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REVIEW

The clinical value of T-wave alternans derived from Holter monitoring

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Microvolt-level T-wave alternans (TWA) assessed by spectral method during an exercise stress test has been widely studied for risk stratification. Several studies have documented the association of a positive TWA with total mortality and arrhythmic events. Nevertheless, the need to achieve an elevated and stabilized heart rate resulting in a considerable proportion of indeterminate test results constitutes one of the main limitations of this method. It is well recognized that arrhythmic events may be triggered not only by physical but also by mental stress and are not necessarily associated with exercise. Detection of TWA in ambulatory electrocardiogram recordings during daily activities might be a valuable option in risk stratification. This review describes the modified moving average (MMA) technique for detection of TWA and summarizes the results of clinical studies on the prognostic value of MMA-TWA. So far, MMA-TWA has been studied in over 5000 patients including those evaluated during exercise as well as during daily activities with ambulatory ECG recordings. The results of these studies indicate that increased MMA-TWA is associated with higher risk of cardiac mortality and arrhythmic events.

Keywords T-wave alternans • Holter monitoring • Modified moving average technique • Sudden cardiac death

Introduction

Macroscopic beat-to-beat changes in amplitude, shape, or even polarity of T waves on 2:1 basis called T-wave alternans (TWA) have been observed for many years in electrocardiogram (ECG) recordings of patients with Prinzmental angina and in those with long QT syndrome[1,2] (*Figure 1*). Several clinical studies and case reports showed that these clearly visible changes were associated with arrhythmic events.[3–5] Such an increased propensity to life-threatening arrhythmias in patients with alternating T waves is believed to be related to an underlying increased spatial heterogeneity of the repolarization process of the myocardium. Various cellular and molecular mechanisms including mostly calcium and potassium homeostasis are involved in this process.[6,7]

Development of technology over the last two decades brought evidence that subtle, non-visible with naked eye, microvolt changes in the ECG basis could be detected by special algorithms. Several technologies to evaluate TWA have been developed over the last decade; however, only two of them have been studied in sizeable clinical studies, namely the *spectral method* and the *modified moving average (MMA) method*. While the first method is applied during exercise test, the latter one (MMA) allows for estimation of TWA both during exercise and in ambulatory long-term ECG recordings during daily activities. Such an approach allows for detection of repolarization abnormalities that occur during normal activities and does not require a target heart rate, which is a major limitation of the traditional spectral method.[8–13]

Following first enthusiastic reports on high predictive value of a spectral method in predicting sudden cardiac death (SCD), TWA assessment was recommended as a Class IIa in risk stratification of patients with ventricular arrhythmias.[14–19] However, the first interventional trial revealed that TWA, while still predictive for all-cause mortality, was unable to predict sudden death or arrhythmic events in patients who were subjected to implantable cardioverter-defibrillator (ICD) implantation (MASTER trial).[20] Subsequently, the SCD-HEFT trial failed to demonstrate the usefulness of TWA in predicting arrhythmic events defined as SCD, sustained ventricular tachycardia (VT)/fibrillation, or appropriate ICD in patients with heart failure.[21] However, negative findings in MASTER and SDC-HEFT trials could have an alternative explanation. A meta-analysis of the spectral method TWA studies by Chan *et al.* showed significant reduction of the hazard ratios after the washout of β-adrenergic blockade, as was performed in the MASTER study.[22] This result was partly related to the fact that, consistent with their capacity to reduce SCD rate, β-blockers suppress TWA. Therefore, their resumption after the test would necessarily disrupt the predictive capacity of the test results. The conflicting results between risk stratification and interventional studies were addressed in a

