Temporal Variations in Microvolt T-Wave Alternans Testing after Acute Myocardial Infarction

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Background: Microvolt T-wave alternans (TWA) have been accepted as a tool for assessing vulnerability to ventricular tachyarrhythmias. There is lack of data concerning prospective temporal variations in TWA measurements after acute myocardial infarction (AMI). We analysed the temporal patterns of TWA in post-AMI patients.

Methods and Results: TWA tests were performed <1 month (TWA_{early}) and 6 months (TWA_{late}) after AMI in 51 consecutive patients treated with successful percutaneous coronary intervention (PCI). Twenty seven patients (53%) had anterior wall infarctions and 24 (47%) had inferior/lateral wall infarctions. TWA was measured during a treadmill manual exercise protocol and defined as positive, negative and indeterminate. Group A included patients with TWA negative in both tests and Group B included those with TWA abnormal (positive or indeterminate) at first or second determinations. TWA_{early} was negative, positive and indeterminate in 38 (74.6%), 8 (15.6%) and 5 (9.8%) patients, respectively, whereas TWA_{late} was negative, positive and indeterminate in 30 (58.9%), 14 (27.4%) and 7 (13.7%) patients, respectively. TWA_{early} was classified as normal in 74.6% and abnormal in 25.4% of the cases, and TWA_{late} was normal in 58.9% and abnormal in 41.1%. TWA tests were concordant in 36 patients (70.6%) and discordant 15 patients (29.4%). At TWA_{late}, 10 patients (19.6%) changed from TWA negative to TWA abnormal and 4 patients (7.8%) from TWA abnormal to TWA negative. After TWA_{early}+TWA_{late}, 45% of the patients had 1 test classified as abnormal. Left ventricular ejection fraction was <50% in 22% of Group A and 52% of Group B ($P = 0.037$).

Conclusions: In the era of primary PCI, temporal changes in TWA measurements may occur frequently during the first 6 months post-AMI. These findings should be considered in risk stratification strategies following AMI.

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T-wave alternans; myocardial infarction; risk stratification

INTRODUCTION

Sudden cardiac death (SCD) remains a major public health problem responsible for about 50% of cardiac mortality and 20% of all deaths.¹ Acute myocardial infarction (AMI) survivors represent an important risk population for the occurrence of SCD due to ventricular tachyarrhythmias.^{2,3} Several risk stratification methods, based on different noninvasive diagnostic techniques, accepted as risk markers of serious ventricular arrhythmias, have been proposed in clinical practice but they either lack adequate sensitivity or tend to show limited positive predictive value.³⁻⁵ Microvolt T-wave alternans

(TWA) has recently been recognized as a tool for the assessment of vulnerability to ventricular arrhythmias. A number of authors demonstrated TWA to be a strong independent predictor of arrhythmic events and SCD in a number of diverse disease states.⁶⁻⁹ In some studies, TWA performed better than signal-averaged ECG, nonsustained ventricular tachycardia, left ventricular ejection fraction and electrophysiologic study in predicting arrhythmia vulnerability.¹⁰⁻¹³ The optimal timing of TWA assessment in post-AMI patients remains to define because there is lack of data concerning prospective temporal variations in TWA measurements in this population. Also, inconsistency remains in the

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Table 1. Clinical Characteristics of the Patients

Characteristic	All Patients	Group A (n = 28)	Group B (n = 23)	P-Value (A vs B)
Age (yr)	58 ± 11 (35-81)	58 ± 11	59 ± 10	NS
Males	42 (82%)	23 (82%)	19 (83%)	NS
No. of vessels diseased				
1	28 (55%)	15 (54%)	13 (57%)	NS
2/3	23 (45%)	13 (46%)	10 (43%)	NS
Site of infarction				
Anterior	27 (53%)	15 (54%)	12 (52%)	NS
Inferior/lateral	24 (47%)	12 (43%)	12 (52%)	NS
PCI after thrombolysis	8 (16%)	4 (14%)	4 (17%)	NS
Complete revascularization	20 (39%)	12 (43%)	8 (35%)	NS
LVEF <50%	18 (35%)	6 (21%)	12 (52%)	0.037
History				
Smokers	21 (42%)	12 (43%)	9 (39%)	NS
Hypertension	19 (37%)	10 (36%)	9 (39%)	NS
Hyperlipidemia	19 (37%)	10 (36%)	9 (39%)	NS
Diabetes	14 (27%)	8 (29%)	6 (26%)	NS
Familiar history of CAD	7 (13%)	4 (14%)	3 (13%)	NS

