Late Potential as a Predictor of re-Hospitalization after Percutaneous Coronary Intervention for Acute Coronary Syndrome

Mari NAKAMURA[*1], Koichiro YOSHIOKA[*1], Mari AMINO[*1], Eiichi WATANABE[*2], Toshiharu FUJII[*1], Tadashi HASHIDA[*1], Daisuke FUJIBAYASHI[*1], Shigetaka KANDA[*1], Yoshinori KOBAYASHI[*1], Teruhisa TANABE[*3] and Yuji IKARI[*1]

[*1]*Department of Cardiovascular Medicine, Tokai University School of Medicine*
[*2]*Department of Cardiology, Fujita Health University School of Medicine*
[*3]*Department of Cardiology, Ebina General Hospital*

(Received February 12, 2016; Accepted July 20, 2016)

Objective: The aim of this study was to investigate the significance of late potential (LP) after percutaneous coronary intervention (PCI) in acute coronary syndrome (ACS).
Method: We enrolled 135 consecutive patients with ACS admitted to Tokai University Hospital from February to December 2012. Twenty-four hour high-resolution ambulatory electrocardiogram was performed between post-PCI procedure and hospital discharge. The patients were divided into the LP-positive (33 patients) and LP-negative (102 patients) groups, and the relationship between LP and re-hospitalization was prospectively investigated.
Results: The body mass index, serum creatinine, and creatine phosphokinase-MB were higher in the LP-positive group than in the LP-negative group ($p < 0.05$). The re-hospitalization rate was higher in the LP-positive group. (9 patients, 27.3% vs. 10 patients, 9.8%; $p = 0.03$). There were no significant differences in the occurrence of ventricular tachycardia or cardiac death between the groups. According to Kaplan-Maier analysis, proportion of re-hospitalization was significantly lower in the LP-positive group than in the LP-negative group ($p = 0.01$; average follow-up, 451.4 ± 25.9 days). The odds ratio of LP presence was 3.45 (highest among all variables; 95% confidence interval, 1.3–9.4; $p < 0.01$).
Conclusion: Positive LP in patients with ACS after PCI may predict re-hospitalization.

Key words: Late potential, high-resolution ambulatory electrocardiogram, acute coronary syndrome, percutaneous coronary intervention

INTRODUCTION

It is known that > 60,000 people die of sudden cardiac death every year in japan. Among them, about 80 % are caused by lifethreatening ventricular arrhythmias and a greater part of them based on ischemic cardiac disease. Percutaneous coronary intervention (PCI) procedures has been developing since the 1990s, and the prognosis of acute myocardial infarction (acute MI) has markedly improved subsequently. Myocardial salvage achieved by early reperfusion therapy is beneficial for preventing arrhythmia in acute MI. Late potential (LP) has been shown to be predictive of lethal arrhythmia and sudden cardiac death for old myocardial infarction [1–3].

Development of high-resolution 24-hour ambulatory electrocardiogram (HR- ambulatory ECG) in recent years has enabled the simultaneous monitoring of multiple predictive factors of sudden cardiac death. In addition to LP, which is a major index for ventricular depolarization, atrial late potential (atrial LP) can be recorded [4]. As indexes for disparity of repolarization, the T-wave alternate [5], T-wave variability of amplitude [6], and QT/RR slope are used. As indices of the autonomic nervous system activity, heart rate variability are well known, and variables of the standard deviation of the NN interval (SDNN) and standard deviation of the sequential 5-min NN interval (SDANN) have been used as prognostic factors of myocardial infarction (MI) [7, 8]. In addition, heart rate turbulence [9] and deceleration capacity [10, 11] are known to be useful predictive factors for sudden cardiac death. Combinations of these multiple predictive factors are expected to improve the positive predictive value for arrhythmic events.

The efficacy and significance of LP values recorded in the acute phase of ACS are rarely examined. In this study, the relationship between LP determined by HR-ambulatory ECG in the acute phase of acute coronary syndrome (ACS) and re-hospitalization event due to ACS re-attack, in-stent restenosis, coronary new lesion, heart failure, or sustained ventricular tachycardia/ventricular fibrillation (s-VT/VF), was prospectively investigated.

PATIENTS AND METHODS

1. Study population

This was a preliminary report for multicenter prospective observational study (TWIST study, director Eiichi Watanabe). The study population was restricted

Koichiro YOSHIOKA, Department of Cardiovascular Medicine, Tokai University School of Medicine, 143 Shimokasuya, Isehara, Kanagawa 259-1193, Japan
Tel: +81-463-93-1121 Fax: +81-463-93-6679 E-mail: ko1@is.icc.u-tokai.ac.jp

to only our hospital data included the 140 consecutive patients who had been transferred to Tokai University Hospital (Isehara, Japan) and diagnosed as having ACS from February to December in 2012. Among them, patients with a pacemaker, right/left bundle branch block, or chronic atrial fibrillation were excluded because of the difficulty of analyzing LP, T-wave variability of amplitude, and heart rate variability. After the exclusions, 135 patients were included in the study. The internal review board of our institution approved the study protocol, and all patients gave written informed consent before participation. This investigation conformed to the principles outlined in the Declaration of Helsinki (Cardiovascular Research 1997; 35: 2–4).

2. Analysis of HR-ambulatory ECG

We used high-resolution digital HR-ambulatory ECG (2.5 μV, 1000 Hz; Ela Medical Co. Ltd.) during 24 h. All patients underwent HR-ambulatory ECG before hospital discharge 5.8 ± 0.3 days (average, 5 days) after PCI. This study used a bipolar X, Y, and Z lead system (CC5R, ML, CB2). Standard silver–silver chloride electrodes were used (Blue Sensor). The data obtained were analyzed automatically using Syne Scope 3.10 and then manually confirmed by two experienced cardiologists. Analysis items included total heartbeats, frequency of arrhythmias, LP, atrial LP, T-wave variability of amplitude, QT/RR slope, heart rate variability, heart rate turbulence, and deceleration capacity.

