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Quantification of left ventricular regional functions using ECG-gated myocardial perfusion SPECT —Validation of left ventricular systolic functions—

Akira YAMAMOTO,* Tetsuo HOSOYA,** Naoto TAKAHASHI,***
Shin-ichiro IWAHARA*** and Kazuo MUNAKATA***

*Department of Radiology, Nippon Medical School Musashikosugi Hospital
**Department of Clinical Application Technology, Daiichi Radioisotope Laboratories, Ltd.
***Department of Internal Medicine, Nippon Medical School Musashikosugi Hospital

Objective: We have developed a program to quantify regional left ventricular (LV) function and wall motion synchrony using ECG-gated myocardial perfusion SPECT (MPS). This preliminary study was undertaken to validate the use of this program for estimating regional LV systolic function. ***Methods:*** Patients were subjected to MPS by ^{99m}Tc-sestamibi at rest. The study included 20 patients who were confirmed to have a low probability of coronary artery disease (LPG; low probability group), 19 heart disease patients who were examined by MPS and equilibrium radionuclide angiography (ERNA) (ERG; ERNA group), and 24 patients who were examined by MPS and 2-dimensional echocardiography (2DE) (2DEG; 2DE group). The values of the ejection fraction (EF) and peak ejection rate (PER) were estimated. The global functions evaluated by this program were compared with those obtained by ERNA in the ERG. For regional assessment, the reference values of the functional indices were obtained for 17 LV segments in LPG. The Z score, (reference average value of the segment – patient's value of the segment)/reference standard deviation of the segment, was used for the evaluation of regional functions; a score equal to or greater than 2 was defined as abnormal. Semiquantitative visual interpretation of 2DE was used as the standard to assess wall motion. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of these criteria and the relationship between 2DE grading and Z scoring were validated in 2DEG. ***Results:*** The values of the global EF and PER evaluated by this program correlated with those determined by ERNA ($r = 0.76$ and 0.58, respectively; $p < 0.005$ and 0.01, respectively). The sensitivities of regional EF and PER for segmental wall motion abnormalities were 86.7% and 68.7%, respectively; their specificities were 86.7% and 95.5%, respectively; their PPVs were 64.3% and 79.2%, respectively; and their NPVs were 96.0% and 91.7%, respectively. The Z scores of these indices significantly correlated with the scores determined by 2DE ($rs = 0.70$ and 0.68, respectively; $p < 10^{-10}$). ***Conclusion:*** The potential of this program to quantify the regional systolic function was validated.

Key words: gated myocardial perfusion SPECT, quantitative analysis, left ventricle, regional function

INTRODUCTION

THE DEVELOPMENT of ^{99m}Tc-labeled perfusion tracers has enabled the assessment of left ventricular (LV) functions by using ECG-gated myocardial perfusion SPECT (MPS).[1–5] However, while MPS is useful in the evaluation of global LV function, regional LV functions still cannot be assessed sufficiently. We have developed a new MPS

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For reprint contact: Akira Yamamoto, M.D., Department of Radiology, Nippon Medical School Musashikosugi Hospital, 1–396, Kosugi-machi, Nakahara-ku, Kawasaki, Kanagawa 211–8533, JAPAN.
E-mail: a-kira@nms.ac.jp.

Table 1 Patients' characteristics

	LPG (n = 20)	ERG (n = 19)	2DEG (n = 24)
Age (y)	51 ± 12	64 ± 11	63 ± 14
Male	9	16	15
History of myocardial infarction	0	9	7
Typical angina	0	3	5
Congestive heart failure	0	3	1
Cardiomyopathy	0	1	2
Recent chest pain	19	8	15
Recent shortness of breath	1	4	4
Resting HR	63 ± 10	66 ± 9	68 ± 11

