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RESEARCH ARTICLE

Prognostic Value of Early Evaluation of Left Ventricular Dyssynchrony After Myocardial Infarction

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Abstract

Purpose: Dispersion in the contraction of the normally coordinate ventricular system, referred to as left ventricular (LV) dyssynchrony, is constantly observed at different grades of severity after myocardial infarction (MI). We aimed to investigate the prognostic value of early dyssynchrony in adverse cardiac events after MI in a rat model using the quantified gated single photon emission tomography (SPECT; QGS) software.

Procedures: After thoracotomy, the left coronary arteries of 16 rats were occluded and reperfused. SPECT was performed with [^{99m} Tc]methoxyisobutylisonitrile 3 days, 1 week, 2 weeks, 4 weeks, and 8 weeks after MI. The phase analysis parameters including mean phase standard deviation (PSD), bandwidth (BW), entropy, and LV function were analyzed by the QGS software. A receiver operating characteristic curve was used to explore the predictors for cardiac death and severe cardiac failure (ejection fraction [EF] < 35 %). A Kaplan–Meier event-free survival analysis, univariate, and multivariate Cox proportional hazards regression analyses were conducted.

Results: Four rats had died, whereas another four rats presented with severe heart failure. LV end-diastolic volume was increased during follow-up, but no significant changes were noted in the other parameters. The prognosis of rats with lower EF and higher end-diastolic and end-systolic volumes (ESV), PSD, BW, and entropy at 3 days after MI was poor. Adverse cardiac events were associated with lower EF (relative risk [RR] 13.1, 95 % confidence Interval [CI]: 2.1–259.9, $P = 0.003$), higher ESV (RR 6.4, CI 1.4–45.9, $P = 0.01$), and higher entropy (RR 4.3, 95 % CI: 1.0–21.8, $P = 0.04$) by univariate analysis. Multivariate analysis showed that lower EF was the most powerful independent predictor of adverse cardiac events (RR 16.0, CI 1.1–429.2, $P = 0.03$).

Conclusions: Severe early dyssynchrony evaluated by QGS after MI could predict cardiac events in the rat model in the same way as other cardiac function parameters including EF and ESV. The early assessment of dyssynchrony after MI may provide helpful information for the prediction of cardiac events in the future.

Key words: Dyssynchrony, Phase analysis, Acute myocardial infarction

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Introduction

Dispersion in the contraction of the normally coordinate ventricular system is referred to as left ventricular (LV) dyssynchrony. It is not an all-or-none phenomenon and has been observed continuously at different grades of severity after myocardial infarction (MI). LV dyssynchrony relates to impaired LV systolic function, perfusion defect size, and poor prognosis during chronic heart failure in patients with known coronary artery diseases [1].

LV dyssynchrony has been evaluated in patients with severe heart failure due to ischemic cardiomyopathy and idiopathic dilated cardiomyopathy, using myocardial perfusion gated single photon emission tomography (SPECT), in order to identify the responders to resynchronization therapy [2]. The addition of phase analysis to conventional perfusion and LV function analysis enables better differentiation of the etiology of LV remodeling, which is a well-known complication characterized by changes in size, shape, structure, and function of the heart after MI [3–5]. However, it remains unclear as to whether the severity of early LV dyssynchrony evaluated by the Quantified Gated SPECT software (QGS, Cedars-Sinai Medical Center, Los Angeles, CA, USA), after MI, is altered during the longitudinal evaluation process and has a prognostic value for adverse cardiac events.

Recently, it has been shown that ultra-high-resolution SPECT using multiple pinhole collimators in small rodents can provide a resolution of less than 1 mm [6, 7]. This advance in technology makes it possible to evaluate myocardial perfusion defects and LV dyssynchrony and measure LV ejection fraction (EF) and ventricular volume by [^{99m}Tc]methoxyisobutylisonitrile ([^{99m}Tc]MIBI) gated SPECT in small animals in the same manner as was described previously in clinical patients. Hence, this method might aid in the study of disease pathology or treatment efficacy in detail before clinical application using laboratory rat hearts with a size of 10 to 15 mm in diameter.

