

Positron emission tomography in coronary artery disease

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Purpose of review

Mortality and coronary events are dramatically reduced in coronary artery disease by intense lifestyle and pharmacologic management without further improvement by revascularization procedures, thereby requiring definitive noninvasive diagnostic imaging. Consequently, this review summarizes the evidence supporting cardiac positron emission tomography as a definitive, noninvasive, 'one-stop' test for routine management of coronary artery disease that is well validated in the scientific literature and illustrated by clinical cases.

Recent findings

Substantial evidence documents accuracy of positron emission tomography for identifying early or advanced coronary artery disease, quantifying its severity, risk stratification, deciding on revascularization procedures, following progression or regression and for evaluating coronary endothelial function as the basis for preventive treatment. Recent technology like positron emission tomography-computed tomography, however, requires advanced knowledge, training and attention to technical details to avoid common artifactual results and to provide definitive conclusions illustrated in this review.

Summary

Cardiac positron emission tomography, done correctly with attention to technical details, provides definitive noninvasive assessment of early or advanced coronary atherosclerosis as the basis for invasive procedures or for lifelong intense risk factor management, demonstrates progression or regression of disease, predicts clinical outcomes and serves as the primary definitive noninvasive guide for managing coronary artery disease.

Keywords

CAD, cardiac PET, noninvasive management of CAD, perfusion imaging

Abbreviations

CAD	coronary artery disease
CT	computed tomography
LAD	left anterior descending coronary artery
PET	positron emission tomography

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0268-4705

Introduction

With strong evidence supporting noninvasive medical treatment of coronary artery disease (CAD), definitive noninvasive imaging is becoming increasingly central to the comprehensive integrated tasks of identifying early coronary artery stenosis or diffuse disease, assessing its quantitative severity, objectively determining need for revascularization procedures, following progression or regression of disease and for directly evaluating endothelial function of the coronary arteries due to early atherosclerosis needing intense preventive management. Cardiac positron emission tomography (PET) provides a noninvasive 'one-stop' test for routine management of CAD that is well validated in the scientific literature for all of these tasks as outlined here.

This review documents the unique accuracy of cardiac PET for accomplishing each of these tasks as the single most definitive basis for the routine management of CAD. It also addresses the substantial pitfalls of cardiac PET, particularly PET-computed tomography (CT) that may give rise to erroneous results and clinical errors. Like all tomographic technologies including CT and MRI, definitive clinical applications require advanced knowledge, training, attention to technical details and integration into the new paradigms of primarily medical treatment of atherosclerosis. Since some readers may not be familiar with the precision and definitive information provided by properly done cardiac PET, several case examples are presented followed by systematic review of the literature.

Diagnostic accuracy and 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 are rotated into true long and short axis views and compiled or stacked into a quantitative three-dimensional 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

Curr Opin Cardiol 22:422-428. © 2007 Lippincott Williams & Wilkins.

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Current Opinion in Cardiology 2007, 22:422-428

wall. Four views of the heart are displayed at 90° angles as if walking around the heart looking at left lateral, inferior, right lateral (septal) and anterior views.

