Nuclear medicine—the past predicts a bright future

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**Keywords:** Nuclear medicine; Harmonic imaging; Radiopharmaceuticals

Nuclear medicine, a field characterized by innovation since the time Becquerel and Curie defined the basic properties of radionuclides, continues to evolve in this seventh decade of the isotope scan. Nuclear medicine has always been ‘molecular’ [1] with early studies defining the avidity of the reticuloendothelial system, identifying the flux of ions across membranes and defining the size and turnover of important compartments, pools and spaces in the body. In contrast to anatomic imaging technology, nuclear medicine has made great strides in the development of new radiopharmaceuticals but has made little progress in imaging devices.

Technical progress in technologies such as ultrasound and multidetector CT are remarkable. Harmonic imaging of native tissue (without added contrast) with ultrasound is an example of this. Harmonic imaging detects the second harmonic of the transmitted ultrasound pulse rather than imaging the fundamental frequency. Harmonic imaging provides better contrast than fundamental imaging as demonstrated in Fig. 1 of a complex renal cyst. Harmonic imaging has been applied to the heart to enhance delineation of lesions and perfusion. Heinle et al. [2] compared harmonic ECHO (with added echo contrast) to myocardial perfusion imaging with $^{99m}$Tc–sestamibi at rest and pharmacological stress. Images were obtained at baseline and during adenosine infusion in three apical views in 123 patients. Agreement between the two methods for detecting coronary disease in each of the three coronary territories was 81% for the left anterior descending artery, 76% for the right coronary artery and 72% for the left circumflex artery. Discrepancies between the two techniques were most notable in the circumflex territory, where fixed defects were observed in 33% by harmonic Doppler contrast ECHO but in only 14% by SPECT. This study concluded that harmonic Doppler contrast ECHO could reliably detect myocardial perfusion during pharmacological stress although there was a significantly higher number of false positive results in the circumflex territory.
In addition to ultrasound, improvements in multidetector X-ray-computed tomography has made CT angiography a standard practice and enhanced the availability of calcium screening for coronary artery disease. The improved spatial resolution of CT and ultrasound make these technologies major contributors in the evaluation of anatomic lesions. Nuclear medicine retains a unique place in the evaluation of disease with its exquisite sensitivity for the detection of extremely small quantities of biologically important substances. Radionuclide techniques are increasingly applied to depict the functional aspects of cells as they respond to their environment with changes in receptor expression, metabolism and signaling systems. Identifying these parameters utilizes the exquisite sensitivity of radionuclide techniques to detect very low concentrations of substrates or ligands as they signal the cell or tissue to perform in a specific fashion.

1. Molecular imaging

Small changes in circulating hormone levels have a marked influence on the localization of tracers as demonstrated by the influence of insulin on the distribution of thallium-201 in the myocardium of diabetic patients. Following insulin administration, there is increased thallium concentration in the myocardium overall and increased regional thallium uptake in the zones of ischemia [3]. This is illustrated in Fig. 2, a rest-injected thallium-201 myocardial perfusion scan of a diabetic patient studied on two successive days. On the first day, top panels, she was fasting prior to injection of thallium at rest. On the second day, middle panels, she had taken her dose of insulin and had a light breakfast prior to injection. Note the difference in the extent of perfusion in the apex, inferior and lateral walls as a result of insulin. Detecting such changes requires the unique sensitivity of radionuclide imaging.

Other factors such as the type of stress can have a major influence on the distribution of regional perfusion. While the overall sensitivity of stress testing with vasodilators and exercise stress is equivalent in patients with significant coronary artery disease [4,5], the appearance of the lesions are not the same. David et al. [6] illustrate this point in patients who had both dipyridamole and exercise studies. Fig. 3, based on the article by David, depicts tomographic reconstructed data on two patients, each studied with both exercise and
dipyridamole stress. There is a remarkable difference in the extent of the perfusion abnormality observed in these patients, with one case larger on the dipyridamole study, while in the other, larger on the exercise study. The relationship of lesion size with each stress was depicted on the graph. Note the wide disparity of lesion extent with the two stress techniques. In patients unable to perform a maximal exercise test, dipyridamole imaging demonstrated more extensive disease than exercise studies. However, lesions were more extensive on exercise studies in patients who were able to perform a maximal exercise test.

