A Nonparametric Surrogate-Based Test of Significance for T-Wave Alternans Detection

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***Abstract*—We present a nonparametric adaptive surrogate test that allows for the differentiation of statistically significant T-wave alternans (TWA) from alternating patterns that can be solely explained by the statistics of noise. The proposed test is based on estimating the distribution of noise-induced alternating patterns in a beat sequence from a set of surrogate data derived from repeated reshuffling of the original beat sequence. Thus, in assessing the significance of the observed alternating patterns in the data, no assumptions are made about the underlying noise distribution. In addition, since the distribution of noise-induced alternans magnitudes is calculated separately for each sequence of beats within the analysis window, the method is robust to data nonstationarities in both noise and TWA. The proposed surrogate method for rejecting noise was compared to the standard noise-rejection methods used with the spectral method (SM) and the modified moving average (MMA) techniques. Using a previously described realistic multilead model of TWA and real physiological noise, we demonstrate the proposed approach that reduces false TWA detections while maintaining a lower missed TWA detection, compared with all the other methods tested. A simple averaging-based TWA estimation algorithm was coupled with the surrogate significance testing and was evaluated on three public databases: the Normal Sinus Rhythm Database, the Chronic Heart Failure Database, and the Sudden Cardiac Death Database. Differences in TWA amplitudes between each database were evaluated at matched heart rate (HR) intervals from 40 to 120 beats per minute (BPM). Using the two-sample Kolmogorov–Smirnov test, we found that significant differences in TWA levels exist between each patient group at all decades of HRs. The most-marked difference was generally found at higher HRs, and the new technique resulted in a larger margin of separability between patient populations than when the SM or MMA were applied to the same data.**

***Index Terms*—ECG, noise, surrogate analysis, T-wave alternans (TWA).**

I. Introduction

T-WAVE alternans (TWA), referring to beat-to-beat variability in the timing or shape of ST-T complex on the surface ECG, was first reported in 1908 by Hering [1]. Although the phenomenon is widely understood to be an important indicator of risk of sudden cardiac death (SCD) [2]–[4], until the 1980s, TWA was believed to be rare. In 1981, Adam *et al.* first reported the existence of the microvolt level TWA, which are too small in amplitude to be visually detected at standard ECG display scales [5]. Follow-up studies 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 SCD [6], [7]. A positive finding in such a patient, though less specific, may indicate that an implantable cardiac defibrillator would be appropriate, which is an indication that can be confirmed using invasive testing. However, the positive predictive value of TWA remains low [8], and it is yet to be determined whether further improvements in the methodology of TWA detection/quantification can improve the positive diagnostic power of the TWA test.

One unresolved issue in the area of TWA analysis is that of noise modeling and rejection of false detections while maintaining a low level of missed detections [9]–[11]. A comprehensive list of various TWA estimation and detection techniques is provided by Martínez and Olmos [12]. Two of the most common shortcomings of the discussed methods of TWA detection are: 1) unjustified assumptions about the nature of the physiological noise (e.g., Gaussian or Laplacian distributions) [11] and 2) arbitrary detection thresholds, often tuned on patient populations that are judged as healthy [13], [14].

In this paper, we seek to determine if in the presence of noise (due to exogenous sources, such as electrode movements or endogenous interferences, such as muscle artifacts), alternating-like patterns can appear in the data, and whether in the absence

Manuscript received October 16, 2009; revised January 8, 2010 and March 10, 2010; accepted March 15, 2010. Date of publication April 19, 2010; date of current version April 20, 2011. The work of S. Nemati was supported by the National Institutes of Health under Training Grant T32-HL07901. This work was supported by the U.S. National Institute of Biomedical Imaging and Bioengineering under Grant RO1 EB001659, by the National Institutes of Health (NIH) under Grant RO1-HL73146, by the NIH Research Resource for Complex Physiologic Signals under Grant U01EB008577, by the Centro de Investigación Biomédica en Red de Bioingeniería, Biomateriales y Nanomedicina through ISCIII, by the Comisíon Interministerial de Ciencia y Tecnologia under Project TEC2010-21703-C03-02 of Ministerio de Ciencia e Innovación (MICINN), and GTC T-30 from DGA (Spain). *Asterisk indicates corresponding author.*

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Digital Object Identifier 10.1109/TBME.2010.2047859

of an appropriate statistical test, such patterns can be mistaken for physiological-based TWA. We propose a nonparametric test to mitigate the problem of TWA false detection. The proposed test makes no assumption concerning the distribution or stationarity of the noise or the TWA in the data, and therefore, it is robust under varying recording conditions. The purpose of this paper is to devise a robust statistical test to assist in accurate detection of TWA, independent of the particular estimation algorithm being used. To the best of our knowledge, this paper is the first to propose a statistical test for TWA detection that is completely nonparametric and makes no assumption about the nature (distribution or dynamics) of the underlying noise or the TWA activity itself.

To provide a comparative study of the proposed TWA detection algorithm, we used an open-source TWA analysis tool to evaluate current standards for TWA metrics on four datasets. First, by using a model of TWA, to which realistic noise is added, we created a gold-standard dataset in which the existence and magnitude of TWA is completely known. We then evaluated the concept of false estimation of TWA amplitude by the standard TWA analyzers at low levels of TWA amplitude and varying noise level to determine the sensitivity floor of various noise-rejection techniques. Once the range of the standard TWA analysis techniques was determined, we investigated the feasibility of assessing statistical significance of a given alternans amplitude via a nonparametric surrogate test that allows for the differentiation of statistically significant TWA from alternating patterns, which can be solely explained by the statistics of noise. Our surrogate method is similar to the one described by Small and Judd [15] and Theiler *et al.* [16], [17]; except that all the computations are performed in the time domain rather than the frequency domain. We also note that our approach is related to the approximate permutation test, Monte Carlo permutation tests or random permutation tests [18]. The proposed statistical significance test was then applied to three publicly available databases to investigate reports that TWA manifest more significantly at higher heart rates (HRs) in both normal and cardiac-impaired populations [19].

