

Positron Emission Tomography in the Routine Management of Coronary Artery Disease

a report by

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Clinical applications of cardiac positron emission tomography (PET) have made dramatic advances over the past three years, particularly in myocardial perfusion imaging. These advances include cardiac-specific PET technology, specialized software, and profound biological insights into myocardial perfusion far beyond the traditional binary interpretation of perfusion images as normal or abnormal requiring arteriographic confirmation.

The advances in cardiac PET also interact powerfully with documentation that vigorous pharmacologic and lifestyle management stabilize plaque, partially reverse coronary artery disease (CAD), and decrease cardiac events by 90% at long-term follow-up.¹⁻³ While not widely recognized, cardiac PET—including PET-computed tomography (CT), has been demonstrated to be the single most powerful non-invasive tool for the integrated tasks of identifying early coronary artery stenosis or diffuse disease, assessing severity of stenosis, objectively determining need for revascularization procedures, following progression or regression of disease, and directly evaluating endothelial function of the coronary arteries as a marker of early atherosclerosis.

The integration of diagnostic imaging with intense medical treatment as a combined subspecialty service has catapulted cardiac PET treatment programs into the same conceptual category as diagnostic therapeutic invasive cardiology. This article outlines these scientific advances that are now routinely applicable for physicians and patients who recognize and wish to pursue this approach to the management of CAD.

Precise Myocardial Perfusion Anatomy

Myocardial perfusion images by PET are acquired in tomographic slices corrected for attenuation loss, random coincidences, scattered radiation, dead time losses, and variation in detector sensitivity. The tomographic data is rotated into true long and short axis views and compiled or stacked into a quantitative three-dimensional (3-D) topographic display of cardiac activity as a thin shell in the shape of the left ventricle displaying the normalized maximum activity across the

left ventricular (LV) wall. Four views of the heart are displayed at 90° angles as if walking around the heart from left lateral to inferior to right lateral (septal) to anterior views. The activity is normalized to the top 2% of activity in the whole heart data set and scaled from the maximum of 100% in white with stepped downward increments to red, yellow, green, blue, and black being progressively more severe defects as in the PET perfusion images of *Figure 1*.

An arterial map is overlaid on the 3-D topographic display of rest perfusion images (upper row) of *Figure 1*. Alternatively, a map of the coronary artery distribution regions is overlaid on the myocardial perfusion images after dipyridamole stress (lower row) of *Figure 1*. These overlays of the coronary arteries or their regions were developed as a precise, detailed perfusion atlas for every coronary artery and all secondary branches by correlating myocardial perfusion defects objectively quantified on PET perfusion images, with stenosis in every specific coronary artery and their individual branches, on coronary arteriograms for over 1,000 patients.⁴

Figure 1 illustrates the remarkable accuracy of PET for assessing the location and severity of mild or severe stenosis of specific coronary arteries and secondary branches. In this example, the PET shows a severe stenosis of the second diagonal branch, a milder stenosis of a small first obtuse marginal branch, and mild diffuse disease of the left circumflex coronary artery, all confirmed by arteriography. Every coronary artery and secondary branches have been mapped like this example.⁴ Sub-endocardial underperfusion manifests as milder decreased activity in the 3-D topographic display compared with a more severe defect for transmural perfusion defects.

Cardiac PET and CT for Coronary Calcification or CT Arteriography

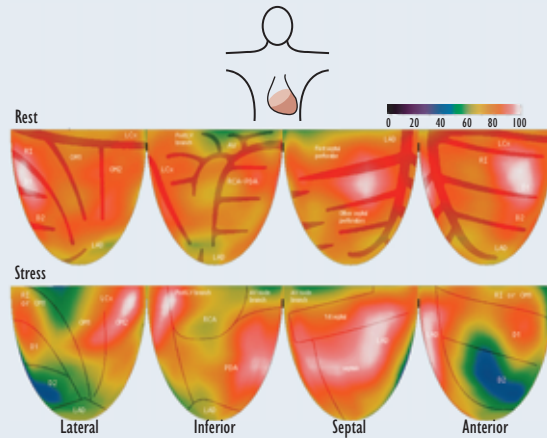
Coronary calcium by CT scanning is an important marker of coronary atherosclerosis. However, early lipid-rich coronary atheroma in young people with premature CAD may cause plaque rupture and coronary events without calcification. At the other extreme, heavy coronary calcification with no flow-



