International Journal of Cardiology 279 (2019) 100–104

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Prevalence and significance of T-wave inversion in children practicing sport: A prospective, 4-year follow-up study

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ARTICLE INFO

Article history:
Received 29 August 2018
Accepted 19 September 2018
Available online 21 September 2018

Keywords:
Electrocardiography
Negative T waves
Cardiomyopathy
Pre-participation screening
Athlete's heart

ABSTRACT

Background: T-wave inversion (TWI) is rare in athlete's heart but is a common manifestation in cardiomyopathies. Although TWI has been extensively investigated in adult athletes, the ability of this ECG pattern to distinguish between a physiological variant and a developing heart muscle disease in children is controversial. The aim of this longitudinal study was to establish the prevalence, changes and clinical significance of TWI in a large cohort of pre-adolescent athletes.

Methods: 2227 children (mean age 12.3 ± 2.0 years) undergoing sports preparticipation screening were included. Children with TWI underwent yearly follow-up until the positivisation of TWI for a maximum follow-up of 4 years.

Results: Among 2227 children, 358 (16%) had TWI. Children with TWI were younger (11.4 ± 2.1 vs. 12.5 ± 2.0 years, $p < 0.0001$) and had a lower BSA than children without TWI ($p < 0.0001$). 97% of children showed anterior TWI while only 3% had infero-lateral TWI. Anterior TWI became positive in 94% of children during the 4-year follow-up ($p < 0.0001$ vs. baseline) and the remaining 6% did not show abnormal clinical findings. Conversely, in the group of 9 children with infero-lateral TWI, only 1 showed normalisation during follow-up ($p = 0.81$) and 1 was found to have a cardiomyopathy.

Conclusions: Anterior TWI is common in children and generally becomes positive by the age of 14 years. Conversely, infero-lateral TWI is rare, persistent and may be associated with structural heart disease. Therefore, infero-lateral TWI should not be interpreted as physiologically related to age, development or training and children with infero-lateral TWI should remain under strict clinical surveillance.

1. Introduction

Intense physical training is usually accompanied by electrical and structural adaptations that are collectively referred to as the 'athlete's heart' [1]. The 12-lead electrocardiogram (ECG) is commonly used for evaluating athletes and is recommended by the European Society of Cardiology as part of the pre-participation cardiovascular screening (PPS) for athletes [1]. While some ECG patterns are common in athletes and related to training, other ECG abnormalities, specifically T-wave inversion (TWI), are rare in athletes but are common manifestations in patients with cardiomyopathies such as hypertrophic (HCM) and arrhythmogenic cardiomyopathy (AC), which account for over one-third of all sudden cardiac deaths in young athletes [2]. Although the prevalence and significance of TWI has been extensively investigated in adult athletes, little is known about their significance in the paediatric athletic population despite an increasing level of competitiveness and training demands on the paediatric athlete. Furthermore, the interpretation of 12-lead ECG in children is challenging because anterior (V1–V3) TWI is common. Although this repolarisation pattern is traditionally considered as the benign juvenile ECG pattern that regresses with age, [3,4], anterior TWI is also the most common ECG abnormality observed in AC. Therefore, the interpretation of anterior TWI in children requires a differential diagnosis between a physiological variant and the potential for developing heart muscle disease [5]. Furthermore, while training-induced changes on the ECG are well established in adult athletes, few studies have investigated the influence of training on the ECG in children practising sports [6,7]. Traditionally ECG data on athletes have been obtained from cross-sectional studies. The aim of

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https://doi.org/10.1016/j.ijcard.2018.09.069
0167-5273/

this longitudinal study was to establish the prevalence of TWI in a large cohort of pre-adolescent athletes undergoing PPS and to monitor the time frame for regression to the adult form.

2. Methods

2.1. Study population

We enrolled 2277 consecutive children practising sports who underwent PPS at the Sports Medicine Center in Siena, Italy, from January 2011 to February 2014. Children practised competitive sports on a regional level and the amount of training per athlete averaged 7 ± 3 h/week. All children underwent PPS in accordance with the Italian protocol [8,9] which includes family and personal history, physical examination and 12-lead resting ECG. Children with abnormal findings underwent further examinations based on the Italian protocol for sports eligibility and disqualification [8,9]. The study was approved by the local ethics Committee.

