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T-wave Alternans Dependency on T-wave Amplitude in Exercise Electrocardiographic Recordings

Laura Burattini[a], Sum C Man[b], and Cees A Swenne[b]
[a]*Department of Information Engineering, Polytechnic University of Marche, Ancona, Italy*
[b]*Department of Cardiology, Leiden University Medical Center, Leiden, The Netherlands*

Laura Burattini, Polytechnic University of Marche, Department of Information Engineering, Via Brecce Bianche, 60131 Ancona, Italy. Email: l.burattini@univpm.it, phone +39 071 220 4461, fax +39 071 220 4224

Abstract. T-wave alternans (TWA), an electrophysiologic phenomenon which manifests as an every-other-beat alternation of the electrocardiographic (ECG) T-wave amplitude or shape, is generally associated to malignant ventricular arrhythmias and sudden cardiac death. TWA is usually identified with no adjustment for T-wave amplitude. However, a possible dependency of TWA on T-wave amplitude has been recently hypothesized. Evaluation of such dependency in exercise ECG tracings was the aim of the present work. Exercise ECG recordings from 58 patients with an implanted cardiac defibrillator were analyzed. TWA was identified using our heart-rate adaptive match filter based method, whereas T-wave amplitude was quantified as the absolute value of the ECG amplitude along the repolarization segment. Inter-patients and intra-patient (inter-leads) TWA dependency on T-wave amplitude was evaluated by computing the correlation coefficient (ρ) between the two quantities. Results indicate a weak ($0.28 \le \rho \le 0.51$, $P<0.05$) inter-patients association between TWA and T-wave amplitude, which were instead linked by a strong ($r=0.86$, $P<0.05$) intra-patient (inter-leads) association.

Keywords: Digital ECG Signal Processing; Exercise ECG; Repolarization Variability; T-wave Alternans; Ventricular Arrhythmias

1. Introduction

T-wave alternans (TWA) consists of every-other-beat shape or amplitude alternation of the electrocardiographic (ECG) repolarization segment (T wave) at fixed heart rate. A link between TWA and malignant ventricular arrhythmias [Rosenbaum et al., 1994; Narayan, 2006; Hohnloser , 2008] and sudden cardiac death [Verrier et al., 2003; Ikeda et al., 2006; Leino et al., 2009] is generally recognized. For this reason TWA is generally accepted as a marker of cardiac electrical instability, and several efforts have been done to identify thresholds values over which TWA levels of patients at increased risk are expected to fall [Bloomfield et al., 2002; Burattini et al., 2009b]. Being TWA a regionally specific phenomenon [Salerno et al., 1986; Nearing et al., 1994], it is generally identified in every available ECG lead independently, and no adjustment for T-wave amplitude is usually performed. However, a possible dependency of TWA on T-wave amplitude has been recently hypothesized [Madias, 2010], and investigations on this topic have became desirable. In a previous study by ourselves, we investigated inter-patients and intra-patient TWA dependency on T-wave amplitude in resting Holter ECG recordings of healthy subjects and coronary artery disease patients, and found no significant association between TWA and T-wave amplitude [Burattini et al., 2012]. Evaluation of inter-patients and intra-patient (inter-leads) TWA dependency on T-wave amplitude in exercise ECG tracings was the aim of the present work.

2. Material and Methods

2.1. Clinical data

Our study population consisted of 58 patients (46 males; age: 59±11 years; body-mass-index: 27±4 Kg/m^2; left ventricular ejection fraction: 29±9%) from the Leiden University Medical Center (The Netherlands) with a cardiac defibrillator (ICD) implanted for primary prevention because of a

depressed left ventricular ejection fraction (less than 35%). All patients were receiving standard care and underwent a bicycle ergometer test, the exercise phase of which consisted of an approximately 10-min bicycle test during which the workload was incremented every minute by 10% of his/her expected maximal exercise capacity. The test was considered valid if the heart rate was within the 95-110 bpm range for at least one minute. During the test, a 12 standard lead (I, II, III, V1, V2, V3, V4, V5, V6, aVR, aVL, aVF,) exercise ECG tracing was recorded from each patient using the GE CASE 8000 stress test system (sampling frequency: 500 Hz; resolution: 4.88 μV/LSB).

