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Evaluation of alternation in T wave amplitude during exercise testing

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ABSTRACT

T wave alternans, alternating amplitude from beat to beat on the T wave of the electrocardiogram, is common among patients at increased risk for life-threatening ventricular arrhythmias, and in dog experiments, cardiac susceptibility to fibrillation was reduced by tachycardia. At sufficiently high heart rates during exercise, alternans can occur even in normal subject, but the extent to which the heart rate threshold might be prognostically significant is not known. The purpose of this study is to establish clinical cutoff value for TWA screening through measurement of exercise induced TWA in normal and patients with elevated risk for SCD.

With the use of microvolt level alternans analysis, during exercise-induced tachycardia, we investigated the alternans power, the alternans ratio, expressed as the ratio of the alternans power to the standard deviation of the background noise, the threshold heart rate of the T wave alternans, and the threshold-to-maximum predicted heart rate (T/M-ratio). Then, we studied the difference in indices of T wave alternans between patients with low T/M-ratio and those without it. During bicycle exercise with gradually increasing workload (such as 20, 40, 60, 80, …watts increasing every three minutes) in 13 normal and 8 heart disease male, we monitored the Frank X, Y, Z leads and nine standard leads (aVR, aVL, aVF,V1-6) of ECG, and microvolt level alternans was analyzed by spectral technique. Left ventricular ejection fractions (LVEF) were also measured by means of ultrasound cardiography in patient group.

Microvolt level alternans was seen in 75% of 6/8 patients and also seen in 38.5% of 5/13 normal subjects. T/M-ratio was not less than 0.706 in all normal subjects. The patient group was divided into 5 positive patients with low T/M-ratio <0.706 and 3 negative patients with normal T/M-ratio≧0.706. The positive patient group presented with significantly higher indices of T wave alternans in comparison with the negative patient group ; the voltage of T wave alternans was 15.0±10.0 and 5.0±1.3 μV, respectively (p=0.036), the ratio of T wave alternans was 72.0±67.5 and 6.5±1.6, respectively (p=0.039), and the LVEF was 56.2±9.0 and 79.3±1.5 %, respectively (p=0.0048). By contrast, there was no significant difference in ST segment changes between low and normal T/M-ratio group.

Our results suggested that microvolt level T wave alternans can occur even in normal subjects and T/M-ratio (<0.706) might be practical index of exercise-induced tachycardia for stratifying patients at risk of ventricular arrhythmias.

KEY WORDS

ECG, T wave alternans, Ventricular Arrhythmia, Sudden cardiac death

Introduction

Beat to beat alternation of the electrocardiogram (ECG) is defined as a change in the amplitude and/or morphology of T wave of the ECG that was first reported by Hering[1] in an experimental animal. In 1910 Thomas Lewis[2] observed alternans in man during paroxysmal atrial tachycardia, leading him to hypothesized that "alteration occurs either when the

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Table 1 : Characteristics of the subjects and underlying heart disease of patients.

	Patients	Normal Subjects
Sex Male	8	13
Mean (±SD) age— year	50.0±13.1	22.1±1.5
Type of heart disease		
Coronary artery disease— no (%)	4 (50.0)	
Mitral - valve stenosis	1 (12.5)	
Aortic - valve regurgitation	1 (12.5)	
WPW	1 (12.5)	
PVC (No organic heart disease)	1 (12.5)	

heart muscle is normal and the heart rate is very fast, or when there is serious cardiac disease and the rate is normal". Every-other-beat alteration of T wave amplitude, termed T wave alternans (TWA), has since been reported under a wide variety of clinical situations such as Prinzmental's angina[3], acute myocardial infarction[4], antiarrhythmic drug therapy[5], and long QT syndrome[6]. Recently, TWA has recognized as a promising phenomenon for cardiac electrical instability. However, at a stage of TWA occurring at levels detectable by visual observation, it is too late to use for purpose of prevention of arrhythmias-related sudden cardiac death (SCD). Adam and co-workers developed the spectral analysis method for detecting microvolt-level TWA (mTWA), undetectable by visual observation alone, in experimental animals[7], which was later refined for use in humans[8].

