Time Course and Spatial Distribution of T Wave Alternans Induced by Coronary Artery Occlusion in Pigs

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Abstract

T-wave alternans (TWA) has been linked to increased vulnerability of the myocardium to ventricular fibrillation in different clinical conditions. Our aim in this work was to study and characterize TWA in an animal model of myocardial ischemia and infarction. Infarction was induced in 29 pigs by a 40-minute-long balloon inflation on the left anterior descending coronary artery. The occlusion recording, as well as a previous baseline recordings were analyzed using the Laplacian Likelihood Method together with Periodic Component Analysis. TWA was found in 27 occlusion recordings and in only 4 baseline recordings. A two/three-peaked pattern was commonly found in the time-course of TWA, where the first peak of TWA was attained at 5 to 7 minutes from the onset of occlusion and the second at about 15 to 20 minutes. After 24 min of occlusion TWA had faded in most recordings. Analysis of the TWA amplitude lead distribution revealed that maximum TWA appears in leads V3 and V4, in consonance with human studies, confirming the regional nature of ischemia-induced TWA.

1. Introduction

T-wave alternans (TWA) is a consistent beat-to-beat alternation in the morphology of the ST segment and / or the T wave, reflecting temporal and spatial heterogeneity of repolarization. TWA is presently regarded as a marker of increased risk for ventricular vulnerability and sudden cardiac death [1]. The mechanisms underlying TWA and the link to vulnerability are still not completely known, and may be different depending on the accompanying clinical conditions [1].

Balloon angioplasty provides an excellent model to investigate the electrophysiological changes of acute transmural ischemia, allowing the study of the initial minutes of the ischemic process and the development of infarction. TWA occurring during the first minutes of occlusion has been investigated and characterized in patients undergoing a percutaneous coronary intervention (PCI) [2]. However, those studies are obviously limited to the very few first minutes of ischemia.

The goal of the present study was to characterize TWA (prevalence, magnitude, time-course as occlusion persist, lead distribution and alternant waveform) during long-lasting coronary artery occlusions in a porcine model of myocardial infarction. To detect and estimate TWA, a multilead approach combining the technique of periodic component analysis (πCA) with the Laplacian Likelihood Ratio method (LLRM) was used [2, 3].

2. Material and methods

2.1. Experimental data

After being anaesthesized, twenty-nine pigs underwent the inflation of an angioplasty balloon for 40 min in the mid portion of the left anterior descendant (LAD) coronary artery.

12-lead ECG monitoring was initiated before starting the occlusion and lasted throughout the occlusion and continued until 4 hours after reperfusion when the experiment was terminated, using a "Kardiotechnica-04-8m" ECG monitor (Incart, St. Petersburg, Russia) at a sampling frequency of 1024 Hz and an amplitude resolution of 1.4 μV. In this work, we analyzed the baseline and occlusion recordings. The experiments were performed at the animal lab of the Biomedical Center (BMC) at Lund University, Lund.

The study conformed to the Guide for the Care and Use of Laboratory Animals, US National Institute of Health (NIH Publication No. 85-23, revised 1996) and was approved by the local animal research ethics committee. See [4] for more information about the experimental data.

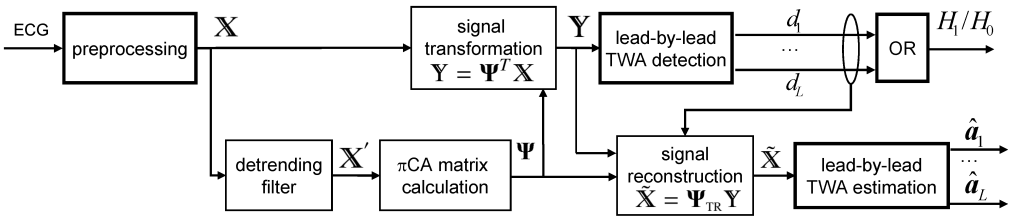

Figure 1. Scheme of the multilead TWA analysis combining πCA and the Laplacian Likelihood Ratio method.

