HEART-RATE ADAPTING MATCH FILTER DETECTION OF T-WAVE ALTERNANS IN EXPERIMENTAL HOLTER ECG RECORDINGS

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ABSTRACT
T-wave alternans (TWA) is an electrophysiological phenomenon associated with cardiac electrical instability. Recently we proposed a new heart-rate adapting match filter (AMF) to detect TWA in ECG tracings affected by baseline wanders. AMF performance was tested against the third-order spline (TOS) interpolation baseline-removal technique, the only other baseline-removal method proposed in literature for TWA-detection purposes. Using simulated data, we proved that our AMF-method increased correct TWA identification by significantly reducing the number of TWA false-negative detections. The aim of the present study was to test AMF performance in Holter ECG recordings from 15 patients with acute myocardial infarction (AMI) and 15 healthy (H) subjects. Comparison with TOS was also made. Four AMI patients and two H subjects were identified as TWA-positive after application of AMF. By contrast, eight AMI patients (p<0.05) and nine H subjects (p<0.05) were identified as TWA-positive after application of TOS-method. According to clinical observations TWA is infrequent, especially in H-subjects. Thus, our results suggest that TOS-based technique may introduce false-positive TWA detections. In conclusion, compared to TOS-method, our AMF-based method reduces both false-positive (experimental study) and false-negative (simulation study) TWA detections, thus yielding an improvement over the TOS in the effectiveness of automatic TWA detection.

KEY WORDS
ECG baseline removal; Repolarization; T-wave alternans.

1. Introduction
T-wave alternans (TWA) consists of a beat-to-beat alternation of the T-wave morphology (amplitude, shape and, sometimes, polarity). Visible TWA is an infrequent phenomenon associated with an increased propensity to life-threatening ventricular arrhythmias [1, 2]. Automatic analysis of digital ECG made possible to unmask and detect non-visible, microvolt TWA, so that both visible and non-visible TWA could be associated with electrical instability [3–12]. Various techniques have been reported to detect microvolt TWA [5–8]. All of them require signal preprocessing to control for possible effects of factors that may affect TWA identification [13–15]. Among these factors, the removal of baseline deviation from the isoelectric line (referred to as baseline wandering) is a major issue that becomes critical when Holter recordings are analyzed. These tracings are indeed recorded under uncontrolled conditions, with baseline components of unknown frequencies. In a recent study [16] based on simulated data, we demonstrated that baseline wandering might cause erroneous detection of TWA from TWA-free ECG tracings, or prevent correct detection of TWA, whenever it was present. To improve effectiveness of TWA detection, we proposed a new heart-rate adaptive match filter (AMF). This filter had a narrow pass-band around the typical TWA frequency, and, in simulated data, allowed TWA detection almost independently of baseline frequency components [16].

The present study was finalized to a further evaluation of the effectiveness of the AMF technique in detecting TWA from Holter ECG recordings of patients with acute myocardial infarction (AMI), who have been found to be at increased risk to develop TWA [17–20], and healthy (H) subjects. Our method was again tested against the traditional technique that uses a third-order spline (TOS) interpolation to identify the baseline, which is subsequently subtracted from the ECG tracing for TWA detection. The TOS-method is the only technique proposed in literature to remove baseline for TWA-detection purposes [13-14].

2. Method

- Experimental data: The present study involved 15 patients who survived an acute myocardial infarction
(AMI; RR=817±168 msec), and 15 healthy subjects (H; RR=963±177 msec). From each patient, a three-channel (X,Y,Z) digital Holter recording was obtained using Burdick recorders (Burdick Inc., Milton, WI), that sampled the ECG signal at 200 samples per second. A series of 128 consecutive sinus beats recorded in resting conditions was used to detect and quantify TWA.

