

Comparison of three commercially available softwares for measuring left ventricular perfusion and function by gated SPECT myocardial perfusion imaging

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Background. The three softwares, Quantitative Perfusion SPECT (QPS), Emory Cardiac Toolbox, and 4 Dimension-Myocardial SPECT (4DM) are widely used with myocardial perfusion imaging (MPI) to determine perfusion defect size (PDS) and left ventricular (LV) function. There are limited data on the degree of agreement between these methods in quantifying the LV perfusion pattern and function.

Methods and Results. In 120 consecutive patients who had abnormal regadenoson SPECT MPI with a visually derived summed stress score ≥ 4 , the correlation between the softwares for measurements of PDS, reversible, and fixed defects was poor to fair (Spearman's $\rho = 0.18-0.72$). Overall, estimation of defect size was smaller by QPS and larger by 4DM. There was discordance among the softwares in 62% of the cases in defining PDS as small/moderate/large. The correlation between the softwares was better for measuring LVEF, volumes and mass ($\rho = 0.84-0.97$), and discrepant results for defining normal/mild-moderate/severe LV systolic dysfunction were prevalent in 28% of the patients.

Conclusion. There are significant differences between the softwares in measuring PDS as well as LV function, and more importantly in defining small, moderate, or large ischemic burden. These results suggest the necessity of using the same software when assessing interval changes by serial imaging. (J Nucl Cardiol 2014;21:673–81.)

Key Words: Myocardial perfusion imaging • single-photon emission-computed tomography • left ventricular ejection fraction • perfusion defect size

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INTRODUCTION

ECG-gated myocardial perfusion imaging (MPI) with single-photon emission-computed tomography (SPECT) is the most widely used imaging modality in the diagnosis and risk assessment of patients with ischemic heart disease.¹⁻³ MPI generates information on myocardial perfusion [reversible defects (ischemia) and fixed defects (scar)], left ventricle (LV) ejection fraction (EF), volumes, mass, regional wall motion, and thickening. The visual interpretation of MPI is dependent on observer's expertise and is less reproducible than automated methods.^{4,5} There are three widely used commercial softwares for automated measurements; Quantitative Perfusion SPECT (QPS, Cedars-Sinai Medical Center, Los Angeles, CA, USA), Emory Cardiac Toolbox (ECTb, Emory University, Atlanta, GA, USA), and 4 Dimension-Myocardial SPECT (4DM, University of Michigan, Ann Arbor, MI, USA).

Several studies have demonstrated that the above mentioned softwares have a strong correlation with each other, and with an independent "gold standard" in estimating LV function and volumes.⁶⁻¹³ In contrast, there are limited data on the degree of agreement between these programs in assessing perfusion abnormalities,^{5,14-16} and no data regarding agreement of the three softwares in measuring perfusion defect size (PDS) and the size of reversible perfusion defects using polar maps.

The aim of this study was to examine the correlation and agreement between the three programs in assessing PDS, and reversible defect size (by polar maps) as well as LVEF, end-diastolic volume (EDV), end-systolic volume (ESV), and mass.

METHODS

Study Population

Data were collected from 120 consecutive patients who had abnormal regadenoson MPI with a visual SSS ≥ 4 performed between July and September 2008 at University of Alabama at Birmingham Medical Center. All studies were performed using a stress/rest sestamibi protocol, in which MPI data were acquired without attenuation correction. The Institutional Review Board for Human Research at the University of Alabama at Birmingham approved this study.

Imaging Protocol

SPECT images were acquired and processed using previously described methods from our laboratory and in accordance with the guidelines of the American Society of Nuclear Cardiology.¹⁷ Image interpretation was done without attenuation or scatter correction. In order to determine inter-observer variability, 35 studies were reanalyzed by a second observer who was blinded to the initial results.

