Prevalence of Cardiomyopathy in Italian Asymptomatic Children with Electrocardiographic T-Wave Inversion at Pre-Participation Screening

Running title: Migliore et al.; Pre-participation ECG screening in Italian children

Federico Migliore, MD1; Alessandro Zorzi, MD1; Pierantonio Michieli, MD, PhD2; Martina Perazzolo Marra, MD, PhD1; Mariachiara Siciliano, MD1; Ilaria Rigato, MD, PhD1; Barbara Bauce, MD, PhD1; Cristina Basso, MD, PhD1; Daniela Toazza, MD2; Maurizio Schiavon, MD2; Sabino Iliceto, MD1; Gaetano Thiene, MD1; Domenico Corrado, MD, PhD1

1Department of Cardiac, Thoracic and Vascular Sciences, University of Padova, Padova, Italy; 2Center for Sports Medicine and Physical Activity, Department of Social Health, Padova, Italy

Correspondence:
Domenico Corrado, MD, PhD
Inherited Arrhytmogenic Cardiomyopathy Unit
Department of Cardiac Thoracic and Vascular Sciences
University of Padova
Via N. Giustiniani 2 35121
Padova, Italy
Phone: +39 049 8212458
Fax: +39 049 8212309
E-mail: domenico.corrado@unipd.it

Abstract:

**Background** - T-wave inversion on 12-lead electrocardiogram (ECG) is usually dismissed in young people as normal persistence of the juvenile pattern of repolarisation. However, T-wave inversion is a common ECG abnormality of cardiomyopathies (CMPs), such as hypertrophic cardiomyopathy (HCM) and arrhythmogenic right ventricular cardiomyopathy (ARVC), which are leading causes of sudden cardiac death (SCD) in athletes. We prospectively assessed the prevalence, age-relation and underlying CMP of T-wave inversion in children undergoing pre-participation screening (PPS).

**Methods and Results** - The study population included 2,765 consecutive children (1,914 males; mean age 13.9±2.2 years; range 8-18 years) undergoing PPS including ECG. Of 229 (8%) children who underwent further evaluation because of positive findings at initial PPS, 33 (1.2%) were diagnosed with a cardiovascular disease. T-wave inversion was recorded in 158 children (5.7%) and was localized in the right precordial leads in 131 (4.7%). The prevalence of right precordial T-wave inversion decreased significantly with increasing age (8.4% in children <14 years vs 1.7% ≥14 years; P<0.001), pubertal development (9.5% of children with incomplete vs 1.6% with complete development; P<0.001) and body mass index <10th percentile (P<0.001). Incomplete pubertal development was the only independent predictor for right precordial T-wave inversion (OR 3.6; 95%CI 1.9-6.8; P<0.001). Of 158 children with T-wave inversion, 4 (2.5%) had a diagnosis of CMP, including ARVC (n=3) and HCM (n=1).

**Conclusions** - The prevalence of T-wave inversion decreases significantly after puberty. Echocardiographic investigation of children with post-pubertal persistence of T-wave inversion at PPS is warranted because it may lead to pre-symptomatic diagnosis of a CMP at risk of SCD during sports.

**Key words:** arrhythmogenic right ventricular cardiomyopathy (ARVC), ECG Screening, hypertrophic cardiomyopathy, athletes, children
Introduction

T-wave inversion is a normal feature of 12-lead electrocardiogram (ECG) in paediatric age. Inversion of T-wave in the right precordial leads occurs in infants older than 48 hours of age and persists during childhood because of the right ventricle (RV) dominance with a repolarisation polarity directed posteriorly. During the first decade of life, changes of electrical predominance from the RV to the left ventricle (LV) result in a gradual reversal of T-wave polarity, which progresses from left to right precordial leads as children grow older and leads after the puberty to the adult ECG pattern, characterized by negative T-wave limited to V1. T-wave inversion in leads V1-V2/V3 may be occasionally observed in post-pubertal adolescents as persistence of the normal children’s pattern. This ECG pattern known as “persistence of the juvenile pattern of repolarisation”, is traditionally considered non-specific and not associated with an increased cardiovascular risk.

On the other hand, T-wave inversion in ≥ 2 adjacent leads is the most common ECG abnormality of cardiomyopathies (CMPs), such as hypertrophic cardiomyopathy (HCM) and arrhythmogenic right ventricular cardiomyopathy (ARVC), which are recognized leading causes of sudden cardiac death (SCD) in young people and athletes. These heart muscle diseases are genetically-determined and show an age-related phenotype. Because early clinical manifestations of such CMPs usually occur after the puberty, the persistence of right precordial T-wave inversion (beyond V1) in the post-pubertal age raises the problem of the differential diagnosis between a benign juvenile pattern of repolarisation and a developing heart muscle disease. Identification by pre-participation screening (PPS) and disqualification from competitive sport activity of adolescents and young adults with ARVC and HCM has been demonstrated to significantly reduce in-the-field mortality.
The aim of the present study was to prospectively assess the prevalence, age-relation and underlying heart diseases of T-wave inversion on resting ECG in a large series of children undergoing PPS.

