

Calculating Coronary Flow Reserve with CZT SPECT

Fundamentals and Applications

White Paper

Introduction

For over half a century, detection of coronary artery stenosis and evaluation of their physiologic significance (i.e., myocardial ischemia) has remained the central paradigm of diagnosis and management of coronary artery disease (CAD). Within this paradigm, myocardial perfusion imaging has played (and will likely continue to play) a central role in noninvasive diagnosis, risk assessment, and guiding management decisions. The significant advances in our understanding of the mechanisms that initiate and facilitate the progression of coronary atherosclerosis have greatly improved our ability to target therapies aimed at prevention, halting progression, or promoting regression of atherosclerosis before it becomes clinically overt. Thus, cardiovascular medicine is witnessing a dramatic shift from the “traditional” paradigm of diagnosing obstructive CAD, to a “new” paradigm in which the central goal is to detect patients who are at risk for developing CAD or who already have pre-clinical (albeit not obstructive) disease.[1]

One tool that has the potential to identify at risk patients and complements the information obtained from traditional MPI SPECT studies is measurement of Coronary Flow Reserve (CFR). CFR measures integrated hemodynamic effects within the epicardial arteries, prearterioles, and arterioles; and is calculated by examining the myocardial blood flow at peak hyperemia (stress) vs. the myocardial blood flow at rest. While CFR measurements are routinely performed in major academic labs with access to PET systems, more generally there is limited access to cardiac PET, and therefore a viable SPECT alternative presents an attractive option. With new technologies, such as the D-SPECT[®], with greater count sensitivity and temporal resolution than traditional Anger SPECT, there is the potential to examine CFR on a more widely available modality.

While traditional MPI SPECT imaging has relatively high sensitivity [2, 3, 4], it has the potential to underestimate the true level of disease (low sensitivity). Adding CFR quantification to an MPI workup enables the clinician to potentially exclude the presence of high-risk CAD in the presence of normal CFR values. [5] In measures of CFR by PET, the presence of impaired function is common among patients with both ischemic and non-ischemic cardiomyopathy and is associated with major adverse cardiac events (MACE). [6] In addition, CFR provides the potential to detect incidences of so called “balanced ischemia” and provides information about the possible presence of micro-vascular dysfunction or multi-vessel disease.

Dynamic-SPECT utilizing D-SPECT system

Introduced to the market in 2007, the D-SPECT dedicated cardiac system utilizes novel CZT (cadmium zinc telluride) SPECT technology with tungsten collimation, thus providing the ability to detect gamma emissions with higher spatial, temporal and energy resolution than is possible with conventional Anger systems. During clinical testing Gambhir and colleagues demonstrated that the sensitivity of the D-SPECT system, with tungsten parallel hole collimators that make use of relatively large 2.26 mm square holes aligned to the CZT crystals, was 10 times higher than that of a conventional Anger camera with sodium iodide scintillation detectors. [7] See Figure 1 for comparative images.

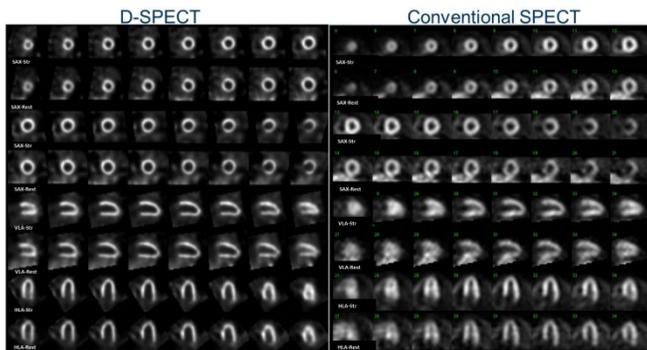


Figure 1: Comparative D-SPECT and Conventional SPECT Stress and Rest images.