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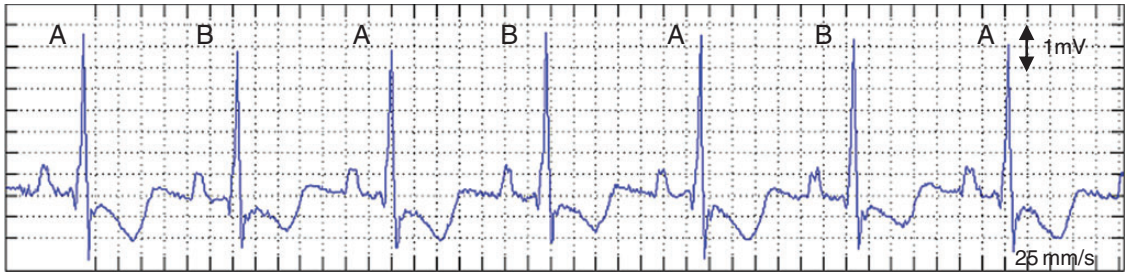

Figure 1 Macroscopic TWA (A–B–A–B) observed in ambulatory ECG recording of a 62-year-old male with heart failure due to ischaemic cardiomyopathy.

meta-analysis by Hohnloser *et al.*[23] They found that the predictive value of TWA was high in those studies with low number of patients with ICDs (HR 13.6; 95% CI 8.5–30.4 for abnormal vs. negative TWA). In contrast, it was low in studies of patients with frequent ICD use (HR 1.6; 95% CI 1.2–2.1). These results support the hypothesis that ICD shocks represent a surrogate endpoint of arrhythmogenic death and reduce the predictive value of TWA.[23]

Since the classical spectral method is limited by a considerable proportion of non-determined results, more attention is being paid to another method of TWA evaluation in ambulatory ECG recordings, which does not require meeting a target heart rate and drugs' washout. This review focuses on clinical trials that evaluated the prognostic value of MMA-TWA with regard to arrhythmia risk stratification.

Rationale for T-wave alternans evaluation from ambulatory electrocardiogram recordings

Several case reports demonstrated significant alterations in autonomic nervous system and repolarization in periods preceding life-threatening arrhythmias. Holter studies showed that this period is characterized by sudden increase in heart rate, decrease in heart rate variability, and abrupt prolongation of QT interval.[5] Progressive changes in MMA-TWA in the period preceding life-threatening arrhythmias were first shown in an experimental study by Nearing and Verrier[24] on the ventricular fibrillation (VF) induced by the occlusion of left anterior descending coronary artery in a canine model of ischaemia. The epicardiac ECG recordings showed progressive changes in T-wave morphology from the uniform morphology to TWA (2:1) and then to more complex forms like tripling or quadrupling in dogs with VF induced by myocardial ischaemia. A similar phenomenon was reported by Shusterman *et al.*[5] in humans in periods preceding ventricular tachyarrhythmias. The magnitude of TWA significantly increased in a period of 30 min before onset of sustained ventricular tachyarrhythmias in patients from the ESVEM (*Electrophysiologic Study versus Electrocardiographic Monitoring*) trial.

It is well recognized that ventricular repolarization and its heterogeneity are influenced not only by physical exertion with an elevated heart rate but also by variety of factors like autonomic nervous system balance, electrolytes, hormones, drugs, etc. A large number of sudden deaths occur unrelated to exercise, and the risk of arrhythmia may be increased also by mental stress.[25–27] Thus, evaluation of TWA during daily activities on the basis of the ambulatory ECG monitoring might be considered as a reasonable alternative. Such a monitoring covers early morning period, known as a risky due to arousal-related cardiac events as well as allows for correlation between repolarization changes and arrhythmic or ischaemic episodes. Furthermore, MMA analysis does not require elevated and stabilized heart rate. Such requirement is considered to be a limitation of the spectral method. Up to 50% of heart failure patients may be ineligible for TWA evaluation by spectral method due to atrial fibrillation or paced rhythm or due to physical inability to perform exercise. Inability to achieve target heart rate is the most common reason of indeterminate results in this population.[28] More importantly, MMA method can also be evaluated in an exercise protocol, in which case it uses routine, symptom-limited exercise, not target-heart-rate exercise.

