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NUCLEAR CARDIOLOGY: 2014 INNOVATIONS AND DEVELOPMENTS

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Abstract

Nuclear cardiac imaging is acknowledged as a robust technique for clinically assessing patients with a wide spectrum of cardiac illnesses. Recent technical, radiotracer, and stressor advancements continue to expand the role of nuclear cardiology for the accurate diagnosis and prognostication of patients with known or suspected coronary artery disease. The introduction of I-123 MIBG represents another advance for assessing risk in patients with congestive heart failure and depressed left ventricular (LV) function. Software and hardware innovations and recent shifts in acquisition protocols have greatly improved image quality, reduced cost and radiation exposure, and continue to promote patient and physician satisfaction. The following article will highlight recent achievements in the field that continue to foster a patient-centered imaging approach.

Introduction

Nuclear cardiac imaging is time-honored in its ability to accurately diagnose and risk stratify patients across the entire spectrum of coronary artery disease.¹⁻⁵ With the use of quantitative techniques, nuclear cardiac imaging can also monitor the success of anti-ischemic therapies^{5,6} and track individual patient risk based on changes in stress-induced perfusion abnormalities (Figure 1).^{7,8} Despite this well-recognized track record, the field has seen many advances in recent years. These include the development of new pharmacologic stressor agents, advances in gamma camera technology, and the discovery of new radiotracers for improving the detection of coronary artery disease and predicting outcomes in special populations, such as patients with congestive heart failure and depressed LV function. There also has been a paradigm shift in image acquisition protocols that will lead to marked reductions in radiation exposure, improved laboratory efficiency, and reduced cost. Together, these developments have led to a patient-centered imaging approach for obtaining the most accurate diagnostic imaging results with the least amount of radiation exposure.

Advances in Pharmacologic Stressor Agents

Pharmacologic stressor agents were introduced several decades ago to increase the availability of myocardial perfusion imaging (MPI) to patients who could not perform adequate exercise stress due to noncardiac medical conditions. The past decade has seen an increasing reliance on pharmacologic stressor agents over treadmill exercise due to the aging population. The traditional pharmacologic stressor agents were the pharmacologic vasodilators (intravenous dipyridamole and adenosine) and the beta-agonist dobutamine. Pharmacologic vasodilators, particularly adenosine, enjoyed great success and were used in almost all patients who could not perform adequate exercise stress.

Fundamental Basis of Myocardial Perfusion Imaging

Adenosine and dipyridamole increase myocardial blood flow based on activation of the alpha-2 adenosine receptor (A_{2A}) with

subsequent coronary arteriolar vasodilation. Resting myocardial blood flow in a normal person can increase by 2- to 4-fold during times of increased demand, and this is termed “coronary flow reserve.” With physical activity, there is depletion of adenosine triphosphate that degrades to adenosine. The accumulation of adenosine in the peripheral coronary bed stimulates the A_{2A} receptor, thereby increasing coronary blood flow relative to physical needs. Without this coronary flow reserve, we would be unable to perform any physical activity. With increasing epicardial coronary artery stenosis, resting myocardial blood flow is maintained through utilization—and therefore depletion—of coronary flow reserve. Thus, with increasing coronary artery stenosis, there is a decreasing ability to augment flow during exercise or pharmacologic stress. Myocardial radiotracer uptake is relatively linear to myocardial blood flow, which means that 2- to 4-times as much radiotracer count activity is noted in normally perfused muscle compared to myocardium supplied by significantly stenosed arteries. This results in stress-induced perfusion defects and is the basis for both single photon (SPECT) and positron emission (PET) tomographic cardiac MPI. Dobutamine also increases myocardial blood flow but by directly increasing myocardial oxygen demands through increases in heart rate and myocardial contractility. Due to its cumbersome administration and significantly greater side-effect profile versus pharmacologic vasodilators, dobutamine is reserved for patients with contraindications to pharmacologic stress.

Adenosine Receptors

Adenosine and dipyridamole stimulate a variety of adenosine receptors that have different physiologic effects. As stated above, stimulation of the A_{2A} adenosine receptor induces coronary vasodilation, but stimulation of the A_1 adenosine receptor decreases atrioventricular (AV) nodal conduction and can result in second- and third-degree atrioventricular block. Stimulation of the A_{2B} receptor induces peripheral vasodilation and potential hypotension, and stimulation of the A_3 adenosine receptor can

