RELATIONSHIP BETWEEN QUANTITATIVE T-WAVE ALTERNANS ESTIMATES AND PARAMETERS DESCRIBING CLINICAL STATUS OF PATIENT IN ACCUTE PHASE OF MYOCARDIAL INFARCTION AND OUTCOME RESULTS

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Keywords: T-wave alternans, Principal component analysis, Myocardial infarction.

Abstract: Relationship between parameters describing clinical status of the patient in acute phase of myocardial infarction, outcome results and quantitative estimates of T-wave alternans, known prognostic factor of severe cardiac arrhythmias or sudden cardiac death, was investigated in aim to reveal their usefulness and incremental diagnostic utility. Integrated estimate, reflecting differences between S-T,T complexes of odd and even cardiocycles, obtained by means of Principal Component Analysis showed significant correlation with Left Ventricular Ejection Fraction and rehospitalization of patient within 6 months.

1 INTRODUCTION

ECG T-wave alternans (TWA), a beat-to-beat alternation in the morphology and amplitude of the ECG ST segment or T wave, reflects temporal-spatial heterogeneity of repolarization (Nearing et al. 2003). The evidence linking TWA with arrhythmias spans more than a century, dating from the pioneering observations reported in (Hering in 1909). Macroscopic levels of TWA have been detected under diverse clinical conditions in association with life-threatening arrhythmias, including acute myocardial ischemia and infarction, Prinzmetal's angina, heart failure, and channelopathies such as the Brugada and long QT syndromes (Nieminen et al. 2010). Numerous studies have demonstrated that screening with microvolt T-wave alternans (MTWA) testing in patients with ischemic cardiomyopathy is effective in identifying patients at high and low risk for sudden cardiac death (Chow et al. 2006); (Bloomfeld et al. 2004). Gehi with co-authors reporting results of meta-analysis about TWA as predictor of ventricular tachyarrhythmic events (Gehi et al. 2005) acknowledge that incremental prognostic value of MTWA when used with other known risk factors for cardiac arrhythmia, such as Left Ventricular Ejection Fraction (LVEF) in patients with ischemic cardiomyopathy, remains unclear. Replying to this publication Chan with colleagues (Chan et al. 2006) rises the question whether TWA is simply a surrogate marker of patients with greater disease burden and severity, or it is an *independent* predictor of cardiac arrhythmias. To answer this question multivariable modelling that adjusts for demographics, LVEF, clinical comorbidities, medication treatment, as well as electrophysiologic variables (e.g., Holter monitoring, ECG QRS duration, electrophysiologic study) should be done.

On the other hand evaluation of TWA over the last two decades has evolved from visual inspection of the ECG to the use of computerized analytical methods for detection of non-visible TWA in the microvolt range. However clinical performance of the methods differs and there is no "Golden Standard" method for detection and evaluation of TWA so far. Results of "Physionet Challenge 2008" (Moody 2008) revealed big variety in results between the methods for detection and evaluation of TWA even on simulated data. Analysis of clinical recordings in critical situations is another challenge for the methods.

Known methods of detection of TWA are giving more or less comparable results, however estimate indicating simply presence or absence of the

Krisciukaitis A., Simoliuniene R., Macas A., Petrolis R., Puodziunaite E., Bertasiene Z. and Saferis V..
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DOI: 10.5220/0003856404480452
In *Proceedings of the International Conference on Bio-inspired Systems and Signal Processing* (BIOSIGNALS-2012), pages 448-452
ISBN: 978-989-8425-89-8

phenomena is never used. There is big variety of methods of quantitative evaluation of TWA giving sometimes mutually incomparable results. Review of methods is given in (Martínez et al., 2005). Some methods give estimates in mV as for alternans only in amplitude, others give non linear energy estimates obtained from spectral analysis. There are also methods based on multivariate analysis (Principal Component Analysis (PCA) or Karhunen Loeve Transform) giving linear estimates, but incomparable with amplitude evaluation, because they depend on basis functions used for truncated expansion of the signals. Most of methods are elaborated using simulated signals (e.g. Clifford et al. 2008) and tested with clinical recordings where TWA was evoked by atrial pacing or comparing recordings of healthy and ichaemic patients. Such rough evaluation usually does not reveal any incremental prognostic usefulness and could be the main reason for hesitations expressed by Gehi (Gehi et al., 2005) and Chan (Chan et al., 2006).

