

## Original article

# Ventricular arrhythmias in competitive athletes: risk stratification with T-wave alternans

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**ABSTRACT:** Introduction: *Aim of our study is to evaluate the role of TWA to stratify the risk of sudden cardiac death in athletes (Ath) with complex ventricular arrhythmias (VA), and to document a possible correlation between TWA and electrophysiological testing (EES) results.*

Methods: *We studied 43 Ath with VA (31 M, mean age 34 ± 12 years). In all cases a cardiological evaluation was performed, including TWA and EES. The patients were evaluated during a follow-up of 25 ± 22 months. The end-point was the occurrence of sudden death or malignant ventricular tachyarrhythmias (VT).*

Results: *TWA was negative in 28 Ath (65%), positive in 8 (19%) and indeterminate in 7 (16%). All subjects with negative TWA did not show induction of VT at EES, with significant correlation between negative TWA and negative EES ( $p < 0.001$ ). All Ath with positive TWA also had VT induced by a EES, but without significant correlation between positive TWA and positive EES. In 2 Ath with undetermined TWA (29%) VT were induced at EES. Our data did not show significant correlation between indeterminate TWA and positive or negative EES. However, logistic regression analysis showed significant correlation between abnormal TWA test (positive or indeterminate) and inducibility of VT at EES ( $p < 0.001$ ). During follow-up we observed a significant difference in end-point occurrence between Ath with negative or positive TWA and between Ath with negative or positive EES.*

Conclusion: *TWA confirm its role as a simple and non-invasive test, and it seems useful for prognostic stratification of Ath with VA. (Heart International 2007; 3: 58-67)*

**KEY WORDS:** *T-wave alternans, Sudden death, Ventricular arrhythmias, Sport activity*

## INTRODUCTION

Sudden cardiac death (SCD) related to ventricular tachyarrhythmia in young athletes is a dramatic event that has emotional and social impact on the media and the medical community. Ventricular ectopic beats (VEB), even with frequent and/or complex forms, have frequently been described on 24-hour ECG in 25-65% of athletes. For athletes with ventricular arrhythmias who have no evidence of underlying heart disease or who have an unsuspected cardiovascular disease, identifying subjects at risk of serious ventricular tachyarrhythmias is often problematic. Corrado et al (1) reported

that, while sporting activity is not the cause of sudden cardiac death, it can trigger cardiac arrest in subjects whose cardiovascular conditions engender a risk of life-threatening arrhythmias during athletic activity. Frequent ventricular premature beats with complex morphology and couplets and non-sustained ventricular tachycardia (NSVT) may be detected in a competitive athlete during ambulatory clinical screening, without evidence of underlying cardiovascular disease. Despite the increased availability of non-invasive and invasive clinical diagnostic methods, such cases pose a diagnostic dilemma for physicians called upon to assess the subject's eligibility to practice sport. It is necessary to

make a precise differential diagnosis between an expression of athlete's heart, which may mimic cardiovascular disease, and "silent" cardiovascular abnormalities that may progress to sustained tachyarrhythmias and/or sudden death with long-term intensive training. Systematic diagnostic methods, including ECG, Holter monitoring, stress testing and echocardiography, are sometimes unable to reveal an underlying structural heart disease, and further evaluations are required in order to determine whether the arrhythmia is benign or potentially life-threatening. Many non-invasive markers of SCD, such as depressed left ventricular ejection fraction, late potentials, QT dispersion, heart rate variability and baroreflex sensitivity, play a role in risk stratification, but are limited by their low specificity. It is crucial to precisely identify athletes at increased risk for serious ventricular tachyarrhythmias in order to exclude them from competitive sport and implement an effective strategy to prevent sudden cardiac death.

