

## Assessment of left ventricular function by gated myocardial perfusion and gated blood-pool SPECT: Can we use the same reference database?

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The purpose of this study was to compare left ventricular (LV) volume and ejection fraction (LVEF) measurements obtained with electrocardiographic gated single-photon emission computed tomographic (SPECT) myocardial perfusion imaging (GS-MPI) with those obtained with gated SPECT cardiac blood-pool imaging (GS-pool). Fifteen patients underwent GS-MPI with technetium-99m-tetrofosmin and GS-pool with technetium-99m-erythrocyte, within a mean interval of  $8 \pm 3$  days. Eight patients had suspected dilated cardiomyopathy and seven patients had angiographically significant coronary artery disease. End-diastolic volume (EDV), end-systolic volume (ESV) and LVEF measurements were estimated from GS-MPI images by means of Cedars-Sinai automatic quantitative program and from GS-pool images by the threshold technique. Mean differences between GS-MPI and GS-pool in EDV, ESV and LVEF measurements were  $-2.8 \pm 10.5$  ml [95% confidence interval (CI):  $-8.6 \pm 3.0$  ml],  $2.6 \pm 7.3$  ml (CI:  $-1.4 \sim 6.6$  ml) and  $-2.3 \pm 5.1$ % (CI:  $-5.1 \sim 0.6$ %), respectively. No significant difference in the mean differences from 0 was found for EDV, ESV or LVEF measurements. Bland-Altman plots revealed no trend over the measured LV volumes and LVEF. For all parameters, regression lines approximated lines of identity. The excellent agreement between GS-MPI and GS-pool measurements suggests that, for estimation of LV volumes and LVEF, these two techniques may be used interchangeably and measurements by one method can serve as a reference for the other.

**Key words:** left ventricular volumes, ejection fraction, gated SPECT, myocardial perfusion imaging, blood-pool imaging

### INTRODUCTION

THE IMPORTANCE of estimating the left ventricular (LV) volume<sup>1,2</sup> and ejection fraction (LVEF)<sup>3,4</sup> in various cardiac diseases has been established. For many years, LVEF is considered as the single most representative index of global left ventricular function.<sup>4</sup> LV volume also provides the basis for the calculation of other functional indices

such as cardiac output, stroke volume and absolute ventricular filling and emptying rate.

Several studies have demonstrated that electrocardiographic gated single-photon emission computed tomographic (SPECT) acquisition of myocardial perfusion or cardiac blood-pool images can reliably estimate LV volumes and LVEF. LV functional indices obtained with gated SPECT myocardial perfusion imaging (GS-MPI)<sup>5-10</sup> or gated SPECT blood pool imaging (GS-pool)<sup>11-15</sup> have been reported to agree reasonably with acceptable standards, but the comparison between these two independent scintigraphic measurements in the same patient has not been reported. Recent advances in camera, computer and processing algorithms shorten the acquisition and processing time significantly and have made both these techniques more practical in clinical settings. It is,

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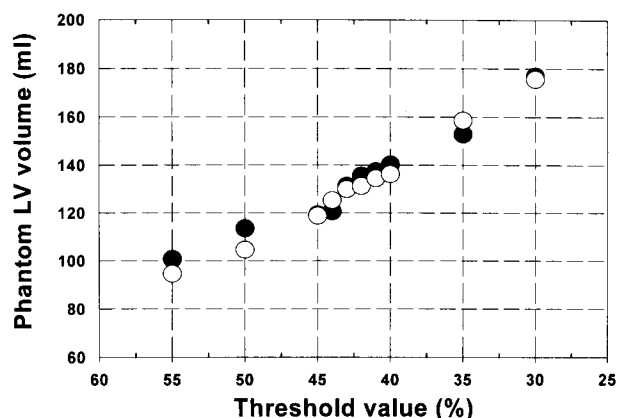
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therefore, important to know whether these techniques can be used interchangeably and whether measurements by one technique can be used as a reference for the other. The aim of this study was to compare LV end-diastolic volume (EDV), end-systolic volume (ESV) and LVEF measurements obtained with GS-MPI with those obtained with GS-pool.

