

Nuclear Imaging

Imaging the Heart: The Role of Nuclear Imaging of Cardiac Perfusion & Function as an Endpoint in Clinical Trials

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Introduction

There is increasing interest in the role of cardiac imaging in clinical trials of new pharmacological agents. One possibility may be to use cardiac imaging results to select appropriate patients for a study of a new cardiovascular therapy. The imaging data may serve as a “surrogate” efficacy end-point to allow early decision-making, in the absence of clinical outcomes data (cardiac mortality or morbidity), or as a primary efficacy end-point in studies of potential cardiovascular therapies. In addition, there is a current focus on the role of cardiac imaging in assessing the cardiac safety of non-cardiac drugs, such as treatment of arthritis and diabetes.

Many different types of cardiac imaging modalities are available in clinical practice and use technologies such as ultrasound (echocardiography), radiopharmaceuticals (nuclear cardiology), X-rays (computed tomography and angiography), and magnetic fields (magnetic resonance imaging). New and novel modalities often hold great potential and attract much attention, but prove to be difficult to implement and use effectively in the clinical trial setting.

What is Cardiac SPECT?

Cardiac SPECT imaging is a nuclear medicine procedure that involves the intravenous injection of a radiopharmaceutical product that is taken up in the cardiac muscle tissue or myocardium. The product emits small amounts of radioactivity in the form of gamma rays

which are “collected” by a gamma camera positioned over the patient’s chest. This energy collected by the gamma camera is converted into an electrical signal and displayed as a digital image of the heart. The camera is rotated around the long axis of the patient, and images are collected from a number of different positions. These digital images are combined into a three-dimensional

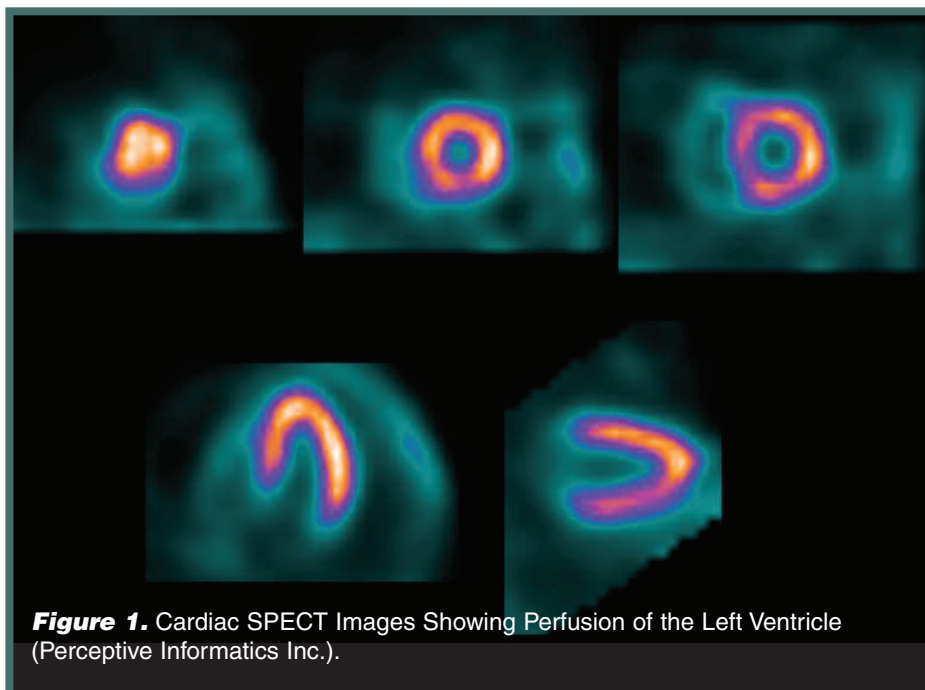


Figure 1. Cardiac SPECT Images Showing Perfusion of the Left Ventricle (Perceptive Informatics Inc.).

picture of the heart muscle and typically displayed as a series of “slices” or tomograms, of the myocardium (Figure 1).

The radiopharmaceutical is taken up by the myocardium in proportion to the amount of blood flow to a given area of the heart. If blood flow is absent or reduced as a result of an obstruction (eg, after a heart attack) or a narrowing (eg, due to atherosclerosis), the energy collected by the gamma camera over that area is consequently absent or reduced, relative to the normal areas of the heart. The area of absent or reduced blood flow is seen on the images as a “defect” or “cold spot.” Thus, these images represent a clear picture of the blood flow through the coronary arteries to the myocardium and provide an accurate, non-invasive assessment of myocardial perfusion.

The timing of the collection of the images is now typically linked (gated) to the cardiac cycle (the contraction and relaxation of the heart) using the patient’s electrocardiogram (ECG). This gating allows a relatively easy assessment of the contraction or function of the myocardium, specifically the left and right ventricles.

In addition to the qualitative interpretation of the gated SPECT images to assess myocardial perfusion and function, several software programs are available that allow accurate and reproducible quantification of perfusion and function. As well as improving the diagnostic utility of cardiac SPECT, this ability to reliably quantify perfusion and function has facilitated the use of cardiac SPECT in the serial assessment of the natural history a patient’s coronary artery disease or their response to therapy.

