ORIGINAL ARTICLE

Early repolarization pattern as a predictor of atrial fibrillation recurrence following radiofrequency pulmonary vein isolation

Burak Hunuk¹ | Carlo de Asmundis² | Giacomo Mugnai² | Vedran Velagic² | Erwin Ströker² | Darragh Moran² | Diego Ruggiero² | Ebru Hacıoglu² | Vincent Umbrain³ | Christian Verborgh³ | Stefan Beckers³ | Jan Poelaert³ | Pedro Brugada² | Gian-Battista Chierchia²

¹Department of Cardiology, Yeditepe University School of Medicine, Istanbul, Turkey

²Heart Rhythm Management Centre, Universitair Ziekenhuis Brussel-Vrije Universiteit Brussel, Brussels, Belgium

³Department of Anesthesiology, Universitair Ziekenhuis Brussel-Vrije Universiteit Brussel, Brussels, Belgium

Correspondence

Burak Hunuk, Department of Cardiology, Yeditepe University School of Medicine, Istanbul, Turkey.
Email: burakhunuk@hotmail.com

Funding information

Burak Hunuk received a postdoctorate international research grant (grant number: BIDEB-2219) from "The Scientific and Technological Research Council of Turkey—TUBITAK".

Abstract

Background: Early repolarization patterns (ERP) have been found to be associated with poor cardiovascular end points. We aimed to evaluate the ERP prevalence among patients with structurally normal hearts undergoing radiofrequency (RF) pulmonary vein isolation (PVI) for paroxysmal atrial fibrillation (AF) ablation and its association with the AF recurrence.

Methods: All consecutive patients who underwent RF-PVI as index procedure for paroxysmal AF in our center were evaluated. Exclusion criteria: structural heart disease, ongoing use of Class I/III antiarrhythmics, complete-bundle-branch-block. Lateral (I, aVL, V₅–V₆), inferior (II, III, aVF), or infero-lateral (both) ERP were defined in baseline ECG as horizontal/downsloping J-point elevation ≥ 1 mm in two consecutive leads with QRS slurring/notching. Documented episodes of AF lasting ≥ 30 s were considered recurrence.

Results: Of 701 cases, 434 patients (305 males, 58 ± 11 years) were included for analysis. ERP observed in 67 patients (15.4%) (Infero-lateral $n = 26$, inferior $n = 23$, lateral $n = 18$) which were significantly younger, demonstrating longer PR-interval and lower heart rates. At a mean follow-up of 22.1 ± 9.7 months, AF recurrences were found in 107 patients (24.6%). In middle-aged patients (≥ 40 – < 60 years; $n = 206$, 79% male), those with an infero-lateral ERP had higher recurrence compared with the ones without (56.3% vs. 19%; $p = 0.002$). Infero-lateral ERP was significantly predicting recurrence (HR 2.42, 95% CI 1.21–4.82; $p = 0.01$).

Conclusion: Early repolarization patterns was more prevalent in our AF population than in the general population. Infero-lateral ERP in baseline ECG might predict AF recurrence in the follow-up after RF-PVI in middle-aged patients.

KEYWORDS

atrial fibrillation, early repolarization pattern, electrocardiography, pulmonary vein isolation, radiofrequency ablation

1 | INTRODUCTION

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in humans, is associated with higher morbidity and mortality, and has become a major health issue with aging populations in the last decades (Kirchhof et al., 2016). Altered atrial Na^+ , K^+ and Ca^{+2} channel functions taking part in the action potential of atrial cells were shown to be responsible in focal triggers by enhancing the automaticity and perpetuating reentry in the left atrium and surrounding structures (Iwasaki, Nishida, Kato, & Nattel, 2011; Mahida & Ellinor, 2012). It is known that 90% of paroxysmal AF is driven by pulmonary vein (PV) sources and responds well to PV-directed procedures, "Pulmonary vein isolation" (PVI) by means of "point by point" radiofrequency (RF) ablation has already become an established technique with acceptable AF recurrence rates and complications (Calkins et al., 2017; Haïssaguerre et al., 1998).

Early repolarization pattern (ERP) on surface 12-lead ECG, generally defined as an elevation of the junction between the end of the QRS complex and the beginning of the ST segment (the J-point) from isoelectric line in leads except $\text{V}_1\text{--V}_3$, which has traditionally been considered to be a benign finding, has recently been associated with an increased risk of sudden cardiac death and lethal ventricular arrhythmias by multiple case-control and population-based studies (Haïssaguerre et al., 2008; Tikkanen et al., 2009). ERP with clinical/lethal ventricular arrhythmias is defined as Early Repolarization Syndrome (ERS) and takes part in a spectrum called "J-wave Syndromes" including Brugada Syndrome and Idiopathic Ventricular Fibrillation sharing similar physiopathological characteristics such as mutations in the genes leading to loss of function in cardiac Na^+ and Ca^{+2} channels as well as to a gain of function in K^+ channels (I_{to} or [ATP dependent] $I_{\text{K-ATP}}$; Antzelevitch, 2013). The prevalence of ERP controversially ranges between 1% and 5% on large population-based studies whereas reaching up to 35%, depending on age (predominant in young athletic adults), sex (prevalent in males), race (common in black populations), and definition of ERP (i.e., J-point elevation >0.05 or 0.1 mV or more; Antzelevitch, 2013; Maury & Rollin, 2013; Patton et al., 2016; Tikkanen et al., 2009). In general population, the inferior/infero-lateral distribution of ERPs with horizontal/downsloping ST-segments has previously been shown to confer an increased risk of lethal arrhythmias, whereas lateral manifestations especially with upsloping ST-segments have not predicted any increased risk of lethal arrhythmic events (Antzelevitch, 2013; Haïssaguerre et al., 2008; Macfarlane et al., 2015; Maury & Rollin, 2013; Patton et al., 2016; Tikkanen & Huikuri, 2015; Tikkanen et al., 2009). ERP has also more recently been shown as a sign for increased mortality and morbidity in many cardiac conditions such as coronary artery disease (Patel et al., 2010) and heart failure (Furukawa et al., 2013).

