T wave alternans detection during exercise stress test and during dobutamine stress.
A comparative study in patients with a recent myocardial infarction

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Key words:
Adrenergic activity; Dobutamine; Exercise test; Myocardial infarction; Signal-averaged electrocardiogram.

Background. **Beat to beat electrical alternans of the T wave (TWA) on the electrocardiogram is a risk marker for the occurrence of life-threatening ventricular tachyarrhythmias. Atrial pacing or exercise are commonly used to increase heart rate to the critical level for TWA detection. However, atrial pacing requires invasive procedures while exercise may cause significant noise on the electrocardiographic recording or may be not performed by a number of patients with cardiac diseases. Dobutamine stress testing is routinely used in post-myocardial infarction patients and may represent an alternative means to detect TWA. However, the comparability of data obtained with exercise and dobutamine needs to be proven.**

Methods. **We measured TWA during exercise and/or dobutamine stress in 42 patients with a recent myocardial infarction. TWA was detected using a commercially available software while the heart rate was increased to the target range of 105-130 b/min. Each patient performed the two tests in random order with an adequate recovery time in between.**

Results. **The mean level of noise during data acquisition for TWA detection was significantly lower during the dobutamine test than during exercise (1.003 ± 0.67 vs 1.46 ± 1.20 μV, $p < 0.01$). With exercise, 32 (78%) patients had a determinable TWA. Of these, 9 (27%) were TWA positive and 23 TWA negative. In the other patients noise (n = 8) or exercise-induced arrhythmias (n = 1) prevented an appropriate TWA determination. One patient could not exercise. With dobutamine stress, 38 (87%) of the 42 patients studied had a determinable TWA. Arrhythmias prevented TWA determination in the remaining 4 patients. Dobutamine and exercise testing provided comparable proportions of TWA determinability. However, by combining exercise and dobutamine testing, a greater ($p = 0.0071$) proportion of the patients (41/42, 98% vs 32/42, 76%) had a determinable TWA when compared with exercise alone. A comparative TWA study could be performed in 29 patients who completed both the dobutamine and the exercise stress tests. All 22 patients TWA negative at exercise were so at dobutamine testing also. On the other hand, 5 of the 7 patients TWA positive at exercise were so at dobutamine testing also. Overall, 27 (93%) of the 29 patients in whom internal comparison could be performed showed a concordant result.**

Conclusions. **Dobutamine testing allows TWA detection with results comparable to those obtained at exercise testing. Combining exercise and dobutamine stress allows TWA determination in most of post-myocardial infarction patients. The present study provides the evidence for a safe and effective TWA determination for risk stratification after myocardial infarction.**

(Ital Heart J 2001; 2 (4): 265-270)

Received October 26, 2000; revision received January 5, 2001; accepted January 18, 2001.

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Introduction

Beat to beat electrical alternans of the T wave (TWA) on the electrocardiogram (ECG) is a risk marker for the occurrence of life-threatening ventricular tachyarrhythmias[1,2]. Macroscopic alternans of repolarization was first described in the early 1900s[3] and, thereafter, in several cardiac pathologies but never linked to arrhythmogenesis until 1975 when it was observed to precede malignant arrhythmias in long QT syndrome patients[4]. Clinical and experimental evidence documents that TWA develops mostly in the presence of an elevated heart rate[5,6] and sympathetic activity, as may occur under stress[4,7] or, in the experimental setting, during stimulation of the cardiac sympathetic nerves[4,8].

The interest for this phenomenon has grown in the last few years with the development of computerized methods able to

detect microscopic TWA[1,9]. The availability of such a technology has indeed allowed TWA detection in different clinical conditions associated with an elevated arrhythmic risk such as myocardial infarction (MI)[10] or hypertrophic cardiomyopathy[11]. A recent investigation indicates that TWA may provide meaningful information for the appropriate prediction of internal cardiac defibrillator discharge independently of other traditional risk factors, such as the left ventricular ejection fraction or arrhythmia inducibility during electrophysiological evaluation[12].

