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The presence of late potentials after percutaneous coronary intervention for the treatment of acute coronary syndrome as a predictor for future significant cardiac events resulting in re-hospitalization

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ABSTRACT

Introduction: We previously reported that LP positive patients after percutaneous coronary intervention (PCI) had higher rate of re-hospitalization in the small-scale study (135 patients). In this study, we evaluated correlation between LP and later cardiac events leading to re-hospitalization more extensively in greater population.
Methods and results: A 24-h high-resolution (HR) ambulatory electrocardiogram (ECG) was performed in 421 patients that received PCI for the treatment of acute coronary syndrome (ACS) within 30 days. Various baseline characteristics and post-PCI ECG parameters including LP were examined for correlation with later re-hospitalization. LP was evaluated based on 3 different conditions, i.e., the worst, mean and best values, from 24-h signal-averaged QRS wave data. During the post-PCI follow-up period (611 ± 489.0 days), 90 patients were re-hospitalized due to cardiac events. Multivariate analysis identified only positive LP based on the worst value as an independent predictor for re-hospitalization with OR 2.26. Most of re-hospitalization cases (>75%) were predominantly attributed to ischemic events. LP positive population had significantly higher incidences of ischemic events as well as overall re-hospitalization compared to LP negative population. The predictive power of LP was decreased when it was combined with other variables. The receiver operating characteristic analysis determined the LP cut-off values consistent with the LP positive criteria previously reported and standardized.
Conclusion: The presence of LP in the 24-h HR ambulatory ECG post-PCI was an independent predictor for a risk of re-hospitalization due to ischemic cardiac events in ACS patients.

Introduction

Ventricular late potentials (LPs) on the signal-averaged electrocardiogram (SAECG) have been widely used to predict ventricular tachycardia/ventricular fibrillation (VT/VF) after acute myocardial infarction (AMI) by providing information about the arrhythmogenic substrate [1]. It has been also reported that LPs are useful in tracking coronary occlusion severity. In one of those studies, LPs were observed in none of 38 patients with a patent infarct-related artery after thrombolytic therapy, but 2 of 6 patients with an occluded infarct-related artery [2]. Chew et al. (1990) [3] also reported that 17 of 26 patients with infarct-related arteries had LPs while only 2 of 40 patients with patent infarct-related arteries had LPs.

Based on the evidence from the above-mentioned studies, we hypothesized that LPs might be useful to predict future ischemic cardiac events after reperfusion therapy in patients with acute coronary syndrome (ACS). We extracted our single center subjects from the parent population of "TWIST study" (Prognostic significance of Holter-derived T wave variability in patients with acute coronary syndrome, https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000017531), and preliminary analyzed potential correlation between LPs and later re-hospitalization [4]. The result of 135 patients found that the LP positive cases had a significantly higher proportion of

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re-hospitalization; however, the small sample size of the preliminary assessment did not allow further detailed analysis. In this new study, therefore, we increased the sample size from 135 to 421 study subjects for more extensive analysis for correlation between positive LP and later cardiac events leading to re-hospitalization.

Patients and methods

Study population

This was an ancillary study to a registered two-center, non-interventional, prospective, observational study (Study title: Prognostic significance of Holter-derived T wave variability in patients with acute coronary syndrome, TWIST study, https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000017531). The investigation conformed to the principles outlined in the Declaration of Helsinki. The internal review board of our institution approved the study protocol, and all patients gave written informed consent before participation. ACS was clarified as either unstable angina or AMI including both non-ST elevation and ST elevation types.

Among 556 ACS patients who were hospitalized at Tokai University Hospital (Isehara, Japan) or Fujita Health University Hospital (Toyoake, Japan) from April 2012 to March 2013, 519 consecutive patients treated with PCI were examined for the study enrollment. All PCIs were performed to achieve residual stenosis of <20% in coronary angiography (CAG) and good blood flow with thrombolysis in myocardial infarction (TIMI) flow grade 3 [5]. Patients with a pacemaker, right/left bundle branch block, or persistent atrial fibrillation (AF) were excluded because detailed analysis of HR-ambulatory ECG was limited. PAF/PAFL are defined as self-terminating episode of <7 days of AF and/or AFL waves according to the Japanese circulation society guideline (http://www.j-circ.or.jp). However in this study, only extremely transient events with a duration of <10 min and a small frequency within 2 times were included in the subject for the analysis of accurate heart rate variability (HRV). After the exclusions, 421 patients (81%) were finally included as subjects (224 patients at Tokai University Hospital, and 197 at Fujita Health University Hospital).

As endpoints after hospital discharge, re-hospitalization due to cardiac events with ACS recurrence, effort angina, congestive heart failure, or sustained VT/VF was investigated. Follow up was continued until January 2018 (up to 6 years). Interviews were performed in the out-patient clinics of the two study institutions or referring hospitals, or by telephone. When contact with patients was lost because they had moved or dropped out, the patients were excluded from the study at that time.

The population was divided into two groups, those with and without re-hospitalization. With respect to patient background, 9 variables consisting of age, sex, history of smoking, body mass index (BMI), and medical history (dyslipidemia, hypertension, diabetes mellitus, chronic kidney disease, and previous AMI) were investigated. Other clinical variables studied included ST-segment elevation, culprit lesions, laboratory data (hemoglobin, triglycerides, LDL-cholesterol, hemoglobin A1c, creatinine, glomerular filtration rate [GFR], max creatine phosphokinase [CPK], max CK–MB, brain natriuretic peptide), left ventricular ejection fraction (LVEF), admission duration, and medicines prescribed. Table 1 compares those variables between the groups. Oral medications were started immediately after PCI.

