Usefulness of Continuous 24-hour Ventricular Late Potential to Predict Prognosis in Patients with Heart Failure

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Objectives: An estimated 50,000 patients have heart failure (HF) in Japan, and the left ventricular ejection fraction (LVEF) is the typical predictor of prognosis. The identification of a noninvasive marker to predict most high-risk patients is urgently needed. This study aimed to log the continuous ventricular late potential (LP) by using high-resolution ambulatory monitoring in patients with HF with non-sustained ventricular tachycardia, and determine the association between the LP variation and prognosis. Methods: The 90 hospitalized patients were classified into cardiogenic death (n = 10) and non-death (n = 80) groups. The LVEF, LP, and coefficient of variation (CV) of the filtered QRS (fQRS), and low-amplitude signal < 40 μV for the terminal QRS portion of (LAS40) of both groups were evaluated. The maximum fQRS over 24 h was defined as the maximum fQRS (Max-fQRS). Results: The results were as follows: (1) cardiogenic death occurred in 32% (10/31 patients) with an LVEF ≤ 45% and a Max-fQRS ≤ 114 ms; (2) cardiogenic death occurred in 38% (10/26 patients) with a LAS40-CV ≥ 0.09; and (3) using LVEF, Max-fQRS, and LAS40-CV as the three predictors, the specificity and accuracy were 83% and 82%, respectively, with an odds ratio of 12.3. Conclusions: LAS40 variations and increases might be new risk indicators of prognosis.

Key words: high resolution ambulatory monitoring, prognostic value, cardiogenic death

INTRODUCTION

According to a survey by the Japanese Ministry of Health, Labour and Welfare, approximately 47,500 and 52,700 patients had heart failure in 2008 and 2011, respectively, showing an increasing tendency [1, 2]. Although a certain degree of improved prognosis associated with oral angiotensin-converting enzyme inhibitor or β-blocker use has been observed, the number of patients with heart failure is expected to increase steadily due to the increasing proportion of elderly members of society. Non-sustained ventricular tachycardia (NSVT) is a prognosis-related factor in addition to typical left ventricular ejection fraction (LVEF) for the prediction of cardiogenic death in patients with heart failure [3]. The identification of a highly precise but noninvasive marker for predicting high-risk patients among the increasing number of patients with heart failure is urgently needed. According to the recent large-scale Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan, the predictors for readmission within 1 year and for mortality in patients with heart failure were cardiovascular symptoms recorded in a health-status questionnaire, lower leg edema, and brain natriuretic peptide (BNP) level [4]. However, both cardiovascular symptoms recorded in the health-status questionnaire and lower leg edema lack objectivity because the subjectivity of each patient caused inconsistent responses to the health-status questionnaire and the subjectivity of each physician was involved in determining the presence or absence of lower leg edema. BNP level was superior in objectivity but since interpretations using BNP level only are limited [5], it may not be considered as an indicator of long-term prognosis.

Here we focused on ventricular late potential (LP) obtained through signal-averaged electrocardiography findings. LP is detected noninvasively and is highly useful as an indicator to predict lethal ventricular arrhythmia and sudden cardiac death in organic heart diseases [6, 7]. On the other hand, it has been reported that LP is detected in a high percentage of patients with symptomatic Brugada syndrome without organic heart disease [8]. Yoshioka *et al.* observed the LP of the patients with Brugada syndrome over time and found a marked diurnal variation pattern in those with symptomatic Brugada syndrome [9]. However, when the LP alone was used, its negative predictive value was high but its positive predictive value was not high [10]. One report stated that combination LVEF and LP may increase the positive predictive value by about two-fold in patients with myocardial infarction [11].

This study aims to determine the association between heart death and a predictor consisting of LVEF and the variation rate of LP in patients with heart failure and NSVT.

