New Developments in Nuclear Cardiac Imaging

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This article will attempt to cover the areas of historic background, current status, newer applications of existing tracers, attenuation correction, metabolic imaging, sympathetic imaging, new stress agents, molecular imaging, and positron emission tomography (PET) without on-site cyclotron. By no means is it meant to be inclusive of all that is currently happening but rather to illustrate some points of what can be seen as potential and what is needed.

Background

The introduction of the gamma camera in 1965 paved the way in 1973 for the use of Potassium-43 (K-43) for myocardial perfusion imaging, a tracer of only historic interest at present. At almost the same time, thallium-201 came aboard and was the only tracer available for ~15 years because it was not until 1990 that the US Food and Drug Administration (FDA) approved the first technetium-based perfusion tracer. In 1999, gated single positron emission computed tomography (SPECT) imaging was described and soon gained wide acceptance. The FDA approved Adenoscan as a stress agent in 1995. Adenosine, Tc-99m Sestamibi and Tc-99m Tetrofosmin heralded the era of clinical phase 3 trials in nuclear cardiology and in the process paved the way for rapid growth in this field. These applications were the subject of two prior presentations in US cardiology by Hendel and by Noble and Heller. Alongside the technological advance, the American Society of Nuclear Cardiology (ASNC) was created in 1993 (its official journal was first published in 1994) and the Certification Board of Nuclear Cardiology (CBNC) was established in 1996. There are a large number of educational programs sponsored by the American Heart Association (AHA), American College of Cardiology (ACC), ASNC, and working groups at regional and state levels. The annual program of the ASNC now provides the venue for original research presentations and breaking news from large trials. Despite the emergence of other imaging modalities (echocardiography (ECG), magnetic resonance imaging (MRI) and CT) nuclear cardiology continues to grow and is by far the most widely used method in ischemia work-up. The growth has been in office-based and out-patient facilities, where turf issues are avoided to a large extent. Imaging accounts for almost US$100 billion in health expenditure annually and there is no end in sight in terms of containment. The political ramifications and power struggles are beyond the scope of this presentation although the ACC is hard at work to produce documents that deal with appropriateness and quality, including the uniform requirements for certification and laboratory accreditation.

Current Status

Gated SPECT imaging provides information on myocardial perfusion and function—perfusion pattern (normal, ischemia, and scar), left ventricular (LV) ejection fraction (EF), LV wall motion and wall thickening, LV size at end-diastole and end-systole, LV muscle mass, transient ischemic dilation, right ventricular (RV) size and function, and more. Both the LV perfusion pattern and EF have independent and incremental prognostic power as previously discussed and summarized in Figure 1 and 2.

Newer Applications of Existing Methods

Recent work suggests that it may be feasible to use gated SPECT imaging to assess LV asynchrony by extracting...
Cardiolite® is not specifically indicated for patients with diabetes. In 3 pivotal trials enrolling 1596 patients and including 311 patients with diabetes, Cardiolite® was shown to be an effective prognostic tool in the evaluation of patients with known or suspected coronary artery disease.

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A nuclear stress test with Cardiolite® may:
- Detect ischemia, including atypical presentation2,3
- Provide information that may assist you in making confident patient management decisions4

Indications and Usage: Cardiolite®, Kit for the Preparation of Technetium Tc99m Sestamibi for Injection, is a myocardial perfusion agent that is indicated for detecting coronary artery disease by localizing myocardial ischemia (reversible defects) and infarction (non-reversible defects), in evaluating myocardial function and developing information for use in patient management decisions. Cardiolite® evaluation of myocardial ischemia can be accomplished with rest and cardiovascular stress techniques (eg, exercise or pharmacologic stress in accordance with the pharmacologic stress agent’s labeling).

It is usually not possible to determine the age of a myocardial infarction or to differentiate a recent myocardial infarction from ischemia.