We start with a brief description of the datasets utilized in this paper, followed by an introduction to the most commonly utilized TWA analysis methods, and a discussion of false detections in the presence of noise. Next, we describe the proposed nonparametric statistical test to separate real TWA effect from the noise-induced alternans-like artifacts. Finally, we evaluate the performance of the proposed approach compared to the standard approaches using simulated vectorcardiographs (VCGs) with known TWA amplitude and three publicly available databases.

II. Materials and Methods

Four datasets were used for the analysis; one set of computer-simulated VCGs with known TWA amplitude and additive physiological noise [from the MIT-BIH Noise Stress Test Database (NSTDB)], one set of recordings from healthy subjects, one set with chronic heart failure, and one set of recordings from SCD patients.

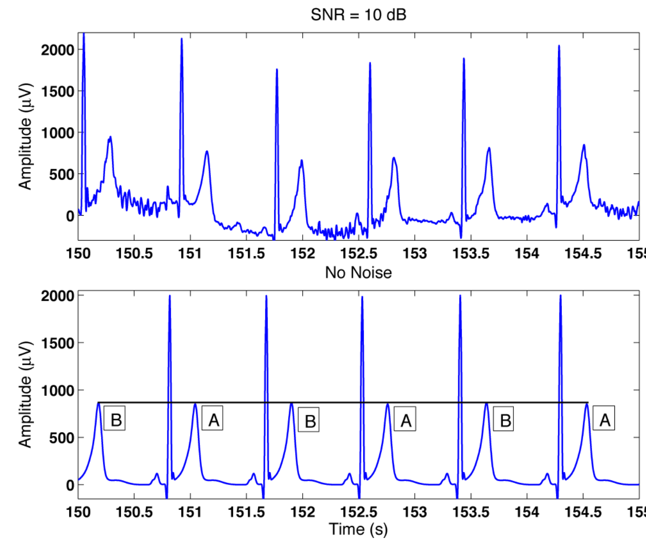

Fig. 1. Examples of simulated VCG with TWA amplitude of 23 μV. Physiological noise consisting of a mixture of muscle artifacts, electrode movements, and baseline wander are added to each record. Only simulations at (top) SNR of 10 dB and (bottom) clean VCG are shown here. Zooming into the bottom plot, one can observe the microvolt variations from a normal beat (type-A) to an abnormal beat (type-B). The maximum amplitude variation between a type-A and a type-B beat is concentrated around the T-wave peak.

A. Simulated TWA

Five minutes duration records with TWA amplitudes of 0 through 100 μV were generated using an artificial multilead VCG model with realistic TWA-like effects [20] and the x-axis of the VCG was chosen as the test signal. Next, noise segments of 5 min duration with random starting points were selected from the MIT-BIH NSTDB [21]. The NSTDB comprises recordings of three different types of noise, namely baseline wander, electrode movement, and muscle artifacts. The additive noise was constructed by mixing all three noise types, and the power of the noise with respect to the VCG signal was adjusted to simulate records of SNR of 10, 20, and 30 dB and no noise (due to space limitations only results from SNR of 10 dB and no noise are reported). For a given SNR level and TWA amplitude, we generated 50 VCG records of 5 min each at a sampling frequency of 500 Hz and 16-bit resolution per sample, which is sufficient to prevent significant quantization noise [10], [22]. Individual records differ in that: 1) the underlying VCGs were generated using a stochastic model of HR variability (70 $\pm$ 5 beats/min) [23] and 2) the additive noise was taken from random 5 min segments of the NSTDB. A short segment from one of the simulated records with a TWA amplitude of 23 μV with additive noise at 10-dB SNR and no noise is shown in Fig. 1.

B. Real ECG Recordings

To assess the effectiveness of the proposed statistical test, we compared the performance of each of the described TWA detection methods for separating patient populations according to the magnitude of TWA activity they manifest. To this end, we employed three publicly available databases to investigate reports that TWA manifest more significantly at higher HRs, and more often within the cardiac-impaired populations [19].

1) Normal Sinus Rhythm Database: This database includes 18 long-term (at least 8 h long) ECG recordings of subjects referred to the Arrhythmia Laboratory at Boston's Beth Israel Deaconess Medical Center. Subjects included in this database were found to have no significant arrhythmias; they include 5 men, aged 26 to 45, and 13 women, aged 20 to 50 years. Recordings were performed at 128 Hz sampling frequency and 12-bit resolution [24].

2) Chronic Heart Failure Database: This database includes long-term ECG recordings from 15 subjects (11 men, aged 22 to 71, and 4 women, aged 54 to 63 years) with severe congestive heart failure. 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 250 Hz sampling frequency and 12-bit resolution [24].

3) SCD Database: 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 sampling frequency of 250 Hz and 12-bit resolution [24].

C. TWA Estimation and Detection

Since the purpose of this study was to propose a robust test of significance of TWA patterns, independent of the particular preprocessing (i.e., prefiltering, QRS detection, and beat alignment) or estimation method, we utilized the same preprocessing steps across all methods. (For a more thorough description, see [25].) Our implementations of the modified moving average (MMA) and spectral method (SM) are based on descriptions given in [12] and [26] and are described in the following sections.

The algorithms and metrics chosen for comparative study in this paper were intended to mimic the approaches employed in commercial equipment and are most often used by clinicians rather than to provide an exhaustive comparison of all TWA analysis techniques. To facilitate comparisons across various methods, an analysis window of length $L = 64$ beats with 32 beats overlap was utilized independent of the particular TWA algorithm. All the analyses in this paper were performed on a single lead of the ECG records (lead I). Although different subjects may manifest maximal TWA activity across different leads, we expect the differences to average out over our databases.

