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## Original Article

## Prevalence of early repolarization pattern and its association with sudden cardiac death and arrhythmia over one-year follow-up in an Egyptian cohort

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## ABSTRACT

**Background and objectives:** Early repolarization pattern (ERP) is not uncommon electrocardiography (ECG) finding and could be associated with arrhythmia and sudden cardiac death (SCD). We aimed to prospectively determine the prevalence of ERP and its association with arrhythmia and SCD during one-year follow-up in an outpatient Egyptian cohort.

**Methods:** Clinical assessment and ECG were performed to 1850 consecutive individuals presented at the outpatient clinic of Suez Canal University Hospital (SCUH). Then, the ERP group and 100 age and gender-matched ERP –ve controls had undergone echocardiography, 24-h Holter ECG and exercise stress ECG.

**Results:** ERP was found in 124 individuals (6.7%); we excluded 24 patients with structural heart disease. ERP group (No. = 100) were relatively young (80% <50 years-old) and showed male preponderance (60%). ERP frequencies were: inferolateral (50%), antero-lateral (38%), inferior (10%), and global (2%). ERP subjects were leaner than controls (BMI was 25.3 vs. 30 kg/m<sup>2</sup>, P value < 0.001) and achieved more metabolic equivalents (METs) on stress ECG (10.7 vs. 8.5 METs, P value < 0.01). Only 4% in the ERP group had horizontal/descending ST slope, while 8% had ST elevation  $\geq$  2 ms. No arrhythmia or SCD were reported during 1-year follow-up in both groups. Regression analysis showed that male gender, Sokolow-Lyon criteria and short QTc were significant independent predictors of ERP, P value < 0.05.

**Conclusions:** In outpatient-based Egyptian cohort, the prevalence of ERP was 6.7%, mostly the inferolateral pattern. Our ERP subjects had low-risk clinical and ECG criteria for malignant ERP. Further epidemiological studies are needed to explore the natural history of ERP.

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## 1. Introduction

There is an increasing concern of ERP among the cardiologists, due to emerging publications correlating ERP to ventricular fibrillation (VF) and SCD. ERP is defined as ST-segment elevation of  $\geq$ 1 leads in 12-lead ECG in the absence of chest pain with terminal QRS notching (J-wave) or slurring.<sup>1</sup>

The prevalence of ERP is highly variable, it was reported to vary between 4 and 10% in the general population up to 40% in highly trained athletes.<sup>1</sup> Initially, ERP was considered benign phenomenon, but recent researches have shown that ERP could be

correlated with SCD and VF. A triggering retrospective study by Haïssaguerre et al.<sup>2</sup> reported that ERP was significantly more frequent in subjects with idiopathic VF than in control subjects (31% vs. 5%, P value <0.001).

Consequently, many successive studies assessed the association of ERP and risk of arrhythmia and SCD.<sup>3–6</sup> Tikkanen et al. studied the prevalence and prognostic significance of ERP in 10,864 middle-aged subjects and reported that ERP in the inferior leads was associated with cardiac mortality.<sup>4</sup>

However, many critical appraisals proposed that ERP per se is not the actual trigger for VF or SCD. Their rationale was that despite the commonly found ERP in the general population, idiopathic VF is rather rare.<sup>3</sup> Moreover, ERP has been frequently observed in patients with short-QT syndrome (SQTS) which itself is a surrogate for VF and SCD. ERP was found in 65% of patients with SQTS and history of VF and in 30% of patients with SQTS without reported arrhythmia.<sup>3</sup> Furthermore, another study reported that patients with idiopathic VF often have short-QT interval or

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low-normal QT interval. Therefore, they concluded that the etiology of idiopathic VF and SCD in some patients, including patients with ERP, is a genetic mutation responsible for SQTS, not the ERP itself.<sup>5</sup>

We don't have enough literature in Egypt about ERP prevalence or possible associated risk. One study concluded that ERP was prevalent in Egyptian male patients with acute STEMI (42.1%, 42/102) and it was associated with increased risk of ventricular arrhythmias during 48 h of acute STEMI (OR: 3.39, 95% CI: 1.41–8.12,  $P < 0.006$ ).<sup>6</sup>

This study aimed to assess the prevalence and characteristics of ERP in a prospective study involving Egyptian cohort attending SCUH outpatient clinic, and to report its associated risk of arrhythmia and SCD.

