Atherosclerosis: Imaging Techniques and the Evolving Role of Nuclear Medicine

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Quantitative assessment of atherosclerotic or atherothrombotic disease during its natural history and following therapeutic interventions is important for understanding the progression and stabilization of the disease and for selecting appropriate medical or surgical interventions. A number of invasive and noninvasive imaging techniques are available to detect and display different characteristics of vascular lesions of clinical and/or research interest. **Methods:** Angiography, the traditional "gold standard," detects advanced lesions and measures the degree of stenosis. Angioscopy clearly identifies thrombus. In carotid arteries and arteries in lower extremities, duplex ultrasonography is useful for providing the degree of stenosis, as well as plaque morphology, and assessing changes in wall thickness. **Results:** Magnetic resonance angiography, being noninvasive, may replace conventional angiography for anatomical imaging of the vasculature. Ultrafast electron beam CT measures the calcium content in the atherosclerotic lesions. Intravascular ultrasound is the only technique that appears to be clinically useful in imaging the unstable, vulnerable plaques in coronary arteries. Magnetic resonance imaging techniques may be able to image vulnerable plaques and characterize plaques in terms of lipid and fibrous content and identify the presence of thrombus associated with the plaques. In regard to the nuclear scientigraphic imaging techniques, radiolabeled lipoproteins, platelets and immunoglobulins have shown some clinical potential as imaging agents, but due to poor target-to-background and target-to-blood ratios these agents are not ideal for imaging coronary or even carotid lesions. Technetium-99m-labeled peptides and monoclonal antibody fragments that clear from circulation rapidly and bind specifically to different components of the atherosclerotic lesion showed significant potential in animal models and in limited clinical studies. **Conclusion:** Peptides capable of binding to GPIIb/IIIA receptors on activated platelets appear to offer significant diagnostic potential for imaging intra-arterial thrombus. Positron emission tomography with metabolic tracers like [^{18}F]-fluorodeoxyglucose (FDG) also appears to offer new opportunities for noninvasive imaging of atherosclerosis and atherothrombosis.

Key Words: atherosclerosis; atherothrombosis

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Atherosclerosis is a chronic, progressive disease of blood vessels with cellular and metabolic changes in the arterial wall, such as cellular proliferation and accumulation of low-density lipoprotein (LDL) (*1*). It is a disease primarily of the elastic arteries (aorta, carotid and iliac) and of some of the large and medium-sized muscular arteries (coronary and popliteal). The most heavily involved vessels are the coronary arteries, the popliteal arteries, the descending thoracic aorta, the internal carotid arteries and the vessels of circle of Willis. Atherosclerosis starts early in life, but it takes decades to develop the mature plaques responsible for the clinical complications, thrombotic and thromboembolic occlusion and aneurysms. Specifically, coronary, carotid and cerebral arteries and the aorta are the prime foci of atherosclerotic complications, and as a result, thrombotic myocardial infarction, thromboembolic cerebral infarction and aortic aneurysms and dissection are the major consequences of this disease. Atherosclerosis is the leading cause of morbidity and mortality in the Western world, and nearly 50% of all deaths in the U.S. are generally attributed to diseases that are associated with atherosclerosis. Therefore, quantitative assessment of atherosclerotic or atherothrombotic disease during its natural history and after therapeutic interventions is important for understanding the progression and stabilization of the disease and for selecting appropriate medical or surgical interventions.

Several invasive and noninvasive imaging techniques (Fig. 1) are now available for detecting and displaying different characteristics of vascular lesions (Fig. 2) of clinical and/or research interest. The choice and appropriateness of each imaging technique, however, depends on its diagnostic efficacy and, most importantly, on the type of questions being asked. The following will review:

1. The current concepts on the plaque composition and morphology;
2. The clinical use of current imaging techniques, both nuclear (radioisotopic) and non-nuclear;
3. The relative merits of different radiotracers for nuclear scintigraphy; and
4. The relative advantages and disadvantages of new high-resolution biochemical imaging techniques specifically designed to detect lipid-rich plaques as compared to radiotracer techniques based on cellular and biochemical markers for identifying plaque composition and cellularity.

PLAQUE COMPOSITION AND MORPHOLOGY

The mature atherosclerotic plaques typically consist of the atheromatous gruel, which is lipid-rich and soft, and sclerotic tissue, which is collagen-rich and hard (*2*). The basic lesion is an "atheromatous plaque," which appears white or whitish yellow and consists of a raised focal plaque within the intima, having a lipid core and a covering fibrous cap. The core within the plaque contains crystalline cholesterol, cholesteryl esters, phospholipids, cellular degradation products and collagen remnants (*3,4*). The fibrous cap separates the core from the lumen and varies in thickness, number of smooth muscle cells, macrophages and collagen content. As the plaque size increases, it encroaches upon the lumen of the artery, resulting in stenosis. Atherosclerotic plaques have three principal components:

1. Cells such as smooth muscle cells, macrophages and lymphocytes;
2. Connective tissue extracellular matrix, including collagen, fibronectin elastic fibers and proteoglycans; and
3. Intracellular and extracellular lipid deposits.

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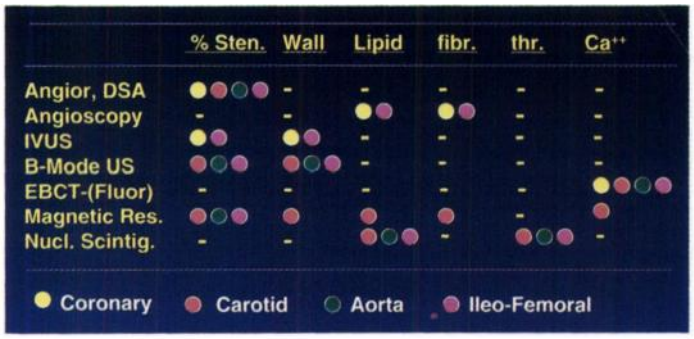

FIGURE 1. Clinical imaging of atherosclerosis and imaging techniques.

