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

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)
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-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 geometrical-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 $^{13}$NH$_3$-ammonia ($^{13}$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). $^{13}$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 $^{13}$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 (99mTc)-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 $^{13}$NH$_3$ is that it is produced by an $^{82}$Sr/$^{82}$Rb generator.
without the need for a cyclotron. Commercial availability of \(^{82}\text{Rb}\) generators in the U.S. has been considered a key element for more widespread application of clinical myocardial perfusion PET.

Another well-established perfusion tracer, \(\text{H}_2\text{\(^{15}\)O}\), is potentially superior to \(^{82}\text{Rb}\) and \(^{13}\text{NH}_3\) because it is metabolically inert and freely diffusible across cell membranes. However, the tracer is not accumulated in myocardium and instead reaches equilibrium between extra- and intravascular compartments. Images of regional myocardial perfusion are not readily obtained, and processing for blood pool subtraction is needed (6). The lack of FDA approval has limited this compound to research applications in the U.S.

**PET Viability Tracers.** \(^{18}\text{F}\)-FDG is an FDA-approved glucose analogue that is widely available due to its success as a metabolic imaging tracer in clinical oncology. The tracer is well established to determine myocardial glucose use as an indicator of myocardial viability. Increased FDG uptake can be observed in ischemic tissue; markedly reduced or absent uptake indicates scar formation (11,48).

FDG uptake is heterogeneous in normal myocardium in the fasting state, so oral glucose loading, nicotinic acid derivatives, or infusion of insulin and glucose have been used to enhance myocardial FDG uptake (44,49). Images obtained in nondiabetic patients and in patients with noninsulin-dependent diabetes are of higher quality after additional insulin infusion than those obtained after oral glucose loading alone. Bolus injections of insulin have been suggested (44,50). When such protocols for patient preparation are followed, cardiac FDG images are generally of high diagnostic quality.

**Radiation exposure.** Radiation exposure from cardiac imaging procedures has increasingly become a matter of discussion (51). An in-depth review of this topic is beyond the scope of this article, and the interested reader is referred to dedicated literature (51). It should be noted, however, that positron emitting tracers typically provide less radiation burden to the patient when compared with SPECT tracers used for the same diagnostic purpose, which is, in part, due to their much shorter half-lives. Also, the radiation burden to staff involved in cardiac PET imaging has been investigated, and due to differences in radiotracer administration, scan acquisition, and stress-testing tasks, doses with PET seem to be lower for staff (as for patients) when compared with single-photon emitting tracers (52).

**Part 2: State-of-the-Art in Clinical Application**

**Myocardial perfusion. Diagnosis of coronary artery disease (CAD).** In a 2005 review, 8 studies that compared perfusion PET with coronary angiography, representing a total of nearly 800 patients, were summarized, and a mean sensitivity of 93% and specificity of 92% for detection of significant CAD were observed (29). A more recent review, reporting a weighted sensitivity of 90% and specificity of 89% from 9 studies including 877 patients, scanned mostly with \(^{82}\text{Rb}\) PET, confirmed these results (36). For detection of myocardial ischemia, myocardial perfusion PET is considered to have superior diagnostic accuracy when compared with the more widely available and more frequently used SPECT technique (Fig. 4).

Available published reports comparing PET and SPECT have also been recently reviewed (36). The robust methods
for attenuation correction with PET reduce the number of false-positive scans due to attenuation artefacts, and specificity is increased. This is of particular importance in obese populations and women, where attenuation artefacts are frequent. Perfusion PET also tends to be more sensitive than SPECT, which can be explained by better spatial resolution and better tracer extraction at high flow, allowing for detection of more subtle perfusion abnormalities. However, the existing literature comparing SPECT and PET has either been published before 1992 or compared both techniques in different, retrospectively matched groups. A prospective head-to-head comparison or randomized study using current state-of-the-art for both techniques is missing and would be desirable to further support the superiority of PET.