Methods

Study population

The study population included 2,765 consecutive children who underwent PPS at the Center for Sports Medicine of Padova, Italy, from January 2007 to June 2009. All individuals were Caucasian and included 1,914 males (70%) and 851 females (30%), with a mean age of 13.9±2.2 years (median= 14 years; range 8-18 years). They were engaged in a variety of sports disciplines reported in Table 1.

Screening protocol

All children underwent PPS according to the Italian protocol\(^\text{15,16}\). The initial cardiovascular evaluation included family and personal history, physical examination (with determination of blood pressure), and ECG. Additional examinations, such as echocardiography, were reserved to athletes who had positive findings at first line screening. Athletes diagnosed with clinically relevant cardiovascular abnormalities were managed according to available guidelines\(^\text{15,17}\).

Medical history

The family history was considered positive when close relative(s) had experienced a premature heart attack or sudden death (<55 years of age in males and <65 years in females), or in the presence of a family history of CMP, Marfan syndrome, long QT syndrome, short QT syndrome, Brugada syndrome, severe arrhythmias, coronary artery disease, or other disabling
cardiovascular diseases. The personal history was considered positive in case of chest pain or discomfort, syncope or near-syncope, irregular heart beat or palpitations on exertion, and in the presence of shortness of breath or fatigue out of proportion to the degree of physical effort.

**Physical examination**

Positive physical findings included musculoskeletal and ocular features suggestive of Marfan syndrome, diminished and delayed artery pulses, mid-or end–systolic clicks, a second heart sound, single or widely split and fixed with respiration, marked heart murmurs (any diastolic and systolic grade ≥ 2/6), irregular heart rhythm, and brachial blood pressure >140/90 mmHg (on > 1 readings). According to the design of the present study, physical examination included the assessment of anthropometric characteristics and degree of pubertal development. The body mass index (BMI) was calculated as weight (Kg) divided by height (m) squared. Subjects with BMI <10\textsuperscript{th} percentile were considered to be underweight\textsuperscript{18}. Stage of pubertal development was assessed according to Tanner staging system based on external primary and secondary sex characteristics, with stage 1 corresponding to infantile and stage 5 to complete puberty\textsuperscript{19,20}.

**12-lead electrocardiogram**

A standard ECG was performed in all subjects in a supine position, during quite respiration, using a Cardioline delta 60 plus recorder. ECGs were recorded at a paper speed of 25mm/sec and at a standard gain of 1 mv/cm. ECG parameters including heart rate; P-wave; PR interval; QRS axis, duration and morphology; T-wave voltages and polarity; ST-segments displacement; and QT-interval (corrected by heart rate according to Bazzett’s formula) were analysed and measured by three experienced physicians; discrepancies were solved by consensus.
ECG abnormalities were interpreted by using Davignon's normative values for ages 8-16 years\textsuperscript{21} and according to the criteria recommended by the section of Sport Cardiology of the European Association of Cardiovascular Prevention and Rehabilitation for subjects >16 years\textsuperscript{22}.

T-wave inversion was diagnosed in the presence of negative T-wave $\geq$1 mm in $\geq$2 contiguous leads. Athletes with T-wave inversion associated with pectus excavatum or completed right bundle branch block were excluded. ECG alterations were classified according to the criteria recommended by the section of Sport Cardiology of the European Association of Cardiovascular Prevention and Rehabilitation, and divided in the following two groups: Group 1 including common and training-related ECG changes; and Group 2 including uncommon and training-unrelated ECG abnormalities\textsuperscript{22}.

**Further clinical evaluation**

Children with a positive history, abnormal physical examination or Group 2 ECG abnormalities underwent further clinical evaluation. All children with T-wave inversion underwent additional study by echocardiography, 24 hour-Holter ECG monitoring and maximal exercise testing. Technical equipment, protocols and references values for such testing have been reported in details elsewhere\textsuperscript{23,24}.

Diagnosis of ARVC and HCM was based on recognized clinical and echocardiographic criteria\textsuperscript{25-27}. According to the recently revised International Task Force (ITF) criteria\textsuperscript{25}, ARVC was diagnosed in the presence of major and minor criteria encompassing genetic, ECG, arrhythmic, morphofunctional, and histopathologic factors, and classified as “definitive” when two major criteria or one major and two minor or four minor criteria from different groups were fulfilled; ARVC was defined as “borderline” in the presence of one major and one minor or three minor criteria. According to these ITF criteria, echocardiographic diagnosis of ARVC relied on
RV wall motion abnormalities (akinesia, dyskinesia, or aneurysm) plus RV dilatation (RV outflow tract $\geq 32$ mm in parasternal long-axis view and $\geq 36$ mm in parasternal short-axis view) and/or RV dysfunction (fractional area change $\leq 33\%$)$^{25}$.

The diagnosis of HCM was based on demonstration of hypertrophied, non-dilated LV with wall thickness $\geq 13$ mm, in the absence of another systemic or cardiac disease that is capable of producing the magnitude of wall thickening (eg, systemic hypertension, aortic valve stenosis etc.)$^{26,27}$.