## MATERIALS AND METHODS

### Phantom study

A standard SPECT chest phantom (RH-2, Kyoto Kagaku Co. Ltd., Japan) was imaged to determine the optimal threshold value for quantification of volumes from GS-



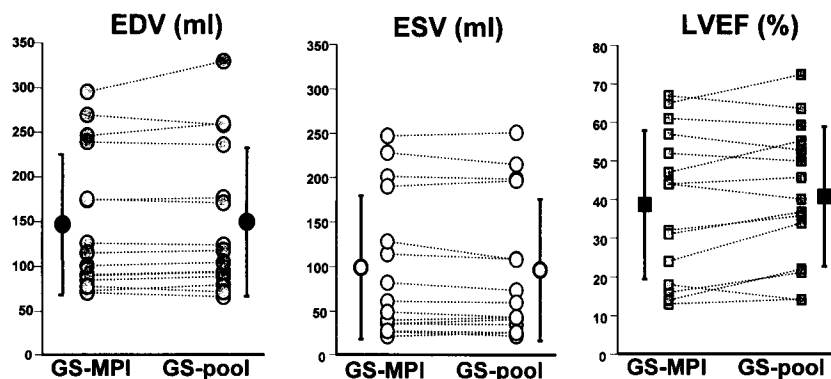
**Fig. 1** Estimated left ventricular (LV) volumes of the phantom plotted against threshold values for two separate gated SPECT acquisitions of blood-pool, with radiotracers in left ventricular cavity (filled circles) and radiotracers in both right and left ventricular cavities (open circles). The two acquisitions provided similar values ( $p = \text{not significant}$ ). At 43% threshold, the phantom volume was estimated as 131.5 ml and 130.0 ml, for former and later acquisitions, respectively; the true volume of the phantom was 130 ml.

pool images. The threshold value was defined as the fraction of peak counts necessary to delineate the LV endocardial edge.<sup>16</sup> The phantom was made of urethane frame and consisted of heart, lung and mediastinal spaces. The heart with right and left ventricular cavities was properly placed and surrounded by lungs (filled with wood powder). The ventricular cavities were filled with technetium-99m (<sup>99m</sup>Tc)-pertechnetate solution at a concentration of ~180 kBq/ml (5  $\mu$ Ci/ml). The mediastinal spaces were filled with water to approximate attenuation by soft tissue.

Phantom images were acquired with the same camera, reconstructed and quantified as in the study of a patient. Threshold values from 30% to 55% of the maximum count per pixel were applied to the reconstructed phantom images. LV volumes were estimated for two different image acquisitions, one set with radiotracer in the LV cavity only and the other set with radiotracer in both right and left ventricular cavities. Both sets provided similar volumes ( $p = \text{not significant}$ ) over the range of thresholds (Fig. 1). This suggested that right ventricular blood-pool activity had no significant effect on quantification of LV volume with this technique. The true volume of the phantom LV cavity was 130 ml. The closest measurements were obtained at 43% threshold, and were 131.5 ml and 130.0 ml, for former and later acquisitions, respectively. The threshold value of 43% of maximal counts/pixel was therefore picked up as an optimal threshold to define LV endocardial edges in GS-pool images.