In experimental animals, threshold of induced ventricular fibrillation decreased significantly associated with atrial pacing rate[9]. Clinical studies revealed that mTWA, induced by elevating heart rate, correlated closely with arrhythmic risk[8]. On the other hand, much exercise is sufficient to induce mTWA even in normal subjects, it is depend on heart rate. We hypothesize that the heart rate threshold for mTWA can be shifted to lower rates by myocardial disease-induced changes, which increase the propensity for life threatening ventricular arrhythmias and SCD. Therefore, we tried to know how much shift in the heart rate threshold of mTWA and other quantitative clinical values, which is a necessary and critical step in establishing TWA study as a clinically-useful marker of risk for SCD.

The purpose of this study is to establish clinical cutoff value for TWA screening through measurement of exercise induced TWA in normal and patients with elevated risk for SCD.

METHODS

1. Subjects

Thirteen normal males (mean age 22.1±1.5 (SD) years, range 18-37 years) who had no cardiac disease (Table 1). Patient population consisted of four males patients with coronary artery disease (mean age 53.3 ±17.0 (SD) years, range 31-68 years), one male patient with mitral valve stenosis (age 45 years), one male patient with aortic valve regurgitation (age 46 years), one male patient with WPW syndrome (age 37 years) and one male patient with non organic heart disease (age 59 years) (Table 1).

2. Measurement of TWA

Fourteen surface electrodes were attached to the chest, abdomen and back to record nine standard leads (AVR, AVL, AVF, V1-V6) and the Frank X, Y, Z leads ECG (Fig 1). All electrode sites achieved a low electrode to skin impedance of 3kΩ or less. Because high risk of patients may exhibit alternans even during sitting rest, measurements include 5 minutes of sitting rest. Exercise protocol starting with gradually increasing workload, every 3 minutes, automatically increasing the pedaling-workload with 20 watts (such as 20, 40, 60...watts increasing every

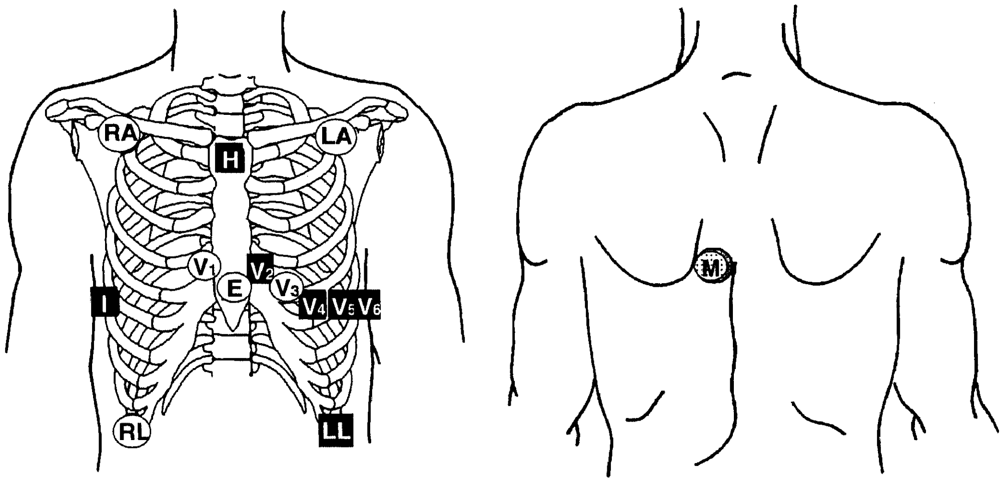

Figure 1 : Electrode placement for standard 12 leads and Frank lead.

