T-Wave Alternans Patterns During Sleep in Healthy, Cardiac Disease and Sleep Apnea Patients

Shamim Nemati[1], Atul Malhotra[1,2], Gari D. Clifford[1,2,3],

[1], Harvard Medical School, Brigham and Women's Hospital, Boston, MA, USA [2], Harvard University, Cambridge, MA, USA, [3], University of Oxford, Dept. Engineering Science, Oxford, UK

Corresponding Author Gari Clifford <gari@robots.ox.ac.uk>.

Abstract

Background
T-Wave Alternans (TWA) activity is known to be a function of heart rate and condition, as well as perhaps physiological state. A recently published non-parametric non-stationary TWA analysis method has been shown to reject nonstationary noise accurately using phase randomized surrogates and has been shown to estimate TWA accurately. This new method was evaluated on multiple databases over a range of heart rates and in healthy subjects, cardiac patients, and obstructive sleep apnea (OSA) patients. We hypothesized that TWA would be lower than previously reported when measured with our new technique and that higher levels of TWA would be observed in OSA patients when compared to normals.

Methods
Five databases were analyzed: 1) Healthy subjects from PhysioNet's Normal Sinus Rhythm Database (NSRDB), 2) Arrhythmia patients from PhysioNet's Chronic Heart Failure Database (CHFDB) and 3) PhysioNet's Sudden Cardiac Death Database (SCDDB), 4) OSA patients from PhysioNet's MIT-BIH Polysomnographic Database (SLPDB), and 5) a private Sleep Apnea Database (SADB) of 85 subjects. TWA magnitudes were calculated for 7 heart rate decades [intervals of 10 beats per minute (BPM) between 40 and 110 BPM] for each database. The Mann-Whitney U-test and the two-sample Kolmogorov-Smirnov test were applied to test for significant differences between data from each database in each heart rate decade interval.

Results
In the healthy population TWA activity level tended to increase with heart rate. Moreover, there appeared to be an unexpected nadir in TWA activity around 60-70 BPM, and a small but significant rise in TWA above and below these heart rates. The rise in TWA at lower heart rates has not been previously reported to our knowledge. We also observed that TWA is unexpectedly lower in OSA patients and did not increase with heart rate.

Conclusion
Although the physiological mechanisms underlying our observations are unclear, there may be clinical implications for TWA testing, particularly at low heart rates, a previously overlooked aspect of TWA.

1. Introduction

The manifestation of microvolt alternations in beat-to-beat T-wave amplitudes, or T-Wave Alternans (TWA), is believed to be related to physiological state, and in particular TWA manifests more significantly at higher heart rates, and particularly within the cardiac populations [1]. However, little is known about the manifestation of TWA during sleep, which is heavily influenced by autonomic state, heart rate (HR) and cardiac condition. It has been demonstrated that the absence of significant TWA in a patient with congestive heart failure, low ejection fraction, or a recent myocardial infarction is strongly predictive of a low risk of sudden cardiac death (SCD) [2, 3]. A positive finding in such a patient, though less specific, may indicate that a further invasive test is required. Although the positive predictive value of TWA assessed through standard methods remains low [4], improvements in the methodology of TWA detection/quantification have recently been proposed which may improve the utility of the TWA test [5, 6]. In this work we employed a recently published non-parametric non-stationary TWA analysis method (together with a standard TWA approach for reference) to analyze a series of databases, including normal subjects, cardiac impaired populations and two databases of patients suffering from obstructive sleep apnea (OSA, a condition associated with risk of nocturnal sudden death). We hypothesized that lower rates of TWA would be observed with our new technique because spurious noise is more effectively rejected with our new technique. Furthermore, we hypothesized that, because OSA patients go on to experience higher than normal rates of cardiac disease, we expected to observe higher rates of TWA in such patients when compared to normal healthy individuals.