Fig. 2. Influence of insulin on thallium uptake. Insulin stimulates the Na/K pump, enhancing the uptake of Tl⁺, changing the appearance of the perfusion image.

Fig. 3. Sensitivity of dipyridamole + LLE vs. exercise in patients with documented CAD: 40 patients (35 with angiography). Larger lesions at exercise were associated with less severe CAD [<70% stenosis and >60 bpm increase in heart rate]. Larger lesions on dipyridamole had lower peak heart rates at exercise [>70% stenosis and <60 bpm increase in heart rate].
The extent of lesions in both scans was equivalent in only 28% of the patients. The best predictors of discrepancies between the two tests were: (A) increase in heart rate with exercise; and (B) an ischemic territory supplied by < 70% coronary stenosis, where lesions were always induced with exercise but in only 30% with dipyridamole.

To enhance the reliability of vasodilator stress testing, it would be helpful to develop agents that specifically activate receptors in the coronary arteries. Adenosine, a commonly used pharmacologic stress agent, is a nucleoside which binds to G-coupled adenosine receptors [7]. At least, four receptor subtypes have been identified: A1, A2A, A2B and A3. In the coronary vessels, receptors A2A and A2B have been found but the predominant receptor responsible for coronary vasodilatation is A2A (Fig. 4). In addition to coronary vasodilatation, adenosine is associated with other undesirable effects like bronchoconstriction and bradycardia and may cause conduction disturbances. The majority of these actions of adenosine are not mediated by the A2A receptor. Therefore, the development of either an adenosine A2A receptor subtype analog or antagonists for the other receptor subtypes would be helpful. He et al. [8] studied the hemodynamic and coronary vasodilatory effects of a potent selective adenosine A(2A) agonist (CGS-21680) in dogs. The study compared adenosine with its A2A analog in (201)Tl (0.5 mCi) and (99m)Tc–sestamibi (5 mCi) cardiac SPECT studies. The study showed that heart rate decreased with adenosine but increased during CGS-21680 infusion ($P < 0.005$). The decrease in systolic blood pressure was more prominent with adenosine than with CGS-21680 ($P < 0.005$).

![Hemodynamics](image)

**He Zx et al Circ 2000; 102:4328-44**

Fig. 4. Selective receptor A2A receptor agonist.
the control LCx zone, maximal myocardial blood flow (measured by radioactive microspheres) increased 3.1-fold during adenosine infusion ($P < 0.005$) and 3.8-fold during CGS-21680 infusion ($P < 0.005$). In the stenotic LAD zone, myocardial blood flow did not change significantly. During adenosine and CGS-21680 infusion, stenosis/control zone MBF ratios were comparable ($0.32 \pm 0.11$ vs. $0.27 \pm 0.10$, $P = \text{NS}$), and transmural (201)TI and (99m)Tc–sestamibi count–activity ratios ($0.48 \pm 0.11$ and $0.51 \pm 0.09$, respectively) were also comparable ($P = \text{NS}$). Myocardial scintigraphy uncovered perfusion defects in all dogs. They conclude that CGS-21680 elicits coronary vasodilation comparable to that of adenosine and produces profound heterogeneity of MBF in (201)TI and (99m)Tc–sestamibi myocardial uptake, rendering it as a promising agent for pharmacological stress testing in conjunction with myocardial perfusion imaging.