Specific forms of electrocardiographic alternans related to cardiac repolarization abnormalities have recently emerged as a cause of serious ventricular arrhythmias. In the 1980s, Adam and Smith (2,3) developed the spectral analysis method for detecting microvolt T-wave alternans in experimental animals and, subsequently, in humans (4,5). These studies showed that microvolt T-wave alternans is a reliable non-invasive risk marker of cardiac electrical vulnerability and a predictor of ventricular arrhythmias (4-13). Electrical alternans is defined as beat-to-beat variation in the vector, amplitude and/or morphology of electrocardiographic signals, due to localized alternation in action potential duration. The presence of amplitude alternans of the T-wave at a periodicity of 0.5 cycles/beat defines T-wave alternans. T-wave alternans (TWA) is a promising new non-invasive clinical tool for identifying patients at risk for sudden cardiac death in a diverse patient population. The usefulness of TWA in predicting the risk of ventricular tachyarrhythmias has been widely reported in several clinical conditions, including coronary artery disease, non-ischemic cardiomyopathy, congestive heart failure and in patients with implantable cardiac defibrillators (14). Recently, several authors have documented the high negative predictive value of TWA in patients with heart disease and low ejection fraction (15,16).

The aim of our study was to evaluate the predictive

value of T-wave alternans in stratifying the risk of severe ventricular tachyarrhythmias and sudden cardiac death in athletes with ventricular arrhythmias, and to investigate the relationship between TWA and the results of programmed ventricular stimulation during electrophysiologic endocavitary study.

## MATERIAL AND METHODS

### *Study protocol*

In this prospective study, we enrolled 43 consecutive athletes (31 males, 12 females), with no history of cardiovascular disease, with age  $34 \pm 11$  years involved in different types of sports. All subjects had been referred to our Cardiology Department following the detection of ventricular arrhythmias during eligibility screening for competitive sports. These arrhythmias included frequent premature ventricular complexes (PVC), arbitrarily defined as  $PVC \geq 2,000$  on 24-h ambulatory Holter monitoring (28 athletes), or NSVT (13 athletes) or sustained ventricular tachycardia (SVT) (2 athletes). All patients underwent a basic cardiological evaluation, which consisted of anamnesis, physical examination, routine blood tests (including fT3, fT4, TSH), ECG, Holter recording, echocardiogram and maximal exercise test. Furthermore, pharmacological testing, specific blood test for myocarditis, coronary angiogram, right and left ventriculogram, magnetic resonance imaging and endomyocardial biopsy were performed, depending on the basic cardiological evaluation. All athletes then underwent electrophysiologic study (EES) with programmed ventricular stimulation (PVS) and microvolt T-wave alternans (TWA) testing. Informed consent was obtained from each subject.

### *T-wave alternans test*

T-wave alternans was measured during a bicycle exercise test after careful skin preparation, including mild abrasion, and placement of high-resolution electrodes (Microvolt Sensors, Cambridge Heart, Inc., Bedford, MA) in order to minimize signal noise. Electrocardiographic leads were placed in the standard 12-lead positions and in a Frank orthogonal configuration (X,Y,Z). Electrocardiographic signals were amplified and digital-

ized, and measurements were taken by means of the CH2000 System (Cambridge Heart, Inc., Bedford, MA) using the spectral method. This technique involved measuring the amplitudes of corresponding points in 128 consecutive T-waves, at the same time after the QRS complex. The amplitude fluctuation was then subjected to spectral analysis. The software then calculated:

- 1) the alternans voltage ( $V_{alt}$ ), defined as the difference in voltage between the overall mean beats and either the even-numbered or odd-numbered mean beats;
- 2) the alternans ratio (K), a measure of the significance of microvolt TWA, defined as the ratio of alternans power divided by the standard deviation of the noise in the reference frequency band. A  $K \geq 3$  was considered to be significant.

TWA was classified as positive if it was sustained (duration  $\geq 1$  min) with onset at heart rate  $\leq 110$  bpm,  $V_{alt} \geq 1.9$  V and  $K \geq 3$ . TWA was considered negative if it did not meet the positivity criteria and if at least 1 minute of artifact-free data was available at heart rate  $\geq 105$  bpm. Otherwise, the test was classified as indeterminate.

Positive or indetermined T-wave alternans test were considered as an abnormal result (16).