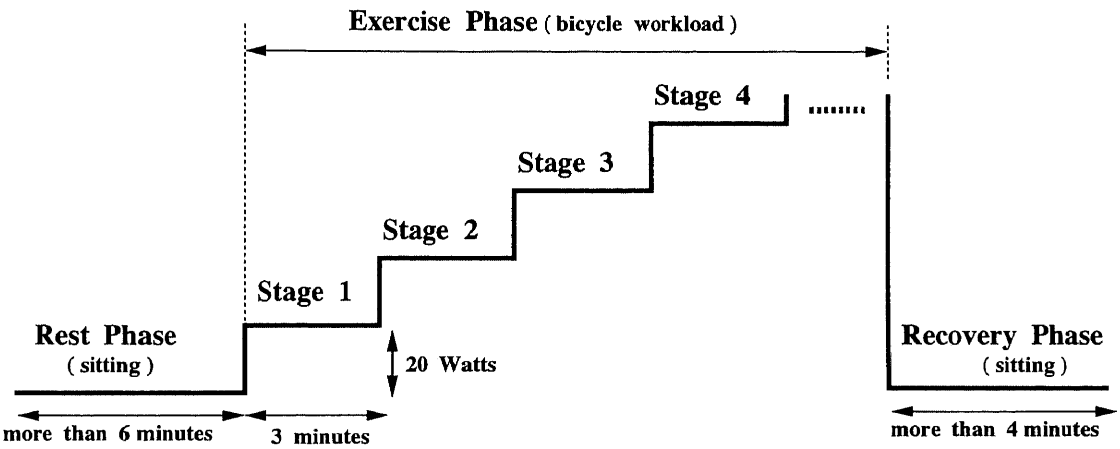

Figure 2 : Exercise protocol. Exercise protocol starting with gradually increasing workload, every 3 minutes, automatically increasing the pedaling-workload with 20 watts(such as 20, 40, 60...watts increasing every three minutes). When the subject show any complaint of fatigue, enter the recovery phase. Pedaling rate of workload was properly at 1/3 or 2/3 of heart rate by following the signal that was generated by the computer. Any protocol for TWA measurement also includes more than 4 minutes of post-exercise recovery process.

three minutes). When the subject show any complaint of fatigue, enter the recovery phase. Pedaling rate of workload was properly at 1/3 or 2/3 of heart rate by following the signal that was generated by the computer. Any protocol for TWA measurement also includes more than 4 minutes of post-exercise recovery process (Fig 2).

A mTWA was measured using a data processa CH2000 (Cambridge Heart, Inc., USA), by which an alternans power spectrum was computed from corresponding samples on 128 consecutive T-waves. Since TWA is every-other beat alteration of T wave amplitude, TWA appears as a peak at exactly one half the beat frequency (0.5 cycles/beat) in the result of power spectral analysis. The amount of alternans power spectrum at 0.5 cycles/beat ($S_{0.5}$) is measured in units of μV^2. Movements or other repetitive artifacts, which may cause peaks at close to 0.5 cycles/beat but not at exactly half the heart rate. Other random white noise raised the entire floor of the spectrum. We used the amount of mean power spectrum of the reference noise band (0.44-0.49 cycles/beat) (S_{NB}) to remove

