

New Imaging Protocols for New Single Photon Emission CT Technologies

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Abstract Nuclear cardiology practitioners have several new technologies available with which to perform myocardial perfusion single photon emission CT (MPS). These include dedicated small-footprint cardiac scanners, new stationary or semi-stationary three-dimensional detectors, and advanced software algorithms for optimal image reconstruction. These new technologies have been employed to reduce imaging time and radiation exposure. They require less technologist and camera time and offer improved patient comfort. They have potential for the overall cost reduction of MPS and at the same time for improved accuracy by increased resolution, or accurate attenuation correction. Furthermore, these new technologies offer potential for new protocols such as simultaneous dual isotope, new combinations of isotopes, stress only MPS, or dynamic first-pass imaging. In addition, new imaging technologies in coronary CT angiography (CCTA) allow novel hybrid stress only MPS/CCTA protocols with reduced radiation burden. Additional developments further improving efficiency and diagnostic accuracy of MPS are on the horizon.

Keywords Myocardial perfusion SPECT · Solid state detectors · Stress-only protocol · Hybrid imaging · Cardiac fusion · Simultaneous dual isotope · Fast cardiac SPECT · Dynamic imaging

Introduction

Myocardial perfusion single photon emission CT (MPS) is a widely used clinical test, with approximately 9 million

studies being performed annually in the United States [1]. Until recently, typical scans were long procedures, requiring 15 to 20 min for each stress and rest MPS acquisition, to allow adequate imaging statistics. Additional consequences of long imaging times were frequent motion artifacts caused by patient motion during the scan and compromised patient comfort. Recent advances in new detector designs allow dramatic reduction of imaging times to less than 2 min in some cases, or alternatively, dramatic reductions in the radiation dose to the patient. Cameras now available from many vendors have increased photon sensitivity achieved by means of custom detector geometry and innovative designs of collimation (including multiple pinhole or slit hole collimators), focusing of the field of view on the heart and using solid-state detectors. The optimized geometry for cardiac imaging allows significantly reducing or totally eliminating the motion of the detector, with simultaneous collections of counts from the whole heart. The new cameras have often reduced footprint and allow easier patient positioning, and in many cases upright imaging. Faster imaging and more comfortable patient position results in reduced patient motion during acquisition. Additionally, three-dimensional (3D) character of the acquisition reduces the effect of patient motion on image quality.

These new camera designs are coupled with novel methods of image reconstruction. Improvements in reconstruction algorithms allow accurate resolution recovery and corrections of physical effects via iterative reconstruction algorithms. These new methods of image reconstruction can be implemented on standard cameras. Combination of the new hardware and the new reconstruction models allows simultaneous improvements in photon sensitivity and image resolution. Furthermore, list mode acquisition capabilities are now available, allowing arbitrary time reformatting of the data after the scan. Consequently, first-pass 3D dynamic imaging and kinetic modeling with

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stationary or semi-stationary single photon emission CT (SPECT) detectors is now possible, similar to what has been available in positron emission tomography (PET). Additionally, increased photon sensitivity can be utilized to pursue novel imaging protocols such as simultaneous dual isotope, or new combinations of isotopes allowing rapid stress/rest assessment. Recently we reviewed new hardware and software developments from a technical perspective [2•]. In this review article, we summarize current clinical applications and trials with emphasis on novel imaging protocols that are possible with the new generation of devices, including hybrid imaging protocols.