CAD = coronary artery disease; LVEF = left ventricular ejection fraction.

predictive value of the TWA when performed in the early post-AMI period.¹³⁻¹⁵ This emphasizes the importance of the timing of TWA assessment after AMI. The present study examines the temporal variations of TWA measurements in patients with an AMI who were treated with percutaneous coronary intervention (PCI).

METHODS

Patients Population

We selected 51 consecutive patients following an ST-segment elevation AMI, submitted to successful PCI on admission, without any major adverse cardiac event during the first 6 months after hospital discharge. All subjects were required to give written informed consent. Patients who had atrial fibrillation or flutter, episodes of chest pain or dyspnea, ventricular pacing, QRS duration >130 ms, >10 ventricular ectopic beats per minute, profound bradycardia (≤ 40 bpm) or current use of antiarrhythmics were excluded from the study. Patients with previous AMI or myocardial revascularization procedure (PCI, bypass surgery), New York Heart Association class IV congestive heart failure and those who were unable to exercise were also excluded. To optimize assessments of TWA, beta-adrenergic blocking agents were withheld at least for 24 hours. Left ventricular systolic function was measured with two dimensional echocardiography

before performing the first TWA testing. The clinical characteristics of the patients are shown in Table 1.

TWA Testing

Patients had a submaximal exercise treadmill test starting at a stage of 25 W following a manual protocol with progressive increments to achieve a stable heart rate between 100 and 110 bpm. TWA testing was performed in a stable clinical condition, within 30 days (TWA_early) and 6 months (TWA_late) after the AMI. The mean number of days post-AMI were 12 ± 7 (range, 5 to 30 days) for TWA_early and 179 ± 5 days for TWA_late (range, 177 to 188 days).

TWA was determined with special equipment (HearTwave System; Cambridge Heart, Inc., Bedford, MA, USA) and according to previously described techniques, using a spectral method of analysis designed to allow detection of alternans in the microvolt range of amplitude.^{16,17} TWA was defined as positive, negative, or indeterminate according to previously described criteria.¹⁸ TWA was classified as indeterminate due to inability to achieve or maintain heart rate >100 bpm, the presence of high noise level or frequent ectopy.

Because previous studies showed that positive and indeterminate TWA tests are strong predictors of death in ischemic heart disease, patients were considered to have an abnormal TWA test when classified as positive or indeterminate and a normal

TWA test when classified as negative.¹⁹ Data were analyzed by an experienced reader who was blinded with respect to the clinical data. The population was divided into those patients with TWA negative in both tests (Group A) and those with a TWA abnormal determination at first or second tests (Group B).

Statistical Analysis

Categorical variables are expressed as frequencies and percentages. Continuous variables are expressed as mean $\pm$ standard deviation. Continuous variables were compared using Student's *t*-test and categorical variables were compared using the chi-square test. A *P* value <0.05 was considered statistically significant. Data were analyzed using SPSS 12.0 (SPSS Inc., Chicago, IL).

RESULTS

All 51 patients were able to complete both TWA assessments. Examples of a negative (left panel) and a positive TWA tracing (right panel) are shown in Figure 1. TWA_{early} was negative, positive and indeterminate in 38 (74.6%), 8 (15.6%), and 5 (9.8%) patients, respectively, whereas TWA_{late} was negative, positive and indeterminate in 30 (58.9%), 14 (27.4%), and 7 (13.7%) patients respectively. TWA_{early} was classified as normal in 74.6% and abnormal in 25.4% of the cases, and TWA_{late} was normal in 58.9% and abnormal in 41.1%. TWA tests were concordant in 36 patients (70.6%) and discordant 15 patients (29.4%). Ten patients (19.6%) changed from TWA normal to TWA abnormal and 4 patients (7.8%) from TWA abnormal to TWA normal (Fig. 2). Analysis of these recordings showed that the TWA results changed in 27.4% of the cases within 6 months after the index AMI. Twenty-eight patients (55%) had both tests negative (group A) and 23 patients (45%) had at least one test classified as abnormal (group B). There were no significant differences with regard to clinical data between the two groups, except for the presence of left ventricular dysfunction (Table 1). Patients of group B were more likely to have left ventricular ejection fraction $<50\%$ (52.2% vs 21.4%; *P* = 0.037).