In the presence of mild left ventricular hypertrophy (13-15 mm), the distinction between HCM and athlete's heart was based on echocardiographic and clinical features, such as the distribution of thickening of the LV wall, the dimension of the left ventricular cavity, the type of sport played, and the results of deconditioning$^{10,28}$.

**Statistical analysis**

Results are expressed as range and mean $\pm$ standard deviation (SD). Regression analysis was performed to assess the relationship between prevalence of T-wave inversion and age. Univariate binary logistic analysis was used to identify variables that were significantly associated with right precordial T-wave inversion. Significantly associated variables ($P \leq 0.15$) were integrated into multivariable analysis using binary logistic analysis to identify independent predictors of the presence of right precordial T-wave inversion in children. A two-tailed $P$ value $<0.05$ was considered statistically significant. Statistics were analyzed using the SPSS version 17 (SPSS Inc.).
Results

One or more ECG alterations were identified in 1,314 of 2,765 (47%) children. ECG changes were classified as Group 1 in 1119 children (40%), and Group 2 in 195 (7%). A total of 229 (8.2%) children were referred for further investigation, 34 (1.2%) because of positive medical history and/or abnormal physical examination and 195 (7%) with Group 2 ECG abnormalities, including 158 (5.7%) with T-wave inversion (Table 2). Additional clinical evaluation led to a diagnosis of heart disease in 33 children (1.2%) (Figure 1).

T-wave inversion

The prevalence and localization of T-wave inversion is shown in Figure 2. T-wave inversion was detected in 158 (5.7%) children and was localized as follows: right precordial leads (V1–V3) in 131 (4.7%), inferior leads (II/aVF) in 24 (0.9%) and lateral precordial leads (V4–V6/I-aVL) in 3 (0.1%).

Right precordial T-wave inversion

T-wave inversion in right precordial leads was observed in 88 of 1914 males (4.6%) and in 43 of 851 females (5%); P=0.15. There was a statistically significant decreasing prevalence of right precordial T-wave inversion with increasing age, both in males (R² = 0.84; P <0.001) and females (R² = 0.86; P <0.001) (Figure 3). Using a cut-off value of 14 years (i.e. median age of study population), T-wave inversion in right precordial leads was recorded in 105 of 1244 (8.4%) aged <14 years vs 26 of 1521 (1.7%) children aged ≥14 years (P <0.001). At the age of 14 years, 241 of 281 males (86%) and 108 of 119 females (91%) showed a Tanner’s stage = 5. All males aged ≥ 17 years and all females aged ≥ 16 had reached a complete pubertal development.

The prevalence of right precordial T-wave inversion was significantly higher in children with incomplete (Tanner’s stage ≤4) vs complete (Tanners’s stage =5) pubertal development
(104 of 1087; 9.5% vs 27 of 1678; 1.6%; P<0.001) and in children with a BMI <10th (33 of 296; 11% vs 98 of 2469; 4%; P<0.001). There was no statistically significant relation between right precordial T-wave inversion and specific sports.

Table 3 shows univariate and multivariable predictors for right precordial T-wave inversion. Univariate predictors were incomplete pubertal development (OR 6.5; 95%CI 4.2-9.9; P<0.001), age <14 years (OR 5.3; 95%CI 3.4-8.2; P<0.001), and BMI <10th percentile (OR 2.4; 95%CI 3.2-1.7; P<0.001). On multivariable analysis, incomplete pubertal development remains the only independent predictor (OR 3.6; 95%CI 1.9-6.8; P<0.001).

Infero-lateral T-wave inversion

There was no statistically significant correlation between T-wave inversion in infero-lateral leads and any clinical variables such as age, sex, pubertal development, BMI and type of sport.

Cardiovascular diagnosis and sport eligibility

Of the 229 children who underwent further additional cardiovascular evaluation because of positive history, abnormal physical examination and type 2 ECG changes, 196 (7%) showed no cardiovascular diseases and were considered eligible for sport participation. Thirty-three (1.2%) were diagnosed as having a cardiovascular disease.

Cardiomyopathies

Four of 158 children (2.5%) with T-wave inversion were diagnosed with a CMP. All showed complete pubertal development (Tanner’s stage =5) (Table 4). Three of 131 children (2.3%) with T-wave inversion in right precordial leads fulfilled diagnosis criteria for ARVC, either “definitive” (n = 1) or “borderline” (n = 2) (Figures 2 and 4). There was no statistically significant association of ARVC with specific sports.
One of 3 children who underwent echocardiographic examination because of T-wave inversion in lateral leads was diagnosed as having HCM (Figures 2 and 5). All received a complete restriction from competitive sports.

**Other cardiovascular disorders**

The following cardiovascular disorders were identified in the remaining 29 children: mitral valve prolapse (n = 16); atrial septal defect (n = 3); ventricular pre-excitation (WPW) (n = 6); long-QT syndrome (n = 2); short QT syndrome (n = 1) and Brugada syndrome (n = 1). There was no statistically significant relation between specific sports and specific forms of cardiovascular disease.

The 16 children with mitral valve prolapse had an echocardiographically trivial mitral valve regurgitation and no significant ventricular arrhythmias on 24 hour-Holter ECG monitoring and maximal exercise testing. Three of them (age 13, 14, and 17 years) had T-wave inversion in inferior leads. They received no sport restriction.