Reports demonstrated an increased prevalence of AF in the effected populations for many channelopathies, including J-wave syndromes and the Long QT syndrome with a poor prognosis (Antzelevitch, 2013; Olesen, Nielsen, Haunsø, & Svendsen, 2014). Most recently, a missense gain-of-function mutation in the gene

encoding the cardiac $I_{\text{K-ATP}}$ Kir6.1 (inwardly rectifying K^+ channel) (KCNJ8), which has previously been shown as a pathogenic substrate for J-wave syndromes has been identified as associated with familial AF (Delaney et al., 2012).

Because of the emerging data suggesting a certain amount of common mechanistic pathways in AF and ERP, we aimed to evaluate the prevalence of ERPs on baseline ECG and the effects of this clinical finding on the clinical outcomes in a population of paroxysmal AF patients who underwent PVI in our center by means of RF.

2 | METHODS

2.1 | Study population

All consecutive patients who underwent PVI as index procedure by RF in our center from 01/01/2013 were considered for our retrospective analysis. The study complies with the Declaration of Helsinki, patients provided informed consent prior to the procedure, and the local ethical committee approval obtained. Patients were affected by drug-resistant paroxysmal AF prior to ablation procedure as stated by the most recent guidelines (Calkins et al., 2017; Kirchhof et al., 2016). Exclusion criteria were as follows: structural heart disease, complete-bundle-branch-block, ongoing use of class I and III antiarrhythmic medications on the time of the baseline ECG recording (in the last month), poor-quality ECGs (≥ 2 uninterpretable leads), ventricular pacemaker stimulation, and any prior PVI procedure. Prior to the procedure, all patients underwent a 2D transthoracic echocardiography to assess left atrial (LA) size and function, left ventricular ejection fraction, and other baseline measurements to rule out any structural and/or valvular disease. A multislice cardiac computed tomography and a transesophageal echocardiography were performed the day before PVI to analyze LA and PV anatomy and to rule out the presence of an intracardiac thrombus together with significant coronary lesions.

2.2 | Electrocardiographic assessment

A simultaneous recording of standard 12-lead ECG was performed in all patients the day before the ablation. The 12-lead ECGs, recorded at 25 mm/s and calibrated to 10 mm/mV, were directly uploaded on the hospital ECG database at 300 DPI. These images were amplified $\times 10$ and then baseline heart rates, PR, QRS, QTc (Bazett) intervals, were manually measured by electronic calipers. The presence of a lateral (I, aVL, $\text{V}_5\text{--V}_6$), inferior (II, III, aVF), or infero-lateral (II, III, aVF, I, aVL, $\text{V}_5\text{--V}_6$) ERP was defined as a prominent J-point elevation of at least 1 mm (0.1 mV) above the isoelectric line in at least two consecutive leads with either QRS slurring (i.e., a smooth transition from the end QRS to the beginning of ST-segment) or notching (a positive deflection [J-wave] occurring immediately after a positive QRS complex at the onset of the ST-segment). In order to be consistent with the proposed terminology stated in the most recent ERP international consensus documents (Macfarlane et al., 2015; Patton et al., 2016), "J peak" was accepted as "J-point" denoting the peak of

TABLE 1 Types of early repolarization patterns for each age group of the study population

Age category (years)	Inferior (n)	Lateral (n)	Infero-lateral (n)	Total number of ERP (% in the age category) (%ERP overall)
≥20–<40	0	3	5	8 (28.6)
≥40–<60	13	8	16	37 (17.9)
≥60	10	7	5	22 (11)
Total (n) (% in ERP)	23 (34%)	18 (26%)	26 (39%)	67 (100%) (15.3%)

Note. ERP: early repolarization pattern.

a notch or onset of a slur. Only the J-wave patterns with horizontal or downsloping ST-segments were accepted as ERP and included in the study. In order to stratify ST-segments, the amplitude of the ST-segment was measured 100 ms after J-terminal (denoting the end of the QRS notch or slur), and it should be less than or equal to the amplitude of J-terminal (Macfarlane et al., 2015; Tikkanen & Huikuri, 2015). All the ECGs were analyzed by two experienced cardiologists blinded for the clinical follow-up or recurrence of the patient with borderline results being reassessed by a third blinded cardiologist for the final classification.

