Sources of variability of gated myocardial perfusion SPECT quantitative parameters

E. Gordon DePuey, MD^{a,b}

^a Mt. Sinai St. Luke's and Roosevelt Hospitals, New York

^b Mt. Sinai Icahn School of Medicine, New York

Received May 6, 2015; accepted Jul 28, 2015

doi:10.1007/s12350-015-0267-4

See related article, pp. 807–817

In the current issue of the Journal of Nuclear Cardiology in a manuscript entitled “Adopting New Gamma Cameras and Reconstruction Algorithms: Do We Need to Establish Normal Reference Values?” by TL Miao et al, the authors demonstrate variability of gated myocardial perfusion SPECT functional parameters attributable to gender and scintillation camera type.¹ As demonstrated previously by others, volumes are smaller in women. In addition, they demonstrated that left ventricular end-diastolic and end-systolic volumes are smaller in SPECT studies acquired with a solid-state CZT camera and processed with the associated software as compared to those acquired with conventional NaI cameras (one supine and the other semi-sitting) and processed with associated software. One factor they acknowledged that confounded their comparisons was a smaller body habitus of patients imaged with the solid-state CZT camera. This report suggests and emphasizes the multitudinous factors that affect quantitative myocardial perfusion function and perfusion SPECT parameters. The reader is reminded of the great many radiopharmaceutical, hardware-, software-, and patient-related factors that influence the quantitative parameters we use routinely to risk-stratify patients and influence their management.

Some of the more common potential sources of variability in quantitative gated myocardial perfusion SPECT studies affecting both functional parameters and perfusion defect characteristics are listed below:

Radiopharmaceutical

Radionuclide (Tc-99m, Tl-201)

Injected activity (low-dose, high-dose)

Hardware

Camera spatial resolution (NaI, CsI, CZT)

Energy resolution (NaI, CsI, CZT)

Collimator

In-plane linear resolution

Depth-dependent resolution (cardio-focused, multi-pinhole collimators)

Attenuation correction (high-flux CT, low-flux CT, Gd-153)

Software

Filtering (filtered backprojection, iterative reconstruction, none)

Myocardial edge detection

Resolution recovery

Noise reduction/modulation

Quantitative analysis

Comparison with software-specific normal limits

Patient-related factors

Gender

Body habitus

Soft tissue attenuation

Scatter

Position for imaging (supine, upright, semi-upright)

Heart rate.

Some of these factors result in only theoretical shortcomings, whereas others may have important clinical significance. Separate normal files have been established due to variability in some of these parameters, whereas there is no consensus opinion indicating which others merit establishment of separate normal limits or normal files. Some critical and some other more

Reprint requests: E. Gordon DePuey, MD, Mt. Sinai St. Luke's and Roosevelt Hospitals, New York; EDepuey@CHPNET.ORG

J Nucl Cardiol 2016;23:818–23.

1071-3581/\$34.00

Copyright © 2015 American Society of Nuclear Cardiology.

theoretical factors impacting quantitative analysis of gated myocardial perfusion SPECT are discussed below.

Myocardial perfusion SPECT image quality is poorer with Tl-201 than with Tc-99m radiopharmaceuticals. Due to the lower energy of Tl-201, there is inferior intrinsic spatial resolution, more marked localized and diffuse soft tissue attenuation, and greater Compton scatter. Moreover, for most nuclear medicine computer systems Tl-201 SPECT data are processed with a lower critical frequency and higher power/order than Tc-99m data. All of these factors result in lower spatial resolution Tl-201 tomographic images. For gated SPECT, the LV cavity appears smaller, especially at end-systole, and perfusion defects may appear smaller with Tl-201 than with Tc-99m. We previously compared 8-frame per cardiac cycle gated Tl-201 and Tc-99m sestamibi SPECT performed on the same patients and observed that although LVEFs correlated well, they were systematically higher for Tl-201 SPECT.² Accurate determination of transient ischemic dilatation using the dual-isotope protocol suffers from these differences in spatial resolution with Tc-99m vs Tl-201 as well. Likewise, Tl-201 and Tc-99m sestamibi SPECT perfusion defects may differ in extent and severity due to differences in spatial resolution, attenuation, and scatter. Therefore, it is advisable to use separate normal perfusion distribution files for Tl-201 and Tc-99m radiopharmaceutical studies.

