Optimal Target Heart Rate for Exercise-Induced T-Wave Alternans

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Objectives: This study was conducted to determine the optimal target heart rate (HR) for the use of exercise-induced T-wave alternans (TWA) as an index for risk of malignant ventricular tachyarrhythmias.

Background: Rate-dependent TWA is an index of vulnerability to ventricular tachyarrhythmias. However, false positive TWA was reported to occur in normal subjects at high HR.

Methods: Two groups were evaluated: Group I: 50 patients with malignant ventricular tachyarrhythmias, who received an implantable cardioverter-defibrillator (ICD); and Group II: 55 age-matched normal subjects. In both Groups, TWA was evaluated during symptom-limited bicycle exercise test.

Results: Peak HR during exercise test was 103 ± 17 beats/min in Group I, versus 124 ± 18 beats/min in Group II ($P < 0.001$). In Group I, 4 patients were excluded from analysis, due to high noise level or frequent ectopy during exercise. Out of the remaining 46 patients, TWA was present in 28 patients (61%), and absent in 18 (39%). In group II, TWA was present in four subjects (7%), and absent in 51 (93%). HR at the onset of TWA was 91 ± 11 /min in Group I, and 119 ± 12 /min in Group II ($P < 0.001$). Receiver operated characteristics curves demonstrated that a HR of 115 beats/min was the cutoff with the best sensitivity and specificity for TWA (100 and 96%, respectively). None of the patients in Group I developed TWA at HR > 115 beats/min, while two out of four in Group II had TWA at HR > 115 /minutes. However, 13 patients in Group I who had no TWA were unable to exercise to a peak HR > 115 beats/min, compared to nine subjects in Group II.

Conclusions: A target HR of 115 beats/min was highly sensitive and specific for determination of exercise-induced TWA as an index of risk of malignant ventricular tachyarrhythmias. However, a significant number of patients may not be able to achieve this target HR, resulting in an indeterminate test. The value of pharmacologic testing in this group should be assessed.

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alternans; electrocardiography; exercise test; ventricular arrhythmia

Alternans of the configuration and/or duration of the T wave, usually referred to as T-wave alternans (TWA) has been described in several clinical situations¹⁻⁴ and may reflect the presence of dispersion of ventricular repolarization, a recognized substrate for malignant ventricular tachyarrhythmias.⁵

Recently, digital processing techniques for detection of subtle degrees of TWA alternans, which may not be visible on conventional electrocardiographic (ECG) recordings, have been introduced.⁶⁻⁸ Microvolt level TWA seems to correlate with vulnerability to ventricular tachyarrhythmias.^{6,9-12}

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However, TWA is rate-dependent and microvolt TWA could develop in normal subjects at sufficiently high heart rate (HR)¹³ In several studies of TWA, a target HR of 100 to 120 beats/min was empirically applied.^{6,8-12} In the present study, the optimal HR for the use of TWA as a index of ventricular vulnerability was systematically investigated in patients with malignant ventricular tachyarrhythmias compared to an age-matched normal group.

METHODS

Patient Selection

This study was approved by the Institutional Review Board and an informed consent was obtained from each individual. Group I comprised consecutive patients who were considered candidates for implantable cardioverter-defibrillator (ICD), based on the presence of symptomatic ventricular tachycardia (VT)/ventricular fibrillation (VF), or inducible sustained VT in high-risk patients. All Group I patients had coronary angiography and programmed ventricular stimulation prior to ICD implantation, according to a standard protocol. Briefly, up to three extrastimuli were delivered to two right ventricular sites at two basic drive cycle lengths (600 and 400 ms). The endpoint of programmed stimulation was induction of a sustained ventricular tachyarrhythmia or completion of the protocol. Patients were excluded from TWA determination if they were unable to exercise, had atrial fibrillation or a permanent pacemaker, or could not tolerate withdrawal from beta-blocking and antiarrhythmic drugs prior to testing.

Group II was selected to include age-matched subjects with no history of organic heart disease, normal 12-lead and stress ECG tracings, and no significant abnormalities detected by echocardiogram and/or coronary angiography.

Exercise Testing

Bicycle exercise testing and TWA determination were performed with commercially available equipment (CH2000, Cambridge Heart, Inc., Bedford, MA, USA) and according to standard techniques.^{8,9} After electrode placement to record standard 12-lead ECG leads and Frank orthogonal leads (X, Y, and Z), 5 minutes of resting ECG tracing were obtained. Then, bicycle ergometry was started with increasing workloads at 3-minute intervals,

and the patients were asked to pedal at 1/3 or 2/3 of their HR to keep the frequency of motion artifacts distinct from the alternans frequency. The test was terminated when maximal HR was achieved or the patient complained of fatigue, dyspnea, or chest pain. Continuous ECG recordings were obtained during the exercise phase and for at least 5 minutes of the recovery phase and sampled at 1 KHz with 2.5 μ V resolution, filtered (bandwidth 0.05 to 250 Hz), and digitized (1,000 Hz with 12-bit resolution).

