Characterization of Repolarization Alternans During Ischemia: Time-Course and Spatial Analysis

Juan Pablo Martínez*, Salvador Olmos, *Member, IEEE*, Galen Wagner, and Pablo Laguna, *Member, IEEE*

***Abstract*—T-wave alternans (TWA) has been linked to increased vulnerability to ventricular fibrillation in different settings including myocardial ischemia. In this study, we propose a methodology for the characterization of TWA induced by transient, regional ischemia. We studied the prevalence, magnitude and spatio-temporal relationship between TWA and ischemia in 95 patients undergoing percutaneous transluminal coronary angioplasty (PTCA). Two electrocardiogram records of each patient, a control recording before PTCA and the PTCA record, were analyzed using a robust, recently proposed method for TWA analysis. The detected episodes were characterized in terms of their time-course, lead distribution and alternans waveform. One third of the patients (33.7%) showed TWA episodes during PTCA. The highest prevalence (51.7%) and amplitude were found in patients with left anterior descendent artery occlusion. The onset of TWA was detected after the first 1–2 min of occlusion, suggesting that some level of ischemia must be attained before TWA arises, while disappearance of TWA following reperfusion was much more rapid. The TWA lead distributions and waveforms showed distinct distributions according to the occluded artery reflecting the regional nature of the TWA phenomenon.**

***Index Terms*—Alternans, angioplasty, electrocardiography, ischemia, repolarization.**

I. Introduction

REPOLARIZATION alternans, more widely known as T-wave alternans (TWA), is a phenomenon appearing in the surface electrocardiogram (ECG) as a consistent fluctuation in the repolarization morphology (ST segment and T wave) on an every-other-beat basis.

TWA is presently regarded as a promising marker of increased risk for ventricular vulnerability and sudden cardiac death [1], [2]. The mechanisms underlying TWA and the link to vulnerability are still not completely known, and may be different depending on the accompanying clinical conditions [3]–[5].

It has been shown that alternans is a regionally specific phenomenon in the ischemic myocardium, confined to the hypoperfused region [6], [7]. Animal experiments [6] have provided evidence that ischemia-induced TWA in the surface ECG arises from alternans in the action potential morphology.

Percutaneous transluminal coronary angioplasty (PTCA) provides an excellent model to investigate the electrophysiological changes of acute transmural ischemia. The sudden complete coronary occlusion produced by balloon inflation allows the study of the initial minutes of the ischemic process. Additionally, PTCA supplies valuable information about spatio-temporal features of ischemia since the coronary occlusion is perfectly defined both in time (period of occlusion) and in space (occlusion site). PTCA-induced TWA have been reported in several studies, either in surface [8]–[14] or in intracoronary ECG (ic-ECG) [11]–[13]. The reported prevalences present a wide range of variation (from 1.2% to 27% in surface ECG and from 7.7% to 43% in ic-ECG). With the exception of [10], [14], only visible TWA were considered and their magnitude was not quantified.

The goals of the present study involving patients undergoing PTCA in the main coronary arteries are: 1) quantify the prevalence and magnitude of TWA in the first minutes of transmural ischemia as a function of the occlusion site; 2) characterize and investigate the evolution of alternans as the occlusion persists; 3) inquire into the spatial relationship between regional ischemia and TWA measured in the ECG. For those purposes, the robust Laplacian Likelihood Ratio (LLR) [15], [16] method was used to detect and estimate TWA in the ECG.

In the last two decades, several analysis methods have been proposed to detect and estimate TWA in the ECG. A general framework for TWA analysis methods has been proposed in a recent methodological review, highlighting the current state of the art [17]. The most widely used approaches are the Spectral method [18], [19] and the complex demodulation method [20], both based on linear spectral estimation. Alternative nonlinear approaches, such as the modified moving average method [21] and the Laplacian likelihood ratio method [15], [16] have been recently proposed and validated. The Laplacian likelihood ratio method computes beat-to-beat the maximum likelihood estimate (MLE) of the alternans voltage under the assumption of nonstationary Laplacian noise. Since the measured voltage can be produced just by the recorded noise, a generalized likelihood ratio test (GLRT) [22] is applied to decide whether TWA is present or not.

Detected TWA episodes were analyzed in three domains: 1) the beat-to-beat course of TWA amplitude as a function of the coronary occlusion timing (time course analysis); 2) the alternans waveform or temporal distribution of TWA within the repolarization phase (waveform analysis); 3) the spatial distribu-

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tion of TWA amplitude in the standard ECG leads (lead distribution analysis).

II. Data Set

The study group consisted of 102 patients at the Charleston Area Medical Center in West Virginia undergoing elective prolonged (>100 s) balloon occlusion during PTCA in one of their major coronary arteries (STAFF-III study). Informed consent was obtained from each subject. This study was approved by the Investigational Review Board and conforms with the principles outlined in the Declaration of Helsinki. Seven patients were excluded because the electrodes were misplaced (3 cases), signal loss was experienced (1 case) or the ECG presented bigeminy (3 cases). The remaining 95 patients (60 males, 35 females), with ages 32 to 85 years (mean 60 ± 11 years) were included in this study. The mean inflation duration was 4 min 28 s with a standard deviation of 74 s. The occlusion period was considerably longer than that of usual PTCA procedures since the treatment protocol included a single prolonged occlusion rather than a series of brief occlusions. No arrhythmic events occurred during the ECG recording.

The locations of the 95 balloon inflations were: left main (LM) in 2 patients, left anterior descending artery (LAD) in 29 patients (22 proximal, 7 distal), right coronary artery (RCA) in 45 patients (20 proximal, 25 distal) and left circumflex artery (LCX) in 19 patients (10 proximal, 9 distal).

According to the Selvester screening criteria [23], 34 patients (36%) had evidence of prior myocardial infarction on the standard ECG recorded at hospital admission.

Nine standard leads (V1-V6, I, II, and III) were recorded using equipment by Siemens-Elema AB (Solna, Sweden) and digitized at a sampling rate of 1 kHz with amplitude resolution of 0.6 μV. Leads aVF, aVR, and aVL were derived from leads I, II, and III. Synthesized orthogonal X, Y and Z leads were also computed using the inverse Dower technique [24].

Two ECG recordings were acquired for each patient at rest in supine position: a control ECG recorded during 5 min before angioplasty and the ECG recorded during the PTCA procedure. Therefore, the patients acted as their own controls. Preliminary results in a subset of the present database were reported in [25].

III. Methods

A. TWA Detection and Estimation

Following the framework proposed in [17], the TWA analysis algorithm can be divided in three stages.

1) Preprocessing: The signals were preprocessed as follows:

First of all, the QRS fiducial points were determined using a wavelet-based algorithm developed in our group [26]. Second, a cubic splines interpolation technique was adopted to remove baseline wandering.

A fixed interval of 450 ms after each QRS fiducial point was selected for repolarization analysis (ST-T complexes). The ST-T complexes were aligned using a two-step method based in maximization of the cross-correlation between the complexes and an average ST-T complex. A matrix $\mathbf{X} = [\mathbf{x}_0\mathbf{x}_1, \ldots, \mathbf{x}_{M-1}]$ was generated, where $\mathbf{x}_i = [x_i[0], \ldots, x_i[N-1]]^T$ is the aligned ST-T complex corresponding to the ith beat ($N = 450$ samples) and M is the number of beats in the ECG record.

