Analysis of vectorcardiographic dynamic changes in patients with acute myocardial ischemia

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Abstract. This work evaluates the vectorcardiographic dynamic changes in ischemic patients before and during Percutaneous Transluminal Coronary Angioplasty (PTCA). Four vectorcardiographic parameters were computed in 51 ischemic and 52 healthy subjects with the objective of assessing the differences between both groups: ST Vector Magnitude Area (ST_{VMa}), T Vector Magnitude Area (T_{VMa}), ST Vector Difference (ST_{VD}), and T Vector Difference (T_{VD}). The conventional ST-Change Vector Magnitude (STC_{VM}) and Spatial Ventricular Gradient (SVG) were also calculated. Results indicate that the most of them show significant differences between healthy and ischemic subjects. Since, the statistical minute-by-minute PTCA comparison against a healthy population shows that ischemic patients monitoring reached values of Sensitivity = **99.5**% and Specificity = **99.4%,** when ST_{VD}, T_{VD} and *SVG* were used in the classification. In conclusion the sensitivity and specificity for acute ischemia monitoring could be increase with the used of only three vectorcardiographic parameters.

1. Introduction

Myocardial ischemia is caused by a decompensation between the oxygen supply and demand; it is frequently associated with coronary atherosclerosis. The temporary occlusion of a coronary artery derives in a reversible ischemia, while a prolonged obstruction leads to myocardial infarction with serious consequences, such as malignant arrhythmias, heart failure and/or sudden cardiac death. Percutaneous Transluminal Coronary Angioplasty (PTCA) is a therapeutic procedure used to reestablish blood flow in narrowed arteries. Such procedure provides an attractive opportunity to study myocardial changes due to lack of coronary patency during its initial minutes [1]. Shortly after the beginning of balloon inflation, some changes can be detected in the electrocardiogram (ECG), such as ST-segment deviation and T-wave modifications, due to alterations in the ventricular repolarization process [2]. Several studies have demonstrated that ventricular depolarization is also modified during acute myocardial ischemia induced by PTCA [3-4]. In this context, other conventional index that

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provides information on the cardiac conduction system operation and on the ventricular action potential duration heterogeneity is the Spatial Ventricular Gradient (SVG) [5]. ter Haar *et al*. have reported that this gradient, in addition to ST analysis, has a potential role in detecting ischemia [6].

Within the vectorcardiography framework, the momentary cardiac electrical activity is representable by a single vector in the Euclidian space, i.e., the heart vector, and the VCG precisely describes both components, magnitude and direction, as time proceeds. Several studies have proposed its use for evaluating cardiac changes during myocardial ischemia or infarction. In a recent work, Hasan *et al*. concluded that vectorcardiographic analysis of beat-to-beat variability in ventricular depolarization and repolarization may provide markers of electrical instability in patients with myocardial infarction [7]. Eriksson used ST_{VM}, ST-Change-vector magnitude (STC_{VM}) and QRS_{VD} monitoring to give valuable prognostic information in cases of unstable angina and acute myocardial infarction, and concluded that vectorcardiography monitoring may identify myocardial reperfusion at an early stage [8]. Jensen *et al.* proposed STC_{VM}= 0.05mV as the best criterion for the detection of myocardial ischemia in VCG studies that monitor coronary angioplasty [9].

Dellborg *et al.* demonstrated that monitoring myocardial ischemia with dynamic computerized continuous vectorcardiography (c-VCG) seems to be more efficient than Holter monitoring and may have a higher sensitivity [10]. Additionally, c-VCG has a full real-time capacity, so allowing monitoring over prolonged periods, while the results are immediately available without time-consuming analysis. Besides, Perez Riera *et al.* showed better specificity, sensitivity and accuracy of the computerized VCG when compared with conventional ECG in several cardiac pathologies [11]. Often, the advantage of the VCG is due to the constancy of the time relations between leads, while conversely, such relationships are lost in separate scalar lead analysis.