Children with complete right bundle branch block (RBBB), repolarization abnormalities other than TWI or with TWI secondary to Wolff-Parkinson-White (WPW) syndrome were excluded from the study. Accordingly, 41 children with RBBB, 2 with WPW syndrome and 6 with long-QT syndrome were excluded. During the initial evaluation 1 child had clinical features consistent with pericarditis and was excluded from the final analysis. The final population consisted of 2227 athletes (mean age: 12.3 ± 2.0 years).

The group of children with TWI underwent yearly assessment, including family and personal history, physical examination and 12-lead resting ECG, until the positivisation of TWI and for a maximum period of observation of 4 years from the beginning of the study. Children with persistent TWI at the end of the observation period underwent further examination with echocardiography and, in selected cases, cardiac magnetic resonance to rule-out an underlying disease.

2.2. Clinical evaluation

Personal history enquired about symptoms suggestive of cardiovascular disease and a family history of cardiomyopathies, premature sudden cardiac death and ischemic heart disease.

Physical examination focused on anthropometric characteristics, precordial assessment, blood pressure, peripheral pulses and musculoskeletal and ocular features of Marfan syndrome. Body mass index (BMI) was calculated by dividing weight in kilograms divided by height in meters and body surface area (BSA) was calculated according to the formula of Dubois and Dubois [10].

2.3. Twelve-lead ECG

A standard 12-lead ECG was performed in all children in the supine position during quiet respiration using a CARDIOLINE Realclick v.3.4. All ECGs were recorded at a paper speed of 25 mm/s and at a standard gain of 1 mV/cm. ECGs were interpreted by experienced cardiologists and discrepancies were solved by consensus among all authors.

Heart rate (HR) at rest, PR interval, QRS duration, QT interval and QRS axis were calculated. Any form of atrioventricular block was sought. Left axis deviation was defined as a QRS axis exceeding −30° and right axis deviation was defined as QRS axis exceeding +120° [11]. Incomplete RBBB was defined as a QRS duration <120 ms, with r′ or R′ wave in lead V1 or V2, an S wave of greater duration than R wave or >40 ms in leads I and V6, and normal R peak time in leads V5 and V6 but >50 ms in lead V1, while complete RBBB was defined as a QRS duration >120 ms in presence of the criteria described earlier. The Sokolow-Lyon voltage criteria were applied for the definition of left ventricular hypertrophy (LVH) [12]. Early repolarization was defined as recommended by the International recommendations [13]. A Q wave was considered abnormal or pathological if it exceeded 0.04 s in duration and/or the depth of the Q wave exceeded 25% of the height of the R wave [11]. The QT interval was calculated manually and was corrected for HR at rest (QTc), according to the Bazzett formula and the QTc interval was considered abnormally prolonged if longer than 440 ms and 460 ms for males and females respectively [14].

TWI was diagnosed in the presence of negative T wave ≥ 1 mm in ≥2 continuous leads except III, V1 and aVR [4]. Deep TWI was defined as a negative T wave ≥ 2 mm in ≥2 continuous leads [15]. Leads V1 to V4 were classified as anterior precordial leads while V5–V6 and/or I-aVL were classified as lateral and II–III/aVF were classified as inferior.

The amplitude of the J point (Jt) was measured at the end of the QRS complex (the onset of the ST-segment) with reference to the onset of the QRS complex. The Jt was considered elevated if Jt ≥ 0.1 mV or depressed if Jt ≤ −0.1 mV. The morphology of the ST-segment in the anterior leads was ascertained during the 100 ms following Jt. The ST-segment was considered elevated if it was above Jt, depressed if it was below Jt, and isoelectric if it was in line with Jt [16]. Ascending ST-segments were categorized as ascending convex or ascending concave [16].

2.4. Statistical analysis

Normal distribution of all continuous variables was examined using the Shapiro-Wilk test, and data are presented as mean ± SD. Categorical variables are expressed as percentages. The unpaired *t*-test and the Mann-Whitney *U* test were used to assess the between-group significance, according to data distribution. The paired *t*-test and the Wilcoxon matched-paired test were used to assess the within group significance in the TWI group according to data distribution. Categorical data were analysed using the chi-squared test. A p value < 0.05 was considered significant. Correlation analysis was performed to find association between the ECG and demographics variables using the Spearman and Pearson methods, as appropriate for data distribution. Statistics were performed using SPSS, version 21.0 (Statistical Package for the Social Sciences Inc., Chicago, Illinois, USA).