Receptor imaging has been used to investigate the pathophysiology of disease. Patients with non-Q-wave infarction do not have a better long-term prognosis than patients with Q-wave infarction in spite of the smaller size of their infarction. The risk of sudden cardiac death is higher in these patients in spite of their better-preserved left ventricular function. Since adrenergic cardiac innervation is very susceptible to ischemia, it has been suggested that the extent of denervation in patients with non-transmural infarction may be broad. A balance of perfusion and innervation (both adrenergic and cholinergeric) is necessary to minimize the likelihood of arrhythmia. To determine if changes in perfusion and adrenergic innervation were similar in patients with non-transmural infarction, Simula et al. [9] used iodine-123–MIBG SPECT and Technetium-99m–sestamibi SPECT to study patients with non-Q-wave and Q-wave infarctions. MIBG and sestamibi lesions were expressed as regional uptake < or $\geq 30\%$ of the maximal myocardial activity. The size of perfusion defects calculated as a percentage of left ventricular mass, was significantly smaller in patients with a non-Q-wave infarction than in patients with a Q-wave infarction. The extent of adrenergic denervation, however, was similar. As a result, patients with non-Q-wave infarcts had areas that were perfused but were denervated, making these areas more prone to arrhythmia.

2. Atherosclerotic plaque

A growing role of molecular Nuclear Medicine is lesion characterization to facilitate a therapy tailored to address the unique nature of specific lesions. In selected tumors, for example, a comparison of regional lesion metabolism with fluorodeoxyglucose imaging and X-ray-computed tomography to define lesion extent, are employed to allow intensity modulated radiation therapy [10]. A family of new radiopharmaceuticals, such as the agent based on identifying apoptosis, $^{99m}$Tc–annexin V [11], is contributing to this process. These techniques work with external imaging. In addition to external imaging, smaller detectors are being built for use in the detection of lesions in the vasculature. The focus is on detecting atheroma, especially characterizing lesions for the likelihood that a plaque will rupture—resulting in thrombosis in the vessel. Characteristics such as receptor expression or metabolism are being evaluated instead of anatomic characteristics [12]. Section 2.1 describes the radiopharmaceuticals that may be employed and the instruments that are being developed to characterize atheroma.
2.1. Characterizing atheroma

Ultrasound, CT, MR and radionuclide imaging have all described approaches to image atheroma. Duplex Doppler ultrasound is widely used to characterize atheroma in the carotid arteries [13] based on vessel diameter, thickness of the media and velocity measurements. Multidetector CT with contrast provides excellent three-dimensional rendering, but despite their high spatial resolution, the images cannot distinguish between moderate degrees of stenosis [14]. Hatsukami et al. [15] describe a high resolution MRI technique to identify carotid plaques at risk of rupture. They suggest that the thickness of the fibrous cap that overlies the necrotic core distinguishes the stable lesion from the one at high risk for rupture and thromboembolism. This high-resolution MRI technique could identify the thickness of the fibrous cap in vivo. The images obtained on 22 subjects scheduled for carotid endarterectomy were compared to histology and gross tissue examination of the lesion ex vivo. The appearance of the fibrous cap was categorized as intact thick, intact thin or ruptured fibrous cap on both MRI, gross and histological sections. Thirty-six sites were compared between MRI and histology. There was 89% agreement between MRI and histological findings, the authors concluding that high-resolution MRI is capable of distinguishing intact thick fibrous caps from intact thin and disrupted caps in atherosclerotic human carotid arteries in vivo. However, the difficulty of identifying the small plaques and particularly coronary lesions due to cardiac movement has lead to more invasive diagnostic techniques.

Intravascular ultrasound (IVUS) and thermography (using a small intravascular temperature-sensing probe) has been a new incorporated intravascular device developed for unstable atherosclerotic plaque detection (Fig. 5) [16]. The technique is based on mapping the temperature on the IVUS image [17]. A major problem with this approach is that temperature elevation is greatest when the lesions are extremely unstable, typically in

![Diagram of plaques](image)
patients with significant symptoms. It is unclear whether this approach can detect lesions of lesser severity.

