ORIGINAL ARTICLE

Importance of over-reading ambulatory ECG-based microvolt T-wave alternans to eliminate three main sources of measurement error

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Abstract

Background: Ambulatory electrocardiogram (ECG)-based microvolt T-wave alternans values measured by the modified moving average method (MMA-TWA) can be disrupted by T-wave changes that mimic true repolarization alternans.

Methods: We investigated potential sources of measurement error by studying 19 healthy subjects (12 men; median age, 25) free of known heart disease with 36-month follow-up to establish freedom from significant arrhythmia or syncope. All participants underwent 24-hr continuous 12-lead ECG monitoring. Causes of automated MMA-TWA ≥ 42 μ V episodes were classified based on visual inspection.

Results: A total of 2,189 episodes of automated MMA-TWA episodes ≥ 42 μ V were observed in all subjects (peak MMA-TWA: median, 94 μ V; interquartile range, 81–112 μ V). All episodes included one or more beats with T-wave deformation which lacked “repeating ABAB pattern” and therefore were identified as TWA measurement error. Causes of such error were categorized as: (a) artifact [72.6% (1,589/2,189), observed in 19 (100%) subjects], more frequently in limb than precordial leads; (b) T-wave changes due to changes in heart/body position [25.5% (559/2,189), observed in 14 (73.7%) subjects], frequently observed in leads V1-2; and (c) postextrasystolic T-wave changes [1.9% (41/2,189), observed in 2 (10.5%) subjects].

Conclusions: Relying only on automated MMA-TWA values obtained during ambulatory ECG monitoring can lead to incorrect measurement of TWA. Our findings offer the potential to reduce false-positive TWA results and to achieve more accurate detection of true repolarization alternans.

KEYWORDS

continuous 12-lead electrocardiography, healthy subject, microvolt T-wave alternans, modified moving average method

1 | INTRODUCTION

Microvolt T-wave alternans (TWA) has been demonstrated to be useful in arrhythmia risk stratification in ample clinical studies (Verrier et al., 2011). Two contemporary techniques used in the clinical studies are the Spectral (Rosenbaum et al., 1994) and the Modified Moving Average (MMA; Nearing & Verrier, 2002) methods. Prospective studies with ambulatory electrocardiogram (ECG)-based TWA analysis with MMA method have yielded significant predictive capacity in patients following myocardial infarction (Hou et al., 2012; Stein, Sanghavi, Domitrovich, Mackey, & Deedwania, 2008; Verrier et al., 2003) and with ischemic or nonischemic cardiomyopathy (Sakaki et al., 2009). The negative predictive value for cardiac death or sudden cardiac death was high, specifically, 97% (Sakaki et al., 2009) and 99% (Hou et al., 2012), whereas the positive predictive value was relatively low, that is, 37% (Sakaki et al., 2009) and 17% (Hou et al., 2012).

We hypothesized that TWA measurement error may limit the specificity of risk stratification with MMA. The purpose of this study was (a) to inspect raw ECG waveforms of automated MMA-based TWA episodes detected during ambulatory ECG monitoring in healthy subjects and (b) to classify the causes of TWA measurement error.

2 | METHODS

2.1 | Study participants

Nineteen healthy volunteers were enrolled between September 2015 and May 2016 with the following exclusion criteria: chest

symptoms, medical therapy, abnormal resting 12-lead ECG, known cardiovascular disease, sudden death in family history, and history of syncope. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee. Informed consent was obtained from each participant.

2.2 | Twenty-four-hour 12-lead continuous ECG monitoring

All participants underwent 24-hr continuous 12-lead ECG (SEER 12 Ambulatory Recorder, GE Healthcare) monitoring. Careful skin preparation and high-resolution electrodes (Blue Sensor L, Ambu A/S) were used to minimize noise. Average 24-hr heart rate was automatically calculated.

