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Early repolarization in adolescent athletes: A gender comparison of ECG and echocardiographic characteristics

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Background: The early repolarization pattern (ERp) is an electrocardiographic finding previously associated with arrhythmic risk in adults. The purpose of this study is to evaluate the prevalence and characteristics of ERp in a group of adolescent athletes according to gender. Furthermore, potential associations with clinical, electrocardiographic, and echocardiographic parameters are explored.
Methods: In this cross-sectional study young athletes (age < 18 years) were consecutively enrolled during the annual pre-participation evaluation, undergoing also transthoracic echocardiography assessment from January 2015 to March 2020.
Results: The prevalence of ERp was 27% in the whole population. Athletes with ERp were more frequently men practicing endurance sports. Women with ERp showed lower heart rate at rest, greater posterior, and relative ventricular wall thickness than those without ERp. Men with ERp presented higher systolic blood pressure at peak exercise, greater septal wall thickness, and indexed left ventricular mass than those without ERp. Both genders with ERp showed increased QRS voltage and narrower QRS duration. The ERp phenotype in men was more frequently notched with higher amplitude and ascending ST segment. Women's ERp presented more frequently a slurred morphology, especially in the inferior leads, and horizontal ST slope. No differences emerged in the occurrence of arrhythmias at rest and during maximal exercise test between groups, even considering higher risk phenotypes.
Conclusions: ERp is an ECG finding compatible with normal cardiac adaptations to training in young athletes. ERp demonstrated gender differences regarding phenotypes previously associated with increased cardiovascular risk, not showing any differences in arrhythmias during maximal exercise test.

KEYWORDS
arrhythmic risk, athlete's heart, early repolarization, pre-participation screening, young athlete

1 | INTRODUCTION

The early repolarization pattern (ERp) is an electrocardiographic (ECG) finding defined as an elevation of the J point ≥0.1 mV in ≥2 contiguous inferior (II, III, aVF) or lateral (I, aVL, V4–V6) leads. The prevalence in the general population ranges from 3% to 13%[1] and is higher in young individuals, males, and the Afro-Caribbean ethnicity.[2] This pattern was considered as a benign electrocardiographic variant until 2008 when some studies challenged this concept correlating ERp with arrhythmic events, idiopathic ventricular fibrillation,[3,4] and increased cardiovascular mortality risk.[5] In particular, the ERp phenotypes characterized by horizontal or down-sloping ST segments,[6] inferior leads involvement,[7] and higher J point amplitude (>0.2 mV),[8] were associated with higher risk of life-threatening ventricular arrhythmias.

The electrophysiological mechanism involved in ERp is still not fully understood. ERp belongs to J-wave syndromes with several underlying shared pathophysiological and morphological mechanisms.[9] ERp seems a consequence of a transmural voltage gradient, caused by an action potential notch only in epicardium (not engaging endocardium), due to a heterogeneous transmural distribution of transient outward potassium current.[10] Precisely, this ion voltage gradient during the early phase of repolarization, could theoretically increase arrhythmia susceptibility caused by local re-excitation.[1]

Adolescent athletes present ERp more frequently than non-athletes,[11] however, no studies in this specific population correlated this pattern with an increased risk of malignant events, including sudden cardiac death (SCD). Indeed, ERp could be considered a benign training-related ECG phenomenon with a dynamic pattern,[12] that not necessarily reflects exercise-induced morphologic remodeling and it seems to be importantly influenced by sexual maturation.[13] Moreover, ERp has been described with a different prevalence of phenotypes previously associated with increased cardiovascular risk in the two genders,[14–16] but no data have yet shown differences regarding ERp phenotypes related to arrhythmic risk and morphological cardiac adaptations in young athletes.

Thus, the aim of this study was to analyze the prevalence and characteristics of ERp evaluating gender differences and its relationship with resting and maximal exercise ECG findings as well as the associated cardiac morphological features.

2 | METHODS

2.1 | Study setting

This cross-sectional study consecutively enrolled adolescent athletes (10–18 years), referred for the annual sport pre-participation evaluation to the Sports and Exercise Medicine Division of the University Hospital of Padova and that also underwent transthoracic echocardiography between January 2015 and March 2020. Exclusion criteria were age > 18 years and known cardiac disease (congenital heart disease, previous cardiac disease, or arrhythmogenic cardiomyopathies such as hypertrophic cardiomyopathy, primary dilated cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, Brugada syndrome, long QT syndrome, and arrhythmic myo-pericarditis). Data regarding patients' medical history, physical examination, ECG characteristics, exercise test outcomes, and transthoracic echocardiography parameters were collected for each participant. A control group of consecutively enrolled young athletes was also analyzed to exclude selection bias. This study was performed in accordance with the Declaration of Helsinki and approved by the local ethics committee (100n/AO/21); all participants provided written informed consent.

