Post-Ventricular Premature Contraction Phase Correction Improves the Predictive Value of Average T-Wave Alternans in Ambulatory ECG Recordings

Alba Martín-Yebra, Violeta Monasterio, Iwona Cygankiewicz, Antoni Bayés-de-Luna, Enrico G. Caiani, Pablo Laguna, and Juan Pablo Martínez

***Abstract*—*Objective*: We proposed and evaluated a method for correcting possible phase shifts provoked by the presence of ventricular premature contractions (VPCs) for a better assessment of T-wave alternans (TWA). *Methods:* First, we synthesized ECG signals with artificial TWA in the presence of different noise sources. Then, we assessed the prognostic value for sudden cardiac death (SCD) of the long-term average of TWA amplitude (the index of average alternans, IAA) in ambulatory ECG signals from congestive heart failure (CHF) and evaluated whether it is sensitive to the presence of VPCs. *Results:* The inclusion of the phase correction after VPC in the processing always improved estimation accuracy of the IAA under different noisy conditions and regardless of the number of the VPCs included in the sequence. It also presented a positive impact on the prognostic value of IAA with increased hazard ratios (from 17% to 29%, depending of the scenario) in comparison to the noninclusion of this step. *Conclusion:* The proposed methodology for IAA estimation, which corrects for the possible phase reversal on TWA after the presence of VPCs, represents a robust TWA estimation approach with a significant impact on the prognostic value of IAA for SCD stratification in CHF patients. *Significance:* An accurate TWA estimation has a potential direct clinical impact on noninvasive SCD stratification, allowing better identification of patients at higher risk and helping clinicians in adopting the most appropriate therapeutic strategy.**

***Index Terms*—Electrocardiogram (ECG), sudden cardiac death (SCD), T-wave alternans (TWA), ventricular premature contraction (VPC).**

I. Introduction

T-WAVE alternans (TWA), also known as repolarization alternans, appear in the electrocardiogram (ECG) as a consistent beat-to-beat alternation in the amplitude, duration or morphology of the ST segment and/or the T wave [1]. This phenomenon is known to reflect temporal and spatial heterogeneity of ventricular repolarization, associated to electrical instability. It is presently regarded as a non-invasive risk marker of ventricular vulnerability and provides valuable information regarding risk stratification for cardiovascular mortality and sudden cardiac death (SCD) [1], [2].

Several methods for TWA detection and estimation have been proposed (a comprehensive review can be found in [3]), being the spectral method (SM) [4] and the modified moving average method (MMAM) [5] the most widely used in clinical research, as they are available in commercial equipment. However, in the clinical practice, an important percentage of indeterminate TWA tests (between 20% and 40% [6]–[8]) is still reported. The main causes that can lead to an indeterminate result are excessive noise, lack of capacity to reach a target heart rate of 105 to 110 beats/min, non-sustained TWA (at least 1 minute) or ventricular ectopic activity, which may directly interfere with the frequency content of alternans [9]. Therefore, from the signal processing viewpoint, robust algorithms able to overcome these limitations are required in order to guarantee the clinical value of TWA. Other methods, such as the Laplacian likelihood ratio (LLR) method [10], have been reported to outperform the accuracy of the SM and MMAM in the presence of impulsive artifacts, as the ones produced in the beat-to-beat amplitude series by ectopic beats or electrode motion [11]. Finally, multilead strategies have been proposed for taking advantage of the

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inter-lead redundancy of TWA and noise components, such as the methods based on principal component analysis (PCA) [12] or periodic component analysis (π CA) [13], thus leading to a more robust and sensitive analysis than lead-by-lead analysis.

In clinical settings, although TWA tests are usually performed under controlled heart rate conditions, typically by exercise-induced stress, the analysis of TWA in ambulatory ECG recordings has become a matter of interest in recent years, yielding promising results [14]–[19]. In particular, long-term averaging of TWA activity in 24-hour Holter recordings (the index of average alternans, IAA) has been shown to be an independent predictor of SCD in chronic heart failure (CHF) patients [20]. In that study, a fully automated method based on LLR method and π CA was used, avoiding the need for visual verification required by other methodologies [14], [17], [18]. The method in [20] discards unstable segments, defined in terms of instantaneous heart rate changes, abrupt baseline wander and the percentage of ectopic beats. Indeed, segments with a low percentage of abnormal beats were still included in the analysis, as the LLR method for TWA estimation is able to cope with a small number of abnormal beats. However, the presence of one or more ventricular premature contractions (VPC) may alter repolarization dynamics, and they may introduce a phase reversal in the sequence of alternant T-wave morphologies [21], which could hamper the estimation of TWA amplitude [22], [23] and, consequently, its potential for risk stratification.

In this work, we propose a method to improve the estimation of TWA amplitude in ambulatory ECG, by dealing with the possible phase reversal induced by the presence of VPCs in the alternans sequence. A simulation scenario was first generated in order to evaluate the performance of the algorithm on synthetic signals. Then, the effect of the proposed method in the prognostic value of TWA amplitude in ambulatory ECG recordings was assessed.

II. Methods

A. Preprocessing

The general scheme for TWA analysis consists of three main stages: ECG pre-processing, signal transformation and TWA detection/estimation.

Preprocessing of ECG recordings included heart beat detection and labelling (including identification of VPCs) using the Aristotle ECG analysis software [24] and linear high-pass filtering (0.5 Hz cut-off frequency) for baseline wander attenuation. Then, the ECG signal was low-pass filtered (15 Hz cut-off frequency) to remove noise out of TWA frequency range, and down-sampled to 100 Hz. Finally, a segmentation of ventricular repolarization phase (ST-T complex) was done at each beat, by defining a fixed interval of 300 ms (30 samples after decimation) after the end of the QRS complex.

ECG signals were processed in segments of $L = 128$ consecutive beats (50% overlapped). Segments were deemed valid for automatic analysis if at least 80% of their beats fulfilled two conditions: (i) they were labelled as normal beats and (ii) there was a difference lower than 200 μV between the baseline voltage measured at the PQ segment in that beat and the one measured in the preceding beat.

