

## Evaluation of right and left ventricular function by quantitative blood-pool SPECT (QBS): Comparison with conventional methods and quantitative gated SPECT (QGS)

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Though quantitative ECG-gated blood-pool SPECT (QBS) has become a popular tool in research settings, more verification is necessary for its utilization in clinical medicine. To evaluate the reliability of the measurements of left and right ventricular functions with QBS, we performed QBS, as well as first-pass pool (FPP) and ECG-gated blood-pool (GBP) studies on planar images in 41 patients and 8 healthy volunteers. Quantitative ECG-gated myocardial perfusion SPECT (QGS) was also performed in 30 of 49 subjects. First, we assessed the reproducibility of the measurements of left and right ventricular ejection fraction (LVEF, RVEF) and left and right ventricular end-diastolic volume (LVEDV, RVEDV) with QBS. Second, LVEF and RVEF obtained from QBS were compared with those from FPP and GBP, respectively. Third, LVEF and LVEDV obtained from QBS were compared with those from QGS, respectively. The intra- and inter-observer reproducibilities were excellent for LVEF, LVEDV, RVEF and RVEDV measured with QBS ( $r = 0.88$  to  $0.96$ ,  $p < 0.01$ ), while the biases in the measurements of RVEF and RVEDV were relatively large. LVEF obtained from QBS correlated significantly with those from FPP and GBP, while RVEF from QBS did not. LVEF and LVEDV obtained from QBS were significantly correlated with those from QGS, but the regression lines were not close to the lines of identity. In conclusion, the measurements of LVEF and LVEDV with QBS have good reproducibility and are useful clinically, while those of RVEF and RVEDV are less useful compared with LVEF and LVEDV. The algorithm of QBS for the measurements of RVEF and RVEDV remains to be improved.

**Key words:** quantitative gated blood-pool SPECT (QBS), quantitative gated SPECT (QGS),  $^{99m}\text{Tc}$ -human serum albumin-DTPA, left ventricular ejection fraction, reproducibility

### INTRODUCTION

FIRST-PASS POOL (FPP) and equilibrium ECG-gated blood-pool (GBP) studies on planar images have been well established for the non-invasive assessment of cardiac functions,<sup>1,2</sup> and have played important roles in the detec-

tion,<sup>3</sup> diagnosis<sup>4</sup> and management<sup>5</sup> of various cardiac diseases. Quantitative ECG-gated blood-pool SPECT (QBS) has advantages over FPP and GBP, regarding the non-invasive and automatic calculation of the left and right ventricular (LV, RV) end-diastolic volume (EDV), end-systolic volume (ESV) and ejection fraction (EF).<sup>6–8</sup> Furthermore, QBS can assess regional wall motions of both LV and RV.

Recently,  $^{99m}\text{Tc}$ -methoxy-isobutyl isonitrile ( $^{99m}\text{Tc}$ -sestamibi) and  $^{99m}\text{Tc}$ -ethylenebis [bis (2-ethoxyethyl) phosphine] ( $^{99m}\text{Tc}$ -tetrofosmin) have been widely used in clinical medicine to assess not only myocardial perfusion, but also global LV function and regional wall motion by

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using quantitative ECG-gated myocardial perfusion SPECT (QGS).<sup>6,9,10</sup> Several studies have reported that the LV volume and LVEF with QGS had a good correlation with magnetic resonance imaging (MRI),<sup>12,13</sup> contrast left ventriculography<sup>10</sup> and GBP.<sup>14,15</sup> However, no report has compared LV volume and LVEF obtained from QBS with those from QGS.

In this study, to evaluate the reliability and reproducibility in the measurements of the cardiac function with QBS, we measured LVEF, LVEDV, RVEF and RVEDV by using QBS, and compared these values with those obtained by FPP, GBP and QGS.

## MATERIALS AND METHODS

### *Study population*

The study population comprised 41 patients with sinus rhythm on ECG and 8 healthy volunteers (27 men and 22 women;  $65.3 \pm 17.4$  years old, mean  $\pm$  SD, ranging from 31 to 90 years). Patients with atrial fibrillation or frequent premature ventricular contractions were not included in this study.