SPECT 1 : Pre-Therapy

SPECT 2 : Post-Therapy

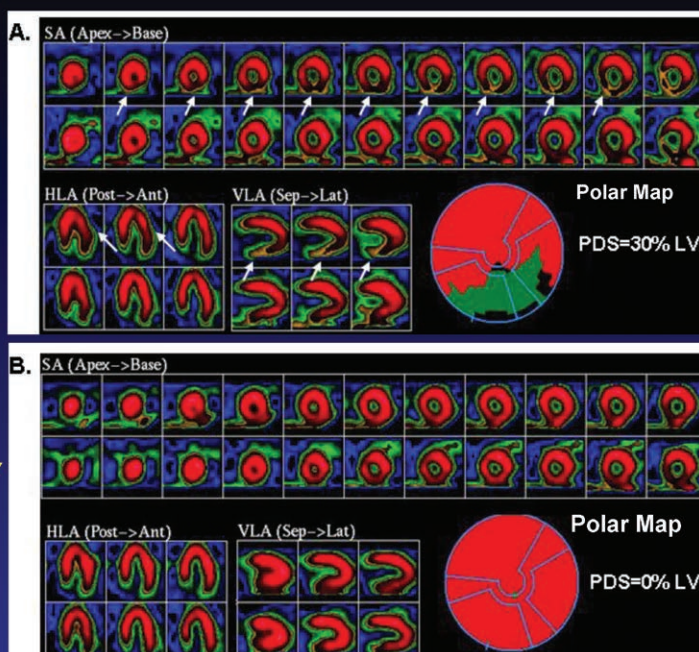


Figure 1. Serial adenosine SPECT imaging over a 1-month interval to assess the success of anti-ischemic medical therapy in a patient with recent myocardial infarction. The pretherapy study (A) shows large inferior and inferolateral ischemic perfusion defects (white arrows on stress study) with a quantified total LV perfusion defect size of 30% (polar map). The post-therapy study (B) is normal. Top panels are stress images and bottom panels are rest images. SA: short axis; HLA: horizontal long axis; VLA: vertical long axis; LV: left ventricular; PDS: perfusion defect size.

cause bronchiolar constriction and wheezing. Adenosine and dipyridamole are contraindicated in patients with hypotension, advanced AV nodal conduction disease/sick sinus syndrome (without a pacemaker), and chronic obstructive pulmonary disease (COPD)/asthma with active wheezing.

Regadenoson: A Selective A_{2A} Adenosine Receptor Agonist

In order to increase availability of MPI, selective A_{2A} adenosine receptor agonists were developed that induce coronary hyperemia but without significant stimulation of other adenosine receptors. Regadenoson was recently approved by the U.S. Food and Drug Administration (FDA) and is currently the only A_{2A} receptor agonist clinically available. Regadenoson was compared to adenosine in two pivotal prospective, randomized, double-blind clinical trials that enrolled over 2,000 patients who had serial adenosine-adenosine vs adenosine-regadenoson SPECT MPI. The ADVANCE 1 and 2 trials demonstrated noninferiority of regadenoson compared to adenosine for detection of myocardial ischemia and with an improved safety profile.^{9,10} We recently reported a quantitative analysis of SPECT images acquired from the ADVANCE 2 dataset.¹¹ In this substudy, regadenoson induced virtually identical total and ischemic perfusion defects as adenosine (Figure 2) and, based on these results, should provide not only similar diagnostic but also prognostic information as observed with adenosine (Figure 3).

Regadenoson has also been evaluated in patients with moderate to severe COPD and in those with mild to moderate asthma in whom adenosine and dipyridamole are contraindicated.¹²⁻¹⁵ In two early, small, double-blind, placebo-controlled, crossover studies, regadenoson did not reduce forced expiratory volume in 1 second (FEV1) on serial pulmonary function testing or oxygen saturation as compared to placebo saline infusion. A more recent double-blind, randomized, placebo-controlled trial of 999 subjects (532 with asthma and 467 with COPD) evaluated the

effects of regadenoson vs saline infusion using serial pulmonary function tests over a several-hour period postinjection.¹³ The primary end point was a > 15% reduction in FEV1 at 2 hours after administration of regadenoson. In this study, there was no significant difference in the percentage of patients who decreased their FEV1 with regadenoson vs placebo. This was true for both the asthmatic and COPD populations. Likewise, oxygen saturations did not significantly decrease with regadenoson vs placebo. There have now been more than 1,300 patients enrolled in four separate studies that demonstrate no adverse effects in COPD or asthmatic patients receiving regadenoson. Consequently, regadenoson is now routinely used in such patients, with no further need for dobutamine except in those with advanced AV conduction abnormalities without a pacemaker. Unlike adenosine, which has a half-life of < 10 seconds and is rapidly neutralized, regadenoson undergoes renal excretion. For this reason, the safety of regadenoson has been studied in patients with stage 3 and 4 renal insufficiency^{16,17} and in patients on hemodialysis.¹⁸ No serious adverse effects were noted with regadenoson compared to controls in any of these studies. In addition, unlike adenosine, regadenoson does not appear to cause conduction abnormalities (i.e., second- or third-degree AV block or sinus pauses) in previous heart transplant recipients and so can be used safely in this population.¹⁹ Other advantages of regadenoson are a standard dose of 400 ug for all patients and a bolus injection over 10 s, with therefore no need for an infusion pump as with adenosine.