For LP analysis, signals from the 200-beat QRS wave were amplified, digitized, and averaged, and then the following three indices at a noise level ≤ 0.8 μV were calculated: filtered QRS (fQRS) duration, duration of the terminal low-amplitude signal < 40 μV (LAS40), and the root mean square voltage of the terminal 40 ms of the filtered QRS (RMS40). The maximum, minimum, and average values of the three indices were calculated, and the worst values (maximum fQRS, maximum LAS40, and minimum RMS40) were used in the LP test. The LP test was defined as positive if > 2 of the following criteria were satisfied: fQRS ≥ 114 ms, LAS40 ≥ 38 ms, and RMS40 < 20 μV [13]. The atrial LP test was defined as positive if the following two criteria were satisfied: filtered P duration ≥ 120 ms and RMS20 < 3.5 μV [4]. The T-wave variability of amplitude measurement method was used after 60 consecutive stable sinus beat clusters acquired according to the time variance method at a noise level of < 10 μV were selected for synchronization with the QRS onset. The maximum T-wave variability of amplitude value of ≥ 59 μV was defined as positive [6, 14]. After the T-wave apex, end point of T wave, and RR duration were checked manually, the QT/RR slope was calculated as the QT slope to RR regarding both after the T-wave apex and end point of T wave [15, 16]. In the heart rate variability analysis, 24 h were divided into three time zones: the entire 24-h period, daytime (0:00–18:00), and nighttime (22:00–06:00). The SDNN, SDANN, and root mean square of the successive differences (RMSSDs) were calculated on the basis of time–domain analysis. Total power, low-frequency (LF) components, high-frequency (HF) components, and the LF/HF ratio were calculated based on frequency–domain analysis. Heart rate turbulence analysis involves determination of the turbulence onset and turbulence slope. Turbulence onset is defined as addition of two beats just after premature ventricular complex (PVC) is subtracted from addition of two beats just before PVC, and the amount is divided by addition of two beats just before PVC. Turbulence slope was defined as the extension velocity of the RR duration, which was defined as the average slope of five RR durations [9]. Deceleration capacity analysis was performed according to the method of Bauer *et al.* [10]. The anchor was defined as an RR duration longer than the predecessor, and chronological order was made with the anchor center. Then, the average of the RR duration was calculated as deceleration capacity. Deceleration capacity was classified according to severity: ≤ 2.5, 2.6–4.5, and > 4.5 ms [10, 17].

3. Indices of population background

The population was divided into two groups: the LP-positive group and LP-negative group. Age, sex, history of smoking, body mass index, family history of ischemic cardiac disease, and medical history, including hyperlipidemia, hypertension, diabetes mellitus, chronic kidney disease, angina pectoris, and proximal atrial fibrillation, were investigated. The ST-T change on ECG, infarction area, culprit lesion, thrombolysis in myocardial infarction trial classification, door-to-balloon time, Killip classification, serum creatinine value at admission, left ventricular ejection fraction (LVEF), peak creatine phosphokinase (CK), peak CK-MB, admission duration, and medicine prescribed were compared and prospectively analyzed (Table 1).

As prognosis indices, re-hospitalization events were defined as ACS re-attack, asymptomatic in-stent restenosis, asymptomatic new lesion stenosis, heart failure, and sustained ventricular tachycardia/ventricular fibrillation. Besides the re-hospitalization events, death events (sudden cardiac death, cardiac failure death and non-cardiogenic death after hospital discharge) were also investigated. The interview was performed in the out-patient clinic of our hospital or those of related hospitals or by telephone. When contact with a patient became impossible because they moved to the other district or dropped out, the patients were excluded from the study at that time.

4. Statistical analysis

Regarding indices of HR-ambulatory ECG and population background, continuous variables are presented as the average standard error, and nominal scales are presented as *n* (%) (Figs. 1 and 2). The structured *t*-test, chi-square test, and Fisher's exact test were used to compare the LP-positive and LP-negative groups. Statistical software (SPSS Statistics 22, IBM) was used to produce Kaplan-Meier curves with readmission as the endpoint. To analyze the two groups, periods to the first events were compared using the log-rank test. In the binomial logistic regression analysis, readmission was used as the response variable, and indices producing significant differences in the clinical background parameters and HR-ambulatory indices between the two groups were determined as predictive variables.