2.2 | Medical history, physical examination, and maximal exercise test

Clinical information, including family and personal medical history were collected through a reproducible and standardized interview. The sport practiced was evaluated qualitatively according to the predominant component of exercise, according to the 2020 ESC Guidelines on Sports Cardiology and Exercise in patients with cardiovascular disease[17] and quantitatively based on weekly hours of training.

Anthropometric parameters and blood pressure values were collected by well-trained nurses. Systolic (SBP) and diastolic blood pressure (DBP) values were manually measured at rest, at peak exercise, and during the recovery phase.

The maximal exercise test was performed on a treadmill with an incremental standardized ramp protocol.[18] Criteria of exhaustion were a Borg rating of perceived exertion ≥18/20 associated with a maximal HR ≥85% of predicted.[19] Exercise capacity was evaluated by metabolic equivalents of task (METs) and test duration at peak exercise. The presence of isolated and/or repetitive ventricular arrhythmias was also analyzed, specifying common, and uncommon characteristics in athletes; morphology, complexity, and interval have been evaluated.[20–22]

2.3 | ECG analyses

All participants were monitored through a 12-lead ECG at rest in supine position, during all phases of the maximal exercise test and for the first 4 min of recovery. The

QT interval measured at rest was corrected using Bazett's formula and the QRS complex duration was detected in those leads where ERp was not present. QRS voltage were assessed using the Sokolow–Lyon voltage criteria (S wave depth in V1 + R wave amplitude in V5/V6 ≥ 35 mm).

The definition and characteristics of ERp were obtained following the MacFarlane criteria presented in the 2015 consensus paper.[23] In particular, ERp was defined as J-point elevation above baseline of at least 1 mm (0.1 mV) in ≥2 contiguous leads. Morphology (notching or slurring), region (inferior if in leads II, III, aVF, or lateral if in leads I, aVL, V4-V6), ST segment (ascending, horizontal, or descending), amplitude (J_o, J_p, and J_t), and duration (D_1 and D_2) were described for each ERp (Figure 1). According to literature, a J_p elevation >0.2 mV was chosen as the cut-off for the definition of marked J wave amplitude.[24] Leads V1, V2, and V3 were intentionally excluded from the analysis to avoid possible confounding with Brugada syndrome or right ventricular cardiomyopathy.[25] All ECG traces were reviewed by two independent physicians and values were digitally obtained zooming into the respective lead.

2.4 | Transthoracic echocardiography analysis

M-mode, two-dimensional, and Doppler echocardiographic examinations were performed using a multi-hertz sector, 2–4 MHz probe-equipped machine (Vivid 7 Pro, GE Healthcare). Cardiac structural and functional measurements were obtained according to European guidelines.[26] Left ventricular end diastolic diameter (LV EDD), left ventricular end systolic diameter (LV ESD), septal (SWT) and posterior wall thickness (PWT), aortic bulb diameter, left ventricular (LV) mass, left atrium (LA) volume, right ventricular end diastolic diameter (RV EDD), tricuspid annular plane systolic excursion (TAPSE), and right ventricular outflow tract diameter (RVOT) were determined. LV mass was calculated using the formula described by Devereux et al. and indexed to body surface area. Ejection fraction (EF) was calculated by the Teichholz method. Relative wall thickness (RWT) was calculated by the equation RWT = 2 × PWT/LV EDD. RWT was considered abnormal if >0.42. LV geometry was categorized according to RWT and LV mass.[26] All examinations were performed by the same experienced operating cardiologist.

2.5 | Statistical analyses

Statistical analyses were performed with the Statistical Package for Social Science (SPSS Inc.; ver. 20). The Shapiro–Wilk test was used to assess normal distribution of all parameters. Continuous variables were expressed as mean ± standard deviation and the comparison between subgroups was performed with the unpaired Student's *T*-test or Mann–Whitney test. The relationship between continuous variables were evaluated by Pearson's or Spearman's correlation coefficients according to the distribution of the variables. Categorical variables were expressed as frequencies and percentages and were compared between groups using Pearson's chi squared test. A general linear model with main effects and interactions between gender and ERp was performed for each quantitative variable. For discrete variable, interaction analysis was performed using a logistic regression model. All reported probability values are two-tailed and a value of $p \leq 0.05$ was considered statistically significant.

