Recent Advances in Cardiac Positron Emission Tomography in the Clinical Management of the Cardiac Patient

Robert J. Gropler, MD and Pablo Soto, MD*

Address
*Cardiovascular Imaging Laboratory, Mallinckrodt Institute of Radiology, 510 South Kingshighway Boulevard, St. Louis, MO 63110, USA.
E-mail: GroplerR@mir.wustl.edu

Current Cardiology Reports 2004, **6:**20–26
Current Science Inc. ISSN 1523-3782

Despite being primarily a research tool, positron emission tomography (PET) has seen slow but steady growth in the clinical management of the cardiac patient. The two major clinical applications of cardiac PET are regional myocardial perfusion imaging to determine the presence and severity of coronary artery disease and metabolic imaging to differentiate viable from nonviable myocardium in patients with ischemic left ventricular dysfunction. Indeed, PET with either nitrogen 13 ammonia or rubidium 82 may offer advantages over current single photon emission computed tomography approaches to assess myocardial perfusion. PET with fluorine 18 fluorodeoxyglucose is considered the current gold standard for identifying viable myocardium. Finally, the use of PET to quantify myocardial perfusion, metabolism, and innervation has led to key insights into the role of altered microvascular function, substrate metabolism, and neuronal function in a variety of cardiac disease processes.

Introduction

Positron emission tomography (PET) has been used to measure myocardial perfusion, metabolism, innervation, and mechanical function for more than 20 years. Although cardiac PET has been primarily a research tool, it is now being used more frequently in the management of patients with ischemic heart disease. The two major clinical applications of cardiac PET are regional myocardial perfusion imaging (MPI) to determine the presence and severity of coronary artery disease (CAD), and metabolic imaging to differentiate viable from nonviable myocardium in patients with ischemic left ventricular (LV) dysfunction. The recent advances of cardiac PET in these two areas as well as the potential future clinical applications of cardiac PET are discussed.

Technical Aspects of Cardiac Positron Emission Tomography

Positron emission tomography takes advantage of the unique decay scheme of the positron-emitting radionuclides, which generate two 511 keV photons emitted at an angle of approximately 180°. It is this colinearity of photons of equal energy that permits localization (called *coincidence detection*) of an annihilation event along the line of coincidence by recording events at opposing detectors within a given time window (typically 5–20 ns). This detection scheme of electronic collimation offers the advantage of improved sensitivity and resolution over lead collimation, which is performed with conventional single photon emission computed tomography (SPECT). Moreover, because of this detection scheme, correction for photon attenuation from overlying breast tissue or diaphragm can be performed more accurately with PET than with the current approaches being implemented for SPECT. A second major attribute of PET is its usage of tracers and physiologic compounds (Table 1). The positron-emitting radionuclides of the biologically ubiquitous elements oxygen (oxygen 15), carbon (carbon 11), and nitrogen (nitrogen 13), as well as fluorine (fluorine 18), substituting for hydrogen, can be incorporated into a wide variety of radiopharmaceuticals to measure myocardial perfusion, metabolism, and innervation. The short physical half life of the positron-emitting radionuclides facilitates the performance of sequential studies with a favorable radiation exposure to the subject when compared with conventional single photon radionuclides. However, because of the short physical half life of these radionuclides and the fact that most of them are cyclotron-produced, an on-site cyclotron is necessary in order to perform such PET studies. Only in situations in which the physical half life of the radionuclide is long enough to permit delivery to PET sites without a cyclotron, such as in the case of fluorine 18 (^{18}F) (half life ~ 110 min), or in the case of generator-produced positron-emitting radionuclides such as rubidium 82 (^{82}Rb), is the need for an on-site cyclotron obviated.

An additional advantage of cardiac PET is its ability to measure myocardial perfusion and metabolism in either relative or absolute terms. In the former case, myocardial

Table 1. Positron-emitting compounds currently used with PET for cardiac studies

Radionuclide	Half life, *min*	Compound	Present use
Cyclotron-produced			
Oxygen 15	2.04	H_2O	Blood flow
		CO	Blood volume
		CO_2	Blood flow
		O_2	Oxygen consumption
Nitrogen 13	10	NH_3	Blood flow
		Various amino acids	Amino acid metabolism
Carbon 11	20.4	Acetate	Oxygen consumption
		Pyruvate	Intermediary metabolism
		Palmitate	Fatty acid metabolism
		Glucose	Glucose metabolism
		HED	Norepinephrine distribution
		MQNB	Muscarinic receptors
		Butanol	Blood flow
Fluorine 18	110	Deoxyglucose	Glucose metabolism
		Dopamine	Dopamine stores
		FHTA	Fatty acid metabolism
Generator-produced			
Rubidium 82	1.25	RbCl	Blood flow
Copper 62	9.73	Cu-ATSM	Hypoxia