## 2. Methods

### 2.1. Study design

This is a single-center, prospective, observational study conducted between January 2015 to December 2015. This study was abiding with the ethical guidelines of the 1975 Declaration of Helsinki and approved by our institutional Ethical Review Board. All subjects had been given information sheet about the study protocol, and they had provided written informed consent to participate in the study.

### 2.2. Study population and data collection

We have evaluated 1850 consecutive subjects who attended the outpatient clinic of cardiology and internal medicine at SCUH, Ismailia, EGYPT. This included detailed medical history, clinical assessment and ECG. Patients on anti-arrhythmic drugs, or with AF, paced rhythm, bundle branch block, Brugada syndrome, long and short QT syndromes, Wolf-Parkinson-White (WPW) syndrome, or documented structural heart disease (i.e. CAD, valvular heart disease and cardiomyopathy) were excluded.

ERP was observed in 124 subjects, of whom 24 were excluded as recent echocardiography revealed structural heart disease. The ERP subjects (no = 100) were further assessed with echocardiography, Holter ECG, and exercise stress test, compared to 100 age and gender-matched controls. Both groups were followed-up for 1-year for occurrence of SCD and arrhythmia.

### 2.3. Electrocardiography

We performed the standard 12-lead ECGs while all subjects in supine position after rest in a quiet room with a quiet respiration. We assessed the presence of ERP by analyzing J wave and ST elevation (STE) according to Antzelevitch et al.<sup>1</sup> and Haissaguerre et al.<sup>2</sup> criteria. All ECGs were recorded at a gain of 10 mm/mV and a velocity of 25 mm/s. ERP was diagnosed when the ECG has: QRS notch or slur on the down-slope of a R wave, J peak is  $\geq 0.1$  mV in 2 contiguous leads, and STE  $\geq 1$  mm of the junction between the QRS offset and ST segment onset (J point) in at least 2 contiguous leads. We further analyzed STE as ascending or horizontal/descending patterns.

ECG tracings were interpreted by 2 cardiologists (MW) and (ATA) for the analysis of J wave and STE. ERP was classified as anterior ( $V_1$ – $V_4$ ), lateral ( $V_5$ – $V_6$ , I, and aVL), or inferior (II, III, aVF) leads. In case of disagreement, a third cardiologist was called (HH) for a blinded ECG interpretation. The clinical characteristics and vital status of participants were blinded during ECG interpretation.

Further ECG analysis included assessment of: heart rate, PR interval, QRS duration, QTc interval (QT corrected with Bazett

formula), and Sokolow-Lyon criterion for left ventricular (LV) hypertrophy ( $SV_1 + RV_{5,6} \geq 35$  mm).

### 2.4. Echocardiography

Echocardiographic studies included M-mode, two-dimensional, and color Doppler flow with subjects in the supine position using Vivid 7 device (General Electric, Dimensions Vingmed) with 2.5-MHz phased array probe. Images were acquired in multiple cross-sectional planes using standard positions. LV cavity measurements, filling and relaxation parameters were obtained following the recommendations of the American Society of Echocardiography.<sup>7</sup>

### 2.5. Ambulatory 24-h Holter ECG

All patients had undergone 24-h Holter ECG at SCUH, using Schiller MT 101 device. This test was done for detection of HR trend, supraventricular and ventricular arrhythmia.

### 2.6. Exercise stress ECG

Exercise stress test was performed using Burdick Quest with a Quinton Q-Stress TM55 treadmill. All enrolled patients underwent a maximal exercise stress test using the Bruce protocol. We reported baseline HR, maximum HR, exercise metabolic equivalents (METs), peak systolic and diastolic blood pressure, and occurrence of arrhythmic events or ST changes.

### 2.7. Laboratory evaluation

Serum potassium, calcium and magnesium levels were checked, and any abnormalities were reported and corrected. Blood samples were collected immediately after admission in the dedicated tubes and processed by personnel blinded to patients' data.

### 2.8. Follow-up

All previous tests were done once at the initial visit. The main study outcomes were occurrence of arrhythmia and/or SCD. SCD was defined as death due to cardiac causes occurring within 1 h of the onset of symptoms. These data were obtained from SCUH registry and clinical records, patients themselves during follow-up at the outpatient clinic or patients relatives (predetermined at the initial visit) by telephone conversation.