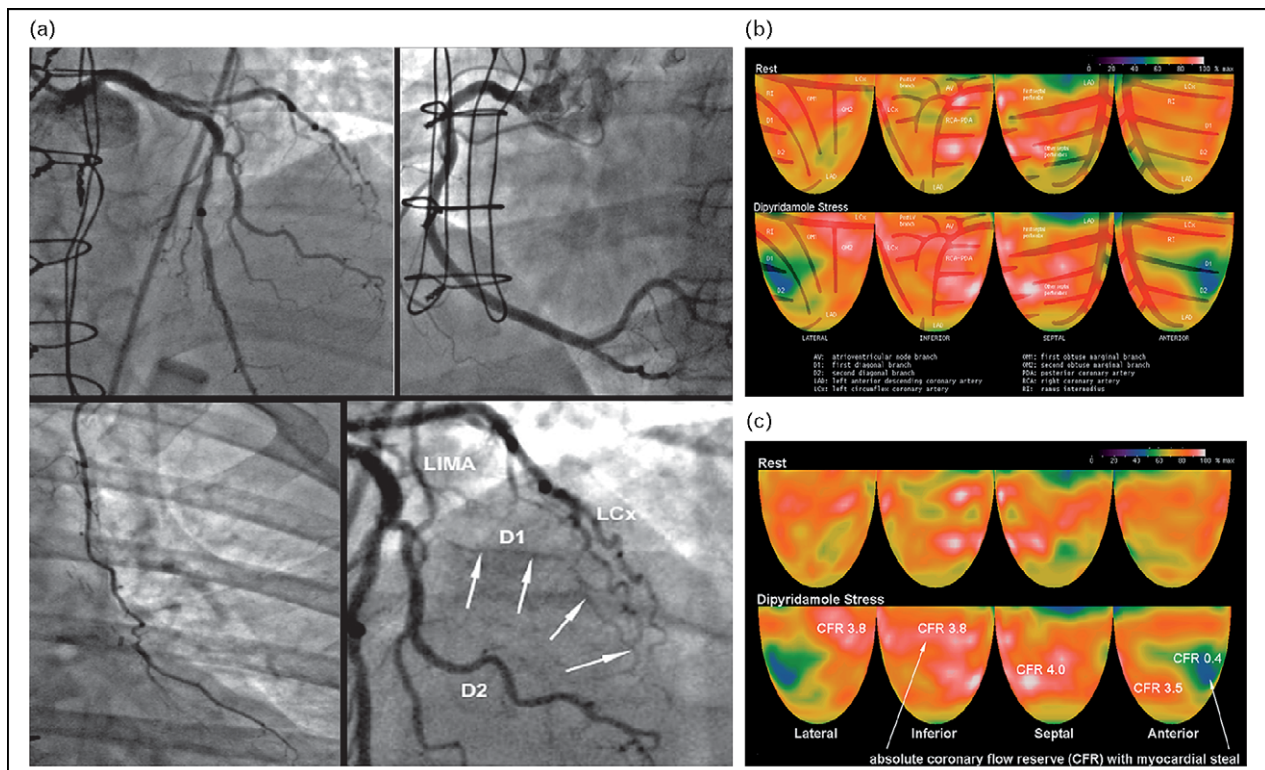
Myocardial activity is normalized to the top 2% of activity in the whole heart data set and scaled from the maximum of 100% in white with stepped downward increments to red, yellow, green, blue and black being progressively more severe defects as in the color bar in the PET perfusion images. This whole heart display provides a more physiologic view of perfusion distribution directly related to the coronary arteries as compared with tomographic 'slices' or the tremendous spatial distortion of the bull's eye display.

A coronary arterial map is overlaid on the three-dimensional topographic display of perfusion images. This overlay of the coronary arteries was 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 an arteriographic stenosis in every coronary

artery and all its branches on coronary arteriograms for over 1000 patients [1].

The patient in Fig. 1a illustrates the remarkable accuracy of PET for assessing the location and severity of specific coronary arteries or secondary branches where anatomic imaging, coronary arteriography, failed to guide appropriate management. She is a 59-year-old with prior four vessel coronary bypass surgery referred for repeat bypass surgery due to persisting angina. Her outside coronary arteriogram showed three bypass grafts closed, an open left internal mammary artery to a diagonal branch and purportedly left anterior descending coronary artery (LAD) stenosis on the arteriogram shown for which percutaneous transluminal coronary angioplasty (PTCA) was done without relief of angina. In view of potential overestimated severity of arteriographic lesions for which she was referred to surgery, a rest dipyrindamole PET scan was done (Fig. 1b). It showed a small severe defect in the distribution of the first diagonal branch of the LAD but no perfusion defects in the distribution of the LAD itself or any other coronary artery.