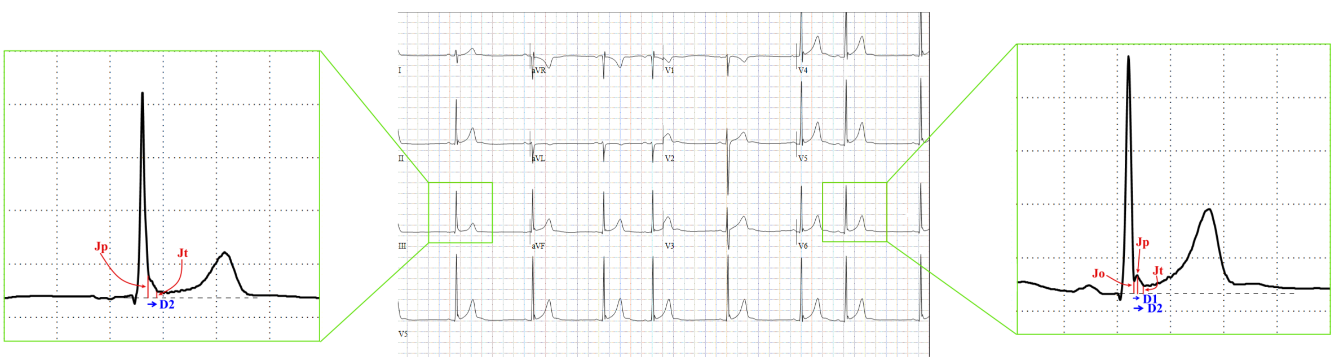

FIGURE 1 Early repolarization patterns. Example of an early repolarization pattern in a male athlete (17 years) with slurred (inferior leads) and notched (lateral leads) morphology. The zoomed images show the identification of the amplitudes *J* onset (J_o), *J* peak (J_p), and *J* termination (J_t), as well as durations D_1 and D_2, in relation to an end-QRS notch. The image on the left shows a zoom on the slurred morphology with identification of J_p, J_t, and D_2. The image on the right shows a zoom on the notched morphology with identification of J_o, J_p, J_t, D_1 and D_2.

3 | RESULTS

3.1 | Clinical characteristics and the prevalence of ERp

A total of 600 adolescent athletes, 210 women (35%) and 390 men (65%), with a mean age of 14.87 ± 1.96 years matched the eligibility criteria. Clinical baseline characteristics of the study sample are shown in Table 1. The overall prevalence of ERp was 27% (127/600) with a higher percentage of men presenting ERp (p = 0.043). Athletes participated in 42 different sports disciplines and data revealed that athletes with ERp showed a higher prevalence of endurance sports participation compared with those without ERp (p = 0.050), but the groups did not differ by total hours of training per week. No difference in the ERp prevalence emerged when the population was divided by age (cut-off used 14 years; p = 0.561). No difference regarding clinical symptoms was observed between groups with and without ERp (syncope, palpitations). Out of the nine Afro-Caribbean athletes in the study, three of them presented ERp (30%). During the mean follow-up time of 4.07 ± 2.62 years, no major cardiovascular events or SCD were recorded.

3.2 | ECG, exercise test, and echocardiography—gender differences

Resting and exercise test ECG parameters and echocardiographic data according to gender are reported in Table 2. Women with ERp showed a significantly lower resting heart rate (HR) than women without ERp (p = 0.005). Resting blood pressure values were similar in subjects with and without ERp, while men with ERp showed a higher systolic blood pressure at peak exercise (p = 0.013) than men without ERp. In both genders, subjects with ERp demonstrated significantly shorter QRS duration (men p = 0.001; women p = 0.003) and higher QRS voltages (both $p < 0.001$) than those without ERp. An interaction analyses have been performed in order to identify whether these differences could be gender related, showing that

TABLE 1 Baseline characteristics

	All (n = 600)	No ERp (n = 438)	ERp (n = 162)	p
Age (years)	14.87 ± 1.96	14.82 ± 1.99	15.01 ± 1.88	0.365
Gender (women %)	215 (35%)	164 (37%)	52 (32%)	0.043
Weight (kg)	59.83 ± 12.89	58.76 ± 13.03	60.92 ± 12.43	0.103
Height (m)	1.67 ± 0.11	1.67 ± 0.12	1.68 ± 0.11	0.091
BMI (Kg/m^2)	21.02 ± 2.98	20.91 ± 2.92	21.34 ± 3.13	0.236
BSA (m^2)	1.66 ± 0.22	1.65 ± 0.23	1.69 ± 0.21	0.149
Sport category				0.050
Endurance	65 (11%)	41 (9%)	24 (15%)	
Power	83 (14%)	69 (16%)	14 (9%)	
Mixed	429 (71%)	312 (71%)	117 (72%)	
Skill	23 (4%)	16 (4%)	7 (4%)	
Training (h/week)	5.70 ± 1.69	5.71 ± 1.75	5.69 ± 1.53	0.773
History of syncope	37 (6%)	32 (7%)	5 (3%)	0.058
History of palpitation	32 (5%)	25 (6%)	7 (4%)	0.682
PVB isolated	217 (36%)	156 (36%)	61 (38%)	0.702
Common morphology[a]	184 (31%)	132 (30%)	52 (32%)	0.690
Uncommon morphology[b]	30 (5%)	22 (5%)	8 (5%)	0.999
Couplets	13 (2%)	8 (2%)	5 (3%)	0.352

Note: It shows anthropometric and clinical parameters of the study population (n = 600). Data are expressed as mean ± standard deviation or frequencies (percentage). All syncopes found can be classified as being of vasovagal/situational origin and not sports related.