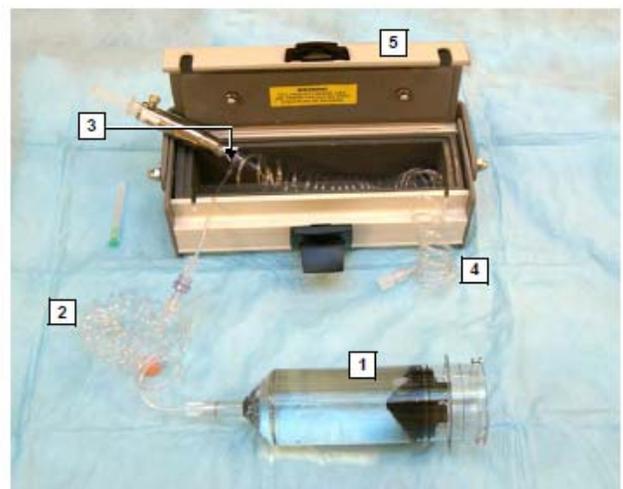
In addition to the benefits of improved sensitivity and spatial resolution, the geometry of the D-SPECT system allows it to be significantly miniaturized and ergonomically optimized for both patients and users. Expected benefits related to the novel D-SPECT technology's increased sensitivity for cardiac imaging include Dynamic SPECT acquisitions that allow kinetic perfusion tracer modeling and measurements of coronary flow reserve, potential reductions in radiation exposure to patients with the ability to use lower radiopharmaceutical doses, and improved patient comfort due to shorter examination times.

Dynamic SPECT Acquisition

The D-SPECT system is comprised of 9 individual detector columns which rotate independently and are able to focus their scanning pattern on a fixed region of interest (ROI) established at the initiation of a dynamic imaging series. Throughout the dynamic scanning process, the detectors perform a continuous step and shoot scanning pattern consisting of multiple sweeps forward and backwards. Each sweep, either forward or backward, is comprised of 10 positions per detector columns (90 positions in total) over approximately 3 seconds. Therefore, a frame of 30 seconds would contain information from 10 sweeps while a frame of 3 seconds would contain information from only a single sweep.

Prior to injection the radioactive tracer is introduced to an injection line, which is then placed in a shielded syringe carrier designed with cutouts at each end for the tubing to pass through. (Figure 2)

The radiopharmaceutical dose is administered using an automatic injector system, with a flow rate of 1-2 cc or mL/sec and a flush volume of 30-40 mL of saline to ensure consistent delivery of a tight bolus. When the dynamic scan is initiated, the injection can be delivered into a patent intravenous line preferentially placed in the antecubital fossa.



No	Details
1	100-200 ml single-use sterile disposable syringe (for injection of sterile saline)
2	Sterile disposable coiled tube (for connection to syringe)
3	Sterile disposable T- or Y-connector with one-way valve for injection of isotope (for drawing the dose into the spiral tube connected to patient)
4	Sterile disposable spiral tube (connects to Patient - via luer connector on IV line)
5	Shielded (lead-lined) accessories case; the spiral tube loaded with the dose is placed inside the case, for radiation safety.

Figure 2

Dynamic images are acquired in list mode over 6 – 8 minutes (with actual timing dependent on the total injected dose).

For rest imaging, an initial dose of approximately 37 MBq (1 mCi) is required in order to position the patient's heart within the field of view and to establish the scanning ROI.

The remaining dose of approximately 148 MBq (4 mCi) is then injected to the patient.

Following the rest dynamic scan, a perfusion scan is acquired per the site's clinical protocol. For rest – stress imaging, no positioning dose is required for the stress injection as the heart location can be identified from the resting activity.

For a stress acquisition, patients receive a pharmacologic stress agent (i.e. Adenosine or Regadenoson) whilst they are positioned on the D-SPECT chair and both the stress radiopharmaceutical injection and the dynamic scan are initiated at peak hyperemia.

Using a dynamic imaging protocol (Figure 3), it is possible to acquire a complete rest – stress dataset for the estimation of CFR in approximately 75 min.

Using the list mode information, a scan can be re-binned into the necessary frame durations required for analysis. Typically, data is re-binned into 32 frames consisting of 3 sec x 21 frames, 9 sec x 1 frame, 15 sec x 1 frame, 21 sec x 1 frame, 27 sec x 1 frame, and 30 sec x 7 frames. An OSEM technique is used for reconstruction of dynamic imaging acquisitions, with 4 iterations and 32 subsets.