2. Materials and Methods

2.1. Data Sources

The five databases used in this study were:

(i) Healthy subjects from PhysioNet's Normal Sinus Rhythm Database (NSRDB). This database includes 18 long-term (at least 8 hour long) ECG recordings of subjects referred to the Arrhythmia Laboratory at Beth Israel Deaconess Medical Center. Subjects included in this database were found to have had no significant arrhythmias; they include 5 men, aged 26 to 45 years, and 13 women, aged 20 to 50 years. Recordings were performed at 128 Hz sampling frequency and 12-bit resolution [7]. Data are freely available from http://www.physionet.org/physiobank/database/nsrdb/.

(ii) Arrhythmia patients from PhysioNet's Chronic Heart Failure Database (CHFDB). This database includes long-term ECG recordings from 15 subjects (11 men, aged 22 to 71 years) with congestive heart failure; New York Heart Association class: III-IV (moderate to severe). This group of subjects was part of a larger study group receiving conventional medical therapy prior to receiving the oral inotropic agent, milrinone. Recordings were performed at a 250 Hz sampling frequency and 12-bit resolution [7]. Data are freely available from http://www.physionet.org/physiobank/database/chfdb/

(iii) Arrhythmia patients from PhysioNet's Sudden Cardiac Death Database (SCDDB). These data include 23 patients with underlying sinus rhythm (four with intermittent pacing), one who was continuously paced, and four with atrial fibrillation. All patients had a sustained ventricular tachyarrhythmia, and most had an actual cardiac arrest. The recordings were performed at a sampling frequency of 250 Hz and 12-bit resolution [7]. Data and are freely available from http://www.physionet.org/physiobank/database/sddb

(iv) Sleep apnea patients from PhysioNet's MIT-BIH Polysomnographic Database (SLPDB). Subjects were monitored in a sleep laboratory for evaluation of OSA, and to test the effects of continuous positive airway pressure (CPAP), a standard therapeutic intervention that usually

prevents airway obstruction in these subjects. The database contains over 80 hours' worth of four-, six-, and seven-channel polysomnographic recordings, each with a single channel of ECG annotated beat-by-beat, and EEG and respiration signals annotated with respect to sleep stages and apnea. The recordings were performed at a sampling frequency of 250 Hz and 12-bit resolution [7, 8]. Data are freely available from
http://www.physionet.org/physiobank/database/slpdb/
(v) A private Sleep Apnea Database (SADB) which comprised 85 subjects undergoing overnight polysomnogram analysis for sleep apnea (6-8 hours of recording, apnea-hypopnea index (AHI) ranging from 0 to 122 events/hour with a mean AHI of 16.0 events/hour). The recordings were performed at a sampling frequency of 250 Hz and 16-bit resolution [9].

Each database contains annotations for locations of R-peak intervals except for the SADB where beat detection was performed using the wavelet-based QRS detector and T-wave detection algorithm of Martínez *et al*. [10].

2.2. Preprocessing

To remove the baseline wander, the ECG was downsampled to 32 Hz and, for a given sample point, a 1.3 s window (0.65 s each side of the point) was sorted and the mean of the central 25 % of the sorted data was then calculated and marked as the baseline for that point. This process was repeated for all the sample points (ignoring boundary conditions). The baseline was then resampled to the original sampling frequency and was subtracted from the original ECG. Next, the ECG was lowpass filtered using an 11 tap Butterworth filter at the cutoff frequency of 40 Hz. Relative timing of points within different repolarization cycles (i.e. successive T-waves) is crucial for any TWA algorithm to avoid introducing false TWA. The beat alignment algorithm utilized a correlation-based method of aligning the beats with respect to the ST-T complex (from the S-point to the T-end). Further steps were taken to replace outlier beats (beats with low correlation with the majority of the beats within the analysis window) with a template beat. Every beat had two optimal correlation values. A beat was considered acceptable if correlation on Q-S interval was higher than 0.9 and correlation on ST-T complex was higher than 0.95. If there were more than 10 % of invalid beats the whole lead was marked as invalid for the given analysis window (for a more thorough description see [11]).