2.2. TWA analysis method

Preprocessing of baseline and occlusion recordings included QRS detection and labelling using the ECG analysis software Aristotle [5], and baseline wander cancellation by cubic-spline interpolation. The signal was then low-pass filtered with a cut-off frequency of 15 Hz and decimated to obtain a sampling frequency of Fs = 31 Hz. In each beat, an interval of 300 ms was selected for TWA analysis (roughly corresponding to the ST-T complex). A linearly independent set of 8 leads (V1-V6, I and II) was used for the rest of the analysis.

Then, TWA analysis was performed automatically on every ECG recording, providing detection of the episodes with consistent TWA, an estimate of the TWA amplitude, its temporal waveform and its lead distribution.

TWA analysis was performed using a sliding 32-beat signal window, applying a multilead processing scheme which makes use of the technique of periodic component analysis (πCA) for multilead ECG processing combined with the Laplacian Likelihood Ratio method (LLRM) to detect and quantify TWA [3]. The scheme of the multilead TWA analysis method is shown in Fig.1.

Signal transformation with πCA. The πCA technique searches for the optimal linear combination of the available leads which maximizes the desired periodicity in the combined lead. For TWA analysis, we are interested in combining the leads in such a way that the 2-beat periodicity is maximized in the resulting signal. As it has been shown elsewhere [6], the optimal combination is given by solving a generalized eigenvalue problem involving the spatial correlation matrix of the segment as well as the spatial correlation matrix of the non-periodic components. Considering all the generalized eigenvectors of this problem, we defined a linear transformation, from the 8 original leads (V1-V6, I, II) to 8 transformed leads (T1...T8). Note that the optimal combination was computed for each 32-beat segment, as it depends on how the alternant components and noise are distributed within the ECG leads.

TWA detection and estimation. We have previously shown that the analysis of the πCA-transformed leads allows the detection of TWA episodes embedded in noise, which remain undetectable when they are analyzed in the original leads [3]. Thus, we used the LLRM [7] to detect and estimate TWA in each of the πCA transformed leads.

TWA was considered to be present at the analyzed segment if it was detected (ie if the generalized likelihood ratio test was above the threshold) in any of the transformed leads (the OR block in Fig.1). To avoid spurious detections, detected episodes with a duration shorter than 64 beats were not considered as reliable detections.

For segments where TWA was detected, the TWA waveform (ie, the median difference between even and odd beats) was estimated in the first πCA transformed lead (the one maximizing the periodicity) using a maximum likelihood estimator for Laplacian noise [7]. The multilead TWA amplitude was defined as the RMS value of the estimated TWA waveform. When no TWA was detected, the TWA amplitude was considered to be zero.

TWA lead distribution. To study and interpret its spatial distribution, TWA must be quantified in the original lead set. For that purpose, we applied the inverse πCA transformation, but only considering those transformed leads where TWA was detected (the other leads were set to zero). In this way, we obtained a reconstructed version of the original signal, which kept essentially unaltered the alternant component and its lead distribution while discarding other non-alternant components [3]. TWA amplitude was then estimated in each reconstructed using the LLRM.

3. Results

TWA episodes were detected in 27 out of 29 occlusion recordings (93.1%) and 4 out of 29 baseline recordings (13.7%) (MacNemar test, $p < 0.001$). The maximum TWA amplitude during occlusions ranged from 45 μV to 831 μV, while TWA amplitude in baseline recordings ranged from 17 μV to 89 μV. There was a slight but significant increase in heart rate during occlusion as compared to the baseline recordings (82.6±20.8 bpm vs 76.6±18.4 bpm, Wilcoxon test $p = 0.02$).

Focusing on TWA episodes induced during occlusions, the mean duration of TWA was of 14.0±8.1 min (ranging from 2.3 min to 32 min). The onset of the detected TWA episodes was 5.4 ± 3.3 min after balloon inflation: in 12 pigs TWA appeared in the first 5 minutes, and in the other 15, TWA appeared between minutes 5 and 10. TWA episodes ended at 25.8 ± 9.3 min from the beginning of

occlusion.

Figure 2 shows the number of recordings where TWA was detected at a given time after the onset of occlusion. The number of recordings with TWA increased until about 4.5 min, where 11 pigs presented TWA, then went down during 2.5 min and increased againg to achieve the global maximum at 11 minutes (24 recordings with TWA). Then, detections decreased until minute 25, and a new lower peak appeared at min 28. Only one record had TWA in the last minute of occlusion.

