Each Nuclear Cardiology lab should have its own lower limit of normal for functional parameters: True or False?

Ahmed Aaty, MD,[a] Alia Abd Al Fattah, MD, FASNC,[b] and Adel Hassan Allam, MD, FASNC[c]

[a] Cardiology, Alexandria University, Alexandria, Egypt
[b] Faculty of Medicine, Critical Care Medicine, Cairo University Kasr Alainy, Cairo, Egypt
[c] Cardiology, Faculty of Medicine, Al-Azhar University, Cairo, Egypt

Received Feb 10, 2017; accepted Feb 10, 2017
doi:10.1007/s12350-017-0830-2

See related article, pp. 652–660

In the field of nuclear cardiology we have three imaging modalities to measure ventricular function: first-pass radionuclide angiography (FPRNA), equilibrium gated radionuclide angiography (ERNA), and ECG-gated myocardial perfusion imaging SPECT (GSPECT) or PET studies.[1] GSPECT was introduced in the 1980s and is considered an ideal technique for combined evaluation of myocardial perfusion and left ventricular function from a single study.[2] Automation of the image processing and quantification has made this technique practical and highly reproducible. In patients with known or suspected coronary artery disease, gating enhances the diagnostic and prognostic capability of myocardial perfusion imaging and provides incremental information over the perfusion data.[3]

During a GSPECT study, a perfusion tracer is injected and is taken up by the LV myocardium. The definitions of the LV myocardium and the LV cavity are achieved by delineating both the endocardium as well as the epicardial edges on the perfusion image. LV regional and global contractile functions are quantified based on the changes in the LV volume, excursion of the endocardium, and brightening of the myocardium from the ECG-gated end-diastole to end-systole.[4]

Reprint requests: Adel Hassan Allam, MD, FASNC, Cardiology, Faculty of Medicine, Al-Azhar University, Cairo, Egypt; *aallamegy@netscape.net*
J Nucl Cardiol 2018;25:661–4.
1071-3581/$34.00

LV volumes and LVEF are usually obtained by applying commercially available software to the reconstructed gated dataset. Software packages developed at Cedars-Sinai Medical Center (QGS), University of Michigan (4D-MSPECT), and Emory University (Emory Cardiac Toolbox)[3–5] are available in many nuclear cardiology labs. Direct comparison between these software packages reveals good correlations in LV volumes as well as LV functional measurements.[6]

In addition to identification of perfusion abnormalities, gated SPECT offers evaluation of systolic functional parameters including LVEF, LVED, and LVES volumes. GSPECT also allows assessment of diastolic parameters such as the peak ejection rate (PER), peak filling rate (PFR), time to peak filling rate (TPFR), and mean filling rate during the first third of diastole (MFR/3). Both systolic and diastolic functional parameters obtained from GSPECT have been validated against similar parameters obtained from other imaging modalities.[7] Other parameters such as transient ischemic dilatation (TID), lung-to-heart (L/H) ratio, and intraventricular synchrony have also been shown to add valuable clinical and prognostic information.[8]

The introduction of ECG gating to MPI allowed the simultaneous assessment of myocardial perfusion and function from a single study. Both global and regional systolic functions have incremental prognostic value over perfusion variables alone. Also, adding ESV or EF to summed stress score (SSS) better predicts mortality in both men and women.[9] On stress SPECT studies, perfusion images capture myocardial perfusion distribution at peak stress, while gated images demonstrate LV contractile function at the time of acquisition. Patients with particularly severe coronary artery disease may show post-stress stunning on SPECT MPI, with regional and global LV dysfunction seen on post-stress images,

but not on the rest images. This finding both confirms myocardial ischemia, and is an adverse prognostic sign. Also, with newer generation cameras, a recent study has shown that it is possible to detect negative EF reserve in patients with significant ischemia using early gated regadenoson stress ultra-fast SPECT.[10]

Impairment of LV diastolic function is defined as abnormalities that exist during LV relaxation and filling. Diastolic dysfunction usually indicates early pathological changes that precede systolic dysfunction and it is particularly seen with hypertension, diabetes, advanced renal disease, and with aging. Diastolic dysfunction carries a substantial risk of heart failure and reduced survival, even in asymptomatic patients. Using echocardiography and Doppler techniques, the LV filling parameters E/A and E/E' ratios provide excellent metrics for the assessment of diastolic function. GSPECT offers PFR, TPFR, and MFR/3 for the evaluation of diastolic function. Good correlation has been found between diastolic parameters measured by these two imaging modalities.[7] Diastolic functional parameters obtained by echocardiography and Doppler techniques are operator dependent and each must be measured separately. However, diastolic parameters obtained by GSPECT are obtained automatically, as a part of routine gated myocardial scintigraphy, and are highly reproducible.[11]

