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CLINICAL RESEARCH

Non-invasive prediction of catheter ablation outcome in persistent atrial fibrillation by fibrillatory wave amplitude computation in multiple electrocardiogram leads



Prédiction non invasive du suivi au décours d'une ablation par cathéter d'une fibrillation atriale persistante par l'analyse informatisée de l'amplitude des ondes de fibrillation atriale sur un tracé ECG à multiples dérivations

Vicente Zarzoso^{a,*}, Decebal G. Latcu^b,
Antonio R. Hidalgo-Muñoz^a, Marianna Meo^c,
Olivier Meste^a, Irina Popescu^b, Nadir Saudi^b

^a I3S Laboratory, University of Nice Sophia Antipolis, CNRS, Sophia-Antipolis, France

^b Cardiology Department, Princess Grace Hospital, Monaco

^c Electrophysiology and Heart Modelling Institute (IHU LIRYC), Bordeaux, France

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KEYWORDS

Atrial fibrillation;
Catheter ablation;
Electrocardiography;
Fibrillatory wave
amplitude;
Therapy outcome
prediction

Summary

Background. – Catheter ablation (CA) of persistent atrial fibrillation (AF) is challenging, and reported results are capable of improvement. A better patient selection for the procedure could enhance its success rate while avoiding the risks associated with ablation, especially for patients with low odds of favorable outcome. CA outcome can be predicted non-invasively by atrial fibrillatory wave (f-wave) amplitude, but previous works focused mostly on manual measures in single electrocardiogram (ECG) leads only.

Aim. – To assess the long-term prediction ability of f-wave amplitude when computed in multiple ECG leads.

Abbreviations: AF, atrial fibrillation; AUC, area under the receiver operating characteristic curve; CA, catheter ablation; CFAE, complex fractionated atrial electrogram; ECG, electrocardiogram; EGM, electrogram; LA, left atrium; LR, logistic regression; PV, pulmonary vein; ROC, receiver operating characteristic.

* Corresponding author. I3S Laboratory, UNS, CNRS, 2000, routes des Lucioles, CS 40121, 06903 Sophia Antipolis cedex, France.

E-mail address: zarzoso@i3s.unice.fr (V. Zarzoso).

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Methods. — Sixty-two patients with persistent AF (52 men; mean age 61.5 ± 10.4 years) referred for CA were enrolled. A standard 1-minute 12-lead ECG was acquired before the ablation procedure for each patient. F-wave amplitudes in different ECG leads were computed by a non-invasive signal processing algorithm, and combined into a multivariate prediction model based on logistic regression.

Results. — During an average follow-up of 13.9 ± 8.3 months, 47 patients had no AF recurrence after ablation. A lead selection approach relying on the Wald index pointed to I, V1, V2 and V5 as the most relevant ECG leads to predict jointly CA outcome using f-wave amplitudes, reaching an area under the curve of 0.854, and improving on single-lead amplitude-based predictors.

Conclusion. — Analysing the f-wave amplitude in several ECG leads simultaneously can significantly improve CA long-term outcome prediction in persistent AF compared with predictors based on single-lead measures.

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MOTS CLÉS

Fibrillation atriale ;
Ablation par cathéter ;
Électrocardiographie ;
Amplitude des ondes de fibrillation atriale ;
Prédiction du suivi

Résumé

Contexte. — L'ablation par cathéter de la fibrillation atriale (FA) persistante demeure un problème difficile et les résultats rapportés sont perfectibles. L'affinement de la sélection des patients pour cette procédure pourrait améliorer le taux de succès en évitant les risques liés à la procédure, notamment chez les patients à faible probabilité de réussite. Le suivi au décours d'une ablation par cathéter peut être prédit de façon non invasive par l'analyse de l'amplitude des ondes de FA mais des travaux précédents se sont focalisés principalement sur des mesures manuelles sur une seule dérivation électrocardiographique (ECG).

Objectifs. — Ce travail évalue la prédiction à long terme du succès d'une ablation par cathéter d'une FA par analyse numérique de l'amplitude des ondes de FA sur des dérivations ECG multiples.

Méthode et résultats. — Soixante-deux patients présentant une FA persistante ont été inclus, 52 hommes, d'âge moyen $61,5 \pm 10,4$ ans. Pendant un suivi moyen de 14 ± 8 mois, 47 patients n'ont pas présenté de récurrence de FA au décours de cette procédure. Un ECG standard a été acquis avant la procédure chez chaque patient. L'amplitude des ondes de FA sur différentes dérivations ECG a été numérisée et un algorithme non invasif utilisé, permettant d'établir un modèle multivarié à partir d'une analyse par régression logistique. Une analyse basée sur l'index de Wald sur les dérivations D1, V1, V2 et V5 permet de prédire au mieux le succès d'une ablation par cathéter à partir de l'amplitude des ondes de FA, fournissant une surface sous la courbe ROC à 0,854, améliorant donc la performance d'une prédiction basée sur l'analyse d'une seule dérivation ECG.

Conclusion. — L'analyse de l'amplitude des ondes de FA sur plusieurs dérivations ECG peut améliorer de façon significative la prédiction du succès d'une ablation par cathéter chez des patients souffrant d'une FA persistante.

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Background

Atrial fibrillation (AF) is the most common sustained arrhythmia encountered in clinical practice [1]. Radiofrequency catheter ablation (CA) of persistent AF is a well-established therapy, with proven efficacy in maintaining sinus rhythm during follow-up [2]. Despite recent significant progress, CA for this form of AF yields less than perfect results, as it remains a costly, time-consuming intervention, with risk of complications for the patient. Hence, accurate selection of long-term responders to CA is crucial for improved patient-tailored management of this cardiac condition.