Table 1
Comparison of baseline characteristics.

	Re-hospitalization (n = 90)	Non-hospitalization (n = 331)	*p* value
Age (years)	65 ± 12.7	66 ± 11.1	0.16
Men	76 (84.4%)	265 (80.1%)	0.35
Current smoker	53 (58.9%)	182 (55.0%)	0.51
Body mass index (kg/m^2)	24.0 ± 5.2	23.5 ± 3.9	0.23
Dyslipidemia	60 (66.7%)	199 (60.1%)	0.26
Hypertension	53 (58.9%)	194 (58.6%)	0.96
Diabetes mellitus	29 (32.2%)	122 (36.9%)	0.42
Chronic kidney disease	23 (25.6%)	82 (24.8%)	0.88
Previous AMI	20 (22.2%)	51 (15.4%)	0.13
ACS characteristics			
STEMI	54 (60.0%)	190 (57.4%)	0.66
NSTEMI	32 (35.6%)	129 (42.6%)	0.55
Unstable angina	4 (4.4%)	12 (3.6%)	0.96
Coronary culprit lesion			
Right coronary artery	29 (32.2%)	109 (32.9%)	0.90
Left anterior descending coronary	46 (51.5%)	156 (47.1%)	0.50
Left circumflex artery	15 (16.7%)	66 (19.9%)	0.48
Laboratory data			
Hemoglobin (g/dl)	14.4 ± 3.4	14.5 ± 6.6	0.45
Triglyceride (mg/dl)	140 ± 121.4	129 ± 120.6	0.23
LDL-cholesterol (mg/dl)	121 ± 38.0	122 ± 31.9	0.41
Hemoglobin A1c (%)	6.5 ± 2.1	6.4 ± 2.2	0.44
Creatinine (mg/dl)	1.2 ± 1.8	1.1 ± 0.8	0.19
GFR (ml/min/1.7 m^2)	59.4 ± 21.2	60.1 ± 20.4	0.18
Maximum CPK (IU/dl)	2052 ± 2501.3	2162 ± 1901.1	0.22
Maximum CPK-MB (IU/dl)	255 ± 237.0	247 ± 291.3	0.45
Brain natriuretic peptide (pg/ml)	144 ± 200.1	158 ± 239.5	0.35
Left ventricular ejection fraction (%)	50 ± 12.5	51 ± 12.8	0.32
Hospital stay (days)	15 ± 13.2	14 ± 12.7	0.46
Medications at hospital discharge			
Anti-platelet	*90 (100%)*	*330 (99.7%)*	0.60
Statin	*88 (97.8%)*	*305 (92.1%)*	0.06
ACE-inhibitor/ARB	*81 (91.1%)*	*299 (90.3%)*	0.82
Beta-blocker	*77 (85.6%)*	*254 (76.7%)*	0.07
Anti-aldosterone	*45 (50.0%)*	*198 (59.8%)*	0.09
Calcium-channel blocker	*18 (20.0%)*	*95 (28.7%)*	0.10
Loop diuretics	*17 (18.9%)*	*64 (19.3%)*	0.92
Hypoglycemic agent	*15 (16.7%)*	*59 (17.8%)*	0.80

AMI, acute myocardial infarction; ACS, acute coronary syndrome; STEMI, ST-segment elevation myocardial infarction; NSTEMI, non ST-segment elevation myocardial infarction; LDL, low-density lipoprotein: CPK, creatine phosphokinase; GFR, Glomerular filtration rate; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; Data are presented as mean ± standard deviation. Nominal scales in each group are shown as number (%).

Analysis of HR-ambulatory ECG

All patients underwent 24-h HR-ambulatory ECG (Ela Medical, France) recordings within 30 days after PCI during hospitalization (8.7 ± 4.4 days). The ECG were recorded at 1000 Hz and 2.5 μV resolution. This study used a bipolar X, Y, and Z lead system (CC5R, ML, and CB2).

Standard silver–silver chloride electrodes were used (Blue Sensor, AMBU Denmark). The data obtained were analyzed automatically using Syne Scope 3.10 software (SORIN GROUP, Italy) and then manually reviewed by two experienced cardiologists blinded to patient outcome. Primary analysis items consisted of parameters commonly available on ambulatory ECG recorders such as total number of heartbeats, mean heart rate (24-h, day time, night time), and frequency of arrhythmic events (non-sustained VT, premature ventricular contractions [PVCs], PAF/PAFL, sinus dysfunction, and atrioventricular block). We defined sinus dysfunction as sinus rate <50 bpm or sinus pause >3 s. Atrioventricular block was defined as second or third degree heart block. Secondary analysis items included LP, T-wave amplitude variability (TAV), and HRV.

Noise reduction is essential for longitudinal LP recording, and thus patients were instructed to keep as quiet as possible over a 24-h recording period and not to use electric appliances. QRS signals were automatically amplified, digitized, and averaged 200 times when the noise level was ≤0.8 μV after filtering, and good recording condition was obtained at least during the sleep in all patients. The average recording time obtained in 24 h was 8.2 ± 3.3 h. The following three indices were calculated for each signal-averaged QRS wave: filtered QRS (fQRS) duration, duration of the terminal low-amplitude signal that was <40 μV (LAS40), and root mean square voltage of the terminal 40 ms of the filtered QRS (RMS40). Each individual value in these 3 indices was

evaluated based on the following positive criteria: fQRS ≥114 ms, LAS40 ≥38 ms, and RMS40 <20 μV [6]. Then, based on the number of positive indices and actual values, the best, mean and worst values during the 24-h recording were determined [7]. The worst and best values were determined at the time points with the most and least positive results of the 3 LP-related indices, respectively (Fig. 1). When >1 time points had the same number of positive or negative indices; therefore the single worst or best time point could not be identified, the time points with the highest and lowest fQRS were used for the worst and best values, respectively. The mean value was obtained from the 24-h recording data for each of 3 indices separately. The presence of LP was determined in each of the worst, best and mean values when at least 2 of 3 indices met positive criteria; therefore, the incidence of LP positive was the highest in the worse value, followed by mean value, then the lest in the best value, All study subjects were classified into 2 groups, LP positive and negative groups based on the worst values.