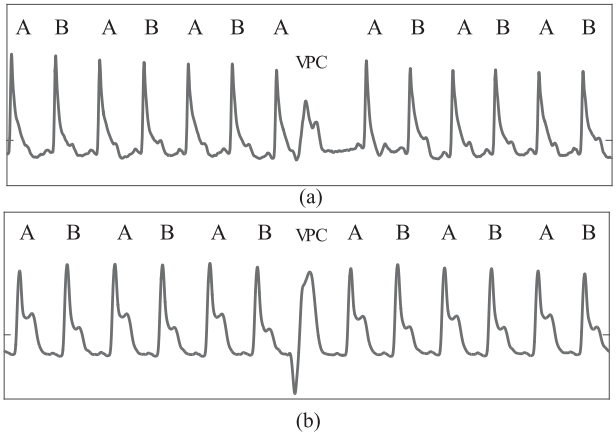

Fig. 1. Two TWA sequences including a VPC extracted from real ECG signals of patients undergoing a percutaneous transluminal coronary angiography (PTCA): in (a), the alternans sequence maintains the phase after the VPC, while in (b), there is a phase shift after the VPC.

An additional criterion based on instantaneous heart rate was applied to ensure heart rhythm stability in the segments accepted for TWA analysis: only segments where the difference between the maximum and minimum RR interval associated only to normal-labelled beats ΔRR^N was lower than 300 ms were included. Thus, with this criterion the RR intervals related to VPCs are not considered to decide whether the segment is included or not.

B. TWA Estimation

The method to estimate the TWA waveform associated to the k^{th} signal segment gives a TWA signal $\boldsymbol{y}_k$, denoted as:

$$\boldsymbol{y}_k = [y_k(1), \ldots, y_k(N)]^T \quad (1)$$

with N the total number of samples within the ST-T complex. It is based on [20]: the three orthogonal leads are linearly combined using π CA, in order to maximize the TWA content in the combined lead [13], where π CA finds the optimal linear combination of leads where the 2-beat periodicity of the ST-T complex (TWA periodicity) is maximized. Then, the LLR method [10] was applied in that new combined lead to estimate the TWA waveform of each segment, disregarding the possible phase shift in the TWA produced by the presence of any VPC (a maximum of 20% allowed). Note also that pre-processing of ECG signal and segments selection criteria defined in this study slightly differs from [20], disallowing for a direct comparison between both studies.

C. VPC Processing

The possible phase shift following a VPC influences TWA estimation. An example of two TWA sequences without and with a phase shift after the VPC is shown in Fig. 1. As the LLR method has been demonstrated to be robust enough to the presence of impulsive noise [3], in the original method [20]

segments with a low percentage of VPC were accepted for TWA analysis and processed in the same way as segments with all normal beats. However, if the ectopic activity produces a phase shift in the sequence of repolarization waveforms during a TWA episode, TWA could be undetected and its amplitude could be underestimated. To avoid this problem, we introduced an additional processing step when VPCs are present in the segment, consisting on controlling the phase of the alternans sequence after the ectopic beat.

Let us consider a VPC within a segment of L beats with TWA. If more than one consecutive VPC appear, the whole sequence of VPCs is considered as a single VPC for the purpose of the algorithm described in this section.

In the following, we will consider, without loss of generality, that an alternant pattern $ABAB\ldots AB$ is present in the signal. Note that if no TWA is present, A and B beats are expected to be similar.

If the ectopic beat lies in an odd position within the series, the sequence of beats before the abnormal beat can be represented as $S_{\rm pre} = \{ABAB\ldots AB\}$. As the abnormal beat may, or may not, reset the phase, the alternant sequence after the ectopic ($S_{\rm post}$) can be either $S_{post1} = \{ABABAB...\}$ or $S_{post2} = \{BABABA...\}$. On the contrary, if the ectopic beat is in an even position, the sequence of beats previous to the VPC will end in an A beat (i.e. $S_{\rm pre} = \{ABAB...ABA\}$) and, again, there are two possible continuations of the series after the VPC: $S_{post1} = \{ABABAB...\}$ or $S_{post2} = \{BABABA...\}$.

The proposed approach consists on determining what is the relative phase of the $S_{\rm post}$ sequence of beats with respect to the $S_{\rm pre}$ sequence, discarding the abnormal beat, and properly concatenating $S_{\rm post}$ at the end of $S_{\rm pre}$. If needed, the first beat of the post-VPC series is also eliminated to keep the continuity of the alternans phase in the resulting series. As an illustrative example, Fig. 2 shows two possible scenarios where $S_{\rm pre}$ and $S_{\rm post}$ are in phase (a) and out of phase (b). In the latter situation, both the ectopic and the following beat need to be discarded in order to preserve the phase of the alternans in the final sequence.

To determine the relative phase between the two subsequences ($S_{\rm pre}$ and $S_{\rm post}$), the following procedure is applied:

1) The TWA waveform of each subsequence ($\boldsymbol{y}_{k,pre}$ and $\boldsymbol{y}_{k,post}$ in $S_{\rm pre}$ and $S_{\rm post}$, respectively) was estimated using the LLR method [10], i.e. as the median of the demodulated differences (alternative sign change) between the consecutive ST-T complexes included in each subsequence.
2) If the mean values of $\boldsymbol{y}_{k,pre}$ and $\boldsymbol{y}_{k,post}$ (defined as $\bar{y}_{k,pre} = \frac{1}{N}\sum_{n=1}^{N} y_{k,pre}(n)$ and $\bar{y}_{k,post} = 1/N\sum_{n=1}^{N} y_{k,post}(n)$, respectively) are both positive or both negative (same sign), this indicates that TWA has the same polarity in both subsequences and, consequently, both of them start with the same phase. On the contrary, if $\bar{y}_{k,pre}$ and $\bar{y}_{k,post}$ have opposite signs, this indicates that both sequences start out-of-phase. Therefore, if the $S_{\rm pre}$ has an even number of beats and both sequences start in phase, only the VPC beat is discarded before concatenation (Fig. 2(a)). The same procedure is applied when the $S_{\rm pre}$ has an odd number of beats and $S_{\rm post}$ starts at the opposite phase. In the remaining two cases, both the VPC and the next beat are discarded before concatenation, in order to keep continuity of the TWA phase.

If there are $M > 1$ non-consecutive abnormal beats in one ECG signal segment, $M+1$ subsequences can be defined. In this case, the same described approach is followed to concatenate the sequence of beats after each VPC to the previous sequence until all VPCs have been processed. Subsequences of just one or two beats are discarded.

Note that in the absence of TWA, the procedure can be applied in the same way, even if the estimated phases are related to other beat-to-beat variability components rather than TWA.