analyzing program that focuses mainly on the simultaneous estimation of regional LV function and wall motion synchrony; this program is named "cardioGRAF" (cardio Gated single photon emission computed tomography Regional Assessment for left ventricular Function). It calculates not only global but also regional LV functional and temporal indices using a regional time-volume curve (TVC) and its first derivative curve (FDC) generated by Fourier fitting using regional volume data determined from 8- or 16-frame MPS as shown in Figures 1 and 2. It also demonstrates LV motion asynchrony with the difference in timing of segmental peak ejection (PE) or end systole (ES) as shown in Figure 2B. This preliminary study was undertaken to validate the use of this program in the evaluation of LV systolic functions at rest by comparing with the results of ERNA regarding global systolic function and those of 2-dimensional echocardiography (2DE) regarding regional wall motion.

MATERIALS AND METHODS

Patient Population

Patients' characteristics are summarized in Table 1. The low probability of coronary artery disease group (LPG) comprised 20 patients who were examined by MPS due to chest pain (n = 19) or due to the presence of a flat T wave on a resting ECG (n = 1). The existence of low probability of coronary artery disease in these patients was confirmed by normal exercise stress ECG and/or normal Holter ECG or normal coronary angiography. 2DE revealed normal wall motion in all the patients. The ERNA group (ERG) comprised 19 patients who were examined by MPS and ERNA within an 8-day interval (3 ± 2 days). The clinical diagnoses were myocardial infarction, congestive heart failure, angina pectoris, cardiomyopathy, and others. The 2DE group (2DEG) comprised 24 heart disease patients who were examined by MPS and 2DE within a 10-day interval (4 ± 4 days). The clinical diagnoses were myocardial infarction, angina pectoris, chest pain syndrome, and others. Patients with severe arrhythmias such as atrial fibrillation and patients with left bundle branch block were not included in any of the 3 groups. In order to confirm the reproducibility of the process, 20 patients were randomly selected from these groups.

ECG-gated MPS

An intravenous injection of 600 MBq ^{99m}Tc-sestamibi was administered to patients at rest, and MPS imaging was initiated after 30–60 min. Data were acquired for 40–50 beats/projection using a parallel dual-detector camera (RC2600-I; Hitachi, Tokyo, Japan), 64 projections during a 360° rotation, with an 8-frame gating, low-energy high-resolution collimation, 64 × 64 matrix, step and shoot. The ECG-gated projection sets were filtered using a 2-dimensional Butterworth filter (Order 8, cutoff = 0.25 cycles/pixel), and reconstructed in a workstation using a filtered back-projection algorithm (RW3000; Hitachi). No attenuation or scatter correction was employed. The short axial data were fed into a personal computer for the subsequent processes.

Preprocessing for cardioGRAF

To determine the inner LV edge, we used a program called "pFAST" (perfusion and function assessment by means of gated SPECT)[3,4] version 2.4.2., which was developed at Sapporo Medical University, Hokkaido, Japan. For optimal LV edge detection, we regulated the magnification for processing axial images and manually adjusted the LV center on short axial images and processing areas. The results thus obtained were saved as files for future processing with cardioGRAF. Inter- and intra-observer reproducibility was also evaluated.

cardioGRAF

The files that were obtained by pFAST contained regional (640 areas that comprised 40 areas/slice × 16 slices) volume data in terms of the number of voxels in each phase. According to the American Heart Association Scientific Statements,[6] we used a 17-segment LV model as shown in Figure 3. In this model, 640 areas were divided into 17 segments as shown in Figure 3. Sixteen slices were divided into 4 layers—basal, mid, apical, and apex—by combining 4 slices. Forty directions in the basal, mid, and apical layers were divided into 48 directions by interpolation. The basal and mid layers were divided into 6 segments each. The apical layer was divided into 4