The aim of this study was to evaluate usefulness of several quantitative estimates obtained by means of method based on Principal Component Analysis analyzing recordings in patients in acute phase of myocardial infarction. We expect that comparison of them to routinely obtained standard estimates of patient status and outcome results can reveal their incremental diagnostic utility.

2 METHODS

2.1 Signal Registration and Pre-processing

Clinical recordings of the signals for investigation we performed during 24h follow up of the patients hospitalized in the acute phase of myocardial infarction in Cardiology Clinics of Lithuanian University of Health Sciences in Kaunas (Permission of Kaunas Region Ethics Committee for Biomedical Research Nr. 169/2004). One lead chest ECG signal was recorded by means of Heartlab™ system (Dregunas, 1999) (certificate No. LS. 08.02.1957) using 12 bit resolution A/D conversion at 1000 Hz sampling rate. The age of patients (64 females and 114 males) was ranging from 35 till 84. Their clinical status according Killip-Kimball classification was following: 50 patients were of class I, 109 – of class II, 10 – of class III and 9 – of class IV.

Signal pre-processing we started with detection of fiducial point of each cardiocycle – peak of ECG R-wave. Advanced two steps R-wave peak time point determination method was necessary to achieve sufficient accuracy according to our experience reported in (Simoliuniene et al., 2008). After preliminary detection using filtered derivative of the ECG signal we maximized cross-correlation of the sliding in time R-wave template with the ECG signal. R-wave template was constructed from first 10 cardiocycles of the recording and updated after every processed cardiocycle. The values of samples of just found R-wave of current cardiocycle was added as 10% of values of updated template shape. Standardized arrays of 428 time points of R-waves corresponding to about 6 minutes duration (depending on actual heart rate) were prepared from every recording for further analysis.

A mean value of 10 consequent samples in interval between the end of T-wave of preceding cardiocycle and beginning of P-wave of current cardiocycle, was considered as a baseline reference point of each cardiocycle. Bicubic spline interpolation using these reference points was used to calculate baseline wander component, which was subtracted from the original ECG signal.

Excerpts of ECG signal samples representing S-T,T complexes of each cardiocycle were taken for further analysis. Number of samples corresponding to 2/3 of mean length of RR intervals in the recording was considered as a length of interval of samples representing S-T, T complex. This interval was starting at 100^{th} sample after fiducial point of cardiocycle. The length of QT interval is varying in regard to heart rate. This variation is tolerable if we want to analyze only amplitude alternans, however it hampering detail shape analysis of S-T, T complex. We applied time stretching of the ordinary S-T,T interval to align it with the others using bicubic spline interpolation, maximizing cross-correlation with the template constructed from the first 10 cardiocycles. Estimated coefficients for QT interval time stretching were close to the values reported by (Sagie et al., 1992), proposed as substitution of classical Bazett formula. Corrected (stretched) arrays of samples from each cardiocycle formed matrix of samples ***X***, which was giving a redundant but comprehensive representation of variety of the shape of S-T,T complexes from the recording considered for analysis:

$$\mathbf{X} = \begin{bmatrix} x_{1,1} & x_{1,2} & \cdots & x_{1,n} \\ x_{2,1} & x_{2,1} & \cdots & x_{2,n} \\ \cdots & \cdots & x_{i,j} & \cdots \\ x_{p,1} & x_{p,2} & \cdots & x_{p,n} \end{bmatrix}, \quad (1)$$

where $x_{i,j}$ is the i^{th} sample of the j^{th} cardiocycle.

2.2 Principal Component Analysis of the S-T,T Complexes

Principal Component Analysis was already successfully used in detection and evaluation of TWA (Simoliuniene et al., 2008) in test recordings of "Physionet Challenge 2008" dataset (Moody, 2008).

