The diagnostic and prognostic evaluation of cardiovascular diseases has been improved considerably by the application of imaging procedures. Among many, scintigraphic procedures have emerged as important diagnostic tools to assess extent, severity, and prognosis in patients with coronary artery disease (CAD). For more than the last 30 years, however, the application of perfusion imaging has been extended to allow the combined evaluation of perfusion, perfusion reserve, and ventricular function. With positron emission tomography (PET), quantitative assessment of perfusion has become possible. In combination with pharmacological stress agents, the coronary flow reserve (CFR) can be quantitatively assessed as an early marker of endothelial dysfunction. PET in combination with metabolic tracers has added the evaluation of cardiac substrate metabolism, which has become an important clinical marker for ischemically jeopardized myocardium. The PET information is widely considered as the gold standard for tissue viability in the management of patients with advanced CAD and impaired left ventricular function (LVF). New tracer approaches include the assessment of cardiac innervation, which plays an increasingly recognized role in the pathophysiology of cardiac diseases. Radiolabeled catecholamine analogues provide visualization of sympathetic nerve terminals that are functionally altered in patients with diabetes mellitus and cardiomyopathy. In addition, this scintigraphic information allows the monitoring of physiological processes such as reinnervation of the transplanted heart. New methods, such as imaging of apoptosis and gene expression, are of interest in cardiology. Combining the therapeutic gene with a reporter gene, the transfection of cardiac tissue can be monitored noninvasively. First results employing the herpes simplex virus thymidine kinase reporter gene (HSV1-tk) are encouraging and represent an attractive approach for the use of PET imaging in the control of cardiac gene therapy. © 2003 Elsevier Science, Inc. All rights reserved.

Key Words: Cardiovascular disease; Scintigraphic; Perfusion; Cardiac gene therapy; PET imaging.

Introduction

In-vivo imaging has become an important tool in medicine, not only to detect the disease process but also to quantify extent and severity, as well as to follow the time course of disease. Starting from the application of X-ray technology to measure the density distribution within the body, new techniques have been introduced during the last century to assess—besides anatomic details—the functional aspects of the disease process. The introduction of dynamic data acquisition allows for the description of organ function (Figure 1). Examples, such as the noninvasive assessment of cardiac pump function using computed tomography (CT), magnetic resonance imaging (MRI), or echocardiography are widely applied clinical tests. In addition to the dynamic data acquisition, the use of contrast agents has improved the diagnostic information obtainable from imaging. X-ray contrast agents not only provide enhancement of vascular structures, but also the estimation of tissue perfusion. With the introduction of tracer techniques, physiological and biochemical processes can be directly visualized. Tracer approaches excel by their high sensitivity and specificity for a given physiological process. The fact that only small amounts of radiolabeled molecules are needed offers the advantage that biological processes are not disturbed. Combining the tracer approach with tracer kinetic modeling, quantitative parameters not only of perfusion but also other tissue function such as metabolism can be derived for diagnosis and prognosis.1 These advances in the area of imaging are paralleled by a change in our understanding of the disease process. Rapid advances in molecular biology led to an improved understanding of the pathophysiology and the
hope to identify patients at risk prior to developing disease with clinical manifestations. It can be foreseen that patients at genetic risk will undergo imaging to define the phenotype using early markers of disease, such as endothelial dysfunction in the case of coronary artery disease (CAD).

In this article, we will review the progress of nuclear cardiology as an example of how imaging technologies adapted to the changing understanding of cardiovascular diseases. We will also try to define future challenges for imaging technologies in a clinical setting, as well as in a research environment.