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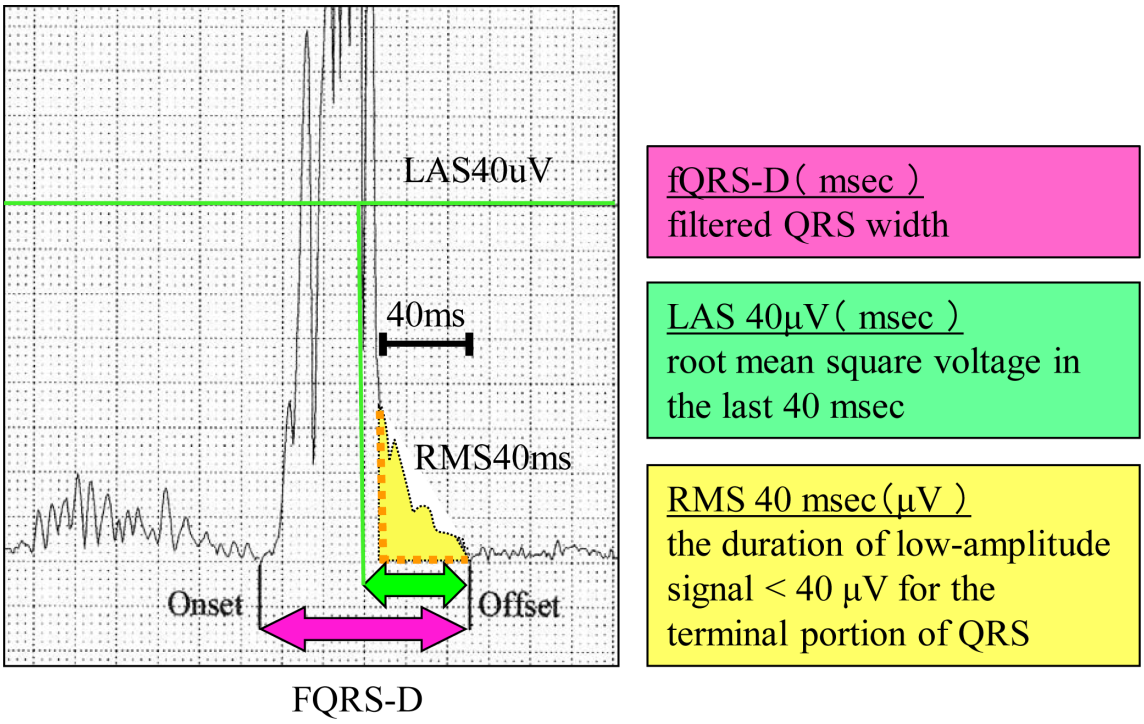

Supple Fig.

PATIENTS AND METHODS

Subjects

Of all 1,583 patients who were diagnosed with heart failure (New York Heart Association II-IV) and hospitalized at Tokai University Hospital (Isehara, Kanagawa Prefecture, Japan) from January 2005 to December 2009, 90 patients (76 men; mean age, 62.1 years) exhibited NSVT during hospitalization and provided consent to participate in this clinical study were included in this study. Patients with bundle branch block or atrial fibrillation were excluded from this study.

Assessment items

These 90 subjects were classified into the death (n = 16) and non-death (n = 74) groups. Furthermore, the patients in the death group were classified into the cardiogenic death (n = 10) and non-cardiogenic death (n = 6) groups. The assessment items included: age; sex; echocardiography-based LVEF; PQ interval, QRS duration, and QTc interval based on a standard 12-leads electrocardiogram; and LP based on ambulatory monitoring. For the LP, the following three indicators were calculated: filtered QRS (fQRS); the duration of low-amplitude signal < 40 μV for the terminal portion of QRS (LAS40); root mean square voltage in the last 40 msec (RMS40). Three LP parameters were schematically shown in the supplemental figure. As a coronary risk factor, the presence or absence of the following items were examined: smoking history, lipid disorder, hypertension, diabetes, and hyperuricemia. The diagnostic criteria of each disease were defined as follows: for hypertension, ≥ 130/85 mmHg; for diabetes, hemoglobin A1c (National Glycohemoglobin Standardization Program level) ≥ 6.5% and fasting blood glucose ≥126 mg/dL; for lipid disorder, low-density lipoprotein cholesterol (LDL-C) ≥ 140 mg/dL, high density lipoprotein (HDL-C) ≤ 40 mg/dL, or triglyceride (TG) ≥ 150 mg/dL; and for hyperuricemia, a uric acid value ≥ 7.0 mg/dL. Patients who were already undergoing drug therapy were classified as having a coronary risk factor for the appropriate disease/clinical condition.

Measurement equipment

A ProSound α10 echocardiograph (HITACHI ALOKA, Japan) was used. The modified Simpson method was used to measure LVEF. An ECG-1500 electrocardiograph (NIHON KOHDEN CORPORATION, Japan) was used (normal values: 120–200 ms, <120 ms, and 350–440 ms for PQ interval, QRS duration, and QTc interval, respectively). For measuring the QTc interval, Bazett's correction formula was used. For measuring LP, high resolution Sine flash digital Holter electrocardiogram (2.5 μV, 1,000 Hz; ELA Medical, Inc. France) was used. The chest XYZ leads (Frank Lead System/CC5R, ML, CB2) were used for the measurements. The recording time was 24 hours. To calculate fQRS, LAS40, and RMS40, 24 hours were divided into 20-minute intervals and the QRS complex was added 200 times and averaged. A noise level of 0.8 μV or less was adopted. In the 24-hour record, the maximal calculated value of fQRS was defined as the maximum fQRS (Max-fQRS), the maximal calculated value of LAS 40 μV was defined as maximum LAS40 (Max-LAS40), while the minimal calculated value of RMS40 was defined as minimum RMS40 msec (Min-RMS40) and the coefficients of variation (CV) for each parameter were calculated. The CV was defined as standard deviation divided by the mean. For LP, a patient who met at least two items of fQRS ≥ 114 msec, LAS40 ≥ 38 msec, RMS40 < 20 μV was defined as positive. Echocardiography, 12-lead electrocardiogram, and high-resolution ambulatory monitoring were