In a previous work, we analyzed a set of VCG parameters computed in the cardiac depolarization phase in ischemic patients [12]. The aim of this study was to differentiate a group of ischemic subjects from a population of healthy ones by VCG analysis of the ventricular depolarization-repolarization process. For that matter, four novel vectorcardiographic parameters (computed on repolarization segments and waves) and three conventional indexes (computed on depolarization-repolarization segments and waves) were evaluated.

As hypothesis, we state that the balloon occlusion modifies the morphology of the ST-T and, thereafter, its parameters can be used to characterize and monitoring the acute myocardial ischemia. To prove this, we evaluated the proposed and the conventional parameters in the classification scheme.

2. Materials

The Raw clinical records were extracted from the PTB diagnostic ECG and STAFF-III databases.

The first one contains the ECG records of 52 healthy subjects (39 men, mean age 42 +/- 14 yrs, and 13 women, mean age 48 +/- 19 yrs). The ECGs in this collection were obtained by Physikalisch-Technische Bundesanstalt (PTB); the National Metrology Institute of Germany. Each record includes 15 simultaneously measured signals: the conventional 12 leads (I, II, III, aVR, aVL, aVF, V1-V6) together with the 3-Frank lead-ECGs (X, Y, Z). Each signal was digitized at 1000 Hz, with 16 bits of amplitude resolution [13].

The second database consists of 51 ischemic patients (33 males, mean age 61 +/- 13 yrs and 18 women, mean age 60 +/- 10 yrs) admitted to the Charleston Area Medical Center in West Virginia, receiving elective PTCA in one of the major coronary arteries (STAFF-III study). The study was approved by the local investigation review board, and informed consent was obtained from each patient before enrollment [4]. The mean occlusion period was 5 min 7s. The locations of the 51 dilations were: Left Anterior Descending Artery in 11 patients, Right Coronary Artery in 14 patients and Left Circumflex Artery in 26 patients. We excluded patients with ECG signal loss during acquisition or with occlusion period less than 4 min 30 sec.

Nine standard leads (V1-V6, I, II, III) were recorded in the study using equipment by Siemens-Elena AB (Solna, Sweden), digitized at sampling rate of 1000 Hz and 0.6 µV amplitude resolution. Synthesized orthogonal X, Y and Z leads were obtained by the Kors transform [14]. A recent study

has demonstrated that Kors synthesis matrix provides a better estimation of Frank leads than the Inverse Dower transform in ischemic patients [15].

For each patient, two ECG records were obtained. One of them (denoted as before-PTCA Record) was acquired continuously at rest in the supine position prior to angioplasty, and the other (denoted as during-PTCA Record) was obtained during the PTCA procedure.

3. Methods

Figure 1 illustrates a block diagram of the different stages of the proposed analysis.
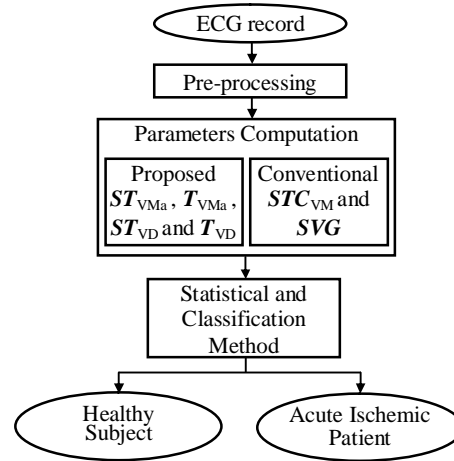

Figure 1. Proposed Analysis General Diagram.

