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Global and regional evaluation of systolic and diastolic left ventricular temporal parameters using a novel program for ECG-gated myocardial perfusion SPECT

—Validation by comparison with gated equilibrium radionuclide angiography and speckle-tracking radial strain from echocardiography—

Akira YAMAMOTO,* Naoto TAKAHASHI,** Kazuo MUNAKATA,** Tetsuo HOSOYA,*** Masato SHIIBA,* Takao OKUYAMA,* Kazuya ABE,* Tadashi KANESHIRO,* Haruko TSURUTA,* Toshi TAKAMA* and Masashi SATO*

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

Background: A newly developed program, named cardioGRAF, enabled the evaluation of left ventricular (LV) systolic and diastolic temporal parameters for the estimation of heart failure using ECG-gated myocardial perfusion SPECT (GMPS). ***Objective:*** The feasibility of those global (g-) and regional (r-) parameters was validated to compare with gated equilibrium radionuclide angiography (ERNA) and speckle-tracking radial strain (STS) from echocardiography. ***Methods:*** Thirty-three patients were studied using GMPS and ERNA (n = 11) or GMPS and STS (n = 22). The following g- or r-parameters obtained by cardioGRAF and ERNA or STS were compared: time to end systole (TES), time from end systole to peak filling rate (TPF1), time from 0 to peak filling rate (TPF2), time to peak radial strain (TPS), time from peak strain to peak negative strain rate (TP-SR1), and time from 0 to peak negative strain rate (TP-SR2). ***Results:*** All g-parameters were successfully obtained by cardioGRAF and ERNA. The results demonstrated good correlations (g-TES: $r = 0.79$, $p < 0.005$; g-TPF1: $r = 0.75$, $p < 0.02$; TPF2: $r = 0.83$, $p < 0.005$). The differences were 11.9 ± 31.8 ms in g-TES, 19.9 ± 65.4 ms in g-TPF1, and 37.7 ± 67.4 ms in g-TPF2. All r-parameters were successfully obtained by cardioGRAF. Eight patients and 12 segments were excluded because of the inadequate quality of routine echocardiography for STS analysis. However, r-parameters obtained by cardioGRAF were significantly correlated with those of STS (r-TES and r-TPS: $r = 0.61$, $p = 1 \times 10^{-8}$; r-TPF1 and r-TP-SR1: $r = 0.69$, $p = 3 \times 10^{-11}$; r-TPF2 and r-TP-SR2: $r = 0.76$, $p = 2 \times 10^{-15}$). The differences were 22.1 ± 38.2 ms between r-TES and r-TPS, 7.0 ± 123.4 ms between r-TPF1 and r-TP-SR1, and 38.1 ± 111.5 ms between r-TPF2 and r-TP-SR2. ***Conclusion:*** The feasibility of evaluating systolic and diastolic temporal parameters by a new program was validated. This program has the potential to evaluate both diastolic and systolic heterogeneous wall motions which express dyssynchrony in heart failure.

Key words: left ventricle, synchrony, gated myocardial perfusion SPECT, speckle-tracking strain analysis

INTRODUCTION

THE DEVELOPMENT of ^{99m}Tc labeled perfusion tracers has enabled assessment of left ventricular (LV) systolic and diastolic functions using ECG-gated myocardial perfusion SPECT (GMPS).[1–7] Recently, cardiac resynchronization therapy (CRT) was developed for severe heart

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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.

failure and was shown to improve cardiac systolic function.[8] The response to CRT was predicted on the basis of radial dyssynchrony which was calculated by regional (r-) temporal parameters using speckle-tracking radial strain (STS) from routine echocardiography.[9] LV synchrony which was calculated by r-systolic temporal parameters was suggested to affect cardiac systolic function in advanced heart failure. On the other hand, diastolic dysfunction has some important role in the early stage of heart failure and the usefulness of global (g-) temporal parameter was reported for the assessment of diastolic function.[5] The r-temporal parameters may also be useful to estimate heart failure in the early stage.