2.2. Evolution of the plaque

Radionuclide approaches can detect disease in evolution based on the biological processes occurring at each phase. Three major events take place in the atherosclerotic plaque: (a) the accumulation of smooth muscle cells within the intima of the vessel together with macrophages and T lymphocytes, (b) the generation of large amounts of connective tissue matrix (collagen, elastic fibers and proteoglycans) by the proliferating smooth muscle, and (c) the accumulation of lipid within the cells as well as in the surrounding connective tissues. There is a great variability in the amount of tissue formed by each of these processes in the lesions. The distribution of the lipid and connective tissue is going to determine whether they are stable plaques or are at risk of rupture.

Since atherosclerosis affects the vessel, the plaque can cause the following changes.

(1) As the lesion develops, the vessel can compensate by dilating, which leads to the formation of an aneurysm as a consequence of overcompensation. There may be a little change in the lumen. These lesions are generally symmetrical and concentric.

(2) The lesion can develop a progressive thickening of the intima, which encroaches upon the lumen of the vessel, resulting in the narrowing of the lumen. These lesions are usually eccentric.

(3) When a plaque ruptures or erodes, a coronary syndrome may be produced as a result of the overlying thrombus which reduces the lumen. If the patient survives the acute episode, the thrombus may partially lyse and the lesion will re-endothelialize. It is likely that the process will be repeated, resulting in further narrowing of the lumen.

2.3. Cells involved in atherosclerosis

Endothelial injury is a key factor in the genesis of atheroma. Elevated levels of lipoprotein/cholesterol, oxidized lipoprotein/cholesterol (although only <1% part of the plaque is composed by them) and persistent high levels of catecholamines are known as important endothelial injury factors. Oxidized low density lipoproteins (LDL) and cholesterol result in toxic injury to the endothelium and can change the surface characteristics of the endothelial cells, circulating leukocytes (particularly circulating monocytes), and possibly, platelets.

2.3.1. Endothelial cells

Endothelial cells present receptors for LDL. LDL is modified by a process of low-level oxidation when bound to LDL-receptors, internalized and transported through the endothelium. Once oxidized, LDL is in the subintimal space and it binds to the scavenger receptor on the surface of macrophages and smooth muscle cells. Once ingested, oxidized LDL is difficult to catabolize and leads to foam cell formation. As the endothelium forms oxidized LDL, the endothelium itself, as well as the underlying cells in the artery wall, may be injured. Arterial endothelial cells are capable of synthesizing and secreting mitogens, one of which is PDGF. PDGF is a growth factor for mesenchymally derived connective tissue (fibroblasts and smooth muscle) but not for arterial endothelial cells. The
capacity of endothelium when it has been appropriately activated to form such growth factors is important in the atherogenic process.

2.3.2. Monocytes and T lymphocytes

Oxidized LDL may cause increased adherence and migration of monocytes and T lymphocytes from the lumen into the artery wall. The inflammation caused by oxidized LDL causes the production of adhesion molecules by the endothelium, causing monocytes and T lymphocytes to stick to the surface of the endothelium through receptor–ligand interactions. After the monocytes adhere, they are attracted to migrate between endothelial cells and localize subendothelially where they can become macrophages.