Advances in Radionuclide Tracers

Cardiac Fatty Acid Metabolism Radionuclide Imaging for Myocardial Ischemia

The principal source of energy for normal myocardium is free fatty acid. During and after myocardial ischemia there is a switch from fatty acid to glucose as a primary source of energy. This change can be imaged with cardiac SPECT using iodine-123 fatty

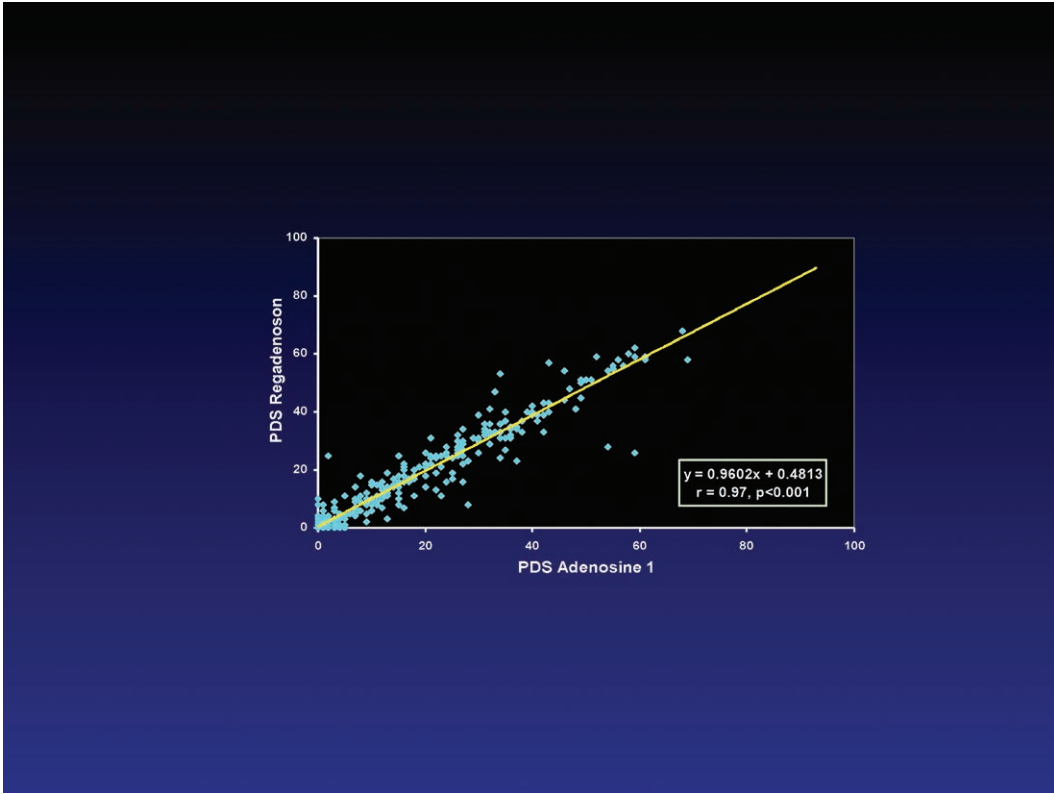


Figure 2. Linear regression showing the close correlation between adenosine and regadenoson induced perfusion defect size (PDS). From Mahmarian et al. JACC: Cardiovascular Imaging; 2009;2:959.