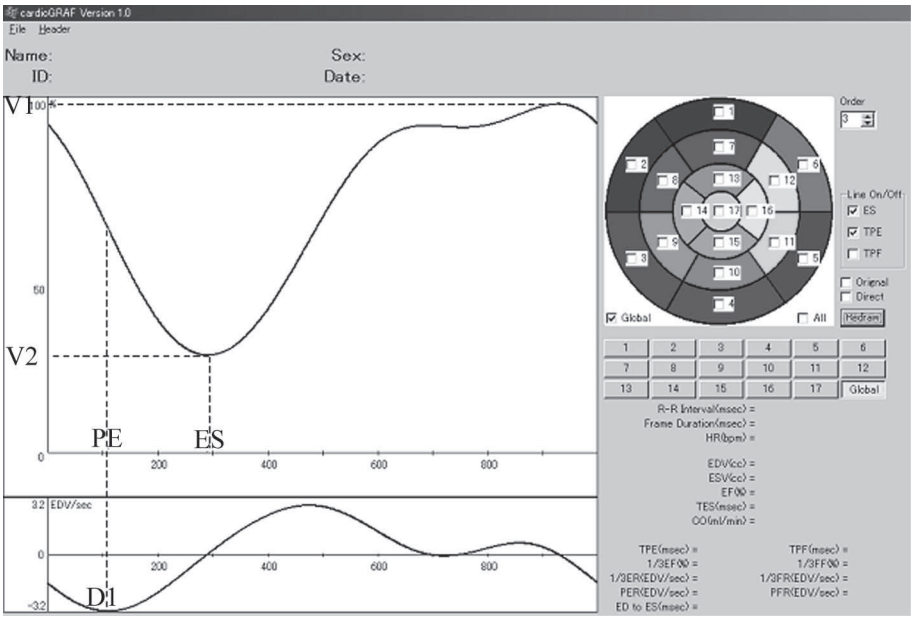

Fig. 1 The main window of cardioGRAF. TVC and FDC of the global left ventricle obtained by MPS at rest in a 58-year-old woman in the LPG.

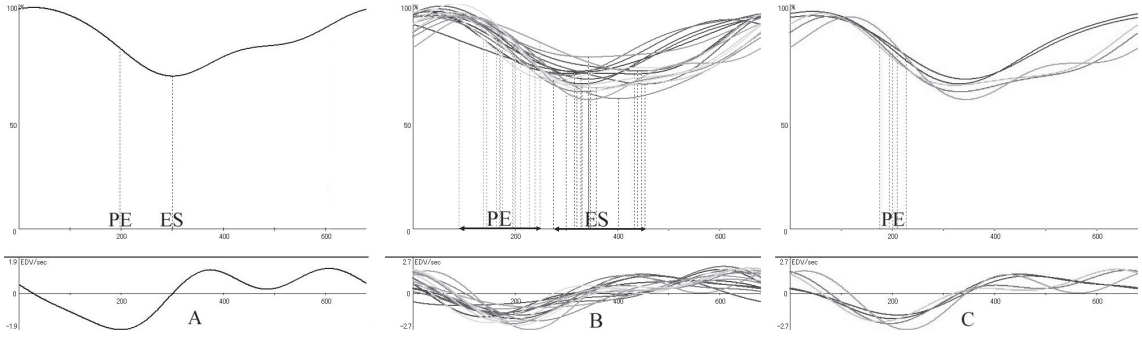

Fig. 2 TVCs and FDCs of the 17 LV segments obtained by MPS at rest in a 75-year-old man with heart failure due to old inferior myocardial infarction. TVC and FDC of the global left ventricle are demonstrated. The dashed lines demonstrate peak ejection (PE) and end systole (ES) (A). TVCs and FDCs of 17 segments of the same patient. The dashed lines demonstrate peak ejection (PE) and end systole (ES). Arrows express the ranges of 17-segmental PE and ES (B). TVCs and FDCs of 5 segments are observed to be abnormal by 2DE but normal by PER; dashed lines demonstrate the regional peak ejection (C).

segments, whereas the apex layer was not divided. The regional volume data of each area were summed up for each segment. The global and segmental TVCs were generated by Fourier curve-fitting analysis by using 1 to 9 harmonics; the FDC was created from the TVC simultaneously as shown in Figures 1 and 2. The values of the global and regional indices were obtained from the TVC and the FDC as shown in Figure 1. The 2 indices were obtained for the estimation of regional LV wall motion:

1) Ejection fraction: EF (%) = (V1 – V2) × 100/V1
2) Peak ejection rate: PER (EDV/s) = |D1|

V1: End-diastolic volume (EDV) (%), V2: End-systolic volume (%), D1: Peak ejection rate (EDV/s)

These indices are output as a spreadsheet that can be used in a calculation program.