D. Alternans Waveform Estimation

Finally, the TWA waveform of the k^{th} segment, $\boldsymbol{y}_k$, was expressed as the median of the demodulated differences between ST-T complexes of even and odd beats [10], after the phase correction is applied to the data.

E. Phase Alignment of Alternans Waveforms

The non-visible microvolt range of TWA, sometimes comparable to the noise level, makes the TWA detection a challenging task. In those cases, the alternans waveform $\boldsymbol{y}_k$ may have an important noise component that should be attenuated in order to properly assess TWA. At this point, a novel methodological step for the computation of the global TWA amplitude was included in the analysis, consisting on the phase alignment of all TWA estimated waveforms, associated to the total K segments, before averaging. This step is needed since the estimated TWA waveform $\boldsymbol{y}_k$ may not have the same polarity, and therefore might cancel out when averaging.

First, a detrended version of each $\boldsymbol{y}_k$, denoted as $\boldsymbol{y}'_k$ was computed:

$$y'_k(n) = y_k(n) - (a_k + b_k n) \tag{2}$$

where the coefficients a_k and b_k were chosen as the ones with the best least-squares fit to the samples of $y_k(n)$ [25], with the aim of eliminating any possible residual baseline component at the alternans frequency. Then, the correlation matrix of all suitable segments, $\mathbf{R}_{\mathbf{Y}'}$, was estimated as

$$\mathbf{R}_{\mathbf{Y}'} = \frac{1}{\rm K}\mathbf{Y}'\mathbf{Y}'^{T} \tag{3}$$

being K the total number of suitable segments for the analysis and $\mathbf{Y}'$ the data matrix built by concatenating all of them $\mathbf{Y}' = [\boldsymbol{y}'_1 \ldots \boldsymbol{y}'_{\rm K}]$.

The dominant alternans waveform was obtained as the first principal component of the spatial correlation matrix [26], by solving the eigenvalue equation:

$$\mathbf{R}_{\mathbf{Y}'}\mathbf{w}_1 = \lambda_1\mathbf{w}_1 \tag{4}$$

where λ_1 is the largest eigenvalue of $\mathbf{R}_{\mathbf{Y}'}$ and $\mathbf{w}_1$ its corresponding eigenvector. At this point, the phase-aligned

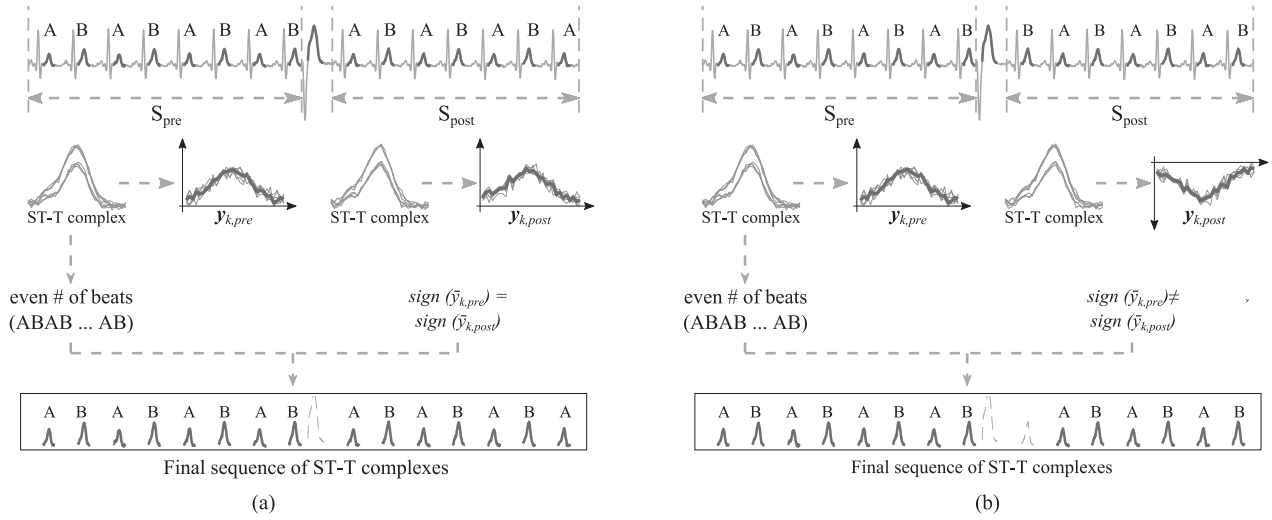

Fig. 2. Two examples of synthetic TWA sequences including the presence of one VPC, and the processing applied for the estimation of the alternans waveform. (a) $S_{\rm pre}$ and $S_{\rm post}$ subsequences start at the same phase ($\bar{y}_{k,pre} > 0$ and $\bar{y}_{k,post} > 0$) and the VPC is in an odd position: only the VPC is excluded in the final sequence considered for the estimation of TWA waveform. (b) $S_{\rm pre}$ and $S_{\rm post}$ subsequences start with the opposite phase ($\bar{y}_{k,pre} > 0$ and $\bar{y}_{k,post} < 0$) and the VPC is in an odd position: both the VPC and the following beat are excluded in this case.

waveform, denoted as $\boldsymbol{y}_k^a$, was estimated as:

$$\boldsymbol{y}_k^a = \text{sign}\left(\boldsymbol{y}_k^{'T}\,\mathbf{w}_1\right)\boldsymbol{y}_k \tag{5}$$

where the function $\text{sign}(x)$ extracts the sign of a real number x (i.e. $\text{sign}(x) = 1$ if $x > 0$, $\text{sign}(x) = 0$ if $x = 0$ and $\text{sign}(x) = -1$ if $x < 0$). Consequently, $\boldsymbol{y}_k^a = \boldsymbol{y}_k$ if $\boldsymbol{y}_k^{'T}\mathbf{w}_1 \geq 0$ and $\boldsymbol{y}_k^a = -\boldsymbol{y}_k$ if $\boldsymbol{y}_k^{'T}\mathbf{w}_1 < 0$. In other words, if the waveform $\boldsymbol{y}_k$ has the same polarity as the dominant $\mathbf{w}_1$, it will remain unchanged, while if it has the opposite polarity, its sign will be changed. In this way, the method aligns the polarities of the estimated TWA waveforms, related to the phase of each alternans sequence, before averaging them.