PROGNOSTIC VALUE. Although meta-analyses confirm a very high diagnostic accuracy, it should be emphasized that the greatest value of perfusion imaging is considered to be its potential to predict adverse cardiac events (53). This incremental outcome information has been shown to be useful as a gatekeeper for invasive procedures and as a guide to appropriate therapy based on individual risk. Studies in very large patient groups have supported the incremental prognostic value for SPECT perfusion imaging, and confirmatory data for myocardial perfusion PET are also available. In one study, 685 patients were scanned with dipyridamole $^{82}$Rb PET and follow-up was obtained over a mean of 41 months. The annual mortality rate for a normal scan was 0.9%; it was 4.3% for an abnormal scan. After a multivariate analysis, PET results had an independent and incremental prognostic value (54). In a more recent study in 367 patients, 3 groups with different stress perfusion abnormalities (normal, mild, moderate to severe) had annual rates of hard event of 0.4%, 2.3%, and 7%, respectively, and PET data were the strongest predictors of total cardiac events. In obese patients, a preferred target group for PET imaging and a group of individuals at higher risk, the annual total event rate was 11% with an abnormal scan and 1.5% with a normal scan (32). Another very recent study confirmed the prognostic value of dipyridamole $^{82}$Rb PET in 1,441 patients with suspected or known CAD, and it demonstrated an incremental value of stress left ventricular ejection fraction from gated PET (55).

ABSOLUTE FLOW QUANTIFICATION. The ability to quantify myocardial blood flow (MBF) and coronary flow reserve (CFR) in absolute terms is another powerful feature of PET. This is achieved by compartmental modeling of multiframe dynamic acquisitions (47,56–60), and it has initially been limited to research applications in selected populations. Early studies showed adverse effects on CFR.
for multiple risk factors such as hyperlipidemia, diabetes, or smoking and supported the beneficial effects of risk-factor modifications and novel medical therapies (61–73). These studies have contributed to a paradigm shift in the perception of CAD, away from a pure macroscopic view of luminal stenoses and toward an emphasis on microcirculation and endothelial function. These are both determinants of CFR and MBF and are key mediators of disease progression and risk. Several studies have suggested the prognostic value of quantitative PET measurements of MBF and CFR for progression toward clinically overt CAD (74) and in idiopathic and hypertrophic cardiomyopathies (75,76).

The growing use of myocardial perfusion PET for the clinical workup of CAD has resulted in stronger efforts to include absolute flow quantification in the analysis of clinical studies. Technical improvements (i.e., more rapid and robust processing and analysis of dynamic data) have expedited these efforts. Algorithms for the most frequently used clinical cardiac PET tracer, 82Rb, are increasingly being validated and used (43,47,60). Quantitative flow measurements may be useful and complementary to the current standard of visual/semiquantitative analysis. Their reproducibility has been demonstrated repeatedly (77–79). They may be useful for detection and evaluation of extensive multivessel CAD with balanced ischemia on qualitative images (80) (Fig. 5), evaluation of the significance of a given lesion (81), evaluation of collateral flow (82), identification of endothelial dysfunction in pre-clinical disease, as well as reliable monitoring of therapeutic strategies.

**Table 2**

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**Figure 3**

PET Perfusion Tracers

Tomographic positron emission tomography (PET) images of myocardial perfusion after administration of adenosine using 3 different tracers, the Food and Drug Administration-approved agents 99mTc-methoxyisobutylisonitrile (99mTc-MIBI) (top) and 13N-ammonia (13NH3) (middle), and the novel compound 18F-fluorobenzyltriphenylphosphonium (18F-FBnTP) (bottom). All images were obtained in a dog model of hemodynamically relevant left circumflex coronary artery stenosis, resulting in reduced perfusion of inferolateral myocardium, as shown by all 3 tracers. Since the canine cardiac anatomy is different from human anatomy, the septum is displayed more superiority in short axis (SA) images. HLA = horizontal long axis; VLA = vertical long axis.

**Figure 4**

Comparison of PET and SPECT Perfusion Imaging

Shown are matched, representative short-axis slices for single-photon emission computed tomography (SPECT) (left) and positron emission tomography (PET) (right) in 2 subjects with suspected coronary artery disease. Panel A illustrates improved specificity with PET. A fixed defect in the inferior wall on SPECT is absent on PET, suggesting the presence of a SPECT attenuation artefact. Panel B illustrates improved sensitivity with PET. Stress-induced perfusion defects in the anterior and inferolateral walls (arrows) are more clearly shown with PET versus SPECT.