Finally, the rows of $\mathbf{X}$ were detrended by computing the difference between each ST-T complex and the previous one. This allowed rejection of the background ECG, as well as other ECG slow variations.

2) Data Reduction: The $N = 450$ samples in each detrended complex were low-pass filtered and decimated by 8 to reduce out-of-band noise as well as the computational load of the method. We denote the decimated, detrended ST-T complex matrix by $\mathbf{Y} = [\mathbf{y}_0\mathbf{y}_1, \ldots, \mathbf{y}_{M-1}]$. No useful information is lost in this process due to the low-frequency characteristics of TWA [27]. The number of samples per ST-T complex after data reduction is $P = 56$.

3) TWA Analysis: Laplacian Likelihood Ratio Method: To be able to follow the dynamic changes in the TWA, a sliding analysis window of L beats is defined. We denote by

$$\mathbf{Y}_l = \left[\mathbf{y}_{l-\frac{L}{2}}, \ldots, \mathbf{y}_l, \ldots, \mathbf{y}_{l+\frac{L}{2}-1}\right] \tag{1}$$

the $P \times L$ matrix to be analyzed when the analysis window is centered on beat l. The GLRT and the MLE are computed on matrix $\mathbf{Y}_l$ for each position l of the analysis window. We used in this work $L = 32$ beats, as a trade-off between noise reduction and dynamic tracking capabilities [17]. Therefore, TWA episodes as short as 32 beats can be detected.

The GLRT and the MLE rely on an assumed model for the signal. The Laplacian Likelihood Ratio method assumes that matrix $\mathbf{Y}_l$ can be modeled as an alternans waveform plus noise (the background ECG was previously removed at the detrending stage)

$$\mathbf{Y}_l = \mathbf{v}_l\mathbf{e}^T + \mathbf{W}_l \tag{2}$$

where $\mathbf{v}_l = [v_l[0], \ldots, v_l[P-1]]^T$ is the decimated alternans waveform (which is deterministic but unknown) and $\mathbf{e}$ is the $L \times 1$ alternans vector $[(-1)^0, \ldots, (-1)^{L-1}]^T$. The rest of nondesired components can be grouped into the noise matrix $\mathbf{W}_l = [\mathbf{w}_{l-L/2}, \ldots, \mathbf{w}_{l+L/2-1}]$. The LLR method assumes that the noise samples of $\mathbf{W}_l$ are uncorrelated and follow a zero-mean Laplacian distribution with unknown standard deviation $\sigma(l)$. Note that in model (2) both the TWA waveform $\mathbf{v}_l$ and the noise level $\sigma(l)$ are assumed to be stationary within the analysis window, but are allowed to change as the analysis windows runs through the record, allowing adaptation to changes in the signal and the noise.

The Laplacian is a heavy-tailed distribution (thus accounting for outliers and extreme values that appear frequently on biomedical signals) and, therefore, provides robust analysis methods [22], while it is mathematically tractable. The details on the derivation of the MLE and GLRT are given in the Appendix.

The MLE of $\mathbf{v}_l$ for this model is given by the P components

$$\hat{v}_l[p] = \text{median}\left(\left\{y_{l+i}[p](-1)^i\right\}_{i=-\frac{L}{2}}^{\frac{L}{2}-1}\right) \quad (\mu V) \tag{3}$$

$p = 0, \ldots, P-1$. Thus, it can be computed beat-to-beat by performing a complex demodulation of the beat-to-beat series $\{y_i[p]\}$ and then applying an L-beat median filter [15].

As a beat-to-beat measure of the estimated TWA voltage, we compute the root mean square (RMS) value across the entire ST-T complex

$$V_l = \sqrt{\frac{1}{P}\sum_{p=0}^{P-1} \hat{v}_l^2[p]} \ (\mu V). \tag{4}$$

In the lead distribution analysis, we are also interested in the relative phase of TWA in the different leads (i.e. whether TWA is concordant or discordant). It is then required to preserve the sign, and we use the mean TWA level through the ST-T complex

$$\bar{V}_l = \frac{1}{P}\sum_{p=0}^{P-1} \hat{v}_l[p] \ (\mu V). \tag{5}$$

The magnitudes of visible TWA episodes were measured manually, confirming the method's output.

The GLRT for this model can be expressed as (see the Appendix for details)

$$T_l = \frac{\sqrt{2}}{\hat{\sigma}_1(l)LP}\sum_{p=0}^{P-1} T_l(p) \underset{\mathcal{H}_0}{\overset{\mathcal{H}_1}{\gtrless}} \gamma' \tag{6}$$

where $T_l(p)$ is computed for each particular sample (p) of the decimated ST-T complex as

$$\begin{aligned} T_l(p) &= 2\sum_{i\in B} \left| y_{l+i}(p)(-1)^i \right| \\ B &= \left\{ i; i \in \left\{ -\frac{L}{2}, \ldots, \frac{L}{2}-1 \right\} \text{ and } \min\left(0, \hat{v}_l[p]\right) \right. \\ &\quad \left. < y_{l+i}[p](-1)^i < \max\left(0, \hat{v}_l[p]\right) \right\}. \end{aligned} \tag{7}$$

$T_l(p)$ is, therefore, proportional to the absolute sum of the terms in the demodulated series $\{y_{l+i}[p](-1)^i\}_{i=-L/2}^{L/2-1}$ whose values lie between zero and the estimated TWA amplitude $\hat{v}_l[p]$.

Note that T_l is inversely proportional to $\hat{\sigma}_1(l)$, i.e. the MLE of $\sigma(l)$ under hypothesis $\mathcal{H}_1$, which indicates the residual noise level after subtracting the estimated alternans component $\hat{\mathbf{v}}_l$ (see the Appendix)

$$\hat{\sigma}_1(l) = \frac{\sqrt{2}}{LP}\sum_{p=0}^{P-1}\sum_{i=-\frac{L}{2}}^{\frac{L}{2}-1} \left| y_{l+i}[p] - \hat{v}_l[p](-1)^i \right|. \tag{8}$$

Thus, the detection statistic T_l is a measure of the statistical significance of the estimated TWA and depends on the noise level $\hat{\sigma}_1(l)$, computed adaptively as the analysis window runs through the record.

TWA is considered to be present in the neighborhood of the ith beat if T_l is above a fixed threshold γ'

$$T_l \underset{\mathcal{H}_0}{\overset{\mathcal{H}_1}{\gtrless}} \gamma' \tag{9}$$

which was set to $\gamma' = 0.15$, according to the validation performed in [16]. Additionally, T_l was required to be above the threshold for at least 32 consecutive beats to consider a significant TWA episode.

The procedure described in this Section is applied to every recorded ECG lead. In the following we will use an extra subindex (as in $T_{l,k}$, $v_{l,k}[p]$, $V_{l,k}, \ldots,$) to denote kth lead.

B. TWA Time Course Analysis

The TWA time course is defined as the beat-to-beat evolution of the TWA amplitude $V_{l,k}$, $l = 0, \ldots, M-1$. In each record showing TWA during the PTCA procedure, the lead with maximum peak TWA level among the 12 standard leads (lead $k_{\max}$) was selected for TWA time course analysis.