1) Proposed Detection Method (Surrogate Data Analysis): In this paper, we propose a nonparametric (assumption-free) statistical test to separate physiologically induced alternans (real TWA) in a beat sequence from alternating patterns that could be a byproduct of the way one measures TWA amplitude and deals with the artifacts of recording noise. The main motivation behind the surrogate data analysis (SDA) method is that if the estimated alternans amplitudes are not artifacts of noise, then by eliminating the temporal relationship between the beats—through shuffling of the beat sequence—the amplitude of the beat-to-beat alternation ought to decrease significantly. Henceforth, we define a noise-induced alternating pattern (NIAP) as

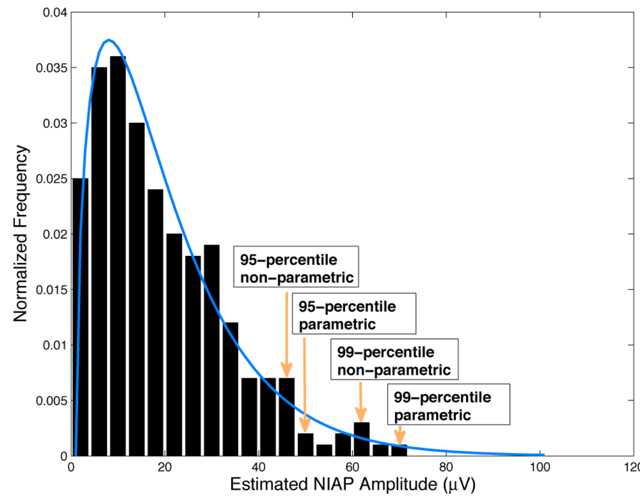

Fig. 2. Normalized histogram of (black) NIAP and (dark blue) fitted gamma distribution calculated from 250 times reshuffling of the beats within an analysis window ($L = 64$ beats). Marked are the 95th and 99th percentiles of the calculated alternans amplitude (nonparametric) and the fitted gamma distribution (parametric). If the estimated TWA is larger than the 95th or 99th percentile, one can confidently reject the null hypothesis at $\alpha = 0.05$ or $\alpha = 0.01$, respectively.

an alternating pattern in a beat sequence that is caused by factors other than alternation in ventricular repolarization on an every-other-beat basis.

To cast the problem into a more rigorous statistical framework, one has to approximate the distribution of NIAP. A surrogate measure of NIAP may be obtained through repeated reshuffling of the beat sequence (say $N = 250$ times) and by estimating the alternans amplitude for each surrogate arrangement of beats. In general, as the number of surrogates (shufflings) increases, the normalized histogram of the measured NIAP will approach the true distribution of NIAP. A statistical test can then be constructed by comparing the measured TWA amplitude against some upper percentile ($(1 - \alpha) \times 100$) of the NIAP estimates (e.g., 95th percentile or 99th percentile for $\alpha = 0.05$ or $\alpha = 0.01$, respectively). If the estimated TWA amplitude is greater than or equal to all the NIAP values up to and including the $(1 - \alpha) \times 100$ percentile, the estimated TWA amplitude is significant and its value is reported. Otherwise, the TWA amplitude is labeled *indeterminate* for the given analysis window. Thus, the indeterminate cases are those for which neither the presence nor the absence of TWA activity can be ruled out. (It is worth noting that in the absence of any TWA activity and no random beat-to-beat variations, all possible random arrangements of beats must result in 0 V TWA amplitude, and thus, alternans-free beat sequences would not be labeled indeterminate. However, in real data due to the presence of noise, certain arrangements of beats will result in nonzero TWA amplitude; therefore, as a consequence of our definition of indeterminacy and noise, 0 V TWA amplitude is almost always labeled indeterminate. However, this does not cause any problem, since in practice, missed or indeterminate 0 V alternans are unimportant.)

Fig. 2 illustrates the normalized histogram of the NIAP (black) calculated (using the simple averaging method (SAM)

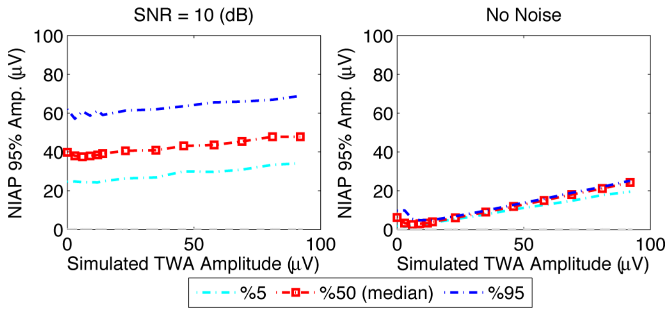

Fig. 3. Range of NIAP amplitudes at 95th percentile significance in reshuffled beat sequences using the SAM (see Fig. 2), representing a statistical measure of the upper limit on the NIAP. (Boxes) Median, (lower line) 5% and (upper line) 95% are plotted to illustrate spread of the 99th percentile at each simulated TWA amplitude and across all simulated records, at SNR of 10 dB and no noise scenario.

described in the following section) from a 64 beats long segment of the simulated ECG, shown in Fig. 1(top). Superimposed on the graph are the fitted gamma distribution (dark blue) calculated from 250 times reshuffling of the beats and the 95th and 99th percentiles of the calculated alternans amplitude (of the empirical distribution) and fitted (parametric) gamma distribution. If the estimated TWA amplitude of the unshuffled beat sequence is larger than the 95th or 99th percentiles of the NIAP distribution, one can confidently reject the null hypothesis (i.e., the alternating pattern in the beat sequence can be explained by the statistics of noise) at $\alpha = 0.05$ or $\alpha = 0.01$, respectively. Note that by introducing a parametric form, one can incorporate a belief pertaining to the tail of the distribution or frequency of rare events (heavy-tailed versus light-tailed), which may not be captured through a moderate number of reshufflings. For instance, a heavy-tailed distribution can further reduce false-alarm rates, since the upper percentiles of such distribution will be further to the right of the corresponding percentiles of the empirical distribution (or normalized histogram). However, this reduction in false-alarm rates comes at a cost of increasing missed detections. This may be a large contributing factor in reports that current TWA analysis approaches are specific, but not sensitive.