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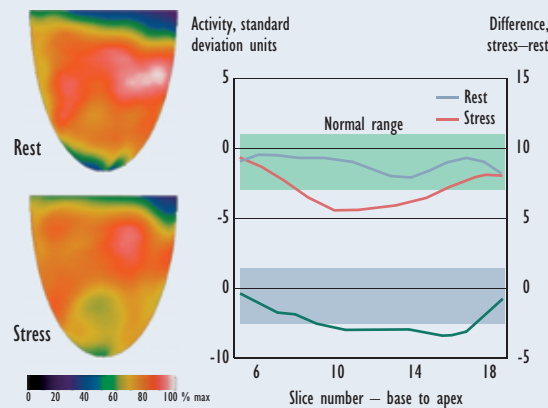


Figure 1: PET Perfusion Images at Rest and After Dipyridamole Stress with Overlay of Coronary Artery Map Based on 1,000 Arteriographic Correlations



All PET images and software displays illustrated in this review were obtained with a Positron PET scanner (Positron Corporation, 1304 Langham Creek Dr., Houston, Texas 77084).

Figure 2: Mild Early CAD with Quantitative Analysis Showing this Mild Abnormality after Dipyridamole Stress (red line) to be Four Standard Deviations Outside Limits of 50 Healthy Subjects without CAD



The black line is the rest to stress change that is also outside normal limits with SD units on the right vertical axis. See text for details of clinical course.

limiting stenosis is common in the author's experience. While valuable as a marker of atherosclerosis, the question of associated stenosis with asymptomatic coronary calcification remains, for which invasive arteriography may not be justified.

The non-invasive CT coronary arteriogram is generating interest for assessing the presence and severity of stenoses. However, the best resolution achievable with a static ideal phantom using the most advanced CT is 1.2 line pairs per millimeter measured personally by the author compared with three- to four-line pairs/mm resolution of invasive cine arteriography that is necessary for assessing stenosis severity quantitatively.⁵ Consequently, careful comparisons of non-invasive CT arteriograms with invasive cine arteriograms demonstrate that severity of coronary artery

stenosis cannot be reliably determined by CT angiography for definitive clinical purposes.⁶⁻⁹ Smaller detector size in CT scanners would improve resolution but would incur prohibitively increased radiation exposure and cost.

However, small changes in coronary artery diameter of tenths of millimeters that cannot be assessed by a CT arteriogram or even by an invasive arteriogram may cause significant changes in coronary flow reserve because flow depends on the fourth power of the arterial radius. PET perfusion images of relative coronary flow reserve, without attenuation artifacts, provide a magnified signal of small changes in arterial diameter as a sensitive specific way of assessing stenosis severity.⁵ Therefore, the combination of PET perfusion imaging with CT as a PET-CT scanner has unique strengths for the comprehensive assessment of CAD or its risk factors.

PET Imaging of Early Coronary Atherosclerosis

With attention to technical details of imaging, PET images small differences in perfusion that reflect mild stenosis of diffuse CAD in the absence of significant flow-limiting stenosis. Diffuse coronary atherosclerosis causes a graded base to apex, longitudinal perfusion gradient along the long axis of the heart.¹⁰⁻¹² This pattern of abnormal perfusion is distinctly different from the circumscribed, regional perfusion defects typical of segmental coronary artery stenosis.

The single view rest-stress perfusion images of Figure 2 show mildly reduced relative perfusion after dipyridamole stress in an asymptomatic lean runner with a father having heart disease and mildly elevated cholesterol levels. The automated quantitative analysis compared with 50 healthy control subjects shows this mild defect to be approximately four standard deviations outside normal limits, indicating diffuse non-obstructive coronary atherosclerosis.