### *Electrophysiologic study*

Electrophysiologic study was performed in the non-sedated, postabsorptive state. A 6-French tetrapolar recording and stimulating catheter was inserted through the right femoral vein and positioned in the right ventricle. A venous access was created in the right femoral vein and a venous introducer was inserted. Thereafter, a quadripolar catheter was advanced to the right ventricular apex under fluoroscopic control and ECG monitoring. Programmed ventricular stimulation was performed through an automatic stimulator (Micropace EPS 320) with up to three extrastimuli at three drive cycle lengths (600, 500, 400 msec). The same protocol was then repeated with the catheter placed in the right ventricular outflow tract. EES was considered positive if SVT or ventricular fibrillation (VF) was induced.

### *Follow up*

All patients were directly evaluated every 6 months and in the event of symptoms. The occurrence of seri-

ous ventricular arrhythmias (SVT or VF) or SCD was regarded as the end-point. SCD was defined as unexpected death occurring within 1 hour of the onset of symptoms or during sleep. The mean follow up was  $25 \pm 22$  months.

### *Statistical analysis*

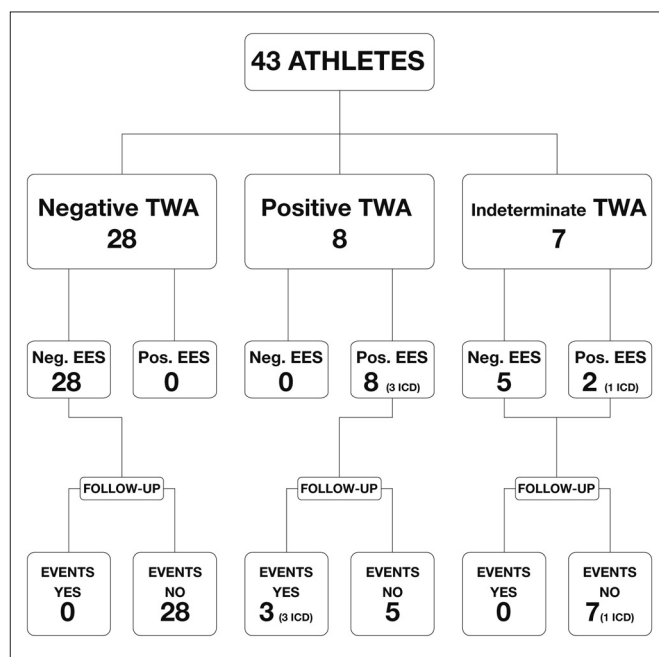
The data were firstly processed using a hierarchical clustering procedure, in order to highlight possible differences among groups of the main available variables (age, sex, ejection fraction, sports activity, clinical presentation) in relationship with the TWA (positive, negative and indeterminate) and EES (positive and negative) variables.

In the following we carried out a set of logistic regression analyses where the dependent dichotomous variables were respectively TWA (positive, negative and indeterminate) and EES (positive and negative), to evaluate the significance of the differences among groups pointed out by the clustering procedure.

Finally, in order to establish a possible significant influence of the TWA and EES variables on the time free from malignant arrhythmic events, we evaluated the follow-up data by generating Kaplan-Meier survival curves where the endpoint was the occurrence of a malignant ventricular arrhythmias and the grouping variables were TWA (positive, negative and indeterminate) and EES (positive and negative).

## RESULTS

At the end of cardiological screening, a structural heart disease was identified in 7 patients (16%). Specifically, arrhythmogenic right ventricular dysplasia was diagnosed in 3 patients and myocarditis in 2. The diagnosis of myocarditis was made on the basis of magnetic resonance imaging, which showed areas of hyper-enhancement with "patchy" distribution, and was confirmed by endomyocardial biopsy. Furthermore, in 2 patients, the echocardiographic picture was borderline for the diagnosis of early-stage dilated cardiomyopathy. Pharmacological antiarrhythmic therapy was started in 15 patients (35%): 7 (47%) were affected by structural heart disease, while in 8 (53%) there was no diagnosis of evident heart disease, therapy being started because



**Fig. 1** - Results of TWA test and EES and occurrence of spontaneous ventricular arrhythmias during follow-up in study population. In brackets it is specified the number of patients who received ICD.