C. TWA Lead Distribution and Waveform Analysis

The relationship between the occlusion site and the TWA spatial features was studied by analyzing both the lead distribution and the alternans waveform at the peak of each alternans episode (beat $l_{\max}$).

The TWA lead distribution was defined as the lead-by-lead mean TWA amplitude through the ST-T complex $\bar{V}_{l_{\max},k}$ in the different leads. On the other hand, the TWA waveform was defined as the alternans waveform in the lead with largest TWA amplitude $v_{l_{\max},k_{\max}}[p]$. For comparison among patients, both lead and temporal distributions were normalized in amplitude so that their maximum value was 1.

D. Statistical Methods

Numerical data are expressed as mean $\pm$ one standard deviation. Two-tailed nonparametric tests (Wilcoxon, Kruskal-Wallis and Mann-Whitney U test) were used where appropriate to test differences between groups. Fisher's exact test was used in 2×2 contingency tables and McNemar analysis for control-PTCA records comparison. Statistical significance was defined as $p < 0.05$.

IV. Results

A. TWA Episodes

TWA episodes during acute ischemia were detected in 32 out of the 95 PTCA records (33.7%), while no alternans episodes were found in the 95 control records acquired before catheterization (McNemar test $p = 5 \cdot 10^{-10}$). We present in Table I the number of patients showing TWA during occlusion in the total study population and several subsets defined by the occlusion location (occluded coronary artery and proximity of occlusion), sex and ECG evidence of previous infarction.

The prevalence of TWA was greater during LAD occlusions (51.7% of 29 patients) than in the other occlusion locations (25.8% of 66 patients) (Fisher's exact test $p = 0.02$). Significant differences in prevalence were also found between proximal LAD occlusions (68.2% of 22 patients) and all other locations (23.3% of 73 patients, $p = 2 \cdot 10^{-4}$) and between proximal and distal occlusions within the LAD group ($p = 0.002$). Indeed, none of the 7 patients with distal LAD occlusion presented TWA.

Differences between the incidences in men and women (38.3% versus 25.7%, NS) and between patients with and without evidence of a previous infarction (44.1% versus 27.9%, NS) were not statistically significant.

The average duration of the balloon inflation was similar in all groups (LAD: 241 $\pm$ 74 s, RCA: 281 $\pm$ 80 s LCX: 276 $\pm$ 44 s) (Kruskal-Wallis test, NS). No significant differences in

TABLE I
CLASSIFICATION OF THE STUDY GROUP ACCORDING TO THE OCCLUDED ARTERY, LOCATION OF THE INFLATION, SEX, AND EVIDENCE OF PREVIOUS INFARCTION

		#	TWA (%)	No TWA (%)	
LM		2	0 (0 %)	2 (100%)	
LAD		29	15 (51.7%)	14 (48.3%)	*
	prox	22	15	7	†/‡
	dist	7	0	7	
LCX		19	5 (26.3%)	14 (73.7%)	
	prox	10	2	8	
	dist	9	3	6	
RCA		45	12 (26.7%)	33 (73.3%)	
	prox	20	5	15	
	dist	25	7	18	
Male		60	23 (38.3%)	37 (61.7%)	
Female		35	9 (25.7%)	26 (74.3%)	
Previous	yes	34	15 (44.1%)	19 (55.9 %)	
Infarction	no	61	17 (27.9 %)	44 (72.1 %)	
Total		95	32 (33.7%)	63 (66.3%)	

* $p = 0.02$ LAD vs other locations (Fisher's exact test)
† $p = 0.002$ prox LAD vs dist LAD (Fisher's exact test)
‡ $p = 2 \cdot 10^{-4}$ prox LAD vs other locations (Fischer's exact test)

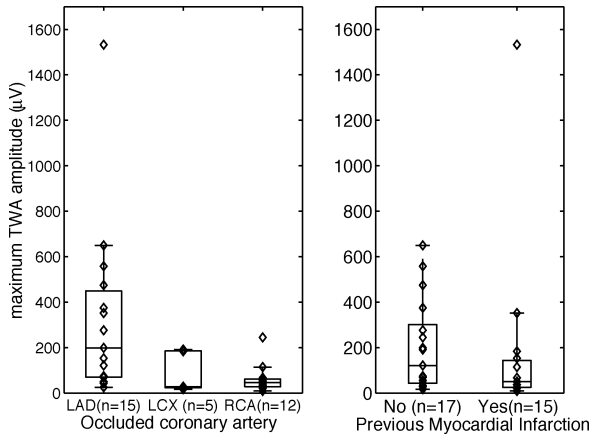


Fig. 1. Box and whisker plots of the maximum TWA amplitudes measured in each patient, classified by (a) occluded artery and (b) according to the evidence of previous MI.

occlusion duration were found between inflations showing and not showing TWA (TWA: 271 ± 84 s versus No TWA: 265 ± 68 s) (Mann-Whitney U test, NS).

Also, no significant HR differences were found during occlusion either between artery groups (LAD:75.2 ± 15.3 bpm; LCX:79.2 ± 13.5 bpm; RCA: 73.1 ± 12.9 bpm; Kruskal-Wallis test, NS) or between patients with and without TWA (TWA: 77.7 ± 11.3 bpm; No TWA: 73.2 ± 15.0 bpm; Mann-Whitney U, NS). The mean HR at which TWA episodes appeared was 79.1 ± 12.6 bpm.

The peak TWA amplitudes ranged in the study group from 10μV to 1533 μV (mean: 192 μV, median: 68 μV). The box and whiskers plots for the subgroups are shown in Fig. 1. Note the single extreme case in the LAD subgroup with a very large amplitude. Significant differences were found according to the occluded artery (LAD: 331 ± 387 μV, median $= 199$ μV; LCX: 90 ± 90 μV, median $= 29$ μV; RCA: 63 ± 63 μV, median $= 47$ μV; Kruskal-Wallis test, $p = 0.007$). However, the differences between the groups with and without evidence of previous MI were not significant (MI: 180 ± 385 μV, no MI: 203 ± 201 μV; Mann-Whitney U, NS).

B. Time Course Analysis

In the 32 occlusions showing TWA, episode durations ranged from 25 s to 375 s (2 min 21 s ± 79 s). The onset time of TWA ranged from 25 s to 245 s after balloon inflation (2 min 6 s ± 64 s). While only 5 episodes started during the first minute of occlusion (four of them at about 45 s), 10 appeared in the second minute, 11 during the third and 4 and 3 respectively during the fourth and fifth minutes of occlusion. The 90% of the maximum amplitude was attained at 3 min 15 s ± 5 s after inflation (69 s ± 47 s after TWA onset).

The end time of the episodes relative to the balloon release ranged from −75 s to +24 s, with negative times meaning before the release. Interestingly, 27 out of the 32 TWA episodes (84%) vanished within the interval lasting from 5 s before the end of the occlusion until 25 s after it (6 s ± 7 s), while only 5 episodes finished well before the balloon deflation (at least 15 s before).

Inter-group differences were found in the delay of TWA onset relative to the balloon inflation (LAD: 91 s ± 40 s; LCX: 120 s ± 55 s; RCA: 172 s ± 66 s; Kruskal-Wallis test $p = 0.009$), but not in TWA duration or in the reaction to the balloon release.

