Depolarization Changes During Acute Myocardial Ischemia by Evaluation of QRS Slopes: Standard Lead and Vectorial Approach

Daniel Romero*, Michael Ringborn, Pablo Laguna, *Senior Member, IEEE*, Olle Pahlm, and Esther Pueyo

***Abstract*—Diagnosis and risk stratification of patients with acute coronary syndromes can be improved by adding information from the depolarization phase (QRS complex) to the conventionally used ST-T segment changes. In this study, ischemia-induced changes in the main three slopes of the QRS complex, upward ($\mathcal{I}_{\mathrm{US}}$) and downward ($\mathcal{I}_{\mathrm{DS}}$) slopes of the R wave as well as the upward ($\mathcal{I}_{\mathrm{TS}}$) slope of the terminal S wave, were evaluated as to represent a robust measure of pathological changes within the depolarization phase. From ECG recordings both in a resting state (control recordings) and during percutaneous coronary intervention (PCI)-induced transmural ischemia, we developed a method for quantification of $\mathcal{I}_{\mathrm{US}}$, $\mathcal{I}_{\mathrm{DS}}$, and $\mathcal{I}_{\mathrm{TS}}$ that incorporates dynamic ECG normalization so as to improve the sensitivity in the detection of ischemia-induced changes. The same method was also applied on leads obtained by projection of QRS loops onto their dominant directions. We show that $\mathcal{I}_{\mathrm{US}}$, $\mathcal{I}_{\mathrm{DS}}$, and $\mathcal{I}_{\mathrm{TS}}$ present high stability in the resting state, thus providing a stable reference for ischemia characterization. Maximum relative factors of change ($\mathcal{R}_{\mathcal{I}}$) during PCI were found in leads derived from the QRS loop, reaching 10.5 and 13.7 times their normal variations in the control for $\mathcal{I}_{\mathrm{US}}$ and $\mathcal{I}_{\mathrm{DS}}$, respectively. For standard leads, the relative factors of change were 6.01 and 9.31. The $\mathcal{I}_{\mathrm{TS}}$ index presented a similar behavior to that of $\mathcal{I}_{\mathrm{DS}}$. The timing for the occurrence of significant changes in $\mathcal{I}_{\mathrm{US}}$ and $\mathcal{I}_{\mathrm{DS}}$ varied with lead, ranging from 30 s to 2 min after initiation of coronary occlusion. In the present ischemia model, relative $\mathcal{I}_{\mathrm{DS}}$ changes were smaller than ST changes in most leads, however with only modest correlation between the two indices, suggesting they present different information about the ischemic process. We conclude that QRS slopes offer a robust tool for evaluating depolarization changes during myocardial ischemia.**

***Index Terms*—Depolarization, ischemia, percutaneous coronary intervention (PCI), QRS slopes.**

I. Introduction

EARLY diagnosis of patients with acute myocardial ischemia is essential to optimize treatment, and hence, clinical outcome. In addition to patient history and clinical examination, the standard 12-lead ECG is the most important tool in the acute evaluation, both in the prehospital setting and in the emergency room. By convention, changes in the repolarization phase (ST-T) are most widely used to detect acute myocardial ischemia. Changes also occur in the depolarization phase (the QRS complex) of the ECG during acute ischemia that could add information beyond the ST-T analysis. However, these changes have historically been more difficult to characterize and have not come into clinical practice. By optimizing the complete information from the ECG signal, detection and localization of myocardial ischemia as well as proper risk stratification of the patient might enable a better tailored treatment regimen and add to improved short- and long-term prognosis.

Several prior studies have reported changes in the depolarization phase both in humans and animals. These include changes in QRS amplitudes [1]–[3], QRS duration [4], Karhunen–Loève transform derived indices [5], and "distorsion of the end of the QRS complex" [6] in the standard ECG. The latter, in addition to relating to more severe ischemia, also correlates to worse clinical outcome in a large cohort. Changes in high-frequency QRS components of the high-resolution signal-averaged ECG have been reported as well [7]–[9]. These methods have, however, not been implemented clinically. Among various limitations, one is the difficulty of correctly delineating the end of the QRS complex when there is pronounced ST elevation. In recent studies, more reliable methods for characterizing changes in the QRS complex due to both amplitude and duration changes have been proposed [10], [11]. Pueyo *et al.* [11] quantified changes in the QRS complex during myocardial ischemia induced by elective percutaneous coronary intervention (PCI) by measuring the upslope and downslope of the R wave. In this study, the variability of the QRS slopes in the control recording was used as a reference for quantification of the ischemia-induced changes. However, the stability of this reference was not further explored by means of the normal or intraindividual variation within or between different recordings, nor was an analysis performed to properly characterize factors that affect the measurement of