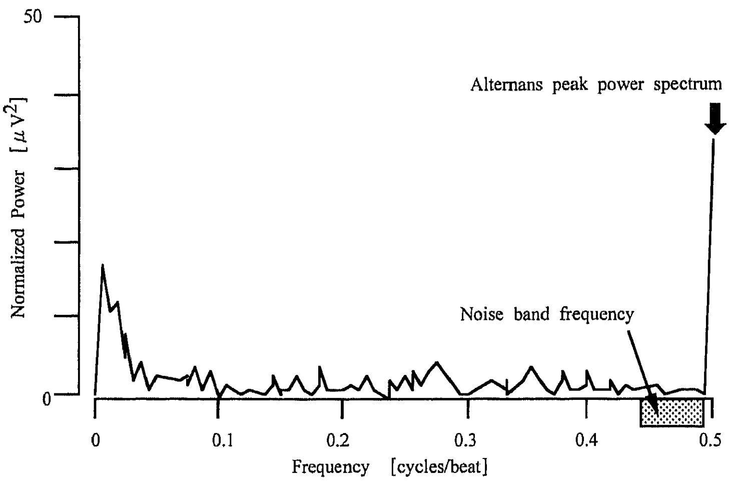

Figure 3 : T Wave Power Spectrum. An alternans power spectrum is computed from corresponding samples on 128 consecutive T wave by the spectral method. Each T wave is measured at the same time relative to the QRS complex. Since this spectrum is created by measurements taken once per beat, its frequencies are in the units of cycles per beat. T wave alternans appears as a peak at exactly one half the beat frequency (0.5 cycles/beat). An estimate of the noise in the alternans power spectrum calculated by taking the average of the spectrum in a noise band correspond to frequencies between 0.44 and 0.49 cycles per beat.

background noise (Fig 3). Thus, the alternans power was calculated by the subtraction of the S_{NB} from the $S_{0.5}$ makes it relatively independent of background noise level.

Alternans Power= $(S_{0.5}-S_{NB})$ [μV^2]

The alternans voltage (V_{alt}), the square root of the alternans power, corresponds to the difference in the voltage (averaged over the T wave) between the overall mean beat and either the even numbered or odd numbered mean beats.

$V_{alt}=(S_{0.5}-S_{NB})^{1/2}$ [μV]

Alternans ratio as a measure of the statistical significance of the alternans was calculated as the ratio of the alternans power to the standard deviation of the noise (σ_{NB}) in the same frequency range used to compute S_{NB}. Alternans ratio corresponds to the number of standard deviations by which the alternans power exceeds the average noise level.

Alternans ratio= $(S_{0.5}-S_{NB})/\sigma_{NB}$

Region for which parameters meet all the following standards was to classify TWA as positive.

There is sustained alternans voltage, which is above $1.9\mu V$[7] and its alternans ratio > 3.0.

The alternans peak in the spectrum is a sharp peak at 0.5 cycles/beat and there are no similar peaks near it and there are no sharp peaks at 0.25 cycles/beat in any lead.

The alternans exist for entire period that the heart rate is above the subject specific threshold and rise with increasing heart rate.

There is a epoch of sustained alternans more than 1 minute and during which noise is less than $1.8\mu V$.

To investigate the extent, to which the heart rate threshold might be prognostically significant, we calculate a parameter (T/M-ratio) as the ratio of the threshold heart rate for the onset of alternans to the maximum predicted heart rate, which is defined as 220-the subjects age in years. The deviation of ST-segment (ΔST) at the maximum heart rate during the exercise was determined. Furthermore, all patients underwent transthoracic echocardiography, and left ventricular ejection fraction (LVEF) was determined to assess the left ventricular function.

3. Statistics

Data were expressed as mean±SD. Patients' characteristics were compared between normal and low T/M-ratio groups with the minimum T/M-ratio (0.706) in the normal subjects group using the Mann-Whitney

Table 2 : Test results for control subjects.

Subject	Age (yr)	⊿ST in V5 (mm)	TWA	Thresh. HR / Max. Pred. HR	T/M-ratio	V_{alt} (μV)	Alt. Ratio
1	19	+1.4	+	148/201	0.736	6.6	8.36
2	18	+2.0	+	152/202	0.752	4.4	7.14
3	22	+0.5	±	141/198	0.712	4.1	4.19
4	19	-0.3	±	142/201	0.706	6.5	6.68
5	25	-0.7	+	150/195	0.769	4.6	7.48
6	19	+0.5	−	142/201	0.706		
7	18	-1.2	−	150/202	0.742		
8	37	0.0	−	130/183	0.710		
9	25	+0.1	−	144/195	0.738		
10	18	-0.5	−	144/202	0.713		
11	24	-0.3	−	149/196	0.760		
12	24	+0.4	−	150/196	0.765		
13	19	-0.3	−	149/201	0.741		
Mean±SD	22.1±5.3	0.1±0.9		145±5.9/198±5.3	0.735±0.023	5.2±1.2	6.78±1.57

The fourth column denotes presence or absence of T wave alternans. ⊿ST in V5=ST segment change in V5 lead ; TWA=T wave alternans ; Thresh. HR=threshold heart rate of T wave alternans in beat per minute ; Max. Pred. HR=maximum predicted heart rate in beat per minute ; T/M-ratio=ratio of the threshold-to-maximum predicted heart rate ; Valt=alternans voltage ; Alt. ratio=alternans ratio.