In this study, we used the QGS software to observe dyssynchrony after MI and investigated the prognostic value of early dyssynchrony for adverse cardiac events in a rat model of severe ischemia and reperfusion.

Material and Methods

Experimental Protocol

The experimental protocol was approved by the animal protection commission of our university. All applicable international, national, and/or institutional guidelines for the care and use of animals were followed. We used 8-week-old male Wistar rats (Charles River, Japan, body weight, 220–240 g) in all experiments. To determine the time course of cardiac perfusion and function after MI, [^{99m}Tc]MIBI myocardial perfusion SPECT imaging was performed in 10 healthy and 16 model rats. In the 16 model rats, LCA was occluded for 20 min ($n = 9$) or 30 min ($n = 7$) followed by reperfusion. The chest was opened under anesthesia (0.05 mg/kg intraperitoneal sodium pentobarbital) to expose the heart. A 7–0 polypropylene suture on a small curved needle was passed under the LCA and ligated to occlude the LCA.

All rats were imaged using a small animal SPECT system (versatile emission computed tomography, VECTor) equipped with a general-purpose rat/mouse collimator (MI-labs, The Netherlands) [8]. The rats received 185 MBq of [^{99m}Tc]MIBI *via* a tail vein 20 min before SPECT, in order to reduce physiological uptake in the liver. The animals were scanned for 15 min under 1–2 % isoflurane anesthesia. *In vivo* 16-frame gated SPECT was performed at 3 days, 1 week, 2 weeks, 4 weeks, and 8 weeks after reperfusion.

SPECT Data Reconstruction

Data were acquired in list mode and photopeak windows (140 keV, 20 % width) were set after acquisition. Triple energy window scatter correction was employed in both phantom and animal experiments (a 20 % photopeak window centered at 140 keV abutting the upper and lower scatter windows 4.5 % in width).

SPECT images were reconstructed using pixel-based ordered-subsets expectation maximization algorithm with 13 subsets and 6 iterations without attenuation correction based on computed tomography [9, 10]. The voxel size ($0.8 \times 0.8 \times 0.8$ mm) was magnified by a factor of 10 to change the size of rat heart to the corresponding of the human heart for analyzing by the QGS/Quantified Perfusion SPECT (QPS) softwares [11]. The heart rate was automatically assumed to be 60/min because the reconstructed data did not include the heart rate information.

QGS/QPS Derivations

Gated [^{99m}Tc]MIBI SPECT was quantitatively analyzed with QGS software, which was used to calculate the end-diastolic volume (EDV), end-systolic volume (ESV), and EF. Phase analysis was performed to calculate phase standard deviations (PSD), bandwidth (BW), and entropy. Phase values were calculated based on the amount of shift of sine curves over the cardiac cycle fitted by the Fourier method. The distribution pattern of phase values was evaluated by phase histogram. PSD and BW were calculated subsequently, based on the histogram analysis. Entropy is an index of "disorder" defined by the summation of $[f_i * \log(f_i)]/\log(n)]$, where f and n denote frequency in the i_{th} bin and number of bins, respectively; it is normalized to its maximum value and reported as a percentage. Measurements of phase values allow evaluating the uniformity and coincidence of the onset of wall movement in the cardiac cycle. To this end, phase BW (95 % interval) and PSD were

determined on the basis of their proven relevance to LV dyssynchrony.

A QPS software (Cedars-Sinai Medical Center, Los Angeles, CA, USA) was applied to assess left ventricular [^{99m}Tc]MIBI distribution and the decreased uptake area semi-quantitatively as a polar map. The relative segment average count level in each 17 segments on polar map was defined as the count ratio value based on the standard normalization factor method given by the QPS software [12]. We used a normal database from our previous study [11], which allowed the comparison of [^{99m}Tc]MIBI distribution of the MI rats with that of the healthy rats. For the analysis of the semiquantitative perfusion distribution in each 17-segment, 5-point defect scoring system was used (0, normal; 1, slight decrease; 2, moderate decrease; 3, severe decrease; and 4, complete defect), and summed defect score (SDS) was calculated. The %SDS was defined as the percentage of SDS in a maximum score of 68.

