

STATE-OF-THE-ART PAPER

Cardiac Positron Emission Tomography

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Positron emission tomography (PET) is a powerful, quantitative imaging modality that has been used for decades to noninvasively investigate cardiovascular biology and physiology. Due to limited availability, methodologic complexity, and high costs, it has long been seen as a research tool and as a reference method for validation of other diagnostic approaches. This perception, fortunately, has changed significantly within recent years. Increasing diversity of therapeutic options for coronary artery disease, and increasing specificity of novel therapies for certain biologic pathways, has resulted in a clinical need for more accurate and specific diagnostic techniques. At the same time, the number of PET centers continues to grow, stimulated by PET's success in oncology. Methodologic advances as well as improved radiotracer availability have further contributed to more widespread use. Evidence for diagnostic and prognostic usefulness of myocardial perfusion and viability assessment by PET is increasing. Some studies suggest overall cost-effectiveness of the technique despite higher costs of a single study, because unnecessary follow-up procedures can be avoided. The advent of hybrid PET-computed tomography (CT), which enables integration of PET-derived biologic information with multislice CT-derived morphologic information, and the key role of PET in the development and translation of novel molecular-targeted imaging compounds, have further contributed to more widespread acceptance. Today, PET promises to play a leading diagnostic role on the pathway toward a future of high-powered, comprehensive, personalized, cardiovascular medicine. This review summarizes the state-of-the-art in current imaging methodology and clinical application, and outlines novel developments and future directions. (J Am Coll Cardiol 2009;54:1-15) © 2009 by the American College of Cardiology Foundation

That is gold which is worth gold.

—George Herbert, English poet, 1593 to 1633 (1)

Since the introduction of the first positron emission tomography (PET) scanner in 1975 (2), PET has been used for noninvasive imaging of the heart (3,4). It has often helped reveal groundbreaking basic science in the areas of myocardial blood flow regulation (5–9), myocardial substrate metabolism (10–14), and cardiac autonomic innervation (15–18).

Due to its inherently quantitative nature, its superior detection sensitivity, and its advantageous spatial and temporal resolution over conventional nuclear techniques, PET has been considered a “gold standard” for noninvasive assessment of myocardial perfusion and viability. In the past, multiple new imaging techniques have been validated with PET as the gold standard (19–26). And in the near future, PET imaging is expected to play a key role in the introduction of novel, molecular-targeted imaging approaches (27,28).

Despite its undisputed value as a high-end diagnostic tool, PET has struggled for many years to expand from its role as a reference standard to broader clinical application. Impeding factors have been the complexity and limited availability of PET cameras, the complexity of production and delivery of short-lived positron-emitting radiotracers, and concerns related to the high cost of the test.

Approval of PET radiotracers for clinical cardiac application by the U.S. Food and Drug Administration (FDA) in 1989 and 2000, followed by reimbursement of their use for myocardial perfusion and viability imaging by the Centers for Medicare and Medicaid Services (CMS) (Table 1), were important first steps toward clinical success (29). In recent years, continuous improvement of scanner systems, commercial marketing of the tracers fluorodeoxyglucose (FDG) and rubidium-82 (⁸²Rb), and increasing availability of the technique, mostly due to its tremendous success in oncology, have all contributed to a rapid growth of PET for clinical cardiac imaging.

Today, many leading nuclear cardiology institutions run high-throughput PET programs and create further evidence for its clinical usefulness (30–33). Large sample-size studies and randomized trials are underway or have been published (34). Industry is introducing novel radiotracers for future commercialization (35). Technical advances such as hybrid imaging systems (36) and molecular-targeted probes (28)

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**Abbreviations
and Acronyms**

CAD = coronary artery disease
CFR = coronary flow reserve
CMS = Centers for Medicare and Medicaid Services
CT = computed tomography
FDA = Food and Drug Administration
FDG = fluorodeoxyglucose
MBF = myocardial blood flow
PET = positron emission tomography
SPECT = single-photon emission computed tomography

continue to drive the field forward. Based on these developments, the notion that PET is “worth gold” to advance cardiovascular medicine stays strong.

