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EDITORIAL

Atherosclerosis Imaging: Pathophysiological Assessment for a New Era

In 1941, Arthur Master introduced the two-step electrocardiogram (*1*) and dramatically altered management decision-making in patients with chronic stable coronary artery disease. Previously, necessary prognostic inferences in such patients were based primarily on subjective complaints. With the new method, the choice of management options could be grounded on objective assessment of the functional consequences of coronary occlusions. In 1941, therapies were few and choices were limited. However, during the ensuing five decades, pharmacologic and surgical treatment modalities proliferated. Ultimately, some were shown to impact positively on the natural history of disease. In this context, easily applied, preferably noninvasive, periodically repeatable approaches to prognostication assumed ever greater importance.

Fortunately, as the need grew, many technical developments enhanced the capacity for noninvasive prognostication. Exercise electrocardiography continues to evolve in diagnostic and predictive accuracy, most recently as computer-based technology permits extraction of new nuggets of information from the sarcolemmal response to ischemia (*2*). However, the current standard for noninvasive prognostication involves radioisotopic imaging during stress to measure the functional importance of occlusive lesions. Beginning with brilliant pioneering efforts in perfusion scintigraphy (*3–5*), shortly thereafter supplemented by direct assessment of ventricular performance during exercise (*6*), scintigraphic stress testing has provided a sound objective basis

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for risk-stratification and management decision making in patients with coronary artery disease (*7–13*).

As data have accumulated, however, it has become increasingly clear that radionuclide-based stress testing, with exercise or with drugs (*14*), falls well short of ideal as a prognostic tool. Scintigraphic methods permit effective determination of relative risk and of risk stratification; comparison of these characteristics with and without therapy is possible, thus fulfilling the requirements for influencing management decisions. However, scintigraphy is woefully lacking in estimation of *absolute* risk. This is particularly true in the target population of greatest interest: patients with stable and tolerable or even absent symptoms and little or no prior myocardial damage for whom therapeutic plans primarily are aimed at preventing death or infarction. This population comprises more than 90% of those presenting for evaluation (*12*). Among such patients, the radionuclide-defined subgroup at highest risk can expect, on average, annual mortality of slightly less than 10% in the absence of surgical therapy; major ischemic event risk is only modestly higher (*13*). These numbers are similar to those achievable in patients with invasive arteriographic evaluation (*15*) and may be far higher than the risk in similarly ischemic patients who undergo coronary bypass grafting (*16*). However, the overwhelming likelihood for the individual patient thus identified is that he or she will be alive a year later irrespective of the management scheme employed. As a corollary, confidence limits for the likelihood of an event in any single patient within the high risk group are 0% and 100% over the same one-year period. In contrast, the ideal prognostic discriminator would provide 100% certainty during the year in question. Life-prolonging therapy thus could be confidently and cost-effectively rationed to those at risk, and ethically and appropriately withheld from those in whom events will not occur. Although such prognostic certainty may never be achievable in biological systems, nonetheless it is reasonable to seek far greater certainty than we can now command.

What is the basis of the mismatch between current objective testing strategies and optimal prognostication? The predictive value of radionuclide-based descriptors now employed is grounded in a statistically valid but biologically indirect association between the functional severity of ischemia caused by an occlusive lesion and the likelihood of sudden anatomic alteration of that lesion. Stated in another way, *people generally do not die because of ischemia induced (and measurable) during exercise; rather, they die of a sudden change in the underlying lesion*, which dramatically alters coronary flow pattern and renders the myocardium electrically unstable and mechanically ineffective. It is fortuitous, but largely coincidental, that lesions which cause the greatest dysfunction during exercise are those that are statistically most likely to undergo sudden alteration. It is, of course, possible that biological linkages may exist between exercise-inducible dysfunction and lesion alteration, e.g., hemodynamic shear stresses on anatomically severe lesions [which are most likely to cause dysfunction (*17*)] often may be greater than those impacting on less severe lesions and may hasten sudden structural alteration. Nonetheless, we now know that sudden change often occurs among anatomically and functionally modest lesions, whereas the most severe stenoses can manifest remarkable stability over time. Thus, the natural history of the patient is determined primarily by the natural history of the atherosclerotic lesion. It follows then that improvement in prognostication and management decision-making must be achieved by providing the "missing link" between testing strategies and the natural history of the coronary lesion. This missing link is direct interrogation of arterial wall biology.