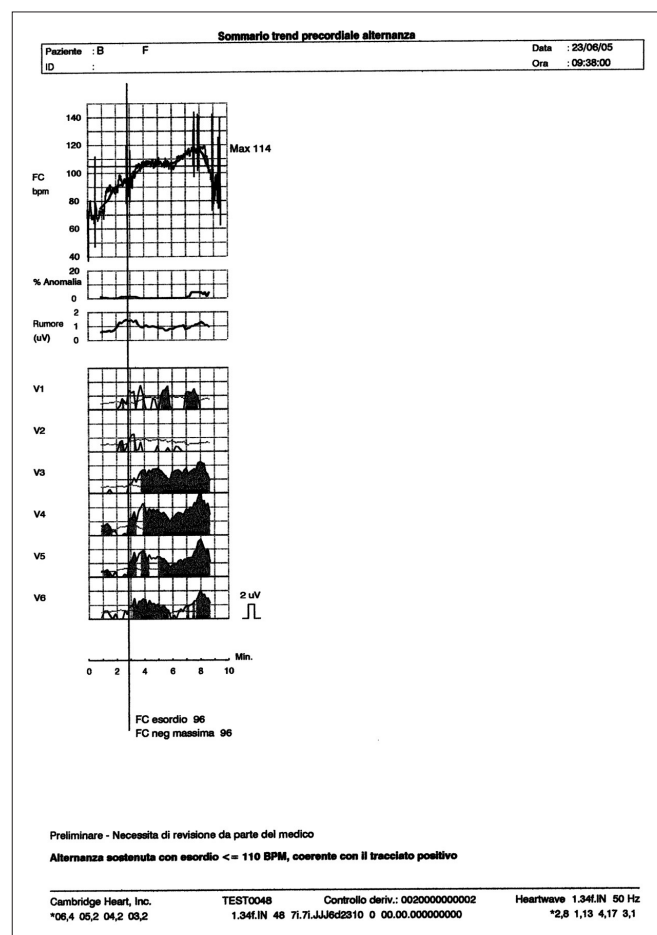
the patients were heavily symptomatic for palpitations. Antiarrhythmic therapy consisted of amiodarone in 7 patients (47%), beta blockers in 3 (20%), sotalol in 3 (20%) and an association of amiodarone and beta blockers in 2 (13%). After cardiological evaluation, an ICD was implanted in 4 subjects (9%): 3 affected by arrhythmogenic right ventricular dysplasia and 1 with myocarditis (Fig. 1).

### Microvolt-TWA test

Microvolt-TWA testing proved negative in 28 patients (65%), positive in 8 (19%) and indeterminate because of excessive noise in 7 (16%) (Fig. 2). Therefore, 15 patients (35%) showed abnormal microvolt-TWA testing. There were no significant differences between patients with positive, indetermined or negative TWA in terms of age, sex, ejection fraction, sports activity, and clinical presentation (Tab. I).

### Electrophysiologic study

Malignant ventricular arrhythmias were induced through programmed ventricular stimulation in 10 pa-



**Fig. 2** - Positive TWA test in a 23-year-old male athlete with ventricular arrhythmias.

tients (23%), and were not induced in 33 (77%) (Fig. 3). There were no significant differences between these patients in terms of age, sex, clinical presentation, ejection fraction, sports activity and clinical presentation.

### Correlation between TWA test and electrophysiologic study

Malignant ventricular arrhythmias were not inducible during electrophysiologic study in any of the subjects in whom the TWA test was negative. Logistic regression analysis demonstrated a significant correlation between a negative microvolt-TWA test and non-inducibility of ventricular arrhythmias during electrophysiologic study ( $p < 0.001$ ). In contrast, in all patients with a positive TWA test, ventricular tachyarrhythmias were inducible during



**Fig. 3** - Induction of VF during programmed ventricular stimulation (double extrastimulus) in the same patient of Figure 2.