**Perfusion Imaging**

In the early 1970s, Strauss and Zaret first introduced thallium-201 scanning as a new method to visualize myocardial perfusion using a potassium analogue, which is highly extracted by the myocardial cell. By injection of this radiopharmaceutical under stress conditions, the relative myocardial perfusion reserve can be estimated and related to coronary anatomy. In subsequent years myocardial perfusion imaging has emerged as one of the most widely used nuclear test. Several studies have shown that the combination of tracer application with physiological or pharmacological stress provides high diagnostic accuracy in the detection of significant CAD. From these studies it also became evident that a normal perfusion during stress is associated with a very favorable prognosis indicating the strength of functional imaging providing independent prognostic information. The same applies to the evidence of stress-induced perfusion abnormalities as a marker of ischemia. It has been shown that perfusion imaging offers incremental and independent prognostic information in comparison to symptoms, stress electrocardiogram and angiography.

Based on this clinical success, the imaging technologies have been further developed in order not only to assess relative perfusion abnormalities but also to measure myocardial perfusion in absolute terms. With the introduction of positron emission tomography (PET) it became possible to quantitate myocardial perfusion in ml/min/100 g tissue. Flow tracers such as N-13 ammonia or O-15 water in combination with tracer kinetic modeling provide accurate flow measurements with high reproducibility. The comparison with reference measurements such as microsphere flow determinations indicates a linear correlation of PET tracer uptake and myocardial flow over a wide range. Clinical applications of quantitative flow measurements are still limited due to their challenging protocols and limited availability of PET. Research data indicate that coronary flow reserve (CFR) is an important marker not only for advanced CAD, but also for early changes in coronary vasoreactivity most likely due to endothelial dysfunction. It is hypothesized that endothelial dysfunction may represent an early and potentially reversible form of atherosclerosis. Recent studies have shown that an abnormal vasoreactivity in the coronary bed is associated with adverse clinical outcome. These data were obtained by invasive measurements in the catheter laboratory. The noninvasive approach by PET represents an attractive alternative to prospectively assess risk populations.

The quantitation of regional CFR has been advocated by Gould et al. for the functional assessment of the severity of coronary artery stenosis in patients with proven CAD. The parameter flow reserve describes not only the functional significance of a given coronary lesion but also vascular reactivity and collateral blood flow in the poststenotic vascular territories. Such functional measurements complement the anatomic description of CAD and link the morphological alterations of epicardial arteries.
with perfusion patterns assessed at the level of microcirculation. Limitations of angiographic characterization of CAD are widely appreciated due to the complex three-dimensional nature of atherosclerotic plaques, as well as considerable interobserver variability in angiographic data interpretation.14–17

A relationship between coronary reserve measurements and age in subjects without CAD has been demonstrated.18 However, there are other factors, such as left ventricular hypertrophy, hypertension, as well as Syndrome X, which may affect coronary reserve measurements in the absence of vascular abnormalities defined by angiography.19,20

In patients with CAD, CFR measurements are reduced.21–25 A correlation between the severity of CAD and severity of flow reserve impairment has been documented.21,24–27

The high incidence (about 30%) of abnormal CFR in territories with only mild CAD is surprising as defined by angiography.28 These data have been confirmed by several laboratories indicating that CFR with pharmacological stress agents may provide more sensitive means to detect early CAD than angiographic criteria alone.21,29 This hypothesis has been addressed by several investigators who have demonstrated that CFR in asymptomatic male patients without clinical evidence of myocardial ischemia, but at high risk for the development of CAD based upon risk factor profile was abnormal.30–33 A significant relationship between the impairment of CFR and plasma cholesterol, LDL, HDL, and oxLDL has been reported. CFR has been shown to be reduced in young men with familial hyperlipidemia, especially with combined abnormalities in cholesterol and triglyceride serum levels (phenotype IIb).34 Furthermore, reduction of flow reserve has been observed in asymptomatic patients with insulin dependent and non-insulin dependent diabetes mellitus.30

The pathophysiological mechanism of the reduced CFR in territories with no, or only mild, angiographic evidence of stenosis is not yet known but may represent complex interplay of vascular alterations, as well as endothelial dysfunction.35 The hemodynamic response to dipyridamole or adenosine can be modified by alpha or beta-receptor blockade, enhancing the range of coronary flow measurements.36,37 First results employing cold pressor stress testing in combination with PET confirm the data obtained in the catheterization laboratory using intracoronary acetylcholine infusion.38–39 In addition, mental stress has been used to investigate coronary vascular reactivity in normals and CAD patients, which demonstrated reduced flow response in this patient group.40