Table 1 Comparison of baseline characteristics of the study groups

Variable	Late Potential		P value
	Positive (n = 33)	Negative (n = 102)	
Age (years)	62.1 ± 2.0	64.1 ± 1.1	0.20
Men	29 (87.9%)	83 (81.4%)	0.55
Smoker	25 (75.8%)	70 (68.6%)	0.58
Body mass index	25.6 ± 0.8	24.2 ± 0.4	0.04 *
Family history of myocardial infarction	9 (27.3%)	17 (16.7%)	0.18
Hyperlipidemia	29 (87.9%)	79 (77.5%)	0.29
Hypertension	20 (60.6%)	75 (73.5%)	0.23
Diabetes mellitus	16 (48.5%)	38 (37.3%)	0.25
Chronic kidney disease	9 (27.3%)	16 (15.7%)	0.22
History of angina	8 (24.2%)	13 (12.7%)	0.11
Old myocardial infarction	6 (18.2%)	13 (12.7%)	0.62
Paroxysmal atrial fibrillation	3 (9.1%)	3 (2.9%)	0.32
Electrocardiogram findings			
STMI	28 (84.8%)	85 (83.3%)	0.95
Non-STEMI	5 (15.6%)	17 (16.7%)	0.95
Ventricular fibrillation	0 (0%)	2 (2.0%)	0.99
Location of myocardial infarction of STEMI			
Antero-septum	10/28 (35.7%)	18/85 (21.2%)	0.20
Anterior	0/28 (0%)	10/85 (11.8%)	0.13
Antero-lateral	5/28 (17.9%)	14/85 (16.5%)	0.90
Lateral	2/28 (7.1%)	5/85 (5.9%)	0.83
Inferior	11/28 (39.3%)	38/85 (44.7%)	0.78
Coronary culprit lesion			
Left anterior descending coronary	14 (42.4%)	49 (48.0%)	0.57
Left circumflex artery	6 (18.2%)	14 (13.7%)	0.73
Right coronary artery	13 (39.4%)	43 (42.2%)	0.94
TIMI category			
Pre PCI	0.5 ± 0.14	0.5 ± 0.08	0.45
Post PCI	2.9 ± 0.06	3.0 ± 0.03	0.16
Time to reperfusion (min)	264.7 ± 38.0 (n = 29)	250.5 ± 13.6 (n = 92)	0.33
Killip class			
1	19 (57.6%)	74 (72.5%)	0.16
2	10 (30.3%)	15 (14.7%)	0.08
3	0 (0%)	5 (4.9%)	0.44
4	4 (12.1%)	8 (7.8%)	0.69
Creatinine (mg/dl) at hospital arrival	1.00 ± 0.06	0.89 ± 0.02	0.04 *
Max creatine phosphokinase(IU/dl)	3195.4 ± 490.3	2350.0 ± 266.2	0.06
Max creatine phosphokinase-MB (IU/dl)	308.4 ± 59.0 (n = 30)	185.4 ± 15.6 (n = 93)	< 0.01 *
Left ventricular ejection fraction(%)	54.4 ± 1.7 (n = 33)	57.7 ± 0.9 (n = 97)	0.04 *
Hospital stay (days)	11.8 ± 1.7	11.1 ± 0.6	0.31
Medical treatment			
Anti-platelet	33 (100%)	100 (87.1%)	0.99
Statin	31 (93.9%)	94 (92.2%)	0.97
ACE-inhibitor/ARB	26/3 (87.9%)	82/12 (92.2%)	0.69
Beta-blocker	26 (78.8%)	89 (87.3%)	0.36
Calcium-channel blocker	6 (18.2%)	15 (14.7%)	0.84
Diuretics	6 (18.2%)	15 (14.7%)	0.84
Hypoglycemic agent	8 (24.2%)	21 (20.6%)	0.84
Amiodarone	1 (3.0%)	1 (1.0%)	0.99
Bepridil	1 (3.0%)	0 (0%)	0.55

STMI, ST elevated myocardialinfarction; TIMI, Thrombolysis in myocardial infarction trial; PCI, percutaneous coronary intervention; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; Data are presented as mean ± standard error. Nominalscales in each group are shown asnumber (%). The Chi-square test for nominal scale between twogroups. The two-sample *t*-test was used to analyze continuous values.

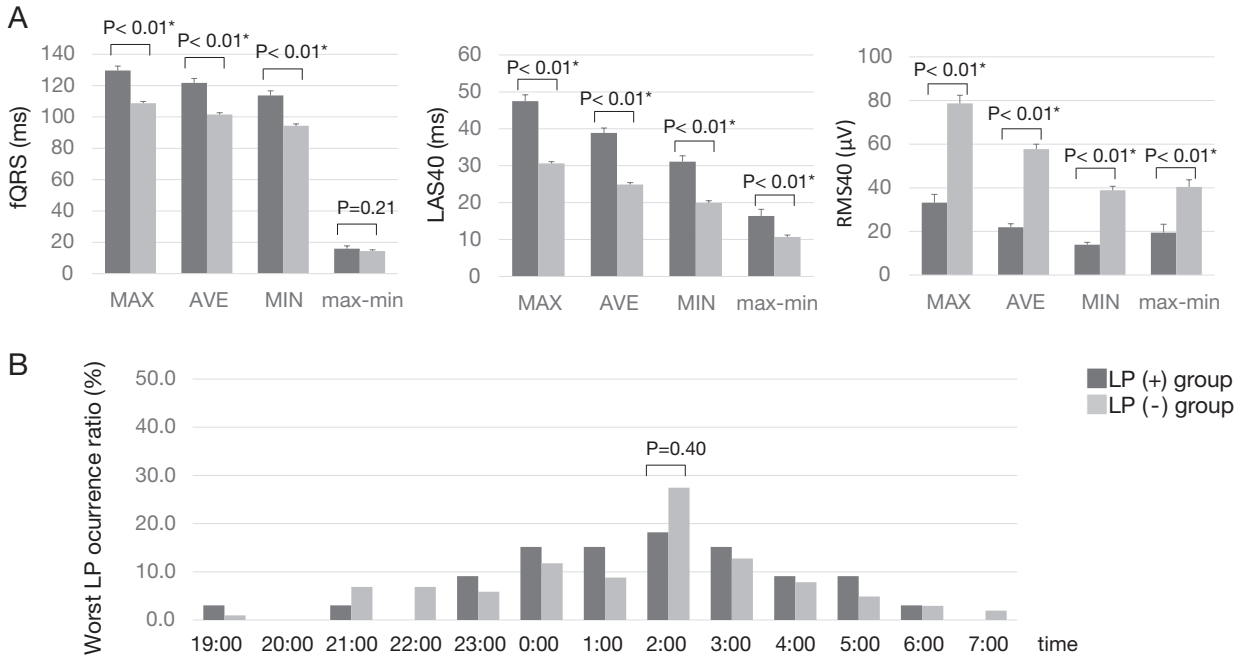

Fig. 1 (A) The maximum value, minimum value, average value, and incremental difference between the maximum values and minimum values of fQRS, LAS, and RMS are shown. (B) The rates of LP-positive values in each time period are shown. The worst values for maximum fQRS, maximum LAS, and minimum RMS were used in the LP test. fQRS, filtered QRS; LAS, low-amplitude signal; RMS, root mean square.