Quantitative SPECT

Automated quantitative analysis was performed using ECTb (version 3.1), 4DM (version 2010.0.1.108), and QPS (version 2008.0.0.14158) on a central workstation with automated processing.¹⁸⁻²⁰ All the analyses were performed as suggested by the manufacturers of the softwares. These programs provide the extent of the stress-induced PDS by polar maps (expressed as percent of LV myocardium), the extent of reversible (ischemia), and fixed defects (scar) as previously described.^{13,21-23} In addition, the following quantitative results were obtained with each software package from the gated SPECT images: LVEF, EDV, ESV, and LV mass.

Statistical Analyses

All continuous observations in this study violated the normality assumption as tested by Shapiro-Wilk test and were therefore compared between the three groups using the Friedman test. To test bivariate correlation among variables, we used the non-parametric Spearman correlation test. For the assessment of agreement, Bland-Altman plots were calculated. For each Bland-Altman plot, the values for the X-axis were calculated by averaging the values obtained from the three softwares. Inter-observer reproducibility was assessed using intra-class coefficient of correlation (ICC).²⁴

An arbitrary classification for Spearman's ρ and ICC was: >0.8 : strong; $0.5-0.8$: fair; <0.5 : poor. All analyses were performed using SPSS version 21 (SPSS, Inc., Chicago, IL, USA). 3D scatter plots were created using data from all three programs for each subject. Scatter plots included a line of unity and a zone of 10% variance created utilizing linear regression. All 3D modeling was carried out using Mathematica version 8 for Windows (Wolfram Research, Champaign, IL, USA). Bland-Altman Plots were generated using Sigmaplot 10.0.0.54. Data are presented as mean \pm standard deviation for variables with normal distribution and as median (interquartile range) for variables without normal distribution. Two-tailed P values $<.05$ were considered statistically significant.

RESULTS

A total of 120 consecutive patients were included in the study. The baseline characteristics of the patients are detailed in Table 1 and are significant for the presence of multiple co-morbidities with a large proportion receiving multiple cardiac medications.

The inter-observer reproducibility of the results was strong for all variables measured using each of the softwares. The ICC ranged from 0.86 to 1.0 for assessment of LVEF, volumes, and mass, and from 0.94 to 0.99 for assessment of PDS (Table S1).

There was poor to fair correlation between the three softwares for assessment of perfusion defect extent (PDS, fixed and reversible defects, Table 2). On Bland-Altman plots, QPS had a bias toward lower values and 4DM toward higher values of defect size

Table 1. Patient characteristics

	Mean ± SD or % (N = 120)
Age (years)	61 ± 13
Male	50%
Race	
Caucasian	64%
Afro-Americans	33%
Diabetes mellitus	51%
Hypertension	86%
Hyperlipidemia	67%
Heart failure	37%
End-stage renal disease	29%
Chronic kidney disease stage ≥3	49%
Prior myocardial infarction	29%
Smoker (current)	25%
Medication use	
Aspirin	60%
Beta blocker	72%
ACE inhibition	60%
Calcium channel blocker	20%
Statin	58%

while ECTb provided values in between (Table S2, Figure 1). The 10% variance zones for PDS and reversible and fixed defect size by the three softwares were wide and a large number of cases lay outside these cones (Figure S1).

In addition to systematic bias, the Bland-Altman plots indicated that there was significant random variance in measurement of PDS (reflected by the spread of the broken lines in Figure 1). In order to assess the random variance, we ranked the PDS values into quartiles (Table S3). Around one half of the patients were ranked in the same quartiles by two different

softwares (47% for QPS and ECTb, 50% for ECTb and 4D-MSPECT, and 44% for 4D-MSPECT and QPS, green shade in Table S3). Majority of the patients were ranked in the same or adjacent quartiles by two different softwares (86% for QPS and ECTb, 93% for ECTb and 4D-MSPECT, and 85% for 4D-MSPECT and QPS, green or orange shade in Table S3).

Figure 2 shows comparison of the three softwares when the defects were categorized into three groups, normal-small (PDS <10%), moderate (PDS 10-19%), and large (PDS ≥20%). There was discordance among the softwares in 62% of the patients (Figure 2A). On pairwise comparisons, the discordance between QPS and ECTb was 50%, between ECTb and 4DM 33%, and between 4DM and QPS 48% (Figure 2B). The corresponding discordances for reversible perfusion defects were 32%, 35%, and 50%, respectively (data not shown). Figure 3 provides an example of a patient with discordant assessment of perfusion defect by the three softwares.

