

Surface ECG–based complexity parameters for predicting outcomes of catheter ablation for nonparoxysmal atrial fibrillation: efficacy of fibrillatory wave amplitude

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Abstract

Catheter ablation (CA) is a well-established therapy for rhythm control in atrial fibrillation (AF). However, CA outcomes for persistent AF remain unsatisfactory because of the high recurrence rate despite time-consuming efforts and the latest ablation technology. Therefore, the selection of good responders to CA is necessary. Surface electrocardiography (sECG)-based complexity parameters were tested for the predictive ability of procedural termination failure during CA and late recurrence of atrial arrhythmias (AA) after CA. A total of 130 patients with nonparoxysmal AF who underwent CA for the first time were investigated. A 10-second sECG of 4 leads (leads I, II, V₁, and V₆) was analyzed to compute the fibrillatory wave amplitude (FWA), dominant frequency (DF), spectral entropy (SE), organization index (OI), and sample entropy (SampEn). The study endpoints were procedural termination failure during CA and late (≥1 year) AA recurrence after CA. In the multivariate analysis, FWA in lead V₁ and DF in lead I were independent predictors of successful AF termination during CA ($P < .05$). The optimal cut-off values for FWA in lead V₁ and DF in lead I were 60.38 μ V (area under the curve [AUC], 0.672; $P = .001$) and 5.7 Hz (AUC, 0.630; $P = .016$), respectively. The combination of FWA of lead V₁ and DF of lead I had a more powerful odds ratio for predicting procedural termination failure (OR, 8.542; 95% CI, 2.938–28.834; $P < .001$). FWA in lead V₁ was the only independent predictor of late recurrence after CA. The cut-off value is 65.73 μ V which was 0.634 of the AUC ($P = .009$).

These sECG parameters, FWA in lead V₁ and DF in lead I, predicted AF termination by CA in patients with nonparoxysmal AF. In particular, FWA in lead V₁ was an independent predictor of late recurrence of AA after CA.

Abbreviations: AA = atrial arrhythmia, AF = atrial fibrillation, AUC = area under the curve, CA = catheter ablation, CFAE = complex fragmented atrial electrogram, DF = dominant frequency, ESAF = event synchronous adaptive filter, FWA = fibrillatory wave amplitude, LA = left atrium, OI = organization index, PVI = pulmonary vein isolation, ROC = receiver operating characteristic, SampEn = sample entropy, SE = spectral entropy, sECG = surface electrocardiography

Keywords: nonparoxysmal atrial fibrillation, radiofrequency catheter ablation, 12-lead ECG, complexity analysis

1. Introduction

Although radiofrequency catheter ablation (CA) is a well-established therapy used to achieve rhythm control in atrial fibrillation (AF), its outcomes for persistent AF, especially long-standing AF, are unsatisfactory despite the use of up-to-date ablation technology.^[1,2] This is because recurrence rates remain high and serious complications can still occur despite time-consuming efforts.^[3,4] Therefore, it is important to identify good responders to CA to ensure better outcomes and avoid unnecessary procedural risks.

Numerous predictors based on AF type, clinical risk factors, imaging, circulating biomarkers, genetic predictors, and

electrocardiographic and electrophysiological parameters have been studied to aid in the identification of patients with AF for a high probability of ablation success.^[5,6] Several scoring systems based purely on clinical parameters have been developed to predict AF recurrence after CA. However, these multivariable scoring systems remain modestly accurate and lack successful implementation in clinical settings.^[7]

Surface electrocardiography (sECG), an easily accessible, noninvasive test used to detect AF, provides key information regarding the integrity and electrophysiological properties of the atrial myocardium.^[8,9] Accordingly, fibrillatory waves on sECG are surrogate markers that represent the atrial electrical and structural status related to AF remodeling.

JIP, S-WP, and M-JK contributed equally to this work.

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Metrics for characterizing fibrillatory electrical activity have focused on quantifying the degree of organization using AF cycle length,^[10–13] dominant frequency (DF),^[14,15] f-wave amplitude (FWA),^[14,16,17] organization index (OI), and related spectral features.^[14,18] Although some of these parameters have been reported to predict arrhythmia recurrence after AF ablation, a single parameter was evaluated in most studies and the results were inconsistent. Therefore, this study aimed to compare the efficacy of various sECG-based complexity parameters in predicting both procedural termination failure and long-term recurrence of nonparoxysmal AF.

2. Materials and Methods

2.1. Study patients

This study enrolled 153 consecutive patients with nonparoxysmal drug-refractory AF who underwent their first CA between March 2018 and March 2020. After excluding 19 patients with corrupted ECG signals and 4 lost to follow-up, 130 patients were ultimately analyzed (Fig. 1). The study protocol was approved by the institutional review board of Yeungnam University Hospital (IRB No.:2021-04-022). The requirement for informed consent was waived because of the retrospective nature of the study. The study complied with the principles of the Declaration of Helsinki.