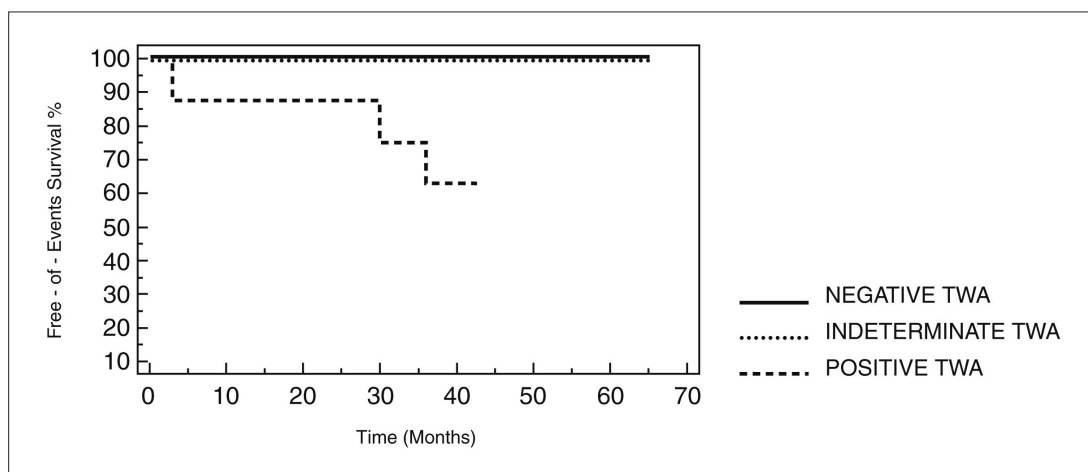
**TABLE I** - COMPARISON OF CLINICAL AND DEMOGRAPHIC CHARACTERISTICS BETWEEN PATIENTS WITH NEGATIVE, INDETERMINATE AND POSITIVE TWA

	Negative TWA	Indeterminate TWA	Positive TWA	p
Age	34 ± 13	33 ± 10	34 ± 9	p=NS
Males	21 (75%)	4 (57%)	6 (75%)	p=NS
Sport				
- Soccer	5 (18%)	2 (28%)	2 (25%)	p=NS
- Running	7 (25%)	3 (44%)	2 (25%)	p=NS
- Skiing	2 (7%)	1 (14%)	0 (0%)	p=NS
- Cycling	4 (14%)	1 (14%)	2 (25%)	p=NS
- Motorcycling	1 (4%)	0 (0%)	0 (0%)	p=NS
- Volleyball	4 (14%)	0 (0%)	1 (12.5%)	p=NS
- Swimming	4 (14%)	0 (0%)	0 (0%)	p=NS
- Climbing	1 (4%)	0 (0%)	0 (0%)	p=NS
- Gymnastics	0 (0%)	0 (0%)	1 (12.5%)	p=NS
EF (%)	66 ± 5	66 ± 5	65 ± 4	p=NS
Arrhythmias				
- VEBs	19 (68%)	5 (71%)	4 (50%)	p=NS
- NSVTs	9 (32%)	2 (29%)	2 (25%)	p=NS
- SVTs	0 (0%)	0 (0%)	2 (25%)	p=NS