In this study, we selected 3 harmonics for the global functional indices and 2 harmonics for the regional indices.

Criteria to Determine Abnormalities of Segmental Function by cardioGRAF

The reference values of the regional function were

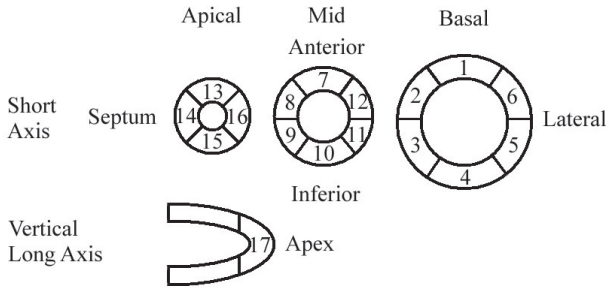

Fig. 3 Assignment of 17 LV segments.

obtained from LPG as shown in Table 2. To assess the regional function in 2DEG, we used the Z score, which is defined as follows.

Z sore = (reference average value of the segment – patient's value of the segment)/referential standard deviation of the segment

A Z score equal to or greater than 2 was defined as abnormal for EF and PER. No geometrical matching was carried out for the rotation or torsion of LV. The score of segment No. 17 was not used because we used the 16-segment model in the 2DE analysis.

Multigated ERNA

Approximately 10 min after injecting ^{99m}Tc-labeled human serum albumin (740 MBq), patients underwent conventional ERNA with a gamma camera (RC2600-I; Hitachi). We acquired 25 frames/cardiac cycle in the left anterior oblique projection with caudal angulations. Data were acquired using an R-wave gate for 500 beats. After semiautomatic determination of the LV region of interest, the time activity curve and its FDC were generated. The EF and PER were calculated in the usual manner.

Semiquantitative Interpretation of 2DE

2DE images were visually scored for the assessment of LV wall motion using the 16-segment model, in which segment No. 17 has been omitted from the 17-segment model of the left ventricle. A 4-degree scale was used to grade the wall motion (2DE scores: 0 = normal, 1 = mild hypokinetic, 2 = severely hypokinetic, 3 = akinetic, dyskinetic). This was done by 2 expert cardiologists who were blinded to the results of MPS and who agreed with regard to the grading in each case.

Statistical Analysis

Values are expressed as mean ± SD. For the global functions, linear regression analysis was performed to determine the correlation coefficients between the data obtained from cardioGRAF and those obtained from ERNA in the ERG. The statistical significance of the correlation was determined using Pearson's correlation coefficient test and a p value of less than 0.05 was considered to be significant. Bland-Altman plots characterized relationships between functional indices determined by ERNA and cardioGRAF.

Table 2 Reference values for segmental function

Segment	EF (%)	PER (EDV/s)
1	65.2 ± 8.3	2.9 ± 0.5
2	61.0 ± 7.9	2.8 ± 0.5
3	59.0 ± 9.0	2.7 ± 0.6
4	60.5 ± 9.8	2.7 ± 0.6
5	62.3 ± 8.9	2.8 ± 0.5
6	61.6 ± 9.8	2.7 ± 0.6
7	64.1 ± 8.5	2.9 ± 0.6
8	64.1 ± 8.2	3.0 ± 0.5
9	62.7 ± 7.9	2.8 ± 0.5
10	63.2 ± 8.9	2.8 ± 0.5
11	61.7 ± 8.3	2.7 ± 0.5
12	59.9 ± 9.4	2.6 ± 0.5
13	65.1 ± 9.9	3.0 ± 0.6
14	66.1 ± 10.5	3.1 ± 0.6
15	66.7 ± 10.5	3.0 ± 0.6
16	61.7 ± 10.5	2.7 ± 0.6
17	72.4 ± 11.5	3.3 ± 0.6