The patient refused lipid or beta-blocker treatment, had a cardiac arrest six months later, and was successfully resuscitated by a physician with him at the time. A coronary arteriogram showed no stenosis but severe coronary atherosclerosis by intravascular ultrasound (IVUS) and a potential site of plaque rupture with probable prior thrombosis dislodged during resuscitation and treatment before the arteriogram.

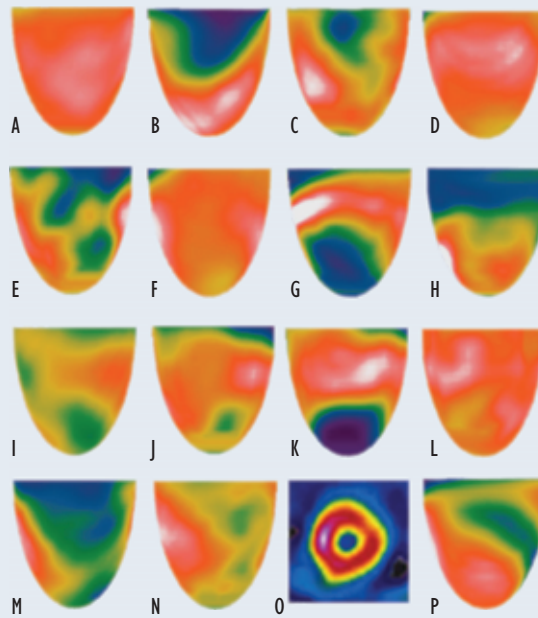
Management Decisions and Second Opinions in CAD Based on PET

Most major management decisions and second opinions in CAD can be satisfactorily resolved based on PET imaging as illustrated in Figure 3. Each PET image of Figure 3 is a single view of perfusion during stress with

normal resting images (not shown) except for the example of hibernating myocardium where the resting images are shown (panels G and H).

- A. Normal myocardial perfusion after dipyridamole stress.
- B. Recurrent angina after bypass surgery with open grafts by arteriogram. PET shows a severe stress-induced, proximal septal defect due to progressive disease involving the first septal perforator proximal to the patent left anterior descending (LAD) graft.
- C. Recurrent resting angina after a successful stent to the left circumflex (LCx) with no residual stenosis anywhere on arteriogram. PET shows a small severe defect in the distribution of a small first obtuse marginal branch with a flush occlusion at the stent site not visible on the arteriogram.
- D. Reportedly 90% stenosis of LAD and 60% to 80% stenosis of LCx and RCA for which bypass surgery recommended. PET shows mild diffuse CAD without localized flow limiting stenosis. Review of arteriogram indicated overestimation of severity. Patient asymptomatic and well 12 years later on medical treatment.
- E. Epigastric pain, CT scan showed no significant calcium, told had no heart disease. PET scan shows severe CAD, confirmed by arteriography.
- F. Asymptomatic person with CT calcium score 2,839; arteriogram recommended. PET shows mild diffuse disease with no significant flow-limiting stenosis, thereby avoiding arteriogram.
- G. Large anterior resting perfusion defect, reduced contraction, occluded LAD and question of transmural scar not suitable for revascularization.
- H. Metabolic image with floro-deoxyglucose of the same patient as in panel G showing metabolically active, viable, hibernating myocardium in the underperfused area for which revascularization is indicated.
- I. Familial CAD—woman with mild diffuse CAD and small acute non-transmural myocardial infarction (MI), wife of man in panel J.
- J. Familial CAD—man with mild CAD by PET, husband of woman in panel I.
- K. Familal CAD—a 46-year-old man with acute MI, son of patients in panel I and panel J. Of asymptomatic people who have a parent or sibling with CAD, 50% have dipyridamole-induced, statistically significant myocardial perfusion abnormalities outside 95%

Figure 3: Single Views of Stress Perfusion by PET, Illustrating most Clinical Decisions and/or Second Opinions in the Diagnosis or Management of CAD



See text for the medical issue in each case.