The 99th percentile of NIAP amplitude in reshuffled beat sequences are shown in Fig. 3 for simulated VCG records at SNR of 10 dB and no noise. Each red square on the graph represents the median over 500 values (50 records of the same TWA amplitude and 10 overlapping windows per record). Within each analysis window (of length $L = 64$ beats), the beat sequence is reshuffled 250 times, the alternans amplitude is calculated for each unique arrangement of the beats, and the 99th percentile of alternans amplitude over all 250 arrangements is recorded. Noteworthy is the tendency of the 99th percentile to increase with the simulated TWA amplitude. Also note that the NIAP is nonzero (even for 0-μV TWA) and that the baseline NIAP increases as the SNR drops. These observations can be explained by the fact that after reshuffling, the number of type-A and type-B beats within the even and the odd group of beats is equal, and then, any difference between the average value of even group and odd group will be due to noise, since the type-A beats (type-B beats) within the even group will cancel the type-A beats (type-B beats) within the odd group. When the reshuffling of the beat sequence is thoroughly random, certain arrangements of beats may result in one of the beat types being overly represented in the odd or even group of beats, and therefore, some of the intergroup differences will be due to the existence of distinct beat types, rather than being purely a noise artifact. In any event, the point of reshuffling the beat sequence is that, if there are two distinct beat types that manifest themselves in an alternating scheme (i.e., $ABABAB\ldots$), then almost all other arrangements of the beats ought to produce an equal or smaller average difference between the odd beats and the even beats.

It should be noted that there are $L!$ ways to arrange L beats, and $(L/2)! \times (L/2)!$ ways to arrange these beats such that the new arrangements result in the same set of even and odd group of beats, as in the original beat sequence. In general, the latter number is negligibly smaller than the former, and thus, the probability of generating beat sequences with even and odd groups of beats similar to the original beat sequence is negligibly small (for 250 shuffles and $L = 64$, this probability is approximately: $250 \times 6.9 \times 10^{70}/1.3 \times 10^{89} \approx 1.4 \times 10^{-16}$). Furthermore, even if by chance shuffling results in such an event, the associated alternans amplitude will belong to the tail of the NIAP distribution, and hence, will not cause a missed detection for even a conservative significance level of $\alpha = 0.01$.

In this paper, the SDA-based detection technique employs a simple averaging-based method for estimating TWA amplitude, which we now describe.

2) Simple Averaging Method: The SAM method is based on calculating the absolute value of the difference between the average of the even and odd groups of beats within the analysis window, at every sample point within the ST-T complex, and by taking the maximum value of the calculated differences within the ST-T complex. The SAM method is only an amplitude-estimation technique and is essentially equivalent to the amplitude estimation part of the SM with a rectangular window.

3) Spectral Method: In our implementation of the SM [5], [27], we utilized Welch's nonoverlapping periodogram method of estimating power spectral density and a Hamming window [12]. The alternans value was considered significant if the k-value was larger than 3 (where the k-value refers to the spectral ratio index utilized within the SM method for detection purposes) [27]. It can be shown that the periodogram calculated at the frequency of 0.5 cycles/beat is proportional to calculating the difference of even and odd group of beats (or a windowed version of the even and odd beat sequences in the case of a Hamming window) [12].

4) Modified Moving Average Method: The MMA method was devised as an *ad hoc* method of calculating average templates for the even and the odd group of beats that are less sensitive to large fluctuations in T-wave amplitude [28]. The reported TWA amplitude is the maximum value of the difference between the calculated even and odd templates. Also note that the MMA method is only a TWA amplitude-estimation technique and does not include any test of significance (i.e., it performs TWA amplitude estimation, but no TWA detection). In practice, certain steps in the preprocessing/alignment step—such as exclusion of beats with abnormal fluctuations in the TP segment (from the end of T-wave to beginning of the P-wave)—are taken to reduce noise artifacts [29]. However, since in this paper, a uniform preprocessing/alignment step is utilized independent of the particular TWA detector, the TP-segment-based noise rejection was omitted.

III. Results

A. Simulated Data

In this section, we compare the performance of the SDA, SAM, SM, and MMA methods on the simulated data described in Section II-A, with and without additive realistic noise. The MMA method, as noted in Section II-C4, is only a metric of TWA amplitude and does not include an explicit detection step. In contrast, SM uses thresholding method to reject noise artifacts. Furthermore, the SAM method is employed with and without our proposed significance testing in order to establish a baseline performance. Note that the significance level for the surrogate test was picked to yield the same level of specificity (i.e., proportion of negatives that are correctly identified) at 0 μV TWA amplitude, as the SM method with a k-value of 3. In general, a more stringent level of specificity would necessarily result in a larger percentage of missed detections and *vice versa*. Thus, by fixing the level of specificity of all detection algorithms, one can compare their missed detection rates as a means to assess their relative performance.