ATSM—diacetyl-bis(N4-methylthiosemicarbazone; FHTA—fluoro-6-thi-hepto-clecanoic acid; HED—hydroxyephedrine; MQNB—methylquinclidinyl benzilate; PET—positron emission computed tomography.

radiotracer activity is referenced to a myocardial wall that is assumed to have normal radiotracer uptake. This is similar to how myocardial SPECT imaging is performed. This approach works fine in situations in which regional differences in perfusion or metabolism exist, typically in CAD. However, the approach is of limited value in situations in which the pathologic process is more diffuse, such as in severe multivessel CAD or microvascular disease associated with diabetes mellitus or hyperlipidemia. PET can also quantify myocardial perfusion in absolute terms (*ie*, in mL/g/min) and metabolism (*ie*, in μmol/g/min). This is done by analyzing the radiotracer kinetics in myocardium using well-validated compartmental models. The strength of this approach is that pathologic processes that effect the heart in a more diffuse pattern can be detected. The disadvantages of quantification are that it is more complex to perform and it may have a greater degree in measurement variability than relative estimates.

Myocardial Perfusion Imaging in the Management of Coronary Artery Disease Patients

Single photon emission computed tomography myocarial perfusion imaging

Currently, SPECT using either thallium 201 (^{201}Tl) or the technetium 99 (^{99}Tc)–labeled perfusion tracers, sestamibi and tetrofosmin, is the most commonly used method for MPI [1]. Typically, myocardial perfusion at rest is compared with perfusion during stress (induced with exercise or pharmacologically). The ability of SPECT rest/stress MPI to accurately diagnose CAD and to risk stratify patients with this disease is well established. As a consequence, SPECT MPI plays a central role in the management of patients with CAD. Despite its importance in the management of patients with CAD, SPECT MPI suffers from several disadvantages. Photon attenuation can result in a distribution of radiotracer in myocardium consistent with infarction where none exists and thus, decrease test specificity. Electrocardiographic (ECG) gating and prone imaging help reduce the impact of attenuation artifacts on image interpretation. Moreover, attenuation correction algorithms are now being added to the SPECT acquisition [2]. However, the experience with this technology is limited and its ultimate usefulness in improving the accuracy of interpretation of SPECT MPI awaits further study. Increased liver uptake of the ^{99m}Tc agents can result in back-projection errors during the tomographic reconstruction, leading to reduced radiotracer activity in the inferior or other adjacent myocardial walls. This is a particular problem during adenosine or dipyridamole stress imaging because splanchnic blood flow is maintained, as opposed to exercise in which it is reduced, leading to increased liver uptake of tracer. Again, test specificity is reduced. Concomitant submaximal exercise to reduce splanchnic blood flow or repeat imaging to let the liver clear the ^{99m}Tc radiotracer activity are approaches used to minimize the effects of increased liver activity [3]. However, many patients cannot exercise (which is why they are undergoing vasodilator stress testing) and repeat imaging can result in a test duration of 4 to 5 hours. Moreover, given the increasing prevalence of obesity (which will increase attenuation artifacts) and advancing age (which will increase the

need for vasodilator stress) in the American population, the confounding of image interpretation by these artifacts will only increase. Finally, with current SPECT cameras it is difficult to obtain simultaneous stress perfusion and LV functional information. Typically, one obtains stress perfusion information and post-stress functional information. PET MPI offers potential solutions to many of these problems.