2.3 | Procedural and postprocedural management

Ablation was performed with RF point by point technique in our center as previously described (Mugnai et al., 2014) using the same electroanatomic mapping and navigation system (CARTO-3; Biosense Webster Inc., USA). RF ablation was performed with an open irrigated cool tip 3.5-mm catheter (NaviStar ThermoCool; Biosense Webster Inc.). Postprocedure, all patients were monitored for 18 hr in a telemetry unit with continuous ECG monitoring. They were discharged on the following day, if clinically stable. Before discharge, a TTE in all patients was performed in order to exclude postprocedural pericardial effusion. Therapy with low-molecular-weight-heparin (LMWH) was commonly started the same day following ablation. Oral anticoagulation (OAC) was started the day following the procedure. Patients were discharged on both OAC and LMWH. When a target international normalized ratio of 2–3 was reached, LMWH was stopped and OAC was continued for at least 3 months. In patients under direct-acting oral anticoagulants, the therapy was generally resumed the same evening of ablation and continued for at least 3 months or lifelong according to the CHADS2-VASC risk score. Antiarrhythmic therapy was administered for 3 months following the procedure and discontinued if the patient was free of AF relapse.

2.4 | Follow-up

After discharge, patients were scheduled for follow-up visits with baseline ECG and 24-hr Holter recordings at 1, 3, 6, and 12 months. Any dysrhythmic symptoms following ablation were deemed as deserving a Holter monitoring. All reports of Holter or ECG recordings having been performed in referring centers were sent to our center for confirmation of the diagnosis of atrial fibrillation recurrence. No

blanking period was considered in the follow-up of the AF recurrences. All documented episodes of AF lasting ≥30 s were considered as a recurrence.

2.5 | Statistical analysis

Continuous variables are expressed as mean ± SD and, if appropriate, were compared using the Student's *t* test. Categorical variables are expressed as numbers and percentages and, if appropriate, were compared with the Chi-square analysis. Univariate analysis was performed using the Cox regression model. Kaplan–Meier survival curves were plotted for ERPs and were compared by means of the log-rank test.

A *p* value <0.05 was deemed statistically significant. Statistical analysis was performed using SPSS 20.0 (IBM Inc., Armonk, NY, USA).

To prevent errors in interpretation, ECGs were assessed for interobserver variability test using “Cohen's Kappa Statistic.” The Kappa value was 0.89 (95% Confidence Interval 0.69–1; Kappa 0.8–1 = Almost perfect) and high statistical agreement between the observers was found (Agreement: 95%; Standard Error: 0.110).

3 | RESULTS

Seven hundred and one consecutive patients having undergone PVI by means of RF were evaluated for our study. Among these patients, 42 were excluded for coronary artery disease, 19 for dilated cardiomyopathy, five for valvular cardiomyopathy, 105 because of class IC antiarrhythmic therapy, 75 because of class III antiarrhythmic treatment, 14 for complete-bundle-branch-block, and seven for ventricular pacemaker stimulation. No ECGs were excluded for poor-quality or uninterpretable leads.

A total 434 patients (305 males, 58 ± 11 years) were finally considered in our analysis. For the ease of analyses and because of the age-specific features of ERP, the study population was divided into three age-related groups as “Young” (≥20–<40 years old; *n* = 28, mean age: 32 ± 7 years), “Middle aged” (≥40–<60 years old; *n* = 207, mean age: 52 ± 6.5 years), and “Elderly” (≥60 years old; *n* = 200, mean age: 67 ± 5.5 years). On the ECGs performed the day before the AF ablation procedure, ERPs was observed in 67 patients (15.4%; Table 1, Figure 1). ERP was more common in infero-lateral leads (6% in overall *n* = 26), and then in inferior leads (5.3%, *n* = 23) and lateral

FIGURE 1 ECG examples of a 42-year-old male patient with paroxysmal atrial fibrillation showing lateral ERP (on left) and a 53-year-old male paroxysmal atrial fibrillation patient with inferior ERP (on right) with horizontal ST-segments. None of them developed a recurrence on the follow-up. ERP: early repolarization patterns

Parameters	Patients with ERP (n = 67) mean $\pm$ SD	Patients without ERP (n = 367) mean $\pm$ SD	p value
Age (years)	53.3 $\pm$ 12.5	58.6 $\pm$ 10.4	<0.001
Male gender (n, %)	59 (88)	246 (67)	0.0004
Duration of symptoms (months)	32.7 $\pm$ 12.8	36.5 $\pm$ 17.6	0.2
Hypertension (n, %)	17 (25)	172 (47)	0.001
Dyslipidemia (n, %)	18 (27)	127 (35)	0.2
Diabetes mellitus (n, %)	2 (3)	30 (8)	0.2
LA diameter (mm)	43.4 $\pm$ 7.9	43.5 $\pm$ 7.5	0.9
Left ventricular ejection fraction (%)	59.4 $\pm$ 2.1	58.9 $\pm$ 3.7	0.3
Body mass index (kg/m ²)	27.3 $\pm$ 4.8	27.1 $\pm$ 4.3	0.8
CHA ₂ DS ₂ -VASc score	0.6 $\pm$ 0.9	1.4 $\pm$ 1.2	<0.001
Follow-up duration (months)	20.6 $\pm$ 7.2	22.7 $\pm$ 10.1	0.1
Oral anticoagulation (n, %)	36 (54)	214 (58)	0.5
Heart rate (bpm)	69.1 $\pm$ 10.4	76.2 $\pm$ 6.3	<0.001
PR interval (ms)	174 $\pm$ 21.8	159.8 $\pm$ 6.1	<0.001
QRS (ms)	96.4 $\pm$ 5.4	95 $\pm$ 6.5	0.1
QT-corrected (Bazett) (ms)	423.6 $\pm$ 8.5	422.5 $\pm$ 5.9	0.19

Note. ERP: early repolarization pattern; LA: left atrium; LVEF: left ventricular ejection fraction. Bold values denote statistically significant clinical and laboratory parameters.

leads (4.1%, $n = 18$) in the study population. ERP was significantly more frequently observed in the young age group (respectively, 28.6% vs. 11.0%; $p = 0.02$) and in the middle age group (respectively, 17.9% vs. 11.0%; $p = 0.05$) compared with the elderly category; otherwise, the ERP prevalence did not significantly differ between

young and middle age categories (respectively, 28.6% vs. 17.90%; $p = 0.2$).