Finally, cardiac-gated SPECT is often used in conjunction with stress testing. Patients with angina pectoris will typically experience chest pain provoked by exertion and relieved by rest. This is usually due a narrowing (or stenosis) in a coronary artery such that blood flow to that area of the myocardium at rest is adequate. However, during exertion, the metabolic demands of the myocardium increase, but the required increase in blood flow to meet these demands is limited by the coronary stenosis. In this situation, a resting gated SPECT

examination may be completely normal. If the patient is then stressed, typically by exercising or pharmacological stress agent (in those unable to exercise adequately), and gated SPECT images obtained at peak stress, there may be evidence of impaired myocardial perfusion (ischemia) and/or function.

Clinical Uses of Cardiac SPECT

Gated cardiac SPECT has now been extensively validated for its ability to provide objective information regarding rest and stress myocardial perfusion and function. It is widely available in mainstream clinical practice and is predominately used to evaluate patients with known or suspected coronary artery disease.¹ Comprehensive guidelines on the clinical use of cardiac SPECT imaging have been developed by the American College of Cardiology (ACC), American Heart Association (AHA), and the American Society of Nuclear Cardiology (ASNC).²

These clinical uses include the following:

- Assessing possible acute coronary syndrome: patients with chest pain in the emergency department;
- Detecting or diagnosing chronic coronary artery disease (CAD): patients with chest pain on exertion;
- Managing patients with known chronic coronary artery disease, including the assessment of disease severity, risk stratification, and prognosis; and
- Detecting coronary artery disease in patients with heart failure, together with the assessment of myocardial viability in patient with CAD and left ventricular (LV) dysfunction.

As defined in the ACC/AHA guidelines for the management of patients with chronic stable angina, stress SPECT has a clear role to play in both the diagnosis and risk stratification of patients with this condition.³

In addition, the recently published ACC Foundation/ASNC Appropriateness Criteria for SPECT Myocardial Perfusion Imaging provide clear guidance on the appropriate clinical use of SPECT imaging, with 27 of 52 possible indications rated as appropriate (ie, SPECT is a generally acceptable and reasonable approach for the indication).⁴

Advantages of SPECT Imaging

As mentioned previously, SPECT myocardial imaging has been extensively studied and validated as diagnostic and prognostic imaging tool in a variety of clinical settings. Protocols for the collection, evaluation, and reporting of SPECT imaging data are well defined, with clear published recommendations.⁵ Substantial advances in computing technology throughout the past decade have facilitated the development and clinical acceptance of software algorithms for the quantitative assessment of myocardial perfusion, significantly improving the reliability and reproducibility of the technology.

The ability to acquire reliable information regarding both myocardial perfusion and function in one examination by using gated SPECT allows for the efficient use of equipment and both staff and patient’s time. In addition, the increasing availability of SPECT imaging in doctor’s offices or free-standing imaging centers has facilitated its accessibility to a broad patient population.

The primary competitive imaging modality is echocardiography, which uses ultrasound (sound waves) to create a real-time, two-dimensional picture of the function of the heart. Although like SPECT, echocardiography can be used at both rest and during stress testing, it only provides an indirect assessment of myocardial perfusion. Echocardiography provides a picture of myocardial contraction, including overall and regional ventricular function. Evidence of a regional wall motion abnormality (reduced or absent contraction of a segment of myocardium) infers reduced or absent blood flow to that area due typically to CAD. Echo is also a very subjective technique,

with the quality of the images obtained dependent on both the skill of the operator and the suitability of the patient. It is estimated that approximately 10% to 20% of patients cannot be imaged adequately with echocardiography.⁶ In contrast, SPECT is a more objective, direct assessment of myocardial perfusion and function and is applicable to a broad patient population.

In general, stress SPECT and stress echocardiography are comparable in their ability to detect CAD (with the use of invasive coronary X-ray angiography as the gold standard for the presence of CAD). The sensitivity (the ability of a positive test to correctly identify CAD) for both tests ranges from 85% to 95% and the specificity (the ability of a negative test to correctly exclude CAD) ranges from 75% to 85%.³ There are more data available on the prognostic utility of SPECT as compared to echo with a normal stress SPECT study conferring a <1% likelihood of a cardiac event over the next year, even in the presence of known CAD.⁷

Limitations of Cardiac SPECT

By its very nature, SPECT involves the injection of a small dose of radiation, although the dose is low when compared to radiation exposure during, for example, computed tomography (a series of X-ray slices of the portion of the body being imaged). The use of the radiopharmaceutical requires appropriate training and licensure to handle radioisotopes.

When compared to echocardiography, SPECT cameras are relatively expensive and, in general, not portable, making examinations of very ill patients impractical. In contrast, echocardiography machines are cheap, widely available, and easily used at the patient's bedside. In addition, the availability of intravenous microbubble contrast agents for use with echocardiography has expanded its use into the patient population with inadequate images. New technologies such as three-dimensional echocardiography and the use of the microbubble contrast agents to directly assess myocardial perfusion offer promise for additional expansion of the use of echocardiography.