Reproducibility of QGS

We assessed the reproducibility of measurements of LV functions from gated SPECT images. All studies were analyzed separately by two experienced nuclear medicine physicians, who applied a quantitative automated algorithm to the same image sets. During this process, some manual steps such as drawing a region of interest over the heart and aligning the two axes can cause variability between operators in cases where the automated algorithm cannot detect the heart.

Statistical Analysis

Results are expressed as mean ± SD, unless stated otherwise. Statistical analyses were performed with the SPSS statistics (Version 23, USA) and the JMP Software (Version 12.2.0, USA). Inter- and intra-observer reproducibility of functional parameters from the gated SPECT images was assessed by the intraclass correlation coefficient (ICC). Analysis of variance (ANOVA) was applied to test differences between variables during observation. Tukey's multiple comparison test was used to compare pairs of values. A receiver operating characteristic (ROC) curve was employed to explore the predictors for cardiac death and severe cardiac failure; in addition, a Kaplan–Meier event-free survival analysis, univariate, and multivariate Cox proportional hazards regression analyses were conducted. Cardiac death and EF < 35 %, calculated by the gated SPECT at 8 weeks after MI, were defined as adverse cardiac events. We examined the following factors for prognostic significance: EDV, ESV, EF, SDS, BD, PSD, and entropy. A P value < 0.05 was considered statistically significant.

Results

Normal Rats

The mean values of the LV parameters were obtained using the QGS/QPS software. As shown in Table 1, significant differences in mean values of parameters were observed between the control and model rats at 3 days ($P < 0.05$).

Model Rats

Early Predictability of Cardiac Adverse Events Eight adverse cardiac events, which included death in four rats and EF < 35 % at 8 weeks after MI in four rats, were observed.

ROC analysis of the parameters 3 days after MI in order to discriminate the adverse cardiac events showed an area under the curve and a cutoff value of 0.90 and 430 μl, respectively, for EDV with a sensitivity 62 % and specificity 100 %. The corresponding values for ESV, EF, SDS, BD, PSD, and entropy were 0.93 and 244 μl, respectively (sensitivity, 87 %; specificity, 100 %), 0.90 and 41 %, respectively (sensitivity, 87 %; specificity, 100 %), 0.92 and 26, respectively (sensitivity, 87 %; specificity, 100 %), 0.86 and 162°, respectively (sensitivity, 62 %; specificity, 100 %), 0.85 and 32.7°, respectively (sensitivity, 87 %; specificity, 85 %), and 0.90 and 68 %, respectively (sensitivity, 87 %; specificity, 100 %).

The cutoff value was applied to divide the groups into two. Kaplan–Meier event-free survival analysis showed that rats with lower EF and higher EDV, ESV, SDS, BW, PSD, and entropy presented with higher frequencies of adverse cardiac events.

Parameters Observed by the QGS/QPS Software All MI rats had perfusion defects based on the normal database. Figure 1 shows the changes in EDV, ESV, EF, SDS, BW, PSD, and entropy in all rats during the observation period. ANOVA test demonstrated an increase in EDV after MI ($P < 0.05$) in all model rats; however, no significant changes in other factors were noted during the observation. Increase in EDV (3 days *vs.* 8 weeks and 1 week *vs.* 8 weeks: $P < 0.01$; 3 days *vs.* 4 weeks: $P < 0.05$) and ESV was observed (3 days *vs.* 8 week: $P < 0.01$; 1 week *vs.* 8 weeks: $P < 0.05$) in rats with adverse cardiac events. Similarly, increased EDV (3 days *vs.* 8 weeks: $P < 0.01$; 1 week *vs.* 8 weeks and 3 days *vs.* 4 weeks: $P < 0.05$) and ESV (3 days *vs.* 8 weeks: $P < 0.05$) values were confirmed in rats with non-adverse cardiac events.

Differences between the adverse and non-adverse cardiac event group were calculated using the t test. Table 2 demonstrates significant differences in all parameters between the two groups at all time points after MI.

