Specificity of the Moving Average Method for Detecting Alternans

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Abstract

The moving average method of detecting alternans, as originally described by Nearing and Verrier, does not address several factors that may impact its specificity. Omitted factors include the influences of RR interval irregularity and the harmonics of 4:1 processes like respiration. Also missing is a test for statistical significance. The relevance of these factors has been tested in a database of 383 recordings from a large trial on chronic heart failure patients (the GISSI-HF study). This database consists of 12-lead 24-hour Holter recordings. Non-overlapping 128-beat segments were analyzed to obtain the average odd minus even beat difference of normal beat pairs. The database provided 284,755 such segments, each with at least 36 odd/even pairs of normal beats. Only lead V5 was evaluated for alternans. Of these, 27,932 distinct 128-beat segments exhibited an alternans amplitude > 20 microvolts in at least one 20ms part of the average ST-T window odd/even differences. After applying tests for RR irregularity/instability, statistical significance, subharmonics, RR alternans, and using wider windows, only 268 events remained. These data suggest that the moving average method previously described exhibits poor specificity without application of additional criteria.

1. Introduction

The moving average method for detection of T wave alternans (TWA) in the ECG, introduced in 2002 by Nearing and Verrier [1], has been the subject of numerous studies. This initial conceptual presentation omitted consideration of several practical factors. A number of these omissions were addressed in Kaiser et al [2]. The purpose of this study is to evaluate the impact on alternans detection of the these factors: (1) a minimum signal to noise ratio, (2) the effects of RR interval irregularity or instability, (3) harmonics of lower frequency patterns masquerading as alternans, (4) RR interval alternans, and (5) the size of the time window used to measure the alternans amplitude.

2. Data acquisition and methods

All data used herein is from 12-lead, 24-hour Holter recordings (H12+, Mortara Instrument) with simultaneous sampling of all leads at 1000s/s. The study population consists of 383 recordings from the GISSI-HF heart failure study [3]. Data preprocessing included baseline drift removal, fully automatic beat detection and labeling, and depolarization and repolarization onset/offset detection by Mortara proprietary algorithms [4].

Since the objective of this study is to evaluate the impact of various additional qualifying criteria for TWA, it seems adequate to study the effects of applying these criteria to a single ECG lead. V5 is the selected lead for the study. A full implementation of the moving average would permit arbitrary blocks of beats to be analyzed for TWA. Instead we have selected consecutive of blocks of 128 beats for TWA analysis employing, a simple average of the valid even/odd beat pair differences within the 128-block is used to measure the alternans amplitude. Valid pairs of beats are defined by normal morphologies for both beats of the pair as well as the preceding beat, and the existence of at least a 100ms window between T end and the next QRS for each beat of the pair. The requirement of a normal preceding beat morphology is to ensure that post-extrasystolic beats (e.g., in a pattern of quadrigeminy) do not contribute to a pseudo-alternans. Two approaches to evaluating the JT interval for alternans are used. The first approach is that of Kaiser [2], using the average amplitudes of successive 20ms windows within the JT interval, and the second approach uses the average amplitudes of two equal time windows spanning the JT interval. A fixed JT interval is used for the entire 128-beat block. The reference isoelectric level for each window is the average amplitude of the 32ms pre-QRS onset window. 128-beat blocks with less than 36 valid even/odd pairs were excluded from further consideration. The alternans amplitude for each time window is then determined from the average of the valid even/odd pair differences, excluding the two largest and two smallest.

The exclusion is made to reduce sensitivity to transient artifact.

The alternans amplitude variance is determined from the variance of the average of two successive even/odd pair differences. This definition of the variance nullifies the spectral component at 0.25 cycle/beat (cpb) and diminishes other likely spectral noise components, reducing the effects of respiration and other rhythmic interference*. The magnitude of the 0.25 cpb spectral component, used as a flag of potential harmonic contributions to alternans at 0.5 cpb, is obtained by taking the magnitude of its two Fourier components, performed by analysis of the 128 beat original samples for each window.

3. Results

The database of 383 recordings provided 284,755 separate 128-beat blocks with at least 36 valid beat pairs for alternans analysis. Of these, 27,932, or 10%, exhibit an alternans amplitude > 20 uV in at least one 20ms window of the JT interval. Limiting the extent of RR interval irregularity or rate change by excluding blocks with an included RR deviating more than 120ms from the mean reduce this number to 18,249. However, only 1792 of these events have an amplitude greater than 3 times the square root of the respective variance. Requiring the alternans amplitude to be at least twice the peak-to-peak 0.25 cpb spectral magnitude reduces this count to 1052 candidate alternans events. RR alternans (RRA) evaluation is also performed, and 430/1052 of the putative alternans events have concurrent RR alternans at the level of 3 standard deviations, leaving 622 events. The median peak-to-peak RRA amplitude of the omitted events is 34ms. Finally, reducing the size, and thereby the number, of time windows examined for a qualifying event from 20ms to ½ of the JT interval reduces the event count to 268. These data are summarized in Table 1.