Lung-heart ratios >55% for TI-201 and >44% for Tc-99m tracers, and transient ischemic dilatation (TID) help better detect patients with severe CAD on MPI.[12] However, in the setting of normal MPI, increased TID ratio has a low prevalence and a poor predictive accuracy and should not be considered as a marker of high risk CAD.[13]

Multiple studies have shown the importance of identifying a normal limit for functional parameters obtained by GSPECT in different geographic regions and different ethnicities. Multiple variables may affect these parameters including biological ones such as age, gender, body surface area (BSA), and heart rate; and imaging variables such as isotope used, filters and reconstruction algorithms, number of frames, new generation cameras, imaging protocols, and even imaging position. Some authors have even suggested that each lab should have its own lower limit of normal for functional parameters.[14,15]

One of the first studies of normal limits for LVEF and volume measurements from GSPECT was by Rozanski et al. These investigators reported Gated SPECT measurements in the evaluation of 214 patients with a low likelihood (<10%) of coronary artery disease (CAD), by 99mTc-sestamibi stress-rest myocardial perfusion. Left ventricular end-diastolic volume index (LVEDVI), end systolic volume (LVESVI), and LVEF were measured. They found that women had significantly higher mean resting LVEF than men and a significantly lower mean resting LVEDVI. A significant relationship was found between LVEDVI and LVEF. The normal limits for women and men were also recorded. Rozanski et al recommended the evaluation of normal limits in other laboratories in order to determine the robustness of their clinical normal ranges.[14]

Peace et al derived male and female reference limits for LV functional parameters and evaluated the effect of age, weight, and body surface area (BSA). The lower reference limits of EF for women and men were recorded as well as the upper reference limits of ESV, indexed to BSA. They found no correlation between EF and age, weight, or BSA. There was only a small decrease in ESV with age and an increase with weight and BSA. The gender-specific differences remained even after adjusting for confounding variables. Peace et al thus obtained their own laboratory reference limits for ESV and EF, which they considered to be transferable to other nuclear cardiology labs using similar protocols.[15]

In a multicenter trial performed in Japan (J-ACCESS study), the investigators reported that three quarters of women with a low likelihood of CAD had small hearts.[16] It is well known that in subjects with a small heart, the LVESV is underestimated and the EF is overestimated and that the errors are greater in women. Thus, different thresholds between normal and abnormal subjects depend on the size of the heart. Nakajima et al tried to develop a new method for delineation of the LV and evaluated it in studies using a digital phantom, normal subjects, and patients. They concluded that the volume-dependent edge correction algorithm was able to effectively reduce the effects on ESV and EF of a small heart. The uniform normal values they derived might be applicable to both men and women and to both small- and normal-sized hearts.[17]

In the current issue of the journal, Kapitan et al reports on the normal limits of LV functional parameters by GSPECT in a Latin American country. The study provides detailed information on most systolic and diastolic indices in a low-risk population both at rest and post exercise. In 90 patients (50 men), GSPECT Tc-99m Sestamibi was performed using 2-day rest-stress protocol, with 16 frames/ R-R cycles. Patients with small hearts (<10 mL ESV) at either rest or post stress were excluded. LVVs were corrected to BSA. ESVi and EDVi were expressed in mL/m^2.

Kapitan et al found that LVVs and LVEF were not different between the rest and post exercise set of images. They also reported a trend for the post-stress LVEF to be higher than the rest LVEF at lower rest LVEF values in a population that is expected to have preserved

contractile reserve. These authors also showed that LVVs and LVEF were significantly different between genders, but they did not find differences between rest and post-stress studies in either men or women. TID was similar for men and women, and they set an upper limit of normal for both genders. In this study, there were no differences in diastolic function parameters between the rest and post-stress images in either sex, except for MFR/3, that was lower in men post stress compared to rest. They also reported that PFR was significantly higher in women compared to men both at rest and post stress.

One of the strong points of this article is that the authors were able to compare their results to those of eight similar trials from different geographical regions and ethnicities, despite the wide variability in the design of those studies. The results were comparable to Kapitan et al's for most of the functional parameters.

As pointed out by Kapitan et al, several limitations in their study design should be considered. The utilization of mainly inappropriate patient studies to define the normal values of functional parameters for patients referred for GSPECT MPI is problematic in the era of patient-centered imaging, ''when the right test for the right patient should be performed at the right time.''[18] This study is an observational retrospective one with a relatively small number of patients. It is also a single center trial that may not represent the country or the region. Also of note, one should consider the hardware, the software packages, and the imaging protocols that were used in the derivation of the defined normal values.

We agree with the author's conclusion that cardiac function parameters and volumes are probably not influenced very much by ethnicity or geographic region. However, variables such as gender and BSA should be considered in defining normative ranges for functional parameters. Also, if a nuclear laboratory is to adopt normal range functional values from a study in the literature, the lab should be using hardware, software, and imaging protocols that are similar to those used in the study.