Important Safety Information: Exercise and pharmacologic stress testing should be performed only under the supervision of a qualified physician. Cardiolite® has been rarely associated with acute severe allergic events of angioedema and urticaria. The most frequently reported adverse events include headache, chest pain/angina, ST segment changes on ECG, nausea, and abnormal taste and smell.

Please see references and brief summary of Full Prescribing Information on the following page.

Visit our website at www.cardiolite.com

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Cardiolite

Cardiolite is a myocardial imaging agent for the detection of myocardial ischemia.

INDICATIONS AND USAGE: Myocardial Imaging. Cardiolite is a myocardial imaging agent for the detection of myocardial ischemia. It is contraindicated in patients with a known history of allergy to any of its components.

Usage Considerations: For Cardiovascular Radiopharmaceuticals. Cardiolite is a radiopharmaceutical product for myocardial imaging. It is intended for use in patients with a known or suspected cardiac disease.

PRECAUTIONS:

GENERAL

The contents of the vial are intended only for use in the preparation of Technetium Tc99m Sestamibi and are not to be administered directly to the patient without first undergoing the preparative procedure.

Lack of specific mention herein does not necessarily imply that the radiation absorbed does not exceed the published organ or tissue limits in the ICRP Publication 103. Kerning of these data is recommended.

Table 9. Selected Adverse Events Reported in > 0.5% of Patients Who Received Technetium Tc99m Sestamibi in Either Breast or Cardiac Clinical Studies*

<table>
<thead>
<tr>
<th>Event</th>
<th>Breast Imaging</th>
<th>Cardiac Imaging</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>13%</td>
<td>12%</td>
<td>0.86</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>7%</td>
<td>4%</td>
<td>0.05</td>
</tr>
<tr>
<td>Chest Pain</td>
<td>1%</td>
<td>0%</td>
<td>0.34</td>
</tr>
<tr>
<td>Anorexia</td>
<td>6%</td>
<td>7%</td>
<td>0.8</td>
</tr>
<tr>
<td>Headache</td>
<td>1%</td>
<td>0%</td>
<td>0.29</td>
</tr>
<tr>
<td>Urinary frequency</td>
<td>6%</td>
<td>6%</td>
<td>0.84</td>
</tr>
<tr>
<td>Sinus Bradycardia</td>
<td>4%</td>
<td>4%</td>
<td>0.84</td>
</tr>
<tr>
<td>Sinus Tachycardia</td>
<td>4%</td>
<td>4%</td>
<td>0.84</td>
</tr>
<tr>
<td>Voice changes</td>
<td>4%</td>
<td>4%</td>
<td>0.84</td>
</tr>
<tr>
<td>Parosmia</td>
<td>3%</td>
<td>3%</td>
<td>0.84</td>
</tr>
<tr>
<td>Taste Perversion</td>
<td>2%</td>
<td>3%</td>
<td>0.84</td>
</tr>
</tbody>
</table>

Adverse Reactions: Adverse reactions seen in breast imaging studies are generally similar to those seen in cardiac imaging studies. The following are selected adverse reactions observed in patients who received Cardiolite in clinical trials:

<table>
<thead>
<tr>
<th>Event</th>
<th>Breast Imaging</th>
<th>Cardiac Imaging</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infraclavicular edema</td>
<td>2%</td>
<td>2%</td>
<td>0.34</td>
</tr>
<tr>
<td>Pruritus</td>
<td>2%</td>
<td>3%</td>
<td>0.84</td>
</tr>
<tr>
<td>Rash</td>
<td>2%</td>
<td>3%</td>
<td>0.84</td>
</tr>
</tbody>
</table>

In the clinical studies for breast imaging, breast pain was reported in 21 (17%) of the patients. In 11 of these patients the pain appears to be associated with myoaspinus.