Abbreviations: BMI, body mass index; BSA, body surface area; PVB, premature ventricular beats.

[a]Common morphology in athletes: infundibular, fascicular.

[b]Uncommon morphology in athletes: atypical right bundle branch block and QRS ≥130 ms, left bundle branch block with superior or intermediate axis.

TABLE 2 Exercise test data, electrocardiographic and echocardiographic parameters

	Men			Women			
	No ERp ($n = 274$)	ERp ($n = 116$)	p	No ERp ($n = 164$)	ERp ($n = 46$)	p	p for interaction
Resting parameters							
HR rest (bpm)	65.99 ± 11.86	65.25 ± 10.55	0.690	74.97 ± 12.85	68.98 ± 9.86	0.005	0.026
SBP rest (mmHg)	113.94 ± 12.18	114.63 ± 12.72	0.621	108.33 ± 10.65	109.24 ± 10.70	0.664	0.925
DBP rest (mmHg)	64.57 ± 8.52	64.56 ± 8.91	0.910	63.02 ± 8.10	61.41 ± 8.07	0.190	0.347
Exercise parameters							
HR peak (bpm)	188.76 ± 8.57	187.17 ± 8.17	0.087	191.16 ± 8.60	191.89 ± 9.50	0.356	0.179
SBP peak (mmHg)	167.39 ± 23.85	172.65 ± 19.89	0.013	151.59 ± 17,01	152.39 ± 15.80	0.885	0.286
DBP peak (mmHg)	46.17 ± 11.24	47.35 ± 12.13	0.195	49.54 ± 12.43	47.17 ± 10.89	0.235	0.132
METs peak	18.47 ± 2.62	18.67 ± 2.66	0.616	15.91 ± 1.88	16.18 ± 2.70	0.817	0.907
Exercise time (s)	451.50 ± 49.13	460.02 ± 51.25	0.112	408.47 ± 48.17	412.11 ± 45.89	0.554	0.620
ECG							
QRS duration (ms)	77.60 ± 11.68	73.28 ± 11.17	0.001	71.72 ± 10.60	66.52 ± 9.48	0.003	0.697
QRS voltage (mm)	32.08 ± 9.17	37.50 ± 9.16	<0.001	25.98 ± 7.01	31.15 ± 7.64	<0.001	0.886
QTc (ms)	388.54 ± 26.39	385.59 ± 23.11	0.484	403.88 ± 24.99	399.63 ± 24.44	0.344	0.799
iRBBB	92 (34%)	15 (13%)	<0.001	36 (22%)	5 (11%)	0.139	0.512
Echocardiography							
LV EDD (mm)	47.38 ± 4.48	47.82 ± 3.53	0.235	44.05 ± 3.95	43.46 ± 3.99	0.252	0.213
LV ESD (mm)	29.09 ± 3.87	28.99 ± 3.58	0.933	26.82 ± 3.73	26.33 ± 2.98	0.369	0.601
EF (%)	68.41 ± 6.34	69.44 ± 6.09	0.170	69.28 ± 6.46	69.89 ± 5.70	0.501	0.736
SWT (mm)	8.59 ± 1.31	8.91 ± 1.32	0.029	7.58 ± 1.05	7.83 ± 0.77	0.112	0.755
PWT (mm)	7.66 ± 1.24	7.98 ± 1.40	0.086	6.62 ± 1.01	7.02 ± 0.86	0.008	0.756
Aortic bulb (mm)	25.21 ± 2.89	25.80 ± 2.65	0.062	23.05 ± 2.52	22.38 ± 2.88	0.271	0.174
LA volume (ml/m^2)	29.72 ± 3.73	30.50 ± 3.39	0.127	27.63 ± 3.28	27.62 ± 3.57	0.873	0.272
LV mass (g/m^2)	76.14 ± 18.24	79.44 ± 15.41	0.031	63.65 ± 14.82	65.78 ± 14.76	0.405	0.727
RV EDD (mm)	34.47 ± 4.40	35.03 ± 4.65	0.288	30.45 ± 4.27	31.36 ± 3.32	0.233	0.685
TAPSE (mm)	24.31 ± 3.11	24.20 ± 3.00	0.859	23.85 ± 2.97	23.31 ± 2.69	0.302	0.489
RVOT (mm)	27.48 ± 3.53	28.07 ± 3.24	0.084	24.33 ± 3.38	24.91 ± 3.37	0.320	0.988
RWT	0.32 ± 0.05	0.34 ± 0.06	0.170	0.30 ± 0.06	0.33 ± 0.06	0.007	0.234

Note: It shows exercise test, ECG, and echocardiography parameters of the study population (n = 600) with inter-group comparisons between those with and without early repolarization pattern (ERp). The last column represents p value for interaction between gender and ERp. Data are expressed as mean ± standard deviation or frequencies (percentage).