1) Performance of the SDA and SAM: Fig. 4(top) illustrates the performance of the SAM without significance testing on the simulated data at SNR of 10 dB and no noise scenario. Represented in each figure are the lower 5%, median, and the upper 95% of the estimated TWA amplitude, as well as the identity line $y = x$ (representing ideal estimation). At each given SNR, there was a noise floor that hindered accurate detection of TWAs with small amplitudes. This noise floor decreased with an increase in SNR and resulted in false quantification of TWA amplitude, particularly at low TWA amplitudes (note that even though only the results for SNR of 10 dB is shown here, these observations were consistent for SNRs of 20 and 30 dB). Even in the absence of background noise, a lower noise floor of 5–10 μV was found below which it was impossible to distinguish real TWA from noise artifacts. Note that since the estimated alternans were all accepted, in Fig. 4(top) (in the absence of significance testing), the percentage of indeterminate cases (or missed detections) were zero in all cases.

Fig. 4(bottom) presents the TWA detection statistics after rejecting cases that were ruled false positives using the SDA method ($\alpha = 0.01$) as well as the percentage of indeterminate cases (gray-color error bar). Also note that at the SNR of 10 dB and TWA amplitude of 0 μV, approximately 99% of the NIAP were rejected. Furthermore, as we show next, the percentage of missed detections at higher TWA amplitudes were notably smaller than the SM (e.g., 20% $\pm$ 15% at the largest simulated TWA amplitude and SNR of 10 dB, as apposed to 50% $\pm$ 20% for the SM).

2) Performance of the SM: Performance of the SM on the equivalent data is presented in Fig. 5(bottom), using a k-value of 3 that is assumed to be constant throughout the analysis.

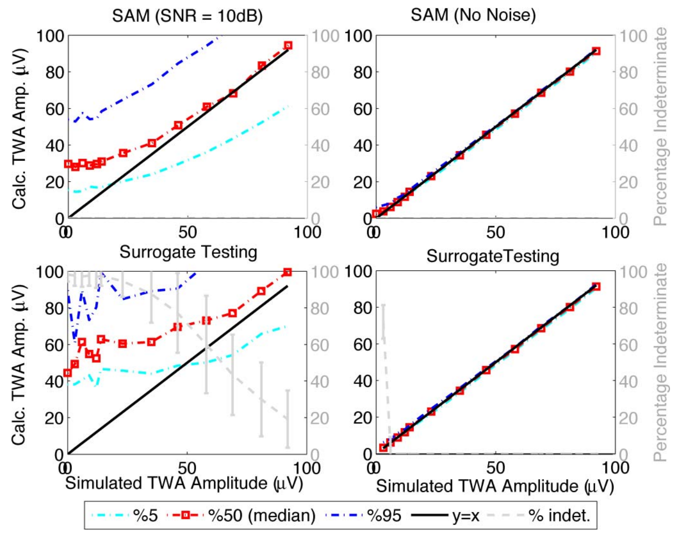

Fig. 4. Performance of the SAM on the simulated data (top) before and (bottom) after application of the SDA method ($\alpha = 0.01$). Estimated TWA amplitude (*Calc. TWA Amp.*) versus simulated TWA amplitude at SNR of 10 dB (left) and noise-free simulated VCGs (right) are shown. Each point on the figure is calculated from 50 simulated VCG records of 5 min length each. At a HR of 70 $\pm$ 5 beats/min, this results in roughly 10 TWA amplitude measurements per record, and thus, a total of 500 estimates. Represented in each figure are the lower 5%, median, and the upper 95% of the estimated TWA amplitude, as well as, the line $y = x$ (representing ideal detection). The gray-color error bars represent the percentage of indeterminate cases (%indet.). Note that at the SNR of 10 dB, application of surrogate testing resulted in rejection of approximately 99% of episodes around 0 μV simulated TWA amplitude, and simultaneously, the percentage of missed detections (or indeterminate cases) at higher TWA amplitudes is notably smaller than the SM method (see Fig. 5).

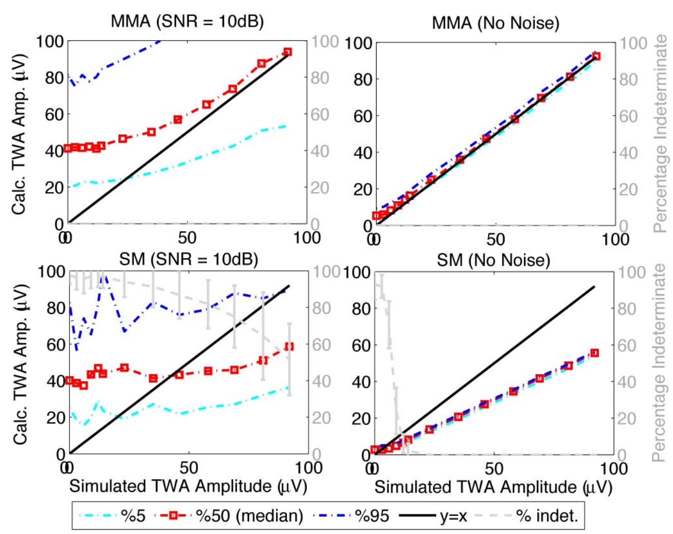

Fig. 5. Performance of (top) MMA method and (bottom) SM using a k threshold value of 3. Note that such choice of k results in rejection of almost 98% $\pm$ 2% of false estimates at 0 μV TWA amplitudes and rejection of 50% $\pm$ 20% of estimated values at the largest simulated TWA amplitude and SNR of 10. See Fig. 4 for explanation of legend.

Note that the SM yielded a substantial rejection rate even at higher TWA amplitudes (e.g., 50% $\pm$ 20% at the largest simulated TWA amplitude and SNR of 10). Also note that the SM underestimated the TWA amplitude by a constant factor.

