The Prevalence and Significance of Anterior T wave Inversion in White, Young Athletes and Non-Athletes

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ABSTRACT

Background: Anterior T wave inversion (ATWI) on an EKG in young white adults raises the possibility of cardiomyopathy, specifically arrhythmogenic right ventricular cardiomyopathy (ARVC). While the 2010 European consensus recommendations for EKG interpretation in young athletes state that ATWI beyond V1 warrants further investigation, the prevalence and significance of ATWI has never been reported in a large white asymptomatic population.

Objective: This study investigated the prevalence and significance of ATWI in a large cohort of young, white adults including athletes.

Methods: 14,646 individuals aged 16-35 years were evaluated with a health questionnaire, physical examination and 12-lead EKG, including 4,720 (32%) females and 2,958 (20%) athletes. ATWI was defined as T wave inversion in ≥2 contiguous anterior leads (V1-V4) and was investigated comprehensively to elucidate cardiac pathology.

Results: ATWI was detected in 338 (2.3%) individuals and was more common in females than males (4.3% vs. 1.4%; $p<0.0001$), and among athletes compared with non-athletes (3.5% vs 2.0%; $p<0.0001$). TWI was predominantly confined to leads V1-V2 (77%). Only 1.2% of females and 0.2% of males exhibited ATWI beyond V2. None of the individuals with ATWI fulfilled diagnostic criteria for ARVC after further evaluation. During a mean follow-up period of 23.1 (±12.2) months none of the individuals with ATWI experienced an adverse event.

Conclusions: Anterior T wave inversion confined to V1-V2 is a normal variant or physiological phenomenon in asymptomatic white individuals without a relevant family history. Conversely, ATWI beyond V2 is rare, particularly in males, and may warrant investigation. These results will have a significant impact on EKG interpretation in young white adults.

Key words: anterior T wave inversion; arrhythmogenic right ventricular cardiomyopathy; EKG screening; ethnicity

Abbreviations:

ARVC- arrhythmogenic right ventricular cardiomyopathy
ATWI- anterior T wave inversion
CMRI- cardiac magnetic resonance imaging
EKG- electrocardiogram
TWI- T wave inversion

Introduction

There is general agreement that T wave inversion (TWI) in the inferior or lateral leads in young individuals warrants further investigation for cardiac disease, particularly cardiomyopathy (1). It is also well-established that adolescent athletes (2-6) and black adult athletes (7) frequently exhibit TWI in the anterior leads as part of the normal physiological or ethnic spectrum respectively. However, the general consensus on the significance of anterior T wave inversion (ATWI), defined as T wave inversion in ≥2 contiguous anterior leads (V1-V4) in white adults varies between expert recommendations for the interpretation of the athlete's EKG. Whereas the European Society of Cardiology recommendations suggest further evaluation of athletes with TWI beyond V1 (8), more recent recommendations from the Seattle criteria advocate investigation only if TWI extends beyond V2 (9).

Both consensus panels have relied on data from unselected (10) or small athlete cohorts (11); however recent studies reveal that TWI in leads V1-V2/V3 is detected in up to 6% of endurance athletes (12). Conversely, ATWI in V1-V2/V3 is a recognized repolarization abnormality in a significant proportion of patients with arrhythmogenic right ventricular cardiomyopathy (ARVC) and a small minority of patients with hypertrophic cardiomyopathy (7) which collectively account for > 40% of all sudden cardiac deaths (SCD) in young athletes (13). The differentiation of potentially pathological ATWI from a pattern that represents a normal variant or physiological remodelling in white adult athletes is essential to minimize the risk and consequences of an erroneous diagnosis (6,14).

Since the prevalence of ATWI has been reported in black athletes and controls of both sexes, and in the adolescent population, this study focused on the prevalence and significance of

ATWI in a large cohort of apparently healthy white adults including a large proportion of athletes.

Methods

Setting

The UK does not support a nationally sponsored screening programme for cardiac disease in young asymptomatic individuals in the absence of a family history of inherited cardiac disease or premature SCD. Several elite sporting organizations finance the evaluation of their athletes through the charitable organization, Cardiac Risk in the Young (CRY). These include premier league football clubs, the Lawn Tennis Association and the English Institute of Sport. Up to 1000 athletes are tested annually at their specific clubs or national training camps, usually with history, examination and EKG. Financially endowed organisations such as the Football Association and the Lawn Tennis Association also incorporate echocardiography as standard.