2.3.3. Macrophages

Macrophages in the lesions are derived from circulating monocytes. They scavenge oxidized LDL, become foam cells and release enzymes, which lead to further oxidation of LDL in the lipid pool of the lesion. Macrophages can replicate in the atheroma, and the factors associated with their turnover, replication and apoptosis are important in the genesis of the lesions. These cells secrete growth factors for monocyte/macrophages and mesenchymal cells (smooth muscle cells and fibroblasts), produce chemotactic agents and generate oxygen metabolites that can be toxic to other cells. Activated foam cells also produce chemotactic agents that attract smooth muscle cells to migrate from the media into the intima, proliferate within the intima and set up conditions that lead to the formation of an intimal, fibromuscular and proliferative lesion. Macrophages have a key role in the induction and maintenance of smooth muscle cell proliferation because of their production of PDGF_BB, one of the most potent growth factors and mitogens stimulating smooth muscle cell chemotaxis and proliferation. PDGF_BB is involved in both the attraction of smooth muscle cells into macrophage-rich fatty streaks and in the progression of these fatty streaks to intermediate or fibro-fatty lesions, which may ultimately become advanced occlusive lesions or fibrous plaques. If the cycle of endothelial injury and macrophage accumulation and stimulation is repeated, at least, two cells capable of releasing growth factors into the intima (activated endothelial cell and activated macrophage) may continue to contribute to the progression of the lesions.

2.3.4. T lymphocytes

T lymphocytes (CD-8+ and CD-4+) have been observed in all phases of atherogenesis. Their involvement supports the notion that these lesions may develop at least in part as a result of an immune or possible autoimmune response. Oxidized LDL may serve as one of the potential major antigens that stimulate macrophage–T cell interactions. If oxidized LDL proves to be the antigen principally responsible for T-lymphocyte activation, this would provide a new approach to the therapy and immune response in the process of atherogenesis. The progressive accumulation of lymphocytes and macrophages alters the plaque, transforming the lesion into a plaque at risk of rupture (vulnerable plaque).

2.3.5. Smooth muscle cell

The cell that proliferates in the arterial intima to form the intermediate and advanced lesions, the smooth muscle cell, is originally derived from the media. These cells must
migrate into the intima where they can respond mitogenically. Smooth muscle cells as fibroblast contain specific high affinity receptors like LDL, growth stimulators (PDGF) and growth inhibitors. They can present two different phenotypes: (a) contractile (do not respond to mitogens (PDGF)) and (b) synthetic (formation of connective tissue matrix macromolecules). When smooth muscle cells become appropriately stimulated, they lose their contractile phenotype and change to a synthetic phenotype. The smooth muscle cells are the principal contributors to the reparative and fibroproliferative process in the development of the lesions of atherosclerosis. They can accumulate lipids resulting in foam cells. Smooth muscle cells and macrophages are the major source of foam cells in the plaque, being the principal cells in the fatty streak.

2.3.6. Platelets

The role of platelets in the genesis of the plaque is uncertain. They are, however, involved in one of the principal sequelae of atherosclerosis and thrombosis.

2.4. Evolution and classification of atherosclerotic plaque’s histology [18]

The American Heart Association has proposed a six-stage classification of atherosclerotic plaque.

Stage I: Smooth muscle proliferation with minimal monocyte/macrophage infiltration.
Stage II: Fatty streak with foam cells (lipid-containing macrophages) in the intima.
Stage III: Pools of extracellular lipid but with no necrotic core.
Stage IV: Core formation with overlying caps of smooth muscle and collagen.
Stage V: Cap and core formation. Fibroatheroma with thick cap and necrotic core (often with calcium).
Stage VI: Plaque rupture with thrombus.

2.4.1. Fatty streaks

Fatty streaks (lesion types I–III) have been observed in children and young adults. The fatty streak appears as an area of yellow discoloration due to the large amount of lipid deposited in the foam cells. Lipid enters the fatty streak by transport of lipoproteins from the plasma via the endothelial cells. They are hydrolyzed and reesterified once they have been taken up. Fatty streaks consist principally of lipid-laden macrophages and T lymphocytes together with small and variable numbers of smooth muscle cells.

2.4.2. Diffuse intimal thickening

Diffuse intimal thickening (lesion type IV) consists of increased numbers of intimal smooth muscle cells surrounded by variable amounts of connective tissue. They may have also diffusely extracellular lipid intermixed with smooth muscle cells, macrophages T cells and connective tissue.

