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Combined Assessment of T-Wave Alternans and Late Potentials Used to Predict Arrhythmic Events After Myocardial Infarction

A Prospective Study

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OBJECTIVES The aim of the present study was to determine whether the combination of two markers that reflect depolarization and repolarization abnormalities can predict future arrhythmic events after acute myocardial infarction (MI).

BACKGROUND Although various noninvasive markers have been used to predict arrhythmic events after MI, the positive predictive value of the markers remains low.

METHODS We prospectively assessed T-wave alternans (TWA) and late potentials (LP) by signal-averaged electrocardiogram (ECG) and ejection fraction (EF) in 102 patients with successful determination results after acute MI. The TWA was analyzed using the power-spectral method during supine bicycle exercise testing. No antiarrhythmic drugs were used during the follow-up period. The study end point was the documentation of ventricular arrhythmias.

RESULTS The TWA was present in 50 patients (49%), LP present in 21 patients (21%), and an EF $<$40% in 28 patients (27%). During a follow-up period of 13 $\pm$ 6 months, symptomatic, sustained ventricular tachycardia or ventricular fibrillation occurred in 15 patients (15%). The event rates were significantly higher in patients with TWA, LP, or an abnormal EF. The sensitivity and the negative predictive value of TWA in predicting arrhythmic events were very high (93% and 98%, respectively), whereas its positive predictive value (28%) was lower than those for LP and EF. The highest positive predictive value (50%) was obtained when TWA and LP were combined.

CONCLUSIONS The combined assessment of TWA and LP was associated with a high positive predictive value for an arrhythmic event after acute MI. Therefore, it could be a useful index to identify patients at high risk of arrhythmic events. (J Am Coll Cardiol 2000;35:722–30) © 2000 by the American College of Cardiology

Following myocardial infarction (MI), serious ventricular arrhythmias are the most frequent mechanisms responsible for sudden cardiac death. Therefore, identification of patients at high risk for sudden cardiac death is very important in clinical cardiology. At present, various noninvasive indices, such as late potentials (LP) determined by signal-averaged electrocardiography (ECG) (1–3), left ventricular ejection fraction (EF) (1–3), ventricular ectopy determined by Holter monitoring (4), heart rate variability (5), and QT dispersion (6), have been used to identify patients at risk for the development of ventricular arrhythmias. In particular, LP, which reflects abnormalities of depolarization, and EF have been shown to be predictors of ventricular arrhythmic events in patients after acute MI (1–3). However, the predictive values of LP or EF alone in predicting future serious ventricular arrhythmias have low positive predictive values (17% to 29%) (1–3).

Recently, microvolt-level electrical alternans of the T-wave ("microscopic" T-wave alternans [TWA]) has been proposed to be a predictor of life-threatening ventricular arrhythmias (7,8), and it is now feasible during exercise as a noninvasive test (8,9). However, no studies have shown the predictive assessment of TWA according to arrhythmic events in the setting of acute MI. The TWA represents

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Abbreviations and Acronyms

CI = confidence interval
ECG = electrocardiogram, electrocardiography
EF = ejection fraction
LP = late potentials
MI = myocardial infarction
PTCA = percutaneous transluminal coronary angioplasty
TWA = T-wave alternans

beat-to-beat variability in the amplitude of the T wave. It is believed to reflect abnormalities of ventricular repolarization. We hypothesized that TWA and LP may be combined (i.e., the combination of two noninvasive markers of repolarization and depolarization abnormalities) to predict future ventricular arrhythmic events, and that the measurement could be used as a useful noninvasive predictor of high-risk patients. In the present study, we prospectively determined the predictive values of TWA, LP, and EF alone, and in combination in identifying patients at risk for developing ventricular arrhythmias after acute MI.

METHODS

Patient population. We screened a total of 142 consecutive patients with acute MIs who were admitted to the coronary care unit of our institute between February 1997 and November 1998. Patients who died soon after admission were not included. The diagnosis of acute MI was based on clinical course, serum creatine kinase activity, and ECG findings corresponding to ST-segment elevation (i.e., transmural MI). All the screened patients underwent screening coronary angiography on admission. Primary percutaneous transluminal coronary angioplasty (PTCA) was performed in most of the patients (98%) as the standard of practice at our institute (10). None of the patients had received thrombolytic therapy. The method of primary PTCA utilized was either stent implantation (58%) or conventional balloon angioplasty (42%). The success rate of PTCA was 94% in this study period. Coronary bypass surgery was performed when PTCA was done unsuccessfully. Therefore, most patients had undergone successful revascularization procedures in this patient population.

