

Diagnostic and Clinical Significance of T Wave Inversion in Athletes

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ABSTRACT: Electrocardiographic abnormalities are a common finding in athletes. To facilitate the differentiation of physiological adaptation versus pathological remodeling, a series of guidelines has emerged in the past decade that attempt to improve specificity while maintaining a high sensitivity. Recently, T wave inversion in the athletic population gained more attention, resulting in accelerated research leading to novel findings not yet integrated into clinical practice. We aim to simplify the knowledge to date and integrate it into one easy-to-use practical flowchart.

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KEY WORDS: T wave inversion (TWI), athletes, screening, electrocardiography (ECG)

Abnormalities in electrocardiography (ECG) tracings are a common finding in athletes. They usually reflect morphofunctional remodeling and adaptation to physical training, referred to as the “athlete’s heart” [1]. It is important to remember that these changes might also represent an underlying pathology that subjects an athlete to risk of sudden cardiac death (SCD) during sports [2]. The understanding that an athlete’s heart undergoes physiological adaptation to strenuous physical activity, and that these changes stem from a broad range of ECG abnormalities similar to pathologic ones, led to attempts to understand the underlying mechanism of these ECG patterns among athletes and identifying red flags for an existing pathology. The ECG changes include those associated with alterations in parasympathetic and sympathetic tone, which result in rhythm and conduction abnormalities, structural adaptations that induce morphological changes of the QRS complex, and repolarization abnormalities that result from both structural and parasympathetic predominance [3-6].

To differentiate physiological adaptations from pathological ones, a series of guidelines have emerged during the past decade to improve specificity while maintaining a high sensitivity. The European guidelines published in 2010 were the first

Exclusion criteria by electrocardiography screening are intended to minimize the rate of false positive results without missing any life threatening pathology in apparently healthy young athletes

to introduce ECG changes and group them into physiologic and pathologic [1]. In 2012, the Seattle Criteria published new criteria incorporating physiologic ethnic-related changes [7]. Refined criteria were introduced in 2014 [8], which led to a significant reduction in the number of false positive ECGs in Middle Eastern, Black, and Caucasian athletes, while maintaining 100% sensitivity for serious cardiac pathologies [9].

T wave inversion (TWI) is among the more controversial and less discussed ECG changes in athletes. These changes are prevalent in healthy endurance athletes, and are commonly found in association with many of the causes of SCD in athletes [10]. To date, no validated guidelines incorporating TWI observed in athletes are available. The objective of this review is to consolidate the current knowledge and try to integrate it into one easy-to-use and practical flowchart [Figure 1].

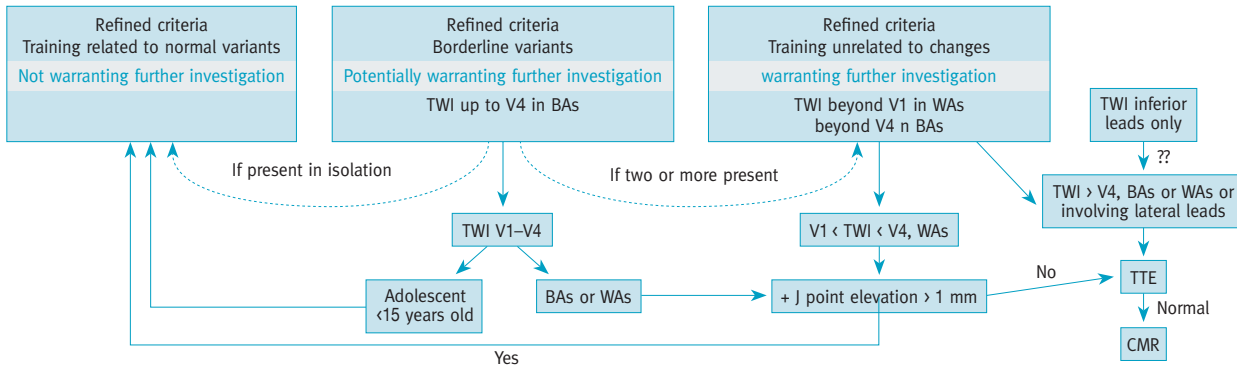
T WAVE INVERSION IN ATHLETES

Inverted T waves are present in a variety of clinical syndromes, both benign and life-threatening, and a prevalence of approximately 30% was observed in the athletic population [4]. The mechanism of TWI is unclear, but it is likely related to ST-segment abnormalities due to early repolarization [11]. Pelliccia et al. [10] followed athletes with their matched controls for almost a decade and found TWI to be a significant marker for cardiomyopathy among these athletes.