Baseline characteristics of patients with ERP compared with those without are listed in Table 2. The clinical characteristics for each age category are shown in Table 3. It can be observed that

TABLE 2 Comparison of baseline characteristics between patients with early repolarization pattern and those without

TABLE 3 Characteristics of patients with ERP and without ERP for each age group of study population

Parameters	≥20–<40 (32 ± 7)			≥40–<60 (52 ± 6.5)			≥60 (67 ± 5.5)		
	ERP (n = 8)	No ERP (n = 20)	p	ERP (n = 37)	no ERP (n = 169)	p	ERP (n = 22)	no ERP (n = 178)	p
Age (years)	31.0 ± 6	33.0 ± 5.6	0.4	50.4 ± 6.2	52.8 ± 5.1	0.01	66.3 ± 5.6	66.8 ± 4.8	0.6
Male gender (n, %)	8 (100)	16 (80)	0.3	33 (89)	127 (75)	0.08	18 (82)	103 (58)	0.04
Duration of symptoms (months)	14.5 ± 6.2	18.3 ± 9.8	0.3	26.4 ± 10.8	30.1 ± 16.2	0.6	27.5 ± 13.9	31.5 ± 10.2	0.1
Hypertension (n, %)	0	1 (5)	1.0	6 (16)	66 (39)	0.007	11 (50)	105 (59)	0.5
Dyslipidemia (n, %)	2 (25)	3 (15)	0.6	7 (19)	43 (25)	0.3	7 (32)	83 (47)	0.3
Diabetes mellitus (n, %)	0	1 (5)	1.0	1 (3)	11 (7)	0.7	1 (5)	18 (10)	0.7
LA diameter (mm)	39.8 ± 5.8	35.9 ± 5.9	0.1	42.9 ± 6.7	42.6 ± 6.7	0.8	46.3 ± 10.3	45.3 ± 7.6	0.6
LVEF (%)	59.7 ± 0.7	58.5 ± 3.3	0.3	59.6 ± 1.8	58.8 ± 4.4	0.3	59.1 ± 2.9	58.4 ± 2.7	0.9
Body mass index (kg/m ²)	26.9 ± 5.2	25.2 ± 3.5	0.3	27.0 ± 3.6	27.1 ± 4.6	0.9	28.1 ± 16.5	27.5 ± 4.2	0.6
CHA ₂ DS ₂ -VASc score	0.2 ± 0.7	0.4 ± 0.5	0.5	0.4 ± 0.7	0.9 ± 0.9	0.004	1.2 ± 1.1	2.0 ± 1.2	0.003
Follow-up duration (months)	18.4 ± 8.1	19.8 ± 9.5	0.5	21.6 ± 9.7	23.9 ± 11.8	0.2	17.3 ± 11.1	20.1 ± 7.7	0.1
Oral anticoagulation (n, %)	2 (25)	4 (20)	1.0	19 (51)	90 (53)	0.9	15 (68)	120 (67)	1.0

Note. ERP: early repolarization pattern; LA: left atrium; LVEF: left ventricular ejection fraction. Bold values denote statistically significant clinical and laboratory parameters.

patients with ERP were significantly younger, predominantly male, demonstrating longer PR intervals and lower basal heart rates, also the CHADS₂-VaSC scores and previous hypertension diagnosis were also significantly lower which might be attributable to their subgroup characteristics. Other baseline characteristics did not differ significantly.

At a mean follow-up of 22.1 ± 9.7 months, recurrences of atrial fibrillation were found in 107 patients (24.6%). The episodes of AF recurrence occurred after a mean time of 9.5 ± 6.1 months from the AF ablation procedure in the general population. In our follow-up, no patients demonstrated any lethal ventricular arrhythmias and there were also no difference in the major procedure-related complications between patients with ERPs (one pseudoaneurysm) and without (eight vascular complications, six tamponades, two thromboembolic events; 1.5% vs. 2.5%, *p* = 0.5).

The overall rate of AF recurrence was significantly higher in the elderly age category compared with the young (respectively, 30.0% vs. 7.1%; *p* = 0.01; Table 4). However, the recurrence rate did not differ between young and middle age categories (respectively, 7.1% vs. 21.8%; *p* = 0.08) and also between middle and elderly age groups (respectively, 21.8% vs. 30%; *p* = 0.07). The rate of recurrence in patients with ERP was higher than in those without (respectively, 32.8% vs. 23.2%; *p* = 0.1), but it did not reach statistical significance.

Among all patients with ER, the recurrence rate did not significantly differ between the different types of ER (inferior vs. lateral pattern: *p* = 0.2; lateral vs. infero-lateral pattern: *p* = 0.2; inferior vs. infero-lateral pattern: *p* = 0.9). However, in the group of middle-aged patients (≥40–<60 years old), the rate of AF recurrence was significantly higher in those with ERP compared with those without ERP (respectively, 28.9% vs. 18.9%; *p* = 0.046; Table 4 and Figure 2). In the remaining age groups, the rate of AF recurrence did not significantly differ between patients with ERP and those without ERP (in the young age group, respectively 12.5% vs. 5%, *p* = 0.5; in the elderly group, respectively, 36.3% vs. 29.2%, *p* = 0.6).

