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LEFT VENTRICULAR GEOMETRY CORRELATES WITH EARLY REPOLARIZATION PATTERN IN ADOLESCENT ATHLETES

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LEFT VENTRICULAR GEOMETRY CORRELATES WITH EARLY REPOLARIZATION PATTERN IN ADOLESCENT ATHLETES

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Short title: Early repolarization in adolescent athlete

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Abstract

Some forms of early ECG repolarization QRS pattern (ERp) with J-point elevation of 0.1mV in two contiguous inferior and/or lateral leads with or without ST elevation are potentially associated with a higher arrhythmic risk in adults. We assessed the prevalence of ERp among non-professional adolescent athletes and correlated it with age, sex, ethnicity and structural and electric cardiac parameters.

We retrospectively analyzed 414 ECGs obtained from young athletes referred to our centre from 2006 to 2017. We found ERp in 22% of cases. In the ERp group, we found a greater percentage of blacks, a higher systolic blood pressure, and lower heart rate (HR) compared with the group without ERp. This pattern was less frequent in female athletes. In athletes with ERp, the occurrence of ventricular ectopic beats was less frequent and QRS duration was shorter. They also exhibited greater i) ECG-based left ventricular hypertrophy (LVH), ii) left ventricular mass, and iii) relative wall thickness (RWT), suggesting a tendency to concentric geometry. At logistic regression analysis, we found that HR (OR 0.98 [0.96-0.99] p= 0.013), QRS duration (OR 0.96 [0.94-0.99], p= 0.003), LVH (OR 1.09 [1.05-1.12], p< 0.001), and RWT (OR 1.08 [1.01-1.16] p= 0.032) were significant predictors of ERp incidence.

ERp is quite common in adolescent athletes and correlates with concentric LV remodeling. Specific clinical and ECG-findings related to training such as lower HR, LVH, and QRS duration are also predictors of ERp. In adolescent non-professional athletes, ERp is a benign finding associated with some structural and electric cardiac modifications induced by training.

KEY WORDS: arrhythmic risk; left ventricular remodeling; adolescent athlete's heart, ethnicity.

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1 INTRODUCTION

Resting 12-lead electrocardiogram (ECG) is part of the pre-participation screening of athletes, to diagnose underlying cardiovascular conditions. In Italy, this procedure reduced the incidence of sudden cardiac death (SD) in athletes to levels that are lower than those of non-athletes.[1] However, the accurate interpretation of athletes' ECG requires continuous investigation, to reduce false positives and improve specificity. There is consensus among cardiologists that we need to refine the criteria used to accurately discriminate sport-related ECG modifications from findings suggestive of cardiac pathologies.[2-6] Frequently, exercise-related ECG abnormalities depend not only on type of sport and intensity of training, but also on variables such as age, sex, and ethnicity. Early repolarization (ER) is one of such "common" abnormalities and is defined as an elevation of the QRS-ST junction of at least 0.1 mV in anterior precordial leads, with morphologies that are different between Caucasians and Africans. In particular, the former is characterized by an elevation of ST-segment with an upward concavity, ending in a positive T-wave, whereas the latter exhibits ST-elevation with an upward convexity, followed by a negative T-wave.[2-6]

In 2008, Haïssaguerre et al.[7] introduced a new definition of early repolarization based on the presence - in the infero-lateral leads - of J waves at the end of QRS, with slurred or notched morphology that might or might not be associated with ST-segment elevations. This pattern (ERp) increases the risk of arrhythmic death in the absence of cardiovascular disease, as confirmed by others.[8-11]

Tikkanen et al.[12] prospectively demonstrated that a horizontal or descending type is accompanied by an increased risk for arrhythmic death; conversely, the ascending one is not associated with such risk. Therefore, ERp could be conveniently subdivided into two forms: a) the upsloping or ascending ST-segment type, which is benign and frequent in athletes, and

b) the horizontal or descending ST-segment one, which is malignant and associated with an increased arrhythmic risk.[13,14]

Cappato et al.[10] compared 21 athletes (mean age 27 years, who experienced cardiac arrest or SD) to 365 age-matched healthy athletes. The authors demonstrated that a J wave, in the absence of ST-elevation in inferior-lateral ECG leads, was associated with a marginally increased risk of cardiac arrest or SD, whereas the presence of ST-segment elevation did not increase such risk.

Unfortunately, ERp is still not thoroughly assessed in young trans-pubertal athletes, who are at higher arrhythmic risk.[15] From a United Kingdom Regional Registry, the etiology of SD in sports varied with age and sudden arrhythmic death with structurally normal heart is most common in younger (< 18 years) cases, accounting for 56% of deaths in children and adolescents (compared with only 26% in adults >35 years of age[15] in whom the most frequent cause of death is coronary artery disease).[16]

In adolescent athletes, ERp's prevalence and clinical significance deserve to be elucidated. Because our Center routinely performs cardiovascular screening for eligibility for competitive sport in adolescent athletes, we evaluated the prevalence of ERp and its relationship with clinical variables, i.e age, gender, ethnicity, history of arrhythmias, and electrical and structural findings derived from ECG and echocardiographic techniques, in this specific setting.

2 METHODS

2.1 Participants

The local ethics' committee approved this study (Prot. 883/2013 and Prot. 486/2018/OSS*/AOUPR) and written informed consent was obtained from the parents of athletes.

This study is a retrospective analysis of ECGs obtained from consecutive young adolescent athletes referred to the University-Hospital of Parma - from 2006 to 2017 - for echocardiographic inspection during sport pre-participation screenings. In Italian pre-participation screening programs, echocardiographic examination is usually indicated in case of systolic murmur, symptoms as palpitations, extrasystoles, or ECG abnormalities such as LVH o T wave inversion. The occurrence of ventricular ectopic beat (VEB) during ECG screening was included as clinical feature. Case subjects were excluded if they had cardiac abnormalities (arrhythmic syndrome, pathological Q wave, ST-depression, deep T-wave inversion) as detected by ECG or by echocardiography.[17,18]

We retrieved 414 ECGs (age of healthy athletes 13.6±1.8 years, age range 12-17). Twenty-eight percent of athletes were female, 17% were black and 83% were white. All black athletes were coming from Central/West Africa. Participants entered the study and, under their physician's and parents' supervision, completed a questionnaire that included their and their family's cardiovascular and clinical history as well as detailed information on type, intensity, and duration of sport activity, as previously reported.[19]

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Blood pressure (BP) was assessed on two occasions, with three consecutive measurements each (OMRON 705 IT).

2.2 ECG analysis

Two trained medical specialists screened all ECGs for the presence of ERp, in a double-blind experimental condition. In case of discrepant opinions, a third reader interpreted the ECG and a conclusive diagnosis was reached. An ERp was defined as elevation of the QRS-ST junction (J point) of at least 0.1mV over the isoelectric line, associated with notching or slurring of the terminal QRS complex in the inferior and/or lateral leads with ascending or descending/horizontal ST segment (Figure 1).[20]

QRS-duration and corrected QT-interval (Bazett formula) were also measured. S1+R5 in precordial leads were calculated using the Sokolow-Lyon voltage criteria (positive if $\geq$ 35mm) to define the presence of LVH.

2.3 Transthoracic echocardiography

M-mode, two-dimensional, and Doppler Echocardiographic examinations were performed by an ultrasonography-experienced cardiologist, using a multi-hertz sector, 2-4 MHz probe-equipped machine (Vivid S5, GE Healthcare, USA). The interventricular septal (SWT) and posterior (PWT) left ventricular (LV) wall thicknesses, systolic and diastolic (EDD) LV diameters and volumes, absolute LV mass (LVM) and indexed to body surface area (LVM/BSA), were calculated as previously described.[19] RWT was calculated as: (SWT+ PWT)/EDD, using the 0.42 cut-off to define eccentric ($\leq$0.42) or concentric ($\geq$0.42) remodelling.[21]

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2.4 Statistical analysis

Data are expressed as mean ± standard deviation. The two groups, i.e. with and without ERp, were compared using two-tailed Student's *t* test (SPSS 20.0 software package, IBM, Armonk, New York, USA). χ-square or Fisher F-test, when appropriate, were used to compare between-group frequencies. Binary logistic regression model was performed to define the variables predictor for ERp. Clinical variables were age, sex, ethnicity, heart rate (HR), VEB. We also computed two structural cardiac parameters such LVM and RWT in addition to ECG-based LVH and QRS- duration. All these measures were assessed as continuous variables.

A 2-tailed $p < 0.05$ was considered as statistically significant. The goodness of fit for logistic regression models was tested looking at the non-significance in the Hosmer Lemeshow test and anomalous distributions of data in the Contingency Table for Hosmer-Lemeshow statistics.

3 RESULTS

3.1 Clinical data

All athletes were engaged in organized amateur-level training for approximately six hours/week. They played in different endurance disciplines, predominantly soccer (177/414, 43% of the total), but also volleyball (n=62, 15% of the total), athletics (n=54, 13%), basketball (n=30, 7%), rugby (n=16, 4%), tennis (n=11, 3%), judo (n=10, 2%), baseball (n=9, 2%), swimming (n=8, 2%), water polo (n=5), gymnastics (n=6), karate (n= 4), softball (n=3), triathlon (n=3), skating (n=3), cycling (n=2). Subjects also played handball, fencing, kickboxing, sport dance, table tennis, flag football, synchronized swimming, and squash (one sport/subject). The clinical characteristics of all adolescent athletes are shown in Table 1 and ECG and echocardiographic data are reported in Table 2.

3.2 Early Repolarization patterns

ERp was found in 92 athletes (i.e. 22%). In the group with ERp (ERp^{+}), inferior, lateral, and both sides, were involved in 25%, 32% and 43% of cases, respectively (Figure 2). The pattern of terminal QRS changes, notching, slurring or both and morphology of ST (elevation or horizontal/downsloping ST-segment) are depicted in Figure 3. Notched morphology with ascending ST (NA) was prevalent in all sites (76%, 48% and 52% in lateral, inferior, and both sites, respectively) followed by slurring with ST-elevation (SA) in lateral and inferior leads (17% and 22%, respectively) whilst in the subjects with inferior and lateral NA/SA was detected in 32.5% of cases. J wave with horizontal or downsloping of ST-segment was uncommon (7%, 13%, and 1% in lateral, inferior, or both sides).

3.3 Characteristics of athletes with ERP

Black male athletes exhibited a higher prevalence of ERp than their Caucasian male counterparts (50% vs 17 %, respectively).

When we compared ERp^+ and the group without ERp (ERp^-), we did not record significant differences for age, BSA, diastolic BP, and hours of training (Table 1).

We found a greater percentage of black, higher systolic BP and lower HR in the ERp^+ group compared with the ERp^- group. This pattern was significantly less frequent in female athletes. History of VEB, assessed during cardiovascular screening at 12-lead resting or during effort ECG, as performed in Italy, was lower in ERp^+ (Table 1).

In the comparison of ECG parameters between the two groups, QRS-duration was shorter in athletes with ERp^+, who had greater LVH without significant differences in QTc (Table 2).