Finally, the index of average alternans including the VPC processing $IAA_{\rm VP}$ was defined as the mean absolute value of the average of the phase-aligned waveforms $\boldsymbol{y}_k^a$:

$$IAA_{\rm VP} = \frac{1}{\rm N}\sum_{\rm n=1}^{\rm N}\left|\frac{1}{\rm K}\sum_{k=1}^{\rm K} y_k^a\,(n)\right| \tag{6}$$

F. Statistical Analysis

Data are presented as mean ± standard deviation for continuous variables, unless otherwise specified. Prognostic value of TWA indices in predicting SCD was determined with univariate Cox proportional hazards analysis. Survival analysis was performed by using Kaplan-Meier estimator and comparison of cumulative events by log-rank test. For all tests, the null hypothesis was rejected for p $\leq$0.05.

III. Datasets

A. Simulated Data

The effect of VPCs and the possible phase resetting of the alternans sequence was assessed by simulating controlled TWA sequences of different amplitudes and under the presence of different sources of noise.

We created 2080-beat series by replicating one beat extracted from an actual Holter recording (sampling frequency 200 Hz), with synthetic TWA generated by adding and subtracting a given waveform (modelled as a Hamming window, with peak amplitudes varying from 0 to 300 μV in steps of 50 μV) to the repolarization phase of the beat (i.e, the ST-T complex).

Moreover, three real sources of noise: electrode motion (em), muscular activity (ma) and baseline wander (bw)-obtained from the Physionet MIT-BIH Noise Stress Test Database (NSTDB) [27]- and Gaussian noise (gn) were independently added to the simulated ECG in order to create a more realistic scenario. For a given TWA amplitude, baseline wander segments (beginning at a random position in one of the 2 available leads of the NSTDB, also randomly selected at each realization) properly scaled to present different standard deviations, σ_{bw} , varying from 0 to 800 μV, in 100 μV steps, were added to the synthetic ECG. The same procedure was replicated for the ma and em noises, with σ_{ma} and σ_{em} ranging from 0 to 200 μV, in 25 μV steps, and Gaussian noise (σ_{gn} varying from 0 to 100 μV).

A total of 100 realizations were generated for each combination of noise and TWA amplitudes in order to have a robust characterization. For each realization, VPCs were randomly allocated along the 2080-beat sequence. The phase of the alternans sequence in the next beat after each one labelled as VPC was randomly selected, with a 0.5 probability of a phase shift. Additionally, the effect of the presence of ectopic beats in the TWA estimation was also evaluated for low, medium and high levels of noise, varying the percentage of VPCs included in the sequence from 0 to the 20%.

B. Ambulatory ECG

A total of 992 consecutive patients with symptomatic CHF corresponding to New York Heart Association (NYHA) classes II and III were enrolled in the multicenter MUSIC (MUerte Súbita en Insuficiencia Cardiaca) study, a prospective study designed to assess risk predictors for cardiovascular

TABLE I
CHARACTERISTICS OF PATIENTS

Variable	Overall population (n = 651)
Age (years)	62.9 ± 11.9
Gender (males)	464 (71.3%)
LVEF ≤ 35%	356 (54.7%)
NYHA class III	115 (17.7%)
Diabetes	244 (37.5%)
Beta-blockers	455 (69.9%)
Amiodarone	61 (9.4%)
ARB or ACE inhibitors	576 (88.5%)
QRS ≥ 110 ms	322 (49.5%)

Data are presented as mean± standard deviation and as absolute frequencies (percentages). LVEF: Left ventricular ejection fraction, NYHA: New York Heart Association; ARB: angiotensin receptor blocker; ACE: angiotensin-converting enzyme.

mortality in ambulatory CHF patients [28]. Patients were enrolled from the specialized CHF clinics of eight University Hospitals between April 2003 and December 2004. The original MUSIC study included patients with both reduced and preserved left ventricular ejection fraction (LVEF). Patients with preserved LVEF were included if they had CHF symptoms, a prior hospitalization for CHF or objective CHF signs confirmed by chest X-ray and/or echocardiography. Patients were excluded if they had recent acute coronary syndrome or severe valvular disease amenable for surgical repair. Patients with other concomitant diseases expected to reduce life-expectancy were also excluded. Originally, patients in sinus rhythm, atrial fibrillation, atrial flutter, permanent supraventricular arrhythmia and in pacemaker rhythm were included. Collection of clinical data for the overall population was already reported in [28]. The 24-hour Holter ECG recordings of 651 patients (187 females) in sinus rhythm, aged 18–89 years (62.9 ± 11.9 years) were analysed in the present study. ECG signals were acquired by using SpiderView records (ELA Medical, Sorin Group, Paris, France) and two or three (96.8%) orthogonal leads (X, Y, Z) sampled at 200 Hz were available for each subject. Most patients (82.3%) were in NYHA class II. Ischemic etiology of CHF was present in 50.2% of patients. Mean LVEF was 36.9 ± 13.8% (range 10−70%), and half of patients (54.7%) presented LVEF <35%. Intraventricular conduction delay, defined as QRS duration >0.11 s, was present in 322 patients. Some relevant patient characteristics are summarized on Table I.

Patients were followed up every 6 months during 48 months. A total of 55 victims of SCD, 59 of other cardiac causes, 26 non-cardiac deaths and 511 survivors were included. SCD, defined as (i) a witnessed death occurring within 60 minutes from the onset of new symptoms unless a cause other than cardiac failure was obvious, (ii) an unwitnessed death (≤24 hours) in the absence of pre-existing progressive circulatory failure or other causes of death, or (iii) death during attempted resuscitation, was considered as an independent endpoint in this study. Endpoints were reviewed and classified by the MUSIC Study Endpoint Committee. The study protocol was approved by institutional investigator committees and all patients gave written informed consent.