3.1. Preprocessing

First, all ECG records were preprocessed with a band-pass filter (Butterworth, 4th order, 0.2–100 Hz, bidirectional) to reduce low and high frequency noise and a notch filter (Butterworth, 2th order, 50/60 Hz, bidirectional) to minimize the power line interference. A cubic spline interpolation filter was used to attenuate ECG baseline drifts and respiratory artifacts. Thereafter, the QRS complexes, T waves and their endpoints were detected in each ECG record using a wavelet-based technique [16]. Beats with a RMS noise level >40 µV (measured within a 40 ms window located at 2/3 of the RR interval) were excluded. In addition, ectopic beats were also eliminated by comparing incoming signals against a previously established template with the use of a cross-correlation technique. Additionally, with this technique, we also make the time alignment of beats, required to obtain an average beat, used in the parameters computation [17]. In this study, a visually low-noise normal beat extracted from the ECG record was selected as template (or reference) beat.

3.2. Parameters Computation

Four VCG parameters and two conventional indexes were computed for each detected beat.

- ST Vector Magnitude Area (ST_{VMa}): It is defined as the magnitude of the vector composed by the X, Y and Z Area between the amplitude of the ECG signal interval from each J-point to J-point+80ms (ST-segment) and the isoelectric level, that is,

$$ST_{VMa} = \left(aST_X^2 + aST_Y^2 + aST_Z^2 \right)^{1/2} \tag{1}$$

This parameters is, a modification of the STC_{VM} widely used in the monitoring of cardiac ischemia [7, 8], The principal differences is STC_{VM} is evaluated at the one point on de signal (usually j-point, or j-point+60ms), by the contrast the proposed ST_{VMa} is computed during all ST segment (figure 2a).

- T Vector Magnitude Area (T_{VMa}): It is defined as the magnitude of the vector composed by the X, Y and Z Area between the amplitude of the ECG signal at interval of each T wave and the isoelectric level (figure 2b), that is,

$$T_{VMa} = \left(aT_X^2 + aT_Y^2 + aT_Z^2 \right)^{1/2} \tag{2}$$

- ST-T-Vector Difference ($ST\text{-}T_{VD}$): It was defined as the difference area between the ECG signal at the current ST-T intervals (from each J-point to the T wave ends) and the reference of ECG signal (at ST-T intervals too) evaluated at the first 30s of each ECG record, that is,

$$ST\text{-}T_{VD} = \left(dA_X^2 + dA_Y^2 + dA_Z^2 \right)^{1/2} \tag{3}$$

The objective of this parameter is estimated all changes produced during left Ventricular repolarization (figure 2-c).

- T-Vector Difference (T_{VD}): It was defined as the difference area between the ECG signal at the current T wave intervals and the reference of ECG signal (at T intervals too) evaluated at the first 30s of each ECG record, that is,

$$T_{VD} = \left(dT_X^2 + dT_Y^2 + dT_Z^2 \right)^{1/2} \tag{4}$$

The objective of this parameter is estimated all changes produced in the T wave (figure 2-d).

- ST-Change Vector Magnitude (STC_{VM}): The ST-vector is composed of the (X, Y and Z) ST-segment deviations from the isoelectric level, measured as the ECG signal amplitude at the J-point (Fig. 2-e); it is a widely used parameter when monitoring cardiac ischemia [7,8]. This vector is the difference between the ST-vector of the current beat and the averaged beat evaluated at the first 30s of each ECG record, that is,

$$STC_{VMi} = \left[\left(ST_{Xi} - ST_{Xr} \right)^2 + \left(ST_{Yi} - ST_{Yr} \right)^2 + \left(ST_{Zi} - ST_{Zr} \right)^2 \right]^{1/2} \tag{5}$$

where r denotes the reference beat, i is the current beat, with $i = 1, ..., N$, and N stands for the total number of analysed beats(Fig. 2-b).

- Spatial Ventricular Gradient (SVG): It is defined as the vectorial QRS-T integral, that is:

$$SVG = \left[\left(aQRS_X + aT_X \right)^2 + \left(aQRS_Y + aT_Y \right)^2 + \left(aQRS_Z + aT_Z \right)^2 \right]^{1/2} \tag{6}$$

where, $aQRS_X$, $aQRS_Y$, $aQRS_Z$ and aT_X, aT_Y, aT_Z are the QRS-complex and T-wave areas on the orthogonal leads, respectively, and all having units of mV·ms. Then, *SVG* has the same units. Unlike most other ECG parameters, the *SVG* is not influenced by changes in ventricular conduction pattern; it only changes if the distribution of the ventricular action potential morphology and/or duration is altered [6].