Table 1 Comparison in age, number of males, LVEF, electrocardiological parameters and coronary artery disease risk factors between cardiac death and surviving groups

	Cardiac death (n = 10)	Non-cardiac death (n = 6)	Survive (n = 74)	P value (Mann-Whitney U test &Fisher test)
Age (years)	72.7 ± 7.6	67.3 ± 8.7	60.2 ± 13.7	n.s
Male	9 (90%)	5 (83%)	62 (84%)	n.s
UCG				
Case of LVEF ≦45%	10 (100%)	1 (17%)	29 (39%)	P < 0.001
12-leads ECG				
PQ (ms)	176.8 ± 26.0	153.3 ± 19.2	166.5 ± 23.3	n.s
QRS (ms)	106.2 ± 12.6	86.3 ± 6.6	97.0 ± 14.8	P = 0.03
QTc (ms)	445.5 ± 30.3	441.3 ± 24.0	431.0 ± 31.8	n.s
HR-Holter ECG				
< Positive criteria >				
Max-fQRS ≧114ms	10 (100%)	1 (17%)	23 (31%)	P < 0.001
Max-LAS40≧38ms	5 (50%)	0 (0%)	20 (27%)	n.s
Min-RMS40< 20μV	5 (50%)	0 (0%)	19 (26%)	n.s
LP positive case	8 (80%)	2 (33%)	44 (59%)	n.s
Coronary risk				
Hypertension	5 (50%)	3 (50%)	24 (32%)	n.s
Diabetes Mellitus	5 (50%)	2 (33%)	17 (23%)	n.s
Dyslipidemia	4 (40%)	0 (0%)	40 (54%)	n.s
Hyper uric acid	3 (30%)	0 (0%)	16 (22%)	n.s
Smoking history	4 (40%)	4 (68%)	39 (53%)	n.s

Data given as mean ± SD or n (%) or (range). LP defined as positive when 2 of 3 criteria (fQRS ≧ 114ms, LAS40 ≧ 38ms, RMS40 < 20μV) were met. Statistical significance was analyzed by Mann-Whitney U test &Fisher test. The difference was considered at P < 0.05 CV, Coefficient of variance; LVEF, left ventricular ejection fraction; ECG, electrocardiogram; HR, high resolution; Max-fQRS, maximum filtered QRS duration; Max-LAS40, maximum duration of the terminal low-amplitude signal < 40μV; Min-RMS40, minimum root mean square voltage of the terminal 40ms of the fQRS; LP, late potential.

performed on day 18 ± 8 of hospitalization.

Statistical analysis

For the statistical analysis, StatView Version 5 (SAS Institute Inc.) was used. In a comparison between the cardiogenic death and survival groups, an unpaired t-test (Mann-Whitney U-test) and Fisher's exact probability test were used. For the calculation of cumulative survival rate, the Kaplan-Meier method was used. To identify the ideal boundary value, diagnostic yield, sensitivity, specificity, positive predictive value, and negative predictive value, ROC analysis was used. P values < 0.05 were considered statistically significant.

RESULTS

Patient characteristics in the death group

Age, sex, LVEF, PQ interval, QRS duration, QTc interval, LP parameters, and coronary risk factors were examined in the cardiogenic death, non-cardiogenic death, and survival groups. The results are shown in Table 1. The number of patients with LVEF ≤ 45%, extended QRS duration, and Max-fQRS ≥ 114 ms were significantly higher in the cardiogenic death group. Regarding LVEF, the patients were classified into two groups: the LVEF > 45% group (good EF group: n = 50); the LVEF ≤ 45% group (low EF group: n = 40) to examine age, sex, ischemic/non-ischemic heart disease, PQ interval, QRS duration, QTc interval, LP parameters, and coronary risk factors (Table 2). The mean age was lower in the low EF group (P = 0.07). The underlying diseases in the good EF group included old myocardial infarction (21patients),acute myocardial infarction (7 patients), vasospastic angina (5patients), hypertrophic cardiomyopathy (2patients), dilated cardiomyopathy (1 patients), idiopathic ventricular tachycardia (8 patients), idiopathic ventricular fibrillation (4patients), arrhythmogenic right ventricular dysplasia (1patient) and left ventricular noncompaction (1 patient): in the low EF group, the underlying diseases were old myocardial infarction (25 patients), acute myocardial infarction (4 patients), hypertrophic cardiomyopathy (3 patients), dilated cardiomyopathy (7 patient), and aortic stenosis (1 patient). Proportion of ischemic heart disease is quite important. In total, ischemic heart disease (IHD) was 33 (66%) in the good EF group and 29 (73%) in the low EF group, respectively. There was no significance about the subject number of ischemic/non-ischemic heart disease among 2 groups. The mean LVEF level was 58.6 ± 6.0% and 34.3 ± 9.7% in the good EF group and low EF group, respectively (P < 0.001). For 12-leads electrocardiogram indicator, QRS duration was prolonged in the low EF group (P = 0.008). For LP indicator, Max-fQRS was prolonged in the low EF