CRY also offers cardiac screening to all young (14- 35 years old) individuals who wish to be assessed even in the absence of symptoms, past history of cardiac disease or a family history of inherited cardiac diseases or SCD. Such screenings are conducted at community centres and high schools and are limited to history, examination and EKG with referral for further assessment only in those with abnormal preliminary investigations or if participating as controls for research studies. Screening events are advertised via the local media and on the CRY website (www.c-r-y.org.uk). Individuals from the general population, including those from local high schools, self-present to screening events whereas competitive athletes attend specified screening events mandated by their relevant sporting bodies. The CRY screening program is supervised by S.S. (principal investigator).

Subjects

Between 2007 and 2013, 14,646 young, white adults aged between 16 and 35 years, underwent cardiac evaluation through CRY at various testing centres in England. Ethnicity was self-reported through the questionnaire that included terms such as white British, white Irish, white European and white other.

Athletes

The study included 2958 (20.2%) athletes competing at regional, national or international level who performed ≥8 hours of exercise per week. Sporting disciplines were categorized as predominantly endurance or strength. Endurance sports were defined as those typically resulting in >70% of maximal oxygen uptake ($VO_{2\ max}$) (15) and included badminton, basketball, canoeing, cycling, hockey, middle and long-distance running, rowing, rugby, soccer, squash, swimming, tennis and triathlon. All other sports were deemed strength disciplines, including cricket, diving, sailing, volley ball, water polo, weight-lifting and wrestling.

Non- Athletes

Non-athletes comprised of 11,688 (79.8%) individuals, whose primary inclusion criterion was a sedentary lifestyle (≤ 2 hours organized physical activity per week). Individuals with symptoms suggestive of cardiac disease, previous cardiac history or a family history of premature cardiac disease or SCD (<50 years) were excluded.

Investigations

<u>Electrocardiogram</u>

A standard 12-lead EKG was performed in a supine position using a Marquette Hellige recorder (Milwaukee, USA) at a paper speed of 25 mm/s. P, Q, R, S, T wave voltages, ST segments, QRS, PR, and QT intervals were measured in each lead as described elsewhere (16). Leads V1-V4 were classified as anterior precordial leads. T wave deflection ≥ -0.1mV in these

leads was regarded as abnormal T wave inversion. Deep T wave inversion was defined as a T wave amplitude ≥ -0.2mV. In cases of biphasic T waves we applied the above definition to the negative component of the T wave. In cases with ATWI, the EKG was repeated ensuring that the leads were correctly positioned according to standard recommendations. In women the EKG electrodes were placed under the breast tissue as per American Heart Association recommendations (17). Partial right bundle branch block (pRBBB) was defined as QRS duration >0.1 but <0.12 seconds, with rSR' morphology in lead V1 and qRS in V6 (18). Individuals with TWI and complete right bundle branch block (QRS ≥0.12 seconds) were excluded from the ATWI group. Additional EKG markers compatible with ARVC were also sought, including terminal activation duration of the QRS complex ≥ 55msec in leads V1, V2 or V3, and the epsilon wave (19).

The amplitude of the J-point (Jt) (20) 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 ≥0.1mV or depressed if Jt ≤ -0.1mV. The morphology of the ST segment in the anterior leads was ascertained in the M interval (the 100ms following Jt) (20). Accordingly, the ST segment at the onset of the M interval, i.e. Jt, was considered elevated if it were above Jt, depressed if it were below Jt and isoelectric if it were in line with Jt. Ascending ST segments were categorised as ascending convex or ascending concave (figure 1).

Echocardiogram

Two-dimensional (2D) transthoracic echocardiography was performed on all subjects with ATWI, with Philips (CPX50, iE33, Sonos 7500) and GE Vivid I (Tiral, Israel) machines. Standard views were obtained and dimensions of cavities and wall thickness measurements, pulsed colour and tissue Doppler measurements were made in accordance with established

guidelines (21-23) Right ventricular (RV) assessment was performed as outlined previously (14). RV regional wall-motion abnormalities (WMAs) were defined as akinetic, dyskinetic, or aneurysmal, in accordance with diagnostic criteria for ARVC (19).