3.3. Statistical and Classification Methods

All parameters were computed for each detected sinus beat in every ECG record. First, we analysed the normality of these values using the D'Agostino-Pearson's test with the aim of quantifying the discrepancy between the parameters' distribution and the Gaussian distribution. It has been observed that the underlying variables' distribution is non-Gaussian. Afterwards, comparisons between healthy (mean of each parameter values of all ECG records) and ischemic subjects (parameters computed before and during PTCA, the last one grouped at 1 min intervals) were made using the non-parametric Mann-Whitney test.
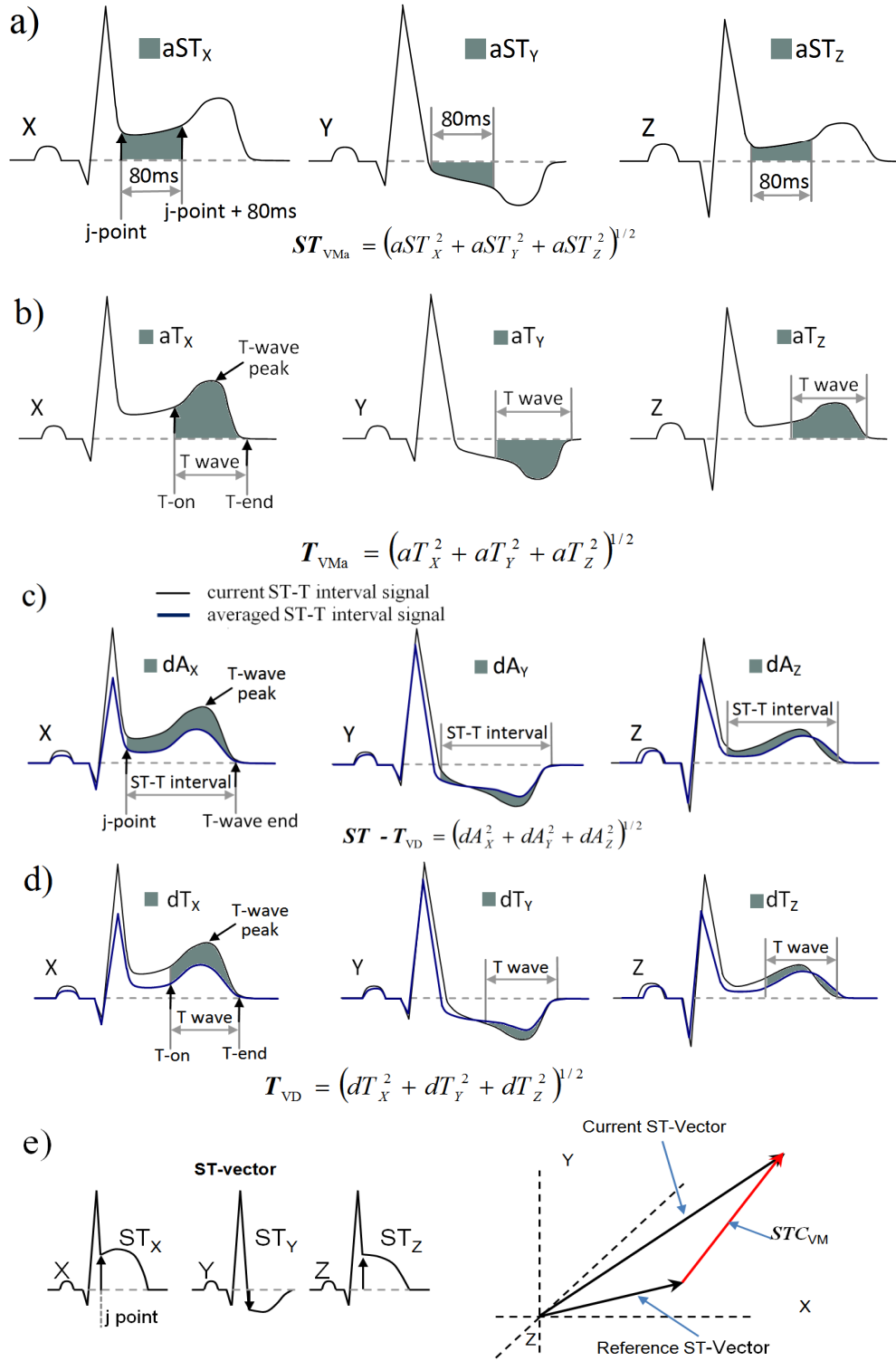
a)