The TAV was calculated from 60 consecutive stable sinus beat clusters acquired by the time variance method at a noise level of <10 μV. Beats were synchronized using QRS onset. We adopted the current criterion for positive in MI patients, namely TAV ≥59 μV [8]. In the HRV analysis, data were analyzed for three time periods: the entire 24-h period, day time (waking period), and night time (while sleeping). With respect to time domain analysis, 2 variables were calculated: root mean square of the successive differences (RMSSDs), and proportion of NN50 divided by the total number of NN (R-R) intervals PNN50 (%). With respect to frequency domain analysis, low-frequency (LF) components, high-frequency (HF) components, and LF/HF ratio were calculated.

Statistical analysis

Continuous variables are presented as the mean and standard deviation, and nominal variables are presented as *n* (%). The Student *t*-test and chi-square test were used to compare the re-hospitalization and non-hospitalization groups. Subsequently, the occurrence of the re-hospitalization due to cardiac events was designated an objective variable, and univariate analysis and multivariate analysis were performed by logistic regression analysis. The odds ratio (OR), 95% confidence interval (CI), and *p*-value were calculated. Discriminant analysis was carried out with LP positive as a single variable or in combination with other parameters as combined variables for identification of re-hospitalization. Kaplan-Meier curves of event free survival were produced between the LP positive and negative groups. Time to the first event post-PCI was compared using the log-rank test. Finally, receiver operating characteristic (ROC) analysis was performed to estimate the most appropriate threshold value for each of 3 indices for LP analysis (fQRS, LAS40, or RMS40). All analyses were performed with SPSS Statistics 22 (IBM). A *p*-value of <0.05 was taken as a statistically significant difference.

Results

Clinical background of the subjects

After PCI, 90 of 421 patients (21.4%) were re-hospitalized due to cardiac events (follow-up observation duration: 611 ± 489.0 days, median: 491 days, range 2–2166 days) (Table 1). None of the variables of clinical baseline characteristics had statistically significant differences between the re-hospitalization and non-hospitalization groups.

Arrhythmia event counts and HR-ambulatory ECG parameters

The interval between PCI and 24-hoour ECG recording was comparable (mean value: 9 days) between the re-hospitalization and non-hospitalization groups (Table 2). Although there was no statistically significant difference in any of heart beat/rate parameters, the values tended to be lower in the non-hospitalization group compared to the re-hospitalization group ($p = 0.05$–0.07 in total heart beats, mean heart rate over 24 h and night time) except for day time heart rate. The incidence of concomitant arrhythmic events was relatively low (<10% for non-sustained VT, <5% for the other types), and there was no significant difference in incidence of any arrhythmic events between

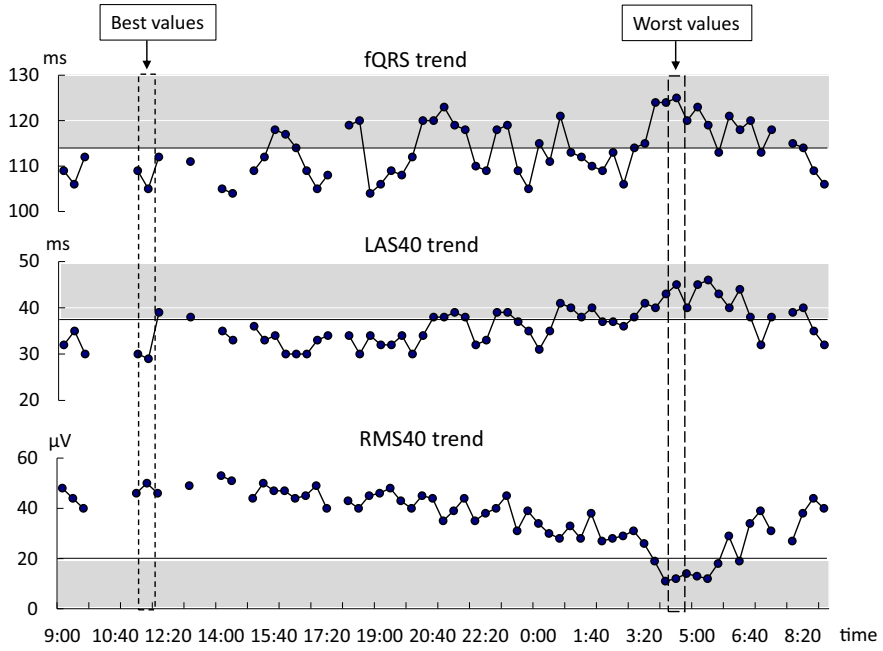


Fig. 1. Definition of the worst and best value for LP determination. The figure shows a plot of the three indices of VLP over time from one patient. The horizontal black line indicates the standard cut-off value of LP for each parameter, namely the values in gray zone in each parameter are determined as LP positive while values in white area as LP negative. In this case example, from 3:20 AM to 6:20 AM, all three indices are in gray zone (i.e., LP positive). Among these multiple data points showing positive LP in all 3 indices, the time point with the greatest fQRS is determined as the worst value at 4:20 AM (large dashed box). From 9:00 AM to 8:00 PM, none of 3 indices are in gray zone (i.e., LP negative). Therefore, the time point with the smallest fQRS was selected as the best value at 11:40 AM (small dotted box). fQRS, filtered QRS; LAS, low-amplitude signal; RMS, root mean square.

