

ORIGINAL ARTICLES

Microvolt T-Wave Alternans as Predictor of Electrophysiological Testing Results in Professional Competitive Athletes

Francesco Furlanello, M.D.,* Giorgio Galanti, M.D.,** Paolo Manetti, M.D.,** Andrea Capalbo, M.D.,** Nicola Pucci, M.D.,** Antonio Michelucci, F.A.A.C.,** Daniele Marangoni, M.S.,† Francesco Terrasi, M.D.,‡ Giacinto Pettinati, M.D.,¶ and Riccardo Cappato, F.A.A.C.*

From the *Department of Clinical Arrhythmia and Electrophysiology, San Donato Milanese Hospital, Milano; **Sport Medicine Centre, University of Florence; †University of Verona; ‡Villa Bianca Hospital, Trento; and ¶Cardiology Department, Ferrari Hospital, Casarano, Lecce, Italy

Background: Several studies have confirmed the equivalence of the microvolt T-Wave alternans (mTWA) and the electrophysiology (EPS) tests in cardiac disease. No data are available in populations of competitive athletes with arrhythmias that might jeopardize the pursuit of their professional career.

Methods: We prospectively studied 100 trained competitive athletes, including elite types (72/100), (mean age $\pm$ standard deviation: 26.1 ± 4.5 years). Forty-eight of them were wholly normal (Group A, mean age: 24.5 ± 8.5 years) and 52 of them had severe arrhythmias (Group B, mean age: 28.2 ± 11.5 years) and were symptomatic in 85% of cases for prolonged palpitations and syncope, but lacked any overt structural heart disease at standardized cardiological screening.

All athletes were evaluated with the microvolt T-wave alternans exercise-stress test, using the Heart Wave System with Microvolt Sensors. Group B underwent EPS to evaluate inducibility to sustained ventricular tachycardia (VT) during programmed electrical stimulation.

Results: In Group A, the mTWA outcome was determinate in 45 subjects (94%) and indeterminate in 3 (6%). No symptomatic event was reported in a follow-up of 36.1 months. In Group B, the mTWA test was positive in 7 symptomatic subjects (15%), indeterminate in 3 (7%), and negative for the remaining 42 subjects (76%). Forty-one of 42 negative mTWA subjects were also negative in the EPS test, without any syncope or sustained VT during 25.3 months of follow-up. In the positive mTWA test subjects, 5 (72%) were positive for inducibility of rapid sustained monomorphic VT in EPS, 1 was positive for severe sustained atrial tachyarrhythmias, and 1 refused EPS. We were able to pronounce a correct diagnosis of lymphocytic myocarditis for only 1 mTWA and EPS-positive subject. For the other 4 positive patients with arrhythmogenic micropathology, severe arrhythmic events were revealed in the follow-up and aggressive hybrid treatment was necessary.

Conclusion: Microvolt-TWA study seems to be a useful, noninvasive, and feasible tool for evaluating arrhythmic risk in the athletic population. The mTWA test showed a high negative predictive value, using both EPS and the follow-up observation for severe arrhythmic cardiac events as an end-point. The positive predictive value was present in a limited number of cases that were, however, subjects with a high risk of sudden arrhythmic death. **A.N.E. 2004;9(3):1-6**

Electrocardiographic T-wave alternans is a heart-rate-dependent measure of repolarization that has been associated with a higher risk of ventricular tachyarrhythmias in many physiopathological

conditions.^{1,2} Computerized analysis techniques are able to measure microvolt T-wave alternans (mTWA) in subjects in whom mTWA is not visible at surface ECG.^{3,4} Microvolt TWA has been

demonstrated to be a sensitive and specific marker of malignant ventricular tachyarrhythmias that is equivalent or superior to programmed stimulation during electrophysiology testing in patients with heart disease.^{5–7} Accurate identifications of patients at increased risk for sustained ventricular arrhythmias are critical for the development of effective strategies to prevent sudden cardiac death.

In normal populations the incidence of positive mTWA is less than 1%.^{8,9} No data are available in athletic populations with significant arrhythmias, where it is important to stratify the risk for severe cardiac events on field such as syncope, cardiac arrest (CA), and sudden death (SD), and hence for athletic eligibility.¹⁰ In fact, recent studies show that young competitive athletes with silent arrhythmogenic heart disease have a higher risk of sudden death than sedentary subjects of the same age and similar latent pathological substrate.^{11–13}

The objectives of this study were (1) to assess the feasibility of the mTWA test in competitive athletes including elite subjects; (2) to compare mTWA and EPS for arrhythmia risk stratification in athletes with complex and severe ventricular arrhythmias including nonsustained and sustained ventricular tachycardia (VT); and (3) to verify the negative predictive value of mTWA study for sustained VT, CA, and SD for a follow-up >24 months of clinical observation.