It is important to state that defining the normal limits for functional parameters on GSPECT is not only important for use in clinical reporting, but that such parameters should also be incorporated into scores that also include clinical, exercise, and perfusion parameters. Such scoring systems may improve the diagnostic accuracy of GSPECT, as well as provide incremental prognostic information in different patient populations.

So the answer to our question posed in the title of this article is, No. Some nuclear cardiology labs can adopt normal limits of their functional parameters from studies in the literature provided that these labs use the same hardware, software, and imaging protocols as these studies. Gender and BSA should be considered.

We believe Kapitan et al in this article succeeded to answer an important question for all nuclear cardiology labs.

References

1. Paul AK, Nabi HA. Gated myocardial perfusion SPECT: Basic principles, technical aspects, and clinical applications. J Nucl Med Technol. 2004;32:179-87.
2. Cullom SJ, Case JA, Bateman MD. Electrocardiographically gated myocardial perfusion SPECT: Technical principles and quality control considerations. J Nucl Cardiol. 1998;5:418-25.
3. Germano G, Kiat H, Kavanagh PB, et al. Automatic quantification of ejection fraction from gated myocardial perfusion SPECT. J Nucl Med. 1995;36:2138-47.
4. Germano G, Erel J, Lewin H, Kavanagh PB, Berman DS. Automatic quantitation of regional myocardial wall motion and thickening from gated technetium-99m Sestamibi myocardial perfusion single-photon emission computed tomography. J Am Coll Cardiol. 1997;30:1360-7.
5. Faber TL, Cooke CD, Folks RD, et al. Left ventricular function and perfusion from gated perfusion images: An integrated method. J Nucl Med. 1999;40:650-9.
6. Nakajima K, Higuchi T, Taki J, Kwano M, Tonami N. Accuracy of ventricular volume and ejection fraction measured by gated myocardial perfusion SPECT: Comparison of 4 software programs. J Nucl Med. 2001;42:1571-8.
7. Persson E, Carlson M, Palmer O, Arheden H. Evaluation of left ventricular volumes and ejection fraction by automated gated myocardial SPECT versus cardiovascular magnetic resonance. Clin physiol Funct Imaging. 2005;25:135-41.
8. Chen J, Garcia EV, Folks RD, Cooke CD, Faber TL, Tauxe EL, Iskandrian AE. Onset of left ventricular mechanical contraction as determined by phase analysis of ECG-gated myocardial perfusion SPECT imaging: Development of a diagnostic tool for assessment of cardiac mechanical dyssynchrony. J Nucl Cardiol. 2005;12:687-95.
9. America YG, Bax JJ, Boersma E, Stokkel M, van der Wall EE. The additive prognostic value of perfusion and functional data assessed by quantitative gated SPECT in women. J Nucl Cardiol. 2009;16:10-9.
10. Miao TL, Kansal V, Glenn Wells R, Ali I, Ruddy TD, Chow BJ. Adopting new gamma cameras and reconstruction algorithms: Do we need to re-establish normal reference values? J Nucl Cardiol. 2016;23(4):807-17.
11. Nakae I, Matsuo S, Matsumoto T, Mitsunami K, Horie M. Clinical significance of diastolic function as an indicator of myocardial ischemia assessed by 16-frame gated myocardial perfusion SPECT. Ann Nucl Med. 2008;22:677-83.
12. Sareen N, Ananthasubramaniam K. Left main coronary artery disease: A review of the spectrum of noninvasive diagnostic modalities. J Nucl Cardiol. 2016;23:1411-29.
13. Mandour Ali MA, Bourque JM, Allam AH, et al. The prevalence and predictive accuracy of quantitatively defined transient ischemic dilation of the left ventricle on otherwise normal SPECT myocardial perfusion imaging studies. J. Nucl. Cardiol. 2011;18:1036.
14. Rozanski A, Nichols K, Yao SS, Malholtra S, Cohen R, DePuey EG. Development and application of normal limits for left ventricular ejection fraction and volume measurements from 99mTc-sestamibi myocardial perfusion gated SPECT. J Nucl Med. 2000;41:1445-50.

15. Peace RA, Adams PC, Lloyd JJ. Effect of sex, age, and weight on ejection fraction and end-systolic volume reference limits in gated myocardial perfusion SPECT. J Nucl Cardiol. 2008;15:86-93.
16. Nakajima K, Kusuoka H, Nishimura S, Yamashina A, Nishimura T. Normal limits of ejection fraction and volumes determined by gated SPECT in clinically normal patients without cardiac events: A study based on the J-ACCESS database. Eur J Nucl Med Mol Imaging. 2007;34:1088-96.
17. Nakajima K, Okuda K, Nyström K, Richter J, Minarik D, Wakabayashi H, Matsuo S, Kinuya S, Edenbrandt L. Improved quantification of small hearts for gated myocardial perfusion imaging. Eur J Nucl Med Mol Imaging. 2013;40:1163-70.
18. Hendel R. Professionalism in cardiac imaging. J Nucl. Cardiol. 2016;23(5):1041-52.