The 41 patients consisted of 19 with ischemic heart disease (9 with prior myocardial infarction, 9 with acute myocardial infarction (AMI) and 1 with vasospastic angina), and 22 patients with non-ischemic heart disease (9 with cardiomyopathy, 7 with valvular heart disease, 2 with chronic pericarditis, 2 with hypertensive heart disease, 1 with chronic pulmonary thromboembolism, 1 with pulmonary hypertension). QGS was performed in 30 of the 49 subjects (17 with ischemic heart disease, 13 with non-ischemic heart disease). QGS and QBS were performed within 141 days ( $25 \pm 32$  days, mean  $\pm$  SD).

### *First-pass planar studies (FPP)*

A dose of 740 MBq of <sup>99m</sup>Tc-human serum albumin-DTPA was introduced into the right antecubital vein. Imaging was performed with a single-head gamma camera (E.CAM, Toshiba Medical Co., Japan) equipped with a high-resolution parallel hole collimator. From the 30 degrees right anterior oblique view of the gamma camera, data were acquired with ECG gating for 51 seconds in list mode and 20% energy window centered at 140 keV. The data were processed on a dedicated computer (GMS 5500 API, Toshiba Medical Co., Tokyo, Japan) with the GCA software program. The regions of interest (ROIs) were set over the LV and RV on the end-diastolic frames by the operator. Ventricular edges were determined as 75% and 55% thresholds of the ventricular peak counts for the LV and RV, respectively, on the images without background subtraction. LVEF and RVEF were calculated from the count in the ROIs, based on the equation  $EF = [(c_{ED} - c_{ES}) / c_{ED}] \times 100$ , where  $c_{ED}$  is the end-diastolic count, and  $c_{ES}$  is the end-systolic count.

### *Equilibrium ECG-gated blood-pool studies on planar images (GBP)*

Ten minutes after the acquisition of FPP data, conventional GBP was performed with a single-head gamma camera (E.CAM) equipped with a high-resolution parallel hole collimator. From the left anterior oblique projection (best septal view), data were acquired with 24 frames per cardiac cycle with ECG gating during the equilibrium state for 300 beats, on  $64 \times 64$  matrices, with a  $\pm 35\%$  R-R acceptance window, and 20% energy window centered at 140 keV. The data were processed on a dedicated computer (GMS 5500 API) with the GCA software program. The ROIs were set over the RV on the end-diastolic frame by the operator and over the LV automatically. Ventricular edges were determined as 75% and 55% thresholds of the ventricular peak counts for the LV and RV, respectively, on the images with background subtraction used for the setting of ventricle edges. LVEF and RVEF were calculated from the count in the ROIs, based on the equation  $EF = [(c_{ED} - c_{ES}) / c_{ED}] \times 100$ , where  $c_{ED}$  is the background corrected end-diastolic count, and  $c_{ES}$  is the background corrected end-systolic count.

### *Quantitative ECG-gated blood-pool SPECT (QBS)*

SPECT imaging was performed immediately after an equilibrium ECG-gated blood-pool study on a planar image acquisition utilizing a dual-head gamma camera (E.CAM) equipped with two high-resolution parallel hole collimators. SPECT data were acquired from 44 projection views over 360 degrees, with 20 seconds per view, on  $64 \times 64$  matrices, 16 frames per cardiac cycle with ECG gating,  $\pm 35\%$  R-R acceptance window, and 20% energy window centered at 140 keV. The data were processed on a dedicated computer (E soft, Toshiba Medical Co., Tokyo, Japan) with the QBS software program. The images were reconstructed by ramp filter back projection after prefiltering the projection data with a Butterworth filter (cut-off frequency 0.35 Nyquist and 8th order). LVEF, LVEDV, LVESV, RVEF, RVEDV and RVESV were calculated by the QBS. In case of failure of the algorithm, the operator drew an ellipsoid around the LV.