PET flow measurements offer a unique opportunity to follow the change of vascular reactivity during risk factor modification. It has been shown that lowering lipid levels is associated with improvement of CFR. This is, however, delayed as compared to the decrease of lipid levels in plasma.41 In patients undergoing interventions that acutely change cholesterol levels such as lipid apheresis, the lowering of cholesterol was not associated with improvement of CFR. The studies indicate that vascular reactivity is not only related to plasma cholesterol levels, but may represent a complex adaptation of vascular structures to high concentrations of circulating lipids. Although myocardial perfusion imaging using thallium-201 or technetium-99m flow markers remains the most widely used clinical test to assess myocardial flow characteristics, PET may gain clinical importance with the increasing availability of this technique. Cost effectiveness studies will have to examine if using PET instead of single photon emission computed tomography technology results in improvements in the diagnostic, as well as prognostic evaluation of patients with proven or suspected CAD.

Assessment of Cardiac Metabolism

Early after the introduction of PET, imaging laboratories concentrated on evaluation of cardiac metabolism using tracer techniques (Figure 2).42 Since the myocardial cell primarily relies on the oxidation of long chain fatty acids for its production of high-energy phosphates, the use of C-11 palmitate was thought to provide a noninvasive parameter of cardiac metabolism. Studies with this tracer have shown that uptake and oxidation of fatty acids can be studied and related to the dietary state, cardiac work and extent, and severity of hypoxia.43,44 However, since C-11 palmitate undergoes a complex metabolic pathway within the myocardial cells, the interpretation of tracer kinetics remained challenging. The complexity of metabolism of C-11 palmitate prevented the development of a simple tracer kinetic model that allows for quantitation of myocardial fatty acid metabolism. With the introduction of F-18 thia heptadecanoic acid (FTHA) that accumulates in the myocardium as a function beta-oxidation, fatty acid metabolism can be quantified.45

An alternative metabolic probe is C-11 acetate as a marker of the TCA cycle and, thus, the oxidative metabolism of the heart. C-11 acetate offers the advantage that its uptake and metabolism is independent of substrate interaction.46 C-11 acetate is rapidly converted to C-11 acetyl-CoA, which is the preferred substrate for the TCA cycle. The disappearance of radioactivity from tissue closely correlates with the release of C-11 CO2, allowing simple curve fitting procedures for quantitation of myocardial oxidative metabolism.47 There are methods to quantitate myocardial oxygen consumption by calibrating the clearance half time of C-11 activity with direct measurements of oxygen consumption in the experimental setting.48 Relating myocardial oxygen
consumption to mechanical work of the ventricular indices of metabolic efficiency of the heart can be derived.\textsuperscript{49} Several studies have shown that this parameter is altered in patients with ventricular dysfunction.\textsuperscript{50} Using the combination of PET metabolic imaging and functional assessment by echocardiography or MRI, unique measurements can be obtained in patients and related to parameters of disease severity. Recent studies in our laboratory have shown that myocardial efficiency is altered in conditions such as hypothyroidism and left ventricular dysfunction.\textsuperscript{51,52} It has also been shown that the efficiency can be improved by therapeutic interventions in patients with congestive heart failure.\textsuperscript{48,53} Infusion of nitroprusside or dobutamine improved the relationship between oxygen expenditure and mechanical performance of the heart. These research studies suggest the potential of PET imaging to perform in vivo measurements of regional metabolism. Previously, these were only possible in complex experimental settings. Further studies will address the question if such measurements provide endpoints for the assessment of therapy in patients with left ventricular dysfunction.