2.2. sECG analysis and data processing

All the patients had AF when they entered the electrophysiology laboratory. Each 12-lead sECG was collected using an EP Workmate system (EP WorkMate™ System, Abbott, St. Paul, MN, USA) at a sampling rate of 2 kHz for at least 60 seconds before the CA. A 60-second 12-lead ECG recording was exported for later analysis, from which a 10-second ECG epoch was selected for the primary analysis. Among the 12 leads of the conventional ECG, the tracings of 4 lead sets (leads I, II, V₁, and V₆), which are known to reflect localized right and left atrial activity and show optimal prediction performances, were selected for ECG analysis.^[19–21] To extract an atrial activity signal from each of the leads, an event synchronous adaptive filter (ESAF)-based method previously developed by the authors was used.^[22] In detail, a wavelet filter, of which passing bandwidth corresponds

to approximately 1–32 Hz, was applied to reject motion artifacts and power-line interference. Then, R peaks were detected from the filtered lead signal and those were converted into an impulse train signal, of which impulses are synchronized with the R peaks. The filtered lead and the impulse train signals were fed to the ESAF as a primary input and a reference signal, respectively. Finally, as an output of the ESAF, a ventricular activity canceled atrial activity signal was obtained. This atrial activity signal was used for further analysis. The DF (expressed in Hertz),^[23] OI,^[24] spectral entropy (SE)^[24] for the frequency domain analysis, sample entropy (SampEn),^[25] and FWA^[11] were computed for the time-domain analysis. The computational formula for each parameter has been described elsewhere.^[23–26] All computations were performed using custom-made software (developed by J Lee) in MATLAB (Mathworks Inc., Natick, MA, USA).

2.3. CA protocol

Our routine approach for AF ablation has been previously described.^[26] Briefly, left atrial (LA) geometry was acquired using a spiral mapping catheter (IBI Inquiry Optima, St. Jude Medical, Inc., St. Paul, MN, USA) in combination with the EnSite NavX™ system (Endocardial Solutions). A TactiCath™ contact force ablation catheter (St. Jude Medical, Inc.) was used in all cases. Wide circumferential pulmonary vein isolation (PVI) across the ipsilateral pulmonary veins was performed, and PVI was confirmed by the loss of pulmonary vein potentials (entry block) and failure to capture the LA during pacing from all bipoles of the circular ring catheter (output: 10 mA; pulse width: 2 ms; exit block). Power-controlled RF energy was delivered at 25–35 W for 20–40 seconds for each lesion. Lower power (20–25 W) and duration settings were used for ablation of the posterior LA wall close to the esophagus. After PVI, if AF persisted, then a 3D-electroanatomical LA complex fragmented atrial electrogram (CFAE) map was constructed using an Advisor™ HD Grid mapping catheter (Abbott). CFAE was ablated in the LA until complete elimination of the fractionated atrial electrograms.

A CFAE was identified when the mean fractionation interval was <120 ms in the following settings: 6-second-long acquisition with a 50-ms refractory period (width, 10 ms; sensitivity, 0.5–1.0 mV).^[27] After CFAE ablation, if patients remained in AF, the sinus rhythm was restored by cardioversion.

