Left Ventricular Mechanical Dyssynchrony after Acute Myocardial Infarction Assessed by CardioGRAF Analysis Is a Predictor of Subsequent Cardiac Events

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Abstract

Objective: Left ventricular mechanical dyssynchrony (LVMD) is associated with deterioration of systolic function and adverse clinical outcomes. This study investigated whether LVMD influenced subsequent cardiac events (CEs), including cardiac death, recurrent nonfatal myocardial infarction, hospitalization for heart failure, and ventricular tachycardia/ventricular fibrillation in patients with acute myocardial infarction (AMI).

Methods: Two hundred and six AMI patients aged 64 ± 11 years (163 men) who underwent successful percutaneous coronary intervention between April 1998 and December 2007 were enrolled. All patients received myocardial \(^{99}\)Tc-sestamibi or \(^{99}\)Tc-tetrofosmin perfusion imaging at rest, and the total defect score was calculated as the sum of the defect scores in 17 standard myocardial segments. Indicators of left ventricular (LV) function were acquired with quantitative gated SPECT software, including the LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV), and LV ejection fraction (LVEF). Then the LVMD index was evaluated by using CardioGraf software.

Results: The follow-up period was 63 ± 31 months. Cardiac events (CEs) occurred in 30 patients, including 15 patients hospitalized for congestive heart failure, 8 patients with recurrent AMI, 4 patients with ventricular tachycardia, and 3 patients with cardiac death. These patients were classified as the CE group, while the other 176 patients without CEs formed the non-CE group. According to univariate analysis with the Cox proportional hazards model, the maximum creatine kinase, frequency of multivessel disease (2-vessel or 3-vessel disease), total defect score, LVEDV, LVESV, and dyssynchrony index were all significantly higher in the CE group than the non-CE group. In contrast, LVEF and the peak ejection rate were significantly lower in the CE group than in the non-CE group. Multivariate analysis showed that multivessel disease (p=0.003) and the LVMD index (p=0.047) were independent prognostic factors for CEs.

Conclusion: LVMD contributes to the risk of subsequent cardiac events in AMI patients.

Keywords: Acute myocardial infarction, Gated myocardial perfusion SPECT, Left ventricular mechanical dyssynchrony

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It has been demonstrated that detection of left ventricular mechanical dyssynchrony (LVMD) by echocardiography can provide prognostic information in patients with acute coronary syndrome (1). Phase analysis on gated SPECT shows a good correlation with speckle tracking echocardiography and is suitable for assessment of LVMD (2). In addition, Civa et al. reported that LVMD measured by tissue Doppler imaging echocardiography in patients with acute ST elevation...
myocardial infarction (STEMI) undergoing primary percutaneous intervention is a prognostic factor for LV dilation and deterioration of LV systolic and diastolic function during follow-up for 6 months (3). It has also been reported that LVMD assessed by gated SPECT phase analysis is an independent predictor of death in patients with advanced coronary artery disease (4).

After STEMI, patients develop LVMD on gated SPECT phase analysis without evidence of electrical dyssynchrony and improvement of this LVMD is correlated with beneficial ventricular remodeling (5). So, assessment of LVMD is thought to be important for risk classification and careful follow up in patients after AMI. But there are few studies to validate whether LVMD assessed by SPECT phase analysis affects their prognosis in patients after AMI.

In the present study, we retrospectively investigated whether LVMD measured by gated SPECT phase analysis was a predictor of cardiac events in patients with acute myocardial infarction (AMI), including cardiac death, recurrent nonfatal myocardial infarction, hospitalization for heart failure, and ventricular tachycardia (VT) or ventricular fibrillation (VF).

### Materials and methods

#### Study population and protocol

This study included patients with AMI who underwent successful percutaneous intervention (PCI) at Gunma Prefecture Cardiovascular Center between April 1998 and December 2007. A total of 347 patients underwent myocardial $^{99m}$Tc-sestamibi or $^{99m}$Tc-tetrofosmin perfusion imaging at rest in the subacute phase (3–30 days after the onset) of AMI. Baseline data were extracted from the medical records with regard to hypertension, diabetes mellitus, hyperlipidemia, smoking, and body mass index in the acute and subacute phases of AMI. Among the 347 patients, 117 patients were ineligible for this study because of the lack of important clinical data (such as SPECT findings or the past medical history) and 15 patients were excluded because the follow-up period was too short (<12 months). We defined cardiac events (CE) as cardiac death, recurrent AMI, hospitalization for heart failure, symptomatic VT or VF requiring an implantable cardioverter defibrillator, or antiarrhythmic therapy for sustained VT.