Table 2 Comparison in age, number of male, LVEF, electrocardiological parameters and coronary artery disease risk factors between patients with EF > 45% and EF ≦ 45%.

	total (n = 90)	EF > 45% good EF group (n = 50)	EF ≦45% low EF group (n = 40)	P value (Mann-Whitney U test &Fisher test)
Age (years)	62.2 ± 13.5	65.9 ± 10.4	59.0 ± 14.9	P = 0.007
Male	76 (84%)	42 (84%)	34 (85%)	n.s
Baseline disease				
IHD	63 (70%)	33 (66%)	29 (73%)	n.s
Non-IHD	27 (30%)	17 (34%)	11 (27%)	n.s
LVEF (%)	49.5 ± 16.8	58.6±6.0	34.3 ± 9.7	P < 0.001
12-leads ECG				
PQ (ms)	166.8 ± 23.6	164.1 ± 25.0	170.1 ± 21.7	n.s
QRS (ms)	97.3 ± 14.6	94.0 ± 13.5	101.5 ± 15.1	P = 0.008
QTc (ms)	433.2 ± 31.2	430.1 ± 28.0	437.1 ± 34.9	n.s
HR-Holter ECG				
Max-fQRS (ms)	122.6 ± 20.3	114.8 ± 14.5	132.4 ± 22.4	P = 0.001
Max-LAS40 (ms)	44.3 ± 13.5	42.7 ± 9.7	46.3 ± 17.1	n.s
Min-RMS40 (μV)	17.7 ± 13.4	18.0 ± 13.4	17.3 ± 13.5	n.s
< Positive criteria >				
Max-fQRS ≧114ms	33 (37%)	11 (22%)	22 (55%)	P = 0.001
Max-LAS40≧38ms	25 (28%)	12 (24%)	13 (33%)	n.s
Min-RMS40< 20μV	24 (27%)	11 (22%)	13 (33%)	n.s
LP positive case	54 (60%)	31 (62%)	23 (58%)	n.s
Coronary risk				
Hypertension	42 (47%)	23 (46%)	19 (48%)	n.s
Diabetes Mellitus	24 (27%)	8 (16%)	16 (40%)	P = 0.005
Dyslipidemia	44 (49%)	23 (46%)	21 (53%)	n.s
Hyper uric acid	19 (21%)	9 (18%)	10 (25%)	n.s
Smoking history	47 (52%)	29 (58%)	18 (45%)	n.s

Data given as mean ± SD or n (%) or (range). LP defined as positive when 2 of 3 criteria (fQRS ≧ 114 ms, LAS40 ≧ 38 ms, RMS40 < 20μV) were met. Statistical significance was analyzed by Mann-Whitney U test & Fisher test. The difference was considered at P < 0.05 IHD, Ischemic heart disease; N-IHD, Non ischemic heart disease; CV, Coefficient of variance; LVEF, left ventricular ejection fraction; ECG, electrocardiogram; HR, high resolution; Max-fQRS, maximum filtered QRS duration; Max-LAS40, maximum duration of the terminal low-amplitude signal < 40μV; Min-RMS40, minimum root mean square voltage of the terminal 40 ms of the fQRS; LP, late potential.

Table 3 Receiver operating characteristic (ROC) analysis for LVEF, Max-fQRS and LAS-CV

	Sensitivity (%)	Specificity (%)	Accuracy (%)	PPV (%)	NPV (%)	OR	AUC	P-value
LVEF	80	74	74	28	97	8.4 (95%CI: 1.8–39.5)	0.838	P < 0.001
Max-fQRS & LAS-CV	80	65	67	22	96	6.0 (95%CI: 1.3–28.0)	0.748	P = 0.01
LVEF & Max-fQRS & LAS-CV	80	83	82	36	97	12.3 (95%CI: 2.6–57.9)	0.869	P < 0.001

PPV, positive predictive value; NPV, negative predictive value; OR, odds ratio, AUC, area under the curve. Other abbreviations as in Table 1.