DIFFERENTIATING T WAVE INVERSION BY ECG LOCATION AND MORPHOLOGY

It has been established that TWI in leads aVR, V1, and lead III alone (i.e., without II and AVF) are actually a normal finding. When preceded by domed ST segments in asymptomatic Afro-Caribbean athletes, TWI in V1–V4 was attributed to athlete’s heart syndrome [8,12,13]. Pathological TWI (PTWI) is defined as a depth of > 1 mm in ≥ 2 of the following leads: V2–V6, II and aVF, or I and aVL (because isolated inverted T waves in III, aVR, and V1 are normal). The presence of a TWI > 2 mm in > 2 adjacent leads in an athlete is a non-specific, but still a warning sign of a potential cardiovascular disease carrying a risk for SCD during sports. Deep TWI in the midprecordial-to-

Figure 1. Interpretation of T wave inversion in athletes



TWI = T wave inversion, BAs = Black athletes, WAs = Caucasian athletes, TTE = transthoracic echocardiography, CMR = cardiac magnetic resonance

lateral precordial leads (V4–V6) should raise the suspicion of apical hypertrophic cardiomyopathy (HCM) [14].

The significance of minor T wave changes, such as flat and/or minimally inverted (< 2 mm) T waves in > 2 leads (mostly inferior and/or lateral), is unclear. Those changes usually revert to normal with exercise and are considered a benign ECG phenomenon resulting from increased vagal tone. However, similar to deep inverted T waves, these minor T wave abnormalities are more common in cardiomyopathies [15]. These findings suggest a pathological basis and should be investigated in depth and followed up over time before they can definitively be ascribed to physiologic neuroautonomic remodeling [16].

INVERTED T WAVES IN THE INFERIOR AND INFEROLATERAL LEADS

TWI in the lateral or inferolateral leads is commonly observed in HCM. Zaidi and colleagues [17] found that inferior TWI was present in almost one-quarter of an arrhythmogenic right ventricular cardiomyopathy (ARVC) cohort, a characteristic that is not featured in current diagnostic criteria.

Papadakis and colleagues [18] revealed a significant difference in the presence of TWI in the inferior and/or lateral leads of adolescent athletes compared to sedentary individuals, who had none. These athletes had a high prevalence of left ventricular hypertrophy (LVH), considered to be part of an athlete’s heart rather than HCM based on other ECG findings.

TWI in inferior (L2, L3, aVF) and/or lateral (L1, aVL, V5–V6) leads of adult athletes raises the suspicion of ischemic heart disease, cardiomyopathy, aortic valve disease, systemic hypertension, and LV non-compaction [16].

When comparing HCM between Black athletes to non-Black controls, the prevalence of TWI in the inferior leads was similar for all groups [14]. Isolated inferior TWI in all tested athletic groups commonly involved leads III and aVF,

which in the authors’ experience do not represent a malignant phenotype [12].

Females do not exhibit TWI in the inferior and/or lateral leads, and when they do, it is likely to represent a pathological process that warrants further investigation regardless of ethnicity [17,19].

INVERTED T WAVES IN THE ANTEROSEPTAL LEADS

TWI in the right precordial leads V1–V3 are a common finding in children and adolescents [20], and some persist into adulthood. These persistent juvenile TWI are present in 0.1–3% of healthy adults [21,22]. The post-pubertal persistence of TWI in the right precordial leads beyond V1 (particularly beyond V2) may also reflect an underlying congenital heart disease leading to a right ventricular volume or pressure overload state, as in ARVC [16,23].