$$ST_{VMa} = \left(aST_X^2 + aST_Y^2 + aST_Z^2\right)^{1/2}$$

b)

$$T_{VMa} = \left(aT_X^2 + aT_Y^2 + aT_Z^2\right)^{1/2}$$

c)

— current ST-T interval signal
— averaged ST-T interval signal

$$ST\text{-}T_{VD} = \left(dA_X^2 + dA_Y^2 + dA_Z^2\right)^{1/2}$$

d)

$$T_{VD} = \left(dT_X^2 + dT_Y^2 + dT_Z^2\right)^{1/2}$$

e)

$$STC_{VM} = \left[\left(ST_{Xi} - ST_{Xr}\right)^2 + \left(ST_{Yi} - ST_{Yr}\right)^2 + \left(ST_{Zi} - ST_{Zr}\right)^2\right]^{1/2}; \quad i = 1 - N$$

Figure 2. Vectorcardiographic Parameters computation.

The mean values of each parameter across the entire record for healthy subjects, and at 1 min interval for ischemic patients, were calculated. These values were used as inputs to a classifier based on *Linear Discriminant Analysis (LDA)* to distinguish (or separating out) ischemic patients from healthy subjects. Basically, the LDA classifier is a linear combination of variables, as follows. The LDA classifier is a linear combination of variables, as follows,

$$y = \mu_0 + \mu_1 X_1 + \mu_2 X_2 + \ldots\ldots + \mu_p X_p \tag{7}$$

where y is the output value of the discriminant function; μ_n (with $n=1,\ldots, p$) stand for the coefficients of the discriminate function; X_n are the discriminate variables (QRS-loop and/or ST-T parameters) and p is the number of variables in the analysis.

The resulting discriminant function can be used to assign each ECG record to a particular class, ischemic patient or healthy subject, based on its values of discriminate variables. The model coefficients are estimated with a subset of ECG records for which the group is known. This subset of observations is sometimes referred to as the **training subset** (we used the 70% of ECG records of both populations). In order to validate the model, this discriminant function was used to predict the group of another different subset (referred to as **validation subset**) of the ECG records (we used the remaining 30% of the ECG records).

To evaluate the performance of the LDA classifier, we computed the **Receiver Operating Characteristic** (ROC). It plots the Sensitivity (Se) against the 1-Specificity (Sp) values for the different possible cut-off points (cut-off values were swept between -5 and 5 in 0.01 steps) of the discriminant function. Then, the optimal cut-off point in the ROC curve was computed as the point nearest the top left-hand corner. This selection maximizes the Se and Sp sum, when it is assumed that the 'cost' of a false negative result is the same as that of a false positive one. Finally, the global performance of the classifier was evaluated with the Area Under the ROC Curve (AUC).