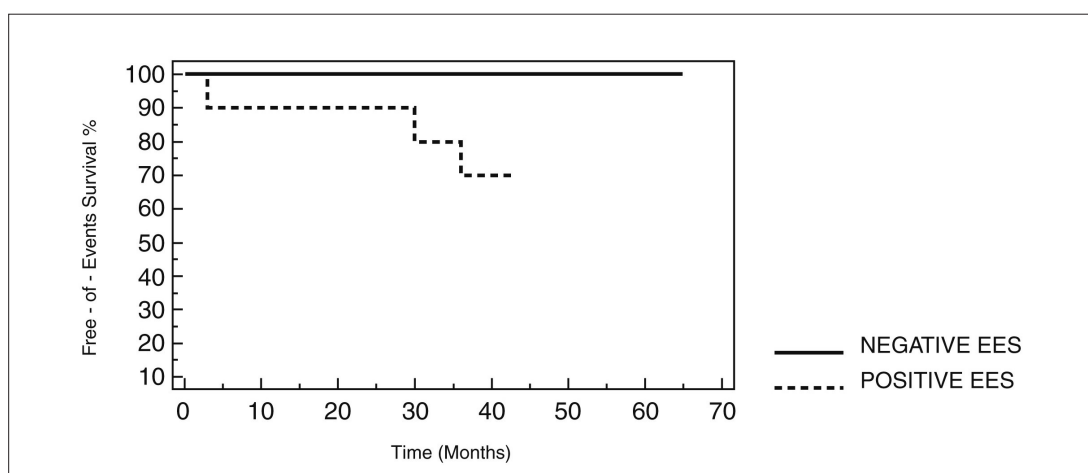
electrophysiologic study (SVT requiring external defibrillation in 6 patients and ventricular fibrillation in 2 patients). However, logistic regression analysis did not show a significant correlation between a positive TWA test and inducibility of ventricular arrhythmias during

electrophysiologic study. Of the patients in whom the TWA test was indeterminate, 2 (29%) showed inducibility of ventricular arrhythmias during electrophysiologic study (sustained ventricular tachycardia requiring external defibrillation in all patients), while in 5 (71%) the

**Fig. 4** - Kaplan-Meier survival curves comparing end-point occurrence between patients with negative, indeterminate and positive TWA.



**Fig. 5** - Kaplan-Meier survival curves comparing end-point occurrence between patients with negative and positive EES.



**TABLE II** - CORRELATION BETWEEN TWA TEST AND ELECTROPHYSIOLOGIC STUDY

	Negative EES	Positive EES	p
Negative TWA	28 (100%)	0 (0%)	p<0.001
Indeterminate TWA	5 (71%)	2 (29%)	p=NS
Positive TWA	0 (0%)	8 (100%)	p=NS
Abnormal TWA (Indeterminate + Positive)	5 (33%)	10 (67%)	p<0.001

electrophysiologic study was negative. Logistic regression analysis did not show a significant correlation between an indeterminate TWA test and inducibility or

non-inducibility of ventricular arrhythmias during electrophysiologic study (p>0.05). However, logistic regression analysis showed significant correlation between abnormal TWA test (positive or indeterminate) and inducibility of ventricular arrhythmias at electrophysiologic study (p<0.001). Our data demonstrate that the TWA test has a positive predictive value (PPV) of 100% for positive TWA test and of 67% for abnormal TWA, and a negative predictive value (NPV) of 100% in predicting the inducibility of ventricular arrhythmias during electrophysiologic study (Tab. II).

*Follow up*

During a mean follow-up of 25 months, 3 patients (7%) experienced an arrhythmic event regarded as the end-point of the study (VF in 1 patient, SVT in 1 and

both arrhythmias in 1). The difference in end-point occurrence rate was significant between patients with a negative TWA test (0%) and those with a positive TWA test (37.5%) ( $p < 0.01$ ). The difference in end-point occurrence was significant also considering patients with negative (0%) or abnormal TWA test (20%) ( $p < 0.05$ ). In our study, the TWA test predicted the occurrence of malignant ventricular arrhythmias with an NPV of 100% and a PPV of 37.5% for positive TWA and 20% for abnormal TWA (Fig. 4).

Similarly, there was a significant difference in end-point occurrence rate between patients in whom the electrophysiologic study proved positive and those in whom it was negative (30% vs 0%) ( $p < 0.01$ ). The electrophysiologic study predicted the occurrence of malignant ventricular arrhythmias with an NPV of 100% and a PPV of 30% (Fig. 5).