2.2. T-wave alternans identification

TWA was identified using our heart-rate adaptive match filter (AMF) method [Burattini et al., 2008], a technique previously tested and prospectively validated in both clinical and simulated settings [Burattini et al., 2006; Burattini et al., 2009a; Burattini et al., 2009b; Burattini et al., 2010; Burattini et al., 2011; Burattini et al., 2012b]. Each lead was analyzed independently. More specifically, 16-beat ECG windows were recursively (every 2 s) extracted from each lead to be preprocessed for noise and baseline removal, and for noisy and ectopic beats replacement [Burattini et al., 2006; Burattini et al., 2011]. Heart-rate stability (NN standard deviation, in s, less than 10% of mean NN, in s) was also tested. ECG windows with more than one replaced beat or with unstable heart rate were rejected. Instead, the accepted ECG 16-beat windows were submitted to our AMF, which consists of a 6th order bidirectional Butterworth band-pass filter (Eq. 1), whose 0.12 Hz wide passing band is centered in the TWA typical frequency (f_{TWA}), by definition equal to half heart rate. Technically, the AMF was implemented as a cascade of a low-pass filter (LPF; cut-off frequency $f_{LPF}=f_{TWA}+df_{TWA}$, with $df_{TWA}=0.06$ Hz) and a high-pass filter (HPF; cut-off frequency $f_{HPF}=f_{TWA}-df_{TWA}$), and was characterized by a transfer function whose squared module is expressed by the following equation:

$$\left|H_{AMF}(f)\right|^2=\left|H_{LPF}(f)\right|^2\cdot\left|H_{HPF}(f)\right|^2=\frac{1}{1+\left(\frac{f}{f_{LPF}}\right)^6}\cdot\frac{\left(\frac{f}{f_{HPF}}\right)^6}{1+\left(\frac{f}{f_{HPF}}\right)^6}. \quad (1)$$

To avoid group delay, the AMF was applied in a bidirectional fashion. Thus, the AMF was designed to filter out every component of the input ECG (included those related to noise) but the one related to TWA. Indeed, the output signal of the AMF was a sinusoidal signal, called TWA signal, with maxima or minima occurring over the ECG repolarization segments. A TWA amplitude (TWAA, μV) parameter was defined (Eq. 2) as the mean of the TWA signal amplitudes in correspondence of these maxima ($i_{max}=1,2,3\ldots N/2$, N=16) and minima ($i_{min}=1,2,3\ldots N/2$) to characterize a 16-beat ECG window:

$$TWAA=\frac{\sum_{i_{max}=1}^{N/2}\left|TWAsignal(i_{max})\right|+\sum_{i_{min}=1}^{N/2}\left|TWAsignal(i_{min})\right|}{N}. \quad (2)$$

Eventually, the TWAA values obtained from all the accepted 16-beat windows of a single-lead 10-min ECG recording were averaged (MTWAA, μV) to provide an overall characterization of the lead.

2.3. T-wave amplitude quantification

T-wave amplitude was evaluated in the same ECG windows which were considered suitable for TWA identification. More specifically, a TA parameter was defined for each window as the mean (over the N=16 beats) value of the differences between the maximum (T_{max}) and the minimum (T_{min}) ECG amplitude throughout the T waves [Burattini et al., 2012a]:

$$TA=\frac{\sum_{i=1}^{N}\left|T_{max}(i)-T_{mnin}(i)\right|}{N}. \quad (3)$$

Eventually, the TA values obtained from all accepted ECG windows were averaged (MTA, μV) to provide an overall estimate of T-wave amplitude in one lead.

2.4. T-wave alternans dependency on T-wave amplitude

Two kinds of TWA dependency on T-wave amplitude were analyzed, which were the inter-patients dependency, and the intra-patient (inter-lead) dependency, respectively.

Inter-patients dependency

In the presence of an inter-patients dependency, the patients showing high values of TWA also show high values of T-wave amplitude, and vice versa. For this reason, the inter-patients dependency was evaluated in each lead independently by computing the correlation coefficient linking the MTWAA and MTA distributions over the 58 ICD patients.

Intra-patient (inter-leads) dependency

In the presence of an intra-patient (inter-leads) dependency, the ECG leads showing high levels of TWA also show large T-wave amplitudes, and vice versa. Thus, this analysis of TWA dependency on TA was evaluated by first computing, for each lead, the mean values of MTWAA and MTA parameters over the ICD population, and then computing the correlation coefficient for the mean MTWAA vs. mean MTA distribution over the 12 standard leads.