There was strong correlation between the three softwares for assessment of LVEF, volumes, and mass (Table 2). On Bland-Altman analyses, QPS had a bias toward lower values (Table S2, Figure 4) while ECTb had a bias toward higher values for EDV, ESV, and LVEF (Table S2, Figure 4). 4DM had a bias toward lower values for EDV and ESV and higher values for LVEF (Table S2, Figure 4). There were no systematic differences between the three softwares for estimation of LV mass (Table S2, Figure 4). LV volumes, EF, and mass had relatively narrow zones of 10% variance by the three softwares and most cases lay inside these variance cones (Figure S2).

On comparing the three softwares in categorizing LVEF as normal (LVEF ≥50%), mild to moderate (LVEF 35-49%), and severe (LVEF <35%) dysfunction, there was discordance among the softwares in 28% of

Table 2. Bivariate Spearman correlations between values derived from Emory Cardiac Toolbox (ECTb), Quantitative Perfusion SPECT (QPS), and 4D-MSPECT (4DM) programs

	ECTb – 4DM	ECTb – QPS	QPS – 4DM
PDS (%)	0.72	0.56	0.56
SSS	0.45	0.46	0.59
RPD (%)	0.42	0.18	0.40
FPD (%)	0.65	0.44	0.62
LVEF (%)	0.92	0.91	0.92
EDV (mL)	0.96	0.96	0.96
ESV (mL)	0.97	0.96	0.96
LV mass (g)	0.93	0.90	0.84

All *P* values were <.001 except for correlation between ECTb and QPS for evaluation of RPD which was not significant
EDV, End-diastolic volume; *ESV*, end-systolic volume; *FPD*, fixed perfusion defect; *LV*, left ventricular; *LVEF*, left ventricular ejection fraction; *PDS*, perfusion defect size; *RPD*, reversible perfusion defect; *SSS*, summed stress score