## DISCUSSION

Ventricular ectopic beats have been detected by surface electrocardiogram in 1% of the general population, and by 24-hour ambulatory ECG Holter monitoring in 40% to 75% of apparently healthy subjects (16-19). However, athletes constitute a particular population of healthy people, in that they show a high prevalence of morphological cardiac alterations (a condition known as athlete's heart), electrocardiographic abnormalities (wave voltage modification, ST and T wave changes) and frequent and/or complex ventricular beats. Athletes' hearts undergo morphological adaptations which can mimic a cardiovascular disease. Consequently, it is not easy to make a differential diagnosis with heart diseases at risk of sudden death, such as, for example, hypertrophic and dilated cardiomyopathy and arrhythmogenic right ventricular cardiomyopathy, which are often difficult to diagnose in their initial phase. The onset of these alterations in the athlete's heart can be due to adaptation to dynamic sports activity and the impact of training on cardiac cavity size. Several prospective studies have shown that detraining and physical deconditioning can result in cardiac reverse remodeling, with a reduction in cavity size, and in the reversibility of ventricular arrhythmias, which is complete in about 25% of subjects and partial in 50% (20-22). Biffi et al (23) reported that the presence of frequent and/or com-

plex ventricular beats in competitive athletes did not indicate an adverse prognosis in subjects without underlying structural heart disease. Nevertheless, the detection of frequent and complex ventricular arrhythmias in a competitive athlete requires particular attention on the part of cardiologists and sports physicians in order to determine whether these arrhythmias have a good prognosis or are potentially life-threatening. In recent studies, several authors have reported that competitive athletes with silent arrhythmogenic heart disease have a higher risk of sudden death than sedentary subjects of the same age and with a similar latent cardiac substrate (24-27).

When frequent and complex ventricular arrhythmias are diagnosed in a young athlete, physicians are faced with medical, ethical and legal problems. Firstly, it is mandatory to clarify whether there is an undiagnosed structural heart disease. If diagnostic screening does not demonstrate the presence of heart disease, there are other issues to consider: the role of intense training on the arrhythmic pattern in young athletes and the potential usefulness of detraining, the criteria of eligibility for sports activity, the importance of the athlete's own wishes and the pressure exerted by family members and coaches.

The value of TWA in predicting ventricular tachyarrhythmias in patients with congestive heart failure and with previous myocardial infarction has been evaluated in several clinical studies (7, 13, 28). These reports document a highly significant statistical association between positive TWA and ventricular tachyarrhythmic events. Gehi et al (29) recently conducted a meta-analysis of the results of 19 studies carried out on a wide range of subjects, including those with ischemic or non-ischemic congestive heart failure, coronary artery disease, athletes and healthy individuals. These authors found that the risk of tachyarrhythmic events was nearly four-fold higher in subjects in whom TWA testing was positive than in those in whom it was negative, and that there was no difference between patients with ischemic or non-ischemic heart failure. The positive predictive value of TWA varied in the meta-analysis from 0% to 51%, depending on the patient population studied, while the negative predictive value was 97% (29). Very few data are available on the risk stratification of sudden cardiac death and severe ventricular tachyarrhythmic events in athletes with ventricular arrhythmias. In a

multi-center study of 52 competitive athletes with severe arrhythmias, Furlanello et al (27) found a high negative predictive value of TWA when both programmed ventricular stimulation and follow up were used as end-points. Unfortunately, the limited number of athletes with positive TWA in this study did not allow to obtain a significant positive predictive value.

In our population of athletes undergoing TWA evaluation and programmed ventricular stimulation, we documented a significant correlation between TWA test negativity and non-inducibility of ventricular arrhythmias through programmed ventricular stimulation. In contrast, our study did not show a significant correlation between positive or indeterminate TWA testing and the result of electrophysiologic study, although we found a non-significant trend towards correlation with inducibility of ventricular arrhythmias. However, this correlation become significant if we consider patients with abnormal TWA (positive and indeterminate). The pathophysiological reason for this trend may be that TWA testing often proves indeterminate in patients with very frequent and complex ventricular ectopic beats; in such subjects, programmed ventricular stimulation can induce ventricular arrhythmias, and arrhythmic events may occur during follow up.