3. Results

3.1. Demographics characteristics

The demographic characteristics of the study population are reported in Table 1. All children were white Caucasian. Among 2227 children included in the study, 358 (16%) had TWI. The percentage of female children was greater in the group of children with TWI ($p = 0.003$). Moreover, children with TWI were younger and had lower BSA than children without TWI ($p < 0.0001$).

3.2. Prevalence, distribution and characteristics of TWI

In the TWI group, 18 (5%) children were lost at follow up because of withdrawal from competition and all had anterior TWI. 340 children were available for the analysis during the follow-up: 331 (97%) children had anterior TWI and 9 (3%) infero-lateral TWI. Among children with infero-lateral TWI, 2 had inferior TWI, 6 both inferior and lateral TWI and 1 had lateral TWI. None experienced symptoms during the study. Prevalence, distribution and characteristics of anterior TWI are reported in Table 2. In the group with anterior TWI, 37 children (11%) had TWI from V1 to V4, 168 (51%) from V1 to V3, 71 (21%) from V1 to V2 and 55 children (17%) had isolated TWI in V3 (Fig. 1). Children with TWI from V1 to V3 were younger and had a smaller BSA as compared to children with TWI in the other anterior leads ($p < 0.0001$ for both).

Deep TWI was less common in the subgroup of children with TWI from V1 to V2 (18%) and more common in the subgroup with TWI from V1 to V3 (54%).

There were no differences in the characteristics of JT elevation and ST-segment morphology preceding anterior TWI among the groups ($p = 0.58$). None of the participants had depressed ST-segment morphology.

Table 1
Demographic and ECG characteristics of children with and without T-wave inversion.

	Children with TWI (n = 358)	Children without TWI (n = 1869)	*p* value
Demographics			
Age (yrs)	11.4 ± 2.1	12.5 ± 2.0	<0.0001
Male (n/%)	189/53	1142/61	0.003
Height (cm)	150.2 ± 13.2	158.7 ± 12.8	<0.0001
Weight (kg)	42.4 ± 12.4	51.3 ± 13.4	<0.0001
BSA (m^2)	1.3 ± 0.24	1.5 ± 0.3	<0.0001
ECG parameters			
Resting heart rate (bpm)	93 ± 16	90 ± 16	0.001
Non-sinus rhythm (n/%)	0/0	3/0.2	0.68
PR interval (ms)	126.1 ± 16.0	128.8 ± 17.0	0.002
First AV block (n/%)	1/0.3	2/0.1	0.41
Second AV block (n/%)	0/0	0/0	NA
Pathological Q waves (n/%)	0/0	0/0	NA
QRS duration (ms)	86.4 ± 9.5	85.4 ± 9.2	0.092
Incomplete RBBB (n/%)	157/44	557/30	<0.0001
Undetermined QRS axis (n/%)	7/2.0	31/1.7	0.69
Left axis deviation (n/%)	0/0	5/0.3	0.33
Right axis deviation (n/%)	0/0	1/0.1	0.66
LVH (n/%)	30/8.4	172/9.2	0.62
Early repolarization			
Anterior (n/%)	25/7.0	552/29.5	<0.0001
Inferior (n/%)	9/2.5	57/3.1	0.58
Lateral (n/%)	15/4.2	99/5.3	0.38
QTc interval (ms)	413.0 ± 25.6	407.6 ± 25.1	<0.0001

TWI, T-wave inversion; BSA, body surface area; AV, atrioventricular; RBBB, right bundle branch block; LVH, left ventricular hypertrophy; QTc, Qt corrected for resting heart rate.

Table 2
Demographic and ECG characteristics of children according to the localisation of anterior TWI, at the beginning of the study and at time of positivisation.

Anterior TWI (n = 331)	V1–V4 (n = 37)	V1–V3 (n = 168)	V1–V2 (n = 71)	Isolated V3 (n = 55)	Overall *p* value
Baseline					
Demographics					
Age (yrs)	12.1 ± 1.7	10.8 ± 1.9*	11.5 ± 2.0	12.0 ± 2.2‖	<0.0001
Height (cm)	157 ± 9	147 ± 12*	150 ± 13†	153 ± 14‡	<0.0001
Weight (kg)	49 ± 9	40 ± 12*	42 ± 13†	44 ± 13	<0.0001
BSA (m^2)	1.47 ± 0.17	1.27 ± 0.23*	1.33 ± 0.24†	1.37 ± 0.25	<0.0001
TWI characteristics					
Deep TWI (%)	46	54	18†,‖	44§	<0.0001
ST-segment preceding TWI (%)					0.58
Ascending convex	38	41	12	38	
Ascending concave	19	23	6	31	
Isoeletric	43	36	82	31	
Depressed	0	0	0	0	
At time of positivisation of TWI					
Demographics					
Age (yrs)	13.8 ± 1.6	12.6 ± 1.9†	13.0 ± 2.0	13.5 ± 2.4	<0.004
Height (cm)	164 ± 8	158 ± 12	159 ± 12	157 ± 24	0.23
Weight (kg)	56 ± 8	48 ± 12†	50 ± 13	49 ± 11	0.014
BSA (m^2)	1.30 ± 0.64	1.41 ± 0.35	1.49 ± 0.24	1.30 ± 0.53	0.038