Informed consent was not obtained because this was a retrospective study. We determined the current status of patients from the medical records, or we sent a letter informing the patient about this study and asking their status if there was no current information in the record. We failed to obtain information about the current status of 9 patients. As a result, 206 patients were investigated. This study was approved by the Ethical Review Board of Gunma Prefecture Cardiovascular Center. All procedures were in accordance with the ethical standards of this committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

#### Myocardial perfusion imaging

Patients underwent myocardial perfusion imaging with $^{99m}$Tc-sestamibi (MIBI, n=127) or $^{99m}$Tc-tetrofosmin (TF, n=79) at rest in the subacute phase of AMI. Each patient received an intravenous injection of 740 MBq of $^{99m}$Tc-MIBI or $^{99m}$Tc-TF, and gated SPECT images were acquired after 30 min. Myocardial SPECT imaging was performed using a three-headed IRIX SPECT system (Picker, Cleveland, OH) with low-energy, all-purpose resolution, parallel-hole collimators. The detector system was linked to a dedicated nuclear medicine computer. A total of 72 projection images were obtained over a 360° arc in 5° increments, with acquisition for 40 s/view for $^{99m}$Tc-MIBI. Data were recorded on a 64 × 64 pixel matrix, and short-axis and long-axis slices (5.4 mm thick) were generated. Regional tracer uptake was scored semiquantitatively on a five-point scale: 0) normal uptake; 1) slightly reduced uptake; 2) moderately reduced uptake; 3) severely reduced uptake; and 4) no uptake. The total defect score was calculated as the sum of the scores for all 17 segments.

All patients were in sinus rhythm during image acquisition. Commercially available quantitative gated SPECT software (Cedars-Sinai Medical Center, Los Angeles, CA) with a temporal resolution of 16 frames per RR interval was used to create a 3-dimensional cine mode display. Then this cine mode display was employed to calculate the left ventricular ejection fraction (LVEF), left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), peak ejection rate, peak filling rate (PFR), and time to peak filling (TPF) throughout the cardiac cycle by using an automatic edge detection algorithm (6-8).

#### Image analysis

Perfusion and function assessment for myocardial SPECT (p-FAST2, Sapporo Medical University, Japan) is a free software program for quantitative analysis of myocardial perfusion and left ventricular function (6). After obtaining short axial SPECT images in each of the 16 periods of the cardiac cycle by the above-mentioned method, we determined the endocardial contour with p-FAST software. After we determined the image mode processing range of this program, abstraction of the endocardial contour was performed automatically.

We also used the free CardioGRAF software program (Fujifilm RI Pharma Co., Ltd. Japan) to compute the timing and visualize regional LV contraction as time-volume curves. This program allowed us to draw time-volume curves for each of the 17 segments by performing Fourier transformation to...
improve temporal resolution (6, 7). Next, we determined the
time to end-systole in each segment and calculated its standard
deviation (SD). Finally, we obtained the dyssynchrony index
(DI), after correcting the SD of the time to end-systole by the
heart rate using the following formula:
\[ DI = \frac{SD \times 100}{RR} \text{ (milliseconds)} \] (8).

Statistical analysis
Continuous variables are expressed as the mean +/- SD, and
categorical variables are presented as percentages. Statistical
analysis was performed with SPSS software (ver. 22; IBM, Armonk, NY, USA). The unpaired two-tailed t-test was used for comparisons between the CE and non-CE groups. Cox proportional hazard models were employed to identify variables with a significant influence on CE, and only variables showing p<0.1 were considered in the multivariate analysis. Kaplan-Meier curves were drawn to estimate the prognosis. For all analyses, p<0.05 was considered statistically significant.

Results
The follow-up period was 63+/−31 months. CEs occurred in
30 patients, including 15 patients hospitalized for congestive
heart failure, 8 patients with recurrent AMI, 4 patients with
VT (no VF was observed), and 3 patients with cardiac death.
These 30 patients were classified as the CE group, while the
other 176 patients without cardiac events during the
observation period formed the non-CE group.

