Beat-to-beat ventricular repolarization variability evaluated during acute myocardial ischemia[☆]

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ABSTRACT

Experimental and clinical studies have shown that beat-to-beat variability of ventricular repolarization morphology, which can be measured by T-wave spectral variance (TSV) index based on the two-dimensional Fourier transform, is associated with an increased risk of developing malignant ventricular arrhythmias.

In the present study we tested TSV index during percutaneous coronary intervention (PCI) procedure in the 12 standard ECG leads and in the orthogonal X, Y and Z leads. In addition, we analyzed the intrasubject and intersubject variability of TSV index, in order to determine reliable limits of significant repolarization variability due to an ischemic cardiac process. A total population of 62 patients, in which two ECG controls and one ECG recording during PCI procedure, were obtained. Results indicate that TSV index showed significant differences during PCI procedure with respect to control situation in all ECG leads ($p < 0.0001$).

The relative change between PCI procedure and control situation showed that there is a preferential ECG lead to analyze the TSV index depending on the occlusion site. Moreover, TSV index presented a high stability in each patient and a significant larger variability among patients. Finally, we conclude that TSV index offers a robust tool for evaluating beat-to-beat repolarization variability during acute myocardial ischemia.

1. Introduction

Ventricular repolarization dispersion (VRD) is a measure of inhomogeneous recovery of excitability during repolarization process. This ventricular heterogeneity is mainly attributable to differences in activation times and action potential duration (APD) in different heart areas. The APDs differs not only between myocytes of different ventricular layers [1] but also between posterior and anterior endocardial layers, apex and base [2], and left and right ventricles [3]. Thereby, increments in VRD values that are higher than normal are associated with an increased risk of developing reentrant arrhythmias [4,5].

Experimental and clinical studies have demonstrated a relationship between VRD and severe ventricular arrhythmia and/or sudden cardiac death [6,7]. Also, it was shown that modifications in the morphology of the T-wave are associated with an increased VRD

[8,9]. Several techniques have been presented to analyze and quantify the temporal variability of ventricular repolarization [10,11]. Moreover, beat-to-beat measurement of the QT interval is based on the exact delineation of the T-wave end point, which frequently fails in automatic ECG analysis [12,13]. Low level beat-to-beat variations in ventricular repolarization (both amplitude and/or time duration) can be detected by using high resolution techniques in ECG recordings [14]. Also, the beat-to-beat changes were evaluated by using the T-wave spectral variance (TSV) index method, based on the two-dimensional Fourier transform (2D-FFT), which allows to detect dynamic changes in the repolarization pattern independently of the exact definition of the end point of the T-wave [15–17].

Steinbigler et al. showed that TSV index reveals an increased VRD in patients prone to ventricular tachycardia and ventricular fibrillation after myocardial infarction, while the corrected QT interval showed no signficant differences [15]. On the other hand, Valverde et al. observed that TSV index detects the presence of temporal repolarization variability in a model of chronic infarcted animals [16]. Later, in another work, Steinbigler et al. showed that TSV index was significantly higher in patients with idiopathic dilated cardiomyopathy prone to ventricular fibrillation respect to no ventricular fibrillation group [17]. However, all these authors did not study the TSV index in different ECG projections. As far as

we know, there are no results indicating the role of the TSV index from different ECG leads by other authors. Moreover, we analize the TSV index in different ECG projections during acute myocardial ischemia induced by percutaneous coronary intervention (PCI) procedure. The TSV index can be calculated without the necessity of exact delineation of the T-wave endpoint and it might allow the detection of spatial ventricular repolarization dispersion if enough numbers of leads were used in the ECG acquisition [15].

The aims of this work were to: (1) Evaluate the presence of beat-to-beat repolarization variability during PCI procedure in the 12 standard ECG leads and in the orthogonal X, Y and Z leads. (2) Analyze the intrasubject and intersubject variation of TSV index at control ECG recordings before PCI procedure. (3) Conclude the advantages and disadvantages of TSV index during acute myocardial ischemia to optimize cardiac risk stratification of patients which might enable a better treatment and a good improved short and long-term prognosis.