Twenty-three patients were excluded from the study because they had evidence of the following conditions at the time of three tests:

1) atrial fibrillation,
2) frequent extrasystoles (≥10 beats/min),
3) sinus bradycardia (<40 beats/min),
4) wide QRS complex including bundle branch block,
5) a severely reduced ejection fraction (<20%),
6) congestive heart failure,
7) implanted permanent pacemaker or cardiac defibrillator, or
8) use of antiarrhythmic drugs and medicines (except beta-blockers), which influence depolarization and repolarization.

Entry criteria were when exclusion criteria were not met, and when the three tests would be feasible and be analyzable. Of 142 patients screened, 119 patients underwent the assessment of the three indices (TWA, LP, and EF). The signal-averaged ECG and TWA tests were sequentially performed. The mean number of days that tests were performed was 20 ± 6 (range, 7 to 30 days) after the acute MI.

In this study, a relatively broad range of testing days was utilized because these tests were performed just prior to hospital discharge. The EF by left ventriculography was assessed within two days prior to the two noninvasive tests. At that time, coronary angiography was also performed in all patients to ensure patency after angioplasty. No arrhythmic drugs were used before and during the tests in all patients. Indeterminate TWA results were obtained in 17 patients due to extrasystoles (11 patients), a failure to achieve heart rate ≥105 beats/min (4 patients), or other clinical reasons (2 patients). An indeterminate signal-averaged ECG result was obtained in one patient because of right bundle branch block at the time of recording; patients with wide QRS complex, including bundle branch block before the tests, had already been excluded from the study. This patient also had an indeterminate TWA result. These 17 patients with indeterminate results of TWA and signal-averaged ECG were excluded from the study. Therefore, 102 patients (83 men and 19 women; mean age: 60 ± 9 years) were prospectively assessed as the final study population. Fifty patients (49%) had anterior wall infarctions, 35 (34%) had inferior wall infarctions and 17 (17%) had lateral wall infarctions. This study included seven patients with previous MI. None of the patients had other organic heart disease (e.g., cardiomyopathy, myocarditis, or valvular disease).

Informed consent was obtained from all patients prior to enrollment in the study. The Committee on Clinical Research of Toho University Ohashi Hospital approved the study protocol.

Measurements. LATE POTENTIALS. Before TWA assessment, LP were analyzed using a signal-averaged ECG system (model 1200EPX, Arrhythmia Research Technology, Austin, Texas). The analysis is based on the quantitative time-domain measurements of the filtered vector magnitude of the orthogonal Frank X, Y, and Z leads. The QRS complexes (≥200 beats) were amplified, digitized, averaged, and filtered with a high pass filter (40 Hz). Three parameters were assessed via a computer algorithm: 1) the filtered QRS duration (f-QRS), 2) the root mean square voltage of the terminal 40 ms of the filtered QRS (RMS_{40}), and 3) the duration of signals <40 μV in the terminal filtered QRS (LAS_{40}). The LP were considered to be present when at least two of three criteria (f-QRS >114 ms, RMS_{40} <20 μV, or LAS_{40} >38 ms) were met (11). Patients with wide

QRS complex had been already excluded from the assessment of the study.

T-WAVE ALTERNANS. After LP acquisition, in keeping the same supine position as the signal-averaged ECG recordings, the orthogonal Frank X, Y, and Z leads and associated vector magnitude (VM), and nine standard ECG leads (aV_R, AV_L, aV_F, V_1 through V_6) were recorded with newly developed electrodes (Cambridge Heart, Bedford, Massachusetts), which reduce electrical noise, after careful skin preparation (12). The presence of TWA was assessed using a CH2000 System (Cambridge Heart), which allows the detection of microvolt electrical alternans of the T wave using power spectral analysis (7). The spectral method of TWA analysis using this system has been described previously (7,13).

In brief, the magnitude of TWA was determined from power spectra by calculating the squared magnitude of the fast Fourier transformation of beat-to-beat fluctuations in the amplitudes of T waves from 128 consecutive beats. Alternans voltage (Valt) and alternans ratio (Ralt) were computed from the beat domain power spectrum. The Valt was calculated as the square root of the difference between the alternans peak voltage and the mean noise voltage in the power spectrum. The Ralt was calculated as the ratio of the squared alternans voltage and the standard deviation of the noise voltage and reflects the uncertainty in the T-wave Alternans measurements. Alternans are identified in the power spectrum at a frequency of 0.5 cycles/beat. This method selectively isolates alternans variability from other fluctuations caused by noise and respiration. If ectopic beats represented less than 10% of beats and the noise for the VM was less than 1.5 μV, the data were considered to be valid for analysis. The TWA was defined as positive if sustained alternans (i.e., alternans with duration $\geq$1 min) occurred with onset heart rate $\leq$110 beats/min in the Valt $\geq$1.9 μV during exercise or 1.0 μV at rest, and a Ralt $\geq$3.0 in single orthogonal leads or two adjacent precordial leads. The TWA was defined as negative if the criteria for positivity were not met while maintaining heart rate at a level $\geq$105 beats/min (14). Patients with indeterminate TWA results were not included in the present study.

