ORIGINAL ARTICLE

In-Hospital Heart Rate Turbulence and Microvolt T-Wave Alternans Abnormalities for Prediction of Early Life-Threatening Ventricular Arrhythmia after Acute Myocardial Infarction

[Correction added on 06 November 2013, after first online publication: The title has been amended from "Microwave T-Wave Alternans Abnormalities" to "Microvolt T-Wave Alternans Abnormalities".]

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Background: In the setting of primary prevention, most implantable cardiac defibrillators (ICD) are implanted more than 6 months after acute myocardial infarction (AMI). Abnormal heart rate turbulence (HRT) and T-wave alternans (TWA) are predictors of long-term sudden cardiac death (SCD). We intended to assess the predictive value of HRT and TWA for early post-AMI SCD and life-threatening ventricular arrhythmias (VA).

Methods: One hundred ninety-nine consecutive patients with AMI were prospectively included (age 61.7 years, LV ejection fraction 45%). One hundred eighty-three patients (92%) underwent percutaneous coronary intervention. We assessed HRT using turbulence slope (TS), turbulence onset (TO), and TWA on channels 1 and 2 (TWA1 and TWA2) using the modified moving average method. Predictive performance for SCD/VA was assessed by area under the receiver operating curve characteristic (ROC-AUC).

Results: Within 6 months after AMI, 2 patients (1%) developed life-threatening VA and 3 (1.5%) experienced SCD. TO and TWA1 had poor ROC-AUC (both 0.64) whereas TS and TWA2 failed to show any predictive performance (ROC-AUC 0.48 and 0.57, respectively). When combining TO and TWA1, ROC-AUC increased to 0.80. Importantly, when considering the subset of patients with a LV ejection fraction ≤40%, the combined variable of TO and TWA1 remained strongly predictive of a short-term event (ROC-AUC 0.86).

Conclusions: Combined assessment of HRT and TWA showed a high predictive performance for SCD or life-threatening VA within 6 months after AMI. This combined Holter ECG index could be useful to identify high-risk patients who might benefit from early ICD implantation.

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acute myocardial infarction; heart rate turbulence; T-wave alternans; sudden death

Patients with a history of myocardial infarction (MI) are at increased risk for sudden cardiac death (SCD), most often due to ventricular arrhythmia (VA). Approximately one-half of arrhythmic deaths occur within the first year and one-quarter within the first 3 months after MI.[1,2] There is still some

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debate regarding the ideal timing for implantable cardiac defibrillator (ICD) placement.[3,4] While current guidelines recommend implantation of ICDs in patients with decreased LV ejection fraction (LVEF) no less than 40 days after acute MI,[5,6] some data suggest that the benefit from ICD implantation may exist only when patients are selected for ICD implantation at a longer period after the index MI.[3–5,7] In the "real world," most patients with a theoretical post-MI indication for ICD implantation undergo actual ICD implantation more than 6 months after MI.[4] It thus appears critically important to better assess the risk for sudden death immediately after acute MI in order to more appropriately select the subset of patients who would benefit from early ICD implantation.

Heart rate turbulence (HRT) and T-wave alternans (TWA) are noninvasive measurements of VA vulnerability that can be performed during standard Holter ECG recordings. HRT is an autonomic marker that indirectly measures the baroreflex-dependent blood pressure response after single ventricular premature contractions (VPC).[8] TWA, which is thought to be due to dispersion of repolarization, is a marker of electrical substrate to VA. Both HRT[1,9,10] and TWA[11–15] correlate with the incidence of sudden death after MI in patients with or without LV dysfunction.

There is still debate regarding the best timing for performance of HRT and TWA measurements. Both HRT and TWA values can change with time after MI. The International Society for Holter and Noninvasive Electrophysiology Consensus focusing on HRT did not specifically address the timing for Holter recordings to be performed.[8] The yield of HRT and TWA measurements in the first days or weeks following MI has been criticized, and poor predictive value of such measurements is reported.[16] Additionally, most Holter ECG recordings were performed 7 days or longer after the index MI in studies assessing the predictive performance of HRT and TWA for clinical outcome after MI.[1,9,16] As the mean hospitalization stay after a first MI is rarely greater than 7 days,[17] it is difficult to identify a useful application of Holter variables to identify patients at high risk for early SCD.