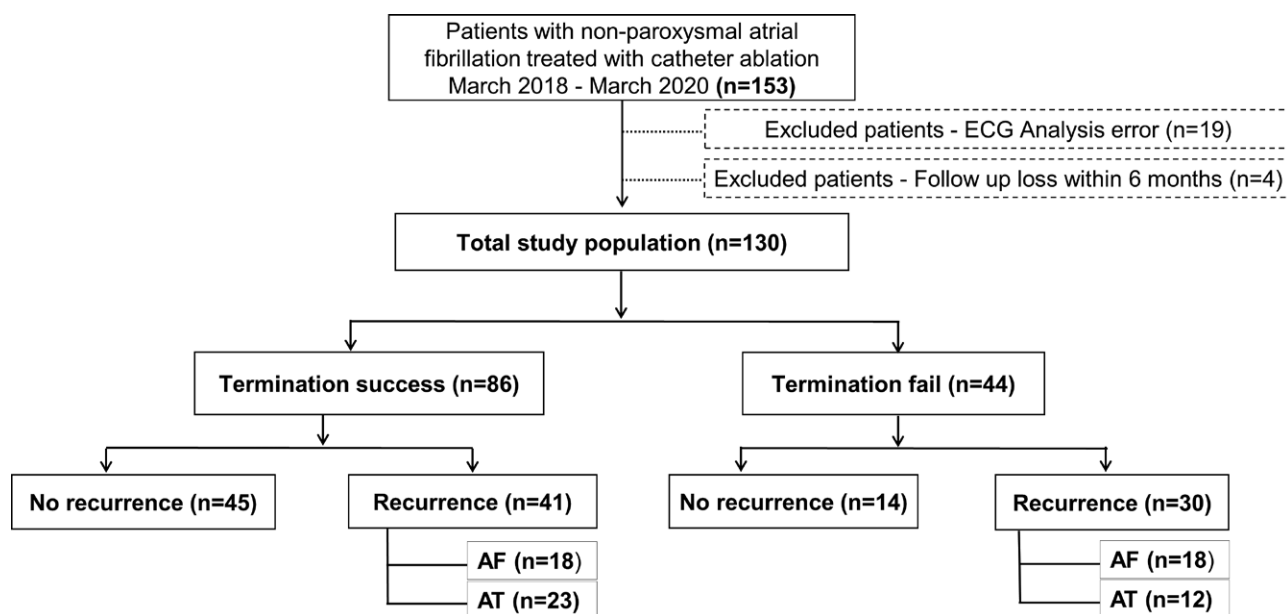


Figure 1. Study population selection process. AF = atrial fibrillation, AT = atrial tachycardia, ECG = electrocardiogram.

2.4. Study endpoints

The study endpoints were AF termination during ablation and recurrence 1 year after ablation in patients with nonparoxysmal AF. AF termination was defined as the conversion of AF to atrial tachycardia, atrial flutter, or sinus rhythm. An attempt was made to map and ablate all mappable atrial tachyarrhythmias when the AF was organized into atrial tachycardia or atrial flutter. Recurrence at 1 year was defined as symptomatic or asymptomatic atrial arrhythmia (AF, atrial flutter, or atrial tachycardia) lasting > 30 seconds documented on sECG, Holter monitor, or event recorder after 3 months of ablation procedure without antiarrhythmic use.

2.5 Postablation management and follow-up

Outpatient visits were made 1 week after discharge and then every 1 or 2 months thereafter. Standard sECG was performed at each visit, and the patient's symptoms were checked. Holter monitoring was performed when symptoms were present; otherwise, the subjects underwent Holter monitoring every three months from the end of the blanking period.

2.6. Echocardiographic examination

All echocardiographic measurements were performed according to the American Society of Echocardiography recommendations. The left ventricular ejection fraction (LVEF) was examined using Simpson's method. We measured LA dimensions as the antero-posterior diameter in the parasternal long-axis view. We measured the LA volume by the prolate ellipse method using apical 4-chamber and parasternal long-axis views at ventricular end-systole.^[28] The LA volume index was calculated as the LA volume corrected by body surface area. Right ventricular systolic pressure (RVSP) was measured as the sum of the trans-tricuspid gradient and estimated right atrial pressure. The trans-tricuspid gradient was estimated using the modified Bernoulli equation: $P = 4 \times V^2$, where V is the peak tricuspid regurgitation velocity in m/s. The right atrial pressure was estimated using the caval respiratory index.^[29]

2.7 Statistical methods

Data are expressed as a number (%) for categorical variables and as mean \pm standard deviation or median and interquartile range (25th–75th) for continuous variables. We checked the distribution normality of continuous variables using the Kolmogorov–Smirnov test. If data normality was proven, these variables were analyzed using parametric Student's t -test. Nonnormally distributed data were examined using the nonparametric Mann–Whitney U -test. Categorical data were compared using the chi-squared test or Fisher's exact test. Next, a logistic regression model was applied for variables with P values <.05 in the univariate analysis, and the odds ratio (OR) was calculated to find independent predictors of success during and after the procedure. For each sECG parameter that showed a significant intergroup difference, receiver operating characteristic curves were computed to obtain cut-off values for optimal sensitivity and specificity. The area under the curve (AUC) was calculated using a prediction performance index. Statistical analyses were performed using IBM SPSS version 22.0 (IBM Corp., Armonk, NY, USA). Statistical significance was set at $P < .05$.