2.4.3. Fibrous plaque

The fibrous plaque (lesions types V and VI) is the advance lesion of atherosclerosis. When they are involved with thrombosis, hemorrhage and/or calcification, they are called
complicated lesions. They are white and usually protrude into the lumen. They consist of large numbers of intimal smooth muscle cells together with numerous macrophages and T cells. Collagen, elastic fibers, proteoglycan and lipids are surrounding the proliferated smooth muscle cells. A fibrous cap characteristically covers these fibrous plaques. The fibrous cap consists of a particular form of smooth muscle cells surrounded by numerous lamellae of basement membrane, proteoglycan and collagen. The connective tissue is very dense. Beneath the fibrous cap lies a mixture of smooth muscle cells, macrophages and numerous lymphocytes. Beneath the cell-rich region, a zone of necrotic tissue and debris may contain cholesterol crystals and calcium as well as enlarged foam cells. The principal clinical results of advanced lesions are derived either from the fact that they partially or totally occlude the lumen or because cracks and fissures developed in the lesions leading to thrombosis and embolism or to aneurysmal dilatation. Many advanced lesions appear to be quite unstable and represent the principal cause of myocardial infarction and sudden ischemic death [19].

Regardless of the stage, the physical detection of atheroma is challenging due to the small size of the lesion. The diameter of a coronary vessel itself is around 3 mm, and the atheroma is usually an eccentric circumferential lesion with a depth of < 1 mm and a length of 3–15 mm. The problem of detection is even more complex because of the motion of the heart.

A strategy to identify plaque should consider whether it is equally important to detect all plaques. Stages I–IV are not likely to cause an acute event. On the other hand, stage V and VI plaques are more likely to rupture causing erosion. From a clinical perspective, it is more important to identify some lesions more than others. Based on their inflammatory characteristics, stage V and VI lesions fall into the category of vulnerable plaques because they have a significant likelihood of thrombosis. Autopsy studies demonstrate that these plaques are responsible for the acute coronary events [20].

### 3. Radionuclide approaches to imaging atheroma

Three classes of radiopharmaceuticals have been suggested to image atheroma:

(a) Agents that label plaque components (Fig. 6)

1. Radiolabeled low density lipoproteins (LDL)
2. Cells that have arrived at the lesion using chemotactic peptides that localize in up-regulated receptors expressed by monocytes and macrophages in the lesions, such as MCP-1

(b) Identifying changes in normal components of the vessel that are responding to the inflammation associated with the atheroma

1. Increased expression of somatostatin receptors by smooth muscle cells that have transformed from the contractile to the secretory/proliferative phenotype
2. Endothelin receptors up-regulated by both endothelial and smooth muscle cells in the region of the lesion
Identifying the increased metabolism of cells in the lesion

1. Utilizing fluorodeoxyglucose as a marker for macrophage activity.

In 1983, Lees et al. [21] used autologous plasma (low density) lipoproteins labeled with I-125 as a tracer to identify atherosclerotic plaques in the carotid arteries. Images were obtained in three patients with known carotid disease and one control subject. The carotid lesions confirmed by angiography were imaged successfully in all three patients, whereas no focal LDL accumulation was visible in the carotid arteries of the control subject, nor in the relatively uninvolved portions of the carotid artery in the three patients.

In addition to the work of Lees et al., other investigators describe the use of radiolabeled autologous lipoproteins [22–26]. In acute/unstable lesions, several agents associated with thrombus formation have shown to be local. These include radiolabeled platelets and platelet specific antibodies [27–29], localized agents that bind to activated IIb/IIIa receptors expressed on an active platelet [30]. A $^{99m}$Tc-labeled adenine nucleotide analog, Ap$_4$A, was directed at the adenosine diphosphate association sites on platelets [31] and radiolabeled fibrinogen [32,33]. The change in the smooth muscle phenotype can be imaged with the Fab fragment of a monoclonal IgM antibody [34,35] which recognizes proliferating arterial smooth muscle cells found in the active plaque. Recent studies of human atheroma demonstrated striking changes associated with apoptosis [36], especially of cells derived from monocytes and lymphocytes. It is likely that $^{99m}$Tc–annexin V can identify such lesions. Unfortunately, none of these agents have demonstrated disease in coronary vessels.