### 2.9. Statistical analysis

We have conducted the statistical analyses with SPSS (version 21.0; SPSS Inc., Chicago, IL, USA). Quantitative data were expressed as means  $\pm$  SD and compared by using Student's T-test while qualitative data were expressed as numbers and percentages and compared by using chi-square tests. Stepwise logistic regression analysis of ERP risk factors was performed by assessment of odds ratio (OR) of the study variables and reported as OR and 95% confidence interval (CI). This included age, gender, smoking, hypertension, diabetes mellitus (DM), RR interval, QTc interval, QRS duration, and Sokolow Lyon criteria.  $P$  value  $< 0.05$  was considered statistically significant.

## 3. Results

Initially, this study included 1850 individuals who attended the outpatient clinic of SCUH between January and December 2015. Clinical evaluation and ECG were done for all participants. ECG

with ERP was prevalent in 124 individuals (6.7%). We excluded 24 patients with structural heart disease from the study. The most frequent ERP was the inferolateral (50%), antero-lateral (38%), while other patterns were less common, (Fig. 1 and 2, and Table 1).

We further characterized the ERP group by analyzing the ECG components of ERP. STE  $\geq 0.2$  mV was only found in 8 patients (8%), and horizontal or descending ST segment slope was only found in 4 patients (4%).

Then, we conducted 24-h Holter ECG, echocardiography and exercise stress ECG test to the ERP group (100 individuals) and the control group (100 individuals, ERP -ve, age and gender matched). Furthermore, both groups were followed-up for 1 year after enrollment to report arrhythmia and/or SCD. We were able to follow-up 97 subjects in the ERP group (97%) and 95 subjects in the control group (95%) for one year. Interestingly, no reported SCD or arrhythmia in both groups during 1-year follow-up.

Individuals with ERP were relatively young (mean age  $\pm$  SD:  $37.7 \pm 13.6$  years-old, 80% were  $<50$  years-old) with male preponderance (60%). The ERP +ve group had less BMI than the control group (mean  $\pm$  SD,  $25.3 \pm 4.1$  versus  $30.3 \pm 5.0$  kg/m<sup>2</sup>, respectively, P value  $< 0.001$ ). the prevalence of hypertension, DM, and smoking was comparable in both groups. Only 1 individual in each group reported family history of SCD, while no reported history of syncope or resuscitated SCD in both groups. Serum electrolytes were comparable in both groups, Table 2.

ECG analysis showed that Soklow-Lyon criteria for LVH was significantly higher in the ERP group than in the control cohort (mean  $\pm$  SD,  $3.37 \pm 0.96$  vs.  $2.72 \pm 0.89$  mV, respectively, P value 0.01). On the other hand, the corrected QT interval (QTc) was significantly shorter in the ERP group than in the control cohort (mean  $\pm$  SD,  $412.7 \pm 18.9$  vs  $419.7 \pm 21.1$  ms, respectively, P value  $< 0.05$ ). However, other parameters like HR, PR interval and QRS duration were comparable in both groups, Table 3.

Exercise stress ECG showed that individuals of the ERP group had a positive trend to achieve better maximum predicted HR (MPHR) than control cohort, but this wasn't statistically significant. However, the individuals with ERP were more physically fit and achieved more metabolic equivalents (METs) than their ERP -ve counterparts, (mean  $\pm$  SD,  $10.7 \pm 2.3$  vs  $8.5 \pm 2.2$  METs, respectively, P value  $< 0.02$ ). Peak systolic and diastolic blood pressure were comparable in both groups.

Only 13 subjects had their test terminated before they achieved their MPHR due to ischemic ECG changes and fatigue, 7 subjects in the ERP +ve group and 6 subjects in the control group. No reported serious arrhythmia during exercise stress test in both groups. Echocardiographic and Holter ECG (24-h recording) findings were comparable in both groups, Table 3. A stepwise multivariate logistic regression analysis revealed that male gender, Sokolow-Lyon voltage, and shorter QTc interval were the most significant independent risk factors for development of ERP, respectively (Table 4).