We have developed a novel GMPS analyzing program which focuses mainly on the simultaneous estimation of r-LV functional and temporal parameters; this program is named "cardioGRAF" (**cardio G**ated single photon emission computed tomography **R**egional **A**ssessment for left ventricular **F**unction) as shown in Figures 1 and 2. We have reported the validation to quantify r-LV systolic function by using this program.[10] It also reveals that synchronous or dyssynchronous diastolic wall motion using the wave forms as shown in Figure 2. We speculated that the dyssynchronous peak filling, which is demonstrated in Figure 2B, also affects the diastolic function. The feasibility of systolic and diastolic temporal parameters which are obtained by this program has to be certified before the evaluation of heart failure. In this study, we validated the feasibility of g- and r-temporal parameters to compare with those of the multigated equilibrium radionuclide angiography (ERNA) or STS for further estimation of synchronous disorder in heart failure.

Table 1 Patients' characteristics

	ERG (n = 11)	STG (n = 22)
Age	65 ± 8	64 ± 11
Male	9	15
Typical angina	1	0
History of myocardial infarction	4	0
Arrhythmia	1	0
Cardiomyopathy	1	0
Valvular disease	3	0
Other cardiac disease	2	22
History of coronary angioplasty	0	4
NYHA I	2	22
NYHA II	6	0
NYHA III	2	0
NYHA IV	1	0
LVEF	46 ± 13	63 ± 14
Resting HR	74 ± 11	69 ± 12

Data are expressed as mean ± SD

Table 2 Reproducibility of various parameters

	Inter-observer %CV	Intra-observer %CV
g-TES (F4)	2.7%	7.1%
g-TPF1 (F2)	5.5%	0.9%
g-TPF2 (F2)	2.0%	3.4%
r-TES (F2)	4.8%	3.2%
r-TPF1 (F2)	12.9%	11.0%
r-TPF2 (F2)	4.8%	4.4%

Intra parentheses express Fourier harmonics
Data are expressed as mean value

METHODS

Patient Populations

Thirty-three patients were studied. The patient characteristics are summarized in Table 1. The ERNA group (ERG) comprised 11 patients who were examined by using GMPS and ERNA within a 7-day interval (3 ± 2 days) and it included various kinds of heart disease. The STS group (STG) comprised 22 non-symptomatic hypertensive patients who were examined using GMPS and echocardiography within the same day and analyzed by STS. Patients with severe arrhythmias such as atrial fibrillation were not included.

ECG-GMPS

An intravenous injection of 600 MBq ^{99m}Tc-sestamibi was administered to the patients at rest, and GMPS 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 16-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 3, 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)[6,7] version 2.4, which was developed at Sapporo Medical University, Hokkaido, Japan. In order to obtain 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 the pFAST data files for future processing along with the cardioGRAF. Inter- and intraobserver reproducibility was also examined.

cardioGRAF

The files obtained by pFAST contained regional volume data in terms of the number of voxels in each phase. In keeping with the American Heart Association Scientific Statements,[11] we used a 17-segment LV model and