The average TWA responses to the onsets of acute ischemia and reperfusion are shown in Fig. 2. All episodes were aligned so that the time origin in Fig. 2(a) corresponds to the balloon inflation and the origin in Fig. 2(b) corresponds to the balloon release. Note that in Fig. 2(a) the averages after the fifth minute have little significance as the number of averaged records quickly declines around that time.

As the detected TWA episodes presented a wide range of amplitudes (see Fig. 1), the time courses with higher amplitude can mask those with small amplitudes when averaging them. As an alternative representation, Fig. 3 shows the average normalized TWA time courses, with all episodes normalized so that the maximum amplitude is 1. Thus, Fig. 3(a) and (b) shows respectively the dynamic response of the TWA phenomenon to the onset of acute ischemia [Fig. 3(a)] and reperfusion [Fig. 3(b)].

The ECG tracings in Fig. 4 (lead V3), recorded at different times of a PTCA procedure on the proximal LAD artery, illustrate the time course of a visible TWA episode.

C. Spatial Analysis

Fig. 5 shows the percentage of patients with TWA where alternans was detected at a given lead (light bars). The dark bars represent the percentage of patients with the maximal TWA amplitude at a given lead.

Fig. 6 shows the mean and standard deviation of the normalized lead distributions for the three artery groups. In LAD subgroup, TWA was predominant at chest leads V2–V4; in RCA subgroup it was in V1–V3, II-aVF-III, while in LCX group, it was in V4–V6, giving an idea of the damaged region location.

In LAD artery occlusions, TWA is predominant at chest leads V2–V4 [Fig. 6(a) which cover the anterior wall of the left ventricle. The leads with maximum amplitude are V3 (60% of the cases), V4 (33%) and V2 (7%) [Fig. 5(a)]. TWA induced by LCX occlusions is most prominent at precordial leads V4-V6,

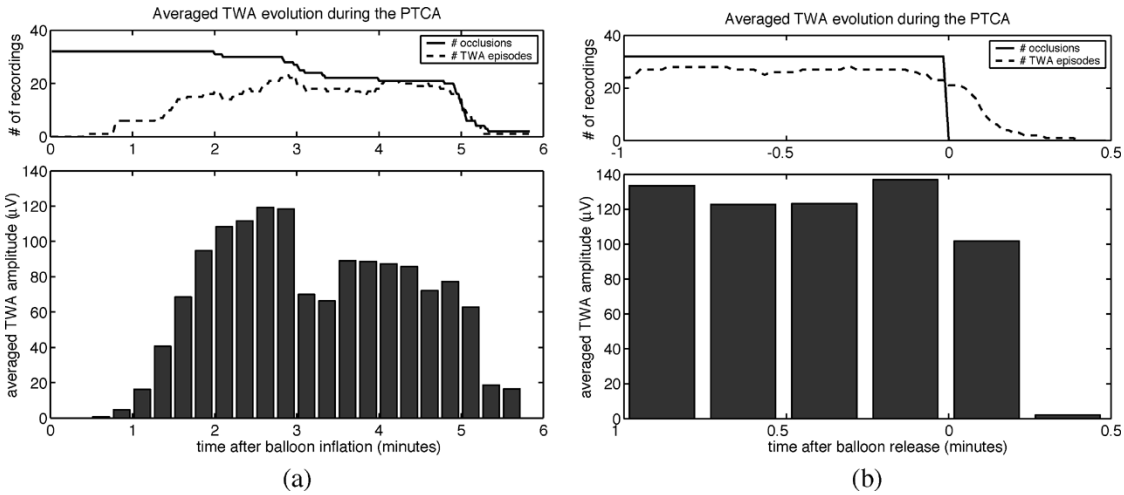


Fig. 2. (a) Averaged time-course of TWA at a given time relative to the balloon inflation and (b) relative to the balloon release (between one minute before and after the release). The upper panels show the number of recordings with occlusion (solid line) and with TWA (dashed line) at a given time.

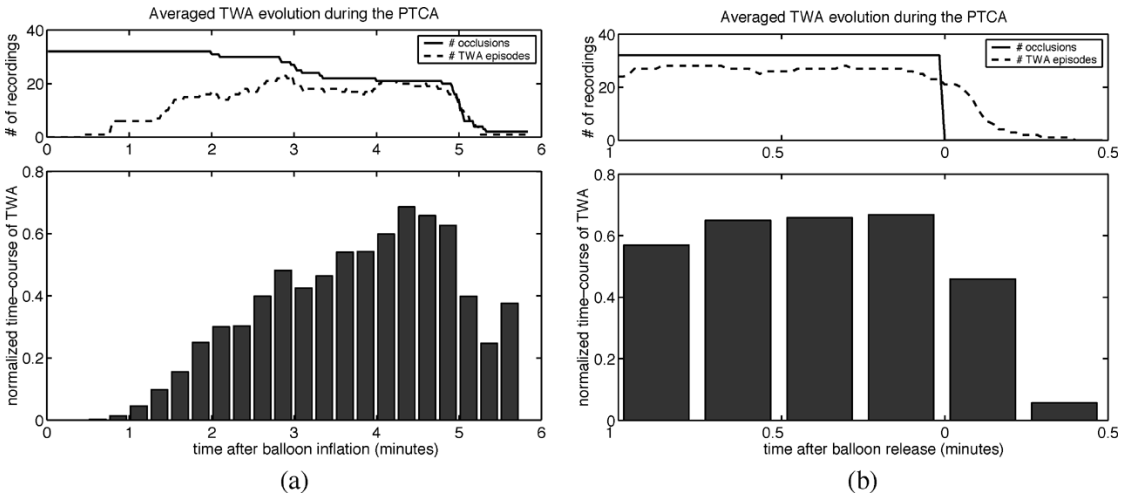


Fig. 3. Similar to Fig. 2, but normalizing the time courses before averaging.

which look at the lateral wall. Half of the LCX-related episodes present the maximum magnitude at V5. In RCA occlusions, the maximum values are found in V1–V3 and the bipolar leads II-aVF-III. Interestingly, TWA is discordant between TWA at right (V1–V2) and left (V5–V6) precordial leads for LCX and RCA occlusions. Conversely, TWA is concordant in precordial leads when occlusion is at LAD.

The frontal, transversal and sagittal projections of the normalized TWA mean electrical axes are shown in Fig. 7 for each artery group. The lines represent the group average vectors, with circular sectors covering twice the standard deviation of the axes' magnitude and angle.

Fig. 8 (upper panels) shows the mean and standard deviations of the normalized TWA waveforms for each artery group. Three illustrative alternans waveforms measured at the peak of TWA in a patient of each group are shown in Fig. 8 (lower panels). Two consecutive ECG beats are presented superimposed as a reference. Though the frequency content of TWA is similar to that of the T wave, alternans waveform is advanced with respect to the T wave. In LAD and LCX groups, alternans was concentrated in the first 250 ms after the QRS fiducial point (corresponding to the ST segment and the first half of the T wave). In the RCA group, alternans spreads further within the repolarization phase. We quantified the TWA timing in terms of the half-area time, i.e. the interval between the QRS fiducial point and the point at which the area under the TWA waveform attains half the total TWA area. This parameter presented significant inter-group differences (LAD: 184 ± 44 ms; LCX: 195 ± 18 ms; RCA: 236 ± 59 ms; Kruskal-Wallis test: $p = 0.025$).