Figure 1 The remarkable accuracy of PET for assessing the location and severity of specific coronary arteries or secondary branches



(a) Coronary arteriograms of patient with three closed bypass grafts, a patent left internal mammary artery (LIMA) to a diagonal branch and persisting angina after PTCA of the LAD, referred for repeat bypass surgery. Top left panel, left coronary; top right panel, right coronary; bottom left panel, LIMA to the second diagonal branch; bottom right panel, in retrospect after the PET scan, contrast-enhanced magnified view of occluded first diagonal branch filling faintly via small collaterals corresponding to the PET defect. (b) PET perfusion images at rest and after dipyrindamole stress of the patient with overlay of a generalized coronary artery map based on 1000 arteriograms correlated with PET perfusion imaging. White indicates the highest myocardial uptake of Rb-82, reflecting the highest myocardial perfusion with red being the next highest and progressively lower perfusion indicated by color gradations from red to yellow, green and blue in the color bar. (c) Absolute coronary flow reserve (CFR) based on absolute perfusion measured in cubic centimeters per minute per gram overlaid on the PET images of the same patient in Figs. 1 and 2.

Absolute coronary flow reserve based on absolute perfusion measured in cubic centimeters per minute per gram showed myocardial steal in the small severe defect indicating collateralization of the first diagonal branch with a flush occlusion at its origin not seen on the coronary arteriogram. Coronary flow reserve throughout the rest of the heart was normal thereby documenting the absence of flow-limiting stenosis elsewhere and making further bypass surgery inappropriate (Fig. 1c).

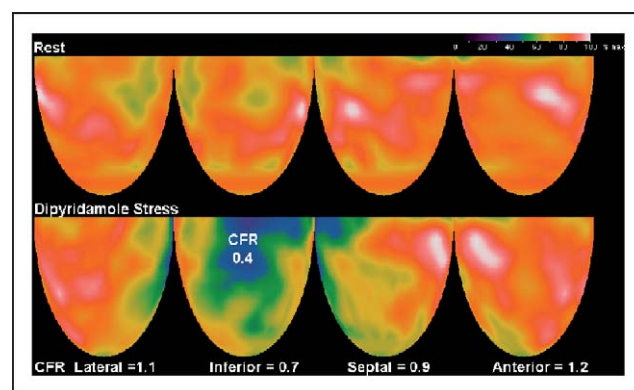
By slowing heart rate with larger doses of beta blocker and more aggressive lipid therapy, both of which improve collateral flow, her angina resolved within 3 days. After the PET had documented the problem, re-review of the outside arteriogram with marked contrast enhancement confirmed a faintly visible occluded first diagonal branch corresponding to the PET defect as the cause of angina (Fig. 1a, bottom right panel). This source of her angina was not identified on any prior coronary arteriogram, was not relieved by prior bypass surgery and PTCA for reported severe stenosis of coronary arteries that were free of flow-limiting stenosis by quantitative PET imaging. This example illustrates how cardiac PET resolves complex problems and second opinions not possible by even a high-quality coronary arteriogram. The diagnostic accuracy of PET imaging is well established in the scientific literature [1,2^{••},3–10].

Who needs revascularization procedures?

Cardiac PET perfusion imaging reliably identifies and quantifies functional severity of flow-limiting coronary artery stenosis thereby avoiding unnecessary diagnostic arteriograms and unnecessary revascularization procedures. It is particularly useful for second opinions by documenting absence of significant flow-limiting stenosis the severity of which is visually overestimated on arteriograms, as in the above example.

Cardiac PET, however, may also confirm that coronary bypass surgery is mandatory, as for this patient with mild angina and an abnormal stress PET (Fig. 2) showing a severe inferior stress-induced defect and reduced left ventricular ejection fraction. The relative uptake images do not show significant perfusion defects elsewhere so that the flow capacity of the normal-appearing areas is not known. Absolute coronary flow reserve based on absolute perfusion measured in cubic centimeters per minute per gram [11], however, showed severely reduced coronary flow reserve of 1.2 throughout the rest of the heart, where 3.5 to 4.0 is normal, thereby indicating severe three vessel disease in the most normal appearing areas, confirmed by arteriography as appropriate for bypass surgery. CFR of 0.4 indicates myocardial steal and collateralization of an occluded right coronary artery.