Cardiac positron emission tomography

Currently, cardiac PET is clinically approved to perform MPI with nitrogen 13 (^{13}N)-ammonia and ^{82}Rb. ^{13}N ammonia is a cyclotron-produced, partially extracted perfusion radiotracer. ^{82}Rb is also a partially extracted flow radiotracer that is a potassium-analog with kinetics similar to ^{201}Tl. It is obtained from a commercially available generator. To assess CAD, a typical study includes a transmission scan to correct for photon attenuation, a rest imaging, and then imaging during vasodilator stress induced with either dipyridamole or adenosine [4]. Potentially, dobutamine could be used as well. ECG gating can be performed both at rest and during stress. Because of the requirements to begin imaging almost immediately following tracer injection, and for the patient to lie still during imaging, exercise is not feasible. Thus, the additional diagnostic and prognostic information associated with the occurrence of angina, exercise duration, and hemodynamic responses are lost. Due to the short physical half life of these radiotracers, rapid sequential imaging is possible. A ^{13}N-ammonia study can be completed in about 60 to 75 minutes, whereas an ^{82}Rb study (half life of 76 sec) requires about 30 to 45 minutes to complete. An important consideration is that the patient remains in the same position for the transmission and emission scans. Misalignment of the transmission and emission scans will lead to significant image artifacts. Strategies designed to reduce this occurrence include using multiple localizing low-energy lasers to ensure the patient is in the same position or performing multiple transmission scans (such as before and after the emission scan) in order to correct for patient motion.

Because of its intrinsic advantage of being generator produced, ^{82}Rb has been more extensively studied than ^{13}N-ammonia for the detection of CAD. However, with either PET radiotracer, sensitivity ranges from 79% to 97% and specificity has been reported at between 85% and 100%, when compared with coronary angiography [5–14]. Of note, nearly all of these studies occurred more than 10 years ago. Thus, comparisons with SPECT were only performed using ^{201}Tl without ECG gating, prone imaging, or attenuation correction [8,13,14]. In these cases PET imaging with either ^{82}Rb or ^{13}N-ammonia exhibited similar sensitivity for detecting coronary disease. However, PET with its superior correction for photon attenuation (particularly in the inferior wall due to overlying diaphragm) exhibited higher specificity compared with SPECT. In a small number of studies, PET with ^{82}Rb has been shown to accurately risk stratify patients and provide additional prognostic information over above clinical and angiographic findings [15]. In addition, it has been suggested that PET MPI may be a more cost-effective approach to evaluate for CAD than exercise electrocardiography, SPECT MPI or coronary angiography in patients with a low to intermediate pretest likelihood of disease [16]. Of note, the capability of PET MPI to simultaneously measure myocardial perfusion and LV function has been demonstrated. Thus, it may be possible to determine when abnormalities in myocardial perfusion during stress reflect solely abnormal vasodilator capacity (normal stress wall motion) as opposed to frank ischemia (presence of a stress wall motion abnormality).

Clearly, further studies are required to demonstrate the usefulness of PET MPI compared with SPECT MPI in the clinical management of the CAD patient. For example, the accuracy of PET MPI must be compared with SPECT using the ^{99m}Tc agents and acquisition schemes that incorporate ECG gating, prone imaging, and/or attenuation correction.

Positron Emission Tomography Myocardial Perfusion Imaging in Microvascular Disease

It is becoming increasingly apparent that abnormalities in myocardial microvascular function are involved in the pathogenesis of a variety cardiovascular disorders such as hyperlipidemia, LV hypertrophy, diabetic heart disease, and dilated cardiomyopathy. Moreover, abnormal microvascular function may be an early manifestation of disease. One example is in CAD in which abnormalities in microvascular function precede the development of angiographically significant epicardial stenoses. In addition to characterizing the pathogenesis of disease, in many cases identification of microvascular dysfunction likely represents a stage of disease that may still be reversible. As mentioned previously, current SPECT MPI approaches are of limited value in this situation because in most cases microvascular dysfunction is a diffuse process. Because PET MPI can quantify myocardial perfusion in mL/g/min it can be used to identify and quantify abnormalities in myocardial microvascular dysfunction. Moreover, by performing these measurements during intravenous adenosine or dipyridamole administration or during cold-pressor testing the relative contributions of primarily endothelial-independent vasodilation (in the former case) and endothelial-dependent vasodilation (in the latter case) to microvascular dysfunction can be determined. Demonstration that chronic hyperglycemia plays a key role in the microvascular dysfunction of diabetics, that acute homocysteinemia impairs myocardial microvascular dilation and that myocardial vasodilator function is impaired in otherwise healthy subjects with familial combined hyperlipidemia are but three examples of the potential usefulness of the quantitative PET MPI method [17•,18,19]. PET measurements of microvascular function

may the have potential to assign prognosis and demonstrate the beneficial effects of therapies designed to reduce impact of various contributors to microvascular dysfunction. For example, in patients with hypertrophic cardiomyopathy, the degree of microvascular dysfunction as measured by PET is a strong independent predictor of clinical deterioration and death [20•]. In patients with mild to moderate hypercholesterolemia and minimal CAD, treatment with a statin results in an improvement in the lipid profile that is paralleled by improved myocardial vasodilator function [21••].