The 3 children with atrial septal defect had a mild shunt and received no sport restriction.

The 6 children with ventricular pre-excitation underwent transoesophageal electrophysiologic study for risk stratification: 3 of them had an anterograde effective refractory period of the accessory pathway <240 msec and received a temporary sport restriction until they underwent successful radiofrequency catheter ablation; the remaining 3 children had an anterograde effective refractory period of the AV accessory pathway >240 msec and received no sports restriction.

A child with a family history of SCD and ajmaline-induced “coved-type” ST-segment elevation in leads V1 and V2, consistent with Brugada syndrome, was deemed as non eligible for competitive sport activity.
Two children with long QT interval (QTc = 510 msec and 530 msec) and one child with short QT interval (QTc = 300 msec) were detrained for a 6 month period without significant changes of the QTc interval and received complete competitive sport restriction. Both children with long QT interval showed mutations of KCNQ1 gene consistent with LQTS 1 and were treated with beta-blockers agents.

**Discussion**

ECG changes are common in athletes and usually reflect the structural and electrical remodelling of the heart as an adaptation to regular physical exercise (“athlete’s heart”)\(^{29,30}\). However, T-wave inversion may be the expression of an underlying heart disease at risk of SCD during sport\(^{11,31-37}\).

This study was designed to prospectively assess the prevalence of T-wave inversion, the relation to age and gender, and the presence of an underlying CMP in a large cohort of children undergoing PPS. The major findings were: 1) in this age group T-wave inversion was documented in 5.7% of cases and was predominantly localized in the right precordial leads; 2) right precordial T-wave inversion significantly decreased with increasing age and pubertal development; 3) T-wave inversion reflected an underlying CMP in 2.5% (4 of 158) of cases.

**T-wave inversion**

Inverted T-waves beyond lead V1 are common in children. By studying the ECGs of 50 healthy children from 2 weeks to 15 years of age Lepeschkin et al.\(^1\) demonstrated that the T-wave is inverted on the right chest, upright on the left, and biphasic in the precordial lead transition. This transition is more to the left in children than in grown ups. After pubertal development, T-wave is usually inverted in lead V1 and upright in leads V2 to V6. When T-
waves remain inverted beyond lead V1 in children >14 years, the ECG pattern is generally deemed as the result of the persistence of the juvenile pattern of repolarisation of no clinical significance. On the other hand, the presence of T-wave inversion beyond lead V1 is a typical ARVC feature with a sensitivity of 87% among patients fulfilling the ITF criteria\textsuperscript{25,38}. Because early clinical manifestation of ARVC occurs usually after the puberty, the persistence of right precordial T-wave inversion (beyond V1) in the post-pubertal age raises the problem of a differential diagnosis between a benign juvenile pattern of repolarisation and a developing ARVC. This is particular important in young competitive athletes.

The concern arises as to the specificity of the juvenile T-wave pattern for ARVC because it has been reported to occur in a sizeable proportion of healthy children. It is unclear what is the prevalence of the juvenile T-wave pattern in a child who has a normal heart and how often the persistence of the juvenile pattern of repolarisation is associated with a CMP. Review of the literature show that the prevalence of T-wave inversion varies according to the age of study population. Suarez et al.\textsuperscript{3} reported the following prevalence of precordial T-wave inversion in children <12 years of age: lead V2 in 45%–65% of children, lead V2-V3 in 30%–40% and beyond lead V3 in 5%–20%. In individuals age 12 to 18 years old, the prevalence of T-wave inversion decreased to 10%–20% in lead V2 and to 5% in lead V3, with no patients showing T-wave inversion beyond lead V3. In older healthy population, 19 to 45 years, the prevalence of juvenile pattern of right precordial T-wave inversion was only 13% in lead V2 and 3% in lead V3.

The traditional idea that ST-T–wave abnormalities are more common in trained athletes than in a sedentary population may be explained by the high prevalence of early repolarisation changes in the athlete’s heart, with J point-ST-segment elevation often followed by a terminal
negative T-wave, which simulates T-wave inversion\textsuperscript{22}. The true prevalence of T-wave inversion in competitive athletes overlaps that of non-athletes of the same age and sex, ranging from 2.7\% in the series of top level athletes (mean age 22.3 ± 12.5 years) reported by Pelliccia et al.\textsuperscript{34} to 4\% in the junior elite athletes (mean age 16 ± 1.7 years) reported by Papadakis et al.\textsuperscript{37}.

Recent studies revealed that athletes of Afro-Caribbean origin exhibit a grater prevalence of T-wave inversion than Caucasian competitors\textsuperscript{39-41}. Papadakis et al\textsuperscript{41} reported that T-wave inversion, predominantly confined to anterior leads (V1-V4), are more common in black athletes than in white (22.8\% vs 3.7\%, respectively).