4. Results

Figures 3 depict the results of the statistical analysis described in section 3.3.The former, shows the mean and Standard Error of the Mean (SEM) of each computed parameter in healthy and ischemic populations before and during the PTCA procedure. The values marked with * indicate the statistical significance (*p*-value < 0.05).
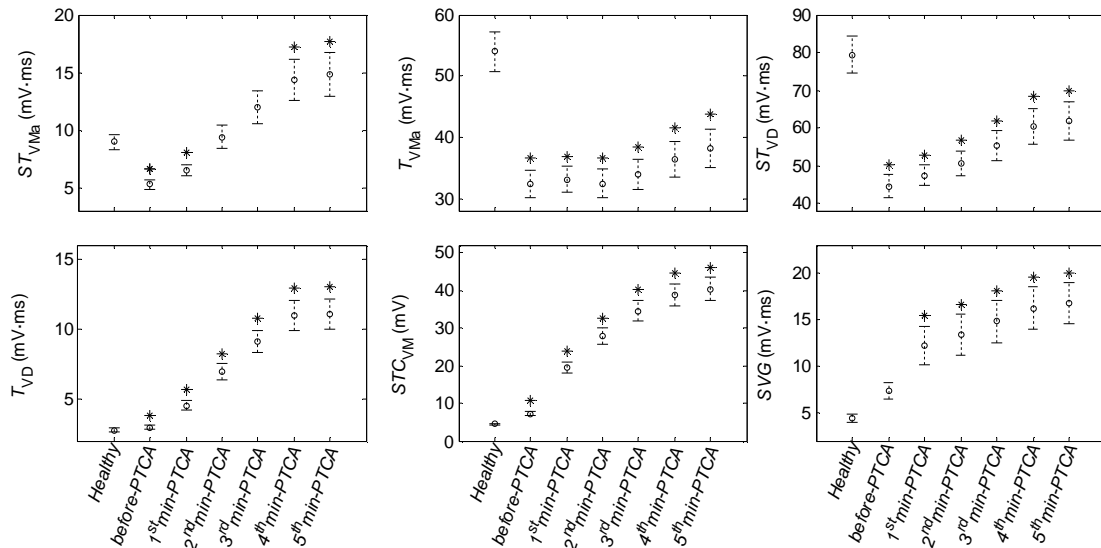

Figure 3. Mean and standard error of the mean of each parameter computed in healthy and acute ischemic subjects (the parameters for the acute ischemic patients were grouped at intervals of 1 min, thereby obtaining 5 groups for each record).
*Denoted statistical significance, p_value< 0.05 (see section 3.3).

Table I show the classification results (Sens and Spec mean values) for each vectorcardiographic parameters studied and for the best combination of them ($ST\text{-}T_{VD}$, T_{VDa} and SVG), before and during PTCA procedure.

Table I: Classification outcomes for each computed index and for the best combination of them

		ST_{VMa}		T_{VMa}		$ST\text{-}T_{VD}$		T_{VDa}		STC_{VM}		SVG		$ST\text{-}T_{VD}$, T_{VDa} and SVG	
		Sens	Spec	Sens	Spec	Sens	Spec	Sens	Spec	Sens	Spec	Sens	Spec	Sens	Spec
before-PTCA		63.93	69.25	82.80	69.75	67.07	69.88	58.07	79.50	71.33	54.50	69.53	81.25	90.07	84.31
during-PTCA	1st min	75.00	50.88	82.67	67.38	88.40	94.19	80.80	83.38	75.07	76.94	68.80	73.75	92.40	93.31
	2nd min	44.53	46.88	75.07	72.69	92.53	96.38	85.07	84.00	83.87	78.63	60.87	81.88	94.60	96.88
	3rd min	53.40	55.06	79.93	70.69	95.07	97.56	86.27	88.88	84.47	81.88	57.27	76.56	96.87	97.56
	4th min	51.87	63.25	78.20	68.69	95.00	97.63	89.00	88.81	88.87	82.00	66.67	61.19	97.60	98.19
	5th min	46.20	75.81	72.60	70.56	96.53	98.25	91.13	90.50	87.07	83.50	62.20	63.00	99.53	99.38

Table II shows the Area Under the ROC Curve (AUC), for classification schemes using only one index at a time and using the parameters $ST\text{-}T_{VD}$, T_{VDa} and SVG combined.