The small size of atheroma in the coronaries is a major challenge for imaging with a gamma camera. Gamma cameras typically have a spatial resolution of about 5–8 mm.

Fig. 6. Components of plaque.
through the collimator at the depth of the heart. This resolution makes it difficult to detect a lesion as small as an atheroma. It would take a target to background ratio of about 20:1 to see small lesions reliably. To enhance the likelihood of detecting these lesions, the detector must be brought close to the site of the lesion. This can be accomplished if the radionuclide detector is mounted on a catheter (Fig. 7) [37].

Such a device is feasible and could be constructed using either a scintillator (plastic or crystal) mated to a fiberoptic fiber to conduct the light to an external detector, or a solid state detector, such as cadmium telluride, which could be used to detect the signal directly. An additional consideration requires a background of minimization from nonspecific tracer localization in tissue adjacent to the coronary vessel. This can be accomplished by making the detector sensitive to low energy X-ray, beta and conversion radiation rather than gamma radiation. Prototypes of a catheter-based radiation detector are under development.

In parallel with the development of the catheter, studies are underway to identify radiopharmaceuticals that will localize lesions in stages V and VI. Using the rabbit balloon-injured aortas in animals fed with a high fat/high cholesterol diet, eight different tracers were studied. These tracers were ¹²⁵I–albumin (inflammatory nonspecific protein space-control), ⁹⁹ᵐTc–depreotide (increased somatostatin receptors on activated lymphocytes and proliferative smooth muscle cells), ⁹⁹ᵐTc–apcitide (increased IIb/IIIa receptors in activated platelets), ¹²⁵I–monocyte chemotactic protein-1 (MCP-1) (activated monocytes/macrophages/foam cells), ⁹⁹ᵐTc–annexin V (apoptotic cells), ²⁰¹thallium (neovascularization), ¹⁸F–FDG (macrophage metabolism) and ¹²⁵I–endothelin (increased endothelin receptors due to inflammation). Excellent localization was seen with several agents, including FDG, thallium, annexin, MCP-1 and endothelin. To determine if tracer localization will occur in the absence of physical injury to the vessel, another study is underway in Gs alpha transgenic mice. These mice are genetically predisposed to
cardiomyopathy and heart failure but not atherosclerosis. They were fed with a high fat diet for several months in order to test a diet model of atherosclerotic plaques. In this model, tracers that characterize different components and metabolic changes of the atheroma are being studied as described above. Success in this model will establish the ability of tracers to localize in lesions that result from vascular injury from hyperlipidemia alone. An agent then localizes in both the rabbit injury model, and the mouse model is more likely to work in humans.

4. Molecular imaging in small animals

Imaging small lesions or small animals requires a high-resolution imaging device. A pinhole collimator with a small aperture can be used effectively to image small objects. If the intrinsic resolution of the gamma camera is improved, the spatial resolution of the system can be enhanced. To effectively image lesions within the mice, high-resolution pinhole imaging is required. Single photon agents, with their wide availability can be used with a high-resolution pinhole collimated single photon instrument to image receptor expression, perfusion and many other biologic processes in mice. Novel ligands can be iodinated, chelated with indium-111 or bound to technetium-99m for high-resolution imaging.

A combination of new radiopharmaceuticals and advances in high resolution instrumentation will enhance the clinical value of radionuclide imaging. Nuclear imaging is being used in the operating room environment, primarily for the identification of sentinel lymph nodes. This instrumentation will soon expand from probes to small hand-held gamma cameras. In addition, catheter cameras are in development to detect lesions in the vasculature. All of these advances will keep Nuclear Medicine where it needs to be, near the patient, available to make measurements that will be pivotal to decision making in patient care.

References

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