The echocardiographic assessment confirmed the ECG data, because the ERp^+ group had more pronounced LV hypertrophy as appraised by a higher SWT, PWT, LVM and LVM/BSA associated with an increase of RWT, suggesting a tendency to concentric remodeling (Table 2). No significant differences were observed for LV and volumes and diameters.

3.4 Predictors of ERp incidence

To analyze the clinical ECG- and Echocardiographic-parameters potentially dictating this pattern, we performed a binary logistic regression model analysis in 365 athletes in which all variables were present. The predictors of incidence of ERp were lower HR (OR 0.98 [0.96-

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0.99] p=0.013) QRS-duration (OR 0.96, [CI 0.94-0.99], p=0.003), ECG-based LVH (OR 1.09 [CI 1.05-1.12], p< 0.001) and RWT (OR 1.08 [CI 1.01-1.16], p=0.032) (Table 3). Sex, age, ethnicity , history of VEB , and LVM/BSA were not significant determinants of ERp (Table 3). Systolic BP was not included in the analysis because we could not retrieve enough data.

Role of geometry vs. ethnicity

We repeated the same analysis by taking only Caucasians into consideration. The data confirmed the same determinants of ERp noted in the global analysis. From the electrical changes we observed, as expected[11,22]: HR (OR 0.98 [0.95-1.00], p=0.035), QRS duration (OR 0.96 [0.94-0.99], p=0.007), ECG-based LVH (OR 1.08 [1.05-1.13], p<0.001). Interestingly, we observed significant association between ERp and RWT (OR 1.10 [1.01-1.20], p=0.031) observed by echocardiography, indicating that geometry plays a pivotal role in ERp (Table 4A).

To corroborate this observation, we performed an additional analysis, by reintroducing black athletes, but excluding geometry (RWT) in the logistic binary regression. The data underscored that ethnicity is as well a determinant (OR 2.52 [1.21-5.26], p=0.014) of ERp as the aforementioned electrical parameters (Table 4B).

4 DISCUSSION

We characterized ECG and echocardiographic examinations and evaluated the prevalence of ERp in 414 adolescent non-professional athletes, who underwent cardiovascular screening for competitive sport.

Our results demonstrate that ERp is frequent in trans-pubertal athletes (especially in male and black subjects) and could be computed as a benign ECG variant not necessary associated with an increased arrhythmic risk, but associated with some electrical and structural cardiac findings related to training, such as classic anterior ST-elevation.

Since it was first described, ER has historically been considered as a benign ECG variant, more frequent in young boys, in athletes, and in Afro-Americans.[23] However, the 2008 publication of Haissaguerre et al.[7] associating ERp with idiopathic ventricular fibrillation, challenged this notion and led to a critical reappraisal of this finding, casting doubts on the real consequences of this pattern. The prevalent hypothesis is that ERp, in inferior and lateral leads associated with horizontal or descending ST-segments, increases the risk of future arrhythmic death in the absence of cardiovascular disease both in general population and in athletes.[10,12,14]

These observations have raised concerns among physicians involved in cardiovascular screening to prevent SD in athletes where ERp is more frequent stimulating research on the clinical significance of this pattern.

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Noseworthy et al.[22] analyzed ERp and the impact of 90 days of vigorous exercise training on its prevalence, in competitive athletes (mean age 18 years) of different sex and ethnicity (males 62%, black ethnicity 10.5%). ERp was found in 25.1% of participants, 99% of whom had an ascending ST-segment morphology. ERp was more common in male, black, taller athletes with slower HR, higher ECG-based LVH and was associated with previous exercise training, i.e. they were better trained when they accessed screening. At multivariate analysis, male sex, black race, increased QRS voltage, and slower HR were predictors of ERp. The prevalence of this pattern increased after more vigorous exercise training in addition to a more pronounced left ventricular remodeling, but the authors did not detect any correlation with echocardiographic measures.

These data suggest that exercise-related ERp is as frequent in athletes as is classic anterior ST-elevation and may be an isolated electric phenomenon rather than the result of structural myocardial remodeling, because it correlates with some ECG signs typical of electrical remodeling induced by training, e.g. increased LVH and lower HR, but not with LV structural echocardiographic-derived measures such LVM and RWT.

Similar to those findings, Juntilla et al.[11], in adult athletes, reported a significant relation between ERp and male sex and higher QRS voltage.

De Asmundis C. et al.[24], in a population of 121 young teen athletes (mean age 13.5±2.7) who underwent a clinical evaluation probably during cardiovascular screening for eligibility to sport, found 36% a prevalence of ERp; the most common subtype was at both inferior and lateral sites, in agreement with our data; however, this study included males only and did not report ST morphology or echocardiographic data. The conclusion was that ERp is a frequently occurring phenomenon not just in adults, but also in adolescent athletes.

Ahmed H et al. [25] analyzed the prevalence of ERp in young pubertal (between 13 and 18 years) athletes, in which between-sex differences also involving the heart became apparent. This study is a retrospective analysis of 575 consecutive healthy adolescents who underwent ECG and limited echocardiographic examination for pre-participation screening. The authors demonstrated that ERp is frequent (they observed it in 40% of cases), but they did not specify the characteristics of the ST-segment. No relationship with sex and ethnicity was detected; however, the authors included only 4% of young Africans in their cohort. The group with ERp, compared with the no-ERp group, did not differ in terms of clinical features such as height, weight, systolic/diastolic BP, HR, or clinical history of arrhythmias, but also LVM.

Our results confirm that ERp is quite frequent, i.e. 22% of cases in young athletes, with a greater and significant prevalence in African ethnicity, similarly to what observed in young adult athletes (25% of cases, mean age 18.4±0.8).[22] As regards sex, ERp is less recurrent in female athletes, confirming the data of a previous study by Pelà and coworkers[26] showing that both the electrical LV remodeling and the structural one are less frequent in females even in adolescence.

Systolic BP was higher in ERp^+ athletes compared with ERp^-, but no significant differences were found for diastolic BP and BSA. As regards ECG parameters, significant differences were observed between the two groups for the main "common" ECG changes induced by exercise according to the ESC guidelines[2] published in 2010: subjects with ERp had lower HR, narrower QRS interval, and greater LVH, suggesting that ERp is influenced by training, as already observed by Noseworthy et al.[22] At difference from the authors, however, we observed that, upon echocardiographic examination, athletes ERp^+ had more significant LV structural changes typical of athlete's heart such as higher LVM and RWT values and, in turn, greater left ventricular hypertrophy associated with a tendency to a more concentric geometry.

The binary logistic regression analysis to assess the determinants of ERp demonstrated that ERp was influenced not only by some ECG parameters, such as HR, QRS interval, and LVH, but also by a structural one such as LV geometry. LVM did not contribute.

We have previously demonstrated that a concentric geometry is peculiar of adolescent athlete of African ethnicity, who also develop greater LV hypertrophy, similar to adult athletes.[19,26-28] African adolescents, even if undergoing resistance training, develop a concentric than eccentric hypertrophy rather like in power sports.[29-31] These data explain the greater incidence of ERp in adolescent athletes of African ethnicity. However, RWT rather than ethnicity was a predictor of ERp after binary logistic global analysis. This role was confirmed in the group of only Caucasian athletes, suggesting that RWT impacts on ERp independently from the ethnicity. The significant role of the ethnicity on ERp rise up in the sub-analysis that did not take in consideration RWT confirming the relationship between ethnicity and concentric remodeling.[19,27]

Finally, we analyzed the distribution of ERp by sites. This pattern was prevalent in both infero-lateral and – to a lesser extent - in the lateral and inferior leads (in 43, 32, and 25% respectively). These findings agree with those of Ahmed et al.[25], where ERp was more frequent in the inferior-lateral sites (48%), but the inferior site prevailed on the lateral one (42% vs. 10%) and the incidence of this pattern was greater (41 vs. 22%). Juntilla et al.[11], in young athletes (age range, 17-24 years), found ERp in 30% of cases, with lateral location being the most common (21%) one. These discrepancies can be tentatively explained by the difficulty of diagnosing ERp. Indeed, we used a double reading by two different cardiologists with a third independent reading in case of disagreement, to reach unambiguous interpretation.

Regarding the morphology of J wave and ST-segment in lateral, inferior or both inferior and lateral leads, the most observed pattern was wave J "notch" or "slur" with ascending ST, while horizontal ST was found in a very small percentage of athletes.

LIMITATIONS

Some limitations of the present study are noteworthy. First, we emphasize that – in our cohort - the overwhelming majority of athletes with ERp exhibited J wave morphology with ascending ST; therefore, we cannot conclude on the impact of the horizontal/descending ST type, which could be potentially malignant yet poorly represented in our sample. Second, the absence of female black athletes in this study is certainly a limitation for elucidating comparison with Caucasian ones. Third, our healthy population is selected for echocardiography analysis during the cardiovascular screening for sport eligibility and, therefore, there cannot be a control group.[31] Non-professional athletes played different

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disciplines that induce different LV remodelling. [29-31] The largest group was mixed sports (n= 316) followed by endurance sports (n= 71). The other groups were poorly represented (power group, n= 18 and skill group, n= 6). ERp prevalence did not differ among the 4 different groups: Mixed 74/242, 23.4%; Endurance 12/59, 16.9%; Power 4/14, 22.2%; Skill 1/5, 16.6%. Therefore, we did not find any significant ECG differences among the different sport disciplines. We also do not have follow-up data for this population. Finally, our study does not include the analysis of functional remodeling derived by Doppler Tissue imaging or speckle tracking echocardiography because we focused our attention to the electrical and structural remodeling.[32] Due to the current screening recommendations, echocardiography or Cardio-MRI should be considered. [33-35]

CONCLUSIONS

Our research supports the hypothesis that ERp is a "benign" pattern of adolescent athletes, correlated with other ECG findings that reflect changes induced by training; ERp is less frequent than the "classic early repolarization" in anterior leads, classified among the "common abnormalities" of the athlete's heart. Our results suggest ERp as a possible marker linking electrical and geometrical remodeling of the LV. Further studies are warranted to confirm our results and clarify the clinical significance of ERp, especially in adolescent athletes who are most at risk of SD.[15]

5 PERSPECTIVE

In this cohort of 414 adolescent athletes, 22% were found to have ERp; the overwhelming majority of them exhibited J wave morphology with ascending ST. Specific clinical and

ECG-findings related to training such as lower HR, LVH, and QRS duration are also predictors of ERp which also correlates with concentric left ventricular remodeling**.** This study of adolescent athletes, less frequently recruited in clinical studies compared with adult athletes, adds new insight to the context of cardiovascular screening program for eligibility to sports in the prevention of juvenile cardiac sudden death.

CONFLICT OF INTEREST

None the authors declare any conflict of interests

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REFERENCES

1. Corrado D, Basso C, Pavei A. Trends in Sudden Cardiovascular Death in Young Competitive Athletes After Implementation of a Preparticipation Screening Program. *JAMA.* 2006;296(13):1593-1601.

2. Corrado D, Pelliccia A, Heidbuchel H, Sharma S, Link M, Basso C, Biffi A, Buja G, Delise P, Gussac I, Anastasakis A, Borjesson M, Bjørnstad HH, Carrè F, Deligiannis A, Dugmore D, Fagard R, Hoogsteen J, Mellwig KP, Panhuyzen-Goedkoop N, Solberg E, Vanhees L, Drezner J, Estes NA 3rd, Iliceto S, Maron BJ, Peidro R, Schwartz PJ, Stein R, Thiene G, Zeppilli P, McKenna WJ. Recommendations for interpretation of 12-lead electrocardiogram in the athlete. *Eur Heart J.* 2010;31:243-259.