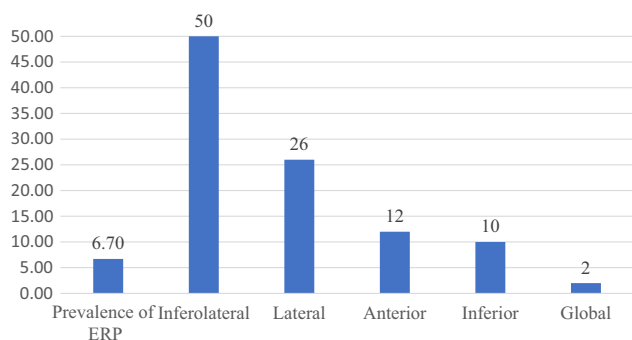


Fig. 1. Prevalence and Distribution of ERP among individuals of the study group.

## 4. Discussion

### 4.1. Prevalence of ERP, demographic and clinical characteristics

Up to our knowledge, this is the first study to address the prevalence of ERP in Egypt in an outpatient-based cohort. ERP was prevalent in 124 individuals (6.7%) in the ECG tracings of a prospective 1850 individuals, attended the outpatient clinic of SCUH during one year. Generally, the prevalence of ERP is variable across different studies, some studies reported a close prevalence to our work i.e. 5%<sup>2</sup> and 5.8%<sup>3</sup> while others reported higher prevalence, i.e. 18.6% in hospital-based cohort<sup>8</sup> and up to 40% in highly trained athletes.<sup>1</sup>

We excluded 24 patients with ERP and documented structural heart from our study to avoid potential confounders in their Holter ECG, stress ECG assessment, and 1-year outcome.

The most frequent ERP was the infero-lateral (50%), antero-lateral (38%), while other patterns were less common. These patterns are close to the results of Diab and co-workers<sup>6</sup> in Egyptian patients with acute STEMI; the inferolateral ERP was 51.8% and the lateral ERP was 24.1%. However, our findings are different from other studies conducted in China and USA.<sup>9,10</sup> A large population-based study in China reported that the inferolateral ERP was 21% and lateral ERP was 66.1% in 2642 individuals.<sup>9</sup> Another study in USA involved 704 athletes reported that the ERP was global in 72% of subjects, 25% in the lateral leads, and only 3% in the inferior leads.<sup>10</sup> These variations in the ERP distribution could be due to ethnic or genetic variations, and variable characteristics of the individuals enrolled in these studies.

Our study reported a low prevalence of ECG criteria suggestive of high risky ERP. In the ERP group, ST segment elevation  $\geq 0.2$  mV was only found in 8 patients (8%), while horizontal or descending ST segment slope was only found in 4 patients (4%). These criteria were proposed by findings of post VF arrest survivors with ECG showing ERP.<sup>1,2,4</sup> This is going with the clinical history reported by our cohort with ERP; they didn't report syncope attacks, they haven't been resuscitated from sudden cardiac arrest and only 1 participant (1%) in ERP group reported family history of SCD. Moreover, they were clinically well with relatively lean body weight and physically fit as proved by exercise stress ECG. These clinical criteria are matching the low-risk ERP as reported by many studies.<sup>1,2,4,10</sup>

Our ERP group were young (80% were  $<50$  years-old) with male predominance (60%). These findings were reported by Sun et al. 2017 in a large prospective Chinese population (11,956 subjects), as male gender constituted 92% of the ERP group and  $>50\%$  of them were  $<54$  years-old.<sup>9</sup> Another study reported that 87% of ERP group were males and 66% were  $<40$  years old.<sup>11</sup> Male gender is strongly associated with ERP as more than 70% of individuals with ERP were men in different ethnic studies.<sup>3,8–11</sup> However, this male predominance was not explained by most of the studies. It was suggested that this may result from large density of epicardial channels of the transient outward potassium current (Ito) caused by higher levels of testosterone, which could be responsible for shortening of action potential duration (APD) and occurrence of ERP and J wave consequently.<sup>1,12</sup>

ERP was associated with younger age in most of the studies<sup>9–12</sup>, and it was declining with advanced age in some studies.<sup>8,10</sup> However, no explanation was provided for this observation. The CARDIA study investigated 5069 participants and found that ERP was common in young adults (18.6%, mean age 25 years), and many of these patients had their ERP vanished at their middle age.<sup>8</sup>

We reported that the ERP group significantly had less BMI than the control group (mean  $\pm$  SD,  $25.3 \pm 4.1$  vs.  $30.3 \pm 5.0$  kg/m<sup>2</sup>, respectively, P value  $< 0.001$ ). The CARDIA study<sup>8</sup> and another large



#### Case 1:

A 21-year-old gentleman, boxing player. He has sinus bradycardia (HR 48 bpm). ERP involves inferolateral leads. Note that notching is not apparent in all leads, even within the same lead.