### Patients

A total of 15 patients (11 men, 4 women; mean age  $56 \pm 14$  years) underwent GS-MPI and GS-pool within a mean interval of  $8 \pm 3$  days. No patient had any intervening cardiac event. Eight patients had suspected dilated cardiomyopathy (DCM) on the basis of clinical and echocardiographic findings and normal coronary arteries on coronary angiography. Seven patients had documented



**Fig. 2** Left ventricular end-diastolic volumes (EDV, *left*), end-systolic volumes (ESV, *middle*) and ejection fractions (LVEF, *right*) obtained with gated SPECT myocardial perfusion imaging (GS-MPI) and gated SPECT blood-pool imaging (GS-pool). For all parameters, the differences between GS-MPI and GS-pool were not statistically significant. Some of the data points represent more than one patient.

angiographic evidence of coronary artery disease (CAD), and of these three had a previous history of myocardial infarction. Coronary angiography demonstrated significant stenosis ( $\geq 50\%$  reduction in luminal diameter) of all three major epicardial coronary arteries in two patients, of two coronary arteries in two patients and of one coronary artery in three patients. Myocardial infarction was diagnosed on the basis of a combination of typical anginal pain of at least 30 min duration, serial electrocardiographic changes consisting of new pathological Q wave or ST change, and a typical rise and fall in the level of serum myocardial enzymes, including CK-MB. None had primary valvular disease, intracardiac shunts or cardiac arrhythmia. All patients gave written informed consent for the study procedure. The study protocol was approved by the ethics committee of Osaka University Graduate School of Medicine and Hospital.

#### Image acquisition

After an overnight fast, each patient had an intravenous injection of 740 MBq of  $^{99m}\text{Tc}$ -tetrofosmin (Myoview, Nihon Medi-Physics Co., Tokyo, Japan) at rest. GS-MPI was performed 60 min later with a rotating triple-detector SPECT system (GCA-9300A/HG, Toshiba Medical Co., Tokyo, Japan) equipped with a low-energy general-purpose collimator. A total of 60 projections of 90 sec each in a 20% window centered on a 140 keV photopeak were

acquired over a 360° circular orbit in a 64 × 64 pixel image matrix. Acquisitions were gated for 10 frames per cardiac cycle with  $\pm 10\%$  gated tolerance. GS-pool imaging was performed similarly. After *in-vivo* labeling of autologous erythrocytes with 740 MBq of  $^{99m}\text{Tc}$ -pertechnetate, images were acquired with the same camera and acquisition parameters. Total acquisition time for the GS-MPI or the GS-pool was about 30 min.

#### Data processing and quantification

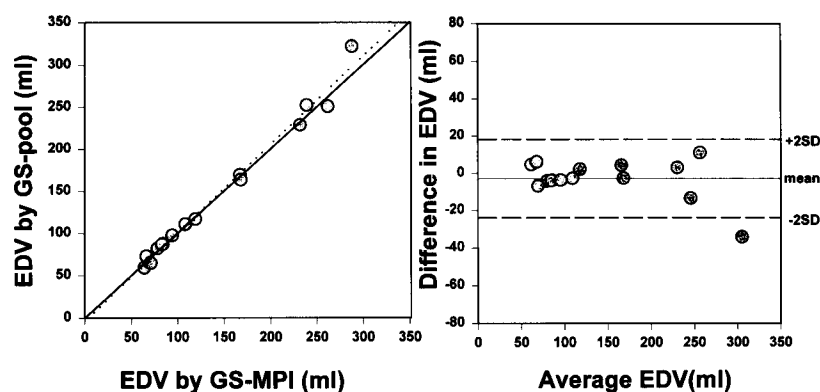
All acquired data were transferred and processed at a workstation (GMS-5500, Toshiba Medical Co., Tokyo, Japan). Projection data set were prefiltered with a two dimensional Butterworth filter (order 8, critical frequency 0.28 cycles/pixel) and reconstructed with filtered back projection method using a Shepp and Logan filter and without attenuation correction.