Abbreviations: DBP, diastolic blood pressure; EDD, end diastolic diameter; EF, ejection fraction; ESD, end systolic diameter; HR, heart rate; iRBBB, incomplete right bundle-branch block; LA, left atrium; LV, left ventricle; PWT, posterior wall thickness; QRS voltage, voltage criteria (Sokolow-Lyon index); RV, right ventricle; RVOT, right ventricular outflow tract diameter; RWT, relative wall thickness; SBP, systolic blood pressure; SWT, septal wall thickness; TAPSE, tricuspid annular plane systolic excursion.

only resting HR remains significant. Athletes with ERp demonstrated increased wall thickness (men ERp SWT: $p = 0.029$; women ERp PWT: $p = 0.008$). Moreover, male athletes with ERp also presented a higher LV mass indexed to body surface area ($p = 0.031$) and women with ERp showed higher RWT ($p = 0.007$). Most athletes showed a normal left ventricular geometry according to LV mass and RWT without inter-group differences regarding ERp. There was no significant interaction between gender and echocardiographic parameters.

3.3 | ERp phenotype—gender difference

ERp phenotypes according to gender are represented in Table 3. 29% of subjects presented ERp in lateral leads, 38% in inferior leads, and 33% in both regions. No difference in ERp location emerged between genders. A notched morphology alone was present in 62% of young athletes with ERp and was more frequent in men ($p = 0.004$). The slurred morphology was present in 14% of athletes with ERp and more common in women ($p = <0.001$), especially

TABLE 3 ERp phenotypes

	ERp men ($n = 116$)	ERp women ($n = 46$)	p
Region			
Lateral	34 (30%)	13 (28%)	0.528
Inferior	41 (35%)	20 (44%)	0.371
Combined	41 (35%)	13 (28%)	0.461
Morphology			
Notched	80 (69%)	20 (44%)	0.004
Slurred	8 (7%)	14 (30%)	<0.001
Both	28 (24%)	12 (26%)	0.841
ST Segment			
Ascending	103 (89%)	30 (65%)	0.001
Horizontal	13 (11%)	16 (35%)	0.001
J Amplitude (mV)			
J_o	0.05 ± 0.02	0.04 ± 0.01	0.868
J_p	0.19 ± 0.07	0.15 ± 0.05	<0.001
J_p>0.2 mV	30 (26%)	1 (2%)	<0.001
J_t	0.06 ± 0.03	0.02 ± 0.01	<0.001
D_1 (ms)	20.20 ± 1.98	20.56 ± 3.29	0.453
D_2 (ms)	40.04 ± 5.13	41.00 ± 6.32	0.127

Note: It shows the early repolarization pattern (ERp) characteristics in both genders, considering the population with ERp ($n = 162$). Data are expressed as mean ± standard deviation or frequencies (percentage). J_o, J onset; J_p, J peak; J_t, J termination; D_1, duration in milliseconds (ms) between J_o and J_p if end-QRS is notched; D_2, duration in milliseconds (ms) between J_o and J_t if end-QRS is notched or J_p and J_t if end-QRS is slurred; mV, millivolts.

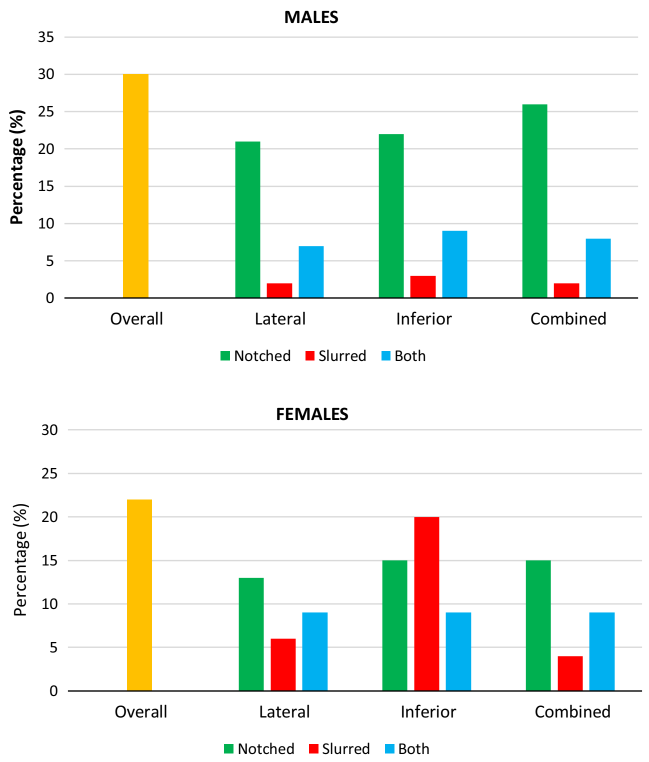

FIGURE 2 Region and morphology of early repolarization patterns. Distribution and gender comparison regarding the morphology of early repolarization patterns in lateral, inferior, and combined (inferior and lateral) leads. Yellow columns represent the overall prevalence of ERp within the study population. Notched, slurred, and both morphologies are shown in green, red and blue, respectively.

in the inferior leads ($p = 0.024$; Figure 2). The association of these two morphologies was present in 24% of the subjects with ERp, with no gender differences.