TWA Determination

This was performed using previously published spectral methods.^{6,8,9} The onset and the end of the T wave were selected by a computer algorithm. Fluctuations in T-wave morphology were analyzed obtaining the power spectrum of beat-to-beat fluctuations in the amplitude of corresponding sample points in a series of time-aligned ECG complexes. Power spectra calculated for each point within the T wave were averaged to create a composite power spectrum. In this spectrum, alternans appeared as a peak corresponding to a frequency of 0.5 cycles/min. Two indices were derived from the composite power spectrum: (1) the alternans voltage, (V alt), which is the square root of the alternans power (i.e., the height of the peak above the background noise level); V alt is measured in μ V; and (2) the alternans ratio (k), which is the alternans power measured in units of standard deviations of the background noise. K is a measure of the statistical significance of the alternans peak, representing the number of standard deviations by which it exceeds the background noise level. Trend plots were created by computing V alt at intervals of 16 beats throughout the exercise test. The trend plots also identified data segments suitable for analysis, based on the absence of excessive noise ($> 1.9 \mu$ V), frequent ectopy ($> 10\%$ of total beats), and improper respiratory or pedaling rate.

Definitions

Sustained TWA was considered to be present when V alt was $> 1.0 \mu$ V at rest or $> 1.9 \mu$ V during exercise and $k \geq 3$ for > 1 artifact-free minute in ≥ 1 orthogonal leads or > 1 adjacent precordial leads. The HR at the onset of alternans was assessed. Peak HR during exercise test was tabulated in all Group I and II patients.

Table 1. Clinical Characteristics of 46 Group I Patients with Analyzable TWA Recordings during Symptom-Limited Bicycle Exercise Test

	TWA Present (n = 28)	TWA Absent (n = 18)	P Value
Coronary artery disease (n)	26	17	NS
Nonischemic dilated cardiomyopathy (n)	2	1	NS
Left ventricular ejection fraction (%)	29 ± 9	36 ± 13	0.036
Spontaneous arrhythmia (n)			
Nonsustained VT	7 (25%)	2 (11%)	NS
Sustained VT	17 (61%)	12 (67%)	NS
VF	4 (14%)	4 (22%)	NS
Induced arrhythmia (n)			
No sustained VT/VF	3 (11%)	4 (22%)	NS
Sustained VT	24 (86%)	12 (67%)	NS
VF	1 (4%)	2 (11%)	NS

NS = not significant.

Statistical Analysis

All values are expressed as mean ± standard deviation. Comparisons between groups were made by *t*-test, chi-square, or Fisher's exact test, as appropriate. A probability (P) value < 0.05 was considered significant. Receiver operated characteristics curves were calculated to evaluate the target HR with the best sensitivity and specificity for TWA detection. HR values between 90 and 130 beats/min, at 1-beat intervals, were included in this analysis.¹⁴

RESULTS

Patient Characteristics

Group I included 50 patients (46 males, 4 females, age: 66 ± 8 years, range: 42-80). The indication for ICD was symptomatic VT in 33 patients, VF in eight, and nonsustained VT with inducible sustained VT in nine. Group II included 55 normal male subjects with a mean age of 63 ± 7 years (range: 45-81). Peak HR during exercise test was 103 ± 17 beats/min in Group I, versus 124 ± 18 beats/min in Group II (P < 0.001).

TWA Determination

In Group I, four patients showed high noise level or frequent ectopy during exercise and were excluded from the analysis. Of the remaining 46 patients, TWA was present in 28 (61%), and absent in 18 (39%). There was no statistically significant difference in the etiology of organic heart disease, as well as the type

of spontaneous and induced ventricular tachyarrhythmias in Group I patients in whom TWA was present, compared to those in whom TWA was absent (Table 1). However, left ventricular ejection fraction was lower in patients with TWA (P = 0.036) (Table 1). The HR at the onset of TWA was 91 ± 11 beats/min. Figure 1 shows an example of TWA during exercise in a patient from Group I.

In Group II, TWA was present in four cases (7%). The HR at the onset of TWA was higher in Group II compared to Group I (119 ± 12 vs 91 ± 11 beats/min, P < 0.001).

TWA Detection

Figure 1. Sensitivity, specificity, and total accuracy curves plotted to identify the optimal target HR for TWA detection. HR: heart rate (in beats/min).

Figure 2. TWA determination during bicycle exercise test in a 62-year-old male patient with coronary artery disease, prior myocardial infarction, spontaneous and inducible sustained monomorphic ventricular tachycardia. Marked TWA developed when the patient's heart rate reached 85 beats/min during stage I of exercise, increased until peak exercise, and gradually decreased during the recovery phase.