Figure 2 Rest dipyridamole PET in a patient undergoing PET for a question of bypass surgery with absolute coronary flow reserve overlaid on the relative uptake images

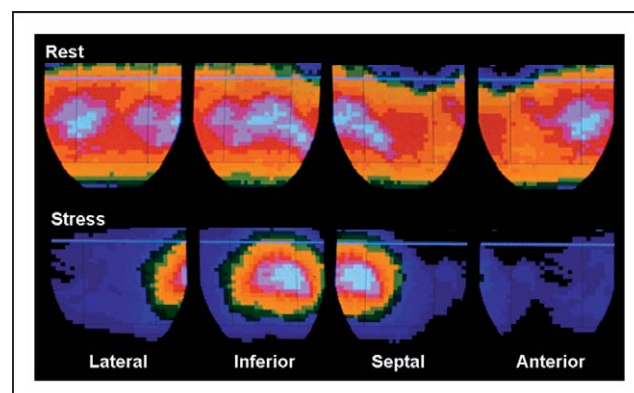


CFR, coronary flow reserve.

In randomized trials, revascularization procedures improve survival only in significant three vessel disease with reduced left ventricular function or left main disease of greater than 60% diameter stenosis. Consequently, noninvasive prognosis, risk stratification and quantitative analysis of severity are essential for optimal management and well documented for cardiac PET imaging [12^{••},13[•],14]. In addition, PET imaging of myocardial uptake of fluorodeoxyglucose is the 'standard' for differentiating myocardial scar from 'hibernating' myocardium that is underperfused and poorly contracting but viable with functional recovery after revascularization [15].

Significant left main coronary artery stenosis, or not, is also readily determined by PET perfusion imaging (Fig. 3). In this case without angina, the stress PET image shows a severe, large, stress-induced perfusion defect indicating severe left main stenosis of a dominant left coronary artery wrapping around the left ventricular

Figure 3 Rest and dipyridamole PET showing previously undiagnosed severe left main stenosis with a left dominant coronary circulation and a small nondominant right coronary artery distribution



apex with the left circumflex supplying the posterior descending coronary artery. The right coronary artery is small and nondominant, all confirmed by arteriography and bypass surgery.

Positron emission tomography imaging in diffuse coronary atherosclerosis

With attention to technical details of data acquisition, PET images small differences in perfusion that reflect mild stenosis or diffuse coronary artery disease in the absence of significant localized flow-limiting stenosis. Diffuse coronary atherosclerosis causes a graded base-to-apex, longitudinal perfusion gradient along the long axis of the heart (Fig. 4) [6,9,10]. This pattern of abnormal perfusion is distinctly different from the circumscribed, regional perfusion defects typical of segmental coronary artery stenosis.

Differentiating diffuse disease from significant flow-limiting left main stenosis may also be done with PET (Fig. 5). This patient is a 76-year-old woman presenting with recurrent angina who had a prior stent to her right coronary artery with a reported 50% left main stenosis. Relative uptake PET images showed small lateral stress-induced defects and a base-to-apex perfusion gradient characteristic of diffuse disease. Absolute coronary flow reserve was moderately but relatively uniformly reduced throughout the heart at 2.0 to 2.3 except for the small lateral defects that had severely reduced absolute coronary flow reserve of 1.2, the source of her angina. The combination of uniform moderately reduced flow reserve and a base-to-apex longitudinal gradient indicate diffuse disease, not flow limiting left main, with a small obtuse marginal branch that is severely narrowed but too small for revascularization, indicating intense medical management.