2. Materials and methods

2.1. Database

In the present work we used the STAFF III database, which comprised 108 patients obtained from the Charleston Area Medical Center in West Virginia, receiving elective PCI (nonperfusion balloons) in one of the major coronary arteries (STAFF III study). Twenty-five patients were excluded from further analysis because they suffered from ventricular tachycardia, had undergone an emergency procedure or presented signal loss during ECG acquisition. A population of 83 patients was included, 55 males and 28 females, ages 32–78 years (mean 60 ± 12 years). The population consist of: *leftmain* (LM) occlusion artery in 2 patients, *leftanteriordescending* (LAD) coronary occlusion artery in 28 patients, *rightcoronaryartery* (RCA) occlusion in 37 patients and *leftcircumflex* (LCx) coronary occlusion artery in 16 patients. The study was approved by the local investigational review board, and informed consent was obtained from each subject before enrolment. A data form indicating the anatomic site and the exact times of inflation and deflation of the balloon was completed. If a patient received more than one balloon inflation during the same procedure, only the first inflation was considered. The mean inflation duration was 4 min 28 s with a standard deviation of 74 s. Eight leads (v1-v6, I, II) were recorded using equipment by Siemens-Elena AB (Solna, Sweden) and digitized at sampling rate of 1000 Hz and amplitude resolution of 0.6 μV. Leads III, aVR, aVL and aVF were derived from leads I and II. Synthesized orthogonal X, Y and Z leads were obtained by the Kors transform [18] obtaining a total of 15 ECG leads.

Three ECG records were acquired for each patient. First, two control recordings were acquired continuously for five min in supine position prior to the PCI procedure in clinical stable conditions, within a time interval of maximum 1 hour in the room and/or catheterization laboratory. The electrodes were maintained on the patients between both recordings with their positions marked, to enable accurate comparisons of the ECG variables. Second, one continuous ECG was recorded during PCI procedure, starting before and ending after balloon inflation and deflation respectively. Therefore, the patients behaved as their own controls. One example of ECG recordings for a particular patient of the STAFF III database before (control situation) and during PCI procedure is shown in leads I (Fig. 1a), v2 (Fig. 1b) and X (Fig. 1c).

2.2. ECG preprocessing

We applied a signal pre-processing to the 15 leads ECG records during control and PCI procedure respectively. Both controls and

PCI ECG records were filtered with a notch filter (Butterworth, 2nd order, 60 Hz) to minimize the power-line interference. A cubic spline interpolation filter was used to attenuate ECG baseline drifts and respiratory artifacts [19]. Thereafter, QRS complexes and their endpoints were detected in each ECG-lead using a modified version algorithm proposed by Pan and Tompkins [20].

In each ECG lead (both controls and PCI procedure), one QRS template was constructed by calculating the median of the total QRS complexes. After that, if the cross-correlation coefficient between QRS complexes and each QRS template was greater than 98%, a new jitter-corrected QRS complex is obtained, otherwise the complex was rejected. Taken 80 ms from fiducially jitter-corrected QRS endpoint, a T-wave window of 250 ms duration was defined in order to construct an aligned T-waves matrix (Fig. 2a). This determined the input matrix containing arranged T-waves for the 2D-FFT process, as can be observed in Fig. 2b.

2.3. T-wave spectral variance index

We computed the TSV index with an algorithm described by Steinbigler et al. [15]. The basement of the algorithm is the 2D-FFT. First, a one-dimensional FFT (1D-FFT) is applied to each T-wave of the T-waves matrix, and the frequency contents were determined. The result is a matrix containing the power spectrum of each T-wave, in which the x-axis correspond to the frequency content in Hertz and the amplitude (z-axis) correspond to the magnitude of the power spectrum expressed in μV^2. A second 1D-FFT is applied to the assembly of the power spectrum of each T-wave in order to evaluate the periodic appearance of each frequency content (y-axis), expressed in cycles-per-beat (cpb), as shown in Fig. 2c.