- **Baseline Removal Techniques for TWA Detection**

  **Purposes:** Our heart-rate adapting match filter (AMF) was used to remove baseline wanderings. Differently from the traditional techniques finalized to baseline estimation and successive subtraction from the ECG tracing, the goal of our AMF was to emphasize the TWA signal by filtering out everything else (the baseline and the ECG components other than TWA). After identification of R peaks, estimated mean RR was used to identify the filter passing TWA frequency (f_{TWA}=1/(2*meanRR)). To allow some physiologic variation of the RR interval, this filter was implemented as a 6th order bidirectional Butterworth band-pass filter (rather than a single frequency-pass filter) with a very narrow bandwidth of f_{TWA}±∆f, with ∆f=0.06 Hz [16].

  Effectiveness of AMF was tested against a classical baseline estimation and removal by means of a third-order spline interpolation (TOS) of fiducial points in the PR intervals [21].

- **TWA Detection Methods:** Automatic detection of TWA was accomplished after filtering the ECG tracings with AMF or with TOS interpolation.

  When using AMF, the TWA signal, as seen at the output of the AMF, is a time-domain, constant-phase and eventually amplitude-modulated sinusoid, with its maxima and minima over the T waves. A local estimate of the TWA amplitude is directly given by the sinusoid amplitude in correspondence of the T-wave apex. Consequently, both local (i.e. relative to a single beat) and global (i.e. relative to the entire analyzed ECG tracing) measurements are available. In fact, from the local measure of TWA amplitude (A_{TWA}), it is possible to obtain the following global measurements: mean TWA amplitude (A_{TWA} averaged over all the alternating T waves), TWA duration (given by the total number of alternating T waves), and TWA magnitude (defined as the product of TWA amplitude by TWA duration).

  When using the TOS, TWA detection was accomplished by applying the correlation method (CM) [13, 14], that uses the median T wave (T_{mdn}) to compute the alternans correlation index (ACI) of individual T_j waves in comparison to T_{mdn}:

  \[ \text{ACI}_j = \frac{\sum_{i=1}^{N} T_j(i)T_{mdn}(i)}{\sum_{i=1}^{N} T_{mdn}^2(i)} \quad j = 1:128. \]  

  Since the correlation method is also a time-domain technique, the definitions of TWA amplitude, TWA duration and TWA magnitude still hold.

  When using TOS, alternations of ACI_j (and, indirectly, of T wave) have to be larger than a certain threshold (THR_{ACI}) to limit false detections due to noise (Fig. 1). To evaluate possible distortions and side effects of TOS application, when analyzing H subjects we considered two values of THR_{ACI}: THR_{ACI}=0 (i.e. no threshold), and THR_{ACI}=0.06, a value already used in our previous works [8, 13, 14]. Only THR_{ACI}=0.06 was considered for AMI patients.

[Fig. 1. Trend of ACI in case of TWA. ACI values have to alternate around the value of one (dashed line). The oscillations have to be larger than a threshold (dotted line) to be considered as TWA and not noise.]

3. **Results**

Analysis of H subjects with TOS, under assumption of THR_{ACI}=0 (that is no threshold on amplitude oscillations), resulted in the detection of some levels of TWA in all 15 (100%). Indeed, TWA was characterized by an appreciable duration (TWA duration: 37±10 out of 128 T waves) and amplitude (TWA amplitude: 31±15 µV; TWA magnitude: 1139±552 µV). Number of TWA-positive H individuals reduced to 9 (60%) for THR_{ACI}=0.06, with TWA being characterized by a shorter duration (TWA duration: 10±12 out of 128 T waves) and smaller amplitude (TWA amplitude: 18±18 µV; TWA magnitude: 326±468 µV).
Table 1. TWA characteristics of AMI- and H-populations, when applying AMF and TOS techniques.

<table>
<thead>
<tr>
<th></th>
<th>AMF</th>
<th>TOS</th>
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<tbody>
<tr>
<td>#TWA+ subjects</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>TWA duration</td>
<td>21±37</td>
<td>9±24</td>
</tr>
<tr>
<td>TWA A (µV)</td>
<td>15±29</td>
<td>6±17</td>
</tr>
<tr>
<td>TWA M (µV)</td>
<td>1218±2565</td>
<td>413±1113</td>
</tr>
</tbody>
</table>

#TWA+ subjects: number of TWA positive subjects; TWA A: TWA amplitude; TWA M: TWA magnitude. All the TWA measurements are averaged over the entire populations.