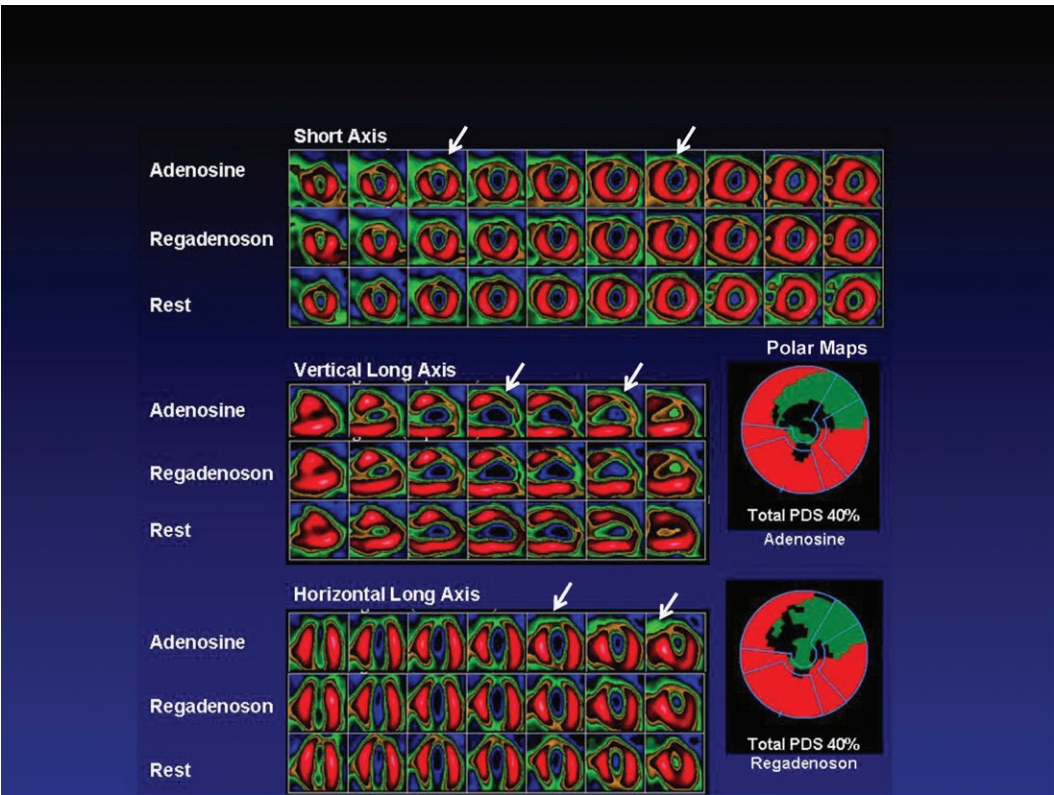


Figure 3. Representative SPECT images in all three cardiac planes following adenosine and regadenoson stress and then at rest. The images and corresponding polar maps show a comparable total left ventricular perfusion defect size (PDS) of 40% (black and green areas) with a comparable extent of ischemia (green area). White arrows indicate areas of stress perfusion abnormalities.

acid radiotracers such as β -methyl iodophenyl-pentadecanoic acid (BMIPP). The impaired utilization by beta oxidation leads to prolonged retention in the cardiac myocyte that persists even after blood flow is restored. The abnormal myocardial BMIPP uptake at rest, after resolution of ischemia, reflects continued metabolic alterations caused by the preceding ischemia, termed

“ischemic memory.” In patients with acute chest pain presenting to the emergency department, a cardiac BMIPP scan within 30 hours of the last episode of chest pain provides incremental value to clinical data in establishing the early diagnosis of acute coronary syndromes.²⁰ An abnormal BMIPP study also has been shown to have good diagnostic accuracy and prognostic utility in

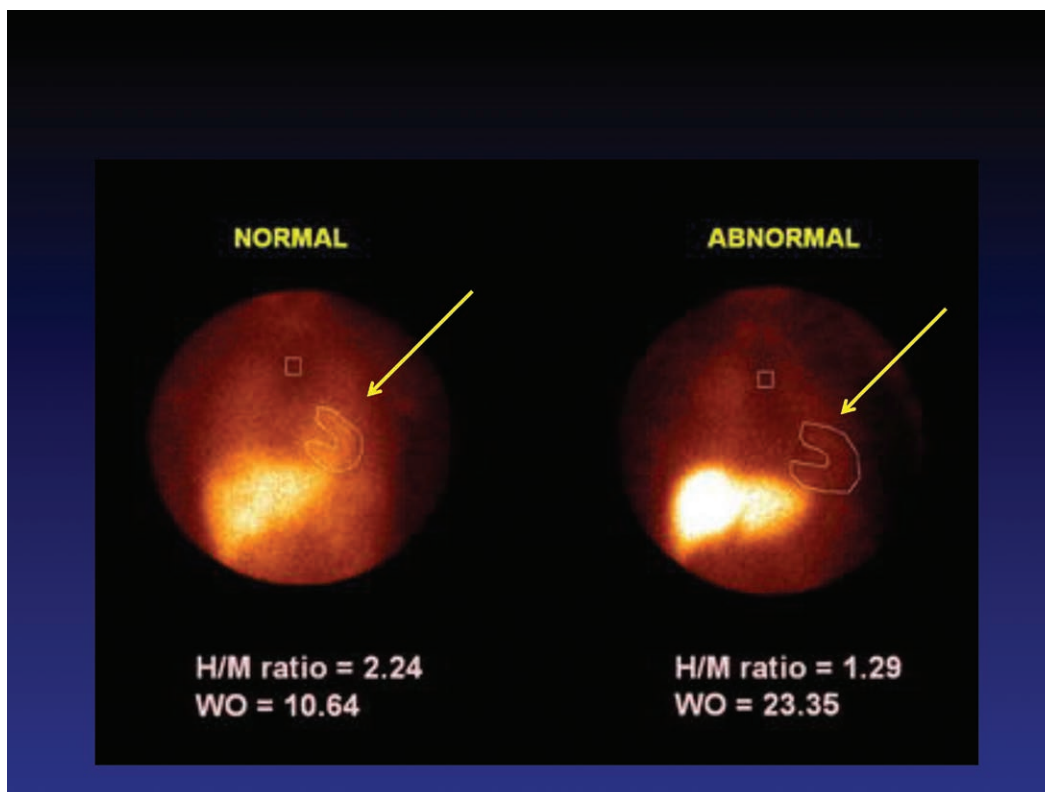


Figure 4. Normal and abnormal planar images showing heart-mediastinal (HM) ratios and tracer washout (WO) in two patients undergoing evaluation with I-123 mIBG. The arrows show the location of the left ventricle and the box shows the mediastinal area of interest. From Ji et al. J Nucl Cardiol; 2010;17:655.

