Putting gated SPECT and PET left ventricular function computations in perspective

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Left ventricular ejection fraction (LVEF) is frequently cited as the single parameter which has the greatest value in predicting survival for a wide variety of cardiac diseases, particularly ischemic heart disease.¹ Early studies showed that therapeutic interventions, such as coronary bypass, that were directed toward patients with coronary disease and reduced LVEF had the greatest potential for showing a benefit.^{2,3} Originally LVEF was determined by x-ray contrast left ventriculography, but efforts quickly were devoted to validate nuclear techniques such as ERNA to determine EF, which was then used to analyze prognosis in coronary disease and valvular heart disease.⁴ Subsequently, the introduction of gated imaging to myocardial perfusion studies allowed visualization and analysis of regional wall motion, and algorithms incorporating LV modeling assumptions were developed to demonstrate the correspondence between LVEF obtained by gated SPECT (GSPECT) and various established reference standards such as ERNA⁵ and X-ray contrast angiography.⁶ Numerous studies have examined relationships between LVEF measured by gated perfusion imaging using various GSPECT or gated PET (GPET) radionuclides (¹⁸F-FDG, ¹³NH, ⁸²Rb), and have differed according to the patient groups examined and patients' extent of CAD, particularly the degree of resting perfusion abnormality,

which may pose difficulties for algorithms relying on myocardial wall counts.⁷

Along those same lines, the current issue of the Journal includes an informative article comparing GSPECT and GPET LV volume and EF computations to one another, and to cardiac magnetic resonance imaging (CMRI) computations, in patients with prior myocardial infarction.⁸ The algorithms tested included QGS,⁹ ECTB,¹⁰ and 4DM. In establishing the validity of scintigraphic approaches to compute physiologic parameters, reliance on a reference standard is of course important. CMRI frequently is quoted as being the most accurate method for assessing LV volumes and EF,¹¹ because of the relatively higher spatial and temporal resolution attainable by this imaging technology¹² and as a result of its documented reproducibility.^{13,14}

One approach to gauging the reliability of comparing scintigraphic values against CMRI is an examination of the range of results reported in the literature. The article by Yao et al. found limits of agreement of ¹⁸F-FDG PET vs CMRI end diastolic volume (EDV) to be – 143 to + 15 mL for QGS and – 131 to + 48 mL for 4DM,⁸ while a 2004 paper reported much narrower limits of agreement of ¹⁸F-FDG PET vs CMRI EDV of – 40 to + 40 mL for QGS and – 40 to + 38 mL for 4DM.¹¹ Likewise, the article by Yao et al. found limits of agreement of ^{99m}Tc-MIBI SPECT vs CMRI EDV to be – 86 to + 74 mL for QGS, – 88 to + 94 mL for ECTB, and – 165 to + 45 mL for 4DM,⁸ but a 2005 publication found narrower limits of agreement of ^{99m}Tc-MIBI SPECT vs CMRI EDV of – 13 to + 46 mL for QGS, – 31 to + 43 mL for ECTB, and – 30 to + 49 mL for 4DM.¹⁵

Which results are correct? Do GPET and GSPECT EDV computations underestimate true EDV or are values similar? It is not surprising that technical differences in data acquisition and handling methods for GPET and

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GSPECT could be expected to play a role in the details of correlations and agreements among methods. PET scanners of different manufacturers have varying reconstruction algorithms that will influence signal-to-noise ratios as well as spatial and temporal resolution of acquired and reconstructed data. Likewise, CMRI systems using different pulse sequences would not be expected to produce identical data sets for the same patients. Just one CMRI variable is the choice to manually include or exclude visually perceived trabeculations and valve plane leaflets, which will influence CMRI LV volume values.