Echocardiography was also performed as standard on 1079 athletes and 769 non-athletes without ATWI of similar age and sex proportion who had normal physical examination and EKG. The echocardiogram was part of a mandatory pre-participation cardiac evaluation in athletes whereas the echocardiogram was conducted as part of research in volunteering non-athletes. These cohorts served as comparative groups for athletes and non-athletes with ATWI respectively.

All EKG and echocardiograms were performed by nationally-accredited cardiac physiologists. Echocardiography was conducted by physiologists blinded to the EKG findings. All EKG and echocardiogram images were reviewed by 2 independent cardiologists with the principal investigator (S.S.) adjudicating any queries.

Further Investigations

All subjects with ATWI underwent additional investigations to detect the broader phenotypic features of a primary cardiomyopathy, particularly ARVC, hypertrophic cardiomyopathy and dilated cardiomyopathy. Pre-determined diagnostic criteria for ARVC were based on the 2010 Modified Task Force criteria (19). Hypertrophic cardiomyopathy was considered in individuals with left ventricular hypertrophy where septal or wall thickness measured ≥15mm in any myocardial segment in the absence of another condition capable of producing left ventricular hypertrophy of the same magnitude (24,25). Dilated cardiomyopathy was considered in individuals with a dilated LV (males >59mm and females >53mm) when

accompanied by a reduced ejection fraction (< 52%) (29). The vast majority (1396; 95%) of further investigations were performed at our institution.

Ambulatory EKG monitoring

Ambulatory 24-hour EKG recording (Lifecard CF Holters, Spacelabs Healthcare, USA) was used to detect ventricular arrhythmias. Subjects were encouraged to continue day-to-day activities including exercise during monitoring.

Exercise-testing

Exercise testing was performed upright on a treadmill using the standard Bruce protocol (27). Subjects were exercised to volitional exhaustion and assessed for cardiac symptoms, ischaemic changes, attenuated blood pressure response or arrhythmias.

Signal-averaged EKG

Signal-averaged EKG was acquired according to accepted methodology using the same machines used for standard electrocardiography, with use of a 40Hz high-pass bi-directional filter (28). Late potentials were defined as abnormal values in one or more of the parameters in accordance the diagnostic criteria for ARVC (19).

Cardiac Magnetic Resonance Imaging

CMRI was performed using a Philips Achiever 3.0T TX scanner (Amsterdam, the Netherlands). Delayed gadolinium enhancement (DGE) images were acquired as previously described (29). Ventricular volumes and function were measured for both ventricles using standard techniques and analysed using semi-automated software (Extended MR workspace, Philips, Amsterdam, the Netherlands) (30). All measures were indexed to body surface area.

Ethical approval

Ethics approval was granted by the National Research Ethics Service, Essex 2 Research Ethics Committee in the United Kingdom. Written consent was obtained from all subjects.

Statistical analysis

Data are expressed as mean (±SD) or percentages as appropriate and analyzed with SPSS software, version 20 (Chicago, IL). Comparison between groups was performed using Student t-test for continuous variables with adjustment for unequal variance if needed and χ^2 tests or Fisher Exact Tests for categorical variables. Univariate analyses were performed to determine variables (gender, age, athletic status, left ventricular end diastolic diameter and right ventricular outflow tract size (parasternal long and short axis measurements)) associated with ATWI. Multivariate logistic regression analyses were used to determine the independence of these associations. Significance was defined as $p<0.05$.

Results

Demographics

The mean age of the cohort was 21.7 (±5.4) years. Of the 14,646 subjects, 9,926 (67.8%) were male. 2063 (20.8%) males and 895 (19.0%) females were athletes. Athletes exercised for an average of 15.7 (±5.1) hours/ week compared with 1.8 (±0.6) hours/ week in non-athletes.