Varying proportions of these three components occur in different plaques, thus giving rise to a spectrum of lesions. Atherosclerotic lesions (Fig. 2) may be clinically characterized by their morphological features, such as lesion length, smoothness or roughness of lumen outline, eccentricity of the lumen, abrupt or tapered shoulders, defects due to thrombus and, finally, presence of calcification. Current understanding of pathophysiology and progression of atherosclerosis has shown that the composition and vulnerability of the plaque is related to the clinical status of the patient. An event known as plaque fissuring, rupture or disruption appears to be responsible for the sudden conversion of a stable atherosclerotic plaque to an unstable and life-threatening atherosclerotic lesion or vulnerable plaque (*5–7*).

According to the criteria set forth by the American Heart Association Committee on Vascular Lesions, plaque progression in coronary arteries can be subdivided into five phases and various types of lesions (*3,4,8,9*), as shown in Figures 3 and 4. Phase 1 consists of a small lesion of the kind commonly found in people under the age of 30. Such lesions may progress over a period of years and are categorized as type I, II and III lesions. Phase 2 consists of a plaque that, although not necessarily stenotic, may be prone to disruption because of high lipid content. The lesions are categorized as type IV or Va. Phase 2 can evolve into acute phase 3 or 4, and either of these can evolve into fibrotic phase 5. Phase 3 consists of the acute "complicated" type VI lesions with a mural thrombus that may or may not occlude the artery. Phase 4 consists of the acute complicated type VI lesion with an occlusive thrombus and it results in an acute coronary syndrome. In Phase 5, changes in geometry of the disrupted plaque and organization of connective tissue can lead to the more occlusive and fibrotic type Vb or Vc lesions. These occlusive lesions can be clinically silent or produce angina.

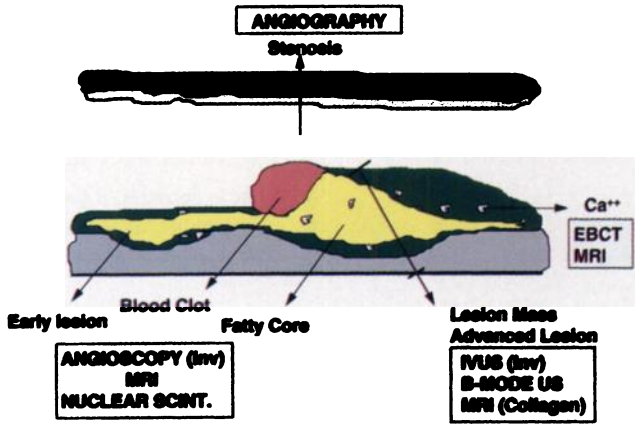

FIGURE 2. Atherosclerotic plaque: morphology, composition and imaging techniques. Modified from Lees and Lees (*57*).

Vulnerable Plaques

Coronary occlusion and myocardial infarction most frequently evolve from mild-to-moderate stenosis of lipid-rich lesions. Specifically, in most patients, acute ischemic events appear to be due to the disruption of lipid-rich lesion types IV and Va, which are often not even visible angiographically. Therefore, less obstructive lipid-rich plaques vulnerable to rupture would be important to image to identify their presence before a clinical event. In contrast, it appears that, in carotid arteries, the vulnerable plaques are severely stenotic and appear to be ulcerated and disrupted. In lipid-rich coronary plaques, the fibrous cap may disintegrate, tear or break and expose the thrombogenic gruel to the flowing blood (*5*). The risk associated with disruption of vulnerable plaques is due to the subsequent thrombus formation (*5*), and, as a result, a type IV or Va lesion suddenly evolves into an acute complicated type VI lesion. In contrast, the vulnerable carotid plaques are not necessarily lipid-rich, but rather heterogeneous, and they are very stenotic; their rupture or dissection probably relates to the impact of blood during systole against the resistance that they may offer by being stenotic.

The major factors that determine coronary plaque's vulnerability to rupture are:

1. The size and lack of consistency of the atheromatous core;
2. Thickness of the fibrous cap; and
3. Inflammation within the cap (*3,6*).

Plaques with large and soft cores containing liquid cholesterol esters are more vulnerable and are at high risk of rupture and thrombosis (*5*). In contrast, hard sclerotic plaques with a high content of smooth muscle cells and collagen and less lipid are less susceptible for rupture. Fibrous caps vary widely in thickness, cellularity, matrix, strength and stiffness; the caps are often thinnest at their shoulder regions where macrophages (*10*) and mast cells (*7*) accumulate and disruption often occurs. In vitro studies suggest that macrophage infiltration and their release of metalloproteinases weakens the caps locally (*11*). It has been shown recently that macrophage-rich areas are more frequently found in coronary artery specimens of patients with unstable angina and non-Q-wave myocardial infarction. This suggests that the macrophage content of the lesion is a marker of unstable atherosclerotic plaques (*6*). In addition, atherosclerotic plaques express endothelial adhesion and chemotactic molecules (such as ox-LDL MCP-1 for monocytes) (*12*), which indicates the inflammatory nature of disrupted, vulnerable plaque (*6,7*).

IMAGING TECHNIQUES

Several invasive and noninvasive techniques are routinely used to image atherosclerosis and to assess progression and stabilization of the disease. Most of the standard techniques identify some of the morphological (decreased luminal diameter or stenosis and increased wall thickness) and functional parameters of the atherosclerosis and provide qualitative or semiquantitative assessment of the relative risk associated with the disease. These techniques, however, neither characterize nor correlate the image parameters with histopathological lesion types, which are more clinically relevant. The relative advantages and disadvantages of these techniques are discussed below.