The patient characteristics that correlate most to CA outcome are unclear [3–5]. The atrial fibrillatory waves (f-waves) observed in the surface electrocardiogram (ECG) reflect the electrical behaviour of the atria in a non-invasive fashion, and their analysis in time [6,7] or frequency domains [8,9], or using more elaborate complexity indices [10], has been shown to correlate with CA outcome. In previous studies, f-wave amplitude has been measured manually in single leads separately (such as II, aVF or V1), thus neglecting information from the remaining leads that may be relevant for AF characterization. Indeed, the link between f-wave amplitude and long-term outcome has not

been clearly established [7] or has been demonstrated with limited accuracy only [6].

To overcome these drawbacks, the present study analysed whether the consideration of multiple ECG leads simultaneously could improve CA long-term outcome prediction based on automated f-wave amplitude measures.

Methods

Study population

All patients underwent radiofrequency ablation for persistent and long-standing persistent AF [2] at Princess Grace Hospital (Monaco). The study was approved by the Institutional Committee on Human Research, and all patients gave written informed consent. Anti-arrhythmic drugs (except amiodarone) were withdrawn at least five half-lives before the study. Rate control drugs were interrupted just before CA. Before the procedure, all patients had echocardiographic assessment of the left atrium (LA; anteroposterior diameter in the parasternal long-axis view; two-dimensional surface in the apical four-chamber view) and the left ventricular ejection fraction by Simpson's biplane method. A computed tomography scan acquisition of the LA was also performed for each patient before the procedure. The LA three-dimensional volume was calculated and reconstructed on the computed tomography scan.

Signal acquisition

For every patient, a 1-minute standard 12-lead ECG was recorded at a sampling rate of 977 Hz immediately before the start of ablation. ECG signals were acquired on a digital electrophysiological recording system (Prucka Engineering, Inc., Houston, TX, USA), including 0.05 to 40 Hz bandpass and 50 Hz notch filters. For patients who underwent repeat procedures, only the ECG recorded before the first intervention was considered in our prediction analysis.

Ablation procedure

The procedural approach for LA arrhythmia ablation in the study's institution has been described elsewhere [11]. In short, we performed coronary sinus catheterization using a decapolar diagnostic catheter, double transseptal puncture, systemic anticoagulation with heparin, with a target activated clotting time >350 seconds, and electroanatomical mapping of the LA with the Carto system (Biosense-Webster Inc., Diamond Bar, CA, USA). Mapping and ablation catheters were inserted transseptally via a non-steerable (Fast-Cath SL1; St. Jude Medical, Minnetonka, MN, USA) or steerable (Agilis, St. Jude Medical; or V-Cas Deflect, Stereotaxis, St. Louis, MO, USA) sheath. A 20-pole circular mapping catheter (Lasso 2512; Biosense-Webster Inc.) was used to assess pulmonary vein (PV) potentials.

LA shell for anatomical definition was done with either standard electroanatomical (Carto XP; Biosense-Webster Inc.) or adjusted fast anatomical (Carto 3; Biosense-Webster Inc.) techniques. Image integration with the LA computed tomography scan reconstruction was always used. Detailed mapping of electrical activation of the LA (and, in selected

cases, of the right atrium) was performed, with visual annotation of complex fractionated atrial electrograms (CFAEs) [12]. Ablations were carried out in a stepwise manner, with endpoints of circumferential PV disconnection, ablation at CFAE sites and block across the lines (if performed). In all procedures, the operator systematically delivered point-by-point ablation lesions for at least 30 seconds to create a contiguous antral circumferential line around the PV pairs. Catheter-tissue contact was optimized before each radiofrequency delivery, using catheter motion on fluoroscopy, near-field electrogram (EGM) stability, impedance drop during radiofrequency delivery and morphological EGM changes suggestive of lesion creation [11]. Whenever available, contact force was also taken into account to optimize catheter-tissue contact. If a significant lesion (based on local EGM modification) was not obtained, reablation at the same site, with further optimization of contact (at times requiring the use of a steerable sheath) and energy increase, was performed. Irrigated radiofrequency was delivered with a Stockert 70 generator (Biosense-Webster Inc.), a 42 °C limiting temperature and 30–40 W for the endocardial part of the line. Baseline irrigation flow was 17 to 30 mL/min, with an increase to 60 mL in case of excessive heating. If PV isolation (entry block) was not obtained at the end of the circular lesion, the lines were remapped and the gaps reablated. If needed, further lesions guided by the circular catheter were delivered.

In case of ongoing AF after PV isolation, additional lesions targeting fractionated EGMs in the LA as well as the roof and, in a few cases, the left isthmus lines (with endpoints of block across the line) were performed. Further lesions were delivered, in selected cases, within the coronary sinus (20 W) and, in some cases without AF termination, in the right atrium, targeting fractionated EGMs.

AF termination during ablation was defined as sinus rhythm resumption or its change to a stable atrial tachyarrhythmia. Nevertheless, this was not a procedural endpoint, and operators ended the procedures after PV isolation, ablation of the annotated CFAE sites and, when appropriate, block across the lines. Associated atrial tachyarrhythmia ablation was performed, and the critical isthmus or focal origin was specifically targeted up to sinus rhythm resumption and reconfirmation of PV isolation before catheter withdrawal.

In cases without AF or atrial tachyarrhythmia termination after catheter withdrawal, a loading dose of amiodarone (30 mg/kg) was administered, unless contraindicated. An electrical cardioversion (150 to 200 J, repeated up to three times under general anaesthesia) was performed if the arrhythmia was ongoing 24 to 48 hours afterwards.

Follow-up

After the 3-month blanking period recommended by current guidelines [2], patients were followed for clinical and asymptomatic recurrences. Follow-up was performed in a "real-life" setting, by regular visits to the treating cardiologist, with repeated ECG and 24-hour Holter monitoring in all cases (every 3 months during the first year after ablation; every 6 months afterwards). Supplementary documentation by ECG or Holter was sought in case of recurring symptoms suggestive of arrhythmia. Any recurring, sustained

(> 30 seconds), symptomatic AF or flutter was considered for a repeat procedure. Absence of any AF recurrence during follow-up defined the CA success group of our study, while patients with documented AF recurrences after the last procedure constituted the CA failure group.

