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ORIGINAL ARTICLE

Assessment of diastolic function using 16-frame ^{201}Tl gated myocardial perfusion SPECT: a comparative study of QGS2 and pFAST2

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Abstract
Objective The objective of the present study is to investigate the correlations across various types of interface software for ^{201}Tl gated myocardial perfusion SPECT (MPS) in calculating two common diastolic function parameters (DFx), peak-filling rates (PFR), and time-to-peak filling (TTPF).
Methods A total of 109 patients (66 men and 43 women; age 35–78 years) were studied. All patients were classified into three groups (i.e., ND, no-defect group; SD, small-defect group; LD, large-defect group) to clarify the influence of perfusion defects possibly affecting the analysis. Two kinds of available software, namely, quantitative gated SPECT (QGS2) and perfusion and functional analysis for gated SPECT (pFAST2) with cardioGRAF were used to obtain PFR and TTPF. Finally, we analyzed the correlation between DFx obtained with the two different kinds of software.
Results The values of LVEF, PFR, and TTPF were assessed in all patients. In both the ND (correlation coefficients were 0.92, 0.79, and 0.99, respectively) and SD groups (correlation coefficients were 0.74, 0.88, and 0.98, respectively), a strong correlation was observed. In contrast, PFR did not show a significant correlation in the LD group.
Conclusions With the two different kinds of software, QGS2 and pFAST2, the calculated PFR was almost equal and showed good correlations in both ND and SD groups. In contrast, the numerical value varied between the two methods, and its correlation was poor in the LD group. However, TTPF showed a good correlation regardless of the presence of perfusion defects, and the values were equal. TTPF was confirmed to be a stable diastolic index across the two kinds of software, QGS2 and pFAST2, in ^{201}Tl gated MPS.

Keywords Left ventricular diastolic function · ^{201}Tl gated myocardial perfusion SPECT · QGS2 · pFAST2

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Introduction

Abnormality of left ventricular (LV) diastolic function (DFx) is frequently the earliest indicator of LV dysfunction in many diseases, including coronary artery disease (CAD) [1], congestive heart failure (CHF), cardiomyopathy [2], valvular heart disease [3], and diabetes mellitus [4]. In particular within heart failure, isolated diastolic dysfunction in which systolic function is normal as diastolic function is disturbed, is really present in 40%–50% of cases [5]. It is, therefore, extremely important to diagnose cardiac diastolic dysfunction.

In addition to myocardial perfusion, gated myocardial perfusion SPECT (MPS) is widely used for the assessment of systolic function (SFx) by the measure-

ment of LV ejection fraction (LVEF) and LV volumes using a variety of commercially available software programs [6–8]. For the evaluation of DFx, Doppler echocardiography and, although the versatility is limited, first-pass and gated blood pool scintigraphy (GBPS) are the established procedures [9–11]. The assessment of DFx has also been shown to be feasible with gated MPS [12–15]. The stability of DFx variables estimated by ^{99m}Tc-MIBI gated MPS has been reported recently [16]. However, the stability of DFx variables is unclear, and normal values for DFx parameters using ^{201}Tl gated MPS have not yet been described. Furthermore, there is no agreement as to which DFx variables are likely to be most effectively measured with ^{201}Tl gated MPS. Although ^{201}Tl is inferior to ^{99m}Tc in image quality [17], we can diagnose multivessel disease by the washout rate of ^{201}Tl [18]. On the basis of the uptake mechanism, it is effective in the estimation of myocardial viability [19, 20]. It is, therefore, still used routinely for practical purposes.

Several kinds of gated SPECT software are available for clinical use, and diastolic parameters can be calculated by software such as quantitative gated SPECT (QGS2, Cedars-Sinai Medical Center, Los Angeles, CA, USA) [6] and perfusion and functional analysis for gated SPECT (pFAST2; Sapporo Medical University, Sapporo, Japan) [8]. This software, pFAST2, is released to general institutions freely, and installation is possible with a PC. The software, therefore, is used for clinical purposes at many hospitals. These programs have correlated well with conventional methods for calculating EF [6, 8, 21, 22]. With regard to systolic indices, a correlation between different software is reported [23]. However, only a few clinical studies have been conducted regarding the cardiac diastolic function parameters estimated by gated MPS [12, 16, 24].