LEFT VENTRICULAR EJECTION FRACTION. Left ventriculography was performed in a 30° right anterior oblique projection with contrast medium in all patients prior to TWA and LP assessment. The EF was assessed by the area-length method. If patients had an EF less than 20%, they were excluded from the present study before the TWA and LP assessments. An abnormal EF was defined as an EF $<$40%. A left ventricular aneurysm was defined as the presence of regional paradoxical systolic wall motion.

Exercise protocol. For the TWA analysis, a graded bicycle ergometer (8,9) was used to increase the heart rate to 110 beats/min because most patients have a patient-specific heart rate threshold for the development of alternans between 80 and 110 beats/min (9,15). Because muscle contraction artifact during exercise can obscure electrical alternans, the bicycle ergometry was performed in the supine position. In addition, electrical alternans were measured in a quiet room with copper shielding to reduce outside electrical noise. After obtaining a resting ECG, bicycle exercise was started and gradually increased to a workload of $\leq$15 W, to increase heart rate slowly to approximately 110 beats/min. Patients adjusted their pedaling rate to match a frequency that was either 33% or 67% of the heart rate using continuous auditory and visual feedback from the CH2000 system. Controlling the pedaling rate was important to ensure reliable TWA assessment, because pedaling at a frequency that was 50% of the heart rate would introduce an artifact into the alternans power.

Follow-up and study end point. All patients were followed as outpatients at our institute. Regular follow-up contact was obtained by a hospital visit at every two or four weeks. Although three patients had arrhythmic events before hospital discharge (see Results for details), we counted them as follow-up events because days at which these events occurred were remote from onset of acute MI. In these patients, the assessment of three indices was performed just after the events. In this study protocol, 24-h Holter ECG recordings were performed using a portable two-channel tape recorder (Fukuda Denshi, Tokyo, Japan) at one and six month(s) after hospital discharge (2.1 $\pm$ 3.1 times/patient; range: 1 to 6). Follow-up angiography was also performed in all patients to confirm maintenance of patency after angioplasty at six months after the MI as the standard of practice at our institute. The end point of the study was the documentation of spontaneous ventricular arrhythmias. When patients had symptomatic episodes, such as palpitation, dizziness, syncope, and so on, we instructed the patients and their families to come to an emergency room of our institute as soon as possible. Although physicians taking care of patients in the emergency room were informed of our study protocol, results of the three tests were not disclosed. Treatment of ventricular arrhythmias was not standardized. If we failed to record ECG during their symptoms, additional Holter ECG recordings were performed to identify symptomatic ventricular arrhythmias. No patients who enrolled in this study received antiarrhythmic drugs except beta-blocker before the documentation of ventricular arrhythmias.

Definition of arrhythmic events. We prospectively assessed the development of spontaneous ventricular arrhythmias during the follow-up period. Ventricular arrhythmias were defined as symptomatic, sustained ventricular tachycardia ($\geq$120 beats/min lasting $>$30 s) or ventricular fibrillation. In this study, hemodynamically stable and sustained ventricular tachycardia was also included into arrhythmic events if symptomatic. Nonsustained ventricular tachycardias lasting less than 30 s were excluded from arrhythmic events. Although sustained ventricular tachycardia or fibril-

Table 1. Clinical Characteristics of 102 Patients With and Without Arrhythmic Events After Acute MI

Variable	Arrhythmic Event (n = 15)	No Arrhythmic Event (n = 87)	p Value
Age (mean ± SD), yr	61 ± 6	59 ± 10	NS
Gender, male	13	72	NS
Heart rate at rest, beats/min	66 ± 7	72 ± 14	NS
Site of infarction			
Anterior wall	11	39	0.04
Inferior wall	4	31	NS
Aneurysm	4	7	0.03
No abnormal Q waves	0	9	NS
Coronary intervention	14	81	NS
Coronary bypass surgery	2	10	NS
Beta-blocker use	5	27	NS
History of			
Myocardial infarction	3	4	NS
Hypertension	9	36	NS
Diabetes mellitus	4	27	NS
T-wave alternans	14 (93%)	36 (41%)	0.0002
Late potential	8 (53%)	13 (15%)	0.002
Ejection fraction (<40%)	9 (60%)	19 (22%)	0.004

Arrhythmic events include symptomatic, sustained ventricular tachycardia and ventricular fibrillation.

lation occurring during the hospitalization was counted as follow-up events, the arrhythmias in acute phase (i.e., the first seven days) of MI were not included into arrhythmic events.