In the present study, T-wave inversion was found in 5.7\% of our large cohort of 2,765 children and was localized in the right precordial leads in 4.7\%. This relatively greater prevalence of T-wave abnormalities is explained by the expected higher rate of physiologic right precordial T-wave inversion in our study population which included a sizeable proportion of pre-pubertal children. The prevalence of right precordial T-wave inversion decreased significantly with increasing age (8.4\% in those age <14 years vs 1.7\% of children age ≥14 years), complete pubertal development and greater BMI. Incomplete pubertal development was the only independent predictor of right precordial T-wave inversion.

In our large series of children, T-wave inversion in inferior-lateral leads was an uncommon finding, not exceeding 1\% (0.9\% in inferior leads and 0.1\% in lateral leads). This low prevalence of T-wave inversion in infero-lateral leads was similar to that of 1.5\% previously reported by Papadakis et al.\textsuperscript{37}. Unlike right precordial T-wave inversion, we did not find any correlation between infero-lateral T-wave inversion and gender, age, anthropometric characteristic and pubertal development.
T-wave inversion and cardiomyopathy

In the Papadakis study, the prevalence of right precordial T-wave inversion beyond V2 in athletes ≥16 years was 0.1% and despite intensive cardiovascular evaluation no athletes were diagnosed with CMP. Our study confirmed and extended these previous observations by showing that T-wave inversion in children with complete pubertal development, though uncommon, may reflect an early CMP. Indeed, a cardiomyopathy was diagnosed in 4 children with T-wave inversion: ARVC in three with T-wave inversion in right precordial leads and HCM in one with T-wave inversion in lateral leads.

The discrepancy between the previous and the present study may be explained by the differences in the study population and study design. Our study included a larger cohort of 2,765 children who had a greater likelihood to be affected by cardiomyopathies, whose estimated prevalence in the general population is 1:500 for HCM and 1:2000 for ARVC. Although the role of genetic factors in the population of the Veneto region of Italy can not be excluded, the relatively high prevalence of ARVC in our study is reasonably explained by the use of “revised” ITF criteria for ARVC diagnosis, which have increased the sensitivity for early/minor ARVC variants, as indicated by the identification of two “borderline” ARVC cases, which would have been missed by the “old” ITF criteria.

We found a relatively low prevalence of HCM in our study population of children with a mean age ~14 years. This may be explained by the fact that HCM is an inherited heart muscle disease whose phenotypic manifestations are age-dependent and occur during adolescence in association with accelerated body growth, with morphologic expression usually completed during young adulthood when physical maturity is achieved. Therefore, screening of
children is expected to have a low sensitivity for detection of HCM which usually develops during a later period of life.

**Implications for pre-participation screening**

The present study showed that echocardiographic evaluation of children with persistence of T-wave inversion beyond puberty on PPS, allowed identification of ARVC and HCM, which are recognized leading causes of SCD in young competitive athletes. These results have significant implications for PPS, clinical diagnosis, and risk stratification for prevention of SCD. In this regard a previous study demonstrated that identification and disqualification of young competitive athletes with ARVC and HCM actually reduce mortality during sport activity.

According to our study findings, echocardiographic study to exclude an underlying cardiomyopathy is warranted for athletes with post-pubertal persistence of T-wave inversion in ≥2 contiguous leads on resting ECG regardless of age.

In our study, PPS led to identification of additional ECG-detectable cardiovascular diseases potentially at risk of SCD, such as, WPW, long and short QT syndrome, and Brugada syndrome. These conditions have been implicated in most SCD occurring without postmortem evidence of structural heart abnormalities. Unlike cardiomyopathies, most of cardiac ion channel disorders have been discovered only recently, so that diagnosis at PPS is being increased over time and its impact on mortality will be assessed on the near future.

The ECG is traditionally considered a non-specific and non-cost-effective tool for cardiovascular evaluation of athletes because of the presumed high level of false-positive results. This concept was based on few studies of small and selected series of highly trained athletes from a limited number of sports disciplines. More recent studies on large athletes cohorts have disproved the traditional idea that ECG is a non specific screening test.
In the present study, among 2,765 children undergoing PPS, 229 (8%) were referred for additional testing because of positive findings, such as positive medical history, abnormal physical examination, or ECG abnormalities. Further clinical work-up led to identification of heart diseases in 33 children (1.2%). Hence, the estimated percentage of false-positives (i.e. athletes with abnormal PPS findings in the absence of heart disease) was 7%. These figures are in keeping with those from a previous prospective Italian study on 42,386 athletes undergoing PPS, which reported a 9% prevalence of athletes with positive findings requiring further examination, and a 2% prevalence of total cardiovascular disorders (~7% of false-positive results)\textsuperscript{12}.

It is noteworthy that if in the present study we had not further investigated athletes with right precordial T-wave inversion due to incomplete pubertal development, the proportion of false-positives would have been reduced to 3.3%, without altering the screening power for detection of cardiomyopathies and, thus, resulting in a more favourable screening cost-effectiveness.