In their article, Yao et al. compare CMRI to GPET values computed by three different algorithms, each of which has its own underlying LV modeling assumptions. While these three algorithms utilize validated normal limits of relative perfusion databases that are unique for PET radionuclides as opposed to SPECT isotopes, their approaches to the calculation of LVEF and volumes for PET have not been appreciably changed from that of SPECT. All of the algorithms handle the LV outflow tract differently from one another. All assume that regional changes in myocardial wall thickness from diastole to systole are manifest as changes in regional myocardial counts, by way of the partial volume effects,¹⁶ but the manner in which these changes are handled differ among the three algorithms. QGS estimates endocardial and epicardial boundary locations by asymmetric Gaussian fitting functions across myocardial count profiles, and then adjusts these through the heart cycle to increase as apparent myocardial counts increase, while keeping total computed myocardial mass constant throughout the cardiac cycle.⁹ ECTB assumes that all patients have a 1-cm-thick myocardial wall at diastole, and then adjusts wall thickness linearly as maximum myocardial counts change through the heart cycle.¹⁰ 4DM uses gradient images to estimate endocardial and epicardial boundaries, and then applies 1- and 2-dimensional weighted spline functions to generate 3D endocardial and epicardial estimated surfaces.¹¹ All of these algorithms compute EF from changes in LV volumes from diastole to systole, and all were originally developed for ^{99m}Tc GSPECT data; none were originally devised for GPET data.

Partial volume effects may contribute to variations in calculated LV volumes and EFs between SPECT, PET, and CMR. For GSPECT imaging partial volume effects have long been known to cause an underestimation of the smallest volumes,¹⁷ particularly of the smallest ESVs, causing EFs of small hearts and hypercontractile hearts to be overestimated.¹⁸ Previous studies have shown that myocardial counts increase in a reliably

linear fashion with myocardial wall thickening for GSPECT data acquired by conventional rotating Anger cameras, even for patients with known LV hypertrophy.¹⁹ Similar studies have yet to be conducted for the different PET isotopes imaged by modern PET/CT systems, which have higher temporal resolution, and higher spatial resolution for ¹⁸F. Details of these partial volume relationships may vary between SPECT data and PET data, and among the different PET isotopes. The most energetic positrons that are emitted range from a low of 0.64 MeV for ¹⁸F to a high of 3.35 MeV for ⁸²Rb. The more energetic the emitted positron, the further it migrates from the origin of the nucleus that emitted it before annihilating with an electron to produce the pair of 511 keV gamma rays.²⁰ Consequently, ¹⁸F PET images have better spatial resolution than ⁸²Rb PET images, with different details as to partial volume effects. A recent paper suggests that LVEF normal ranges should be established specifically for the individual PET isotopes, such as for ⁸²Rb.²¹

In clinical practice, difficulties in comparing LVEF derived from different algorithms are superimposed on other variables affecting ventricular function, including age, gender, pre-load, and afterload. The latter two may vary significantly between determinations made by different modalities, even if the intervening time interval is short. Some authors suggest that a value of LVEF should specify the blood pressure at time of assessment.²² The extent of perfusion/metabolism mismatch also affects LV volumes and EF. Yao et al. found that GPET, but not GSPECT, underestimated LV volumes at three levels of viability.⁸ However, with sample sizes of only 20 to 31 patients in the subgroups, it would be advisable to confirm these results in larger patient groups.

Consistent with the vast majority of publications that have compared LV function measurements among imaging modalities and algorithms, Yao et al. found significant correlations of GSPECT and GPET LV volumes and EFs with CMRI, and among the different algorithms, but also significant differences among mean values. Most investigations have reported that mean LV volume and EF values and their normal limits are not interchangeable among imaging modalities and between scintigraphic algorithms. Given this state of affairs, what are clinicians to make of the LV volume and EF computations obtained at their particular site, using a specific scintigraphic imaging technology and set of data processing algorithms?

First, though LV volume and EF measurements are important considering their influence on cardiac outcomes,¹ they represent only one component of ventricular function that can be obtained from nuclear

imaging. In the study of Yao et al., the precise numerical values of LVEF for the three modalities differed, but all were in the < 30% range, and on a clinical basis would be considered severely reduced. However, current practice in evaluating cardiac prognosis and the components of ventricular function, particularly using GPET, now go well beyond measuring LVEF. Certainly, the measurement of absolute myocardial blood flow and myocardial flow reserve are required. Recently, Gupta et al. demonstrated that global myocardial flow reserve < 2.0 had a highly significant effect on mortality, even controlling for multiple clinical risk factors including LVEF.²³ Dorbala et al.²⁴ and Van Tosh et al.²⁵ have demonstrated that coronary anatomy, rest and stress myocardial blood flow, and myocardial flow reserve are directly related to resting LVEF and the change in LVEF from rest to stress. Synchronicity of LV contraction is also recognized as a significant component of overall cardiac function, which is now analyzed reproducibly by GSPECT and GPET.^{26,27} It may be helpful to some physicians less familiar with these data to refer to an alternative technology with which the cardiologist is already familiar. For instance, if the institution has more experience with echocardiography than any other approach, then connecting echocardiographic computations to the particular scintigraphic technology being employed would make sense. Some authors advocate that the most important ventricular function parameter in an individual patient is the one most relevant to determining the next best step in the patient's care.²²