Figure 2 illustrates the sensitivity and specificity curves plotted to identify the optimal target HR for TWA detection. A HR ≤ 115 beats/min showed the best sensitivity (100%) and specificity (96%). None of the patients in Group I developed TWA at HR > 115 beats/min, while two out of four in Group II had TWA at HR > 115 beats/min. However, 13 of 18 patients in Group I who did not show TWA could not reach HR > 115 beats/min, compared to 9 of 55 subjects in Group II.

DISCUSSION

The present study was designed to establish in a rigorous statistical fashion the optimal target HR for the use of exercise-induced TWA as an index for ventricular vulnerability. For the purpose of this analysis, we investigated two groups of age-matched elderly subjects. Group I comprised patients who were "true positive" high risk for malignant ventricular tachyarrhythmias, while Group II consisted of subjects considered "true negative" for

arrhythmic risk. The best sensitivity and specificity could be achieved at a target HR of 115 beats/min (100 and 96%, respectively). A target HR of 110 beats/min had a similar specificity (98%), but a lower sensitivity (82%). Lower target HRs were associated with rapid decline of the sensitivity of the test, while maintaining a relatively high specificity.

This study was not designed to investigate the predictive value of exercise-induced TWA for malignant ventricular tachyarrhythmias at large or to compare it with other indices of arrhythmic risk, such as programmed stimulation or the signal averaged ECG. However, in Group I, that comprised patients at very high risk for arrhythmic death in whom the ICD was indicated according to currently approved guidelines,¹⁵ a TWA utilizing a target HR of 115 beats/min had only a 61% positivity. On the other hand, 11% of these patients had false negative results, while in the remaining 28% the test was indeterminate, because the patients could not exercise up to a target HR of 115 beats/min. In this group, it could be argued that the use of a pharmacologic agent, e.g., isoproterenol, to increase HR to the target level may be advised and could conceivably enhance the sensitivity of the test. However, before such a protocol is to be recommended, the difference in the electrophysiologic mechanism of rate-dependent TWA when HR is increased by exercise, by atrial pacing, or by a pharmacological agent, should be investigated. Experimental evidence suggests that TWA is dependent on both HR and the sympathetic nervous system.^{16,17} In a recent study, the prevalence and HR threshold for TWA were compared in the same group of patients during exercise and atrial pacing.⁸ This study showed that, during both exercise and atrial pacing, TWA developed when the HR reached a patient-specific threshold and that the average threshold for TWA was similar whether the HR was increased by exercise or with pacing. This would suggest that the increase in HR rather than autonomic changes is primarily responsible for TWA. However, in this study a submaximal exercise was utilized which may not have been associated with significant activation of the sympathetic nervous system.¹⁸

The contribution of exercise-induced myocardial ischemia to the development of TWA should also be considered, especially since patients with coronary artery disease represent the majority of those at high risk for malignant ventricular tachyarrhyth-

mias.¹⁸ Transient myocardial ischemia has been shown to be associated with TWA.^{2,19} This is particularly relevant in our group of patients, among whom the majority had coronary artery disease and who were exercised to a symptom-limited or maximal HR. However, irrespective of the pathophysiology of TWA in these patients, the test would retain its predictive value as an index of ventricular vulnerability.

The present study raises the issue of sensitivity versus specificity of a diagnostic test in relation to the degree and severity of the risk investigated in a given population. For example, if TWA is to be used as a screening test for malignant ventricular tachyarrhythmias in a population with low-to-moderate risk, it is comforting to know that the specificity of the test remains high up to a HR of 115 beats/min. However, in a high risk population, e.g., those with coronary artery disease and left ventricular dysfunction, to achieve a high degree of sensitivity for identification of those at risk (and who could, for example, receive a prophylactic ICD) it may be necessary to achieve a high target HR.

Study Limitations

The two study groups with markedly contrasting arrhythmic risk are not appropriate for evaluating the predictive value of TWA for malignant ventricular tachyarrhythmias, nor for comparing TWA with other potential risk stratifiers. The study utilized an analysis algorithm for defining TWA that has been previously reported.⁹ It is possible that a different algorithm would have resulted in a different optimal target HR. A recent study has shown that the use of individual orthogonal leads plus a vector magnitude lead (as was utilized in the present study) results in increased sensitivity of the test as a predictor of VT inducibility.¹³

CONCLUSIONS

The present study shows that an optimal target HR of 115 beats/min is highly sensitive and specific for the use of TWA as an index of ventricular vulnerability. However, since a significant number of patients could not exercise up to this optimal target HR, means other than exercise that could achieve the target HR should be investigated.

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