3. Drezner JA, Ackerman MJ, Anderson J, Ashley E, Asplund CA, Baggish AL, Börjesson M, Cannon BC, Corrado D, DiFiori JP, Fischbach P, Froelicher V, Harmon KG, Heidbuchel H, Marek J, Owens DS, Paul S, Pelliccia A, Prutkin JM, Salerno JC, Schmied CM, Sharma S, Stein R, Vetter VL, Wilson MG. Electrocardiographic interpretation in athletes: the "Seattle criteria". *Br J Sports Med.* 2013;47:122-124.

4. Riding NR, Sheikh N, Adamuz C, Watt V, Farooq A, Whyte GP, George KP, Drezner JA, Sharma S, Wilson MG. Comparison of three current sets of electrocardiographic interpretation criteria for use in screening athletes. *Heart.* 2015;101(5): 384-390.

5. Drezner JA, Sharma S, Baggish A, Papadakis M, Wilson MG, Prutkin JM, Gerche A, Ackerman MJ, Borjesson M, Salerno JC, Asif IM, Owens DS, Chung EH, Emery MS, Froelicher VF, Heidbuchel H, Adamuz C, Asplund CA, Cohen G, Harmon KG, Marek JC, Molossi S, Niebauer J, Pelto HF, Perez MV, Riding NR, Saarel T,

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Schmied CM, Shipon DM, Stein R, Vetter VL, Pelliccia A, Corrado D. International criteria for electrocardiographic interpretation in athletes: consensus statement. *Br J Sports Med.* 2017;51:704-731.

6. McClean G, Riding NR, Arden CL, Farooq A, Pieles GE[5], Watt V, Adamuz C, George KP, Oxborough D, Wilson MG. Electrical and structural adaptations of the paediatric athlete's heart: a systematic review with meta-analysis. *Br J Sports Med.* 2018;52:230.
7. Haïssaguerre M, Derval N, Sacher F, Jesel L, Deisenhofer I, de Roy L, Pasquié JL, Nogami A, Babuty D, Yli-Mayry S, De Chillou C, Scanu P, Mabo P, Matsuo S, Probst V, Le Scouarnec S, Defaye P, Schlaepfer J, Rostock T, Lacroix D, Lamaison D, Lavergne T, Aizawa Y, Englund A, Anselme F, O'Neill M, Hocini M, Lim KT, Knecht S, Veenhuyzen GD, Bordachar P, Chauvin M, Jais P, Coureau G, Chene G, Klein GJ, Clémenty J. Sudden Cardiac Arrest Associated with Early Repolarization. *N Engl J Med.* 2008;358:2016-2023.
8. Rosso R, Kogan E, Belhassen B, Rozovski U, Scheinman MM, Zeltser D, HaLKIN a, Steinvil A, Heller K, Glikson M, Katz A, Viskin S. J-Point Elevation in Survivors of Primary Ventricular Fibrillation and Matched Control Subjects. *J Am Coll Cardiol.* 2008;52:1231-1238.
9. Tikkanen JT, Anttonen O, Junttila MJ, Aro AL, Kerola T, Rissanen HA, Reunanen A, Huikuri H. Long-term outcome associated with early repolarization on electrocardiography. *N Engl J Med.* 2009;361:2529–2537.
10. Cappato R, Furlanello F, Giovinazzo V, Infusino T, Lupo P, Pittalis M, Foresti S, De Ambroggi G, Ali H, Bianco E, Riccamboni R, Butera G, Ricci C, Ranucci M, Pelliccia A, De Ambroggi L. J-wave, QRS Slurring and ST Elevation in Athletes

with Cardiac Arrest in the Absence of Heart Disease: Marker of Risk, or Innocent Bystander? *Circ Arrhythm Electrophysiol.* 2010;3:305-311.

11. Juntilla MJ, Sager SJ, Freiser M, McGonagle S, Castellanos A, Myerburg RJ. Inferolateral early repolarization in athletes. *J Interv Card Electrophysiol.* 2011;31:33-38.
12. Tikkanen JT, Junttila MJ, Anttonen O, Aro AL, Luttinen S, Kerola T, Sager SJ, Rissanen HA, Myerburg RJ, Reunanen A, Huikuri HV. Early Repolarization. Electrocardiographic phenotypes associated with favorable long-term outcome. *Circulation.* 2011;123:2666-2673.
13. Rosso R, Glikson E, Belhassen B, Katz A, Halkin A, Steivil A, Viskin S. Distinguishing "benign" from "malignant early repolarization": the value of the ST segment morphology. *Heart Rhythm.* 2012;9:225-229.
14. Tikkanen JT, Huikuri HV. Characteristics of "malignant" vs "benign" electrocardiographic patterns of early repolarization. *J Electrocardiol.* 2015;48: 390-394.
15. Finocchiaro G, Papadakis M, Robertus J, Dhutia H, Steriotis AK, Tome M, Mellor G, Merghani A, Malhotra A, Behr E, Sharma S, Sheppard MN. Etiology of Sudden Death in Sports: Insights From a United Kingdom Regional Registry. *J Am Coll Cardiol.* 2016;67:2108-2115.
16. Schmied C, Borjesson M. Sudden cardiac death in athletes. *J Int Med*. 2014;275:93-103.
17. Thompson AJ, Cannon BC, Wackel PL, Horner JM, Ackerman MJ, O'Leary PW,, Eidem BW, Johnson JN. Electrocardiographic abnormalities in elite high school athletes: comparison to adolescent hypertrophic cardiomyopathy. *Br J Sports Med*. 2016;50(2):105-10.

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18. Maron BJ, Maron BA. Revisiting Athlete's Heart Versus Pathologic Hypertrophy: ARVC and the Right Ventricle. *JACC Cardiovascular imaging*. 2017;10:395.

19. Pelà G, Li Calzi M, Crocamo A, Pattoneri P, Goldoni M, Anedda A, Musiari L, Biggi A, Bonetti A, Montanari A. Ethnicity-related variations of left ventricular remodeling in adolescent amateur football players. *Scand J Med Sci Sports.* 2015; 25: 382-389.

20. Macfarlane PW, Antzelevitch C, Haïssaguerre M, Huikuri HV, Potse M, Rosso R, Sacher F, Tikkanen JT, Wellens H, Yan G-X. The Early Repolarization Pattern. A consensus paper. *J Am Coll Cardiol.* 2015;66:470-477.

21. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JU. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging.*2015;16:233-270.

22. Noseworthy PA, Weiner R, Kim J, Keelara V, Wang F, Berkstresser B, Wood MJ, WaNG tj, Picard MH, Hutter AM, Newton-Cheh C, Baggish AL. Early Repolarization Pattern in Competitive Athletes. Clinical Correlates and the Effects of Exercise Training. *Circ Arrhythm Electrophysiol.* 2011;4:432-440.

23. Klatsky A, Oehm R, Cooper RA, Udaltsova N, Armstrong MA. The Early Repolarization Normal Variant Electrocardiogram: Correlates and Consequences. *Am J Med.* 2003;115:171-177.

24. De Amundis C, Conte G, Levinstein M, Chierchia G-B, Sieira J, Di Giovanni G, Baltogiannis G, Park MH, Sarkozy A, Brugada P. *Acta Cardiol.* 2014;69:3-6.

25. Ahmed H, Czosk RJ, Spar DS, Knilans TK, Anderson JB. Early Repolarization in Normal Adolescents is Common. *Pediatr Cardiol.* 2017;38:864-872.

26. Pelà G, Crocamo A, Li Calzi M, Gianfreda M, Gioia MI, Visioli F, Pattoneri P, Corradi D, Goldoni M, Montanari A. Sex-related differences in left ventricular structure in early adolescent non-professional athletes. *Eur J Prev Cardiol* . 2016;23: 777-784.

27. Demola P, Crocamo A, Ceriello L, Botti A, Cremonini I, Pattoneri P, Corradi D, Visioli F, Goldoni M, Pelà G. Hemodynamic and ECG responses to stress test in early adolescent athletes explain ethnicity-related cardiac differences. *Int J Cardiol.*2019;289:125-130

28. Basavarajaiah S, Boraita A, Whyte G, Wilson M, Carby L, Shah A, Sharma S. Ethnic differences in left ventricular remodeling in highly-trained athletes relevance to differentiating physiologic left ventricular hypertrophy from hypertrophic cardiomyopathy. *J Am Coll Cardiol.* 2008;51:2256–2262.

29. Pluim BM, Zwinderman AH, van der Laarse A, van der Wall EE. The athlete's heart a meta-analysis of cardiac structure and function. *Circulation*. 2000;101(3):336-44.

30. Leischik R, Spelsberg N. Endurance sport and "cardiac injury": a prospective study of recreational ironman athletes. *Int J Environ Res Public Health*. 2014;11(9):9082-100.

31. Degens H, Stasiulis A, Skurvydas A, Statkeviciene B, Venckunas T. Physiological comparison between non-athletes, endurance, power, and team athletes. *European J ApplPhysiol.* 2019;119:1377-1386.

32. D'Ascenzi F, Caselli S, Solari M, Pelliccia A, Cameli M, Focardi M, Padeletti M, Corrado D, Bonifazi M, Mondillo S. Novel echocardiographic techniques for the evaluation of athletes' heart: A focus on speckle-tracking echocardiography. *EurJ Prev Cardiol.* 2016;23(4):437-46.

33. Paterick TE, Gordon T, Spiegel D. Echocardiography: profiling of the athlete's heart. *JASE*. 2014;27(9):940-8.

34. Paterick Z, Paterick T. Preparticipation Cardiovascular Screening of Student-Athletes with Echocardiography: Ethical, Clinical, Economic, and Legal Considerations. *Curr Cardiol Rep.* 2019;(3):1-12.

35. Grazioli G, Sanz de la Garza M, Vidal B, Montserrat S, Sarquella-Brugada G, Pi R, et al. Prevention of sudden death in adolescent athletes: Incremental diagnostic value and cost-effectiveness of diagnostic tests. *Eur J Prev Cardiol*. 2017;24:1446-1454.