Signal-processing and statistical analysis

F-wave amplitude computation

The signal-processing algorithm used to compute the f-wave amplitude in each lead is illustrated in Fig. 1. First, ECG fiducial points were detected to properly segment TQ intervals, where atrial activity can be measured free from QRST complexes of ventricular interference (Fig. 1, top). R-wave time instants were located on lead V1 by applying the Pan-Tompkins algorithm [13], and Q-wave onsets were simply obtained by subtracting 40 ms, a typical ventricular activation time. From the lead where the most prominent T-waves could be visually identified, T-wave offsets were estimated by an adapted Woody's method [14]; then, the segmented intervals were mean centred and concatenated (Fig. 1, middle). In the concatenated TQ segments, the local maxima were detected, and an upper envelope was estimated by interpolation; the lower envelope was estimated in an analogous manner from the local minima (Fig. 1, bottom). Finally, the average difference between both envelopes along time

was computed as an estimate of the f-wave mean amplitude in the lead examined. The mathematical details of this amplitude measurement algorithm have been described by Meo et al. [15].

Of the six frontal leads, only two provide linearly independent voltages [16]. Hence, to avoid redundancy, only leads I, II and V1–V6 were considered in subsequent analyses. Amplitude computation was performed using MATLAB, version 2011a (MathWorks, Natick, MA, USA).

For each patient, the f-wave amplitude used for prediction was computed in every lead, using the available duration of atrial activity signal after TQ segment concatenation. To validate the temporal stability of this measurement method, the f-wave mean amplitude was also computed on initial 10-second and 30-second segments of atrial activity in the recordings, where such lengths were available, and Pearson correlation coefficients were then determined for every lead.

Univariate analysis

Distribution normality was first checked for the variables under examination by the Kolmogorov–Smirnov test. Levene's correction was applied when homoscedasticity (homogeneity of variance) could not be assumed. Under data normality, groups were compared by a parametric Student's *t*-test, whereas a non-parametric Mann–Whitney *U*-test was

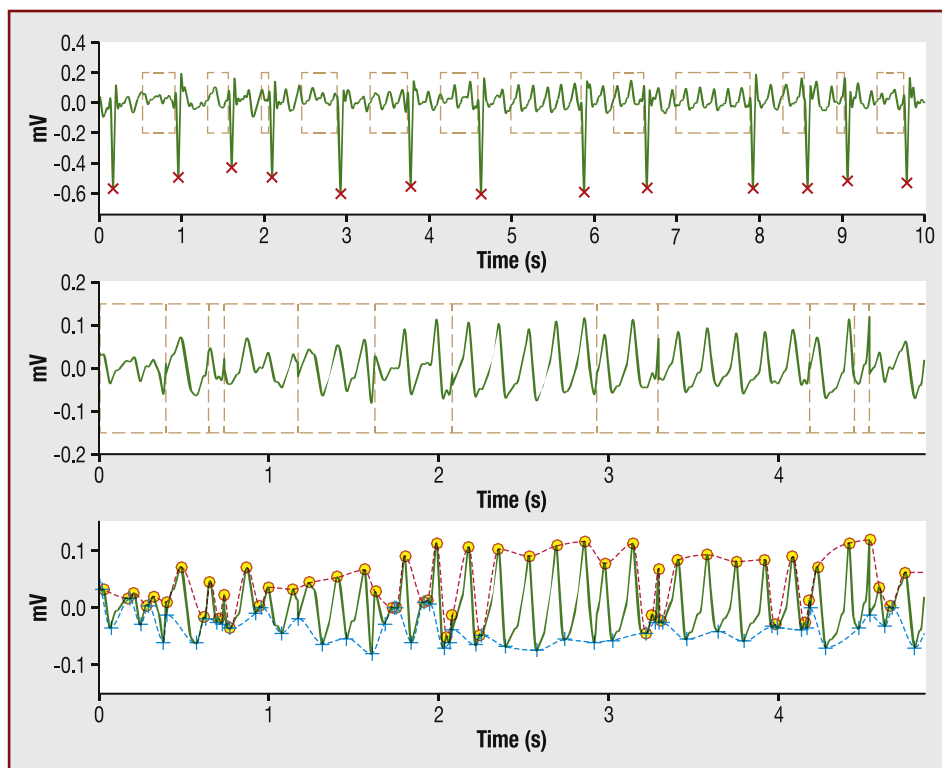


Figure 1. The f-wave amplitude measurement algorithm used in this study. Top: electrocardiogram (ECG) from the first patient of the database (to ease visualization, only 10 seconds are shown); the TQ intervals (dashed boxes) are segmented after detecting the R-wave peaks (red crosses) as well as the Q-wave onset and T-wave offset locations. Middle: the TQ segments (dashed boxes) are mean centred and concatenated. Bottom: local maxima (red circles) and minima (blue crosses) are detected in the concatenated TQ segments, and then interpolated to yield an estimate of the upper and lower envelopes (red and blue dashed line, respectively) of the atrial activity signal; at each time instant, the difference between the two envelopes provides an instantaneous estimate of f-wave amplitude in the ECG lead considered.

used when the variables did not show a normal distribution. Proportion analysis was based on the χ^2 test. For each univariate predictor of CA outcome, receiver operating characteristic (ROC) curves were computed to find the cut-off point providing the optimal trade-off between sensitivity and specificity, and the area under the ROC curve (AUC) was used as a prediction performance index. This statistical analysis and the logistic regression (LR) model described next were performed with SPSS software, version 13.0 (IBM, Armonk, NY, USA).

Multivariate analysis

An LR model was constructed from a linear combination of f-wave amplitudes computed in the ECG leads, acting as multiple predictor variables. Optimal linear combination coefficients were determined by maximum likelihood estimation from the available dataset [17]. After estimating the model coefficients, the LR score was computed from the f-wave amplitude set of each patient. The numerical value of the LR score is directly related to the estimated odds of CA success (not a voltage), and was then used as a CA outcome predictor. Using the LR score, ROC-based indices were derived to quantify the multivariate model predictive performance, as in the univariate analysis above. A backward elimination technique based on the Wald index [17] was employed to select the ECG leads whose f-wave amplitudes contributed to the LR prediction score in a statistically significant manner.