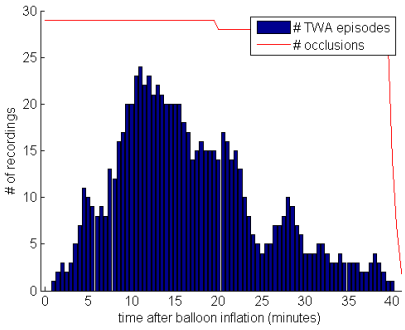

Figure 2. Number of recordings with TWA at a given time after balloon inflation. The red line represents the total number of recordings with occlusion at that time.

The average time-course of TWA amplitude during occlusion is shown in Fig. 3. A pattern with two peaks was observed: the mean TWA amplitude attained a first maximum at 5 min of occlusion (32 μV), then the mean amplitude decreased in 1 min until 8 μV, and grew again to attain an absolute maximum at 12 min, with a mean amplitude of 92 μV. Then, TWA amplitude decreased monotonically to achieve at min 25 levels similar to those at the two first minutes of occlusion.

When observing the TWA time-course in individual pigs, we found typical patterns of two or three peaks in most records, being the first at 5-7 min from occlusion and the second at 15-20 min. Figure 4 illustrates a typical time-course of TWA.

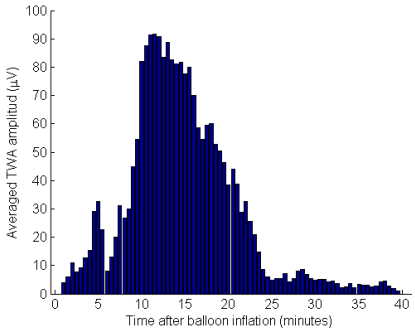

Figure 3. Time-course of the TWA amplitude during occlusion.

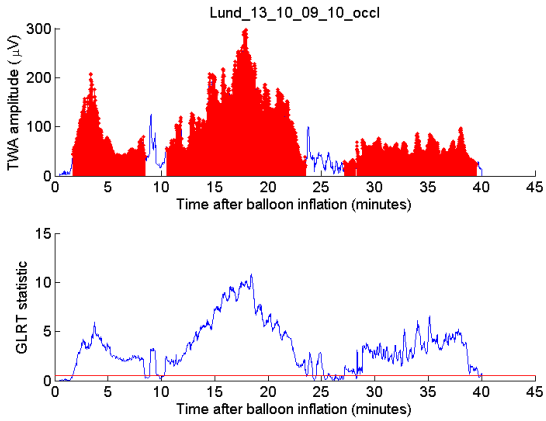

Figure 4. Top panel shows Time-course of the estimated TWA amplitude in one occlusion. The red filling shows when TWA has been detected. Bottom pannel shows the detection statistic (the generalized likelihood ratio test), with the detection threshold in red.

During the occlusion, the average RR interval ranged from 750 to 840 ms. Maximal heart rate occurred in the first minutes of occlusion, while the slowest rhythm appeared by the middle of the record. Therefore, the evolution of TWA was not accompanied by changes in the heart rate.

Figure 5 shows the mean and standard deviation of the normalized lead distribution of TWA amplitude in all occlusion recordings with TWA. Before averaging, lead distributions of amplitudes were normalized so that its maximum was one. Maximum TWA amplitude was induced mainly in precordial leads, and especially in lead V3 and V4.

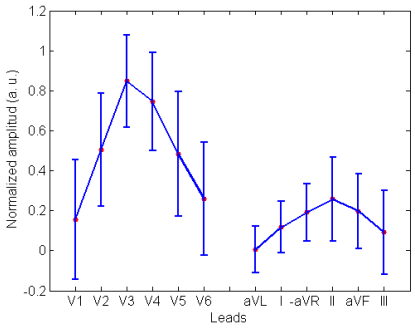

Figure 5. Mean ± standard deviation of the TWA amplitude distribution within the 12 standard leads.

Similarly, Fig. 6 shows the mean and standard deviation of the normalized TWA waveform measured in all occlusion recordings with TWA. Before averaging, waveforms were normalized so that its maximum was one. TWA appeared mainly between 100 and 300 ms after the QRS fiducial point, having the maximum at 210 ms.

