Striving for consistency in the measurement of LVEF and left ventricular volume

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Myocardial perfusion imaging (MPI) with positron emission tomography (PET) is a robust imaging modality for evaluation of patients at risk for developing or with known coronary artery disease and it has several advantages over other nuclear imaging modalities. The advantages of PET include high spatial and temporal resolution, routine use of either 68-Germanium source or computed tomography (CT) for attenuation correction, use of short-lived radiotracers such as ⁸²Rb or ¹³NH₃ and low radiation exposure.¹ ECG-gated PET permits assessment of left ventricular ejection fraction (LVEF) and volumes, and also has the additional advantage of the ability to measure myocardial blood flow (mL/min/g) and flow reserve. All of those cardiac PET imaging parameters have been well studied and play an important role in diagnosis and prognosis of coronary disease.¹ Given that many critical prognostic and therapeutic decisions are based on left ventricular size and function, LVEF, LV end-diastolic volume (LVEDV), and LV end-systolic volume (LVESV) need to be accurately measured.² In addition to accuracy, reproducibility is also important as are intra-observer and inter-observer variability. Software vendors do their best to demonstrate those qualities before they market their product. However, there is no independent, accepted, gold standard to which a vendor can compare its product. Therefore, demonstration of the reproducibility and the accuracy of the measurement of those variables is of great importance in clinical practice.

Using ECG gating, functional and volumetric measurements are typically performed in conjunction with myocardial perfusion imaging. LVEF is defined quantitatively by analysis of a reconstructed three-dimensional data set using software with automated edge detection where few geometric assumptions need to be made about the LV cavity shape.²

Several different proprietary, quantitative software products such as QPET (Cedars-Sinai), Syngo MBF (Siemens Healthcare), FlowQuant (University of Ottawa Heart Institute), and Corridor4DM (INVIA, LLC, Ann Arbor, USA) and others are currently available for PET MPI processing. They differ in subtle and sometimes, not so subtle ways that may result in differing quantitative results as has been demonstrated for SPECT imaging.³ We know from previous studies of SPECT imaging,^{4–6} that there is variability among the different software products especially in regard to the quantitative assessment of ventricular size and function. Bravo et al evaluated reference values for LVEF, LVESV, and LVEDV in gated ⁸²Rb Cardiac PET/CT using four different commercial software packages (CardIQ Physio (a dedicated PET software)) and three SPECT software packages (Emory Cardiac Toolbox, Quantitative Gated SPECT, and 4DM-SPECT) applied to the PET data and found that LVEF and LV volumes from gated ⁸²Rb PET/CT varied significantly among available software programs and therefore could not be used interchangeably.⁷ Additionally, Oliveira et al also demonstrated that when using different PET software products, the mean values of myocardial blood flow and myocardial perfusion reserve were statistically significantly different.⁸ The authors of that study advised caution when using different software packages as the differences may introduce quantitative variation which could be clinically significant.

In this issue of the *Journal*, Byrne et al also discovered poor concordance in healthy volunteers between the measurements of LVEF and LV volume when comparing two different PET software packages.⁹ Forty

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healthy volunteers were recruited and underwent a standard rest and adenosine stress ^{82}Rb PET/CT protocol twice within 17 ± 14 days. With healthy normal individuals and limited time between acquisitions, they minimized the likelihood of changes in the functional parameters due to varying physiology. That said, there was a statistically significantly lower HR at rest at the second scan, perhaps attributable to a decrease in anxiety that may have been present prior to the first study. The functional PET parameters in those subjects were analyzed with Corridor4DM v 2015.0.0.44 (INVIA, LLC, Ann Arbor, USA) and Quantitative Gated SPECT (QGS) v. 2015.5 (Cedars-Sinai Cardiac Suite, Los Angeles, USA).

Data quantification with 4DM was automatically processed while with QGS, many cases required operator intervention to improve the edge detection results. In addition, the authors quantified LV mass which was only available from 4DM.