DISCUSSION

The present study was designed to evaluate temporal variations of TWA measurements in the first 6 months after an AMI in patients treated suc-

Figure 1. Example of (A) normal TWA and (B) abnormal TWA measurements during an exercise testing. Top panel represents heart rate. The middle panels represent TWA from the vector magnitude lead and from the vector leads X, Y, Z. TWA = microvolt T-wave alternans.

cessfully with a PCI. In our analysis, temporal changes of TWA results occurred in 27.4% of the patients, either from TWA normal to TWA abnormal (19.6%) or from TWA abnormal to TWA normal (7.8%). The TWA test changed from positive to negative in only 1 patient (1.9%), while it changed from negative to positive in 7 patients (13.7%). All the other qualitative changes in TWA classification were due to an indeterminate test. Numerous studies have provided a scientific basis for using TWA as a marker of vulnerability to ventricular tachyarrhythmias.^{3,6-9} Nevertheless, there is lack of data analysing prospectively the modifications of qualitative assessment of TWA in post-AMI patients. There is evidence that TWA is linked to alternations in cellular calcium homeostasis, which

Figure 2. Variations of TWA 6 months after AMI. TWA_early = first TWA test (<30 days post-AMI). TWA_late = second TWA test (6 months post-AMI), pts = patients, abnormal = positive or indeterminate.

significantly influence the action potential duration (APD).²⁰ Beat-to-beat fluctuations in APD from neighboring regions of cells alternate with opposite phase that greatly amplifies spatial dispersions of ventricular repolarization, which, in turn, fractionates the wavefront and facilitates reentry.²¹ Clinical and experimental evidence relate APD alternans to ischemic heart disease and ventricular arrhythmias.^{22,23} Our results suggest that post-AMI left ventricular dysfunction may be associated with the temporal modification of TWA results. In these serial determinations of TWA, at least one test abnormal was found in 52.2% of the patients with left ventricular dysfunction. TWA measurements changed from indeterminate to negative in three cases (5.9%). These variations could be due to a better ability to exercise 6 months after AMI. However, we included in the study only those patients who were able to complete the exercise testing required to obtain both TWA assessments. Also, our results showed that TWA indeterminate changed from 9.8% to 13.7% in TWA_early and TWA_late, respectively. Indeterminate results have been described in 12–47% of the cases when TWA is assessed during exercise testing.²⁴ Our lower rate of TWA indeterminate supports the fact that temporal TWA changes were not due to technical conditions causing indeterminate tests. This emphasizes the importance of dynamic variations of TWA and

should be pointed out in risk stratification strategies.

Temporal TWA variations could be associated with ventricular remodeling or residual ischemia after AMI. In fact, 45% of this population had multivessel coronary disease with complete myocardial revascularization obtained in 39% of the patients. Nevertheless, there was no difference between the groups for the clinical and angiographic characteristics and only patients without post-AMI ischemic events were included in the study. Despite these findings, in the absence of serial determinations of left ventricle characteristics it is not possible to define a relationship between temporal variations of TWA and ventricular remodeling post-AMI. It is also possible that the development of the arrhythmic substrate related to the infarct scar formation is a time-dependent phenomenon which may lead to temporal TWA changes. This might provide a more powerful prognostic information later on, after formation of a permanent scar with a substrate more stable.