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TABLE 1 Anthropometry and clinical data in adolescent athletes

Clinical Characteristics	All (n=414)	ERp^- (n=322)	ERp^+ (n=92)	p value
Age (years)	13.6±1.8	13.5±1.8	13.8±1.8	=0.11
Female (n, %)	114 (28%)	96 (30%)	18 (19%)	**=0.05**
White (n, %)	345 (83%)	287 (89%)	58 (63%)	**<0.001**
Black ethnicity (n, %)	69 (17%)	35 (11%)	34 (37%)	
BSA (m^2)	1.58±0.23	1.58±0.24	1.58±0.22	=0.92
***Systolic BP (mm Hg)**	109±13	108±13	112±13	**=0.027**
***Diastolic BP (mm Hg)**	68±9	67±9	69±9	=0.18
Heart rate (beats-per-minute)	78±18	80±18	73±14	**<0.001**
****Premature ventricular Complex (n, %)**	73 (18%)	65 (20%)	8 (9%)	**=0.018**
Hours of sport played in a week	6±2	6±2	6±2	=0.73

Data are means ± standard deviation or number of subjects with corresponding percentage. BSA, Body surface area; BP, blood pressure; ERp^+ and ERp^-, athletes with and without Early Repolarization pattern; *Data available for 331 subjects; ** Data available for 406 subjects

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TABLE 2 Electrocardiographic and echocardiographic data in adolescent athletes

ECG parameters	All (n=414)	ERp⁻ (n=322,78%)	ERp⁺ (n=92, 22%)	P value
QTc (ms)	362.7±37.6	362.0±38.9	365.4±32.3	0.46
QRS (ms)	87.7±17.6	88.7±18.7	84.1±12.3	**=0.032**
LVH (mV)	30±10	28±10	36±10	**<0.001**

LV Echocardiographic data	All	ERp⁻	ERp⁺	P value
EDD (mm)	45.8±4.2	46.0±4.1	45.5±4.3	=0.32
ESD (mm)	28.4±3.7	28.4±3.6	28.5±4.1	=0.79
SWT (mm)	7.9±1.3	7.8±1.3	8.4±1.3	**<0.001**
PWT (mm)	7.9±1.5	7.8±1.4	8.5±1.6	**<0.001**
EDV (ml)	101±26	100±26	103±25	=0.43
ESV (ml)	33±11	33±11	33±10	=0.80
RWT	0.35±0.05	0.34±0.05	0.37±0.06	**<0.001**
LVM (g)	149±49	146±48	160±51	**=0.019**
LVM/BSA (g/m²)	93±21	91±20	99±23	**=0.002**

Data are means ± standard deviation. EDD and EDS, end diastolic and end systolic diameter; EDV and EDS, end diastolic and end systolic volumes; ERp^+ and ERp^-, athletes with and without Early Repolarization pattern; LV, left ventricle; LVM, absolute left ventricle mass; LVM/BSA, indexed LVM; LVH, left ventricular hypertrophy; ms, millisecond; mV, millivolt; QTc, corrected of QT-interval in D2 lead; QRS, QRS- duration in D2 lead; RWT, relative wall thickness.

TABLE 3 Binary Logistic regression analysis of the predictor for ERp (values as odds ratio with 95% confidence interval)

Variable	OR (CI)	Sig.
Age (years)	1.02 (0.84-1.22)	ns
Sex	1.67 (0.76-3.67)	ns
Ethnicity	1.73 (0.77-3.89)	ns
VEB	0.77 (0.32-1.85)	ns
HR (bpm)	0.98 (0.96-0.99)	=**0.013**
QRS interval (ms)	0.96 (0.94-0.99)	**=0.003**
LVH (mV)	1.09 (1.05-1.12)	**<0.001**
RWT	1.08 (1.01-1.16)	**=0.032**
LVM/BSA (g/m^2)	1.00 (0.98-1.02)	**ns**

Data available for 365 subjects. Age, Sex, Ethnicity, History of BEV, HR, ECG based LVH, LVM/BSA and RWT were considered as covariates.
VEB, ventricular ectopic beat, HR, Heart rate; LVM/BSA, left ventricular mass normalized by body surface area; LVH, left ventricular hypertrophy assessed by ECG, RWT, relative wall thickness; OR, odds ratio; IC, confidence interval.
OR for continuous variables was calculated for incremental delta of 1, except RWT (incremental delta of 0.01).

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TABLE 4 Binary Logistic regression analysis of the predictor for ERp (values as odds ratio with 95% confidence interval)

A : Black athletes not included

Variable	OR (CI)	Sig.
Age (years)	1.41 (0.85-1.28)	ns
Sex	1.63 (0.71-3.77)	ns
VEB	0.82 (0.31-2.14)	ns
HR (bpm)	0.98 (0.95-1.00)	=**0.035**
QRS interval (ms)	0.96 (0.94-0.99)	**=0.007**
LVH (mV)	1.08 (1.05-1.13)	**<0.001**
RWT	1.10 (1.01-1.20)	**=0.031**
LVM/BSA (g/m^2)	1.00 (0.98-1.02)	**ns**

Data available for 307 subjects.

B : RWT not included

Variable	OR (CI)	Sig.
Age (years)	1.04 (0.87-1.24)	ns
Sex	1.66 (0.76-3.64)	ns
Ethnicity	2.52 (1.21-5.26)	**=0.014**
VEB	0.81 (0.35-1.87)	ns
HR (bpm)	0.98 (0.96-1.00)	=**0.019**
QRS interval (ms)	0.96 (0.94-0.99)	**=0.002**
LVH (mV)	1.09 (1.05-1.12)	**<0.001**
LVM/BSA(g/m^2)	1.00 (0.99-1.02)	ns

Data available for 365 subjects.

VEB, ventricular ectopic beat, HR, Heart rate; LVM/BSA, left ventricular mass normalized by body surface area; LVH, left ventricular hypertrophy assessed by ECG, RWT, relative wall thickness; OR, odds ratio; IC, confidence interval.
OR for continuous variables was calculated for incremental delta of 1, except RWT (incremental delta of 0.01).

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FIGURE LEGENDS

Figure 1 A: Example of ERp (male Caucasian athlete, 16 years old) with slurred (inferior site, A1) notched (lateral site, A2) and QRS morphology and ascending ST (A). B: Example of ERp (male African athlete, 15 years old) in lead V4-V6 with notched QRS morphology and horizontal ST (B1). See also Fig 1 in the ref. 22.

Figure 2 ECG lead distribution in percentage of non-anterior early repolarization pattern (92 on 414 athletes, 22% of participants) among adolescent amateur-level athletes.

Figure 3 Distribution in percentage of morphology of early repolarization pattern (ERp) in lateral (top), inferior (middle) and inferior& lateral (bottom) leads. NA= notching ascending; SA= slur ascending; NA/SA= combination of NA and SA; NH=notch horizontal; SH= slur horizontal

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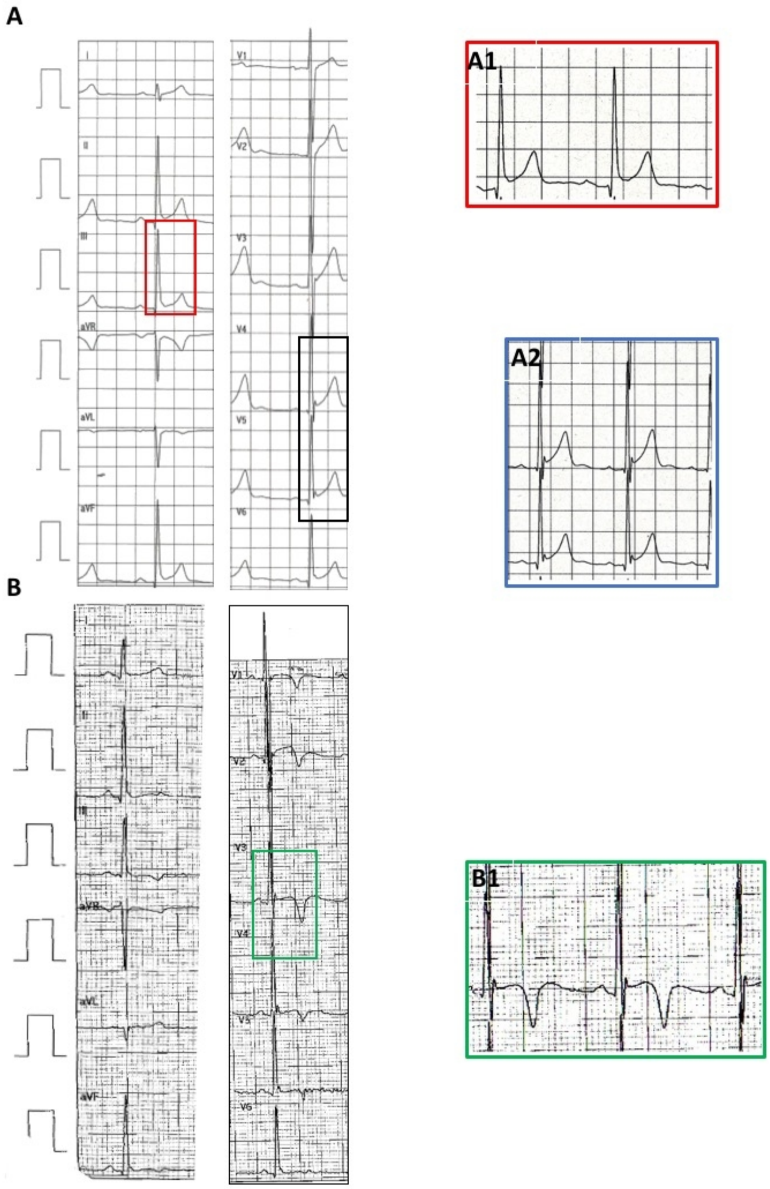

190x275mm (96 x 96 DPI)