### *Quantitative gated SPECT (QGS)*

Twenty minutes after the intravenous injection of 740 MBq of <sup>99m</sup>Tc-sestamibi, an ECG-gated myocardial perfusion SPECT was obtained at rest with a dual-head gamma camera (E.CAM) equipped with low energy general-purpose collimators. SPECT data were acquired from 44 projection views over 180 degrees, with 20 seconds per view, on  $64 \times 64$  matrices, 16 frames per cardiac cycle with ECG gating,  $\pm 35\%$  R-R acceptance window, and 20% energy window centered at 140 keV. The data were processed on a dedicated computer (E soft) with the QGS software program (Cedars-Sinai Medical Center, CA, USA). The images were reconstructed by ramp filter back projection after prefiltering the projection data with a

**Table 1** Linear regression equation and Bland-Altman analysis for evaluating intra-observer reproducibility of LVEF, LVEDV, RVEF and RVEDV obtained from quantitative blood-pool SPECT (QBS)

	Scatter plots		Bland-Altman plots	
	Value	95% CI	Value	95% CI
<b>LVEF</b>				
Intercept	7.20	-5.91 to 20.1	-0.90	-14.4 to 12.6
Slope	0.94	-0.70 to 0.17	-0.053	-0.29 to 0.18
r value	0.89		0.11	
p value	< 0.001		0.64	
<b>LVEDV</b>				
Intercept	0.85	-12.2 to 12.9	2.75	-10.1 to 15.5
Slope	0.93	0.80 to 1.06	0.032	-0.14 to 0.17
r value	0.96		0.12	
p value	< 0.001		0.63	
<b>RVEF</b>				
Intercept	13.1	-6.45 to 25.8	-5.96	-22.8 to 10.9
Slope	0.82	0.58 to 1.05	0.061	0.20 to 0.32
r value	0.87		0.11	
p value	< 0.001		0.64	
<b>RVEDV</b>				
Intercept	-1.76	0.82 to 1.17	-6.22	-7.51 to 19.9
Slope	1.00	-16.0 to 12.5	0.057	-0.023 to 0.11
r value	0.94		0.16	
p value	< 0.001		0.49	

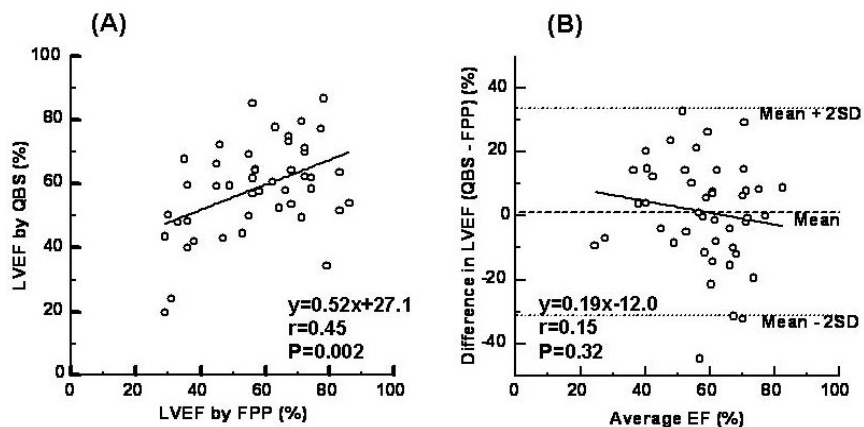
**Table 2** Linear regression equation and Bland-Altman analysis for evaluating inter-observer reproducibility of LVEF, LVEDV, RVEF and RVEDV obtained from QBS

	Scatter plots		Bland-Altman plots	
	Value	95% CI	Value	95% CI
<b>LVEF</b>				
Intercept	0.96	-13.1 to 15.0	5.87	-7.78 to 19.5
Slope	0.95	-0.70 to 1.27	-0.079	0.32 to 0.16
r value	0.88		0.16	
p value	< 0.001		0.50	
<b>LVEDV</b>				
Intercept	1.18	-19.9 to 22.3	7.19	-14.4 to 28.8
Slope	0.89	0.68 to 1.08	0.27	-0.18 to 0.24
r value	0.91		0.064	
p value	< 0.001		0.79	
<b>RVEF</b>				
Intercept	-27.1	-44.7 to -9.35	29.4	19.6 to 41.9
Slope	1.26	1.01 to 1.51	-0.31	-0.50 to -0.13
r value	0.93		0.064	
p value	< 0.001		0.02	
<b>RVEDV</b>				
Intercept	4.89	0.82 to 1.17	2.53	-13.6 to 23.3
Slope	0.73	-16.0 to 12.5	0.20	0.56 to 0.92
r value	0.90		0.08	
p value	< 0.001		0.40	