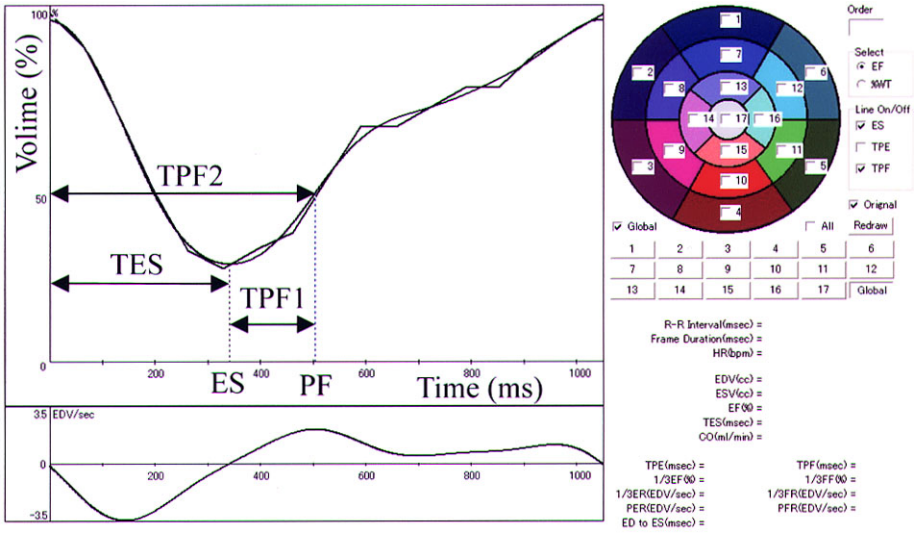

Fig. 1 The main window of cardioGRAF. Original graph and TVC of global left ventricle (*upper*) and FDC (*lower*) obtained by GMPS at rest in a 57-year-old woman who demonstrated normal wall motion and LV function. The dashed lines demonstrate end systole time (ES), and peak filling time (PF). TES: Time to end systole (ms), TPF1: Time from end systole to peak filling rate (ms), TPF2: Time from 0 to peak filling rate (ms)

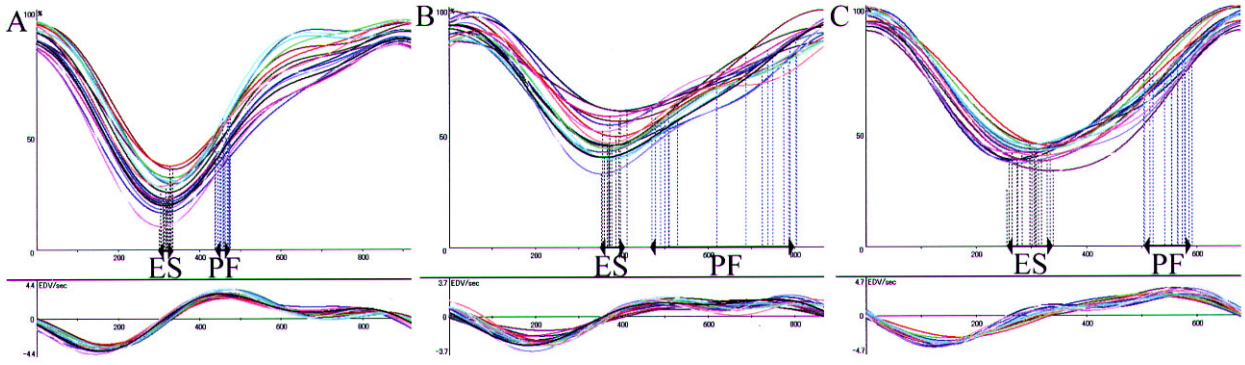

Fig. 2 The regional TVCs and FDCs of LV obtained by cardioGRAF at rest in a 63-year-old woman (A), 79-year-old man (B), and 56-year-old man (C) with hypertension. The dashed lines demonstrate end systole (ES) and peak filling time (PF). Arrows show the range of r-TES and r-TPF2.

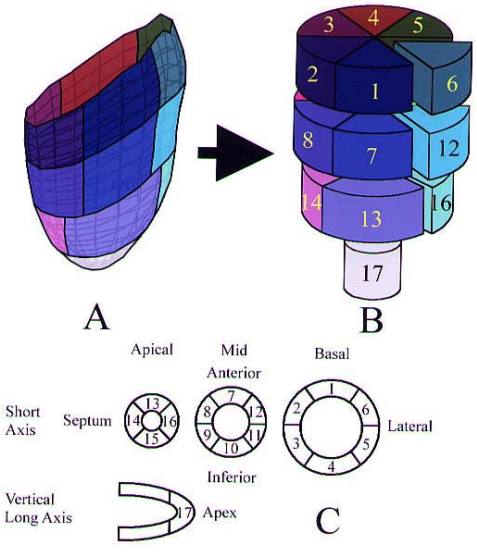

Fig. 3 The 3D image of LV endocardium at end diastole (A). The 3D schema of 17 LV segments (B). Assignment of 17 LV segments (C).

