Molecular and Metabolic Imaging of Atherosclerosis*

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Atherosclerosis is a systemic disease that affects most major arteries of the body and is the most common cause of premature death in the western world. It develops slowly and often asymptomatically, so that for many patients its first manifestation is sudden cardiac death, stroke, or myocardial infarction. The current gold standard for imaging atherosclerosis is x-ray angiography. However, recent advances in understanding of the pathobiology of atherosclerosis have highlighted the inadequacies of this technique and the need for better imaging approaches. The purpose of this article is to briefly outline the biology of atherosclerosis and to review the techniques available to image it, concentrating specifically on those that detect metabolic or inflammatory changes within the atherosclerotic plaque.

Key Words: atherosclerosis; nuclear medicine; PET; radionuclide; thrombus

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BIOLOGY OF ATHEROSCLEROSIS

Atherosclerosis is characterized by accumulation of lipids, inflammatory cells, and connective tissue within the arterial wall (*1*). It is a chronic, progressive disease with a long asymptomatic phase. The initial abnormality is the fatty streak, a white/yellow linear discoloration, visible macroscopically on the endothelial surface of an artery and caused by accumulation of lipids and macrophages. This develops into a mature atherosclerotic plaque consisting of a central lipid core bounded on its lumen side by an endothelialized fibrous cap containing vascular smooth muscle cells and connective tissue, in particular collagen. As the plaque grows, the vessel expands, so that the lumen diameter and, therefore, blood flow are preserved, a process know as positive remodeling. Consequently, large atherosclerotic lesions can accumulate without compromising flow or producing symptoms. The artery eventually can expand no farther, and the plaque begins to encroach into the lumen of the vessel, causing obstruction to blood flow.

Atherosclerosis remains clinically silent until either of 2 occurrences. The lesion can expand to the point at which it limits flow, producing symptoms of reversible ischemia, such as angina, during periods of high demand. Alternatively, the fibrous plaque can erode or rupture, resulting in the exposure of subendothelial collagen and lipid (*2*). The latter leads to activation of circulating platelets and clotting cascade proteins. Platelet activation produces an upregulation of glycoprotein IIb/IIIa (GPIIb/IIIa) receptors on the platelet surface which, when stimulated, promote platelet aggregation. Activation of clotting factor proteins VII and XI results in the production of thrombin, fibrinogen, and fibrin through the so-called extrinsic and intrinsic coagulation pathways respectively. The result is the formation of thrombus composed of both fibrin and platelets. The consequences of plaque rupture range from complete lysis of the thrombus by endogenous fibrinolytic pathways with subsequent healing of the fibrous cap and overlying endothelium to unchecked thrombosis and complete lumen occlusion. Thus, such an event can range from being clinically silent at one extreme through precipitation of an acute vascular event, such as unstable angina, myocardial infarction, or stroke (depending on the vessel involved), to sudden death at the other extreme (*3*).

Recent research has provided valuable insight into the molecular and cellular biology of atherosclerosis and, in particular, plaque rupture. This research is driving a reevaluation of the approach to investigation and management of the patient with atherosclerosis. Endothelial cell dysfunction is the earliest detectable physiologic manifestation of atherosclerosis (*4*). The major atherogenic risk factors, such as smoking, high low-density lipoprotein (LDL) levels, hypertension, and diabetes, have all been shown to impair endothelial function. Normal endothelium has antithrombotic, antiinflammatory, and vasomodulatory functions through secretion of substances, such as prostacyclin and

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nitric oxide (NO), which inhibit platelet activation and promote vasodilatation (*5,6*). In addition, NO inhibits expression of the adhesion molecules responsible for inflammatory cell recruitment. Both the barrier function and secretory capacity of the endothelium are disrupted in atherosclerosis. This manifests as an increase in permeability to lipids and inflammatory cells (mainly monocytes and T lymphocytes) derived from the blood. Several techniques have been devised to test endothelial function in humans, and all demonstrate impaired endothelial function in the context of atherosclerosis and, of note, in patients at risk of atherosclerosis but without overt disease (*7*).

The combination of endothelial dysfunction and high circulating levels of atherogenic lipoproteins leads to the accumulation of lipid-laden, monocyte-derived foam cells in the subendothelial layer, forming the early atherosclerotic lesion. Accumulation of foam cells and their subsequent death produces an acellular core of cholesterol esters and cell debris. Vascular smooth muscle cells (VSMCs) migrate from the medial layer of the vessel and synthesize extracellular matrix components, such as elastin and collagen, to form the fibrous cap. The fibrous cap contains inflammatory cells, predominantly macrophages, but also some T lymphocytes and mast cells (*1*).