In summary, the article in this month's Journal by Yao et al. reports results that are consistent with the majority of the scientific literature, namely, that correlations of LV volumes and EFs are high among algorithms and between modalities but that mean values, and by implication normal limits, differ. This report provides the opportunity to examine the commonalities and differences among LV function parameters in detail, and for patients with prior myocardial infarction and sub-grouped according to extent of viable myocardium. Thus, this investigation reinforces the practice of including GSPECT and GPET measurements of LV function along with the many other clinical parameters in forming a diagnosis, but with the caveat that it is necessary to interpret LV volumes and EF measurements in the context of values that would be obtained by other imaging modalities with which the clinician may be familiar, such as magnetic resonance imaging.

Disclosures

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References

1. White HD, Norris RM, Brown M, Brandt PW, Whitlock RM, Wild CJ. Left ventricular end-systolic volume as the major determinant of survival after recovery from myocardial infarction. *Circulation* 1987;76:44-51.
2. Alderman EL, Fisher LD, Litwin P, Kaiser GC, Myers WO, Maynard C, et al. Results of coronary artery surgery in patients with poor left ventricular function (CASS). *Circulation* 1983;68:785-95.
3. Pfeffer MA, Braunwald E, Moye LA, Basta L, Brown EJ Jr, Cuddy TE, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. *N Engl J Med* 1992;327:669-77.
4. Bonow RO, Green MV, Bacharach SL. Radionuclide angiography during exercise in patients with coronary artery disease: diagnostic, prognostic and therapeutic implications. *Int J Cardiol* 1984;5:229-33.
5. Nichols K, DePuey EG, Rozanski A. Automation of gated tomographic left ventricular ejection fraction. *J Nucl Cardiol* 1996;3:475-82.
6. Williams KA, Taillon LA. Left ventricular function in patients with coronary artery disease assessed by gated tomographic myocardial perfusion images comparison with assessment by contrast ventriculography and first-pass radionuclide angiography. *J Am Coll Cardiol* 1996;27:173-81.
7. Wei H, Tian C, Schindler TH, Qiu CM, Lu M, Shen R, et al. The impacts of severe perfusion defects, akinetic/dyskinetic segments, and viable myocardium on the accuracy of volumes and LVEF measured by gated ^{99m}Tc-MIBI SPECT and gated ¹⁸F-FDG PET in patients with left ventricular aneurysm: cardiac magnetic resonance imaging as the reference. *J Nucl Cardiol* 2014;21:1230-44.
8. Yao Y, Wang D-W, Fang W, Tian Y-Q, Shen R, Sun X-X, et al. Evaluation of left ventricular volumes and ejection fraction by ^{99m}Tc-MIBI gated SPECT and ¹⁸F-FDG gated PET in patients with prior myocardial infarction. *J Nucl Cardiol current issue*.
9. Germano G, Kiat H, Kavanagh PB, Moriel M, Mazzanti M, Su HT, et al. Automatic quantification of ejection fraction from gated myocardial perfusion SPECT. *J Nucl Med* 1995;36:2138-47.
10. Faber TL, Cooke CD, Folks RD, Vansant JP, Nichols KJ, DePuey EG, et al. Left ventricular function and perfusion from gated SPECT perfusion images: an integrated method. *J Nucl Med* 1999;40:650-9.
11. Schaefer WM, Lipke CSA, Nowak B, Kaiser H-J, Reinartz P, Buecker A, et al. Validation of QGS and 4D-MSPECT for quantification of left ventricular volumes and ejection fraction from gated ¹⁸F-FDG PET: Comparison with cardiac MRI. *J Nucl Med* 2004;45:74-9.
12. Dulce MC, Mostbeck GH, Friesse KK, Caputo GR, Higgins CB. Quantification of the left ventricular volumes and function with cine MRI: comparison of geometric models with three-dimensional data. *Radiology* 1993;188:371-6.
13. Sandstede J, Lipke C, Beer M, Hofmann S, Pabst T, Kenn W, et al. Age- and gender-specific differences in left and right ventricular cardiac function and mass determined by cine magnetic resonance imaging. *Eur Radiol* 2000;10:438-42.
14. Moon J, Lorenz C, Francis J, Smith G, Pennell D. Breath-hold FLASH and FISP cardiovascular MR imaging: left ventricular volume differences and reproducibility. *Radiology* 2002;223:789-97.
15. Schaefer WM, Lipke CSA, Standke D, Kuhl HP, Nowak B, Kaiser H-J, et al. Quantification of left ventricular volumes and ejection fraction from ^{99m}Tc-MIBI: MRI Validation and comparison of the