TWI, T-wave inversion; BSA, body surface area; AV, atrioventricular; RBBB, right bundle branch block; LVH, left ventricular hypertrophy; QTc, Qt corrected for resting heart rate.
* $p < 0.0001$ vs. V1–V4.
† $p < 0.05$ vs. V1–V4.
‡ $p < 0.05$ V1–V3 vs. V3.
§ $p < 0.05$ vs. V1–V2.
‖ $p < 0.0001$ vs. V1–V3.

3.3. Follow up of children with TWI

Anterior TWI became positive in almost all (94%) of the children during the 4-year follow-up period ($p < 0.0001$ vs. baseline). Conversely, among the children with infero-lateral TWI, only 1 child (11%) showed complete normalisation during follow up, at the age of 17 years old ($p = 0.81$ vs. baseline). This child had inferior TWI. The number of children with anterior and infero-lateral TWI at the beginning of the study and after the 4-year follow up is shown in Fig. 2. All children with infero-lateral TWI as well as children with persistent anterior TWI underwent echocardiography. Among children with infero-lateral TWI, 5 had a normal echocardiogram; 1 had mild left ventricular hypertrophy; 1 had a mitral valve prolapse (anterior leaflet); 1 with TWI both in the inferior and in the lateral leads showed echocardiographic findings consistent with left ventricular non-compaction that was confirmed by cardiac magnetic resonance, 1 child had moderate left ventricular hypertrophy

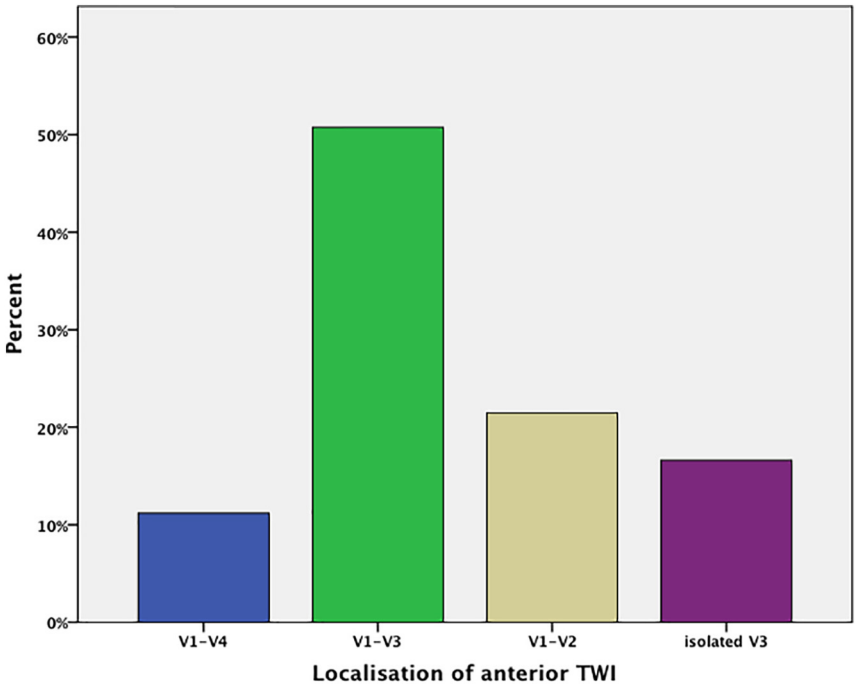

Fig. 1. Distribution of anterior T-wave inversion in children according to the localisation in the anterior leads.