TABLE I
PERFORMANCE SUMMERY OF THREE TWA DETECTION ALGORITHMS DISCUSSED IN THIS PAPER AT LOW SNR OF 10 dB, BASED ON FIGS. 4(BOTTOM-LEFT) AND 5(BOTTOM-LEFT)

Detection Method	% False Alarm at 0 μV, SNR=10 dB	% missed detections at 50 μV, SNR=10 dB	100 μV, SNR=10 dB
SM (spectral ratio test)	$2\% \pm 2\%$	$80\% \pm 13\%$ †	$50\% \pm 20\%$ †
SDA	$1\% \pm 1\%$	$60\% \pm 25\%$ †	$20\% \pm 15\%$ †

In the case of the SM, the spectral ratio index k was set equal to 3. The significance level of the SDA method ($\alpha = 0.01$) was chosen to yield similar false-alarm rate at 0 μV as the SM with $k = 3$ (i.e., $2\% \pm 2\%$). Application of the Wilcoxon rank-sum test indicates significance differences (indicated by †) between the two algorithms in terms of percentage of missed detections, at every simulated TWA amplitude level from 50 to 100 μV ($p < 0.001$). (Due to space limitations, only results for 50 and 100 μV are presented here.)

3) Performance of the MMA Method: Fig. 5(top) illustrates the performance of the MMA method on the simulated ECG. Comparing with the Fig. 4(top), it can be seen that the modified averaging method employed by the MMA method tended to amplify the noise. For instance at the SNR of 10 dB, and in the absence of TWA, the median of the MMA estimates was 40 μV compared with 30 μV in the case of the SAM. This observation affirms and complements the observations made by Cox *et al.* [30], who conclude that: "MMA amplifies TWA compared to traditional spectral analysis, but both likely reflect similar pathophysiology." However, our simulations indicate that MMA amplifies both TWA as well as the effect of the recording noise. Due to the nonlinear nature of the MMA method, we were not able to single out a unique cause for this behavior.

Table I summarizes the performance of the two TWA detection algorithms discussed in this paper.

4) Effect of Window Size: Although we fixed the number of beats in our analysis to 64 beats, to allow direct comparison between different detection techniques for noise rejection, different studies have employed varying analysis window lengths, ranging from 16 beats [29] for the MMA method to 128 beats for the SM [27]. To determine the influence of the analysis window length on the results reported in this paper, we repeated all the simulation studies with a 32 beats and a 128 beats window. Decreasing the analysis window length led to a raising of the noise floor and an increase in the percentage of indeterminate cases, since the noise-reduction effect of averaging was less marked when using fewer beats, but did not influence the trend observed in our results. On the other hand, increasing the number of beats in a qualitatively similar way decreased the NIAP level across all the methods.

B. Real ECG Recordings

In this section, we present results of a comparative TWA analysis of three publicly available databases using the SAM and the SDA methods. Our goal was to investigate the effects of the proposed statistical test to facilitate analysis of the data (in terms of separability of patient populations according to their level of TWA activity) independent of the particular method of estimation of the TWA amplitude. To this end, we applied the SAM (the simplest estimation method) without and with significance testing to the three databases. To facilitate comparison, we also present the performance of the SM and the MMA method on the same databases.

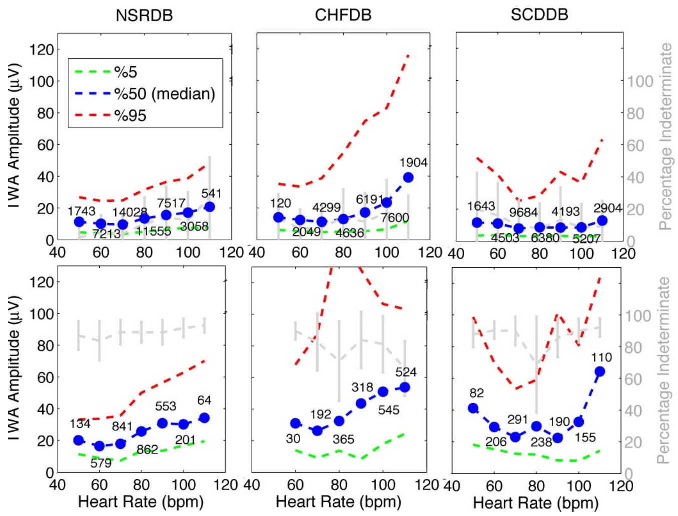

Fig. 6. Comparison of the NSRDB, the CHFDB, and the SCDDB patient populations (at matched HRs) using (top) SAM and (bottom) SDA method. The small numbers by the open blue circles indicate the number of detected episodes of TWA for the given HR range. The gray error bars signify the percentage of indeterminate cases at each HR range over the entire population. Note that in the top panels, the indeterminate cases are caused by preprocessing failure of associated analysis windows, while in the indeterminate cases in the bottom panels are an aggregate result of preprocessing failure and application of the SDA method ($\alpha = 0.05$). In comparison to the top panels, the number of detected episodes of TWA in the bottom panels are greatly reduced (see numbers by the open blue circles), and the margin of separability among patient populations is increased (see Table II).

Fig. 6 compares the effects of significance testing on three different patient populations. The top panels show the estimated TWA amplitude on the Normal Sinus Rhythm Database (NSRDB), Chronic Heart Failure Database (CHFDB), and SCD Database (SCDDB) patient populations at matched HR decades using the SAM with no surrogate testing. We chose to break down the data into HR decades because TWA is hypothesized to be an HR-dependent phenomenon [19]. By doing so, we avoid any bias due to the expected differences in HRs between each population or for any differences in the noise-rejection abilities of each TWA method, which may be HR-dependent. Note that in the case of real data, the definition of *indeterminate* is further extended to include preprocessing failure (due to misalignments, excessive ectopic beats within the analysis window, etc.). Fig. 6(bottom) present results of applying the proposed SDA method. Setting $\alpha = 0.05$ resulted in rejection of a large number of alternans-like episodes that did not pass the test of significance.