V. Discussion

The first characterizations of TWA in the surface ECG induced by the occlusion of one of the major coronary arteries were provided in experimental animal studies [28], [29], and during ambulatory Prinzmetal's angina [30], [31]. Until the early 1990's, TWA during human PTCA interventions were rarely noticed [32]. Gilchrist [8] and Shah and Subramanyan [12] report 5 and 9 cases respectively, but no quantification of TWA was provided. The studies by Okino *et al.* [9], Nearing *et al.*. [10], Kwan *et al.* [11] provide a deeper insight into PTCA-induced TWA, but TWA was only reported on LAD

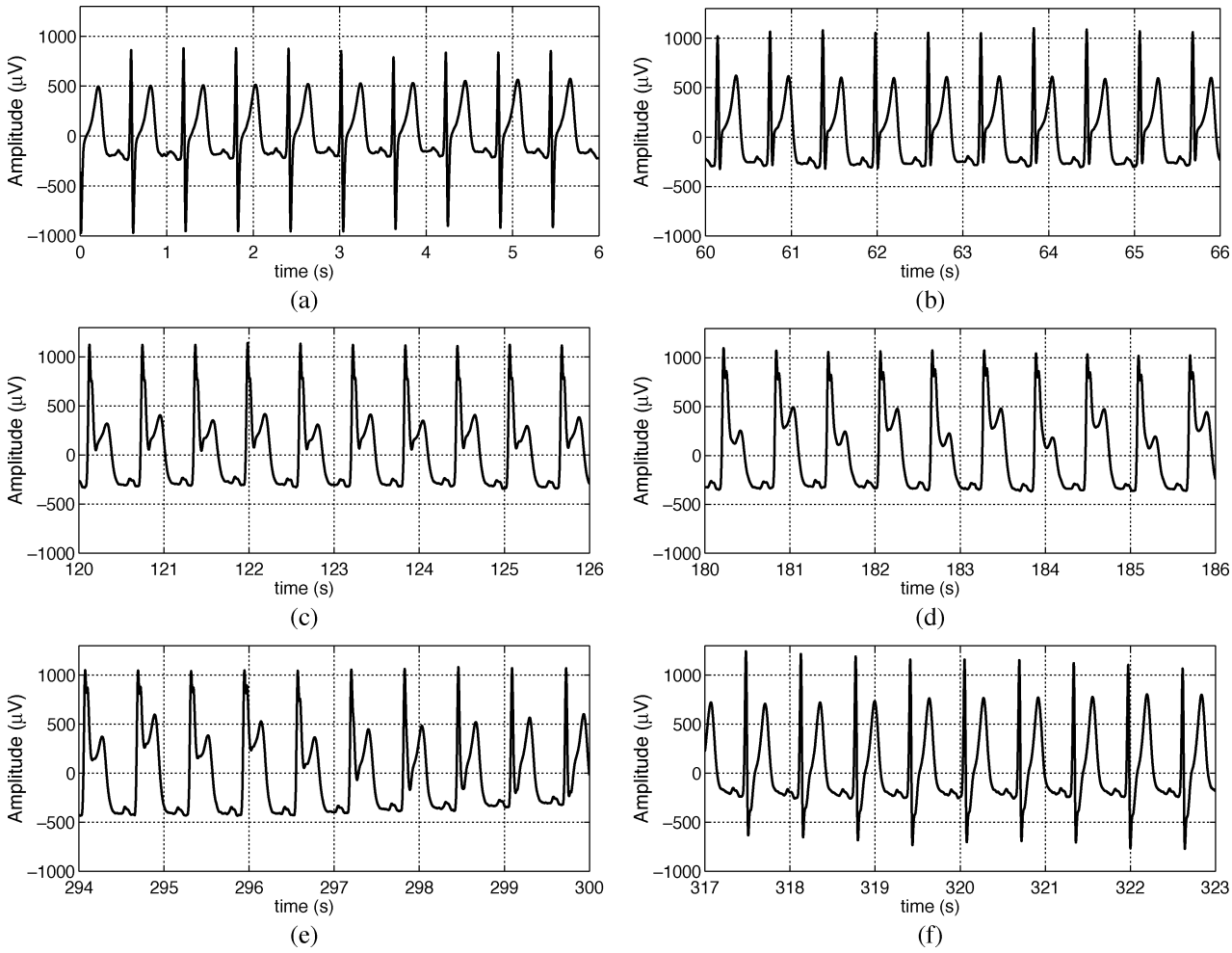


Fig. 4. ECG signal excerpts (lead V3) recorded during a PTCA of the LAD artery. (a) Onset of occlusion (no TWA detected). (b) One minue after occlusion (no TWA detected). (c) Two minutes after occlusion (TWA detected, $V = 52\ \mu\mathrm{V}$). (d) Three minutes after occlusion (TWA detected, $V = 172\ \mu\mathrm{V}$). (e) Vanishing of TWA, seconds after balloon deflation. (f) Reperfusion (no TWA detected).

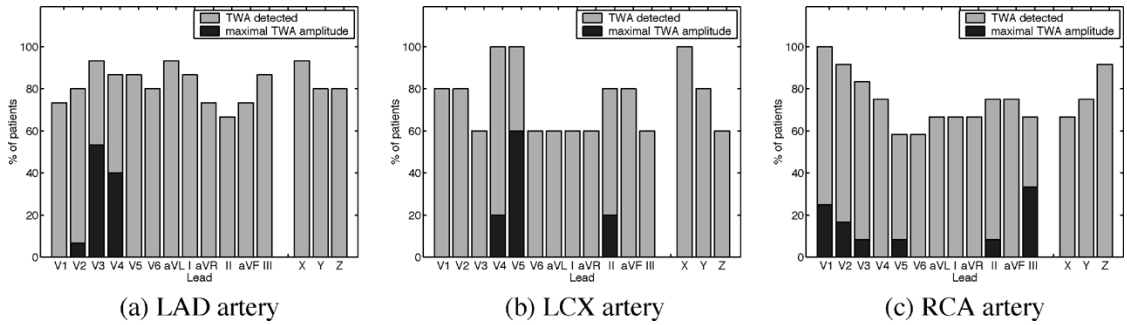


Fig. 5. Percentage of patients with detected TWA (light bars) and with maximum TWA level (dark bars) in each individual lead. The patients with available TWA data in the (a) LAD, (b) RCA, and (c) LCX groups are presented.

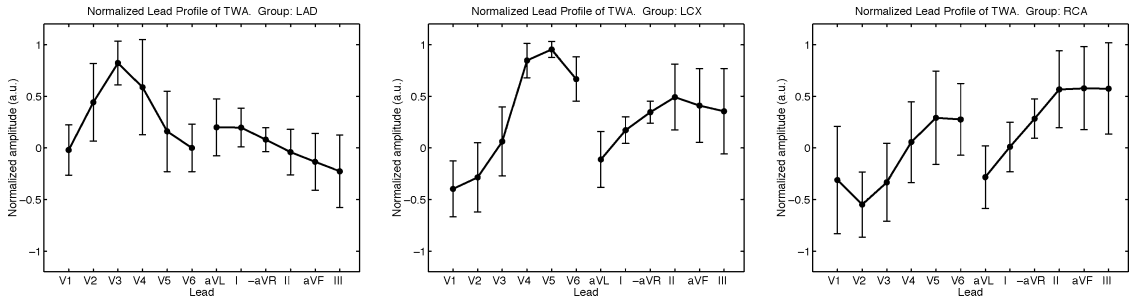
occlusions. Batur *et al.* quantified the TWA magnitude before, during and 24 hours after the PTCA procedure in 97 patients with occlusion in the 3 main arteries.