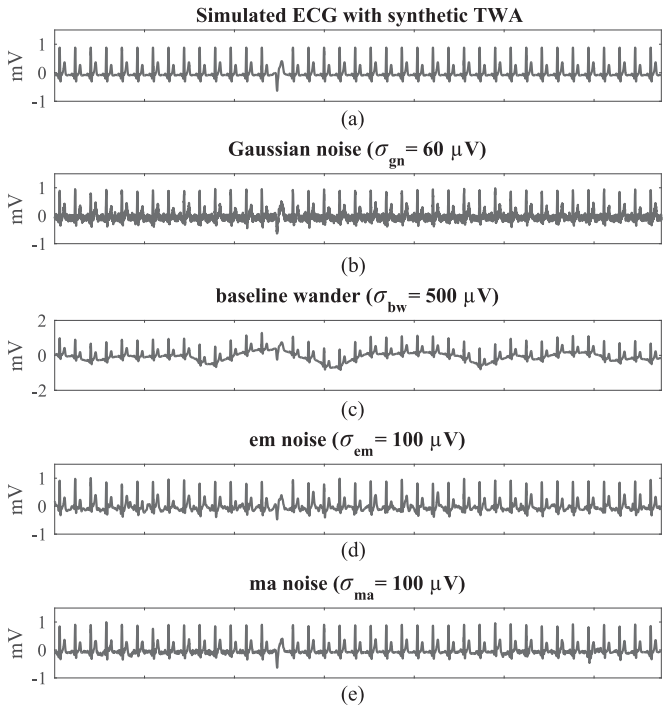

Fig. 3. Simulated ECGs with added artificial TWA (a) and corrupted by different noises: Gaussian noise (b), baseline wander (c), electrode motion (d) and muscular activity (e).

IV. RESULTS

A. Simulation Study

The effect of VPCs and the possible phase resetting of the alternans sequence in the estimation of the IAA index were evaluated using synthetic signals. Fig. 3 shows examples of simulated beat sequences with artificial TWA and four additive noises: Gaussian noise, baseline wander, muscular activity and electrode motion.

For each TWA level, noise type, noise level and VPC probability, 100 different realizations were generated, randomizing the presence of the VPCs along the whole beat sequence, as well as the posterior phase resetting of the alternans sequence. Fig. 4 shows the mean and standard deviation of the estimated IAA index, computed including the VPC processing and phase alignment (IAA_{VP}, blue line) and when these steps are not included, i.e. analyzing raw beat segments (IAA_{nVP}, grey dashed line) , under different levels of noise (σ_{gn}, σ_{bw}, σ_{em} and σ_{ma}), for a VPC probability of 2%. Each curve is associated to a different TWA simulated amplitude. From top to bottom, peak amplitudes of alternans waveform were set to 300, 250, 200, 150, 100, 50 and 0 microvolts, which corresponds to average alternans amplitudes (IAA_{sim}) of 159.8, 133.2, 106.6, 79.9, 53.3, 26.6 and 0 microvolts, respectively.

Additionally, the effect of the number of VPCs present in the segment was also evaluated. For low, medium and high noise levels, the IAA was estimated by varying the probability of having a VPC from 0 to the 20% (Fig. 5). Peak alternans amplitudes were incremented from 0 to 200 μV in steps of

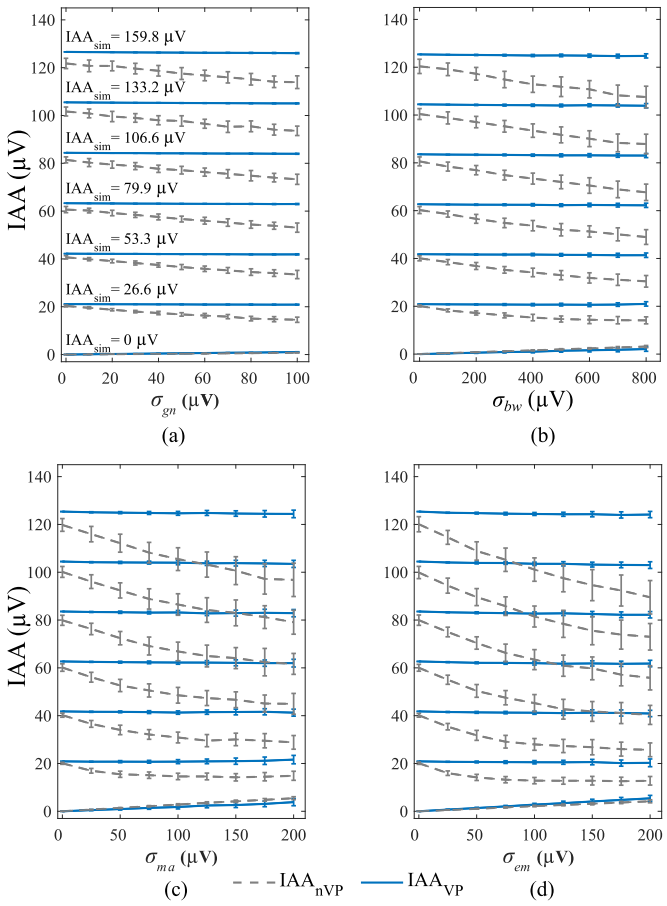

Fig. 4. IAA estimation on synthetic signals with different noises types and levels (σ_{gn}, σ_{bw}, σ_{ma}, and σ_{em} in panels (a), (b), (c), and (d), respectively) when the probability of VPCs is limited up to the 2%. Results are represented as mean $\pm$ std of 100 realizations for each combination of σ and alternans amplitude. From top to bottom, the curves represent the measured IAA with both methods when the simulated mean TWA amplitude (IAA_{sim}) was, respectively, of 159.8, 133.2, 106.6, 79.9, 53.3, 26.6, and 0 μV (corresponding with the alternans peak amplitudes of 300, 250, 200, 150, 100, 50, and 0 μV). Blue line corresponds to the IAA estimated with the ectopic protection and phase alignment (IAA_{VP}) and grey dashed line represents the IAA estimation without any protection (IAA_{nVP}).

50 μV (corresponding to IAA_{sim} of 0, 26.6, 53.3, 79.9 and 106.6 μV).

B. Ambulatory ECG

Holter ECG signals from CHF patients were processed using the same methodology. We computed both IAA_{VP} and IAA_{nVP} indices, as a measurement of the average TWA amplitude for the 24h recording, and compared the associated prognostic values. Patients were classified as TWA(+) or TWA(−) based on a risk threshold (TWA(+) if $IAA \geq th_{\text{risk}}$, TWA(−) otherwise). This th_{risk} threshold was defined as the third quartile of the total distribution of IAA indices. Accordingly, the TWA(+) group is composed by the 25% of patients (n = 163) with the largest IAA values each time. See Table II for the distribution of SCD events in the TWA(−) and TWA(+) groups.