Prevalence of Anterior T wave Inversion

338 individuals (2.3%) exhibited ATWI. Individuals with ATWI were of similar age and had a similar mean body surface area compared to those without ATWI (**Table 1**). Anterior T wave inversion was more common in females compared with males (n= 203; 4.3% vs n= 135; 1.4%: p<0.0001) and was more common in athletes than non-athletes (n= 103; 3.5% vs. n= 235; 2%; p<0.0001) in both sexes (females: n= 58; 6.5% vs. n= 145; 3.8%; p= 0.0005, and males: n= 45; 2.1% vs. n= 90; 1.1%; p= 0.0004) (**Central Illustration**). Among athletes, ATWI was more

prevalent in those engaging in endurance sports compared to strength sports (n= 82; 5.6% vs. n=41; 2.8%: p<0.0001). The prevalence of ATWI among those aged 16-21 years was not dissimilar to those aged above 21 years (2.28% vs 2.46%; p= 0.52).

Distribution of Anterior T wave Inversion

260 individuals (1.8%) revealed TWI confined to V1-V2. TWI confined to V1-V2 constituted 77% of all ATWI. Only 78 (0.5%) individuals demonstrated TWI beyond V2 which was present in 56 (1.2%) females vs. 22 (0.2%) males (p<0.0001). Among athletes, TWI in V1-V3 was detected in 19 (2.1%) females vs. 7 (0.3%) males (p<0.0001) (figure- central illustration). Four females, but none of the males, showed TWI extending to V4, which equated to just 2% of all ATWI in females.

Deep ATWI was more common in males than females (55.6% vs. 33%; p=0.0166) but did not differ between athletes and non-athletes. 50 individuals with ATWI (14.8%) exhibited incomplete RBBB which never extended beyond V2.

Jt elevation and ST segment morphology preceding ATWI

Among individuals with ATWI, Jt elevation was more common in athletes than non-athletes (49% vs. 29%; p=0.0008) and more common in males than females irrespective of athletic status (athletes: 71.1% vs. 31.0%, p= 0.0004; non-athletes: 58.9% vs. 10.3%, p< 0.0001). None of the individuals with ATWI demonstrated a depressed Jt.

Males frequently showed an elevated ST-segment that of ascending convex morphology (42%), followed by an ascending concave morphology (33%) and an isoelectric pattern (25%). In females with ATWI the ST segment was most commonly isoelectric (57%), followed by ascending convex (24%) and ascending concave (19%) morphologies. Only one individual with ATWI demonstrated a depressed ST segment (**Figure 2**).

Cardiac Structure and Function in Individuals with ATWI

The echocardiographic results of all 338 individuals with ATWI (athletes= 103, non-athletes= 235) were compared with the results of 1848 individuals without ATWI (athletes= 1079, non-athletes= 769). Athletes revealed larger ventricular dimensions compared to non-athletes irrespective of ATWI. There were no differences in left or right ventricular dimensions or function in individuals (athletes and non-athletes) with ATWI compared to those without AWTI (**Table 2**).

CMRI was performed on 250 (74%) subjects with ATWI. Athletes demonstrated larger left and right ventricular volumes and masses compared to non-athletes (**Table 2**). Following gadolinium there was no evidence of late enhancement in any subject. None of the individuals with ATWI showed unequivocal diagnostic features of ARVC, hypertrophic cardiomyopathy or dilated cardiomyopathy.

Other Investigations

Signal-averaged Electrocardiogram

316 (93%) individuals with ATWI underwent SAEKG and 21 (7%) showed an abnormality in one of the three parameters. The most common abnormality was filtered QRS prolongation (60%), a phenomenon that has been reported previously in healthy individuals (31,32).

Exercise Stress Testing and Ambulatory EKG Monitoring

274 (81%) individuals with ATWI underwent an exercise stress test and 293 (87%) had 24 hour EKG monitoring. None of the individuals with ATWI exhibited an arrhythmia during exercise, other than occasional isolated ventricular ectopics (n= 10; 3%) of right or left

ventricular origin in the early stages of exercise. Similarly, none showed >500 ventricular ectopics or runs of non-sustained ventricular tachycardia during Holter monitoring (19).