2.3 TWA Algorithms and Significance Testing

The TWA analysis algorithms we employed were described in detail in Nemati *et al*. [5]. For this work we used two TWA detection and estimation techniques; 1) A simple averaging method (SAM) which we have previously shown to be equivalent to the Modified Moving Average Technique [5], and 2) the SAM with a non-parametric non-stationary noise rejection technique. The latter approach involves randomly shuffling the time series of T-wave amplitudes and recalculating the resultant TWA magnitude. If most (95%) of the TWA amplitudes calculated form the time-shuffled data are smaller than the original T-wave time series, we can be confident of our detection of real TWA (rather than random noise). Otherwise the TWA is considered Non-significant (indeterminate). See Nemati *et al*. [5] for more details. An analysis window of length 64 beats with a 32 beat overlap was used for both TWA algorithms. All the analyses in this article were performed on a single lead of the ECG records (lead I). TWA magnitudes were calculated for 7 heart rate decades (with intervals of 10 BPM) between 40 and 110 BPM for each database. Indeterminate episodes were then omitted. All remaining episodes are reported as means ± one standard deviation. Significant differences between data in each heart rate decade interval between databases were tested for using the two-sample Kolmogorov-Smirnov test.

3. Results

Figure 1 illustrates the TWA detection statistics after eliminating indeterminate TWA episodes (for a summary see Tables 1 and 2). Note that, in the top panels of Figure 1 the indeterminate cases were caused by preprocessing failure of associated analysis windows, while in the indeterminate cases in the bottom panels result from a combination of preprocessing failure and application of surrogate significance testing ($p< 0.05$). Results indicate that in the healthy population the TWA activity level tended to increase with heart rate. However, in the sleep apnea patients there was no apparent increase in TWA activity with an increase in heart rate. Moreover, we note that there appeared to be a nadir in TWA around 60-70 BPM, and a small but significant rise in TWA above and below these heart rates.

Table 1 compares TWA activity at different heart rates in the NSRDB, SLPDB, and SADB populations using the SAM without significance testing (top) and after significance testing with $p< 0.05$ (bottom). Differences between median TWA estimates are given for all combinations of databases tested with numerical subscripts 1 through 3 indicating the SLPDB, NSRDB and SADB populations respectively. A negative sign therefore indicates that the patients in the first database exhibited a higher median TWA amplitude. The symbol † indicates a significant difference between TWA amplitudes at a given HR range using the Mann-Whitney U-test (of medians) with $p< 0.05$ (with †† indicating significance with $p< 0.0001$). A significant difference in distribution of TWA amplitudes at a given heart rates was assessed using the two-sample Kolmogorov-Smirnov test (with significance at a level of $p< 0.05$ indicated by an asterisk). The lack of few comparable episodes in the NSRDB-SADB database after significance testing was due to the lack of events in the SADB data, rather than the normal data, indicating that the two sleep populations may have been exhibiting differing cardiac activity, or perhaps the SADB is comprised of noisier recordings, leading to more event rejection. We note however, that this does not indicate that lower TWA amplitudes were rejected because of the higher noise levels, particularly as our results indicate that the SADB exhibits TWA amplitudes lower than the other databases at matched heart rates.

Table 2 illustrates the comparison of TWA activity at different heart rates in the NSRDB, CHFDB, and SCDDB populations using the SAM without significance testing (top) and after significance testing with $p< 0.05$ (bottom). For a given heart rate range, $\Delta_{med(1,4)}$ was the median TWA amplitude of CHFDB population minus the median TWA amplitude in the NSRDB population. Similarly, $\Delta_{med(1,5)}$ was the median TWA amplitude of SCDDB population minus the median TWA amplitude in the NSRDB population. Interestingly, the application of surrogate testing changes the interpretation of the effect of SCD on TWA; that is, without significance testing, TWA appears to have been higher in the normal patients. After significance testing, this observation is reversed and the TWA appears to have been higher in the SCD population, as expected, except at very low heart rates (40-50 BPM).