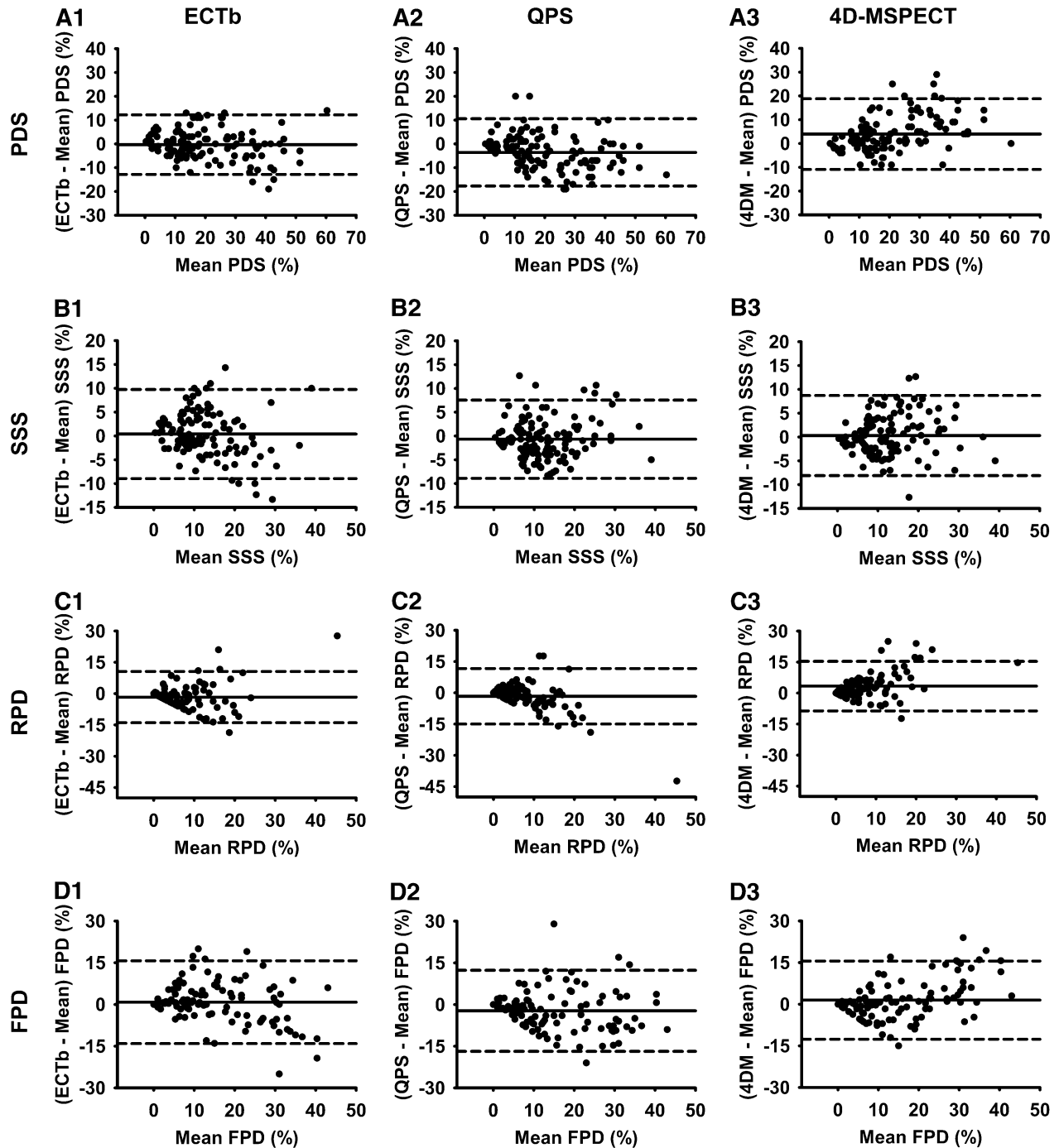


Figure 1. Bland-Altman Plots for (A) PDS, (B) SSS, (C) RPD, and (D) fixed perfusion defect (FPD) for (1) Emory Cardiac Toolbox (ECTb), (2) Quantitative Perfusion SPECT (QPS), and (3) 4 Dimension-Myocardial SPECT (4DM). Solid line represents mean and broken line represents ± 1.96 SD.

patients (Figure 5A). On pairwise comparison, the discordance between QPS and ECTb was 21%, between ECTb and 4DM 20%, and between 4DM and QPS 14% (Figure 5B).

DISCUSSION

An important finding from our study is that for the assessment of PDS and reversible perfusion defects