2.5. Statistics

The MTWAA and MTA characterizing the ICD population were expressed as mean ± standard deviation (sd). The Kruskal-Wallis test was used to perform the one-way ANOVA test to evaluate if MTWAA and MTA parameters distributions over the 12 standard leads were characterized by the same median value. Information about which pairs of leads had different median values was obtained using the multiple comparison procedure. Agreement between two parameter distributions was evaluated by computing the correlation coefficient (ρ) and the regression line that best interpolates the data in the least squares sense. The statistical significance level was set at 5%.

3. Results

The MTWAA and the MTA values characterizing the ECG tracings of our ICD population are reported in Table 1.

Table 1. *Mean TWA amplitude (MTWAA) and mean T-wave amplitude (MTA) values (mean±sd over our 58 ICD patients) measured in the 12 standard leads.*

Lead	***MTWAA (μV)***	***MTA (μV)***
I	12±6	171±94
II	24±15	418±202
III	25±18	406±233
V1	17±12	316±209
V2	21±13	538±327
V3	26±21	605±339
V4	22±13	505±262
V5	19±13	388±211
V6	17±9	315±187
aVR	15±9	255±118
aVL	16±15	230±140
aVF	23±11	405±210

ANOVA analysis showed that some significant differences were only occasionally detectable among the 12 standard leads, so that it was not possible to identify a specific lead characterized by the highest or the lowest MTWAA and/or MTA values, compared to all the other leads of the system. Moreover, the lead for which MTWA and MTA was maximum was patient dependent (Table 2).

Table 2. *Number of ICD patients, out of 58, for which mean TWA amplitude (MTWAA) and mean T-wave amplitude (MTA) values were maximum in correspondence of a specific lead.*

Lead	***max MTWAA***	***max MTA***
I	0 (0.0%)	0 (0.0%)
II	9 (15.5%)	8 (13.8%)
III	9 (15.5%)	4 (6.9%)
V1	2 (3.5%)	0 (0.0%)
V2	8 (13.8%)	11 (19.0%)
V3	14 (24.1%)	22 (37.9%)
V4	6 (10.3%)	11 (19.0%)
V5	3 (5.2%)	2 (3.5%)
V6	4 (6.9%)	0 (0.0%)
aVR	1 (1.7%)	0 (0.0%)
aVL	0 (0%)	0 (0.0%)
aVF	2 (3.5%)	0 (0.0%)

The analysis of TWA dependency on T-wave amplitude highlighted a weak ($0.28 \leq \rho \leq 0.51$, $P<0.05$) inter-patients association between MTWAA and MTA (Table 3), whose mean values over the 58 ICD patients were instead linked by a strong ($r=0.86$, $P<0.05$; Fig. 1) intra-patient (inter-leads) association.

Table 3. *Correlation values (ρ) between mean TWA amplitude (MTWA) and mean T-wave amplitude (MTA) in the 12 standard leads, indicating the degree of inter-patients dependency of TWA on T amplitude.*

Lead	***ρ (MTWAA vs. MTA)***	***P***
I	0.39	$<10^{-2}$
II	0.28	<0.05
III	0.39	$<10^{-2}$
V1	0.36	$<10^{-2}$
V2	0.45	$<10^{-3}$
V3	0.48	$<10^{-3}$
V4	0.51	$<10^{-4}$
V5	0.49	$<10^{-3}$
V6	0.51	$<10^{-4}$
aVR	0.28	<0.05
aVL	0.39	$<10^{-2}$
aVF	0.30	<0.05