TABLE II
NUMBER OF SCD EVENTS INCLUDED IN TWA(−) AND TWA(+) GROUPS AS A RESULTS OF THE ANALYSIS WITH THE ECTOPIC PROCESSING (IAA_{VP}) AND WITHOUT ANY PROTECTION (IAA_{NVP})

	IAA_{nVP}		IAA_{VP}	
	TWA(−) (n = 488)	TWA(+) (n = 163)	TWA(−) (n = 488)	TWA(+) (n = 163)
$\Delta RR^N < 300$	37 (7.6%)	18 (11.0%)	–	–
$\Delta RR^N < 300$ with $\leq$ 1 VPC	34 (7.0%)	21* (12.9%)	32 (6.6%)	23** (14.1%)
$\Delta RR^N < 300$ with $\leq$ 2 VPCs	36 (7.4%)	19 (11.7%)	34 (7.0%)	21* (12.9%)
$\Delta RR^N < 300$ with $\leq$ 3 VPCs	37 (7.6%)	18 (11.0%)	34 (7.0%)	21* (12.9%)
$\Delta RR^N < 300$	36 (7.4%)	19 (11.7%)	37 (7.6%)	18 (11.0%)

Data are expressed as absolute frequencies and percentages within TWA groups. Significant differences between the number of SCD events in TWA(−) and TWA(+) groups are indicate by *($p < .05$) and **($p < .005$).

TABLE III
ASSOCIATION OF IAA INDICES WITH SUDDEN CARDIAC DEATH COMPUTED IN PATIENTS WITH CHRONIC HEART FAILURE

	Average # of segments	Risk threshold (th_{risk})	Hazard ratio (95% CI)	p-value
$\Delta RR^N < 300$ with 0 VPC	527 ± 414	$th_{\text{risk}}^{\text{nVP}} = 1.394\ \mu$V	1.590 (0.901,2.808)	0.11
$\Delta RR^N < 300$ with $\leq$ 1 VPC	669 ± 448	$th_{\text{risk}}^{\text{nVP}} = 1.381\ \mu$V	**2.030** (1.174,3.509)	**0.011**
		$th_{\text{risk}}^{\text{VP}} = 1.470\ \mu$V	**2.386** (1.391,4.092)	**0.002**
$\Delta RR^N < 300$ with $\leq$ 2 VPCs	749 ± 455	$th_{\text{risk}}^{\text{nVP}} = 1.354\ \mu$V	1.708 (0.977,2.987)	0.060
		$th_{\text{risk}}^{\text{VP}} = 1.544\ \mu$V	**2.026** (1.172,3.502)	**0.011**
$\Delta RR^N < 300$ with $\leq$ 3 VPCs	804 ± 458	$th_{\text{risk}}^{\text{nVP}} = 1.339\ \mu$V	1.582 (0.898,2.786)	0.112
		$th_{\text{risk}}^{\text{VP}} = 1.649\ \mu$V	**2.035** (1.177,3.518)	**0.011**
$\Delta RR^N < 300$	1018 ± 423	$th_{\text{risk}}^{\text{nVP}} = 1.509\ \mu$V	1.657 (0.950,2.889)	0.075
		$th_{\text{risk}}^{\text{VP}} = 2.282\ \mu$V	1.502 (0.885,2.638)	0.157

Results from the analysis with the ectopic processing (IAA_{VP}) and without any protection (IAA_{nVP}) are included. Hazard ratios significantly greater than 1 are indicated in bold.

Finally, we evaluated the effect of including additional VPCs in the processing and we assessed the prognostic value of IAA indices in SCD prediction by performing a univariate Cox proportional hazards analysis. Results are summarized on Table III. We started by including in the analysis only those VPC-free segments with $\Delta RR^N < 300$ ms, i.e. stable rhythm segments containing only normal beats. TWA(+) outcome was not associated with SCD. By sequentially adding segments containing a maximum of 1, 2 and 3 VPCs, TWA(+) outcome according to IAA_{VP} was in all cases successfully associated to SCD when the ectopic processing was included in the