#### Case 2:

A 49-year-old gentleman. ERP involves inferior leads only. Note that notching (arrows) is apparent in all inferior leads.

**Fig. 2.** Examples of ECG with ERP.

hospital-based study conducted by Klatsky et al.<sup>11</sup> found that one of the characteristics of patients with ERP was low BMI. However, they didn't provide an explanation for this observation.

#### 4.2. Echocardiographic findings

Our study showed no significant difference between both groups in echocardiographic measurements or Holter ECG record-

ing. These findings were reported by Quattrini et al.<sup>10</sup> who reported that no difference between ERP group (102 subjects) and normal group (602 subjects) in arrhythmia or main echocardiographic parameters. Only LV mass, LV wall thickness and LVEDD were slightly higher, but still significant, in the ERP group versus the control group. However, both groups had comparable LVEF and other tissue Doppler parameters. Moreover, both groups were athletes which could affect LV wall thickness and dimensions, as

**Table 1**  
ECG characteristics of ERP group.

Variable, No. (%)	ST Elevation		ST Slope	
	< 0.2 mv	≥ 0.2 mv	Ascending	Horizontal/Descending
Infero-lateral, 50 (50%)	47	3	48	2
Antero-lateral, 38 (38%)	35	3	37	1
Inferior, 10 (10%)	9	1	9	1
Global, 2 (2%)	1	1	2	0
Total, 100 (100%)	92	8	96	4

**Table 2**  
Demographic and clinical characteristics of the study participants.

Variable	ERP –ve group (n = 100)	ERP +ve group (n = 100)	P Value
<i>Demographic and Anthropometric characteristics</i>			
Gender			0.08
Male, No (%)	47 (47%)	60 (60%)	
Female, No (%)	53 (53%)	40 (40%)	
Age, years, mean ± SD	38.9 ± 10.4	37.7 ± 13.6	0.46
Weight, kg, mean ± SD	84.04 ± 14.9	75.52 ± 11.2	0.001*
Height, cm, mean ± SD	166.8 ± 9.7	173.2 ± 9.0	0.01*
BMI, kg/m <sup>2</sup> , mean ± SD	30.3 ± 5.0	25.3 ± 4.1	0.001*
<i>Clinical characteristics</i>			
SBP, mmHg, mean ± SD	136 ± 19	133 ± 21	0.09
DBP, mmHg, mean ± SD	82 ± 11	79 ± 13	0.11
DM, %	10	6	0.43
Hypertension, %	12	19	0.24
Smokers, %	24	21	0.73
Family History of SCD, %	1	1	NA
<i>Electrolytes</i>			
Sodium	137.8 ± 14.9	139.2 ± 16.2	0.41
Potassium	3.9 ± 0.32	4.0 ± 0.39	0.38
Magnesium	1.9 ± 0.19	1.9 ± 0.21	0.46

ERP early repolarization pattern, kg kilogram, BMI body mass index, m meter, SBP systolic blood pressure, DBP diastolic blood pressure, DM diabetes mellitus.

\* Significant difference.