The technological armamentarium for characterizing lesions in vivo has grown rapidly in recent years. Both invasive (digital contrast angiography, echocardiographic catheterization, angioscopy) and noninvasive (transesophageal echocardiography, magnetic resonance imaging) modalities not employing radioisotopes have proliferated to describe lesion shape and anatomic structure. Relatively poor spatial resolution inherently limits radionuclide-based methods from characterizing lesions in this way. However, radioisotopic techniques possess inherent advantages unique among current imaging modalities: in theory, virtually any metabolically active molecule can be isotopically labeled, permitting direct interrogation of biochemical/metabolic processes. (Indeed, historically, this fact was crucial in the development of nuclear medicine as endocrinologists first married biology and imaging technology in the thyroid.) In the heart, this capacity has been employed most dramatically in the application of positron emission tomography to interrogate myocyte energy metabolism. The resulting insight into the biology of ischemic myocardium has served as the technological template for the clinically important assessment of myocardial viability (*18*). As illustrated by the outstanding study by Demacker et al. in this issue of the *Journal*, radionuclides can be employed to characterize arterial wall biology as well (*19*). Thus, together with the capacity to identify lesions by external imaging, radioisotopes may help to improve the certainty of prognostication by highlighting important biochemical/metabolic characteristics.

Several groups of investigators have contributed importantly to the present state of atherosclerosis imaging. Nonetheless, the development of this field is largely attributable to the pioneering work of Robert Lees and his coworkers (*20–25*) who brought to their task a background of 30 yr of well-recognized research in atherogenesis. Lees conceived the in vivo tracking of arterial lipoprotein metabolism with radiolabeled atherogenic molecules, published the first preliminary results of ^{125}I-LDL imaging in rabbits with balloon-deendothelialized aortas in 1980 (*24*) and later developed

^{99m}Tc-LDL for imaging both rabbits and human subjects (*23,25*). Lees' initial efforts were instructive but were of limited practical utility: target-to-background activity ratios were suboptimal for external imaging of the arteries. Target-to-background ratio, or contrast, in this setting is affected by several factors, including the absolute and relative affinities of the labeled ligand for its receptor, the duration of its residence at the target site, the clearance rate of background activity from the blood and the photon flux achievable at the target site, itself in part a function of the size of the carrier molecule and the number of photon-emitting nuclei which can be carried. LDL, a large (2.5×10^6 Daltons) molecule, is not filtered through the renal glomeruli and is cleared slowly from the blood. LDL can bind to multiple sites, including the so-called "LDL receptor," in many tissues besides the arterial wall, thus adding to background. Finally, Lees' labeling resulted in relatively few emitter-nuclei per LDL molecule, limiting achievable photon flux at the target.

In theory, the atherosclerotic lesion can be imaged using probes other than atherogenic molecules. Thus, for example, imaging might be achieved with ligands to platelet or fibrin receptors to make use of the propensity of lesions to cause in situ thrombi; alternatively, endothelial or other cell surface receptors, altered or otherwise characteristic of atherosclerotic lesions, might be identified by appropriately structured and labelled ligands. The latter option was explored in a brilliantly innovative series of studies by Fischman et al., first reported in 1989 (*26*). These investigations were based on the observation that macrophage-derived foam cells, heavily represented in "fatty plaques", express a high density of cell-surface Fc receptors (*27*). Fischman and his coworkers correctly reasoned that nonspecific polyclonal immunoglobulin G (each molecule of which contains an Fc subunit) when appropriately radiolabeled would target the foam cells and permit identification of lesions.

The work of Demacker et al. extends Fischman's pioneering observation; in testing a number of crucial hypotheses, it is of major importance on several levels. The noteworthiness of this effort rests as much on its critical negative results as on its important positives in response to the following hypotheses:

1. Polyclonal IgG and, specifically, its Fc subunit, is preferentially bound to atherosclerotic plaque, in confirmation of Fischman's original observation.
2. Fc uptake is a function of the foam cell content of the plaque (itself inferred from the age of the rabbit).
3. Uptake is modifiable by therapies which lower cholesterol or otherwise minimize atherosclerosis development.
4. The relationship of ligand-receptor affinity and blood clearance of tracer provide a target-to-background ratio adequate for recognition of lesions by external imaging in an animal model of spontaneous atherosclerosis.
5. As a corollary, the balloon deendothelialized aorta model employed by Fischman is an adequate imaging surrogate for atherosclerosis resulting spontaneously from genetic predisposition and normal diet.