3. Results

3.1. Patients' characteristics

The mean age was 60 ± 10 years (female, 16.9%). Patients who had prior ablation, prior cardiac surgery, valvular heart diseases or implantable cardiac devices and were older than 80 years were

excluded. The median AF duration was 23 (5–64) months. The mean follow-up duration was 16 ± 8 months. The CHADS2VASc score was 2.36 ± 1.29 . Long-standing persistent AF was observed in 80 patients (62%). The clinical characteristics of all study patients and differences in the characteristics according to end-points are summarized in Table 1. The demographic variables, AF duration, frequency of long-standing AF and comorbid diseases were similar between the groups, regardless of whether AF was terminated during the procedure. The patients in whom AF was terminated during the procedure were more likely to have a smaller LA AP diameter (41.5 ± 5.1 mm vs. 46.5 ± 4.9 mm), LA volume (59.9 ± 17.8 mL vs. 80.2 ± 24.8 mL), LAVI (33.2 ± 10.0 vs. 43.0 ± 12.7), LA CT volume (139.0 ± 34.4 mL vs. 173.2 ± 44.7 mL) than those of not terminated patients ($P < .001$ for all). No differences in the demographic variables, AF duration, frequency of long-standing AF and comorbid diseases, and LA size were found between groups according to late recurrence.

3.2 sECG-based complexity parameters

The sECG parameters according to the study end-points are summarized in Table 2. In patients in whom AF was terminated during the procedure, the FWA in lead V_1 was significantly larger (75.47 ± 26.18 vs. 64.76 ± 29.79 , $P = .038$), and the DF of lead I (5.549 ± 1.011 vs. 6.036 ± 1.057 , $P = .012$) and lead II (5.505 ± 0.918 vs. 5.886 ± 0.992 , $P = .031$) were significantly smaller than those of patients in whom AF was not terminated. The SE of lead II was lower (3.009 ± 0.579 vs. 3.277 ± 0.482 , $P = .006$) in patients in whom AF was terminated. As a predictor of late recurrence, the FWA of lead V_1 was larger (77.96 ± 27.51 vs. 66.80 ± 27.24 , $P = .023$), and the SE of lead V_1 was smaller (2.625 ± 0.706 vs. 2.925 ± 0.721 , $P = .032$) in patients with no recurrence of AF did not recur. No differences were found in other sECG parameters. Table 3 shows the results of univariate and multivariate analyses for predicting procedural termination failure or late recurrence (bad outcomes). In the univariate analysis of procedural termination failure, LA CT volume, FWA in lead V_1 , DF in lead I, DF in lead II and SE in lead II were statistically significant (all, $P < .05$). In the univariate analysis of late recurrence, the FWA in lead V_1 ($P = .027$) and SE in lead V_1 ($P = .040$) were statistically significant. Multivariate analysis revealed that, LA CT volume (OR, 1.029; 95% CI, 1.015–1.043; $P < .001$) was an independent predictor of procedural termination failure during CA. Among the sECG parameters, FWA in lead V_1 (OR, 0.981; 95% CI, 0.964–0.999; $P = .034$) and DF in lead I (OR, 2.037; 95% CI, 1.297–3.197; $P = .002$) were powerful predictors of procedural termination failure. A low FWA in lead V_1 or a high DF in lead I predicted procedural termination failure. For the prediction of late recurrence, FWA in lead V_1 was the only independent predictor of late recurrence of AF after CA (OR, 0.985; 95% CI, 0.972–0.998; $P = .027$). A low FWA in lead V_1 predicted late recurrence of AF after CA.

3.3. Optimal cut-off value for predicting procedural termination failure and recurrence after CA

Figure 2 shows the receiver operating characteristic (ROC) curves for the optimal cut-off values that predict procedural termination failure and late recurrence after CA (bad outcomes). The AUC for predicting AF termination during CA was 0.672 for the FWA in lead V_1 and 0.630 for the DF in lead I. When the cut-off value of the FWA in lead V_1 was 60.38 μ V, the sensitivity and specificity were 70.6% and 63.6%, respectively (95% CI, 0.569–0.775, $P = .001$). When the cut-off value of the DF in lead I was 5.70 Hz, the sensitivity and specificity were 59.1% and 51.2%, respectively (95% CI, 0.530–0.729, $P = .016$). The AUC for predicting late AF recurrence of FWA in lead V_1 was 0.634 and the cut-off value was 65.73 μ V. Sensitivity and specificity were 69.0% and 62.0%, respectively.