**Table 3**  
ECG, Echocardiographic, 24-h Holter and stress ECG findings.

Variable	ERP –ve group (n = 100)	ERP +ve group (n = 100)	P Value
<i>Electrocardiographic characteristics, mean ± SD</i>			
HR, bpm	81.2 ± 12.5	78.7 ± 10.3	0.09
PR interval, ms	155.8 ± 19.7	157.3 ± 22.5	0.08
QTc interval, ms	419.7 ± 21.1	412.7 ± 18.9	0.05*
QRS duration, ms	93.8 ± 11.4	95.2 ± 9.6	0.2
Sokolow-Lyon, mV	2.72 ± 0.89	3.37 ± 0.96	0.01*
<i>Echocardiographic characteristics, mean ± SD</i>			
LVEF, %	61.5 ± 7.8	63.7 ± 8.4	0.1
LVEDD, mm	48.6 ± 5.2	49.9 ± 6.4	0.1
LVESD, mm	30.9 ± 4.6	32.1 ± 5.4	0.09
<i>Holter ECG (24-h recording)</i>			
SDNN, ms, mean ± SD	105.39 ± 28.45	108.29 ± 31.13	0.09
Maximum HR, bpm, mean ± SD	122.3 ± 33.9	127.5 ± 25.6	0.06
Minimum HR, bpm, mean ± SD	49.5 ± 7.9	46.4 ± 14.2	0.13
Average HR, bpm, mean ± SD	73.1 ± 11.2	69.3 ± 6.4	0.11
Paroxysmal AF > 1%, %	2	3	0.08
SVT > 1%, %	3	4	0.18
Frequent PVCs, %	1	1	NA
<i>Exercise stress ECG, mean ± SD</i>			
Maximum Predicted HR reached %	92.7 ± 7.1	94.2 ± 6.3	0.06
Exercise METs	8.5 ± 2.2	10.7 ± 2.3	0.02*
Peak systolic blood pressure, mmHg	187 ± 21	185 ± 91	0.13
Peak systolic blood pressure, mmHg	95 ± 8	93 ± 6	0.16

HR hear rate, ms millisecond, LV left ventricle, EF ejection fraction, EDD end-diastolic diameter, ESD end-systolic diameter, mm millimeter, SDNN mean of the standard deviation of normal to normal R-R intervals, bpm beats per minute, AF atrial fibrillation, SVT supraventricular tachycardia, PVCs premature ventricular complexes, METs metabolic equivalents.

\* Significant difference.

stated by the study investigators.<sup>10</sup> We have excluded patients with ERP and structural heart disease (n = 24 patients) to avoid confounder factors which could affect the study outcomes at 1-year follow-up. Then, we have chosen the control group age and gender matched. These factors might be responsible for the similarity of both groups in echocardiographic measurements and Holter ECG recording.

#### 4.3. Baseline and Holter ECG findings

ECG analysis showed that Sokolow-Lyon criteria for LVH was significantly higher in the ERP group than in the control cohort (mean ± SD, 3.37 ± 0.96 vs. 2.72 ± 0.89 mV, respectively, P value 0.01). This was reported in previous ERP studies<sup>2,4,8–10</sup>, as they reported that electrocardiographic LVH was prevalent in ERP and is considered as a predictor of ERP. However, none of these studies reported associated increased risk of arrhythmia or SCD with LVH in ERP.

**Table 4**  
Stepwise logistic regression analysis of ERP risk factors.

Variable	P Value	OR	95% C.I. for OR	
			Lower	Upper
Age	0.64	0.99	0.96	1.02
Gender	0.03*	2.08	1.06	4.12
Smoking	0.17	1.79	0.77	4.18
Hypertension	0.19	0.53	0.21	1.38
Diabetes	0.2	2.36	0.63	8.88
RR interval	0.08	0.79	0.63	0.99
QTc interval	0.041*	1.41	1.29	2.18
QRS duration	0.1	1.06	0.95	1.24
Sokolow-Lyon LVH criteria	0.022*	1.98	1.57	2.48

LVH left ventricular hypertrophy, OR odds ratio.

\* Significant difference.

On the other hand, the corrected QT interval (QTc) was significantly lower in the ERP group than in the control cohort (mean  $\pm$  SD,  $412.7 \pm 18.9$  vs  $419.7 \pm 21.1$  ms, respectively,  $P$  value  $< 0.05$ ). Many studies reported the same finding<sup>2,9,13</sup> including a recent study of 2950 subjects with ERP in Korea which reported that ERP was associated with short QT interval.<sup>13</sup>

We reported that PR interval and QRS duration were comparable in both groups. QRS duration was reported to be comparable in the ERP group versus control subjects previously.<sup>2,9</sup> Haïssaguerre et al.<sup>2</sup> reported that PR interval was comparable in both groups, while Sun et al.<sup>9</sup> reported that PR is longer in the ERP group than in controls.