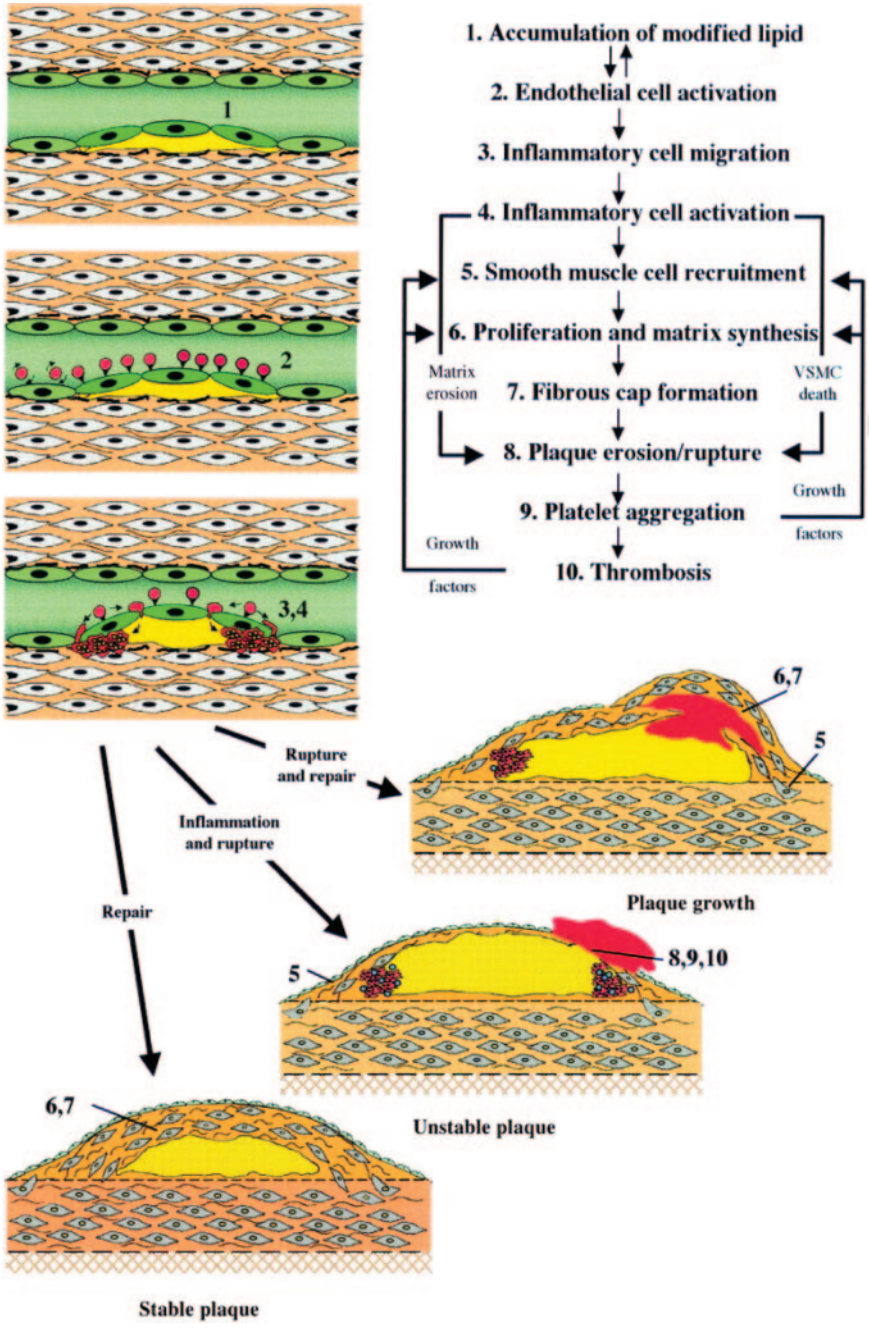

FIGURE 1. Cellular interactions in development and progression of atherosclerosis. VSMC = vascular smooth muscle cell. (Reprinted from *Heart*. 2000;83:247–252, with permission from BMJ Publishing Group).

TABLE 1
Modalities for Imaging Atherosclerosis

Invasive	Noninvasive
X-ray angiography	B-mode ultrasound
Intravascular ultrasound	CT
Angioscopy	MRI
Intravascular thermography	SPECT
	PET

Figure 1 is a schematic representation of the atherosclerotic disease process.

It has become clear that the cellular and extracellular composition of the plaque is a primary determinant of plaque stability. Lesions with a large lipid core, thin fibrous cap, a preponderance of inflammatory cells, and a relative paucity of VSMCs are at the highest risk of rupture (*8*). Inflammatory cells, particularly macrophages, produce metalloproteinases, which break down the matrix proteins in the fibrous cap (*9*). In addition, they secrete inflammatory cytokines, in particular interferon γ (IFN γ), which inhibit VSMC proliferation and collagen synthesis. Other cytokines secreted by inflammatory cells, such as interleukin 1β and tumor necrosis factor α are cytotoxic to VSMCs, and activated macrophages can induce VSMC death by direct cell-to-cell contact. Furthermore, VSMCs in the fibrous cap have a reduced proliferative capacity and a propensity to apoptosis (*10,11*). Consequently, the inflammatory process within the lesions tends toward destruction of the fibrous cap and subsequent thrombosis. There is a dynamic balance within the plaque between macrophages, which promote erosion and rupture of the fibrous cap, and VSMCs, which nourish and repair it. These processes are independent of plaque size. Consequently, small asymptomatic and angiographically invisible plaques can rupture to precipitate a fatal clinical event, whereas some large plaques that obstruct flow to produce symptoms such as angina may be stable and not life threatening. There is an urgent need to discriminate stable from potentially unstable lesions in clinical practice.

IMAGING OF ATHEROSCLEROSIS

Many different techniques for imaging atherosclerosis aid both in diagnosis and in guiding future management (Table 1). These can be categorized into invasive and noninvasive techniques.

Invasive Imaging

X-ray angiography remains the current gold standard imaging technique, although it has considerable limitations (*12–14*). Because angiography simply images the lumen of the vessel, it fails to detect atherosclerotic lesions that do not protrude into the lumen and provides very little information on atherosclerotic plaque composition. Thus, it cannot differentiate between unstable and stable plaques and, therefore, is unable to predict the risk of plaque rupture. Consequently, because it is mostly symptom driven, its main value is in delineating the causative lesion in a symptomatic patient. However, because of positive remodeling, a 'normal' angiogram cannot be interpreted as indicating an absence of atherosclerosis.

Intravascular ultrasound (IVUS), in which a small ultrasound probe mounted on the end of a catheter is passed into a vessel, permits direct imaging of atheroma and can provide a 2-dimensional cross-sectional image of the entire plaque and vessel wall (*15*). Thus, IVUS is able to define angiographically invisible, nonstenotic atheromatous plaques (Fig. 2). In addition, the acoustic properties of plaques allow

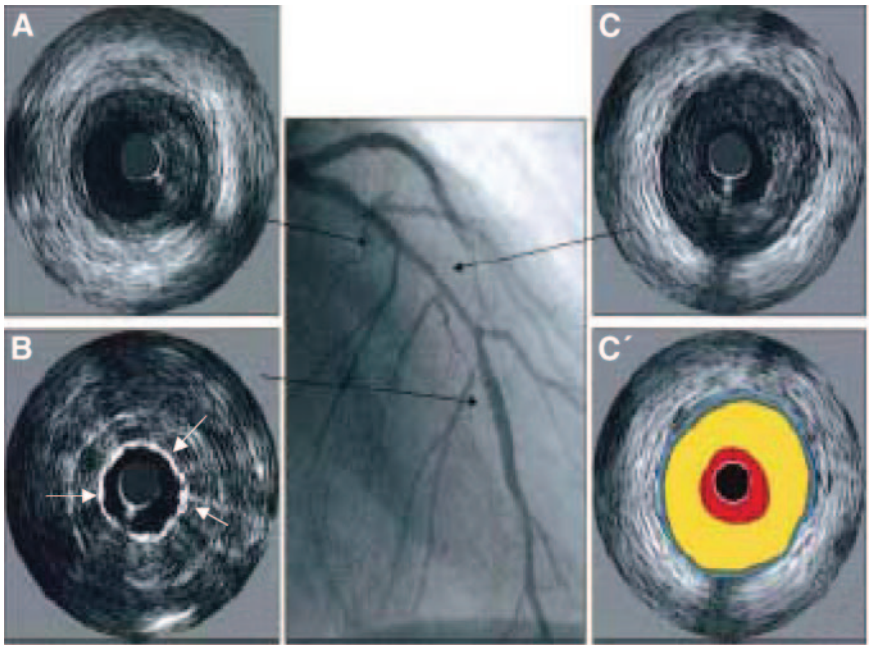

FIGURE 2. Representative intravascular ultrasound images of left anterior descending coronary artery with corresponding x-ray coronary angiogram. (A) Crescent-shaped atheroma is evident despite normal appearance on the corresponding segment of coronary angiogram. (B) Segment of coronary artery in which a stent has been deployed (arrows) to dilate a previously narrowed lumen. (C) Intravascular ultrasound appearance of a circumferential atheroma, which is seen on angiogram as gradual tapering of the lumen. (C′) Different areas represented on intravascular ultrasound image have been color-coded: black = intravascular ultrasound probe; red = vessel lumen; yellow = atheroma; light blue = internal elastic lamina. (Reprinted from *Heart*. 2002;88:91–96, with permission from BMJ Publishing Group).

them to be categorized as soft, fibrous, or calcified, although the clinical significance of such distinctions remains to be determined. However, because IVUS is invasive and demands considerable time, expertise, and expense, its use is currently confined to research and determining the success of interventions, such as balloon angioplasty in single atherosclerotic lesions.

Angioscopy is a catheter-based technique that allows direct visualization of the arterial surface (*16*). Thus, some assessment of the plaque composition can be made through direct visualization of thrombus and the color of the plaque surface. However, there is limited evidence to suggest that this technique is able reliably to identify unstable plaques and predict adverse outcomes (*17–19*). This, coupled with its high cost and invasive nature, confine its use to research.