Adverse cardiac events were associated with lower EF (relative risk [RR] 13.1, 95 % confidence interval [CI]: 2.1–259.9, $P = 0.003$), higher ESV (RR 6.4, CI 1.4–45.9, $P =$

Table 1. SPECT parameters at 3 days

Parameters	Control ($n = 10$)	3 days	
		Non-adverse cardiac event group ($n = 8$)	Adverse cardiac event group ($n = 8$)
EDV (μl)	320 ± 32	315 ± 65	458 ± 98 *
ESV (μl)	107 ± 13	154 ± 38 *	302 ± 98 **
EF (%)	67 ± 3	50 ± 6 ***	34 ± 12 ***
SDS	1 ± 1	19 ± 5 ***	31 ± 8 ***
BW (degrees)	18 ± 3	74 ± 51 *	165 ± 64 **
PSD (degrees)	4 ± 1	20 ± 17 *	49 ± 22 *
Entropy (%)	23 ± 4	47 ± 11 **	68 ± 12 ***

EDV end-diastolic volume, *ESV* end-systolic volume, *EF* ejection fraction, *SDS* summed defect score, *BW* bandwidth, *PSD* phase standard deviation
*$P < 0.05$, **$P < 0.001$, and ***$P < 0.0001$

0.01), and higher entropy (RR 4.3, 95 % CI: 1.0–21.8, $P = 0.04$) by univariate analysis. Multivariate analysis showed that lower EF was the most powerful independent predictor of adverse cardiac events (RR 16.0, CI 1.1–429.2, $P = 0.03$).

Reproducibility of Cardiac Function Parameters by QGS
An ICC analysis demonstrated high intra- and inter-observer (two observers) reproducibility of EDV, ESV, EF, PSD, BW, and entropy (ICC > 0.9, $P < 0.001$) in all rats at 3 days after MI.

Discussion

The current study demonstrates that QGS analysis can be successfully used to evaluate dyssynchrony after MI. QGS/QPS software is commercially available for clinical use with SPECT and can be readily utilized by most researchers. We also confirmed the high performance of SPECT to monitor LV functions, perfusion defect, and dyssynchrony in a rat model.

To the best of our knowledge, this is the first study to evaluate LV dyssynchrony using QGS software in a rat model. The dyssynchrony parameters in normal rats (BW, 18 ± 3°; PSD, 4 ± 1°; and entropy, 28 ± 4 %) were very similar to those in humans reported in a Japanese database