Table II summarizes the differences between the NSRDB, CHFDB, and SCDDB populations, as depicted in Fig. 6. For the purpose of comparison, Tables III and IV summarize the performance of the MMA method and the SM to the same databases.

Fig. 6 and Tables II–IV demonstrate that the SDA method is effective in separating the three patient populations according to the median of their TWA activity. For instance, before significance testing, the difference of median TWA amplitude between the NSRDB and SCDDB populations for HR band of 110–120 was -1.35 μV (see the fourth column of Table III). However, after removing episodes of false positive—using the

TABLE II
COMPARISON OF TWA ACTIVITY AT DIFFERENT HR IN NSRDB, CHFDB, AND SCDDB POPULATIONS USING SAM (TOP) WITHOUT SIGNIFICANCE TESTING AND (BOTTOM) AFTER SIGNIFICANCE TESTING WITH $\alpha = 0.05$

HR Band (*beats/min*)	NSRDB/CHFDB/SCDDB (*% indeterminate*)	$\Delta_{med(1,2)}$ (μV)	$\Delta_{med(1,3)}$ (μV)
	SAM		
40-50	1±5 / - / 20±20	-	-2.28†
50-60	1±7 / 14±15 / 20±23	0.03†	-2.58†
60-70	4±11 / 7±12 / 16±20	-1.67†	-3.14†
70-80	4±11 / 8±14 / 10±16	-2.82†	-6.23†
80-90	10±17 / 14±18 / 8±16	-1.08†	-5.50†
90-100	14±19 / 11±18 / 13±20	3.05†	-5.70†
100-110	12±18 / 17±21 / 8±15	9.28†	-5.60†
110-120	27±25 / 14±14 / 9±16	25.05†	-1.35†
	After Significance Testing (SDA method)		
40-50	88±4 / - / 80±11	-	-2.70†
50-60	86±9 / - / 88±8	-	18.41†
60-70	83±12 / 89±5 / 90±5	8.01†	6.47†
70-80	88±8 / 82±18 / 90±9	3.45†	0.11†
80-90	88±7 / 70±25 / 68±30	9.60†	6.95†
90-100	88±8 / 84±18 / 86±12	20.71†	0.43†
100-110	91±6 / 81±18 / 90±8	28.09†	9.69†
110-120	92±4 / 66±17 / 92±6	30.96†	41.51†

For a given HR range, $\Delta_{med(1,2)}$ is the median TWA amplitude of CHFDB population minus the median TWA amplitude in the NSRDB population. Similarly, $\Delta_{med(1,3)}$ is the median TWA amplitude of SCDDB population minus the median TWA amplitude in the NSRDB population. †indicates a significant difference between TWA amplitudes at a given HR range using the Kolmogorov–Smirnov test (p <0.0001). The empty entries (−) indicate that there were less than ten detected episodes of TWA activity in the corresponding patient populations, and thus not amenable to significance testing using the Kolmogorov–Smirnov test.

TABLE III
COMPARISON OF NSRDB, CHFDB, AND SCDDB USING SM WITH A SPECTRAL RATIO THRESHOLD VALUE OF $k = 3$

HR Band (*beats/min*)	NSRDB/CHFDB/SCDDB (*% indeterminate*)	$\Delta_{med(1,2)}$ (μV)	$\Delta_{med(1,3)}$ (μV)
40-50	- / - / -	-	-
50-60	87±10 / - / 92 ± 6	-	12.12†
60-70	91±6 / 85±15 / 93±4	-1.37†	-4.57†
70-80	93±4 / 78±21 / 91±6	3.91†	-5.79†
80-90	94±3 / 87±11 / 87±13	3.68†	-5.33
90-100	95±3 / 87±10 / 88±9	9.15†	-4.21†
100-110	95±2 / 76±13 / 91±7	28.14†	-4.25†
110-120	95±2 / 74±15 / 90±8	21.95†	3.24†

See Table II, for a description of the presented items.

TABLE IV
COMPARISON OF NSRDB, CHFDB, AND SCDDB USING MMA METHOD

HR Band (*beats/min*)	NSRDB/CHFDB/SCDDB (*% indeterminate*)	$\Delta_{med(1,2)}$ (μV)	$\Delta_{med(1,3)}$ (μV)
40-50	1±5 / - / 20±20	-	-2.94†
50-60	1±7 / 14±15 / 20±23	-2.14	-2.63†
60-70	4±11 / 7±12 / 16±20	-1.56†	-4.28†
70-80	4±11 / 8±14 / 10±16	-4.54†	-8.64†
80-90	10±17 / 14±18 / 8±16	-2.33†	-7.85†
90-100	14±19 / 11±18 / 13±20	1.53†	-7.86†
100-110	12±18 / 17±21 / 8±15	9.36†	-7.92†
110-120	27±25 / 14±14 / 9±16	23.19†	-3.43†

See Table II, for a description of the presented items.

SDA method–this difference was 41.51 μV, thus indicating a much higher level of TWA activity among the SCDDB patient population.

IV. DISCUSSION

TWA analysis generally leads to a large number of indeterminate cases [4], [6], [7]. Furthermore, "natural" TWA activity of normal subjects of up to 10 μV has been reported in healthy subjects [19]. The results of our study suggest that these observations may be explained by the high number of false-positive TWA events, particularly during periods of higher noise (such as during exercise/stress test when the signal quality is qualitatively similar to the 10 dB simulated records studied here). In addition, our simulation study indicates that in the absence of appropriate (adaptive nonparametric) significance testing, even a relatively small amount of noise (due to muscle artifact, baseline wander, or electrode motion) can lead to the raising of the noise floor to clinically significant levels (10 μV or much more).