Particularly, in the group of middle-aged patients, those with an infero-lateral ERP had significantly higher AF recurrence rates compared with all the other patients recurrences in the same age group (respectively, [9/16] 56.3% vs. [36/190] 19%; *p* = 0.002; Table 4). However, recurrence rates in patients with inferior ERP (respectively, [3/13] 23.1% vs. 19%; *p* = 0.7) and lateral ERP (respectively, [1/8] 12.5% vs. 19%, *p* = 0.3) did not significantly differ with all the remaining patients of the above-mentioned age group. Finally, the Cox regression analysis showed that, in the group of patients between 40 and 60 years old, only the presence of the infero-lateral ERP was significantly able to predict AF recurrence in the follow-up (Hazard ratio: 2.42, 95% CI: 1.21–4.82; *p* = 0.01; Table 5).

Patients with ERPs developed AF recurrence after a mean follow-up of 5.2 ± 5.1 months while the ones without ERPs after 9.2 ± 9.6 months; showing a trend for an earlier recurrence without significance (*p* = 0.054). Figure 3 shows the Kaplan–Meier event-free survival analysis curve demonstrating the significantly higher AF recurrence events in the follow-up of patients with infero-lateral ERP in the middle-aged group (*p* = 0.02).

TABLE 4 Atrial fibrillation recurrences observed in patients with and without ERP for each age group of study population

Age group (n = patients with ER)	Inferior ERP n = patients with recurrence (n = total patients in group)	Lateral ERP n = patients with recurrence (n = total patients in group)	Infero-lateral ERP n = patients with recurrence (n = total patients in group)	Total recurrences in ERP N (% overall)	Recurrences in patients without ERP (n = total patients in group) (% recurrence overall)	Overall recurrences (n = total patients in age group) (% recurrence overall)
≥20–<40 years (n = 8)	0 (0)	0 (3)	1 (5)	1 (12.5)	1 (20) (5)	2 (28) (7.1)
≥ 40–<60 years (n = 37)	3 (13)	1 (8)	9 (16)	13 (28.9)	32 (169) (18.9)	45 (206) (21.8)
>60 years (n = 22)	4 (10)	2 (7)	2 (5)	8 (36.3)	52 (178) (29.2)	60 (200) (30)
Total n of recurrence (n = total patients in group)	7 (23)	3 (18)	12 (26)	22 (32.8)	85 (367) (23.2)	107 (434) (24.6)

Note. ERP: early repolarization pattern.

Bold values denote evident and significant numbers of recurrences detected in the middle age category.

4 | DISCUSSION

4.1 | Early repolarization patterns and prevalence

Our single-center retrospective study demonstrated a higher prevalence of ERPs with malignant characteristics (downsloping-horizontal ST segment, dominantly infero-lateral distribution) in our AF population than were observed in other similar western community-based population cohorts demonstrating prevalences between 1% and 7% (Maury & Rollin, 2013; Rollin et al., 2012; Sinner et al., 2010). Our finding of 15.3% far exceed the revealed 13.1% prevalence of ERP in the recent MONICA/KORA prospective, population-based case-cohort study conducted in Germany by Sinner et al. (2010) even though the population studied in that study was younger (mean age 52 vs. 58 in our work) and the ST segment elevation/slope was not taken into consideration while defining the ERPs. Previous studies put forward that some distinct ECG characteristics observed in ERPs are associated with an increased arrhythmic risk. Observations from population-based studies suggest that lateral ERP carries the lowest risk, whereas risk progressively increases with inferior ERP and prominently increases in combined infero-lateral J-wave distribution. ERP with a horizontal/descending ST segment has also been shown to possess the highest risk of arrhythmic events in J-wave syndromes, patients with myocardial ischemia and general population samples (Antzelevitch, 2013; Haïssaguerre et al., 2008; Patton et al., 2016; Tikkanen et al., 2009).

More recently, Rollin et al. (2012) conducted a similar population-based study in Southwestern French subjects 35- to 64-years old giving out a similar 13.3% prevalence like MONICA/KORA investigators; however, only 64.8% of evaluated ERPs were with an horizontal/descending type ST segment and this type of ERPs with a notching QRS were found to be strongly associated with the highest risk of all-cause and cardiovascular deaths while ERPs with an ascending type ST segment were not found to be correlated with any increased cardiac/all-cause death consistent with numerous published data.

We also demonstrated a potential association between the recurrence of atrial fibrillation after PVI by means of RF and the existence of ERPs in the infero-lateral leads in the middle-aged study population. Our data might suggest a common potential mechanism that also exists in the atrial tissue increasing the risk of atrial arrhythmias.