Table 2. TWA characteristics of AMI patients and H subjects with detected TWA, when applying AMF and TOS techniques.

<table>
<thead>
<tr>
<th></th>
<th>AMF</th>
<th>TOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMI+ (4)</td>
<td>80±15</td>
<td>66±25</td>
</tr>
<tr>
<td>H+ (4)</td>
<td>14±8</td>
<td>17±11</td>
</tr>
<tr>
<td>TWA duration</td>
<td>55±29</td>
<td>48±6</td>
</tr>
<tr>
<td>TWA A (µV)</td>
<td>4569±3209</td>
<td>3096±849</td>
</tr>
<tr>
<td>TWA M (µV)</td>
<td>386±292</td>
<td>544±500</td>
</tr>
</tbody>
</table>

AMI+ : AMI patients with detected TWA; H+: H subjects with detected TWA; TWA A: TWA amplitude; TWA M: TWA magnitude. All TWA measurements are averaged over the TWA-positive individuals of a population.

Application of AMF to AMI- and H-groups yielded the results reported in Table 1 (where the TWA measurements are averaged over the entire populations) and Fig. 2. TWA was detected in 4 (27%) AMI patients and 2 (13%) H subjects. On average, TWA episodes were longer (TWA duration: 21±37 and 9±24 T waves) and larger (TWA amplitude: 15±29 and 6±17 µV; TWA magnitude: 1218±2565 and 413±1113 µV) for AMI than H subjects, respectively (Table 1).

Application of TOS interpolation, under assumption of THR=0.06, yielded in AMI and H groups the results shown in Table 1 and Fig. 3. TWA was detected in 8 (53%) AMI and 9 (60%) H individuals. On average, all TWA measurements were slightly lower for AMI than for H subjects (Table 1: TWA duration: 7±9 and 10±12 T waves; TWA amplitude: 16±24 and 18±18 µV; TWA magnitude: 206±287 and 326±468 µV for AMI and H subjects, respectively).
A comparison between TWA-positive AMI patients and H subjects (denoted as AMI+ and H+, respectively) showed that (Table 2, with TWA measurements averaged only over those individuals of a population with detected TWA), after application of our AMF, TWA episodes in AMI+ were longer (TWA duration: 80±15 T waves) and had larger amplitude (TWA amplitude: 55±29 µV; TWA magnitude: 4569±3209 µV) than those detected in H+ (TWA duration: 66±25 T waves, TWA amplitude: 48±6. µV; TWA magnitude: 3096±849 µV). After applying the TOS, the two populations showed no appreciable differences between any of the TWA parameters (Table 2: TWA duration: 14±8 and 17±11 T waves; TWA amplitude: 30±26 and 29±13µV; TWA magnitude: 386±292 and 544±500 µV; for AMI+ and H+, respectively). Three AMI patients and one H subject were detected as TWA positive with both techniques.

4. Discussion

TWA is an infrequent electrophysiological phenomenon strictly associated with cardiac electrical instability and life threatening ventricular arrhythmias [1-12]. Since in most circumstances this phenomenon is not visible in ECG tracings, efforts have been put in setting up computerized procedures that allow detection of TWA from standard Holter ECG recordings, thus making available a non-invasive and clinically useful marker of sudden cardiac-death risk [8, 14].

Fluctuations of isoelectric line may induce failure in detection of TWA from ECG recordings [13, 16]. These fluctuations depend on various causes of ‘internal’ (such as respiration and muscular electric noise) and ‘external’ (such as electrical interferences) nature [13, 22, 23] that make it hard to determine the baseline frequency components. Baseline removal, however, is beneficial to TWA detection, as well as to any signal processing technique finalized to measure ECG amplitude. Several techniques have been proposed in the literature for estimation and successive removal of isoelectric line fluctuations [21, 24-30]; some examples are cubic-spline interpolation [21], linear filtering [26, 27], and adaptive filtering [28-30]. All of them are designed to achieve precise goals (analysis of heartbeat dynamics [28], analysis of ST segment [30], etc). As far as we know, no specific adaptive filter, rather than our own [16], was reported for TWA purposes.