FIGURE 2

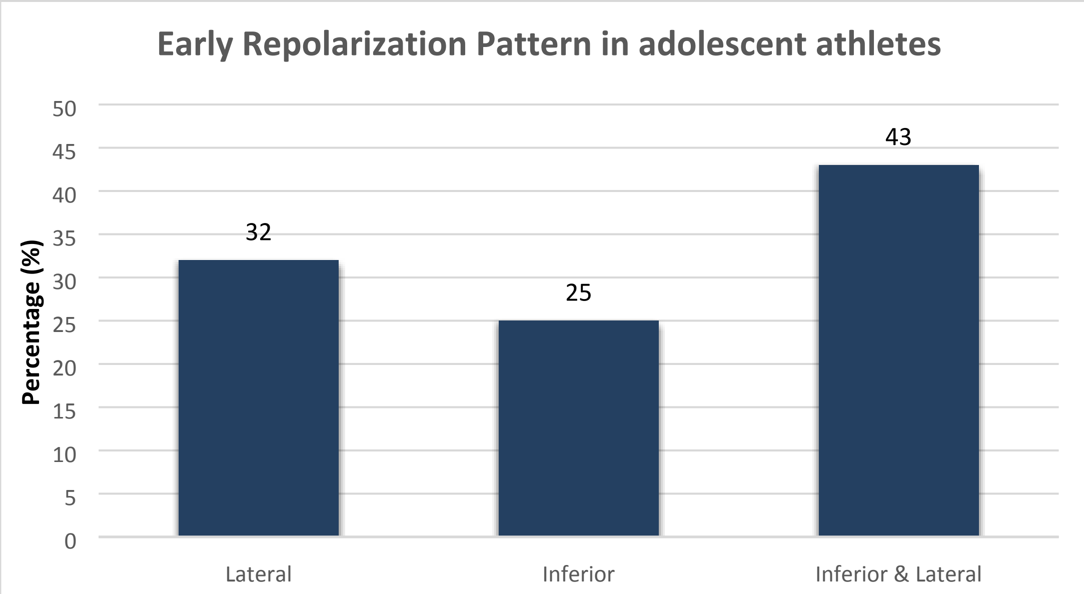

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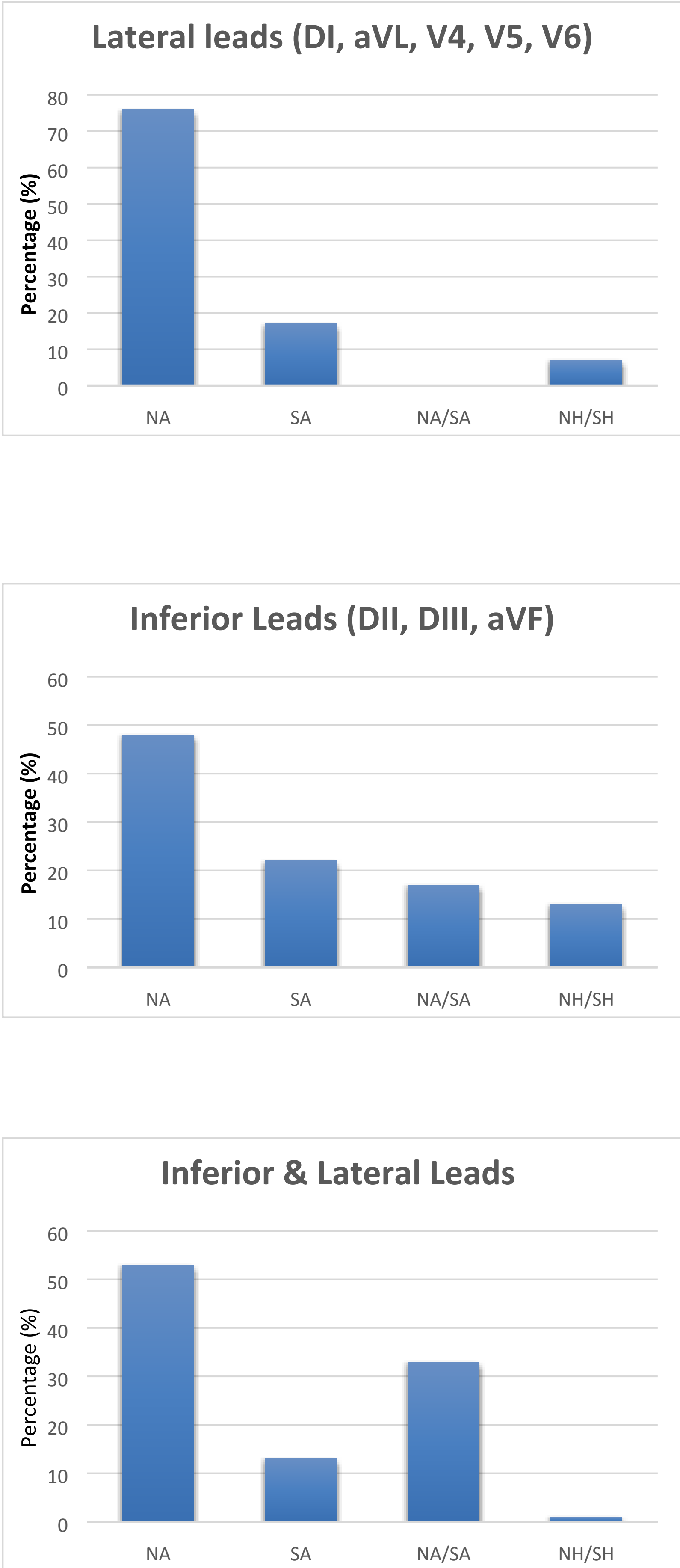
FIGURE 3


Lateral leads (DI, aVL, V4, V5, V6)
Percentage (%)
80
70
60
50
40
30
20
10
0
NA
SA
NA/SA
NH/SH
Inferior Leads (DII, DIII, aVF)
Percentage (%)
60
50
40
30
20
10
0
NA
SA
NA/SA
NH/SH
Inferior & Lateral Leads
Percentage (%)
60
50
40
30
20
10
0
NA
SA
NA/SA
NH/SH

LEFT VENTRICULAR GEOMETRY CORRELATES WITH EARLY REPOLARIZATION PATTERN IN ADOLESCENT ATHLETES

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Short title: Early repolarization in adolescent athlete

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Abstract

Some forms of early ECG repolarization QRS pattern (ERp) with J-point elevation of 0.1mV in two contiguous inferior and/or lateral leads with or without ST elevation are potentially associated with a higher arrhythmic risk in adults. We assessed the prevalence of ERp among non-professional adolescent athletes and correlated it with age, sex, ethnicity and structural and electric cardiac parameters.

We retrospectively analyzed 414 ECGs obtained from young athletes referred to our centre from 2006 to 2017. We found ERp in 22% of cases. In the ERp group, we found a greater percentage of blacks, a higher systolic blood pressure, and lower heart rate (HR) compared with the group without ERp. This pattern was less frequent in female athletes. In athletes with ERp, the occurrence of ventricular ectopic beats was less frequent and QRS duration was shorter. They also exhibited greater i) ECG-based left ventricular hypertrophy (LVH), ii) left ventricular mass, and iii) relative wall thickness (RWT), suggesting a tendency to concentric geometry. At logistic regression analysis, we found that HR (OR 0.98 [0.96-0.99] p= 0.013), QRS duration (OR 0.96 [0.94-0.99], p= 0.003), LVH (OR 1.09 [1.05-1.12], p< 0.001), and RWT (OR 1.08 [1.01-1.16] p= 0.032) were significant predictors of ERp incidence.

ERp is quite common in adolescent athletes and correlates with concentric LV remodeling. Specific clinical and ECG-findings related to training such as lower HR, LVH, and QRS duration are also predictors of ERp. In adolescent non-professional athletes, ERp is a benign finding associated with some structural and electric cardiac modifications induced by training.

KEY WORDS: arrhythmic risk; left ventricular remodeling; adolescent athlete's heart, ethnicity.

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1 INTRODUCTION

Resting 12-lead electrocardiogram (ECG) is part of the pre-participation screening of athletes, to diagnose underlying cardiovascular conditions. In Italy, this procedure reduced the incidence of sudden cardiac death (SD) in athletes to levels that are lower than those of non-athletes.[1] However, the accurate interpretation of athletes' ECG requires continuous investigation, to reduce false positives and improve specificity. There is consensus among cardiologists that we need to refine the criteria used to accurately discriminate sport-related ECG modifications from findings suggestive of cardiac pathologies.[2-6] Frequently, exercise-related ECG abnormalities depend not only on type of sport and intensity of training, but also on variables such as age, sex, and ethnicity. Early repolarization (ER) is one of such "common" abnormalities and is defined as an elevation of the QRS-ST junction of at least 0.1 mV in anterior precordial leads, with morphologies that are different between Caucasians and Africans. In particular, the former is characterized by an elevation of ST-segment with an upward concavity, ending in a positive T-wave, whereas the latter exhibits ST-elevation with an upward convexity, followed by a negative T-wave.[2-6]

In 2008, Haïssaguerre et al.[7] introduced a new definition of early repolarization based on the presence - in the infero-lateral leads - of J waves at the end of QRS, with slurred or notched morphology that might or might not be associated with ST-segment elevations. This pattern (ERp) increases the risk of arrhythmic death in the absence of cardiovascular disease, as confirmed by others.[8-11]

Tikkanen et al.[12] prospectively demonstrated that a horizontal or descending type is accompanied by an increased risk for arrhythmic death; conversely, the ascending one is not associated with such risk. Therefore, ERp could be conveniently subdivided into two forms: a) the upsloping or ascending ST-segment type, which is benign and frequent in athletes, and

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b) the horizontal or descending ST-segment one, which is malignant and associated with an increased arrhythmic risk.[13,14]

Cappato et al.[10] compared 21 athletes (mean age 27 years, who experienced cardiac arrest or SD) to 365 age-matched healthy athletes. The authors demonstrated that a J wave, in the absence of ST-elevation in inferior-lateral ECG leads, was associated with a marginally increased risk of cardiac arrest or SD, whereas the presence of ST-segment elevation did not increase such risk.

Unfortunately, ERp is still not thoroughly assessed in young trans-pubertal athletes, who are at higher arrhythmic risk.[15] From a United Kingdom Regional Registry, the etiology of SD in sports varied with age and sudden arrhythmic death with structurally normal heart is most common in younger (< 18 years) cases, accounting for 56% of deaths in children and adolescents (compared with only 26% in adults >35 years of age[15] in whom the most frequent cause of death is coronary artery disease).[16]

In adolescent athletes, ERp's prevalence and clinical significance deserve to be elucidated. Because our Center routinely performs cardiovascular screening for eligibility for competitive sport in adolescent athletes, we evaluated the prevalence of ERp and its relationship with clinical variables, i.e age, gender, ethnicity, history of arrhythmias, and electrical and structural findings derived from ECG and echocardiographic techniques, in this specific setting.

2 METHODS

2.1 Participants

The local ethics' committee approved this study (Prot. 883/2013 and Prot. 486/2018/OSS*/AOUPR) and written informed consent was obtained from the parents of athletes.

This study is a retrospective analysis of ECGs obtained from consecutive young adolescent athletes referred to the University-Hospital of Parma - from 2006 to 2017 - for echocardiographic inspection during sport pre-participation screenings. In Italian pre-participation screening programs, echocardiographic examination is usually indicated in case of systolic murmur, symptoms as palpitations, extrasystoles, or ECG abnormalities such as LVH o T wave inversion. The occurrence of ventricular ectopic beat (VEB) during ECG screening was included as clinical feature. Case subjects were excluded if they had cardiac abnormalities (arrhythmic syndrome, pathological Q wave, ST-depression, deep T-wave inversion) as detected by ECG or by echocardiography.[17,18]

We retrieved 414 ECGs (age of healthy athletes 13.6±1.8 years, age range 12-17). Twenty-eight percent of athletes were female, 17% were black and 83% were white. All black athletes were coming from Central/West Africa. Participants entered the study and, under their physician's and parents' supervision, completed a questionnaire that included their and their family's cardiovascular and clinical history as well as detailed information on type, intensity, and duration of sport activity, as previously reported.[19]

Blood pressure (BP) was assessed on two occasions, with three consecutive measurements each (OMRON 705 IT).

2.2 ECG analysis

Two trained medical specialists screened all ECGs for the presence of ERp, in a double-blind experimental condition. In case of discrepant opinions, a third reader interpreted the ECG and a conclusive diagnosis was reached. An ERp was defined as elevation of the QRS-ST junction (J point) of at least 0.1mV over the isoelectric line, associated with notching or slurring of the terminal QRS complex in the inferior and/or lateral leads with ascending or descending/horizontal ST segment (Figure 1).[20]

QRS-duration and corrected QT-interval (Bazett formula) were also measured. S1+R5 in precordial leads were calculated using the Sokolow-Lyon voltage criteria (positive if ≥ 35mm) to define the presence of LVH.