Dynamic Imaging Protocol

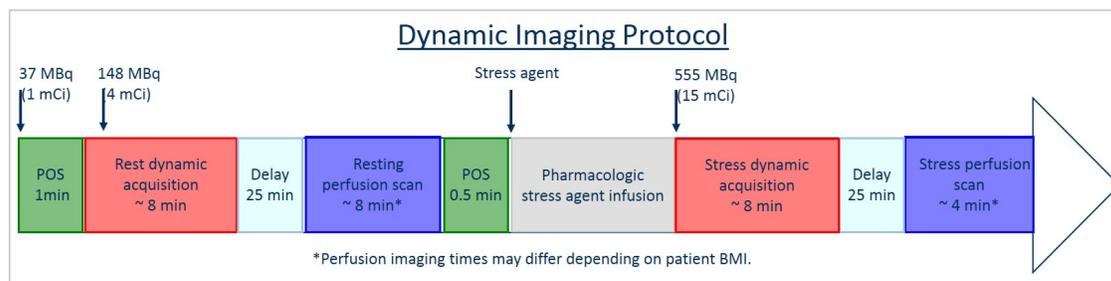


Figure 3: Dynamic Imaging Protocol

**Protocol only compatible with D-SPECT (9 detectors)*

Dynamic SPECT Analysis

Dynamic imaging data and corresponding perfusion information are analyzed using semi-quantitative methods in commercially available software. Left ventricular (LV) endocardial and epicardial surfaces are algorithmically estimated from summed myocardial images beyond the two minute mark. A midwall surface, determined equally distant between the endocardial and epicardial surfaces, is divided into 460 polar map sectors, where LV myocardial tissue time activity curves (TAC) are nearest-neighbor sampled at the center of each sector across all time frames.

Global and regional TACs, vascular (LAD, LCX, RCA) or 17-segmental, are averaged from the polar map sector TACs. The CFR analysis makes use of ROI blood sampling by averaging a box-shaped region in the LV blood pool, specifically in the center of the LV in the short axis and centered at the basal valve plane along the long-axis, across all time frames. The size of the ROI is two pixels wide in the short axis and 30mm long in the long-axis to sample both the LV and left atrial cavities. [8, 9]

A net retention model proposed by Jeffrey Leppo [10] and Katsuya Yoshida [8] using the following modified equation to calculate the retention rate R:

$$R = MBF \times E = \frac{1}{PV \times (t_3 - t_2) \int_{t_2}^{t_3} P(t) - S_m \times C_a(t) dt} \int_{t_2}^{t_3} P(t) - S_m \times C_a(t) dt$$

$$R = MBF \times E = \frac{1}{(CF) \int_0^{t_1} C_a(t) - S_b \times P(t) dt}$$

MBF is the myocardial blood flow. E is the extraction fraction. P(t) is the total myocardial tracer concentration or tissue TAC. C_a(t) is the arterial concentration of the tracer or blood TAC. PV is the partial volume value where for example a system with resolution of 11mm and a myocardium width of 10mm would have a value of 0.63. CF is the correction factor for myocardial density for which is 1.0 if no correction is necessary. S_m is the spillover from the blood pool activity to the myocardium empirically estimated from compartmental analysis [11, 12]. S_b is the spillover from the myocardium to the blood pool activity which can be set to 0.0 assuming the ROI is narrow in the LV and includes the left atrium [13]. Integration limit t₁ denotes the end of the blood pool phase typically at 1.5 minutes while t₂ and t₃ denote integration limits of the average tissue activity typically from 1.5min to 2.5min. Alternatively the integration limits can be offset from the peak of the blood TAC to adjust for the variability of the time between the start of data acquisition and peak time of the blood TAC.

An alternative to the net retention model is the 2-compartment (or 1-tissue compartment) kinetic model with washout parameter k₂ fixed to 0. This is the case for published analysis from initial feasibility cases using D-SPECT and a dynamic imaging protocol performed at Brigham and Women's Hospital, Boston, MA and University College London Hospital, London, UK. They have demonstrated that imaging and quantification of coronary flow reserve is feasible in a human population using the D-SPECT system [14].

Leppo also presented the parameters to relate uptake K₁ to MBF in the following Renkin-Crone equation:

$$K_1 = MBF * (1 - A * e^{-\frac{B}{MBF}})$$

where A=0.874 and B=0.443.