In an important study which assessed benign versus malignant inferolateral ERP, Roten et al.<sup>14</sup> studied 92 patients with history of aborted SCD due to VF and baseline ERP ECG versus another 247 subjects with asymptomatic ERP. They concluded that QRS duration and PR interval were comparable in both groups, while QTc duration was significantly longer in the ERP and VF group than in the asymptomatic ERP group.<sup>14</sup>

Our study showed that Holter ECG didn't reveal significant difference between both groups. There was a trend that ERP group has slower average HR, but this wasn't statistically significant. The frequency of paroxysmal AF, SVT and PVCs were comparable in both groups. Quattrini et al. reported that athletes with and without ERP had comparable Holter ECG findings regarding prevalence of SVT or PVCs.<sup>10</sup>

#### 4.4. Exercise stress ECG findings

Exercise stress ECG showed that individuals of the ERP had a positive trend to achieve better maximum predicted heart rate (MPHR) than control cohort, but this wasn't statistically significant (mean  $\pm$  SD,  $94.2 \pm 6.3\%$  vs  $92.7 \pm 7.1\%$ , respectively,  $P$  value  $< 0.06$ ). However, the ERP individuals were more physically fit and achieved more metabolic equivalents (METs) than their control group, (mean  $\pm$  SD,  $10.7 \pm 2.3$  vs  $8.5 \pm 2.2$  METs, respectively,  $P$  value  $< 0.02$ ). No reported serious arrhythmia during exercise stress test in both groups.

Quattrini et al.<sup>10</sup> reported that peak workload achieved by athletes with ERP was higher than what was achieved by athletes without ERP. Klatsky et al.<sup>11</sup> reported that individuals with ERP were practicing exercise more than control group without ERP; the same was reported by Ahmed et al.<sup>15</sup> in USA who reported that subjects with ERP (no = 228) were practicing sports more than control subjects without ERP, especially playing football, indicating more physical fitness.<sup>15</sup>

Klatsky et al.<sup>11</sup> explained the association between ERP and physical fitness; they proposed that predisposing genetic traits could be common in athletics and ERP. One more explanation was the assumption that ERP was a sequel of exercise. Factors that favored these assumptions were lower body mass index and low HR and in the ERP group.<sup>11</sup> Walsh et al.<sup>8</sup> reported that ERP was associated with increased vagal tone and better cardiovascular fitness.

#### 4.5. Predictors of ERP

We reported in a stepwise multivariate logistic regression analysis that male gender, Sokolow-Lyon voltage, and shorter QTc interval were the most significant independent risk factors for the development of ERP in this Egyptian cohort, respectively.

Quattrini et al.<sup>10</sup> reported that ERP was associated with Sokolow score, ST segment elevation and male gender. Likewise, Sun et al.<sup>9</sup> demonstrated that age, male gender, SBP, stroke, QTc duration, Sokolow-Lyon voltage, and QRS duration were significant indepen-

dent clinical factors for development of ERP. Male gender was the most powerful predictor of ERP.<sup>9</sup>

As explained earlier, male gender is associated with increased level of testosterone is associated with large density of epicardial channels of the transient outward potassium current (Ito), which could be responsible for shortening of action potential duration (APD) and occurrence of ERP.<sup>1,12</sup> Shorter QTc intervals are associated with shortening of APD as well which leads to occurrence of ERP and J wave.<sup>5</sup> It was suggested that lean subjects, who constituted most of ERP individuals in our study, usually have a high Sokolow-Lyon index.<sup>15</sup>

#### 4.6. Risk of arrhythmia and mortality in ERP

Interestingly, we didn't report SCD or arrhythmia in both groups during the 1-year follow-up. Data from large epidemiological studies and case-control studies were conflicting regarding the association of ERP with arrhythmia and SCD. This could be explained by interaction of heritable and environmental influences which contribute to the presence of ERP and could determine its phenotype and the likelihood of arrhythmia and/or SCD.<sup>1</sup>

Regarding history, our ERP group have low-risk profile, which was reported by other studies. Ahmed et al.<sup>15</sup> studied 575 adolescents in USA and reported that 40% (n = 228) had ERP. They reported no difference in history of syncope, family history of (SCD, arrhythmia or ICD/pacemaker requirement) in ERP subjects versus controls. They further reported that subjects with ERP were physically fit, compared to controls. Moreover, they didn't report mortality or arrhythmia at follow-up.<sup>15</sup>

Quattrini et al.<sup>10</sup> studied 102 athletes with ERP and 602 athletes without ERP. No significant difference between 2 groups in clinical variables, echocardiographic or Holter ECG findings. They concluded that ERP was common in highly trained athletes and didn't carry risk for adverse cardiac events, arrhythmia or SCD.<sup>10</sup>