Results

Study population

Sixty-two consecutive patients (52 men; mean age 61.5 ± 10.4 years) were included in the study. Patient characteristics are summarized in Table 1. Patients had a mean AF history of 61.5 ± 56.1 months. AF was persistent in 54 patients (87.1%) and long-standing persistent in eight patients (12.9%). Duration of the actual AF episode (ongoing at the time of CA) was 7.3 ± 11.1 months. AF was idiopathic in 26 patients (41.9%).

Ablation procedure and follow-up

The flowchart of the ablation procedure is presented in Fig. 2. PV isolation was achieved in all patients. AF termination by CA was accomplished in 23 cases (37%), after a loading dose of amiodarone in three cases (5%) and by electrical cardioversion in 36 cases (58%). Procedure duration was 263.5 ± 64.0 minutes, fluoroscopy time was 14.1 ± 6.3 minutes and radiofrequency delivery time was 47.5 ± 25.7 minutes. Two major complications occurred: one arteriovenous femoral fistula requiring surgery; and one intra-alveolar haemorrhage prolonging hospitalization.

Five patients had a redo procedure for AF recurrence. With 1.08 procedures per patient and a follow-up of 13.9 ± 8.3 months after the last procedure, AF recurred in 15 patients. Recurrences occurred after a delay of 5.5 ± 4.2 months. Four additional patients had an atrial tachycardia recurrence, for which they were successfully

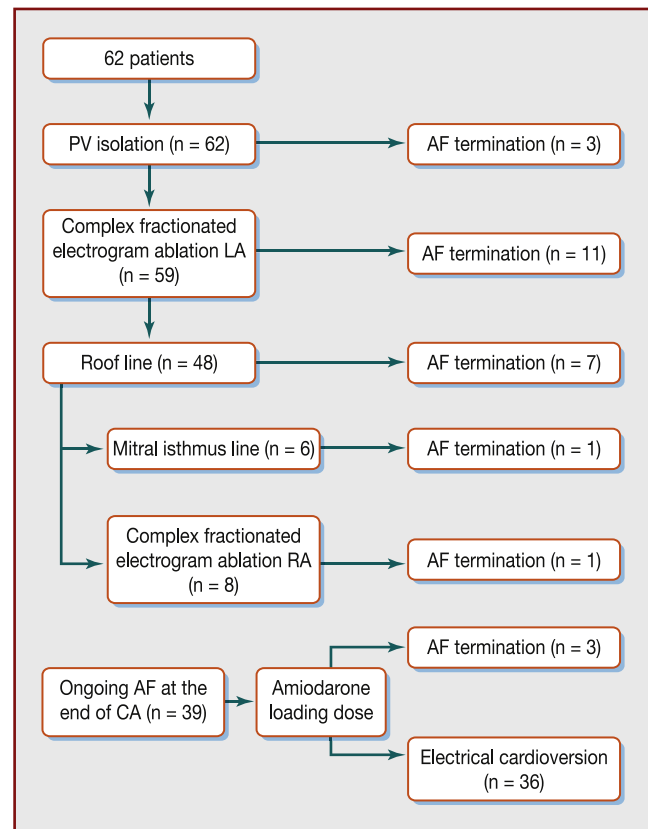


Figure 2. Flowchart of the ablation procedure steps and endpoints used in this study. AF: atrial fibrillation; CA: catheter ablation; LA: left atrium; PV: pulmonary vein; RA: right atrium.

reablated (classified in the CA success group). In the CA success group ($n=47$), 40 patients were off anti-arrhythmic drugs and seven patients were still on amiodarone, despite absence of AF recurrence (as per their cardiologist's prescription).

Validation of f-wave measurement

For the 34 patients with concatenated atrial signal segments of over 30 seconds, Pearson correlation of f-wave amplitude measures using 10-second and 30-second segments was at least 0.98 ($P < 0.001$) in all leads.

When comparing the amplitude computed over the original atrial signal (actual length dependent on the patient) with that over 10-second segments for the same patient population, the minimum correlation remained at 0.97 ($P < 0.001$), keeping at least at 0.9 in all leads for segments as short as 5 seconds. In addition, the minimum correlation between amplitudes measured in initial and final 5-second segments was 0.799, obtained in lead V1. Full details of the validation study can be found in [18].

Univariate analysis

Table 1 shows the results of the univariate analysis performed on the usual clinical data. Only AF history duration presented a significant intergroup difference, with the highest AUC (54.7 ± 53.5 vs. 87.0 ± 61.0 months; $P = 0.047$;

Table 1 Patient characteristics for the overall population, and comparison between the CA success and CA failure groups by univariate analysis.

Patient characteristics	Overall (n = 62)	CA success (n = 47; 75.8%)	CA failure (n = 15; 24.2%)	P
Men	52 (83.9)	40 (85.1)	12 (80.0)	0.64 ^a
Age (years)	61.5 ± 10.4	60.3 ± 10.4	65.1 ± 9.7	0.12 ^b
Hypertension	22 (35.5)	19 (40.4)	3 (20.0)	0.15 ^a
Sleep apnoea syndrome	5 (8.1)	4 (8.5)	1 (6.7)	0.82 ^a
Diabetes	8 (12.9)	8 (17.0)	0 (0)	0.09 ^a
Body mass index	27.6 ± 4.4	27.6 ± 4.6	27.8 ± 3.7	0.90 ^b
Obesity	14 (22.6)	10 (21.3)	4 (26.7)	0.66 ^a
Coronary heart disease	7 (11.3)	7 (14.9)	0 (0)	0.11 ^a
Hypertensive cardiomyopathy	6 (9.7)	2 (4.3)	4 (26.7)	0.011 ^{a,d}
Dilated cardiomyopathy	8 (12.9)	4 (8.5)	4 (26.7)	0.07 ^a
Valvular heart disease	4 (6.5)	2 (4.3)	2 (13.3)	0.21 ^a
Hypertrophic cardiomyopathy	2 (3.2)	2 (4.3)	0 (0)	0.42 ^a
AF history (months)	61.5 ± 56.1	54.7 ± 53.5	87.0 ± 61.0	0.047 ^{c,d}
Current AF episode	7.3 ± 11.1	6.8 ± 12.0	8.8 ± 7.3	0.06 ^c
LA anteroposterior diameter (mm)	47.2 ± 7.1	47.1 ± 7.3	47.5 ± 6.4	0.86 ^b
LA surface (cm ²)	29.1 ± 5.9	28.4 ± 5.8	31.5 ± 5.5	0.09 ^b
LVEF (%)	59.4 ± 15.6	61.5 ± 13.5	53.1 ± 19.7	0.07 ^b
LA CT scan maximal volume (mL)	141.0 ± 44.9	135.7 ± 42.7	158.6 ± 49.1	0.11 ^b
Patients on amiodarone before CA	26 (41.9)	19 (40.4)	7 (46.7)	0.67 ^a
Patients with repeat procedure	5 (8.1)	4 (8.5)	1 (6.7)	0.82 ^a