Our study results demonstrated that athletes diagnosed with heart diseases at pre-participation screening were not indiscriminately disqualified for sport competitions. Rather, various heart conditions required different management strategies: i) follow-up without sport restriction (for instance MVP); ii) return to sports participation after treatment (for instance WPW syndrome); and iii) definitive, complete sport restriction (for instance cardiomyopathies and channelopathies). It is noteworthy that only 8 of 2,765 (0.3%) children were diagnosed with cardiomyopathies and channelopathies (Figure 1), which carry a high risk of SCD as to mandated disqualification from competitive sport activity.
Study limitation

Our results were derived from a population of athletes of Caucasian descent and should not be generalized to populations of different ethnic origin. There is emerging evidence that racial factors have a significant impact on the physiological adaptation to exercise\textsuperscript{39}. In this regard, current data reveal that black athletes, either male or females, develop a greater magnitude of LV hypertrophy and a higher prevalence of ECG abnormalities, such as increased QRS voltages and T-wave inversion, compared with Caucasian athletes\textsuperscript{40,41}. As a corollary, the implementation of PPS in countries with a large proportion of black athletes may prove problematical and result in a high number of false-positive tests. Recent data, however, suggest that athletes with Afro-Caribbean origin showing T-wave inversion in the right precordial leads do not have echocardiographic evidence of cardiomyopathy and subsequent follow-up does not reveal any cardiac morbidity or mortality\textsuperscript{41}. This indicates that the higher proportion of ECG abnormalities observed in this athletic population much more often represents an ethnic variants rather than cardiac pathology.

According to the study design and the screening protocol, clinical evaluation and follow-up were reserved to the subgroup of children engaged in competitive sports activity who showed positive findings at pre-participation screening. Because of this selection biases, the study results on the prevalence of ECG abnormalities and underlying cardiomyopathy may not be generalised to the general population of children not involved in sports.

Conclusions

ECG abnormalities are relatively common in children undergoing PPS. Most ECG abnormalities reflect the physiologic pre-pubertal ECG repolarisation pattern and/or physiologic
ECG changes related to the cardiac adaptation to physical exercise (athlete’s heart). After complete pubertal development, T-wave inversion in children becomes significantly less common than traditionally believed and may reflect an underlying heart muscle disease such as ARVC and HCM. Our study results suggest that demonstration of post-pubertal persistence of T-wave inversion in children engaged in competitive sport activity justifies an echocardiographic investigation which may lead to pre-symptomatic identification of early cardiomyopathy at risk of SCD during sports.

**Funding Sources:** This study was supported by Ministry of Health, Rome; Fondazione Cariparo, Padova and Rovigo, Italy and Registry of Cardio-Cerebro-Vascular Pathology, Veneto Region, Venice, Italy

**Conflict of Interest Disclosures:** None

**References:**


**Table 1.** Type of sport practiced by the 2,765 athletes

<table>
<thead>
<tr>
<th>Type of sport</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soccer</td>
<td>1057 (38.2)</td>
</tr>
<tr>
<td>Volleyball</td>
<td>571 (20.6)</td>
</tr>
<tr>
<td>Basketball</td>
<td>456 (16.5)</td>
</tr>
<tr>
<td>Skating</td>
<td>134 (4.8)</td>
</tr>
<tr>
<td>Swimming</td>
<td>112 (4.0)</td>
</tr>
<tr>
<td>Martial arts</td>
<td>86 (3.1)</td>
</tr>
<tr>
<td>Tennis</td>
<td>75 (2.7)</td>
</tr>
<tr>
<td>Rugby</td>
<td>55 (2.0)</td>
</tr>
<tr>
<td>Artistic gymnastics</td>
<td>53 (1.9)</td>
</tr>
<tr>
<td>Athletics</td>
<td>47 (1.7)</td>
</tr>
<tr>
<td>Fencing</td>
<td>33 (1.2)</td>
</tr>
<tr>
<td>Hockey</td>
<td>16 (0.6)</td>
</tr>
<tr>
<td>Ski</td>
<td>14 (0.5)</td>
</tr>
<tr>
<td>Horse-riding</td>
<td>12 (0.4)</td>
</tr>
<tr>
<td>Cycling</td>
<td>8  (0.3)</td>
</tr>
<tr>
<td>Baseball</td>
<td>8  (0.3)</td>
</tr>
<tr>
<td>Diving activities</td>
<td>6  (0.2)</td>
</tr>
<tr>
<td>Triathlon</td>
<td>6  (0.2)</td>
</tr>
<tr>
<td>Others</td>
<td>16 (0.6)</td>
</tr>
</tbody>
</table>
Table 2. Classification of ECG abnormalities