Cedars-Sinai automatic quantitative gated SPECT program, developed by Germano et al.,<sup>5</sup> was applied to reconstructed short-axis tomograms of GS-MPI to obtain EDV, ESV and LVEF. Details of this program has been described elsewhere.<sup>5</sup> This program segments the left ventricle, estimates endocardial and epicardial surfaces for all gating intervals in the cardiac cycle, calculates EDV and ESV, and derives the LVEF by dividing stroke volume by EDV and expressing it as a percentage. For interpretation of the perfusion scan, GS-MPI projection

**Table 1** Difference between GS-MPI and GS-pool measurements

	EDV (ml)	ESV (ml)	LVEF (%)
Mean difference $\pm$ SD	$-2.8 \pm 10.5$	$2.6 \pm 7.3$	$-2.3 \pm 5.1$
Range of difference	$-34.0 \sim 11.1$	$-19.9 \sim 6.5$	$-4.0 \sim 10.0$
Standard error of differences	2.7	1.9	1.3
95% confidence interval	$-8.6 \sim 3.0$	$-1.4 \sim 6.6$	$-5.1 \sim 0.6$
Limits of agreement	$-23.9 \sim 18.3$	$-11.9 \sim 17.1$	$-12.4 \sim 7.9$

GS-MPI, Gated SPECT myocardial perfusion imaging; GS-pool, gated SPECT blood-pool imaging; EDV, end-diastolic volume; ESV, end-systolic volume; LVEF, ejection fraction; SD, standard deviation



**Fig. 3** Scatter plot (left) and Bland-Altman plot (right) for end-diastolic volume (EDV) between gated SPECT myocardial perfusion imaging (GS-MPI) and gated SPECT blood-pool imaging (GS-pool). Dotted and solid lines in the scatter plot represent the regression line ( $y = 1.1 \cdot x - 3.8$ ,  $r = 0.99$ , standard error of the estimate = 10.2 ml) and line of identity, respectively.

data were converted to summed nongated data, and vertical long-axis, horizontal long-axis and short-axis images were reconstructed.

GS-pool data were quantified with a program based on the threshold technique, originally described by Tauxe and associates.<sup>16</sup> LV regions of interest were delineated manually from reconstructed transaxial image sets. The threshold of 43% was applied as determined from the phantom study. To calculate the volume of a frame, the number of pixels within the threshold-defined region of interest was multiplied by the volume (0.25 ml) of a voxel of the imaging system. Volumes were plotted against the corresponding frames to generate a volume curve. EDV and ESV were the maximum and minimum volumes of this curve, respectively. LVEF was derived from EDV and ESV.

#### Statistical analysis

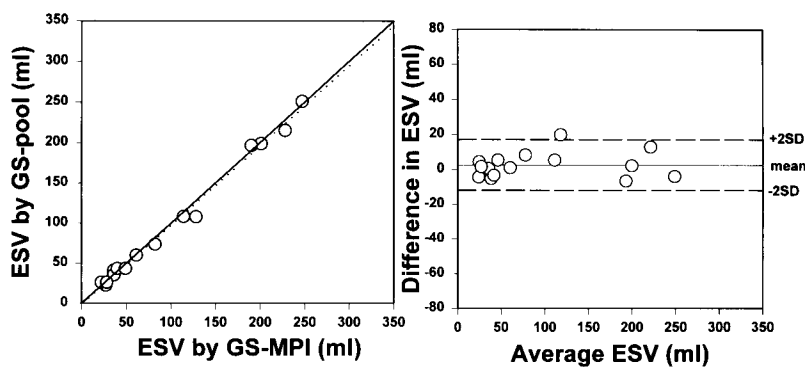
Data are expressed as mean  $\pm$  standard deviation. Systemic error and degree of agreement on LV volumes and LVEF obtained by GS-MPI and GS-pool were assessed according to the method of Bland and Altman.<sup>17</sup> The degree of agreement was determined as the mean differ-

ence (bias), standard deviation of the differences, limits of agreement (mean  $\pm$  2SD), standard error of the mean difference, and 95% confidence interval of the mean difference. Student's t-test at the 5% significance level was used to determine whether data obtained with one method was substantially different from the other. Linear regression analysis (Pearson correlation coefficient,  $r$ ) was used to correlate the measurements obtained by GS-MPI and GS-pool. A probability value ( $p$ ) of less than 0.05 was considered statistically significant.