Data are expressed as number (%) or mean ± standard deviation. CA: catheter ablation; CT: computed tomography; LA: left atrium; LVEF: left ventricular ejection fraction.

^a P value computed according to the χ^2 test.

^b P value computed according to Student's *t*-test.

^c P value computed according to the Mann–Whitney *U*-test.

^d Statistical significance.

Table 2 Results from the univariate analysis on atrial fibrillatory amplitudes computed in the electrocardiogram leads separately.

Lead	CA success	CA failure	P ^a	AUC
I	30.76 ± 23.27	43.1 ± 26.13	0.039	0.678
II	50.87 ± 31.75	51.57 ± 21	0.38	0.576
V1	72.95 ± 70.24	59.43 ± 32.24	0.55	0.552
V2	81.30 ± 194.9	74.69 ± 70	0.36	0.579
V3	87.69 ± 217.8	63.5 ± 52.42	0.84	0.518
V4	78.7 ± 169.1	55.57 ± 55.29	0.93	0.508
V5	56.57 ± 71.28	40.24 ± 14.56	0.90	0.511
V6	40.93 ± 41.87	33.99 ± 14.08	0.88	0.513

Data are expressed as mean ± standard deviation (μ V) for both groups of interest. AUC: area under the receiver operating characteristic curve; CA: catheter ablation.

^a P values computed according to the Mann–Whitney *U*-test.

AUC = 0.687). There were more hypertensive heart disease patients in the CA failure group (4.3% vs. 26.7%; $P = 0.01$). No other differences between the groups were significant.

Table 2 summarizes the univariate analysis results for the f-wave amplitudes computed on the ECG leads separately. Owing to the high dispersion of the data, no significant

differences are found between groups for any lead considered on its own, except for lead I, with a maximal AUC value of 0.678. The corresponding ROC curve is displayed in **Fig. 3**, resulting in 66% sensitivity, 73.3% specificity and 67.7% accuracy at the optimal amplitude cut-off of 0.029 mV.

Multivariate analysis

After applying LR with backward elimination on the available clinical data (**Table 1**), no combination of clinical variables was retained. Concerning the f-wave amplitude values, a total of five iterations of the same LR with backward elimination protocol were run before all remaining variables reached the significance level ($P < 0.05$). The leads selected were: I (Wald index = 6.882; $P = 0.009$), V1 (Wald index = 5.311; $P = 0.021$), V2 (Wald index = 6.826; $P = 0.009$) and V5 (Wald index = 5.038; $P = 0.025$). When clinical and ECG data were taken together, the model selected the same remaining variables.

Fig. 4 illustrates the ROC of the LR score based on the four selected leads resulting in the best CA prediction performance. The optimal cut-off value was 1.732, yielding 83% sensitivity, 73.3% specificity and 80.6% accuracy, as summarized in **Table 3**. The LR score and thus its optimal cut-off value are not expressed in mV, but as the estimated odds

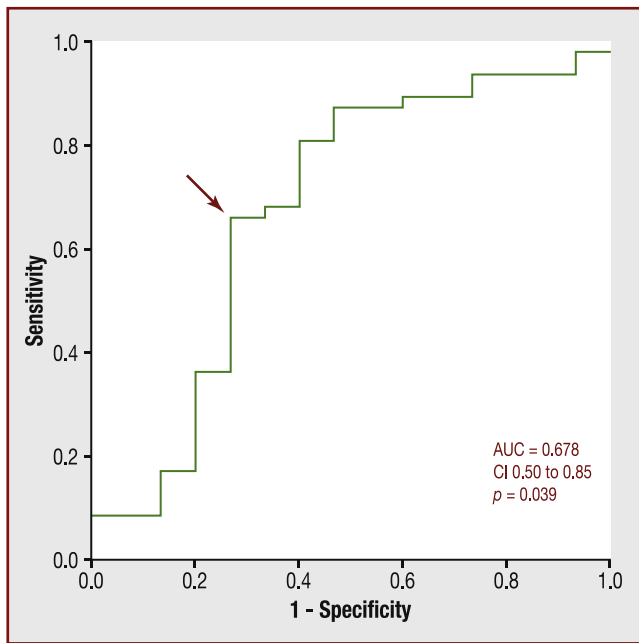


Figure 3. Receiver operating characteristic curve of the fibrillatory amplitude computed in lead I, yielding the best prediction among f-wave amplitudes measured in electrocardiogram leads separately (univariate analysis). Arrow indicates optimal cut-off point. AUC: area under the receiver operating characteristic curve; CI: confidence interval.