asymptomatic hemodialysis patients with no history of coronary artery disease.²¹

Cardiac Sympathetic Nerve Function Radionuclide Imaging for Heart Failure

Heart failure has become the most important cardiac cause of morbidity and mortality. Accurate risk assessment with multiple clinical and echocardiographic indices remains suboptimal. It is well-established that cardiac autonomic regulation is often altered with heart failure progression. Patients with depressed LV function often have decreased *catecholamine* sensitivity and beta-adrenergic receptor activity. Presynaptic energy-dependent uptake of norepinephrine is therefore decreased, resulting in higher concentrations in the synaptic cleft for interaction with beta receptors. Cardiac iodine-123 metaiodobenzylguanidine (MIBG) is an analog of guanethidine with similar uptake as norepinephrine, but since it is not metabolized by catechol-O-methyltransferase, presynaptic retention is high. Iodine-123-labeled MIBG molecular imaging with SPECT can be used to evaluate cardiac sympathetic nerve function in the failing heart based on its uptake and retention. The MIBG heart-to-mediastinum ratio (HMR) compares MIBG count activity in the entire heart vs the upper-third of mediastinum from an anterior planar image (Figure 4). The HMR and the washout rate (by comparing heart counts in the early 15-minute to the delayed 4-hour acquisition) predict cardiac and arrhythmic death as well as heart failure progression. Although a normal HMR is considered to be ≥ 1.6 , patient outcome varies across the entire spectrum of HMR. In the ADMIRE study, 2-year mortality was 22% in patients with an HMR of < 1.2 but only 3.3% in patients with an HMR ≥ 1.6 (Figure 5).²²

In addition, the HMR further risk-stratified patients beyond that provided by initial *brain natriuretic peptide* and left-ventricular ejection fraction (LVEF). Likewise, in the study by Ketchum et al., MIBG HMR significantly improved risk stratification

beyond the well-recognized Seattle Heart Failure Model.²³ A recent Japanese meta-analysis in 1,322 heart failure patients corroborated the strength of the HMR for predicting outcome over a 5-year period, showing 50% mortality in patients with an HMR ≤ 1.14 but only 8% when the HMR was > 2.0 .²⁴ In addition to its established prognostic ability, there are preliminary data pointing to a potential role of cardiac MIBG imaging in guiding AICD implantation for prevention of sudden cardiac death and in guiding medical therapy with beta blockers.²⁵⁻²⁷ Cardiac MIBG is currently FDA approved for assessing prognosis in patients with class II-III congestive heart failure who have an LVEF $\leq 35\%$.

Myocardial Perfusion Tracers with Flurpiridaz F-18 PET

Both SPECT with technetium Tc 99m-labeled tracers and PET with rubidium chloride Rb 82 represent major advances for myocardial perfusion and functional imaging compared to thallium Tl 201, which has low energy, significant scatter, and the highest radiation exposure due to its long half-life. However, they are far from being ideal perfusion tracers primarily due to dosimetry issues and, most importantly, nonlinear uptake of these radiotracers at high coronary blood flows during hyperemia (i.e., during exercise or pharmacologic stress), which can limit diagnostic accuracy.

One of the most promising PET tracers is flurpiridaz 18F, which is a radionuclide-labeled analog of myocardial mitochondrial complex I inhibitors such as pyridaben. Compared to other tracers, it has been shown to have near-linear myocardial extraction across all coronary blood flows (less roll-off) and exhibits minimal redistribution. Resting and postvasodilator global and regional myocardial blood flow assessed with this tracer correlate very well with results using microspheres,²⁸ which should improve sensitivity for detection of coronary artery disease and particularly lesions of intermediate stenosis. Due to its lower energy and the much shorter positron range of flurpiridaz 18F (7-times less than rubidium chloride Rb 82), it provides higher spatial resolution.

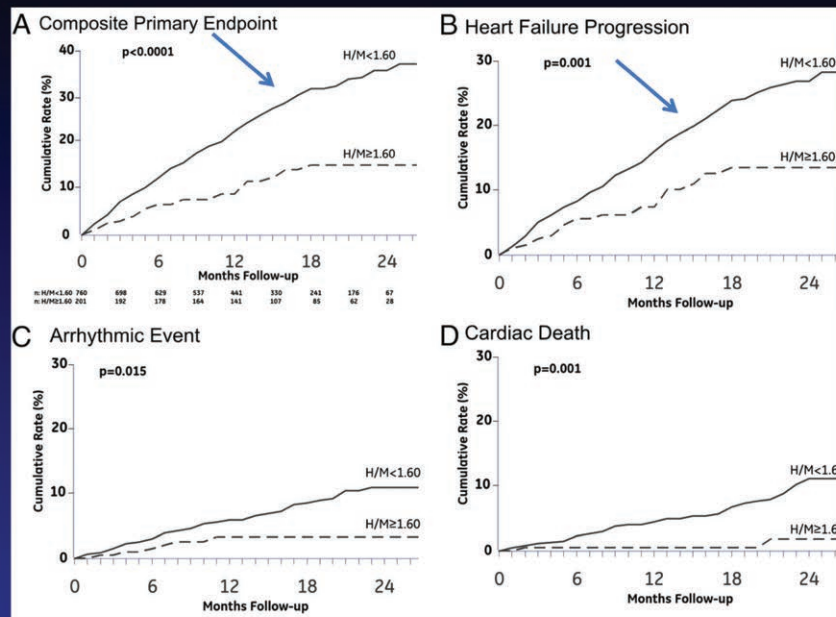


Figure 5. The ADMIRE study results in 961 patients followed for 17 months. I-123 mIBG was able to identify patients at high and low risk based on the heart/mediastinal (H/M) ratio even though all had congestive heart failure symptoms and a low left ventricular ejection fraction (< 35%). Composite end point was heart failure progression, arrhythmic event, and cardiac death. From Jacobson et al. *J Am Coll Cardiol*; 2010;55:2212.