The majority of laboratories in the United States use a single-day rest/stress protocol. The count density of resting images is less than one-third that of the stress images, necessitating filtering with a lower critical frequency and higher power/order. Due to the lower count density and the “smoothing” associated with processing, the quality and spatial resolution of the resting gated SPECT images are inferior to those of the stress images. There is consequently potential error in comparing post-stress and resting LVEFs, cavity size for determination of transient ischemic dilatation (TID), and even perfusion stress vs rest defect extent and severity. Despite these potential limitations, a decrease in LVEF from rest to stress and significant TID have nonetheless been demonstrated to serve as important markers of the presence of coronary artery disease and high risk of cardiac morbidity and mortality.

Energy resolution and spatial resolution with solid-state CsI and CZT cameras are superior to those with conventional NaI cameras. This results in sharper definition of the myocardial borders. This difference is accentuated by the fact that all of these new solid-state cameras incorporate advanced software (see below) that further improves resolution and contrast. Therefore, as Miao et al demonstrated in the article in this month’s

Journal, CZT cameras yielded larger LVEDVs and LVESVs.¹

Scintillation camera resolution is also dependent upon collimator characteristics. High-resolution collimators are recommended for Tc-99m myocardial perfusion SPECT studies. Although collimator characteristics vary slightly among vendors, similar clinical results should be anticipated. However, some laboratories instead use low-energy all-purpose collimators. An associated advantage is a more than doubling of counting statistics; however, spatial resolution declines significantly, with a resulting decrease in LV volumes and decrease in resolution of perfusion defects. With standard scintillation cameras equipped with parallel-hole collimators, only such alterations in linear, in-plane (*X* and *Y* planes) spatial resolution are of concern. However with “cardio-focused” collimators such as IQ-SPECT™ from Siemens Medical Solutions, the scanning focused parallel-hole collimators on the CZT D-SPECT™ camera from Spectrum Dynamics, and the multiple multi-pinhole collimators on the Discovery 530c™ from GE Healthcare, differences in depth resolution (*Z* plane) must also be considered. With improved depth resolution, there is better definition of deeper cardiac structures, including the valve plane, which may affect determinations of LV volumes.

Attenuation correction (AC) is an important adjunct to myocardial perfusion SPECT, yielding higher specificity and possibly higher sensitivity in the detection of coronary artery disease. The quality of AC images obtained with x-ray transmission sources is superior to those obtained with Gd-153 scanning line sources. Comparison of AC data to non-AC normal perfusion distribution files, which account for breast and diaphragmatic soft tissue attenuation, will clearly yield erroneous results. Therefore, comparison to gender-matched attenuation-corrected files is strongly advised (Figure 1). The effect on LV volumes is not as significant, although some differences cannot be total discounted.

Filtering, or smoothing, improves image quality by decreasing noise. However, the associated image “blurring” likewise decreases spatial resolution and myocardial border definition. This effect can be quite dramatic with filtered backprojection. With iterative reconstruction, the effect is considerably less marked. However, because iterative reconstruction may increase image noise, most vendors apply some filtering following the iterative reconstruction process. The lower the critical frequency and higher the order/power, the greater the degree of blurring is introduced. The implementation of filters varies among vendors. As for many other parameters discussed above, LV volumes progressively decrease and perfusion defect definition progressively

Figure 1. Composite normal files for men and women obtained with patients imaged supine on a standard dual-head NaI camera (*top row*), upright using the X-ACT™ camera from Digirad Inc. (*middle row*), and upright with low-dose x-ray attenuation correction (*bottom row*).

diminishes with greater degrees of smoothing. Therefore, ideally for perfusion defect definition and LV volume determination a laboratory should use the same, or nearly the same filter that was used to generate the associated normal file.

For the determination of LV volumes, software algorithms delineate the endocardial border at end-diastole and end-systole. Edge-detection methods vary among vendors. In one software package, Emory Tool-box™, the user even has a choice of three different algorithms, R_0 , R_1 , and R_2 , each of which incorporates a different regression equation to determine the LV end-systolic endocardial border.³ More than one option was devised since the initial algorithm did not yield results consistent with common comparators. These different algorithms yield significantly different LV volume and

LVEF results. In Table 1, Tc-99m sestamibi functional gated myocardial perfusion SPECT data processed using these three available algorithms are presented from two patients from our laboratory with non-ischemic cardiomyopathies. Comparison is made with an Ordered Subset Expectation Maximization (OSEM) software program, Evolution™, used by another vendor, GE Healthcare. For both patients computed values vary significantly, with possible clinical consequences. Clearly, if follow-up studies will be performed, it is imperative that the same processing algorithm be applied to both sets of data.