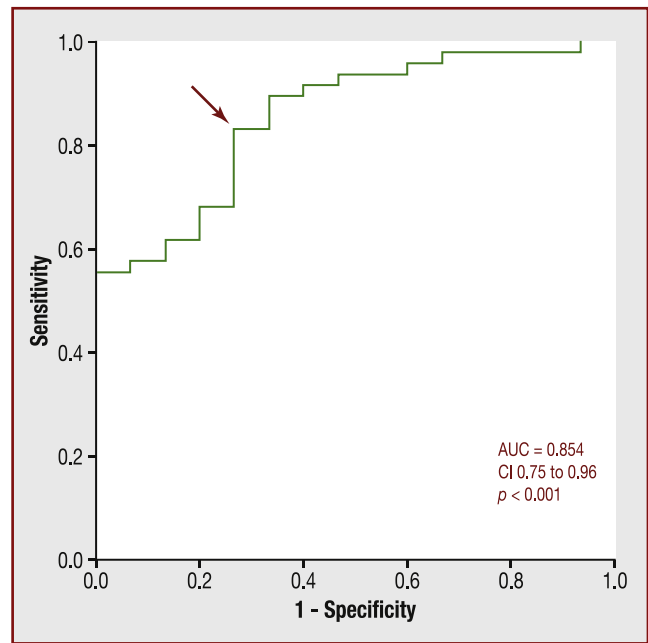


Figure 4. Receiver operating characteristic curve of the logistic regression score based on f-wave amplitudes computed in leads I, V1, V2 and V5, yielding optimal performance in multivariate prediction analysis. Arrow indicates optimal cut-off point. AUC: area under the receiver operating characteristic curve; CI: confidence interval.

of CA success according to the multivariate model based on f-wave amplitudes (see methods section).

Discussion

This work shows that the simultaneous analysis of f-wave mean amplitude, automatically computed in multiple ECG leads, improves the prediction of CA long-term outcome compared with single-lead amplitude measures in patients with persistent AF. Our analysis points to I, V1, V2 and V5 as the optimal leads for CA outcome prediction based on f-wave amplitude. The LR score derived from these leads predicts CA success with over 80% accuracy. With the clinical goal of predicting therapy outcome before CA referral, and thus avoiding unnecessary procedures, we focused exclusively on variables acquired before the intervention as the most suitable for patient selection.

F-wave amplitude as a predictor of ablation outcome

A variety of clinical and signal features have been explored as predictors of CA outcome in the literature [3–9,15]. Frequency-domain analysis has received particular attention, especially the AF cycle length, which is linked to the atrial myocytes’ refractory period [19], and has been associated with acute AF termination by CA [5,9]. The AF cycle length’s link with sinus rhythm maintenance after CA has also been demonstrated [9], but has lacked reproducibility in further studies [5,20,21], thus questioning the spectral features as markers of long-term CA outcome. To illustrate this limitation, the AF dominant frequency in lead V1 yielded an AUC of 0.662 ($P=0.06$) in our database. Similarly, the phase-lock index [10] was not predictive of CA outcome in our study (AUC = 0.536; $P=0.68$), probably because that index has been proposed in the context of a specific ablation

Table 3 Confusion matrix of the final logistic regression model with optimal cut-off.

	Positive outcome (CA success)	Negative outcome (CA failure)	
Predicted positive outcome (CA success)	True positives = 39	False positives = 4	PPV = 90.7%
Predicted negative outcome (CA failure)	False negatives = 8 Sensitivity = 83.0%	True negatives = 11 Specificity = 73.3%	NPV = 57.9%
			Accuracy = 80.6%

NPV: negative predictive value; PPV: positive predictive value.

procedure, aiming at the suppression of focal impulse and rotor modulation sources [22].

F-wave amplitude on the surface ECG is related to the magnitude of the underlying atrial voltage, which is also related to the amount of viable atrial muscle [6,7]; it has been associated with AF duration and patient age, both in V1 and II, with higher values linked to AF acute termination by CA [7]. However, anatomical characteristics, such as LA size and left ventricular end-diastolic diameter do not seem to correlate consistently with f-wave amplitude in different leads [7]; a lack of correlation between LA anatomy and CA outcome is observed in our study (Table 1). Similarly, the long-term prediction ability of f-wave amplitude measured in a single lead has so far remained tenuous, or has only been demonstrated with limited accuracy, depending on the lead considered [6,7]. Electrical dipoles associated with atrial activation wave fronts during AF may cancel out, as a result of local interactions, and cancellation effects may reflect differently depending on the ECG lead, which may explain the spatial variability of f-wave amplitude. Moreover, spatial variability is likely to increase in persistent forms of AF, where atrial electrical activation becomes more complex. As an illustration of the consequences of this hypothesis, the amplitude of lead I in Table 2 is higher for failing ablations, which is inconsistent with the expected results, pointing out the lack of reliability of single-lead measures, and confirming the value of considering multiple leads, as in the present approach.

The algorithm for f-wave amplitude computation described in the methods section only considers the atrial signal during the TQ intervals, as in the studies by Cheng et al. and Nault et al. [6,7], but, unlike those works, it is not manual. Also, in contrast to the study by Cheng et al. [6], our estimation procedure does not require an intracardiac EGM input as time reference, and is thus fully non-invasive. The high correlation results in our study show the good temporal stability and reproducibility of the automated f-wave amplitude measures. This study focused on an automated computation of f-wave amplitude in order to avoid the subjectivity of human operators in manual measurement methods requiring visual inspection. Hence, a comparison with manual methods was not considered relevant.

Multivariate analysis of ablation outcome

Most of the existing works aiming at CA outcome prediction consider each variable separately from the rest by means of univariate analyses, and the whole set of variables is only introduced into a multivariate model, such as LR, to identify independent predictors [6,7,9]. By contrast, the present work directly exploits the LR score as a prediction index, based on the multiple variables incorporated into the model. A backward elimination procedure is employed to select the most discriminant variables in this multivariate setting. By considering multiple ECG leads simultaneously, this approach is able to stress the long-term outcome prediction capabilities of the f-wave amplitude in the context of the CA therapy, as shown in Table 3, Figs. 3 and 4. Such long-term prediction capabilities are superior to those previously reported [6,7]. Optimally combining ECG leads through suitable signal decomposition techniques has also recently been proposed by Meo et al. [15]. Although that approach yielded

improved prediction of acute CA outcome, it did not provide satisfactory results in the long-term prediction goal of the present investigation.