The objective of the present study is to evaluate correlations between the two software programs (QGS2 and p-FAST2) in computing gated SPECT diastolic function parameters in both patients with and without perfusion defects. We also discuss whether we might compare diastolic function parameters calculated by different software in the follow-up of the same patient.

Materials and methods

Patient population

The study population comprised 109 patients referred for stress/rest gated MPS who met the following criteria: technically acceptable normal rest and gated MPS, achieving 85% of maximum predicted heart rate during symptom-limited treadmill exercise (Bruce protocol). The diagnoses for these patients consisted of old myocardial infarction (n = 31), old myocardial infarction with angina pectoris (n = 25), angina pectoris (n = 43), and finally diagnosed as normal (n = 10). No patients had valvular regurgitation. The so-called small heart patients were excluded from the present study. Namely, such cases, in which the lumen of left ventricle could not be visualized separately owing to its low volume even after the enlargement procedure, were excluded from the study. All patients signed informed consent forms prior to the study, and the study protocol was approved by the research council of our institution.

According to Nakajima et al. [23], all the patients were classified into three groups on the basis of the myocardial SPECT findings. The no-defect (ND) group comprised 35 patients in whom resting perfusion SPECT found no perfusion defect. The small perfusion defect (SD) group comprised 54 patients with a small perfusion defect. The large perfusion defect (LD) group comprised 20 patients with a large perfusion defect. The criteria were visually assessed by two nuclear medicine physicians, who reached a consensus on the polar map images. On the polar map image, which consisted of 20 segments (six basal portion, six mid-portion, six apical portion, and two apex), four-point scoring analysis was done. The defect score was defined as follows: 3, perfusion defect; 2, severe low perfusion; 1, moderate low perfusion; and 0, normal perfusion. On the basis of the total number of segments with severe low perfusion or perfusion defect (score 2 or 3), we classified the patients into three subgroups such as the LD group that included more than seven segments whose defect score was 2 or 3; the ND group that consisted of all segments with defect score 0, and we defined the other patients as the SD group.

Image acquisition/reconstruction

All patients underwent ^{201}Tl MPS following 111 MBq ^{201}Tl injection at peak exercise. Images were acquired with a two-detector camera (e-CAM, Siemens Medical Systems, USA) using elliptic 360° acquisition with 92 projections at 15 s per projection and 16 frames per R–R interval. The projection data were reconstructed into tomographic transaxial images using the filtered back projection (FBP) method and automatic reorientation. Tomographic short-axis images were reconstructed with a Butterworth filter that had a cutoff frequency of 0.4 cycles per centimeter (order 8). No attenuation or scatter correction was used. The pixel size was 5.32 mm.

Assessment of DFx and SFx by the two different kinds of software

For this study, a new version of QGS2 software was used (QGS Companion; Cedars-Sinai Medical Center), which quantifies DFx parameters using the bicubic spline interpolation of the LV volume/time curve. The algorithm for determining edges and calculating volume has been described and validated by Germano et al. [6, 21]. At the same time, we used version 2 of the pFAST2 software [8], which is designed to operate on Windows for personal computers and transfers data online from a SPECT system. After the myocardium was automatically extracted, a region of interest was set using spine interpolation. When the myocardial perfusion defect was large and the fitting deemed inappropriate, the shape would then be adjusted manually. The radial profile curves were generated from the center. The distance from the myocardial maximum point to the epicardial border was defined as 50% of the maximum count. The endocardial border was calculated as the distance from the center to the myocardial peak count plus k times wall thickness, where k was empirically determined to be 0.35.

Automatic processing was initially used for both software programs. When the wall tracing was visually judged inappropriate in using pFAST2, the operator modified the ventricular border surrounding the ventricle and reprocessed the edge.