Steinbigler et al. considered the frequency content of the T-wave less than 50 Hz, and they calculated the TSV index as a non-units (n.u.) ratio of the spectral energy with beat-to-beat variability greater than 0 cpb and the total spectral energy, from 0 Hz to 50 Hz [15]. This assumption is supported by Thakor et al., who separated the power spectrum of the QRS complexes and, P- and T-waves in healthy and abnormal patients, and observed that the power spectrums of these complexes and waves were less than 40 Hz [21]. In consequence, we computed the beat-to-beat variability of the T-wave less than 50 Hz as following:
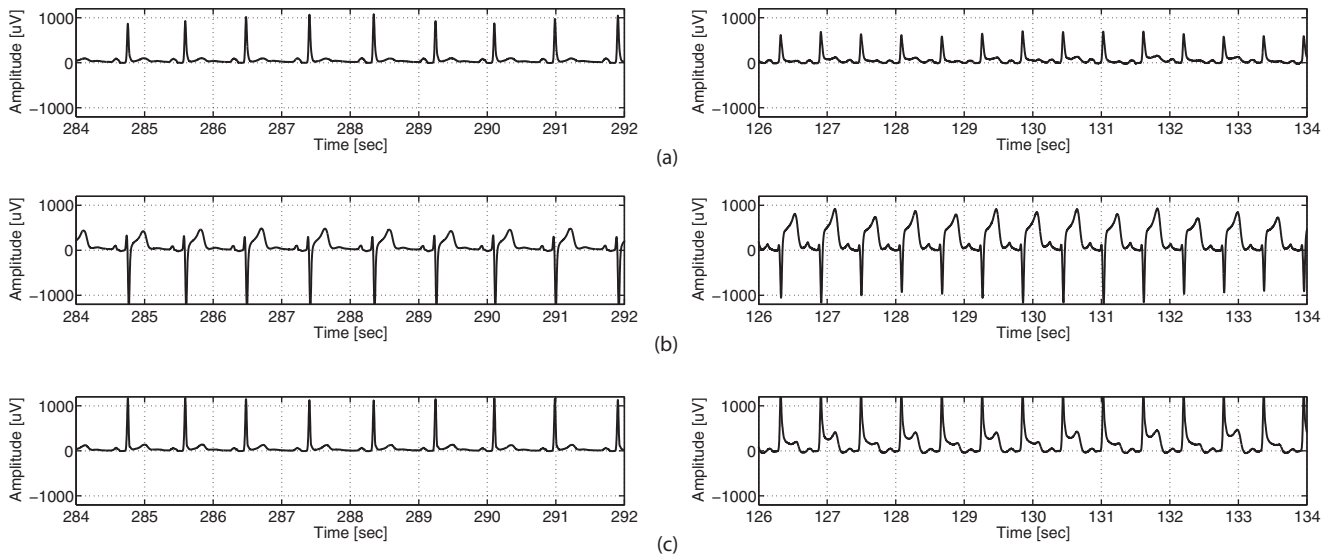
$$TSV = \left. \frac{\text{Spectral Energy} > 0cpb}{\text{Total Spectral Energy}} \right|_{<50\,Hz} \qquad (1)$$

A TSV index near 0 is indicative of a constant T-wave morphology in all the beats included for the analysis. In contrast, if different degrees of variability in the shape of the T-wave are present, the TSV index tends to 1. Beat-to-beat variability appearing at frequencies from 50 Hz to 100 Hz can be considered as noise because no spectral components of the T-waves appear at these frequencies. We evaluated the noise/T-wave amplitude ratio (NTR) in this technique as the ratio between the total spectral energy from noise bandwidth respect to the total spectral energy of the T-wave [16].

$$NTR = \frac{\text{Total Spectral Energy } (50–100)\,Hz}{\text{Total Spectral Energy} < (50)\,Hz}. \qquad (2)$$

2.4. Exclusion criteria of ECG recordings

Those patients who have shown at least one T-waves matrix with less than 64 consecutive T-waves were rejected. The noise ratio was obtained for each matrix and those patients with a NTR greater than 0.30 times were considered noisy and rejected. Using these exclusion criteria, a total population (TP) group of 62 patients in this work were analyzed. Finally, the location of 62 balloon inflations were: LM in 2 patients, LAD in 21 patients, LCx in 12 patients and RCA in 27 patients.