Cardiac Positron Emission Tomography for the Detection of Viable Myocardium

It is now apparent that in patients with CAD, the presence of resting LV dysfunction can represent either irreversibly damaged tissue or scar or tissue with the potential for functional recovery. Irreversibly damaged tissue is considered nonviable myocardium, whereas reversibly damaged tissue is considered viable. The distinction has relevance because restoration of perfusion to viable myocardium by coronary artery bypass surgery or percutaneous coronary intervention will likely result in improved systolic function, whereas function will not improve in nonviable tissue. The differentiation of viable from nonviable tissue is typically needed in patients with ischemic cardiomyopathy in whom the decision of high-risk coronary revascularization as opposed to medical therapy or heart transplantation is being contemplated. Thus, it is key that the magnitude and extent of viable myocardium be determined accurately. Metabolic imaging with cardiac PET is currently considered the gold standard in this regard.

Assessment of Cardiac Metabolism

Under normal resting conditions the myocardium produces energy from the oxidation of either fatty acids or glucose and to a lesser extent lactate. The relative contribution of fatty acids or glucose to overall oxidative metabolism is dependent upon a variety of factors such as the level of fatty acids in the blood, insulin levels, and the level of cardiac work. For example, under fasting conditions where plasma fatty acid levels are elevated and insulin levels are low, the myocardium oxidizes fatty acids primarily. In contrast, in the postprandial state when insulin levels rise slightly and plasma fatty acid levels decline, glucose becomes a preferred oxidative substrate. Under conditions of mild to moderate myocardial ischemia, oxidation of fatty acids ceases and anaerobic metabolism supervenes. Glucose becomes the primary substrate for both increased anaerobic glycolysis and for continued, albeit diminished, oxidative metabolism. With more marked reductions in myocardial blood flow, myocardial oxidative metabolism ceases, glycolysis diminishes via end-product inhibition, and myocardial necrosis ensues. Consequently, the preservation of myocardial glucose metabolism is a marker of ischemic but viable myocardium.

Taking advantage of this metabolic switch, PET imaging is performed typically using the glucose analog ^{18}F-fluorodeoxyglucose (FDG). The initial uptake and phosphorylation of FDG parallels that of glucose. However, unlike glucose, once phosphorylated, FDG is not further metabolized and is retained within the myocardium. Consequently, the higher the degree of FDG accumulation in the myocardium the higher the level of overall glucose metabolism. Viability assessments are performed with PET and FDG in conjunction with measuring myocardial perfusion. Perfusion can be measured with either ^{13}N-ammonia or ^{82}Rb, as described above. Or the assessments of regional perfusion can be performed using conventional SPECT radiotracers. Identification of viable and nonviable myocardium is based on the patterns of metabolism in relation to perfusion [22]. Tissues are identified as viable when myocardial perfusion is normal regardless of the degree of FDG uptake. This most likely represents a intermittent myocardial stunning [23]. However, when FDG uptake is increased in the presence of a perfusion defect (perfusion-metabolic mismatch) this is most consistent with myocardial hibernation and is also indicative of viable tissue. In contrast, when there is a concordant decrease in regional myocardial perfusion and FDG uptake, the pattern is consistent with predominately nonviable or necrotic myocardium. Of note, these defects can be graded for their severity based on the level of FDG uptake. For example, when FDG uptake is approximately 50% to 60% of peak activity, it would be most consistent with a nontransmural myocardial infarction; whereas, when FDG uptake is only 10% to 20% of peak activity this is more consistent with transmural scar.