Angiography

The angiogram simply reflects luminal diameter and provides a measure of stenosis with excellent resolution, but does not image the vessel wall and its various histopathological components (Figs. 1, 2). Nevertheless, this technique has become the

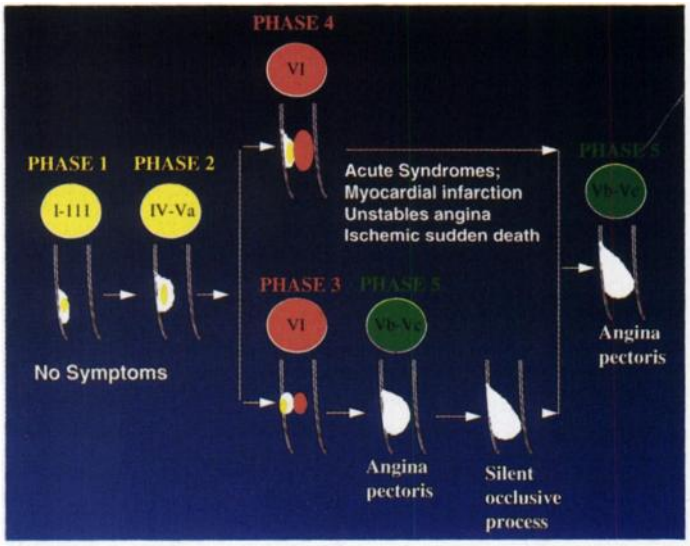

FIGURE 3. Phases and lesion morphology of the progression of coronary atherosclerosis. From Fuster et al. (8,9).

mainstay of the diagnosis of coronary (*11,13*), carotid (*14*) and peripheral artery lesions (*15*) and is the "gold standard" for anatomic diagnosis despite limited specificity and sensitivity. Nevertheless, angiography may reveal advanced lesions, plaque disruption, luminal thrombosis and calcification. In regard to sensitivity, histological lesion types I, II and III are not detected by angiography. Some IV and V lesion types with a smooth surface and a perfectly round lumen cannot be detected. Angiography lacks specificity because the technique does not identify and image vulnerable lipid-rich atherosclerotic plaques and other histopathological components. Although quantitative coronary angiography has improved the reproducibility of coronary luminal measurements, the technique is limited by magnification errors, the inability to detect disease at the reference segment and by the small number of projections available (*13*). The degree of stenosis of a lesion reflects clinical flow impairment and percentage diameter stenosis is clinically useful as a measure of obstruction to blood flow, especially if the stenosis is <50% or >70%. The calculation of the stenosis, however, depends on proper designation of a normal reference segment. One of the major limitations of the technique is that diffuse atherosclerotic disease may narrow the entire lumen of the artery, and, as a result, angiography underestimates the degree of stenosis. In addition, because the atherosclerotic plaques are displaced outwards of the vessel wall, the luminal diameter may appear to be normal.

Angioscopy

Visualization of arterial wall rather than the lumen is important for characterizing atherosclerotic disease. The angioscopy technique reveals the plaque and surface features not seen angiographically (*16,17*). In addition, it allows the observation of the color (red, white or yellow) of the material in the artery, and it is therefore highly sensitive for the detection of thrombus (Fig. 1). It views only the lesion surface and is not representative of the internal heterogeneity of the plaque. As a routine clinical tool, it may not be practical due to the thickness of the catheter. Two recent clinical trials, however, suggest the potential clinical use of angioscopic technique. In patients with different coronary syndromes, the angiographic findings were directly compared with histomorphology and ex vivo angioscopy of atherectomized material (*18*). This study concluded that yellow plaque color is closely related to degenerated plaques or atheroma and is associated with acute coronary syndromes. Another clinical study also concluded that angioscopic identification of plaque rupture and thrombus were independently associated with adverse outcome in patients with complex

Plaque Progression	Lesion Type	Lesion Morphology	Clinical Symptoms
Phase 1	I	foam cells	No Symptoms
	II	foam cells, smooth muscle cells and extracellular lipid droplets	
	III	smooth muscle cells surrounded by extracellular connective tissue, fibrils and lipid deposits	
Phase 2	IV	confluent cellular lesions with a great deal of extracellular lipid, intermixed with fibrous connective tissue	
	Va	extracellular lipid covered by thin fibrous cap	
Phase 3	VI	Disruption of IV or Va lesion with a mural thrombus which may or may not occlude the artery	
Phase 4	VI	Disruption of IV or Va lesion with an occlusive thrombus	Acute syndromes, myocardial infarction, unstable angina, ischemic sudden death
Phase 5	Vb-Vc	Changes in geometry of the disrupted plaque, and organization of mural thrombus by connective tissue may lead to formation of occlusive and fibrotic type	Silent occlusive process or Angina pectoris

FIGURE 4. Phases and lesion morphology and histopathology of coronary atherosclerotic plaque.

lesions after interventional procedures, and in addition, these features were not identified by either angiography or intravascular ultrasound (*19*).

Intravascular Ultrasound

Catheter-based ultrasound is a new approach to the imaging of vascular anatomy. This technique permits direct imaging of atheroma and provides a cross-sectional, tomographic perspective of the vessel and the atherosclerotic disease (*20–22*). The diagnostic applications of intravascular ultrasound include detection of angiographically unrecognized disease, detection of lesions of uncertain severity (40%–75% stenosis) and risk stratification of atherosclerotic lesions in interventional practice. The current generation catheters (incorporating a transducer), ranging in size from 0.96 to 1.17 mm, provide very high image quality. The axial resolution is about 80 μm, and the lateral resolution is depth-dependent, averaging 200 μm. Based on plaque echogenecity, the coronary atheroma can be differentiated into three categories: soft, fibrous or calcified. In normal subjects, the intimal thickness is 0.15 ± 0.07 mm. The intravascular ultrasound can delineate the thickness and echogenicity of vessel wall structures (Fig. 1), but it does not provide full histopathological information. In the near future, catheters with transducers of <0.025 inches will enable imaging of virtually any coronary stenosis.