Table II Area Under the ROC Curve (AUC) for different classification schemes

		ST_{VMa}	T_{VMa}	$ST\text{-}T_{VD}$	T_{VDa}	STC_{VM}	SVG	$ST\text{-}T_{VD}$, T_{VDa} and SVG
before-PTCA		0.73	0.78	0.76	0.68	0.63	0.83	0.91
during-PTCA	1st min	0.64	0.77	0.95	0.85	0.82	0.81	0.98
	2nd min	0.43	0.78	0.98	0.89	0.89	0.77	0.99
	3rd min	0.55	0.75	0.98	0.91	0.92	0.72	1.00
	4th min	0.62	0.73	0.99	0.92	0.94	0.67	1.00
	5th min	0.61	0.70	0.99	0.93	0.94	0.66	1.00

5. Discussion and Conclusions

Several studies have demonstrated the potential automated vectorcardiographic analysis usefulness to evaluate cardiac changes during ischemia or infarction [5-11]. Furthermore, in [9], Jensen *et al.* compared on-line computerized VCG's derived from 12-lead ECG's, and concluded that the first one is a more sensitive method for detecting myocardial ischemia during coronary angioplasty. However, most of the studies based on VCG use the STC_{VM} and SVG parameters.

Also these two conventional indexes, here in we examined 4 vectorcardiographic parameters computed in the ST-T interval to further describe cardiac dynamic changes during an episode of acute ischemia induced by PTCA.

On the basis of the statistical analysis, it can be observed in figure 3 that all the vectorcardiographic parameters (with same exception: the ST_{VMa} for 2nd and 3rd min during PTCA and SVG before-PTCA) produced significant differences (p-value < 0.05) between healthy and ischemic populations, before and during PTCA. Besides, the four proposed parameters, similar to conventional indexes, tend to gradually increase its mean value during angioplasty. This similar behaviour could be used in a combined analysis to improve monitoring of acute myocardial ischemia.

The discriminant analysis (see Table I) indicates that the vectorcardiographic parameter with the best global performance was $ST\text{-}T_{VD}$, which reached Sen=96.5%, Spec=98.2%, and AUC=0.99.

Moreover, minute-by-minute statistical comparison of the PTCA against a healthy population shows that acute ischemic patients monitoring is greatly enhanced when the parameters $ST\text{-}T_{VD}$, T_{VDa} and SVG are used in the classification, reaching **Sens = 99.5% and Spec = 99.4%**, at the 5th minute of the PTCA. Meanwhile, the best classification using only the conventional STC_{VM} or SVG indexes, reaching values of Sens = 88.9 % and Spec = 82.0% at the 4th minute the occlusion, which are lower

than those reported above. Additionally, the best AUC value (see Table II), using the parameters ST-T_{VD}, T_{VDa} and SVG is $AUC = 1.00$, after the 3th minute of the balloon inflation. Thus, it indicates high effectiveness for the proposed classification technique. This AUC value is considered of high accuracy in diagnostic tests [18].

In conclusion: The proposed technique based on vectorcardiographic study could be used in addition to the conventional ST-T analysis for a better monitoring of ischemic patients. From the clinical point of view, the most important future application would be the ambulatory monitoring of ischemic patients in Holter or stress tests studies.

Reference

[1]   Engblom H and Strauss DG 2011 Electrocardiography of ischemic heart disease. In: *Multimodal cardiovascular imaging: Principles and clinical applications,* Edited by Pahlm O and Wagner G, 1sted, (New York, USA: McGraw-Hill Medical, c2011) 128-145.

[2]   Bayés de Luna A 1999 Electrocardiografía Clínica, 1st Ed. (Barcelona, Spain: ESPAXS S.A.)