Baseline clinical characteristics of the two groups are
summarized in Table 1. The mean age of the patients was
64+/−11 years, and 163 patients (79%) were men. There were no significant differences between the two groups with regard to age, sex, BMI, and the prevalence of diabetes mellitus, dyslipidemia, hypertension, or smoking. There were also no significant differences in the time from onset of AMI to recanalization (p=0.162) or the number of days from onset of AMI to performance of SPECT (p=0.460). The maximum creatine kinase level showed no significant difference between the CE group and the non-CE group (p=0.079). We classified the patients into 2 groups based on the number of vessels involved, which were 1-vessel disease vs. a combination of 2-vessel disease and 3-vessel disease (multivessel disease). The CE group had a higher proportion of patients with multivessel disease than the non-CE group (p=0.034). Complete right bundle branch block was found in 6 patients from the non-CE group, but did not occur in the CE group, while complete left bundle branch block was identified in 2 patients from the CE group and was not seen in the non-CE group. QRS duration was significantly longer in the CE group than the non-CE group (p=0.032), and use of β-blocker use (p=0.257) showed a significant difference between the two groups by Student’s t-test, but were not significant predictors according to Cox proportional hazards analysis. Variables showing p<0.1 in univariate analysis were selected for multivariate analysis, including the QRS duration, multivessel disease, maximum creatine kinase, total defect score, LVEDV, LVESV, peak ejection rate, and DI. The results of multivariate analysis are summarized in Table 3. Both multivessel disease (p=0.003) and DI (p=0.047) were found to be independent prognostic factors for CEs, while the maximum creatine kinase (p=0.470), QRS duration (p=0.125), total defect score (p=0.496), EDV (p=0.947), ESV (p=0.101), and peak ejection rate (p=0.961) were not significant predictors.

Next, a receiver operating characteristic (ROC) curve was drawn for the relation between DI and CE, revealing that the area under the curve was 0.653 (Fig. 2). Then Youden’s index was determined to identify the optimum DI threshold for predicting CEs, and we found that DI ≥ 4 could predict CEs with a sensitivity of 0.67 and a specificity of 0.64. When we defined severe LVMD as DI ≥ 4 (n=82) and mild LVMD as DI < 4 (n=124), Kaplan-Meier analysis demonstrated that patients with severe LVMD had a significantly worse prognosis than patients with mild LVMD (p<0.001, log-rank test; Fig. 3).

Representative examples of mild and severe LVMD are shown in Fig. 4-7.

**Discussion**

This study demonstrated that LVMD in the subacute phase of AMI is a valuable predictor of subsequent CEs, including chronic heart failure, recurrent AMI, ventricular arrhythmias, and cardiac death. LVMD measured by tissue Doppler imaging has been reported to be a predictor of LV remodeling (9). Though the echocardiography field has made various advances, many echocardiographic clinical studies of LVMD have yielded negative results (11-12). Several investigations of cardiac resynchronization therapy in patients with systolic heart failure, a narrow QRS complex, and LVMD on echocardiography have been terminated prematurely because cardiac resynchronization showed no benefit and was possibly harmful (10-12).

Nuclear imaging techniques have been adopted relatively recently for assessment of LVMD. The chief advantages of gated SPECT are excellent repeatability and reproducibility owing to automated processing of digital data (13). SPECT data are averaged over thousands of cardiac cycles, while...
echocardiographic data are derived from only a single cardiac cycle (14). It is still unclear whether LVMD determined by gated SPECT is a good indicator for cardiac resynchronization therapy, but it may be a useful prognostic factor.

In patients with heart failure, Nagao et al. analyzed LVMD by cine-tagged MRI and revealed that basal/apical dyssynchrony is an independent predictor of major adverse cardiac events, although septal/lateral dyssynchrony is not (15). We did not precisely assess LVMD geometry in the present study, but patients with the LAD as the culprit vessel would be expected to have basal/apical dyssynchrony, and they were more likely to show larger LVMD (n=120, number of DI ≥4 patients=62) than patients with non-LAD culprit vessels (n=86, number of DI ≥4 patients=20) (p<0.001, chi-square test).

In our study, recurrent AMI was classified as one of the major CEs. Studies using tissue Doppler echocardiography have shown that diastolic dysfunction is correlated with LV remodeling and recurrent myocardial ischemia in patients with unstable angina (16), but no previous study has revealed a relation between LVMD and recurrent AMI, although multivessel disease is reported to be a predictor of reinfarction after AMI (17). In the present study, a higher proportion of patients with recurrent AMI had multivessel disease (4/8 patients) than patients without recurrent AMI (54/198 patients). Though there was no significant difference in the frequency of multivessel disease between these groups (p=0.07 by the chi-square test with Yates’ correction), such disease may influence the recurrence of CEs. In our study,