- confidence intervals of normal controls, indicating preclinical CAD independent of other risk factors.¹³
- L. CT arteriogram showed '60% stenosis' with question of needing an invasive arteriogram. PET showed no significant flow-limiting stenosis thereby avoiding invasive arteriogram.
- M. PET showed severe defects with myocardial steal after dipyridamole stress—indicating an occluded collateralized LCx, confirmed by arteriogram with no procedure done but intense pharmacologic and lifestyle program instituted.
- N. PET of the same patient in panel M conducted four years later showing such well developed collaterals that dipyridamole stress caused no myocardial steal and only a mild perfusion defect.
- O. Normal stress SPECT perfusion scan of a patient with risk factors, also had PET.
- P. PET perfusion scan of the same patient in O showing a stress-induced defect typical of severe stenosis of the ramus intermedius starting at the basal anterior wall and extending infero-laterally.

Following Regression/Progression of CAD by PET During Intense Medical Treatment

Over the past 10 years, large randomized trials have demonstrated that lipid-lowering improves perfusion

Figure 4: Progression and Regression of CAD by PET in a Poorly Treated and Maximally Treated Patient

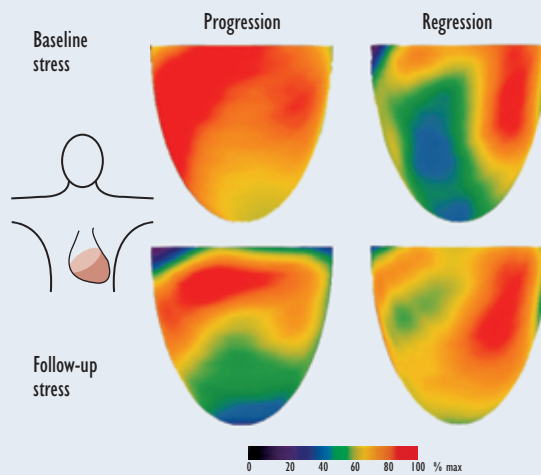
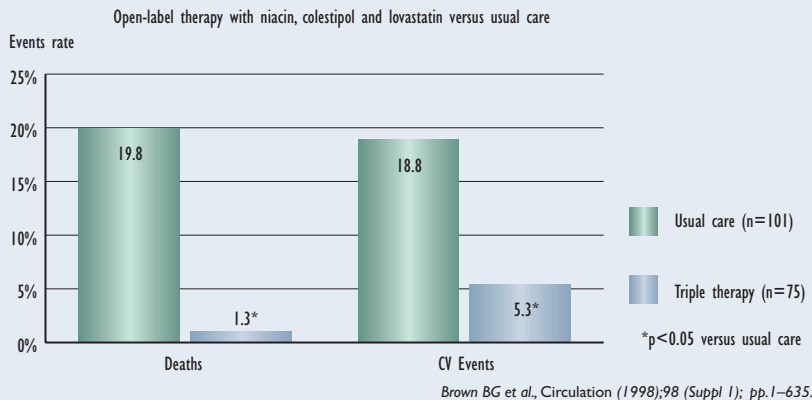
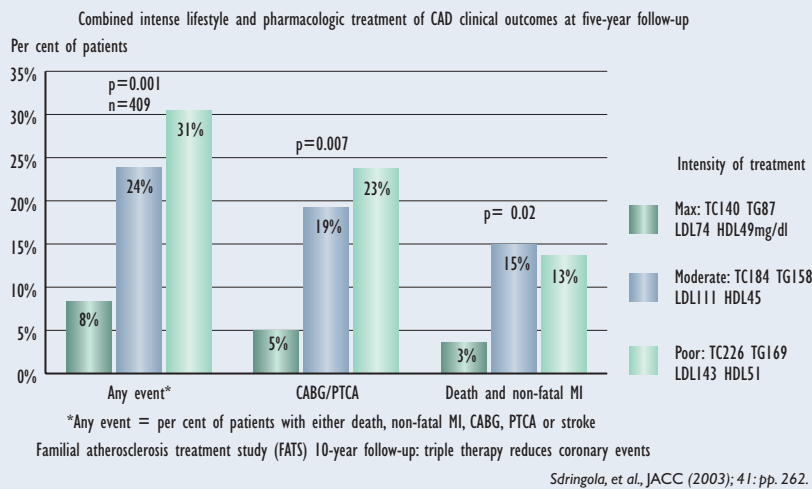