Clinical Trial Applications

There are relatively few examples of the use of cardiac SPECT in clinical trials assessing the efficacy of new or existing therapeutic interventions in patients with CAD. However, a number of significant studies have been published in recent years in patients with both chronic CAD and acute coronary syndromes.

One recent example was the use of gated cardiac SPECT in a subset of patients in the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial.⁸ This landmark sub-study compared the effectiveness of percutaneous coronary intervention (PCI - invasive dilatation of a narrowed coronary artery using a balloon catheter inserted through the major artery in the groin) for improving myocardial ischemia when added to optimal medical therapy (OMT). Gated SPECT was used as the technique to assess the changes in myocardial ischemia over time. The sub-study concluded that adding PCI to OMT resulted in a greater reduction in ischemia when compared to OMT alone. The greatest benefit was seen in patients with more severe baseline ischemia. This sub-study proved to be a clear example of the use of SPECT in providing essential clinical data to facilitate effective and objective assessment of the effects of alternative therapeutic strategies in the management of patients with chronic CAD.

Another recently published study assessed the role of gated SPECT in the risk stratification and determination of initial management of high-risk, but stable, survivors of an acute heart attack.⁹ This study demonstrated that gated stress SPECT performed early after the attack accurately identified a sizeable, low-risk group who has a < 2% risk of cardiac death or another heart attack after 12 months. Thus, gated SPECT has the potential to identify low-risk patients who after a heart attack could be suitable for early discharge from the hospital, with a consequent saving of healthcare resources. This same study also demonstrated that sequential gated stress SPECT can effectively monitor changes in myocardial ischemia after medical or surgical treatment.¹⁰

Finally, gated SPECT has also been

shown to be a potentially useful tool in evaluating patients who come to the emergency room with chest pain.¹¹ In this study, the use of gated SPECT reduced the frequency of unnecessary hospitalization in patients without evidence of myocardial ischemia.

The development of new imaging modalities is often quickly followed by pharmaceutical companies wishing to use the new modality to demonstrate the improved safety or efficacy of a new compound, expand the use of an existing compound, or decrease the astronomical costs associated with clinical trials and the drug development process. However, this can be a double-edged sword. Although new modalities may offer innovation over older methods, new modalities are usually not typically accepted by regulatory agencies without adequate demonstration of their reliability and reproducibility.

In discussions with Dr. George Mills, who until recently served as Division Director, Medical Imaging and Hematology Products in the Office of Oncology Drug Products, part of the FDA Center for Drug Evaluation and Research, no pharmaceutical product used to treat a disease has ever achieved approval based on cardiac SPECT imaging. He conceded, however, that several radiopharmaceuticals have been approved for the diagnosis of cardiac disease, not for therapy. While cardiac SPECT clearly has a very important place in the diagnosis and management of patients with known or suspected CAD, it has not yet been validated to the extent that it is acceptable to the FDA as a tool to prove the efficacy of a potential therapeutic product.

Although discouraging on the surface, Dr. Mills explained that SPECT imaging can play a valuable role in the early clinical evaluation of a potential therapeutic agent. For example, during early clinical trials (Phase II) in patients with CAD, gated SPECT can be used to provide objective evidence of a possible response to the new treatment and corroborate an improvement in the patient's clinical condition. This can allow effective decision-making regarding moving the clinical program into the large, expensive Phase III studies used to support a New Drug Application, and also influence the design of

those studies. Factors such as detailed imaging protocols, intensive site training, good quality control of image acquisition, and appropriately documented and conducted “blinded” reading of the images (where the readers of the images are not aware of any of the clinical or other details regarding the patients), are critical in the conduct of such studies.

As noted by Dr. Mills, detailed discussions and appropriate buy-in from the FDA is critical at each stage of the process. A sponsor that simply arrives with a completed Phase III study using only SPECT may be disappointed. Sponsor companies should expect (and indeed demand) a thorough protocol review and agreement on both study design and statistical analysis plans from any regulatory agency before beginning the SPECT acquisition phase of a trial, let alone the image analysis. If done appropriately, SPECT imaging can be used as an imaging endpoint.

Summary

Cardiac SPECT imaging is a well-established clinical modality for the effective, quantitative evaluation of myocardial perfusion and function in patients with known or suspected coronary artery disease. Three-dimensional imaging, simultaneous assessment of cardiac perfusion and function, and the availability of well-validated, quantitative software are but a few of the advantages of this technology. Recent clinical data have demonstrated the role of cardiac SPECT in evaluating anti-ischemic therapy and also in risk stratification and decision-making in patients with known or suspected coronary artery disease. However, cardiac SPECT has not yet been accepted by regulatory authorities as a primary endpoint for the approval of

therapeutic pharmaceuticals. Experts in the field indicate that with proper planning, and if used appropriately, cardiac SPECT can become an acceptable imaging endpoint for clinical trials. ♦

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