4. Discussion and Conclusions

In this article we have investigated TWA activity at different heart rates in various patient populations using a recently proven more accurate TWA estimation analysis tool. Our aim was to identify TWA patterns in normal patients, cardiac impaired patients and sleep apnea patients, and compare inter-patient differences. In particular we investigated the hypothesis that TWA may be lower than previously reported and that, for OSA patients, TWA manifests more strongly than normal patients. We observed some unusual previously unreported dynamics. First we noticed that in normal and cardiac patients, there was a significant rise in TWA levels at lower heart rates. The conventional understanding of TWA indicates that lower heart rates should be associated with lower TWA activity [1]. We also note that even when controlling for heart rate, TWA is

lower in sleep apnea patients. Moreover, TWA in these patients does not increase with heart rate as we see for other patient populations. Since sleep apnea patients are prone to cardiac arrhythmias [12], one might expect a higher level of TWA. However, since these patients are undergoing overnight studies, they may have a lowered sympathetic tone compared to the general population (or cardiac patients) and hence may have lower TWA activity. It is unclear whether the lower TWA is simply a phenomenon related to the clinical protocol, or if it reveals some underlying physiological mechanism. We note some limitations of this study. First, all the analyses were performed on a single lead of the ECG records (lead I). Different subjects may manifest maximal TWA activity across different leads, and in fact the location of the dominant TWA may change over time. Although we have no reason to suppose that the lead dependency is correlated to heart rate, autonomic state or medical condition, it would be interesting to explore these issues using more complete lead sets via methods appropriate to multilead analysis, such as in Monasterio *et al*. [6]. The other main limitation of this study is that physiological sleep states in the cardiac and normal populations were not available. However, when segmenting those data using a 6 hour period of the lowest heart rate (during the night) when sleep can be assumed, we saw little change in our results.

In summary, our analyses add to the literature for a number of reasons. First, we have shown the feasibility of our validated TWA analytical approach on various databases of interest. Second, we have confirmed the heart rate dependence of TWA in various databases including normal subjects and cardiac patients. Third, we have observed a lack of heart rate dependence of TWA in sleep apnea, a finding that we had not anticipated. Moreover, the low value of TWA observed in sleep apnea raises interesting questions including possible protective mechanisms which may be invoked to prevent arrhythmias in this vulnerable population. Fourth and finally, we have observed elevations in TWA at low heart rates, a finding that we believe has interesting implications for further study. For instance, whether pharmacological lowering of heart rate (e.g. using beta-blockers) has similar effects to spontaneous reductions in heart rate is unknown and untested. Thus, we believe our findings provide important future directions for research into the clinical use of TWA and its interpretation in relation to cardiac states and diseases.

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HR band (BPM)	**Δmed(1,2)** (μV)	**Δmed(1,3)** (μV)
	SAM	
35-45	--	-7.1 [-4.5, -11.5] ††*
45-55	-5.9 [-4.4, 2.5] ††*	-7.6 [-5.0, -5.5] ††*
55-65	-8.8 [-5.2, -3.0] ††*	-8.4 [-5.3, -7.3] ††*
65-75	-9.9 [-5.9, -10.0] ††*	-8.9 [-5.8, -9.0] ††*
75-85	-8.8 [-5.6, -8.4] ††*	-9.2 [-5.7, -8.4] ††*
85-95	-8.0 [-4.9, -10.8] ††*	-9.1 [-5.8, -7.4] ††*
95-105	-8.0 [-4.6, -12.3] ††*	-8.0 [-5.7, -7.9] ††*
105-115	--	-7.5 [-4.5, -13.9] ††*
	After Significance Testing	
35-45	--	-4.4 [-8.1, -5.8]
45-55	--	-5.1 [-12.9, -7.0] †
55-65	--	-7.9 [-12.0, 22.2] †*
65-75	--	-8.6 [-14.0, 8.6] ††*
75-85	--	-8.3 [-8.5, -1.7] ††*
85-95	--	-7.9 [-10.8, -6.9] ††*
95-105	--	1.1 [-4.5, -4.9] †*
105-115	--	--

