《招請講演》

Why New Cardiac Imaging Agents?

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The first two decades of cardiovascular nuclear medicine has witnessed the experimental and clinical validation of thallium-201 myocardial perfusion imaging and technetium-99m radionuclide angiography. Despite changing patient referral patterns and laboratory utilization profiles, these radionuclide studies have persistently demonstrated high sensitivity for disease detection and significant positive predictive accuracy for adverse cardiac events, particularly in the setting of ischemic heart disease. Industry-investigator collaborations have yielded quantitative image analytic techniques which demonstrate excellent transportability between medical centers and high interstudy reproducibility.

In this setting, newly developed cardiovascular radiopharmaceuticals must offer improved dosimetry, image resolution (temporal or spatial), or provide diagnostic information on a previously-unmeasurable, but relevant biological parameter. As with medicinal pharmaceutical agents, diagnostic radiopharmaceutical research and development is proceeding at a rapid pace. An expanded range of radiopharmaceuticals has been developed for the evaluation of myocardial perfusion, ventricular function, myocardial viability, and cardiovascular substrate metabolism. Single photon and positron nuclear medicine camera computer systems have been reconfigured to accommodate the physical characteristics and biological behavior of these new radioisotopes. As with thallium-201 imaging, standardized image acquisition protocols, radiopharmacy dose preparation and quality control, dissemination of validated quantitative software and standardized normal files are essential if new radiopharmaceuticals are to have a significant diagnostic impact in clinical medicine.

The goal of this review will be to evaluate the evolution of cardiovascular nuclear medicine in several specific areas which demonstrate considerable promise for probable integration into the daily practice of cardiovascular nuclear medicine within the next decade. These areas are:

1. Myocardial *perfusion* imaging (Tc-99 sestamibi, copper-62 PTSM, etc.);
2. Myocardial *viability* (dual isotope imaging: thallium-sestamibi; thallium-antimyosin, iodine-123 fatty acids, carbon-11 acetate, etc.);
3. Myocardial *neuro-adrenergic* state (fluorine-18 ACE inhibitor, carbon-11 metahydroxy ephedrine, iodine-123 meta iodobenzyl guanidine, fluorine-18 fluorodopamine, etc.);
4. De novo *metabolic* pathways (i.e. carbon-11 acetate, iodine-123 methyl IPPA, fluorine-18 fluoromisonidazole, etc.).

The refinement of several radiochemistry techniques has been critical to the initial success enjoyed by the above radiopharmaceuticals. For example, advances in technetium-99m radiochemistry have permitted the labeling of a wide variety of compounds not previously accessible for imaging. The development of monoclonal antibodies with high specificity for epitopes on the surface of cells, platelets and thrombotic proteins has permitted *in vivo* studies of plaque instability which were previously relegated to indium-111 labeling of autologous platelets. Hybridoma and recombinant DNA technology has permitted the cloning and genetic manipulation of cell lines suitable for the production of large quantities of highly purified monoclonal antibody. "Kit" labeling techniques are also more available.

Advances in single photon emission tomography equipment now permit dual acquisition of the myocardial distribution of perfusion and infarction. In addition, continuous SPECT imaging allows for acquisition of tomographic data from agents that are rapidly cleared by the myocardium. Having established the poor relationship between a "fixed" 4-hour thallium-201 defect and viability,

a range of SPECT and PET radiopharmaceuticals have been tested to improve the visualization of severely ischemic, but viable myocardium (i.e. stunned or hibernating) with the potential for mechanical recovery following revascularization. Reinjection of thallium, and/or late (18–24 hour) thallium imaging are adequate for the detection of viability in most clinical settings. The relationship of technetium-99m myocardial perfusion agents to viability is under investigation. PET imaging of FDG-ammonia "mismatch", supplemented in some cases by carbon-11 acetate, are increasingly applied for the detection of myocardial viability.

The advent of these new cardiovascular diagnostic radiopharmaceuticals has significantly improved the range of diseased states which can be studied by nuclear medicine physicians and their clinical colleagues. This array of new imaging agents and techniques has been developed in direct response to a clinical need and improved understanding of the *in vivo* metabolism of the myocardium and vascular tissues. New radiopharmaceuticals must fulfill at least one of the following prerequisites: improved dosimetry, ease of dose preparation, improved dose availability, improved image resolution, unique radiotracer kinetics, enhanced clinical patient throughput, and/or measurement of a previously unmeasurable physiologic parameter. Tc-99m sestamibi imaging meets each of these criteria.

Considerable effort is being directed towards the detection of disease in the "pre-clinical" state, prior to the obvious clinical manifestation of symptoms or pathology. Improved specificity of radiotracers and sensitivity of detection systems should permit continued advances in cardiovascular nuclear medicine in the ensuing decade. Thallium-201 myocardial perfusion imaging remains the mainstay of cardiovascular nuclear medicine, and has shown tremendous resilience and adaptability to the diagnostic demands of clinical cardiologists. The role of new cardiovascular nuclear medicine studies for the assessment of myocardial perfusion, cardiac metabolism, neuro-adrenergic activation, and vascular disease (i.e. hypertensive, atherosclerotic) is being evaluated.

In response to the question, "Why new cardiac imaging agents?", one can point to the dramatic evolution of molecular and cellular biology, which has directly lead to advances in therapeutic pharmaceutical agents. Also, the ability to aggressively treat a broad spectrum of cardiovascular disease has created a demand for nuclear medicine technology to keep up with these significant clinical and pharmaceutical advances. Tc-99m sestamibi and other novel radiopharmaceuticals reviewed have been developed as a direct response to this clinical impetus.

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