The accuracy of PET with FDG to predict improvement in regional systolic function following coronary revascularization was summarized recently [24]. This technique demonstrated a sensitivity of 88%, a specificity of 73%, a positive predictive value of 76%, and a negative predictive value of 86%. These values compare favorably with SPECT using either ^{201}Tl or the ^{99m}Tc agents and dobutamine stress echocardiography. The caveat here is that myocardial viability detection with PET and FDG is much less accurate in patients within 2 weeks of a myocardial infarction [25]. This is most likely due to the variable levels in myocardial glucose use following ischemia with reperfusion. In addition to demonstrating improvement in regional systolic function, PET with FDG has shown that coronary revascularization can have a favorable effect on global LV function. Most importantly, PET and FDG studies in patients with ischemic cardiomyopathy have demonstrated that the presence of viable myocardium is marker of high cardiac risk if coronary revascularization is not performed. Indeed, a recent meta-analysis that included PET and FDG, MPI with ^{201}Tl, and low-dose dobutamine echocardiographic methods to detect viable myocardium

demonstrated that coronary revascularization of patients with viable myocardium was associated with an 80% reduction in annual mortality compared with a similar group of patients treated medically [26••]. Moreover, in these patients there was a direct relationship between the severity of LV dysfunction present initially and the degree of benefit with revascularization. Importantly, annual mortality following revascularization was significantly higher in patients with predominantly nonviable tissue (7.7%) compared with patients with predominantly viable myocardium (3.2%). Of note, there was no difference between the three methods in predicting the magnitude of benefit following revascularization. This would imply that PET with FDG is no better that SPECT with ^{201}Tl or low-dose dobutamine stress echocardiography for evaluating patients with ischemic cardiomyopathy for the presence of viable myocardium. However, the detection of viable myocardium is frequently required in obese patients with severe LV dysfunction (ejection fraction value < 25%). It is in this situation where the accuracy of SPECT and echocardiographic approaches to differentiate viable from nonviable myocardium declines. Consequently, it is in these patients where PET with FDG is of most use.

Other Metabolic Applications

There is a rapidly growing body of evidence to suggest that abnormalities in myocardial substrate metabolism play a central role in a variety cardiac disorders. For example, a decline in myocardial fatty acid metabolism with a shift to glucose use is seen in the aging heart, LV hypertrophy, and dilated cardiomyopathy. Conversely, an overdependence on fatty metabolism typifies the diabetic heart. This loss in plasticity in myocardial substrate metabolism may contribute to the diastolic and systolic dysfunction as well as the adverse outcome observed in these conditions. Until recently, this evidence was based on studies in rodent models of these cardiac disorders where marked alterations were observed in the gene expression of key enzymes that regulate myocardial fatty acid and glucose metabolism. Results of recent PET studies in humans have shown the expected metabolic phenotype observed in rodent models of aging, LV hypertrophy, dilated cardiomyopathy, and diabetic heart disease occur in humans with these conditions [27•,28–30]. Moreover, PET measurements of metabolism have been able to show that therapies designed to improve LV function are associated with improvements myocardial metabolism. For example, the improvment in LV remodeling and function by cardiac resynchronization therapy in patients with dilated cardiomyopathy is paralleled by a reduction in the regional disparities in myocardial glucose metabolism [31]. Moreover, the salutary effects of endurance exercise training in patients with dilated cardiomyopathy on exercise tolerance and LV function are associated with a decline in myocardial oxygen consumption by both the right and left ventricles and an improvement in LV efficiency [32••]. Thus, although the number studies are small, their results demonstrate the potential clinical role PET measurements of myocardial metabolism in patients with a variety of cardiac disorders.

Myocardial Sympathetic Neurotransmitter Imaging

It is well recognized that abnormalities in the sympathetic nervous system play a key role in the pathogenesis of a wide range of cardiac disorders. For example, increased adrenergic activity leading to down-regulation of myocardial β-receptor function is a critical part of the pathophysiology of congestive heart failure. Age-related decline in cardiac function, hypertension-induced LV hypertrophy, and diabetic heart disease are a few other examples of the contribution of reduced myocardial sympathetic innervation to observed cardiac pathophysiology. In contrast, the pattern of myocardial sympathetic innervation may be as important as the degree of heterogeneity in LV sympathetic innervation may correlate with arrhythmogenic potential. Iodine 123 (^{123}I) metaiodobenzylguandine (MIBG) is the most commonly used SPECT radiotracer to assess myocardial sympathetic innervation. MIBG is an analogue of guanethidine and its cellular uptake is similar to norepinephrine at the sympathetic nerve terminals. Higher uptake of ^{123}I MIBG correlates with higher adrenergic function. The most common PET radiotracer is carbon 11 (^{11}C)-hydroxyephedrine (HED), which is also taken up in sympathetic nerve terminals. Again increased tracer uptake indicating increased adrenergic activity. Using this method has helped clarify the pathophysiology of a variety of cardiac disorders. Numerous investigators have shown that reinnervation of cardiac allografts occurs, particularly in younger individuals in whom the transplant procedure was uncomplicated and the rate of allograft rejection was low [33]. It is well known that sympathetic autonomic neuropathy is a marker of poor prognosis patients with diabetes mellitus. Measurements of cardiac sympathetic innervation in diabetic patients using PET and ^{11}C-HED have demonstrated that abnormalities in sympathetic innervation are associated with impaired myocardial vasodilator responses to sympathetic stimulation, thus shedding light on the potential mechanism responsible for the adverse outcome in these patients [34]. As mentioned above, the distribution of sympathetic innervation may have relevance in cardiac disease, particularly with respect to arrhythmias. Mutations in the genes regulating sodium and potassium channels have been implicated in the pathogenesis of arrhythmia in patients with congenital long QT syndrome. Measurements of sympathetic innervation with PET and ^{11}C-HED demonstrated a greater degree of heterogeneity in innervation in the patients compared with controls, suggesting abnormal sympathetic function amplifies the severity of disease