Table 1**Clinical characteristics of the study patients, and difference of characteristics according to the end-points.**

Variable	Overall population (n = 130)	Procedural termination (n = 130)			Late recurrence (n = 130)		
		Yes (n = 86)	No (n = 44)	P value	No (n = 59)	Yes (n = 71)	P value
Clinical parameter							
Age (y)	59.7 ± 9.6	60.8 ± 10.0	57.6 ± 9.3	.081	60.6 ± 10.9	59.0 ± 8.5	.356
Female	22 (16.9)	18 (13.8)	4 (3.1)	.137	11 (18.6)	11 (15.5)	.403
BMI (kg/m ²)	26.1 ± 3.4	25.8 ± 3.1	26.7 ± 3.7	.151	26.3 ± 3.6	25.8 ± 3.1	.324
Long standing persistent AF duration (mo)	80 (61.5)	54 (41.5)	26 (20.0)	.411	33 (55.9)	47 (66.2)	.155
Hypertension	23.0 (5.0–64.0)	23.0 (6.5–61.0)	20.0 (4.0–72.0)	.890	16.0 (5–51.5)	25.5 (5.5–67.5)	.390
Diabetes	70 (50.8)	42 (32.3)	28 (21.5)	.138	35 (59.3)	35 (49.3)	.167
Congestive heart failure	26 (20.0)	17 (13.1)	9 (6.9)	.549	14 (23.7)	12 (16.9)	.227
Vascular disease	55 (42.3)	35 (26.9)	20 (15.4)	.369	25 (42.4)	30 (42.3)	.565
Stroke	29 (22.3)	21 (16.2)	8 (6.2)	.282	16 (27.1)	13 (18.3)	.161
CHADS ₂ VASc score	30 (23.1)	17 (13.1)	13 (10.0)	.151	11 (18.6)	19 (26.8)	.189
Echocardiographic parameter	2.36 ± 1.29	2.40 ± 1.37	2.30 ± 1.13	.660	2.54 ± 1.39	2.21 ± 1.19	.147
LVEF	57.6 ± 8.5	57.6 ± 8.4	57.6 ± 8.8	.964	57.2 ± 8.8	58.0 ± 8.3	.588
LA AP diameter (mm)	43.2 ± 5.6	41.5 ± 5.1	46.5 ± 4.9	<.001	42.9 ± 5.3	43.5 ± 5.8	.532
LA volume (mL)	62.7 ± 22.5	59.9 ± 17.8	80.2 ± 24.8	<.001	65.4 ± 21.0	67.9 ± 23.8	.523
LAVI (mL/m ²)	36.5 ± 11.9	33.2 ± 10.0	43.0 ± 12.7	<.001	36.0 ± 10.9	37.0 ± 12.7	.617
RVSP (mmHg)	25.7 ± 10.5	28.6 ± 6.7	31.3 ± 8.8	.063	25.5 ± 12.0	25.8 ± 9.3	.875
3D CT findings							
LA CT volume (mL)	150.7 ± 41.4	139.0 ± 34.4	173.2 ± 44.7	<.001	148.8 ± 39.4	152.2 ± 43.2	.641
Catheter ablation strategy							
CFAE	93 (71.5)	52 (60.5)	41 (93.2)	<.001	39 (66.1)	54 (76.1)	.244

Values are presented as mean ± standard deviation or number (%).

AF = atrial fibrillation, BMI = body mass index, CT = computed tomography, LA = left atrium, LA AP = left atrial anteroposterior, LAVI = left atrial volume index, LVEF = left ventricular ejection fraction, RVSP = right ventricular systolic pressure, CFAE = complex fractionated atrial electrogram.