Figure 5: Coronary Events in Two Studies of Maximal Multi-drug and/or Combined Pharmacologic with Lifestyle Treatment of CAD Compared with Usual Care^{1,3}



and reduces risk of coronary events such as MI, death, hospitalization, balloon angioplasty, and bypass surgery in patients with established CAD.

Figure 4 illustrates progression and regression of CAD in single views of dipyridamole stress images obtained at

baseline and two or more years follow-up from two different patients. Worsening is characteristic of patients without adequate risk factor treatment. Improvement in these perfusion patterns is typical of vigorous risk factor management^{1,14,15} associated with marked reduction in cardiovascular events. Changes objectively quantified by PET are greater with greater statistical significance than changes by quantitative coronary arteriography.¹⁵

Figure 5 shows clinical outcomes at five-year follow-up in PET studies and at 10-year follow-up of the Familial Atherosclerosis Treatment Study (FATS) using multi-drug treatment³ comparable with outcomes of the HDL (high density lipoprotein) Atherosclerosis Treatment Study (HATS) of combined statin and niacin.² In the author's PET study, 'maximal treatment' indicates food with <10% of calories as fat, regular exercise and lipid active drugs dosed to target goals of LDL <2.3mmol/L (90 mg/dl), HDL >1.2mmol/L (45mg/dl), and triglycerides <1.1mmol/L (100mg/dl). 'Moderate treatment' indicates an American Heart Association (AHA) diet and lipid-lowering drugs not dosed to goals or on strict low fat diet (<10% of calories) without lipid drugs. 'Poor treatment' indicates no diet or lipid drugs, or smoking. Over five years of follow-up, coronary events occurred in 6.6%, 20.3%, and 30.6% of patients on maximal, moderate and poor treatment, respectively (p=0.001).¹ The HATS trial had comparable results,³ both better than statin monotherapy trials.

Combined intense lifestyle change plus lipid-active drugs and severity/change of perfusion abnormalities independently predicted cardiac events. By stepwise multivariate logistic regression analysis, independent predictors of the combined end-point (MI, death, percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG)) were:

- severity of myocardial perfusion abnormalities on dipyridamole PET scans;
- change in myocardial perfusion abnormalities between the baseline and follow-up PET scans;
- combined intense lifestyle changes plus lipid-active drugs;
- lipid-active medications;
- regular exercise;
- LDL and triglyceride levels; and
- diabetes and coronary heart disease in a mother, father, or sibling.

Endothelial and Microvascular Dysfunction by PET as Markers of the Earliest Stage of CAD

Coronary endothelial dysfunction is closely associated with microvascular dysfunction, and CAD or its risk factors¹⁶ may be familial as an independent risk factor¹⁷

and predicts future coronary events¹⁸⁻²¹ or clinically manifest disease up to 10 years later.²¹ The three principle methods for assessing coronary endothelial function reflect different aspects of its complex multifaceted behavior with specific limitations in their clinical application.

The method using intracoronary acetylcholine requires coronary arteriography and provides information only on epicardial coronary arteries, not endothelial function of the microvasculature that is an essential component of preclinical coronary atherosclerosis. Forearm arterial vasodilation during reactive hyperemia by ultrasound is non-invasive but does not correlate specifically with coronary endothelial dysfunction.²² The cold pressor test involves complex sensory and efferent vasomotor control mechanisms separately from endothelial function with substantial variability in normal subjects that may limit its diagnostic utility in individuals.²³