Fig. 1. ECG recordings for a particular patient for both control situation (left panels) and during PCI procedure (right panels). (a) I lead, (b) the v2 lead and (c) X lead.
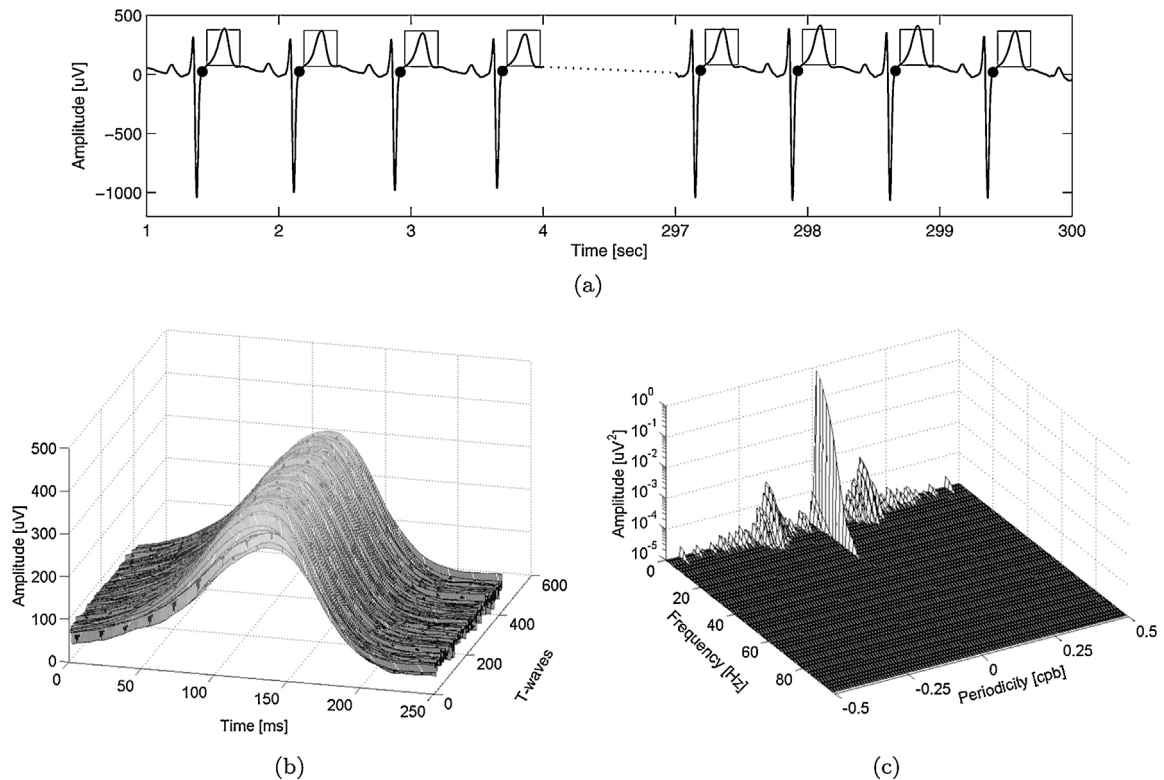
2.5. Statistical analyses

2.5.1. TSV control vs. PCI test

For each patient, $j = 1 \dots J$, and for each lead, $k = 1 \dots K$, the $TSV_k(j)$ was calculated. Also, in order to determine the statistical significance of TSV index between control situation and PCI procedure, the D'Agostino–Pearson normality test was applied with the aim of quantify the discrepancy between the distribution of TSV index an ideal Gaussian distributions. If the TSV index followed a normal distribution, a parametric two-tailed Student's t-test was used. Otherwise, a non-parametric two-sided Mann–Whitney U test was used instead. When p value was < 0.05, differences were considered statistically significant. Moreover, the mean value $\overline{TSV}_k^C$ of all the patients for each lead was obtained for control situation and similarly, $\overline{TSV}_k^P$, was calculated for PCI procedure. The results were presented as mean $\pm$ standard error of the mean (SEM).

2.5.2. RR analysis

To evaluate the influence of the heart rate in the estimation of T-wave variability, we analyzed the RR interval along the total beats

Fig. 2. Representative example of calculation of the TSV index. (a) Consecutive T-waves were acquired through 250 ms windows taken 80 ms after the jitter-corrected QRS endpoint (represented by • markers), to build the assembly of the T-waves matrix as shown in (b). In (c), the TSV was calculated from the two-dimensional Fast Fourier Transform (2D-FFT) applied to the assembly of T-waves matrix.

considered for both control situation and PCI procedure. Mean values of RR intervals for both groups were obtained by averaging the mean RR interval of each subject. A non-parametric two-sided Mann–Whitney U test was used. When p value was <0.05, differences were considered statistically significant. We also evaluated the individual variation of the heart rate by comparing the difference of the RR intervals between the beginning and the end of each study. A Wilcoxon signed rank test was used and a p value <0.05 was considered significant.

2.5.3. Intrasubject variability analysis

To assess the intrasubject variability [22] of TSV index, the difference between TSV index of both control recordings, $c = 1, 2$, was calculated as

$$D_k(j) = TSV_{k,1}(j) - TSV_{k,2}(j) \tag{3}$$

for each patient, $j = 1 \ldots J$, and for each lead, $k = 1 \ldots K$. Then, a statistical Wilcoxon signed rank test was applied to the difference $D_k(j)$ for the TP group and for each lead, with the aim to evaluate the next hypothesis:

- H_0: the intrasubject change ($\overline{D}_k$) is zero.
- H_1: the intrasubject change ($\overline{D}_k$) is different to zero.

where the mean value $\overline{D}_k$ for all the patients, $j = 1 \ldots J$, for each lead, $k = 1 \ldots K$, was calculated.