In the REFINE study,[16] the combination of HRT and TWA allowed a more precise risk-stratification of sudden death in patients after MI than the variables taken separately. There is strong pathophysiological rationale for the combined use of markers of autonomic tone and electric substrate to assess the risk for life-threatening VA.

We aimed to determine if in-hospital Holter ECG measurements performed days after MI could predict early SCD or life-threatening VA. Specifically, we hypothesized that the combined use of TWA and HRT measured during the initial hospital stay of patients with a first MI could adequately predict the risk of sudden death within 6 months after MI.

METHODS

Patient study group

Between November 2009 and April 2011, we prospectively enrolled 201 patients admitted to the intensive care unit (ICU) of our institute for a first acute MI. Inclusion criteria were presence of chest pain associated with ST-segment elevation $\geq$0.1 mV in at least two leads of the surface ECG and elevated troponin levels. Exclusions criteria were left bundle branch block, pacemaker rhythm, rhythm other than sinus, and prior MI or coronary artery bypass graft (CABG). The institutional review board approved the study. All patients gave informed consent for the research protocol.

Clinical characteristics upon hospital arrival were assessed through a standardized form. All patients had complete invasive and noninvasive cardiac evaluation during their ICU stay. Antegrade perfusion was graded according to the classification of the Thrombolytic in MI Trial. LVEF was evaluated in all patients at discharge from the ICU. Patient's clinical characteristics and percutaneous coronary intervention data were prospectively collected and entered in a computerized database.

Holter ECG recordings

Two-channel 24-hour Holter ECGs were systematically performed within the first week following MI (mean 2.38 $\pm$ 0.79 days, range 2–7 days) in the ICU (n = 177, 88.1%) or in the cardiology unit (n = 24, 11.9%) immediately after ICU discharge. All recordings were performed using SEER Light Extend Digital Holter recorders (GE Healthcare, Vélizy, France) and analyzed with the MARS Holter proprietary software. Two patients were excluded from the study due to excessive noise or artifact on Holter recording. The remaining 199 patients were considered in our analysis. No antiarrhythmic drugs other than beta-blockers and calcium channel blockers were used before

or during Holter ECG recordings. Nonsustained ventricular tachycardia (VT) was collected and coded during Holter ECG and from telemetric data obtained during the ICU stay.

Turbulence slope (TS) and turbulence onset (TO), parameters derived from HRT, as well as TWA were assessed. TWA analyses could be performed in all patients whereas measurement of HRT was impossible in one patient (1/199, 0.5%).

HRT measurement

TO is a measure of the relative shortening of R-R intervals immediately after the pause of the index ventricular premature beat (i.e., the percentage difference between the heart rate immediately following and preceding VPC). It is calculated using the equation: TO = ((RR1 + RR2) – (RR – 2 + RR – 1)) / (RR – 2 + RR – 1)*100, with RR-2 and RR-1 being the first two normal intervals preceding the VPC and RR1 and RR2 the first two normal intervals following the VPC.[8]

TS describes the subsequent lengthening of RR intervals, is quantified by the steepest linear regression between the RR interval count and the RR interval duration. It is defined as the maximum positive steepest slope of the linear regression line for each sequence of five consecutive normal intervals in the local tachogram.[8]

Values for TO <0% and for TS >2.5 ms/RR interval were considered normal.[8]

TWA Analysis

Two methods currently exist to perform microvolt TWA analysis—the spectral analytic method and the modified moving average method. In this study we used the modified moving average method.[18] TWA was calculated as the maximum difference between successive T waves of the respective moving averages for each 15-second beat stream. Additional algorithms minimized the effect of noise and artifact. TWA measurements were made from normal beats with accurately detected beat onsets only. In a manner similar to that used for routine Holter-based ST segment analysis, the greatest TWA magnitudes were separately examined for each of the two leads, starting at the maximum value detected. For each value of TWA, the associated ECG strip and superimposed A and B waveforms from the modified moving average algorithm were displayed. TWA values were determined and used as the peak TWA for each lead. TWA >46 μV was considered abnormal.[18]

Outcomes

The primary outcome was a composite endpoint of sudden death and sustained VA treated with external electric cardioversion. Secondary outcomes were: (1) all cause death and (2) the composite endpoint of all cause death and sustained VA treated with electric cardioversion. No patients were lost to follow-up.