**Part 1: State-of-the-Art
in Imaging Technology**

Strengths of PET methodology. Beta (+) decay of a nucleus results in emission of a positron, which rapidly annihilates with an electron, giving off two 511-keV photons, which travel in opposite directions. The basic principle of PET is detection of these photons as coincidences in a ring scanner (Fig. 1A). The spatial resolution of reconstructed clinical PET images is currently in the range of 4 to 7 mm (37), and it is superior to conventional nuclear

imaging techniques. Superior detection sensitivity allows for identification of radiotracer at nano- to picomolar concentrations. PET also has high temporal resolution, which allows for creation of dynamic imaging sequences to describe tracer kinetics. Together with readily available correction algorithms for photon attenuation, scatter, and random events, these characteristics make PET a truly quantitative imaging tool that measures absolute concentrations of radioactivity in the body and allows for kinetic modeling of physiologic parameters such as absolute myocardial blood flow or glucose use.

In recent years, several technical innovations have contributed to a steady improvement in the performance of clinical PET systems (Figs. 1B to 1D). New detector materials have enhanced coincidence detection yield and reduced system dead time (37). Three- rather than 2-dimensional coincidence detection is being used to maximize count yield, improve image statistics, and/or reduce injected dose (38,39). Reconstruction algorithms have been introduced that decrease noise and correct for geometry-related loss of resolution with increasing distance from the center of the field-of-view (40). All of these advances make implementation of the time-of-flight (the difference between arrivals of coincidence photons on both sides of the

detector ring, which is in the range of picoseconds) close to becoming a clinical reality. This will increase spatial information and improve the signal/noise ratio (37).

On the acquisition side, collection of data in list mode has become available for routine use, allowing for multiple image reconstructions from a single dataset, including static, gated, and dynamic images (Fig. 2). This increases flexibility and provides various options for advanced image processing. Electrocardiogram-gated datasets can be created for complementary functional analysis (41). The addition of respiratory gating may allow for creation of “motion-frozen” images, which will reduce distortion and facilitate correction for respiratory misalignment (42).

These advantages may be combined with creation of dynamic imaging sequences for routine measurement of tracer kinetics and noninvasive absolute quantification of biological and physiological processes by compartmental modeling (43). **Positron-emitting radiotracers for cardiac imaging.** Table 1 lists current FDA-approved tracers for cardiac PET, and Table 2 lists other cardiac tracers that are not FDA approved but have been successfully applied in humans.

PET PERFUSION TRACERS. FDA-approved ^{82}Rb and ^{13}N -ammonia ($^{13}\text{NH}_3$) allow for short imaging protocols and same-day repeated studies due to their short half-lives. A PET perfusion study can be readily accomplished in a fraction of the time necessary for single-photon emission tomography (SPECT) myocardial perfusion imaging (29,44). $^{13}\text{NH}_3$ has a first-pass extraction of 80% and requires energy for myocardial retention. The images are of high quality and resolution, and uptake is linear over a wide range of myocardial blood flow except at very high flow rates (45). Imaging with $^{13}\text{NH}_3$ requires either an on-site cyclotron or close proximity to a regional radiopharmaceutical production center.

^{82}Rb is a potassium analog that has a first-pass extraction of 65% and also requires energy for myocardial uptake via Na/K-ATPase. With ^{82}Rb , the extraction fraction decreases in a nonlinear manner with increasing blood flow, and this effect is more pronounced when compared with ammonia, although still superior when compared with technetium-99m ($^{99\text{m}}\text{Tc}$)-labeled SPECT compounds (46,47). Image resolution and quality are somewhat compromised due to the high energy of positrons emitted during the decay of ^{82}Rb and due to lower count rates as a result of the ultrashort half-life (Fig. 3). A major advantage of ^{82}Rb over $^{13}\text{NH}_3$ is that it is produced by an $^{82}\text{Sr}/^{82}\text{Rb}$ generator

Table 1 FDA-Approved Cardiac PET Tracers

Tracer	Half-Life	Tissue Positron Range (mm)	Myocardial Uptake Mechanism	FDA Approval	CMS Reimbursement Since
^{82}Rb	78 s	2.6	Na/K-ATPase (perfusion)	December 1989	March 1995
$^{13}\text{NH}_3$	10 min	0.7	Diffusion/metabolic trapping (perfusion)	March 2000	October 2003
^{18}F -FDG	110 min	0.2	Glucose transport/hexokinase (viability)	March 2000	July 2001

CMS = Centers for Medicare and Medicaid Services; FDA = Food and Drug Administration; FDG = fluorodeoxyglucose; Na/K-ATPase = sodium/potassium-ATPase; PET = positron emission tomography; Rb = rubidium.

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