The ST segment was found mainly ascending (82%) but a horizontal slope was more frequent in women (35%; $p = 0.001$). No athletes presented a ST descending slope.

Most athletes with ERp (72%) showed an amplitude of the *J*-point ≤2 mV. Men presented more often an amplitude >2 mV when compared with women (26% vs 2%; $p < 0.001$) and had consequently higher J_p and J_t points (both $p < 0.001$). The J_p amplitude showed a correlation with age ($r = 0.310$, $p < 0.001$), BSA ($r = 0.215$, $p = 0.006$), QRS voltage ($r = 0.231$, $p = 0.003$), and exercise capacity expressed as METs at peak exercise ($r = 0.306$; $p < 0.001$) and exercise test duration ($r = 0.217$; $p < 0.001$). J_p amplitude was associated also with several echocardiographic measurements such as left ventricular wall thicknesses and diameters (LV EDD: $r = 0.223$, $p = 0.004$; LV ESD: $r = 0.184$, $p = 0.019$; SWT: $r = 0.180$, $p = 0.022$; PWT: $r = 0.207$, $p = 0.008$). Age-corrected partial correlation analyses showed a significant association only between J_p amplitude and QRS voltage (Sokolow–Lyon index) ($r = 0.249$, $p = 0.001$). No differences emerged regarding ERp duration. The same gender differences on ERp phenotypes were confirmed also in the control group of unselected athletes (Supplementary Table S2).

3.4 | ERp and arrhythmic risk

Young athletes with ERp did not present an increased occurrence of ventricular arrhythmias during exercise testing ($p = 0.702$), neither for isolated premature ventricular beats nor for couplets. No couplet presented short coupling interval. No triplets or ventricular tachycardia have been reported. No difference was found in arrhythmia morphology between subjects with and without ERp (common pattern: $p = 0.690$; uncommon pattern: $p = 0.999$). No difference was found in premature ventricular beats classification between subjects with and without ERp. Gender analysis also revealed no increase in ventricular arrhythmias in men or women with ERp (men $p = 0.909$; women $p = 0.302$).

Finally, a sub-analysis on ERp phenotypes previously associated with an increased arrhythmic risk has been conducted. ERp in the inferior leads, regardless of morphology, did not show an increased number of ventricular arrhythmias, neither for isolated ventricular premature beats (notched: $p = 0.199$; slurred: $p = 0.436$) nor for couplets (notched: $p = 0.326$; slurred: $p = 0.308$). Moreover, athletes with ST horizontal slopes (isolated: $p = 0.399$; couplets: $p = 0.632$) or a J_p amplitude above 0.2 mV (isolated: $p = 0.542$; couplets: $p = 0.584$) did not present an increased number of arrhythmias during maximal exercise testing.

4 | DISCUSSION

The prevalence and characteristics of ERp were evaluated in 600 adolescent athletes, who underwent the periodical cardiovascular pre-participation evaluation for competitive sports, according to Italian law. To the best of our knowledge, this is the largest study on ERp in a population of young athletes, the first study to specifically evaluate gender differences and to analyze ERp parameters according to the 2015 consensus paper.[23] This work underpins ERp as a frequently present benign ECG pattern in young athletes, adding an interesting gender comparison between ERp phenotypes.

The main outcomes of this study are threefold and summarized in Figure 3:

1. ERp is associated with other exercise-induced ECG and echocardiographic findings of cardiac adaptations.
2. ERp phenotypes show gender differences in young athletes. Men presented predominantly a notched morphology and higher J_p amplitude, while women showed mainly a slurred morphology and higher prevalence of horizontal sloping ST segment.
3. Young athletes with ERp do not present an increased arrhythmic risk, independently from ERp phenotype.

4.1 | ERp in the whole population

Although the interest in ERp has dramatically increased over the past two decades,[7,27] only few studies investigated the prevalence and characteristics of ERp in young athletes. The ERp prevalence in our study (27%) is in line with previous publications showing that it is common in young athletes and more frequent in the male gender.[24,28–30] This pattern seems not particularly influenced by genetic predisposition[31] but more significantly by environmental factors, such as exercise training.[32] Moreover, in our study, ERp is more frequently present in endurance sports although cumulative total training hours seem not to affect these ECG presentations. This may suggest that ERp is probably more related to the training method rather than the total volume. The link between training and ERp has not yet been clarified. Some studies showed a correlation between high load