**SUMMARY.** Table 3 summarizes the evidence and potential clinical role of PET myocardial perfusion imaging.

**Myocardial viability.** Clinical value. Therapeutic decision making is difficult in patients with advanced CAD and severe left ventricular dysfunction because revascularization has
a high procedure-related risk. Viability testing has been developed to serve as a guide to the most appropriate therapy. Initially, PET techniques played a key role in understanding the myocardial response to severe ischemic damage and in establishing the identification of myocardial viability as a diagnostic target. Metabolic imaging has been used to support the notion that assessment of perfusion alone may not be enough to predict functional recovery after revascularization. The pathophysiology of hibernating myocardium has been characterized by PET imaging as resting hypoperfusion and dysfunction with preserved glucose metabolism (11) (Fig. 6).

It is now well known that PET, using the metabolic tracer FDG, is accurate to predict improvement of regional wall motion and global left ventricular ejection fraction after revascularization. When comparing PET with alternative viability imaging techniques such as low-dose dobutamine echocardiography, SPECT imaging with perfusion tracers, or delayed enhancement magnetic resonance imaging, differences exist that are mostly related to the pathophysiological target of each imaging test. A detailed comparison between techniques is beyond the scope of this article, and readers are referred to dedicated reviews (83–85).

PET is most predictive of improvement of function after revascularization when blood flow is reduced by >50%, with relatively high glucose uptake. A recent pooled analysis of 24 studies in 756 patients, demonstrated a weighted mean sensitivity and specificity of 92% and 63%, respectively, for regional functional recovery, with positive and negative predictive values of 74% and 87%, respectively (85).

It has been shown that it is critical to revascularize patients with PET-defined hibernating myocardium as soon as possible because improvement is less likely to occur when surgery is delayed after documentation of dysfunctional but viable myocardium (86). This has recently been confirmed in a large study analyzing more than 700 patients who all underwent 18F-FDG PET. Patients with rapid intervention had significantly better outcomes when compared with a propensity-matched group with delayed or no intervention (33).
Other studies have shown that PET can also be used to predict improvement of heart failure symptoms and improvement of exercise capacity (87). Several retrospective studies have focused on the outcome of patients with ischemic heart disease and ventricular dysfunction relative to their PET results and their treatment strategy. A recent meta-analysis summarized 10 studies in 1,046 patients and found annualized mortality rates of 4% for those with viable myocardium who underwent revascularization versus 17% for those with viability who did not undergo revascularization. The mortality was 6% for those without viability undergoing revascularization versus 8% for those without viability not undergoing revascularization (85).

**RANDOMIZED TRIALS.** Assessment of myocardial viability by PET is one of the few diagnostic approaches that have been explored in randomized diagnostic studies. Such studies are difficult to design because therapeutic decision making (which will influence outcome) is difficult to control. The field should be commended for having conducted such studies. Despite the strength of randomization, results of these studies must be interpreted with caution. Inclusion criteria as well as management algorithms need to be taken into consideration. One early randomized study assigned patients to either SPECT or PET and found no difference in accuracy between techniques for viability assessment (88). However, the study included patients with relatively preserved ejection fractions, where differences between techniques may be minimal.

The benefits of PET are expected to be greater in a target population with severe heart failure and an ejection fraction below 35%. A group of patients fulfilling these criteria was studied in another recent randomized trial that assigned 430 patients to either management assisted by FDG PET or standard care. The study overall showed only a nonsignificant trend toward reduction in cardiac events for FDG PET-assisted management versus standard care. But it needs to be emphasized that alternative viability testing was allowed in the control arm and that nonadherence to PET-based recommendations was found in a significant subfraction of patients in the PET arm. Importantly, in those who adhered to PET recommendations regarding therapy, significant survival benefits were observed (34). Although PET has been used in large and powerful viability studies, the results of these studies are still controversial and it is difficult to find a unifying conclusion. The evidence in support of the usefulness of PET is growing, but the use of viability imaging at a given center is still defined mostly by local expertise and availability.

**SUMMARY.** Table 4 summarizes the evidence and potential clinical role of PET myocardial viability imaging.
Cost-effectiveness considerations. In cardiology, imaging options are extensive and often redundant. Because financial resources in health care are increasingly limited, the question of cost-effectiveness is crucial. The value of PET as a research tool and as a gold standard for other diagnostic imaging techniques is not in question, but reimbursement and general clinical application of the technique is under more scrutiny because a PET procedure is more expensive than other noninvasive procedures.