Duplex Imaging (B-Mode Ultrasound)

Extracranial carotid atherosclerosis is a major cause of ischemic cerebrovascular disease; stroke and transient ischemic attacks are associated with advanced atherosclerosis at the carotid bifurcation (*14*). Accurate determination of the degree of stenosis and plaque morphogenesis is critical for therapeutic decisions and surgery. Two recent clinical trials (the North American Symptomatic Carotid Endarterectomy Trial and the Asymptomatic Carotid Artery Stenosis Study) have shown that the degree of stenosis and the hemodynamic factors play a significant role in producing stroke (*23,24*). High-resolution (<0.4 mm axial), real-time B-mode ultrasonography with Doppler flow imaging (Duplex scanning) has emerged as one of the best modalities for visualization of carotid arteries (*14,25,26*). Measurements of wall thickness and quantitative analysis of plaque mass and area can be determined (Fig. 1). The echogenicity of the plaque reflects plaque characteristics; echoluscent heterogeneous plaque is associated with both intraplaque hemorrhage and lipids, whereas echodense homogeneous plaque is mostly a fibrous plaque. In addition, the configuration of the plaque (mural versus nodular) can identify active (mural) lesions that are more prone to proliferation and thromboembolism (*26*). Because the technique is noninvasive, it can be used to evaluate the efficacy of drugs (*27*) and study the natural history of atherosclerosis (longitudinal studies) by after-up individuals at increased risk of atherosclerosis (*23*). In coronary and peripheral arteries of lower extremities, Duplex scanning is clinically not as useful as the traditional angiographic techniques.

Electron Beam CT

Atherosclerotic calcification is an organized and regulated process and is found more frequently in advanced lesions, although it may occur in small amounts in earlier lesions (*28*). There is a strong association between coronary calcium and obstructive coronary artery disease, and it was clearly shown that the amount of coronary calcium was a useful predictor of the extent of coronary artery disease (*29*). Magnetic resonance imaging (MRI), fluoroscopy, electron beam CT (EBCT) and helical CT can identify calcific deposits in blood vessels. However, only EBCT can quantitate the amount or volume of calcium (*28*). In addition, the EBCT images of the myocardium can be obtained in 0.1 sec, and, because of the rapid image acquisition time, motion artifacts are eliminated (*30*). It has been well-documented that the presence of coronary artery calcium, detected by EBCT, may be a sensitive early marker for the presence and progression of atherosclerotic lesion before the development of a complicated lesion (*31*).

Magnetic Resonance Angiography

Magnetic resonance techniques using gradient echo methods to generate images of flowing blood as positive contrast within the lumen of the vessel are similar to conventional angiography techniques (*32,33*). The magnetic resonance angiography (MRA) of coronary arteries is currently under development, and the resolution is in the range of 1 mm^3. In a recent study (*34*), the coronary artery stenosis estimated by MRA was compared with angiographic results, and the authors concluded that accurate localization of coronary stenosis was possible with MRA, but the stenosis length was overestimated. In extracranial carotid arterial disease and in peripheral vascular disease, two- or three-dimensional time-of-flight and phase-contrast MRA techniques have been evaluated. In several clinical studies comparing MRA with angiography, the diagnostic accuracy was in the range of 87%–100% in patients with carotid disease (*33*).

MRA techniques provide images of the vessel lumen, whereas MRI studies are often performed to evaluate the effects of the disease on the tissue supplied by the vessel. Recent developments in high-resolution (0.4 mm), fast spin-echo imaging and computer processing techniques visualize in vivo, atherosclerotic plaque activity and intimal thickening (*35*). Proton spectroscopic studies show that fibrous plaques and fat had unique spectra, and these two tissues also have different T2 relaxation times, the fibrous plaques having a short T2 compared to that of fat (*36*). Recently, it has been reported that MRI techniques are useful for studying the progression of experimental atherosclerosis in hypercholesterolemic rabbits and for imaging the plaque components such as fibrous caps, necrotic cores and intraplaque hemorrhage (*37*). In a recent clinical study in patients with carotid atherosclerosis, MRI was the first noninvasive imaging technique (Fig. 1) to allow the discrimination of lipid cores, fibrous caps, calcification, normal media, adventia, intraplaque hemorrhage and acute thrombosis (*38,39*).

RADIOTRACERS AND ROLE OF NUCLEAR MEDICINE

The principal mechanisms involved in human atherogenesis are lipid infiltration, cellular invasion and proliferation and thrombus formation. In the last 20 yr, many radiotracers have been developed based on several molecules and cells involved in atherogenesis, and the potential diagnostic utility of these radiotracers for imaging atherosclerotic lesions have been studied by many investigators in animal models (*40,41,42*). These radiotracers were primarily designed to image atherosclerotic lesions or to detect the intra-arterial thrombus associated with these lesions (Table 1). The ideal radiotracer(s) for imaging atherosclerosis and atherothrombosis:

1. Must be able to detect the presence of disease and be specific for lipid core, macrophage density and thrombus;
2. Must be able to detect lesions in coronary, carotid and ileo-femoral arteries;
3. Must be able to assess progression–regression of atherosclerosis;
4. Must be able to predict clinically significant events;