Intravascular thermography, in which a highly sensitive thermistor is introduced into an artery and applied to the vessel wall, is the most recent innovation in catheter-based technology aimed at defining plaque composition (*20*). Because of their inflammatory cell content, atherosclerotic plaques emit more heat than adjacent normal vessel wall, and unstable plaques emit more heat than stable ones. Thus, intravascular thermography is the first clinical technique to measure plaque metabolism, and numerous studies are currently under way to assess its role in predicting clinical events and monitoring changes in plaque composition (*21,22*). Despite its promise, it is an expensive and invasive technique that is unlikely to gain widespread clinical application.

In summary, although some catheter-based techniques, such as IVUS and thermography, can provide important information on the composition of individual plaques, their invasive nature limits their use to only a few patients with well-defined disease.

Noninvasive Imaging

Because of the difficulty in accessing the coronary bed, most noninvasive imaging of atherosclerosis has been targeted at other arteries. B-mode duplex ultrasound allows noninvasive imaging of large, superficial arteries and has become routine in the assessment of patients with suspected carotid artery disease. Carotid atherosclerosis is a major cause of ischemic cerebrovascular disease producing the clinical syndromes of stroke and transient ischemic attack (*12*). Through its ability to quantify blood flow velocity and to define vascular wall boundaries, ultrasound can accurately measure lumen stenosis as well as arterial wall thickness, measured as combined intima media thickness (IMT). Numerous population studies have now shown that mean IMT predicts risk of both cerebrovascular and myocardial events, presumably because atherosclerosis is a systemic disease in which extent in a single vascular bed reflects that in another (*23,24*). Moreover, in experienced hands, carotid ultrasound can provide some information on plaque morphology based on acoustic impedance, in which heterogeneous echolucency represents intraplaque hemorrhage and lipids (instability), whereas homogeneous echodensity indicates a fibrous plaque (stability). In addition, surface nodularity can indicate lesions that are more prone to thromboembolism (*25,26*). Because carotid ultrasound is noninvasive, safe, and inexpensive, it has become a useful tool for the diagnosis, assessment, and follow-up of atherosclerosis. Nevertheless, it provides no useful information on plaque inflammation or risk of plaque rupture (*27*).

Because surface ultrasound has no real potential for imaging the coronary circulation, attention has focused on other noninvasive techniques, such as CT and MRI. Both CT and MRI can detect flow-limiting lesions in the proximal coronary arteries, particularly when combined with appropriate intravenous contrast agents. Either or both may someday provide a noninvasive substitute for conventional angiography, once problems with motion artifact and image resolution have been resolved (*28,29*). However, the fundamental criticisms of angiography as a means of evaluating atherosclerosis, discussed previously, will still apply.

However, both CT and MRI can provide more than simple angiographic data. In particular, electron-beam CT (EBCT) scanning can accurately quantify coronary calcium. Because calcification is an early manifestation of atherosclerosis and is an almost ubiquitous feature of advanced plaque, its presence or absence can include or exclude a diagnosis of coronary atheroma (*30,31*). EBCT is increasingly used in the United States as a screening technique for coronary atheroma.

Recent studies have shown that MRI is capable of discriminating between lipid core, fibrous cap, intraplaque hemorrhage, calcification, and acute intralumenal thrombosis in patients with carotid artery atheroma (*32,33*). When combined with administration of ultra-small paramagnetic iron oxide particles (USPIOs) that are taken up by macrophages, MRI has the potential to discriminate macrophage-rich from macrophage-poor lesions (*34*). However, considerably more work is required to overcome problems caused by motion artifact, lack of resolution, and interpretation of signal heterogeneity before MRI can realistically be used to assess coronary artery plaque composition.

FUNCTIONAL IMAGING OF ATHEROSCLEROSIS

Most of the techniques described so far, with the possible exception of thermography, have been aimed at providing anatomic detail of plaque size and, to a limited extent, composition. However, none is able to provide information on cell biologic events that determine risk of plaque rupture. Several radiolabeled tracers have been developed that will bind to or be taken up by constituents of the atherosclerotic plaque or associated surface thrombus (Fig. 3), so that 2-dimensional tomographic and 3-dimensional reconstructive images can be extrapolated from emitted γ-rays, usually by means of SPECT, or positrons by means of PET.

An ideal radiotracer to image atherosclerosis should have a high sensitivity and specificity for the detection of ather-

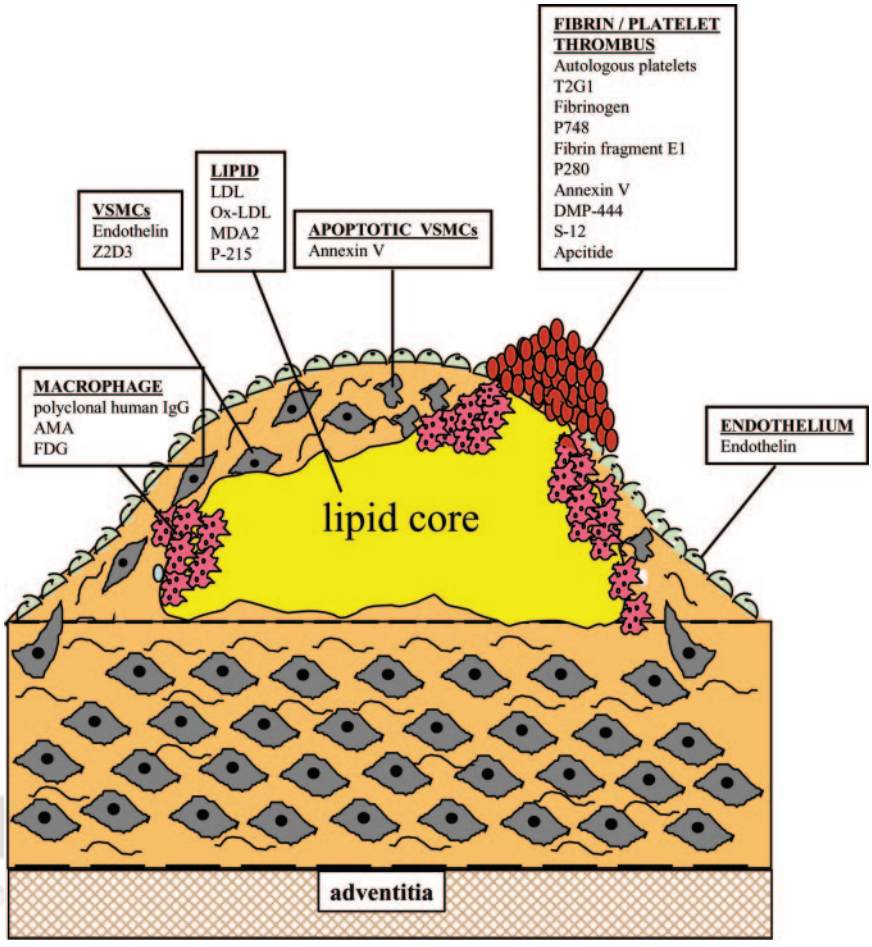

FIGURE 3. Schematic representation of ruptured atherosclerotic plaque with surface thrombus formation. Text boxes represent substrates that have been labeled with radiotracer molecules related to their targets within the plaque. AMA = amino malonic acid; LDL = low-density lipoprotein; Ox-LDL = oxidized low-density lipoprotein.

oma, be able to detect lesions in all vascular beds, and provide information about the probability of adverse outcome in both symptomatic and asymptomatic individuals. To obtain clear images, it is imperative that tracers have rapid clearance from the circulation and high target-to-background ratios. Some of the more successful approaches are discussed here.