Right precordial TWI in leads V1–V3 is a relatively rare finding in the middle-age general population, especially in men [24]. As such, TWI beyond V2 in any athlete older than 16 years of age warrants a detailed investigation. It is noteworthy that ARVC can exhibit a normal ECG in some cases with a severe structural phenotype [17]. Zaidi and colleagues [17] concluded that TWI and a balanced biventricular dilatation are

likely to represent benign manifestations of intensive training in the majority of asymptomatic athletes without a relevant family history.

Black athletes exhibited a greater prevalence of TWI confined to the anterior leads suggesting this probably represents an ethnic response to physiologic adaptation to exercise rather than an ethnic effect alone [12]. A more meticulous investigation confirmed that TWI in asymptomatic Afro-Caribbean athletes in V1–V4 preceded by domed ST segments is attributed to athlete’s heart syndrome [12].

INVERTED T WAVES IN THE LATERAL AND ANTEROLATERAL LEADS

TWI in the lateral or inferolateral leads is commonly seen in HCM [25], and > 90% of these patients will have an abnormal ECG [26]. TWI in the lateral leads are uncommon in healthy athletes, thus, regardless of ethnicity, it is considered abnormal and requires additional investigation to rule out HCM. In their editorial, Sharma and Papadakis [27] concluded, based on earlier studies [12, 25-28], that most PTWI affect the lateral leads and are commonly present in inferolateral territories. Lateral TWI is a common manifestation of cardiomyopathy, especially HCM, and has been shown to correlate with cardiac disease in athletes [29]. They concluded that deep TWI affecting the lateral leads (I, AVL, V5, and V6) should always be viewed with a high index of suspicion.

Calò et al. [28] provided new data on young athletes and found that the prevalence of TWI decreased with age and when it persisted in inferolateral leads, it was mostly associated with a cardiomyopathy, while TWI in other leads did not. TWI are more common in lateral leads of Black patients with HCM [12].

INVERTED T WAVES IN THE ANTERIOR LEADS

TWI in anterior leads may be present in HCM [12] and ARVC [23,31,24], but also in perfectly healthy athletes, including those who are Caucasian [12,23,37], Black [12,13], and mixed ethnicity [36]. Calore and colleagues [30] published a report on ECG parameters that can help differentiate physiologic anterior TWI in athletes from pathologic. After analyzing ECG patterns from HCM, ARVC, and healthy athletes of different ethnicities, they proposed a flowchart for the interpretation of anterior TWI based on a combination of J point elevation and TWI confined to V1–V4, with a 100% negative predictive value and halving the number of false positive results.

INVESTIGATION OF T WAVE INVERSION IN ATHLETES

When TWI is demonstrated in the ECGs of athletes, the recommendations are designed to further determine an underlying pathology [1,7,8]. The extent of such an investigation is not clear. Schnell and co-authors [35] prospectively studied the prevalence of cardiac pathology in athletes presenting with PTWI and examined the efficacy of including a cardiovascular magnetic resonance (CMR) evaluation in the diagnostic battery. They found that when incorporating CMR, a pathologic process was demonstrated in 45% of athletes presenting with PTWI. They proposed a new algorithm that includes CMR as a mandatory secondary test for these athletes.

We tested our flowchart on four abnormal ECGs from three athletes examined at our facility. Figure 2 displays the ECG findings of three athletes. Figure 2A depicts a tracing of a 50 year old male Caucasian triathlon athlete. The extensive TWI in all precordial leads mandated an immediate transthoracic echocar-

We emphasize the importance of defining the area of the leads in which T wave inversion is present

diographic (TTE) examination that diagnosed HCM. Figure 2B is a tracing of a 44 year old Caucasian male athlete, demonstrating a small TWI up to V4. In line with the flowchart in Figure 1, we examined the J point and found no elevation, thus a TTE exam was performed, which revealed the presence of ARVC. The athlete in Figure 2B was followed for 1 year. During this time his TWI extended and deepened in all precordial leads [Figure 2C]. However, Figure 3 exhibits an ECG tracing of a 28 year old male Caucasian athlete with persistent TWI up to V3 combined with lead III and AVF. As proposed by the flowchart in Figure 1, the J point was examined for elevation and demonstrated an elevation of more than 1 mm in V2–V3, meaning a normal variation of an