The LV-filling rate/time curve was composed from the first derivative of the volume/time curve. The peak-filling rate (PFR) was defined as the maximum dV/dt value divided by end-diastolic volume (per second) [16], and a unit of PFR was expressed in EDV/S. The time-to-peak filling (TTPF), expressed in milliseconds, is the interval between end-systole (ES) and PFR. For SFx, LVEF (%) was calculated from the LV volume/time curves as commonly used [6, 16]. Recent QGS2 software computes the DFx parameters in their corresponding units, rather than providing raw frame numbers in brackets, which needed further calculations to find the final unit values like in the previous version.

We also analyzed the differences in percentage (% difference), correlation, and Bland Altman plot in two kinds of DFx parameters and LVEF between QGS2 and pFAST in each group.

Statistical analysis

The results are expressed as mean ± standard deviation. The comparisons between groups were made with the Mann–Whitney U test. The comparisons of proportions were made using Fisher's exact test. The correlations between diastolic function parameters calculated by QGS2 and those calculated by pFAST2 were determined using Pearson's correlation coefficient. At the same time, % differences of all the data were calculated, and the mean value of each of the three groups was compared. Finally, the Bland Altman Plot analysis was performed to evaluate the bias [25] and to establish 2SD values between the two studies. Statistical analysis was performed using the GraphPad Prism 4 for Windows statistical application program. In all assessments, $P < 0.05$ was considered to be statistically significant.

Results

There were no significant differences in clinical parameters among the three subgroups. Regarding mean ventricular volumes, both values of EDV and ESV in the LD group were statistically significantly higher than those in the other subgroups (Table 1). We examined the inter-observer and intra-observer reproducibility of the data from 16 R-R interval gated SPECT in using pFAST2. The inter-observer analysis was performed by two independent observers. The intra-observer analysis was done twice by the same observer. The reproducibility was good in respect to all the LV systolic and diastolic functional variables (Table 2). The values of LVEF,

Table 1 Patients' characteristics

	ND group	SD group	LD group	
Age (years)	67.3 ± 13.1	65.7 ± 10.2	65.6 ± 8.6	NS
M : F	21 : 14	31 : 23	15 : 5	NS
Diagnosis				
Normal	10	0	0	
AP	25	18	0	
AP + old MI	0	12	13	
Old MI	0	24	7	
HR (bpm)	74.8 ± 9.5	69.9 ± 11.7	67.6 ± 4.6	NS
EDV (ml)	58.3 ± 19.2	59.5 ± 19.5	102.1 ± 50.2[a]	<0.05
ESV (ml)	19.0 ± 14.1	26.8 ± 17.9	56.5 ± 43.8[a]	<0.05

AP angina pectoris, *MI* myocardial infarction, *NS* not significant, *HR* heart rate during gated, MPS acquisition, *EDV* end diastolic volume, *ESV* end systolic volume, *M* male, *F* female

[a] Both EDV and ESV were measured by QGS2

Table 2 Reproducibility of various parameters in using pFAST2

	Inter-observer, %CV	Intra-observer, %CV
LVEF	1.32 ± 0.52	1.12 ± 0.51
PFR	1.29 ± 0.86	1.23 ± 0.71
TTPF	1.17 ± 0.62	1.12 ± 0.42

Data are expressed as mean ± SD

Table 3 Differences in percentage of parameters

	ND group	SD group	LD group
PFR (EDV/s)			
QGS2	2.33 ± 0.74	2.55 ± 1.05	1.77 ± 0.61
pFAST2	2.58 ± 0.78	2.61 ± 0.86	1.95 ± 0.52
Difference (%)	14.3 ± 14.3	15.8 ± 20.9	40.2 ± 44.3
TTPF (ms)			
QGS2	195.8 ± 97.6	231.8 ± 90.5	264.7 ± 144.7
pFAST2	195.6 ± 100.6	236.1 ± 98.5	254.5 ± 122.3
Difference (%)	5.1 ± 3.7	6.5 ± 4.8	23.6 ± 48.0
LVEF (%)			
QGS2	73.6 ± 13.0	63.1 ± 13.1	44.8 ± 11.8
PFAST2	74.8 ± 12.6	66.6 ± 14.0	51.3 ± 11.1
Difference (%)	5.9 ± 4.2	10.0 ± 7.3	25.7 ± 24.7