Statistical analysis. Data are expressed as the mean ± SD. Comparisons between arrhythmic events and clinical variables were evaluated by a contingency chi-square analysis. For the analysis of the association among arrhythmic events and TWA, LP, and an abnormal EF, and their combination, univariate and multivariate Cox regression analyses were performed. Results of event-free analyses are presented with the relative hazard and 95% confidence intervals (CIs). Sensitivity, specificity, positive and negative predictive values, and predictive accuracy of event-free prediction were also evaluated. Differences in arrhythmic event-free rates were determined using the Kaplan-Meier method and the log-rank test. A value for $p < 0.05$ was considered statistically significant.

RESULTS

Patient characteristics and arrhythmic events. The duration of follow-up was 13 ± 6 months (range: 3 to 23 months). The clinical characteristics of 102 patients after acute MI are summarized in Table 1. No patients had congestive heart failure that was refractory to medical therapy or other organic heart disease during the follow-up period. In this study population, most of the patients received coronary revascularization procedures during the acute phase of MI. Furthermore, nine patients (9%) had no abnormal Q waves on standard 12-lead ECG at the time of noninvasive testing.

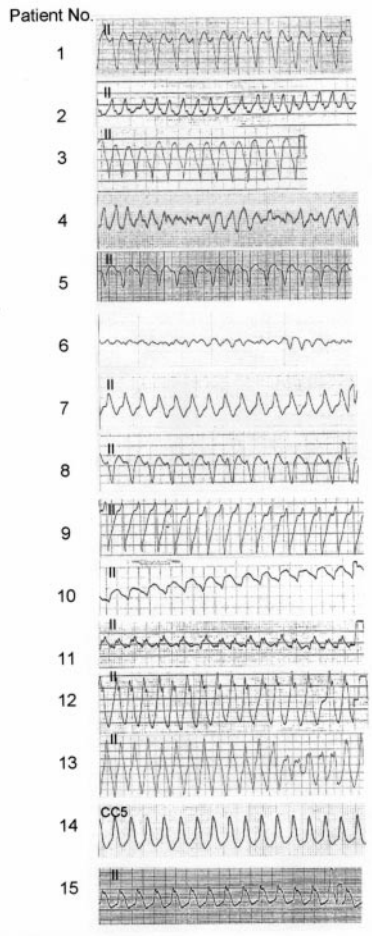

Figure 1. Individual ECG tracings in 15 patients revealing the occurrence of spontaneous, sustained ventricular arrhythmias. These tracings were recorded by any standard 12-lead ECG (patients 1–3, 5, 7–13, 15), conventional monitor ECG recorders (patients 4, 6), or 24-h Holter monitoring (patient 14). **II** indicates lead II in standard 12-lead ECGs, and **CC5** indicates lead CC5 in Holter monitoring. Patient number corresponds to the number in Table 2.

During the follow-up period, 15 patients (15%) had documented symptomatic, spontaneous ventricular arrhythmias as shown in Figure 1. The arrhythmic events occurred within six months after acute MI (mean: 2.5 ± 1.9 months). Characteristics of documented ventricular arrhythmias and results of three indices in the 15 patients are shown in Table 2. Patient number in Table 2 corresponds to the number in Figure 1. In this study, three patients (Patients 3, 4, 11) with the events that occurred at days 14, 17, and 24, respectively, after MI during their hospitalization were included among patients who experienced the events because these days were remote from the onset of acute MI. Sustained ventricular arrhythmias were terminated by defibrillation shocks in 2 patients, cardioversion in 11 patients,

Table 2. Characteristics of Documented Ventricular Arrhythmias and Results of Three Indices in 15 Patients

Patient No.	Age/Gender	Symptom	Type of Arrhythmia	Tachycardia Rate (beats/min)	Duration (min)	Mode of Termination	TWA	LP	EF
1	56/M	Palpitation	Sustained monomorphic VT	152	90	Cardioversion	+	+	36
2	51/M	Dizziness	Sustained monomorphic VT	210	60	Cardioversion	+	−	59
3	66/M	Palpitation with hypotension	Sustained monomorphic VT	182	10	Cardioversion	+	+	34
4	59/M	Syncope	VF	>300	5	Defibrillation shocks	+	+	39
5	56/M	Palpitation with hypotension	Sustained monomorphic VT	140	100	Procainamide	+	−	24
6	74/M	Syncope	VF	>300	30	Defibrillation shocks	+	+	36
7	71/M	Dizziness	Sustained monomorphic VT	190	90	Cardioversion	+	−	37
8	69/M	Palpitation	Sustained monomorphic VT	156	100	Cardioversion	−	−	65
9	73/M	Palpitation with hypotension	Sustained monomorphic VT	204	60	Cardioversion	+	+	38
10	45/M	Palpitation	Sustained monomorphic VT	166	120	Cardioversion	+	−	53
11	67/M	Palpitation with hypotension	Sustained monomorphic VT	192	20	Cardioversion	+	−	48
12	57/M	Presyncope	Sustained monomorphic VT	210	40	Cardioversion	+	+	46
13	53/M	Presyncope	Sustained polymorphic VT	250	30	Cardioversion	+	+	58
14	69/M	Palpitation	Sustained monomorphic VT	190	4	Spontaneously	+	+	35
15	43/M	Palpitation with hypotension	Sustained monomorphic VT	168	90	Cardioversion	+	−	33