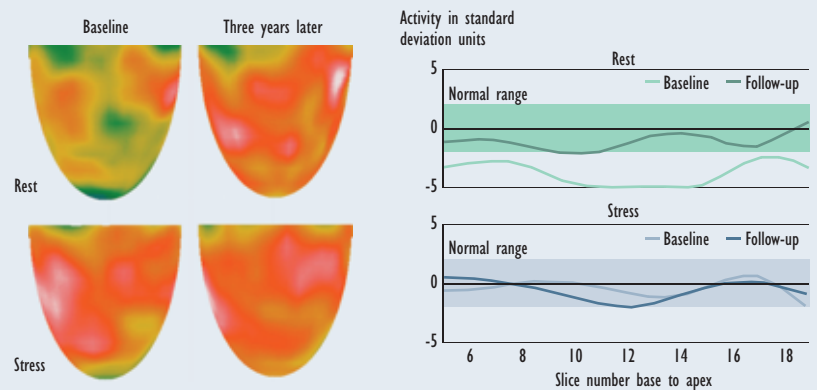
Coronary endothelial dysfunction is heterogeneous within different locations of a single coronary artery and among coronary arteries affecting both the macro and micro-circulation. This heterogeneous coronary endothelial dysfunction causes heterogenous arteriolar vasoconstriction at resting conditions apparent on resting PET perfusion images as a ‘moth-eaten’ appearance that may improve after dipyridamole or adenosine stress, resulting in more homogeneous perfusion in areas without flow-limiting stenosis,^{5,24} illustrated in *Figure 6* at baseline and after intense treatment of risk factors. The automated quantification of relative activity on baseline to follow-up resting scans is shown on the upper right graph and the corresponding baseline to follow-up stress comparisons on the lower right graph. This diffuse patchy heterogeneous resting myocardial perfusion by PET may be quantified objectively by Markovian homogeneity analysis and/or its improvement during dipyridamole stress.²⁴ These perfusion patterns by PET are powerful predictors of even mild stress perfusion abnormalities, more than standard risk factors, consistent with coronary microvascular dysfunction as an early marker of CAD.²⁴

Clinical PET Integrated with Current Pathophysiologic Concepts of CAD

Based on current knowledge and technology, the clinical guidelines for applying and interpreting cardiac PET imaging require a radical departure from traditional nuclear cardiology using standard single photon emission computed tomography (SPECT) imaging summarized as follows:

- Due to accurate attenuation correction, high-resolution and improved counting statistics, PET perfusion imaging conducted and viewed correctly is

Figure 6: Resting Perfusion Changes Associated with Endothelial Dysfunction Due to Coronary Atherosclerosis in a Patient with Risk Factors and Scattered Mild Non-flow-limiting Stenosis by PET and Coronary Arteriography



a definitive, stand-alone diagnostic procedure that does not require diagnostic arteriographic confirmation and provides the basis for revascularization decisions.

- Coronary atherosclerosis is a diffuse disease with a graded range of severity of narrowing. PET perfusion imaging shows a corresponding range of abnormalities. Consequently, binary classification as normal or abnormal with an associated binary decision for or against coronary arteriography is inadequate as the basis for managing CAD in view of current knowledge about coronary plaque rupture, diffuse disease, endothelial function, prognosis, vigorous risk factor treatment, and unaltered risk of clinical events after revascularization procedures.
- The severity of perfusion abnormalities quantifies the severity of coronary artery stenosis, its precise anatomic location in the coronary artery tree, diffuse disease and effects of multiple stenoses in addition to diffuse disease that is not possible with any other invasive or non-invasive technology.
- Mild perfusion abnormalities by PET indicate the substrate for plaque rupture and cardiovascular events that requires vigorous, lifelong risk factor management. A mild perfusion defect by PET implies the same long-term risk as a severe defect by virtue of identifying subjects with CAD subject to plaque rupture. Both mild and severe PET perfusion defects mandate equally vigorous cholesterol-lowering and risk factor treatment.
- Changes in perfusion abnormalities by follow-up PET studies indicate progression or regression of CAD with an accuracy greater than the arteriogram due to perfusion reflecting diffuse changes throughout the length of the coronary arteries, depending on radius changes raised to the fourth

power and due to altered endothelial mediated vasomotor function.