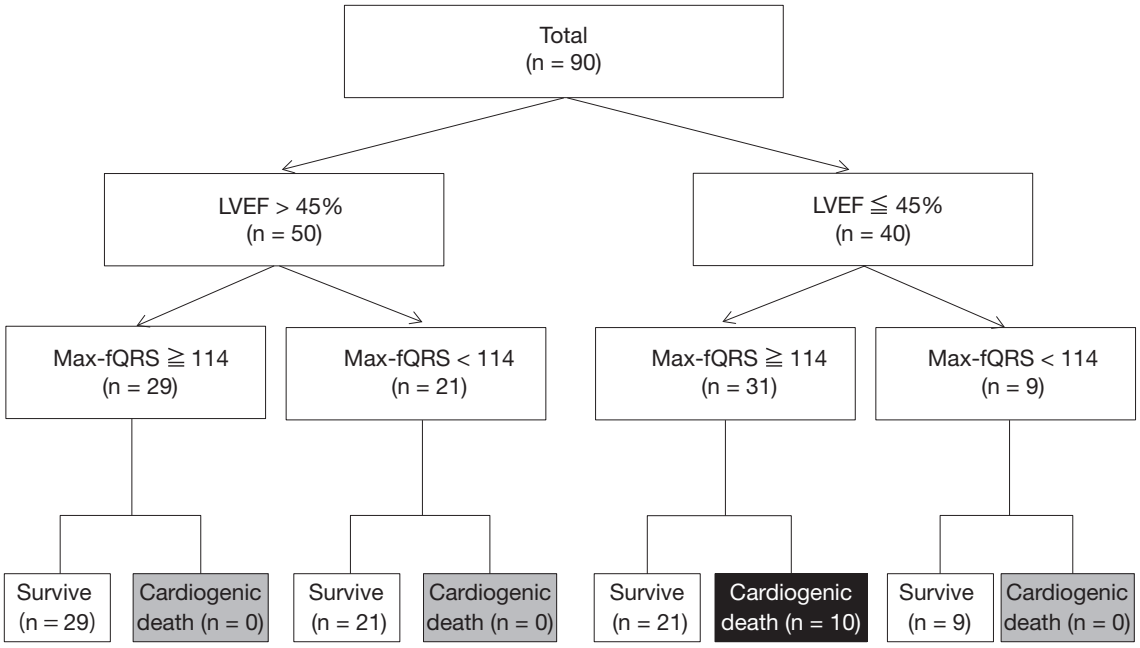

Fig. 1 Ratio of cardiac death according to the parameters with LVEF and Max-fQRS
Based on the criteria with cutoff values of LVEF 45% and Max-fQRS of 114 ms, cardiogenic death in all 90 patients was classified and the characteristics of the results are shown in Fig. 1. Of the 31 patients who met the criteria (LVEF ≤ 45% and Max-fQRS ≥ 114 ms), 10 (32%) were cases of cardiogenic death. No cardiogenic death was found in the other groups.
LVEF, left ventricular ejection fraction; Max-fQRS, maximam filterd QRS duration.

group (P = 0.001). More patients in the low EF group met the positive criteria (P = 0.001). Regarding risk factors of coronary arteriosclerosis, the low EF group showed a high incidence of comorbidity with diabetes (16% vs. 40%; P = 0.005), whereas there was no difference in smoking history, lipid disorder, hypertension, and hyperuricemia between both groups.

Based on the examination mentioned above, with cutoff values of LVEF 45% and Max-fQRS of 114 ms, cardiogenic death in all 90 patients was classified and the characteristics of the results are shown in Fig. 1. Of the 31 patients who met the criteria (LVEF ≤ 45% and Max-fQRS ≥ 114 ms), 10 (32%) were cases of cardiogenic death. No cardiogenic death was found in the other groups.

Kaplan-Meier analysis using LVEF, Max-fQRS, and CV of LP as predictors

To increase the predicted value of prognosis, the CV of LP was added to the two predictors consisting of LVEF ≤ 45% and Max-fQRS ≥ 114 ms groups to calculate a survival curve up to 3,000 days. The cutoff value of CV was set at 0.05, 0.09, and 0.2 for fQRS, LAS40, and RMS40, respectively. For fQRS-CV ≥ 0.05 and fQRS-CV < 0.05, cardiogenic death was found in 2/10 patients (20%) and 8/21 patients (38%), respectively (Fig. 2A, P = 0.43). For LAS40-CV set at 0.09, cardiogenic death was found in 10/26 patients (38%) and 0/5 patients (0%), respectively (Fig. 2B, P = 0.07). For RMS40-CV set at 0.2, cardiogenic death was found in 5/22 patients (23%) and 5/9 patients (56%), respectively (Fig. 2C, P = 0.20). In Kaplan-Meier analysis with fQRS-CV, LAS40-CV, and RMS40-CV as additional indicators, there were no significant differences among any of the groups. However, in the group of patients who met the LVEF ever, in the group 114 ms, and LAS40-CV < 0.09, there was no case of death (Fig. 2B).