In addition, its relatively long half-life of 109 min allows for 1) delivery of unit doses on a daily basis rather than reliance on an on-site cyclotron (as with nitrogen N13-ammonia) or a generator (as with rubidium chloride Rb 82), and 2) performance of exercise stress PET imaging, which cannot be performed with any other currently available PET tracer. The excellent safety profile of this tracer has been established in phase 1 and 2 clinical trials. A recent phase 2 clinical trial in 132 patients showed a higher percentage of good image quality and diagnostic certainty compared to technetium Tc 99m SPECT imaging.²⁹

In the subgroup of 86 patients undergoing invasive angiogram, flurpiridaz 18F had higher sensitivity and similar specificity. Based on its favorable dosimetry, linear extraction across all myocardial blood flows, improved spatial resolution, and longer half-life (allowing performance of exercise studies), this tracer should provide a major advancement in current imaging of coronary artery disease. Two phase-3 multicenter trials are currently ongoing to assess this new tracer agent compared to conventional SPECT imaging.

Advances in Software and Hardware

One major limitation of cardiac SPECT compared to other techniques has been long acquisition times to obtain adequate count statistics and diagnostic images. A variety of software and hardware solutions have been developed that significantly reduce imaging times and radiopharmaceutical doses while maintaining excellent image quality.

Software Advances

The traditional reconstruction method for processing raw SPECT projection image data is filtered back projection (FBP). FBP suppresses high-frequency image data, resulting in less noise but with a smoother image that may variably obscure perfusion abnormalities. Conversely, iterative reconstruction (IR) compares

the original projection data with estimated projections and updates the image based upon the difference between the calculated and actual projections.³⁰ Ordered subset expectation maximization (OSEM) is the most commonly used version of IR and produces images of higher quality than with FBP, with less noise, sharper definition of myocardial borders, and improved contrast. IR is most advantageous when applied to low-count imaging studies and in those where high subdiaphragmatic radiotracer activity is present, which creates artifacts when using the ramp filter.

All SPECT cameras are equipped with lead collimators that are placed in front of the imaging crystal to register photons emitted perpendicular to the crystal surface. The distance of the collimator from the source and the particular geometry of the collimator (length, thickness, septal width) strongly influence image spatial resolution. Resolution recovery (RR) is a method that models the collimator's geometry and, when incorporated with IR, compensates for any image blurring.³¹ IR with resolution recovery reduces noise and improves spatial resolution, particularly when study count statistics are suboptimal.³²

Due to generally poor count statistics, SPECT images have noise. Noise compensation techniques have been developed that maintain signal-to-noise ratio (SNR) while suppressing high-frequency components of the image.³² By suppressing noise and enhancing SNR, resolution and contrast are maintained. All vendors possess advanced software packages incorporating all current advanced software processing methods: IR, RR, and noise compensation. Some of these include nSPEED™ (Digirad, Suwanee, GA), Evolution® (GE Healthcare, Pittsburgh, PA), Astonish® (Philips, Amsterdam, The Netherlands), and Flash-3D® (Siemens, Malvern, PA).

Hardware Advances

Standard SPECT systems use sodium iodide crystals to register a scintillation event when photons strike the crystal. An array of