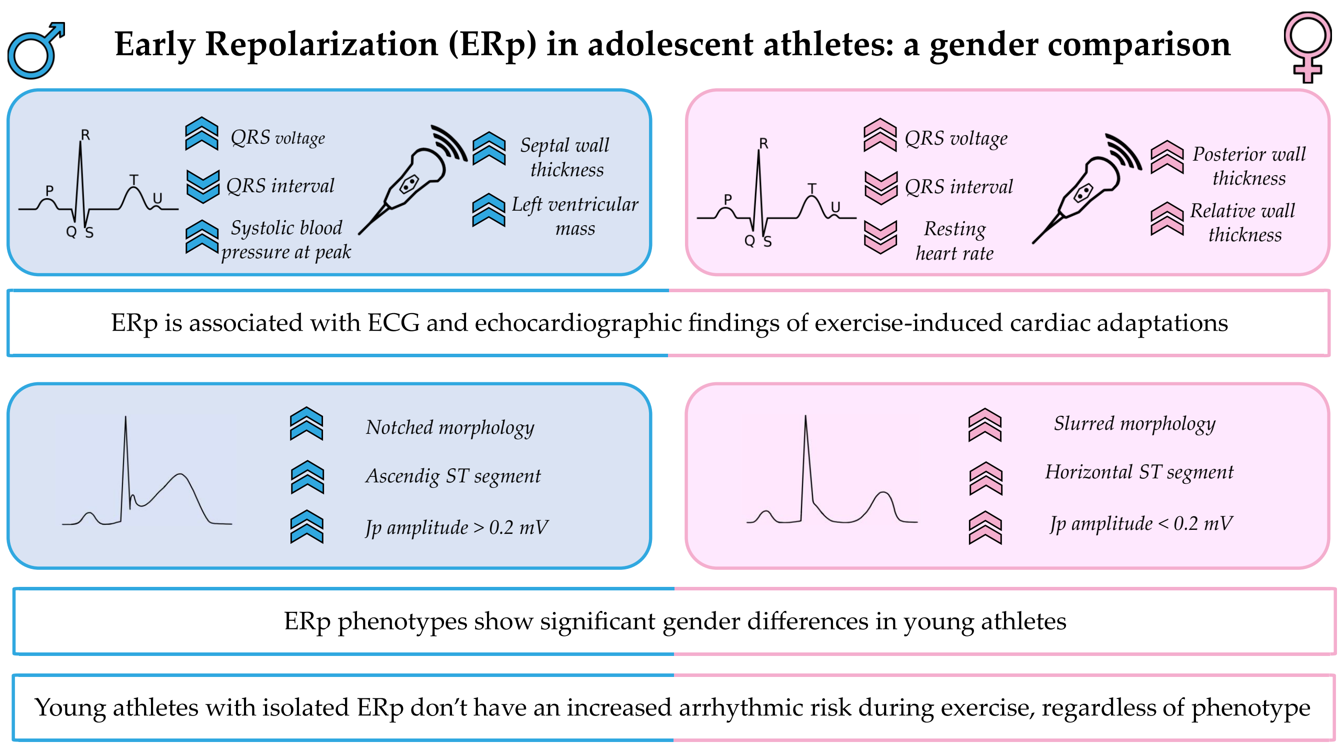

FIGURE 3 Gender differences in adolescent athletes with early repolarization patterns. Early repolarization patterns (ERp) are associated with electrical and morphological exercise-induced cardiac adaptations in both genders. The ERp phenotypes show significant gender differences in young athletes without a distinctive increased occurrence of cardiac arrhythmias during maximal exercise testing

sports and ERp for pediatric populations,[33] while others showed no difference in the ERp prevalence in children before and after endurance training.[13] It is possible that this pattern in adolescent athletes is influenced more by age and sexual maturation than by training, as already seen in other repolarization abnormalities.[13] In our cohort, no significant differences in ERp prevalence emerged between adolescent and preadolescent athletes. However, the use of an age-correlated cut-off makes it difficult to interpret these data particularly in this population because pubertal maturity is not strictly related to a specific age and differs between the two genders.

Furthermore, ERp seems to be more frequently associated with common training-related physiological cardiac adaptations. Athletes with ERp presented narrower QRS intervals and higher QRS voltages. Women with ERp showed a lower HR at rest, suggesting how this is strictly related to exercise adaptations.[24,32] Moreover, our study showed a lower presence of iRBBB in young male athletes with ERp, suggesting that ERp may mask or influence the appearance or the interpretation of iRBBB.[30]

Gender differences on echocardiographic measurements showed possible exercise-induced small adaptations, typical of the athlete's heart. Nevertheless, interaction analysis did not confirm the gender effect when comparing young athletes with e without ERp, as also described in a recent study in elite adult athletes. This may suggest that only some of these differences are strictly gender related.[34] Moreover, it is likely that some of the differences in exercise-induced parameters such as voltage amplitude and QRS duration are independent of gender while others are more influenced. Further studies with larger sample sizes and a specific study design could ensure more reliable and robust considerations.