Table 1. Comparison of TWA activity at different HR in the NSRDB, SLPDB, and SADB populations using the SAM without significance testing (top) and after significance testing with $p < 0.05$ (bottom). For a given HR range, Δmed(1,2) is the median TWA amplitude of SLPDB population minus the median TWA amplitude in the NSRDB population. Similarly, Δmed(1,3) is the median TWA amplitude of SADB population minus the median TWA amplitude in the NSRDB population. For every pair of populations and each matched heart rate, the two numbers inside a bracket are the differences between the lower 5-percentiles and the upper 95-percentiles of the values across the populations, respectively. † indicates a significant difference between TWA amplitudes at a given HR range using the Mann-Whitney U-test (of medians) with $p < 0.05$ (similarly, †† signifies $p < 0.0001$). A significant difference in distribution of TWA amplitudes at a given heart rates was assessed using the two-sample Kolmogorov-Smirnov test ($p < 0.05$, indicated by an asterisk *). The empty entries (−) indicate that there were fewer than 10 detected episodes of TWA activity in the corresponding patient populations, and thus not amenable to significance testing.

HR band (BPM)	$\Delta_{med(1,4)}$ (μV)	$\Delta_{med(1,5)}$ (μV)
	SAM	
35-45	-	-2.3 [-3.1, 8.2] ††*
45-55	0.0 [-1.1, 9.8] ††*	-2.6 [-3.9, 26.4] †*
55-65	-1.7 [-2.0, 8.1] ††	-3.1 [-3.7, 15.9] ††*
65-75	-2.8 [-2.6, 13.3] ††	-6.2 [-4.3, -0.2] ††*
75-85	-1.1 [-2.3, 27.2] *	-5.5 [-4.2, 3.0] ††*
85-95	3.1 [-1.9, 48.0] ††*	-5.7 [-4.2, 17.4] ††*
95-105	9.3 [-0.8, 56.0] ††*	-5.6 [-4.5, 11.0] ††*
105-115	25.1 [4.5, 80.7] ††*	-1.4 [-4.3, 36.2] ††*
115-125	2.4 [-2.6, 59.0] †*	-2.0 [-4.6, 16.1] ††*
	After Significance Testing	
35-45	-	-2.4 [-7.1, 17.3] *
45-55	-	18.4 [0.4, 65.6] ††*
55-65	8.0 [-3.9, 35.0] ††*	6.5 [-2.5, 36.8] ††*
65-75	3.5 [-8.6, 54.4] ††*	0.1 [-5.2, 20.3] ††*
75-85	9.6 [-4.2, 95.2] ††*	6.9 [-5.8, 26.0] ††*
85-95	20.7 [-9.5, 85.1] ††*	-0.7 [-9.5, 64.2] ††*
95-105	28.1 [0.1, 71.7] ††*	9.7 [-9.7, 47.9] *
105-115	31.0 [6.5, 67.0] ††*	41.2 [-3.4, 85.8] †*
115-125	--	--

Table 2. Comparison of TWA activity at different HR in the NSRDB, CHFDB, and SCDDB populations using the SAM without significance testing (top) and after significance testing with $p< 0.05$ (bottom). For a given HR range, $\Delta_{med(1,4)}$ is the median TWA amplitude of CHFDB population minus the median TWA amplitude in the NSRDB population. Similarly, $\Delta_{med(1,5)}$ is the median TWA amplitude of SCDDB population minus the median TWA amplitude in the NSRDB population. See Table 1 for more information.