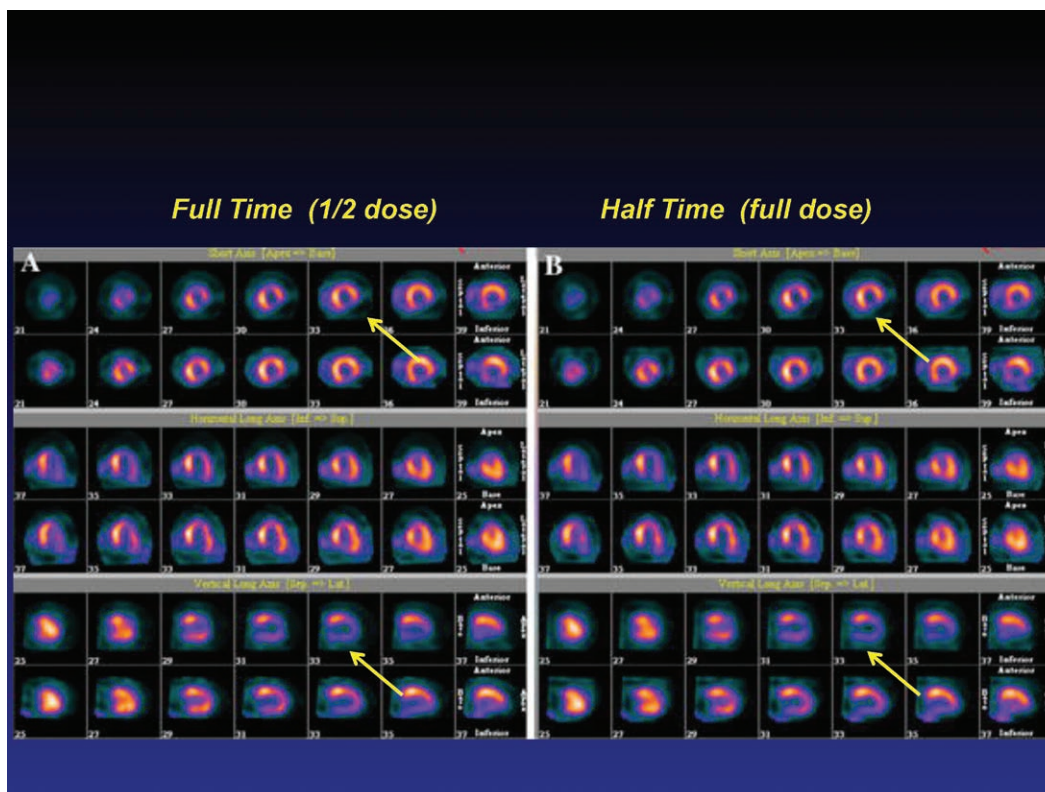


Figure 6. Representative patient images showing comparable quality and diagnostic accuracy using new gamma camera hardware technology. In panel A, the patient received one-half of the radiotracer dose (with one-half of the radiation exposure) and was imaged for twice as long. In panel B, the patient received a full radiotracer dose but with the standard 2- to 4-minute acquisition. The arrows show comparable perfusion defects on both acquisitions. From Maddahi et al. *J Nucl Cardiol.* 2009;16:351.

photomultiplier (PM) tubes then detect this light signal, localize the scintillation event, and convert it to an electrical signal. Unfortunately, the number of steps involved with sodium iodide (NaI) detectors leads to degradation of information and loss of both energy and spatial resolution with resultant object blurring. New solid-state detectors employ cadmium-zinc-telluride (CZT) crystal detectors that are divided into an array of individual detector elements. Each of these 2.46 mm pixelated detectors directly convert the scintillation event, without the need for photomultiplier tubes, into an electrical output signal resulting in improved count sensitivity and accurate localization of the event. When compared with thallium-activated sodium iodide (NaI(Tl)) crystals, CZT detectors optimize energy, spatial and contrast resolution.³³

New-generation cardiac scanners are innovatively designed with particular goals in mind. Many scanners today (Digirad Cardius®, Siemens C-Cam®, Data Spectrum D-SPECT®) employ upright or semi-upright positioning options to increase patient comfort, decrease motion artifact, and limit diaphragmatic attenuation artifacts over the inferior wall. Optimized detector geometry with focused collimation, to image just the cardiac field of view, provides a dramatic 5- to 10-fold increase in count sensitivity. Digirad Cardius®, Spectrum Dynamics D-SPECT® (Spectrum Dynamics Medical, Inc., Round Rock, TX), and GE Discovery 530c® incorporate cardiocentric SPECT orbits that allow the heart to remain in the center of the field of view for each detector, thereby eliminating blurring and artifacts.³⁴ Multiple pixelated CZT detectors with a fanning motion and cardiac-focused tungsten parallel-hole collimators, as seen with the D-SPECT camera, preferentially sample photons emanating from the heart rather than surrounding structures.³⁵ Its unique L shape also allows for closer positioning of the camera to the chest wall. The GE Healthcare Discovery NM 530c® employs 16 CZT pixelated detectors with focused pinhole collimators

simultaneously imaging the heart without moving parts during data acquisition.³⁶ Both the detector and patient are stationary, reducing motion and attenuation artifacts, and imaging can be performed in either the supine or prone positioning.

The application of software and hardware improvements allows for a significant increase in count sensitivity and image quality with high energy, spatial, and contrast resolution. Routine stress and rest images can be completed in 4 to 6 minutes compared to 25 minutes with conventional cameras, thereby improving laboratory efficiency and reducing cost. Rapid image acquisitions reduce the likelihood of suboptimal image quality due to patient motion and add flexibility for a more patient-centered imaging approach.³⁷ In this regard, cooperative patients can be imaged for twice as long (i.e., 8-12 minutes) but be administered one-half the standard radiopharmaceutical dose, resulting in radiation exposures of only 1 to 2 mSv (Figure 6).³⁸