TABLE 1
Radiotracers for Imaging Atherosclerosis and Intra-Arterial Thrombus

	Radiotracers
For imaging atherosclerosis	
LDL	^{125}I- or ^{123}I-LDL, ^{111}In-LDL, ^{99m}Tc-native LDL and ^{99m}Tc-ox-LDL
Immunoglobulins	
Nonspecific	^{111}In-DTPA-human polyclonal IgG (may bind to Fc receptors on macrophages)
Specific monoclonal	^{111}In-(DTPA-PL)-Z2D3 F(ab')$_2$ IgM (against smooth muscle cells)
Specific	^{131}I-anti-ICAM-1 monoclonal IgG (against endothelial adhesion molecule)
Peptides	^{123}I-SP-4, ^{99m}Tc-199 and ^{99m}Tc-P215 (peptides based on apo-B)
	^{99m}Tc-endothelium-derived peptides
Monocytes	^{111}In-monocytes
Metabolic tracer	^{18}F-fluorodeoxyglucose (FDG) (may reflect macrophage density)
For imaging intra-arterial thrombosis	
Platelets	^{111}In-platelets and ^{99m}Tc-HMPAO-platelets
Fibrinogen	^{125}I- or ^{123}I-fibrinogen
Plasminogen activator	^{131}I- or ^{123}I-[DLT-PPACK]-t-Pa
Immunoglobulins	
Specific	^{99m}Tc-S-12, monoclonal IgG Fab' fragments (against GP GMP-140 on activated platelets)
Specific	^{99m}Tc-T2G1, monoclonal IgG Fab' fragments (against fibrin only)
Peptides	^{99m}Tc-P280, ^{99m}Tc-P748 and ^{99m}Tc-RP-431 (against GP IIb/IIIa receptor on platelets)

5. Must be able to provide prognostic indicators in population studies; and
6. Must have kit formulation for instant preparation, high specificity and sensitivity, fast blood clearance and high lesion-to-blood ratios.

Based on these criteria, a single radiotracer is not ideally suited to image atherosclerosis and provide prognostic and clinical indicators necessary for medical and surgical interventions. Preliminary clinical evaluations of some of these tracers were performed in patients with carotid atherosclerotic disease. Very few clinical studies, however, have been performed to correlate in vivo imaging data with histopathology of plaques. A clear understanding of the cellular and biochemical composition of the vulnerable plaques and the mechanisms involved in plaque rupture are crucial for the development of nuclear scintigraphic techniques needed to:

1. Identify clinically relevant "unstable vulnerable plaques";
2. Quantitate the natural progression of atherosclerotic disease; and
3. Assess the therapeutic effectiveness of various drugs on the stabilization and regression of plaques.

The advantages and disadvantages of some of these radiotracers are discussed below.

Radiotracers to Image Atherosclerosis

Low-Density Lipoprotein. Atherogenic molecules such as plasma LDL accumulate in the arterial lesions. In a balloon catheter deendothelialized aorta of a rabbit, focal LDL accumulation is predominantly seen in the edges of regenerating endothelial islands (*43*). Based on this observation, Lees et al. (*44*) first developed radioiodinated LDL and demonstrated the diagnostic utility of radiolabeled LDL for imaging carotid atherosclerotic lesions in patients. Subsequently, LDL was labeled with several radionuclides with different physical half-lives, such as ^{123}I, ^{99m}Tc and ^{111}In, and the uptake in atherosclerotic lesions was demonstrated in a variety of hypercholesterolemic rabbit models (*40,45,46*) and in patients (*47–51*). In patients with carotid atherosclerosis, the uptake of ^{99m}Tc-LDL was seen in soft lesions rich in macrophages, whereas the mature fibrocalcific plaques did not accumulate radiolabeled LDL (*47,48*). In two clinical studies, the tendon xanthomas in hypercholesterolemic patients and the expanded bone marrow in myeloproliferative patients also showed intense uptake of ^{99m}Tc-LDL, which correlated with increased macrophage content in these tissues (*49,50*). Even though the potential for diagnostic imaging of radioiodinated LDL and ^{99m}Tc-LDL was demonstrated in patients with carotid and femoral atherosclerosis (lesion types III–V), clinical use of this technique remains elusive. In coronary arteries, ^{99m}Tc-LDL imaging does not detect lesions for two reasons: the absolute and specific uptake of radiotracer in the lesion is very low (<0.1% of the injected dose), and the blood-pool activity is very high due to slow plasma clearance of the radiotracer.

Monocyte-derived macrophages in atheroma appear to sequester oxidized LDL more efficiently than did native LDL (*1*). Therefore, oxidized LDL labeled with ^{99m}Tc would be expected to be more selective than radiolabeled native LDL for imaging atherosclerotic lesions in vivo. This hypothesis was recently tested in a clinical study with patients who were candidates for carotid endarterectomy (*52*). Both planar and SPECT imaging studies were performed in the same subject with both tracers. Technetium-99m uptake in carotid lesions was slightly greater with ox-LDL than it was with native LDL. There were no significant differences, however, between the two tracers regarding lesion detectability, even though the blood clearance of LDL was enhanced due to oxidation (*52*). Similar results were also reported in animal studies, in which the aortic focal uptake of modified LDL was similar to that of native LDL, suggesting that the focal uptake of LDL in arterial lesions is mediated by specific, oxidation-independent patterns of charge and polarity (*53*).

Peptides. Lipoproteins are large molecules and consequently clear from circulation very slowly. By contrast, peptides are very small molecules (normally 10–20 amino acids) and clear from the circulation very rapidly, and therefore, they provide high target-to-background ratios within minutes postinjection. Two different classes of peptides molecules have been evaluated as potential atherosclerosis imaging agents: peptides based on the apo-B portion of LDL and endothelin analogs. Specific cellular uptake of LDL by fibroblasts and hepatocytes involves the classic LDL receptor that recognizes a particular portion of apo-B. This LDL receptor binding domain, however, is not involved in focal accumulation of LDL by monocyte macrophages in atheroma because homozygous familial hypercholesterolemic patients, with absent LDL receptors, also develop atherosclerotic lesions. Therefore, a synthetic peptide (SP-4) was developed (*54*), and radioiodinated SP-4 showed significant accumulation in experimental atherosclerotic lesions (*55*). Since then, other synthetic peptides have been developed (P-199 and P-215) that can be radiolabeled with ^{99m}Tc (*56*). The principal advantage of ^{99m}Tc-labeled peptides compared to ^{99m}Tc-LDL is that imaging can be performed within 1 hr postinjection because the peptides clear much faster than LDL from the circulation. In pilot studies involving patients with carotid atherosclerotic lesions documented by ultrasound, ^{99m}Tc-P215 SPECT images showed some uptake in the atherosclerotic lesions immediately postinjection (*57*). The diagnostic

value of this tracer, however, has not yet been evaluated in well-controlled clinical trials.