ND no-defect group, *SD* small-defect group, *LD* large-defect group, *PFR* peak-filling rates, *QGS2* quantitative gated SPECT, *pFAST2* perfusion and functional analysis for gated SPECT, *TTPF* time-to-peak filling, *LVEF* left ventricular ejection fraction

Table 4 Differences in percentage of left ventricular volume

	ND group	SD group	LD group
EDV (ml)			
QGS2	58.3 ± 19.2	59.5 ± 19.5	102.1 ± 50.2
pFAST2	76.2 ± 25.1	79.1 ± 29.7	169.7 ± 97.3
Difference (%)	31.4 ± 13.6	35.7 ± 3.7	44.4 ± 7.7
ESV (ml)			
QGS2	19.0 ± 14.1	26.8 ± 17.9	56.5 ± 43.8
pFAST2	22.0 ± 18.7	29.5 ± 22.6	78.9 ± 72.0
Difference (%)	20.8 ± 19.1	17.5 ± 15.7	30.1 ± 17.4

PFR, and TTPF in the three groups of patients are summarized in Table 3. Similarly, both the values of ESV and EDV are summarized in Table 4. Both EDV and ESV estimated by QGS2 were apparently lower than those with pFAST2. The tendency was prominently noted in the LD group.

Correlations of LV systolic and diastolic functional parameters measured by the two different methods

Regarding LVEF, the correlation was good in all groups ($r = 0.92$ in the ND group, $r = 0.74$ in the SD group, and $r = 0.65$ in the LD group, Fig. 1a). The limits of agreement for LVEF were −11.2 to 8.7, −28.2 to 19.5, and −26.5 to 14.5 between the ND, SD, and LD groups, respectively (Fig. 2a).

In both the ND and SD groups, the value of PFR showed an excellent correlation ($r = 0.79$ in the ND group and $r = 0.88$ in the SD group). In contrast, there was no correlation in the LD group (Fig. 1b). The limits of agreement for PFR were −0.61 to 0.58, −1.0 to 0.89, and −1.59 to 1.23 between the ND, SD, and LD groups, respectively (Fig. 2b).

Regarding TTPF, they also showed good correlations ($r = 0.99$ in the ND group, $r = 0.98$ in the SD group, and $r = 0.91$ in the LD group, Fig. 1c). The limits of agreement for TTPF were −20.3 to 20.8, −40.1 to 32.5, and −107.9 to 128.3, respectively (Fig. 2c).

Discussion

The present study demonstrated a good correlation between diastolic function indexes obtained from two different software packages (QGS2 and pFAST2) using different algorithms. Conventionally, ^{201}Tl has been used routinely for the following three reasons. The first is that ^{201}Tl is the agent of choice in identifying myocardial viability on the basis of the assessment of sarcolemma integrity [26, 27]. The second is that ^{201}Tl offers the possibility of assessing LV function at rest and immediately after stress [28]. The third is that it offers indirect signs of LV dysfunction, which are associated with multivessel or severe coronary disease and a poor prognosis [29]. An earlier report confirmed the reliability of ^{201}Tl gated SPECT as a tool for the assessment of LVEF and regional wall motion abnormality (WMA) [30].

However, ^{201}Tl became useless because of its low energy with a lack of feasibility. In particular, plenty of time is needed to acquire counts in gated myocardial SPECT. Recently, a myocardial collimator (Siemens) has been developed and has become widely used. Because of its higher sensitivity, the time necessary to acquire data has been shortened. This instrument will help overcome the drawbacks of ^{201}Tl.