Radiotracers for Imaging Atherosclerosis

As outlined earlier in this review, LDL accumulates within atherosclerotic plaques, where it plays a pathogenic role in the formation, progression, and destabilization of lesions. LDL has been labeled with various radioisotopes, including ^{123}I, ^{99m}Tc, and ^{111}In (*35–40*). Studies have shown that radiolabeled LDL is taken up into experimental atherosclerosis in rabbits (*40*). Subsequent clinical studies showed that ^{99m}Tc-LDL could be imaged in coronary, carotid, iliac, or femoral arteries in 7 of 17 patients with proven atheroma. Analysis of endarterectomy specimens 1 d after imaging in 6 of the patients revealed 2–4 times greater uptake into lesions rich in macrophages than in those containing few macrophages (*38,39*). However, because of slow radiotracer clearance from the blood, the authors concluded that radiolabels with improved kinetics were needed to provide useful clinical information.

Because macrophages take up oxidized LDL via the scavenger receptor much more readily than native LDL, a logical step was to attempt to image atherosclerosis using radiolabeled oxidized LDL (*41–43*). In a study of 7 patients with symptomatic carotid artery disease, uptake of ^{99m}Tc-oxidized LDL was seen in 10 of 11 atheromatous lesions, with ^{99m}Tc-oxidized LDL target-to-background ratios approximately 1.5 times higher in diseased than normal carotid arteries (*44*). When compared with native LDL, oxidized LDL has a higher sensitivity for detecting atheromatous lesions as well as a more rapid blood clearance, allowing imaging 1 h after injection.

Radiolabeled antibodies raised against epitopes on the LDL particle, such as the antibody MDA2, have also been studied. MDA2 recognizes malondialdehyde-lysine epitopes on oxidized LDL particles and has been studied in rabbits (*45*). ^{125}I-MDA2 was injected intravenously into 7 LDL receptor-deficient Watanabe heritable hyperlipidemic (WHHL) rabbits and 2 normal New Zealand White rabbits, and aortic plaque uptake was evaluated by way of autoradiography. Uptake of ^{125}I-MDA2 was found to be 17 times higher in the hyperlipidemic rabbits than in the normal rabbits. Autoradiography confirmed that the uptake was preferential in diseased segments of the artery. Imaging then

was performed in similar groups of rabbits using ^{99m}Tc-MDA2. Unfortunately, uniplanar images revealed a visible signal in only 50% of hyperlipidemic rabbits. Suboptimal imaging technique may have accounted for the poor result, but no other studies have been published. Human studies have not been performed because of the possibility of mutagenic metabolites.

In comparison with lipoproteins, peptides clear from the circulation quickly and theoretically could improve the target (atherosclerotic plaque)-to-background (blood pool) ratio, potentially making the identification of atherosclerosis easier. Radiotracers based on the apo-B portion of LDL were the first peptides to be evaluated. Injection of a radioiodinated synthetic apo-B analog, SP-4, resulted in significant uptake into experimental atherosclerotic lesions in WHHL rabbits (*46*). A human pilot study using a ^{99m}Tc label on a synthetic apo-B analog, P-215, showed uptake into human carotid lesions (*47*). However, larger studies with improved design have not been published. Radiolabeled endothelin peptides have been derived and investigated. Endothelin production by smooth muscle and endothelial cells is upregulated in the presence of endothelial dysfunction and, therefore, provides a potential target for identifying atheroma. Both iodinated and ^{99m}Tc-labeled endothelin and its derivatives have been shown to accumulate in experimental atherosclerotic lesions in rabbits, but to date no human studies have been published (*48,49*).

Macrophages within atherosclerotic plaques express cell surface Fc receptors. ^{111}In-Labeled polyclonal human IgG contains an Fc subunit that binds to these macrophage receptors. Its use has been evaluated in patients with carotid atheroma, where it was found to identify 86% of lesions detected by ultrasound. Uptake of ^{111}In-polyclonal human IgG did not correlate with morphology suggestive of a large lipid core on ultrasound. However, ultrasound is not a well-validated method of delineating plaque composition, and the lack of a correlation is as likely to represent the shortcomings of ultrasound as it is the failings of ^{111}In-polyclonal human IgG (*50*). Imaging studies on WHHL rabbits with aortic atherosclerosis were unsuccessful because of poor target-to-background ratios. In addition, autoradiographic analysis revealed that uptake was not reduced in rabbits treated with lipid-lowering therapy (*51*). Taken together, these results suggest that ^{111}In-polyclonal IgG is not an appropriate tracer to identify unstable atherosclerotic lesions.

Radiolabels have been produced with the potential to provide an indirect measure of macrophage content. An example is the radioiodinated monoclonal antibody against amino malonic acid (AMA), a molecule vital to monocyte recruitment and foam cell production within atherosclerotic lesions (*52*). ^{131}I-AMA was assessed in an experimental rabbit model of atherosclerosis. As with ^{111}In-polyclonal human IgG, biodistribution studies revealed significantly increased uptake in diseased as compared with normal aortic tissue, but the slow radiotracer clearance from the circulation meant that in vivo imaging of aortic plaque was unsuccessful.

Antibodies directed against other cells and antigens present in atheromatous lesions have been studied. In preliminary experiments, Z2D3 F(ab′)$_2$ IgM, an antibody fragment that binds to antigen on the surface of VSMCs, has been shown to localize in experimental lesions in rabbits (*53*). Z2D3 has been evaluated in humans in a small study of 11 patients with carotid disease (*54*). Planar and SPECT images revealed focal uptake of the antibody in all symptomatic plaques within 4 h of injection. The location of uptake corresponded with the anatomic location of the plaque as delineated by angiography. Uptake of tracer was also seen in the contralateral asymptomatic carotid artery in approximately 50% of the patients. Subsequent immunohistochemical analysis of carotid endarterectomy specimens confirmed the uptake of Z2D3 into areas of the plaque rich in smooth muscle cells. The results of this study need to be interpreted carefully and in conjunction with current theories regarding plaque instability and rupture. As stated previously, plaque rupture appears to correlate with lesions with a thin fibrous cap containing many macrophages and relatively few VSMCs. Therefore, imaging with Z2D3 is unlikely to provide information about risk of plaque rupture. Further studies are clearly needed.

Radiotracers for Imaging Intraarterial Thrombosis

As discussed previously, plaque rupture leads to thrombus formation which, if not fatal, becomes incorporated into an enlarged atherosclerotic plaque. Therefore, detection of thrombus on the surface of or within atherosclerotic lesions could aid identification of vulnerable plaques.

Imaging approaches have targeted 3 components of the hemostatic process: platelets, fibrinogen, and fibrinolytic molecules. Conflicting results have been found in studies using radiolabeled autologous platelets in patients with carotid, femoral, and aortic atherosclerosis (*55–57*). These studies have had important design differences that could explain the discrepancy in outcome. In a study of 60 patients, 38 of whom had cerebrovascular events referrable to the carotid system, Moriwaki et al. (*55*) showed that ^{111}In-labeled platelet accumulation correlated with overall plaque burden and plaque ulceration as detected by careful B-mode ultrasound examination. In contrast, Minar et al. (*56*) in a similar study found no correlation between radiotracer uptake and ultrasound parameters (*56*). Of note, in the first study, antiplatelet medications were stopped 3 wk before imaging, which was performed 48 h after injection of the radiotracer, whereas, in the second study, antiplatelet medications were continued and images were taken 24–26 h after injection. Therefore, the conflicting results may be the result of differences in study design. Nevertheless, the need to image 48 h after tracer injection in patients not receiving antiplatelet therapy would seriously limit the applicability of this technique to patients with suspected vascular events.