<table>
<thead>
<tr>
<th>Group 1 ECG abnormalities (≥1)</th>
<th>N (%)</th>
<th>Group 2 ECG abnormalities (≥1)</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinus bradycardia</td>
<td>172 (6.2)</td>
<td>T-wave inversion</td>
<td>158 (5.7)</td>
</tr>
<tr>
<td>First degree AV block</td>
<td>6 (0.2)</td>
<td>Deep T-wave inversion (≥2mm)</td>
<td>139 (5)</td>
</tr>
<tr>
<td>Incomplete RBBB</td>
<td>285 (10.3)</td>
<td>Minor T-wave inversion (≥1mm)</td>
<td>19 (0.7)</td>
</tr>
<tr>
<td>Early repolarisation pattern</td>
<td>332 (12)</td>
<td>ST-segment depression</td>
<td>-</td>
</tr>
<tr>
<td>Isolated QRS voltage criteria for LVH</td>
<td></td>
<td>Abnormal Q-waves</td>
<td>2 (0.07)</td>
</tr>
<tr>
<td><strong>Sokolow-Lyon criteria</strong></td>
<td>67/414 (16)</td>
<td>Left atrial enlargement</td>
<td>-</td>
</tr>
<tr>
<td><strong>Davignon criteria (≥1)</strong></td>
<td>282/2351 (12)</td>
<td>Left axis deviation (≤-30 °) †</td>
<td>13 (0.5)</td>
</tr>
<tr>
<td>SVI</td>
<td>217 (9.2)</td>
<td>Left anterior hemiblock</td>
<td>3 (0.1)</td>
</tr>
<tr>
<td>RV6</td>
<td>244 (10.3)</td>
<td>Right axis deviation (≥+120 °) †</td>
<td>5 (0.2)</td>
</tr>
<tr>
<td>RV6 + SVI</td>
<td>275 (11.6)</td>
<td>Left posterior hemiblock</td>
<td>-</td>
</tr>
<tr>
<td>Q III</td>
<td>181 (7.6)</td>
<td>Ventricular pre-excitation</td>
<td>6 (0.2)</td>
</tr>
<tr>
<td>Q V6</td>
<td>179 (7.6)</td>
<td>Complete RBBB</td>
<td>13 (0.5)</td>
</tr>
<tr>
<td>Q III</td>
<td>181 (7.6)</td>
<td>Complete LBBB</td>
<td>-</td>
</tr>
<tr>
<td>Q V6</td>
<td>179 (7.6)</td>
<td>Long QT interval</td>
<td>2 (0.07)</td>
</tr>
<tr>
<td>Q V6</td>
<td>179 (7.6)</td>
<td>Short QT interval</td>
<td>1 (0.03)</td>
</tr>
<tr>
<td>Q V6</td>
<td>179 (7.6)</td>
<td>Brugada-like early repolarisation</td>
<td>2 (0.07)</td>
</tr>
</tbody>
</table>

AV, atrio-ventricular; LBBB, left bundle branch block; LVH, left ventricular hypertrophy; RBBB, right bundle branch block.
† In the age group 8-16 years by using Davignon’s normative values²¹
Table 3. Univariate and multivariable predictors for T-wave inversion in right precordial leads

<table>
<thead>
<tr>
<th>Variables</th>
<th>Univariate Analysis</th>
<th>Multivariable Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Incomplete pubertal development</td>
<td>6.5</td>
<td>4.2-9.9</td>
</tr>
<tr>
<td>Age &lt; 14 years</td>
<td>5.3</td>
<td>3.4-8.2</td>
</tr>
<tr>
<td>BMI &lt;&lt;10th percentile</td>
<td>2.4</td>
<td>3.2-1.7</td>
</tr>
<tr>
<td>Male gender</td>
<td>1.1</td>
<td>0.8-1.6</td>
</tr>
</tbody>
</table>

BMI = body mass index
Table 4. Clinical and instrumental findings in 4 children with T-wave inversion and cardiomyopathy

<table>
<thead>
<tr>
<th>Clinical findings</th>
<th>HCM</th>
<th>ARVC “Definitive”</th>
<th>ARVC “Borderline”</th>
<th>ARVC “Borderline”</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>15</td>
<td>14</td>
<td>15</td>
<td>17</td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td>Pubertal development (Tanner’s stage = 5)</td>
<td>Complete</td>
<td>Complete</td>
<td>Complete</td>
<td>Complete</td>
</tr>
<tr>
<td>Type of sport</td>
<td>Soccer player</td>
<td>Soccer player</td>
<td>Soccer player</td>
<td>Soccer player</td>
</tr>
<tr>
<td>Family history</td>
<td>Positive</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Physical examination</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Symptoms</td>
<td>No T-wave inversion in I-aVL; Q-wave in inferior leads</td>
<td>No T-wave inversion in V1-V2</td>
<td>No T-wave inversion in V1-V3</td>
<td>No T-wave inversion in V1-V3</td>
</tr>
<tr>
<td>Resting ECG</td>
<td>Maximal septal thickness 31 mm</td>
<td>RV postero-basal (subtricuspidal) akinesia; RVOT dilatation (37 mm at PLAX view and 39 mm at PSAX view)</td>
<td>RV antero-lateral akinesia; RVOT dilatation (30 mm at PLAX view and 32 mm at PSAX view)</td>
<td>RVOT akinesia: RVOT dilatation (31 mm at PLAX view and 35 mm at PSAX view)</td>
</tr>
<tr>
<td>Echocardiographic findings</td>
<td>Negative</td>
<td>Positive</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>24 h (12-lead) ECG</td>
<td>No arrhythmias</td>
<td>2782 PVBs and non sustained VT (4 beats, 170/min, LBBB/superior axis pattern)</td>
<td>357 PVBs (LBBB/inferior axis pattern)</td>
<td>389 PVBs (LBBB/inferior axis pattern)</td>
</tr>
<tr>
<td>Maximal exercise testing</td>
<td>No ST-segment ischemic changes; no arrhythmias</td>
<td>No ST-segment ischemic changes; Coupled PVBs at maximal exercise</td>
<td>No ST-segment ischemic changes; no arrhythmias</td>
<td>No ST-segment ischemic changes; no arrhythmias</td>
</tr>
</tbody>
</table>