Statistical analysis

Continuous variables are expressed as means ± standard deviation (SD) and proportions are expressed as percentages. Variables were visually checked for nonnormal distribution and log-transformed if necessary. Unpaired *t*-tests, chi-square test, and Fisher's exact test were used when appropriate.

Receiver operating curve (ROC) analysis was performed to determine the predictive performance of each Holter ECG parameter for the considered outcomes. Predictive performance was measured with the area under the ROC curve (ROC-AUC). ROC-AUC values range from 0 to 1, with 0 and 1 representing perfect predictive performance and 0.5 representing chance prediction. ROC-AUC was considered as poor if ranging from 0.6 to 0.7, fair if ranging from 0.7 to 0.8 and good if >0.8.

As a sensitivity analysis, Cox survival models were fitted to determine the association between Holter variables and outcome.

Statistical analyses were performed using SPSS 15 software (SPSS Inc., Chicago, IL, USA). A P value <0.05 was considered statistically significant.

RESULTS

The majority of the 199 patients were male (77%, N = 154) and half were smokers (47%, N = 98) (Table 1). Mean LVEF was 45.3 ± 9.5%. All patients underwent coronary angiography and 10 (5%) had no invasive treatment because coronary spasm was diagnosed or suspected. More that 95% of the patients were prescribed beta-blockers and/or angiotensin converting enzyme inhibitors during their ICU stay (96.5% for beta blockers, 99% for angiotensin converting enzyme inhibitors).

Table 1. Patient Characteristics

Patients, n	**199**
Age (years)	61.7 ± 14.8
Female gender	22.6%
Body mass index (kg/m^2)	27.0 ± 3.7
Diabetes	18.7%
Hypertension	20%
Current smoker	46.7%
Hypercholesterolemia	28.6%
Myocardial infarction site	
Anterior	49.2%
Inferior	47.2%
Lateral	17.6%
Killip class>1	26.6%
Preadmission cardiac arrest	7.0%
Coronarography data	
Left anterior descending artery	
Stenosis ≥70	17.6%
Occluded or suboccluded	46.7%
Left circumflex artery	
Stenosis ≥70	12.6%
Occluded or suboccluded	12.1%
Right coronary artery	
Stenosis ≥70	7.0%
Occluded or suboccluded	42.7%
Two vessel disease	27.6%
Three vessel disease	7.0%
Initial treatment by PCI/CABG	92%/3%
Number of stents during the index procedure	1.21 ± 0.68
Peak Troponin I (ng/l)	84.5 ± 97.61
LVEF%	45.3 ± 9.5
LVEF ≤ 40%	31.7%
ECG data	
PR (ms)	167.3 ± 22.7
QRS (ms)	82.7 ± 13.2
QTc (ms)	406.7 ± 41.7

There was no significant association between gender, MI territory, diabetes, smoking status, LVEF, and **abnormal values** of TO, TS, or TWA (Table 2, all $P > 0.05$). Patients with **abnormal values** of TO were significantly older compared to patients with negative TO (mean age 68.0 ± 15.8 vs. 59.7 ± 14.0, $P = 0.001$). In contrast, age was not significantly associated with the prevalence of **abnormal values** of TS or TWA (all $P > 0.25$). **Abnormal values** TO, TS, or TWA was not significantly associated with the occurrence of in hospital nonsustained VT (all $P > 0.1$).