New Cardiac SPECT Technologies

Several vendors have developed hardware and software technologies allowing reduced imaging or dose time, improved patient comfort, and improved image quality. Digirad Inc. (Poway, CA) has developed a cardiac Cardius XPO camera, which is coupled with new reconstruction technology (n-speed). For imaging, the patient sits on a chair with his or her arms placed on an armrest above the detectors [3]. Digirad has also incorporated a low-cost approach to obtain x-ray transmission scans for attenuation correction that can be implemented with the XPO camera. Another dedicated cardiac camera was developed by CardiArc (Canton, MI), optimized specifically for cardiac imaging and upright patient position [4]. Spectrum Dynamics (Haifa, Israel) has manufactured a solid-state dedicated cardiac system called D-SPECT with semi-stationary detectors, high-sensitivity collimation, and reconstruction optimized specifically for cardiac imaging. The patient is imaged in a semi-upright position with the left arm placed on top of the camera or in the supine position. General Electric Healthcare has developed a stationary imaging camera based on the multi-pinhole design, an alternative technique for photon collimation [5–7], and an array of cadmium zinc telluride pixilated detectors [8]. Patients are imaged in a supine position with their arms placed over their heads. Two examples of studies obtained with D-SPECT and GE Discovery NM 530c with comparable acquisition times and doses are shown in Fig. 1. Siemens has combined an astigmatic collimator, an optimized organ-of-interest centered acquisition, and iterative reconstruction in their IQ•SPECT system with CT-based attenuation correction (on Symbia platform) and energy window-based scatter correction [9]. This system allows hybrid MPS-CT imaging.

In parallel, efforts have been undertaken to improve image contrast and reduce noise levels by reconstruction algorithms that incorporate physical modeling of the detectors based on ordered subsets expectation maximization (OSEM) [10] and applied to data acquired on standard

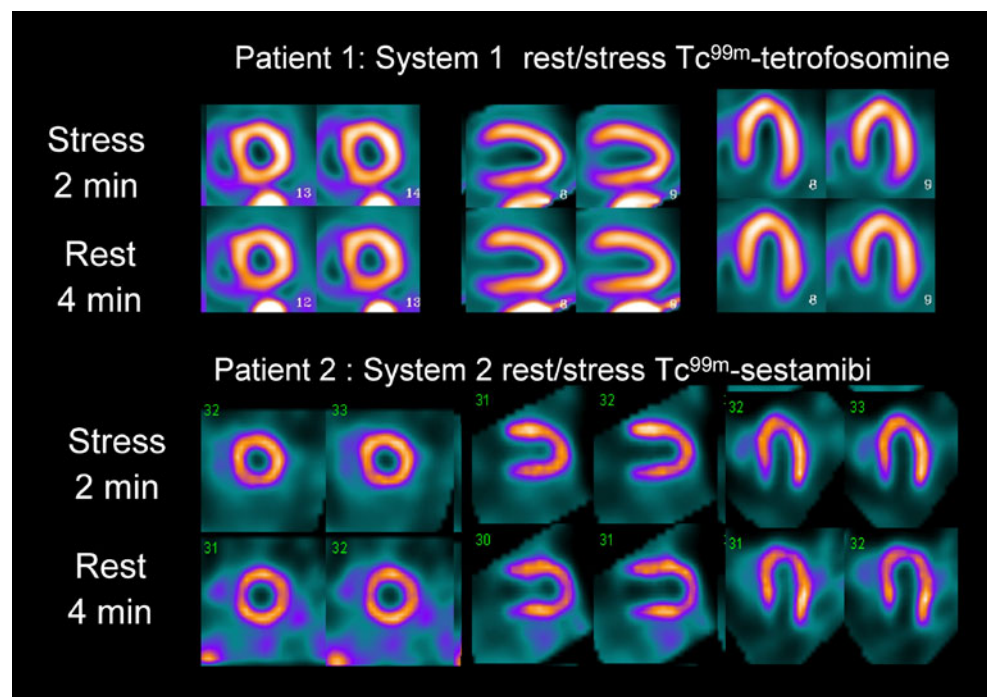
scanners. Philips (San Jose, CA) has developed a fast SPECT reconstruction algorithm (Astonish) that includes corrections for photon scatter, photon attenuation, and variations in spatial resolution and allows reduced imaging time. UltraSpect Inc. (Haifa, Israel) has developed a standalone workstation that utilizes the patented Wide Beam Reconstruction (WBR) algorithm [11, 12].