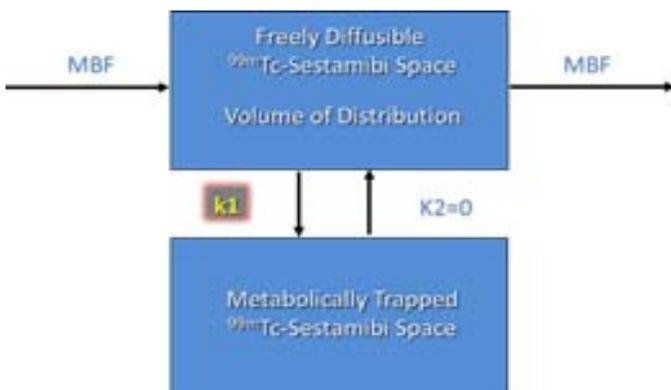


Figure 5 shows normal perfusion Stress and Rest Images from a 73 y/o male.

Figure 6 shows the corresponding Coronary flow reserve data is normal and all vascular territories were confirmed by FFR (LAD – 1.0, LCX, - 1.0, RCA -0.97).

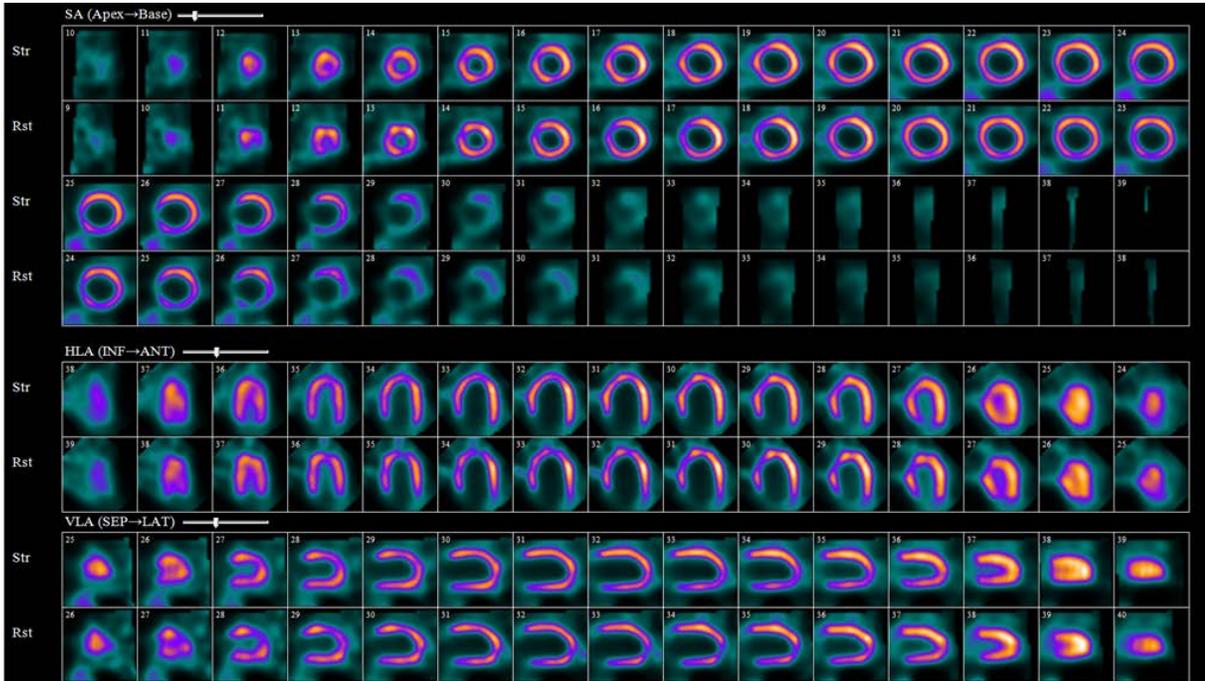


Figure 5