To our best knowledge, this study is the first one to measure and characterize the spatio-temporal features of TWA in patients undergoing PTCA in the RCA and LCX arteries, thus complementing the previous works. Moreover, our methodology allows to robustly measure nonvisible TWA (at the level of a few microvolts), quantifying the time-course, lead distribution and alternans waveform in each episode. Within the previous PTCA studies, only Nearing and coworkers [10] and Batur *et al.* [14] had measured nonvisible TWA.

A. Laplacian Likelihood Ratio Method

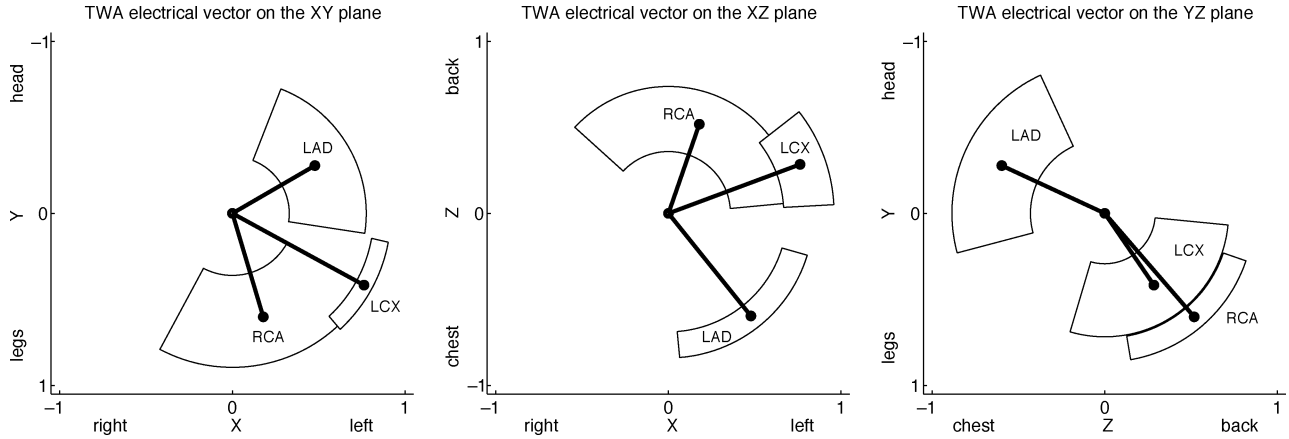
We used the recently proposed Laplacian Likelihood Method [16]. This method has been shown to outperform other linear techniques, based on Gaussian noise distributions, in simulated as well as real noise conditions [15], [16].

Among the features of the LLR method, we must highlight its intrinsic robustness: the underlying Laplacian model and the use



(a) LAD artery group (b) LCX artery group (c) RCA artery group

Fig. 6. Average lead distributions of TWA in the (a) LAD, (b) RCA, and (c) LCX. The error bars represent ±SD.



(a) frontal (XY plane) (b) transversal (XZ plane) (c) sagittal (YZ plane)

Fig. 7. Average normalized electrical axis of TWA in the three subgroups in the (a) frontal, (b) transversal, and (c) sagittal projections. The circular sectors cover 2 SD of the electrical axis magnitude and angle in each plane.

of the median operator make the method robust to outliers (such of the presence of noise bursts, sudden artifacts or ectopic beats). Also, the sensitivity of the detector is adapted to the noise level (in this study, alternans as low as 5 μV were measured using standard electrodes).

B. Incidence and Magnitude

Previous studies have reported in general a lower prevalence of PTCA-induced TWA in the surface ECG than the 33.7% incidence in this study. Gilchrist reports only 1.2% of 407 patients with visible ST alternans [8], Kwan *et al.* [11] TWA ($\geq$0.1 mV) in 2 of 65 patients. With the same criterion, Shah and Subramanyan [12] report a 7.7% incidence in 78 patients, and Okino *et al.* [9] found marked alternans ($\geq$0.2 mV) in 27% of 41 patients with LAD occlusion. On the other side, Nearing *et al.* [10] reported significant levels of TWA above baseline in all 7 patients studied during LAD angioplasty. In general, studies on ic-ECG report higher magnitudes and incidences of TWA (achieving up to 43% in proximal LAD studies) than in surface ECG [11]–[13].

The diversity of the reported prevalences in different studies may be explained by the sensitivity to low-level alternans. Using the LLR, TWA onsets were detected in our dataset at the level of 5 μV, with some detected episodes presenting peak amplitudes as low as 9.7 μV. The sensitivity of this method allows detection of nonvisible low-level TWA in surface ECG. Considering a visual detection criterion of 100μV (as in [11] and [12]), the number of visible episodes would reduce to 14 (during 10 LAD, 2 RCA and 2 LCX occlusions), while only 8 patients in our study group (7 LAD, 0 LCX, 1 RCA) showed TWA $\geq$ 200 μV (which is the criterion in [9]). These numbers agree with the prevalences of visual TWA reported in 12 lead ECG [9].

The greatest prevalence and amplitude of TWA were found in our study during proximal LAD artery occlusion. This supports the hypothesis that a large region of the myocardium must be affected to observe TWA in surface ECG [11]–[13]. Batur *et al.* do not present data about TWA incidence, but report a higher TWA magnitude in patients undergoing LAD angioplasty as compared to other coronary arteries. This fact, together with the low sensitivity of visual TWA assessment, may also explain why most of the episodes reported in the literature were induced by LAD artery occlusions [8], [9], [11], [13]. The observed differences among individuals with occlusion in the same arteries can be influenced by medication, but also by other factors determining the extent and severity of the ischemia in each patient, such as collateral circulation, coronary anatomy or the precise location of the occlusion.

We found a higher TWA incidence in patients with previous MI than in patients without MI (44% versus 28%) but, given the size of our sample, this difference was not statistically significant. A wider study group, as well as more information about the infarction extension and site in each patient would be necessary to obtain relevant conclusions. Other studies, such as Okino *et al.*, found no TWA in 15 post MI patients, while they found