From their data, Demacker et al. legitimately could conclude that polyclonal IgG and, specifically, Fc fragments, indeed are preferentially bound to atherosclerotic lesions, most particularly in young lesions in which the putative macrophage target, the foam cell, is most abundant. The latter observation is potentially important. In man, the foam cell-laden fatty plaque appears to be relatively unstable, more likely to rupture with consequent sudden thrombus formation than is the fibrous plaque in which foam cells are less numerous. Demacker further observed, however, that uptake was not modifiable by therapies believed to beneficially alter the atherosclerotic process. Since the therapies employed in the study are not of proven efficacy clinically in reducing ischemic events, unequivocal interpretation of this negative is not possible. However, the result may indicate the inadequacy of the cell-surface Fc receptor as a target for probing the biology of atherosclerosis to inform management decision making: inability to assess the effectiveness of therapy would be an unfortunate limitation for such a technique. Most importantly, though, Demacker et al. found that, in the setting of spontaneous atherosclerosis, the relationship of target affinity and blood clearance of the large antibody molecule and of the antibody fragment is inadequate to permit resolution of atherosclerotic lesions by external imaging. By extension, these workers have highlighted the importance of the surrogate selected to model human disease. The deendothelialized aorta was chosen to model human atherosclerosis based on the belief that most lesions are initiated by nonspecific endothelial injury (*28*). However, the regrowth of endothelium after injury in the rabbit may fail to adequately model the process which occurs spontaneously in man. The WHHL rabbit employed by Demacker et al. is deficient in LDL receptors and thus, on a normal diet, abnormally accumulates arterial wall cholesterol to form lesions reminiscent histologically of those found in man. Although Demacker's negative results may have been influenced by sex distribution within the rabbit population (sex and gravidity directly affect lesion cholesterol metabolism in the WHHL rabbit and sex distribution is not reported by the investigator), it is more likely that the tracer, itself, was not adequate to its task. Several inferences may be drawn from this finding. First, judicious selection among the available animal models may be critical in identifying clinically useful atherosclerosis imaging agents. Second, if the ingenious Fc fragment approach is to be further developed to interrogate the biology of atherosclerosis by external imaging, then the specific Fc receptor binding site must be identified and maintained while the remainder of the peptide must be engineered to facilitate blood clearance.

Although the latter task is formidable, the work of Fischman and of Demacker suggests that the effort may be handsomely repaid.

A precedent now exists for such molecular engineering to facilitate atherosclerosis imaging. As noted above, Lees' early approach foundered primarily on the same rocky shores as Demacker's: given its target affinity, the large LDL molecule is cleared too slowly from the blood to permit useful external imaging. In response to this problem, Lees and his coworkers went about the painstaking task of identifying a small LDL fragment which would overcome the technical roadblock. Reasoning that the apoprotein determines lesion binding, they split lipid-free apolipoprotein B into several domains, some sufficiently small to permit rapid renal clearance. In choosing a peptide for further development, they avoided the LDL receptor domain to preclude the extensive and potentially confusing noncardiac binding caused by the wide distribution of the LDL receptor. The result of their search was an 18 amino acid, 2000 Dalton nonantigenic peptide fragment, now manufactured synthetically and known as SP-4 (*29*). When labeled with radioiodine or technetium, SP-4 manifests high affinity for atherosclerotic plaque and rapid blood clearance by renal excretion. The molecule not only is avidly taken up by the growing endothelial edge in balloon-denuded aorta but recently has been demonstrated to manifest similarly high affinity for spontaneous atherosclerotic plaques in WHHL and cholesterol-fed New Zealand white rabbits (*30–33*). The latter studies, performed in my laboratory (*30–32*) and in a sister institution (*33*), also have demonstrated the feasibility of lesion detection by external imaging and have been sufficiently promising that they have spawned the first clinical trial of the technetium-labeled agent, which is now under way. In addition, these studies highlighted the critical importance of subtle variations in secondary and tertiary molecular structure resulting from radiolabeling: both clearance rate and target residence time were significantly affected by replacing the tyrosine-bound iodine label with the chelator-bound technetium and by altering the position of the chelated technetium. Although its binding site has not yet been directly identified, SP-4, like the Fc fragment, appears to be relatively specific for fatty plaque.

Finally, and perhaps most importantly, the growing interest in radioisotope imaging and characterization of atherosclerotic plaque carries potential for an extraordinary therapeutic byproduct: in binding to the lesion, the carrier molecule may, at least transiently, alter the capacity of the lesion to receive other ligands. If appropriately engineered, the diagnostic tool (minus its label) could thus become a therapeutic agent. Moreover, since prevention and treatment meet at the molecular level where pathophysiological processes are fundamentally expressed, one might even foresee the development of agents, analogous to those of Fischman, Demacker and Lees, for prevention of the very disease they have been designed to identify! Perhaps the most exciting aspect of the growing interest in radioisotopic atherosclerosis imaging therefore is the inherent property which makes it most unique: the capacity to explore molecular pathophysiology. It is here that nuclear medicine may have its most important role in the future.

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