Fast Imaging and Dose Reduction in Clinical Studies

In the past 2 years, these new hardware systems and reconstruction techniques have been utilized clinically to reduce patient imaging time and radiation dose. Typically, these studies have been validated by comparing to studies performed with the same injected dose during the same patient visit on a conventional dual head SPECT camera. Data were analyzed by blinded visual or by quantitative analysis. Several of these studies combined data from multiple centers. Herzog et al. [13] performed phantom and clinical studies to establish the most optimal imaging time for the solid-state multi-pinhole Discovery NM 530c detectors and found that scan as short as 2 min with 327 MBq mean dose and 3-minute rest scan with 915 MBq provide equivalent images to 15-minute acquisitions with the standard camera. A similar protocol was followed in 75 patients by the same group, and excellent correlation for per-vessel and per-patient perfusion defects was found with conventional SPECT [14]. In the United States, the Discovery NM 530c system was evaluated by the Emory University group [15•]. Similarly high correlations with conventional SPECT were found for perfusion defects and for left ventricular ejection fractions (LVEFs).

The D-SPECT camera was compared with a standard dual detector in 44 patients and reported shorter imaging times and higher MPS quality for the new camera, with high correlations in visual perfusion scores [16]. In another study, a novel stress TI-201/rest Technetium-99m protocol, with total stress/rest imaging time reduced to less than 20 min, including additional supine views, was described and compared to a standard Tc/Tc protocol on the same fast camera (Fig. 2) [17•]. They concluded that TI/Tc protocol offers similar image quality and dosimetry (11.9 mSv vs 11.2 mSv; P =not significant), but results in much shorter total imaging time and offers potential for better depiction of stress lesions with physiologically superior TI-201 agent (Fig. 3). Furthermore, this study demonstrated possibility of dual-position imaging for these new cameras with patient imaged in upright and supine positions. Two-position imaging allows improved diagnostic accuracy by resolving of subtle attenuation artifacts or patient motion as demonstrated in prone-supine conventional SPECT imaging [18]. In another large study of D-SPECT data from four US

Fig. 1 Examples of two patient studies obtained with Discovery NM 530c (system 1; images courtesy of Dr. Ernest Garcia) and D-SPECT (system 2; images courtesy of Dr. Jack Ziffer), showing good-quality studies with comparable acquisition protocols (2-minute stress, 4-minute rest)

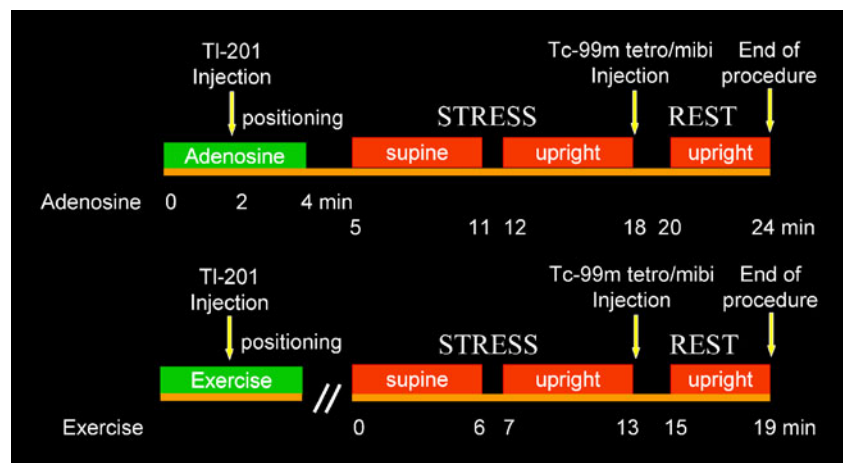


centers, Sharir et al. [19••] used fully automated quantitative software with normal limits developed for the new camera for their data analysis. They demonstrated that the quantitative total perfusion deficit [20] obtained with the fast protocol correlated linearly with stress and rest conventional SPECT ($r=0.95$ and $r=0.97$, respectively; $P<0.0001$), and that the average amount of ischemia was higher in the high-likelihood patients, as compared to conventional SPECT. Similarly, LVEFs and LV volumes obtained with fully quantitative analysis [21] were highly correlated.

