Clinical PET—A Modest Proposal

It is impossible for ideas to compete in the marketplace if no forum for their presentation is provided or available.
Thomas Mann

All great ideas are controversial; or have been at one time.
George Selder

As PET emerges from the cocoon of investigation into the harsh reality of clinical practice, it is useful to look at the issues raised by the supporters and critics of this technology. PET has been praised for its remarkable resolution and its ability to make quantitative measurements. PET has been condemned for its cost, complexity and its competition with single-photon techniques. The arguments against PET have gained momentum with the publication of studies showing nearly comparable results for PET and SPECT in areas where both techniques make similar measurements. In contrast, studies reporting measurements that are unique, such as determination of regional glucose utilization with ^{18}FDG, make a compelling case for PET as a major contributor to the clinical care of patients with tumors or coronary artery disease. Since new technologies win their spurs either by making new measurements or by performing existing measurements better, faster or cheaper, let us take a more detailed look at how well PET ranks.

Argument: PET Procedures Are Too Complex

This criticism focuses on two points: the preparation of PET radiopharmaceuticals and the acquisition and analysis of PET studies. Currently, the level of expertise required to prepare PET radiopharmaceuticals is no greater than that needed for the preparation of single-photon studies about 20 years ago. The technology is well understood, the chemistry is reliable, and the final products can be routinely prepared by trained individuals. Image acquisition, reconstruction, and interpretation require the same range of skills and experience as other radionuclide procedures. Proficiency in the performance and interpretation of PET studies can be readily acquired by interested individuals in a similar fashion to that of other new technologies such as MRI or intravasculas ultrasound. The extraordinary quality of state-of-theart PET images, as with MRI, actually makes the data easier to interpret. In contrast to research studies, which may require many hours of imaging and even more time for data analysis, clinical PET studies can be executed rapidly, often with shorter imaging times than conventional single-photon radionuclide procedures.

Argument: PET Offers Little Additional Value When Compared with SPECT

Although comparative studies of comparable PET and SPECT procedures in the same subjects are limited, several have been reported in the evaluation of patients with coronary artery disease. SPECT studies typically utilize ^{201}Tl, while PET studies employ ^{82}Rb or $^{13}NH_3$. The ^{99m}Tc-labeled agents, with their potential advantages of greater photon flux and more favorable energy for imaging with an Anger camera, are unlikely to enhance the sensitivity and specificity of myocardial perfusion imaging in comparison to the results available with ^{201}Tl (*1–5*). Likewise, the total imaging time is likely to remain at about 1 hr. A PET myocardial perfusion study using ^{13}N-ammonia or ^{82}Rb requires about the same amount of time, including two transmission scans. The PET study eliminates attenuation artifacts and provides higher count density images of consistently high resolution for interpretation. These advantages notwithstanding, the results of single-photon studies are so good that improvements in sensitivity or specificity are difficult to detect. However, considering the high prevalence of coronary artery disease and the consequences of a misdiagnosis, even if the sensitivity and specificity of PET are only slightly higher than single-photon techniques, PET procedures could have significant diagnostic value.

In studies by Stewart et al. (*6*) and Tamaki et al. (*7*), PET with ^{82}Rb or ^{13}N-ammonia was shown to have higher sensitivity and specificity than ^{201}Tl SPECT for diagnosing coronary artery disease. However, a difficulty in evaluating these results is the fact that in both investigations, the PET and SPECT studies were separated by 2–4 wk. In a prospective study where ^{82}Rb PET and ^{201}Tl SPECT studies were performed on the same day, Go et al. (*8*) demonstrated that PET had significantly higher sensitivity and accuracy for the diagnosis of coronary artery disease. Unfortunately, these investigations compared PET techniques to thallium stress-redistribution studies, which have been shown to be less sensitive than stress-reinjection for detecting viable/ischemic myocardium (*9*). Despite the lack of extensive comparative data, based on clinical experience in hundreds of cases, PET enthusiasts such as Gould (*10*) identify a

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substantial advantage of PET in terms of specificity. Thus, in the case of PET versus SPECT for myocardial perfusion imaging, the jury is still out.