Determinants of Anterior T wave Inversion

Univariate predictors of ATWI were female gender and athletic status. Stepwise logistic regression identified female gender (OR 3.1, 95% CI 1.96-4.90, p<0.001) and athletic status (OR 3.3, 95% CI 1.91-5.63, p=0.001) as being independently associated with ATWI in the screened adult population, irrespective of age.

Detection of Cardiac Pathology

Following comprehensive clinical evaluation of 274 (81%) individuals with ATWI (including echocardiography in all 338 individuals) and a mean follow-up period of 23.1 ±12.2) months, we could not diagnose ARVC or any other cardiomyopathy. However, 16 athletes and 10 non-athletes with ATWI fell into the gray zone, in which structural changes attributed to physiological adaptation needed to be differentiated from primary cardiomyopathies. These included: 2 athletes and 3 non-athletes with an indexed $RVOT_{plax} \geq 19$ mm/m^2; 1 athlete with a maximal left ventricular wall thickness of 13mm; and 6 non-athletes who initially demonstrated an absolute LVEDD above the upper limit of normal (non-athletes: LVEDD; males >59mm and females >53mm[26] and athletes with an LVEDD > 60mm[33]).

Identification of Minor Cardiac Pathology

Echocardiography in all 338 subjects with ATWI failed to show akinetic segments or regional wall motion abnormalities affecting the right ventricle. A small proportion revealed minor pathology in 5 (1.5%) including: bicuspid aortic valve (n= 2; 0.6%), mitral valve prolapse with moderate mitral regurgitation (n= 1; 0.3%); atrial septal defect (n=1; 0.3%) and patent

ductus arteriosus (n= 1; 0.3%). 7 (2%) individuals had a patent foramen ovale noted and pectus excavatum was noted in 2 (0.6%) cases.

Discussion

The detection of lateral or infero-lateral T wave inversion in young black or white individuals has a relatively high yield for the diagnosis of cardiomyopathy (1). Whereas ATWI is a benign variant in healthy adolescents of all ethnic origins and in black adolescent and adult athletes, its significance in asymptomatic white adults is unknown. However, between 50-60% of probands with ARVC show ATWI in leads V1-V3 (34). This study of almost 15,000 healthy, white adults, including 4,720 females and almost 3,000 athletes, showed that ATWI beyond V1 was present in a small proportion of individuals (2.3%) and this prevalence fell to just 0.5% beyond V2. ATWI was more common in females than males irrespective of athletic status and validates data from much smaller studies from 6- 7 decades ago (35,36). Several postulations for this gender difference have been proposed including varying levels of sympathetic innervation and anatomical differences in chest wall structure, specifically breast tissue. Based on the fact that the prevalence of anterior T wave inversion is almost identical in prepubertal males and females (3) we suspect that sex differences in adults are likely to reflect differences in lead placement as a result of increased breast tissue in females.

Prevalence of Anterior T wave Inversion in Athletes

Athletes demonstrated a greater prevalence of ATWI than non-athletes, particularly those engaging in >15 hours/ week of exercise. Such intense exercise regimes, particularly in endurance sports, place a greater haemodynamic load on the right ventricle that may manifest on the EKG as ATWI. Our study however, was unable to demonstrate any structural differences in the right ventricle between individuals with ATWI and those without.

Significance of Extrapolating Data from Probands with Cardiomyopathy to low-risk Populations

There are justifiable concerns about the association of ATWI with an underlying cardiomyopathy such as ARVC or hypertrophic cardiomyopathy. While isolated ATWI is rare in hypertrophic cardiomyopathy is a rare finding (2), ATWI beyond V2 in probands with ARVC is common and classified as a major repolarization abnormality in the Revised Task Force Criteria for ARVC (19). In this study, none of the athletes with ATWI in V2/V3 fulfilled diagnostic criteria for ARVC based on a combination of health questionnaire, EKG, and echocardiography in 100% of cases, SAEKG in 93%, 24 hour EKG in 87%, exercise testing in 81% and CMRI in 74% . This observation highlights that data derived from probands with ARVC for generating diagnostic criteria lack specificity in low risk populations (29). However, TWI beyond V2 was present in just 1 in 200 white adult athletes and could justify detailed assessment to exclude ARVC or any other cardiomyopathy. Our data supports the consensus based Seattle recommendations, which pragmatically suggest that only TWI beyond V2 in asymptomatic white athletes requires further evaluation (9). However, these recommendations are at odds with the European Society of Cardiology recommendations and the recently published refined criteria (8,37). Given the potentially sinister ramifications of false negative tests with regard to ARVC in particular more robust data is necessary before such criteria can be adopted with more certainly in future updates for EKG interpretation in athletes. This comprehensive study of a large population of athletes with ATWI provides support for the Seattle consensus.