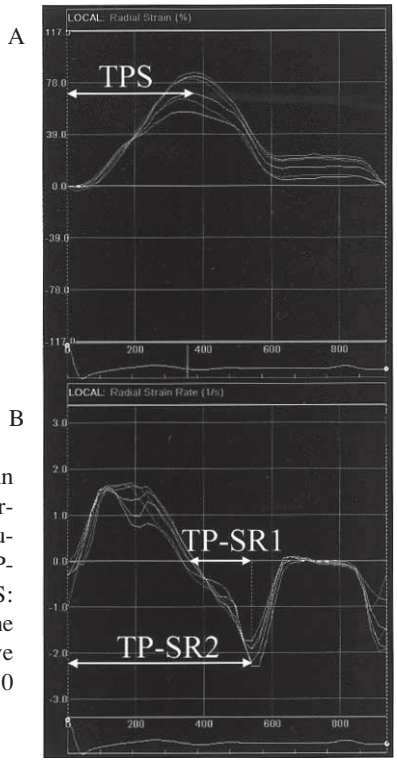

Fig. 4 Wave forms of radial strain (A) and radial strain rate (B). Arrows show r-TPS of mid ventricular anterior segment (A) and r-TP-SR of same segment (B). TPS: Time to peak strain, TP-SR1: Time from peak strain to peak negative strain rate, TP-SR2: Time from 0 to peak negative strain rate.

divided regional volume data into 17 segments by the procedure which is previously described[10] as shown in Figure 3. The g- and r-time volume curves (TVCs) were generated from time-volume data by Fourier curve-fitting analysis with 2 or 4 harmonics; the first derivative curve (FDC) was simultaneously created from the TVC as shown in Figures 1 and 2. The values of the g- and r-parameters were obtained from the TVC and the FDC as shown in Figure 1. The selected temporal parameters were as follows:

1) Time to end systole: TES (ms)
2) Time from end systole to peak filling rate: TPF1 (ms)
3) Time from 0 to peak filling rate: TPF2 (ms)

TES is assumed to be the systolic temporal parameter. TPF1 and TPF2 are assumed to be the diastolic temporal parameters. These parameters are available for output in a spreadsheet to be used for further calculation with a personal computer. In this study, we selected 4 harmonics for the calculation of g-TES and 2 harmonics for the calculation of the other temporal parameters.

Multigated ERNA

Approximately 10 min after injecting ^{99m}Tc-labeled human serum albumin (740 MBq), patients underwent conventional ERNA for which a gamma camera was used (RC2600-I; Hitachi). We acquired 25 frames/cardiac-cycle from 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, g-TES, g-TPF1, and g-TPF2 were calculated using the standard method.

Routine Echocardiography and Speckle-Tracking Radial Strain Analysis

The examinations were performed with Vivid 7 system (GE-Vingmed, Houten, Norway) for further STS analysis. For the evaluation by STS, the midventricular short-axis images were selected the same as in a previous report which compared STS with tissue Doppler examination.[9] Offline analysis of radial strain was performed on digitally stored images (Echo PAC, GE-Vingmed). STS was performed by 2 well trained people who were blinded to the results of GMPS. The short-axis images were divided into 6 segments automatically. The segments which were poorly tracked or included artifacts were omitted by the other observer who was also blinded to the results of GMPS. By using those radial strain and strain rate data, we measured temporal parameters as follows (Fig. 4):

1) Time to peak radial strain: TPS (ms)
2) Time from peak strain to peak negative strain rate: TP-SR1 (ms)
3) Time from 0 to peak negative strain rate: TP-SR2 (ms)

Those r-TPS, r-TP-SR1, and r-TP-SR2 were compared with r-TES, r-TPF1, and r-TPF2, respectively.

Statistical Analysis

Values are expressed as the mean ± SD. For the g- or r-temporal parameters, linear regression analysis was performed to determine the correlation coefficients of those obtained by cardioGRAF and ERNA in ERG or STS in STG. The Bland-Altman plots for the g- and r-temporal parameters were also examined. The statistical significance of the correlation was determined using Pearson's correlation coefficient test, and a p value < 0.05 was considered to be significant.