Figure 4 Single views of rest dipyridamole PET images for three different people demonstrating normal images, segmental stenosis and diffuse coronary artery disease

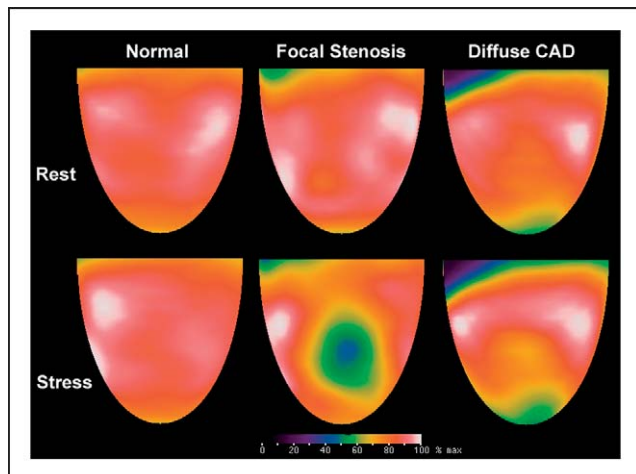
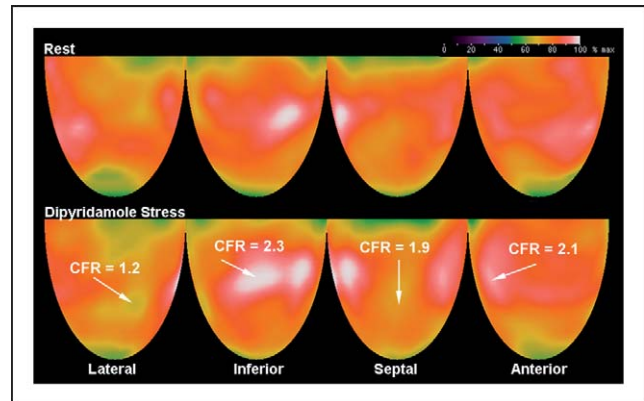


Figure 5 Rest dipyridamole PET of mild left main and diffuse coronary artery disease with absolute coronary flow reserve overlaid on the relative uptake images



CFR, coronary flow reserve.

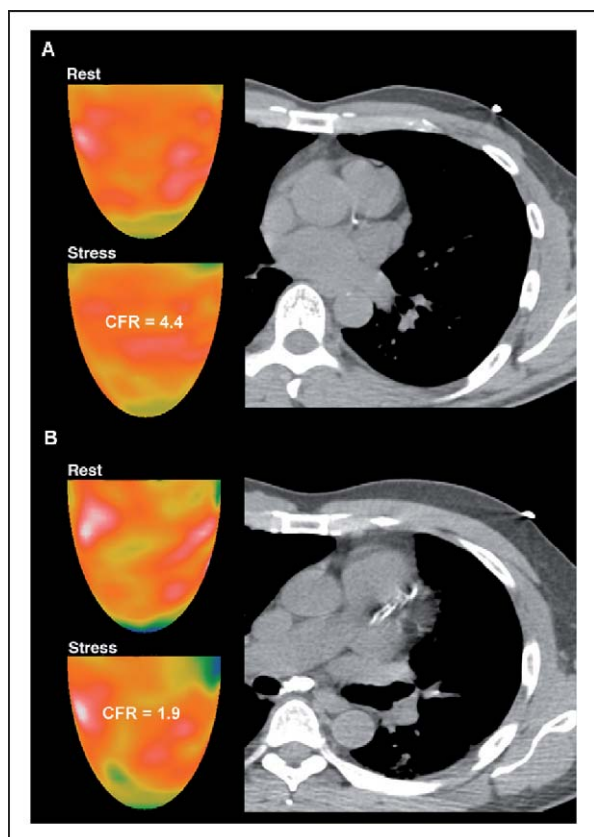
The dilemma of asymptomatic coronary calcification

Coronary calcium by CT scanning is an important marker of coronary atherosclerosis. Early lipid-rich coronary atheroma in young people with premature coronary artery disease, however, may cause plaque rupture and coronary events without calcification. At the other extreme, heavy coronary calcification without flow-limiting stenosis is common. While valuable as a marker of atherosclerosis, coronary calcification fails to identify whether there is an associated coronary artery stenosis. Moreover, atherosclerosis identified by coronary calcification may be associated with endothelial dysfunction, diffuse disease, or small vessel disease either with or without localized stenosis or none of these abnormalities. Absolute coronary flow reserve based on absolute perfusion measured in cubic centimeters per minute per gram provides definitive assessment of coronary calcification (Fig. 6). In these case examples, both patients had coronary calcification by CT and stress PET scans showing no flow-limiting stenosis, thereby eliminating any need for arteriography. In one patient, however, coronary flow was excellent at 4.4 whereas in the other patient coronary flow reserve was moderately uniformly reduced to 1.9 without a base-to-apex longitudinal perfusion gradient characteristic of diffuse coronary artery narrowing. This pattern of reduced coronary flow reserve without a significant base-to-apex longitudinal perfusion gradient characterizing diffuse disease indicates primarily small vessel dysfunction associated with atherosclerosis.