Modified moving average analysis methodology

Modified moving average analysis is a non-spectral, time-domain-based method of TWA measurement in which a stream of beats is divided into odd and even bins. Subsequently, the morphology of the beats in each bin is averaged over a few beats successively to create a moving average complex, and TWA is then defined as the maximum difference in amplitude between the odd-beats and the even-beats complexes from the J point to the end of T wave (*Figure 2*).[29] Detailed methodological guidelines including technical requirements, electrode types, and lead configuration for MMA-TWA assessment were published in a consensus guideline prepared by the International Society for Holter and Noninvasive Electrocardiology.[13] Taking into account pathophysiological factors related to an increased risk of arrhythmias, it would be reasonable that TWA should be measured at the peak heart rate, at morning hours, and at the peak ST deviation from the baseline as it was previously suggested.[29] However, current recommendations are to use only the maximum TWA level recorded without regard for heart rate, time of a day, or/and ST-segment deviation with cut-points of 47 and 60 μV defining abnormality and severe abnormality, respectively.[13] T-wave alternans should be calculated from precordial

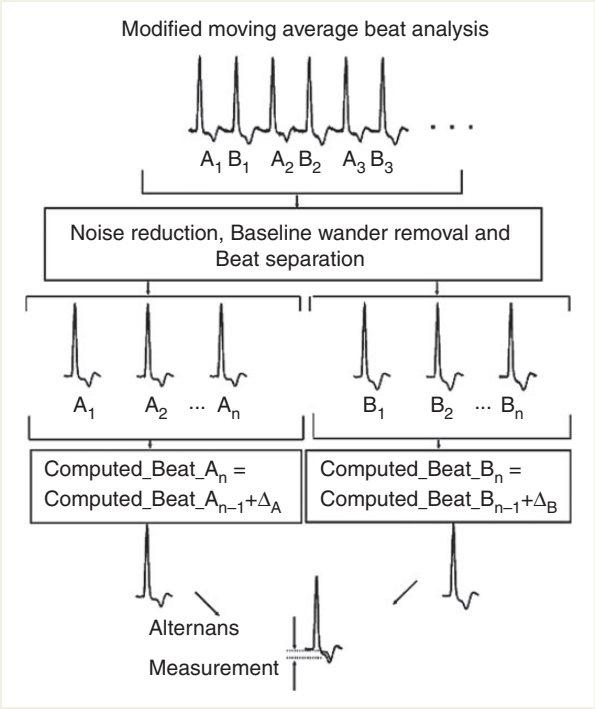

Figure 2 Modified moving average technique.

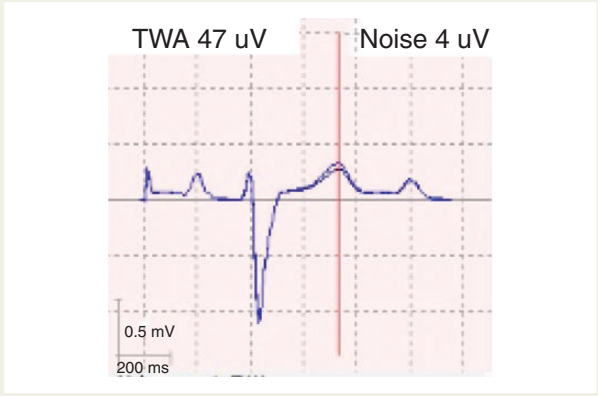

Figure 3 Modified moving average TWA in a patient with heart failure (an image of QRS-aligned templates generated by the MMA method, where the vertical line represents the point of maximum TWA 47 μV, noise 4 μV).

leads, as limb leads are prone to provide unreliable results due to motion artifacts.[13] Furthermore, it seems that TWA from particular leads has greater prognostic value than that from the others.[30–32] Verrier *et al.* found that TWA is lead specific, with higher values in V5 than in V1.[30] Similarly, a study by Leino *et al.* showed that TWA assessed from lead V5 exceeded single leads and combinations of leads for all-cause mortality prediction.[33]