- Emory Cardiac Tool Box with QGS and 4D-MSPECT. *J Nucl Med* 2005;46:1256-63.
16. Galt JR, Garcia EV, Robbins WL. Effects of myocardial wall thickness of SPECT quantification. *IEEE Trans Med Imaging* 1990;9:144-50.
17. Ford PV, Chatziioannou SN, Moore WH, Dhekne RD. Overestimation of the LVEF by quantitative gated SPECT in simulated left ventricles. *J Nucl Med* 2001;40:650-9.
18. Khalila MM, Elgazzara A, Khalilb W, Omarc A, Ziadaa G. Assessment of left ventricular ejection fraction by four different methods using ^{99m}Tc tetrofosmin gated SPECT in patients with small hearts: correlation with gated blood pool. *Nucl Med Commun* 2005;26:885-93.
19. Nichols K, DePuey EG, Friedman MI, Rozanski A. Do patient data ever exceed the partial volume limit? *J Nucl Cardiol* 1998;5:484-90.
20. Cherry SR, Sorensen JA, Phelps ME. Positron emission tomography. In: Cherry SR, Sorensen JA, Phelps ME, editors. *Physics in nuclear medicine*. 4th ed. Elsevier Saunders: Philadelphia, PA; 2013. p. 307-44.
21. Bravo PE, Chien D, Javadi M, Merrill J, Bengel FM. Reference ranges for LVEF and LV volumes from electrocardiographically gated ^{82}Rb cardiac PET/CT using commercially available software. *J Nucl Med* 2010;51:898-905.
22. Marwick TH. Ejection fraction pros and cons. *J Am Coll Cardiol* 2018;72:2360-79.
23. Gupta A, Taqueti VR, van de Hoef TP, Bajaj NS, Bravo PE, Murthy VL, et al. Integrated noninvasive physiological assessment of coronary circulatory function and impact on cardiovascular mortality in patients with stable coronary artery disease. *Circulation* 2017;136:2325-36.
24. Dorbala S, Vangala D, Sampson U, Limaye A, Kwong R, Di Carli MF. Value of vasodilator left ventricular ejection fraction reserve in evaluating the magnitude of myocardium at risk and the extent of angiographic coronary artery disease: A ^{82}Rb PET/CT study. *J Nucl Med* 2007;48:349-58.
25. Van Tosh A, Votaw JR, Reichek N, Palestro CJ, Nichols KJ. The relationship between ischemia-induced left ventricular dysfunction, coronary flow reserve and coronary steal on regadenoson stress gated ^{82}Rb PET myocardial perfusion imaging. *J Nucl Cardiol* 2013;20:1060-8.
26. Cooke CD, Esteves FP, Chen J, Garcia EV. Left ventricular mechanical synchrony from stress and rest ^{82}Rb PET myocardial perfusion ECG-gated studies: Differentiating normal from LBBB patients. *J Nucl Cardiol* 2011;18:1076-85.
27. Zhou Y, Faber TL, Patel Z, Folks RD, Cheung AA, Garcia EV, et al. An automatic alignment tool to improve repeatability of left ventricular function and dyssynchrony parameters in serial gated myocardial perfusion SPECT studies. *Nucl Med Commun* 2013;34:124-9.

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