However, heart rate turbulence analysis was excluded because there were many missing values. The odds ratio, 95% confidence interval, and *p*-value were calculated. A *p*-value of < 0.05 was taken as indicating a statistically significant difference.

RESULTS

1. Clinical background of the subjects

Among 135 study patients, 33 (23.9%) were LP positive and 103 (75.6%) were LP negative. As shown in Table 1, the body mass index, serum creatinine at admission, and maximum CK-MB value were significantly higher, and the LVEF was significantly lower in the LP-positive group than in the LP-negative group ($p < 0.05$, in all). There were no significant differences in age, sex, family history, complications, ST-T change in ECG, culprit lesion, thrombolysis in myocardial infarction trial classification, door-to-balloon time, Killip classification, or the number of days spent in hospital. In medical therapy, no significant differences were observed in the use of antiplatelet agents, hydroxymethylglutaryl-CoA reductase inhibitors, angiotensin converting enzyme inhibitors/Angiotensin II receptor blocker, β-blocker, diuretics, hypoglycemic agents, or antiarrhythmic agents.

2. Indices of HR-ambulatory ECG

The arrhythmic events in the two groups are shown in Table 2−1. HR-ambulatory ECG was performed at an average of 5.8 days after PCI in both groups. There were no significant differences in total heartbeats and occurrence of bradycardia or tachycardia between the two groups. As shown in Table 2−2, the HR-ambulatory ECG variables with significant differences between the two groups included LP parameters (maximum fQRS, maximum LAS40, minimum RMS40), night-time RMSSD, night-time HF, and heart rate tubulence (turbulence onset). The maximum fQRS and maximum LAS40 were significantly higher, and the minimum RMS40 was significantly lower in the LP-positive group than in the LP-negative group. Night-time RMSSD and night-time HF were higher in the LP-positive group than in the LP-negative group. Heart rate turbulence analysis could be performed for 60 (44%) of the 135 study patients, and TO was significantly lower in the LP-positive group ($p < 0.04$). There were no significant differences in atrial LP, T-wave variability of amplitude, QT/RR slope, SDNN, SDANN, TP, LF/HF, deceleration capacity, and acceleration capacity.

There were significant differences in the maximum, average, and minimum values of fQRS, LAS40, and RMS40 between the groups (Fig. 1A). Especially, the rate of LP positive was highest from 00:00 to 03:00. However, at any time period, there were no significant differences in worst LP occurrence rate between the two groups (Fig. 1B). Especially, because the noise level during daytime exceeded the standard, effective analysis of this time period was not possible.

3. Occurrence of re-hospitalization and death events

As for the analysis of re-hospitalization events, 9 patients (27.3%) in the LP-positive group and 10 patients (9.8%) in the LP-negative group required re-admission ($p = 0.03$). Among the nine patients in the LP-positive group, three (9.1%) were for ACS re-attack, two (6.1%) were for asymptomatic in-stent restenosis, two (6.1%) were for asymptomatic new lesions, two (6.1%) were for heart failure, and no occurrence of s-VT/VF (0%)

Table 2-1 Comparison of arrhythmic events in high resolution ambulatory electrocardiogram

Variable	Late Potential		P value
	Positive (n = 33)	Negative (n = 102)	
Days from onset to Holter recording	5.8 ± 0.4	5.8 ± 0.3	0.50
Total heat beats/24hours	97315.0 ± 3124.8	96570.3 ± 1315.9	0.40
Heart rate			
24-hours	69.5 ± 2.3	69.5 ± 1.0	0.49
Day	72.0 ± 2.3	72.4 ± 1.0	0.44
Night	64.9 ± 2.4	64.7 ± 1.0	0.46
Arrhythmia event			
Non -sustained ventricular tachycardia	1 (3.0%)	7 (6.9%)	0.67
PVCs > 10% in total heart beats	0 (0%)	0 (0%)	-
AF/AFL	2 (6.1%)	3 (2.9%)	0.77
Sick sinus syndrome	2 (6.1%)	1 (1.0%)	0.30
Atrioventricular block	0 (0%)	0 (0%)	-

PVCs, prematureventricular constructions; AF/AFL, atrial fibrillation/atrial flutter; Data are presented as mean ± standard error. Nominal scales in each group are shown as number (%). The Chi-square test for nominal scale between two groups. The two-sample *t*-test was used to analyze continuous values. Values of $p < 0.05$ were considered significant.

(Fig. 2A black bar). Among the 10 patients in the LP-negative group, 4 (3.9%) were for ACS re-attack, 4 (3.9%) were for asymptomatic in-stent restenosis, 2 (2.0%) were for new lesions, and no occurrence of s-VT/VF (0%) (Fig. 2A gray bar).

As for the death events, there was no occurrence of sudden cardiac death, cardiac failure death and non-cardiogenic death in the LP-positive group. In the LP-negative group, there was no patient with sudden cardiac death (0%), two patients (2.0%) who died of cardiac failure, and three patients (2.9%) who died from non-cardiac causes. These three non-cardiac death patients died from pneumonia, malignant tumor, or physical trauma.

In the long term follow-up until re-admission, the mean time from the last hospital discharge after PCI was 177 ± 37.8 days (range 6–308 days) in the LP-positive group and 299 ± 37.6 days (range 119–538 days) in the LP-negative group ($p = 0.02$). Kaplan–Meier analysis for a mean period of 451.4 ± 7.8 days showed that the event-free rate of re-hospitalization was significantly lower in the LP-positive group than in the LP-negative group ($p = 0.01$; Fig. 2B).