The current guidelines indicate that TWA assessment should be performed on pharmacotherapy.[13] Drugs, such as β-blockers, influence TWA magnitude; however, the predictive value of TWA remains unchanged despite the intake of drugs.[13,22] T-wave alternans may also be influenced by revascularization and/or moderate physical activity during rehabilitation.[22,34–36]

Since the MMA is the only FDA-approved method for analysing TWA from Holter monitoring records, the present review is targeting that methodology. However, other methods have also been proposed for the evaluation of alternans and variability of TWA in ambulatory Holter recordings.[2,8,9,12] Average TWA activity was found to be predictive of SCD in heart failure patients.[9,37] The so-called transient variability of T-wave morphology (TWV) was shown to be predictive for ventricular tachyarrhythmias in MADIT II population[38] or congenital long QT syndrome patients.[39]

Prognostic value of Holter-derived T-wave alternans in clinical studies

Initial observational data on the potential role of increased ventricular heterogeneity detected by MMA technique led to studies evaluating the predictive value of MMA-TWA in different subsets of patients. First, data on potential value of MMA-TWA in assessment of arrhythmia vulnerability came from a study published in 2003 by Verrier *et al.*[30] The authors compared MMA-TWA in post-infarction patients who experienced cardiac arrest due to VF or arrhythmic death and matched controls from the ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) study. T-wave alternans was assessed in three pre-specified time periods from 24-h Holter monitoring: the maximum heart rate, morning hours (at 8 AM), and at the maximum ST deviation. In both cases and controls, TWA amplitude was significantly higher at each of these predetermined time periods when compared with baseline. 'High-risk' TWA cut-offs were defined as those above 75th percentile (from 42.5 to 74 μV depending on the lead and a studied period time). Increased TWA at the maximum heart rate as well as at morning hours was associated with arrhythmic events. The results confirmed the hypothesis that TWA should be looked for not only at the maximum heart rate that can be achieved by exercise but also during high-risk day periods, i.e. morning hours.

A case-control study matched for age, gender, and diabetes, including post-myocardial infarction (MI) patients with heart failure and/or diabetes from the EPHESUS (*Eplerenon Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study*) trial,[40] confirmed that MMA-TWA assessed from 24 h ambulatory ECG monitoring is a strong predictor of SCD. T-wave alternans was higher in patients who died suddenly. The cut-off point of TWA >47 μV (based on cut-offs reported by ATRAMI investigators) was associated with SCD with RR 5.2 (95% CI 1.8–14.6, $P = 0.002$) for a lead V1 and RR 5.5 (95% CI 2.2–13.8, $P < 0.001$) when evaluated in a lead V3. In this study, the highest levels of TWA were observed in the afternoon hours, which is compatible with the fact that heart failure patients typically die in the afternoon (*Figure 3*).[41]

A prospective study by Sakaki *et al.*[31] that included patients with left ventricular dysfunction due to ischaemic and non-ischaemic cardiomyopathy evaluated TWA in predicting cardiac mortality. Kaplan-Meier analysis revealed significant separation of survivors and non-survivors by the TWA cut-off value. Abnormal TWA was the strongest multivariate risk predictor for cardiac mortality (HR

17.1, $P < 0.001$) and was predictive in both ischaemic and non-ischaemic sub-groups.[31]