The following adverse reactions have been reported in a 0.5% of patients and symptoms consistent with allergy occurring shortly after administration of the agent: urticaria, angioedema, bronchospasm, rhinitis, dizziness, syncope, abdominal pain, vomiting, and severe hypersensitivity characterized by hypotension, hypoxemia, anaphylaxis, angioedema, and generalized urticaria. There were no second cases of injection of Technetium Tc99m Sestamibi. A few cases of flushing, wheezing, injection site irritation, dry mouth, fever, pruritus, rash, urticaria and fatigue have also been attributed to administration of the agent.

Dosage and Administration: For Myocardial Imaging. The suggested dose range for IV administration of Cardiolite in a single dose to be employed in the average patient (78 Kg) is 570-1110 MBq (15.6-30 mCi) Technetium Tc99m Sestamibi. The recommended dose range for IV administration of MIRALUMA is 1 single dose of 740-1110 MBq (20-30 mCi).

Use in Pregnancy: Cardiolite contains Technetium Tc99m Sestamibi and is not to be administered directly to the patient without first undergoing the preparative procedure.

Cardiolite is contraindicated in patients with a known history of allergy to any of its components.

Warnings: In patients with in whom cardiac disease is known or suspected, care should be taken to assure continuous monitoring and treatment in accordance with safe, accepted clinical procedure.

In the clinical studies, cardiovascular disease was demonstrated by localizing myocardial ischemia (reversible defects) and myocardial infarction (non-reversible defects), in evaluating myocardial function and in detecting infarction in patients having management decisions. Cardiolite evaluation of myocardial ischemia can be accomplished with rest and pharmacologic stress techniques (e.g., exercise or pharmacologic stress in accordance with the physiologic stress agent's labeling).

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amplitude and phase changes in the regional LV counts throughout the cardiac cycle. Normal values in men and women have been derived and dynamic displays of the activation sequence with automated programs that measure the degree of asynchrony are being tested. If validated, this method will be of considerable help in heart failure (HF) patients being considered for resynchronization therapy. Many in the field believe there must be better criteria than the presence of left bundle-branch block (LBBB) on surface ECG.

Another example arises in outcome studies. Although a large body of evidence shows that SPECT imaging effectively stratifies patients into different risk group, this in itself is not sufficient. Firstly, the data are mostly from single center studies or registries and the analysis is retrospective—there is surely a need for prospective large-scale trials. Secondly, if the notion that a high risk-group has an event rate of more than 3% per year (based on ACC/AHA guidelines) is accepted, most patients will still not have events, no matter what the odd ratio is between those with abnormal versus normal images. Thirdly, it is not know whether a given high risk is modifiable and, if so, whether all interventions are created equally. To put this last point in perspective, two examples from contemporary medicine can be examined. The first is the saga of ventricular premature beats (VPC) after acute MI—the means to detect and suppress these VPC were available, yet the Cardiac Arrhythmia Suppression Trial (CAST) study showed that this therapy is detrimental to such patients, a practice that has since been abandoned. The second example is depression after acute MI. The means to diagnose and treat depression are available, but will such a therapy alter the outcome of these patients? It is simply not known. With regard to SPECT imaging and CAD patients, it is known that abnormal SPECT identifies a high-risk group, but it is not known whether therapy changes the outcome. Is the change in outcome parallel to the change in SPECT results qualitatively and quantitatively, and is one type of therapy superior to another type (medical, percutaneous coronary intervention (PCI), coronary artery bypass grafting, (CABG))? It is not known for sure, but retrospective data suggest that high-risk patients progress more with coronary revascularization than medical therapy in stable patients. After acute MI, it seems that abolition of ischemia rather than mode of therapy is the important determinant of outcome. Most of these data do not reflect current advances in either medical or revascularization therapy. The Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial, which completed patient recruitment and the BAR12D trial, which also completed recruitment may provide valuable data. The COURAGE trial has a sub-study with a small number of patients while the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) has the nuclear sub-study in all patients.