Table 2
Comparison of parameters in high resolution ambulatory electrocardiogram.

	Re-hospitalization (n = 90)	Non-hospitalization (n = 331)	*p* value
Heart rates and arrhythmic events			
Days from PCI to 24-h ECG	9 ± 5.1	9 ± 5.6	0.32
Total heart beats (beats/24-h)	101,907 ± 23,611.7	93,567 ± 14,901.6	0.06
Mean heart rate			
24-h (beat/min)	71 ± 13.4	69 ± 10.2	0.07
Day time (beat/min)	73 ± 13.7	71 ± 10.3	0.42
Night time (beat/min)	67 ± 11.6	64 ± 10.6	0.05
Patients with arrhythmia events			
Non-sustained VT	8 (8.9%)	24 (7.3%)	0.60
PVCs >10% of total heart beats	1 (1.1%)	2 (0.6%)	0.61
PAF/PAFL	4 (4.4%)	9 (2.7%)	0.40
Sick sinus dysfunction	3 (3.3%)	15 (4.5%)	0.62
II AV block	1 (1.1%)	5 (1.5%)	0.78
Non-invasive parameters			
LP analysis			
Worst values			
Maximum fQRSD (ms)	119 ± 18.8	110 ± 17.2	<0.01*
Maximum LAS40 μV (ms)	38 ± 11.4	34 ± 10.1	<0.01*
Minimum RMS40 ms (μV)	21 ± 12.3	37 ± 26.7	<0.01*
LP positive ratio	39 (43.3%)	71 (21.5%)	<0.01*
Mean values			
Mean fQRSD (ms)	113 ± 18.9	104 ± 15.8	<0.01*
Mean LAS40 μV (ms)	33 ± 10.5	28 ± 9.9	<0.01*
Mean RMS40 ms (μV)	35 ± 19.1	56 ± 30.9	<0.01*
LP positive ratio	18 (20.0%)	25 (7.6%)	<0.01*
Best values			
Minimum fQRSD (ms)	107 ± 19.7	97 ± 15.6	<0.01*
Minimum LAS40 μV (ms)	26 ± 10.9	24 ± 9.8	<0.01*
Maximum RMS40 ms (μV)	45 ± 27.8	76 ± 51.3	<0.01*
LP positive ratio	14 (15.6%)	12 (3.6%)	<0.01*
T wave amplitude variability (TAV)			
Value (μV)	42.7 ± 22.4	42.5 ± 21.3	0.48
Patients with TAV positive	19 (21.1%)	54 (16.3%)	0.29
HRV parameters			
RMSSD (ms) – 24-h	27.1 ± 26.7	29.5 ± 36.7	0.34
– Day time	26.8 ± 22.8	29.0 ± 33.5	0.26
– Night time	30.0 ± 27.5	31.0 ± 39.8	0.37
PNN50 (%) – 24-h	4.7 ± 10.8	5.4 ± 12.0	0.38
– Day time	4.2 ± 10.1	5.1 ± 11.9	0.29
– Night time	5.9 ± 11.7	6.9 ± 13.5	0.21
LF (ms^2) – 24-h	364 ± 503.5	442 ± 1040.1	0.34
– Day time	299 ± 511.2	410 ± 1009.2	0.11
– Night time	381 ± 568.3	569 ± 1225.6	0.27
HF (ms^2) – 24-h	188 ± 571.5	346 ± 1023.2	0.24
– Day time	160 ± 500.2	301 ± 1494.5	0.21
– Night time	224 ± 661.4	436 ± 1960.4	0.04*
LF/HF – 24-h	4.1 ± 5.5	3.2 ± 4.6	0.09
– Day time	4.3 ± 6.7	3.4 ± 3.1	0.08
- Night time	4.0 ± 6.6	3.0 ± 2.2	0.04*

VT, ventricular tachycardia; PVCs, premature ventricular contractions; PAF/PAFL, paroxysmal atrial fibrillation/atrial flutter; II AV block, Second-degree atrioventricular block; Data are presented as mean ± standard error. Nominal scales in each group are shown as number (%). LP, late potential; fQRSD, filtered QRS duration; LAS40 μV, the duration of the terminal low-amplitude signal <40 μV; RMS40 ms, root mean square voltage of the terminal 40 ms of the fQRS; HRV, heart rate variability; RMSSD, root mean squared differences of successive RR intervals; PNN50 (%), proportion of NN50 divided by the total number of NN (R-R) intervals; LF, low frequency; HF, high frequency; Data are presented as mean ± standard deviation.
* *P*-value <0.05 was considered to indicate a statistically significant difference.

the two groups. The duration of PAF/PAFL was 4.3 ± 3.2 min in the re-hospitalization group and 5.2 ± 2.5 min in the non-re-hospitalization group (p = n.s). All cases of sinus dysfunction were sinus pause within 2.9–3.9 s, or sinus bradycardia within 44–49 bpm. The atrioventricular block were all second-degree heart block.