PCA is used to reduce dimensionality of redundant representation of S-T,T complexes. The PCA transforms the original data set into a new set of vectors (the principal components) which are uncorrelated and each of them involves information represented by several interrelated variables in the original set. The calculated principal components are ordered so that the very first of them retain most of the variation present in all the original variables. Thus it is possible to perform a truncated expansion of S-T,T complexes representing vectors by using only the first several principal components. Every vector $\boldsymbol{x}_i$ representing ordinary S-T,T complex is then represented by linear combination of the principal components $\boldsymbol{\phi}_k$ multiplied by coefficients $w_{i,k}$:

$$\mathbf{x}_i = \sum_{k=1}^{p} w_{i,k}\varphi_k \quad . \tag{2}$$

Variation of coefficients $w_{i,k}$ represents variation in shape of S-T,T complexes. It was shown in our previous works that TWA is represented by beat-to-beat variation of one or mostly few coefficients w (Simoliuniene et al., 2008).

Minimal yet sufficient number of principal components to be used for truncated representation of the signals was determined by means of Wold's criteria (Wold, 1978):

$$PR(m) = \frac{PRESS(m)}{PRESS(m-1)} \ , \tag{3}$$

where PRESS(m) is calculated as following:

$$PRESS(m) = \sum_{i=1}^{n}\sum_{j=1}^{p}({}_m\hat{x}_{ij} - x_{ij})^2 \quad . \tag{4}$$

${}_m\hat{x}_{ij}$ here is the estimate of the original data set based not on all but the first m principal components; x_{ij} - the original data set. Final determination of number was done according to our experience (Krisciukaitis et al. 2006).

2.3 Detection of T-wave Alternans

Detection of TWA was performed step by step in consequent intervals of the recordings. TWA was detected by two methods. First method uses normalized estimate of power spectral density of the coefficients w at the highest frequency. Episode of TWA was registered in case when this estimate at the highest frequency in 128 coefficients interval was at least two times bigger then mean of 10 neighbouring lower frequency estimates (Simoliuniene et al., 2008). Second method is based on the idea used by (Nearing et al., 2002), that shape of S-T,T complexes in odd and even cardiocycles should be similar between each other in the groups and different between these groups. Unlike moving average complexes used by (Nearing et al., 2002) we used derivative quantitative estimates of shape of the S-T,T complexes – coefficients of principal components. The shape of ordinary S-T,T complex is optimally represented by several coefficients of principal components as a point in multidimensional orthogonal space. Performing a t-test for means between two 32 coefficient sets of such coefficients formed from odd and even cardiocycles (64 is a total number of cardiocycles in the tested interval) we can reveal even fine differences in their shape. TWA was detected when means of two sets were statistically different at significance level $p<0.05$.

Final detection of TWA was performed consolidating results of these two methods, taking into account only episodes where results of methods coincided.

2.4 Evaluation of T-wave Alternans

Four quantitative estimates of TWA were selected for testing:

nTWA – Number of TWA episodes over tested interval;

siTWA – sum of absolute value of integrated differences between S-T,T complexes restored using first five principal components and mean coefficients of odd and even cardiocycles;

smTWA – maximal amplitude of difference between restored cardiocycles;

scTWA – sum of absolute values of highest frequency component of coefficient sequences extracted by means of hi-pass filter.

All estimates are normalized due to the fixed length of processed recording interval and give comprehensive representation of phenomena in terms of presence/absence, frequency and amplitude. siTWA and smTWA could be comparable with estimates used in (Nearing et al. 2002), however giving better representation being more robust to noise.

2.5 Estimates of Patient Status and Outcome Results

Following standard estimates of patient status and clinical outcome were used:

- Killip-Kimball class index;
- Left Ventricular Ejection Fraction (LVEF);
- Localization of injury by infarction;
- Rehospitalization within 6 months;
- Rehospitalization within 12 months;

In addition mean heart rate and triangular heart rate variability index (HRVi) were estimated according (Eur Heart J 1996).