A critical aspect for the appropriate identification of TWA is a heart rate > 105 b/min. In order to achieve this target heart rate TWA is currently investigated during atrial pacing or during an exercise stress test. However, atrial pacing requires invasive procedures and cannot be performed in a routine protocol. On the other hand, the exercise stress test is commonly used in noninvasive laboratories but it is associated with elevated ECG noise that may impair appropriate TWA detection. The dobutamine stress test is also routinely used for post-MI studies and may represent an alternative and effective means of raising the heart rate by direct adrenergic receptor stimulation. TWA is modulated by autonomic activity. In fact, sympathetic activity can enhance it and vagal activity may blunt it[5]. Exercise implies both neural and humoral adrenergic activation while dobutamine testing results exclusively in humoral stimulation. Thus, a comparable response to exercise and dobutamine should not always be considered as expected. The present study was designed to determine whether exercise stress testing and dobutamine stress may provide comparable information. Accordingly, we studied TWA in a group of patients with a recent MI during a standard exercise stress test and we compared this information with that observed during a dobutamine stress test.

Methods

Patient population. The study protocol was approved by the ethical committee of the S. Matteo Hospital in Pavia, Italy. Forty-two patients discharged from the Coronary Care Unit of the S. Matteo Hospital, with diagnosis of acute MI, were selected for the present study. All patients were enrolled in the study 1 month after the index event, at the time of the follow-up visit for risk stratification. TWA measurement is part of the algorithm that includes standard tests and autonomic evaluation according to the ATRAMI[13] criteria, used at our institution for post-MI risk stratification. TWA testing was performed within 1-2 months of the index event. The inclusion criteria were: a documented recent MI and the capability of performing an exercise stress test. The exclusion criteria were: angina, residual ischemia, permanent pacemaker, major atrial or ventricular cardiac rhythm disturbances at the basal ECG, and ventricular bundle branch block.

At the time of study, all patients were free of medication with known influences on cardiac repolarization. Beta-blocking agents were withheld for at least 5 days prior to performing the test and none of the patients received antiarrhythmic drugs. All patients performed the test after signing the informed consent form.

Measurement of T wave alternans. Standard ECG leads along with the Frank orthogonal (XYZ) configuration leads were recorded. Multicontact silver-silver chloride electrodes were used for noise reduction. ECG signals were amplified, filtered (bandwidth 0.05 to 250 Hz) and digitized (1000 Hz with 16-bit resolution). TWA was measured using a commercially available software (CH 2000 system, Cambridge Heart Inc., Bedford, MA, USA). Using this software, the beat domain power spectrum of the T wave (J point + 60 ms through the end of the T wave) was calculated every 16 beats from the sequential, overlapping 128-beat sequence. The following measures were computed: alternans voltage (V_{alt}), which corresponds to the characteristic difference in voltage (averaged over the T wave) between the overall mean beat and either the even numbered or odd numbered mean beats. Clinical studies[2,12] have described that a sustained $V_{alt} > 1.9$ μV during exercise or > 1.0 μV at rest should be considered significant; the alternans ratio (k), which represents the height of the alternans peak above the background noise level was measured as the standard deviation of the noise. The alternans ratio represents a measure of the statistical significance of V_{alt}: for one to be confident that T wave alternans is present, k must be ≥ 3.

TWA was considered to be present when a sustained $V_{alt} \geq 1.9$ μV occurred when the heart rate was still below 70% of the maximum predicted heart rate, or when the V_{alt} at rest was > 1.0 μV for a period of at least 1 min, provided that the k was ≥ 3. TWA was considered to be negative if the criteria for positivity were not met and at least 1 min of artifact-free data were available for a heart rate maintained at a level ≥ 105 b/min. TWA was otherwise defined as undeterminable.

Exercise protocol. TWA were measured during submaximal bicycle exercise. Having placed the electrodes, a resting ECG was recorded for 5 min and bicycle ergometry was subsequently started. The workload was increased stepwise by 25 W every 3 min in order to raise the heart rate up to the target range of 105-130 b/min. The desired pedaling rate was reached at either one third or two thirds of the expected heart rate. The pedaling rate was monitored throughout the test to prevent artifacts in the alternans power spectrum that could mimic physiological alternans. At the end of exercise ECG signals were recorded for another 5 min.

Dobutamine testing. For pharmacological testing, dobutamine infusion was used according to standard pro-

tocols for the echocardiographic stress test[14]. Using an infusion pump, the dosage was increased stepwise every 3 min from an initial dose of 5 μg/kg/min up to 40 μg/kg/min until the heart rate reached values ranging between 105-130 b/min. As for the exercise test, the ECG was recorded throughout the test using the TWA measurement equipment. Atropine (0.4 mg i.v.) was added only in those cases (n = 2) in which dobutamine was not sufficient to achieve an adequate increase in heart rate.