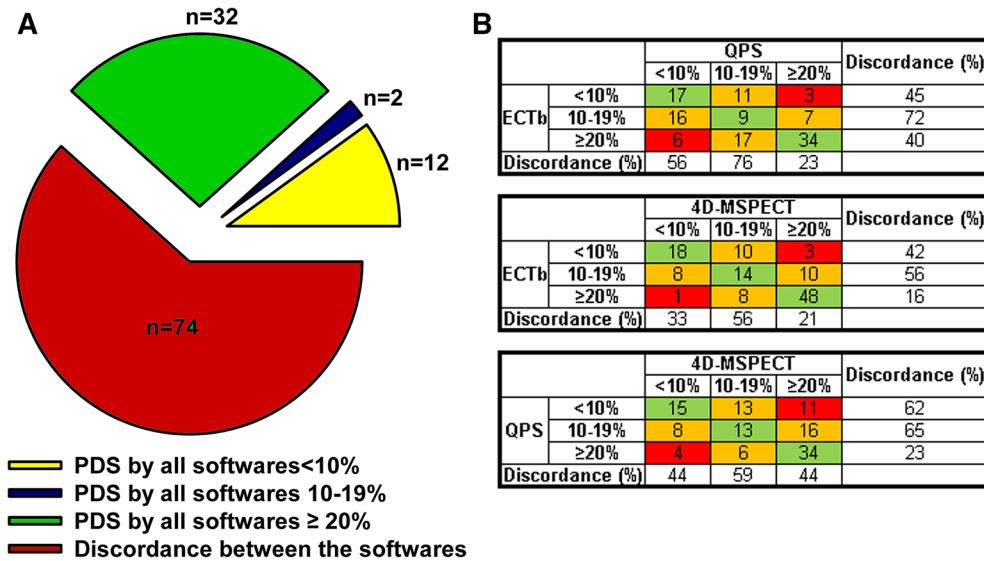


Figure 2. Discordance between the softwares for estimation of categories of PDS as defined by normal to mild (<10%), moderate (10-19%), and severe (≥20%). (A) Pie chart showing percentage of patients with concordance and discordance between the softwares for categories of PDS. (B) Bivariate comparison of softwares for discordance for the three categories of PDS. Last column and row represent the percentage of patients with discordant results for each row and column, respectively.

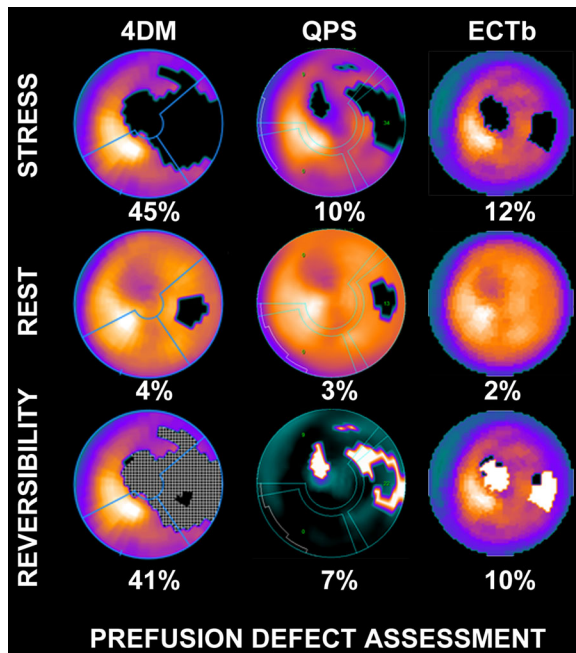


Figure 3. Representative example of a patient with discordant assessment of perfusion defect with the three softwares. Whereas 4DM assessed the reversible perfusion defect as severe (45%), ECTb measured it as moderate (10%), and QPS as mild (7%).

(fixed defects are derived as PDS-reversible defects), the correlation between QPS, ECTb, and 4DM is poor to fair. For measurement of PDS, QPS exhibited a

systematic bias toward lower values and 4DM toward higher values. For measurement of reversible defect size, 4DM showed a systematic bias toward higher values than the other two programs. For assessment of LV volumes and function, there was a strong correlation between the three softwares but significant differences were still detected in ~1/3 of the patients. QPS exhibited a systematic bias toward lower values and ECTb toward higher values of LV volumes. When compared with the other two softwares, QPS exhibited a bias toward lower LVEF. There was a significant discrepancy between the softwares for classification of patients as having mild, moderate, or severe perfusion abnormality (reversible defect or PDS), and depressed LVEF.

Knollmann et al assessed summed stress score (SSS) in 60 randomly selected men with coronary artery disease and found that there was a high correlation between 4DM and QPS.¹⁴ In contrast, three other studies with larger samples sizes have shown significant disagreement between the three softwares for assessment of SSS.^{5,15,16} In our study, based on polar maps analysis, there was discordance among the three softwares in 62% of cases for classification of PDS as mild, moderate, or severe.