Although the reliability of DFx has been established in gated blood-pool studies [31, 32], it has not been confirmed in gated myocardial SPECT using ^{201}Tl. The most commonly used parameters for assessing DFx are the PFR and the TTPF. Using a new algorithm in QGS2 and pFAST2 software, we evaluated the correlation between these parameters obtained with two kinds of software in patients with suspected ischemia under rest conditions. The TTPF showed good correlations in every group. In contrast, PFR showed poor correlations in the group with large perfusion defects. In an earlier

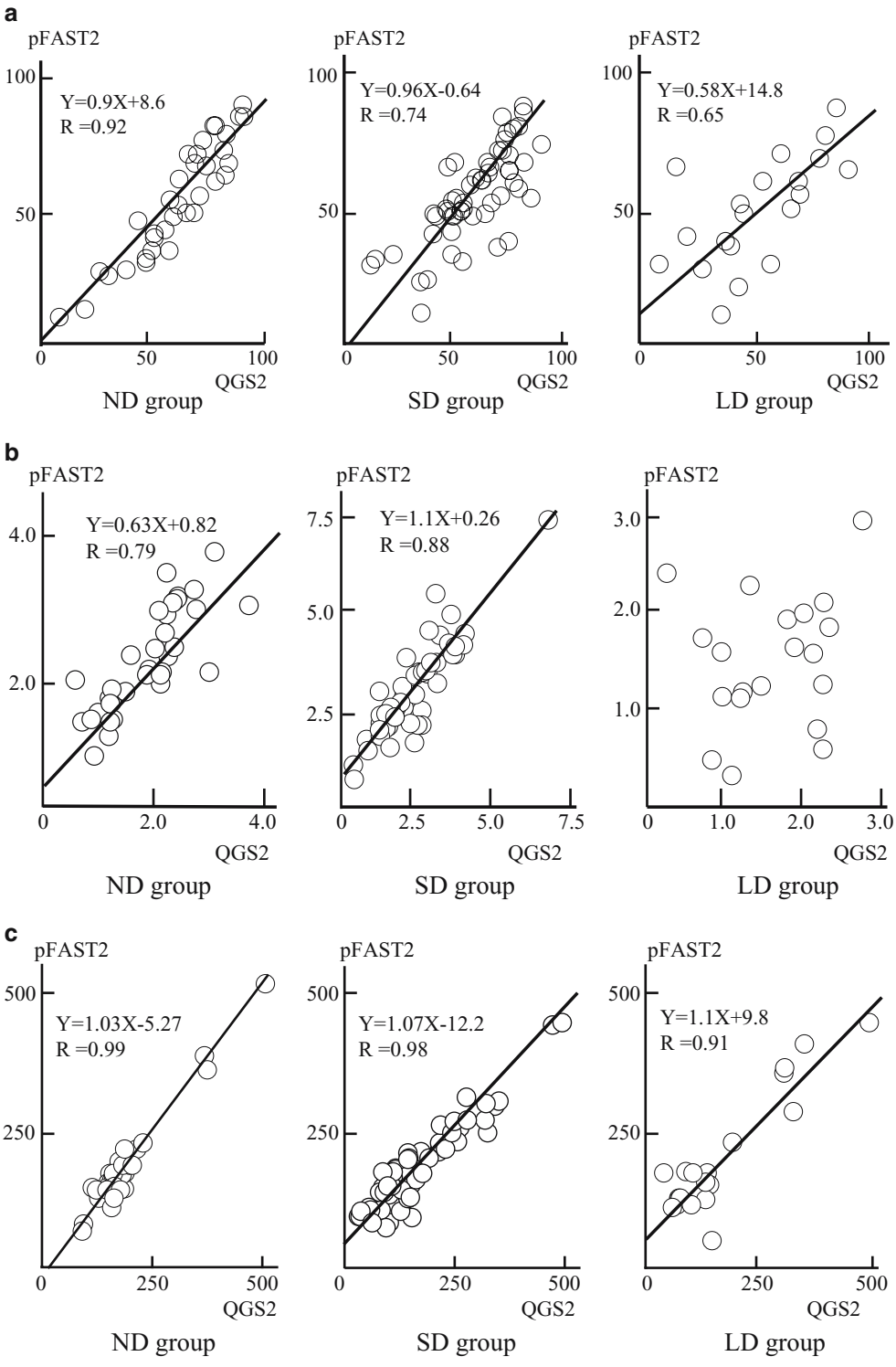

Fig. 1 Correlation of left ventricular ejection fraction (LVEF) obtained from quantitative gated SPECT (QGS2) and perfusion and functional analysis for gated SPECT (pFAST2). Although positive correlations are noted in every condition, the correlation coefficient in the large-defect (LD) group is lower than that in the other two conditions (**a**). Correlation of peak-filling rates (PFR) obtained from QGS2 and pFAST2. Although positive correlations are noted in both the no-defect (ND) and small-defect (SD) groups, there is no significant correlation in the LD group (**b**). Correlation of time-to-peak filling (TTPF) obtained from QGS2 and pFAST2. Significant positive correlations are noted in all three conditions (**c**)