TWA = T-wave alternans; LP, late potentials; EF = left ventricular ejection fraction; VT = ventricular tachycardia; VF = ventricular fibrillation.
Patient number corresponds to the number in Figure 1.

an intravenous administration of procainamide in 1 patient, and spontaneously in 1 patient. Eight of 12 patients followed as outpatients were hospitalized to treat the arrhythmias because the arrhythmias were associated with severe symptoms, such as syncope, dizziness, and palpitations with hypotension. The remaining four patients were also not hospitalized because in three patients (Patients 1, 8, 10), the arrhythmias were hemodynamically stable and the symptoms were not so severe, and in one patient (Patient 14), the arrhythmia was recorded on 24-h Holter monitoring (Fig. 2). A rapid polymorphic sustained ventricular tachycardia was documented in a patient (Patient 13) who received resuscitation. This event was not associated with acute MI because of the confirmation by coronary angiography after the event.

Although two patients (Patients 4 and 6) had ventricular fibrillation, both patients were rescued by resuscitations with several defibrillation shocks. Three patients with either rapid polymorphic sustained ventricular tachycardia or ventricular fibrillation and one patient with monomorphic sustained ventricular tachycardia that was refractory to antiarrhythmic drugs received subsequent implantation of a

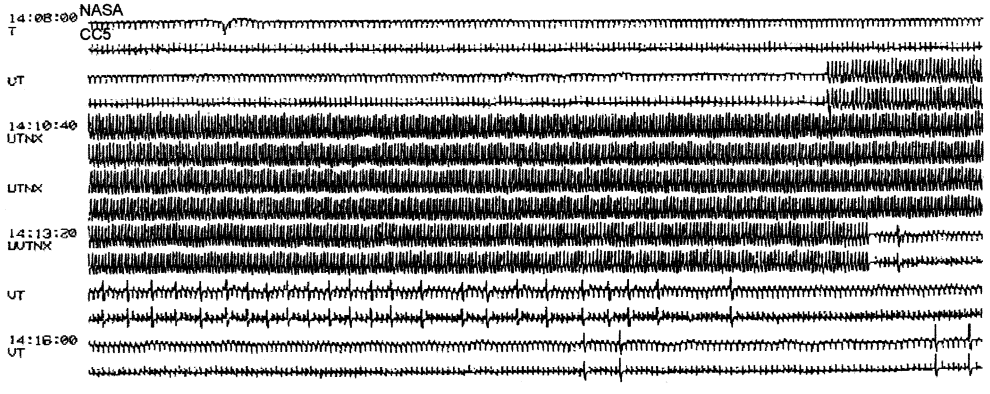

Figure 2. Holter recording revealing spontaneous onset and termination of sustained ventricular tachycardia documented in Patient 14. **NASA** and **CC5** indicate lead NASA and CC5, respectively, in Holter monitoring.

cardiac defibrillator. The remaining 11 patients were treated with amiodarone or class I antiarrhythmic drugs. In patients with arrhythmic events, the incidences of an anterior wall infarction and left ventricular aneurysm were higher than in patients without arrhythmic events (Table 1). With respect to other clinical features, no significant differences existed between patients with and without arrhythmic events.

Presence of abnormal noninvasive markers. **T-WAVE ALTERNANS.** Of the 102 patients, 50 patients (49%) had evidence of TWA. Of the patients with TWA, 34 (68%) did not have LP, and 27 patients (54%) had a normal EF. In patients with TWA, eight had TWA at rest with a mean heart rate of 94 ± 8 beats/min. The remaining 42 patients developed TWA as their heart rate increased during exercise stress testing (Fig. 3). During the TWA determination test, none of the patients complained of chest pain; none had significant ST-segment depression. The maximum Valt for patients with TWA was 4.9 ± 4.8 μV, and the maximum Ralt was 47 ± 70. The incidence of TWA in patients with arrhythmic events was significantly higher ($p = 0.0002$) than that in patients without arrhythmic events (Table 1).

LATE POTENTIALS. Twenty-one of the 102 patients (21%) had LP. Of the patients with LP, five (24%) did not have TWA and three patients (14%) had a normal EF. In patients with arrhythmic events, the incidence of LP was significantly higher ($p = 0.002$) than in patients without arrhythmic events. An f-QRS >114 ms was observed in 23 patients, a RMS_{40} <20 μV was noted in 20 patients, and an LAS_{40} >38 ms was present in 21 patients.