4. Predictive factors of re-hospitalization

In the univariate analysis, body mass index, serum creatinine level at admission, maximum CK-MB value, LVEF, LP-positive status, maximum fQRS, maximum LAS40, minimum RMS40, night-RMSSD, and night-HF were used (Table 3). There were significant differences in the odds ratios (OR) of event occurrences for body mass index (OR: 1.17), maximum CK-MB value (OR: 1.002), LVEF (OR: 0.92), LP positive (OR: 3.45), and maximum LAS40 (OR: 1.05). The OR for LP positive was the strongest confounding factor. In the multivariable analysis, two clinically important variables (LP and LVEF) were selected as predictive variables. The OR of LVEF was 0.94, and significant ($p = 0.03$), while LP was 2.65, but not significant ($p = 0.08$).

DISCUSSION

The findings in this study were described below; we examined prospectively feasibility of LP values by HR-ambulatory ECG of ACS patients in terms of predicting re-hospitalization. The LP positive group shows higher re-hospitalization rate. Kaplan Meier analysis with readmission endpoint shows event free rate is significantly lower in LP positive group. The highest odd ratio of readmission by univariate logistic analysis among all variables is one of LP positive.

Predictive value of LP for arrhythmic event in MI patients

Development of treatments for ischemic heart disease, including thrombolytic therapy, percutaneous transluminal coronary angioplasty/PCI, antiarrhythmic agents, interpretational change of β-blocker, and implantable cardioverter defibrillator, has been ongoing since the 1980s. The LP value determined by signal-averaging electrocardiography was shown to be predictive of future cardiac events in the early 1980s [1]. Therefore, the accuracy of LP values has also increased with development of heart disease treatments. Kuchar *et al.* reported in 1986 that the sensitivity of LP in patients with arrhythmic events who survived acute MI was 92% with a specificity of 62% (during follow-up of ≤ 20 months; median, 11 months) [2].

El-Sherif N *et al.* discussed effective time period of LP recorded by signal-averaging electrocardiography to 156 patients with acute MI, which showed that based on logistic analysis, the second phase of post acute MI (6–30 days after acute MI) was most significantly related to arrhythmic events [18].

Savard *et al.* investigated the relation between LP and the occurrence of lethal ventricular arrhythmia during the 1983–1990 period with that during the 1990–1995 period [3]. The occurrence rate of ventricular arrhythmia was 9.6% and 5.8% respectively, and there was no difference in the sensitivity or specificity of LP during the two periods. Although treatment of heart disease has developed with time, it has been difficult to improve the positive predictive value only

Table 2-2 Comparison of electrophysiological parameters in high resolution ambulatory electrocardiogram

Variable		Late Potential		P value
		Positive (n = 33)	Negative (n = 102)	
Ventricular late potential				
Positive ratio (%)		33 (100%)	0 (0%)	-
Maximum fQRS (ms)		129.6 ± 2.9	108.7 ± 1.2	< 0.01 *
Maximum LAS40 (ms)		47.5 ± 1.7	30.7 ± 0.5	< 0.01 *
MinimumRMS40 (μV)		13.8 ± 1.1	38.7 ± 1.8	< 0.01 *
Atrial late potential		N = 25	N = 81	
Positive ratio (%)		10 (40.0%)	37 (45.7%)	0.62
Maximum fPD (ms)		137.9 ± 2.8	135.3 ± 1.5	0.20
Minimum RMS20 (μV)		4.8 ± 0.7	5.4 ± 0.6	0.29
T wave amplitude of variability		N = 31	N = 97	
Positive ratio (%)		9 (29.0%)	27 (27.8%)	0.92
Maximum value (μV)		44.0 ± 5.3	46.6 ± 2.4	0.33
QT/RR slope		N = 33	N = 102	
QT-apex/RR slope		0.15 ± 0.01	0.15 ± 0.01	0.39
QT-end/RR slope		0.15 ± 0.01	0.15 ± 0.01	0.47
HRV parameters		N = 31	N = 97	
SDNN (ms)	- 24hrs	95.0 ± 6.5	95.3 ± 3.4	0.48
	- Day time	86.1 ± 5.8	84.4 ± 2.9	0.39
	- Night time	72.0 ± 5.7	69.7 ± 2.4	0.34
SDANN (ms)	- 24hrs	79.3 ± 5.5	80.1 ± 2.9	0.45
	- Day time	71.0 ± 3.2	69.5 ± 2.4	0.38
	- Night time	45.8 ± 3.9	47.5 ± 1.8	0.32
RMSSD (ms)	- 24hrs	28.8 ± 2.8	23.8 ± 1.9	0.09
	- Day time	27.1 ± 3.0	22.9 ± 2.3	0.17
	- Night time	31.9 ± 3.6	24.3 ± 1.3	0.01 *
Total power (ms^2)	- 24hrs	2205.8 ± 348.6	2024.9 ± 172.0	0.31
	- Day time	1923.8 ± 288.0	1898.3 ± 218.4	0.48
	- Night time	2811.1 ± 543.3	2237.9 ± 167.0	0.09
LF (ms^2)	- 24hrs	344.6 ± 62.7	318.5 ± 41.0	0.37
	- Day time	316.3 ± 59.6	314.8 ± 51.8	0.49
	- Night time	428.3 ± 98.8	323.5 ± 36.8	0.11
HF (ms^2)	- 24hrs	163.1 ± 28.6	139.8 ± 40.6	0.38
	- Day time	139.1 ± 31.7	150.6 ± 69.4	0.46
	- Night time	221.9 ± 45.2	139.5 ± 21.2	0.04 *
LF/HF	- 24hrs	2.9 ± 0.5	4.0 ± 0.7	0.18
	- Day time	3.0 ± 0.4	4.4 ± 0.7	0.14
	- Night time	2.9 ± 0.8	3.7 ± 0.5	0.23
HRT parameters		N = 16	N = 44	
TO (%)		-0.009 ± 0.005	-0.001 ± 0.002	0.04 *
TS (ms / RRI)		4.03 ± 0.95	4.61 ± 0.72	0.33
HRT score: Score 0		8 (50.0%)	14 (31.8%)	0.32
Score 1		5 (31.3%)	20 (45.5%)	0.49
Score 2		3 (18.8%)	10 (22.7%)	0.98
Deceleration capacity		N = 31	N = 93	
Value		5.9 ± 0.38 (n = 31)	5.4 ± 0.17 (n = 93)	0.09
≤ 2.5 ms		2 (6.5%)	3 (3.2%)	0.79
2.6–4.5 ms		6 (19.4%)	29 (31.2%)	0.30
> 4.5 ms		23 (74.2%)	61 (65.6%)	0.51
Acceleration capacity		-6.4 ± 0.47 (n = 31)	-5.8 ± 0.20 (n = 93)	0.08