They found high reproducibility both at rest and stress for all parameters between two scans using the same software package. In contrast, when comparing LVEF, ESV, EDV at rest and during stress between the two different software packages, they found significant differences and poor concordance in the parameters.

Overall, both rest and stress LVEF were higher on QGS software as compared to 4DM software. They found a mean difference in resting LVEF of 8.7 (8.1 to 9.4, 95% CI) and 8.0 (7.4 to 8.5, 95% CI) for stress LVEF. Interestingly, resting and stress ESV were lower on QGS as compared to 4DM. There was a mean difference of -18.2 (-20.0 to -16.5 , 95% CI) for resting ESV and -13.4 (-14.7 to -12.1 , 95% CI) for stress ESV. Resting and Stress EDV also were lower for QGS as compared to 4DM. Resting EDV showed a mean difference -17.2 (-18.6 to -15.9 , (95% CI) and -6.9 (-8.3 to -5.4) for stress EDV.

Those findings are not completely surprising and were also consistent with similar observations made in the analysis of gated myocardial SPECT data using different software packages.⁴⁻⁶

Overall, different studies by different authors have led to similar conclusions, resonating a message of the importance of selecting a single software package for valid comparisons and the warning that software processing products should not be used interchangeably.⁶

There are many differences which could account for inter-software variabilities. Since ECG gating is a sine qua non, arrhythmias and R-wave recognition errors may contribute to the LVEF variability. Bravo et al speculated that differences in the automatic algorithms for definition of endocardial and epicardial borders and definition of the base and valve planes are the most likely explanation for these differences.⁷ For example,

QGS uses a 3-dimensional model of the heart without specific geometric assumptions of horizontal or transversal long axes and 4DM requires the heart base to be perpendicular to the chosen long axis.^{7,10} Additionally, the QGS valve-plane definition model assumes that the septal wall is shorter than the lateral wall and the basal limits are independently estimated on the septal and lateral walls of the left ventricle, whereas in 4DM, the basal limits are the same in the septal and lateral walls.^{7,11,12} Those, seemingly minor, differences may contribute to quite discrepant results because the calculation of LVEF, for example, is exquisitely sensitive to very minor differences in the location of the valve plane. Moreover, the characteristics of ^{82}Rb itself may lead to increased variability. The 75 s half-life of ^{82}Rb results in rapidly decreasing count rates during the acquisition which may compromise data quality, especially gated data quality. The relatively high energy of the ^{82}Rb positron results in greater positron travel in tissue prior to annihilation which degrades image resolution. It would be very interesting to see if inter-software variability was improved with use of $^{13}\text{NH}_3$. Additionally, variation may be introduced by operator intervention, which is often required when extra-cardiac activity compromises the accuracy of automated edge detection which may also widen inter-software variation.^{3,13} Those variances may become even more pronounced when evaluating structurally abnormal hearts. ESV is often overestimated resulting in underestimation of LVEF due to failure of automatic processing to accurately track the endocardial border in very hypertrophic hearts. Hypertrophy may also influence the measurement of myocardial blood flow with PET. Yalcin et al have shown that there are poorer correlations between software products for measurement of myocardial blood flow with PET when comparing patients with to those without hypertrophic cardiomyopathy.¹⁴ It would have been interesting had Byrne et al included myocardial blood flow data in their comparisons.

The study by Byrne et al does add to the body of literature demonstrating that inter-software differences must be kept in mind when serial evaluations are performed in the clinical setting. Those of us with the “good” fortune or misfortune, as the case may be, of having routine exposure to multiple software products are keenly aware of the differences demonstrated in the current study. Laboratories with access to more than one software product should be especially cognizant of the potential differences so that attempts are made to apply the same processing method to any given patient during longitudinal clinical follow-up and certainly during any clinical trial.

Disclosure

The authors Patrycja Galazka and Steven Port have no conflicts to disclose in reference to this work.

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