In conditions associated with endothelial cell injury, the peptide endothelin has been shown to be present in vascular smooth muscle cells and endothelial cells of human atherosclerotic lesions. Radioiodinated endothelin was shown to accumulate in experimentally induced arterial wall injuries in rabbits (*58*). Recently, several endothelin derivatives have been labeled with ^{99m}Tc and have been shown to accumulate in significant amounts in experimental atherosclerotic lesions in rabbits (*59*). The diagnostic significance and clinical use of these peptides, however, has not been well-established.

Immunoglobulins. Macrophage-derived foam cells are present in abundant quantity in the fatty streaks and vulnerable plaques. These cells specifically express cell surface Fc receptors. It has been hypothesized that radiolabeled immunoglobulin, IgG, which contains an Fc subunit, would be an appropriate radiotracer to image macrophage density in the atherosclerotic lesions (*60*). The potential diagnostic value of ^{111}In-labeled polyclonal human IgG was evaluated in patients with carotid atherosclerosis. Indium-111-IgG identified 86% of the lesions determined by ultrasonography. However, it did not correlate with plaque morphology and clinical stage of the disease, as determined by ultrasound (*61*). Indium-111-IgG imaging studies in Watanabe heritable hyperlipidemic rabbits also failed to detect the early lesions in the aorta. In addition, treatment of the rabbits with antioxidants and a hypolipidemic drug did not reduce the lesion uptake of the radiotracer. (*62*). Because the plasma clearance of the tracer is very slow, the images obtained even after 4–5 days postinjection would not provide adequate target-to-blood ratios for visualizing coronary artery lesions. The clinical and animal data clearly suggest that the accumulation of the tracer in the lesion may be nonspecific, and radiolabeled IgG may not be an appropriate radiotracer to image and identify vulnerable atherosclerotic lesions.

To circumvent the problem of nonspecific localization of IgG, monoclonal antibodies were developed against different cells and antigens present in the atherosclerotic lesions. Smooth muscle cell proliferation is one of the major consequences of atherosclerotic disease. Targeting these cells with a specific radiolabeled antibody is expected to image metabolically active atherosclerotic lesions. A mouse/human chimeric monoclonal IgM antibody fragment, Z2D3 F(ab')$_2$ IgM, was developed with specificity for an antigen associated with smooth muscle cells (*63*). Indium-111-(DTPA-PL)-Z2D3 F(ab')$_2$ IgM-negative charge-modified antibody fragments were shown to localize in experimental atherosclerotic lesions (*64*).

Amino malonic acid (AMA) has been isolated from human atherosclerotic plaques. This molecule has possible calcium-binding properties and is crucial to progressive stages of atherosclerotic process to include monocyte intimal recruitment and foam cell production. Radioiodinated monoclonal antibody against AMA (^{131}I-AMA) was shown to localize in experimental atherosclerotic lesions (*65*).

Radiotracers to Image Intra-Arterial Thrombus

In coronary, cerebral and peripheral vascular beds, atherothrombotic events underlie acute clinical vascular syndromes (*2,5,8*). Identification of the ruptured plaque or the clinically so-called "culprit lesion" is crucial in clinical management and therapeutic intervention. Loscalzo and Rocco (*66*) have clearly pointed out that the lack of a simple, relatively noninvasive method for identifying an acute atherothrombotic process is a notable deficiency in current cardiovascular practice. The search for thrombus-specific agents began almost two decades ago, and three principal elements of thrombus have been selected as targets for developing radiotracers. These include fibrin, platelets and fibrinolytic molecules (Table 1). Radiotracers that would localize in forming thrombi will be ideal for imaging fresh propagating thrombi. Several radiotracers have been developed to detect forming thrombi and the relative advantages, and the clinical use of these will be discussed.

Platelets. Platelets have been implicated in the pathogenesis of atherosclerosis. They play an important role in the initial steps of lesion development by adhering to subendothelial connective tissue. Platelet mural thrombi have been associated with lesion formation during all phases of the disease, and especially massive thrombi are seen in advanced lesions. Autologous platelets can be labeled efficiently with ^{111}In or ^{99m}Tc lipophilic complexes. Platelets labeled with ^{111}In have been evaluated as a radiotracer for the detection of complicated unstable plaques because radiolabeled platelets were presumed to accumulate only in an active thrombus that is being formed. Several clinical studies showed ^{111}In-platelet uptake in atherosclerotic lesions of carotid and femoral arteries and in the abdominal aorta (*41,67*). Recently, several groups of investigators have reevaluated the potential diagnostic and clinical use of In-platelet imaging technique in patients with carotid atherosclerosis (*68,69*). The ^{111}In-platelet uptake in the carotid arteries did not correlate with clinical symptomatology, angiographic or ultrasound results or pharmacological intervention. In a recent review, however, it was pointed out that platelet scintigraphy has a sensitivity of 43%–73% and a specificity of 87%–100%, compared with angiographic abnormalities (*67*). In a recent clinical study with 60 patients with carotid atherosclerosis who were not receiving antithrombotic medication, In-platelet uptake was shown to be significantly greater in ulcerated plaques characterized by B-mode ultrasonography (*69*). In spite of this optimistic clinical finding, In-platelet imaging has significant limitations. Due to slow clearance of platelets from circulation, imaging has to be performed at least 48 hr after reinjection of platelets. The count density in the image is very poor due to the limitations on the amount of radioactivity that can be injected. Finally, like radiolabeled LDL, ^{111}In-platelets are also not useful in detecting vulnerable plaques in the coronary arteries due to very high blood-pool activity.