2.3 | Measurement of microvolt TWA

Microvolt TWA values were calculated by the time-domain MMA method (Nearing & Verrier, 2002) using MARS Holter Analysis Workstation Software Version 8 (GE Healthcare). In brief, a stream of beats is divided into odd and even bins and the morphology of the beats in each bin is averaged over a few beats successively to create a moving average complex. Average morphologies of both the odd and even beats are continuously updated by a weighting factor of one-eighth of the difference between the ongoing average and the new incoming beats. T-wave alternans is computed as the maximum difference in amplitude between the odd-beat and the even-beat

TABLE 1 Participant characteristics and results of 24-hr ambulatory ECG

Participant number	Sex	Age (years)	Average heart rate (bpm)	PVC (beat/day)	PAC (beat/day)	QTc (ms)
1	F	6	86	0	26	395
2	F	37	69	0	31	431
3	M	40	72	0	3	409
4	M	9	80	0	3	431
5	F	11	80	0	52	438
6	F	24	76	0	0	412
7	F	24	69	1	8	422
8	M	28	91	17	4	404
9	M	15	61	0	19	428
10	M	19	86	0	12	432
11	M	59	73	1,672	103	420
12	M	26	75	715	474	430
13	F	55	69	1	28	434
14	M	24	70	0	11	404
15	M	50	80	0	2	437
16	M	26	65	0	11	411
17	F	25	62	0	17	434
18	M	26	61	1	2	404
19	M	25	58	6	11	404

Abbreviations: F, female; M, male; PAC, premature atrial contraction; PVC, premature ventricular contraction.

TABLE 2 Peak TWA measurement error values and frequency of episodes $\geq 42 \mu V$

Participant number	Total episodes $\geq 42 \mu V$ (μV)	Motion artifact errors (μV)	Heart/body position change errors (μV)	Postextrastystolic errors (μV)	Total TWA ≥ 42 frequency (events/day)	Motion artifact errors frequency (events/day)	Heart/body position change errors frequency (events/day)	Postextrastystolic errors (events/day)
1	174	174	47	<42	68	66	2	0
2	81	73	81	<42	70	18	52	0
3	81	81	<42	<42	44	44	0	0
4	112	112	53	<42	171	160	11	0
5	172	172	50	<42	271	264	7	0
6	61	61	<42	NA	18	18	0	NA
7	94	94	60	<42	81	80	1	0
8	106	106	54	<42	104	102	2	0
9	112	110	112	<42	402	166	236	0
10	129	129	88	<42	260	110	150	0
11	89	89	75	42	27	14	12	1
12	97	97	64	68	174	114	20	40
13	101	101	<42	<42	43	43	0	0
14	81	73	81	<42	70	18	52	0
15	152	152	<42	<42	277	277	0	0
16	62	62	58	<42	15	9	6	0
17	92	92	64	<42	80	77	3	0
18	87	87	<42	<42	3	3	0	0
19	47	47	45	<42	11	6	5	0

Abbreviations: NA, not applicable; TWA, T-wave alternans.

average complexes from the J point to the end of the T wave for each 15 s beat stream.

The data were visually inspected and scored by one clinical technologist who was blinded to information on the subjects. TWA values at heart rate >120 bpm or those with noise levels >20 μV were excluded from the analysis. The lowest cut point TWA value at the present time ($\geq 42 \mu\text{V}$) was used (Takasugi et al., 2016, 2018; Verrier et al., 2011).

2.4 | Classification of “automatically generated” microvolt TWA $\geq 42 \mu\text{V}$ episodes

Automated TWA episodes were defined as TWA measurement error if they fulfilled the following criteria: (a) episode includes one or more beats with deformation of T wave, and (b) the T-wave deformation does not appear from beat-to-beat (lack of repeating ABAB pattern). Causes of T-wave deformation leading to TWA measurement error were categorized as: (a) artifact; (b) T-wave changes due to change in heart/body position; and (c) postextrasystolic T-wave changes.

2.5 | Statistical analysis

Statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). Continuous variables were presented as median (interquartile range).

3 | RESULTS

3.1 | Participant characteristics

The characteristics of the 19 participants and results of 24-hr ambulatory ECG are summarized in Table 1. During a median follow-up

of 36 (33.5–37) months, none of the participants experienced arrhythmias or syncope. All participants except for #6 exhibited atrial or ventricular extrasystoles.

3.2 | Results of microvolt TWA derived from 24-hr continuous 12-lead ECG in healthy subjects

The daily peak value of automated TWA was 94 (81–112) μV . A median of 75 (39–195.5) episodes of automated TWA $\geq 42 \mu\text{V}$ was observed in all subjects enrolled. All the episodes included one or more beats with T-wave deformation and lacked “repeating ABAB pattern.” A total of 2,189 instances of TWA measurement error episodes $\geq 42 \mu\text{V}$ were categorized into: (a) artifact [72.6% (1,589/2,189), observed in 19 (100%) subjects]; (b) T-wave changes due to change in heart/body position [25.5% (559/2,189), observed in 14 (73.7%) subjects]; and (c) postextrasystolic T-wave changes [1.9% (41/2,189) observed in 2 (10.5%) subjects]. Peak TWA measurement error values and daily frequency of TWA measurement error episodes according to the causes are summarized in Table 2.