### Table 2: Univariate analysis, CE group vs. non-CE group

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Cox proportional hazard modeling</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard Ratio</td>
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<tr>
<td>Age (years)</td>
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<tr>
<td>Male sex, n (%)</td>
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<tr>
<td>Body mass index</td>
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<tr>
<td>Maximum Creatine kinase (U/L)</td>
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<tr>
<td>Recanal time, h</td>
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<tr>
<td>From onset to SPECT, day</td>
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<tr>
<td>Diabetes Mellitus, n (%)</td>
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<tr>
<td>Dyslipidemia, n (%)</td>
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<tr>
<td>Hypertension, n (%)</td>
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<tr>
<td>Current smoker, n (%)</td>
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</tr>
<tr>
<td>QRS duration time (msec)</td>
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</tr>
<tr>
<td>Multiple Diseased Vessels, n (%)</td>
<td>2.450</td>
</tr>
</tbody>
</table>

Medication

| β-blocker, n (%) | 1.539 | 0.730-3.242 | 0.257 |
| ACE/ARB, n (%)   | 1.302 | 0.619-2.738 | 0.486 |
| Ca channel blocker, n (%) | 1.170 | 0.474-2.886 | 0.733 |
| Nitrates, n (%)  | 1.281 | 0.560-2.928 | 0.558 |
| DAPT, n (%)      | 1.170 | 0.474-2.886 | 0.733 |

SPECT

| TDS | 1.069 | 1.028-1.111 | 0.001 |
| LVEDV (ml) | 1.017 | 1.009-1.026 | <0.001 |
| LVESV (ml) | 1.024 | 1.015-1.033 | <0.001 |
| LVEF (%) | 0.933 | 0.900-0.966 | <0.001 |
| PER (EDV/sec) | 0.613 | 0.397-0.947 | 0.028 |
| PFR (EDV/sec) | 0.635 | 0.357-1.131 | 0.123 |
| TPF (msec) | 1.000 | 0.997-1.003 | 0.900 |
| mean TES (msec) | 1.003 | 1.000-1.006 | 0.059 |
| Standard Deviation of TES | 1.008 | 1.003-1.013 | 0.003 |
| DI | 1.072 | 1.021-1.126 | 0.005 |
| R-R interval (msec) | 1.000 | 0.998-1.002 | 0.908 |

Data are expressed as means +/- SD (%).
ACE: angiotensin converting enzyme; ARB: angiotensin II receptor blocker; DAPT: dual antiplatelet therapy; MVD: multi vessel disease (2 Vessel Disease or 3 Vessel Disease); TDS: total defect score; LVEDV: left ventricular end diastolic volume; LVESV: left ventricular end systolic volume; LVEF: left ventricular ejection fraction; PER: peak ejection rate; PFR: peak filling rate; TPF: time to peak filling; TES: time to end systole; DI: dyssynchrony index.
ventricular arrhythmias were also included among CEs. Hage et al. reported that LVMD is independently associated with the potential for sudden cardiac death in patients with systolic heart failure (18). In addition, Aljaroudi et al. reported that the severity of LVMD (evaluated by phase analysis of gated SPECT images) was associated with the risk of cardiac death and appropriate shock responses in patients with an implantable cardioverter defibrillator (19). On the other hand, LVMD did not predict ventricular arrhythmias with/without death in patients who had mild heart failure with or without left bundle branch block (LBBB) in the MADIT-CRT trial (20). However, if LVMD is correlated with progression of LV remodeling after AMI, the risk of ventricular arrhythmia may possibly be increased. Turan et al. reported that LVMD was a strong predictor of LV remodeling after acute AMI (21). Also, a recent study employing speckle tracking echocardiography revealed that LVMD is independently associated with VT after AMI (22).

Because we did not analyze changes of LVMD during the follow-up period, it is not clear whether improvement of LVMD can contribute to reduction of CEs. However, some previous studies have shown that LVMD evaluated by phase analysis improves within six months after revascularization in AMI patients and that dyssynchrony parameters are not independent predictors of adverse LV remodeling (23).

Hida et al. reported that stress-induced LVMD assessed by phase analysis is of diagnostic value in patients with multivessel disease (24). Tanaka et al. also reported that ATP-
induced LVMD is useful for diagnosis of multivessel disease (25). In the present study, both groups had patients with multivessel disease and all SPECT data were obtained before PCI for residual stenosis. However, it was considered that there was little risk of overestimating LVMD caused by non-culprit vessels, because we evaluated LVMD without stressors such as exercise or dobutamine.

This study had several limitations. First, CardioGRAF is designed to automatically assess LVMD, but we often encountered difficulty in determining whether the p-FAST program traced the inner contour...
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