Proteins. Radioiodinated fibrinogen was the first scintigraphic agent used successfully to detect thrombus (*40,70*). The tracer localizes only in actively growing thrombus, but requires delayed imaging (several days) for optimal diagnostic accuracy because the plasma clearance of the tracer is very slow. In addition, the thrombus-to-blood ratios are suboptimal for the detection of intra-arterial lesions because arterial thrombi are not rich in fibrin. Fibronectin is a relatively large glycoprotein (440 kDa) known to interact with fibrin, collagen and proteoglycans. It is present in atherosclerotic lesions of the intima, especially in developing fibrous plaques. Iodine-131-labeled fibronectin is taken up by the deendothelialized lesions in rabbit aortas (*71*). No clinical studies have been reported with this tracer. Because blood clearance of the tracer is very slow, optimal imaging time might be 2–3 days postinjection, and the diagnostic potential of this tracer may be low.

Within hours after acute thrombus formation, several fibrin degradation products are formed. Fibrin fragment E1 is a 60-kDa fragment of human fibrin that binds specifically to fibrin polymers, but not to fibrin monomer or fibrinogen (*72*). Both ^{123}I- and ^{99m}Tc-labeled fibrin fragment E1 showed excellent thrombus uptake in vivo, in a canine deep vein thrombosis model. Images can be obtained within 1 hr postinjection, and thrombus-to-blood ratios are higher than fibrinogen and platelet

ratios because the blood-pool activity is minimal (*72*). The tracer has not yet been tested in an intra-arterial thrombus in animal models or in patients.

Annexin V is a human protein (36 kDa) of 319 amino acids, which binds with very high affinity to a phosphatidylserine moiety that is exposed on activated platelets (*73*). Because there is no circulating pool of annexin V and platelets in circulation are quiescent, the plasma clearance of this protein is very rapid compared to fibrinogen, fibronectin and immunoglobulins. Technetium-99m-labeled annexin V showed intense localization in an acute porcine left atrial thrombus within 2 hr postinjection. The thrombus-to-blood ratios of 14–22 suggest that this tracer has a great potential for intra-arterial thrombus detection (*74*).

Immunoglobulins. In the last two decades, several radiolabeled antibodies against platelets and fibrin have been evaluated in animal models and in patients as potential thrombus imaging agents (*40,72,75*). To date, no radiolabeled antibody, however, has been approved by the Food and Drug Administration specifically for thrombus detection. Recent animal and clinical studies have indicated the potential use of certain new radiolabeled immunoglobulins. Monoclonal antibodies have been developed against two sites, which become exposed on activated platelets: GPIIb/IIIa (fibrinogen receptor) and GPGMP-140 (the alpha-granule membrane glycoprotein). The antibody, S-12, is specific for GMP-140 and expressed on activated platelets only. Technetium-99m-labeled S-12 Fab′ fragment showed significant localization in an acute animal model with intra-arterial thrombi that were rich in platelets (*75*). Secretion of platelet alpha-granule contents, such as platelet derived growth factor (PDGF) and platelet factor-4 occurs at lower thrombin concentrations, whereas high thrombin concentrations would secrete serotonin from the dense granules. Therefore, it is hypothesized that ^{99m}Tc-S-12 Fab′ antibody uptake in an arterial lesion would be a marker for PDGF release and thus would reflect postangioplasty hyperproliferative response (*75*).

Antifibrin antibodies (T2G1s) bind specifically to fibrin, but not to circulating fibrinogen or fibrin degradation products. Animal and human studies have demonstrated the uptake of radiolabeled T2G1 antibody in both venous and intra-arterial thrombi where there is an active fibrin deposition (*76*). Technetium-99m-labeled T2G1s antifibrin antibody Fab′ fragments were recently evaluated in patients to detect arterial thrombosis, and the results were compared to ^{111}In-platelet thrombus uptake in the same patients (*77*). The study demonstrated that T2G1 antibody scintigraphy was less likely to detect chronic thrombi than ^{111}In-platelets.

Peptides. In the last 2–3 yr, radiolabeled thrombus-binding peptides have shown excellent potential to detect active thrombi in animal models. Several synthetic peptides were prepared, and the targeting sequence of the peptides was derived from the primary binding region of the fibrinogen molecule, which binds to the GPIIb/IIIa (fibrinogen receptor) on activated platelets. The advantage of peptides is that they have rapid blood clearance and are less immunogenic than immunoglobulins. In a canine model of deep vein thrombosis, ^{123}I-bitistatin (*78*), ^{99m}Tc-P280 (*79*), ^{99m}Tc-P748 (*80*) and ^{99m}Tc-RP431 (*81*) demonstrated significant thrombus uptake within 1–2 hr postinjection. In a canine model of intra-arterial thrombus, ^{99m}Tc-P748 localized in thrombus within minutes after injection and showed excellent thrombus-to-blood ratios, similar to those of ^{111}In-platelets (*82*). In a recent clinical study in patients who were candidates for carotid endarterectomy, ^{99m}Tc-P280 SPECT images showed significant localization in atherosclerotic lesions, and the uptake in lesions was independent of percent stenosis (*83*). The clinical significance of these studies and the potential diagnostic value of ^{99m}Tc-P280 studies for intra-arterial thrombus detection are yet to be correlated with lesion histopathology.

PET. The conventional nuclear medicine gamma cameras have a resolution of 1.0–1.5 cm for planar and SPECT imaging techniques. In contrast, the state-of-the-art PET cameras provide 4–5 mm of resolution. Fluorine-18-labeled FDG, an analog of glucose, has been used extensively as a radiotracer to estimate glucose metabolic rates of brain, heart and tumor (*84,85*). This analog competes with glucose for transport into the cell and is subsequently trapped within the cell. While investigating the mechanisms of FDG accumulation in tumor tissue, Kubota et al. (*86*) recently reported that, within the tumor, the uptake of deoxyglucose by macrophages was higher than that by tumor cells. Because atherosclerotic lesions are rich in macrophages, we hypothesized that FDG-PET imaging of atherosclerosis may provide a noninvasive test to image and quantitate the extent of macrophage content in an atherosclerotic lesion. This metabolic tracer showed significant localization in experimental atherosclerotic lesions of hypercholesterolemic rabbits (*87*). In addition, histopathological data also suggest that the amount of FDG uptake in the lesion correlates with the macrophage density in the lesion (*87*). Because FDG clears from circulation rapidly, FDG-PET scans may provide excellent image quality with very high target-to-background ratios within 30 min postinjection.