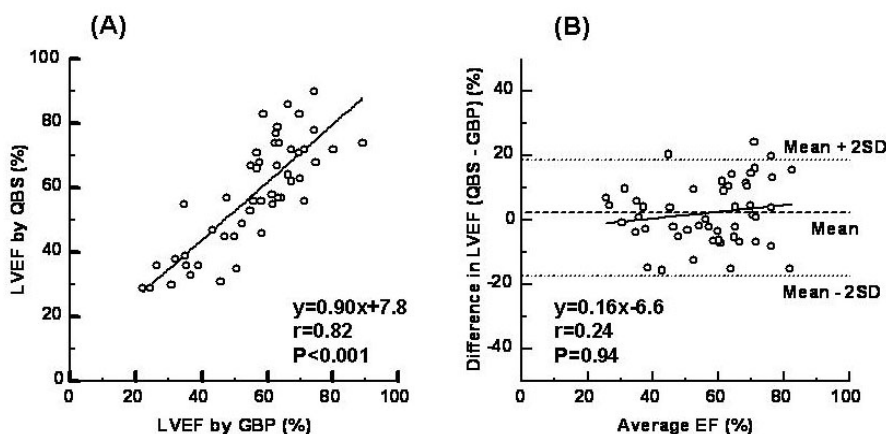
Butterworth filter (cut-off frequency 0.35 Nyquist and 8th order). LVEF, LVEDV and LVESV were calculated by the QGS.

*Statistical analysis*

Statistical analysis was performed with the SPSS program, version 11.0 (SPSS Inc., IL, USA). Continuous data were reported as mean  $\pm$  SD, and categorical data were



**Fig. 1** Comparison of left ventricular ejection fraction (EF) between QBS and first pass pool (FPP). Left panel shows scatter plots and linear regressions; right panel shows the Bland-Altman plots.



**Fig. 2** Comparison of left ventricular ejection fraction (EF) between QBS and equilibrium ECG-gated blood-pool study on planar image (GBP). The left panel shows scatter plots and linear regressions, and the right panel shows the Bland-Altman plots.

reported as a percentage.

Correlations between the two methods were assessed by Pearson's correlation coefficient ( $r$ ). The Bland-Altman method<sup>16</sup> was also performed to evaluate the bias, and to establish 2SD values between two studies. The limits of agreement were considered as the mean  $\pm$  2SD of the difference. A  $p$  value of less than 0.05 was considered statistically significant.

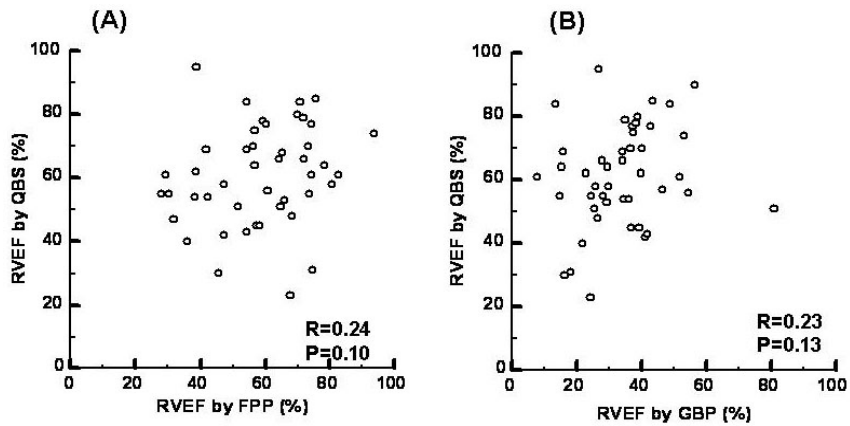
## RESULTS

Automatic processing by QBS was successful in 44 of 49 cases. The unsuccessful automatic processing in the remaining 5 cases was due to the intrusion of LV into the left atrium in 4 cases, and due to the failure of edge-detection of both LV and RV in 1 case.