Data are expressed as mean ± SD; n = 20

Table 3 Reproducibility of various parameters

	Inter-observer %CV	Intra-observer %CV
global EF	3.17 ± 2.06%	2.50 ± 1.72%
global PER	3.28 ± 2.28%	3.18 ± 2.56%
regional EF	10.20 ± 9.88%	7.50 ± 7.93%
regional PER	11.18 ± 9.03%	8.69 ± 8.67%

Data are expressed as mean ± SD

For the regional functions, a regional Z score equal to or greater than 2 was defined as abnormal. In the 2DEG, the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated to compare the results of 2DE for each of the 16 segments (data of the apex layer by cardioGRAF were excluded for the comparison). In addition, Spearman's correlation coefficient by rank test was also performed to determine the correlation between the 2DE score and the Z score. Either Student's t test or Welch's t test was used to compare the Z scores and the 2DE scores for each functional index, and a p value of less than 0.05 was considered to be statistically significant.

RESULTS

Reproducibility of the Analysis with the pFAST Program

Inter-observer reproducibility of manual adjustment with the pFAST program was evaluated by 3 operators and intra-observer reproducibility was evaluated by repeating the process 3 times of one operator in 20 patients, including 4 patients with inferior wall infarctions, 2 with apical infarctions, and 2 with anterior wall infarctions. The

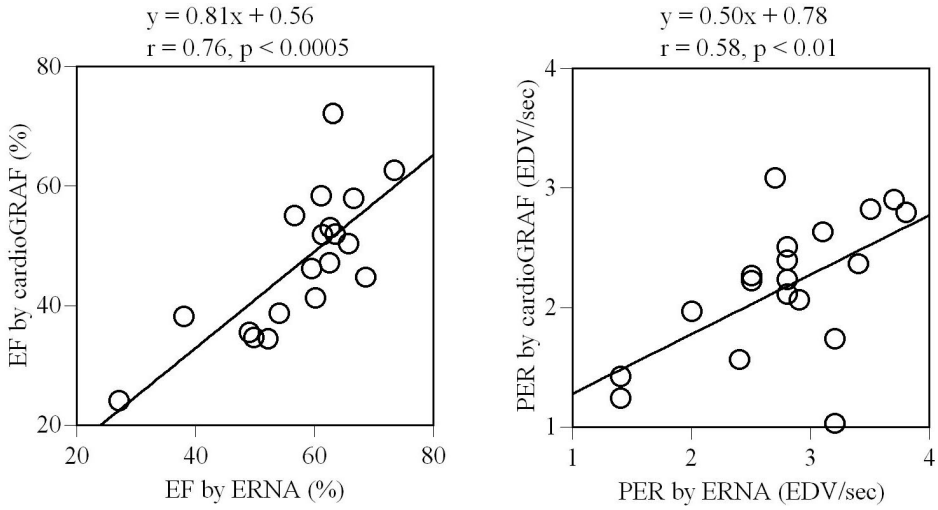

Fig. 4 Correlation of EF and PER values that were determined by ERNA with those obtained by cardioGRAF. Solid lines indicate a linear fit.