MATERIALS AND METHODS

Study Population

This was a multicenter prospective study of 100 athletes aged between 12 and 46 years (mean age: 26.1 ± 4.5 years), practicing 12 different types of competitive sports. Seventy-two of the subjects were high level international “elite” athletes (Table 1).

Inclusion Criteria

We studied 48 (Group A) healthy, well-trained, asymptomatic, competitive athletes (mean age: 24.5 ± 8.2 years) with normal resting and stress ECG, 24-hour Holter (ventricular ectopic beats (VEB) < 10/24 hour, no nonsustained VTs even during intense physical activity), and a normal complete echocardiography study, to evaluate the accuracy rate and the negative predictive value of the mTWA test in normal subjects. After the exercise mTWA test had been performed, Group A subjects were directly observed or questioned by the reference sports physician about their symptoms and athletic activity every 6 months. The follow-up was 36.1 (min–max: 34–37) months.

A second group (Group B) of 52 athletes (mean age: 28.2 ± 11.5 years) with important arrhythmias (VEB > 10/hour or nonsustained and sustained VT) was also studied with standardized diagnostic screening. They were symptomatic in 85% of the cases (prolonged palpitations, syncope, or presyncope). The diagnostic screening protocol consisted of family and personal past history, clinical evaluation, routine blood tests (including thyroid evaluation), resting and stress test ECG, Holter recording comprehensive of intense physical activity, cardiac events recording, implantable loop recording, two Doppler color flow echocardiographies, stress echo, transesophageal echo, CT, MRI, three-dimensional magnetic resonance angiography (MRA), SAECG, Head-up Tilt test, specific blood test (i.e., for myocarditis), pharmacological testing (flecainide administration, isoprotenerol infusion), genetic studies, cardiac catheterization and angiography, and endomyocardial biopsy.¹⁴ Not all tests were performed on every subject, but only according to specific needs. No arrhythmogenic pathology that was identifiable with either the noninvasive or invasive examinations was

Table 1. Clinical Characteristics of the Athletic Study Population

	Healthy (A) (n = 48)	With Arrhythmias (B) (n = 52)	
Age	24.5 ± 8.2	28.5 ± 10.3	P < 0.05
Gender (M/F)	48 M	5 F, 47 M	
Sports	Soccer 40, Basketball 3, Cycling 2, Running 1, Orienteering 2	Soccer 21, Basketball 8, Swimming 7, Running 4, Cycling 3, Rugby 3, Tennis 2, Handball 1, Racing driving 1, Horse-riding 1, Skiing 1	
Ranking	Elite 12/48	Elite 24/52	

detected in any of these cases. Only in a few cases the Doppler color flow echocardiographies were on the borderline. Group B subjects underwent an EPS with programmed ventricular stimulation after mTWA testing. They were directly observed every 6 months or according to the appearance of symptoms. The follow-up was 25.3 (min–max: 11–37) months.

Informed consent was obtained from each subject and the study was approved by the institutional review boards of the participating institutions.

Microvolt-TWA Testing

Careful skin preparation including mild abrasion and high resolution electrodes (Microvolt Sensors, Cambridge Heart, Inc., Bedford, MA) were used to minimize noise. T-wave alternans was measured during the treadmill ($n = 33$) or bicycle ($n = 67$) exercise test to achieve a heart rate (HR) of 105–110 beats/min in 15 minutes.^{15–17} Electrocardiographic measurements were carried out by the CH2000 System (Cambridge Heart, Inc., Bedford, MA), which utilized a spectral method of analysis designed to allow detection of alternans in the microvolt range of amplitude. Microvolt-TWA was prospectively defined as positive when it was sustained with an onset HR of ≤ 110 beats/min with an alternans amplitude of ≥ 1.9 microvolt and an alternans ratio of >3 in the vector magnitude lead, any orthogonal lead, or two consecutive precordial leads.¹⁷ Microvolt-TWA was defined as negative if the criteria for a positive test were not found and if no significant alternans were present for a 1-minute period while the HR was greater than or equal to 105 beats/min, and the tracing was not obscured by noise or ectopic beats. Otherwise the mTWA test was considered indeterminate.

Because of the difficulties for athletes to reach a HR of 120 beats/min, we asked them to perform a morning sport training session so that they could easily reach this rate in the afternoon, due to fatigue.

Microvolt-TWA tests were classified automatically by the Microvolt-TWA software and interpreted by two independent experts blinded to EP (electrophysiological) results with 100% concordance.