Statistical analysis. A Student's t-test for paired data was used to compare noise levels. The occurrence of TWA during the two tests was compared using the χ^2 test. Data are expressed as mean ± SD. A p value of < 0.05 was considered significant.

Results

A total of 42 patients with a history of a recent MI constituted the study group. Thirty-eight (90%) patients were men, the mean age was 55 ± 11 years and the left ventricular ejection fraction averaged 53 ± 10% (Table I).

Table I. Patient characteristics.

Male subjects	38 (90%)
Age (years)	55 ± 11 (range 33-76)
LVEF (%)	53 ± 10
Infarct site	
Anterior	20
Inferior	19
Apical	2
Non-Q wave	1

LVEF = left ventricular ejection fraction.

The flow chart of the study is shown in figure 1. Forty-one patients performed the exercise stress test (one could not exercise because of severe arthritis) while 42 patients underwent the dobutamine test. All patients included in the study reached the target heart rate. The mean level of noise during data acquisition for TWA detection was significantly lower during dobutamine than during exercise testing (1.003 ± 0.67 vs 1.46 ± 1.20 μV, $p < 0.01$).

At exercise testing, 32 (78%) patients had a determinable TWA. Of these, 9 (27%) were TWA positive and 23 TWA negative. In the other patients noise (n = 8) or exercise-induced arrhythmias (n=1) prevented an appropriate TWA determination.

At dobutamine stress testing, 38 (87%) of the 42 patients studied had a determinable TWA. Dobutamine-induced arrhythmias prevented TWA determination in the remaining 4 patients. Overall, dobutamine and exercise testing provided a comparable number of TWA determinations with similar proportions of TWA positive and negative patients (p = 0.33). However, it is worth noting that, by combining exercise and dobutamine testing a significantly (p = 0.0071) greater proportion of patients (41/42, 98% vs 32/42, 76%) had a determinable TWA compared to that observed at exercise testing alone. Specifically, in all 8 patients who, because of noise, had an undeterminable TWA at exercise testing and in the patient who could not exercise, this parameter was determined at dobutamine testing. On the other hand, the overall TWA positivity with combined analysis was 8/42 (19%), similar to that observed in the database of large studies involving post-MI patients[10].

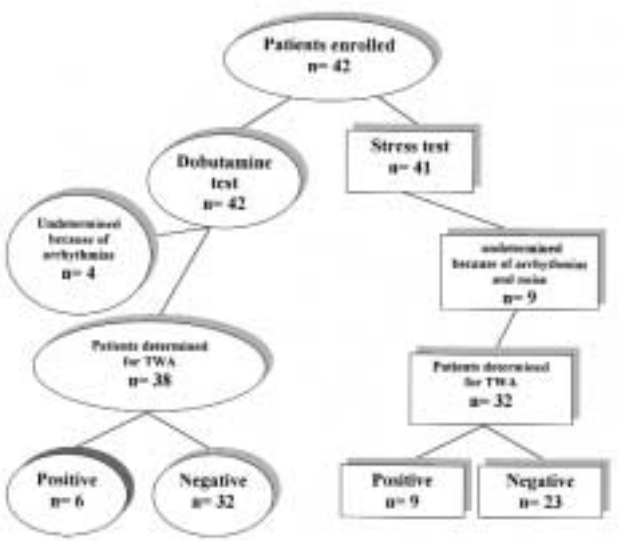

Figure 1. *Flow chart of the study. TWA = T wave alternans.*

A comparative TWA study could be performed in 29 patients who completed both the dobutamine and the exercise stress tests. Table II shows the results. All 22 patients TWA negative at exercise testing were so at dobutamine testing also. On the other hand, 5 of the 7 patients TWA positive at exercise testing were so also at dobutamine testing. Figure 2 illustrates a comparative example in a patient with positive TWA. In this patient, as in the

Table II. Contingency table describing the incidence of T wave alternans in 29 patients who were submitted to both exercise and dobutamine stress testing.