[35••]. Beyond the mechanistic information the study demonstrates the potential role of PET to characterize the phenotype of newly identified genetic disorders.

Conclusions

It is likely that the clinical use cardiac PET will continue to grow in the foreseeable future. The increasing prevalence of metabolic syndrome and advancing age of the American population will increase the demand for accurate pharmacologic stress testing for the management of patients with CAD. Indeed, the need for efficient use of medical resources will also require that false positive studies be kept to a minimum. Through sharing of camera availability, the rapid dissemination of PET cameras for oncologic applications increases the availability of cardiac PET. In addition, there is currently favorable reimbursement of cardiac PET. That being said, more studies are needed to demonstrate the superiority of cardiac PET MPI compared with SPECT MPI. Technologic advances in cardiac PET will also increase its potential clinical applicability. The recent development of PET/CT holds the promise of integrating information regarding coronary artery anatomy with alterations in myocardial perfusion, metabolism, and function. Obtaining all of this information in a single examination will facilitate the management of cardiac patients, particularly those with CAD. The quantitative capability of cardiac PET will be used to improve our understanding of disease processes that manifest as abnormalities in myocardial microvascular function and metabolism. Such information will be key in the development and evaluation of new therapies designed to ameliorate these abnormalities at a stage when disease reversal is still possible. Finally, understanding the role of myocardial innervation in various cardiac diseases will provide for a more complete understanding of these processes and will likely identify new targets for novel therapeutics.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Baird MG, Bateman TM, Berman DS, *et al.*: **ACC/AHA/ASNC guidelines for the clinical use of cardiac radionuclide imaging.** *J Am Coll Cardiol* 2003, **42:**1318–1333.
2. Hendel RC, Corbett JR, Cullom SJ, *et al.*: **The value and practice of attenuation correction for myocardial perfusion SPECT imaging: a joint position statement from the American Society of Nuclear Cardiology and the Society of Nuclear Medicine.** *J Nucl Cardiol* 2002, **9:**135–143.
3. American Society of Nuclear Cardiology: **Updated imaging guidelines for nuclear cardiology procedures.** *J Nucl Cardiol* 2001, **8:**G5–G58.
4. Bacharach SL, Bax JJ, Case J, *et al.*: **ASNC practice guidelines: PET myocardial glucose metabolism and perfusion imaging; Part 1-guidelines for patient preparation and data acquisition. ASNC website.** http://www.asnc.org/
5. Schelbert HR, Wisenberg G, Phelphs ME, *et al.*: **Noninvasive assessment of coronary stenoses by myocardial imaging during pharmacologic coronary vasodilation.VI. Detection of coronary artery disease in human beings with intravenous N-13 ammonia and positron computed tomography.** *Am J Cardiol* 1982, **49:**1197–1206.
6. Gould KL, Goldstein RA, Mullani NA, *et al.*: **Noninvasive assessment of coronary stenosis by myocardial perfusion imaging during pharmacologic coronary vasodilation.VIII. Clinical feasibility of positron cardiac imaging without a cyclotron using generator-produced rubidium-82.** *J Am Coll Cardiol* 1986, **7:**775–789.
7. Yonekura Y, Tamaki N, Senda M, *et al.*: **Detection of coronary artery disease with N-13 ammonia and high-resolution positron-emission tomography.** *Am Heart J* 1987, **113:**645–654.
8. Tamaki N, Yonekura Y, Senda M, *et al.*: **Value and limitation of stress thallium-201 single photon emission computed tomography: comparison with nitrogen-13 ammonia positron tomography.** *J Nucl Med* 1988, **29:**1181–1188.
9. Laubenbacher C, Stevenson L, Kobishagawa J, *et al.*: **An automated analysis program for the evaluation of cardiac PET studies: initial results in the detection and localization of coronary artery disease using N-13 ammonia.** *J Nucl Med* 1991, **34:**968–978.
10. Sand NP, Bottcher M, Madsen MM, *et al.*: **Evaluation of regional myocardial perfusion in patients with severe left ventricular dysfunction: comparison of N-13 ammonia PET and Tc-99m sestamibi SPECT.** *J Nucl Cardiol* 1998, **5:**4–13.
11. Grover-McKay M, Ratib O, Schwaiger MS, *et al.*: **Detection of coronary artery disease with positron emission tomography and rubidium 82.** *Am Heart J* 1992, **123:**646.
12. Simone GL, Mullani NZ, Page DA, Anderson BA: **Utilization statistics and diagnostic accuracy of nonhospital-based positron emission tomography center for the detection of coronary artery disease using rubidium-82.** *Am J Physiol Imaging* 1992, **314:**203–209.
13. Go RT, Marwick TH, MacIntyre WJ, *et al.*: **A prospective comparison of rubidium-82 PET and thallium-201 SPECT myocardial perfusion imaging utilizing a single dipyridamole stress in the diagnosis of coronary artery disease.** *J Nucl Med* 1990, **31:**1899–1905.
14. Stewart RE, Schwaiger M, Molina E, *et al.*: **Comparison of rubidium-82 positron emission tomography and thallium-201 SPECT imaging for detection of coronary artery disease.** *Am J Cardiol* 1991, **67:**1303–1310.
15. Marwick TH, Shan K, Patel S, *et al.*: **Incremental value of rubidium-82 positron emission tomography for prognostic assessment of known or suspected coronary artery disease.** *Am J Cardiol* 1997, **80:**865–870.
16. Patterson RE, Eisner RL, Horowitz SF: **Comparison of cost-effectiveness and utility of exercise ECG, single photon emission computed tomography, and coronary angiography for diagnosis of coronary artery disease.** *Circulation* 1995, **91:**54–65.
17. • Di Carli MF, Janisse J, Grunberger G, *et al.*: **Role of chronic hyperglycemia in the pathogensis of coronary microvascular dysfunction in diabetes.** *J Am Coll Cardiol* 2003, **41:**1387–1393.