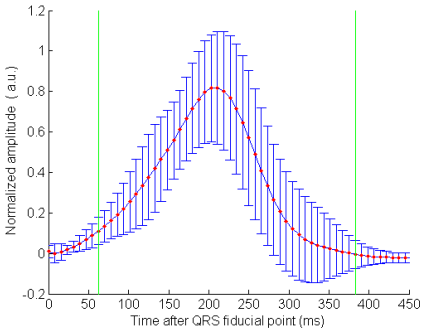

Figure 6. Mean ± standard deviation of the normalized TWA waveforms.

4. Discussion and conclusions

In this work involving LAD coronary occlusion in pigs, we studied the TWA induced during the first minutes of acute myocardial and infarction. In our study group of 29 pigs, 27 presented TWA (93.1%). This is a much higher prevalence than that reported in human PCI studies, which on the other hand, are typically occlusions of 1-2 min, and up to 4-5 min in extreme cases. Taking time into account (Fig. 2), 3 pigs (10.3%) presented TWA during the first two minutes, and 12 (41.4%) during the first five minutes, approaching the 51.7% prevalence that we reported in human LAD occlusions with an average duration of 4.5 min [2].

In that study we showed that the average TWA amplitude monotonically increased during the first 5 min of ischemia. In the present study, we found a similar behaviour up to 5 min of occlusion but we observed an important decay in TWA amplitude between 5 and 6 min, and then, a new and more important increase in amplitude up to a new peak at 12 min with mean amplitude three times higher than at 5 min. From 12 min to 25 min the mean TWA amplitude decreases, and for the rest of the occlusion, TWA amplitude remains at a much lower level, similar to the first minute of occlusion (Fig. 3). This two-peaked pattern resembles the biphasic distribution of early ischemic arrhythmias, where two phases, called Ia and Ib, of increased arrhythmicity have been identified [8]. This suggests that some relation may exist between the amplitude of ischemia-induced TWA and the mechanisms leading to arrhythmia. A third peak of TWA is detected in some recordings, but with much lower amplitude.

At the time of maximal TWA amplitude, the leads with higher TWA amplitude are those facing the anterior wall of the heart, the myocardial region irrigated by the LAD artery: V2-V5, which is in concordance with the observations in humans (compare Fig. 5 with Fig. 6(a) in [2]). The TWA waveform analysis also yields similar results to the study in humans, with TWA peaking at 150-250 ms after QRS fiducial point, corresponding to the ST-T complex and first-half of T wave.

In sum, the TWA spatial and waveform analysis results were were coherent with the regional nature of TWA, and we have identified a typical two/three-peaked temporal pattern, whose relation with the propensity to arrhythmias should be further studied.

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References

[1] Nieminen T, Verrier RL. Usefulness of T-wave alternans in sudden death risk stratification and guiding medical therapy. Ann Noninvasive Electrocardiol Jul 2010;15(3):276–288.

[2] Martinez JP, Olmos S, Wagner G, Laguna P. Characterization of repolarization alternans during ischemia: time-course and spatial analysis. IEEE Transactions on Biomedical Engineering April 2006;53(4):701–711.

[3] Monasterio V, Clifford GD, Laguna P, Martínez JP. A multilead scheme based on periodic component analysis for T-wave alternans analysis in the ECG. Ann Biomed Eng Apr 2010;38(8):2532–2541.

[4] Demidova M, vanderPals J, Ubachs J, Kanski M, Engblom H, Erlinge D, Tichonenko VM, Platonov P. ST-segment dynamics during reperfusion period and the size of myocardial injury in experimental myocardial infarction. Journal of Electrocardiology 2011;44(1):74–81.

[5] Moody GB, Mark R. Development and evaluation of a 2-lead ECG analysis program. In Proc. Computers in Cardiology 1982. 1982; 39–44.

[6] Saul LK, Allen JB. Periodic component analysis: an eigenvalue method for representing periodic structure in speech. NIPS 2000;807–813.

[7] Martinez JP, Olmos S. Methodological principles of T wave alternans analysis: a unified framework. IEEE Transactions on Biomedical Engineering Apr 2005;52(4):599–613.

[8] Smith IV WTS, Fleet WF, Johnson TA, Engle CL, Cascio WE. The Ib phase of ventricular arrhythmias in ischemic in situ porcine heart is related to changes in cell-to-cell electrical coupling. Circulation 1995;92.

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