New software is now commercially available to cope with lower myocardial counting statistics and facilitate reduction of injected activity for myocardial perfusion SPECT scans, thereby decreasing patient

Table 1. Functional parameters determined from gated myocardial perfusion SPECT in two patients with non-ischemic cardiomyopathy using three different software programs: OSEM, Evolution™ from GE Healthcare; OSEM, Emory Toolbox™ (ECT) with the R₀, R₁, and R₂ options; and Wide Beam Reconstruction™ (WBR) from UltraSPECT, Inc., incorporating iterative reconstruction, resolution recovery, and noise reduction/modulation with no filtering

	Evolution	ECT R ₀	ECT R ₁	ECT R ₂	WBR
Patient #1					
LVEF (%)	35	38	31	39	30
LVEDV (mL)	67	83	83	83	77
LVESV (mL)	45	51	57	50	54
Patient #2					
LVEF (%)	55	59	52	65	44
LVEDV (mL)	95	121	123	121	100
LVESV (mL)	43	49	58	42	56

radiation exposure. These software programs incorporate depth-dependent resolution recovery and noise reduction/modulation. Resolution recovery increases resolution with depth and improves definition of structures further from the parallel-hole collimator, including the inferoposterior myocardial wall and valve plane. Noise modulation improves image resolution and contrast without smoothing. In previous studies, we demonstrated that LVEFs were significantly, approximately 8 points, lower using such software implemented in Wide Beam Reconstruction™ (WBR) by UltraSPECT, Inc. as compared to either filtered backprojection or iterative reconstruction with OSEM.^{4,5} We found that the reason for the discrepancy was due to more accurate definition of the basal myocardium and valve plane with WBR. The results of WBR reconstruction are also presented in Table 1 for our two non-ischemic cardiomyopathy patients. Reduced count density software is also available from all of the scintillation camera companies. Of note, however, the means by which noise reduction and resolution recovery are implemented in these programs and the resulting image quality differs among vendors.

Although not applicable to functional parameters, comparison of patient data to gender-matched normal files is essential to quantification of the size and severity of perfusion defects. Each vendor uses a different normal file comprising a unique “normal population.” One file may incorporate data only from normal volunteers, another from patients within a certain body habitus range, whereas another may incorporate low-likelihood patients irrespective of body habitus. The greater the subject variability in a normal file, i.e., chest circumference, bra cup size, abdominal girth, and associated degrees of soft tissue attenuation and scatter, the more specific and less sensitive it will be for the diagnosis of

coronary artery disease when data from a particular patient are compared. Conversely, the more constrained the normal file is, the more sensitive and less specific it will be. For this reason, when a patient is followed with sequential myocardial perfusion SPECT studies, it is imperative that the same gender-matched normal limits are applied to each scan.

Physiologically, LV volumes and LVEF differ among men and women as clearly demonstrated by Miao et al in the current article¹ and demonstrated previously by others.⁶ LV volumes also, of course, are directly proportional to body mass index. These authors therefore appropriately analyzed volume *indices*. Most commercially available software programs do not incorporate individual body surface areas and provide only absolute LV volumes. Therefore, individual users should perform these volume index calculations independently.

Similarly, although LV volume and LVEF may vary slightly with patient position, the effect of patient position on LV functional parameters determined by myocardial perfusion SPECT is probably insignificant. However, patient position can most definitely affect apparent perfusion distribution and therefore should be accounted for when patient data are compared to gender-matched normal files. Patients are routinely imaged supine, as were patients in available gender-matched normal files. Whereas prone imaging is of value in differentiating a diaphragmatic attenuation artifact from a true inferior perfusion defect, it is inadvisable to compare prone patient data to a normal supine patient data file. Likewise, when patients are imaged sitting, as with the X-ACT™ camera from Digirad Corporation, or semi-upright with the C-Cam camera from Siemens Medical solutions, the diaphragm shifts downward, resulting in less diaphragmatic attenuation, and the

Figure 2. Rest (*bottom row*) and post-stress (*top row*) Tc-99m sestamibi SPECT in a patient with post-stress tachycardia (HR 130 bpm).

breast become more pendulous, resulting in less anterior and more apical and inferior attenuation. Differences in apparent tracer distribution in patients with a low likelihood of coronary disease imaged supine using a standard two-headed NaI SPECT camera and also the upright X-ACT™ camera from Digirad Corporation are shown in Figure 1. In the male composite file, higher count density is noted in the inferior wall with upright imaging. In the female composite file, higher anterior count density and lower apical and inferior count density are noted with upright SPECT.