### Hardware and Software

There are currently two methods for attenuation correction: one is based on simultaneous emission-transmission images using line sources; and the other on a hybrid technology of SPCT-CT. Neither method has so far made it to routine clinical use, undoubtedly because both methods continue to have imperfections, though each has made considerable advances. It is believed that radioactivity emanating from the myocardium is subject to scatter, absorption, and in addition regional difference...
might be due to depth resolution rather than biological differences. By correction for all three variables, there is clearly a more uniform tracer distribution and gender differences between activity in the anterior, and inferior walls are no longer present. This makes it feasible to use a gender-neutral database for quantitative analysis. It should be noted that the apex appears more photopenic on attenuation-corrected images, which is most likely due to normal myocardial thinning in this region (see Figure 3).

The count recovery increases in proportion to body mass index (BMI) (see Figure 4). There is also evidence to suggest that using attenuation correction decreases the need for rest imaging and increases the reader’s confidence in interpretation.

A special gamma camera (color decision list (CDL)), designed for motion-corrected first-pass radionuclide angiography (RNA) during treadmill upright exercise, is currently being used. The premise is that the gated SPECT images provide resting LVEF, while the CDL provides peak exercise EF. The combination of rest and peak exercise EF could improve diagnostic accuracy. There are no reliable data at present to substantiate this claim. The addition of another stress is most certainly going to add to the cost of imaging at a time when costs are closely monitored. Another type of gamma camera known as Multiwire camera (Proportional Technologists, Inc.) is based on an entirely different concept and utilizes a short-lived, generator produced tracer (Tantalum 78) with a t1/2 of ~10 minutes. This camera is fitted with online motion correction algorithm that allows performance of high-quality first-pass RNA studies during upright exercise. Furthermore, propriety software has been developed that allows the integration of pressure data and radioactivity data, in order to generate the pressure volume loops. This was tested in the catheterization laboratory with the pressure signal coming from a catheter positioned in the RV.
data are obtained from time activity curve obtained during a first-pass RNA study.

Other Tracers

It is ironic that nuclear imaging has revolved around one set of tracers, collectively known as perfusion tracers (thallium-201, Tc-99m Sestamibi and Tc-99m tetrofosmin). At one time or another infarct-avid imaging tracers and acute inflammatory avid tracers were available (Tc-99m pyrophosphate and In-111 antimyosin) but have either been withdrawn from US market (antimyosin) or almost never used (pyrophosphate). There is still a clear need for both of these indications.

On a brighter note, two other tracers, I-123 beta-methyliodophenyl pentadecanoic acid (BMIPP) and I-123 metaiodobenzyl guanidine (MIBG) are now in clinical trials. Each can be characterized as being a non-perfusion tracer. It is known that the myocardium utilizes several substrates to generate energy—glucose, fatty acids, lactic acid, pyruvate, and amino acids. Under normal conditions, fatty acids are used preferentially while under conditions of hypoxemia, ischemia, and after a large meal, glucose is the preferred substrate. BMIPP is a long-chained straight fatty acid that, because of its methyl group, does not undergo beta-oxidation in the mitochondria, but remains sequestered in the cytoplasm. This makes it suitable for imaging. It seems that during and following an episode of ischemia, changes in myocardial metabolism persist for hours (some believe as long as 24 hours) during which time fatty acid metabolism is suppressed and the ischemic region is depicted as a perfusion abnormality, even though the images are obtained at rest and even though there is no longer active on-going ischemia. This ‘memory’ function makes it feasible to detect ischemia long after the episode has subsided. In fact, the phase 2 trials recently completed addressed this issue in patients presenting to the emergency department (ED) because of chest pain and Philips nuclear scintigraphy revealed evidence of acute MI. The phase 3 trial is scheduled for late 2005 or early 2006. The story of BMIPP does not end here because I-123 seems to be just the first-generation of fatty acid analogs. Second- and third-generation analogs will use technetium-based compounds, which are more attractive than iodine-based compounds. I-123 MIBG is an adrenergic presynaptic analog whose uptake at the nerve terminal is very much like norepinephrine.