ABNORMAL EF. The mean EF for all 102 patients was 49 ± 9%. The EF was <40% in 28 patients (27%) and ≥40% in 74 patients (73%). Eleven patients had evidence of a left ventricular aneurysm. The percentage of patients with an abnormal EF (<40%) was significantly higher ($p = 0.004$) in patients with an arrhythmic event than in patients without an arrhythmic event.

TWA, late potentials and EF as predictors of arrhythmic events. The predictive values of TWA, LP, and EF alone, and the combination of the three markers in predicting arrhythmic events, are shown in Table 3. There were 16 patients with both TWA and LP, 23 patients with TWA and an abnormal EF, 18 patients with LP and an abnormal EF, and 14 patients with all three markers. Using a single marker, TWA had the highest sensitivity (93%) and the highest negative predictive value (98%), although the specificity (59%) and positive predictive value (28%) were lower than for LP or EF. Although LP had a higher specificity (85%) than TWA, the other predictive values were low, especially the positive predictive value. An abnormal EF also had a low positive predictive value. When TWA and LP were combined, the highest positive predictive value (50%) and the highest predictive accuracy (85%) were achieved. This was associated with a sensitivity of 53%, a specificity of 91%, and a negative predictive value of 92%.

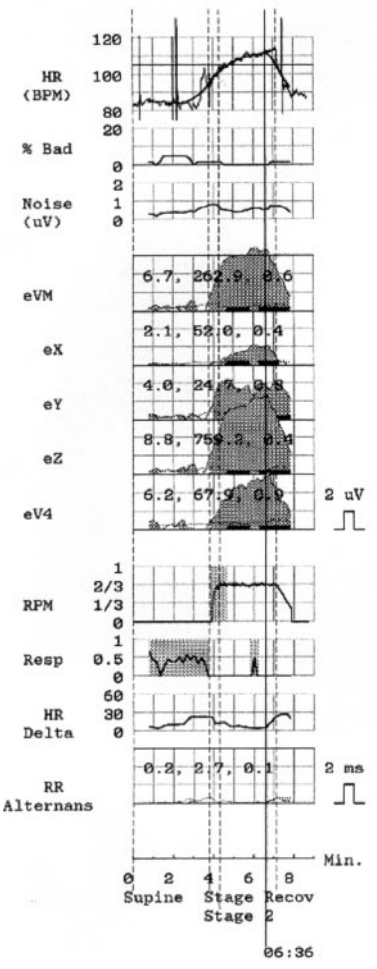

Figure 3. Representative data for a patient with a typical microvolt alternans of the T wave during exercise testing. Alternans analysis for leads VM, X, Y, Z, and V_4 is shown. The **dark shaded areas** for each lead indicate regions for which the Valt has a Ralt ≥3 SD above the level of noise. Dark shaded areas, which also have %Bad, RPM, Resp and HR Delta indices in the acceptable range, are indicated by a black line along the time axis. In this representative patient, the Valt is 8.8 μV and the Ralt is 759 for lead Z. The alternans increased as the heart rate increased. HR, heart rate trend; %Bad, percentage of beats more than 10% premature; Noise, mean noise in lead VM; eVM, eX, eY, eZ, eV_4, enhanced VM, X, Y, Z, and V_4 leads; RPM, bicycle ergometer pedaling rate during exercise; Resp, respiratory frequency (0.25 cycles/beat); HR Delta, the difference between the highest and lowest instantaneous heart rates for a 128-consecutive beat interval; RR Alternans, the amplitude of RR interval alternans.

The other combinations of two markers (TWA and EF, or LP and EF) were inferior to the combination of TWA and LP. If all three markers were combined, the positive predictive value was lower than the combination of TWA and LP.

Univariate Cox regression analyses were performed to identify independent predictors of arrhythmic events (Table 3). In a single use, all three markers were statistically significant. Although TWA alone had the highest relative hazard (16.8 [95% CI 2.2 to 127.8]) among predictors, the

Table 3. Predictive Values and Univariate Cox Regression Analyses Associating Three Indices Used Alone and in Combination With Arrhythmic Events

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	PA (%)	RH (95% CI)	p Value
TWA	93	59	28	98	64	16.8 (2.2–127.8)	0.006
LP	53	85	38	91	80	5.7 (2.1–15.7)	0.0008
EF	60	78	32	92	75	4.7 (1.7–13.2)	0.004
TWA and LP	53	91	50	92	85	8.6 (3.1–23.9)	<0.0001
TWA and EF	60	84	39	92	80	6.3 (2.3–17.8)	0.0005
LP and EF	40	86	33	89	79	3.8 (1.4–10.8)	0.01
TWA and LP and EF	40	91	43	90	83	5.5 (2.0–15.5)	0.001