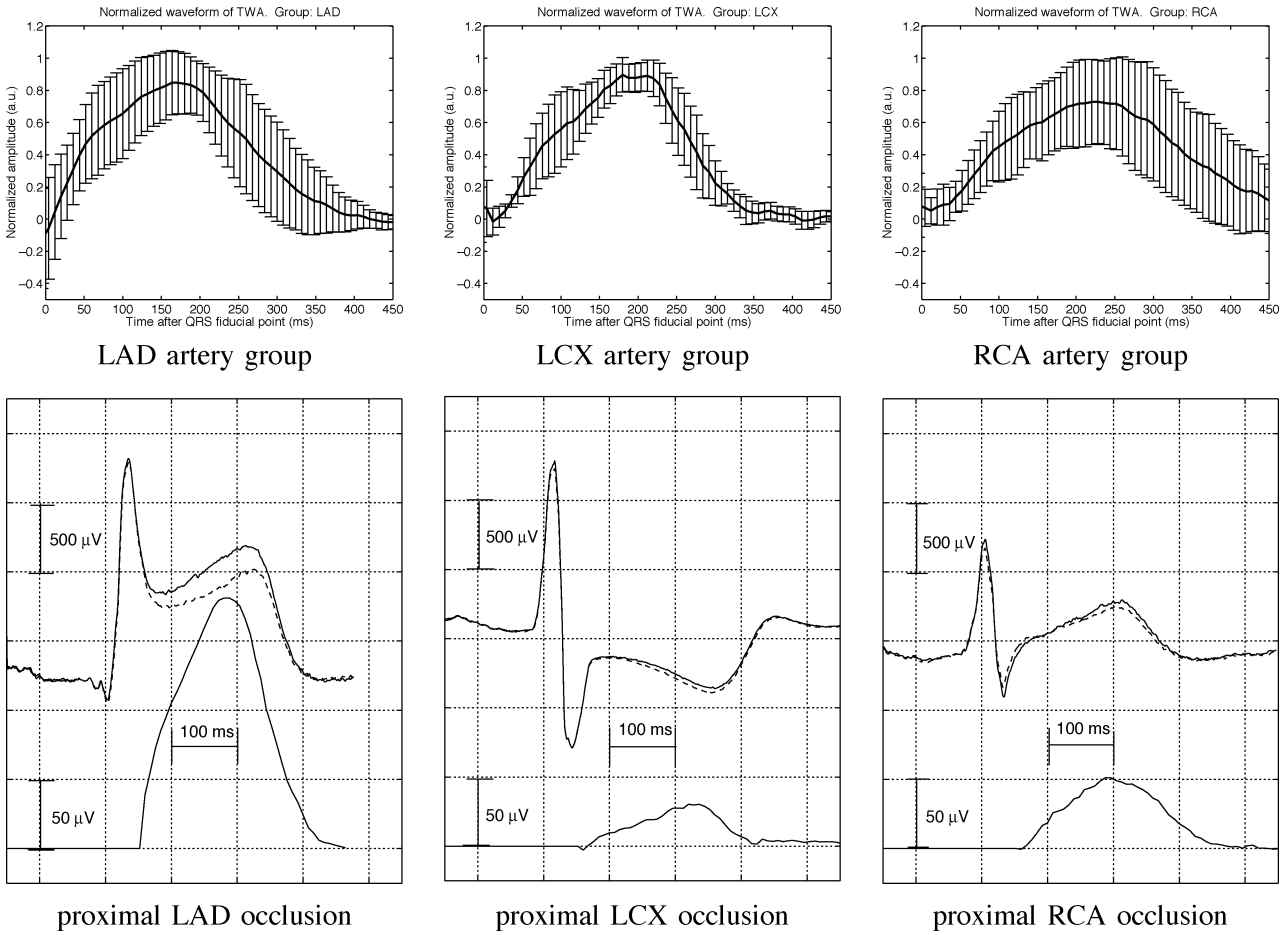


Fig. 8. Upper panels: Average of the normalized alternans waveforms in the LAD, LCX and RCA groups. The error bars represent ± one standard deviation of the normalized waveforms. Lower panels: Examples of alternans waveforms estimated with the LLR method at the peak of TWA for three patients in our study group (Lead V4). Two superimposed ECG beats are also represented as a timing reference. Note that TWA amplitude has been magnified ×10.

TWA in 11 out of 26 patients without previous MI [9]. They argue that when there is a previous MI, the amount of viable myocardium is smaller, and therefore, the ischemic area due to PTCA is not enough to induce measurable TWA at surface ECG. Batur *et al.* did not either report differences according to the existence of prior MI [14].

Experimental and human studies suggest that the incidence and magnitude of TWA is greater at increased heart rates [10], [33]. The heart rate at which TWA appears plays also an important role in the measure of risk [19], [33]. In this study, the patients presented spontaneous sinus rhythm, with an average heart rate of 79 bpm at the onset of TWA, well below the range of heart rates used to induce pacing- or stress-related TWA, showing that in the setting of acute ischemia, TWA can be observed at rest without the need to increase the heart rate.

C. Time-Course of TWA in Occlusion and Reperfusion

To our best knowledge, the quantitative time course of PTCA-induced TWA in humans had only been reported before by Nearing *et al.* [10]. Our time course analysis revealed that the TWA onset was delayed with respect to the balloon inflation (2 min 14 s ± 70 s). Other authors have also reported that alternans arises in the ECG only after some time of occlusion [8]–[11]. We found that the TWA amplitude increases as the time of occlusion elapses, which may indicate a progressive increase of electrical instability within the myocardium. In most of the episodes (79%), the TWA continued until the end of the occlusion, where the maximum level was attained. Nearing *et al.* [10] also reported TWA persisting throughout the occlusion. Shah *et al.* [12] found that alternans coincided with the maximum ST segment elevation in the ECG. Similar patterns have been described in animal experimental settings with longer occlusions (8–10 min) [10], [18].

Upon reperfusion, we observed that the response to the balloon deflation is much quicker than the response to occlusion. TWA vanished in all the cases within the first 25 seconds after the balloon release. We did not find the sudden increase of TWA described by Nearing *et al.* [10] following reperfusion in dogs and humans. This abrupt surge is attributed to the release of ischemia washout products. Other authors, however, report a quick decrease in TWA magnitude just after balloon release [9], [11], [12], similar to the behavior described in this study. Turitto *et al.* also reported an analogous pattern in ambulatory variant ischemia [31], with alternans appearing mainly at the time of maximal ST segment elevation, and disappearing in reperfusion.

The time course of TWA contrasts with the more rapid responses of other PTCA-induced changes, such as ST segment elevation and other repolarization changes [34]. This behavior

has been attributed to the requirement of a certain level of ischemia to induce alternans [8], [11], according to the fact that intracellular calcium alternans have been measured in animal hearts only after 2–3 min of complete ischemia [35]. Other repolarization features, such as the recently proposed inter-lead heterogeneity seem to follow a similarly delayed time-course [36].

D. TWA Lead Distribution

The lead distribution of repolarization alternans indicates how the alternans electrical activity is projected into the different lead vectors.

We found strong regional differences in the lead distribution of TWA depending on the occluded artery. The maximum amplitudes were found in the precordial leads nearest to the region of the myocardium irrigated by the arteries. The mean alternans electrical axis, which indicates the main direction of alternation, was also differently oriented in each of the three subgroups (Fig. 7) indicating the main direction of alternation. This suggests a certain ability of TWA to indicate the location of ischemia.

The lead distribution found in the LAD group is in accordance with that reported by Nearing *et al.* [10] in 7 LAD occlusions. As far as we know, this is the first study of the TWA lead distribution during RCA and LCX artery occlusion. It has also been reported that TWA is better detected in precordial leads than in frontal or the Frank orthogonal leads [10]. Our results (Fig. 5) show that the LLR method attains high detection rates in all standard and orthogonal leads, including those with very slight alternans. This highlights the importance of the methodological approach.

Analogous patterns of lead-specific spatial variation have been found in other occlusion-induced features, such as ST deviation [37], variation of Karhunen-Loève coefficients [37] or high-frequency QRS [38].