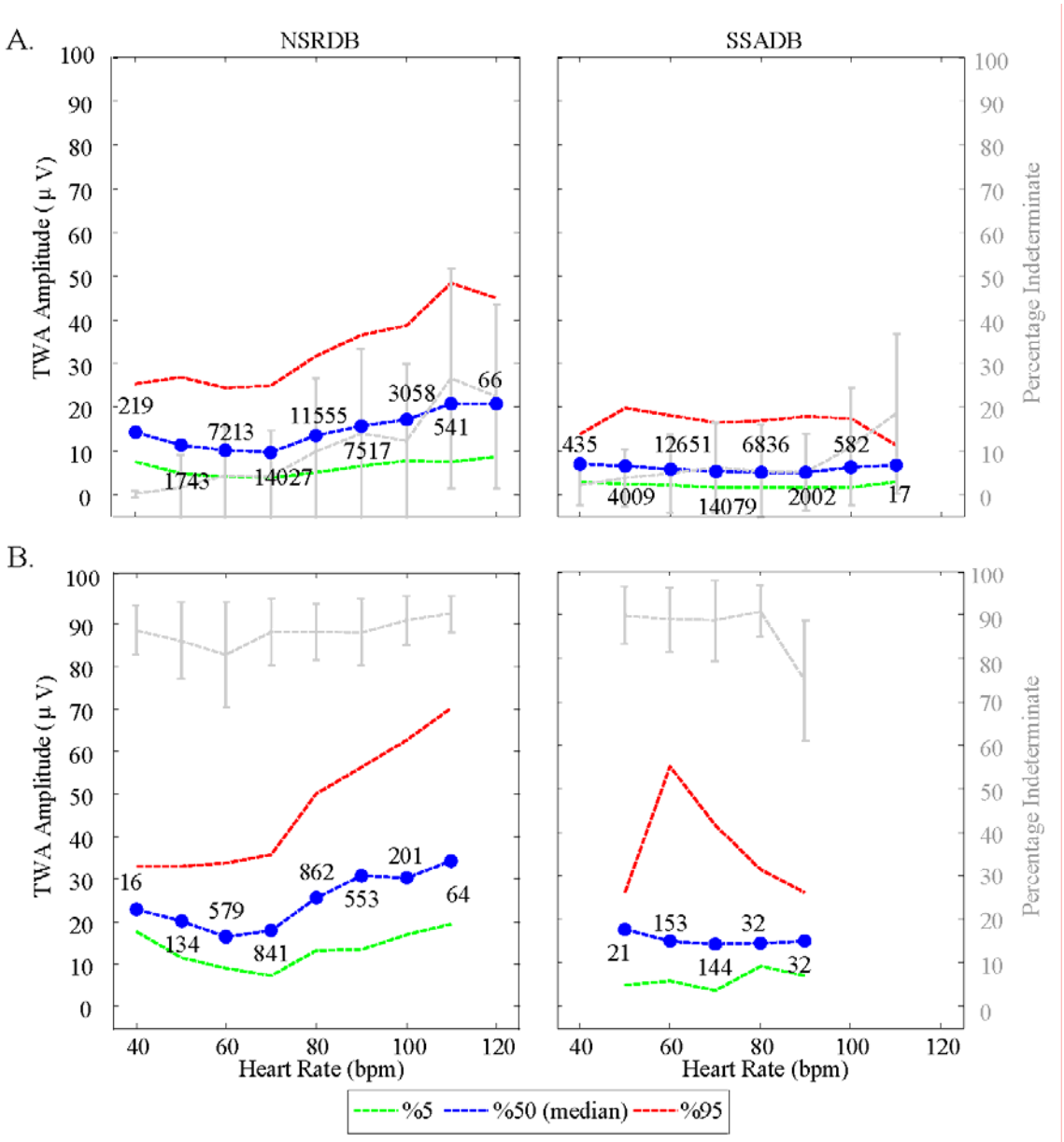

Figure 1. Comparison of the NSRDB and SADB patient populations (at matched HRs) without significance testing (A) and after significance testing (B). In addition to the TWA amplitude medians (blue circles) the upper 95-percentile (green) and the lower 5-percentile (red) values are also shown. The small numbers by the blue circles indicate the number of detected episodes of TWA for the given HR range. The grey error bars signify the percentage of indeterminate cases at each HR range over the entire population.