In the absence of a gold-standard assessment, our previous simulation approach [16] helped to provide insights into the benefits/limitations of our new AMF-based method against the TOS-based method. Simulated time series were obtained from a real ECG complex. Simulation of TWA was performed by varying the T wave amplitude, whereas baseline wanderings were simulated with sinusoids of frequencies lower, equal, and higher than TWA fundamental frequency (fTWA). When no baseline removal filtering was applied, both false-positive and false-negative detections occurred. The presence of baseline oscillations at lower and higher frequency than fTWA prevented TWA detection when TWA amplitude was lower or equal to that of baseline oscillations. On the other hand, the presence of baseline oscillation at the same frequency of TWA resulted in the detection of TWA even when not present. After application of TOS-technique, a suitable detection of TWA occurred only for frequencies lower than fTWA. For baseline oscillations at greater frequency than heart rate, however, TOS application became useless. An advantage of our AMF-based technique over the TOS-based method was that it allowed detection of TWA almost independently of baseline frequency components, when these were different from TWA own frequency. Thus, we concluded that the AMF-based technique was a potentially better tool for automatic TWA detection, that deserved further validation studies [16].

In the present study a comparative test between the two TWA-detection techniques was performed on experimental data. We analyzed Holter ECG recordings from 15 patients with acute myocardial infarction (AMI), who have been found to be at increased risk to develop TWA [17-20], and 15 healthy (H) subjects as control group. Effectiveness of our AMF-based technique was again compared with that of the TOS-based technique, which is the only other baseline-removal technique proposed in the literature for TWA detection purposes.

Our AMF-based technique was able to discriminate the proneness of AMI and H groups to develop TWA. Four AMI patients and two H subjects were identified as TWA-positive after application of AMF, with larger and longer TWA episodes identified in TWA-positive AMI patients compared to TWA-positive H subjects. By...
contrast, eight AMI patients (p<0.05) and nine H subjects (p<0.05) were identified as TWA-positive after application of the TOS-method. Thus, significantly different indications as to the presence of TWA in the two populations are provided by the two competing methods. Judgment of what is most reliable between these methods can only be based on qualitative clinical expectations (it is impossible to know a priori if TWA is present or not) and on previous results found from simulation studies, where it is known a priori if TWA is present or not. Because it is generally accepted in clinics that TWA is an infrequent phenomenon, especially in healthy subjects, the occurrence of TWA in 60% of our H-group detected by the TOS-method, which was even higher that the occurrence in AMI patients (53%), is unlikely. Detection of TWA-positive cases in 13% H-subjects and 27% AMI patients provided by our AMF-method appears more reliable.

False TWA-positive detections by the TOS might be related to the choice of the threshold level introduced in the algorithm. This threshold is necessary since we found that, in the absence of it, all H-subjects showed appreciable levels of TWA. To avoid such a clinically unacceptable behavior, the threshold was given a previously tested value [13, 14], that proved to work well for statistical discrimination between long QT syndrome patients and healthy subjects [8]. AMI patients, however, are less likely to develop TWA than long QT syndrome patients [1, 2, 8, 17-20], where TWA is often present even in its visible forms [1, 2]. Determination of a better threshold does not seem a possible solution to distinguish between AMI and H groups, since TWA measurements are even lower in the former than in the latter group.

From these observations we infer that TOS may cause some ECG distortions that induce false-positive TWA detections. This limitation adds up to that found in our previous simulation study, where the TOS-method underestimated the number of cases where TWA was present [16]. In conclusion, our AMF-based method reduces both false-positive (experimental study) and false-negative (simulation study) TWA detections, thus yielding an improvement over the TOS-based technique in the effectiveness of automatic TWA detection.

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References