Looking only at the costs of a single test is a short-sighted, incomplete approach. Estimation of the total cost of diagnostic tests for CAD requires consideration of indirect and induced costs of management algorithms based on the test. False positives may result in unnecessary subsequent diagnostic or therapeutic procedures, which carry additional costs and risks. A missed diagnosis due to a false-negative test, on the other hand, may result in preventable adverse events that could impair life duration and quality. A comprehensive analysis of utility has to account for the impact of medical care on quality as well as quantity of life.

Patterson et al. (93) used a mathematical model to compare cost-effectiveness of exercise electrocardiography, SPECT, PET, and invasive angiography to diagnose CAD. Their model accounted for costs per effect or cost per utility unit (including cost of diagnostic and therapeutic measures, which included those that yield false-positive results as well as those that yield false-negative results). They observed that PET, despite the high cost of a single test, shows the lowest cost per effect in patients with a pre-test likelihood of CAD below 70%. This was attributed to its superior diagnostic accuracy and avoidance of false-positive and false-negative studies. Only when the pre-test likelihood was above 70% was direct angiography the most cost-effective approach. Gould et al. (94), using a somewhat less complex model, had earlier come to similar conclusions, but both studies were published more than 13 years ago.

Merhige et al. (95) more recently compared the frequency of diagnostic arteriography, revascularization, costs, and 1-year clinical outcomes in 2,159 patients studied with PET with an internal and an external SPECT control group. They showed reduced use of downstream invasive procedures when using perfusion PET versus SPECT, which resulted in lower costs with comparable outcomes.

Similar issues need to be considered for PET imaging of myocardial viability. The costs of a single test are high, but the costs and risk of avoidable surgical or interventional treatment may be even higher. Avoidance of an unnecessary bypass operation, or even of an unnecessary cardiac transplantation, may justify conducting numerous noninvasive tests if they are appropriate for guidance of clinical decision making. It has clearly been shown that PET assessment of viability influences decision making (96), and if PET recommendations are followed, outcomes will improve (34).

One study in the United Kingdom applied an economic model and compared 3 strategies (bypass for all patients,
medical therapy for all patients, and PET-guided decision for bypass or medical therapy). It was concluded that PET may be cost-effective to select patients with poor left ventricular function for coronary artery bypass grafting (97).

Hence, there is some evidence for cost-effectiveness of cardiac PET in the clinical setting. Factors such as higher patient throughput and patient comfort due to shorter imaging protocols for PET versus SPECT have not even been considered in the above analyses. But cost-effectiveness remains complex and difficult to generalize. Further studies using updated clinical algorithms and updated values for accuracy and procedure costs are necessary to support the use of PET in the actual health care environment.

Target populations in which perfusion PET may be especially cost-effective are obese patients and women, although it should be noted that computed tomography (CT) angiography may emerge as a competitor to PET in such situations (98). For viability imaging, end-stage ischemic cardiomyopathy may be the most useful situation. Studying cost-effectiveness in these specific groups in more detail might further support an efficient clinical use of the high-end technique.

**Part 3: New Developments and Future Directions**

**Hybrid PET-CT: the merging of morphology, function and biology.** Due to their success in oncology, all currently offered PET imaging systems are hybrid PET-CT scanners. This has brought challenges for cardiac imaging that are related mainly to the use of a separate CT for attenuation correction of subsequently acquired PET data. Respiratory or patient motion may result in misalignment of CT and PET and artificial heterogeneity in CT-attenuation-corrected cardiac PET images (99). Corrective algorithms have been proposed to address this issue (99–101).

More importantly, the advent of hybrid PET-CT has resulted in the unique opportunity to combine CT-derived morphologic information with PET-derived functional, physiological and biological information. Most PET-CT scanners are now equipped with multislice CT, allowing for CT measurement of coronary calcium and/or CT coronary angiography in addition to PET imaging procedures.

Schenker et al. (31) measured myocardial perfusion and coronary calcium in a single cardiac PET-CT study in 695 patients with an intermediate pre-test likelihood of CAD. They observed an increasing prevalence of abnormal PET with increasing coronary calcium scores. In about 50% of cases with very high calcium, myocardial perfusion was abnormal. But interestingly, abnormal perfusion was also found in 16% of patients with absent calcium.

Risk-adjusted survival analysis demonstrated a stepwise increase in cardiac events with increasing calcium scores in patients with and without ischemia on PET. Among patients with normal PET myocardial perfusion imaging, the annualized event rate in patients with no calcium was lower than in those with high calcium (2.6% vs. 12.3%, respectively). In patients with ischemia demonstrated on PET, the annualized event rate in those with no calcium was also lower than in those with high calcium (8.2% vs. 22.1%). These data suggest that CT calcium scoring and PET perfusion imaging are complementary for the assessment of cardiovascular risk. Both can be integrated to stratify patients into different risk-based categories.