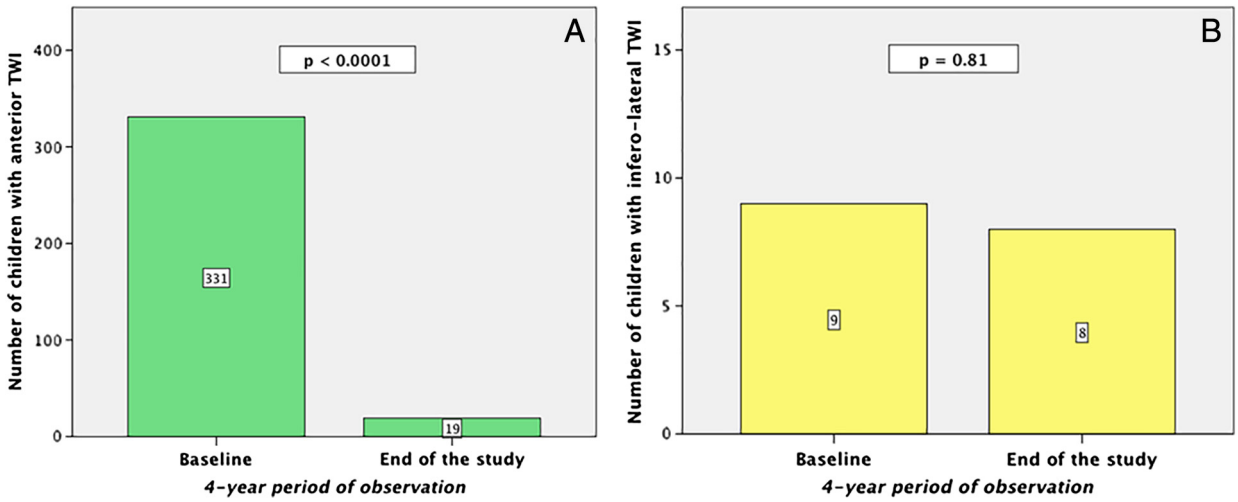

Fig. 2. Changes of anterior (A) and infero-lateral (B) T-wave inversion (TWI) during the follow up. The figure describes the number of children with TWI at the beginning of the study and at the end of the study.

at echocardiography and underwent cardiac magnetic resonance demonstrating a mild increase in left ventricular mass and end-diastolic volume, in absence of a clear diagnosis of hypertrophic cardiomyopathy at the time of evaluation. Conversely, all children with persistent anterior TWI showed a normal echocardiography. None of children with TWI had family history of cardiomyopathies or demonstrated malignant ventricular arrhythmias.

3.4. Correlation analysis

In the population of children with TWI we found that age inversely correlated with presence of anterior TWI ($R = -0.22$, $p < 0.0001$) and TWI V1–V3 ($R = -0.28$, $p < 0.0001$). A mild correlation was found between age and presence of inferior and lateral TWI ($R = 0.21$, $p < 0.0001$ and $R = 0.20$, $p < 0.0001$, respectively). BSA inversely correlated with anterior TWI ($R = -0.21$, $p < 0.0001$) and positively correlated with presence of inferior and lateral TWI ($R = 0.21$, $p < 0.0001$ and $R = 0.20$, $p < 0.0001$, respectively).

4. Discussion

The interpretation of TWI on the 12-lead resting ECG during the PPS can be challenging in children because there are dynamic repolarisation changes in the anterior leads from birth to adolescence. Young athletes often exhibit TWI in the right precordial leads which are considered to represent the normal juvenile ECG pattern but which are also similar to ECGs of patients with AC and sometimes with HCM. Therefore, an accurate differentiation between ECG patterns related to age and development or to cardiomyopathies is crucial in children practising sport during the PPS.

This study of over 2200 children practising sport demonstrates a high prevalence TWI. Indeed, up to 16% of children had TWI. The percentage of athletes exhibiting TWI varies according to age. In a recent cross-sectional study performed in Italy and aimed to derive normal ECG values in children and adolescent practising non-competitive sports, Molinari et al. found that the presence of TWI decreased from 55 to 60% at 3 years to 10% at 14 years [17]. In the study by Migliore et al., in a large population of children with a mean age of 13.9 ± 2.2 years (range 8–18 years), the prevalence of TWI was 5.7% [18]. The prevalence decreases as young athletes progress from childhood to adolescence and young adulthood as demonstrated by Sharma et al. reporting a prevalence of TWI in V2–V3 up to 4% in a population of 1000 junior elite athletes with a mean age of 15.7 years [11]. Similarly, Papadakis et al. found a prevalence of 4% in adolescent athletes with a mean age 16 ± 1.7 (range 14–18) and where TWI extending beyond V2 was rare (0.8%) [15]. Conversely, the prevalence of anterior TWI decreased up to 2.3% in a study by Malhotra investigating a population of young athletes with a mean age of 21.7 ± 5.4 [16]. In the present study we found a high prevalence of TWI that is explained by the lowest mean age of our population as compared to those analysed in the previous studies. Furthermore, when children with TWI were compared with those without TWI, we found that the former were younger, with a lower weight and a higher height as compared to the latter. Notably, the prevalence of females was higher in the group with TWI as compared to the group without TWI.