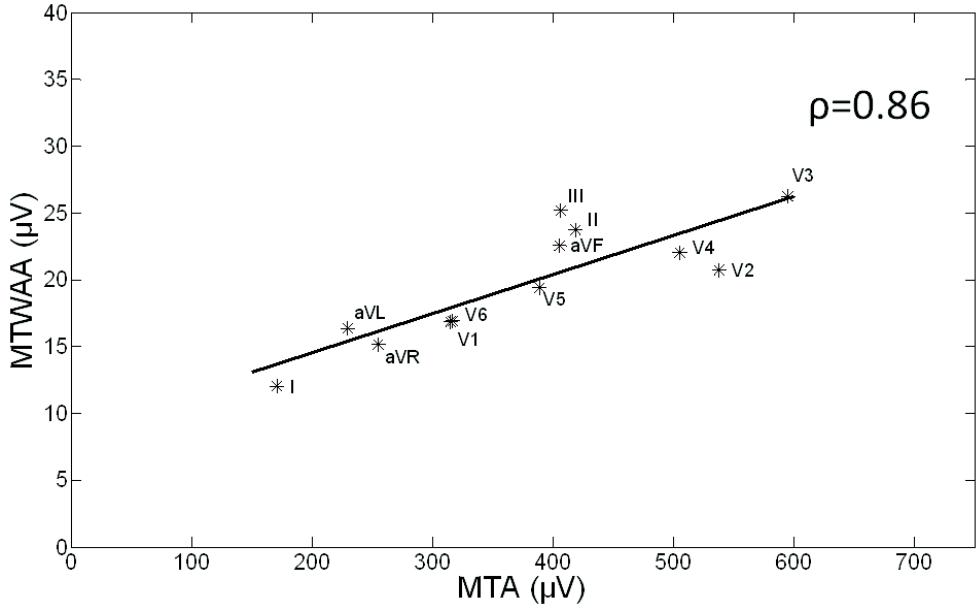

Figure 1. *Regression line and corresponding correlation coefficient (ρ) between mean TWA (MTWAA) and mean T-wave amplitude (MTA), representing the intra-patient (inter-leads) dependency of TWA on T-wave amplitude.*

4. Discussion

This study investigated the existence of a possible dependency of TWA amplitude on T-wave amplitude in 10 min exercise ECG recordings. In the specific, TWA and T-wave amplitude were measured in the 12 standard ECG leads of 58 ICD patients. The ICD patients are indeed particularly prone to develop TWA [de Vilhena Garcia et al., 2009; Man et al., 2011], which is known to increase at high heart rates [Bloomfield et al., 2002], in this study reached by performing the bicycle ergometer test. TWA amplitude and T-wave amplitude values were estimated for each single beat, then averaged over 16 beats for an estimate relative to a single ECG window, and eventually averaged over all accepted ECG windows.

TWA was identified using our AMF-based method, which is particularly robust to noisy interferences affecting the ECG [Burattini et al., 2011], and can also be applied to ECG windows of various length, as long as these are characterized by stable heart rate, so that the periodicity assumed by the filter is satisfied. During the exercise test, the heart rate is constantly increasing, and stable heart rate can be supposed only in short ECG windows, as the ones characterized by 16 beats considered in the present study. Each 16-beat ECG window had to satisfy our heart-rate stability test (NN standard deviation less than 10% of mean NN; see Methods) to be processed for TWA identification. Thus, a small amount of heart-rate variability is allowed, but it is compensated by the fact the AMF is a narrow-band pass filter and not a single-frequency pass filter. Eventually, the 16-beat ECG windows were recursively extracted from the 10 min tracings, so that TWA was here estimated averaging over several 16-beat ECG windows (and, thus, over a larger number of beats overall).

According to our results no lead was characterized by higher TWA compared to all other leads. Rather, the lead showing maximum TWA was patient dependent, so that it was not possible to identify a specific lead more suitable for its detection. Consequently, TWA seems not to affect the same portion of the heart among patients, because in this case, it should appear differently on a given lead among them [Leino et al., 2011].

A statistically significant ($P<0.05$) association was found between TWA and T-wave amplitude. Still, inter-patients association was quite weak ($\rho\leq0.51$), indicating that patients with increased TWA are not necessarily characterized by increased T-wave amplitude. Instead, intra-patient (inter-leads) analysis showed a strong ($\rho=0.86$) dependency of TWA on T-wave amplitude, indicating that the leads characterized by higher TWA are also the ones characterized by higher T-wave amplitude. This finding may suggest that TWA could be a global phenomenon inside the heart, which is reflected proportional to the T wave itself. Indeed, if the phenomenon were local and not global, it will not necessarily imply intra-patient (inter-leads) correlation. Future study on a larger population are needed to confirm the

existence of an the intra-patient (inter-leads) correlation, and eventually, to evaluate the usefulness of considering TWA clinical criteria [Burattini et al., 2009b] adapted to T-wave amplitude [Madias, 2010].

5. Conclusions

In conclusion, in exercise ECG recordings from ICD patients, TWA shows a strong intra-patient (inter-leads) dependency on T-wave amplitude. The inter-patients association, instead, is not relevant.

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