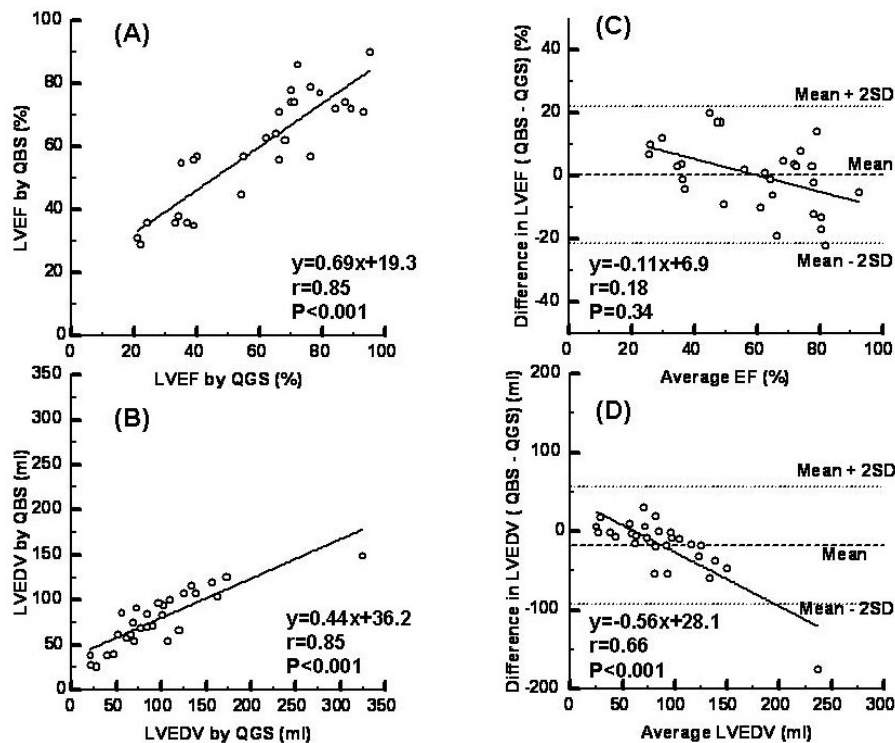
The intra-observer and inter-observer reproducibilities in the measurements of LVEF, RVEF, LVEDV and RVEDV with QBS were evaluated in the first 20 patients. Linear regression analysis and Bland-Altman analysis

were performed for the assessment of their reproducibilities as shown in Table 1. The intra-observer reproducibilities of LVEF, LVEDV, RVEF and RVEDV were calculated as  $y = 0.94x + 7.20$  ( $r = 0.89$ ,  $p < 0.001$ ),  $y = 0.93x + 0.85$  ( $r = 0.96$ ,  $p < 0.001$ ),  $y = 0.82x + 13.1$  ( $r = 0.87$ ,  $p < 0.001$ ) and  $y = 1.00x - 1.76$  ( $r = 0.94$ ,  $p < 0.001$ ), respectively. The limits of agreement calculated using the Bland-Altman analysis were  $1.6 \pm 18.3\%$ ,  $9.8 \pm 36.9$  ml,  $9.8 \pm 16.9\%$ ,  $19.4 \pm 38.7$  ml, respectively. As shown in Table 2, the inter-observer reproducibilities of LVEF, LVEDV, RVEF and RVEDV were calculated as  $y = 0.95x + 0.96$  ( $r = 0.88$ ,  $p < 0.001$ ),  $y = 0.89x + 1.18$  ( $r = 0.91$ ,  $p < 0.001$ ),  $y = 1.26x - 27.1$  ( $r = 0.93$ ,  $p < 0.001$ ) and  $y = 0.73x + 4.89$  ( $r = 0.90$ ,  $p < 0.001$ ), respectively. The limits of agreement calculated using the Bland-Altman analysis were  $-3.8 \pm 16.1\%$ ,  $5.5 \pm 23.8$  ml,  $-2.3 \pm 20.4\%$ , and  $2.1 \pm 25.1$  ml, respectively.

LVEF and RVEF obtained from QBS were compared with those from FPP and GBP using a linear regression and Bland-Altman analyses, respectively. As shown in



**Fig. 3** Comparisons of right ventricular ejection fraction (EF) between QBS and conventional methods. The left panel shows comparison between QBS and FPP, and the right panel shows comparison between QBS and GBP.



**Fig. 4** Comparisons of left ventricular ejection fraction (EF) (A) and end diastolic left ventricular volume (B) between QBS and quantitative gated SPECT. The left panels show scatter plots and linear regressions, and the right panels show Bland-Altman plots.