4. Discussion

The results of this study show that only 268/27932 (~ 1%) of all 128-beat segments with a TWA amplitude > 20uV pass additional scrutiny. A large fraction of the initial number is associated with RR irregularity or instability. More than 90% of the remaining candidate TWA events lack statistical significance. Because the estimate of variance plays a critical role in qualifying events, it is important to recognize that there are different methods of determining the variance. In Kaiser [2], the average of the variances of the even and odd beats is used, whereas the pair sum of pair differences is used here. This results in a shaped noise spectrum as seen in Figure 1(a). The method of Kaiser results in a uniform weighting while the method used here selectively weights the noise spectrum above 0.35 cpb to obtain the estimate of variance. Most importantly, this weighting sharply limits the contribution of modulations at ¼ and 1/3 of the heart rate. The benefit can be inferred by considering the spectral density example shown in panel (c). In this example, the weighted variance is roughly ¼ of the uniformly weighted.

Windows	Alternans Amp > 20uV	RR Dev < 120ms	> 3 SD	No ¼ cpb Harmonic	No RR Alternans
N x 20ms	27932	18429	1792	1052	622
2 x ½ JT	13265	9136	697	499	268

Table 1. Tabulation of alternans qualifying 128 beat blocks. Rows indicate the size of the averaging window within the JT interval and the implicit number of windows. Columns show the results of progressively applied criteria. “Alternans Amp > 20uV” means that at least one window of the JT interval has an average amplitude greater than 20 microvolt. “RR Dev < 120ms” means that no valid RR interval in the 128 beats deviate by much as 120ms from the mean. “> 3SD” means that the qualifying amplitude exceeds 3 times the square root of the variance. “No 0.25cpb Harmonic” means that the alternans amplitude exceeds the ¼ cpb amplitude magnitude by a factor of 2. “No RR Alternans” means that the measured RR interval alternans amplitude is less than 3 times the square root of its variance.