2.5.4. Intersubject variability analysis

To assess the intersubject variability [22] of TSV index, the mean value of both TSV control indexes, $c = 1, 2$, for each patient, $j = 1 \ldots J$, and for each lead, $k = 1 \ldots K$, was calculated as

$$\overline{TSV}_k(j) = \frac{1}{2} \left[TSV_{k,1}(j) + TSV_{k,2}(j) \right] \tag{4}$$

The standard deviation (SD) of $\overline{TSV}_k(j)$ over the TP group was denoted by $\chi_k^{\ddagger}$. Moreover, the SD of the two TSV control indexes for each patient and each lead was denoted as

$$\chi_k^{\leftrightarrow}(j) = \frac{1}{\sqrt{2}} \left| TSV_{k,1}(j) - TSV_{k,2}(j) \right| = \frac{1}{\sqrt{2}} \left| D_k(j) \right| \tag{5}$$

Also, the mean value $\overline{\chi}_k^{\leftrightarrow}$ for all the patients, $j = 1 \ldots J$, for each lead, $k = 1 \ldots K$, was calculated. A statistical Wilcoxon signed rank test was applied to compare the intrasubject variability $\chi_k^{\leftrightarrow}(j)$ with the intersubject variability of the total population $\chi_k^{\ddagger}$.

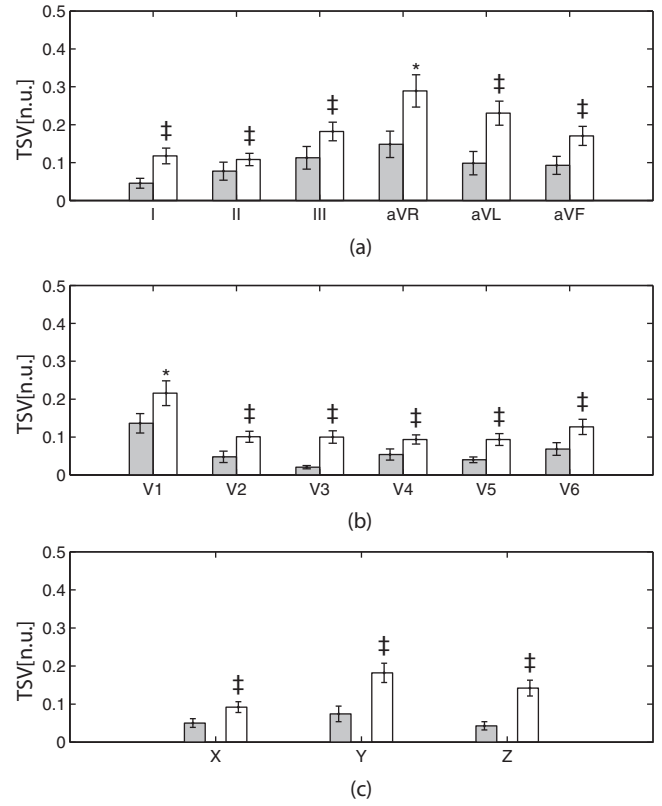### 2.6. Relative change of TSV index

The relative change

$$\mathcal{R}_k = \frac{\overline{TSV}_k^P}{\overline{TSV}_k^C} \tag{6}$$

for each lead, $k = 1 \ldots K$, expressed in times, was calculated. The ECG leads were separated into three groups, being them: (FR) frontal, (PR) precordial and (OR) orthogonal group of leads.

3. Results

3.1. TSV index variation for both control situation and PCI groups

From a TP group subject to balloon inflation procedure in one main coronary artery for each lead, the $TSV_k(j)$ was calculated during control situation and PCI procedure. A non-parametric two-sided Mann–Whitney U test was used. It can be observed that, for TP group, the $\overline{TSV}_k^P$ compared against $\overline{TSV}_k^C$ was statistically significant for all the leads, as shown in Fig. 3. It can be observed in Table 1

Fig. 3. Bar graph showing control (gray bars) and PCI procedure (white bars) TSV indexes for the total population (TP) group, expressed in non-units as *mean* $\pm$ *SEM* ($\overline{TSV}_k \pm$ SEM {TSV_k}) for each lead. (a) The frontal leads, (b) the precordial leads and (c) orthogonal leads. $^*p < 0.05$ and $\ddagger p < 0.0001$.

the $\mathcal{R}_k$ for the TP group, which increased up to almost 2.5 times in lead I for FR, 5 times in lead v3 for PR and 3.5 times in lead Z for OR group of leads.