3.3 | Artifact-induced TWA measurement error

A representative episode of artifact-induced TWA measurement error, which occurs primarily in the limb leads, is demonstrated in Figure 1. Baseline wander caused periodic changes in T-wave morphology, which mimicked polarity alternans of the T wave.

3.4 | Heart/body position-induced TWA measurement error

A representative episode of heart/body position-induced TWA measurement error is presented in Figure 2. Note the periodic

FIGURE 1 Representative case of T-wave alternans (TWA) measurement error due to artifact from participant 13. (a) ECG strips of leads I, II, and III at 20:12:15, show baseline wander. (b) TWA trend in leads I, II, and III from 20:10 to 20:14, showing transient episode of TWA measurement error at 20:12:15. (c) Templates of superimposed waveforms in leads I and II at 20:12:15

FIGURE 2 Representative case of T-wave alternans (TWA) measurement error due to body position (respiration) from participant 11. (a) ECG strips of leads V1, V2, and V3 at 01:30, showing periodic change in amplitude of the QRS complex and the T wave (blue arrows). Note that the lowest amplitude of the QRS complex and the T wave appeared in every fourth beat (red arrows). (b) TWA trend in leads V1, V2, and V3 from 01:28 to 01:32, showing transient episode of TWA measurement error at 01:30. (c) Templates of superimposed waveforms in leads V1 and V2 at 01:30

variation in the amplitude of the QRS complexes as well as the T waves, which might have resulted from respiratory movement. Importantly, the episode lacked “repeating ABAB pattern” and the large change in T-wave amplitude appeared in every fourth beat, which may have affected MMA-based TWA measurement.

3.5 | Postextrasystolic T-wave change-induced pseudo-TWA

A representative episode of pseudo-TWA induced by postextrasystolic T-wave change is demonstrated in Figure 3. Note the reduced

amplitude of the T wave in the beat after the compensatory pause, which may have affected MMA-based TWA measurement.

3.6 | Distribution of TWA measurement error episodes $\geq 42 \mu\text{V}$ in each lead

Distribution of TWA measurement error episodes $\geq 42 \mu\text{V}$ in each lead is shown in Figure 4. Artifact-induced TWA measurement error was observed more frequently in the limb leads than in the precordial leads. Heart/body position-induced TWA measurement error was observed frequently in the leads V1-2.

FIGURE 3 Representative case of T-wave alternans (TWA) measurement error due to postextrasystolic T-wave changes from participant 12. (a) ECG strips of leads V4, V5, and V6 at 12:03, showing postextrasystolic flattening of the T wave (red arrows). (b) TWA trend of leads V1, V2, and V3 from 01:28 to 01:32, showing transient episode of TWA measurement error at 12:03. (c) Templates of superimposed waveforms in leads V5 and V6 at 12:03

FIGURE 4 Number of T-wave alternans (TWA) measurement error episodes ≥ 42 μV in each lead in the entire group of participants studied. (a) TWA measurement error episodes ≥ 42 μV ($N = 2,189$) were most frequent in lead V1 ($N = 359$) and the second most frequent in lead V2 ($N = 294$). (b) TWA measurement error episodes ≥ 42 μV due to artifact ($N = 1,589$) were more frequent in the limb leads, especially in leads I ($N = 198$), II ($N = 188$), and III ($N = 226$), than in the precordial leads. (c) TWA measurement error episodes ≥ 42 μV due to body position ($N = 559$) were most frequent (85.3%; 477/559) in leads V1 ($N = 277$) and V2 ($N = 200$). (d) Only 1.9% (41/2,189) of TWA measurement error episodes ≥ 42 μV were due to postextrasystolic T-wave changes. Nearly all (97.6%, 40/41) of the episodes were from participant 12, and 30 of the 40 episodes were observed in lead V5

4 | DISCUSSION

The present study has shown that automated MMA-TWA episodes derived from 24-hr ambulatory ECG recordings may include TWA measurement error, which can lead to false-positive TWA results. MMA-based TWA values can be influenced by a large change in T-wave morphology in a single beat, although we used a weighting factor of 1/8 (default setting), that is, average T-wave morphology is updated by 1/8 of the difference between ongoing average and new incoming beats. Our results suggest that there are three main sources of TWA measurement error, namely artifact due to movement and baseline wander; body/heart position changes; and postextrasystolic potentiation.