fQRS, filtered QRS duration; LAS40, the duration of the terminal low-amplitude signal < 40 μV; RMS40, root mean square voltage of the terminal 40 ms of the fQRS; fPD, filtered P-wave duration; RMS20, the root mean square voltage of the terminal 20 ms in the filtered P wave; HRV, heart rate variability; SDNN, standard deviation of all normal RR intervals; SDANN, standard deviation of mean of normal RR intervals at each 5-minute segment; RMSSD, root mean squared differences of successive RR intervals; LF, low frequency; HF, high frequency; HRT, heart rate turbulence; TO, turbulence onset; TS, turbulence slope. Data are presented as mean ± standard error. Nominal scales in each group are shown as number (%). The Chi-square test for nominal scale between two groups. The two-sample *t*-test was used to analyze continuous values. Values of $p < 0.05$ were considered significant.

Table 3 Probability of major adverse cardiovascular events on clinical and electrophysiological variables

	Univariate analysis			Multivariat analysis		
	OR	95% CI	P value	OR	95% CI	P value
Body mass index	1.17	1.05–1.30	< 0.01 *			
Cr (mg/dl) at hospital arrival	0.30	0.04–2.59	0.28			
Max CPK-MB (IU/dl)	1.002	1.000–1.004	0.03 *			
LVEF (%)	0.92	0.87–0.98	0.01 *	0.94	0.88–0.99	0.03 *
Presence of late potential	3.45	1.26–9.43	< 0.01 *	2.65	0.88–8.02	0.08
Maximum fQRS (ms)	1.01	0.98–1.04	0.39			
Maximum LAS40 (ms)	1.05	1.00–1.10	0.04 *			
Minimum RMS40 (μV)	0.98	0.94–1.01	0.13			
RMSSDRMSSD (ms) - Night time	1.01	0.98–1.04	0.57			
HF HF (ms^2) - Night time	1.00	0.99–1.00	0.65			

Cr, creatinine; CPK, creatine phosphokinase; LEF, Left ventricular ejection fraction; RMSSD, root mean squared differences of successive RR intervals; HF, high frequency; HR, odds ratio; CI, confidential interval; Values of $p < 0.05$ were considered significant.

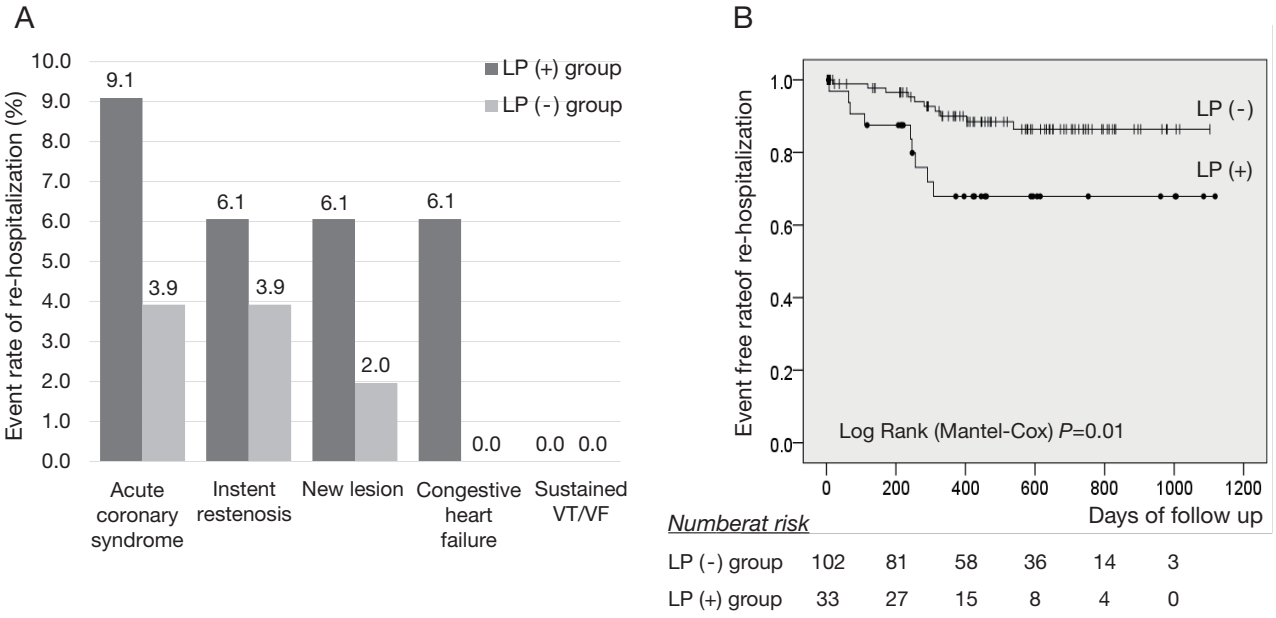

Fig. 2 (A) The rates of re-hospitalization events in the LP-positive group and LP-negative group. s-VT/VF, sustained ventricular tachycardia/ventricular fibrillation. (B) Kaplan–Meier analysis of re-hospitalization events. LP, late potential.

by LP. In the 2000s, in addition to PCI, the use of β-blocker has become common. Huikuri *et al.* analyzed a group in which > 95% of the population used β-blocker. In the group, low LVEF values and LP-positive status were found to be correlated with sudden cardiac death; however, the positive predictive value of low LVEF values was 8% and that using LP-positive status was 13%. They concluded that when β-blocker were used, conventional predictive indices became less accurate.