		EXERCISE +	EXERCISE −
DOBUTAMINE	+	5	0
	−	2	22

others, the threshold and amplitude of TWA with the two methods were comparable. Overall, 27 (93%) of the 29 patients in whom internal comparison could be performed showed a concordant result.

Discussion

The present study documents the effective use of pharmacological stress by dobutamine to study TWA in patients with a recent MI. Dobutamine stress provided results comparable to those obtained at exercise testing and, importantly, allowed TWA determination in most of the patients in whom this parameter was otherwise undeterminable. The present investigation further supports the feasibility of TWA assessment as part of the routine protocol for the risk stratification of life-threatening arrhythmias.

Mechanisms of T wave alternans. Heart rate is a critical determinant for the detection of microvolt-level TWA. Indeed, the occurrence of TWA increases with increasing heart rate. It is now established that a threshold of 105 b/min is critical for appropriate definition of TWA. Two basic mechanisms had been proposed as underlying the electrical alternans of repolarization. In 1984[15] a computer simulation described a possible relationship between dispersion of cellular recovery and electrical alternans leading to reentrant arrhythmias. This evidence generated the hypothesis that electrical activation and recovery alternate on a beat to beat basis. The underlying mechanism would involve a refractory time sufficiently long to prevent a full recovery within a single cycle of at least certain regions of the heart. This would lead to the development of areas of refractory tissue ultimately causing fractionation of the wavefront and reentry[16]. However, this kind of alternating pattern has not been observed in a typical condition of TWA and arrhythmogenesis such as, for instance, during acute myocardial ischemia.

An alternative hypothesis suggests that TWA originates from action potential alternans at the level of the single cell. This latter hypothesis is supported by recent experimental evidence. In Langerdorff-perfused guinea pig hearts, a beat to beat alternation of cellular repolarization with an opposite phase between neighboring cells was observed. A critical aspect of this study was that a heart rate threshold was observed above which a slight shortening in cycle length caused unidirectional block of the impulse propagation, reentrant propagation and initiation of ventricular fibrillation[17].

Exercise and atrial pacing provide comparable effects on TWA[16] and this would imply that autonomic responses to exercise have little influence on this phenomenon. However, heart rate is not the sole mechanism of TWA. Sympathetic activation enhances TWA[5] and it

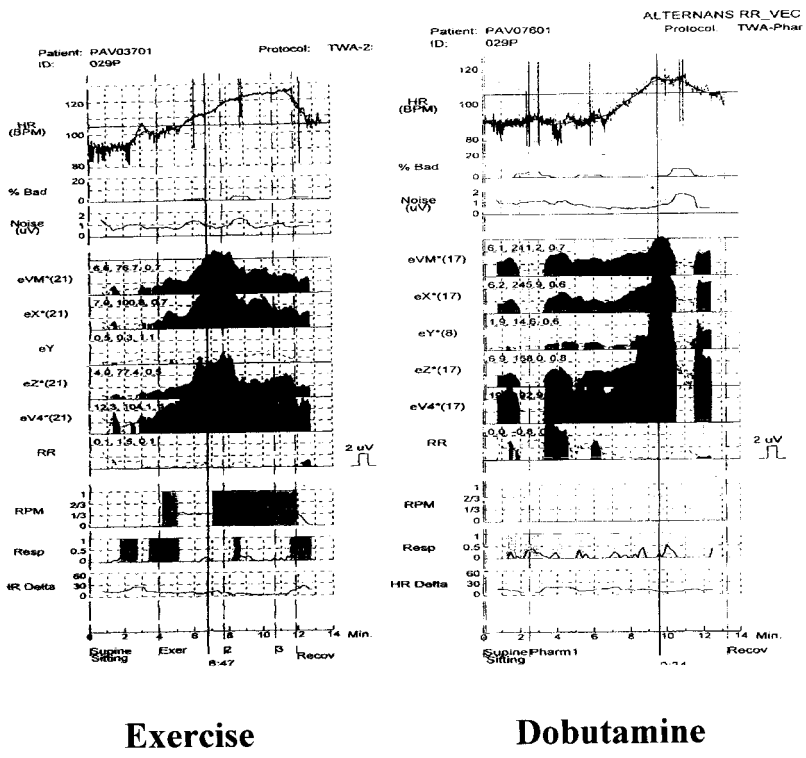

Figure 2. *T wave alternans (TWA) data collected in the same patient both at exercise (*left panel*) and dobutamine (*right panel*) stress testing. Positivity is indicated by the* black shaded areas *in the diagram. Similar levels of TWA occurred in the same leads during the two tests. The noise level was slightly higher at exercise testing. The higher level of TWA occurred in V_4. The heart rate pattern was different in the two tests but at optimal detection (*vertical solid line*) the TWA level was comparable and occurred at the same heart rate. In all other patients a similar behavior was observed.*