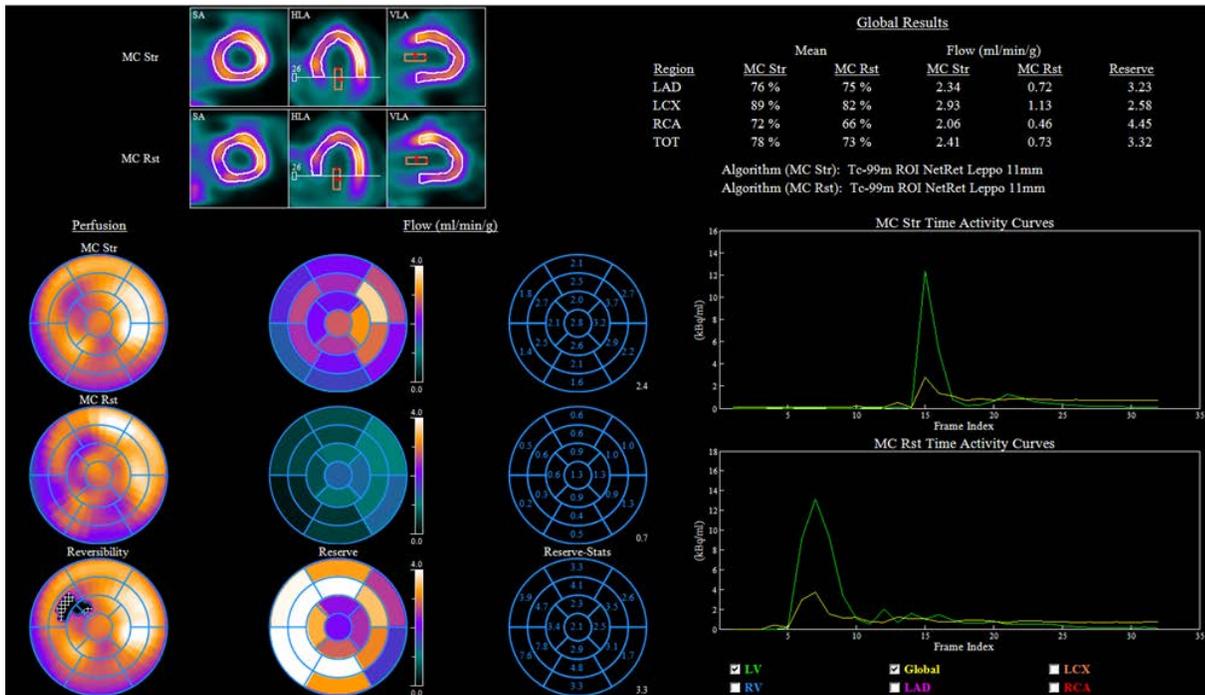


Figure 6

Figure 7 shows a mildly abnormal perfusion study from a 63 y/o female with corresponding flow data showing there is reduced CFR in all vascular territories. Upon further workup of this patient, invasive FFR showed an occlusion in the RCA, FFR of 0.47, 0.74 and 0.72 in the LAC, LCX and Diagonal branch respectively.