Table 2. Data FROM Holter ECG in the Entire Population and in Patients with LVEF ≤40%

	Entire population	**Patients with LVEF ≤40%**
Geometric mean of PVB	25.9 ± 5.0	28.7 ± 6.0
Nonsustained VT (%)	11.7%	11.1%
HRT variables		
Mean TO (%)	−1.12 ± 2.5	−0.64 ± 2.15
TO > 0%	23.1%	28.6%
Geometric mean TS ms/RRI	5.75 ± 2.38	4.17 ± 2.42
TS < 2.5 ms/ RRI	16.6%	25.4%
TWA variables		
Mean TWA on channel 1 (μV)	25.2 ± 14.1	27.0 ± 16.0
TWA > 46 μV on channel 1	8.5%	11.1%
Mean TWA on channel 2 (μV)	23.8 ± 13.7	23.0 ± 13.9
TWA > 46 μV on channel 2	6.0%	6.3%

During the 6-month follow-up period, five patients had an event, including two ventricular tachycardia requiring external electric cardioversion and three SCD. In addition, seven patients died of non–sudden-death causes, mostly during the index hospitalization ($n = 6$, one septic shock, one left ventricular free wall rupture, and four cardiogenic shocks). Consequently, the overall mortality during 6-month follow-up was 5.0% (10/199).

Prognostic performance of HRT and TWA in the entire cohort for the primary outcome

When considered as continuous variables, TO and TWA on channel 1 (TWA1) had poor ROC-AUC with regards to the primary outcome of the study (both 0.64) whereas TS and TWA on channel 2 (TWA2) failed to show any predictive performance (ROC-AUC 0.48 and 0.57, respectively) (Table 3). The predictive performance of the log-transformed variable of TS was similar (ROC-AUC = 0.48).

As TO and TWA1 showed some prognostic performance with regards to the primary outcome, we constructed a combined variable of TO and TWA1. To account for large differences in standard

Table 3. Predictive Performance of Holter ECG Data

	Entire population				Patients with LVEF ≤ 40%			
	SCD or life-threatening VA within 6 months of MI		All cause death or life-threatening VA within 6 months of MI		SCD or life-threatening VA within 6 months of MI		All cause death or life-threatening VA within 6 months of MI	
ROC-AUC	Value	CI	Value	CI	Value	CI	Value	CI
TO	0.64	0.34–0.93	0.69	0.55–0.83	0.71	0.40–1.02	0.69	0.54–0.84
TS	0.48	0.19–0.77	0.31	0.15–0.48	0.51	0.17–0.85	0.35	0.17–0.53
TWA on channel 1	0.64	0.34–0.94	0.63	0.45–0.80	0.59	0.20–0.97	0.59	0.38–0.80
TWA on channel 2	0.57	0.32–0.82	0.63	0.45–0.79	0.52	0.23–0.82	0.59	0.39–0.79
Combination of TO and TWA on channel 1 (TO*6 + TWA1)	0.80	0.65–0.96	0.74	0.63–0.85	0.86	0.77–0.96	0.73	0.60–0.87

deviation of these two variables (SD = 2.5 for TO and SD = 14.1 for TWA1), the following additive variable was constructed: TO*6 + TWA1. This new variable showed good predictive performance with regard to the primary outcome (ROC-AUC = 0.80). A threshold of TO*6 + TWA1 equal to 31.5 (no units) showed a sensitivity of 80% and specificity of 79%. Forty-four patients (22.1%) had a TO*6 + TWA1 ≥ 31.5.

ROC-AUC of age, LVEF, and peak troponin were 0.78 (CI = 0.49–1.00), 0.17 (CI = 0.05–0.29), and 0.65 (CI = 0.41–0.88), respectively.

Survival analyses confirmed the results obtained by ROC curves analyses. TO tended to be associated with the primary outcome (P = 0.07), whereas TS, TWA1, and TWA2 were not significantly associated with the incidence of the primary outcome (P = 0.80, P = 0.15, and P = 0.96, respectively). There was a significant increase in the primary outcome in patients with higher TO*6 + TWA1 (HR = 1.036, 95% confidence interval = 1.004–1.068, P = 0.03).