Additionally, considering the occlusion sites, it can be observed in Table 1 that the greatest values of $\mathcal{R}_k$ for LAD occlusion site were found in lead I for FR, lead v3 for PR and lead X for OR group of leads. With respect to LCx oclussion site, the greatest values of $\mathcal{R}_k$ were found in lead v3 for PR and lead Z for OR group of leads. Also, for RCA occlusion site, the greatest values of $\mathcal{R}_k$ were found in lead aVL for FR, lead v3 for PR and lead Z for OR group of leads. Complementary, Table 1 presents statistical significant differences of the TSV index between control situation and PCI procedure for the analyzed groups of patients (TP, LAD, LCx and RCA) and for each group of leads (FR, PR and OR).

Finally, we have evaluated the NTR in control and PCI procedure and we have not found statistical differences between both groups.

3.2. Evaluation of the RR interval

The RR interval (mean $\pm$ SEM) showed significant differences between control situation and PCI procedure (888 ± 18 ms vs. 812 ± 19 ms). The difference of the individual variation of the heart rate (mean $\pm$ SEM) showed no significant differences (NS) during control situation (1 ± 3 ms), and during PCI procedure (11 ± 11 ms).

3.3. Intrasubject variability of TSV index variation

The low-intrasubject variability of TSV index variation was confirmed by the result of the statistical test applied to $D_k(j)$, which is described in Section 2.5.3. In all leads, except to aVR, aVL and v2, the hypothesis H_0 for $\overline{D}_k$ was accepted. See Fig. 4.

Table 1
Relative changes, expressed in times, for the total population (TP) group and for each oclussion site (LAD, LCx and RCA), separated by the three group of leads: Frontal (FR), Precordial (PR) and Ortoghonal (OR).
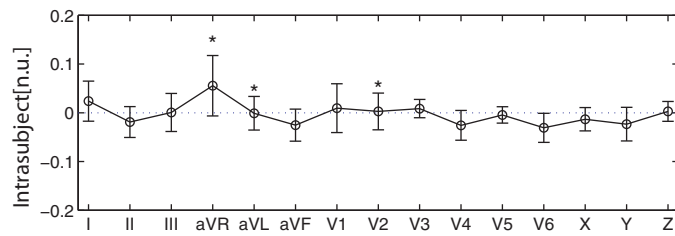
	FR leads						PR leads						OR leads		
	$\mathcal{R}_I$	$\mathcal{R}_{II}$	$\mathcal{R}_{III}$	$\mathcal{R}_{aVR}$	$\mathcal{R}_{aVL}$	$\mathcal{R}_{aVF}$	$\mathcal{R}_{v1}$	$\mathcal{R}_{v2}$	$\mathcal{R}_{v3}$	$\mathcal{R}_{v4}$	$\mathcal{R}_{v5}$	$\mathcal{R}_{v6}$	$\mathcal{R}_X$	$\mathcal{R}_Y$	$\mathcal{R}_Z$
TP	2.59‡	1.40‡	1.62‡	1.95*	2.34‡	1.84‡	1.58*	2.11‡	4.87‡	1.74‡	2.34‡	1.85‡	1.83‡	2.45‡	3.31‡
LAD	4.23*	1.99‡	2.34*	1.68*	2.09*	2.59‡	1.30NS	3.03‡	3.80‡	1.21*	2.27*	2.35*	2.95*	2.86‡	1.99*
LCx	3.58NS	0.74NS	1.17NS	1.21NS	1.20NS	0.77NS	1.77NS	1.90*	5.61*	3.22*	1.89*	1.13NS	2.40*	0.83NS	4.41*
RCA	1.89*	1.42*	1.51*	3.52*	5.72‡	2.08*	2.57*	1.36‡	5.35‡	1.59*	2.61*	2.06*	1.32*	4.75*	6.34‡

Indicating the statistical significant differences between control and PCI procedure of TSV indexes.

 * $p < 0.05$.
 ‡ $p < 0.0001$.
 NS Non significant.

Fig. 4. Figure shows intrasubject variability of TSV index expressed in non-units as $mean \pm SEM$ ($\overline{D}_k \pm \mathrm{SEM}\{D_k\}$) for each lead. * $p < 0.05$.

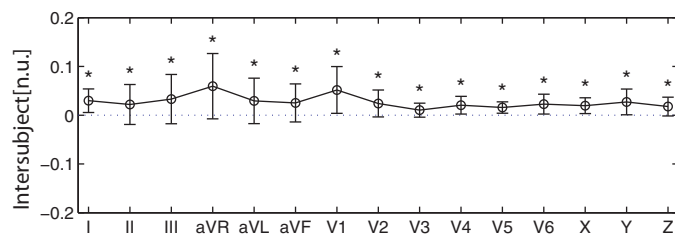### 3.4. Intersubject varability of TSV index variation

The intersubject variability of TSV index was obtained in Section 2.5.4. In all leads, the statistical test showed that the differences between the SD of each control, $\chi_k^{\leftrightarrow}(j)$, and SD of the total population, $\chi_k^{\ddagger}$, were highly significant, $p < 0.05$, being $\chi_k^{\ddagger} > \overline{\chi}_k^{\leftrightarrow}$ in all cases. The intersubject variability of how the SD of the TSV index at resting state during control vary within the total population is showed in Fig. 5.