The metabolic tracer most widely used in cardiac imaging is 2-deoxy-2-\textsuperscript{18}Ffluoro-D-glucose (FDG). The delineation of glucose utilization is of importance, since the glucose extraction by the myocardium is increased in pathophysiological conditions such as ischemia and hypoxia.\textsuperscript{54} Based on this principle, this technology has been applied to assess ischemically compromised myocardium during stress and under resting conditions.\textsuperscript{55,56} It has gained clinical acceptance in the assessment of tissue viability since glucose uptake in normal and ischemically compromised myocardium is associated with cellular integrity. Areas with left ventricular dysfunction that display maintained or relatively increased glucose utilization have shown to benefit from revascularization.\textsuperscript{56,57} The extent of FDG uptake is correlated with the degree of functional recovery following revascularization in the majority of patients with maintained FDG uptake. In addition to the predictive value for functional recovery, several studies have indicated that hibernating myocardium is associated with poor clinical outcome. This clinical observation has led to the hypothesis that upregulation of glucose transport and phosphorylation represents a stress signal for ischemically compromised myocardium. This interpretation has stimulated a number of experimental studies investigating the relationship of FDG uptake in the myocardium, and the expression and translocation of glucose transporters.\textsuperscript{59,60} There are several glucose transporters known to exist in the myocardial tissue. Transporters GLUT1 and GLUT4 are known to play a predominant physiological role in myocardial glucose transport. While GLUT1 primarily determines basal uptake of glucose, GLUT4 is insulin responsive and modulates glucose utilization in response to hormonal stimulation (Figure 3). It has been demonstrated, that insulin and ischemia represent independent stimuli for the translocation of GLUT4 transporters to the cell membrane. In addition, catecholamine induced upregulation of glucose transport may play a pathophysiological role during myocardial ischemia.\textsuperscript{61} It is known that during myocardial ischemia regional catecholamine levels may increase by leaky presynaptic nerve terminals.\textsuperscript{62} The comparison of myocardial FDG uptake, and the expression and translocation of glucose transporters provides unique insights into the molecular regulation of glucose uptake. This technique has been applied to transgenic animals with knockout of GLUT4 transporters. Figure 4 shows PET images in transgenic animals prior to and after exposure to insulin as compared to wild type animals with
intact GLUT4 transporters. The results suggest that GLUT4 knockout animals display the same FDG response to insulin as control animals. Based on the biochemical information provided by FDG-PET, a molecular mechanism is assumed to compensate for the lack of insulin responsive GLUT4 transporters. By relating the genotype information with the phenotype measurements provided by PET, important measurements can be performed in the genetically altered animal model defining phenotypical adaptation to genetic alterations.

The discrepancy between myocardial blood flow and metabolism in patients with advanced left ventricular dysfunction has led to the concept of hibernating myocardium. This concept includes dedifferentiation of myocardial cells and a switch of metabolic pathways in the affected myocardium. The observation of chronically increased FDG uptake in repetitive ischemic segments indicates a preferential glucose metabolism in these myocardial segments as a source for high-energy phosphates. This alteration in glucose utilization is associated with increased glycogen storage and ultra structural changes of the heart. In addition, the longitudinal evaluation of functional recovery following revascularization indicates delayed functional recovery of hibernating myocardium as compared to segments that have the normal metabolic pattern.63

The upregulated FDG uptake in ischemically injured myocardium may represent a stress signal of cells undergoing repetitive ischemia. Animal studies have shown that GLUT1 mRNA expression is increased during prolonged ischemia in the dog model.64 Clinical observations support this notion by reporting a high incidence of cardiovascular complications in patients with hibernating myocardium without revascularization.65,66 In addition, the metabolic signal of increased FDG uptake in the presence of reduced N-13 ammonia uptake was associated with poor clinical outcome in patients waiting for bypass surgery.67 This PET research led to the increasing recognition of hibernating myocardium as frequent clinical sequelae of advanced CAD and plays an important role in the management of such patients.