RESULTS

Reproducibility of Analysis with the pFAST Program

Interobserver reproducibility of manual adjustment with the pFAST program was evaluated by 3 operators, and intraobserver reproducibility was evaluated by repeating the process 3 times in consecutive 20 patients. The reproducibility was assessed by the coefficient of variation error (%CV) as shown in Table 2. The reproducibility of r-TPF1 is less than the other temporal parameters.

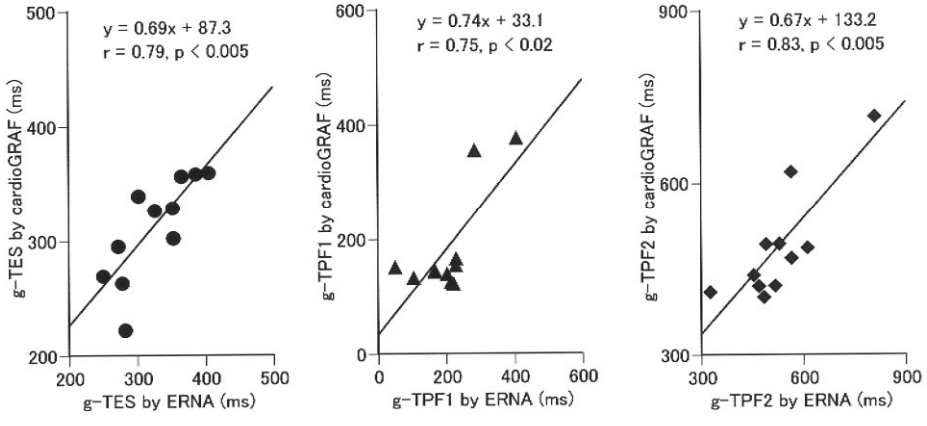

Fig. 5 Correlation of g-temporal parameters between the values determined by ERNA and the values obtained from cardioGRAF. Solid line indicates linear fit.

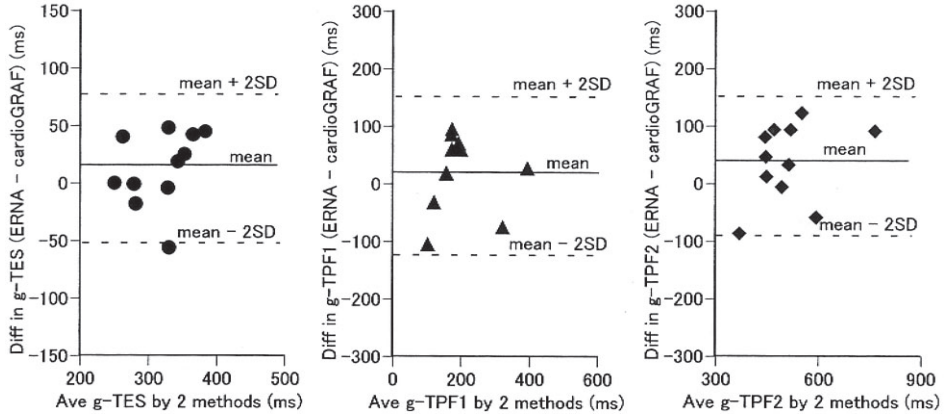

Fig. 6 The Bland-Altman plots for the g-temporal parameters. Ave: average, Diff: difference.