ROC analysis using LVEF, Max-fQRS, and LAS40-CV to predict prognosis

Since the possibility of a good prognosis was suggested in the group of patients who met the LAS40-CV < 0.09 criterion, we conducted ROC analysis using it as a predictor (Table 3). After having calculated the hazard score for cardiogenic death (1) using LVEF alone, (2) using two factors of Max-fQRS and LAS40-CV, (3) when using three factors of LVEF, Max-fQRS, and LAS40-CV, the sensitivity, specificity, accuracy, positive predictive value, negative predictive value, odds ratio (OR), and area under the curve (AUC) were calculated. Using LVEF alone, the sensitivity, specificity, accuracy, and OR were 80%, 74%, 74%, and 8.4 (95% confidence interval [CI], 1.8–39.5) and the AUC was 0.838. On the other hand, when combining Max-fQRS and LAS40-CV, the sensitivity, specificity, accuracy, and odds ratio were 80%, 65%, 67%, and 6.0 (95% CI, 1.3–28.0) and the AUC was 0.748, a decrease in reliability compared to LVEF alone. When combining three factors of LVEF, Max-fQRS, and LAS40-CV, the sensitivity, specificity, accuracy, and OR were 80%, 83%, 82%, and 12.3 (95% CI, 2.6–57.9) and the AUC was 0.869, an increase in predictive reliability.

DISCUSSION

In patients with heart failure and NSVT, the association between the variation rate of LP and prognosis was examined by using a high-resolution ambulatory monitoring. When the three predictors of cardiogenic death (LVEF, Max-fQRS, and LAS40-CV) were com-