Table 2**Surface electrocardiography parameters according to the end-points.**

Variable	Overall population (n = 130)	Procedural termination (n = 130)			Late recurrence (n = 130)		
		Yes (n = 86)	No (n = 44)	P value	No (n = 59)	Yes (n = 71)	P value
f wave amplitude (μV)							
Lead I	44.54 ± 16.38	44.93 ± 16.08	44.78 ± 17.10	.706	45.34 ± 16.91	43.87 ± 16.01	.613
Lead II	65.58 ± 22.18	68.28 ± 22.30	60.30 ± 21.21	.052	69.57 ± 24.46	62.26 ± 19.66	.061
Lead V1	71.82 ± 27.82	75.47 ± 26.18	64.76 ± 29.79	.038	77.96 ± 27.51	66.80 ± 27.24	.023
Lead V6	57.34 ± 25.91	56.50 ± 21.38	58.97 ± 33.26	.609	59.42 ± 21.33	55.60 ± 29.21	.405
Dominant frequency (Hz)							
Lead I	5.714 ± 1.049	5.549 ± 1.011	6.036 ± 1.057	.012	5.563 ± 1.057	5.839 ± 1.032	0.135
Lead II	5.634 ± 0.957	5.505 ± 0.918	5.886 ± 0.992	.031	5.471 ± 0.830	5.769 ± 1.038	.077
Lead V1	5.852 ± 1.211	5.793 ± 1.316	5.968 ± 0.998	.602	5.810 ± 1.185	5.969 ± 1.027	.417
Lead V6	5.585 ± 1.264	5.551 ± 1.248	5.650 ± 1.305	.293	5.542 ± 0.970	5.620 ± 1.470	.447
Organization index							
Lead I	0.698 ± 0.109	0.707 ± 0.115	0.679 ± 0.092	.170	0.705 ± 0.118	0.692 ± 0.101	.540
Lead II	0.705 ± 0.089	0.708 ± 0.082	0.698 ± 0.102	.574	0.694 ± 0.076	0.713 ± 0.098	.232
Lead V1	0.752 ± 0.128	0.754 ± 0.141	0.748 ± 0.099	.482	0.733 ± 0.141	0.768 ± 0.116	.257
Lead V6	0.712 ± 0.102	0.718 ± 0.102	0.702 ± 0.101	.388	0.730 ± 0.108	0.699 ± 0.095	.091
Spectral entropy							
Lead I	3.292 ± 0.507	3.281 ± 0.506	3.314 ± 0.514	.724	3.303 ± 0.529	3.267 ± 0.455	.701
Lead II	3.100 ± 0.561	3.009 ± 0.579	3.277 ± 0.482	.006	3.104 ± 0.562	3.091 ± 0.566	.904
Lead V1	2.715 ± 0.721	2.649 ± 0.754	2.844 ± 0.640	.125	2.625 ± 0.706	2.925 ± 0.721	.032
Lead V6	3.277 ± 0.519	3.274 ± 0.556	3.381 ± 0.426	.078	3.274 ± 0.536	3.285 ± 0.486	.910
Sample entropy							
Lead I	0.127 ± 0.016	0.127 ± 0.015	0.129 ± 0.018	.401	0.127 ± 0.015	0.128 ± 0.017	.884
Lead II	0.124 ± 0.013	0.123 ± 0.014	0.125 ± 0.013	.448	0.122 ± 0.013	0.125 ± 0.013	.261
Lead V1	0.125 ± 0.018	0.123 ± 0.019	0.129 ± 0.012	.052	0.122 ± 0.021	0.127 ± 0.013	.201
Lead V6	0.118 ± 0.016	0.119 ± 0.016	0.117 ± 0.015	.582	0.117 ± 0.015	0.119 ± 0.016	.542

3.4. Combination of FWA in lead V₁ and DF in lead I had higher predictive value for AF termination during CA

Table 4 shows that the combination of a lower FWA in lead V₁ (< 60.38 μV) and a higher DF in lead I (> 5.7 Hz) had a

more powerful odds ratio for predicting procedural termination failure (OR, 8.542; 95% CI, 2.938–24.834; *P* < .001) than a lower FWA in lead V₁ (< 60.38 μV; OR, 4.919; 95% CI, 2.020–11.983; *P* < .001) or a higher DF in lead I (> 5.7 Hz; OR, 3.099; 95% CI, 1.217–7.890; *P* = .018) alone.

Table 3
Multivariate logistic regression analysis for prediction of procedural termination failure or late recurrence.

Variable	Univariate analysis		Multivariate analysis (Model I)	
	OR (95% CI)	P value	OR (95% CI)	P value
Procedural termination failure				
LA CT volume(mL)	1.024 (1.012–1.036)	<.001	1.027 (1.014–1.041)	<.001
FWA V ₁ (μV)	0.985 (0.970–0.985)	.042	0.981 (0.964–0.999)	.034
DF I (Hz)	1.582 (1.097–2.281)	.014	2.032 (1.300–3.177)	.002
DF II (Hz)	1.538 (1.035–2.285)	.033	1.357 (0.810–2.274)	.246
SE II	2.532 (1.232–5.205)	.011	2.129 (0.949–4.778)	.067
Late recurrence				
FWA V ₁ (μV)	0.985 (0.972–0.998)	.027	0.985 (0.972–0.998)	.027
SE V ₁	1.842 (1.027–3.305)	.040	1.041 (0.618–1.753)	.880

CI = confidence interval, CT = computed tomography, DF = dominant frequency, FWA = fibrillatory wave amplitude, LA = left atrium, OR = odds ratio, SE = spectral entropy.