Statistically significant differences between the two groups were observed in all LP indices with lower *p* values ($p < 0.01$). The re-hospitalization group had significantly higher fQRSD, LAS40, and incidence of positive LP and lower RMS40 compared to the non-hospitalization group in all of the worst, mean or best values.

There was no significant difference in any of TAV parameters between the 2 groups. Of the HRV parameters, HF or LF/HF at night time showed a significant difference. HF was lower and LF/HF was higher in the re-hospitalization group compared to the non-hospitalization group.

Table 3-1
Logistic analysis for predictive factors for re-hospitalization.

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	*p* value	OR	95% CI	*p* value
1. Age	0.99	0.94–1.01	0.23	0.98	0.97–1.02	0.39
2. Men	1.77	0.85–3.03	0.12	1.26	0.59–2.19	0.55
3. Body mass index	1.13	0.89–2.10	0.19			
4. Previous AMI	1.77	0.85–3.41	0.18			
5. Creatinine	1.30	0.82–2.16	0.21			
6. Max CPK	0.98	0.98–1.33	0.87			
7. Brain natriuretic peptide	1.35	0.91–1.18	0.26			
8. LVEF	0.99	0.97–1.03	0.23	0.99	0.96–1.04	0.33
9. LP positive in worst value	3.40	1.65–5.14	<0.01*	2.26	1.13–4.14	0.02*
10. LP positive in mean value	3.23	1.57–5.37	<0.01*	2.30	0.98–3.10	0.09
11. LP positive in best value	3.89	1.66–7.58	<0.01*	1.10	0.97–1.25	0.19
12. TAV positive	1.01	0.99–1.02	0.56	1.01	0.98–1.03	0.48
13. RMSSD – Night time	1.00	0.99–1.02	0.47			
14. PNN50 – Night time	0.99	0.97–1.02	0.51			
15. HF– Night time	1.00	0.99–1.04	0.49	1.12	0.99–1.15	0.13
16. LF/HF – Night time	1.04	0.99–1.01	0.56	1.09	0.98–1.22	0.14

AMI, acute myocardial infarction; CPK, creatine phosphokinase; LEF, left ventricular ejection fraction; LP, late potential; TAV, T wave amplitude variability; RMSSD, root mean squared differences of successive RR intervals; PNN50 (%), proportion of NN50 divided by the total number of NN (R-R) intervals; HF, high frequency; LF, low frequency; OR, odds ratio; CI, confidence interval.
* *P*-value <0.05 was considered to indicate a statistically significant difference.

Logistic analysis for predictive factors for re-hospitalization due to cardiac events

In the univariate analysis, 16 explanatory variables that could potentially affect the outcomes were extracted based on the literature and scientific rationale (Table 3-1). Statistically significant difference was observed in all of the 3 LP positive variables (LP positive in the worst, mean and best values) with ORs of >3.0 while none of the other variables demonstrated statistical significance. Subsequently performed multivariate logistic regression analysis identified only LP positive in the worst value as an independent predictor of re-hospitalization ($p = 0.02$, OR: 2.26). None of the other eight parameters tested were independent predictors.

Additional discriminant analysis was performed with LP positive in the worst value as either a single variable, or variable combined with other six variables (Table 3-2). The predictive rate in LP positive alone was greater than that in combination with other six parameters.

Table 3-2
Discriminant analysis for prediction of re-hospitalization with LP positive in worst value alone or in combination with multiple variables.

Single variable	Predictive rate	Multiple variables	Predictive rate
LP positive in worst value	71.1%	LP positive in worst value Age Men LVEF TAV positive HF– Night time LF/HF– Night time	64.8%

LP, late potential; LEF, left ventricular ejection fraction; TAV, T wave amplitude variability; LF, low frequency; HF, high frequency.

Table 4-1
Occurrence of major adverse cardiac events resulting in re-hospitalization, and mortality.

	LP positive n = 110	LP negative n = 311	*p* value
1) Overall of Re-hospitalization	39 (35.5%)	51 (16.4%)	<0.01*
ACS recurrence	16 (14.5%)	21 (6.8%)	0.01*
Effort angina	13 (11.8%)	18 (5.8%)	0.04*
Congestive heart failure	5 (4.5%)	7 (2.3%)	0.21
Sustained VT/VF	5 (4.5%)	5 (1.6%)	0.08
2) Overall of Death	4 (3.6%)	9 (2.9%)	0.90
Cardiogenic	4 (3.6%)	4 (1.3%)	0.25
Non-cardiogenic	0	5 (1.6%)	0.41

* *P*-value <0.05 was considered to indicate a statistically significant difference.

Occurrence of re-hospitalization in patients with and without LP

There 90 cardiac events resulting in re-hospitalization including ACS recurrence, effort angina, congestive heart failure, and sustained VT/VF in order of frequency (Table 4-1). Ischemic cardiac events such as ACS recurrence and effort angina accounted for 75.6% (n = 68) of total re-hospitalization cases. The study subjects were classified into the LP positive group (n = 110) and negative group (n = 311) to assess potential correlation with cardiac events. The LP positive group demonstrated significantly higher rate of overall re-hospitalization as well as ACS recurrence and effort angina compared to the negative population. In contrast to high incidence of ischemic cardiac events, VT/VF accounted for only 11.1% (n = 10) and there was no significant difference in the incidence between the two groups. Overall mortality rate was 14.4% (n = 13) that consisted of 8 cardiogenic (8.9%) and 5 non-cardiogenic (5.6%) cases. Although there was no significant difference in the incidence between the two groups, all of the 4 mortality cases in the LP positive group were cardiogenic. There was no sudden cardiac death (arrhythmic death) among 8 cardiogenic death cases.