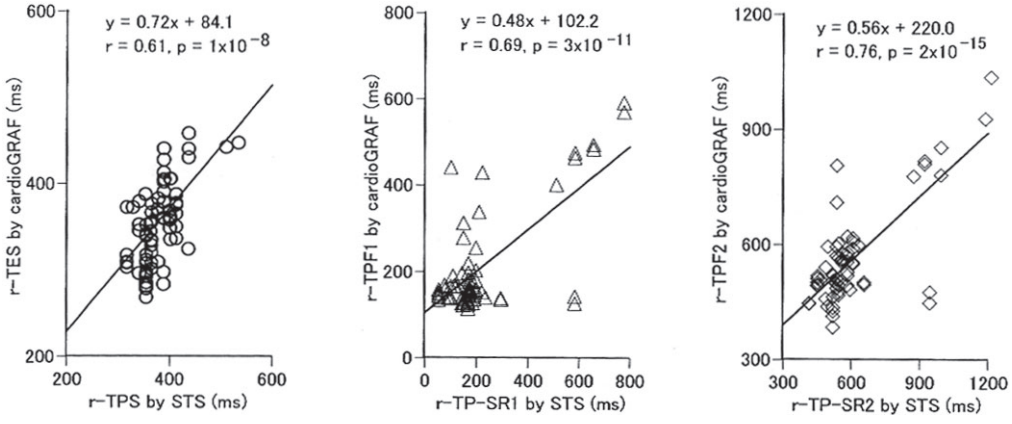

Fig. 7 Correlation between the r-temporal parameters determined by STS and cardioGRAF. Solid line indicates linear fit.

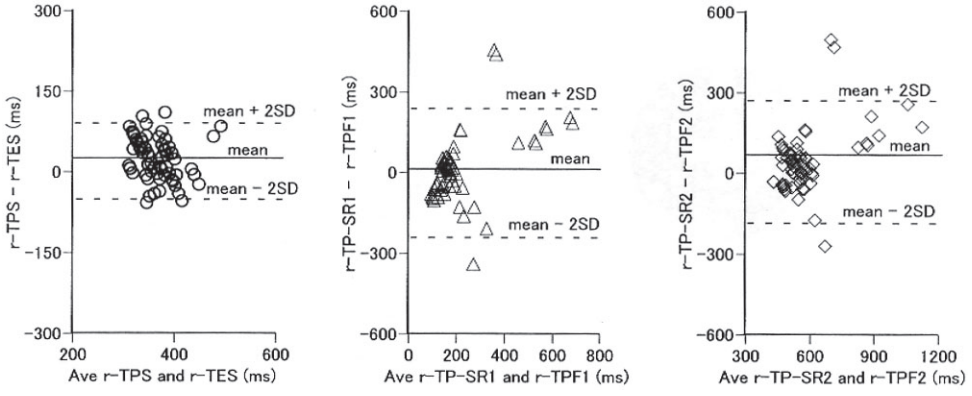

Fig. 8 The Bland-Altman plots for the r-temporal parameters. Ave: average.

Correlation of Global Temporal Parameters between cardioGRAF and ERNA

Figure 5 shows the relationships between the g-temporal parameters determined by ERNA and those obtained from cardioGRAF in ERG. All g-temporal parameters obtained from cardioGRAF demonstrated good correlations with those determined by ERNA.

Figure 6 shows the differences between g-TES, g-TPF1, and g-TPF2 determined by ERNA and cardioGRAF in ERG. The differences are 11.9 ± 31.8 ms in g-TES, 19.9 ± 65.4 ms in g-TPF1, and 37.7 ± 67.4 ms in g-TPF2. All parameters are less well evaluated by cardioGRAF than

ERNA. The Bland-Altman plots for the parameters did not reveal any systematic trend.

Correlation of Segmental Temporal Parameters between STS and cardioGRAF

Eight patients were excluded due to inadeqaute quality of routine echo imaging for STS analysis. In midventricular 84 segments of 14 patients, 12 segments were also omitted for poor tracking because of the presence of artifact or other reasons and 72 segments were examined. The omitted segments were 4 antero-lateral, 2 anterior, 2 inferior, 2 infero-septal, 1 antero-septal, and 1 infero-lateral segments. Frame rates were 41 or 43 Hz (mean 41.3 ± 0.7 Hz). R-R intervals of 15 patients were 973 ± 158 ms in STS and 944 ± 164 ms in GMPS.

Figure 7 shows the relationships between r-temporal parameters obtained from STS and cardioGRAF in STG. Statistically significant correlations were confirmed between all r-temporal parameters obtained from STS and cardioGRAF.

Figure 8 shows difference between r-temporal parameters obtained by STS and cardioGRAF in STG. The differences are 22.1 ± 38.2 ms between r-TES and r-TPS, 7.0 ± 123.4 ms between r-TPF1 and r-TP-SR1, and 38.1 ± 111.5 ms between r-TPF2 and TP-SR2. All parameters were less well evaluated by cardioGRAF than STS. In the case of higher temporal parameters, evaluation by cardioGRAF gave lower values as compared to those by STS. However, the differences were –9.0 ± 47.3 ms in 50 segments of both r-TP-SR1 and r-TPF1 < 200 ms and 15.8 ± 56.3 ms in 51 segments of both r-TP-SR2 and r-TPF2 < 600 ms.