Prior studies have demonstrated that the three software programs yield comparable measures of LVEF and volumes.^{1,6,11,12,21,25,26} Our findings are consistent with these studies but also show that in spite of the

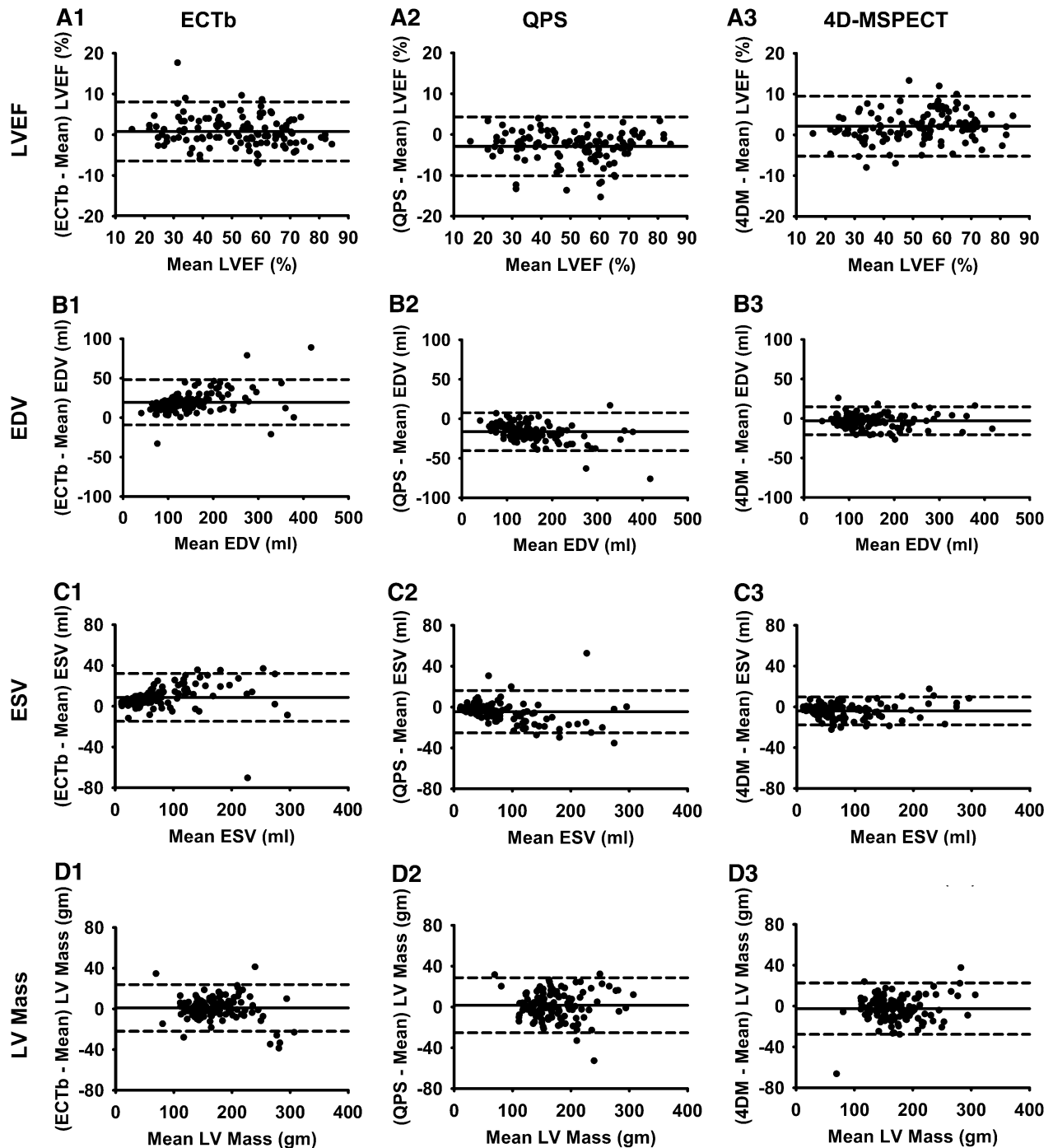


Figure 4. Bland-Altman Plots for (A) left ventricular ejection fraction (LVEF), (B) EDV, (C) ESV, and (D) left ventricular (LV) mass for (1) Emory Cardiac Toolbox (ECTb), (2) Quantitative Perfusion SPECT (QPS), and (3) 4 Dimension-Myocardial SPECT (4DM). *Solid line* represents mean and *broken line* represents ± 1.96 SD.