Table 4-2 summarizes the coronary culprit lesions in cases with ACS recurrence and effort angina. They were classified to re-stenosis of the last treated coronary, newly developed lesion of the last treated coronary, and another coronary lesion. The LP positive group showed significantly higher rate of newly developed lesion of the last treated coronary compared to the negative population (35% vs 10%), while the LP negative group indicated significantly higher rate of another coronary lesion compared to the positive population (0% vs 23%).

Kaplan–Meier analysis showed that the event-free rate of re-hospitalization was significantly higher in the LP-negative group than in the LP-positive group ($p < 0.01$, Fig. 2). Time interval between the first hospital discharge post-PCI and re-hospitalization was significantly shorter in the LP-positive group (540 ± 505.3 days, median: 449 days, range: 2–2166 days) compared to the LP negative group (637 ± 481.4 days, median: 496 days, range: 4–2109 days).

ROC analyses were performed to determine the optimal cut-off values of the three LP-related indices in the worst values for prediction of re-hospitalization (Fig. 3). The optimal cut-off value of fQRS, LAS40 μV, and RMS40 were 112.5 μV, 34.5 ms, and 22.5 μV, respectively, providing favorable sensitivity (≥53%)/specificity (≥63%) as well as the highest AUC values (≥0.60). These optimal cut-off values in this population were similar to the conventional LP positive criteria for SAECG (fQRS ≥114 ms, LAS 40 ≥ 38 ms, and RMS 40 <20 μV) [6].

Table 4-2
Coronary culprit lesion in case with ACS recurrence or effort angina.

	LP positive n = 29	LP negative n = 39	*p* value
Re-stenosis of last treated coronary	19 (65.5%)	26 (66.7%)	0.92
Newly developed lesion of last treated coronary	10 (34.5%)	4 (10.3%)	0.03*
Another coronary lesion	0	9 (23.1%)	<0.01*

LP, ventricular late potential (LP positive/negative based on the worst values); ACS, acute coronary syndrome; VT/VF, ventricular tachycardia/ventricular fibrillation.
* *P*-value <0.05 was considered to indicate a statistically significant difference.

Discussion

Utility of LP for prediction of recurrent ischemic events after PCI

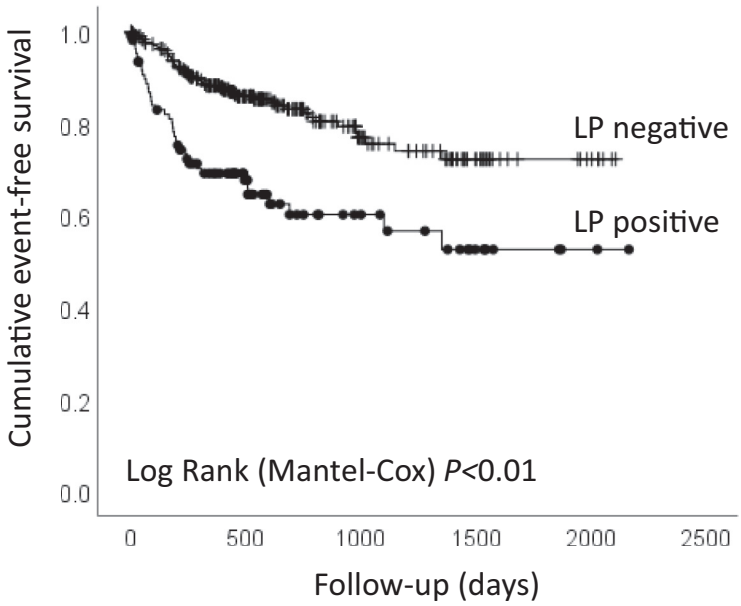
We previously reported that LP positive patients after PCI for the treatment of ACS had higher rate of re-hospitalization compared to LP negative patients, suggesting LP might reflect ischemia associated with future re-hospitalization [4]. The small-scale study in 135 patients, however, did not allow further detailed analysis for potential utility of LP. The logistic analysis revealed a trend toward correlation between LP and re-hospitalization with OR of 2.65, but it was not statistically significant ($p = 0.08$) in a confirmatory multivariate analysis. Because of small sample size, statistical analysis was not achievable for potential correlation between presence of LP and each type of cardiac events leading to re-hospitalization. In this new study, therefore, we increased the sample size from 135 to 421 study subjects and successfully obtained more extensive data supporting strong correlation between LP and re-hospitalization/cardiac events.

The first univariate analysis revealed only LP positive data (in all of the worst, mean and best values) as potential predictive factors for re-hospitalization but not any other factors including clinical and other ECG variables. Then the following multivariate analysis determined the LP positive in the worst value as the only independent predictor for a risk of re-hospitalization. Most of re-hospitalization cases were predominantly attributed to ischemic cardiac events including ACS recurrence and effort angina (>75% of overall re-hospitalization); in contrast, incidence of arrhythmic events was low. The LP positive group demonstrated significantly higher rate of ACS recurrence and effort angina, namely the two most predominant ischemic events, as well as overall re-hospitalization compared to the LP negative population. In addition, LP positive in the worst value alone had a greater predictive power compared with when it was combined with other variables. Furthermore, the ROC analysis determined optimal cut-off values of LP-related indices consistent with the LP positive criteria that were reported with conventional SAECG [6] and used in actual correlation analysis in this study, providing high sensitivity and specificity. These results indicate that the presence of LP after PCI is a useful predictor for a risk of future cardiac ischemic events leading to re-hospitalization.