Figure 1, the correlation coefficient between LVEF from QBS and that from FPP was 0.45 ( $y = 0.52x + 27.1$ ,  $p = 0.002$ ). The mean difference was 1.3% (the limits of agreement were  $-31.1\%$  to  $33.7\%$ ). As shown in Figure 2, the correlation coefficient between LVEF from QBS and that from GBP was 0.82 ( $y = 0.90x + 7.8$ ,  $p < 0.001$ ). The mean difference was 2.2% (the limits of agreement were  $-17.6\%$  to  $18.8\%$ ). The correlation coefficient between LVEF from QBS and that from GBP was better than FPP. RVEF obtained from QBS did not correlate significantly

with those from FPP or GBP (Fig. 3).

When LVEF (Fig. 4A) and LVEDV (Fig. 4B) obtained from QBS were compared with those obtained from QGS, there were significant correlations both in LVEF and LVEDV, respectively. The correlation coefficient between LVEF obtained from QBS and QGS was 0.85 ( $y = 0.69x + 19.3$ ,  $p < 0.001$ ). The comparison of LVEDV obtained from QBS and QGS yielded a correlation coefficient of 0.85 ( $y = 0.44x + 36.2$ ,  $p < 0.001$ ). The limits of agreement were  $-21.5\%$  to  $22.1\%$  for LVEF (Fig. 4C) and



-92.5 ml to 57.0 ml for LVEDV (Fig. 4D). There was no significant difference or bias in LVEF between QBS and QGS, but a large difference and significant bias appeared in LVEDV between QBS and QGS. LVEDV obtained from QBS was overestimated compared with that obtained from QGS in patients in large LV volume (Fig. 4C and 4D).

## DISCUSSION

We evaluated the reliability and reproducibility of the measurements of the LV and RV functions obtained by QBS. The inter- and intra-observer reproducibilities of the LVEF, LVEDV, RVEF and RVEDV measured by QBS were excellent. The LVEF obtained by QBS showed good correlations with conventional blood-pool methods (FPP and GBP), but the correlation coefficient between LVEF from QBS and from GBP was better than FPP, while the RVEF exhibited no significant correlation. There were good correlations in LVEF and LVEDV between QBS and QGS, although there was significant difference between the 2 methods and the regression lines were not very close to the lines of identity.

### *Intra- and inter-observer reproducibility of QBS*

Higuchi et al. reported that the reproducibility of LVEF obtained from QBS was good (intra-observer,  $r = 0.95$ ; inter-observer,  $r = 0.96$ ), whereas that of RVEF was fair (intra-observer,  $r = 0.83$ ; inter-observer,  $r = 0.83$ ).<sup>18</sup> Wright et al. also indicated that the correlation coefficient between repeated measurements was  $r = 0.87$  for QBS.<sup>17</sup> In our study, the intra-observer reproducibilities of LVEF, LVEDV, RVEF and RVEDV were excellent ( $r = 0.88$  to  $0.96$ ,  $p < 0.001$ ), and the regression lines of LVEF and LVEDV were close to the lines of identity in both intra- and inter-observer reproducibility (Tables 1 and 2).

The biases in the measurements of RVEF and RVEDV were relatively large compared with those in LVEF and LVEDV in both inter- and intra-observer reproducibilities. Especially, there was a large bias in the measurements of RVEF and RVEDV in inter-observer reproducibility, and their regression lines were not close to the lines of identity. These results were similar to those of previous studies, and possible explanations are that: (1) the algorithm of QBS was not adequate to detect the edge of RV accurately compared with that of LV, and (2) the inter-observer variability for orienting the resulting axial images to produce images in the short axis projection may be large.