Evaluation of the Presynaptic and Postsynaptic Autonomic Nervous System

The visualization of cardiac innervation by imaging techniques represents a unique application of tracer techniques to monitor neuronal function. It is impossible by anatomic imaging to separate nerve fibers from myocardial or vascular cells. Using tracers, which are specifically retained in neuronal structures, it becomes possible to identify the distribution of cardiac nerves.
The heart is innervated by the parasympathetic and sympathetic nerve fibers. The left ventricle of the heart is primarily supplied by sympathetic nerves that modify cardiovascular performance in adapting to the changing hemodynamic requirements. The parasympathetic nervous system primarily innervates the atria and the conduction system. There is a highly regulated balance in the sympathetic and parasympathetic input to optimize cardiac performance.

A number of radiopharmaceuticals have been developed to identify the presynaptic nerve terminals. In addition, tracers have been introduced to assess the adrenergic receptors of the heart. Among the presynaptic tracers, radioiodinated metaiodobenzylguanidine (MIBG) and C-11-labelled metahydroxyephedrine (HED) have emerged as the most commonly applied radiopharmaceuticals. Both tracers represent false neurotransmitters of the sympathetic system. They resemble in their chemical structure the naturally occurring neurotransmitter norepinephrine, but are not metabolized within the presynaptic nerve terminals. The neuronal uptake of these tracers in the myocardium is mediated through the uptake 1 mechanism, which removes circulating catecholamines from the extra neuronal space in the myocardium.

Initial clinical applications of the PET tracer C-11 HED show excellent image quality with high contrast between myocardial tracer activity and blood pool, as well as lung tissue surrounding the heart (Figure 5). The specificity of the tracer approach for neuronal tissue has been well documented by studies in cardiac transplant patients, which showed a marked reduction of tracer uptake, suggesting only little nonspecific binding of this tracer, which allows for quantitative image analysis. Allman et al. employed C-11 HED in the assessment of patients with acute myocardial infarction undergoing thrombolytic therapy. Experimental data indicated that the extent of neuronal damage following transient ischemia is larger than the area of tissue necrosis. Wolpers et al. demonstrated a decreased retention fraction of C-11 HED in reperfused canine myocardium suggesting a high sensitivity of neurons to ischemic injury. Similar data have been observed in the clinical setting. The area of neuronal dysfunction, as evidenced by I-123 MIBG defects, was significantly larger than the area of perfusion abnormalities in patients with acute myocardial infarction and correlated closely with the area of risk as assessed by Tc-99m Sestamibi imaging in the same patients confirming the experimental data.

Figure 4. PET studies of transgenic mice (GLUT 4 knock-out) under fasting conditions and following insulin stimulation. Under fasting conditions, both the transgenic (A) and the wild type (B) animals have very little FDG uptake in the myocardium. Following insulin stimulation, both the transgenic and the wild type display increased FDG activity within the myocardial structure. Northern blot analysis revealed absence of GLUT 4 messenger RNA in the GLUT 4 knock-out animals. The data suggest the importance of functional tissue characterization to define the compensatory processes occurring in genetically altered animal models.

Figure 5. PET images of left ventricular myocardial distribution of the perfusion tracer N-13 ammonia and the presynaptic sympathetic marker C-11 hydroxyephedrine (HED) in a normal volunteer (SA = short axis; HLA = horizontal long axis, VLA = vertical long axis).
HED PET studies were also performed in patients with diabetic neuropathy. These studies revealed a correlation between the results of autonomic nervous system testing and the abnormalities of HED distribution. The study that found regional cardiac denervation represents a heterogeneous process in patients with diabetic neuropathy was surprising. C-11 hydroxyephedrine defects were most severe in the apical segments of the left ventricle and least severe in the proximal segments of the left ventricle.76–78 Comparison of neuronal dysfunction and blood flow measurements by PET revealed impaired vasodilator response in diabetic patients.79 Alterations of the sympathetic nervous system are a common feature of progressive heart failure. Sympathetic activation results in elevation of systemic catecholamine levels and subsequent downregulation of postsynaptic beta-adrenoceptors, as demonstrated by Merlet et al.80 using PET and the beta-receptor ligand C-11 CGP12177. In addition, presynaptic alterations can be observed, as indicated by globally reduced myocardial uptake of the catecholamine analogue C-11 hydroxyephedrine. In 29 patients, Hartmann et al. observed abnormally low hydroxyephedrine retention in 64 ± 32% of the left ventricle despite nearly normal perfusion. The degree of presynaptic alterations was correlated with reduction of ejection fraction and New York Heart Association (NYHA) status.81 In a more recent study, a correlation with impaired metabolic efficiency was also observed.51 These alterations of presynaptic sympathetic innervation thus seem to reflect the severity of heart failure in dilated cardiomyopathy. It has recently been shown in a follow-up study by Pietila et al.,82 using 46 patients for a period of 55 months, that they also correlate with progression of disease and that PET can be used to predict patient outcome.