Potential Markers of Disease in Individuals with Anterior T wave Inversion

In athletes with TWI beyond V1, information from the preceding Jt or ST segment may provide valuable diagnostic information when considering ARVC. Based on comparisons between 45 athletes with ATWI and 35 patients with ARVC we have previously reported that a

Jt and ST segment in line with the onset of the QRS complex or a depressed ST segment preceding ATWI is a powerful discriminator between the two entities (29). Moreover, a recent study examining ATWI as a marker of cardiomyopathy in a small cohort of athletes of black and white ethnicity, showed that Jt elevation ($\geq$ 0.1mV) preceding the TWI excluded ARVC.[34] Our large study of almost 15,000 white individuals provides validation for these concepts in males but reveals that Jt may be in line with the onset of the QRS complex in as many as 50% of healthy females with ATWI. Importantly, only 1 athlete demonstrated ATWI with preceding ST segment depression and none of the individuals with ATWI showed Jt depression suggesting that the presence of such electrical markers may be pointers for cardiac pathology.

There remains the possibility that ATWI confined to V1-V2 may be a manifestation of ARVC. We have examined our own cohort of 35 probands with ARVC and identified ATWI in V1-V2 alone in 6%. All of these patients either expressed symptoms or other electrical features diagnostic of ARVC (29).

Limitations

This study was cross-sectional in nature and although there were no adverse clinical events in the ATWI group during a follow-up of nearly 2 years, the authors cannot be certain whether ATWI may precede the development of ARVC by several years. Familial evaluation was not performed in any of the individuals with ATWI because none fulfilled overt criteria for a cardiomyopathy. However, the authors concede that such practice may have highlighted some individuals with incomplete expression of disease. A small proportion of ATWI individuals were lost to follow up due to logistical difficulties that could not be overcome (e.g. emigration). Cardiac MRI is the recognized gold standard for the investigation of primary cardiomyopathies but was only performed in 250 (74%) individuals with ATWI. However, 81% of all individuals

with ATWI had all of EKG, echocardiography, SAEKG, Holter and exercise stress test which are sufficient to diagnose ARVC according to modified task force criteria (19). Voluntary cardiac screening programmes of non-athletes in the community conducted through organizations such as CRY do have a potential for inherent selection bias though given the large numbers included in this study of nearly 15,000 participants, the potential of any such bias is significantly mitigated.

Conclusions

ATWI is present in 2.3% of the young white population and is more common in females and in athletes. Almost 80% is confined to V1-V2 and has a poor diagnostic yield for cardiac pathology, implying that this electrocardiographic pattern could be considered a normal phenomenon in asymptomatic individuals without a family history of cardiomyopathy or premature SCD. In contrast, TWI extending beyond V2 is present in only 1% females and 0.2% males and may justify further evaluation in white individuals, particularly when preceded by Jt depression or ST segment depression.

Clinical Perspectives

Competency in Medical Knowledge: Anterior T wave inversion confined to V1-V2 may be a normal variant or physiological phenomenon in asymptomatic white individuals without a relevant family history.

Translational Outlook: The results of this study will have a significant impact on EKG interpretation in young white athletes and non-athletes as the rarity of T wave inversion beyond V2 (1 in 200) may justify further investigation.

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Figure Legends

Central illustration: Prevalence of anterior T wave inversion (ATWI) in the adult white population aged 16-35 years old. The overall prevalence of ATWI in adult white individuals was 2.3%. ATWI was more common in females and in athletes. The prevalence of ATWI beyond V2 was rare, falling to 0.2% in male non-athletes.