### *Comparison between QBS and conventional blood-pool studies*

LVEF obtained from GBP was recognized as highly reproducible and has been widely utilized clinically. In our study, there was a significant but weak correlation

between LVEF obtained from QBS and FPP. The correlation between LVEF obtained from QBS and GBP was better than FPP, and there was no significant difference in LVEF between the 2 methods. The Bland-Altman analysis showed that the limits of agreement of difference between LVEF obtained from QBS and GBP are relatively wide (-17.6% to 18.8%). These data are similar to the range reported in previous studies.<sup>7,17,18</sup>

In the published results, the correlation between RVEF obtained from QBS and conventional blood-pool methods was significant but weaker than that of LVEF.<sup>8,18</sup> In our study, RVEF obtained from QBS did not correlate significantly with those from FPP or GBP. Unlike with our study, Hacker et al. described that RVEF calculated from QBS showed no significant correlation with either FPP or GBP.<sup>19</sup> The discordance may be due to the difficulty to isolate RV from other structures in algorithms of QBS, FPP and GBP, because the shape of RV is more complex than that of LV. Furthermore, we did not validate the reproducibility of FPP and GBP, and we cannot deny the possibility of poor reproducibility of the measurements of RVEF in FPP and GBP. De Bondt et al. reported that the measurement of RVEF had a good correlation with the true value of dynamic 4-chamber cardiac phantom ( $r = 0.84$ ,  $p < 0.001$ ), but the mean difference from the Bland-Altman analysis was high ( $-41.28 \pm 43.66$  ml).<sup>20</sup> Therefore, at least in the present state,<sup>18-20</sup> RVEF calculated from QBS may not be adequate to be applied for the clinical settings.

### *Comparison between QBS and QGS*

To our knowledge, this is the first study to describe the correlation between the values of LVEF and LVEDV obtained from QBS and QGS. LVEF and LVEDV measured from QGS have been reported to correlate well with those from MRI<sup>22,23</sup> and LVG,<sup>10,21</sup> respectively, and the reproducibility of QGS has been well established in research and clinical settings. For LVEF and LVEDV, the correlations between QBS and QGS were fair ( $r = 0.85$  and  $0.85$ , respectively), whereas the regression lines of LVEF and LVEDV were not very close to the lines of identity. In LVEF, there was no significant difference between the two methods, but LVEDV estimated by QBS was apparently lower than that with QGS. Moreover, a significant disagreement and a large bias were found between LVEDV obtained from QBS and QGS, and the limits of agreement were large for LVEF and LVEDV obtained from QBS and QGS. The following 3 reasons may explain the difference and disagreement between LVEDV obtained from QBS and QGS. First, in QBS and QGS, many factors might influence LVEDV and LVEF, including the order and cut off frequency of the Butterworth filter, kinds of reconstruction filter, myocardial counts, matrix size for data acquisition, magnitude of zoom and heart size. Second, in our sequence of acquisition for the

QBS data, the LV counts of tracers might not be sufficient to calculate the accurate value of LVEDV. The algorithm for QBS is geometric, not on count thresholds; that is, it utilizes an ellipsoidal coordinate system computed by an endocardial surface from the relative count and the count density gradients.<sup>7</sup> When the LV counts of tracers are inadequate, LVEDV could be underestimated. Third, in 30 subjects who underwent QGS, 8 patients were categorized as having AMI. Although QGS and QBS were performed within 17 days ( $10.3 \pm 3.8$  days), LVEF and LVEDV might have changed drastically during this interval. Furthermore, large perfusion defects in these patients might have interfered with the accurate measurements of LVEF and LVEDV with QGS. The values of LVEF and LVEDV obtained from QBS might be more accurate than those obtained from QGS at least in patients with large perfusion defects in myocardial perfusion imaging, such as left ventricular aneurysm.

#### Study limitations

In this study, RVEF obtained from QBS did not significantly correlate with those from FPP and GBP. However, FPP and GBP are not the gold standard for the measurement of RVEF. In recent years, magnetic resonance imaging (MRI) is considered to be the gold standard for the measurement of RV functions. Though Kjaer et al. reported that the values of RVEDV were in the same range when measured by MRI and QBS, the limit of agreement was wide.<sup>24</sup> Unfortunately, we did not compare RVEF by QBS with that obtained by MRI. Further studies are needed to clarify the reliability of RV function obtained by QBS.

### CONCLUSION

We demonstrated that the measurements of LVEF and LVEDV obtained by QBS have good reproducibility and reliability that are sufficient for clinical use. For the measurements of RVEF and RVEDV, the reliability of QBS did not reach satisfactory levels. The algorithm of QBS for the measurements of RVEF and RVEDV needs to be improved. In addition, there is a small but significant disagreement between QBS and QGS, which also remains to be improved for establishing the reliability of measurements of LVEF and LVEDV with QBS.

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