report, QGS analysis could not be performed correctly in cases in which the perfusion defect involved more than 50% of the myocardium [33]. Poor correlations of PFR in the group with large defects seemed to be related to these limitations. It seems that the influence of different exhaustion methods of cardiac contour is strong on the analysis of cases having a large defect. As anticipated, both EDV and ESV estimated by QGS2 were apparently lower than those with pFAST2. Because PFR is an inclination of the LV volume curve, prominent differences in such ventricle volumes are likely to have an important influence. Moreover, PFR is normalized to EDV, and so

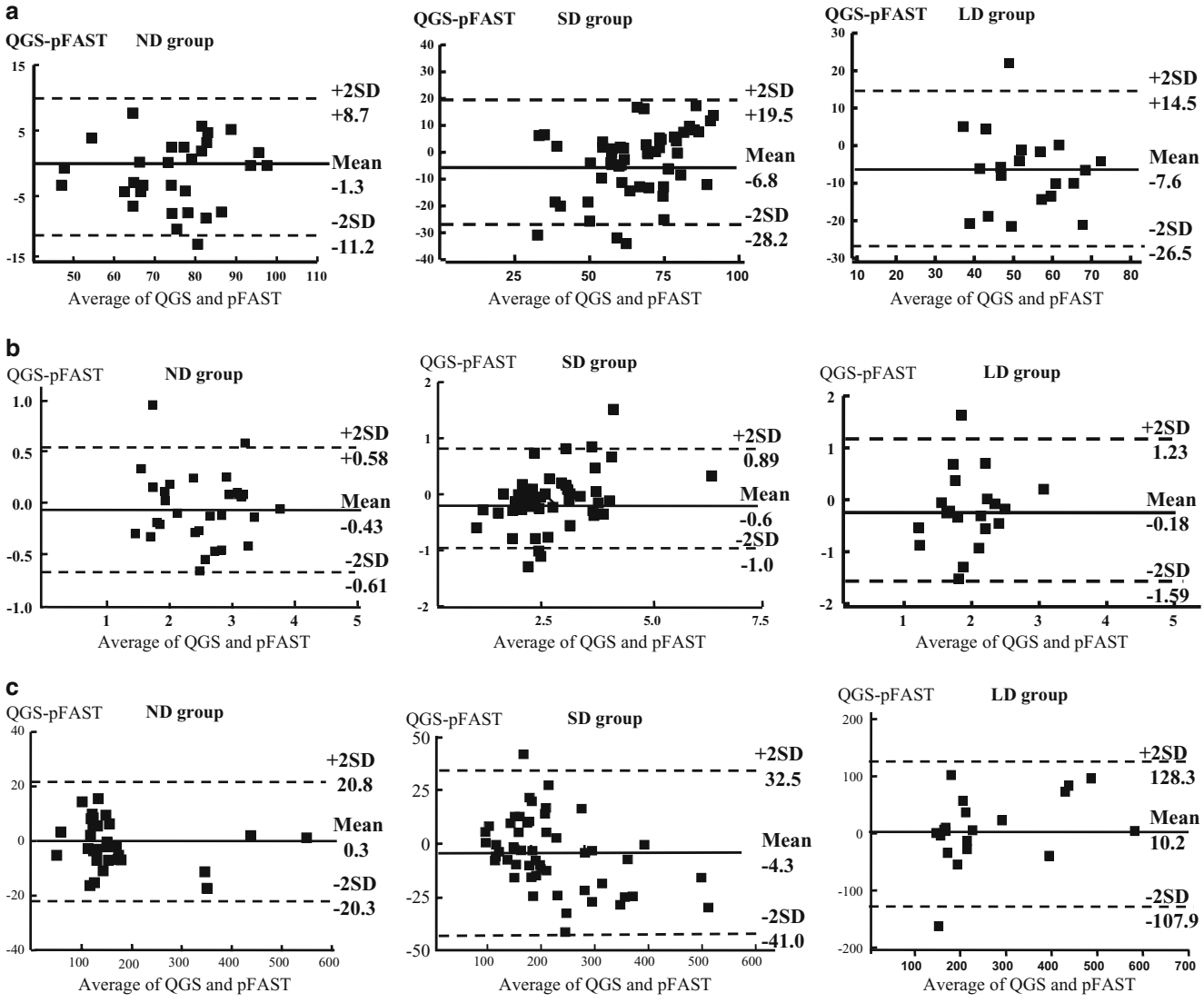

Fig. 2 Comparison of left ventricular function indexes by Bland–Altman plots analysis. *Dotted line* indicates two-SD threshold. Regarding LVEF, the limits of agreement of difference in each of the three conditions are small (**a**). In the LD group, limits of agreement of difference between PFR obtained from QGS2 and pFAST2 are relatively wide (**b**). Regarding TTPF, limits of agreement of difference in each of the three conditions are small (**c**)

the difference in calculated EDV also seemed to be an influential factor.

As TTPF is a timing of volume change, it seemed that there was little influence of different exhaustion methods of contour. As Akincioglu reported, TTPF appears to be a stable and more useful parameter than PFR [16].

Temporal undersampling can adversely affect functional measurements [6]. In general, it has long been considered that an accurate assessment of DFx requires a greater number of frames per cardiac cycle than an assessment of SFx [12, 13, 15], with 32 frames recommended [12, 34]. It is well known that temporal resolution equal to or less than 40 ms/frame is required to estimate diastolic dysfunction using gated pool scintigraphy. This fact indicates that the 16-frame gated MPS will not achieve the basis. However, obtaining adequate counts for evaluation of DFx in a 32-frame gated MPS would require longer acquisitions than gated pool imaging because of the lower counting rates, potentially exceeding 30 min with conventional methods. A recent study has suggested that the impact of fewer frames on these measurements may be less than previously thought of [16]. As the values that we observed in our population were similar to the earlier reported values from GBPS studies with higher frame rates or MPS using ^{99m}Tc-MIBI [16, 35], we consider it likely that 16-frame data will suffice in providing adequate temporal resolution to assess DFx even in ^{201}Tl-SPECT.