3 RESULTS

PCA of several recordings was performed as a pilot study to establish minimal yet sufficient number of principal components to be used for further analysis. Values of Wold's criteria PR and percentage of variation represented by corresponding number of first principal components is presented in Figure 1. First five principal components representing more then 90% of variation in S-T,T complexes were selected according our experience (Krisciukaitis et al. 2006) as minimal yet sufficient set of basis functions for truncated representation of the signals.

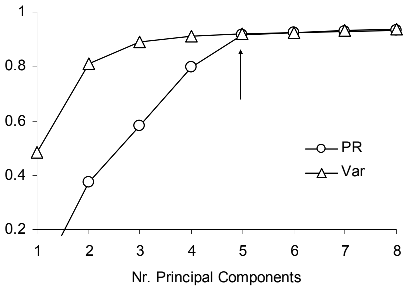

Figure 1: Wold's criteria PR and part of represented variation (Var) in signal for determination of minimal yet sufficient number of Principal components for truncated representation of S-T,T complexes. Specific point in dependency of PR criteria marked by arrow.

We selected 178 recordings for processing, where signals were of acceptable quality and free of power network or other noises and movement artefacts.

Episodes of TWA were found in 41 out of 178 recordings. Visually was possible to observe episodes of alternans in T-wave amplitude and/or shape in some of these 41 recordings and no one such episode was found in the rest of recordings. Interestingly TWA was found not only in the recordings showing low HRVi and high heart rate. Mean values of RR intervals in TWA episodes containing recordings were ranging from 750 ms till 1100 ms with HRVi spanning from 3.27 till 25. Moreover we did not find any episodes of TWA in some recordings with mean RR intervals below 750 ms. We also did not find any significant relationship between heart rhythm parameters and any of TWA parameters. No significant relationship was found also between TWA and Killip-Kimball class estimates.

We found statistically significant correlation between siTWA and LVEF, which was r = -0.456 (p=0.017). Correlation was estimated using Spearman rank correlation because distribution of data was non Gaussian.

Values of siTWA showed also relationship with clinical outcome results: 0.22±0.037 (mean ± SE) in 7 patients who were rehospitalized within 6 months versus 0.19±0.011 for the rest of 32 patients in TWA positive group. There was no significant difference when compared in regard to rehospitalization within 12 months.

TWA estimates obtained using separately only one of the methods, either spectral (Simoliuniene et al., 2008), either t-test for means between odd and even PC coefficient sets, did not show any significant relationship with LVEF, clinical outcome, or other parameters describing status of the patient.

4 DISCUSSION

Importance of aspiration to increase reliability of TWA detection is supported by the fact that only TWA estimates obtained using combined analysis methods involving as much as possible comprehensive information showed significant relationship to LVEF, parameter describing clinical status of the patient in acute phase of myocardial infarction. LVEF was obtained by means of independent from ECG method. Increase in siTWA was related with decrease in LVEF, it complies with data published by other authors (Chan et al., 2008). Another fact, that TWA detection method (Simoliuniene et al., 2008) comparatively good scored up by results on test recordings from PhysioNet database shows in some cases disputable results on clinical recordings, demonstrates that further studies on clinical recordings are of great importance.

We found TWA episodes not only in cases of high mean heart rate and low heart rate variability unlikely results reported in earlier publications concerning phenomena. This fact shows need for further clinical studies.

Prognostic value of siTWA was demonstrated by statistically significant relationship with rehospitalization of patients within 6 months. It complies with the results of survival studies reported in (Nieminen et al., 2010). However, our results at the moment do not provide any significant evidence of incremental prognostic value of estimates of TWA.

Further investigations need database of clinical recordings including as big as possible variety of standardized clinical recordings. A network based databank of such recordings based on international cooperation would be a solution for future investigations.

5 CONCLUSIONS

Elaboration of quantitative estimates of TWA is playing major role in development of diagnostic methods and acquiring by them of wider acceptance as risk stratification tool.

ACKNOWLEDGEMENTS

This research was funded by a grant (No. MIP-68/2010) from the Research Council of Lithuania.

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