4. Discussion

In the present work, we analyzed beat-to-beat repolarization variability in the 12 standard ECG leads and in the orthogonal X, Y and Z leads during complete coronary occlusion produced by balloon inflation. In the TP group analysis we observed that $\overline{TSV}_k^P$ compared against $\overline{TSV}_k^C$ was statistically significant for all the ECG leads. This finding suggests that TSV index result could not be strongly dependent to the ECG lead where it was calculated. However, in a more exhaustive analysis of TSV index, considering the different occlusion sites, we found preferential ECG leads to quantify the beat-to-beat repolarization variability.

When we analyzed the PR group of leads in Table 1, we have observed that lead v3 have shown the maximmum value of $\mathcal{R}_k$, for the TP ($p < 0.0001$), LAD ($p < 0.0001$), LCx ($p < 0.05$) and RCA

Fig. 5. Figure shows intersubject variability of TSV index expressed in non-units as $mean \pm SEM$ ($\overline{\chi}_k^{\leftrightarrow} \pm \mathrm{SEM}\{\chi_k^{\ddagger}\}$) for each lead. *$p < 0.05$.
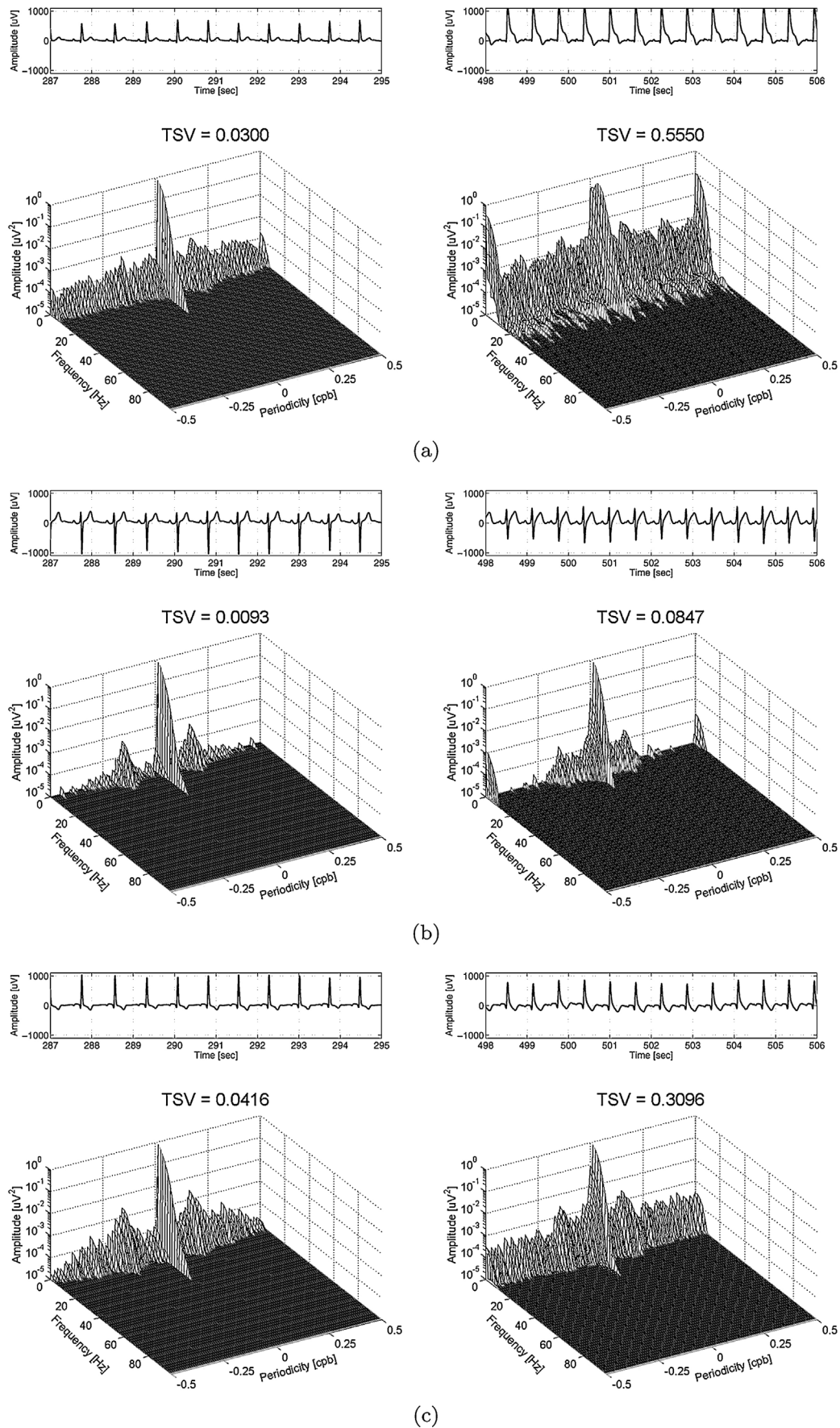
($p < 0.0001$) groups. In our previous work, we analyzed the TSV index in a single precordial lead, located close to v2 and v3, where it was exhibited the larger positive T-wave, before and after occluding the LAD coronary artery [16]. The present results were consistent with the precordial ECG lead location used in Valverde et al. [16]. However, when we considering the FR, PR and OR groups of leads, the greatest values of $\mathcal{R}_k$ were found in lead v3 for TP and LCx groups, lead I for LAD ($p < 0.05$) group and lead Z for RCA ($p < 0.0001$) group. These results could suggest that there is a preferential ECG lead to analyze the TSV index depending on the artery occlusion site. Moreover, LCx occlusion did not produce statistically significant in the TSV indexes for FR group of leads, while LAD and RCA occlusions very well captured the beat-to-beat variability during acute myocardial ischemia in FR group of leads.