ARVC = arrhythmogenic right ventricular cardiomyopathy; HCM = hypertrophic cardiomyopathy; LBBB = left bundle branch block; PLAX RVOT = parasternal long-axis view right ventricular outflow tract; PSAX RVOT = parasternal short-axis view right ventricular outflow tract; PVBs = premature ventricular beats; RV = right ventricle; SAECG = signal averaged electrocardiogram; VT = ventricular tachycardia.
Figure Legends:

Figure 1. Results of pre-participation screening in the overall study population. *Among 9 patients with a positive family history 4 subjects had a family history of premature sudden death in close relatives (<55 years of age in males and < 65 years in females) and 5 had a positive family history of coronary arteries disease or cardiomyopathy. † 19 subjects had a either systolic murmur and or a second heart sound, split and fixed with respiration. PE = physical examination; MVP = mitral valve prolapsed; ASD atrial septal defect; ARVC = arrhythmogenic right ventricular cardiomyopathy; HCM = hypertrophic cardiomyopathy; LQTS = long QT syndrome; SQTS = short QT syndrome; WPW = Wolf-Parkinson-White.

Figure 2. Prevalence and distribution of T-wave inversion and underlying cardiomyopathy in the overall study population. * Male, aged 14 years with a complete pubertal development. † One female aged 15 years, and one male aged 17 years both with complete pubertal development. ‡ Male, aged 15 years, with complete pubertal development. ARVC = arrhythmogenic right ventricular cardiomyopathy; HCM = hypertrophic cardiomyopathy.

Figure 3. Correlation between prevalence (%) of T-wave in right precordial leads and age among males (grey) and females (black).

Figure 4. Electrocardiographic and echocardiographic findings in a 14-year-old male soccer player with ARVC. ECG shows T-wave inversion in right precordial leads (V1-V2) (A). Echocardiographic examination reveals RV dilatation (RVOT diameter of 39 mm on end-
diastolic parasternal short-axis view) (B) and RV dysfunction (akinesia of RVOT and posterobasal, subtricuspidal regions) (not shown).

**Figure 5.** Electrocardiographic and echocardiographic findings in a 15-year-old male soccer player with HCM. ECG shows T-wave inversion in lateral leads (I and aVL) and pathological Q-wave (duration >25% of the height of the ensuing R-wave) in inferior leads (III and aVF) (A). Echocardiogram shows an asymmetric left ventricular hypertrophy with maximal septal thickness of 31 mm (B). VS = ventricular septal; LV = left ventricle; LA = left atrium; AO = aorta.
Children
N=2765

Initial cardiovascular protocol
(Medical history, physical examination, ECG)

Abnormalities in 229 (8%)
- Medical history in 9 (0.32%) *
- PE in 19 (0.68%) †
- Group 2 ECG abnormalities in 195 (7%)
- Medical history/PE/ECG in 6 (0.21%)

No abnormalities in 2536 (92%)
Subjects eligible for sports participation

Echocardiography
and/or additional tests

No heart disease in 196 (7%)
Subjects eligible for sports participation

Heart disease in 33 (1.2%)

Eligible for competitive sports
(n = 19; 0.7%)
- MVP with mild mitral valve regurgitation (16)
- ASD with mild shunt (3)

Non eligible for competitive sports
(n = 8; 0.3%)
- Definitive ARVC (1)
- Borderline ARVC (2)
- HCM (1)
- LQTS (2)
- SQTS (1)
- Brugada syndrome (1)

Eligible for competitive sports after electrophysiologic study and/or ablation
(n = 6; 0.2%)
- Ventricular pre-excitation (WPW) (6)
Children
N=2765

T-wave inversion in ≥2 leads
N=158 (5.7%)

T-wave inversion in inferior leads
(II/aVF)
N=24 (0.9%)
→ Echocardiography
→ No cardiomyopathies

T-wave inversion in right precordial leads
(V1-V3)
N=131 (4.7%)
→ Echocardiography
→ “definitive” ARVC (N=1) *
→ “borderline” ARVC (N=2) †

T-wave inversion in lateral leads
(V4-V6 and/or 1-aVL)
N=3 (0.1%)
→ Echocardiography
→ HCM (N=1) ‡

No T-wave inversion
N=2607 (94.3%)
Prevalence of Cardiomyopathy in Italian Asymptomatic Children with Electrocardiographic T-Wave Inversion at Pre-Participation Screening
Federico Migliore, Alessandro Zorzi, Pierantonio Michieli, Martina Perazzolo Marra, Mariachiara Siciliano, Ilaria Rigato, Barbara Bauce, Cristina Basso, Daniela Toazza, Maurizio Schiavon, Sabino Iliceto, Gaetano Thiene and Domenico Corrado

Circulation. published online December 16, 2011;
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2011 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/early/2011/12/16/CIRCULATIONAHA.111.055673

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/