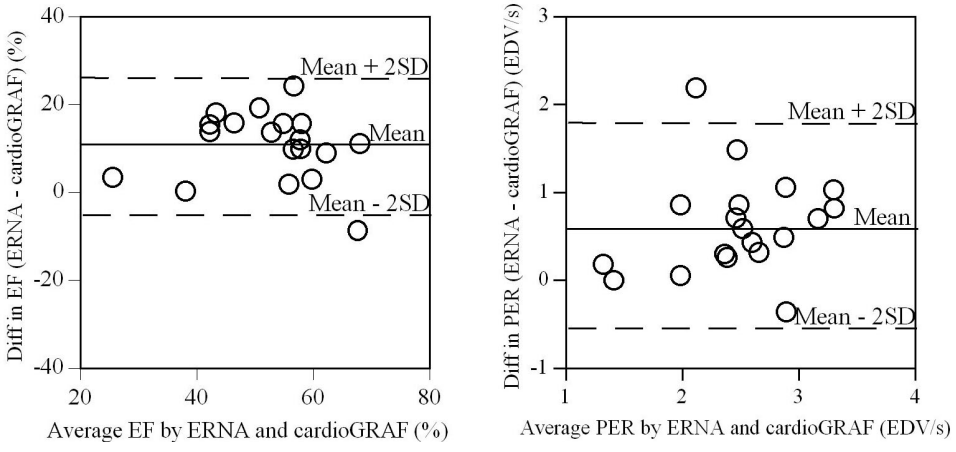

Fig. 5 Bland-Altman plots of EF and PER obtained by ERNA and cardioGARF. *Diff*, Difference.

reproducibility was assessed by the coefficient of variation error (%CV) as shown in Table 3. The reproducibility of the global indices was better than that of the regional indices.

Correlation of Global Functions between cardioGRAF and ERNA

Figure 4 shows the relationships between the global systolic functional indices determined by ERNA and those obtained from cardioGRAF in the ERG. Based on the EF values, a good correlation was confirmed. Based on the PER values, a statistically significant correlation was confirmed.

Figure 5 shows the differences between EF and PER obtained by ERNA and cardioGRAF. The differences were 10.46 ± 7.85% in EF and 0.62 ± 0.58 EDV/s in PER. Both indices were less evaluated by cardioGRAF than ERNA.

Detection of Abnormalities

The reference values of segmental functions are presented in Table 2, which shows normal heterogeneity of the regional LV function in the LPG. Figure 6 shows the overall sensitivity, specificity, PPV, and NPV using the criteria for abnormality that includes the 2 systolic functional indices in the 2DEG. Among the 384 segments in these 24 patients, 2DE detected 83 abnormal segments (22%). With regard to regional EF abnormalities, the sensitivity, specificity, PPV, and NPV were 86.7% (72/83), 86.7% (261/301), 64.3% (72/112), and 96.0% (261/271), respectively. The detection of segmental PER abnormalities revealed that the values of these parameters were 68.7% (57/83), 95.0% (286/301), 79.2% (57/72), and 91.7% (286/312), respectively.

Using the regional EF, false negative results were observed in 7 grade 1 segments and 2 grade 2 segments. With regard to PER, false negative results were observed

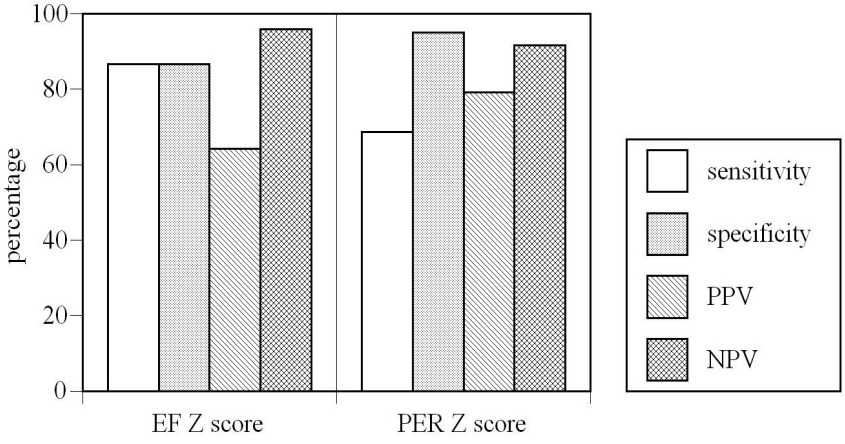

Fig. 6 Sensitivity, specificity, PPV, and NPV obtained by cardioGRAF with regard to the detection of segmental functional abnormalities.