One of the consequences of cardiac transplantation is a complete denervation of the allograft due to surgical transection of autonomic nerve fibers. Sympathetic denervation can be demonstrated by PET and absent cardiac uptake of radiolabeled catecholamine analogues such as C-11 hydroxyephedrine.83,84 Denervation is thought to be the major reason for chronotropic incompetence and impaired exercise capacity in transplant recipients. Metabolic studies using F-18 FDG reported an increase of myocardial glucose utilization in transplanted hearts and attributed this finding to denervation.85 In other studies, however, overall oxidative metabolism86 and myocardial metabolic efficiency87 in transplanted hearts were comparable to normals, rendering negative effects of metabolic alterations at rest unlikely.

PET studies using C-11 hydroxyephedrine have substantially contributed to identify and characterize sympathetic reinnervation that occurs frequently and increases with time after transplantation (Figure 6).88 Reinnervation remains regionally limited, starting in the basal anteroseptal wall and extending towards apex and lateral wall with time, while the inferior wall remains denervated until up to 18 years after transplantation.84 Although regionally incomplete, reinnervation has been shown to improve microvascular reactivity in response to cold,89 and to influence regional substrate utilization by lowering glucose uptake in reinervated myocardium.80 Most importantly, it has been demonstrated recently that reinnervation also improves chronotropic and inotropic response to exercise and thus overall exercise capacity and daily life activity in transplant recipients.91 It has also been understood that reinnervation is not only a function of time, but also determined by other factors such as age of donor and recipient, duration of transplant surgery and rejection frequency.92 Beneficial effects on the patient course late after transplantation and thus on long-term outcome, however, remain to be determined in detail.

**Figure 6.** Representative PET short axis slices of presynaptic sympathetic innervation (assessed with C-11 HED) and myocardial perfusion (assessed with N-13 ammonia) in three patients at various time points after cardiac transplantation (HTX). While complete denervation is indicated by absent HED uptake early after HTX, incomplete reinnervation is observed at later time points, starting in the basal anteroseptal wall, and later extending towards lateral wall and apex.
Detection of Apoptotic Cell Death and Atherosclerotic Plaque Characterization

Recently, Tc-99m labeled annexin V has been introduced as a tracer that allows for identification of apoptotic cell death.

Annexin V binds to phosphatidylserine, a molecule that is expressed on the sarcolemmal membrane during early stages of the apoptotic pathway. Clinical studies have been performed that demonstrate that annexin V specifically accumulates in the area of acute myocardial infarction, and allows for early detection of cardiac transplant rejection. Results are promising and will lead the way to future trials in larger patient groups. Those will be necessary to establish a clinical usefulness for this marker of cell death, and to overcome hurdles which in the past limited the application of previously introduced hot spot tracers, such as radiolabelled antimonyosin antibodies.

Noninvasive characterization of atherosclerotic plaques has become another attractive target for nuclear imaging, although issues of target to background ratios for tracer accumulation and spatial resolution of camera systems are critical for clinical application, especially for a potential assessment of coronary plaques. In-111 labeled ZZD3 antibodies directed against proliferating smooth muscle cells have been introduced and were successfully applied in humans to visualize carotid plaques. Unstable plaques that are prone to rupture are characterized by specific histologic criteria such as large lipid core, thin fibrous cap, and macrophage infiltration/inflammation. Recently, tracer strategies have been introduced to identify some of these characteristics. Plaque inflammation, for example, may be visualized using FDG. More specifically, radiolabeled monocyte chemoattractant protein 1 can be used in the experimental setting to quantify macrophage content of atherosclerotic plaques.