TWA = T-wave alternans; LP = late potentials; EF = ejection fraction; PPV = positive predictive value; NPV = negative predictive value; PA = predictive accuracy; RH = relative hazard; CI = confidence interval.

statistical significance ($p = 0.006$) was inferior to the combined use of TWA and LP ($p < 0.0001$). To test explicitly the statistical significance of the combination of TWA and LP in predicting arrhythmic events, we specifically examined a multivariate Cox regression analysis involving TWA alone and the combination of TWA and other markers (Table 4). The combination of TWA and LP was the most significant ($p = 0.001$) predictor, providing the highest relative hazard (19.9 [95% CI 3.2–125.3]). Figure 4 depicts the event-free curves for TWA, LP and the combination of both tests during a mean follow-up period of 13 months. The combination of TWA and LP was a most significant predictor at this time point ($p < 0.0001$).

DISCUSSION

TWA and arrhythmias. Previously, "visual" TWA, which consists of beat-to-beat changes in the morphology of the T wave on the surface ECG, was reported to be associated with the development of ventricular arrhythmias in experimental and clinical settings, including acute ischemia (16–19), Prinzmetal angina (20,21), long QT syndrome (22,23), and metabolic and electrolyte abnormalities (24). Recently, a spectral analysis technique, incorporating noise reduction signal processing, allows the detection of microvolt electrical alternans of the T wave ("microscopic" TWA) (7,12). In addition, it has been proposed that "microscopic" TWA can be measured during bicycle exercise stress testing (8,9). The presence of "microscopic" TWA has been reported to be associated with an increased risk of ventricular arrhythmias in several clinical settings (8,14,25–27). No studies have demonstrated the predictive significance of TWA with respect to arrhythmic events in the setting of acute MI. The present prospective study suggests that TWA is an independent predictor of arrhythmic events. Because both the sensitivity and negative predictive value of TWA were very high (93% and 98%, respectively), TWA could be utilized in the primary screening of patients for serious ventricular arrhythmias after acute MI. However, the positive predictive value was lower than LP or an abnormal EF.

Table 4. Result of a Multivariate Cox Regression Analysis

	Relative Hazard (95% CI)	p Value
TWA	6.5 (0.7–62.2)	0.11
TWA and LP	19.9 (3.2–125.3)	0.001
TWA and EF	3.1 (0.6–15.3)	0.17
TWA and LP and EF	0.1 (0.01–0.8)	0.03

Comparison with previous studies. The LP are low-amplitude signals in the terminal portion of the QRS complex assessed by signal-averaged ECG (28,29). The prognostic value of LP in predicting sustained ventricular tachycardia or sudden death following acute MI has been evaluated in several studies (1–3,28–30). In these studies, the signal-averaged ECG was performed at a time similar to that in the present study, less than one month after infarction. The LP were found in 12% to 44% of the patients studied. Patients with definite LP had a 4.3% to 14.7% incidence of arrhythmic events during the follow-up period (10 to 12 months). In the present study, LP were noted in 21% of patients, and the arrhythmic events were documented in 15% of those patients during a mean follow-up of 13 months. The incidence of definite LP was comparable to those in previous reports. However, the incidence of arrhythmic events in the present study group was slightly higher.

In several previous reports (1,3), a higher proportion of patients without arrhythmic events received antiarrhythmic drugs or beta-blockers. In the present study, although beta-blockers were occasionally used (no significant difference in beta-blocker use between patients with and without arrhythmic events), antiarrhythmic drugs were not administered during the follow-up period. Moreover, hemodynamically stable and sustained ventricular tachycardias were included in arrhythmic events because the study end point was the documentation of ventricular arrhythmias. These may influence a higher incidence of arrhythmic events.

Recently, Estes at al. (8) have shown that TWA is a predictor of arrhythmic vulnerability in a small patient population ($n = 27$) that included a high proportion of