In the REFINE study,[42] patients after MI with at least mild left ventricular dysfunction [left ventricular ejection fraction (LVEF) <50%] underwent non-invasive risk stratification within 2–4 weeks and 10–14 weeks after infarction. Both methodologies were used to assess TWA: (i) the 'traditional' spectral method from the exercise stress test and (ii) the MMA method from the 20- to 30-min resting ECG recordings immediately following the stress test. The cut-off for increased TWA was established on the basis of ROC curves to provide similar sensitivity and specificity as the exercise TWA at 5 μV. Both TWA techniques were not predictive for the primary endpoint (cardiac death or resuscitated cardiac arrest) when assessed within the first 2–4 weeks after infarction; however, they were found to be independent risk markers when assessed late after acute MI. T-wave alternans detected by MMA technique was related to a nearly three-fold higher risk of cardiac death or resuscitated cardiac arrest during follow-up (HR 2.94; 95% CI 1.10–7.87, $P = 0.031$). The best predictive model was provided by complex analysis of autonomic nervous system impairment assessed by heart rate turbulence (HRT) and the presence of electrical substrate expressed by TWA. The combination of abnormal Holter TWA and impaired HRT provided the highest HR (4.18; 95% CI 2.06–8.32, $P = 0.001$) to predict the primary endpoint. Nonetheless, following the results of the REFINE and other studies, the 2015 ESC Guidelines do not recommend microvolt TWA for risk stratification in the early phase (within 10 days) after MI.[43]

Similar combination of parameters reflecting both autonomic nervous tone and repolarization was tested by other authors. In a study by Arisha *et al.*,[44] combination of turbulence onset (TO) of HRT and TWA in a sub-group of patients with decreased LVEF ≤40% was strongly predictive of SCD or life-threatening ventricular arrhythmias. Sulimov et al. showed that TWA and TO values were significantly higher (83 vs. 79 μV, $P = 0.002$; 0 vs. −0.01, $P = 0.004$, respectively), and turbulence slope significantly lower (3.34 vs. 3.82 ms/RR, $P < 0.001$) in patients who died from cardiovascular causes when compared with survivors.[45] Hoshida *et al.*[46] demonstrated that while both MMA-TWA and HRT are significant predictors for cardiac mortality, TWA is more strongly correlated with arrhythmic events. On multivariate analysis, MMA-TWA was associated with a nearly six-fold higher risk of fatal arrhythmic events during follow-up, whereas HRT had higher predictive value for cardiac mortality.

In a recent subanalysis of a randomized trial on ranolazine (MERLIN-TIMI 36 trial) in patients with non-ST-segment elevation MI and LVEF <40%, an increased TWA at admission (>47 μV) was associated with an increased risk of total and cardiovascular mortality during a 1-year follow-up (OR = 2.35, 95% CI 1.03–5.37, $P = 0.04$ and OR = 2.18, 95% CI 0.93–5.11, $P = 0.07$, respectively) as well as with a higher risk of non-sustained VT episodes (>4 ventricular premature beats at heart rate >100 bpm) during hospitalization (OR = 2.70, 95% CI 1.31–5.56, $P = 0.01$).[47] Hou *et al.*[48] also confirmed that TWA is a useful tool to assess the risk of SCD shortly after acute coronary syndromes (1–15 days). Moreover, they documented that not only positive result of TWA but also the frequency of ≥5 episodes of positive TWA per 24 h has a predictive value for sudden death or life-threatening ventricular arrhythmia.[48]

An association of TWA with non-sustained VT episodes was observed in patients undergoing percutaneous coronary intervention procedures. Interestingly, the amplitude of TWA remained elevated up to 30 min after balloon inflation even in ST-segment elevation MI patients with complete reperfusion and TIMI grade 3 after procedure.[34] Similar results were obtained by Takasugi *et al.*,[35] who studied 20 patients with acute cardiac syndromes. In patients who experienced ventricular tachyarrhythmias following reperfusion, peak MMA-TWA assessed before reperfusion was higher than in the group without arrhythmia (33 ± 4.4 vs. 15.8 ± 4.0 μV, $P < 0.001$). The onset of arrhythmia in two patients was preceded by an elevation of TWA to 75 and 105 μV.[35] Shimada *et al.*[49] showed that in a group of 40 patients with vasospastic angina, those with episodes of VT presented higher values of TWA than those without arrhythmia (83.0 ± 15 vs. 65.9 ± 20 μV, $P < 0.05$).

