Second Annual Mario S. Verani, MD, Memorial Lecture: Nuclear cardiology, the next 10 years

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The nuclear cardiology of the future will be based on new clinical and biologic targets. It will be driven by modern concepts of molecular and cell biology and molecular genetics. A major effort involves detection of atherosclerosis and vascular vulnerability. Approaches include targeting proliferating smooth muscle cells, angiogenesis, vascular injury, inflammation through a variety of mechanisms, defining cell death and protease activation, and imaging gene expression. Another new clinical target involves imaging stem cells and various progenitor cells. To meet these new objectives, advanced imaging technology is required. This involves the development of micro–single photon emission computed tomography and micro–positron emission tomography systems as well as fusion technology involving radiologic computed tomography imaging together with nuclear imaging. Vascular lesion detection imaging may require intravascular detectors. The future of nuclear cardiology, based on molecular imaging, is extraordinarily exciting. The newly defined biologic targets will allow the answering of many of the key clinical questions that will dominate cardiovascular care in cardiovascular investigation over the next decade. (J Nucl Cardiol 2004;11:393-407.)

It is a distinct honor and privilege to deliver the Second Annual Lecture in memory of my friend and colleague, Dr Mario S. Verani. Dr Verani will long be remembered for his very substantive contributions to the field of nuclear cardiology. He was there at the field’s onset and maintained an intellectual zest and vibrancy throughout his all-too-short career. Those of us who knew him well enjoyed our opportunities for interaction, both personal and professional. He stimulated us intellectually and befriended us as individuals. His courage and commitment to life persisted until the end. I had the opportunity to visit him during his last weeks of life, while he was hospitalized in Houston, Tex. His courage and demeanor in the face of ongoing pain and an inevitable outcome will continue to be a source of inspiration throughout my life.

INTRODUCTION

Over the past 3 decades, nuclear cardiology has been established as a viable and clinically meaningful discipline. The field has been driven by the classic principles of systems physiology and pathophysiology: supply/demand imbalance, determinants of myocardial blood flow, determinants of ventricular performance, hibernation, and stunning. As such, nuclear cardiology has appropriately focused on myocardial perfusion, necrosis, viability, and ventricular function. Extraordinary outcome data involving tens of thousands of patients have demonstrated the unequivocal value of this technology in predicting risk and serving as a cost-defective gatekeeper.1,2

The nuclear cardiology of the future will build on these extraordinary experiences but also will clearly take the field in different directions (Table 1). This future will include better perfusion tracers that more effectively track flow at high flow rates.3 These should also maintain the favorable imaging qualities provided currently by technetium 99m labeling. There will be improved imaging technology. This will involve macrotechnologies as well as microtechnologies.4 There also will be emphasis on fusion imaging technologies, linking nuclear imaging to other modalities such as computed tomography (CT) scanning, thereby providing relevant anatomic co-registration for new physiologic image data.5 There will be increasing emphasis on positron emission tomography (PET), with respect to coronary flow reserve measurements, viability, perfusion imaging, and new tracers.6 Most importantly, there will be a large number of new biologic and clinical targets. Imaging these new targets will provide the means for answering key questions that will drive the clinical cardiology of the next era. The field will be driven by modern concepts of molecular and cell biology and molecular genetics rather than solely by...
the classic physiologic principles heretofore used. As such, cardiovascular imaging will remain a relevant part of and contributor to the new “molecular medicine” of this century. It is the early development of this new discipline of nuclear cardiology—molecular nuclear cardiology—that will form the basis of this presentation.

**Clinical Targets**

There are a variety of relevant clinical targets that currently are being evaluated and will form the basis of future studies (Table 2). One such target involves direct evaluation of the blood vessel wall. Of particular interest is definition of unstable or “vulnerable” plaque. Other relevant targets include definition of angiogenesis; characterization of the myocyte with respect to necrosis, apoptosis, ischemia, and viability; and assessment of overall neuronal integrity. There also will be major efforts in the area of imaging gene expression, initially exogenous and, in the future, endogenous gene expression. Finally, the newly developing field of “reparative medicine,” based on delivery of pluripotential stem cells to areas of tissue injury such as myocardial infarction, provides unique imaging opportunities for molecular nuclear cardiology. Many of these specific approaches will be discussed in this lecture.

**Development of Atherosclerosis and Concept of Vulnerability**

At the onset, it is worth thinking in the simplest of terms about the development of atherosclerosis (Figure 1). At least a simplified understanding makes apparent the need for development of numerous new imaging targets to address the development and consequences of this process. The atherosclerotic process involves adhesion of monocytes to the endothelial layer of the vasculature, stimulated by release of adhesion molecules and other cytokines from endothelial cells. There is also the direct absorption of circulating low-density lipoprotein (LDL). The monocytes migrate into the intimal area, where they metabolize the circulating LDL in modified form, creating foam cells. Release of growth factors leads to phenotypic transformation of smooth muscle cells and their subsequent proliferation. Monocytes also release catalytic enzymes such as metalloproteinases, which are capable of digesting matrix.

Plaque vulnerability has been further defined anatomically and biochemically by the presence of substantial monocyte inflammation, development of a thin fibrous cap, presence of a large lipid core with substantial oxidized LDL, presence of red blood cells and platelets in the lesion, apoptosis of macrophages, release of matrix metalloproteinases, and endothelial and smooth muscle cell transformation (Figure 2).

These anatomic and biochemical events thus provide an appropriate framework in which to develop new approaches to imaging the vascular wall. The distinct advantage of nuclear techniques, as opposed to other imaging technologies, involves the definition of relevant biochemical events, directly demonstrated by the uptake of specifically constructed biologically driven novel radioligands. From a biochemical standpoint, the field is limited only by its own imagination.

**Targeting Proliferating Smooth Muscle Cells**

The first substantive approach to imaging the vascular wall involved the development of an antibody against a specific, though poorly defined, epitope expressed on the surface of proliferating smooth muscle cells by Narula et al. This antibody, which was called Z2D3, was labeled with indium 111. In 1995 the authors demonstrated substantial pathologic uptake of this antibody in an atherosclerotic rabbit aorta model. The uptake sites corresponded to areas of high-grade atherosclerosis in the rabbit aorta and also correlated extremely well with autoradiographic imaging of the extirpated aorta.