Many studies reported the association of ERP with SCD, mortality and arrhythmia. Cho et al.<sup>13</sup> reported, in a large epidemiological study, a low mortality of 2.7% over 10 years of follow-up of 2950 with ERP (out of 26,345 Korean subjects). They concluded that ERP with J wave had higher mortality risk, while other ERP varieties had similar survival compared to control group.<sup>13</sup>

The robust study of Haïssaguerre et al.<sup>2</sup> reported an increased prevalence of ERP in 206 subjects with VF compared with 412 control subjects (HR: 2.1; 95% CI, 1.2–3.5;  $P < 0.001$ ). Another study by Rosso et al.<sup>16</sup> also revealed that inferolateral ER was more frequent in 45 patients with VF compared with 121 matched control subjects. However, it is essential to explain that both studies have assessed the ERP prevalence in high risky patients with VF, not in the general population.

A large study of 10,864 individuals in Finland by Tikkanen et al.<sup>4</sup> found that inferolateral ERP was associated with an increased risk of SCD, particularly in patients with inferior ERP  $\geq 2$  mm (relative risk, 2.92; 95% CI).<sup>4</sup> On the other hand, other large studies reported no association between ERP, arrhythmia or SCD. Klatsky et al.<sup>11</sup> reported that patients with ERP were not significantly at greater risk of hospitalization or death. Of 1455 patients hospitalized for chest pain, only 10 (1.5%) had ERP. Interestingly, tachyarrhythmia was less common in the ERP group versus control group,  $P < 0.01$ . Mortality rate was lower in the ERP group (5.6%) than in the control group (10.98%); CV death represented 27% of mortality in the ERP group versus 39% in the control group ( $P$  value  $< 0.2$ ). Therefore, the authors suggested that ERP has a benign prognosis, without an increased risk of CV disease or death.<sup>11</sup>

Tikkanen et al.<sup>4</sup> and Rosso et al.<sup>16</sup> reported that ascending ST-segment slope is a benign finding in ERP which has not predicted mortality or SCD in any of the general population, which is the case in 96% of our ERP group. They concluded that ERP with a horizontal

or downward ST segment slope, which represented 4% of our ERP cohort, was potentially more serious and associated with VF.<sup>16</sup>

Uberoi et al.<sup>17</sup> evaluated resting ambulatory ECGs of 29,281 individuals; ERP prevalence was 2.3%. They reported that all ECG components of ERP were associated with decreased CV mortality. They concluded that no significant association between CV mortality and any ERP components at ECG.<sup>17</sup>

One of the important explanations of this controversy between different hospital or population-based studies of the associated risk of ERP with serious arrhythmia or SCD is that we should differentiate between ER syndrome who should have aborted SCD and ERP versus subjects with ERP at ECG without significant clinical or ECG high-risk profile.<sup>13</sup>

## 5. Conclusion

Up to our knowledge, this is the first work to study the prevalence of ERP (6.7%) in a large outpatient Egyptian cohort (n = 1850). Egyptians with ERP are generally young, mostly males, lean, and physically fit. The most statistically significant ERP predictors are male gender, Sokolow-Lyon voltage criterion and short QTc intervals. ERP in our Egyptian cohort is generally a benign finding (no syncope, no aborted SCD, scarce family history of SCD, and low prevalence of high-risk ECG criteria of malignant ERP). Moreover, we didn't report SCD or significant arrhythmia among ERP cohort at 1-year follow-up. Our study findings and outcome are close to many of the reported ERP literature, involving different methods and population ethnics. However, many other studies reported a malignant nature of ERP, mostly in patients with aborted SCD due to VF. We recommend conducting a larger epidemiological study with a longer follow-up period that should include patients with structural heart disease, reported ventricular arrhythmia and aborted SCD to explain the natural history of ERP in Egyptians.

## Study limitations

This study is a single-center, prospective study with 1-year follow-up period. Despite the initial sample size including 1850 subjects for screening, only 100 subjects with ERP were included. Our ERP subjects had low-risk clinical profile, i.e. no syncope, no history of aborted SCD, and scarce family history of SCD with low-risk ECG criteria for malignant ERP. Altogether, these factors may have led to absence of SCD or arrhythmia at follow-up.

## Conflicts of interest

All authors of this manuscript declare no conflict of interest.

## Financial disclosures

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## Disclosure

All listed authors declare no conflict of interest.

## Authorship declaration

All listed authors are in agreement with the manuscript.

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