Adrenergic receptors are abundant in the myocardium; cholinergic receptors are mainly in the atrium while adrenergic receptors are mainly in the ventricles. There is a base to apex gradient. The α1 and α2 receptors constitute ~15% of total receptors (post-synaptic and pre-synaptic as well) while the β1 and β2~ constitute the remaining 85% and are mostly post-synaptic. There are more β1 than β2 receptors (β1:β2=5:1).

A study of sympathetic innervation is important in a number of diseases such as heart transplantation, HF, diabetes, ischemia and infarction, and sudden death. Sympathetic fibers run along the epicardial surface from base to apex and penetrate the myocardium to reach the endocardial surface. There are α1, α2, β1, and β2 receptors. The α1 and β1 are mostly in large vessels while the other two are mostly in microvasculature. Stimulation of α1 in normal subjects produce no vasoconstriction of conduit vessels and no decrease in coronary blood flow (CBF) probably due to low receptor density and counterbalance by nitric oxide. Stimulation of α2 on the other hand decreases CBF due to micro-vascular vasoconstriction.

There is clear indication that sympathetic surges could produce dramatic changes in myocardial blood flow and ventricular function.

in distal and mid regions), markedly elevated catecholamines blood levels and in those who had biopsy mononuclear infiltrates, and/or contraction band necrosis. This entity has become known as transient LV apical ballooning. The precise mechanism and the reason for sex preponderance in women still remains to be explored, although epicardial vasospasm, microvascular vasospasm or direct myocardial injuries are possibilities. This entity will be another example where MIBG imaging might be useful. Experience in Japan and Europe has clearly shown that MIBG imaging provides independent and incremental prognostic information in HF patients, and the on-going phase 3 trial in the US is addressing the role of MIBG imaging in HF patients.

**Stress Agents**

One of the areas of most rapid growth in nuclear imaging has been in the use of pharmacological stress testing because of the realization that exercise, though ordinarily the preferred mode of stress, may provide misleading results if inadequate. With the increase in the age of patients and the fact that many are on multiple medications that limit the achievement of adequate heart rate response, more of these patients undergo pharmacological stress testing. The available agents are adenosine, dipyridamole, and dobutamine. The latter is the least used in nuclear imaging, unlike stress ECG. Adenosine produces maximum coronary hyperemia by stimulating $\alpha_2$ receptors. Adenosine also stimulates a number of other receptors, which may account for some of the untoward side effects such as chest pain, atrial ventricular (AV) block, and bronchospasm. There are currently a number of selective $\alpha_2$ agonists in phase 3 trials for use in stress testing (see Table 1). These agents differ from each other in potency, selectivity, and affinity. Each could be given as an infusion but also as a bolus, which could simplify and shorten the duration of stress testing. The phase 3 trials with the continuously variable transmission (CVT) product (Regadenoson) is close to completion and early results are to be presented at the 2005 meeting of the ASNC in Seattle, WA.

**Molecular Imaging**

There are many targets of interest for imaging such as angiogenesis, apoptosis, atherosclerosis, and vulnerable plaques. Such imaging has been enhanced by advances in instrumentation such as micro SPECT/CT and micro PET/CT systems. These systems allow imaging of mouse hearts with a resolution of 1–2mm. Thus, in addition to assessment of functional consequences of arteriogenesis therapy (such as improvement in perfusion and functional status), gene products, growth factors, and signaling proteins are therefore possible. This topic has been reviewed elsewhere.

**PET Imaging**

There are sites with on-site cyclotron and sites that use generator-produced Rb-81 or F-18 fluorodeoxyglucose (FDG) that has a long enough half-life to allow shipments from other sites or other states. The uses are summarized in Tables 2–6.