Fast imaging protocol for the Digirad cardiac system (majority with dual or triple head configuration) with optimized image reconstruction has been evaluated in a multicenter trial (11 centers) by Maddahi et al. [22]. They found that images from fast protocols were diagnostically

equivalent in 444/448 (99%) of the patients as determined by blinded visual analysis. Functional parameters ejection fraction, diastolic, and systolic volume were also highly correlated. With a conventional camera, fast imaging by means of optimized WBR reconstruction with image resolution recovery and novel approach to noise control was also evaluated [12]. This reconstruction was applied to data obtained on a conventional dual-head system (GE, Ventr) with high-resolution parallel-hole camera. DePuey et al. [23] reported equivalent summed stress and rest perfusion scores with similar image quality at rest and superior at stress for the in $\frac{1}{4}$ time WBR imaging as compared to full-time standard OSEM reconstruction. Similar to the other studies, functional parameters were also highly correlated.

Fig. 2 Fast TI-201 stress/Tc-99m rest protocol for adenosine (top) and exercise (bottom) myocardial perfusion SPECT protocol. At peak stress, patients were injected with TI-201. After a 5-minute post-stress monitoring period, supine and semi-upright (sitting) acquisitions were performed sequentially. Subsequently, Tc-99m sestamibi (mibi) or tetrofosmin (tetro) was injected, and a single 4-minute sitting rest acquisition was performed. (Modified from Berman et al. [17•])



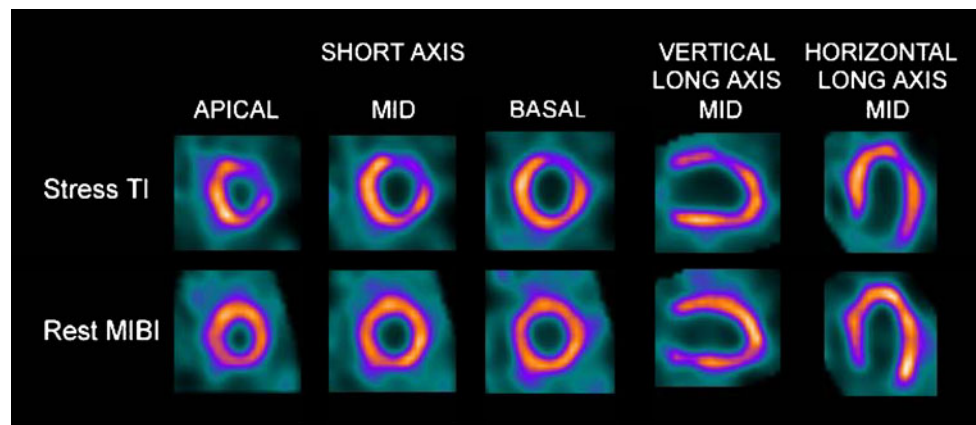


Fig. 3 Images of a 53-year-old man with no known coronary artery disease and hypertension, diabetes, hypercholesterolemia, and shortness of breath, acquired with fast ^{201}Tl exercise stress/ $^{99\text{m}}\text{Tc}$ rest protocol showing large severe reversible defects in the anterior and lateral walls.

Coronary angiography revealed 70% stenosis in the mid left anterior descending artery and the second diagonal branch. Percutaneous coronary intervention and stent implantation were subsequently performed in these two vessels

In other clinical reports, some preliminary results have been presented for the SPECT•IQ system, with imaging times as short as 4 min. The Symbia T series systems also allow for obtaining of CT calcium scan in as little as 30 s during the same imaging session [24]. Preliminary study of fast 3-minute gated imaging with multi-pinhole system on conventional detectors has been also presented by Koss et al. [25], which facilitates the study of segmental LV perfusion and contractile performance during infused dobutamine stress and during the recovery period following stress.

Stress-Only MPS

The effective imaging time and patient dose reduction could also be accomplished by means of eliminating the resting MPS scan. Stress-only MPS protocols with attenuation correction (AC) have been advocated in the past [26]. The stress-only approach increases laboratory efficiency, decreases cost, and improves patient convenience, while reducing radiation dose [27]. The Philips Astonish approach to reducing scan time allows simultaneous AC and MPS acquisition, reducing potential for any misregistration artifacts associated with CT AC. It has been demonstrated that half-time acquisitions, when compared to standard (filtered back-projection) FBP processing, have equivalent diagnostic accuracy with both Astonish [28] and GE Evolution systems [29]. Bateman et al. [30] conducted a study to determine the clinical feasibility of stress-only protocol with reduced scan time and simultaneous acquisition of AC scan. They found that simulated half-time scans (obtained by reconstruction sampling from full-time scans) when compared to standard FBP reconstruction without AC had similar quality and