E. Alternans Waveform

The temporal distribution of alternans within the repolarization interval has been little studied in the literature. Our analysis has shown that alternans is limited to the first 300–350 ms after the QRS fiducial point in LAD and LCX occlusions, corresponding to the ST segment and the first half of the T wave. On the other hand, the TWA produced by RCA occlusion spread in average further in the repolarization interval (vanishing at about 400 ms).

The interpretation of these results is not straightforward. The differences in the temporal distribution of TWA could be attributable to the sequence of repolarization of the different parts of myocardium. Thus, the TWA waveform would be related to the location of the electrically unstable region in the propagation path of the repolarization. Nearing *et al.* [10] found in humans and animals undergoing LAD occlusion that TWA was marked during the first half of the T wave (the vulnerable period of the repolarization), suggesting a link to cardiac vulnerability. Narayan and Smith [39] observed, in patients undergoing programmed electrical stimulation, that TWA distributed later in the repolarization was a more specific predictor of VT inducibility than earlier alternans.

F. Limitations

Although the number of cases is significantly higher than in other studies, the fact that they are distributed in the major coronary arteries makes this number still small to perform finer statistical analysis, such as spatio-temporal differences between proximal and distal occlusions, or the effect of the infarction site in the patients with previous MI.

Furthermore, occlusions in the same site of a coronary artery may result in a different location of the ischemic area in different patients. Inter-subject variations of chest shape, coronary anatomy and collateral circulation may have obscured the spatial characterization of TWA in the three artery subgroups.

The standard 12-lead configuration used in this study performs a good mapping of the anterior and lateral walls of the heart, which are the areas supplied by LAD and partly by LCX. The inferior region of the myocardium, irrigated mainly by RCA and LCX arteries is not so well represented in the standard 12-lead ECG. If the ischemic region produced by the occlusion is mainly at the inferior wall of the myocardium, ECG signals from electrodes placed on the back of the patients, or body surface potential maps could give more representative results of inferior or posterior lesions.

The medication received by the patients was not available in this study. It has been shown that calcium blockers are able to suppress alternans during coronary occlusion [40], [41] and reperfusion [41] in animals. However, the results in other human angioplasty studies are not so conclusive. Some studies show that visible TWA can be induced in patients receiving calcium antagonists [8], [9], [11], [42]. Batur *et al.* did not either find differences in the magnitude of ischemia-induced TWA according to previous medication (nitrates, calcium antagonists and beta blockers).

VI. Conclusion

The electrocardiographic features of PTCA-induced repolarization alternans were analyzed in three dimensions: the time-course, the lead distribution and the alternans waveform. The analysis of these features allowed the characterization of this transient, regional phenomenon during the first minutes of acute ischemia.

Appendix A
GLRT and MLE Derivation for Laplacian Likelihood Ratio Method

Departing from model (2), the TWA detection problem for a given position of the analysis window can be outlined as the hypothesis test

$$\begin{aligned} \mathcal{H}_0 &: \mathbf{v}_l = \mathbf{0} \\ \mathcal{H}_1 &: \mathbf{v}_l \neq \mathbf{0}. \end{aligned} \tag{10}$$

According to the assumptions described in Section III, the likelihood function for the observed data matrix is given by

$$p\left(\mathbf{Y}_l; \mathbf{v}_l, \sigma(l)\right) = \left(\frac{1}{\sqrt{2}\sigma(l)}\right)^{PL} \times \exp\left(-\frac{\sqrt{2}}{\sigma(l)} \sum_{i=-\frac{L}{2}}^{\frac{L}{2}-1} \left\|\mathbf{y}_{l+i} - \mathbf{v}_l(-1)^i\right\|_1\right), \tag{11}$$

where $\|\cdot\|_1$ denotes the ℓ_1 norm (the sum of the component absolute values). The GLRT is given by the likelihood ratio

$$L_G(l) = \frac{p(\mathbf{Y}_l; \hat{\mathbf{v}}_l, \hat{\sigma}_1(l), \mathcal{H}_1)}{p(\mathbf{Y}_l; \hat{\sigma}_0(l), \mathcal{H}_0)} \underset{\mathcal{H}_0}{\overset{\mathcal{H}_1}{\gtrless}} \gamma, \tag{12}$$

where the unknown parameters $\mathbf{v}_l$ and $\sigma(l)$ are replaced by their MLE under each hypothesis ($\hat{\mathbf{v}}_l$ is the MLE of $\mathbf{v}_l$ under $\mathcal{H}_1$, and $\hat{\sigma}_1(l), \hat{\sigma}_0(l)$ are the MLE of $\sigma(l)$ under $\mathcal{H}_1$ and $\mathcal{H}_0$ respectively).

Under $\mathcal{H}_1$, the likelihood maximization condition for $\hat{\mathbf{v}}_l$ can be written as

$$\hat{\mathbf{v}}_l = \arg\min_{\mathbf{v}_l} \sum_{i=-\frac{L}{2}}^{\frac{L}{2}-1} \left\| \mathbf{y}_{l+i}(-1)^i - \mathbf{v}_l \right\|_1. \tag{13}$$

This condition is accomplished when each $\hat{v}_l[p]$ is the median of the demodulated series (3).

Equalling to zero the partial derivatives of (11) with respect to $\sigma(l)$ under both hypothesis, we obtain the MLEs:

$$\hat{\sigma}_0(l) = \frac{\sqrt{2}}{LP} \sum_{i=-\frac{L}{2}}^{\frac{L}{2}-1} \|\mathbf{y}_{l+i}\|_1. \tag{14}$$

$$\hat{\sigma}_1(l) = \frac{\sqrt{2}}{LP} \sum_{i=-\frac{L}{2}}^{\frac{L}{2}-1} \left\| \mathbf{y}_{l+i} - \hat{\mathbf{v}}_l(-1)^i \right\|_1. \tag{15}$$

Substituting the MLE's in (12), we get the GLRT

$$L_G(l) = \left(\frac{\hat{\sigma}_0(l)}{\hat{\sigma}_1(l)} \right)^{PL} \underset{\mathcal{H}_0}{\overset{\mathcal{H}_1}{\gtrless}} \gamma. \tag{16}$$

Applying the monotonically increasing function $f(x) = x^{(1/PL)} - 1$ to both sides of (16) we get the equivalent test

$$T_l = \frac{\sqrt{2}}{\hat{\sigma}_1(l) LP} \sum_{p=0}^{P-1} T_l(p) \underset{\mathcal{H}_0}{\overset{\mathcal{H}_1}{\gtrless}} \gamma', \tag{17}$$

where

$$T_l(p) = \sum_{i=-\frac{L}{2}}^{\frac{L}{2}-1} |y_{i+l}[p]| - \sum_{i=-\frac{L}{2}}^{\frac{L}{2}-1} \left| y_{i+l}[p] - \hat{v}_l[p](-1)^i \right| \tag{18}$$

and $\gamma' = \gamma^{1/PL} - 1$ is the new threshold. After some manipulation, (18) can be written as (7).

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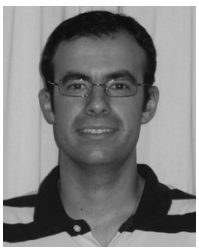

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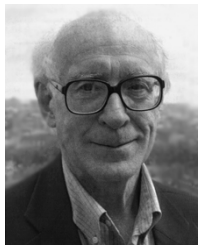

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