Figure 1: ST segment morphology.(A) The vertical solid line and the vertical dashed line define the M interval, which has a duration of 100ms. The horizontal dashed line through the onset of the QRS complex provides the reference point for the measurement of Jt. Jt is elevated at 0.2mV with a convex appearance. ST segment morphologies with anterior T wave inversion in chest leads V2 and V3 are shown as: B) ascending convex; C) isoelectric; D) ascending concave; E) depressed.

Figure 2: Bar graph demonstrating the type of ST segment morphology preceding anterior T wave inversion (ATWI) in healthy individuals and ATWI according to sex. An ascending convex and ascending concave ST segment morphology was more common in males than females. Females more commonly demonstrated an isoelectric ST segment.

Table 1: Demographics and EKG characteristics of individuals with and without anterior T wave inversion

	Characteristic	Anterior TWI population (n =338)	Population without anterior TWI (n=14,308)	p value
Demographics	Age (years)	21.1 ± 5.4	21.7 ± 5.3	0.0398
	Sex (% female)	60.1	31.6	<0.0001
	Athletes (%)	30.5	20.0	0.0003
	BSA (m^2)	1.81 ± 0.3	1.91 ± 0.2	<0.0001
	Blood pressure (mmHg)	121/66 ±12/7	123/80 ±10/6	0.0003
EKG parameters	Heart rate (bpm)	64 ± 14	66 ± 14	<0.0001
	PR (ms)	150 ± 25	151 ± 32	<0.0001
	QRS (ms)	93 ± 12	92 ± 13	<0.0001
	QTc (ms)	421 ± 28	412 ± 20	<0.0001
	Incomplete RBBB (%)	17.7	5.5	<0.0001
	LBBB (%)	0	0.02	0.77
	LVH (%)	17.9	10.1	<0.0001
	RVH (%)	1.2	1.1	0.93
	ER (%)	15.1	9.7	0.0018
	Pathol Q waves (%)	0.5	0.3	<0.0001
	LA enlargement (%)	3.3	1.4	0.002
	RA enlargement (%)	1.4	0.6	0.1

LAD (%)	1.0	1.2	0.83
RAD (%)	0.7	0.4	0.49
Pre-excitation (%)	0.5	0.5	0.93

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501 Values are mean ± SD or % overall population

502 BSA= body surface area; EKG = 12 lead electrocardiogram; ER = early repolarisation; LA = left

503 atrial; LAD = left axis deviation; LBBB= left bundle branch block; LVH= left ventricular

504 hypertrophy; RA = right atrial; RAD = right axis deviation; RVH = right ventricular hypertrophy;

505 TWI = T wave inversion.

Table 2: Echocardiographic and Cardiac Magnetic Resonance Measurements of Athletes and Non-athletes with and without Anterior T wave Inversion.

Measurement	Athletes (n= 1182)			Non-athletes (n= 1,004)		
	With Ant TWI (n= 103)	Without Ant TWI (n= 1079)	p value	With Ant TWI (n=235)	Without Ant TWI (n= 769)	p value
Ao (mm)	28.0 ± 4.3	28.6 ± 4.5	0.2306	27.1 ± 3.6	27.4 ± 3.8	0.2839
LA (mm)	33.1 ± 6.1	33.5 ± 4.9	0.4394	31 ± 4.3	31.3 ± 5.5	0.443
LVEDd (mm)	50.8 ± 5.8	51.5 ± 5.6	0.2272	48.1 ± 4.5	48.5 ± 5.8	0.3315
LVESd (mm)	34.0 ± 6.1	33.9 ± 4.8	0.844	31.1 ± 3.9	31.6 ± 5.1	0.1666
MLVWT (mm)	9.2 ± 2.3	8.9 ± 2.1	0.1699	8.5 ± 2.2	8.3 ± 1.5	0.1126
LVMI (g/m^2)	105 ± 15	103 ± 16	0.2233	94 ± 8	95 ± 9	0.1267
EF (%)	60 ± 9	59 ± 8	0.231	66 ± 8	67 ± 9	0.1267
$RVOT_{plax}$ (mm)	29.9 ± 5.4	29.8 ± 4.8	0.8417	26.0 ± 3.7	25.4 ± 3.6	0.1072
$RVOT_{plax}$ $in_{(mm/m^2)}$	16.7 ± 2.1	16.8 ± 3.7	0.7871	15.2 ± 2.5	14.8 ± 3.1	0.2041
$RVOT_{psax}$ (mm)	31.6 ± 4.9	32.3 ± 5.6	0.221	28.2 ± 5.8	29.1 ± 5.7	0.1266
$RVOT_{psax}in_{(mm/m^2)}$	17.8 ± 2.5	17.5 ± 2.9	0.3106	16.0 ± 2.1	16.1 ± 2.5	0.6945
RVOT2 (mm)	25.8 ± 4.8	25.1 ± 4.4	0.1263	22.6 ± 3.7	23.2 ± 4.3	0.0537