2.3 Transthoracic echocardiography

M-mode, two-dimensional, and Doppler Echocardiographic examinationCHOs were performed by an ultrasonography-experienced cardiologist, using a multi-hertz sector, 2-4 MHz probe-equipped machine (Vivid S5, GE Healthcare, USA). The interventricular septal (SWT) and posterior (PWT) left ventricular (LV) wall thicknesses, systolic and diastolic (EDD) LV diameters and volumes, absolute LV mass (LVM) and indexed to body surface area (LVM/BSA), were calculated as previously described.[19] RWT was calculated as: (SWT+ PWT)/EDD, using the 0.42 cut-off to define eccentric ($\leq$ 0.42) or concentric ($\geq$ 0.42) remodelling.[21]

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2.4 Statistical analysis

Data are expressed as mean ± standard deviation. The two groups, i.e. with and without ERp, were compared using two-tailed Student's *t* test (SPSS 20.0 software package, IBM, Armonk, New York, USA). χ-square or Fisher F-test, when appropriate, were used to compare between-group frequencies. Binary logistic regression model was performed to define the variables predictor for ERp. Clinical variables were age, sex, ethnicity, heart rate (HR), VEB. We also computed two structural cardiac parameters such LVM and RWT in addition to ECG-based LVH and QRS- duration. All these measures were assessed as continuous variables.

A 2-tailed $p < 0.05$ was considered as statistically significant. The goodness of fit for logistic regression models was tested looking at the non-significance in the Hosmer Lemeshow test and anomalous distributions of data in the Contingency Table for Hosmer-Lemeshow statistics.

3 RESULTS

3.1 Clinical data

All athletes were engaged in organized amateur-level training for approximately six hours/week. They played in different endurance disciplines, predominantly soccer (177/414, 43% of the total), but also volleyball (n=62, 15% of the total), athletics (n=54, 13%), basketball (n=30, 7%), rugby (n=16, 4%), tennis (n=11, 3%), judo (n=10, 2%), baseball (n=9, 2%), swimming (n=8, 2%), water polo (n=5), gymnastics (n=6), karate (n= 4), softball (n=3), triathlon (n=3), skating (n=3), cycling (n=2). Subjects also played handball, fencing, kickboxing, sport dance, table tennis, flag football, synchronized swimming, and squash (one sport/subject). The clinical characteristics of all adolescent athletes are shown in Table 1 and ECG and echocardiographic data are reported in Table 2.

3.2 Early Repolarization patterns

ERp was found in 92 athletes (i.e. 22%). In the group with ERp (ERp^+), inferior, lateral, and both sides, were involved in 25%, 32% and 43% of cases, respectively (Figure 2). The pattern of terminal QRS changes, notching, slurring or both and morphology of ST (elevation or horizontal/downsloping ST-segment) are depicted in Figure 3. Notched morphology with ascending ST (NA) was prevalent in all sites (76%, 48% and 52% in lateral, inferior, and both sites, respectively) followed by slurring with ST-elevation (SA) in lateral and inferior leads (17% and 22%, respectively) whilst in the subjects with inferior and lateral NA/SA was

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detected in 32.5% of cases. J wave with horizontal or downsloping of ST-segment was uncommon (7%, 13%, and 1% in lateral, inferior, or both sides).

3.3 Characteristics of athletes with ERP

Black male athletes exhibited a higher prevalence of ERp than their Caucasian male counterparts (50% vs 17 %, respectively).

When we compared ERp$^+$ and the group without ERp (ERp$^-$), we did not record significant differences for age, BSA, diastolic BP, and hours of training (Table 1).

We found a greater percentage of black, higher systolic BP and lower HR in the ERp$^+$ group compared with the ERp$^-$ group. This pattern was significantly less frequent in female athletes. History of VEB, assessed during cardiovascular screening at 12-lead resting or during effort ECG, as performed in Italy, was lower in ERp$^+$ (Table 1).

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In the comparison of ECG parameters between the two groups, QRS-duration was shorter in athletes with ERp$^+$, who had greater LVH without significant differences in QTc (Table 2).

The echocardiographic assessment confirmed the ECG data, because the ERp$^+$ group had more pronounced LV hypertrophy as appraised by a higher SWT, PWT, LVM and LVM/BSA associated with an increase of RWT, suggesting a tendency to concentric remodeling (Table 2). No significant differences were observed for LV and volumes and diameters.

3.4 Predictors of ERp incidence

To analyze the clinical ECG- and Echocardiographic~~CHO~~-parameters potentially dictating this pattern, we performed a binary logistic regression model analysis in 365 athletes in which all variables were present. The predictors of incidence of ERp were lower HR (OR

0.98 [0.96-0.99] p=0.013) QRS-duration (OR 0.96, [CI 0.94-0.99], p=0.003), ECG-based LVH (OR 1.09 [CI 1.05-1.12], p< 0.001) and RWT (OR 1.08 [CI 1.01-1.16], p=0.032) (Table 3). Sex, age, ethnicity , history of VEB , and LVM/BSA were not significant determinants of ERp (Table 3). Systolic BP was not included in the analysis because we could not retrieve enough data.

Role of geometry vs. ethnicity

We repeated the same analysis by taking only Caucasians into consideration. The data confirmed the same determinants of ERp noted in the global analysis. From the electrical changes we observed, as expected[11,22]: HR (OR 0.98 [0.95-1.00], p=0.035), QRS duration (OR 0.96 [0.94-0.99], p=0.007), ECG-based LVH (OR 1.08 [1.05-1.13], p<0.001). Interestingly, we observed significant association between ERp and RWT (OR 1.10 [1.01-1.20], p=0.031) observed by echocardiography, indicating that geometry plays a pivotal role in ERp (Table 4A).

To corroborate this observation, we performed an additional analysis, by reintroducing black athletes, but excluding geometry (RWT) in the logistic binary regression. The data underscored that ethnicity is as well a determinant (OR 2.52 [1.21-5.26], p=0.014) of ERp as the aforementioned electrical parameters (Table 4B).

4 DISCUSSION

We characterized ECG and echocardiographic examinations and evaluated the prevalence of ERp in 414 adolescent non-professional athletes, who underwent cardiovascular screening for competitive sport.

Our results demonstrate that ERp is frequent in trans-pubertal athletes (especially in male and black subjects) and could be computed as a benign ECG variant not necessary associated with an increased arrhythmic risk, but associated with some electrical and structural cardiac findings related to training, such as classic anterior ST-elevation.

Since it was first described, ER has historically been considered as a benign ECG variant, more frequent in young boys, in athletes, and in Afro-Americans.[23] However, the 2008 publication of Haissaguerre et al.[7] associating ERp with idiopathic ventricular fibrillation, challenged this notion and led to a critical reappraisal of this finding, casting doubts on the real consequences of this pattern. The prevalent hypothesis is that ERp, in inferior and lateral leads associated with horizontal or descending ST-segments, increases the risk of future arrhythmic death in the absence of cardiovascular disease both in general population and in athletes.[10,12,14]

These observations have raised concerns among physicians involved in cardiovascular screening to prevent SD in athletes where ERp is more frequent stimulating research on the clinical significance of this pattern.

PROOF

Noseworthy et al.[22] analyzed ERp and the impact of 90 days of vigorous exercise training on its prevalence, in competitive athletes (mean age 18 years) of different sex and ethnicity (males 62%, black ethnicity 10.5%). ERp was found in 25.1% of participants, 99% of whom had an ascending ST-segment morphology. ERp was more common in male, black, taller athletes with slower HR, higher ECG-based LVH and was associated with previous exercise training, i.e. they were better trained when they accessed screening. At multivariate analysis, male sex, black race, increased QRS voltage, and slower HR were predictors of ERp. The prevalence of this pattern increased after more vigorous exercise training in addition to a more pronounced left ventricular remodeling, but the authors did not detect any correlation with echocardiographic measures.

These data suggest that exercise-related ERp is as frequent in athletes as is classic anterior ST-elevation and may be an isolated electric phenomenon rather than the result of structural myocardial remodeling, because it correlates with some ECG signs typical of electrical remodeling induced by training, e.g. increased LVH and lower HR, but not with LV structural echocardiographic-derived measures such LVM and RWT.

Similar to those findings, Juntilla et al.[11], in adult athletes, reported a significant relation between ERp and male sex and higher QRS voltage.

De Asmundis C. et al.[24], in a population of 121 young teen athletes (mean age 13.5±2.7) who underwent a clinical evaluation probably during cardiovascular screening for eligibility to sport, found 36% a prevalence of ERp; the most common subtype was at both inferior and lateral sites, in agreement with our data; however, this study included males only and did not report ST morphology or echocardiographic data. The conclusion was that ERp is a frequently occurring phenomenon not just in adults, but also in adolescent athletes.

Ahmed H et al. [25] analyzed the prevalence of ERp in young pubertal (between 13 and 18 years) athletes, in which between-sex differences also involving the heart became apparent. This study is a retrospective analysis of 575 consecutive healthy adolescents who underwent ECG and limited echocardiographic examination for pre-participation screening. The authors demonstrated that ERp is frequent (they observed it in 40% of cases), but they did not specify the characteristics of the ST-segment. No relationship with sex and ethnicity was detected; however, the authors included only 4% of young Africans in their cohort. The group with ERp, compared with the no-ERp group, did not differ in terms of clinical features such as height, weight, systolic/diastolic BP, HR, or clinical history of arrhythmias, but also LVM.

Our results confirm that ERp is quite frequent, i.e. 22% of cases in young athletes, with a greater and significant prevalence in African ethnicity, similarly to what observed in young adult athletes (25% of cases, mean age 18.4±0.8).[22] As regards sex, ERp is less recurrent in female athletes, confirming the data of a previous study by Pelà and coworkers[26] showing that both the electrical LV remodeling and the structural one are less frequent in females even in adolescence.

Systolic BP was higher in ERp^+ athletes compared with ERp^-, but no significant differences were found for diastolic BP and BSA. As regards ECG parameters, significant differences were observed between the two groups for the main "common" ECG changes induced by exercise according to the ESC guidelines[2] published in 2010: subjects with ERp had lower HR, narrower QRS interval, and greater LVH, suggesting that ERp is influenced by training, as already observed by Noseworthy et al.[22] At difference from the authors, however, we observed that, upon echocardiographic examination, athletes ERp^+ had more significant LV structural changes typical of athlete's heart such as higher LVM and RWT values and, in turn, greater left ventricular hypertrophy associated with a tendency to a more concentric geometry.

The binary logistic regression analysis to assess the determinants of ERp demonstrated that ERp was influenced not only by some ECG parameters, such as HR, QRS interval, and LVH, but also by a structural one such as LV geometry. LVM did not contribute.

We have previously demonstrated that a concentric geometry is peculiar of adolescent athlete of African ethnicity, who also develop greater LV hypertrophy, similar to adult athletes.[19,26-28] African adolescents, even if undergoing resistance training, develop a concentric than eccentric hypertrophy rather like in power sports.[29-31] These data explain the greater incidence of ERp in adolescent athletes of African ethnicity. However, RWT rather than ethnicity was a predictor of ERp after binary logistic global analysis. This role was confirmed in the group of only Caucasian athletes, suggesting that RWT impacts on ERp independently from the ethnicity. The significant role of the ethnicity on ERp rise up in the sub-analysis that did not take in consideration RWT confirming the relationship between ethnicity and concentric remodeling.[19,27]

Finally, we analyzed the distribution of ERp by sites. This pattern was prevalent in both infero-lateral and – to a lesser extent - in the lateral and inferior leads (in 43, 32, and 25% respectively). These findings agree with those of Ahmed et al.[25], where ERp was more frequent in the inferior-lateral sites (48%), but the inferior site prevailed on the lateral one (42% vs. 10%) and the incidence of this pattern was greater (41 vs. 22%). Juntilla et al.[11], in young athletes (age range, 17-24 years), found ERp in 30% of cases, with lateral location being the most common (21%) one. These discrepancies can be tentatively explained by the difficulty of diagnosing ERp. Indeed, we used a double reading by two different cardiologists with a third independent reading in case of disagreement, to reach unambiguous interpretation.