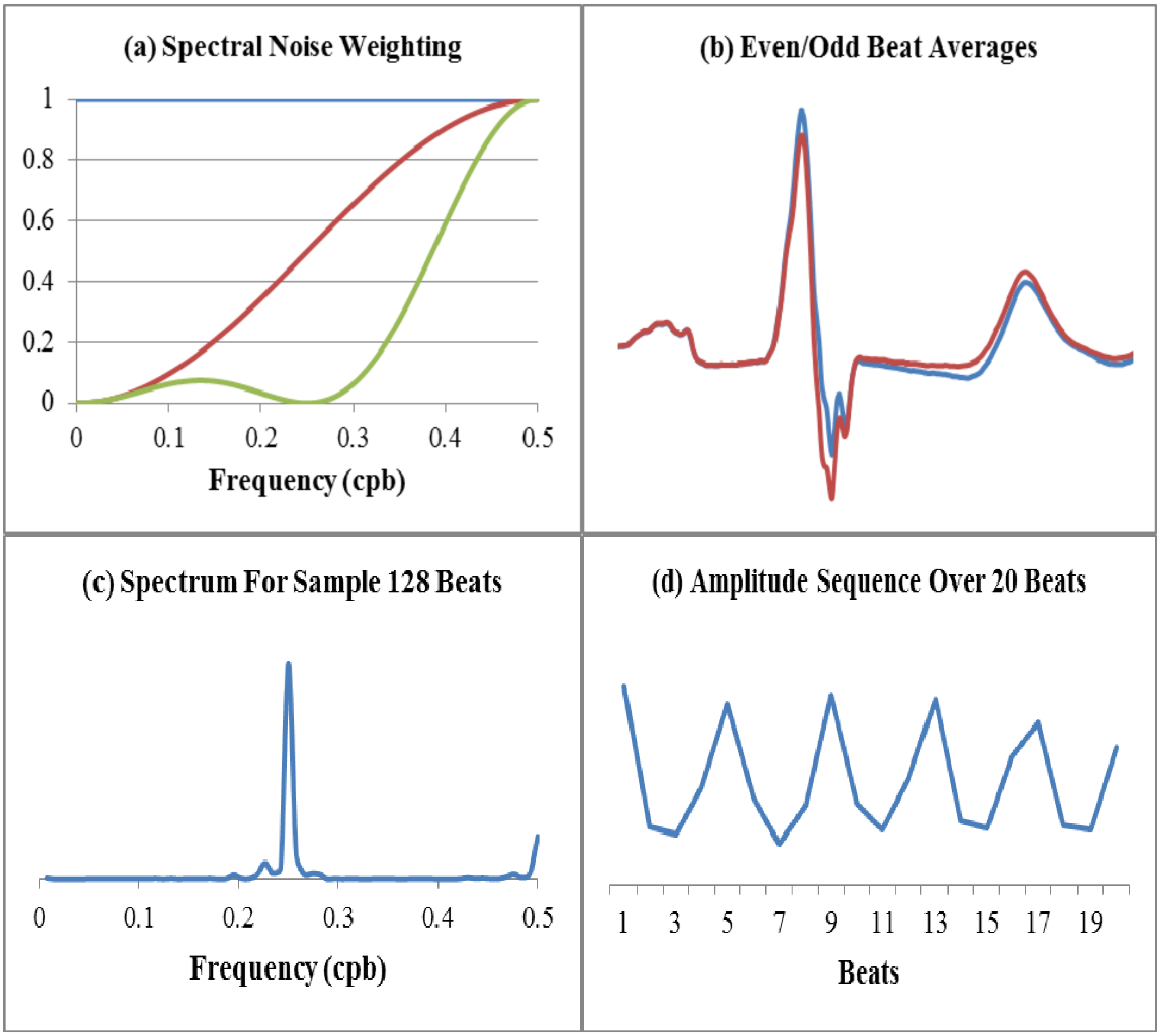

Figure 1. Panel (a) Weights applied to different parts of the noise spectrum to estimate the variance of the alternans signal. Blue line: uniform weights as in Kaiser [2]. Red line: weighting implied by taking the variance of even/odd pair differences (for illustration only, and not used herein). Green line: weighting implied by taking the variance of successive pair sums of even/odd pair differences. Panel (b) Blue/red lines are the averages of the even/odd beats in a 128 beat block. Panel (c) Power spectrum for one window of the JT interval. Panel (d) The window amplitude for the first 20 beats of the block.

Figure 1(b-d) is an example of a harmonic, presumably of respiration, producing "alternans-like" even/odd beat differences. Panel (b) of the figure shows the even/odd averages, panel (c) shows the spectral analysis of the amplitudes from one of the time windows, and panel (d) shows the window amplitude over a subset of the 128 beats. These three panels illustrate a misleading feature of the even/odd difference approach to alternans detection. The existence of the subharmonic of alternans is completely masked by the even/odd difference, but is readily apparent in the spectral analysis and the amplitude sequence. What looks like a perfect example of TWA (and, incidentally, QRS alternans) is almost certainly an artifact.

Atrial bigeminy may exhibit TWA as a secondary effect, and this is one reason that an RR irregularity test is applied. But what of less visible RRA? The results in Table 1 show that RRA occurs in a large percentage of the apparent TWA cases. TWA in the presence of RRA has an uncertain etiology. It may reflect entrainment, it may be induced by differences of stroke volume, or it may be secondary to QT adaptations to changing RR intervals among other possibilities. In any case, it seems warranted to distinguish TWA events with and without RRA.

The two rows of Table 1 show that the number of detected TWA events is highly dependent on the window size used. In the absence of evidence that the alternans waveform is more complex than the T wave in morphology, it would seem obvious that using fewer, wider windows is preferable.

Summarizing, alternans detection by comparison of even/odd beat averages requires a series of selection criteria to avoid oversensitivity. Moreover, some of these selection criteria involve spectral analysis of the signal. Prudent future studies employing even/odd beat comparison will need to address estimates of signal variance, RRA, subharmonics, and window size.

Acknowledgements

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References

[1] Nearing BD, Verrier RL, Modified moving average analysis of T-wave alternans to predict ventricular fibrillation with high accuracy. J Appl Physiol 2002;92:541-549.

[2] Kaiser W, Findeis M, Young BJ, Improving T-wave alternans measurement quality by reducing noise and artifacts. Computing in Cardiology 2004;31:445-448.

[3] Tavazzi L, Tognoni G, Franzosi MG, Latini R, Maggioni AP, Marchioli R, Nicolosi GL, Porcu M on behalf of GISSI-HF Investigators. Rationale and design of the GISSI Heart Failure Trial: a large trial to assess the effects of n-3 polyunsaturated fatty acids and rosuvastatin in symptomatic congestive heart failure. Eur J Heart Fail 2004;6:635-641.

[4] Mortara D, Automated QT Measurement and Application to Detection of Moxifloxacin-induced Changes. Ann Noninvasive Electrocardiol 2009; 13(Suppl. 1):S30-S34

*Note

In principle, a further narrowing of the spectral weighting can be achieved by widening the beat range of the effective filter. But the concomitant reduction in the number of independent samples increases the dispersion of the resulting variance estimate. This observation is particularly relevant when blocks smaller than 128 beats are used for even/odd beat average comparison. For example, if 32 beat blocks are used, there are only 8 independent components of the variance as defined in this study – each component being the sum of two pair differences. This results in a statistical 35% dispersion (1/√8) of the standard deviation.

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