[3]   Surawicz B, Orr CM, Hermiller JB, Bell KD, Pinto RP 1997 QRS changes during percutaneous transluminal coronary angioplasty and their possible mechanisms. *J Am CollCardiol* **30**:452-458.

[4]   Ringborn M, Pettersson J, Persson E, Warren SG, Platonov P, Pahlm O, Wagner GS 2010 Comparison of high-frequency QRS components and ST-segment elevation to detect and quantify acute myocardial ischemia. *J. Electrocardiol* **43**:113–120.

[5]   Draisma HHM, Schalij MJ, van der Wall EE, Swenne CA. Elucidation of the spatial ventricular gradient and its link with dispersion of repolarization. *Heart Rhythm* 2006; 3:1092.

[6]   ter Haar CC, Maan AC, Schalij MJ, Swenne CA 2012 ST and ventricular gradient dynamics during percutaneous transluminal coronary angioplasty. *Computing in Cardiology* **39**:341-345.

[7]   Hasan MA, Abbott D, Baumert M. 2012 Beat-to-beat vectorcardiographic analysis of ventricular depolarization and repolarization in myocardial infarction. *PLoS ONE* **7**(11) :e49489.doi:10.1371/journal.pone.0049489

[8]   Eriksson SV 1999 Vectorcardiography: a tool for non-invasive detection of reperfusion and reocclusion. *Thromb Haemost* **82**:64-67.

[9]   Jensen SM, Johansson G, Osterman G, Reiz S, Näslund U 1994 On-line computerized vectorcardiography monitoring of myocardial ischemia during coronary angioplasty: comparison with 12-lead electrocardiography. *Coronary Artery Dis* **5**:507-514.

[10]   Dellborg M, Malmberg K, Ryden L, Svensson AM, Swedberg K 1995 Dynamic on-line vectorcardiography improves and simplifies in-hospital ischemia monitoring of patients with unstable angina. *J Am Coll Cardiol* **26**:1501-1507.

[11]   Pérez Riera AR, Uchida AH, Ferreira Filho C, Meneghini A, Ferreira C, Schapacknik E, Dubner S, Moffa P 2007 Significance of vectorcardiogram in the cardiological diagnosis of the 21st century. *Clin Cardiol* **30**:319-323.

[12]   Correa R, Arini P, Valentinuzzi M, Laciar E 2013 Novel set of vectorcardiographic parameters for the identification of ischemic patients. *Med EngPhys* **35**:16-22.

[13]   Bousseljot R, Kreiseler D, Schnabel A 1995 Nutzung der EKG-Signal daten bank CARDIODAT der PTB über das Internet. *Biomedizinische Technik, Band 40, Ergänzungsband* **1**:317.

[14]   Kors JA, van Herpen G, Sittig AC, van Bemmel JH 1990 Reconstruction of the Frank vectorcardiogram from standard electrocardiographic leads: diagnostic comparison of different methods. *Eur Heart J* **11**:1083-1092.

[15]   Man S, Algra AM, Schreurs CA, Borleffs CJ, Scherptong RW, van Erven L, van der Wall E, Cannegieter SC, Schalij MJ, Swenne CA 2011 Influence of the vectorcardiogram synthesis matrix on the power of the electrocardiogram-derived spatial QRS-T angle to predict arrhythmias in patients with ischemic heart disease and systolic left ventricular dysfunction. *J of Electrocardiol* **44**:410-415.

[16]   Martinez JP, Almeida R, Olmos S, Rocha AP, Laguna P 2004 A wavelet-based ECG delineator: Evaluation on standard databases. *IEEE Trans Biomed Eng* **51**(4):570-581.

[17]   Laciar E, Jané R, Brooks DH 2003 Improved Alignment Method for Noisy High Resolution ECG and Holter Records using Multi-Scale Cross-Correlation. *IEEE Trans Biomed Eng* **50**(3):344-353.

[18]   Swets JA 1988 Measuring the accuracy of diagnostic systems. *Science* 240:1285-1293.