Regarding the morphology of J wave and ST-segment in lateral, inferior or both inferior and lateral leads, the most observed pattern was wave J "notch" or "slur" with ascending ST, while horizontal ST was found in a very small percentage of athletes.

PROOF

LIMITATIONS

Some limitations of the present study are noteworthy. First, we emphasize that – in our cohort - the overwhelming majority of athletes with ERp exhibited J wave morphology with ascending ST; therefore, we cannot conclude on the impact of the horizontal/descending ST type, which could be potentially malignant yet poorly represented in our sample. Second, the absence of female black athletes in this study is certainly a limitation for elucidating comparison with Caucasian ones. Third, our healthy population is selected for echocardiography analysis during the cardiovascular screening for sport eligibility and, therefore, there cannot be a control group.[31] Non-professional athletes played different disciplines that induce different LV remodelling. [29-31] The largest group was mixed sports (n= 316) followed by endurance sports (n= 71). The other groups were poorly represented (power group, n= 18 and skill group, n= 6). ERp prevalence did not differ among the 4 different groups: Mixed 74/242, 23.4%; Endurance 12/59, 16.9%; Power 4/14, 22.2%; Skill 1/5, 16.6%. Therefore, we did not find any significant ECG differences among the different sport disciplines. We also do not have follow-up data for this population. Finally, our study does not include the analysis of functional remodeling derived by Doppler Tissue imaging or speckle tracking echocardiography because we focused our attention to the electrical and structural remodeling.[32] Due to the current screening recommendations, echocardiography or Cardio-MRI should be ~~performed~~considered. [33-35]

CONCLUSIONS

Our research supports the hypothesis that ERp is a "benign" pattern of adolescent athletes, correlated with other ECG findings that reflect changes induced by training; ERp is less frequent than the "classic early repolarization" in anterior leads, classified among the "common abnormalities" of the athlete's heart. Our results suggest ERp as a possible marker linking electrical and geometrical remodeling of the LV. Further studies are warranted to confirm our results and clarify the clinical significance of ERp, especially in adolescent athletes who are most at risk of SD.[15]

5 PERSPECTIVE

In this cohort of 414 adolescent athletes, 22% were found to have ERp; the overwhelming majority of them exhibited J wave morphology with ascending ST. Specific clinical and

ECG-findings related to training such as lower HR, LVH, and QRS duration are also predictors of ERp which also correlates with concentric left ventricular remodeling**.** This study of adolescent athletes, less frequently recruited in clinical studies compared with adult athletes, adds new insight to the context of cardiovascular screening program for eligibility to sports in the prevention of juvenile cardiac sudden death.

CONFLICT OF INTEREST

None the authors declare any conflict of interests

FUNDING

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PROOF

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REFERENCES

1. Corrado D, Basso C, Pavei A. Trends in Sudden Cardiovascular Death in Young Competitive Athletes After Implementation of a Preparticipation Screening Program. *JAMA.* 2006;296(13):1593-1601.

2. Corrado D, Pelliccia A, Heidbuchel H, Sharma S, Link M, Basso C, Biffi A, Buja G, Delise P, Gussac I, Anastasakis A, Borjesson M, Bjørnstad HH, Carrè F, Deligiannis A, Dugmore D, Fagard R, Hoogsteen J, Mellwig KP, Panhuyzen-Goedkoop N, Solberg E, Vanhees L, Drezner J, Estes NA 3rd, Iliceto S, Maron BJ, Peidro R, Schwartz PJ, Stein R, Thiene G, Zeppilli P, McKenna WJ. Recommendations for interpretation of 12-lead electrocardiogram in the athlete. *Eur Heart J.* 2010;31:243-259.

3. Drezner JA, Ackerman MJ, Anderson J, Ashley E, Asplund CA, Baggish AL, Börjesson M, Cannon BC, Corrado D, DiFiori JP, Fischbach P, Froelicher V, Harmon KG, Heidbuchel H, Marek J, Owens DS, Paul S, Pelliccia A, Prutkin JM, Salerno JC, Schmied CM, Sharma S, Stein R, Vetter VL, Wilson MG. Electrocardiographic interpretation in athletes: the “Seattle criteria”. *Br J Sports Med.* 2013;47:122-124.

4. Riding NR, Sheikh N, Adamuz C, Watt V, Farooq A, Whyte GP, George KP, Drezner JA, Sharma S, Wilson MG. Comparison of three current sets of electrocardiographic interpretation criteria for use in screening athletes. *Heart.* 2015;101(5): 384-390.

5. Drezner JA, Sharma S, Baggish A, Papadakis M, Wilson MG, Prutkin JM, Gerche A, Ackerman MJ, Borjesson M, Salerno JC, Asif IM, Owens DS, Chung EH, Emery MS, Froelicher VF, Heidbuchel H, Adamuz C, Asplund CA, Cohen G, Harmon KG, Marek JC, Molossi S, Niebauer J, Pelto HF, Perez MV, Riding NR, Saarel T,

Schmied CM, Shipon DM, Stein R, Vetter VL, Pelliccia A, Corrado D. International criteria for electrocardiographic interpretation in athletes: consensus statement. *Br J Sports Med.* 2017;51:704-731.

6. McClean G, Riding NR, Arden CL, Farooq A, Pieles GE[5], Watt V, Adamuz C, George KP, Oxborough D, Wilson MG. Electrical and structural adaptations of the paediatric athlete's heart: a systematic review with meta-analysis. *Br J Sports Med.* 2018;52:230.
7. Haïssaguerre M, Derval N, Sacher F, Jesel L, Deisenhofer I, de Roy L, Pasquié JL, Nogami A, Babuty D, Yli-Mayry S, De Chillou C, Scanu P, Mabo P, Matsuo S, Probst V, Le Scouarnec S, Defaye P, Schlaepfer J, Rostock T, Lacroix D, Lamaison D, Lavergne T, Aizawa Y, Englund A, Anselme F, O'Neill M, Hocini M, Lim KT, Knecht S, Veenhuyzen GD, Bordachar P, Chauvin M, Jais P, Coureau G, Chene G, Klein GJ, Clémenty J. Sudden Cardiac Arrest Associated with Early Repolarization. *N Engl J Med.* 2008;358:2016-2023.
8. Rosso R, Kogan E, Belhassen B, Rozovski U, Scheinman MM, Zeltser D, HaLKIN a, Steinvil A, Heller K, Glikson M, Katz A, Viskin S. J-Point Elevation in Survivors of Primary Ventricular Fibrillation and Matched Control Subjects. *J Am Coll Cardiol.* 2008;52:1231-1238.
9. Tikkanen JT, Anttonen O, Junttila MJ, Aro AL, Kerola T, Rissanen HA, Reunanen A, Huikuri H. Long-term outcome associated with early repolarization on electrocardiography. *N Engl J Med.* 2009;361:2529–2537.
10. Cappato R, Furlanello F, Giovinazzo V, Infusino T, Lupo P, Pittalis M, Foresti S, De Ambroggi G, Ali H, Bianco E, Riccamboni R, Butera G, Ricci C, Ranucci M, Pelliccia A, De Ambroggi L. J-wave, QRS Slurring and ST Elevation in Athletes

with Cardiac Arrest in the Absence of Heart Disease: Marker of Risk, or Innocent Bystander? *Circ Arrhythm Electrophysiol.* 2010;3:305-311.

11. Juntilla MJ, Sager SJ, Freiser M, McGonagle S, Castellanos A, Myerburg RJ. Inferolateral early repolarization in athletes. *J Interv Card Electrophysiol.* 2011;31:33-38.
12. Tikkanen JT, Junttila MJ, Anttonen O, Aro AL, Luttinen S, Kerola T, Sager SJ, Rissanen HA, Myerburg RJ, Reunanen A, Huikuri HV. Early Repolarization. Electrocardiographic phenotypes associated with favorable long-term outcome. *Circulation.* 2011;123:2666-2673.
13. Rosso R, Glikson E, Belhassen B, Katz A, Halkin A, Steivil A, Viskin S. Distinguishing "benign" from "malignant early repolarization": the value of the ST segment morphology. *Heart Rhythm.* 2012;9:225-229.
14. Tikkanen JT, Huikuri HV. Characteristics of "malignant" vs "benign" electrocardiographic patterns of early repolarization. *J Electrocardiol.* 2015;48: 390-394.
15. Finocchiaro G, Papadakis M, Robertus J, Dhutia H, Steriotis AK, Tome M, Mellor G, Merghani A, Malhotra A, Behr E, Sharma S, Sheppard MN. Etiology of Sudden Death in Sports: Insights From a United Kingdom Regional Registry. *J Am Coll Cardiol.* 2016;67:2108-2115.
16. Schmied C, Borjesson M. Sudden cardiac death in athletes. *J Int Med*. 2014;275:93-103.
17. Thompson AJ, Cannon BC, Wackel PL, Horner JM, Ackerman MJ, O'Leary PW,, Eidem BW, Johnson JN. Electrocardiographic abnormalities in elite high school athletes: comparison to adolescent hypertrophic cardiomyopathy. *Br J Sports Med*. 2016;50(2):105-10.

18. Maron BJ, Maron BA. Revisiting Athlete's Heart Versus Pathologic Hypertrophy: ARVC and the Right Ventricle. *JACC Cardiovascular imaging*. 2017;10:395.

19. Pelà G, Li Calzi M, Crocamo A, Pattoneri P, Goldoni M, Anedda A, Musiari L, Biggi A, Bonetti A, Montanari A. Ethnicity-related variations of left ventricular remodeling in adolescent amateur football players. *Scand J Med Sci Sports.* 2015; 25: 382-389.

20. Macfarlane PW, Antzelevitch C, Haïssaguerre M, Huikuri HV, Potse M, Rosso R, Sacher F, Tikkanen JT, Wellens H, Yan G-X. The Early Repolarization Pattern. A consensus paper. *J Am Coll Cardiol.* 2015;66:470-477.

21. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JU. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging.*2015;16:233-270.

22. Noseworthy PA, Weiner R, Kim J, Keelara V, Wang F, Berkstresser B, Wood MJ, WaNG tj, Picard MH, Hutter AM, Newton-Cheh C, Baggish AL. Early Repolarization Pattern in Competitive Athletes. Clinical Correlates and the Effects of Exercise Training. *Circ Arrhythm Electrophysiol.* 2011;4:432-440.

23. Klatsky A, Oehm R, Cooper RA, Udaltsova N, Armstrong MA. The Early Repolarization Normal Variant Electrocardiogram: Correlates and Consequences. *Am J Med.* 2003;115:171-177.