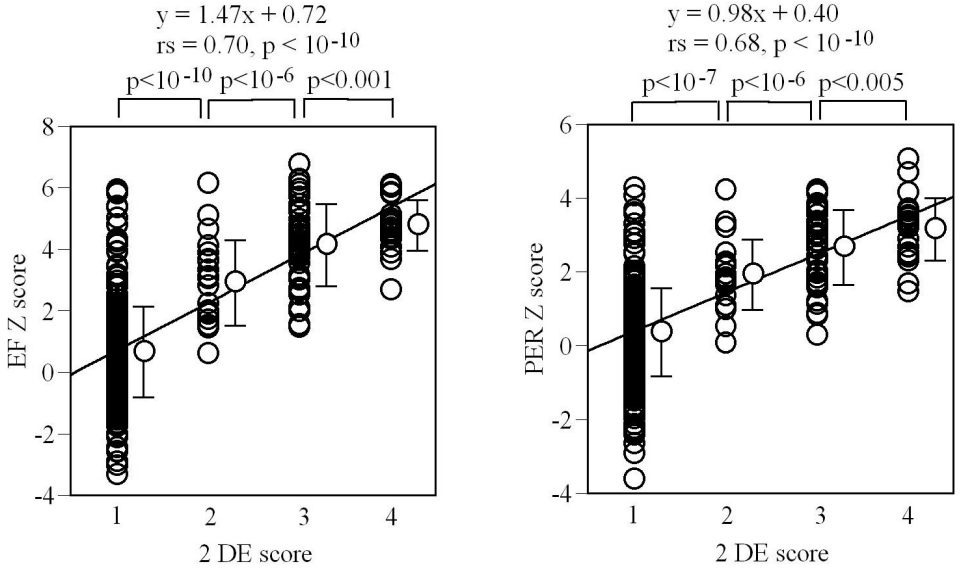

Fig. 7 Correlation of the scores determined by 2DE and their EF's and PER's Z scores obtained by cardioGRAF. Solid lines indicate a linear fit. Data are also expressed as mean and SD.

in 9 grade 1 segments, 12 grade 2 segments, and 2 grade 3 segments. Figure 2C shows false negative results of 5 grade 2 low regional EF segments evaluated by PER.

Correlation between 2DE Scores and Z Scores of Regional Indices by cardioGRAF

Figure 7 shows the correlation between the scores determined by 2DE and the regional Z scores of EF and PER obtained by cardioGRAF in 384 segments of 24 patients in the 2DEG. The 2DE scores correlated with the Z scores of regional EF and PER obtained by cardioGRAF. The Z scores of EF were 0.66 ± 1.48, 2.91 ± 1.40, 4.14 ± 1.34, and 4.78 ± 0.83 in 2DE score 0, 1, 2, and 3, respectively. The Z scores of PER were 0.36 ± 1.19, 1.92 ± 0.95, 2.66 ± 1.02, and 3.15 ± 0.85 in 2DE score 0, 1, 2, and 3, respectively. There was a significant difference between a lower 2DE score group and a higher 2DE score group in EF and PER.

DISCUSSION

We have developed a new program that focuses on regional wall motion and its synchrony. The validation of this program was divided into 2 steps. The first step validated the evaluation of regional function, and the second step validated the regional wall motion synchrony, because it is impossible to estimate wall motion synchrony without employing a method that evaluates the regional function. In this preliminary study, we focused on the validation of the systolic functions by comparing with the results obtained by ERNA and semiquantitative evaluation by 2DE.