The risk of SCD remains high in the first 6 months after AMI.^{25,26} However, as pointed out by Huikuri et al., the incidence and temporal distribution of SCD is significantly lower during the early time period after AMI in the beta-blocking era.²⁷ In our study, despite the assessment of the presence of TWA only in patients submitted to successful ICP without angina recurrence or major adverse events, the results of TWA testing changed significantly in the first 6 months after AMI, with 25.4% and 41.1% of the tests classified as abnormal at TWA_early and TWA_late, respectively. In particular, changes between TWA normal and TWA abnormal may be of greatest importance concerning clinical implications in identifying patients at high risk for the development of ventricular tachyarrhythmias. Thus, in the modern era of primary PCI therapy, the prevalence of TWA, accepted as a risk marker with a predictive accuracy superior to other conventional markers of arrhythmic events, seems to depend on left ventricular ejection fraction rather than on infarct-related artery patency. The impact of these TWA changes in risk stratification post-AMI has not been well studied. The occurrence of temporal changes of TWA testing may also contribute to explain the contrasting results reported by Tapanainen et al on 379 patients who underwent TWA measurements in the early post-AMI period.¹⁴ The presence of TWA during a predischARGE exercise test was not predictive for increased risk

Table 2. TWA Results <30 Days (TWA_Early) and 6 Months (TWA_Late) After Acute Myocardial Infarction

Concordant	TWA+/TWA+	TWA-/TWA-	TWAind/TWAind			
36 (70.6%)	6 (11.8%)	28 (54.9%)	2 (3.9%)			
Discordant	TWA-/TWA+	TWA-/TWAind	TWA+/TWA-	TWA+/TWAind	TWAind/TWA-	TWAind/TWA+
15 (29.4%)	7(13.7%)	3(5.9%)	1 (1.9%)	1 (1.9%)	3(5.9%)	0

Data represented as TWA_early/TWA_late. TWA+ = TWA positive; TWA- = TWA negative, TWAind = TWAindeterminate.

of SCD, rather, inability to complete the exercise test required for TWA testing had a high correlation with subsequent cardiac death. The utility of TWA for the identification of patients at high and low risk for arrhythmic events needs to be further clarified, not only in the remote but also in the recent post-AMI phase. In fact, risk variables may be unstable early in the post-AMI course and, therefore, unreliable for the prediction of long-term outcome. Better understanding of dynamic changes in pathophysiologic processes, such as postmyocardial infarction remodeling and the transition to heart failure will help to improve both risk stratification and management among patients surviving an AMI.

Study Limitations

One of the limitations of our study is related to the period of time after AMI with unchanged TWA results. Although all the patients performed a second TWA test, we did not assess TWA between the first and the sixth month. Therefore, it is not possible to define the moment where the TWA changes occur. The Alternans Cardiac Electrical Stability Study reported that TWA evolves from early (5 to 21 days) to later (28 to 56 days) measurements, with only 67% concordance.²⁸ These changes, within 2 months after AMI, could be due to the fact that TWA measured during exercise testing has a reproducibility between 82% and 93%,^{29,30} but also associated with evolution of ischemic and structural disease. Secondly, this is a selected population, with a limited number of patients, not representative of all AMI survivors. We have tried to determine temporal variations of TWA in a homogeneous population with AMI but, given the importance of optimal risk stratification strategies, it should be applied across the general AMI population in clinical practice. In fact, the absence of a group of AMI survivors not treated with PCI makes

not possible to accept these temporal variations of TWA as a common post-AMI finding. Finally, the absence of angina pectoris or major adverse events between the two tests, can not exclude the presence of ischemic areas causing variations of conduction and refractoriness. Transient myocardial ischemia could not be completely ruled out in our study population. However, Ikeda, in a study to assess the association between TWA and ambulatory ischemia did not found association between TWA and ST-segment depression during exercise in postinfarction patients.³¹ In addition, the inclusion of a test such as the nuclear myocardial scan, for the detection of myocardial ischemia, could introduce confounding data to our analysis, for it has been demonstrated that ischemic "memory images" obtained on myocardial scintigraphy are a common phenomenon in post-AMI patients.³²

CONCLUSIONS

In summary, temporal variations of TWA measurements occur frequently in the post-AMI course despite successful myocardial revascularization. This may partially explain the discrepancies in the ability to identify patients at risk for SCD and cardiac mortality reported by some authors. We found that in relatively low-risk patients, the most common change is from a TWA normal to a TWA abnormal. Despite a higher prevalence of this temporal variation of TWA in patients with depressed left ventricle function, further longitudinal studies with serial characterization of postinfarction ventricular remodeling should evaluate the effects of ventricular remodeling on TWA determinations. Temporal variations of TWA measurements following an AMI should be considered given the challenge of risk stratification for sudden death in post AMI patients for today's clinical practice.

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