strong correlation between the softwares, there are significant differences for the measurement; there was disagreement regarding classification into the clinically significant categories of normal, mild-moderate, and

severe LV systolic dysfunction in 28% of the patients. This misclassification is smaller than the discrepancy in the assessment of PDS. However, a measurement of LVEF $<35\%$ is used to guide placement of an

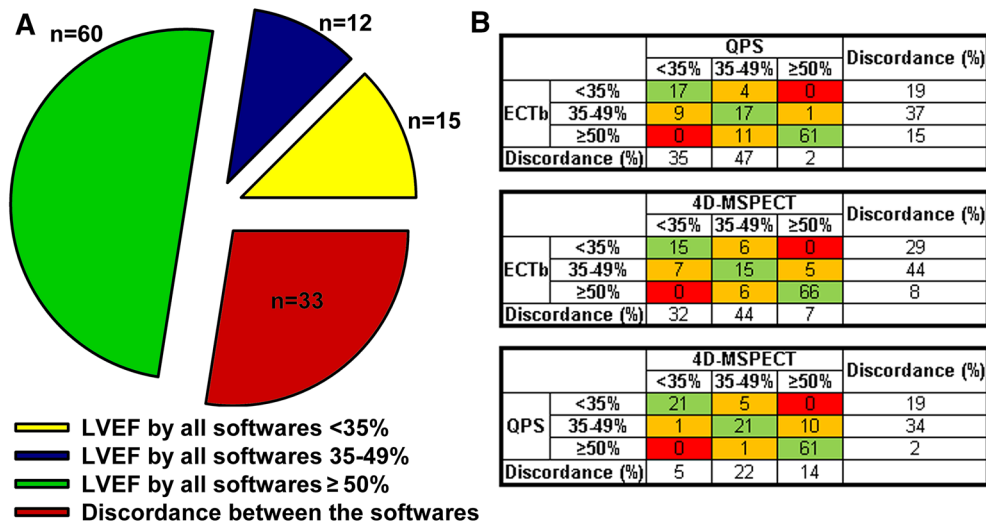


Figure 5. Discordance between the softwares for estimation of categories of LVEF as defined by normal ($\geq 50\%$), mild-moderate (35-49%), and severe ($<35\%$). (A) Pie chart showing percentage of patients with concordance and discordance between the softwares for categories of LVEF. (B) Bivariate comparison of softwares for discordance for the three categories of LVEF. Last column and row represent the percentage of patients with discordant results for each row and column, respectively.

implantable cardioverter-defibrillator in patients with heart failure.²⁷ Due to the high prevalence of heart failure,²⁸ this may translate into a large number of patients either being at increased risk of sudden cardiac death without the protection of a defibrillator, or an increased burden on our health care system with expensive devices placed in patients who may not derive benefits from implantable cardiac defibrillators.

In our study, based on polar maps analysis, there was discordance among the three softwares in 62% of cases for classification of PDS as mild, moderate, or severe. To the best of our knowledge, this is the first study that has compared the performance of the three softwares in assessing PDS and reversible perfusion defects. There are several possible reasons for the differences in results obtained with the three software packages. First, the algorithms used to generate the semi-quantitative polar maps are different. Polar maps provide a standardized 2D representation of the 3D LV myocardium for reproducible comparisons of rest and stress studies or follow-up of a patient over time. Although the three softwares use cylindrical sampling around the basal and mid-ventricular walls, the methods differ in their samplings of the apical region. QPS and ECTb map spherical sampling coordinates in the apical region into polar coordinates in the polar map,⁹ while 4DM maps the entire LV myocardium by cylindrical sampling.²¹ Second, each program defines the count threshold for an abnormal pixel and its reversibility differently. Third, each of these softwares are systematically being refined and updated over time