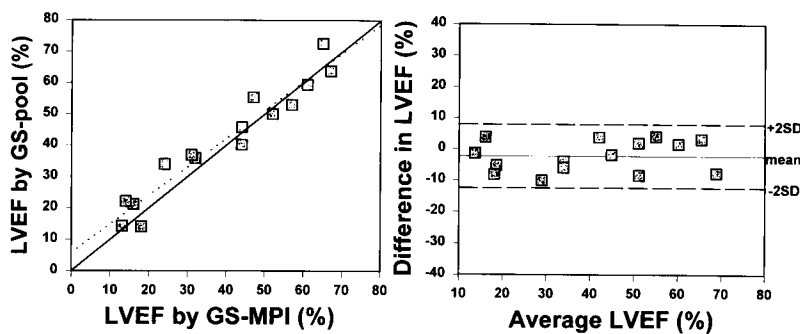
## RESULTS

Among eight patients with DCM, resting perfusion scan showed nonhomogeneous uptake of radiotracer in LV myocardium of five patients, localized defect in the inferior wall of one patient and no perfusion abnormalities in two patients. Three patients with previous myocardial infarction showed perfusion defects in the anterior wall in one patient, lateral wall in one patient, and anterior and inferior walls in one patient. The remaining four patients had a normal resting perfusion scan.

Figure 2 shows EDV, ESV and LVEF obtained with



**Fig. 4** Scatter plot (left) and Bland-Altman plot (right) for end-systolic volume (ESV) between gated SPECT myocardial perfusion imaging (GS-MPI) and gated SPECT blood-pool imaging (GS-pool). Dotted and solid lines in the scatter plot represent the regression line ( $y = 0.99x - 1.2$ ,  $r = 0.99$ , standard error of the estimate = 7.4 ml) and line of identity, respectively.



**Fig. 5** Scatter plot (left) and Bland-Altman plot (right) for ejection fraction (LVEF) between gated SPECT myocardial perfusion imaging (GS-MPI) and gated SPECT blood-pool imaging (GS-pool). Dotted and solid lines in the scatter plot represent the regression line ( $y = 0.91x + 5.8$ ,  $r = 0.97$ , standard error of the estimate = 5.0%) and line of identity, respectively.

GS-MPI and GS-pool. The ranges of EDV, ESV and LVEF, estimated by GS-MPI were 64–288 ml, 22–247 ml and 13–67%, respectively. The ranges of GS-pool measurements were 59–322 ml, 22–251 ml and 14–73%, for EDV, ESV and LVEF, respectively.

The results of Bland-Altman analysis are summarized in Table 1. The regression plots and Bland-Altman plots (difference plotted versus means of paired values) for EDV, ESV and LVEF are shown in Figures 3, 4 and 5, respectively. There was no significant degree of directional measurement bias in any of the comparisons of GS-MPI data and GS-pool data. No significant difference in the mean difference from 0 was found for EDV, ESV or LVEF measurements. The regression lines for EDV, ESV and LVEF measurements between GS-MPI and GS-pool were very close to the lines of identity.

## DISCUSSION

In this study, LV EDV, ESV and LVEF measurements obtained with GS-MPI and GS-pool were directly compared. Close agreement between these two methods was found over a wide range of volumes and LVEFs. For all parameters, mean differences were small, limits of agreement were reasonable and regression lines approximated lines of identity. No significant difference in the mean differences from 0 was found for any of the measurements.