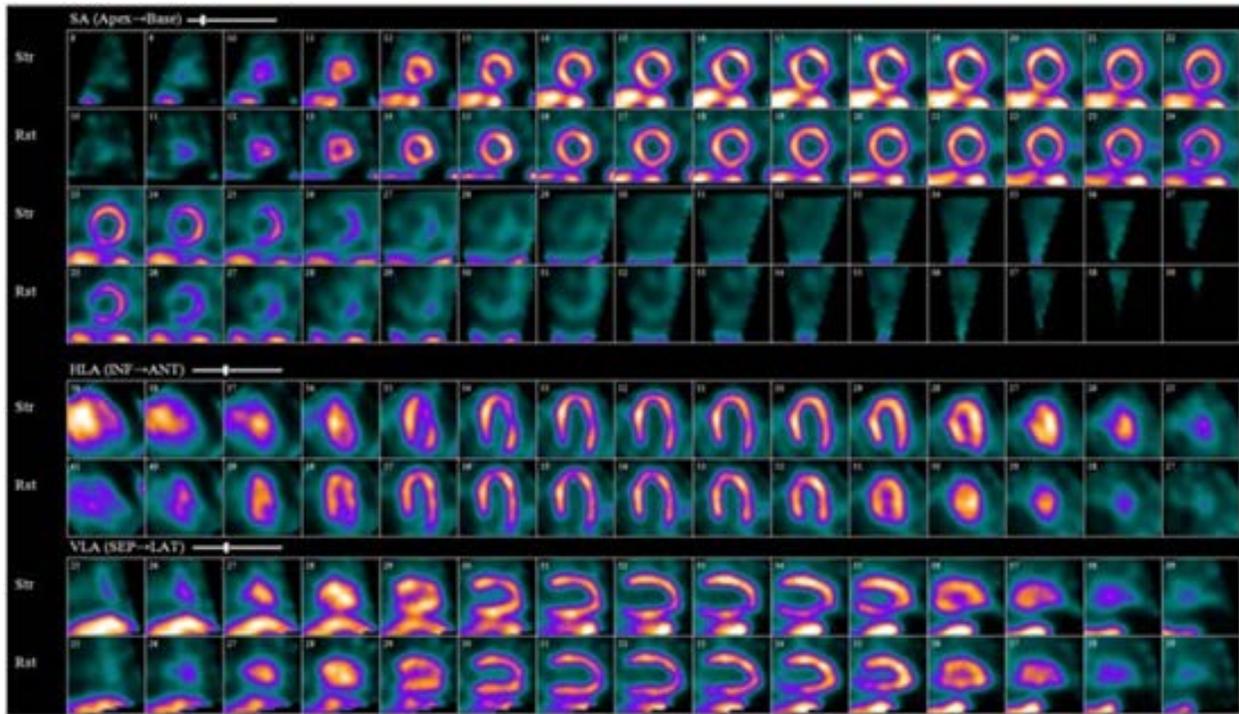


Figure 7

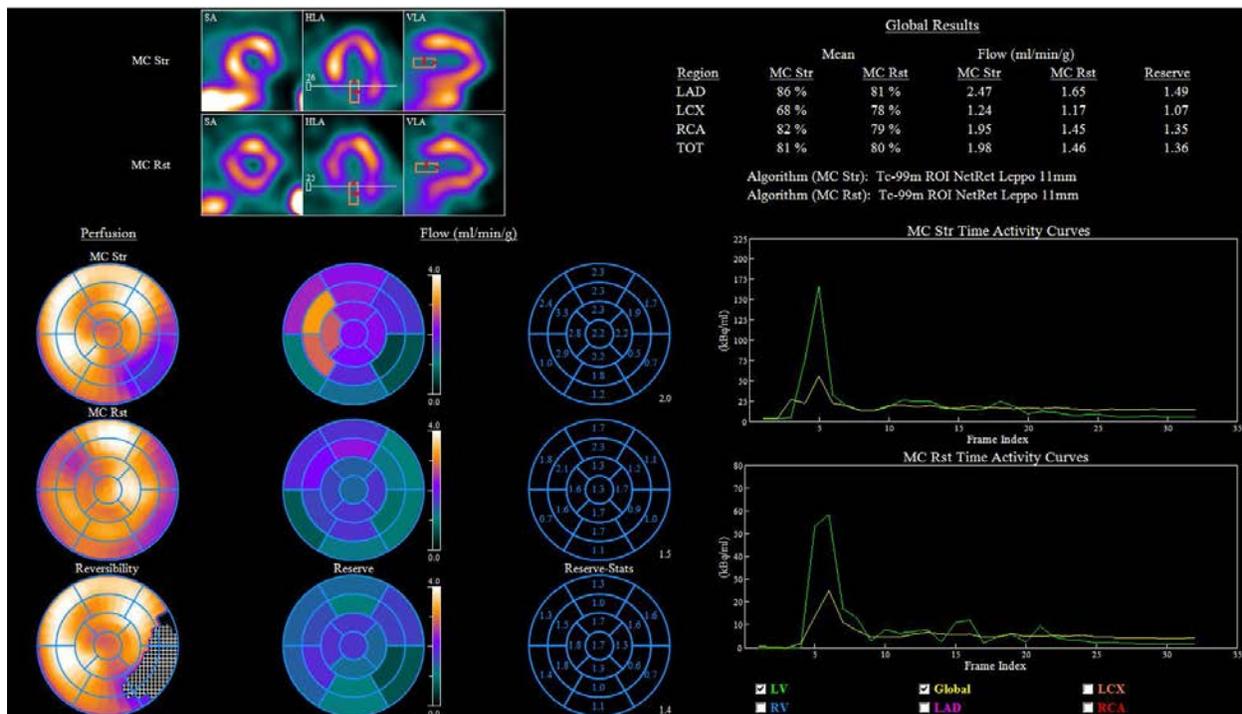


Figure 8

CONCLUSION

Based on interim results from an ongoing trial at multiple large academic centers and previously published data, it appears that it is feasible to calculate coronary flow reserve values that are reproducible using **the** D-SPECT cardiac SPECT device. Having these quantitative values available as part of the standard MPI work up, may allow clinicians to detect multi vessel disease and or “balanced reduction in flow.”

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