Even though MMA-TWA has been analysed predominantly in post-infarction patients, there are substantial data supporting its prognostic role in other populations. Increased average TWA was associated with SCD in ambulatory patients with mild-to-moderate heart failure.[9] An increase in TWA amplitude was observed in periods preceding ventricular tachyarrhythmias in patients admitted to a hospital due to decompensated acute heart failure (from 18.6 ± 2.1 to 27.9 ± 4.6 μV in V5 lead at 15–30 min before VT, $P < 0.05$).[50] Chiu *et al.*[51] showed higher TWA values in patients with repaired tetralogy of Fallot when compared with controls (25.1 ± 14.0 vs. 17.6 ± 9.2 μV, $P < 0.001$). More importantly, in patients with congenital heart disease, a trend to higher TWA values was observed in those who developed late ventricular arrhythmias (34.0 ± 16.5 vs. 24.2 ± 13.5 μV, $P = 0.053$).[50] In patients with chronic heart failure, increased TWA levels correlated significantly with apnoea–hypopnoea index, which suggests that obstructive sleep apnoea may contribute to an increased risk of arrhythmia in this population.[52] Increased TWA was also proposed as a method to stratify patients with inherited primary arrhythmia syndromes. In patients with Brugada syndrome, positive TWA (defined as >60 μV in lead V2 or >57 μV in lead V5) was significantly associated with a history of VF.[53] Not surprisingly, higher TWA values were observed during night-time periods.[54] On the other hand, Yalin *et al.* found no relationship between TWA and ICD discharge in a small group of patients with Brugada syndrome.[55] However, in a letter to the editor, the authors admitted that TWA assessment during ambulatory ECG analysis might be superior to exercise-based TWA analysis as performed in their study.[56] A recently published study by Takasugi *et al.* showed evidence of the utility of Holter-based TWA to assess risk for torsade de pointes in long QT patients. More importantly, the study revealed that microvolt TWA is more frequent in patients with LQTS than it was previously reported.[57]

The prognostic role of TWA with regard to predicting arrhythmic risk in a general population was assessed in the Cardiovascular Health Study. In subjects older than 65 years, MMA-TWA >37 μV predicted SCD. More importantly, having both higher VPCs count and higher TWA was associated with eight-fold higher risk of sudden death.[58]

Conclusions

Modified moving average technique evaluating TWA from ambulatory ECG recordings has been largely studied in clinical trials and proved to be associated with unfavourable outcome. Being somehow independent on target heart rate, it offers some advantages over the spectral method, thus possibly resolving the problem of undetermined TWA tests and allowing for detection of repolarization instability during daily activities and those induced by other than physical activity causes such as mental stress.

Up to date, MMA-TWA has been studied in over 5000 patients from both smaller clinical and large randomized trials. Recently published meta-analysis by Quan *et al.* on MMA-TWA including patients with both ischaemic and non-ischaemic cardiomyopathies showed that positive MMA-TWA is associated with 7.5-fold higher risk of SCD, 4.75-fold higher risk of cardiac mortality, and 6-fold higher risk of a composite endpoint defined as sudden death, cardiac mortality, and severe arrhythmic events.[59]

According to 2006 ACC/AHA/ESC guidelines[14] on management of patients with ventricular arrhythmias and the prevention of SCD, TWA monitoring was recommended to improve diagnosis and risk stratification in patients with ventricular arrhythmias (Class IIa, level of evidence A). Recently published ESC guidelines on ventricular arrhythmias[41] do not recommend non-invasive risk stratification by means of TWA in the *early* post-infarction phase. However, these recommendations refer to spectral rather than MMA-TWA. AHA/ACC/HRS recommendations on non-invasive techniques in risk stratification[60] emphasize that even though the majority of data support a role of TWA in risk stratification, there is still a need of further prospective randomized trials to prove efficacy of TWA-guided antiarrhythmic therapy.

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