Presently, the concept that combinations of clinical parameters should be useful has led to the common use of the LVEF and ECG indices for prediction of heart diseases. Ikeda *et al.* reported that the combined assessment of T-wave alternate and LP was associated with a high predictive value for an arrhythmic event after acute MI [5].

Indices of autonomic activity as prognostic predictor

In addition to ECG indices regarding depolarization and repolarization, indices of autonomic activity are important prognostic factors. Kleiger *et al.* first reported that heart rate variability had univariate correlation with mortality. They also reported that lower SDNN was correlated with a higher mortality rate [20]. SDNN is considered to be effective not only as a predictor of total death of patients with MI but also as a predictor of sudden cardiac death [7, 8, 21]. However, since β-blocker has been used commonly, SDNN is sometimes not reflective of the true activity of the cardiac autosomal system. Heart rate variability is a cumulative value of basic autosomal activity and reflex autosomal activity; therefore, it is difficult to evaluate instant activity. In contrast, in heart rate turbulence, it is possible to evaluate instant activity as an increase or decrease in heart rate after PVC. Compared with conventional methods, such as baroreflex sensitivity, heart rate tur-

bulence is a less invasive and more accurate predictor of sudden ischemic death [9, 22]. However, heart rate turbulence has one disadvantage that when the patients do not have PVCs, heart rate turbulence cannot be analyzed. deceleration capacity is another promising index of heart rate variability. The first evidence of deceleration capacity was reported by Bauer *et al*. in a cohort study, which showed that a decrease in deceleration capacity of patients with MI was a stronger prognostic factor than was LVEF or conventional measures of heart rate variability, such as SDNN [10, 11].

With the increased use of PCI, many studies regarding prognosis of patients with ACS have been conducted. According to Nakatani *et al*., clinical factors, such as diabetes mellitus, history of MI, and advanced age, appear to be associated with the occurrence of recurrent MI after hospital discharge, and recurrent MI carries a great risk for subsequent mortality [23]. Murata *et al*. suggested that chronic exacerbation of renal function is related to major cardiovascular events and mortality risk [24]. A common clinical background among these patients could have led to progressive coronary stenosis due to arteriosclerosis, but functional impairment caused by the autonomic system, transient reversible ischemia or metabolic abnormality appears to have been involved also.

Possibility of LP as ischemic predictor in MI patients

At this point, the usefulness as predictor of future cardiac events of noninvasive indices in the acute phase of MI is controversial, but risk stratification of patients with MI is still important. Conventionally, LP was considered to be a predictive factor of fatal arrhythmic events or sudden cardiac death. However, few studies have been conducted to investigate the relationship between LP and re-hospitalization due to ACS re-attack or heart failure. In our study, in the LP-positive group, 27% required re-hospitalization, whereas 0% of the patients experienced ventricular arrhythmia or sudden cardiac death, suggesting that LP could be used as a predictive factor for future re-hospitalization by cardiovascular events. One of the reason for inhibiting effect of the fatal arrhythmia and sudden cardiac death possibly related with the oral medication by β-blocker over the approximately 80%. Why the rate of re-hospitalization was significantly higher in the LP-positive group than in the LP-negative group is not clear, but it is possible that micro-vascular lesions not reflecting coronary angiography or 12-lead ECG at rest were involved. Assuming that multiple micro-vascular lesions evoked by vasospasm or plaque rapture exist in the LP-positive patients, which will be not treatable by PCI, and silent myocardial ischemia may produce the conduction abnormalities in the ventricle muscle. In other words, such fine ischemia may be reflective of functional LP with transient positive conversion, not reflective of substantial LP caused by structural myocardial substrate.

CONCLUSION

LP in patients with acute ACS after PCI may predict re-hospitalization.

LIMITATIONS

A limitation of this study is that this was a preliminary observational study because the number of patients and events was small. At present, we are analyzing data from other institutions with the goal of determining the best noninvasive combination of predictive factors of cardiac events and to create an objective prognostic system in which each factor of the best combination is scored.

ACKNOWLEDGEMENTS

Data analysis was performed with the kind cooperation of Keiko Yamaguchi Base Line Inc. and Mayumi Kitahara Tokai University Hospital Cardiology.

DISCLOSURES

This study was supported by a subsidy from a public interest incorporated foundation, the Suzuken Memorial Foundation 2014 (Amino *et al*., Research Papers of the Suzuken Memorial Foundation Vol.33. [in Japanese]).