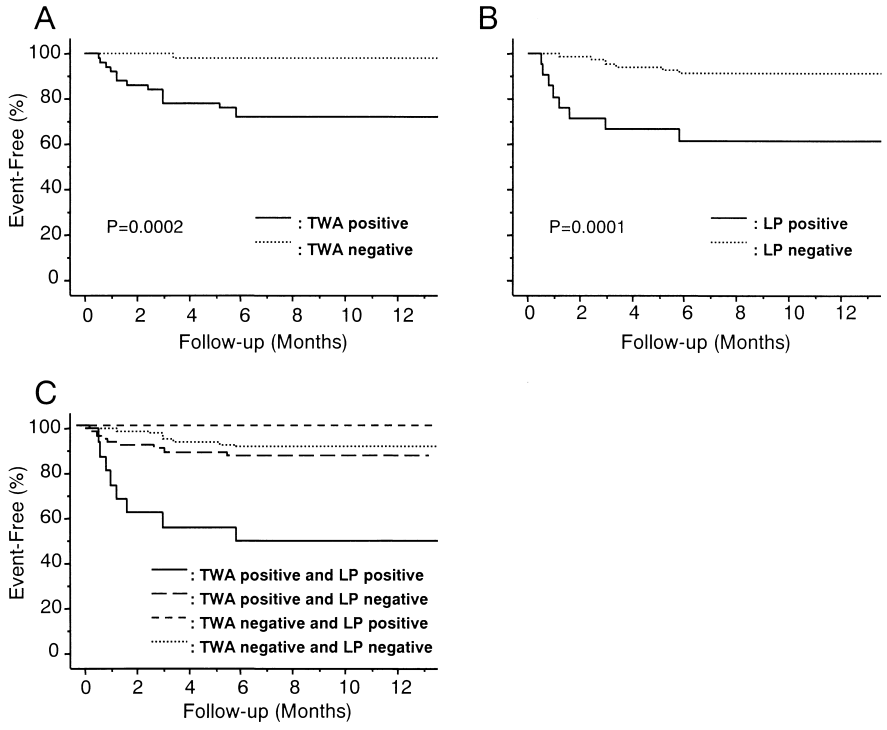

Figure 4. Kaplan-Meier actuarial curves for arrhythmic event-free rates based on positive or negative for T-wave alternans (TWA) **(A)**, late potentials **(B)**, and the combination of the two noninvasive tests **(C)** following acute myocardial infarction. The combination of TWA positive and LP positive had poorer event-free ($p < 0.0001$) than the other.

patients with syncope, while LP is not a predictor of arrhythmic events. More recently, Hohnloser et al. (14) have also found that in recipients of an implantable cardioverter defibrillator (75% of the study group had coronary artery disease), determinate TWA (n = 62) is a most predicting marker for recurrent ventricular arrhythmias, while LP (n = 85) is not. In our study of patients with acute MI (n = 102), both TWA and LP were significant predictors of first onset of ventricular arrhythmias.

The EF, determined by echocardiography, radionuclide ventriculography or ventriculography, is commonly used in clinical practice. A number of studies have shown that an EF <40% predicts serious arrhythmic events and sudden cardiac death in patients after infarction (1–3). Although an EF <40% was an independent predictor of future arrhythmic events in the present study, the positive predictive value was lower than for LP, which is in keeping with several previous studies (1–3,28–30).

Predictive significance of combined noninvasive indices. The single use of either TWA, LP, or EF has limited usefulness in predicting arrhythmic events after acute MI in this study. Specifically, the positive predictive value is 28% to 38%, although the negative predictive value is very high (91% to 98%). Previous prospective studies have assessed the combination of several noninvasive predictors, including LP and EF, to identify patients at risk for arrhythmic events and sudden cardiac death. Kuchar et al. (2) and Gomes et al. (3) have found that in patients with LP and a reduced EF (<40%), the risk of arrhythmic events (i.e., the positive predictive value) was 34% to 36%. In the present study, the combination of TWA and LP had the highest positive predictive value (50%) with the highest predictive accuracy (85%), providing the most significant value in both univariate and multivariate analyses. The combination of both markers therefore could be a useful noninvasive index reflecting abnormalities of both ventricular depolarization and repolarization. When all three markers were combined, the positive predictive value was no better than for the combination of TWA and LP. This may be due to the fact that we excluded patients with a severely reduced EF (<20%). This exclusion criterion was necessary to ensure the performance of a successful TWA determination test during exercise.

Study limitations. In previous prospective studies (1–3), the use of antiarrhythmic drug therapy was not controlled in the study group. In the present study, antiarrhythmic drugs were not administered during the follow-up period. However, our study population was limited because of testing constraints. First, patients with frequent extrasystoles (≥10 beats/min) and a high degree of R-R interval variability (<85% or >115% of qualified sinus beats) were excluded from the study. Previous reports have suggested that the detection of ventricular ectopy by Holter monitoring and abnormal heart rate variability were both predictors of

arrhythmic events (4,5). Therefore, our results may not be applicable to patients with significant accounts of ventricular ectopy or abnormal heart rate variability. However, TWA, LP, and an abnormal EF seem to be important prognostic factors in identifying patients with the substrate for reentrant ventricular arrhythmias. Second, we excluded patients with a very low EF (<20%), who are at most concern for risk stratification. Our data may not be applied to patients with severe congestive heart failure.

Clinical implications. Although previous reports have suggested that programmed ventricular stimulation can identify patients at high risk for ventricular arrhythmias (30), noninvasive measurements are more desirable as a screening test in a large number of patients with acute MI. This study shows that TWA is a useful marker to identify such patients because the sensitivity and the negative predictive value were very high. Second, the combination of TWA and LP can be used to identify patients at high risk for the development of ventricular arrhythmias following acute MI.

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