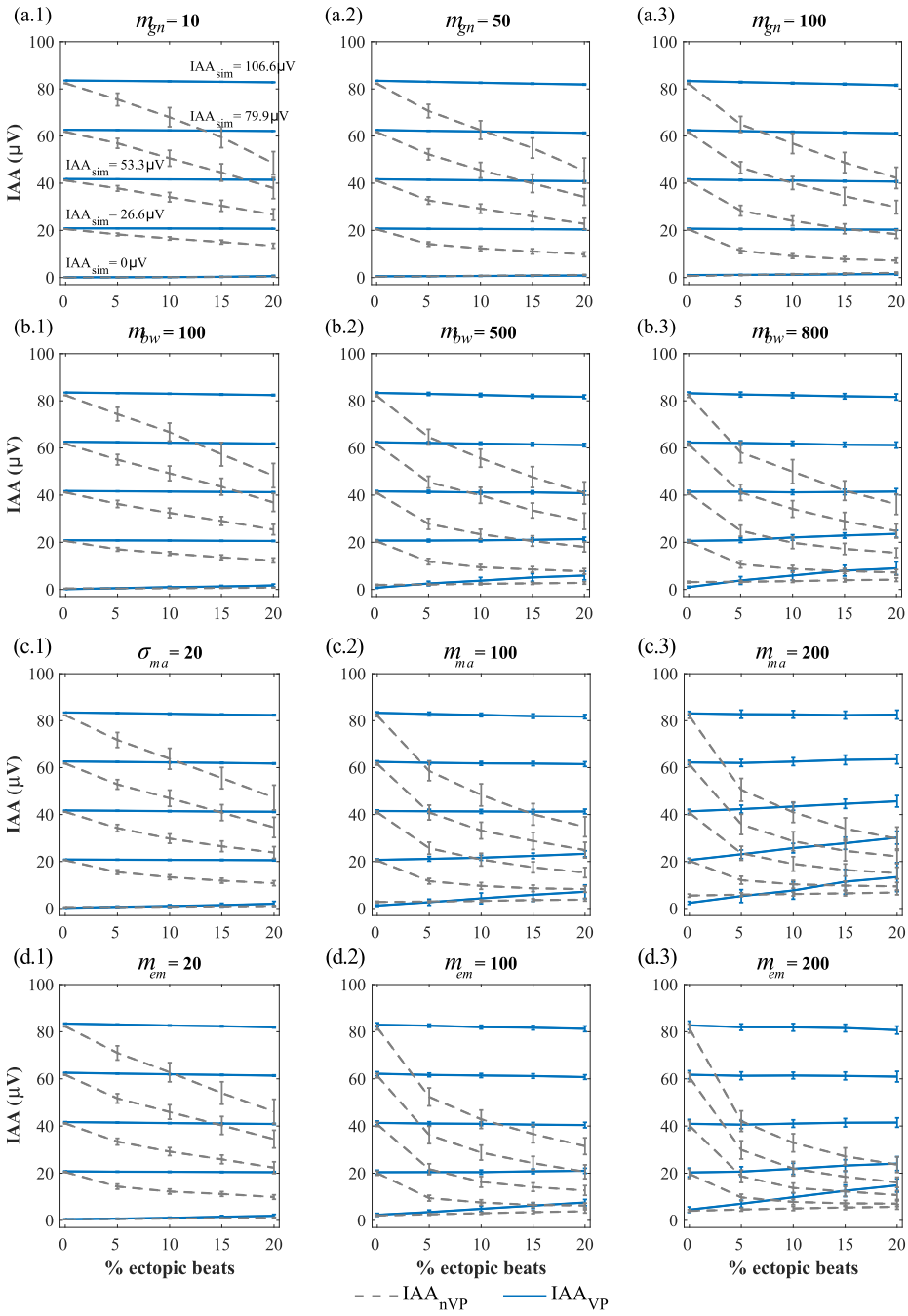

Fig. 5. Effect of the number of VPCs present in the segment on IAA estimation for a low (left column), medium (middle column) and high (right column) levels of noise, from top to bottom σ_{gn}, σ_{bw}, σ_{ma}, and σ_{em}. Results are represented as mean $\pm$ std of 100 realizations, where blue line corresponds to the IAA estimated with the VPC processing and phase alignment (IAA_{VP}) and grey dashed line represents the IAA estimation without any protection (IAA_{nVP}). In each panel, from top to bottom, the curves represent the measured IAA with both methods when the simulated mean TWA amplitude (IAA_{sim}) was, respectively of 106.6, 79.9, 53.3, 26.6, and 0 μV (corresponding with the alternans peak amplitudes of 200, 150, 100, 50, and 0 μV).

processing. In contrast, no association was found between IAA indices obtained from IAA_{nVP} and SCD, except when a maximum of 1 VPC was allowed, being the hazard ratio in all cases lower than the one obtained with the ectopic processing (IAA_{VP}). Hazard ratios were increased by 17%, 19%, 29% when including 1, 2 and 3 VPCs, respectively. Finally, when all segments with $\Delta RR^N < 300$ ms regardless of the number of VPCs were included in the analysis, neither IAA_{nVP}, nor IAA_{VP} preserved the alternans predictive value (see Table III).

Survival probability curves for the most significant predictive indices are shown on Fig. 6. Results associated to both IAA_{nVP} and IAA_{VP} indices are included in grey and blue lines, respectively.

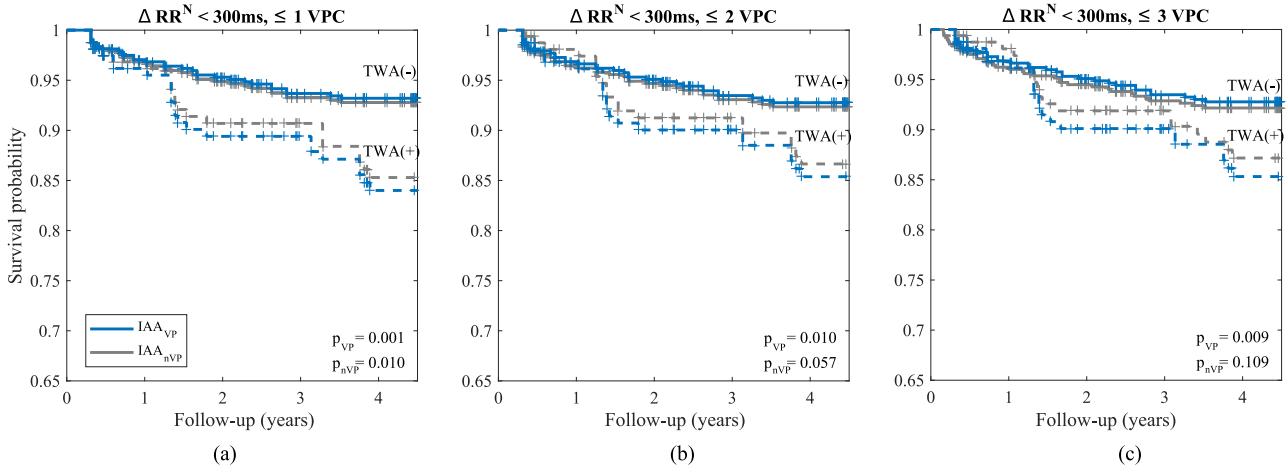

Fig. 6. Survival probability curves of sudden cardiac death associated with IAA_{nVP} (grey lines) and IAA_{VP} (blue) in the chronic heart failure population. Each panel includes results corresponding to different selection criteria: (a) segments with $\Delta RR^N < 300$ ms with a maximum of one VPC allowed; (b) segments with $\Delta RR^N < 300$ ms with a maximum of two VPCs and (c) segments with $\Delta RR^N < 300$ ms with a maximum of three VPCs.

V. Discussion

In this study, we have proposed a method to improve the long-term quantification of TWA activity by overcoming the presence of VPCs and the possible associated phase shifts in the alternans sequence, as well as other sources of noise that could lead to the underestimation of TWA amplitude.

TWA testing, usually performed using the spectral method, provides a positive, negative or indeterminate test result [9]. However, the high rate of indeterminate tests (up to 40%) [6]–[8] has yielded to the analysis of TWA on ambulatory ECG recordings as an alternative [14]–[19]. In that setting, fully-automatic long-term averaging has been already shown to provide a risk stratifying in 24h-ECG recordings [20].

Both unaltered and reversed phase of the alternans sequence following a premature beat have been described in the literature [21], [29]. Although the LLR method has been proved to be more robust than other methods to the presence of impulsive noise [3], [11], as the one produced in the beat-to-beat series when isolated abnormal beats are present in the analyzed segment, the potential phase resetting can still have a relevant impact on TWA estimation [5], [22], [30]. In particular, if the phase reversal occurs in the central beat of the segment, it can lead to measuring a zero-voltage alternans when spectral analysis is used [23]. To overcome this limitation, our approach introduces an additional control of phase reversal after the presence of each VPC ensuring the phase continuity if alternans is present in the segment. For that purpose, the VPC and, if needed, the following beat are discarded before estimating TWA magnitude in the segment. As a note, this methodology requires prior beat classification and VPC identification.