and therefore even the same software may provide different results when newer versions are used. Fourth, these softwares use different approaches to generate polar maps and to normalize patient data to normal count distributions.^{5,29} Each program automatically detects the orientation of the LV myocardium and places the LV long axis and the apex in default positions based on the contours of the LV myocardium. In addition to defining the epicardial and endocardial borders, the most basal portion of the LV also needs to be defined. The membranous septum and the valve plane do not contain myocardium and are, therefore, not visible on the images and are modeled differently by the softwares. ECTb and QPS assume that the septal wall is shorter than the lateral wall while 4DM assumes that the basal limits are the same in both walls. Therefore, both ECTb and QPS independently estimate the basal limits on each side of the LV, while 4DM presumes that the basal limits are the same but allows the user to override automated defaults. Further, if the perfusion defect involves the basal region, the deficiencies in counts may be ignored to various degrees depending on the software algorithm.

Implications and Limitations

These results have important implications regarding patient care, as accurate assessment of PDS is vital in guiding clinical decision making. For example, observational data indicate that coronary revascularization is associated with improved survival compared with

medical therapy only in patients with moderate-large perfusion defects.³⁰ The ongoing International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) is randomizing patients with stable ischemic heart disease and moderate-severe reversible perfusion defect ($\geq 10\%$ LV myocardium) to an invasive strategy with cardiac catheterization and optimal revascularization plus optimal medical therapy versus a conservative strategy with optimal medical therapy alone and catheterization reserved for patients who fail medical therapy.³¹

These results are also vital for planning future multicenter studies that involve assessment of PDS, as use of different softwares will result in significant heterogeneity. Lastly, the heterogeneity between the results of the three softwares needs to be taken into account when comparing studies using different softwares for analyses of PDS. The message is simple, results by one software should not be generalized into other softwares unless systematic adjustments are made, and the same software should be used in studies that involve serial testing to assess the impact of therapeutic interventions such as coronary revascularization, medical therapy or gene therapy, for example.²² Our study results should not be extrapolated to the performance of the three softwares in identifying presence or absence of PDS, as we did not include normal studies. The agreement between the softwares for presence or absence of a perfusion defect, although not tested here, is expected to be better than the quantitation of PDS.

Currently, there is no valid “Gold standard” to determine which software is correct. Recently, Chrysanthou-Baustert et al have shown that a pumping cardiac phantom can be used as a model to assess the performance of SPECT MPI.³² Future studies are required to see whether this model can be used to compare the performance of the three programs and standardize the measurement of PDS. In the absence of a gold standard, the best surrogate endpoint would be the relative performance of the three programs in predicting outcome in same patient population. Such data are not difficult to generate from existing databases and registries, and can be generated by image analyses using the three programs by an unbiased observer. These data can also be used to categorize PDS size in a clinically meaningful manner, which correspond to outcomes.

CONCLUSIONS

Although the three softwares produce highly reproducible results for automated measurements of PDS and reversible perfusion defects, the correlation between the softwares is only fair to poor. Importantly, the softwares provided discrepant results for important end-points of moderate to severe PDS and reversible perfusion defect,

in a large proportion of patients. The softwares provided discrepant results in a smaller, but still clinically significant, proportion of patients for assessment of depressed LV function. These findings are important for patient care, interpretation of published studies, and planning for upcoming trials. Future studies are required to address the relative prognostic values of the three softwares in same patient population and to develop algorithms to standardize reporting in order to allow for conversion of results from one software to another.

NEW KNOWLEDGE GAINED

There is significant discordance among the three widely used commercial softwares in assessing PDS. This discordance is due to systematic bias and significant random error. In contrast, there is strong correlation between the softwares for assessment of LV size and function. Further, there is significant discordance among the softwares in categorizing perfusion defects into small, moderate or large. The corresponding discordance in categorizing LVEF into normal, mild-moderate and severe dysfunction is smaller but also clinically relevant.

Conflict of interest

The authors have indicated that they have no financial conflict of interest.

Disclosure

Dr Iskandrian is a scientific advisor for Rapidscan, Pharma and has received research grants from Astellas Pharma USA. Dr Hage is a scientific advisor for Astellas Pharma USA and has received investigator-initiated grant support from Astellas Pharma USA. The other authors report no financial disclosures.

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