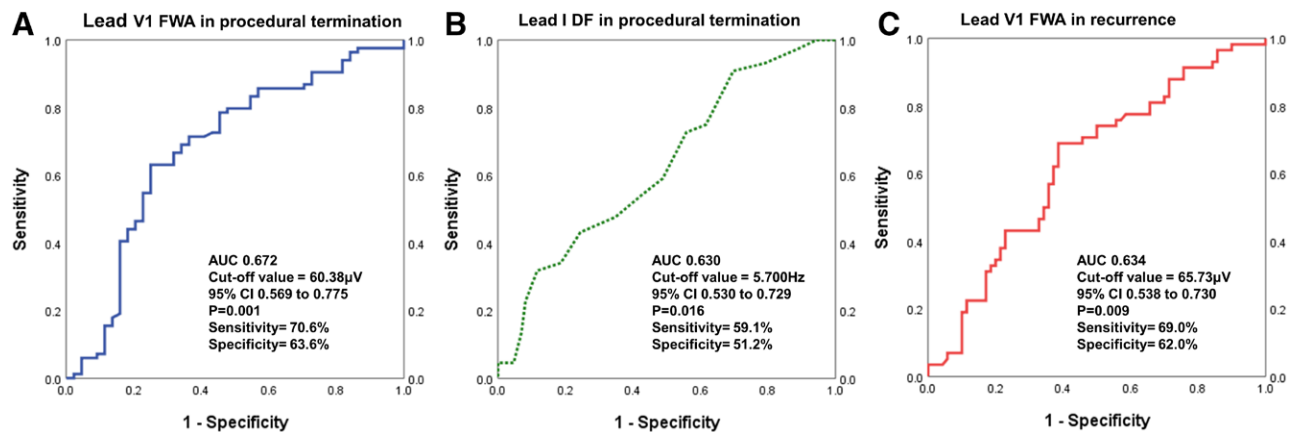


Figure 2. Receiver operating characteristic curve of FWA in lead V₁ and DF in lead I according to the outcomes of CA. ROC curve of lead V₁ FWA (A) and lead I DF (B) for procedural termination failure, and lead V₁ FWA for late recurrence (C). The area under the curve (AUC), cut-off value, P-value, 95% confidence interval (CI), sensitivity, and specificity of each parameter are shown. CA = catheter ablation, DF = dominant frequency, FWA = fibrillatory wave amplitude.

Table 4
Multivariate analysis of the cut-off value depending on the surface electrocardiography parameters in procedural termination failure.

Variable	Multivariate analysis (Model II)		Multivariate analysis (Model III)	
	OR (95% CI)	P value	OR (95% CI)	P value
Procedural termination failure				
LA CT volume(mL)	1.029 (1.015–1.044)	<.001	1.030 (1.016–1.044)	<.001
Low FWA V ₁ (< 60.38 μV)	4.919 (2.020–11.983)	<.001		
High DF I (> 5.700 Hz)	3.099 (1.217–7.890)	.018		
Combination of low FWA V ₁ and high DF I			8.542 (2.938–24.834)	<.001

AF = atrial fibrillation, CI = confidence interval, CT = computed tomography, DF = dominant frequency, FWA = fibrillatory wave amplitude, LA = left atrium, OR = odds ratio.

4. Discussion

The main findings of the present study were that sECG-based complexity parameters are useful for predicting procedural termination failure of AF and late recurrence of atrial arrhythmias (bad outcomes) after CA for nonparoxysmal AF. In particular, FWA in lead V₁ is a powerful independent predictor of both procedural termination failure and late recurrence. DF in lead I was also an independent parameter for predicting procedural termination failure during CA. The combination of the FWA of lead V₁ (< 60.38 μV) and the DF of lead I (> 5.70 Hz) was 8.54 times more likely to predict failure of AF termination during CA. In the present study, LA CT volume was the only parameter, except for sECG, that predicted procedural termination failure during CA. Previous studies have shown a statistically significant relationship between CA success and LA size.^[30,31]

4.1. sECG-based complexity parameters as predictors of CA outcome

The clinical risk prediction of AF recurrence in patients who have undergone CA is limited.^[7] The standard 12-lead ECG is an attractive method for the assessment of AF complexity level because it is an easily accessible, noninvasive test. Recently, many complexity parameters derived from the 12-lead ECG, such as the AF cycle length,^[10,12,13] FWA^[11,14,16,17,32] DF^[14,15,23,33,34] OI,^[14,24,32] SE,^[14,24] and SampEn^[14,25,32] have been proposed. Although several parameters showed encouraging results in predicting treatment outcomes, the results were not consistent.^[32] A single parameter has been tested in most previous studies. In the present study, we adopted five parameters (FWA and SampEn for the time-domain analysis, and DF, OI, and SE for the frequency domain analysis of fibrillatory waves) and compared them.