4.2 | Common proposed mechanisms of atrial fibrillation and early repolarization

In cardiac cells, electrical properties are adjusted by cell membrane ion channels and increased inward currents (Ca^{+2} and Na^{+}) depolarize the cell prolonging action potential duration (APD), whereas enhanced outward currents (carried by K^{+}) repolarize the cell and shorten APD (Antzelevitch, 2013; Delaney et al., 2012; Iwasaki et al., 2011; Olesen et al., 2014). The determinants of conduction velocity (CV) include phase 0 inward currents (particularly Na^{+}) that provide

FIGURE 2 ECG example of a 45-year-old male paroxysmal atrial fibrillation patient who had a recurrence on the 7th month of follow-up after pulmonary vein isolation-radiofrequency demonstrating infero-lateral early repolarization patterns

energy for conduction and gap junction connexin channels, which allow electric flow between cardiomyocytes.

Atrial fibrillation can be maintained by reentry circuits producing a rapidly firing driver with fibrillatory propagation or with multiple irregular reentry circuits depending on atrial/substrate properties requiring a convenient balance between refractory and excitability determinants that are currently explained by leading circle or spiral wave models (Iwasaki et al., 2011; Kirchhof et al., 2016; Mahida & Ellinor, 2012). Increased outflow K currents or decreased Ca currents shorten APD, refractory periods (RP), and promote reentrant AF, while reduced Na^+ current and connexin dysfunction promote AF by slowing conduction (Iwasaki et al., 2011).

For both reentry models, it can be seen that, shortened RP, CV, and APD promotes AF by leading to a shortened wavelength than its path length creating a good environment for reentry circuits and might explain familial AF cases caused by gain-of-function K^+ channel mutations, the antiarrhythmic effects of APD-prolonging drugs, the AF-promoting effects of CV slowing with loss-of-function Na^+ channel and connexin mutations (Iwasaki et al., 2011; Mahida & Ellinor, 2012; Olesen et al., 2014). Consequently, atrial electrical remodeling occurs mainly to protect atrial cells from an excess Ca^{+2} accumulation due to fast rates by some auto-protective mechanisms such as Ca^{+2} current inactivation, L-type Ca^{+2} channel down-regulation, and inward rectifier K current enhancement (both I_{K1} and acetylcholine-dependent current [$I_{K\text{-ACh}}$]) that decreases Ca^{+2} loading by reducing APD. With shortened APD, atrial reentry rotors are stabilized increasing AF sustainability (Iwasaki et al., 2011; Olesen et al., 2014).

In J-wave syndromes, main mechanism leading to ERPs and Brugada pattern is explained by an outward shift in cardiac action

TABLE 5 Univariate regression analyses of atrial fibrillation specific clinical parameters as a predictor of atrial fibrillation recurrence in the follow-up of middle-aged patients

Variables	Hazard ratio	p value
Age	0.98 (95% CI, 0.92–1.03)	0.44
Hypertension	0.97 (95% CI, 0.51–1.85)	0.93
Left atrial diameter	1.04 (95% CI, 0.99–1.09)	0.15
Body mass index	1.01 (95% CI, 0.93–1.08)	0.96
DM type II	1.11 (95% CI, 0.81–1.4)	0.80
Infero-lateral ERP	2.42 (95% CI, 1.21–4.82)	0.01

Note. ERP: early repolarization pattern.

Bold value denotes statistically significant parameter.

potential repolarizing current due to a decrease in Na^+ or Ca^{+2} channel currents or an increase in outward currents (I_{to} , $I_{\text{K-ATP}}$, $I_{\text{K-ACh}}$, or other) giving rise to a transmural voltage gradient between endocardium and epicardium on partial regions of the heart leading to lethal ventricular arrhythmias (Antzelevitch, 2013). ERPs seen in J-wave syndromes depend on the part of the heart that is principally affected and which ion channels involved, together with accentuation of the epicardial action potential notch and transmural voltage gradient in different regions of heart (Antzelevitch, 2013; Haïssaguerre et al., 2009). It has previously been shown that there is an abundance of AF and atrial arrhythmias in Brugada Syndrome (Amin et al., 2011) which follows similar ionic mechanisms while giving rise to the distinct J-wave patterns like ERP. Theoretically, diminished cardiac Na^+ current and slowed CV present also in atrial tissue leads to a convenient substrate for reentry waves and excitable tissues could also find enough time to recover from refractoriness creating a suitable environment for AF maintenance.

FIGURE 3 Kaplan–Meier event-free survival curves for middle-aged (≥ 40 – < 60 years) patients being followed up for atrial fibrillation recurrence after pulmonary vein isolation by radiofrequency in patients with and without infero-lateral early repolarization pattern (ERP) on admittance surface ECG

Although it is still yet controversial and hypothetical by which extent does delayed Na current and SCN5A/connexin mutations or other causative mutations taking part in J-wave syndromes play role in initiating, perpetuating, and maintaining an atrial arrhythmia, the ideas about potential common links and overlap between similar existing pathways in AF and ERP/J-wave syndromes are also supported by similar ion channel mutations demonstrated in familial/idiopathic atrial fibrillation patients (Amin et al., 2011; Antzelevitch, 2013; Delaney et al., 2012; Mahida & Ellinor, 2012; Olesen et al., 2014).

4.3 | Autonomic remodelling

In our study, patients with ERPs were demonstrating longer PR intervals and lower basal heart rates. Enhanced vagal autonomic modulation in AF observed in previous studies might be proposed explaining that finding and also ionic changes previously suggested for both ERP and atrial fibrillation (especially reduced Na^+ current) might be speculated about this finding (Gould et al., 2006). Vagal discharge enhances IK_{ACh} , reducing APD and stabilizing reentrant rotors and contributes promoting AF persistence and recurrence (Gould et al., 2006; Iwasaki et al., 2011). Suppression of autonomic signaling may contribute to the efficacy of PV-directed ablation procedures for AF, since model-specific autonomic ganglion ablation effects depend on autonomic innervation changes in some experimental AF models (Nishida et al., 2011). In a recent study, ERPs were found to be associated with both increased vagal tonus and increased left atrial filling pressures, also reflecting a structural left atrial remodeling (Wilhelm et al., 2010). However, in our study, we could not demonstrate any significant difference in the cardiac structures of the patients with or without ERPs by means of 2D transthoracic echocardiography.