Surface ECG lead selection

Typically, only one lead (e.g., II, aVF or V1) is considered separately, without exploiting the intrinsic spatial variability of the f-waves across ECG leads [6,7,9]. The multivariate LR model used in this work points to leads I, V1, V2 and V5 as the most discriminant to determine mid- and long-term CA outcome based on f-wave amplitude, with a prediction accuracy exceeding 80%, while keeping acceptable values of specificity and sensitivity. To support the consistency of our analysis, an alternative feature selection approach based on support vector machines [23] was also tested, retaining the same set of leads, and yielding equivalent prediction results even after cross-validation. These results stress the benefits of taking into consideration the information from several leads that are often neglected in AF analysis. By virtue of their spatial location, the selected leads V2 and V5 may offer a more distinctive view of LA activity, which may be insufficiently represented by V1, yet could play a significant role in AF characterization and prediction of therapy outcome.

Clinical implications

Proposing CA to a patient with persistent AF is a difficult clinical decision. Current guidelines [2] state that the indication class for persistent forms of AF is weaker than for paroxysmal AF. Suboptimal results with CA are notorious for such forms, and the ablation technique still exposes patients to a significant risk of major complications [24]. This decision may rely only on clinical and imaging information, but the most valuable predictors of CA results (such as magnetic resonance imaging-based quantification of atrial fibrosis [25]) are not available in the majority of electrophysiology laboratories.

Hence, developing a standard 12-lead ECG-based predictor of CA outcome in the context of persistent AF may have major clinical value, by providing a rapid tool for patient selection. Software may be easily integrated in ECGs, and can provide an instantaneous multilead computation of the f-wave amplitude that clinicians may use for fine-tuning the clinical indication for ablation.

Study limitations

Although the multivariate classification and lead selection approaches (LR, support vector machines) considered in the analysis are in close agreement, their generalization ability may be hampered by the relatively small sample size available in our study. This sample size, however, is similar to that in similar studies recently reported in the literature [6,20].

The stepwise ablation procedure implies a certain degree of interpatient variability, which may represent a bias for CA outcome. Nevertheless, among the described strategies of persistent AF ablation, the stepwise approach is adopted in many ablation centres, and encompasses widespread strategies, such as circumferential PV isolation alone and isolated CFAE ablation [5–7,9,20]. While electrical cardioversion might be considered as a confounding factor when evaluating CA outcome, its ability to maintain sinus rhythm when

applied on its own to treat persistent AF remains controversial [26]. In any case, the proportions of patients who had received cardioversion in the CA success and failure groups of our database were not significantly different. Likewise, the continued use of amiodarone before ablation and the application of repeat procedures do not seem to influence CA outcome (Table 1). Thus, we consider that the prediction value of the computational method on the surface ECG may be extrapolated widely in clinical practice.

AF termination rate during CA was inferior in our study compared with some published series [27,28]. Nevertheless, as stated in the methods section, AF termination by ablation was not an endpoint, and operators performed limited radiofrequency deliveries outside the PV antra; this did not hamper the long-term outcome of CA in this form of AF, which is in accordance with the recent literature [29]. Indeed, AF termination by ablation is debatable, and several series have shown no predictive value of AF termination during ablation for long-term outcome [30]. The best choice of extravenous ablation targets in persistent AF is currently being investigated, with different concepts and technologies other than CFAE ablation, but without consensus for the time being [31,32].

Anti-arrhythmic drugs were continued in a minority of patients in the CA success group, without evidence of arrhythmia recurrence. As follow-up was performed in a "real-life" setting, drug prescription was continued as deemed necessary by the cardiologist treating the respective patients. We consider the potentially induced bias as limited, as only a few patients were concerned, and the same drugs had been ineffective in these same patients before the ablation procedure. Clinical improvement being a certainty in these patients, the results reflect CA outcome in an "intention-to-treat" real-life setting even better.

Follow-up was performed with systematic 24-hour Holter ECG monitoring (and additional ECG or Holter in case of symptoms), according to current guidelines [2], as in similar studies [6,7,9]. However, the recurrence rate may be underestimated compared with implantable loop recorders.

Finally, as in other prediction studies (e.g. [5–7,9,10]), our results are based on retrospective data, and should be confirmed by further prospective analyses.

Conclusions

Surface ECG recordings provide useful non-invasive information for identifying persistent AF positive responders to CA. This work has shown that considering the f-wave amplitude across multiple ECG leads jointly yields improved long-term outcome prediction compared with single-channel amplitude measures. The novel predictor enhances patient selection for CA, and can thus contribute to the patient-tailored treatment of AF.

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Disclosure of interest

The authors declare that they have no competing interest.