4.1 | TWA measurement error due to artifact

Continuous ECG monitoring during daily activities such as exercise, eating, sleeping or emotional stress, which dynamically affect physiological conditions, may offer a more practical means of risk stratification compared to exercise stress ECG only (Steinberg et al., 2017). However, accurate TWA measurement in freely moving subjects is technically challenging due to noise such as from movement or myopotentials, particularly in the limb leads. Indeed, the leading cause of TWA measurement error in the present study was artifact despite the fact that episodes with noise levels >20 μV were excluded

from the analysis. Visual inspection to exclude artifact-induced TWA measurement error is not difficult.

4.2 | TWA measurement error due to change in body or heart position

Shift in electrical axis or transitional zone can be caused by change in heart position due to respiration or change in body position. The shift in depolarization typically alters subsequent repolarization (Rautaharju, Surawicz, Gettes, & Wellens, 2009). Theoretically, QRS axis (amplitude) is directly proportional to T-wave axis (amplitude) as demonstrated in Figure 3. If the large change occurs every second/fourth/sixth/... beat, the automated MMA-TWA value will be overestimated. It is of interest that the TWA measurement error induced by changes in heart position appeared in a specific narrow region, namely precordial leads V1 and V2. This finding is important because TWA frequently appears in the precordial leads V1 and V2 in patients with long QT syndrome (Takasugi et al., 2016, 2018) and Brugada syndrome (Nishizaki, Fujii, Sakurada, Kimura, & Hiraoka, 2005).

4.3 | Pseudo-MMA-TWA due to postextrasystolic T-wave changes

Postextrasystolic T-wave changes, that is, changes in the T-wave amplitude, shape, or polarity of the sinus beats immediately following

ventricular extrasystoles, appear neither sensitive nor specific in the identification of patients with cardiac disease and can be deemed benign (Fagin & Guidot, 1958; Leachman et al., 1981). The mechanism is unknown, but is considered to be related to cardiac memory (Batchvarov, Bajpai, & Camm, 2007) or to mechano-electrical feedback, that is, shortening of repolarization time resulting from increased ventricular filling pressure during compensatory pause (Franz, 1996). Of the 19 healthy subjects enrolled, only 2 subjects exhibited postextrasystolic T-wave change-induced pseudo-TWA. However, exclusion of such postextrasystolic T-wave episodes of pseudo-TWA is important in risk stratification of patients with heart disease, since such patients may exhibit extrasystoles more frequently than healthy subjects.

4.4 | Limitations

First, sample size of our study was small. Second, the present study did not include subjects with cardiac disease and the applicability of the current findings to these populations requires further study. Third, apparently normal 12-lead ECGs may have led to information bias although the examiner was blinded to information about the subjects. Finally, significant transmural dispersion of repolarization (TDR) may not always be manifested as "ABAB pattern" (Takasugi et al., 2018). However, in the presence of such large TDR, the "ABAB pattern" should appear during heart rate increase at different times of day.

5 | CONCLUSIONS

The present findings emphasize the importance of over-reading ambulatory ECG-based microvolt TWA to eliminate the main sources of measurement error. Precordial leads, particularly V3-V6 are generally preferred, as they minimize the main source of measurement error due to artifact, namely motion, which is often observed in the limb leads, and are less sensitive to changes in body position. Close attention to changes in the ABAB pattern during atrial and ventricular ectopy is warranted. Adherence to the findings of the present study has the potential to rule out false-positive TWA results and more accurately to detect the presence of true repolarization alternans. Larger methodological studies in patients with different stages of structural heart disease and different quantities of atrial and ventricular ectopic activity are needed in order to classify the incidence and major sources of measurement errors and to define recommendations for over-reading of MMA-TWA in these specific patient populations.

CONFLICT OF INTEREST

R.L.V. receives royalty income from Georgetown University and Beth Israel Deaconess Medical Center for intellectual property on the Modified Moving Average method of TWA analysis, which has

been licensed by GE Healthcare and was used in this study. The other authors have declared no conflicts of interest.

AUTHOR CONTRIBUTIONS

N.T.: conceived and designed the study, collected the data, analyzed and interpreted the data, and drafted the article. M.T. and R.L.V.: conceived and designed the study, analyzed and interpreted the data, and revised the article critically. H.M., K.S., and T.W.: collected the data, analyzed the data, and revised the article critically. H.I.: analyzed the data, revised the article critically, and involved in funding. H.O.: analyzed the data, performed statistics, revised the article critically, and involved in funding.

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