is a critical element of arrhythmogenesis both in the ischemic heart[18,19] and in conditions of iatrogenic or congenital prolongation of repolarization[7]. There is evidence documenting the autonomic influences on ventricular repolarization[20] and experimental data have described that sympathetic and vagal activation have opposite effects on TWA during acute myocardial ischemia[5].

In a large body of evidence describing the arrhythmogenic mechanisms of sympathetic activation a recent one is specifically relevant to TWA. Catecholamines increase transmural dispersion of repolarization by causing different shortening effects on the repolarization phase of myocytes located in different layers of the ventricular wall. This is due to the fact that the catecholamine-sensitive component of I_k, I_{ks} in mid-myocardium cells is underexpressed[21] and thus, in this area, repolarization of the myocardial wall is less sensitive to adrenergic stimulation. A direct consequence of this is a lesser shortening of mid-cells during the action potential triggered by sympathetic activation and thus, an increased dispersion of transmural repolarization that, ultimately, may create the substrate for reentrant ventricular tachyarrhythmia.

Overall, there is a solid rationale to suggest that TWA should be assessed in the condition that more frequently is associated with the onset of arrhythmia, such as during adrenergic activation. In this context dobutamine is a safe means of increasing heart rate by activating adrenergic receptors and represents a valuable alternative to exercise.

Clinical implications. The present investigation was not meant to shed light on TWA mechanisms but provides meaningful information for routine TWA detection. Dobutamine allowed the determination of TWA in most patients in whom this parameter was not determined at exercise testing alone. In only a few patients did the test have to be stopped owing to the arrhythmogenic effects of dobutamine. No patient developed symptoms of angina. It is worth noting that the arrhythmias, although ventricular in origin, were never life-threatening. In the present study a pure adrenergic intervention was preferred and atropine was added to dobutamine only in 2 patients (who had comparable responses, TWA negative at exercise and dobutamine testing) in order to achieve the target heart rate.

An important practical advantage of dobutamine testing relates to the noise reduction that allowed appropriate recording in all patients who did not develop an arrhythmia. TWA detection requires an almost unfiltered ECG recording and, in this condition, the possibility of avoiding muscle exercise, and the consequent noise, is of obvious importance. On the other hand, exercise allowed TWA determination in patients who developed an arrhythmia early during the dobutamine stress test.

All patients enrolled had a recent MI (1-2 months previously) and were submitted to the risk stratification process routinely used at our hospital, including assessment of residual ischemia. It is important to recall that residual ischemia may alter autonomic balance[22] and may be a confounding factor in the use of TWA for prognostic purposes. In our study, residual ischemia was an exclusion criterion. In accordance with our protocol, the absence of ischemia during TWA assessment was also documented by the absence of any symptom of angina during the tests and by a careful review of the ST-T segment in all ECG recordings.

Overall, by combining exercise and dobutamine stress, the presence of TWA could be determined in 98% of all the post-MI patients enrolled in the present study. Side effects were minimal. Both exercise stress testing and dobutamine stress under echocardiographic monitoring are standard aspects of the traditional algorithms for post-MI risk stratification. The overall 19% incidence of TWA may appear elevated if one considers the low arrhythmic risk profile of the study population. However, the TWA incidence in our study matches the one observed in a large study in post-MI patients[10]. It could be speculated that the lower TWA incidence with dobutamine may actually reflect a better specificity, possibly due to a lesser noise interference on TWA detection. At this time, however, this remains a suggestion that may deserve specific investigation in larger populations and, given the present knowledge, exercise testing should remain the first approach for TWA detection.

All patients enrolled in our study had a preserved left ventricular function but large evidence documents the safety of dobutamine stress after MI and in patients with heart failure[23,24]. Overall, the present investigation provides the evidence for a safe and effective method of TWA determination for risk stratification after MI.

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