Several studies have demonstrated that the FWA is a predictor of procedural termination failure and AF recurrence.^[11,14,16,17] Maximal amplitude of ≥ 0.07 mV in V_1 /lead II predicted AF termination by ablation and patients with FWA < 0.05 mV in lead V_1 had higher AF recurrence.^[11] This cutoff value is similar to the FWA cutoff value (< 60.38 μ V) proposed.^[11,16] We showed that the FWA of lead V_1 was a powerful independent predictor of both procedural termination failure and late recurrence. Procedural termination failure during CA is a prognostically important endpoint of CA for nonparoxysmal AF.^[10,35,36]

Regarding the predictive efficacy of DF, patients with a high DF in lead aVL (DF ≥ 6.9 Hz) and V_1 DF of ≥ 7.1 Hz showed a lower success rate of persistent AF ablation.^[33] In another study, the best electrographic predictor of AF termination was DFs in the left atrial appendage (DF < 6.5 Hz) and lead II (DF < 5.9 Hz).^[34] Likewise, the DF of lead I (< 5.7 Hz) was an independent parameter for predicting procedural termination failure during CA in our study. Taken together, patients with a lower FWA of lead V_1 (< 60.38 μ V) and/or higher DF of lead I (> 5.7 Hz) would have a lower AF termination rate and higher late recurrence rate. FWA was the best predictor of the outcome.

4.2. Optimal sECG lead for prediction of CA outcome

The lead that showed the best predictive value was different depending on the study, in which it was lead I in one study,^[16] lead aVF and V_6 in another study,^[14] or lead V_1 ^[11,17] as in our study. The role of lead V_1 FWA in predicting CA outcomes is challenging to determine. Fibrillatory waves of sECG lead V_1 closely reflect the right atrium and, to a lesser degree, the left atrial activity.^[37] On surface ECG, the amplitude of fibrillatory waves is dependent on the magnitude of the underlying voltage, which is related to the magnitude of the remaining viable atrial muscle.^[17] Patients with permanent AF had a greater extent of fibrosis than those with paroxysmal AF.^[38] The structural remodeling of atrial fibrosis theoretically leads to a decrease in muscle fiber activation, which affects the FWA voltage.^[39,40] Therefore, lower FWA in lead V_1 implies a reduction in right atrial voltage with increased low voltage areas as a result of advanced structural remodeling with progression of AF.

The efficacy of sECG-based parameters in predicting treatment outcomes was not consistent. DF, OI, SampEn, and FWA were not able to predict arrhythmia recurrence following ablation in a previous study.^[32] This might be due to the different ablation techniques, strategies, and compositions of the study patients. In this study, SE, SampEn, and OI showed no ability to predict procedural termination failure or arrhythmia recurrence after CA.

4.3. Clinical implications

To date, the selection of patients with nonparoxysmal AF who benefited from CA has been at the physician's discretion. As a noninvasive tool, sECG is being used by physicians to easily treat and evaluate AF patients in real-world practice. These sECG-based complexity parameters from the results of this study can identify patients who are likely to benefit from CA. Among these, FWA was the most powerful sECG-derived predictor. This study proposes the quantitative cut-off value of FWA in lead V_1 (procedural termination failure: 60.38 μ V, late recurrence: 65.73 μ V) and DF in lead I (procedural termination failure: 5.70 Hz) for selecting patients who benefited from CA by predicting procedural termination failure. This can help physicians decide whether to recommend CA to patients with nonparoxysmal AF. AF complexity parameters quantified from sECG can be employed in a clinical setting to predict treatment outcomes and ultimately guide AF management.

The incorporation of artificial intelligence and machine learning technology into AF management in the future would facilitate the selection of nonparoxysmal AF patients who benefit most from CA, the assessment of procedure-related risk, specific ablation target selection, and prediction of ablation outcomes in AF. Overall, this would lead to an improvement in patient-tailored CA procedures for treating nonparoxysmal AF.

4.4. Limitations

In this study, CFAE ablation was used as adjunctive ablation after PVI. CA outcomes, such as AF termination or long-term recurrence, will vary depending on which technique among CFAE ablation or additional linear lesions as adjunctive ablation strategy after PVI is used. The outcomes would also differ depending on electrophysiology laboratory staff experience and proficiency. Since the cut-off values of FWA and DF are determined by the ablation success rate, the cutoff values may vary. For these reasons, this is a major limitation of this study. Second, owing to the small sample size of a single center and relatively short follow-up period, our findings should be validated in a large prospective multicenter cohort study prior to their application in clinical practice. Third, we selected only four leads (I, II, V_1 , and V_6) among the 12 ECG leads for analysis; therefore, we might have missed the optimal lead with better predictability. Simultaneous analysis of the FWA in several ECG leads may improve CA long-term outcome prediction in persistent AF compared with predictors based on a single lead.^[16] The combination of clinical parameters and/or the best-predicting ECG parameters will further improve the prediction performance.

5. Conclusion

Noninvasive sECG-based complexity parameters, especially FWA in lead V_1 and DF in lead I, are effective for prediction of the procedural termination failure of AF by a single-time CA and long-term recurrence of atrial arrhythmias in patients with nonparoxysmal AF.

Author contributions

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