RVD1 (mm)	41.1 ± 6.6	40.6 ± 5.8	0.4093	35.3 ± 4.9	35.6 ± 5.5	0.4534
RVD2 (mm)	34.1 ± 6.4	33.3 ± 5.5	0.165	28.2± 4.5	28.7 ± 5.7	0.2181
RVD3 (mm)	84.2 ± 10.5	82.0 ± 13.2	0.1008	73.5 ± 11.4	74.9 ± 11.1	0.093
RVWT (mm)	4.8 ± 1.5	4.6 ± 1.3	0.1416	4.2 ± 0.8	4.1 ± 1.0	0.1613
TAPSE (mm)	23.4 ± 5.3	23.5 ± 4.2	0.8219	22.8 ± 4.7	22.9 ± 4.5	0.768
PASP (mmHg)	17.6± 7.7	15.9 ± 6.5	0.0128	17.8 ± 3.3	18.3 ± 4.0	0.0816
TV E/A	1.9 ± 0.5	2.0 ± 0.4	0.0181	1.9 ± 0.6	2.0 ± 0.8	0.0771
TV S' (cm/s)	14.8± 2.6	14.9 ± 2.5	0.6992	14.6 ± 2.8	14.2 ± 2.8	0.0556
TV E' (cm/s)	13.9 ± 3.4	14.1 ± 3.1	0.5353	14.9 ± 2.9	15.1 ± 3.5	0.426
RAA (cm^2)	19.2 ± 3.4	18.8 ± 3.7	0.2915	15.2 ± 2.8	15.1 ± 4.8	0.7613
RV FAC (%)	38.7 ± 4.9	39.6 ± 4.8	0.0698	36.2 ± 4.1	37.3 ± 6.2	0.0108

CMR	**ATWI Athletes (n=76)**	**ATWI Non- athletes (n= 174)**	
LVM- i (g/m^2)	105 ± 15	94 ± 9	p<0.05
LVEDV- i (ml/m^2)	105.8 ± 15	94.3 ± 14	p<0.05
RV EF (%)	52.5 ± 5.1	55.5 ± 5.9	p<0.05
RVEDV- i(ml/m^2)	105.3 ± 14	94.3 ± 14	p<0.05

LGE (%)	0	0	-

Values are mean ±SD. Ao= aorta; CMR= cardiac magnetic resonance imaging; EF= ejection fraction by Simpson's biplane; LA= left atrial; LVEDd= left ventricular end diastolic diameter; LVEDV= left ventricular end diastolic volume; LVESd= left ventricular end systolic diameter; LVM i = left ventricular mass index (g/m^2); MLVWT= maximum left ventricular wall thickness; PASP= pulmonary artery systolic pressure; RAA= right atrial area; RVD1= right ventricular basal dimension; RVD2= right ventricular midventricular dimension; RVD3= right ventricular longitudinal dimension; RVEDV= right ventricular end diastolic volume; RV `EF= right ventricular ejection fraction; RVOT1= proximal right ventricular outflow tract dimension; RVOT2= distal right ventricular outflow tract dimension; RVOTplax= right ventricular outflow tract dimension (parasternal); ; RVOTsax= right ventricular outflow tract dimension (short axis); RVWT= right ventricular free wall thickness; S'= peak systolic velocity; TAPSE= tricuspid annular plane systolic excursion; TV= tricuspid valve.