Radioiodinated fibrinogen has been used to detect thrombus in 4 patients with angiographically proven carotid disease (*58*). However, slow fibrinogen accumulation and the low fibrin content in arterial thrombus compared with venous thrombus makes radioiodinated fibrinogen an unlikely candidate for useful clinical imaging of atheroma.

Fibrin degradation products can be detected within hours after thrombus formation and, therefore, provide potential tracer molecules for the detection of thrombus. Fibrin fragment E_1 has been labeled with both ^{123}I and ^{99m}Tc, and its ability to detect the presence of thrombus in animals with deep vein thrombosis (DVT) has been confirmed (*59*). It has a short circulation half-life and, therefore, high target-to-background ratios, making it potentially suitable for vascular wall imaging. However, no studies in animals or humans have been published to date evaluating the detection of thrombus associated with atherosclerosis using fibrin fragment E_1.

Annexin V is a small protein that binds avidly to a phosphatidylserine moiety on the surface of activated platelets and apoptotic VSMCs in the fibrous cap (*60,61*). It has a rapid plasma clearance and, in a porcine model, ^{99m}Tc-annexin V has been found to localize to thrombus generated in the left atrium, giving high thrombus-to-blood ratios and clear resolution (*62*). No in vivo studies, however, have confirmed uptake by intraarterial thrombus.

Research has identified several radiolabeled antibodies against platelets and fibrin with the potential to image thrombus on atherosclerotic plaques. Monoclonal antibodies against the GPIIb/IIIa receptor and the membrane glycoprotein GMP-140 on activated platelets have been developed, raising the possibility of using them to image thrombus. S-12, an antibody against the GMP-140 glycoprotein, has been radiolabeled with ^{99m}Tc and been shown to localize to acute intraarterial thrombus in the animal model (*63*). Antibodies against fibrin (T2G1s) bind solely to fibrin and not fibrinogen, its circulating precursor, or fibrin degradation products. Uptake of radiolabeled T2G1 by acute venous and arterial thrombus has been shown in both animals and humans (*64*). However, it has a sensitivity of only 50% for the detection of chronic arterial thrombi in patients with left ventricular thrombus, aortic aneurysms, and peripheral arterial grafts (*65*).

Several synthetic peptides that bind to thrombus have been radiolabeled. Most target the GPIIb/IIIa receptor on activated platelets. Because of their small size, they have the advantage of rapid clearance from the circulation. They are also less likely to raise an immune response than the immunoglobulin labels. Rapid uptake of ^{99m}Tc-P748, a synthetic peptide ligand to the GPIIb/IIIa receptor, by thrombus in the carotid arteries of dogs (induced by crush injury) has been demonstrated with very favorable thrombus-to-blood ratios (*66*). ^{99m}Tc-P280 was the first GPIIb/IIIa binding peptide to be studied in humans (*67*). A pilot study of 9 patients with carotid atherosclerosis who underwent SPECT of the neck after injection of ^{99m}Tc-P280 demonstrated uptake of tracer in 11 of 18 carotid arteries. There was only moderate correlation when compared with duplex ultrasound findings. Recently Mitchel et al (*68*) have tested the ability of a new GPIIb/IIIa platelet inhibitor, DMP-444, labeled with ^{99m}Tc, to identify platelet-rich thrombus by nuclear imaging in the coronary arteries of a canine model. They found that markedly positive nuclear images could be obtained and that postmortem studies confirmed the presence of radioactive platelet-rich thrombus. In dogs with very little DMP-444 uptake, there were lower postmortem nuclear counts and thrombus weights, a result that reached statistical significance. No DMP-444 human studies have thus far been published. Other similar peptides have been developed and radiolabeled, but few studies have been performed to make them relevant to this review. However, one additional study looking at ^{99m}Tc-apcitide deserves mention because it addressed the question of differentiating between acute and chronic thrombus, albeit in venous thrombosis (*69*). This is clearly a potentially important issue in terms of identifying arterial lesions responsible for recent symptoms. ^{99m}Tc-Apcitide, like the other synthetic peptides mentioned here, binds to the GPIIb/IIIa receptors expressed on activated platelets. Bates et al. (*69*) enrolled patients with newly diagnosed first DVT and patients with previous DVT. With images interpreted in a blinded fashion, they found that the sensitivity and specificity of ^{99m}Tc-apcitide for differentiating between acute and chronic thrombus were 92% and 86%, respectively.

Positron-Emitting Radiotracers

PET has certain advantages over conventional nuclear medicine γ-camera technology. PET can provide 4- to 5-mm resolution compared with 1- to 1.5-cm for planar and SPECT. PET images are derived from the detection of positron-emitting radionuclides, such as ^{11}C and ^{18}F, to label various biochemical and metabolic substrates. PET agents have the potential to provide a better functional assessment of atherosclerotic plaques than tracers used in conventional nuclear imaging, in part as a result of the higher spatial resolution of PET.

Deoxyglucose, a glucose analog, competes with glucose for uptake into metabolically active cells. When labeled with ^{18}F, the resultant ^{18}F-FDG is taken up into metabolically active cells but is not metabolized and so accumulates. ^{18}F-FDG has been used extensively to estimate metabolism in heart, brain, and tumor tissue (*70,71*). Kubota et al. (*72*) first noted uptake of ^{18}F-FDG by macrophages present within tumors. This discovery has led to investigation into the possibility of using ^{18}F-FDG to image macrophages in atherosclerotic plaque.

Preliminary studies using a rabbit model of atherosclerosis confirmed uptake of ^{18}F-FDG in the region of the aortic arch in rabbits fed a high-cholesterol diet (*73*). Normal rabbits did not show uptake above that of background levels. Ex vivo analysis of the aortic arch confirmed ^{18}F-FDG uptake in areas of atherosclerosis rich in macrophages.

A further study by Lederman et al. (*74*) confirmed a 4-fold increase in ^{18}F-FDG uptake by diseased segments of iliac artery when compared with normal segments. A positron-sensitive fiber-optic probe placed in contact with the arterial intima was used to detect ^{18}F-FDG uptake in rabbit iliac artery specimens ex vivo after injection of ^{18}F-FDG 2–4 h earlier. Subsequent histopathology confirmed that injured artery had significantly higher macrophage and smooth muscle cell density than uninjured artery. In preliminary studies, we have recently shown focal areas of ^{18}F-FDG uptake into atherosclerotic lesions in rabbits maintained on a high-cholesterol diet, with markedly reduced ^{18}F-FDG uptake into the same lesions after cholesterol withdrawal (Rudd et al., unpublished data, April 2002). Together these studies suggest that ^{18}F-FDG PET has the potential to monitor plaque inflammation in vivo.

Few studies have been reported in humans. Yun et al. (*75*) reported the incidental observation of vascular ^{18}F-FDG uptake in patients undergoing PET for cancer. They found that in 137 consecutive patients undergoing PET, approximately 50% had vascular wall uptake of ^{18}F-FDG. They made the presumption that the ^{18}F-FDG uptake seen on the scans was representative of atheroma. Post hoc analysis reported a statistically significant difference between vascular wall ^{18}F-FDG uptake in patients with at least one of the traditional atherogenic risk factors and that observed in patients with no risk factors (*76*). Among all risk factors, age was found to be the most significant and consistent factor correlating with ^{18}F-FDG uptake, but hypercholesterolemia also correlated consistently with vascular ^{18}F-FDG levels.