EPS Testing

Sinus and atrioventricular nodal function were assessed, then programmed ventricular stimulation

was performed at two right ventricular sites with up to three extrastimuli at 2-drive cycle length (600 ms, 400 ms).

The endpoint of EPS was the induction of monomorphic sustained VT (>30 s in duration or associated with hemodynamic compromise requiring earlier intervention, or completion of the study protocol).

RESULTS

Results are shown in Table 2.

Group A

The mTWA outcome was negative in 45 healthy competitive athletes (94%) and indeterminate in 3 (6%) due to high noise levels. During the follow-up period (36.1 months) no episode of presyncope, syncope or VT, or important arrhythmias was presented and all the professional athletes are still practicing active competitive sport. The mTWA showed a negative predictive value of 100% using the follow-up observation for severe arrhythmic cardiac events as endpoint.

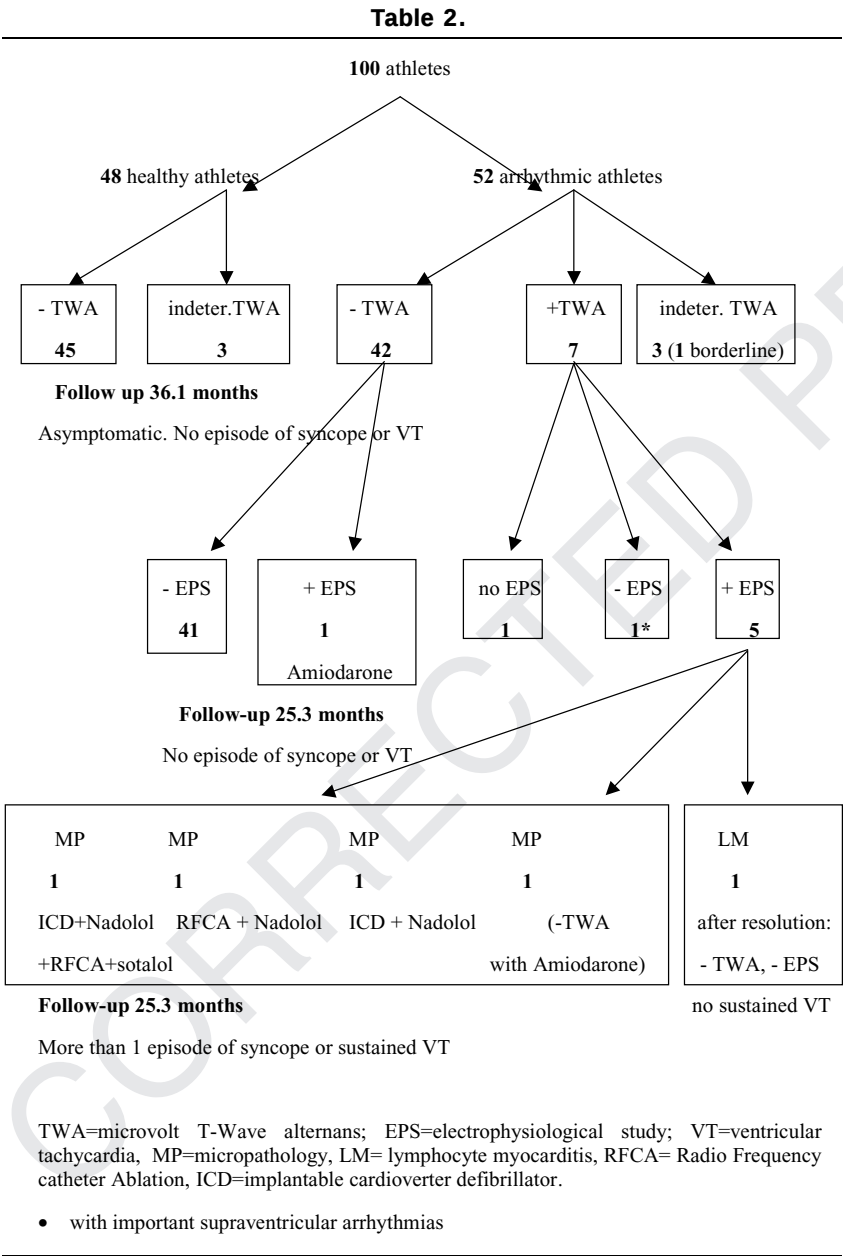
Group B

The mTWA test was negative in 42 competitive athletes (80%), positive in 7 (13%), and indeterminate in 3 (5%).

In 41 of 42 negative mTWA test athletes EPS were also negative (97%); only 1 subject on amiodarone treatment was mTWA-negative and EPS-positive for induction of sustained VTs. During the follow-up period of 25.3 months no episode of syncope or VT was documented.