Although earlier studies have indicated that PFR varies when linked with other parameters, such as HR, EDV, ESV, LVEF, and age, TTPF seems to demonstrate less variability [16, 35]. Akincioglu et al. [16] recently reported that TTPF varies slightly with HR and does not significantly correlate with age, but PFR shows significant correlations with both of these parameters. In contrast, Muntinga et al. [36] observed an intermediate correlation between TTPF and age. As most subjects in the present study had ischemia, we could not obtain sufficient numbers for the analysis. In the future, we should perform a study with adjustment for SFx, HR, and age, even when acquired with 16-frame protocols.

Finally, the correlation of diastolic function parameters was relatively poor in the LD group. Particularly, the measurements of PFR cannot be used interchangeably in the large perfusion defect group by two different software packages (QGS2 or pFAST2). The clinical implication of this is that diastolic indices should be used with caution, when follow-up examinations of DFx are performed in conditions such as severe CADs or ischemic heart failure. In contrast, a follow-up study with two different software packages would be possible in diseases not characterized by large perfusion defects such as DCM. However, in the same patient, sequential studies should ideally be done using the same software package. Determination of the degree to which standard 16-frame gated MPS acquisitions can be useful clinically would require further study of patients with both normal and abnormal DFx.

Conclusions

With two different kinds of software, QGS2 and pFAST2, the value of PFR was almost equal and showed a good correlation in both ND and SD groups. However, in the LD group, numerical values varied between the two methods. In contrast, TTPF showed a good correlation regardless of the presence of perfusion defects, and the values were equal. TTPF was likely to be stable across the two kinds of software, QGS2 and pFAST2, in ^{201}Tl gated MPS.

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