Other factors associated with the patient's myocardial perfusion scan may impact on determination of LV volumes and ejection fraction. A severe perfusion defect may confound endocardial edge detection and may result in overestimation of LV volume.⁷ In patients with left ventricular hypertrophy, endocardial edge detection may also be erroneous with an associated overestimation of LV volumes.⁸ Variations in heart rate and arrhythmias may result in “displacement” of gating markers for end-diastole and end-systole, introducing error in quantification of functional parameters.

Finally, day-to-day and even moment-to-moment physiologic variations can affect some of the parameters we measure. For example, at higher heart rates, there is less left ventricular diastolic filling so LVEDV and often LVESV decrease.⁶ Figure 2 demonstrates a post-stress and rest myocardial perfusion SPECT scan in a patient from our laboratory. Following pharmacologic stress, the patient had persistent sinus tachycardia. The heart rate at the time of the 40-minute post-stress SPECT acquisition was 130 beats per minute, compared to a baseline heart rate of 62 beats per minute at the time of the resting SPECT acquisition. The left ventricular cavity size is much smaller in the post-stress tomograms, and there was “reverse TID,” with a TID ratio of 0.32.

In summary, there are a multitude of radiopharmaceutical, vendor-specific hardware and software instrumentation-related, and patient-related factors that will influence cardiac SPECT quantitative perfusion and functional parameters. Although it would be ideal to establish normal files accounting for each variable (for example, a file for obese, tachycardiac women, imaged semi-sitting, undergoing a dual-isotope protocol without attenuation correction, processed with reduced count density software), this is impractical. As imagers, we should be aware of the sources of variability and error of our quantitative parameters. At the least, we should minimize these sources of variability, particularly for sequential studies in the same patient, and compare patient data to normal files only when appropriate.

Disclosure

The author declares that there is no conflict of interest to disclose.

References

1. Miao TL, Kansal V, Glenn Wells R, Ali I, Ruddy TD, Chow BJW. Adopting new gamma cameras and reconstruction algorithms: Do we need to re-establish normal reference values? *J Nucl Cardiol* 2015. doi:10.1007/s12350-015-0172-x.
2. DePuey EG, Parmett S, Ghesani M, Rozanski A, Nichols K, Salensky H. Comparison of Tc-99m sestamibi and thallium-201 gated perfusion SPECT. *J Nucl Cardiol* 1999;6:278-85.
3. Faber TL, Vansant JP, Pettigrew RI, Galt JR, Blais M, Chatzimavroudis G, et al. Evaluation of left ventricular endocardial volumes and ejection fractions computed from gated perfusion SPECT with magnetic resonance imaging: Comparison of two methods. *J Nucl Cardiol* 2001;8:645-51.
4. DePuey EG, Gadiraju R, Clark J, Thompson L, Anstett F, Shwartz SC. OSEM and wide beam reconstruction (WBR) “half-time” gated myocardial perfusion SPECT functional imaging: A

- comparison to “full-time” filtered back projection. *J Nucl Cardiol* 2008;15:547-63.
5. DePuey EG, Bommireddipalli S, Clark J, Thompson L, Srour Y. Wide beam reconstruction (WBR) “quarter-time” gated myocardial perfusion SPECT functional imaging: A comparison to “full-time” ordered subset expectation maximum (OSEM). *J Nucl Cardiol* 2009;16:736-52.
 6. Rozanski A, Nichols K, Yao SS, Malhotra S, Cohen R, DePuey EG. Development and application of normal limits for left ventricular ejection fraction and volume measurements from ^{99m}Tc -sestamibi myocardial perfusion gated SPECT. *J Nucl Med* 2000;41:1445-50.
 7. Nichols K, DePuey EG, Krasnow N, Lefkowitz D, Rozanski A. Reliability of enhanced gated perfusion SPECT in assessing wall motion of severely hypoperfused myocardia: An echocardiographic validation. *J Nucl Cardiol* 1998;5:387-94.
 8. Nichols K, DePuey EG, Friedman MI, Rozanski A. Do patient data ever exceed the partial volume limit? *J Nucl Cardiol* 1998;5:484-90.