Following regression or progression of coronary artery disease

Small changes in coronary artery diameter of tenths of millimeters that cannot be assessed by an arteriogram may significantly change coronary flow reserve since flow

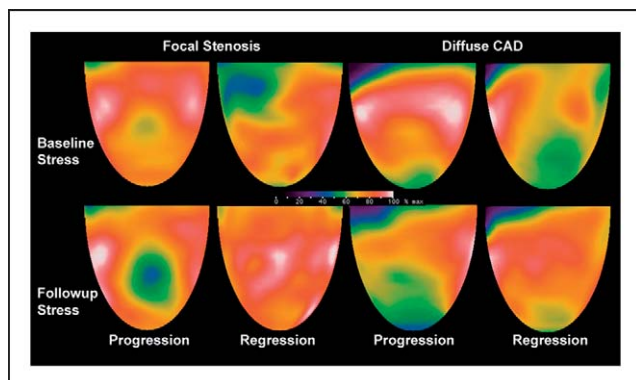
Figure 6 Rest dipyridamole PET and absolute coronary flow reserve in two patients with coronary calcification



CFR, coronary flow reserve.

depends on the fourth power of the arterial radius. PET perfusion images without attenuation artifacts provide a magnified signal of small changes in arterial diameter as a sensitive specific measure of stenosis severity and its changes (Fig. 7). One view of the stress image for each of four different patients at baseline and at follow-up

Figure 7 Single views from four different patients of stress PET images at baseline and at follow-up several years later showing progression or regression of segmental stenosis or diffuse disease



several years later shows typical progression and regression of segmental and diffuse CAD that are objectively quantified for following effectiveness of treatment [12^{**},16^{**},17–21]. The pattern of these quantitative changes on PET perfusion images also indicates non-invasively the mechanism of progression and regression by partial plaque rupture or gradual changes of a prior stenosis [12^{**}].

Worsening PET perfusion images are characteristic of patients without adequate risk factor treatment; improvement in these perfusion patterns is typical of vigorous risk factor management associated with marked reduction in cardiovascular events [12^{**},16^{**},17,19]. Perfusion changes at follow-up PET imaging objectively quantified by automated software are larger with greater statistical significance than changes by quantitative coronary arteriography [19] and are powerful predictors of clinical outcomes [12^{**},16^{**},17,19].

Endothelial and microvascular dysfunction by positron emission tomography in early coronary artery disease

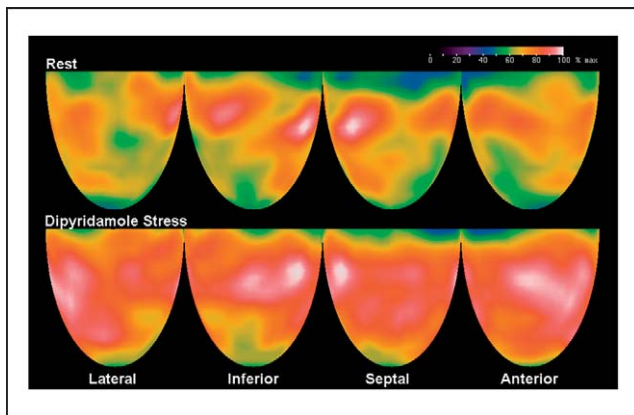
Coronary endothelial dysfunction is closely associated with microvascular dysfunction and CAD or its risk factors, may be familial as an independent risk factor [22], and predicts future coronary events [23–27] or clinically manifest disease up to 10 years later [27]. Forearm arterial vasodilation during reactive hyperemia by ultrasound is noninvasive but does not correlate specifically with coronary endothelial dysfunction [25]. The cold pressor test with PET perfusion imaging has been used to assess coronary endothelial function and associated clinical outcomes [28].