CONCLUSION

The relative advantages and limitations of the many techniques discussed above are summarized in Figure 1. In regard to non-nuclear-related imaging techniques, angiography, the traditional "gold standard," detects advanced lesions and provides a measure of the degree of stenosis. Angioscopy, on the other hand, clearly identifies the presence of thrombus. These techniques, however, are ineffective in detemining the plaques that are unstable and vulnerable to thrombosis and proliferation. In carotid arteries and arteries in lower extremities, duplex ultrasonography is useful for providing the degree of stenosis, as well as plaque morphology, and for assessing changes in wall thickness. Intravascular ultrasound is the only technique that appears to be clinically useful in imaging the unstable, vulnerable plaques in coronary arteries. The technique, however, is very invasive, like angiography and angioscopy, and is, therefore, not practical in evaluating the progression of atherosclerotic disease in patients with stable angina. Magnetic resonance angiography, being noninvasive, may replace angiography for anatomical imaging of the vasculature, but MRA technique is also ineffective in imaging the vulnerable plaques. Magnetic resonance imaging techniques, in the near future, may be able to image vulnerable plaques and characterize plaques in terms of lipid and fibrous content and identify the presence of thrombus associated with the plaques. Ultrafast EBCT is noninvasive and useful for measuring the calcium content in the coronary arteries, but clinical studies have not confirmed that there is a good correlation between calcium concentration and plaque vulnerability.

With regard to the radioisotopic imaging techniques, radiolabeled lipoproteins and platelets have shown some clinical potential as imaging agents, but due to poor target/background and target/blood ratios, these agents are not ideal for imaging coronary or even carotid lesions. Radiolabeled peptides, antibody fragments and metabolic tracers like FDG appear to offer new opportunities for nuclear scintigraphic techniques in the noninvasive imaging of atherosclerosis and atherothrombosis. Specifically, peptides capable of imaging intra-arterial throm-

bus offer significant diagnostic potential. These peptides, however, are not designed to detect vulnerable plaques. Recent advances in molecular biology have shown the potential significance of many molecules, such as PDGF, transforming growth factor-beta, interleukin 1 and tumor necrosis factor in the pathogenesis of atherosclerosis and response to the injury of arterial wall. Radiolabeled antibody molecules against these biochemicals may also provide an excellent opportunity for noninvasive imaging of atherosclerosis.

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EDITORIAL

Camera-Based PET: The Best Is Yet to Come

Radionuclide imaging provides a sensitive method to characterize in vivo chemistry. Imaging studies of bone mineral turnover using ^{99m}Tc-MDP, transferrin receptors using ^{67}Ga-citrate, somatostatin receptors using ^{111}In-pentetreotide, uptake and vesicular storage using ^{131}I-MIBG and radiolabeled monoclonal antibodies now are being used to diagnose diseases by a specific aspect of chemistry. Fluorine-18-2-fluoro-2-deoxyglucose (FDG) has been used for many years in PET facilities throughout the world, and its use in demonstrating glucose metabolism has been well documented. It is now becoming more widely available through multiple distribution sites located in several large metropolitan areas in the U.S.

Imaging from FDG-PET has been demonstrated to have clinical use in several neurologic, cardiac and oncologic diseases (*1–3*). Most recently, the oncologic applications have been validated and accepted (*3–5*). Brain tumor imaging was the first oncologic application of FDG-PET (*6*), and its use is in the characterization of the degree of malignancy of a tumor and in the differentiation of necrosis from tumor after either radiation therapy or chemotherapy (*7*). The use of FDG-PET in lung cancer has been demonstrated to provide unique (*8*) and cost-effective (*9*) information in patient management. It is very accurate in the differentiation of benign and malignant solitary pulmonary nodules that are indeterminate by chest radiograph and CT (*8*), in staging the extent of disease (*10*), and in the differentiation of fibrosis from residual tumor after therapy (*11*).

The use of FDG-PET in other malignancies has achieved very good results (*3*), but its role in these other malignancies is not as well developed as in lung cancer. The other malignancies in which FDG-PET is being used include melanoma, lymphoma, persistent or recurrent colorectal carcinoma, breast cancer, head and neck cancer, gynecologic malignancy and bone and soft tissue malignancies (*3*).

The data, in the literature, that support the clinical applications of FDG have been obtained with dedicated PET scanners. Because of the cost of these scanners and the limited number (approximately 60 in the U.S.), the data to support the clinical applications of FDG-PET have been slow to develop. Nevertheless, the data clearly demonstrate that FDG imaging is going to have an important role in the future of nuclear medicine.

The widespread availability of FDG-PET imaging has been limited because of the cost of the imaging equipment and the need to have a cyclotron and a radiochemistry laboratory to produce the FDG. Availability of FDG is being addressed through the development of multiple distribution sites. The availability of imaging devices is being addressed by several manufacturers of gamma cameras who are modifying their devices to image FDG.

PET scanners, as we know them today, were developed in the early 1970s by Phelps et al. (*12*) at the Mallinckrodt Institute of Radiology. Multiple improvements have been made in the technology since that time. The original scanner was a single slice device with a resolution of 17 mm, and today's scanners have a 15–30 cm axial field of view with a 4–5 mm intrinsic resolution (*13,14*).

In the mid-1970s, Muellehner et al. (*15*) at Searle Radiographics attempted to perform coincidence imaging using opposed gamma cameras. Investigators had proposed the use of coincidence imaging

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