The detection of viable ischemic myocardium is another area where additional data are needed. In a series of 16 patients, Bonow et al. (*11*) suggested that thallium reinjection imaging with SPECT is comparable to PET measurements of perfusion and glucose metabolism for the detection of viable myocardium. In contrast, in a series of 18 patients, Tamaki et al. (*12*) demonstrated that PET is indispensable for the detection of viable ischemic myocardium and cannot be replaced by reinjection studies. It is likely that neither reinjection, with its enhanced sensitivity compared to redistribution alone, nor reinjection and redistribution (*13*) will identify all patients with ischemic viable myocardium. Similarly, perfusion and glucose imaging may fail to identify all zones of ischemic viable tissue. Severely ischemic myocardium can become sufficiently acidotic so that glucose catabolism may be substantially reduced. Hashimoto et al. (*14*) reported a case of one such patient. Whether this will be the rare exception is uncertain, but it serves to illustrate that no single marker will identify all patients with ischemic viable myocardium. A thoughtful position paper on the current state of clinical cardiac PET was recently issued by the Committee on Advanced Cardiac Imaging and Technology of the Council on Clinical Cardiology of the American Heart Association (*15*). This group came to a similar position—preliminary data are tantalizing—but the comparison to single-photon imaging suggests that PET may offer additional data on a subset of patients only. As a result, the wholesale application of PET may increase the cost of health care and should be carefully considered. They added a note of encouragement in their conclusion: "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."

Another area where PET may be compared with single-photon imaging is bone scanning. Fluorine-18-fluoride was one of the first bone scanning agents in the era of rectilinear scanners. It provided images of high contrast with excellent localization in bone (*16,17*). Unfortunately, this radionuclide was not well-suited for imaging with Anger cameras and was replaced by ^{99m}Tc-labeled diphosphonates (*18–20*). Today, whole-body surveys can be performed with either PET or single-photon multidetector devices. Whole-body bone scans with ^{18}F have uniform high resolution, reduce the requirements for spot views, and enhance the certainty of interpretation (*21*).

In addition to myocardial perfusion and bone imaging, many other procedures could be performed by either technology (Table 1). PET procedures are at least equal to single-photon techniques in terms of speed, sensitivity, and resolution.

The detection of neoplasms by their metabolic characteristics is a unique facility afforded by PET. Although the technique is not able to identify all lesions, the enhanced glucose metabolism associated with many tumors makes the approach valuable. The combination of FDG and total-body imaging makes it possible to increase the specificity of findings on bone scans and identify both primary and metastatic lesions arising from colon and breast cancer (*22,23*). Other metabolic substrates, such as methionine, may be better suited for tumors in selected locations, such as the brain (*24*). Several studies recently have been reported that point to the potential utility of PET in treatment planning (*25*). As this data gains clinical acceptance, it is likely that an ever increasing number of patients will insist on PET studies as part of their evaluation.

Argument: PET Is Impractical

For the institution considering the acquisition of either PET or a new multi-headed SPECT camera, the appeal of PET will be dampened by the physical and bureacratic barriers that such a purchase would entail. A fully operational PET facility requires extensive planning, new construction, special permits and a longer training period for technologists and physicians. Yet once in place, PET has at least two important practical advantages when compared to conventional single-photon operations: (1) minimal radioactive waste; and (2) a reliable supply of radionuclides at a known cost. In the present political environment, one cannot minimize the need to be especially sensitive to issues of waste disposal. Fortunately, the commonly used radionuclides for PET imaging have extremely short half-lives, minimizing the disposal problem. The fragility of a reliable supply of nuclides, especially ^{99m}Tc, was underlined by a recent occurrence. Most of the ^{99m}Tc used in the United States is obtained from ^{99}Mo made in nuclear reactors operating in Canada. In March 1991, a technical problem with those reactors resulted in delays of ^{99}Mo shipments to all generator manufacturers (*26*). Although supplies were maintained, this episode identified a potentially weak link in the supplier system. The increasing costs of maintaining these reactors as they age, and the relative monopoly held by virtually a single supplier, make it inevitable that the cost of ^{99}Mo will rise. When this is coupled with the consolidation of radiopharmaceutical manufacturers, it is certain that the cost of ^{99m}Tc radiopharmaceuticals will increase substantially over the next several years.