REFERENCES

1) Kanovsky MS, Falcone RA, Dresden CA, Josephson ME, Simson MB. Identification of patients with ventricular tachycardia after myocardial infarction: signal-averaged electrocardiogram, Holter monitoring, and cardiac catheterization. Circulation 1984; 70: 264–70.
2) Kuchar DL, Thorburn CW, Sammel NL. Late potentials detected after myocardialinfarction: natural history and prognostic significance. Circulation 1986; 74: 1280–9.
3) Savard P, Rouleau JL, Ferguson J, Poitras N, Morel P, Davies RF, *et al*. Risk stratification after myocardial infarction using signal-averaged electrocardiographic criteria adjusted for sex, age, and myocardial infarction location. Circulation 1997; 96: 202–13.
4) Fukunami M, Yamada T, Ohmori M, Kumagai K, Umemoto K, Sakai A, *et al*. Detection of patients at risk for paroxysmal atrial fibrillation during sinus rhythm by P wave-triggered signal-averaged electrocardiogram. Circulation 1991; 83: 162–9.
5) Ikeda T, Sakata T, Takami M, Kondo N, Tezuka N, Nakae T, *et al*. Combined assessment of T-wave alternans and late potentials used to predict arrhtymic events after myocardial infarction. J Am Coll Cardiol 2000; 35: 722–30.
6) Couderc J.P, Zareba W, McNitt S, Maison-Blanche P, Moss A.J, *et al*. Repolarization variability in the risk stratification of MADIT II patients. Europace 2007; 9: 717–23.
7) Hohnloser SH, Klingenheben T, Zabel M, Schöpperl M, Mauss O. Prevalence, characteristics and prognostic value during long-term follow-up of nonsustained ventricular tachycardia after myocardial infarction in the thrombolytic era. J Am Coll Cardiol 1999; 33: 1895–902.
8) Zabel M, Klingenheben T, Franz MR, Hohnloser SH. Assessment of QT dispersion for prediction of mortality or arrhythmic events after myocardial infarction: results of a prospective, long-term follow-up study. Circulation 1998; 97: 2543–50.
9) Schmidt G, Malik M, Barthel P, Schneider R, Ulm K, Rolnitzky L, *et al*. Heart-rate turbulence after ventricular premature beats as a predictor of mortality after acute myocardial infarction. Lancet 1999; 353: 1390–6.
10) Bauer A, Kantelhardt JW, Barthel P, Schneider R, Mäkikallio T, Ulm K, *et al*. Deceleration capacity of heart rate as a predictor of mortality after myocardial infarction: cohort study. Lancet 2006; 367: 1674–81.
11) Bauer A, Barthel P, Schneider R, Ulm K, Müller A, Joeinig A, *et al*. Improved Stratification of Autonomic Regulation for risk prediction in post-infarction patients with preserved left ventricular function (ISAR-Risk). Eur Heart J 2009; 30: 576–83.
12) Yoshioka K, Amino M, Zareba W, Shima M, Matsuzaki A, Fujii

T, *et al*. Identification of high-risk Brugada syndrome patients by combined analysis of late potential and T-wave amplitude variability on ambulatory electrocardiograms. Circ J 2013; 77: 610–8.
13) Breithardt G, Cain M.E, El-Sherif N, Flowers N.C, Hombach V, Janse M *et al*. Standards for analysis of ventricular late potentials using high-resolution or signal-averaged electrocardiography. A statement by a Task Force Committee of the European Society of Cardiology, the American Heart Association, and the American College of Cardiology. Circulation 1991; 83: 1481–8.
14) Sobue Y, Watanabe E, Yamamoto M, Sano K, Harigaya H, Okuda K, *et al*. Beat-to-beat variability of T-wave amplitude for the risk assessment of ventricular tachyarrhythmia in patients without structural heart disease. Europace 2011; 13: 1612–8.
15) Malik K, Färbom P, Batchvarov V, Hnatkova K, Camm A.J. Relation between QT and RR intervals is highly individual among healthy subjects: implications for heart rate correction of the QT interval. Heart 2002; 87: 220–8.
16) Stramba-Badiale M, Locati E.H, Martinelli A, Courville J, Schwartz P.J. Gender and the relationship between ventricular repolarization and cardiac cycle length during 24-h Holter recordings. Eur Heart J 1997; 18: 1000–06.
17) Lewek J, Wranicz J.K, Guzik P, Chudzik M, Ruta J, Cygankiewicz I. Clinical and electrocardiographic covariates of deceleration capacity in patients with ST-segment elevation myocardial infarction. Cardiol J 2009; 16: 528–34.
18) El-Sherif N, Ursell S, Bekheit S, Fontaine J, Turitto G, Henkin R, *et al*. Prognostic significance of the signal-averaged ECG depends on the time of recording in the postinfarction period. Am Heart J 1989; 118: 256–64.
19) Huikuri H.V, Tapanainen J.M, Lindgren K, Raatikainen P, Mäkikallio T.H, JuhaniAiraksinen K.E, *et al*. Prediction of sudden cardiac death after myocardialinfarction in the beta-blocking era. J Am Coll Cardiol 2003; 42: 652–8.
20) Kleiger R.E, Miller J.P, Bigger J.T Jr, Moss A.J. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. Am J Cardiol 1987; 59: 256–62.
21) Huikuri H.V, Raatikainen M.J, Moerch-Joergensen R, Hartikainen J, Virtanen V, Boland J, *et al*. Prediction of fatal or near-fatal cardiac arrhythmia events in patients with depressed left ventricular function after an acute myocardial infarction. Eur Heart J 2009; 30: 689–98.
22) Barthel P, Schneider R, Bauer A, Ulm K, Schmitt C, Schömig A, *et al*. Risk stratification after acute myocardial infarction by heart rate turbulence. Circulation 2003; 108: 1221–6.
23) Nakatani D, Sakata Y, Suna S, Usami M, Matsumoto S, Shimizu M, *et al*. Incidence, predictors, and subsequent mortality risk of recurrent myocardial infarction in patients following discharge for acute myocardial infarction. Circ J 2013; 77: 439–46.
24) Murata N, Kaneko H, Yajima J, Oikawa Y, Oshima T, Tanaka S, *et al*. The prognostic impact of worsening renal function in Japanese patients undergoing percutaneous coronary intervention with acute coronary syndrome. J Cardiol 2015; 66: 326–32.