The mTWA showed a negative predictive value of 97% using both EPS and the follow-up observation for severe arrhythmic cardiac events as endpoint.

Of the 7 mTWA test positives, all elite athletes, 1 refused EPS, and 5 of 6 (80%) athletes undergoing EPS were positive for sustained monomorphic VT during the test, 1 being positive only for severe supraventricular tachyarrhythmias, atrial fibrillation included. We were able to pronounce a correct diagnosis of lymphocytic myocarditis for only 1 positive subject, who tested negative on both mTWA and EPS after 6 months of recuperation. For the other four “positive” patients, we postulated a nondocumentable “micro-pathology” after rigorous cardiological screening



Q5 refractory left epicardial VT. One of four subjects who was mTWA- and EPS-positive for sustained rapid VTs became mTWA-negative on amiodarone therapy.

The mTWA showed a positive predictive value of 71% using both EPS and the follow-up observation for severe arrhythmic cardiac events as endpoint.

Only 1 of 100 athletes had an adverse reaction to abrasion (contact dermatitis) regardless of the type of electrode or sensor: The signs of dermatitis were also present in other parts of the body not abraded for the test.

DISCUSSION

Despite significant improvements in the prevention of sudden cardiac death, many individuals still remain untreated because routine clinical tests do not identify them as being at risk.^{18,19}

Various noninvasive methods, such as determination of left ventricular function or heart rate variability, as well as invasive electrophysiologic testing, are currently used for risk stratification.

Evidence is accumulating that mTWA, a fluctuation in T-wave morphology occurring on an every-other-beat basis, is a marker of increased risk for ventricular tachyarrhythmias.

The present study aims to use the mTWA test in risk stratification in the athlete with serious arrhythmias, whose sporting career is jeopardized because of the risk of life-threatening arrhythmic events.

NORMAL ATHLETES

The mTWA test used in healthy, regularly trained athletes has shown its feasibility in 94% of cases and has had negative results in all cases in which it was performed. All the athletes in question were certainly healthy and competitive, and included elite athletes. They underwent a pre-screening study that was complete with ergometric test, Holter monitoring, complete echocardiographic evaluation, and a 36-month follow-up that was negative for syncope and serious arrhythmic events. All the athletes are still competitive. This result is in agreement with previous studies carried out in normal subjects who showed a mTWA positivity of less than 1%.⁸ A new study has recently been presented showing that where mTWA and EP results are in agreement the event rate is

0% where both are negative, and 38% where both are positive.²⁰

ARRHYTHMIC ATHLETES

These were previously competitive athletes, including 24 of the elite category, who were symptomatic in 70% of the cases. They were submitted to arrhythmological screening for serious arrhythmias that would be incompatible with eligibility for athletic activity, including nonsustained and sustained TV events. The feasibility of the investigation was 94% and was indeterminate in three subjects (6%). All the arrhythmic athletes except one (1/41) with negative mTWA were also negative at the EPS test. None of them presented any significant clinical arrhythmic events, syncope, or VTs in the follow-up period of 25.3 months.

It would seem possible to conclude that the mTWA test documented a negative predictive value of 97% for EPS and follow-up.

ARRHYTHMIC ATHLETES WITH POSITIVE mTWA

Positivity occurred in a limited number of cases (7; [13%]), 1 of whom refused the EPS test. The EPS test was positive in 5 (73%) of the others.

In conclusion, in subjects with positive mTWA there was high positivity in the TV-inducible response to the EPS that made it possible to identify the arrhythmic risk of sudden death in these athletes and to proceed to appropriate therapeutic decisions in subjects with "apparently intact heart" and life-threatening arrhythmias.

LIMITATIONS

A limitation of the article was to use different endpoints of asymptomatic arrhythmia in Group A from symptomatic, documented, or inducible arrhythmia in Group B. This was necessary because of the difficulty in subjecting asymptomatic controls to an invasive study. The control population was not age- and gender-matched, but we suppose this is unlikely to influence the conclusion of the study. In Group B therapy of patients could potentially influence the clinical outcomes with not-known mechanisms.

CONCLUSION

Microvolt TWA seems to be a useful, noninvasive, and feasible tool for assessing arrhythmic risk in a population of competitive athletes including those of the elite category. The mTWA test showed a high negative predictive value utilizing an EPS and the arrhythmic events along the follow-up as endpoint. The limited number of subjects who were positive to the mTWA test means that further verification is necessary to achieve a numerical significance of the sample. All these athletes were, however, subjects with a high risk of sudden arrhythmic death.

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