A good number of studies have reported that LV functional parameters estimated by GS-MPI<sup>5–10</sup> or GS-pool<sup>11–15</sup> correlate well with those of standard techniques. Comparing gated SPECT measurements in reference to those of contrast angiography, we and others have found that ESVs were identical whereas EDV and LVEF were significantly lower than angiographic measurements.<sup>6,7</sup> Similarly, EDV and subsequent LVEF, estimated by GS-pool, tended to underestimate contrast angiographic measurements.<sup>12,13</sup> This might be caused by the limitations of the contrast angiographic technique. Specifically, a) contrast angiographic drawing of endocardium includes more outflow tract than scintigraphy,<sup>7</sup> b) compared with LV autopsy casts, single-plane or bi-plane contrast angiographic LV volume measurements are known to overestimate true ventricular volumes<sup>18</sup> and c) angiographic measurements are based on geometric assumption of LV shape, and are always not applicable, especially for ventricles of irregular shape, extreme dilatation or with asynergy.<sup>19</sup> On the other hand, measurements estimated by GS-MPI or GS-pool were found to agree well with those of magnetic resonance imaging (MRI), presently considered as a standard for volume calculation. Two recent studies<sup>9,10</sup> reported a high degree of agreement between GS-MPI and MRI on LV volume and LVEF measurements. Tadamura et al.<sup>9</sup> reported a mean difference of  $-5.9 \pm 13.0$  ml,  $0 \pm 6.6$  ml and  $-2.8 \pm 5.1\%$ , for EDV, ESV and LVEF, respectively, between GS-MPI

with Tc-99m-sestamibi and MRI. The relationship between GS-pool and MRI has also been reported to be very good for LV volumes ( $r = 0.96$ , slope = 0.88, standard error of the estimate = 18.2 ml) and LVEF ( $r = 0.94$ , slope = 1.1, standard error of the estimate = 9.0%).<sup>15</sup> Based on these observations, SPECT measurements of LV volume may be considered accurate. This also explains the excellent agreement observed in this study between two gated SPECT techniques, when compared directly.

At end-diastole, definition of the mitral valve plane has been reported to be difficult in GS-pool images of some patients, as the left ventricle is dilated, separation between the chambers is at its minimum and the impact of the partial volume effect on the separation is at its peak.<sup>14</sup> In this situation, the accurate assessment of EDV may be problematic. In this study, we could reasonably define the mitral valve plane in all GS-pool images likely due to the relatively better resolution of the triple-detector SPECT system. Another important factor in accurate quantification of GS-pool images by the threshold technique is to optimize the threshold value, which is applied to define the endocardial edges in successive blood-pool slices. The threshold value is determined by phantom imaging by changing the fractional values until the true volume is obtained. The variation in estimated volumes as a result of variation in the threshold value was evident from our result of phantom imaging as shown in Figure 1. Corbett et al. reported that a variation of 5% in threshold value could produce an under- and overestimation of 20% and 22%, respectively, in EDV of 2 control patients.<sup>14</sup> Tauxe et al.<sup>16</sup> found that the threshold varied slightly (about 1%) as a function of phantom size over a wide range of volumes (91–3216 ml), but a subsequent study showed that a single threshold could accurately estimate different phantom volumes below 500 ml.<sup>11</sup> As LV volumes encountered in clinical patients are well within this range, we used a single threshold value, which was determined from the phantom study. Single threshold was also used in other studies.<sup>12–14</sup>

In this study, the study population was small. There were few patients with large perfusion defect, in whom the accuracy of automated edge-detection program is of concern.<sup>20</sup> It has already been shown that severe and extensive perfusion defects did not affect the accuracy of the Cedars-Sinai automatic quantitative program.<sup>5,21</sup> This study included a few patients with a small LV, in whom GS-MPI was reported to underestimate LV volumes.<sup>7,8</sup> Nevertheless, the ranges of volumes examined in this study were reasonably wide. In conclusion, an excellent agreement was found between two gated SPECT techniques in this study for assessment of LV function. This suggests that for assessment of LV volume and LVEF, GS-MPI and GS-pool may be used interchangeably and one method may serve as a common reference for the other.

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