U test. Correlations between 2 variables were determined by linear regression. The significance of the correlation coefficient was assessed using Student t-test. A value of $p<0.05$ was considered to be statistically significant.

RESULTS

The exercise induced TWA were found in 6 (75%) patients and 5 (38.5%) normal subjects (Table 2, 3). T/M-ratio of the normal subjects, who showed exercise-induced TWA, was 0.735±0.023, and those of the minimum value was 0.706. Then, the patients were divided into 2 groups by definition, the T/M-ratio was equal or greater than 0.706 in group normal T/M-ratio and the T/M-ratio was less than 0.706 in group low T/M-ratio. The alternans voltage was smaller in normal T/M-ratio group (5.0±1.3 μV) than in low T/M-ratio group (15.0±10.0 μV) (p=0.036, Figure 4). The alternans ratio was also smaller in normal T/M-ratio group (6.5±1.6) than in low T/M-ratio group 2 (72.0±67.5) (p=0.039, Figure 4). Low T/M-ratio group showed poor contractility of left ventricule in comparison with normal T/M-ratio group ; the LVEF was 56.2±9.0 % and 79.3±1.5%, respectively (p=0.0048, Figure 4). However no significant difference was noted between the 2 groups in ST-segment deviation (p=0.884, Figure 4).

DISCUSSION

mTWA occurred even in normal subjects. In this study, exercise induced mTWA in 38.5% of normal subjects. Therefore, the presence of mTWA alone should not be considered to have prognostic significance. Adam et al[7] and Rosenbaum et al[8] reported that amplitude of alternans can classify vulnerability to ventricular arrhythmias. If all subjects be exercised until 70.6% of maximal heart rate is achieved and background noise is less than 1.8 μV, alternans voltage seem to be able to predict vulnerability. However, elder people tend to quit exercise still low of heart rate. In such case, generally the alternans voltage was not so high. T/M-ratio seems to be a better parameter. Even if the alternans amplitude was not high, if the T/M-ratio was below 70.6% of the maximum predicted heart rate that showed the threshold of alternans was declined.

Closely relationships among sustained ventricular tachycardia, left ventricular dysfunction, and mortality after myocardial infarction were reported[10,11]. Three patients of this study, case no 2, no 3 and no 4, had same heart rate threshold for the onset of the alternans. Case no 2 patient, who had no history of

Table 3 : Test results for control patients.

Underlying heart disease	Age (yr)	⊿ST in V5 (mm)	LVEF (%)	TWA	Thresh. HR / Max. Pred. HR	T/M-ratio	V_{alt} (μV)	Alt. Ratio
1 AP, HT	65	- 0.6	69	+	91/155	0.587	16.7	24.4
2 AP, HT	68	+0.7	79	+	117/152	0.770	3.6	5.1
3 AMI	31	- 1.3	51	+	117/189	0.619	7.4	54.7
4 OMI	49	+0.3	52	+	117/171	0.684	3.7	5.7
5 MS, CHF	45	+0.1	62	+	106/175	0.606	29.3	174
6 AR, HT	46	- 1.7	47	+	97/174	0.557	17.8	101
7 WPW	37	- 1.5	81	-	157/183	0.858	-	-
8 PVC	59	- 0.8	78	-	127/161	0.788	-	-
Mean±SD	50.0±13.1	- 0.6±0.9	65±14		116±20/170±13	0.684±0.11	5.2±1.2	60.8±66.2

The fifth column denotes presence or absence of T wave alternans. ⊿ST in V5=ST segment change in V5 lead ; LVEF=left ventricular ejection fraction ; TWA=T wave alternans ; Thresh. HR=threshold heart rate of T wave alternans in beat per minute ; Max. Pred. HR=maximum predicted heart rate in beat per minute ; T/M-ratio=ratio of the threshold-to-maximum predicted heart rate ; Valt=alternans voltage ; Alt. ratio=alternans ratio.