Analysis of the RR interval showed to be significant shorter in PCI procedure, but no variation of this parameter was found during each individual study. This contribute to shown the lack of influence of the heart rate in ventricular repolarization variability for this work.

Analysis of intrasubject TSV index variability in different ECG control recordings showed that this index has high stability for each patient in all ECG leads, excepts for aVR, aVL and v2 leads, thus giving reliable reference for the evaluation of beat-to-beat repolarization variability during acute myocardial ischemia. However, the intersubject TSV index variability is significantly larger in all ECG leads, being necessary to propose a normalization criteria of the TSV index in order to not have an intersubject dependence.

Previously, several studies reported the presence of T-wave alternant (TWA) during PCI procedure, either in ECG surface [23–29] or in intracoronary ECG [26–28]. In Fig. 6 it can be observed a patient with TWA expressed by the presence of an increased power spectrum lobes at ± 0.5 cpb in right panels with respect to the control situation in the left panels. Also, this example shows an increment of the power spectrum at all the periodicites except to 0 cpb, resulting in a greater TSV index during PCI procedure respect to control situation. TSV index extend the concept of TWA to detect variations at all periodicities and not only at every alternate cardiac beat, that is, a periodicity of ± 0.5 cpb.

We consider that PCI procedure provides a good model to study the electrophysiological changes during acute transmural ischemia [30]. The sudden complete coronary occlusion induced by balloon inflation allows the study of the acute ischemic process. Additionally, PCI procedure supplies valuable information about spatio-temporal features of ischemia process [31]. Finally, the ischemic regions could act like barriers to the activation and recovering of APD favouring division or fractionation of the wavefronts. This phenomena could produce different patterns of activation and recovery in successive beats, giving a plausible explanation for the beat-to-beat changes in the T-wave, expressed as an increment of the TSV index.

Fig. 6. Power spectrum amplitude of the 2D-FFT represented in a logarithmic scale for a particular patient, including a portion of their associated ECG records. (a) Control (left panel) and PCI procedure (right panel) in aVF lead. In (b), it can be observed control (left panel) and PCI procedure (right panel) for v3 lead. Also, (c) Control (left panel) and PCI procedure (right panel) for Z lead.

5. Study limitations

Further clinical trials will be helpful to better assess the accuracy of the TSV index in identifying patients with different degrees of acute ischemia during angioplasty for different occlusion sites. The 2D-FFT does not suppress noise, in consequence, reliable results depend on a low noise/T-wave amplitude ratio. Due to a high inter-subject TSV index variability, a normalization method is needed.

6. Conclusions

In this study we have observed that the proposed TSV index could be used as a robust method to monitor patients undergoing PCI procedure and during ambulatory ECG recordings. It provides additional information, assessing on the changes of T-wave beat-to-beat morphology, to that supplied by other conventional parameters such as computing ST-segment deviation.

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