Dynamicity of J-wave patterns has already been well demonstrated (Antzelevitch, 2013; Tikkanen et al., 2009), and this

characteristic of ERPs makes up one of the most important limitation of our study together with our retrospective design. We only took into consideration the admittance ECGs of the patients and potentially underestimated the real ERP prevalence. However, we tried to overcome this limitation by excluding the relatively “benign” ERP types, including mainly “malignant” type ERPs with an effort to increase the specificity, statistical power and to prevent a potential type I error in price of a probable type II error due to the relatively small sample sizes (recurrences) in each group. No ventricular events were seen in our study; however, our mean follow-up was relatively short (around 2 years) compared with the long-term population-based J-wave/ERP studies (Haïssaguerre et al., 2009; Tikkanen et al., 2009). Genetical data about some common mutations of K^+ and Na^+ channels observed in populations with ERPs might be helpful to comment on some causative relations with AF mechanisms.

In conclusion, ERPs were found strikingly more prevalent in our adult paroxysmal AF population undergoing PVI procedure than the general population. The presence of infero-lateral ERP with a horizontal/downsloping ST segment in baseline ECG might predict AF recurrence in the follow-up after RF PVI in middle-aged subjects. Our findings might be attributed to some common genetic and electrophysiological mechanisms taking part in the pathophysiology of AF and J-wave syndromes/ERPs. The reason behind the age group dependent findings of our study, the mechanisms of relatively early recurrence and long-term prognosis of AF patients demonstrating ERPs on ECG needs to be elucidated by future research on a large scale of AF ablation patients. ERPs observed on surface ECG seem to provide some prognostic insights into the physicians and might be a cheap, safe, and efficient tool for risk stratification of AF patients being clinically followed up or planned for an ablation procedure.