myocardial infarction, had normal left ventricular function (LVEF=79%). In contrast, Case no 3 and no 4 patients whose left ventricular wall motion had been hypokinetic (LVEF=51% and 52%, respectively). Case no 2 patient had normal T/M-ratio (0.770) while case no 3 and no 4 patients showed low T/M-ratio (0.619 and 0.684, respectively). T/M-ratio seemed to be associated with left ventricular function in patients who had history of myocardial infarction. Additionally, in whole patients group there was significant correlation between T/M-ratio and LVEF (r=0.79, P=0.02), though there was no correlation between threshold heart rate and LVEF (p=0.170). These results suggested that T/M-ratio might be better parameter for cardiac electrical instability than threshold heart rate.

Konta et al[12] reported that during the occlusion of the coronary artery of dogs they observed the discordance between the deviation of ST segment and resultant ventricular fibrillation. We also found that there was no significant relation between depression of ST segment at the maximum heart rate during exercise and low T/M-ratio (Fig 4). It seemed disagree with the fact that ischemia is one of the important decision factor of unevenness in cardiac conduction system. ST segment depression is associated with acute myocardial ischemia. The underlying mechanism for TWA was originally thought to be alternating conduction pathways, arising from regional areas of refractoriness that alternated spatially from beat to beat[13]. However, experimentally this was only demonstrable during acute myocardial ischemia[14]. Pastore et al[15] recorded optical action potentials from 128 sites on the epicardial surface of guinea pig heart during ventricular pacing. As heart rate was elevated, alternation of repolarization phase of action potential coincided with alternation of the T wave of the ECG. The mechanism of conduction block is unrelated to repolarization. Additionally, at present, there is no clear clinical or mechanistic relation between ST segment depression and ventricular tachyarrhythmias. In contrast, TWA has been implicated in the pathophysiological mechanism and clinical prognosis of ventricular fibrillation. Therefore, during ischemia the underlying relationship between ST segment depression and arrhythmogenesis may not be mechanistically related.

Although, there was not much correspondent in age between normal control subjects (mean age 22.1±1.5 years) and patients (mean age 53.3± (SD) years), we confirmed the fact that even in normal young subjects who had no organic disorder showed mTWA at heart rates in excess of 70.6% of maximum predicted heart rate.Additionally, the minimum T/M-ratio (0.706) in normal young subjects could classify the patients into normal and low T/M-ratio groups those had