References

- [1] January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS Guideline for the management of patients with atrial fibrillation: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol* 2014;64:2246–80.
- [2] Calkins H, Kuck KH, Cappato R, et al. 2012 HRS/EHRA/ECAS Expert consensus statement on catheter and surgical ablation of atrial fibrillation: recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design. *Europace* 2012;14:528–606.
- [3] D'Ascenzo F, Corleto A, Biondi-Zoccai G, et al. Which are the most reliable predictors of recurrence of atrial fibrillation after transcatheter ablation?: a meta-analysis. *Int J Cardiol* 2013;167:1984–9.
- [4] Ganesan A, Shipp N, Brooks A, et al. Long-term outcomes of catheter ablation of atrial fibrillation: a systematic review. *Heart Lung Circ* 2012;21:S130 [abstract 318].
- [5] Heist EK, Chalhoub F, Barrett C, Danik S, Ruskin JN, Mansour M. Predictors of atrial fibrillation termination and clinical success of catheter ablation of persistent atrial fibrillation. *Am J Cardiol* 2012;110:545–51.
- [6] Cheng Z, Deng H, Cheng K, et al. The amplitude of fibrillatory waves on leads aVF and V1 predicting the recurrence of persistent atrial fibrillation patients who underwent catheter ablation. *Ann Noninvasive Electrocardiol* 2013;18:352–8.
- [7] Nault I, Lellouche N, Matsuo S, et al. Clinical value of fibrillatory wave amplitude on surface ECG in patients with persistent atrial fibrillation. *J Interv Card Electrophysiol* 2009;26:11–9.
- [8] Buttu A, Van Zaen J, Viso A, et al. Termination of atrial fibrillation by catheter ablation can be successfully predicted from baseline ECG. *Comput Cardiol* 2012;39:189–92.
- [9] Matsuo S, Lellouche N, Wright M, et al. Clinical predictors of termination and clinical outcome of catheter ablation for persistent atrial fibrillation. *J Am Coll Cardiol* 2009;54:788–95.
- [10] Jones AR, Krummen DE, Narayan SM. Non-invasive identification of stable rotors and focal sources for human atrial fibrillation: mechanistic classification of atrial fibrillation from the electrocardiogram. *Europace* 2013;15:1249–58.
- [11] Squara F, Latcu DG, Massaad Y, Mahjoub M, Bun SS, Saoudi N. Contact force and force-time integral in atrial radiofrequency ablation predict transmuralty of lesions. *Europace* 2014;16:660–7.
- [12] Nademanee K, McKenzie J, Kosar E, et al. A new approach for catheter ablation of atrial fibrillation: mapping of the electrophysiologic substrate. *J Am Coll Cardiol* 2004;43:2044–53.
- [13] Pan J, Tompkins WJ. A real-time QRS detection algorithm. *IEEE Trans Biomed Eng* 1985;32:230–6.
- [14] Cabasson A, Meste O. Time delay estimation: a new insight into the Woody's method. *IEEE Sign Proc Lett* 2008;15:573–6.
- [15] Meo M, Zarzoso V, Meste O, Latcu DG, Saoudi N. Spatial variability of the 12-lead surface ECG as a tool for noninvasive prediction of catheter ablation outcome in persistent atrial fibrillation. *IEEE Trans Biomed Eng* 2013;60:20–7.

- [16] Malmivuo J, Plonsey R. *Bioelectromagnetism: Principles and Applications of Bioelectric and Biomagnetic Fields*. New York: Oxford University Press; 1995.
- [17] Indrayan A. *Medical Biostatistics*. Chapman & Hall/CRC Biostatistics Series. Boca Raton, FL: CRC Press; 2012.
- [18] Meo M, Hidalgo-Muñoz AR, Zarzoso V, Meste O, Latcu DG, Saoudi N. F-wave amplitude stability on multiple electrocardiogram leads in atrial fibrillation. *Comput Cardiol* 2015;42:505–8.
- [19] Bollmann A, Kanuru NK, McTeague KK, Walter PF, DeLurgio DB, Langberg JJ. Frequency analysis of human atrial fibrillation using the surface electrocardiogram and its response to ibutilide. *Am J Cardiol* 1998;81:1439–45.
- [20] Di Marco LY, Raine D, Bourke JP, Langley P. Characteristics of atrial fibrillation cycle length predict restoration of sinus rhythm by catheter ablation. *Heart Rhythm* 2013;10:1303–10.
- [21] Garibaldi M, Zarzoso V, Latcu DG, Saoudi N. Predicting catheter ablation outcome in persistent atrial fibrillation using atrial dominant frequency and related spectral features. *Conf Proc IEEE Eng Med Biol Soc* 2012;2012:613–6.
- [22] Narayan SM, Krummen DE, Rappel WJ. Clinical mapping approach to diagnose electrical rotors and focal impulse sources for human atrial fibrillation. *J Cardiovasc Electrophysiol* 2012;23:447–54.
- [23] Guyon I, Weston J, Barnhill S, Vapnik V. Gene selection for cancer classification using support vector machines. *Machine Learn* 2002;46:389–422.
- [24] Deshmukh A, Patel NJ, Pant S, et al. In-hospital complications associated with catheter ablation of atrial fibrillation in the United States between 2000 and 2010: analysis of 93 801 procedures. *Circulation* 2013;128:2104–12.
- [25] McLellan AJ, Ling LH, Azzopardi S, et al. Diffuse ventricular fibrosis measured by T(1) mapping on cardiac MRI predicts success of catheter ablation for atrial fibrillation. *Circ Arrhythm Electrophysiol* 2014;7:834–40.
- [26] Abu-El-Haija B, Giudici MC. Predictors of long-term maintenance of normal sinus rhythm after successful electrical cardioversion. *Clin Cardiol* 2014;37:381–5.
- [27] Faustino M, Pizzi C, Capuzzi D, et al. Impact of atrial fibrillation termination mode during catheter ablation procedure on maintenance of sinus rhythm. *Heart Rhythm* 2014;11:1528–35.
- [28] Pascale P, Shah AJ, Roten L, et al. Pulmonary veins to left atrium cycle length gradient predicts procedural and clinical outcomes of persistent atrial fibrillation ablation. *Circ Arrhythm Electrophysiol* 2014;7:473–82.
- [29] Mont L, Bisbal F, Hernandez-Madrid A, et al. Catheter ablation vs. antiarrhythmic drug treatment of persistent atrial fibrillation: a multicentre, randomized, controlled trial (SARA study). *Eur Heart J* 2014;35:501–7.
- [30] Yokoyama Y, Hirao K. Atrial fibrillation (AF) termination by ablation in patients with persistent AF – what is that supposed to mean? *Circ J* 2013;77:1399–400.
- [31] Haissaguerre M, Hocini M, Denis A, et al. Driver domains in persistent atrial fibrillation. *Circulation* 2014;130:508–30.
- [32] Swarup V, Baykaner T, Rostamian A, et al. Stability of rotors and focal sources for human atrial fibrillation: focal impulse and rotor mapping (FIRM) of AF sources and fibrillatory conduction. *J Cardiovasc Electrophysiol* 2014;25:1284–92.