There is less evidence at the moment for the integrated use of CT coronary angiography and perfusion PET, although initial studies suggest that both tests may also be complementary rather than competitive. Not all patients with obstructive atherosclerosis on CT show ischemia on PET and, vice versa, not all patients with nonobstructive CAD have no perfusion abnormalities (102).

Contrast-enhanced CT angiography enables the detection of noncalcified plaque and, if imaging is repeated several minutes after injection, it may allow for detection of infarcts by delayed contrast enhancement (103,104). How this information is best combined with PET for maximization of diagnostic and prognostic accuracy will be a matter of further research in the future. It is likely, however, that increasing availability of 64-slice CT in PET-CT systems, along with new prospectively gated CT acquisition techniques, which lower radiation exposure for CT angiography by more than 70% (105), will contribute to a more widespread use in hybrid PET-CT protocols (Fig. 7). Innovative integrated imaging protocols may include CT for morphologic assessment of coronary arteries and PET for functional assessment of myocardial blood flow. A CT delayed enhancement study may be done after CT angiography to identify the presence or absence of scar (104). This may obviate the need for a rest perfusion study.

**Novel myocardial perfusion tracers.** All established PET perfusion tracers have half-lives that are very short. This limits their applicability for exercise stress, so clinical protocols usually use pharmacologic stress with the patient on the camera table, followed by immediate imaging. Another consequence of the short half-lives is the limited availability of tracers because they require an on-site cyclotron or a significant financial commitment to a strontium/rubidium generator, which needs to be replaced every month and requires high-throughput imaging to be cost-effective. This has generated interest in fluorine-18-labeled perfusion tracers, which may overcome both problems due to a longer, 110-min half-life. Like FDG, which has already been successfully commercialized, these tracers can be produced in regional centers for dose-by-dose delivery to multiple PET sites. Also, they may be injected during exercise stress with enough time to move the patient to the camera after completion of the stress protocol.

Currently, data are available on 2 18F-labeled perfusion compounds. 18F-BMS747158 is a pyridazinone derivative that avidly binds to mitochondrial complex-1 (106). Its first-pass extraction fraction is very high at 94% (107), and it yields high and stable myocardial uptake that is proportional to myocardial blood flow. Myocardial uptake is
greater than that of the SPECT tracers thallium-201 and $^{99m}$Tc-sestamibi (35). The compound is very promising for myocardial perfusion PET imaging and it is currently being tested in clinical phase 1 and 2 studies (Fig. 8).

$^{18}$F-fluorobenzyl triphenyl phosphonium (FBnTP) is another compound that is taken up rapidly by myocardium in proportion to myocardial blood flow (108), with high contrast that is superior to the SPECT tracer $^{99m}$Tc-tetrofosmin. It also targets mitochondria (109) and seems to be promising for myocardial perfusion imaging (Fig. 3), although, unlike BMS747158, it has not entered clinical trials yet.

**Molecular imaging.** Cardiovascular molecular imaging is a rapidly emerging discipline that aims toward visualization of specific molecular targets and pathways that precede or underlie changes in morphology, physiology, and function. Due to its high detection sensitivity, PET is considered a key player in the development and introduction of novel molecular-targeted imaging approaches. The introduction of dedicated small animal imaging systems, which allow for serial in vivo imaging in rodents and facilitate translation of new diagnostic compounds from experimental to clinical practice (Fig. 9), has further contributed to increasing recognition of the future potential of molecular imaging in cardiovascular research and patient care (110–113).

Due to the wide spectrum of novel approaches, a detailed review of PET-based molecular imaging is beyond the scope of this article, and the reader is referred to dedicated articles (27,28,114,115). Some key principles and some examples are highlighted below. First, molecular imaging places an emphasis on the diagnosis (and subsequent treatment) of precursors or the earliest stages of the disease, as opposed to its sequelae. Examples are the use of neuronal imaging to identify subjects at risk for ventricular arrhythmia (116), the development of compounds targeting plaque vulnerability before rupture and subsequent myocardial infarction (117,118), and the targeting of biomechanisms that precede left ventricular remodeling and development of heart failure (119,120).