Furthermore, the inclusion of the sign alignment, based on a correlation criterion, of all estimated alternans waveforms before IAA estimation offers a robust solution, especially when both alternans and noise are at the same amplitude level of a few microvolts.

The accuracy of TWA estimation was assessed in the presence of four different types of noise: Gaussian noise, baseline wander, muscular activity and electrode motion. According to the simulation results, with a fixed VPC probability per beat of 2%, the estimation accuracy is clearly higher when the ectopic processing and phase alignment were included (IAA_{VP}) than when this step is not included (IAA_{nVP}). Note that even in the absence of noise, TWA amplitudes are slightly subestimated as a consequence of the pre-processing baseline removal linear filter.

Results show that TWA amplitude was markedly underestimated and had a larger variance when the VPC processing was not applied, being this bias larger as the noise level increased for a given TWA level. Moreover, both bias and variance were larger as the simulated TWA amplitude increased, but still both parameters, and especially the variance, were greatly reduced when the processing of ectopic beats and phase control were included.

The impact of the number of VPCs on the TWA estimation was also evaluated: while IAA_{VP} values remained essentially unchanged as the VPC probability was increased for low and medium levels of noise, both the bias and variance significantly increased even when a very low percentage of VPCs (5%) was allowed with low noise levels, regardless of its nature, if this step was not included (i.e. in IAA_{nVP}). We obtain a similar pattern of degradation for any gn, bw and ma noises. Still, both methods appeared to be sensitive to high ma and em noise levels (>100 μV) and the presence of VPCs ($>$ 5%), leading to an over-estimation of IAA_{VP} with greater variances, in the absence of TWA, most probably due to noise components overlapping the TWA bandwidth being interpreted as TWA. Even so, our approach represents a robust alternative against the presence of moderate levels of noise and VPCs (with the possible subsequent alternans phase reversal). Nonetheless, only the effect of the possible phase resetting in the alternans sequence after the VPC has been taken into consideration in

simulated data, but not other possible induced changes in TWA morphology and amplitude, which were assumed unaltered. In real ECG signals the presence of a VPC, in addition to the possible phase resetting of alternans sequence, is known to have also an induced effect in subsequent repolarizations (changes in T wave morphology after VPCs have been studied [31]–[33]), thus inducing other possible variations in the sequence of TWA amplitudes that could interfere in TWA measurement.

From a clinical perspective, we have also demonstrated that the inclusion of the VPC processing in the TWA estimation led to an enhanced predictive value of the average TWA activity in the examined CHF population. That is, with the inclusion of the ectopic treatment step, hazard ratios associated to the classification obtained for IAA_{VP} were always increased with respect to those based on IAA_{nVP}. The ability of the index of average alternans (IAA) to predict SCD was already proved in [20]. To note, results here presented are not directly comparable to those obtained in [20]: first, ECG preprocessing and segments selection criteria were improved; secondly, IAA computation took advantage of including a waveform phase alignment step; finally, the conditions to enter the study have changed with respect to [20]: in that work, a previous ECG was used to assess the baseline rhythm of the patient; in this work the baseline rhythm has been assessed in the Holter recording. As a consequence, 16 patients of our study population were not in the study population of [20], while 15 patients from the previous study were discarded here.

The motivation for using the long-term average of alternans activity in ambulatory ECGs was to provide with a reliable and robust measurement of TWA, but this requires for some additional restrictions in order to consider only suitable ECG segments to be included in the automatic analysis. In particular in this study, segments were considered suitable for the automatic analysis based on instantaneous RR-interval changes associated to Normal labelled beats present in the segment ($\Delta RR^N < 300$ ms). Moreover, it becomes necessary to limit the maximum presence of VPCs as, from a physiological view-point, it would not make sense to measure TWA if many VPCs were included, and more than 20% of abnormal beats in the segment led to the direct exclusion of that segment.

Using the most restrictive criterion (discarding segments containing any number of VPCs) led to the loss of predictability of the IAA_{nVP}, which could be explained by the low number of segments that had fulfilled this requirement and, consequently, to the reliability of the long-term average TWA estimation. However, when this restriction was relaxed and segments with one VPC were included, TWA(+) outcome obtained for both IAA_{nVP} and IAA_{VP} was successfully associated to SCD, with more than a 2-fold increased risk in TWA(+) patients than in TWA(−), providing with the best stratification performance. Including in the analysis segments with 2 and 3 VPCs decreased the hazard ratio but still with significant association with SCD outcome for IAA_{VP}. In those cases, when the ectopic protection was not included, then IAA_{nVP} lost its predictive value. Still, when no limitation in the number of VPCs was imposed ($\Delta RR^N < 300$ ms), the predictive value of IAA_{nVP} and IAA_{VP} was lost. Actually, the presence of several VPCs ($m > 2$) in a 128-beat segment, creating $(m + 1)$ shorter subsequences within it, could compromise the local TWA estimation (i.e. $\boldsymbol{y}_{k,pre}$ and $\boldsymbol{y}_{k,post}$) used for the posterior decision in the concatenation of subsequences, especially if it is the case that alternans sequence is also affected by the abnormal beat, being more sensitive as the number of VPCs included in the segment increases. This could explain why the inclusion of all segments with more than 3 VPCs did not add additional prognostic value with respect to the other scenarios. Some studies have already revealed an increment in TWA amplitude after the occurrence of one isolated VPC just in some patients [21], [29], but the effect of more than one VPC within a short period of time (< 128 beats) needs to be investigated. On the other hand, higher th_{risk} values associated to the IAA_{VP} ($th_{\mathrm{risk}}^{\mathrm{VP}}$) were obtained with respect to $th_{\mathrm{risk}}^{\mathrm{nVP}}$, as reported on Table III. This is in agreement with the better estimation accuracy of IAA_{VP} with respect to IAA_{nVP}, already shown in Figs. 5 and 6 using simulated data.

VI. Conclusion

The proposed methodology for computing the index of average alternans, which deals with the presence of ventricular premature contractions and with the possible induction of phase resetting in the alternans sequence, represents an accurate and noise-robust solution for quantifying TWA in ambulatory recordings. Moreover, the analysis of ambulatory ECGs of mild-to-moderate CHF patients demonstrated the enhancement in the predictive value of IAA for SCD stratification by analyzing segments with limited number of VPCs.

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