Relationship between microcirculatory dysfunction and LP

Unfortunately there is no clear answer to the question of why LP can predict recurrent ischemic events several months ahead. However, based on the fact that all recurrent cases in the LP positive group were attributed to the lesions in the previously treated coronary, LP might reflect microcirculatory dysfunction which could not be visualized by CAG. Reperfusion of infarct-related coronary is critical for favorable prognosis [9]. However, even though CAG findings are normalized, the reperfusion therapy does not always resolve ischemia, resulting in "no-reflow" phenomenon [10]. Expected underlying mechanisms of "no-reflow" include superficial thrombosis due to vulnerable plaque, peripheral arterial embolization due to reperfusion, and circulatory defect due to micro-arterial embolism [11]. "No-reflow/slow-reflow" phenomenon has been known to be linked to clinical manifestations of myocardial ischemia, life-threatening arrhythmias, sudden cardiac death, and recurrent ACS [12].

Cardiac syndrome X is known as a pathological condition mostly attributed to coronary microvascular ischemia [13]. It demonstrates a typical angina chest pain and positive results of cardiac stress test but shows normal CAG [14]. LP was present in 15.4% (2.7–42.2%) in the syndrome X [15] and higher than that of healthy subjects (4–6%) [16,17]. Although LP has been thought to represent a fixed arrhythmogenic



Number of residual case					
Days	0	500	1000	1500	2000
LP(-) group	311	157	59	23	6
LP(+) group	110	46	19	8	1

Fig. 2. Kaplan–Meier analysis of cumulative event-free survival in the ventricular late potential (LP)-positive group and LP-negative group.

substrate, it is also affected by the premature extra beat as a trigger, the autonomic nervous system or ischemia as modulating factors, and interaction of electrolyte imbalance and endocrine substance [18]. It is conceivable that the factors of LP formation may be related to the functional variation influenced by the microcirculatory dysfunction, such as disorganized conduction in the depolarization process and the inhomogeneity of the refractory period in the repolarization process [13] [19]. The weight of evidence suggests that the LP may be associated with microcirculatory dysfunction in the treated coronary, which is not completely resolved with the PCI; therefore, it correlates to high risk of future recurrence.

Prevention of microcirculatory disturbance includes aspiration catheter thrombectomy, and distal embolic protection device therapy. It is also preferable to conduct additional intensive drug therapy (nitrate, calcium channel blocker, nicorandil) after distinguishing whether the cause is acute obstruction or spasm. In case that LP becomes positive after PCI despite the above-mentioned preventive intervention, we would like to recommend detailed medical interview during the outpatient clinic, frequent ECG examination, and appropriate follow-up of CAG, to minimize a risk of recurrent ischemic events.

Comprehensive evaluation by HR ambulatory ECG

SAECG has been widely used as a sensitive ECG monitoring especially for potential LP assessment; however, it limits its ability to capture the circadian variation of LP [1]: In contrast, HR ambulatory ECG enables

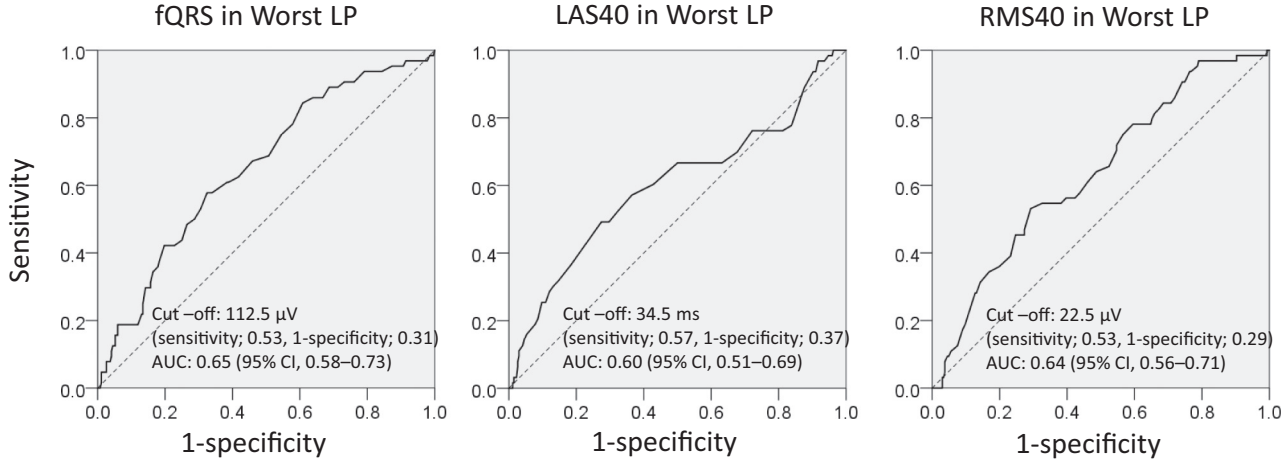


Fig. 3. The ROC curve of the three ventricular late potential (LP) indices, fQRS, LAS40, or RMS40 taken from Worst LP for prediction of re-hospitalization. Sensitivity and specificity to identify high-risk patients were determined by the analysis with area under the curve (AUC). fQRS, filtered QRS; LAS, low-amplitude signal; RMS, root mean square. See text for further discussion.

us to perform a 24-h continuous recording providing robust LP time-course variation data including worst, mean and best values of LP-related indices. Our results indicate that LP positive in only the worst value but not mean or best value obtained from the 24-h continuous QRS wave data can be the statistically reliable predictor for a risk of re-hospitalization. Thus, it is important to assess a potential risk based on the worst value even LP could be observed only transiently during a diurnal variation. Additionally, HR-ambulatory ECG has a significant advantage to record various non-invasive parameters as well as LP simultaneously. It is possible to comprehensive evaluation considering repolarization instability and autonomic nervous function besides basic information of heart rate, arrhythmic event and ST changes.