24. De Amundis C, Conte G, Levinstein M, Chierchia G-B, Sieira J, Di Giovanni G, Baltogiannis G, Park MH, Sarkozy A, Brugada P. *Acta Cardiol.* 2014;69:3-6.

25. Ahmed H, Czosk RJ, Spar DS, Knilans TK, Anderson JB. Early Repolarization in Normal Adolescents is Common. *Pediatr Cardiol.* 2017;38:864-872.

26. Pelà G, Crocamo A, Li Calzi M, Gianfreda M, Gioia MI, Visioli F, Pattoneri P, Corradi D, Goldoni M, Montanari A. Sex-related differences in left ventricular structure in early adolescent non-professional athletes. *Eur J Prev Cardiol* . 2016;23: 777-784.

27. Demola P, Crocamo A, Ceriello L, Botti A, Cremonini I, Pattoneri P, Corradi D, Visioli F, Goldoni M, Pelà G. Hemodynamic and ECG responses to stress test in early adolescent athletes explain ethnicity-related cardiac differences. *Int J Cardiol.*2019;289:125-130

28. Basavarajaiah S, Boraita A, Whyte G, Wilson M, Carby L, Shah A, Sharma S. Ethnic differences in left ventricular remodeling in highly-trained athletes relevance to differentiating physiologic left ventricular hypertrophy from hypertrophic cardiomyopathy. *J Am Coll Cardiol.* 2008;51:2256–2262.

29. Pluim BM, Zwinderman AH, van der Laarse A, van der Wall EE. The athlete's heart a meta-analysis of cardiac structure and function. *Circulation*. 2000;101(3):336-44.

30. Leischik R, Spelsberg N. Endurance sport and "cardiac injury": a prospective study of recreational ironman athletes. *Int J Environ Res Public Health*. 2014;11(9):9082-100.

31. Degens H, Stasiulis A, Skurvydas A, Statkeviciene B, Venckunas T. Physiological comparison between non-athletes, endurance, power, and team athletes. *European J ApplPhysiol.* 2019;119:1377-1386.

32. D'Ascenzi F, Caselli S, Solari M, Pelliccia A, Cameli M, Focardi M, Padeletti M, Corrado D, Bonifazi M, Mondillo S. Novel echocardiographic techniques for the evaluation of athletes' heart: A focus on speckle-tracking echocardiography. *EurJ Prev Cardiol.* 2016;23(4):437-46.

33. Paterick TE, Gordon T, Spiegel D. Echocardiography: profiling of the athlete's heart. *JASE*. 2014;27(9):940-8.

34. Paterick Z, Paterick T. Preparticipation Cardiovascular Screening of Student-Athletes with Echocardiography: Ethical, Clinical, Economic, and Legal Considerations. *Curr Cardiol Rep.* 2019;(3):1-12.

35. Grazioli G, Sanz de la Garza M, Vidal B, Montserrat S, Sarquella-Brugada G, Pi R, et al. Prevention of sudden death in adolescent athletes: Incremental diagnostic value and cost-effectiveness of diagnostic tests. *Eur J Prev Cardiol*. 2017;24:1446-1454.

PROOF

TABLE 1 Anthropometry and clinical data in adolescent athletes

Clinical Characteristics	All (n=414)	ERp^- (n=322)	ERp^+ (n=92)	p value
Age (years)	13.6±1.8	13.5±1.8	13.8±1.8	=0.11
Female (n, %)	114 (28%)	96 (30%)	18 (19%)	**=0.05**
White (n, %)	345 (83%)	287 (89%)	58 (63%)	**<0.001**
Black ethnicity (n, %)	69 (17%)	35 (11%)	34 (37%)	
BSA (m^2)	1.58±0.23	1.58±0.24	1.58±0.22	=0.92
***Systolic BP (mm Hg)**	109±13	108±13	112±13	**=0.027**
***Diastolic BP (mm Hg)**	68±9	67±9	69±9	=0.18
Heart rate (beats-per-minute)	78±18	80±18	73±14	**<0.001**
****Premature ventricular Complex (n, %)**	73 (18%)	65 (20%)	8 (9%)	**=0.018**
Hours of sport played in a week	6±2	6±2	6±2	=0.73

Data are means ± standard deviation or number of subjects with corresponding percentage. BSA, Body surface area; BP, blood pressure; ERp^+ and ERp^-, athletes with and without Early Repolarization pattern; *Data available for 331 subjects; ** Data available for 406 subjects

PROOF

TABLE 2 Electrocardiographic and echocardiographic data in adolescent athletes

ECG parameters	All (n=414)	ERp^- (n=322,78%)	ERp^+ (n=92, 22%)	P value
QTc (ms)	362.7±37.6	362.0±38.9	365.4±32.3	0.46
QRS (ms)	87.7±17.6	88.7±18.7	84.1±12.3	**=0.032**
LVH (mV)	30±10	28±10	36±10	**<0.001**

LV Echocardiographic data	All	ERp^-	ERp^+	P value
EDD (mm)	45.8±4.2	46.0±4.1	45.5±4.3	=0.32
ESD (mm)	28.4±3.7	28.4±3.6	28.5±4.1	=0.79
SWT (mm)	7.9±1.3	7.8±1.3	8.4±1.3	**<0.001**
PWT (mm)	7.9±1.5	7.8±1.4	8.5±1.6	**<0.001**
EDV (ml)	101±26	100±26	103±25	=0.43
ESV (ml)	33±11	33±11	33±10	=0.80
RWT	0.35±0.05	0.34±0.05	0.37±0.06	**<0.001**
LVM (g)	149±49	146±48	160±51	**=0.019**
LVM/BSA (g/m²)	93±21	91±20	99±23	**=0.002**

Data are means ± standard deviation. EDD and EDS, end diastolic and end systolic diameter; EDV and EDS, end diastolic and end systolic volumes; ERp^+ and ERp^-, athletes with and without Early Repolarization pattern; LV, left ventricle; LVM, absolute left ventricle mass; LVM/BSA, indexed LVM; LVH, left ventricular hypertrophy; ms, millisecond; mV, millivolt; QTc, corrected of QT-interval in D2 lead; QRS, QRS- duration in D2 lead; RWT, relative wall thickness.

PROOF

TABLE 3 Binary Logistic regression analysis of the predictor for ERp (values as odds ratio with 95% confidence interval)

Variable	OR (CI)	Sig.
Age (years)	1.02 (0.84-1.22)	ns
Sex	1.67 (0.76-3.67)	ns
Ethnicity	1.73 (0.77-3.89)	ns
VEB	0.77 (0.32-1.85)	ns
HR (bpm)	0.98 (0.96-0.99)	=**0.013**
QRS interval (ms)	0.96 (0.94-0.99)	**=0.003**
LVH (mV)	1.09 (1.05-1.12)	**<0.001**
RWT	1.08 (1.01-1.16)	**=0.032**
LVM/BSA (g/m^2)	1.00 (0.98-1.02)	**ns**

Data available for 365 subjects. Age, Sex, Ethnicity, History of BEV, HR, ECG based LVH, LVM/BSA and RWT were considered as covariates.
VEB, ventricular ectopic beat, HR, Heart rate; LVM/BSA, left ventricular mass normalized by body surface area; LVH, left ventricular hypertrophy assessed by ECG, RWT, relative wall thickness; OR, odds ratio; IC, confidence interval.
OR for continuous variables was calculated for incremental delta of 1, except RWT (incremental delta of 0.01).

PROOF

TABLE 4 Binary Logistic regression analysis of the predictor for ERp (values as odds ratio with 95% confidence interval)

A : Black athletes not included

Variable	OR (CI)	Sig.
Age (years)	1.41 (0.85-1.28)	ns
Sex	1.63 (0.71-3.77)	ns
VEB	0.82 (0.31-2.14)	ns
HR (bpm)	0.98 (0.95-1.00)	=**0.035**
QRS interval (ms)	0.96 (0.94-0.99)	**=0.007**
LVH (mV)	1.08 (1.05-1.13)	**<0.001**
RWT	1.10 (1.01-1.20)	**=0.031**
LVM/BSA (g/m^2)	1.00 (0.98-1.02)	**ns**

Data available for 307 subjects.

PROOF

B : RWT not included

Variable	OR (CI)	Sig.
Age (years)	1.04 (0.87-1.24)	ns
Sex	1.66 (0.76-3.64)	ns
Ethnicity	2.52 (1.21-5.26)	**=0.014**
VEB	0.81 (0.35-1.87)	ns
HR (bpm)	0.98 (0.96-1.00)	=**0.019**
QRS interval (ms)	0.96 (0.94-0.99)	**=0.002**
LVH (mV)	1.09 (1.05-1.12)	**<0.001**
LVM/BSA(g/m^2)	1.00 (0.99-1.02)	ns

Data available for 365 subjects.

VEB, ventricular ectopic beat, HR, Heart rate; LVM/BSA, left ventricular mass normalized by body surface area; LVH, left ventricular hypertrophy assessed by ECG, RWT, relative wall thickness; OR, odds ratio; IC, confidence interval.
OR for continuous variables was calculated for incremental delta of 1, except RWT (incremental delta of 0.01).

FIGURE LEGENDS

Figure 1 A: Example of ERp (male Caucasian athlete, 16 years old) with slurred (inferior site, A1) notched (lateral site, A2) and QRS morphology and ascending ST (A). B: Example of ERp (male African athlete, 15 years old) in lead V4-V6 with notched QRS morphology and horizontal ST (B1). See also Fig 1 in the ref. 22.

Figure 2 ECG lead distribution in percentage of non-anterior early repolarization pattern (92 on 414 athletes, 22% of participants) among adolescent amateur-level athletes.

Figure 3 Distribution in percentage of morphology of early repolarization pattern (ERp) in lateral (top), inferior (middle) and inferior& lateral (bottom) leads. NA= notching ascending; SA= slur ascending; NA/SA= combination of NA and SA; NH=notch horizontal; SH= slur horizontal

PROOF

03-Jul-2019

Dear Professor Pelà,

Manuscript SJMSS-O-248-19.R3 entitled "LEFT VENTRICULAR GEOMETRY CORRELATES WITH EARLY REPOLARIZATION PATTERN IN ADOLESCENT ATHLETES", which you submitted to the Scandinavian Journal of Medicine and Science in Sports, has now been re-reviewed. The comments of the reviewer(s) are included at the bottom of this letter. Your paper is considered to be conditionally acceptable provided that you can respond and modify your manuscript in accordance with the comments made by the reviewers. Therefore, I invite you to respond to the comments of the reviewer(s) and revise your manuscript.

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Yours sincerely,

Professor Jose Calbet
Senior Section Editor, Physiology & Biochemistry Scandinavian Journal of Medicine and Science in Sports
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PROOF

Reviewer(s)' Comments to Author:

Reviewer: 1

Comments to the Author
Thank you for rephrasing some of the language into better English. There are, however, still at least 5 different places in the manuscript where the authors use the term Echo rather than echocardiography. This should be changed.

Response

We overlooked the 5 different places where we use ECHO rather than echocardiography, now corrected.

I would also support Reveiwer 1 in suggesting that (Limitation section) ... echocardiogrphay or CMR should be considered.

The authors state that it should be performed, which i do not think is correct.

Response

The sentence has now been corrected, as suggested

PROOF