Reproducibility is not a matter of concern for this program itself because it does not involve any manual processes. However, some manual adjustments are required during the preparation for pFAST. We validated the reproducibility of these processes. Inter- and intraobserver reproducibility demonstrated acceptable %CV for both global and regional indices.

For the global functional indices, each index determined by ERNA significantly correlated with that obtained by cardioGRAF. Particularly, a good correlation was demonstrated with regard to the EF. Two indices were underestimated by cardioGRAF rather than ERNA. In this study, we examined the data obtained from 8-frame MPS; however, 16-frame data may improve the correlation and difference, similar to quantitative gated SPECT (QGS).[7]

For the regional functional indices, we used the Z score method; this was because of the normal heterogeneity of the LV wall motion, which was reported by Sharir et al.[5] They compared the regional functional values, namely, wall motion distance and wall thickening with semiquantitative optical estimation of a 3D LV motion image in the same program. They also used an adjusted threshold to determine the abnormalities of wall motion and thickening.[5] We used threshold averages under 2SD as generally used and compared these with the 2DE grading that was evaluated separately by 2 cardiologists' who agreed with regard to the grading in each case. For the detection of segmental wall motion abnormalities, the sensitivity with regard to regional EF and the specificity of both indices were either similar to or better than those previously described[5]; however, the thresholds were obtained from a small number of patients. The reason for false negative results was the underestimation of mild hypokinesis or geometrical mismatch while employing regional EF. The sensitivity of PER was less than that of EF. The main reason was that the wall motion rate was maintained within a normal range in low regional EF segments as shown in Figure 2C. The wall motion abnormality detected by 2DE is not defined as an abnormality of contraction, motion distance, or motion rate. The abnormality detected by 2DE might be mainly reflected as a contraction abnormality as revealed by the EF. The number of data acquisitions per R-R interval influences the functional indices in MPS. Generally, the results obtained by 16- and 32-frame examinations are more similar to the ERNA results than with the 8-frame data for the LV function in the case of QGS.[7] In this study, we used the 8-frame data, and the estimation was conducted by comparing the same frame data. This might decrease the influence of a low frame rate.

Regarding the correlation between the 2DE scores and the Z scores of the regional indices obtained by cardioGRAF, the regional Z scores of EF and PER significantly correlated with the regional 2DE scores, particularly with the EF Z scores. Z scores of higher 2DE scores were significantly greater than those of lower 2 DE scores. These imply that cardioGRAF can be used to estimate regional wall motion abnormalities.

We selected pFAST as a method to be employed before cardioGRAF, because we have routinely used this program for the analysis of MPS. Moreover, this program enables the processing of the combined short axial slices. Further, the center of the LV cavity is defined for each slice, and the fan-shaped regional volume, which is divided through the center, of each phase is suitable for creating the regional TVC. A controversy exists regarding the actual existence of the center of the LV cavity, particularly in the case of abnormal wall motion. On the other hand, a virtual center simplifies the analysis of the regional functions using the regional time-volume data. Since it was difficult to define the center of the LV cavity, we had to manually adjust the center of the end-diastolic phase and end-systolic phase in pFAST. An automatic definition of the LV center would further improve the reproducibility of pFAST.

In a recent paper, the LV contraction synchrony was estimated by %WT.[8] For the analysis of %WT of the LV, defining the center of the LV wall is not required, but the results must be highly reproducible. However, the torsion of the LV wall might influence the results. Further, its use in cases with a perfusion defect is difficult. Besides, %WT has not been proved to reflect the wall motion exactly. We plan to proceed with this program in order to enable the simultaneous demonstration of the regional %WT and EF. This new program confirms the relationship between wall thickening and wall motion.

We will report the validation and examination of the regional temporal index and LV motion synchrony, in the next paper.

CONCLUSION

The potential of this program to quantify regional systolic function was validated. This program has already been released as free software. Although the main purpose of myocardial SPECT does not vary, the additional value of MPS needs to be evaluated further. We hope that this program will expand the horizons of nuclear cardiology.

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