Using quantitative measurements of myocardial perfusion demonstrated the central role of chronic hypoglycemia in microvascular dysfunction in patients with diabetes mellitus. Demonstrates the potential of quantitative PET MPI to characterize mechanisms responsible for microvascular dysfunction.

18. Tawakol A, Forgione MA, Stuehlinger M, *et al.*: **Homocysteine impairs coronary microvascular dilator function in humans.** *J Am Coll Cardiol* 2002, **40:**1051–1058.

19. Pitkanen OP, Nuutila P, Raitakari OT, *et al.*: **Coronary flow reserve in young men with familial combined hyperlipidemia.** *Circulation* 1999, **99:**1678–1684.

20.• Cecchi F, Olivotto I, Gistri R, *et al.*: **Coronary microvascular dysfunction and prognosis in hypertrophic cardiomyopathy.** *N Engl J Med* 2003, **349:**1027–1035.

Demonstrated in patients with hypertrophic cardiomyopathy that abnormalities in myocardial microvascular function was an independent predictor of an adverse outcome. This study shows the potential of quantitative PET MPI to risk stratify patients.

21.•• Baller D, Notohamiprodjo G, Gleichmann U, *et al.*: **Improvement in coronary flow reserve determined by positron emission tomography after 6 months of cholesterol-lowering therapy in patients with early stages of coronary atherosclerosis.** *Circulation* 1999, **99:**2871–2875.

An intervention study that demonstrated the salutary effects of lipid-lowering therapy on myocardial vasodilator function in patients with hyperlipidemia and early CAD. Demonstrates the potential of quantitative PET MPI to identify therapeutic strategies that may reverse cardiac disease.