Information from the preceding Jt or ST-segment may provide valuable diagnostic information in adult athletes with anterior TWI [16]. We extended the previous findings reporting for the first time the characteristics of Jt or ST-segment in a paediatric population of athletes. We demonstrated that none of the preadolescent athletes have a depressed ST-segment preceding anterior TWI, in agreement with the interpretation of this pattern as an electrical marker of cardiac pathology [16]. Notably, as compare to the adult population, children tend to exhibit more frequently a TWI preceded by an isoelectric ST-segment and this difference should be taken into account when evaluating TWI in children rather than in adult athletes.

Anterior TWI may persist within the paediatric population, owing to right ventricular dominance [17]. Changes in electrical predominance from the right to the left ventricle result in a gradual reversal of T-wave polarity which leads after puberty to the adult ECG pattern. After puberty, the T wave is usually inverted in lead V1 and upright in leads V2–V6 [18]. In this longitudinal study, we had the opportunity to identify the dynamic changes observed on 12-lead resting. We demonstrated for the first time that, during a 4-year follow up, in the vast majority of children with anterior TWI (94%), negative T waves become positive with only 6% of children still exhibiting anterior TWI after the period of observation, in absence of structural heart disease. Most of the authors identified 14 years as the age threshold after that anterior TWI cannot be classified as normal and should interpret as persistence of the juvenile pattern of repolarisation –with no clinical significance- or a potential feature of cardiomyopathy. Indeed, according to the current Task Force criteria for the diagnosis of AC, the presence of inverted T waves in leads V1 and V2 in individuals >14 years represents a minor criterion for the diagnosis of AC [19]. We demonstrated that in the vast majority of children anterior TWI becomes positive during the years of observation. However, in a small proportion (6%), this peculiar pattern persists, in absence of family history, symptoms or relevant clinical findings, suggesting that, although a yearly follow up is recommended

in these children, this condition should be interpreted as the physiological persistence of the juvenile pattern until proven otherwise.

In the present study we also found that TWI in the infero-lateral leads is rare in preadolescent athletes (3%). Furthermore, one child with infero-lateral TWI was found to have a cardiomyopathy. These findings are in agreement with previous studies demonstrating that TWI in these leads is rare in young athletes and athletes with TWI in the infero-lateral leads should undergo further investigations to identify potential cardiomyopathy at risk of sudden cardiac death [7,15]. Furthermore, in this longitudinal study we had the unique opportunity to demonstrate that, while the vast majority of anterior TWI resolved gradually, only 1 child with inferior TWI showed reversion to normal during the period of observation. Therefore, the present findings further strengthen the interpretation of TWI in the infero-lateral leads as repolarisation abnormalities not physiologically related to age, development or training. Conversely, inverted T waves in the infero-lateral leads should be considered pathological in all cases until proven otherwise and children with these repolarisation abnormalities should undergo a strict follow up to identify the potential development of cardiomyopathies typically characterized by changes at 12-lead resting ECG preceding those found at imaging testing.

4.1. Limitations

The main limitation of this study is represented by the lack of a control's group. However, the aim and the novelty of this study were primarily to identify the dynamic ECG changes observed in children through a longitudinal design and a long-term follow up. Furthermore, the study was planned to characterize TWI and not to identify potential training-induced ECG changes. Therefore, recent evidences suggesting no differences in terms of TWI between young athletes and sedentary controls [15] further strengthen the design of the study.

Previous studies have demonstrated the influence of ethnicity on the pattern of resting ECG [7,20]. Data collected in the present study were derived from an Italian population of white children, therefore, the results of this study may not be applicable to non-white children.

5. Conclusions

The prevalence of anterior TWI is common in children and during a 4-year follow up generally becomes positive by the age of 14 years. Conversely, infero-lateral TWI is rare, persistent and may be accompanied by structural heart disease. Therefore, infero-lateral TWI should not be interpreted as physiologically related to age, development or training and children with infero-lateral TWI should remain under strict clinical surveillance.

Conflict of interest

None declared.

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