Our results on artificial data indicate that the SDA method produces a more accurate detection of TWA patterns in noise, when compared to other standard or more advanced techniques of noise rejection at both low and high values of TWA and noise. Since our technique assumes nothing concerning the noise distribution, we expect (and observe) a lower error rate. The inverse relationship between the false-alarm rate and missed detection rate is well known; reducing one results in increasing the other and *vice versa*. Thus, to facilitate comparison of the three detection algorithms discussed in this paper, we fixed their false-alarm rates at the simulated TWA amplitude of 0 μV to approximately 1%–2% and studied their missed detection rates. As summarized in Table I, the SDA method resulted in a statistically significant reduction in the percentage of missed detections (or indeterminate cases) at every simulated TWA amplitude from 50 to 100 μV (Wilcoxon rank-sum test, $p < 0.001$).

The SAM method is utilized in this paper as a baseline amplitude-estimation technique to demonstrate the applicability of the SDA method for reducing false detections (false alarms) and simultaneously reducing missed detections. Our rational for choosing the SAM method was its ease of interpretation, as that it is based on simple averaging in time domain. Logically, we can expect that more sophisticated TWA amplitude-estimation techniques, in association with the SDA method, will result in further improvements.

When testing the effect of window size, we found that decreasing the window length from 128 to 64–32 beats simply raised the noise floor, but did not affect the trend in our result. These observations are consistent with the previously reported results concerning the influence of window size on the performance of the SM and the MMA method [9]. Nevertheless, increasing the window size is not always practical, since one might wish to decrease the window length to mitigate the nonstationary effects, such as phase changes due to ectopy and HR perturbations and to be able to more rapidly track changes in TWA amplitude. We also demonstrate that the SM technique produces an estimate of the TWA amplitude that is biased toward values lower than simulated values. (This observation can be explained mathematically and is beyond the scope of this paper [31].)

Studies on both artificial data and three different patient populations (using the NSRDB, the CHFDB, and the SCCDB) indicate that our new detection algorithm provides enhanced discriminatory power between patient populations. (The median difference between healthy and unhealthy patients is significantly larger than the other standard techniques at almost all HRs ($p < 0.0001$).) The most marked differences are found at higher HRs, although HRs below standard thresholds [110 beats per minute (BPM)] also allow differentiation of normal and abnormal subjects. Note that, in each case, the application of significance testing increased the margin of separability between the patient populations (see Tables II and III). This improvement can be explained as follows: Before significance testing, the number of reported alternans-like episodes with relatively small amplitudes were much larger, and thus, the quantiles were biased toward zero. After significance testing, a large number of such episodes were marked as indeterminate, and thus, were removed from the quantile calculations, and therefore, each quantile took on a larger value. Therefore, the application of significance testing improved the margin of separability by removing false detections that were negatively weighting the calculations. Furthermore, on average, the surrogate test maintained a lower percentage of indeterminate case than a comparable test (the SM). This observation may be explained by the lower missed detection rate of our surrogate test method.

Note that the SM does include a test of significance (designed under assumption of Gaussianity of the spectral coefficients), while in contrast, the MMA method relies on the preprocessing steps (such as exclusion of beats with abnormal fluctuations in the TP complex) to reduce noise artifacts [28], [29]. We repeated the TWA analysis on the real data using the SM and MMA methods. In the case of the NSRDB–CHFDB, application of the SM resulted in an improvement in interpopulation separability over both the SAM (with no significance testing) and the MMA method. However, in the case of the NSRDB–SCDDB, only the SAM with the surrogate testing method was able to improve the interpopulation margin of separability. The MMA method produced similar results to the SAM (with no significance testing), although with a positive offset at all HRs, as we would expect from our experience on artificial data.

It is worth noting that the SDA method is not computationally more expensive than the standard methods, since the bulk of the computation of TWA algorithms is devoted to preprocessing and alignment of beats, with generation of surrogate data through beat index reshuffling and reestimation of TWA amplitude being only a small portion of the overall computational cost.

Finally, we note that we employed the same preprocessing for all the methods, using the best-available open-source algorithms [25], since this paper focuses on significance testing. The commercial implementations of the MMA and the SM may include additional or alternative preprocessing and noise-reduction steps that are not considered here. However, it is unlikely that even extremely sophisticated preprocessing or estimation methods (such as complex demodulation or time-frequency approaches) would obviate the need for significance testing, since there exits no known technique that completely removes all noise in the ECG.

V. Conclusion

We have described a new application of a nonparametric surrogate test to reject false TWA-like activity (which could have been due to artifacts or noise). The new technique was evaluated on both real and artificial data. Tests on the artificial data demonstrate the superiority of our method over existing TWA detection methods, both at low and high levels of TWA amplitude.

In the absence of background physiological noise, a lower noise floor of 5–10 μV was found, below which the measured TWA is unreliable and could be due to noise alone. This noise floor may account for some reports of TWA in normal patients below 10 μV. Results also demonstrate that the higher the background noise, the more likely it is that a given technique will falsely detect TWA and overestimate the magnitude of the TWA.

When evaluated on three public databases (the NSRDB, the CHFDB, and the SCDDB), our new approach demonstrated significant differences in TWA amplitudes between each database at all HRs intervals between 40 and 120 BPM. The most-marked differences were generally found at higher HRs, and the new technique provided a larger margin of separability between patient populations than the standard methods. Our results also indicate that population separation is possible at lower HRs than current clinically recommended.

Acknowledgment

The content of this article is solely the responsibility of the authors and does not necessarily represent the official views of the U.S. National Institute of Biomedical Imaging and Bioengineering, the NIH, or the ISCIII.

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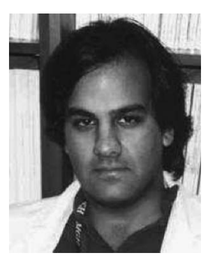

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