The only published study to date looking at ^{18}F-FDG PET of atheroma in symptomatic humans has been performed by our group (*77*). In this study, we tested the ability of ^{18}F-FDG PET to image inflammation within carotid artery atherosclerotic plaques. Eight patients with symptomatic carotid atherosclerosis were imaged with ^{18}F-FDG PET. Uptake of ^{18}F-FDG was seen in all patients within 3 h of injection, and coregistration using CT angiography confirmed that uptake was located within the atherosclerotic plaque (Fig. 4). In those patients with bilateral carotid disease, the ^{18}F-FDG accumulation rate in symptomatic lesions was 27% higher than in contralateral asymptomatic lesions. No measurable ^{18}F-FDG uptake into normal carotid arteries was found. Autoradiography of excised plaques confirmed accumulation of deoxyglucose in macrophage-rich areas of the plaque. This study shows that plaque macrophage activity, the major determinant of plaque rupture, can be imaged and potentially quantified by ^{18}F-FDG PET.

Because ^{18}FDG is taken up by all metabolically active tissues, including myocardium, ^{18}F-FDG PET cannot be used to image coronary atheroma, in which a more macrophage-specific ligand is desirable. Currently, the most promising macrophage ligand in clinical use is PK11195, which binds to peripheral benzodiazepine receptors in mitochondrial membranes, particularly in macrophages (*78*). Studies are currently under way to evaluate the potential of this ligand for imaging atherosclerosis.

CONCLUSION

Until recently, imaging technology for atherosclerosis has focused almost entirely on defining anatomic obstructions to flow. However, advances in our understanding of the cell biology that leads to clinical events in atherosclerosis have highlighted a clear need for imaging techniques that can provide information about plaque composition. These advances are driving the development of more informative imaging techniques. X-ray angiography, the current gold standard imaging tool in clinical practice, is unable to provide such information. Newer imaging modalities, such as IVUS and MRI, are able to provide information on plaque composition in some vascular beds but are unlikely to be able to provide metabolic data on plaque inflammatory cell activity, the major determinant of plaque stability.

Nuclear imaging has the potential to provide invaluable information on the cellular, metabolic, and molecular composition of the plaque. However, both scanning technology and the radiolabeled tracer molecules need to be improved to produce images of sufficient resolution and quality to allow detection and functional assessment of atherosclerotic lesions in medium-to-small arteries, such as those found in the coronary circulation. Recent PET studies in animals and humans suggest that this should be achievable.

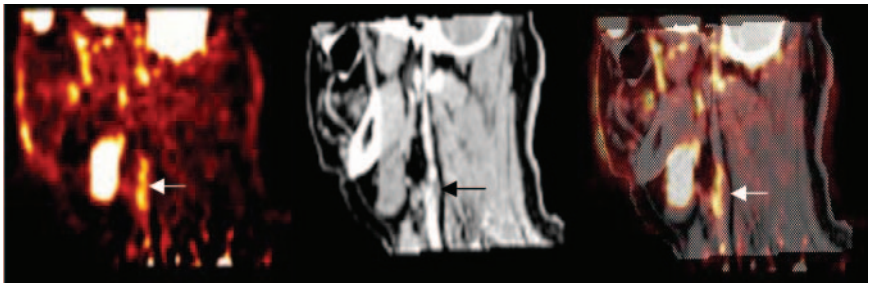

FIGURE 4. PET of symptomatic carotid atherosclerosis. Images (from left to right) show PET, contrast CT, and coregistered PET/CT images in sagittal plane, from 63-y-old man who had experienced 2 episodes of left-sided hemiparesis. Angiography demonstrated 80% stenosis of proximal right internal carotid artery. This was confirmed on CT image (black arrow). White arrows show FDG uptake at the level of the plaque in carotid artery. As expected, there was high FDG uptake in brain, jaw muscles, and facial soft tissues.