In our study, TWA testing showed a very high NPV (100%) and PPV (100% for positive TWA and 67% for abnormal TWA) in predicting the result of programmed ventricular stimulation. However, a larger study population may be needed in order to demonstrate a significant correlation between positive and indeterminate TWA testing and inducibility of ventricular arrhythmias during electrophysiologic study.

### *Comparison between TWA and programmed ventricular stimulation in different populations*

Review of a number of prospective studies conducted in a variety of clinical patient populations, including subjects with non-ischemic or ischemic cardiac disease, syncope, dilated cardiomyopathy and congestive heart failure, suggests that the occurrence rate of severe ventricular tachyarrhythmias in patients with positive TWA is equivalent to that of ventricular tachyarrhythmias in patients with a positive result on programmed ventricular stimulation during electrophysiologic endocavitary study. The event rate among patients

with negative TWA is low, and in many cases lower than the event rate in patients with a negative response to programmed ventricular stimulation (7,12,13,28). Rosenbaum et al (4) evaluated T wave alternans as a predictor of severe arrhythmic events in a group of 83 patients who underwent programmed ventricular stimulation for previous tachyarrhythmic events. During a follow-up of 20 months, Kaplan-Meier survival analysis showed that TWA had a good predictive value, in that the rates of arrhythmia-free survival were 94% in patients with negative TWA and 19% in those with positive TWA.

In a multi-center trial of 313 patients undergoing programmed ventricular stimulation and TWA testing, Gold et al (7) documented that TWA was a highly significant predictor of major ventricular tachyarrhythmias. During follow up, the presence of positive TWA was associated with a relative risk of 10.9, versus 7.1 for EES and 4.5 for signal-averaged electrocardiography (SAECG), for the end-point of sudden cardiac death and sustained ventricular tachycardia, ventricular fibrillation or ICD implantation. In many studies, TWA has proved to be equivalent to programmed ventricular stimulation and better than SAECG in the risk stratification of patients for life-threatening arrhythmias (4, 7, 11, 30-32).

In our study we found a significant difference between patients with positive and negative TWA tests with regard to the occurrence of sudden death, ventricular fibrillation and sustained ventricular tachycardia during an average follow-up of 25 months. Kaplan-Meier survival analysis showed a 100% rate of end-point-free survival in patients with a negative TWA test and a 62.5% rate in subjects with a positive TWA test, suggesting that TWA can also predict spontaneous malignant arrhythmic events in athletes with ventricular arrhythmias. The difference was significant also considering patients with abnormal TWA, in whom there was a 80% rate of end-point-free survival. The NPV (100%) and PPV (37.5% for positive TWA test and 20% for abnormal TWA test) obtained in our study are comparable to those reported by Gehi et al (29) in different populations.

### *TWA and programmed ventricular stimulation in competitive athletes*

Few studies have evaluated T wave alternans as a predictor of arrhythmic events in competitive athletes, and little information is available on the comparison of



TWA and programmed ventricular stimulation in arrhythmia risk stratification in this population (27). In our study, the predictive accuracy of invasive programmed ventricular stimulation during EES was similar to that of TWA. These results, which were obtained in a single-center experience, are in line with those from a multi-center study by Furlanello et al (27) on 52 competitive athletes, and suggest that TWA may play an important role in the prognostic stratification of athletes with ventricular arrhythmias. Unlike electrophysiological study, which is an invasive procedure requiring hospitalization, TWA testing is non-invasive, cheap, easy to perform and repeatable during follow-up.

## CONCLUSION

TWA is an effective non-invasive predictor of the risk of severe ventricular tachyarrhythmias and sudden car-

diac death in competitive athletes, its efficacy being at least comparable to that of invasive programmed ventricular stimulation. In particular, T wave alternans has a high negative predictive value. In athletes with ventricular arrhythmias TWA seems to be useful for improving risk stratification for sudden cardiac death.

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