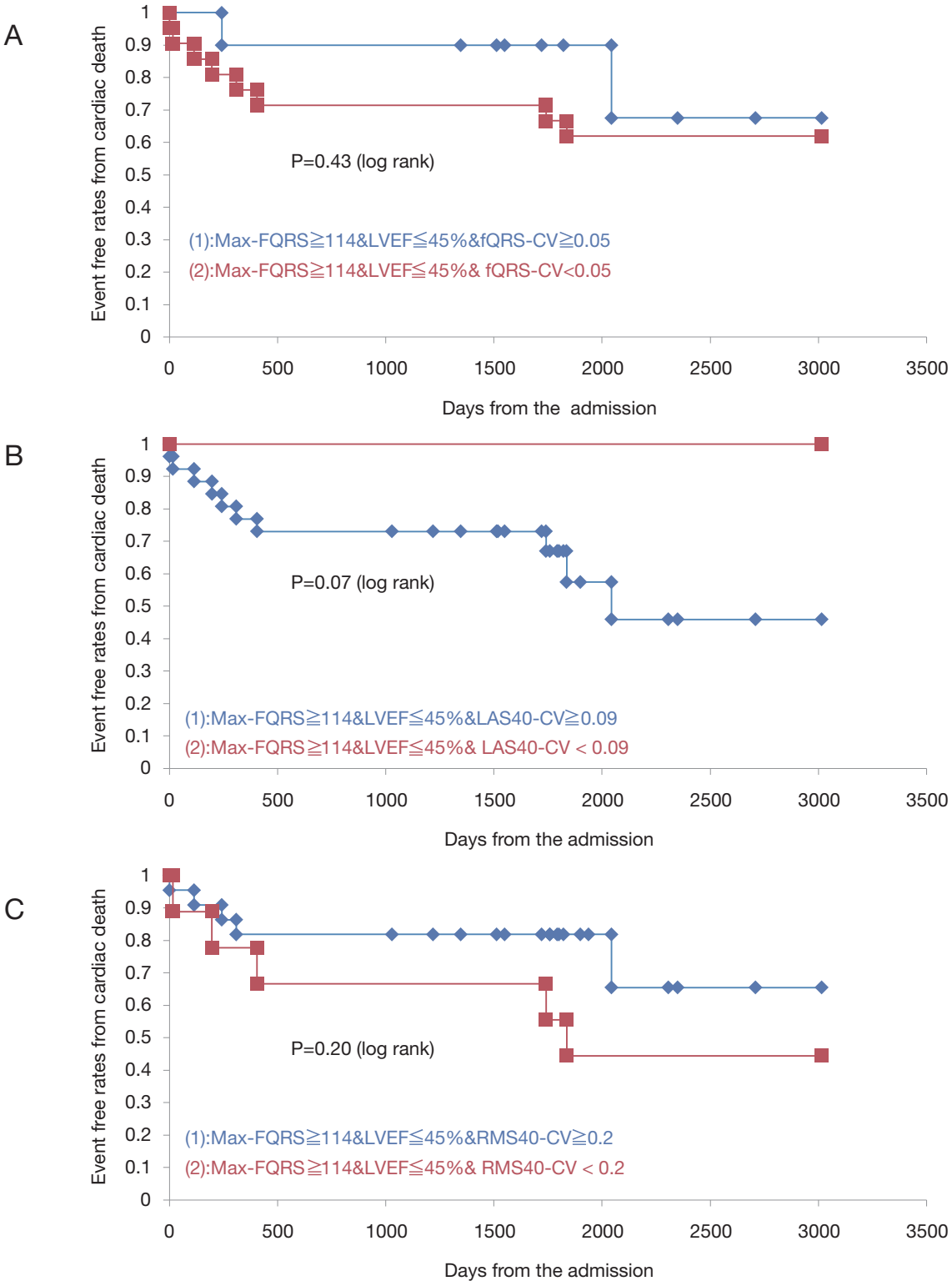

Fig. 2 Kaplan-Meier analysis using LVEF, Max-fQRS, and CV of LP as predictors
The cutoff value of CV was set at 0.05, 0.09, and 0.2 for fQRS, LAS40, and RMS40, respectively.
A is the groups with fQRS-CV ≥ 0.05 and fQRS-CV < 0.05.
B is the groups with LAS40-CV set at 0.09.
C is the groups with RMS40-CV set at 0.2.
fQRS, filtered QRS; LAS40, the duration of low-amplitude signal < 40μV for the terminal portion of QRS; RMS40, root mean square voltage in the last 40 msec; CV, coefficient of variation.

Supple Table Comparison in LVEF, electrocardiological parameters between cardiac death and surviving groups

	Cardiac death (n = 10)	Survive (n = 74)	P value (Mann-Whitney U test)
UCG			
LVEF (%)	29.8 ± 9.8	51.7 ± 16.3	P < 0.001
12-leads ECG			
PQ (ms)	176.8 ± 26.0	166.5 ± 23.3	n.s
QRS (ms)	106.2 ± 12.6	97.0 ± 14.8	P = 0.03
QTc (ms)	445.5 ± 30.3	431.0 ± 31.8	n.s
HR-Holter ECG			
Max-fQRS (ms)	130.6 ± 12.1	112.1 ± 18.1	P < 0.001
Max-LAS40 (ms)	37.8 ± 11.8	34.0 ± 12.2	n.s
Min-RMS40 (μV)	29.0 ± 20.1	37.7 ± 26.9	n.s

Data given as mean ± SD or n (%) or (range). LP defined as positive when 2 of 3 criteria (fQRS ≧ 114ms, LAS40 ≧ 38ms, RMS40 < 20μV) were met. Statistical significance was analyzed by Mann-Whitney U test. The difference was considered at P < 0.05 CV, Coefficient of variance; UCG, ultrasound cardiography; LVEF, left ventricular ejection fraction; ECG, electrocardiogram; HR, high resolution; fQRS, filtered QRS duration; LAS40, duration of the terminal low-amplitude signal < 40μV; RMS40, root mean square voltage of the terminal 40ms of the fQRS.

bined, the sensitivity, specificity, accuracy, and OR were high at 80%, 83%, 82%, and 12.3, respectively.

Preliminary statistical analysis

Another statistical approaches had tried to be done before the current approaches. Firstly, comparison of LVEF, 12-leads ECG findings (PQ, QRS, and QTc), and HR-Holter ECG findings (Max-fQRS, Max-LAS40, and Min-RMS40) was performed between cardiac death patients and survivors by using Man-Whitney U test (supplement table). In the results, LVEF (%) was lower ($p < 0.001$), and extended QRS duration (of 12-leads ECG) and Max-fQRS (of HR Holter ECG) in the cardiogenic death group were higher ($P = 0.03$, $P < 0.001$) than survive group. Then secondly, concerning the significant factors (LVEF, QPS, Max-fQRS), the multivariate analysis was performed by commercially available SPSS software. Ten subjects of cardiac death was set as a dependent variable (objective variable) with binary variable. The statistical significant factors, LVEF, QRS on 12-1eads ECG, and max-fQRS on HR-Holter ECG were set as independent variables (explanatory variables). However multiple logistic regression analysis was impossible to be done for lack of number of event sample. Finally ROC curve analysis applied to determine best cut-off value for LVEF, QRS, and Max-fQRS. As regarding LVEF, optimal value was 45% (the sensitivity, specificity, and accuracy were 76%, 74%, and 72%). As regarding QRS, optimal value was 104 (the sensitivity, specificity, and accuracy were 59%, 55%, and 58%). As regarding Max-fQRS, optimal value was 114 (the sensitivity, specificity, and accuracy were 79%, 70%, and 78%). Based on the preliminary statistical analysis mentioned above, with cutoff values of LVEF 45% and Max-fQRS of 114 ms, cardiogenic death in all 90 patients was classified and the characteristics of the results are shown in Fig. 1.