Prognostic performance of HRT and TWA for the primary outcome in patients with LVEF ≤40%

In the subset of 63 patients (31.7%) with LVEF ≤40%, the percentage of abnormal values TO, TS, TWA1, and TWA2 were not significantly higher than in the entire population (28.6% vs. 23.1%, 25.4% vs. 16.6%, 11.1% vs. 8.5%, and 6.3% vs. 6.0%, respectively, all P > 0.1).

During the 6-month follow-up period, four patients in this group had an event (two ventricular tachycardia requiring electric cardioversion, two sudden deaths).

In the subset of patients with LVEF ≤40%, TO had a fair predictive performance (ROC-AUC 0.71) whereas TS, TWA1, and TWA2 had no predictive performance (ROC-AUC 0.51, 0.59, and 0.52, respectively). The combined variable of TO and TWA1 (TO*6 + TWA1) still showed good predictive performance for the primary outcome (ROC-AUC 0.86). A threshold of TO*6 + TWA1 equal to 31.5 (no units) had a sensitivity of 100% and specificity of 78%, whereas a threshold of 34.8 (no units) had a sensitivity of 75% and a specificity of 85%. And 17 patients (28.3%) had a TO*6 + TWA1 ≥ 31.5 and 12 patients (20.0%) had a TO*6 + TWA1 ≥ 34.8.

Of note, in this subset, age, LVEF, and peak troponin had poor predictive performance with regards to the primary outcome (ROC-AUC 0.70, 0.36, and 0.65, respectively).

Prognostic performance of HRT and TWA for secondary outcomes

The four Holter ECG variables of interest had ROC-AUC ranging from 0.28 to 0.68 when considering all-cause death (data not shown) and ROC-AUC ranging from 0.35 to 0.69 when considering all cause death and VA treated with electric cardioversion (Table 3).

The combined variable of TO and TWA1 (TO*6 + TWA1) had a fair predictive performance when considering all-cause death or all cause death and VA treated with electric cardioversion (0.72 and 0.74, respectively). In patients with LVEF $\leq$40%, similar ROC-AUC were found (0.70 for all cause death and 0.73 for all cause death and VA treated with electric cardioversion).

DISCUSSION

The main finding of our study is that the integrated use of HRT and TWA can be useful in predicting sudden death or life-threatening VA within 6 months after acute MI. This finding appears of great interest considering that (1) most SCD after MI occur within the first year[2] and (2) numerous ICD implantations are performed more than 1-year after MI.[4,19] HRT and TWA might be of interest in identifying patients who could benefit from early ICD implantation.

Usefulness of in hospital TWA and HRT to predict sudden death after MI

The predictive performance of TWA[11–13] and HRT[1,9] for SCD has been proven in previous studies. However, in these studies, Holter recordings were usually performed more than 7 days after MI. In modern cardiology practice, as most MI patients leave the hospital within days of the MI occurrence,[17] this implies an outpatient measurement. However, outpatient recording is probably a great limitation to the widespread utilization of TWA and HRT to assess early post-MI risk of SCD. In the present study, in-hospital measurement of TWA and HRT showed good predictive performance with regards to SCD and life-threatening VA. This finding is in contradiction with results of the REFINE study.[16] Indeed, Exner et al. found that Holter measurements were predictive of clinical outcome only if recordings were made 2 months after MI.[16] However, it should be acknowledge that, as HRT and TWA can change with time.[20] These measures could be associated with clinical outcome only for a limited period of time (i.e., early measurements might predict only early outcome). Our positive results might thus be partly explained by the 6-month follow-up chosen in our study.

In contrast, our findings regarding the cumulative predictive value of TWA and HRT are in line with results of the REFINE study.[16] Indeed, when taken separately, the predictive value of TWA and HRT remained limited (ROC-AUC <0.7) whereas combining these variables showed good predictive value (ROC-AUC 0.80 in the whole population and 0.86 in patients with LVEF <40%). This predictive performance should be compared with the current techniques to predict SCD, which are based on clinical characteristics. In the post hoc analysis of the VALIANT trial published by Piccini et al.,[21] the C-Index of the multivariable model for SCD 30 days to 6 months after MI was 0.747 despite the inclusion of 22 variables. When compared to this result, the assessment of risk for SCD with TWA and HRT measurement based on in-hospital Holter recordings appears of great interest.