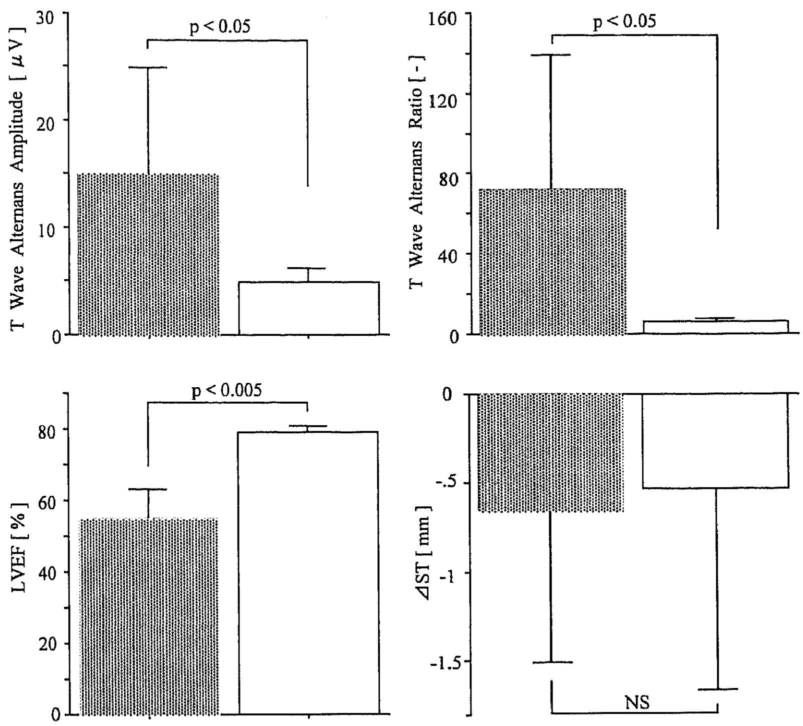

Figure 4 : Comparison of alternans amplitude(upper left), alternans ratio (upper right), LVEF (lower left), and ST segment change(lower right) between positive and negative patient group. The positive patient group with T/M-ratio less than 0.706 are indicated with shaded bars. The negative patient group with T/M-ratio not less than 0.706 are indicated with open bars. Results represent mean +/-1SD.

Upper left : The positive patient group was significantly higher voltage of T wave alternans amplitude than the negative patient group ; the mean (+/-SD) voltage was 15.0 +/-10.0 and 5.0 +/-1.3 μV, respectively.

Upper right : The positive patient group was significantly higher alternans ratio of T wave alternans than the negative patient group ; the mean (+/-SD) alternans ratio was 72.0 +/-67.5 and 6.5 +/-1.6, respectively.

Lower left : The positive patient group showed poor contractility of left ventricule in comparison with the negative patient group ; the mean (+/-SD) LVEF was 56.2 +/-9.0 and 79.3 +/-1.5, respectively.

Lower right : There was no significant difference in ST egment change between positive and negative group. LVEF=Left ventricullar ejection fraction, ⊿ST=ST segment change, NS=Not significant.

significant different mean values in alternans voltage, alternans ratio and LVEF. The result suggested that the minimum T/M-ratio (0.706) in normal young subjects might apply over wide range of age as a useful threshold.

Since the present study was done without follow-up period, we could not investigated actual relationships between low T/M-ratio patients and arrhythmic events. Therefore, follow-up study of normal and low T/M-ratio groups including more severe cases is needed to confirm the usefulness of risk stratification using T/M-ratio (<0.706).

In conclusion, we hypothesized that the shift in the alternans-heart rate relationship towards lower heart rate threshold is an important clue to the mechanism of alternans-related arrhythmogenesis. Then, we calculated a parameter T/M-ratio as the ratio of the threshold heart rate for the onset of alternans to the maximum predicted heart rate, and the minimum T/M-ratio (0.706) of the normal control subjects were applied to the threshold to classify the patients with risk of ventricular arrhythmias and those without it. As a result, there were significant differences in left ventricular function, alternans voltage and alternans ratio between normal and low T/M-ratio patient groups. These results suggested that T/M-ratio (<0.706) might be practical index of exercise-induced mTWA for stratifying patients at risk of ventricular arrhythmias.

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運動負荷時の心電図T波交互振幅変動の評価

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要　旨

心電図のT波振幅が一拍づつ交互に変動を繰り返すT波オルタナンス（TWA）は，通常致死性心室性不整脈のリスクが増加した患者で見られる。T波オルタナンス計測のどのような計測指標がTWA検査の臨床応用に向け適切か検討した。

健常群13名，および心臓疾患群８名を対象とした。自転車エルゴメーターによる運動負荷時の心電図から，0.5cycle／beatにピークを持つ成分のスペクトル・パワー値を求めた。

運動負荷時にTWAは，心疾患群で６名（75.0%）で，健常者群でも５名（38.5%）にみられた。TWA計測指標として閾値心拍数比をTWA出現開始心拍数と被検者の予測最大心拍数との比から求めた。健常者群の最小閾値心拍数比0.705で心疾患群をLow（<0.705），High（≧0.705）の２群に分けた。２群間では，LVEF（p＝0.026），TWA振幅（p＝0.036），オルタナンス比（p＝0.039）と左室収縮性，電気的不安定性の両指標で有意の差が見られた。TWAの計測は，閾値心拍数比（0.705）を指標とすることにより左室機能や心臓の電気的不安定性を判別できることが示され，閾値心拍数比の臨床応用への可能性が示唆された。