ORCID

Burak Hunuk <https://orcid.org/0000-0001-6080-8608>

Carlo de Asmundis <https://orcid.org/0000-0001-9351-0760>

REFERENCES

- Amin, A. S., Boink, G. J. J., Atrafi, F., Spanjaart, A. M., Asghari-Roodsari, A., Molenaar, R. J., ... Tan, H. L. (2011). Facilitatory and inhibitory effects of SCN5A mutations on atrial fibrillation in Brugada syndrome. *Europace*, 13(7), 968–975. <https://doi.org/10.1093/europace/eur011>
- Antzelevitch, C. (2013). J-wave syndromes: Molecular and cellular mechanisms. *Journal of Electrocardiology*, 46(6), 510–518. <https://doi.org/10.1016/j.jelectrocard.2013.08.006>
- Calkins, H., Hindricks, G., Cappato, R., Kim, Y.-H., Saad, E. B., Aguinaga, L., ... Yamane, T. (2017). 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. *Heart Rhythm*, 14(10), e275–e444. <https://doi.org/10.1016/j.hrthm.2017.05.012>
- Delaney, J. T., Muhammad, R., Blair, M. A., Kor, K., Fish, F. A., Roden, D. M., & Darbar, D. (2012). A KCNJ8 mutation associated with early repolarization and atrial fibrillation. *Europace*, 14(10), 1428–1432. <https://doi.org/10.1093/europace/eus150>
- Furukawa, Y., Yamada, T., Morita, T., Iwasaki, Y., Kawasaki, M., Kikuchi, A., ... Fukunami, M. (2013). Early repolarization pattern associated with sudden cardiac death: Long-term follow-up in patients with chronic heart failure. *Journal of Cardiovascular Electrophysiology*, 24(6), 632–639. <https://doi.org/10.1111/jce.12093>
- Gould, P. A., Yui, M., Mclean, C., Finch, S., Marshall, T., Lambert, G. W., & Kaye, D. M. (2006). Evidence for increased atrial sympathetic innervation in persistent human atrial fibrillation. *Pacing and Clinical Electrophysiology*, 29(8), 821–829. <https://doi.org/10.1111/j.1540-8159.2006.00447.x>
- Haïssaguerre, P., Derval, N., Sacher, F., Jesel, L., Deisenhofer, I., de Roy, L., ... Clémenty, J. (2008). Sudden cardiac arrest associated with early repolarization. *New England Journal of Medicine*, 358(19), 2016–2023. <https://doi.org/10.1056/NEJMoa071968>
- Haïssaguerre, M., Jaïs, P., Shah, D. C., Takahashi, A., Hocini, M., Quiniou, G., ... Clémenty, J. (1998). Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. *New England Journal of Medicine*, 339(10), 659–666. <https://doi.org/10.1056/NEJM199809033391003>
- Haïssaguerre, M., Sacher, F., Nogami, A., Komiya, N., Bernard, A., Probst, V., ... Clémenty, J. (2009). Characteristics of recurrent ventricular fibrillation associated with inferolateral early repolarization. *Journal of the American College of Cardiology*, 53(7), 612–619. <https://doi.org/10.1016/j.jacc.2008.10.044>
- Iwasaki, Y., Nishida, K., Kato, T., & Nattel, S. (2011). Atrial fibrillation pathophysiology: Implications for management. *Circulation*, 124(20), 2264–2274. <https://doi.org/10.1161/CIRCULATIONAHA.111.019893>
- Kirchhof, P., Benussi, S., Kotecha, D., Ahlsson, A., Atar, D., Casadei, B., ... Zeppenfeld, K. (2016). 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Europace*, 18(11), 1609–1678. <https://doi.org/10.1093/europace/euw295>
- Macfarlane, P. W., Antzelevitch, C., Haïssaguerre, M., Huikuri, H. V., Potse, M., Rosso, R., ... Yan, G.-X. (2015). The early repolarization pattern: A consensus paper. *Journal of the American College of Cardiology*, 66(4), 470–477. <https://doi.org/10.1016/j.JACC.2015.05.033>
- Mahida, S., & Ellinor, P. T. (2012). New advances in the genetic basis of atrial fibrillation. *Journal of Cardiovascular Electrophysiology*, 23(12), 1400–1406. <https://doi.org/10.1111/j.1540-8167.2012.02445.x>
- Maury, P., & Rollin, A. (2013). Prevalence of early repolarisation/J-wave patterns in the normal population. *Journal of Electrocardiology*, 46(5), 411–416. <https://doi.org/10.1016/j.jelectrocard.2013.06.014>
- Mugnai, G., Chierchia, G.-B., de Asmundis, C., Sieira-Moret, J., Conte, G., Capulzini, L., ... Brugada, P. (2014). Comparison of pulmonary vein isolation using cryoballoon versus conventional radiofrequency for paroxysmal atrial fibrillation. *The American Journal of Cardiology*, 113(9), 1509–1513. <https://doi.org/10.1016/j.amjcard.2014.01.425>
- Nishida, K., Maguy, A., Sakabe, M., Comtois, P., Inoue, H., & Nattel, S. (2011). The role of pulmonary veins vs. autonomic ganglia in different experimental substrates of canine atrial fibrillation. *Cardiovascular Research*, 89(4), 825–833. <https://doi.org/10.1093/cvr/cvq332>
- Olesen, M. S., Nielsen, M. W., Haunsø, S., & Svendsen, J. H. (2014). Atrial fibrillation: The role of common and rare genetic variants. *European Journal of Human Genetics*, 22(3), 297–306. <https://doi.org/10.1038/ejhg.2013.139>
- Patel, R. B., Ng, J., Reddy, V., Chokshi, M., Parikh, K., Subacius, H., ... Kadish, A. H. (2010). Early repolarization associated with ventricular arrhythmias in patients with chronic coronary artery disease. *Circulation: Arrhythmia and Electrophysiology*, 3(5), 489–495. <https://doi.org/10.1161/CIRCEP.109.921130>
- Patton, K. K., Ellinor, P. T., Ezekowitz, M., Kowey, P., Lubitz, S. A., Perez, M., ... American Heart Association Electrocardiography and Arrhythmias Committee of the Council on Clinical Cardiology and Council on Functional Genomics and Translational Biology (2016). Electrocardiographic early repolarization. *Circulation*, 133(15), 1520–1529. <https://doi.org/10.1161/CIR.0000000000000388>
- Rollin, A., Maury, P., Bongard, V., Sacher, F., Delay, M., Duparc, A., ... Ruidavets, J.-B. (2012). Prevalence, prognosis, and identification of the malignant form of early repolarization pattern in a population-based study. *The American Journal of Cardiology*, 110(9), 1302–1308. <https://doi.org/10.1016/j.amjcard.2012.06.033>
- Sinner, M. F., Reinhard, W., Müller, M., Beckmann, B.-M., Martens, E., Perz, S., ... Käbb, S. (2010). Association of early repolarization pattern on ECG with risk of cardiac and all-cause mortality: A population-based prospective cohort study (MONICA/KORA). *PLoS Med*, 7(7), e1000314. <https://doi.org/10.1371/journal.pmed.1000314>
- Tikkanen, J. T., & Huikuri, H. V. (2015). Characteristics of “malignant” vs. “benign” electrocardiographic patterns of early repolarization. *Journal of Electrocardiology*, 48(3), 390–394. <https://doi.org/10.1016/j.jelectrocard.2014.12.020>
- Tikkanen, J. T., Anttonen, O., Junttila, M. J., Aro, A. L., Kerola, T., Rissanen, H. A., ... Huikuri, H. V. (2009). Long-term outcome associated with early repolarization on electrocardiography. *New England Journal of Medicine*, 361(26), 2529–2537. <https://doi.org/10.1056/NEJMoa0907589>
- Wilhelm, M., Brem, M. H., Rost, C., Klinghammer, L., Hennig, F. F., Daniel, W. G., & Flachskampf, F. (2010). Early repolarization, left ventricular diastolic function, and left atrial size in professional soccer players. *The American Journal of Cardiology*, 106(4), 569–574. <https://doi.org/10.1016/j.amjcard.2010.03.072>

How to cite this article: Hunuk B, de Asmundis C, Mugnai G, et al. Early repolarization pattern as a predictor of atrial fibrillation recurrence following radiofrequency pulmonary vein isolation. *Ann Noninvasive Electrocardiol*. 2019;24:e12627. <https://doi.org/10.1111/anec.12627>