interpretive certainty, with equivalent summed perfusion scores obtained by blinded visual analysis. Importantly, in this study 92 of 118 cases had available correlating angiography and the diagnostic performance for the stress-only half-time AC MPS imaging was equivalent to standard full-time FBP studies. Therefore, the authors concluded that the stress-only AC MPS approach with optimized reconstruction has the potential to significantly improve MPS efficiency without reducing test accuracy. Additionally, stress-only scan reduces the patient radiation dose to less than 8 mSv, which could be further reduced by using standard rather than half-time acquisition times.

Recent peer-reviewed clinical studies referenced above, which utilize the new technology in order to reduce imaging time, are summarized in Table 1.

Novel MPS Protocols

Beyond simply reducing the acquisition time or patient radiation dose, there are several reports of novel MPS protocols, which take advantage of superior imaging characteristics of new devices or availability of new modalities for hybrid imaging. These include techniques for simultaneous dual isotope imaging, dynamic imaging, and hybrid coronary CT angiography (CCTA)/MPS imaging.

Simultaneous Dual Isotope

Routine simultaneous dual isotope would reduce the imaging time in half compared to the separate stress and rest study. The superior energy resolution of the new detectors can allow better separation of photons from different isotopes, which can result in much improved cross-talk correction [32]. In addition, stationary detector

Table 1 Recent clinical studies demonstrating possibility of shortened imaging times with MPS

Study	System	N	Protocol	Injected dose	Acquisition time
Herzog et al. [13]	Discovery NM 530c	20	1-day ^{99m}Tc -tetrofosmin adenosine stress-rest	Stress/rest 8.8/25.1 mCi	3 min/2 min optimal
Buechel et al. [14]	Discovery NM 530c	75	1-day ^{99m}Tc -tetrofosmin adenosine stress-rest	Stress/rest 9.1/25.6 mCi	3 min/2 min
Maddahi et al. [22]	Digirad 2/3-head	189 3-head 239 2-head	Rest/stress ^{99m}Tc	Rest/Stress 7–10 mCi/20–30 mCi	4.8 min/4.3 min 6.5 min/4.3 min
Esteves et al. [15•]	Discovery NM 530c	168	1-day ^{99m}Tc -tetrofosmin rest/stress	Rest/stress 10–15/30–45 mCi	4 min/2 min
Sharir et al. [16]	D-SPECT	44	1-day ^{99m}Tc stress/rest sestamibi	Stress/rest 11/28 mCi	4 min/2 min
Berman et al. [17•]	D-SPECT	374	Stress TI/rest ^{99m}Tc	Stress/rest TI/Tc 2–2.5/8–10 mCi;	6 min/4 min
		262	Rest/stress Tc/Tc	Tc/Tc 8–10/25–40 mCi	4 min/2 min
Sharir et al. [19••]	D-SPECT	238	Rest/stress tetrofosmin/ sestamibi ^{99m}Tc	Rest/stress 10/30 mCi	4 min/2 min
Gambhir et al. [31]	D-SPECT	18	1-day ^{99m}Tc -sestamibi stress/rest	Stress/rest 11/28 mCi	4 min/2 min
DePuey et al. [23]	UltraSPECT Widebeam Reconstruction	209	Rest/stress ^{99m}Tc -sestamibi	Rest/stress 9/32 mCi	4.5 min/4 min
Bateman et al. [30•]	Stress only Astonish	110	Stress only ^{99m}Tc -sestamibi	Stress 25–35 mCi	6 min/–