In early atherosclerosis, coronary endothelium may produce excess endothelin and heterogeneous small vessel vasoconstriction associated with resting perfusion heterogeneity (Fig. 8). Objective quantification by Markovian heterogeneity analysis [29] is a powerful predictor of even early mild stress perfusion abnormalities due to CAD, more predictive than standard risk factors, consistent with coronary microvascular dysfunction as an early marker. Myocardial perfusion abnormalities caused by endothelin in an experimental model may disappear, remain the same or become worse after dipyridamole stress depending on the severity of endothelin-induced vasoconstriction [30].

Visual impact on patient motivation

The PET images as displayed here have a profound impact on patient motivation for intense combined lifestyle changes and drug treatment of risk factors with corresponding better outcomes than reported for lipid-lowering monotherapy drug trials [12^{**},17,19]. There is great disparity between proven effective lifestyle–drug

Figure 8 Resting perfusion heterogeneity that improves with dipyridamole stress associated with endothelial dysfunction in a patient with risk factors and scattered mild stenosis on dipyridamole PET images and coronary arteriogram without significant stenosis



treatment to prevent or reverse CAD and the clinical application of this knowledge. The problem was described in the *New York Times*, Sunday, April 8, 2007 referring to Dr Daniel Levy, director of the Framingham study, who is quoted thus, 'Prevention does not have a face. There are no personal stories, no individuals who can be pointed to as the success of prevention. It is just statistics.' While appropriate for statistical analysis, this viewpoint fails to recognize the extensive literature demonstrating early or advanced coronary atherosclerosis by cardiac PET perfusion imaging and its reversal in individual patients as a guide for physicians and a powerful motivator for patients undertaking intense lifestyle-pharmacologic management with dramatic reduction in clinical events over years of follow-up.

Positron emission tomography-computed tomography: the good and the bad

PET-CT uses helical CT for attenuation correction of PET emission images. It shortens total imaging time and identifies coronary calcification. Helical CT images for attenuation, however, are momentary CT 'snapshots' at some point in the respiratory cycle of changing attenuating thoracic-diaphragmatic structures during breathing. These brief CT 'snapshots' commonly do not match the actual average attenuation of the constantly changing thoracic-diaphragmatic structures over longer emission scans during normal breathing. Misregistration of PET emission images and CT attenuation images causes artifactual abnormalities on cardiac PET images that are false positive defects in 20–40% of PET-CT cardiac images or artifactually worsen severity of real perfusion defects [31,32–36]. These artifacts may be avoided by using cine CT that averages CT attenuation data during breathing and by shifting the images for correct visual

coregistration, a function currently lacking in most PET-CT scanners. The suboptimal specificity reported for cardiac PET-CT [1] is likely due to misregistration artifacts since the PET-CT used for that study did not have the capacity for correcting CT-PET misregistration.

Due to the CT scan, the radiation dose to patients undergoing PET-CT is substantially higher than for pure PET using attenuation correction data acquired by a rotating rod. Finally, a number of additional technical factors are crucial for quantitative cold spot imaging illustrated by these examples. These include high count acquisition by early imaging after rubidium infusion, two-dimensional image acquisition with long extended septa, filtered back projection reconstruction, and a scanner capable of very high true count rates for imaging the first pass bolus of full dose rubidium for optimal clinical images as well as absolute perfusion in cubic centimeters per minute per gram. Therefore, technical expertise, specific training, experience and critical examination of every study for artifacts are essential for these advanced routine clinical applications of cardiac PET.

Conclusion

Cardiac PET, done correctly with attention to technical details, provides definitive noninvasive assessment of early or advanced coronary atherosclerosis as the basis for invasive procedures or for life-long intense risk factor management, demonstrates progression or regression of disease, predicts clinical outcomes and serves as the primary definitive noninvasive basis for managing CAD.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 478).

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