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REFERENCES

1. Davies MJ. A macro and micro view of coronary vascular insult in ischemic heart disease. *Circulation.* 1990;82(3 suppl):II38–II46.
2. Fuster V, Fallon JT, Nemerson Y. Coronary thrombosis. *Lancet.* 1996;348(suppl 1):s7–s10.
3. Davies MJ. Acute coronary thrombosis: the role of plaque disruption and its initiation and prevention. *Eur Heart J.* 1995;16(suppl L):3–7.
4. Behrendt D, Ganz P. Endothelial function: from vascular biology to clinical applications. *Am J Cardiol.* 2002;90(10C):40L–48L.
5. Vanhoutte PM, Luscher TF, Graser T. Endothelium-dependent contractions. *Blood Vessels.* 1991;28:74–83.
6. Luscher TF, Tanner FC, Tschudi MR, Noll G. Endothelial dysfunction in coronary artery disease. *Annu Rev Med.* 1993;44:395–418.
7. Bogaty P, Hackett D, Davies G, Maseri A. Vasoreactivity of the culprit lesion in unstable angina. *Circulation.* 1994;90:5–11.
8. Davies MJ. Stability and instability: two faces of coronary atherosclerosis—The Paul Dudley White Lecture 1995. *Circulation.* 1996;94:2013–2020.
9. Libby P. Molecular bases of the acute coronary syndromes. *Circulation.* 1995; 91:2844–2850.
10. Bennett MR, Macdonald K, Chan SW, Boyle JJ, Weissberg PL. Cooperative interactions between RB and p53 regulate cell proliferation, cell senescence, and apoptosis in human vascular smooth muscle cells from atherosclerotic plaques. *Circ Res.* 1998;82:704–712.
11. Ross R, Wight TN, Strandness E, Thiele B. Human atherosclerosis. I. Cell constitution and characteristics of advanced lesions of the superficial femoral artery. *Am J Pathol.* 1984;114:79–93.
12. Kohler T. Imaging of carotid artery lesions: a surgeon's view. In: Fuster V, ed. *Syndromes of Atherosclerosis: Correlations of Clinical Imaging and Pathology.* Armonk, NY: Futura Publishing Co., Inc.; 1996:205–233.
13. Ambrose J. Angiographic correlations of advanced coronary lesions in acute coronary syndromes. In: Fuster V, ed. *Syndromes of Atherosclerosis: Correlations of Clinical Imaging and Pathology.* Armonk, NY: Futura Publishing Co., Inc.; 1996:105–122.
14. Dinsmore R. Imaging techniques in carotid and peripheral vascular disease. In: Fuster V, ed. *Syndromes of Atherosclerosis: Correlations of Clinical Imaging and Pathology.* Armonk, NY: Futura Publishing Co., Inc.; 1996:277–289.
15. von Birgelen C, Slager CJ, Di Mario C, de Feyter PJ, Serruys PW. Volumetric intracoronary ultrasound: a new maximum confidence approach for the quantitative assessment of progression-regression of atherosclerosis? *Atherosclerosis.* 1995;118(suppl):S103–S13.
16. den Heijer P, Foley DP, Hillege HL, et al. The 'Ermenonville' classification of observations at coronary angioscopy: evaluation of intra- and inter-observer agreement—European Working Group on Coronary Angioscopy. *Eur Heart J.* 1994;15:815–822.
17. Feld S, Ganim M, Carell ES, et al. Comparison of angioscopy, intravascular ultrasound imaging and quantitative coronary angiography in predicting clinical outcome after coronary intervention in high risk patients. *J Am Coll Cardiol.* 1996;28:97–105.
18. Thieme T, Wernecke KD, Meyer R, et al. Angioscopic evaluation of atherosclerotic plaques: validation by histomorphologic analysis and association with stable and unstable coronary syndromes. *J Am Coll Cardiol.* 1996;28:1–6.
19. Uchida Y, Nakamura F, Tomaru T, et al. Prediction of acute coronary syndromes by percutaneous coronary angioscopy in patients with stable angina. *Am Heart J.* 1995;130:195–203.
20. Stefanadis C, Diamantopoulos L, Vlachopoulos C, et al. Thermal heterogeneity within human atherosclerotic coronary arteries detected in vivo: a new method of detection by application of a special thermography catheter. *Circulation.* 1999; 99:1965–1971.
21. Stefanadis C, Diamantopoulos L, Dernellis J, et al. Heat production of atherosclerotic plaques and inflammation assessed by the acute phase proteins in acute coronary syndromes. *J Mol Cell Cardiol.* 2000;32:43–52.
22. Verheye S, De Meyer GR, Van Langenhove G, Knaapen MW, Kockx MM. In vivo temperature heterogeneity of atherosclerotic plaques is determined by plaque composition. *Circulation.* 2002;105:1596–1601.
23. Salonen JT, Salonen R. Ultrasonographically assessed carotid morphology and the risk of coronary heart disease. *Arterioscler Thromb.* 1991;11:1245–1249.
24. O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK Jr. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults: Cardiovascular Health Study Collaborative Research Group. *N Engl J Med.* 1999;340:14–22.
25. Patel MR, Kuntz KM, Klufas RA, et al. Preoperative assessment of the carotid bifurcation: can magnetic resonance angiography and duplex ultrasonography replace contrast arteriography? *Stroke.* 1995;26:1753–1758.
26. Eliasziw M, Rankin RN, Fox AJ, Haynes RB, Barnett HJ. Accuracy and prognostic consequences of ultrasonography in identifying severe carotid artery stenosis: North American Symptomatic Carotid Endarterectomy Trial (NASCET) Group. *Stroke.* 1995;26:1747–1752.
27. Weinberger J, Ramos L, Ambrose JA, Fuster V. Morphologic and dynamic changes of atherosclerotic plaque at the carotid artery bifurcation: sequential imaging by real time B-mode ultrasonography. *J Am Coll Cardiol.* 1988;12: 1515–1521.
28. Achenbach S, Giesler T, Ropers D, et al. Detection of coronary artery stenoses by contrast-enhanced, retrospectively electrocardiographically-gated, multislice spiral computed tomography. *Circulation.* 2001;103:2535–2538.
29. Kim WY, Danias PG, Stuber M, et al. Coronary magnetic resonance angiography for the detection of coronary stenoses. *N Engl J Med.* 2001;345:1863–1869.
30. Wexler L, Brundage B, Crouse J, et al. Coronary artery calcification: pathophysiology, epidemiology, imaging methods, and clinical implications—a statement for health professionals from the American Heart Association Writing Group. *Circulation.* 1996;94:1175–1192.
31. Rumberger JA, Simons DB, Fitzpatrick LA, Sheedy PF, Schwartz RS. Coronary artery calcium area by electron-beam computed tomography and coronary atherosclerotic plaque area: a histopathologic correlative study. *Circulation.* 1995; 92:2157–2162.
32. Toussaint JF, LaMuraglia GM, Southern JF, Fuster V, Kantor HL. Magnetic resonance images lipid, fibrous, calcified, hemorrhagic, and thrombotic components of human atherosclerosis in vivo. *Circulation.* 1996;94:932–938.
33. Toussaint JF, Southern JF, Fuster V, Kantor HL. T2-weighted contrast for NMR characterization of human atherosclerosis. *Arterioscler Thromb Vasc Biol.* 1995; 15:1533–1542.
34. Kooi ME, Cappendijk VC, Cleutjens KB, et al. Accumulation of ultrasmall superparamagnetic particles of iron oxide in human atherosclerotic plaques can be detected by in vivo magnetic resonance imaging. *Circulation.* 2003;107:2453–2458.
35. Rosen JM, Butler SP, Meinken GE, et al. Indium-111-labeled LDL: a potential agent for imaging atherosclerotic disease and lipoprotein biodistribution. *J Nucl Med.* 1990;31:343–350.
36. Vallabhajosula S, Paidi M, Badimon JJ, et al. Radiotracers for low density lipoprotein biodistribution studies in vivo: technetium-99m low density lipoprotein versus radioiodinated low density lipoprotein preparations. *J Nucl Med.* 1988;29:1237–1245.
37. Pirich C, Sinzinger H. Evidence for lipid regression in humans in vivo performed by 123-iodine-low-density lipoprotein scintiscanning. *Ann N Y Acad Sci.* 1995; 748:613–621.
38. Lees AM, Lees RS, Schoen FJ, et al. Imaging human atherosclerosis with ^{99m}Tc-labeled low density lipoproteins. *Arteriosclerosis.* 1988;8:461–470.
39. Virgolini I, Rauscha F, Lupattelli G, et al. Autologous low-density lipoprotein labelling allows characterization of human atherosclerotic lesions in vivo as to presence of foam cells and endothelial coverage. *Eur J Nucl Med.* 1991;18:948–951.
40. Chang MY, Lees AM, Lees RS. Time course of ^{125}I-labeled LDL accumulation in the healing, balloon-deendothelialized rabbit aorta. *Arterioscler Thromb.* 1992; 12:1088–1098.
41. Steinberg D, Parthasarathy S, Carew TE, Khoo JC, Witztum JL. Beyond cholesterol: modifications of low-density lipoprotein that increase its atherogenicity. *N Engl J Med.* 1989;320:915–924.
42. Steinbrecher UP, Lougheed M, Kwan WC, Dirks M. Recognition of oxidized low density lipoprotein by the scavenger receptor of macrophages results from derivatization of apolipoprotein B by products of fatty acid peroxidation. *J Biol Chem.* 1989;264:15216–15223.
43. Goldstein JL, Ho YK, Basu SK, Brown MS. Binding site on macrophages that mediates uptake and degradation of acetylated low density lipoprotein, producing massive cholesterol deposition. *Proc Natl Acad Sci USA.* 1979;76:333–337.
44. Iuliano L, Signore A, Vallabajosula S, et al. Preparation and biodistribution of 99m-technetium labelled oxidized LDL in man. *Atherosclerosis.* 1996;126:131–141.
45. Tsimikas S, Palinski W, Halpern SE, Yeung DW, Curtiss LK, Witztum JL. Radiolabeled MDA2, an oxidation-specific, monoclonal antibody, identifies native atherosclerotic lesions in vivo. *J Nucl Cardiol.* 1999;6:41–53.
46. Hardoff R, Braegelmann F, Zanzonico P, et al. External imaging of atherosclerosis in rabbits using an ^{123}I-labeled synthetic peptide fragment. *J Clin Pharmacol.* 1993;33:1039–1047.