Figure 2. Electrocardiogram of pathologic T wave inversion **[A]** A 50 year old male Caucasian triathlon athlete with hypertrophic cardiomyopathy (HCM), **[B]** A 44 year old male Caucasian athlete with arrhythmogenic right ventricular cardiomyopathy (ARVC). **[C]** A 44 year old male Caucasian athlete with ARVC 1 year later

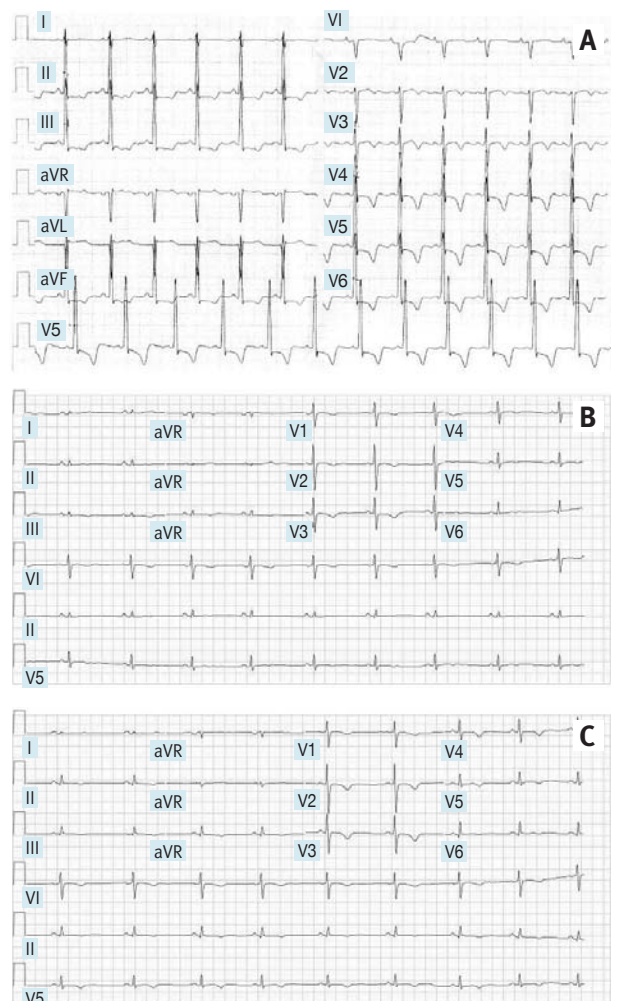
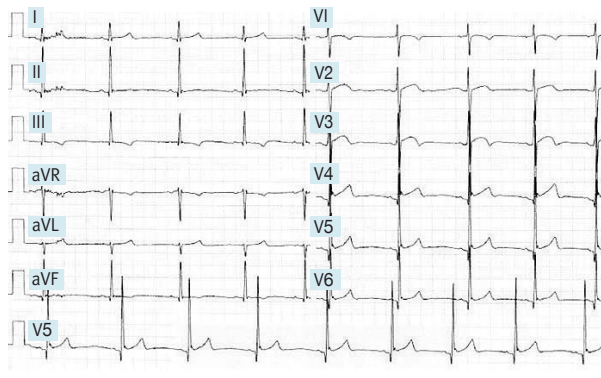


Figure 3. Electrocardiogram of a normal variant of T wave inversion (TWI) This 28 year old male Caucasian athlete had persistent TWI up to V3 and in III and AVF with a normal physical work-up



athlete’s heart. Because of no conclusive guidelines to date, this athlete was followed by serial TTE exams and a cardiac magnetic resonance imaging, revealing a completely normal heart, confirming our flow chart hypothesis. It should be noted that the TWI mentioned here applies to anterior leads alone and must be differentiated from Brugada syndrome utilizing the ratio of the ST elevation at the J point and at 80 msec later as described by Zorzi et al. [36]. This group reported that an upsloping ST segment configuration ($ST_J/ST_{80} < 1$) has a sensitivity of 97%, a specificity of 100%, and a diagnostic accuracy of 98.7% for the diagnosis of early repolarization variants in athletes. This approach helps differentiate TWI in anterior leads, which seem to be most frequently associated with cardiac pathology.