4.2 | ERp phenotypes—gender differences

Different ERp characteristics and phenotypes have been associated with lower or higher cardiovascular risk,[6–8] while the impact of gender has not yet been adequately addressed on this issue, especially in adolescent athletes. ERp is slightly more common in inferior leads and no gender differences regarding ERp region were found. These findings are consistent with those previously described but showing a more equal distribution between the leads.[28,29]

The notching morphology alone was the most common ERp phenotype (62%), and it was more frequent in men without a specific lead preference. On the contrary, the slurring morphology alone was the least frequent one (14%), and in our study, it appeared to be significantly more prevalent in women, especially in the inferior leads. The slurred morphology has already been described as less common in young athletes, but it has been reported more frequently in adults.[29,35,36] This discrepancy may be also due to the difficulties in ERp detection and interpretation, and to the lack of standardization before the MacFarlane consensus paper was introduced.[23] Ascending ST segment of ERp was the most represented (81%) but horizontal sloping was more frequent in women with ERp. The ERp amplitude was significantly higher in men and only one female athlete presented a J_p>0.2 mV. The J_p amplitude correlated positively with age and QRS voltage. Indeed, it is known that exercise training leads to significant increases in the prevalence of ERp,[32] but this is the first study showing that the ERp amplitude is quantitatively associated with exercise capacity. Testosterone levels were reported to be significantly higher among men with ERp, leading to the assumption of a potential involvement of some cardiac ion channels (I_{to}) in ERp generation.[37] Moreover, testosterone levels were closely associated with ERp in the lateral leads and the rapidly ascending ST-segment after J-point elevation. This hypothesis would explain the male predominance, its close relationship with exercise training, the increased prevalence during puberty and the subsequent known decline in later life of this ECG pattern.[1,32] It may also suggest that the inferior or horizontal/descending ST segment ERp phenotype is less related to physiological adaptations, growth hormone levels, or physical exercise, and it may therefore deserve further consideration.

4.3 | ERp and Arrhythmic risk

In our study, no differences in occurrence of cardiac arrhythmias emerged between athletes with and without ERp, also when analyzing complexity and morphologies of ventricular arrhythmias. Thus, ERp could be considered as a benign ECG pattern that in the young does not appear to be associated with increased arrhythmic risk.[38] The evidence of no major cardiovascular events and SCD in the follow-up period emphasizes the possible benign nature of this ECG finding.[36,39] Furthermore, ERp in inferior leads and/or horizontal ST segment as well as a J_p amplitude >0.2 mV did not lead to an increase in the occurrence of ventricular arrhythmias, despite previous publications associated these phenotypes with increased arrhythmic risk.[6–8,24] Thus, our results are in line with previous reports from adult populations[40] and sustain the approach of the current consensus statement, affirming how all ERp in athletes, when present as isolated findings and without clinical markers of pathology, should be considered benign variants and do not need further examination or intervention.[41]

4.4 | Limitations and perspectives

Our study investigated only athletes who underwent echocardiography during the pre-participation evaluation for sports eligibility. Indications to perform echocardiography were linked to various minor diagnostic findings detected at the basic screening examination. Nevertheless, to minimize this possible selection bias, athletes with previous known or new onset cardiomyopathies and severe valvular diseases were excluded. Moreover, after second-line investigations, none of the athletes were found to be not eligible for competitive sports. Furthermore, gender differences regarding ERp phenotypes were also confirmed in the unselected control group. Secondly, our study focused only on standard systolic echocardiographic parameters, while other evaluations such as global longitudinal strain, Doppler tissue imaging, or speckle tracking should be addressed by future investigations. Thirdly, due to the poor representation in our study population of non-Caucasian athletes, no considerations were made regarding ethnicity.[2,29] Finally, the number of young athletes included in this study is robust but still limited when compared with data obtained from population-based epidemiological research projects, especially for further considerations on physiological adaptations to specific exercise training modalities.[5,34]

5 | CONCLUSIONS

This study confirms the high prevalence of ERp in young athletes, especially in men and in those practicing endurance sports. ERp seems to be associated with other exercise-induced ECG and echocardiographic findings of cardiac adaptations, regardless of gender, suggesting ERp as a possible marker of electrical and structural remodeling of the LV. Furthermore, ERp phenotypes show significant gender differences. Men present predominantly a notched morphology and higher J_p amplitude, while women show mainly a slurred morphology, especially in inferior leads, and a higher prevalence of horizontal sloping ST segments. No differences in ventricular arrhythmic events emerged between phenotypes previously considered at increased risk.

AUTHOR CONTRIBUTIONS

MV and DN involved in conceptualization and formal analysis. MV and GS involved in data curation. MV, VB, and GF performed investigation. MV, VB, GQ, GF, FB, DN involved in methodology. AE involved in project administration. FB, DN, and AE contributed to supervision. MV involved in writing—original draft. MV, VB, PEA, GF, FB, and DN involved in writing—review and editing.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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