47. Lees R, Lees A. Radiopharmaceutical imaging of atherosclerosis. In: Fuster V, ed. *Syndromes of Atherosclerosis: Correlations of Clinical Imaging and Pathology.* Armonk, NY: Futura Publishing Co., Inc.; 1996:385–401.
48. Dinkelborg L, Hingler C, Semmier W. Endothelin derivatives for imaging atherosclerosis [abstract]. *J Nucl Med.* 1995;36(suppl):102P.
49. Prat L, Torres G, Carrio I, et al. Polyclonal ^{111}In-IgG, ^{125}I-LDL and ^{125}I-endothelin-1 accumulation in experimental arterial wall injury. *Eur J Nucl Med.* 1993;20:1141–1145.
50. Sinzinger H, Rodrigues M, Kritz H. Radioisotopic imaging of atheroma. In: Fuster V, ed. *Syndromes of Atherosclerosis: Correlations of Clinical Imaging and Pathology.* Armonk, NY: Futura Publishing Co., Inc.; 1996:369–383.
51. Demacker PN, Dormans TP, Koenders EB, Corstens FH. Evaluation of indium-111-polyclonal immunoglobulin G to quantitate atherosclerosis in Watanabe heritable hyperlipidemic rabbits with scintigraphy: effect of age and treatment with antioxidants or ethinylestradiol. *J Nucl Med.* 1993;34:1316–1321.
52. Chakrabarti M, Cheng KT, Spicer KM, et al. Biodistribution and radioimmunopharmacokinetics of ^{131}I-AMA monoclonal antibody in atherosclerotic rabbits. *Nucl Med Biol.* 1995;22:693–697.
53. Narula J, Petrov A, Bianchi C, et al. Noninvasive localization of experimental atherosclerotic lesions with mouse/human chimeric Z2D3 $F(ab')_2$ specific for the proliferating smooth muscle cells of human atheroma: imaging with conventional and negative charge-modified antibody fragments. *Circulation.* 1995;92:474–484.
54. Carrio I, Pieri PL, Narula J, et al. Noninvasive localization of human atherosclerotic lesions with indium 111-labeled monoclonal Z2D3 antibody specific for proliferating smooth muscle cells. *J Nucl Cardiol.* 1998;5:551–557.
55. Moriwaki H, Matsumoto M, Handa N, et al. Functional and anatomic evaluation of carotid atherothrombosis: a combined study of indium-111 platelet scintigraphy and B-mode ultrasonography. *Arterioscler Thromb Vasc Biol.* 1995;15:2234–2240.
56. Minar E, Ehringer H, Dudczak R, et al. Indium-111-labeled platelet scintigraphy in carotid atherosclerosis. *Stroke.* 1989;20:27–33.
57. Smyth JV, Dodd PD, Walker MG. Indium-111 platelet scintigraphy in vascular disease. *Br J Surg.* 1995;82:588–595.
58. Mettinger KL, Larsson S, Ericson K, Casseborn S. Detection of atherosclerotic plaques in carotid arteries by the use of ^{123}I-fibrinogen. *Lancet.* 1978;1(8058):242–244.
59. Knight LC. Scintigraphic methods for detecting vascular thrombus. *J Nucl Med.* 1993;34(3 suppl):554–561.
60. Thiagarajan P, Tait JF. Binding of annexin V/placental anticoagulant protein I to platelets: evidence for phosphatidylserine exposure in the procoagulant response of activated platelets. *J Biol Chem.* 1990;265:17420–17423.
61. Flynn PD, Byrne CD, Baglin TP, Weissberg PL, Bennett MR. Thrombin generation by apoptotic vascular smooth muscle cells. *Blood.* 1997;89:4378–4384.
62. Stratton JR, Dewhurst TA, Kasina S, et al. Selective uptake of radiolabeled annexin V on acute porcine left atrial thrombi. *Circulation.* 1995;92:3113–3121.
63. Miller D. Radionuclide labeled monoclonal antibody imaging of atherosclerosis and vascular injury. In: Fuster V, ed. *Syndromes of Atherosclerosis: Correlations of Clinical Imaging and Pathology.* Armonk, NY: Futura Publishing Co., Inc.; 1996:403–416.
64. Seabold JE, Rosebrough SF. Will a radiolabeled antibody replace indium-111-platelets to detect active thrombus? *J Nucl Med.* 1994;35:1738–1740.
65. Stratton JR, Cerqueira MD, Dewhurst TA, Kohler TR. Imaging arterial thrombosis: comparison of technetium-99m-labeled monoclonal antifibrin antibodies and indium-111-platelets. *J Nucl Med.* 1994;35:1731–1737.
66. Vallabhajosula S. Technetium-99m-P748, platelet specific techtide for imaging arerial thrombus: preclinical studies in a canine model of intra-arterial thrombus [abstract]. *J Nucl Med.* 1996;37(suppl):152P.
67. Lister-James J, Knight LC, Maurer AH, Bush LR, Moyer BR, Dean RT. Thrombus imaging with a technetium-99m-labeled activated platelet receptor-binding peptide. *J Nucl Med.* 1996;37:775–781.
68. Mitchel J, Waters D, Lai T, et al. Identification of coronary thrombus with a IIb/IIIa platelet inhibitor radiopharmaceutical, technetium-99m DMP-444: a canine model. *Circulation.* 2000;101:1643–1646.
69. Bates SM, Lister-James J, Julian JA, Taillefer R, Moyer BR, Ginsberg JS. Imaging characteristics of a novel technetium Tc99m-labeled platelet glycoprotein IIb/IIIa receptor antagonist in patients with acute deep vein thrombosis or a history of deep vein thrombosis. *Arch Intern Med.* 2003;163:452–456.
70. Strauss LG, Conti PS. The applications of PET in clinical oncology. *J Nucl Med.* 1991;32:623–648.
71. Phelps ME, Hoffman EJ, Selin C, et al. Investigation of [^{18}F]2-fluoro-2-deoxyglucose for the measure of myocardial glucose metabolism. *J Nucl Med.* 1978;19:1311–1319.
72. Kubota R, Kubota K, Yamada S, Tada M, Ido T, Tamahashi N. Microautoradiographic study for the differentiation of intratumoral macrophages, granulation tissues and cancer cells by the dynamics of fluorine-18-fluorodeoxyglucose uptake. *J Nucl Med.* 1994;35:104–112.
73. Vallabajosula S, Machac K, Knesaurek J. Imaging atherosclerotic macrophage density by positron emission tomography using F-18-flurodeoxyglucose (FDG) [abstract]. *J Nucl Med.* 1996;37(suppl):38P.
74. Lederman RJ, Raylman RR, Fisher SJ, et al. Detection of atherosclerosis using a novel positron-sensitive probe and 18-fluorodeoxyglucose (FDG). *Nucl Med Commun.* 2001;22:747–753.
75. Yun M, Yeh D, Araujo LI, Jang S, Newberg A, Alavi A. F-18 FDG uptake in the large arteries: a new observation. *Clin Nucl Med.* 2001;26:314–319.
76. Yun M, Jang S, Cucchiara A, Newberg AB, Alavi A. ^{18}F-FDG uptake in the large arteries: a correlation study with the atherogenic risk factors. *Semin Nucl Med.* 2002;32:70–76.
77. Rudd JH, Warburton EA, Fryer TD, et al. Imaging atherosclerotic plaque inflammation with [^{18}F]-fluorodeoxyglucose positron emission tomography. *Circulation.* 2002;105:2708–2711.
78. Anholt RR, Pedersen PL, De Souza EB, Snyder SH. The peripheral-type benzodiazepine receptor: localization to the mitochondrial outer membrane. *J Biol Chem.* 1986;261:576–583.