DISCUSSION

Athletes are being screened because of the occurrence of SCD events in the healthy young population. The burden of false positive ECG findings established the need for revision and improvement of exclusion criteria with the aim of keeping a sensitivity of 100%. New data on the differential diagnosis of TWI in athletes have recently emerged, but have not yet been incorporated or validated in a large cohort of apparently healthy athletes. This review summarizes these findings and attempts to incorporate them together in one simplified algorithm [Figure 1].

The proposed algorithm for discriminating PTWI in athletes is based on the latest validated and refined criteria in which TWI was predominantly abnormal up to V4, except in those of Black ethnicity [8]. In that population, the algorithm differentiates between adolescents and adults; in the former groups TWI may be considered a normal variant in athletes up to the age of 15 years [6,17,23]. The next step integrates the latest findings regarding ethnicity by Calore et al. [30] with no discrimination between different ethnicities, but solely according to the presence of TWI beyond V4, which implicates a pathological

process, or TWI up to V4, which then necessitates examination of J point elevation.

We emphasize the importance of defining the area of the leads in which TWI is present. TWI in the lateral leads was associated with an existing pathology in athletes, putting them at risk for SCD [25,37], while TWI in inferior leads has not yet been well established [27,37]. When taking all of these data into consideration, and studying the impact of TWI in the inferior leads in greater detail, the distribution of TWI might help us to further differentiate which athletes need a more extended work-up. When undertaking a secondary investigation because of a suspicious ECG, Schnell et al. [35] stressed the need for a second look after a TTE turns out to be normal because of a high prevalence of false negative results necessitating the need for a CMR study.

CONCLUSIONS

Exclusion criteria by ECG screening are intended to minimize the rate of false positive results without missing any life threatening pathology in an apparently healthy young athlete whose life could be saved by implementing timely and appropriate measures. TWI remains a controversial issue in the athletic population; therefore, this review attempts to consolidate the latest findings in one algorithm. Further studies are warranted to validate this novel flowchart.

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Capsule

Familial Mediterranean fever and incidence of cancer

Familial Mediterranean fever (FMF) is an autoinflammatory disease manifested as recurrent serosal inflammation. An association between FMF and malignancy has not been evaluated. The aim of this study was to estimate cancer risk in a large cohort of FMF patients from a single institution. **Brenner** and colleagues conducted a study cohort consisting of 8534 FMF patients registered at the National FMF Center in Tel Hashomer, Israel. The authors linked the study cohort to the database of the Israel National Cancer Registry using their national identity number. Cancer incidence in FMF patients was determined and then stratified by age and gender. Standardized incidence ratios (SIRs) for cancers were calculated. Among 8534 FMF patients (4400 men, 4134 women), 350 developed cancer during the years 1970–2011. The overall

cancer risk among patients with FMF was significantly lower than was expected in specific gender and ethnic groups of the Israeli population: for males of Jewish ethnicity, SIR 0.66 (95% confidence interval [95%CI] 0.55–0.77), $P < 0.001$; for females of Jewish ethnicity, SIR 0.75 (95%CI 0.64–0.86), $P < 0.001$; and for males of Arab ethnicity, SIR 0.34 (95%CI 0.07–0.99), $P = 0.024$. The authors conclude that FMF patients have a significantly lower incidence of cancer than the general population of Israel. This pattern was demonstrated in two ethnic populations: Jewish and Arab. The authors speculated that the lower cancer incidence could be attributed to a direct physiologic effect of FMF or to its treatment.

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