PET radiopharmaceuticals do not suffer from these problems. Cyclotron produced short-lived materials are made onsite in the quantities required for the individual institution. The parent for the ^{82}Sr/^{82}Rb generator can be produced

TABLE 1

Standard radionuclide procedure	Pet equivalent	References
Brain Perfusion		
^{99m}Tc-HMPAO	^{15}C-carbon dioxide	27
	^{11}C or ^{15}O-Butanol	28, 29
	^{62}Cu-PTSM	30
Brain Permeability		
^{99m}Tc-DTPA	^{68}Ga-EDTA	31, 32
Blood-Pool imaging		
^{99m}Tc-RBCs	^{11}C-carbon monoxide	
^{99m}Tc-albumin	^{15}O-carbon monoxide	
	^{11}C-albumin	
Bone Imaging		
^{99m}Tc-diphosphonates	^{18}F-fluoride	
Hepatobilliary		
^{99m}Tc-DISIDA	^{68}Ga-HBED	33
Infection Imaging		
^{67}Ga-citrate	^{18}F- or ^{11}C-labeled chemotactic	34
Radiolabeled WBCs	peptides	
Liver-Spleen		
^{99m}Tc-colloid	^{18}F-FDG	35, 36
	^{68}Ga-colloids	
Lung		
^{133}Xe/^{99m}Tc-MAA	^{18}O-carbon dioxide	37
	$^{13}N_2$	
Myocardial Perfusion Imaging		
^{201}Tl	^{13}N-ammonia	38
^{99m}Tc-isonitriles	^{15}O-water	39
^{99m}Tc-teboroxime	^{82}Rb	40, 41
	^{15}O-butanol	
	^{62}Cu-PTSM	42
Renal Imaging		
^{99m}Tc-DTPA	^{68}Ga-EDTA	43
^{99m}Tc-MAG3	^{15}O-water	44
	^{82}Rb	45
Thyroid Imaging		
^{123}I	^{124}I	46
[^{99m}Tc]pertechnetate		
Tumor Imaging		
^{67}Ga-citrate	^{18}F-FDG	47, 48
	^{11}C-methionine	24, 49
	^{11}C-leucine	50
	^{11}C-thymidine	51
	^{124}I-MIBG	
	^{18}F-estradiol	52

by several cyclotrons located throughout the world. The decentralization of isotope production that PET affords minimizes the need for large isotope production facilities with the associated danger of loss of supply to many users.

Argument: PET Is Expensive

The initial cost of establishing a PET facility is high. However, the same is true for an angiographic suite or for state-of-the-art MRI and fast CT. More important than the up-front price is the cost of continued operation. Depending on assumptions about operating hours and patients/hour, costs range from $800/procedure to $2,000/patient scan. As with CT and MRI, it is only cost-effective to perform PET if the facility is operating at least 16 hours/day–6 days/week. Under these assumptions, the costs for PET procedures can be similar to other nuclear medicine examinations.

A Modest Proposal

Opponents and proponents have valid points. Where they fail, however, is in the perception that their preferred modality's existence is contingent upon the demise of the other. This is not the case. The major issue is not whether

PET is better than single-photon imaging, but whether its added value in selected areas makes the technology worthy of the cost and effort needed to make the procedures widely available.

PET is poised to take advantage of new approaches to evaluate pathophysiology. Our field must offer new procedures to grow. Although we have seen recent enhancements to existing procedures through the utilization of new radiopharmaceuticals, the majority of new procedures employ PET. The description of human disease in terms of receptor function and molecular biology are considered by many to be the major advances of twentieth century medicine. PET is the only imaging technique that can apply the in vitro methodologies developed in these areas in a meaningful way in vivo.

It is time to address the issue of clinical PET by permitting reimbursement to at least the level of single-photon imaging. If PET studies provide information of clinical value and the procedures can be performed in a cost-effective manner, the technology will gain an appropriate place in the clinical armamentarium. Only if PET becomes reimbursable can the procedures it offers be applied to the large numbers of patients in varied clinical settings that are required to determine its added value in diagnostic medicine.

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