MPS myocardial perfusion SPECT, SPECT single photon emission CT

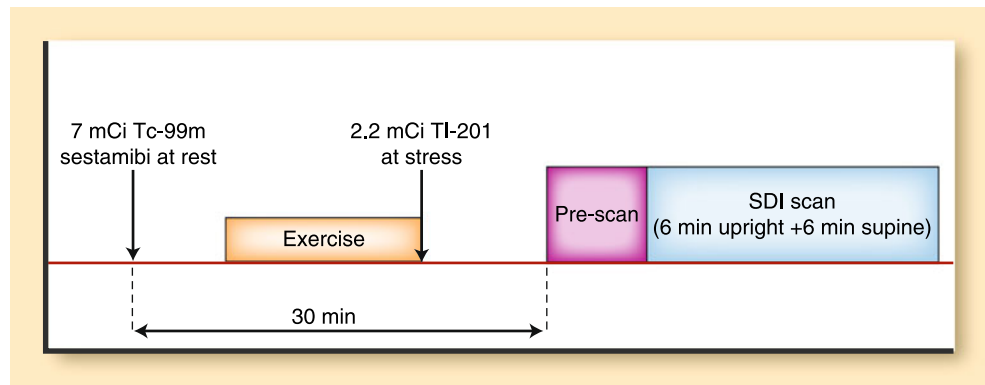
system design eliminates the projection consistencies that would further confound the simultaneous dual isotope imaging. The improved statistical content of new scanners is also a key factor in supporting the ability to image multiple isotopes simultaneously. A natural application is to simultaneously image ^{99m}Tc and ^{201}Tl in a combined rest/stress protocol as originally proposed for standard cameras [33], but never implemented clinically due to technical difficulties.

A proof-of-concept of simultaneous dual-isotope imaging on a multi-pinhole system was recently demonstrated by Steele et al. [34], who used 222 MBq of ^{99m}Tc injected at rest and 148 MBq of ^{201}Tl injected 1 min before the end of exercise and performed simultaneous dual-isotope imaging of ^{201}Tl (stress) and ^{99m}Tc (rest) immediately after completion of exercise, by the three-detector 18-pinhole system, during a single 20-minute imaging session. Ben-Haim et al. [35] reported the feasibility of simultaneous dual-isotope application with the solid-state D-SPECT camera. They studied 24 patients with simultaneous dual-isotope imaging with 80 MBq of ^{201}Tl injected at rest and 250 MBq of ^{99m}Tc sestamibi injected during adenosine infusion. Images were collected in a 15-minute list mode simultaneous dual radionuclide (rest/stress) gated acquisition with a spillover and scatter correction method, specifically designed for solid-state camera. Comparable diagnostic performance and image quality to conventional SPECT with a separate rest ^{201}Tl acquisition on D-SPECT has been demonstrated. The proposed imaging protocol for this application is shown in Fig. 4.

Dynamic Imaging

The potential for absolute measurement of flow and flow reserve has remained the key advantage of PET over SPECT [36]. The new SPECT camera designs, however, with stationary detectors such as the multi-pinhole systems [8, 37], or systems with semi-stationary detectors such as D-SPECT design, where the whole 3D view is captured with limited detector motion in a few seconds, may allow first-pass MPS imaging. The proof-of-concept of such studies for the Discovery NM 530c platform has been demonstrated by Huang et al. [38] with the NCAT digital phantom simulations and one-compartment modeling, for ^{99m}Tc -teboroxime. They concluded that this stationary MPS system can provide a parametric image of myocardial blood flow for this myocardial perfusion agent. A group at Brigham and Women's Hospital in Boston, MA, in collaboration with our center, is currently exploring the quantification of regional and global estimates of coronary flow reserve on the D-SPECT system with ^{99m}Tc sestamibi [39]. MPS imaging is performed with 10 and 30 mCi of ^{99m}Tc sestamibi injected at rest and during vasodilator stress, respectively, with imaging starting immediately with the intravenous bolus injection of radiotracer. Using list mode capabilities of D-SPECT device, the 4-minute stress and rest image data are reconstructed into 70 3.5-second frames. Estimates of the myocardial perfusion reserve can be derived with one-compartment model implemented within the Cedars-Sinai kinetic modeling QPET software in a fully automated mode [40]. Estimates of myocardial reserve can be obtained on a per-vessel or per-

Fig. 4 Illustration of the simultaneous dual isotope (SDI) protocol for the solid state camera



segment basis. Example of dynamic MPS images obtained with this novel imaging protocol is shown in Fig. 5.