DISCUSSION

For severe heart failure, CRT is a very hopeful treatment and the evaluation of LV synchrony is a requisite for predicting the response to this therapy.[9,13–15] With the exception of CRT, LV dyssynchrony may play an important role in cardiac dysfunction. The evaluation of r-temporal parameters is necessary for the evaluation of LV dyssynchrony. For the estimation of heart failure, diastolic function is very important and g-diastolic temporal parameter is one important factor to estimate diastolic function.[5] The r-diastolic temporal parameter may also contribute to evaluate the heart failure. For further clinical investigation of heart failure, we developed a new program that focuses mainly on the evaluation of r-LV systolic and diastolic temporal parameters by using GMPS. It enables evaluation of not only systolic but also diastolic wall motion dyssynchrony as shown in Figure 2B by using r-temporal parameters. In this study, the validation of g- and r-temporal parameters obtained from a new program was performed by comparison with ERNA and STS.

This program does not involve any manual process, but preparation with pFAST requires manual adjustments. We validated inter- and intrareproducibility of this process. Three attempts with pFAST demonstrate good %CV for g- and r-temporal parameters. However, reproducibility of some r-temporal parameters was less than that of global ones. Especially, the reproducibility of r-TPF1 was less than the others, but it is still the same as the global diastolic functional parameters of echocardiography which were recently reported.[12] Hence, we used medians of these parameters to reduce the influence of manual adjustment in this study.

The g-temporal parameters obtained by cardioGRAF demonstrated good correlations with those of ERNA. This means that g-temporal parameter obtained by cardioGRAF is available for further evaluation.

Regarding STS analysis, the speckle tracking was frequently disturbed by artifacts. Higher quality image is required for the STS analysis than the routine optical interpretation. The r-TES demonstrated a significant correlation but its correlation coefficient was less than the others. One reason is that the range of r-TES was not as wide as the other temporal parameters in this study. The other reason was the impossibility to adjust the segments of GMPS and echocardiography completely as a comparison between Doppler echocardiography and STS analysis.[9]

Regarding the r-peak filling, it occasionally happened that the filling rate in rapid filling is greater than the filling rate in atrial filling but the r-strain rate in rapid filling was less than the r-strain rate in atrial filling because of segmental mismatch between 2 different modalities. Moreover, it was difficult to decide the peak filling or peak strain rate, when the r-filling rate or r-strain rate in rapid filling was the same as the r-filling rate or r-strain rate in atrial filling. These were reasons for the differences between r-TPF1/2 and r-TP-SR1/2. Using the median of parameter was a possible solution to select the optimum regional peak filling under the present conditions. STS uses only one heart beat but cardioGRAF uses an averaged heart beat. The respiration influences the R-R duration. It was not statistically significant but the average R-R interval of STS was larger than that of GMPS. All GMPS examinations were performed 2 to 3 hours later than the echocardiography for STS analysis. These may be the other possibilities for the difference. At least, the differences between r-TPF and r-TP-SR in the early diastole, which were r-TP-SR1 and r-TPF1 < 200 ms or r-TP-SR2 and r-TPF2 < 600 ms, were smaller than the differences of others.

Although the r-volume is different from r-wall strain, each regional temporal parameter is significantly correlated between cardioGRAF and STS. In view of this condition, the regional temporal parameters obtained by a new program are also available to evaluate the timing of regional contraction and dilatation for the estimation of LV wall motion in the early stage of heart failure.

In this study, we validated the regional temporal parameters in the early stage of heart failure only. Therefore, validation of those parameters is needed in advanced heart failure as well.

CONCLUSIONS

The feasibility of systolic and diastolic temporal parameters evaluated by a new program was validated. This program has the potential to evaluate both diastolic and systolic heterogeneous wall motions which express dyssynchrony in heart failure.

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