22. Schelbert H, Beanlands RSB, Bengel F, *et al.*: **ASNC practice guidelines: PET myocardial glucose metabolism and perfusion imaging; Part 2-guidelines for interpretation and reporting. ASNC website.** http://www.asnc.org/

23. Conversano A, Walsh JF, Geltman EM, *et al.*: **Delineation of myocardial stunning and hibernation by positron emission tomography in patients with advanced coronary artery disease.** *Am Heart J* 1996, **131:**440–450.

24. Bax JJ, Poldermans D, Elhendy A, *et al.*: **Sensitivity, specificity, and predictive accuracies of various noninvasive techniques for detecting hibernating myocardium.** *Curr Probl Cardiol* 2001, **26:**141–186.

25. Rubin PJ, Lee DS, Davila-Roman VG, *et al.*: **Differentiation of viable from nonviable myocardium by positron emission tomography in patients with recent myocardial infarction: superiority of C-11 acetate compared with F-18 fluorodeoxyglucose.** *Am J Cardiol* 1996, **78:**1230–1236.

26.•• Allman KC, Shaw LJ, Hachamovitch R, Udelson JE: **Myocardial viability testing and impact of revascularization on prognosis in patients with coronary artery disease and left ventricular dysfunction: a meta-analysis.** *J Am Coll Cardiol* 2002, **39:**1151–1158.

Demonstrated the importance of the presence of viable myocardium as a marker of adverse outcome unless coronary revascularization is performed.

27.• Kates AM, Herrero P, Dence C, *et al.*: **Impact of aging on substrate metabolism by the human heart.** *J Am Coll Cardiol* 2003, **41:**293–299.

Demonstrated that aging is associated with a shift in myocardial substrate metabolism to a greater dependence on glucose use. The results show the potential of quantitative PET measurements to identify subtle changes in myocardial substrate metabolism.

28. De las Fuentes L, Herrero P, Peterson LR, *et al.*: **Myocardial fatty acid metabolism: independent predictor of left ventricular mass in hypertension and in left ventricular dysfunction.** *Hypertension* 2003, **41:**82–87.

29. Davila-Roman VG, Vedala G, Herrero P, *et al.*: **Altered fatty acid and glucose metabolism in idiopathic dilated cardiomyopathy.** *J Am Coll Cardiol* 2002, **40:**271–277.

30. Monti LD, Lucignani G, Landoni C, *et al.*: **Myocardial glucose uptake evaluated by positron emission tomography and fluorodeoxyglucose during hyperglycemic clamp in IDDM patients. Role of free fatty acid and insulin levels.** *Diabetes* 1995, **44:**537–542.

31. Nowak B, Sinha AM, Schaefer WM, *et al.*: **Cardiac resynchronization therapy homogenizes myocardial glucose metabolism and perfusion in dilated cardiomyopathy and left bundle branch block.** *J Am Coll Cardiol* 2003, **41:**1523–1528.

32.•• Stolen KQ, Kemppainen J, Ukkonen H, *et al.*: **Exercise training improves biventricular oxidative metabolism and left ventricular efficiency in patients with dilated cardiomyopathy.** *J Am Coll Cardiol* 2003, **41:**460–467.

Demonstrated that in patients with dilated cardiomyopathy, endurance exercise training decreases oxidative metabolism in both ventricles and improves the efficiency of the LV. The study shows how quantitative PET measurements of metabolism can be used measure the effects of a specific therapy.

33. Bengel FM, Uerberfuhr P, Hesse T, *et al.*: **Clinical determinants of ventricular sympathetic reinnervation after orthotopic heart transplantation.** *Circulation* 2002, **106:**831–835.

34. Di Carli MF, Bianco-Battlles D, Landa ME, *et al.*: **Effects of autonomic neuropathy on coronary blood flow in patients with diabetes mellitus.** *Circulation* 1999, **100:**813–819.

35.•• Mazzadi AN, Andre-Fouet X, Duisit J, *et al.*: **Cardiac retention of carbon-11 HED in genotyped long QT patients: a potential amplifier role for the severity of the disease.** *Am J Physiol Heart Circ Physiol* 2003, **2285:**H1286–H1293.

Demonstrated that in patients with mutations in the sodium and potassium channel genes and long QT syndrome heterogeneity in sympathetic innervation was increased. Beyond the mechanistic information, the study demonstrates the potential role of PET to characterize the phenotype of newly identified genetic disorders.