Hybrid Imaging

A novel concept in modifying the imaging protocols is to employ hybrid technology [41] that may include novel

software tools for image fusion. Specifically, recent advances in CCTA allow routine dose reduction in prospective mode to the 2 mSv range [42]. CCTA has been shown to have a very high negative predictive value in detection of coronary artery disease. These new developments allow a combined CCTA-MPS imaging protocol with acceptable radiation burden. Exploiting this concept,

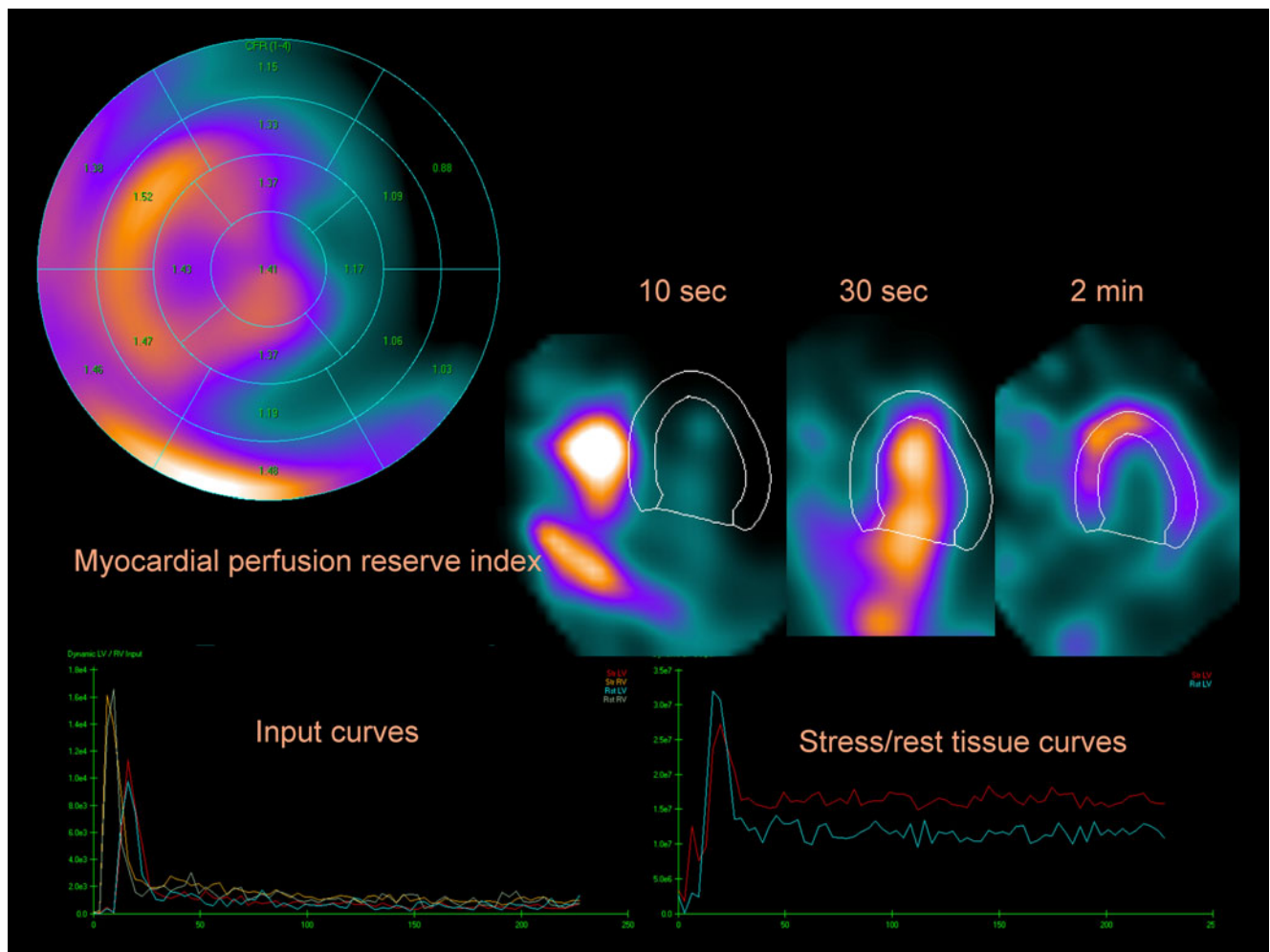


Fig. 5 Dynamic quantitative analysis of abnormal study obtained on D-SPECT system showing segmental analysis of myocardial perfusion index with segmental values (top left), dynamic images, myocardial

perfusion SPECT images (top right), input curves (bottom left), and output stress and rest curves (bottom right). (Data courtesy of Marcelo Di Carli, Brigham & Women’s Hospital)