Combination use of multiple predictors

From the results of preliminary ROC analysis, the discriminant power of any single parameter of LVEF, QRS, and Max-fQRS was less than 80% and insufficient. Multiple logistic regression analysis was impossible because of the number of subjects. We, therefore, performed further Kaplan-Meier analysis by combination of the LVEF, Max-fQRS, and LAS40-CV. The possibility of a good prognosis was suggested in the group of patients who met the LAS40-CV < 0.09 criterion by the ROC analysis. When combining three factors of LVEF, Max-fQRS, and LAS40-CV, the sensitivity, specificity, and accuracy were more than 80% and the AUC was 0.869, an increase in predictive reliability. Comparing with the ROC analysis for single parameter, it became clearly variable to detect the prognosis of cardiac death by setting certain boundary values. These observations suggest that analysis of both fQRS and LAS40-CV in ambulatory HR-Holter ECG is quite useful in the stratification of CHF patients with NSVT, in addition to the traditional assessment procedure as LVEF. However the predictors is not enough to be applied to every heart disease with sudden death or fatal arrhythmia, because we had a wide variety of underling disease in this time.

Prognosis evaluation using LVEF

The accurate predictor of cardiogenic death is contractility of the left ventricle. Kawashiro *et al.* [12] conducted a prognosis survey in patients with ischemic/non-ischemic heart diseases (n = 3578; mean LVEF, 42%) and reported a high frequency of sudden death in patients with an LVEF ≤ 35%. LVEF is the strongest independent indicator of heart death. In the United States and Europe, implantation criteria for implantable cardioverter defibrillators (ICD) have been established based on LVEF. According to the Multicenter Automatic Defibrillator Implantation Trial II [13], ICD implantation decreased all-cause mortality by approximately 30% in patients with post-infarction cardiac hypofunction (n = 1234, LVEF < 30%). According to the Sudden Cardiac Death in Heart Failure Trial study [14], ICD implantation decreased all-cause mortality by approximately 23% in patients with ischemic/non-

ischemic heart disease (n = 2521, LVEF ≤ 35%). Also in this study, all 10 cardiogenic deaths showed LVEF ≤ 45%.

Prognosis evaluation using the LP

The Cardiac Arrhythmia Suppression Trial/Signal-Averaged Electrocardiogram study [7] reported that fQRS (≥ 120 ms) along with LVEF was useful for predicting lethal arrhythmia in 1,158 patients with myocardial infarction (mean observation period, 10 months). According to De Chillou C *et al.* [6], signal average electrocardiography (SAECG) revealed that LAS40 was a predictor of lethal arrhythmia along with LVEF in 244 patients with myocardial infarction. In this study, cardiogenic death was significantly common in the Max-fQRS ≥ 114 msec group calculated by using a high-resolution ambulatory monitoring, while no significant difference was found with Max-LAS40. Therefore, we examined the CV of each LP parameter (fQRS, LAS40, and RMS40) as an additional indicator and found that the specificity, accuracy, and odds ratio for cardiogenic death increased when LAS40-CV was used. Many prognosis evaluations in previous studies were based on a single measurement of LP with SAECG and did not consider diurnal variation. However, by adding the CV of LP to the predictor, we found what might be a new indicator to predict cardiogenic death in patients with heart failure.

Repolarization indicator and autonomic nervous function indicator

LP is a typical indicator reflecting myocardial depolarization. To predict ventricular arrhythmias, the usefulness of other indicators reflecting repolarization abnormalities such as T-wave alternans [11] and T-wave variability [9] has also been reported. As indicators of autonomic nervous function, in addition to conventional heart rate variability, new indicators such as heart rate turbulence [15] and deceleration capacity [16] have been developed. Thus, it has become possible to analyze the attenuation functions of sympathetic nervous activity. In our study, the evaluation was conducted by combining LVEF, fQRS, and LAS40-CV, which improved the predictive precision. However, the positive predictive value increased by only 8% compared with LVEF alone. To further improve reliability, examinations that consider abnormal repolarization and autonomic nerve indicators will be necessary.

LIMITATIONS

In this examination, the number of the subjects was limited to 90 patients including both patients with ischemic heart disease and those with non-ischemic heart disease. It has been reported that there is no significant correlation between sudden death and LP in patients with non-ischemic heart disease [17]. Therefore, it is necessary to accumulate more cases and distinguish the targeted heart disease. In addition, because the data were continuous records obtained by using ambulatory monitoring, physical exertion influenced the noise level and there were few daytime LP data available for analysis. We believe that there is high demand for further examinations that consider the impact of postural change on LP.

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DISCLOSURES

Conflict of Interest: None declared.

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