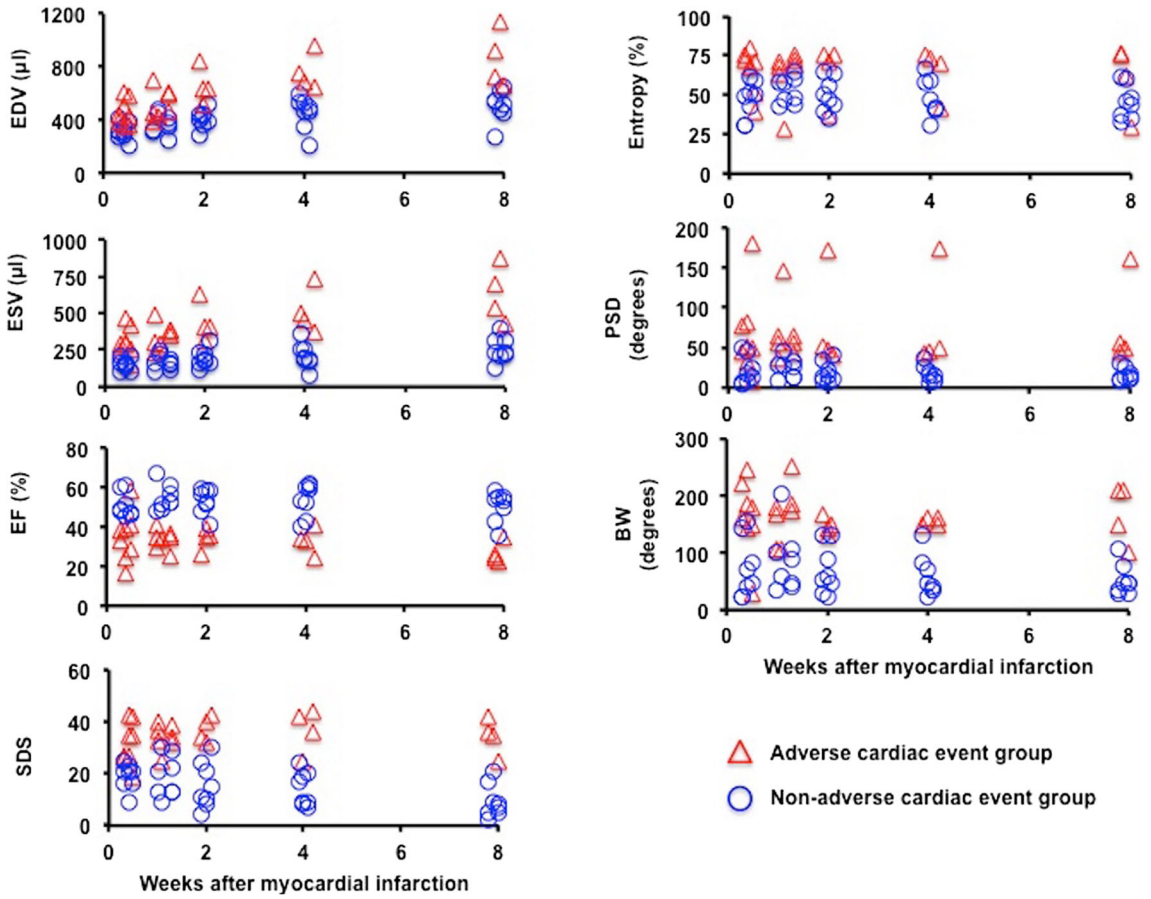

Fig. 1. The change of parameters during observation changes in end-diastolic volume (EDV), end-systolic volume (ESV), ejection fraction (EF), summed defect score (SDS), entropy, bandwidth (BW), and phase standard deviation (PSD) in the adverse cardiac event (red triangle) and non-adverse cardiac event (blue circle) groups during the observation period. EDV was increased in both adverse and non-adverse cardiac event groups longitudinally (ANOVA test; $P < 0.05$); no significant changes were noted in the other parameters.

Table 2. The differences of SPECT parameters between adverse and non-adverse cardiac event group

Parameters	Adverse cardiac event group vs. non-adverse cardiac event group				
	3 days ($n=8$ *vs.* 8)	1 week ($n=7$ *vs.* 8)	2 weeks ($n=4$ *vs.* 8)	4 weeks ($n=4$ *vs.* 8)	8 weeks ($n=4$ *vs.* 8)
EDV (μl)	458 ± 98 *vs.* 315 ± 65 *	521 ± 114 *vs.* 369 ± 77 *	657 ± 134 *vs.* 409 ± 70 *	760 ± 142 *vs.* 455 ± 122 *	858 ± 214 *vs.* 510 ± 117 *
ESV (μl)	302 ± 98 *vs.* 154 ± 38 *	346 ± 84 *vs.* 168 ± 46 **	439 ± 130 *vs.* 195 ± 57 *	517 ± 154 *vs.* 213 ± 79 *	634 ± 196 *vs.* 255 ± 83 *
EF (%)	34 ± 12 *vs.* 50 ± 6 *	33 ± 5 *vs.* 54 ± 6 **	34 ± 5 *vs.* 53 ± 6 *	33 ± 6 *vs.* 53 ± 8 *	27 ± 5 *vs.* 50 ± 7 **
SDS	31 ± 8 *vs.* 19 ± 5 *	34 ± 5 *vs.* 18 ± 7 **	37 ± 5 *vs.* 15 ± 8 **	36 ± 8 *vs.* 14 ± 6 *	34 ± 7 *vs.* 9 ± 6 *
BW (degrees)	165 ± 64 *vs.* 74 ± 51 *	168 ± 49 *vs.* 88 ± 55 *	148 ± 15 *vs.* 71 ± 42 *	156 ± 6 *vs.* 59 ± 35 **	168 ± 52 *vs.* 53 ± 26 *
PSD (degrees)	49 ± 22 *vs.* 20 ± 17 *	49 ± 14 *vs.* 23 ± 12 *	43 ± 5 *vs.* 18 ± 12 **	44 ± 3 *vs.* 16 ± 10 **	44 ± 10 *vs.* 15 ± 7 *
Entropy (%)	68 ± 12 *vs.* 47 ± 11 *	69 ± 3 *vs.* 52 ± 8 **	72 ± 2 *vs.* 49 ± 10 **	70 ± 4 *vs.* 48 ± 11 *	70 ± 7 *vs.* 45 ± 10 **