Husmann et al. [43•] demonstrated the feasibility of stress-only MPS/CCTA protocol. In the study, 1-day adenosine stress/rest MPS using a dose of 300 and 900 MBq of ^{99m}Tc -tetrofosmin, respectively, for stress and rest, with low-dose CT attenuation correction, was combined with CCTA obtained on a separate GE VCT 64-slice scanner in 100 patients. The total patient time scheduled on the hybrid CCTA/stress-MPS examination protocol was 130 min, which is shorter than total times during current 1-day stress/rest MPS protocols. It should be noted that this protocol could be significantly shortened if rest scans were not performed. All CCTA examinations in this study were performed in the 90 min between the first injection of ^{99m}Tc -tetrofosmin and stress data acquisition. They have shown that by using stress-only and prospectively gated CCTA data the combined dose would be 5.4 ± 0.8 mSv, and such hybrid combination offers additional diagnostic information as compared to stress/rest study, without increased radiation exposure [43•]. Furthermore, hybrid cardiac imaging offered a high confidence in image interpretation, as equivocal findings in either of the scans can be resolved by the complementary modality. The principal drawback of this approach is that clinicians usually do not know ahead of time which patients will require both CCTA and MPS studies, such that sequential application of the methods, only when needed, may prove to be the more cost effective approach.

Future Directions

To summarize, many novel protocols have been described recently taking advantage of new detector design and new algorithms for software reconstruction. Primarily, the new clinical studies have aimed to reduce the total imaging time and scanning efficiency. However, in view of recent increased awareness of potential radiation exposure risks, it is possible that these protocols will be modified to reduce the radiation dose instead. It is conceivable that this can be customized based on the patient age, for example [44], since the radiation risk models assume that risk is inversely proportional to patient age. Similarly, to date, stress-only protocols have been demonstrated with conventional patient dosing. It is feasible that an aggressive dose-reducing protocol could involve full-time stress-only scan with reduced dose. Similarly, the hybrid CCTA/stress MPS protocol could be performed with the use of the new efficient detectors, allowing a further dose reduction. The CCTA technology is also advancing rapidly, and recently excellent image quality was reported for new high-pitch spiral CCTA at a consistent dose below 1.0 mSv [45]. In addition, it should be possible to selectively eliminate the stress MPS scan, for example if CCTA was normal [41], reducing the effective radiation burden and procedure cost. Additional improvements in hybrid imaging diagnostic

accuracy could be accomplished by accurate image fusion aiding visual [46] or quantitative [47] analysis.

As the new efficient MPS hardware and software designs are being evaluated clinically, there are preclinical efforts ongoing that demonstrate that even higher sensitivity and efficiency can be achieved in cardiac SPECT. For example, Zeng and Stevens [48] theoretically demonstrated that multi-divergent-beam collimators could be used for stationary cardiac SPECT and that this design has the potential to be superior to currently available multi-pinhole systems in terms of sensitivity by a factor of 2, maintaining the same image resolution. In another report, theoretical calculations for multi-pinhole designs with curved detectors fitted to pinholes demonstrated potential of close to 50% improvement [49] as compared to the latest multi-pinhole designs clinically available.

Conclusions

Nuclear cardiology equipment and associated software have undergone very significant advances in the recent years. These new developments have been employed to test new imaging protocols with improved patient comfort, reduced imaging time, and reduced radiation dose. Novel protocols such as simultaneous dual-isotope, stress-only acquisitions, dynamic imaging, and hybrid multimodality protocols are being explored to further reduce imaging time and also improve the diagnostic information. Additional improvements in efficiency of cardiac SPECT technologies are possible, allowing further reductions in imaging time and radiation dose.

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