Advances in Image Acquisition Protocols

There has been a concerted effort by the American Society of Nuclear Cardiology (ASNC) to promote reductions in radiation exposure.^{39,40} This can be achieved by 1) imaging only patients that have appropriate indications for testing, 2) substituting high-exposure radiotracers such as thallium Tl 201 for technetium Tc 99m, and 3) individualizing acquisition protocols. When patients typically are referred for stress MPI, they are imaged under resting conditions after injection of approximately 10 mCi technetium Tc 99m followed by imaging after injection of 30 mCi during either exercise or pharmacologic stress, which is the standard rest-stress acquisition protocol. For many years we have championed stress-rest imaging protocols that allow for stress-only imaging if the initial stress images are normal. By avoiding the generally higher second technetium Tc 99m dose, radiation exposure can be reduced from approximately 11 mSv to 2.5 mSv. A stress-only imaging approach also significantly reduces radiation exposure

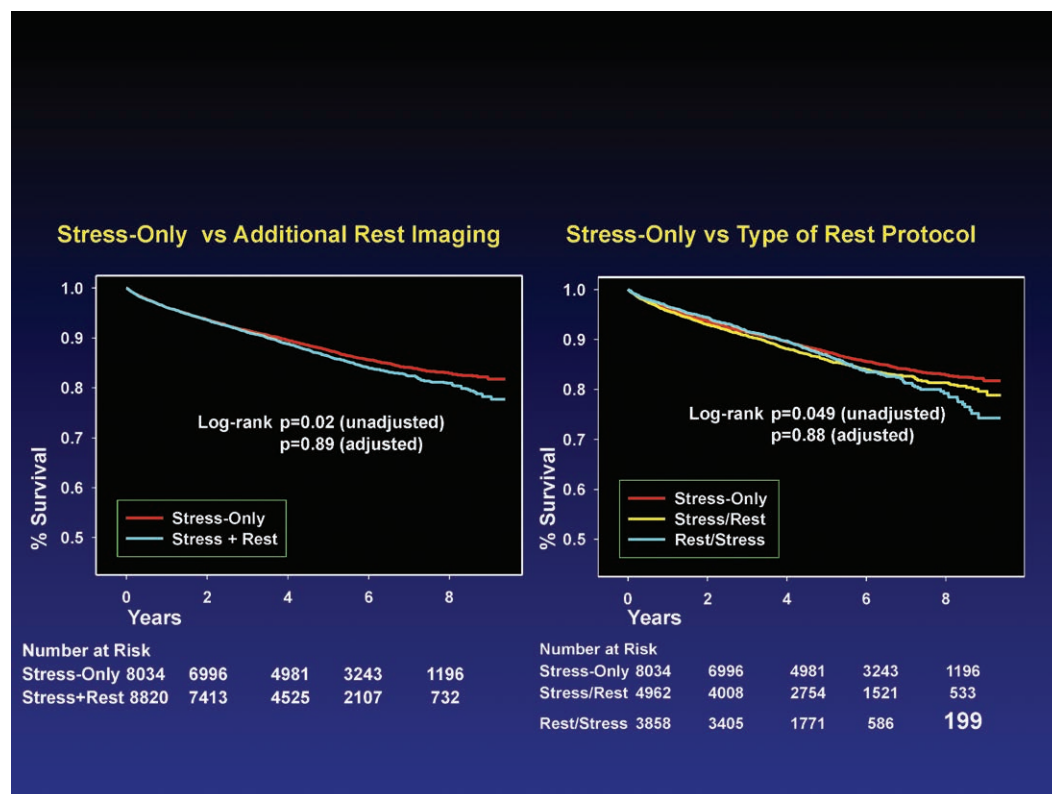


Figure 7. Comparable long-term survival (median 4.5 years) in 16,854 patients who underwent stress-only vs stress-rest imaging. From Chang et al. *J Am Coll Cardiol.* 2010;55:221.

to technologists and other workers involved in patient imaging.⁴¹ Recent publications by our group⁴² at the Houston Methodist DeBakey Heart & Vascular Center and others⁴³ have shown similar low event rates in patients who undergo stress-only imaging compared to standard stress-rest acquisition protocols. In our analysis of more than 27,000 patients, 16,000 (61%) had a normal study with stress-only imaging performed in 50% of those with a normal SPECT (Figure 7). With the incorporation of attenuation correction techniques, even large patients who commonly have image artifacts can undergo successful stress-only imaging procedures.^{44,45} Furthermore, incorporation of stress-only techniques into new camera technology can reduce radiation exposure to approximately 1 to 2 mSv.⁴⁶ To put this into context, annual radiation exposure at sea level from natural sources is approximately 5 mSv per year. In addition to being safe and significantly reducing radiation exposure, a stress-only imaging approach conserves technetium Tc 99m (which is in short supply), improves laboratory efficiency, increases patient satisfaction and convenience, and reduces cost by eliminating the second higher dose of radiotracer and the second imaging procedure. The ASNC has recently endorsed stress-only imaging and promoted awareness of this important advance to the nuclear imaging community.

Conclusion

Technical, radiotracer, and stressor advancements continue to expand the role of nuclear cardiology for the accurate diagnosis and prognostication of patients with known or suspected coronary artery disease. The introduction of iodine I 123 MIBG represents a further advance for assessing risk in patients with congestive heart failure and depressed LV function. Software and hardware innovations and recent shifts in acquisition protocols have greatly improved image quality, reduced cost and radiation exposure, and continue to promote patient and physician satisfaction.

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