The same abbreviations are used as in Table 1
*$P < 0.05$ and **$P < 0.001$

(BW, 21 ± 8°; PSD, 5 ± 3°; and entropy, 24 ± 8 %) [13]. Furthermore, phase distribution was nearly symmetrical, whereas phase histogram was highly peaked with a narrow distribution in normal rats in the present study.

Early dyssynchrony parameters at 3 days after MI including BW, PSD, and entropy showed good predictive performance with an area under the curve of ROC of ≥ 0.85. Additionally, adverse cardiac events were associated with higher entropy by univariate analysis. The QGS software has been expanded to provide quantitative parameters of LV dyssynchrony, in addition to the previously reported LV functional parameters [2]. Although several variables including higher SDS and ESV by gated SPECT have been identified as interrelated risk factors of LV remodeling after MI, none of them was currently considered as a definite risk factor. The results of the current study are in agreement with that of a recent study, which reported that LV dyssynchrony measured by gated SPECT had a prognostic value in acute MI with multivessel disease [14]. The early assessment of dyssynchrony by gated SPECT after acute MI may provide helpful information in order to predict further adverse cardiac events in the same way as cardiac echo imaging and cardiac contrast-enhanced magnetic imaging [15].

The observation period after MI in the current study was longer than that in other rat studies (2–4 weeks) [16–18] in order to recognize the LV remodeling in chronic phase in model rats with MI. At 8 weeks after MI, higher LV volume because of LV remodeling and increased severity of LV dyssynchrony were confirmed in the adverse cardiac event group. LVEF < 35 % was adopted as a cardiac event in the present study, because values less than 30–35 % are generally representative of severe heart failure [19, 20]. Considering the fact that the LVEF of the normal rats (67 % ± 3 %) in the current study was very similar to that of humans (66 % ± 6 %) in the Japanese database [21], an LVEF < 35 % might adequately reflect severe heart failure in the rats. Our study demonstrated that 8 weeks was sufficient to monitor LV remodeling and the severity of dyssynchrony in the model rats after MI.

Although phase analysis has been validated for the measurement of LV dyssynchrony in perfusion defect regions *via* gated SPECT imaging [22], accurate regional phase analysis by gated SPECT in severe perfusion defect areas is sometimes difficult because of large variability, heterogeneity, and attenuation artifacts [23–25]. A modest correlation between phase analysis of gated-SPECT MPI and tissue Doppler imaging data has been reported, especially in heart failure patients [26]. Therefore, considering the weakness of the software, only the global and not regional phase analysis parameters were used in the current study. Interestingly, the global phase analysis parameters demonstrated significant differences between the adverse and non-adverse cardiac event group.

Conclusions

Severe early dyssynchrony evaluated using QGS after MI could predict cardiac events in the rat model in the same way as other cardiac function parameters including EF and ESV. Severity of dyssynchrony did not change during longitudinal observation; therefore, early assessment LV dyssynchrony could be useful in predicting adverse outcomes and optimizing therapeutic management.

Compliance with Ethical Standards. The experimental protocol was approved by the animal protection commission of our university. All applicable international, national, and/or institutional guidelines for the care and use of animals were followed.

Conflict of Interest

The authors declare that they have no competing interests.

Ethical Approval

All applicable international, national, and/or institutional guidelines for the care and use of animals were followed.

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