Imaging of Cardiac Transgene Expression

Myocardial gene therapy is rapidly evolving and holds promise for treatment of diseases, such as heart failure and ischemia. It has reached the stage of human application, and several clinical trials for treatment of ischemia using vectors expressing angiogenesis-inducing genes have been conducted. Currently, the success of cardiac gene delivery in the clinical setting can only be monitored by indirect measures such as symptomatic improvement or clinical test results, while direct assessment of gene expression has been feasible only. A noninvasive, clinically applicable method for imaging of successful myocardial gene transfer is of considerable value as it allows for monitoring of gene therapy by defining localization, extent, magnitude and persistence of gene expression over time.

The herpes simplex virus type 1 thymidine kinase gene (HSV1-tk) has been used as marker gene. HSV1-tk is normally not present in host tissue and encodes for an enzyme catalyzing phosphorylation and thus intracellular accumulation of marker substrates. Among various substrates, radiolabeled 2'-fluoro-2'-deoxy-5-iido-1β-D-arabinofuranosyluracil (FIAU) demonstrated high sensitivity and selectivity for detection of HSV1-tk expression. FIAU is trapped intracellularly only in presence of HSV1-tk. This tracer has been used successfully for imaging of HSV1-tk expression in tumors in vivo. In first experiments in cardiac cells, it has been shown at our lab that the uptake of FIAU is comparable following adenoviral transfer of HSV1-tk in cardiac and tumor cells in vitro. Additionally, specific FIAU accumulation could be demonstrated autoradiographically in the myocardial region of HSV1-tk expression after intramyocardial application of adenovirus in rats in vivo. These data suggested the usefulness of reporter gene imaging not only in tumors, but also in

Figure 7. PET images and polar maps of left ventricular perfusion and regional uptake of I-124 FIAU in a pig 48 hours after injection of 1 X 10^10 pfu of adenovirus carrying the herpesviral thymidine kinase reporter gene (HSV1-tk) into the mid anterolateral wall following lateral thoracotomy. Specific FIAU uptake in anterolateral wall allows for identification of regional reporter gene expression in the myocardium.
the heart. More recently, using other reporter genes and reporter substrates, Wu et al. \(^{105,106}\) demonstrated that reporter gene expression in the heart can be imaged in living rats using micro-PET or optical imaging devices, thus giving further support to the feasibility of cardiac exogenous gene product imaging. Consistently, images of regional HSV1-tk expression can also be obtained in the pig heart using I-124 FIAU and a clinical PET camera (Figure 7).

Ultimately, marker genes can be coexpressed with effector genes for subsequent imaging of therapeutic gene transfer. Approaches to enhance cell type specificity of reporter gene expression and to reduce immunogenicity are being developed. Finally, the use of reporter genes also appears to be transferable to studying cell trafficking and stem cell therapy in the future.

**Summary**

This short review summarizes the development of cardiac imaging with tracer techniques over the last 35 years. Perfusion imaging remains to be one of the most important physiological signals employed in the management of patients with CAD. The introduction of PET technology, however, may provide the opportunity to quantitate regional myocardial blood flow and deliver a sensitive marker of early atherosclerotic disease. The tracer techniques are of particular interest for research applications in the heart. Conventional markers such as radiolabeled glucose or fatty acids may help to define metabolic phenotypes in the presence of various disease processes. New techniques, such as gene imaging, will be uniquely suited to evaluate new therapeutic strategies. With the success of PET in the area of oncology, the availability of PET instrumentation will significantly increase in the near future. This penetration of technology should help to revitalize the clinical and academic interest in cardiac PET imaging.

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