- Heterogeneity of resting myocardial perfusion outside of the normal limits indicates microvascular dysfunction and is a powerful independent predictor of coronary atherosclerosis requiring vigorous treatment of risk factors.
- Clinical reports of PET perfusion images need to be written in a way that incorporates this new information while still recognizing the traditional viewpoints of most physicians (or patients) reading PET reports who may not be familiar with the implications of this integrated new knowledge about high-quality perfusion imaging, related coronary pathophysiology, and its treatment.

A New Cardiovascular Subspecialty Service—Non-invasive PET or PET-CT Imaging Integrated with Intense Preventive-reversal Treatment

For the comprehensive non-invasive diagnosis and management of coronary heart disease based on reversal treatment, myocardial PET perfusion imaging provides the following:

- non-invasive other than an intravenous injection;
- high diagnostic accuracy that is definitive, comparable with, or better than coronary arteriography as the basis for lifelong reversal treatment;
- accurate assessment of severity in specific coronary arteries or branches for deciding on invasive procedures;
- proven accuracy for following progression or regression of CAD as well as or better than coronary arteriography;
- capacity for identifying early, non-stenotic coronary atherosclerosis or diffuse disease before significant segmental stenoses, ischemia, symptoms, or contractile dysfunction develop; and
- visualizing and objectively quantifying abnormal endothelial function associated with early or diffuse atherosclerosis.

Therefore, non-invasive diagnostic PET imaging has advanced beyond the accuracy and clinical utility of most visually interpreted diagnostic coronary arteriography as the optimal approach for principally non-invasive management of CAD. PET perfusion images need to be interpreted in the context of the documented role of endothelium and plaque rupture in the patho-physiology and treatment of CAD. Diagnostic interpretation of PET perfusion images must recognize and be influenced by the newer therapeutic options of treatment to stabilize or partially

reverse coronary atherosclerosis based on intense comprehensive risk factor management.

Essential Technical Details for Clinical Cardiac PET

Cold area imaging for perfusion defects using short half-life perfusion radionuclides is substantially more difficult than using longer half-life fluorodeoxyglucose (FDG) or hot-spot imaging for cancer due to greater technical demands for the cardiac applications demonstrated here. In the author's experience, good cardiac perfusion images require 40 to 50 million total counts or at least 12 to 15 million true coincidence counts for adequate cold area imaging, for quantifying defect severity and for identifying early mild perfusion changes due to preclinical CAD.

With generator-produced Rb-82 having a half-life of 75 seconds, 40 to 50 mCi have to be infused quickly intravenously. Data acquisition has to be completed in five minutes with high count rates early in acquisition, 2M to 3M cps. Consequently, random coincidences, dead time and scatter are high with potentially high noise and poor signal to noise ratio. In the author's experience of reducing noise and acquiring sufficiently high true counts, 2-D imaging with long extended septa, filtered back projection reconstruction and a scanner capable of high true count rate are essential for the advanced cold area imaging demonstrated in these examples. Acquisition of 3-D image and ordered-subset expectation maximization (OSEM) reconstruction techniques are not satisfactory for high-quality cardiac perfusion imaging using Rb-82.

Misregistration of attenuation and emission images is common in cardiac PET imaging, and causes artifactual defects in 20% of patients, predicted by diaphragmatic displacement, body mass index, and heart size.²⁵ Software for visually optimizing co-registration of attenuation and emission images is essential for eliminating artifacts. Recognizing and correcting these misregistration artifacts are essential for reliably identifying mild perfusion defects of early non-obstructive coronary atherosclerosis as the basis for intense lifestyle and pharmacologic treatment.

Summary

Cardiac PET, conducted correctly with attention to technical details, provides definitive non-invasive assessment of early or advanced coronary atherosclerosis as the basis for invasive procedures or lifelong intense risk factor management, demonstrates progression or regression of disease, predicts clinical outcomes, and may serve as the primary basis for managing CAD. ■

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