In the SHIFT study (Systolic Heart Failure Treatment with the If Inhibitor Ivabradine Trial) for patients with coronary artery disease (LVEF <35% and a resting heart rate ≥ 70/min), the higher heart rate at the enrollment was associated with the higher incidence of cardiovascular events [20]. The meta-analysis on the prognosis of coronary artery disease performed by Diaz et al. [21] also reported that total mortality and cardiovascular mortality increased as heart rate increased. The onset of ACS is triggered by hyperactivation of sympathetic nerve system, large fluctuations of blood pressure, coronary plaque rupture, etc., and plaque rupture can occur more easily with higher heart beats. Heidland et al. [22] performed CAG twice in 6 months and investigated the risk of new plaque rupture at the second time, the hazard ratio was 4.92 in left ventricular hypertrophy (≥270 g), then 3.19 in the higher heart rate (≥80/min). On the other hand, the hazard ratio in taking beta-blockers was as low as 0.32.

Interestingly, the re-hospitalization group in our study tended to have higher total heart beats/24-h and mean heart rate compared to the non-re-hospitalization group despite the higher usage rate of beta-blockers. In the HRV analysis, the re-hospitalization group exhibited decreased vagal nerve tonus and increased relative sympathetic nerve tonus at night, suggesting insufficient suppression of sympathetic nerve activity likely due to insufficient dosage of beta-blockers or non-responder. Although the target dosage of beta-blockers has not been standardized yet, physicians should make efforts to administer optimal dose of beta-blockers avoiding side effects such as bradycardia and hypotension are not observed.

Utility of LP for prediction of arrhythmia events and cardiac death

There are several published reports indicating that LP in combination with other factors may increase its predictability compared to LP alone [23,24]. Those reports, however, investigated LP primarily as a predictor for arrhythmia in early 2000s. After beta-blockers have been widely used in >95% of AMI populations in the mid-2000s, predictability of LP and LVEF for cardiac death significantly decreased [25]. In our study, beta-blockers were used in approximately 80% of the study subjects, and there was no statistically significant difference in LVEF between re-hospitalization and non-hospitalization groups. The predictability of LP positive alone for re-hospitalization was 71%; however, it decreased significantly to 65% in combination with LVEF and repolarization indices such as TAV. These results indicate that early intervention including perfusion therapy and beta-blockers provides significant benefit for cardiac function, but at the same time limits the values of LVEF or repolarization indices as prognostic predictors.

LPs had been used as an effective prognostic predictor for fatal arrhythmia, especially as a complication of AMI for a long time [26,27]. The predictive power of LPs, however, largely decreased with the significant changes in AMI disease circumstance due to advancement of medical interventions including PCI, beta-blockers, amiodarone, and implantable cardioverter-defibrillators, and improved management of risk factors and lifestyles [28,29]. Bauer et al. [30] reported LPs were no longer an effective predictor for cardiac death or severe arrhythmic events based on his study using SAECG in 968 patients receiving PCI for the treatment of AMI. Our study also revealed that a majority of post-PCI cardiac events were associated with ischemia (75.6%). In contrast, arrhythmia accounted for only 11.1% and cardiac death accounted for 8.9% (sudden death 0%) of the overall events; and there was no significant difference in its incidence between LP positive and negative groups. Based on the evidence above, we may need to accept the limitation of LP as a prognostic predictor for arrhythmia and sudden cardiac death post-PCI.

Limitations

The following three points were limitations of this research. (1) LP recording was not analyzed when noise was over 0.8 μV. In this study, all subjects were examined during hospital stay. Therefore, patients maintained a supine resting position for relatively long periods during the day time reducing motion artifact. Nevertheless, few patients produced full 24 h LP data. (2) Two HR-ambulatory ECG technicians and two cardiologists visually reviewed the automatically determined onset and offset of P and QRS waves, and excluded false positive data. In order to use HR-ambulatory ECG as a versatile and common examination, further improvements such as more accurate automatic analysis would be necessary. (3) Unlike the SAECG, ambulatory ECG is affected by posture changes. In a previous study of SAECG, we found that the decubitus or prone position exacerbated LPs [31]. However, because a position detecting sensor was not available on the devices used in the current study, further investigation for potential effects of posture on our results may be warranted. (4) Conventionally, Simson's method has been used for obtaining spatial vector magnitude from X, Y, Z bipolar leads [32], however vector electrocardiogram could not be sufficient to detect the LP in pathological condition with local depolarization abnormality such as MI. On the other hand, the multipoint monopolar leads method may be able to capture the LP just under the electrode, but it is susceptible to the influence of the physique of the patient or artifacts. Our study did not investigate multipoint monopolar leads method, warranting an additional examination to identify the distribution and direction of the conduction delay.

Conclusion

The presence of LP in the worst value obtained from 24-h HR ambulatory ECG post-PCI was an independent predictor for a risk of re-hospitalization due to later ischemic cardiac events in ACS patients. The ROC analysis determined optimal cut-off values of LP-related indices to predict a risk of re-hospitalization, which were consistent with the LP positive criteria previously reported with conventional SAECG.

Disclosure

The authors declare no conflicts of interest associated with this manuscript. All members participated in the current study. 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]).

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