Second, molecular imaging has great potential to facilitate discovery and development of novel therapies through improved target identification and implementation of more efficient end points for clinical trials. Examples are the
measurement of myocardial efficiency to identify the benefits of therapies for heart failure (121,122) and imaging the beneficial effects of metabolic interventions (123).

Third, visualization of cellular and subcellular target structures has contributed to advances in fundamental cardiac research such as cell trafficking, myocardial regen-

**Figure 8** PET-CT Perfusion Imaging at Rest and With Physical Exercise Using the Novel $^{18}$F-Labeled Compound BMS747158

The injected dose was 1.5 mCi at rest and 3.5 mCi at peak stress. Shown are static attenuation-corrected PET images acquired from 5 to 10 min after injection (left), as well as PET-CT fusion images documenting good alignment of PET and CT (right). Rest and stress studies were obtained on subsequent days as part of a clinical phase-1 study in healthy volunteers. Abbreviations as in Figures 3 and 7.

**Figure 9** Translational Molecular Cardiac PET Imaging

Shown are representative midventricular short-axis slices of myocardial sympathetic innervation imaged with $^{11}$C-epinephrine, in the healthy human, pig, and rat heart. For size comparison, images are shown at the same scale (A) and after zooming to comparable image size (B). Human and pig hearts were imaged with a clinical scanner and the rat heart with a dedicated small animal scanner.
eration, and heart failure-specific functional genomics and proteomics. Examples are the development of reporter gene imaging techniques (28) and the implementation of cell labeling for imaging of engraftment after transplantation (28,124).

And fourth, the need to visualize small amounts of molecular-targeted compounds in small target areas drives advances in the imaging sciences such as instrumentation, reconstruction algorithms, and probe design to improve the detection sensitivity, molecular specificity, and translational potential of molecular imaging.

The vision is that novel molecular-targeted approaches will guide early disease detection and therapeutic/preventive decision making based on an individual’s biology. PET as a key modality may thereby contribute to further personalization of cardiovascular medicine.

Synergies between oncologic and cardiovascular PET. Although PET is on the move in cardiovascular medicine and new developments are likely to increase its application and impact in clinical practice, some similarities and interrelationships between its cardiac applications and applications for tumor imaging should be noted. First, the success of PET as a key modality in tumor staging and evaluation of anti-tumor therapy has resulted in dissemination of the technique and in improved availability for cardiac imaging. Second, expensive equipment, such as scanners, radiochemistry laboratories, and cyclotrons, is most effectively used when it serves multiple areas of PET imaging applications. And finally, many existing and novel biologic targets for PET imaging are important not only in heart and vessels, but also in tumors (Table 5). This is highly relevant not only because advances in tumor biology may help advance cardiovascular biology via improved understanding of related biomechanisms, but also because multiple applications in heart, vessels, and tumors will be helpful to stimulate interest in commercialization of compounds with a broader spectrum of target groups.

Summary and Conclusions

Cardiac PET is a powerful, quantitative, noninvasive imaging technique that is increasingly penetrating the clinical arena. For clinical assessment of myocardial perfusion and viability, evidence for diagnostic and prognostic usefulness is increasing and cost-effectiveness due to high accuracy despite high single-test costs is suggested. The advent of hybrid imaging enables routine combination of PET with CT-derived morphologic parameters. New molecular imaging compounds will be key elements in the emerging paradigm of personalized medicine.

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REFERENCES


Table 5 Examples of Common Imaging Targets in Myocardium, Vessel Wall, and Tumors

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<tr>
<td>Glucose use</td>
<td>↑ (when damaged)</td>
<td>↑ (when inflamed)</td>
<td>↑</td>
</tr>
<tr>
<td>Apoptosis</td>
<td>↑ (when damaged)</td>
<td>↑ (when inflamed)</td>
<td>↑ (in therapy response)</td>
</tr>
<tr>
<td>Integrin expression/angiogenesis</td>
<td>↑ (when damaged)</td>
<td>↑ (when damaged)</td>
<td>↑ (some tumors)</td>
</tr>
<tr>
<td>Matrix metalloproteinase expression</td>
<td>↑ (when damaged)</td>
<td>↑ (when vulnerable)</td>
<td>↑ (some tumors)</td>
</tr>
</tbody>
</table>
Cardiac PET


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Key Words: positron emission tomography • myocardial perfusion • myocardial viability • hybrid imaging • molecular imaging.