Timing of ICD implantation

ICD implantation rates have increased in Europe during the decade[22] but remains much lower than the US implantation rates. Numerous patients who meet the guidelines criteria for ICD implantation still do not beneficiate from ICD implantation.[23] The debate regarding the optimal timing for ICD implantation after MI is possibly one of the factors that precludes a larger adherence to guidelines. Most patients included in the MADIT I and II studies were enrolled greater than 6 months after MI (75% and 88%, respectively).[3] Some data suggests that LVEF continue to increase more than 6 months after AMI.[24] In addition, some studies suggest a lack of efficiency of ICDs to prevent all-cause mortality when implanted early after MI.[4,7,25] As a consequence, most ICDs are implanted distantly from the initial MI.[4,19] In our study, we found that the combined variable of TWA and TO has a good predictive value for

SCD or life-threatening VA within six months after index MI. This variable could consequently help to identify patients who would most benefit from early ICD implantation. Patients with a combined Holter variable value (TO*6 + TWA1) > 31.5 might beneficiate from an ICD implantation within the first months after MI. Nonetheless, owing to the limited power of our study, further investigations should be conducted in similar settings to ascertain the predictive performance of in-hospital Holter recording to assess early arrhythmic risk after a first MI.

It was suggested from available data[25] that the prevention of early SCD after MI would only translate into higher rates of early nonarrhythmic deaths. However, this assertion is mainly based on the results of a study published in the mid 2000s.[25] The management of severe cardiac pump failure has considerably improved over the past 10 years.[26] Consequently, we could hypothesize that the prevented SCD might translate, currently, into higher rates of nonlethal severe heart failure events rather than higher rates of lethal heart failure events. For instance, ventricular assist devices have greatly improved over the past years.[27] From our point of view, identifying patients with very high arrhythmic risk remains of crucial interest.

Limitation of the study

This is a moderately sized cohort study. As SCD or life-threatening VA within 6 months of MI is a fairly rare event, we had limited statistical power for our analyses. Consequently, it was impossible to performed multivariable analyses. Importantly, we could not adjust for LVEF. However, Holter variables and LVEF are poorly correlated, and might thus be complementary with regards to sudden death prediction. Besides, within the subset of patients with LVEF <40%, our combined variable of HRT and TWA remained highly predictive of an arrhythmic event.

We could not determine the information gain of our combined Holter variable over other patient characteristics. However, no clinical risk score for SCD after MI is currently sufficiently accurate to guide therapy. Ejection fraction, which is virtually the only variable used in clinical practice to guide treatment, is known to suffer from a low sensitivity and specificity.[28] In our study, the predictive performance of our combined Holter variable was similar to that of LVEF (ROC-AUC 0.80 vs. 0.17, delta between 0.5, with the two ROC-AUC being 0.30 and 0.33, respectively).

As the Holter recordings were performed during the initial hospital stay, mostly in the ICU, patients had no or very limited physical activity. Patients were also receiving variable doses of beta-blockers, which can impact Holter variables. However, these limitations are due to the timing of the Holter recording itself. Importantly, despite the setting in which the Holter measurements were performed, we found a good predictive performance of the combined TWA-HRT variable. This good predictive performance is, in the end, the most important feature. As discussed earlier, we feel that the measurement of HRT and TWA during the index hospital stay is a way to promote its use in clinical practice.

CONCLUSION

Our study demonstrates that abnormal values of HRT and TWA are useful predictors of early SCD or life-threatening VA after acute MI. A combined variable including HRT and TWA data (TO and TWA on channel 1) showed good predictive ability for early post-MI events and should be further evaluated in larger studies. This combined variable could help identify patients who would benefit from early ICD implantation after MI.

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