Manuscript received April 13, 2010; revised July 8, 2010; accepted August 22, 2010. Date of publication September 13, 2010; date of current version December 17, 2010. This work was supported by MCyT and FEDER Spain under Projects TEC2010-21703-C03-02 and TEC2010-19410 and in part by the Grupo Consolidado T30, DGA, Spain, and the Lund University Hospital, Sweden. The work of D. Romero was supported by Santander Central Hispano bank and the University of Zaragoza. The work of M. Ringborn was supported by The Southern Region of Healthcare, Lund, Sweden and Blekinge Scientific Council, Sweden. *Asterisk indicates corresponding author.*

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Digital Object Identifier 10.1109/TBME.2010.2076385

the QRS slopes by modulation of the QRS amplitude. Another way to evaluate depolarization changes during ischemia is by projecting the signals into a 3-D vector-based loop derived from the orthogonal ECG leads as in [12] and [13]. Prolonged PCI provides an excellent human model to investigate the electrophysiological changes during the initial minutes of transmural ischemia [5], [7]. During this procedure, a balloon is inserted and inflated inside a coronary artery to induce controlled ischemia due to the balloon occlusion. After deflation, the blood flow is immediately restored. During the PCI, the occlusion site is perfectly defined in space and time, and therefore, allows to study the ischemia-induced changes in both domains.

The aims of this study were to: 1) evaluate the normal variation of the QRS slopes in the standard 12 leads at resting state (control recordings) in a large population, with the purpose of determining reliable limits of significant QRS slope changes due to an ischemic pathophysiological process; 2) apply a normalization procedure to both control and PCI recordings to attenuate low-frequency variation in the slopes and stabilize the slope reference for better quantification of pathophysiologically significant changes; 3) test the performance of this improved method in monitoring QRS slope changes along the dynamic ECG recordings during PCI-induced ischemia on the standard 12-lead ECG and leads derived from the spatial QRS loop; and 4) determine the timing of significant changes during PCI.

II. Materials and Methods

A. Population

The total study population comprised 152 patients, 73 of whom were referred to the Department of Clinical Physiology at Lund University Hospital, Sweden for exercise testing (STRESS dataset). The other 79 patients were taken from the STAFF III dataset, with patients admitted to the Charleston Area Medical Center in West Virginia, for prolonged, elective PCI due to stable angina pectoris [1], [5]. The following inclusion criteria had to be met for both subpopulations: no clinical or ECG evidence of an acute or recent myocardial infarction, no intraventricular conduction delay with QRS duration equal to or more than 120 ms [including left bundle branch block (LBBB) and right bundle branch block (RBBB)], no pacemaker rhythm, low voltage, atrial fibrillation/flutter, or any ventricular rhythm at inclusion (or during the PCI for this subpopulation). We also excluded patients either if they underwent an emergency procedure, or presented signal loss during acquisition.

1) ECG Acquisition: All ECGs were recorded using the same equipment provided by Siemens–Elema AB, Solna, Sweden. Nine standard leads (V1–V6, I, II, and III) were recorded and digitized at a sampling rate of 1 kHz with an amplitude resolution of 0.6 μV. The three augmented leads aVL, -aVR, and aVF were then generated from the limb leads to yield the complete standard 12-lead ECG. For each patient of the two datasets, two control recordings were acquired continuously for 5 min, at rest in supine position prior to the stress test or PCI procedure, respectively, during clinical stable situations, within a time interval of maximum one hour. The electrodes were either retained on the patient between the recordings, or removed and their positions marked, to enable accurate comparisons of the ECG variables.

These control recordings from all 152 subjects were later used for determining the intra and interindividual variation of the QRS slopes.

2) PCI Recordings: In the subset of 79 patients from the STAFF III dataset, another continuous ECG was acquired during the PCI, starting before and ending after balloon inflation and deflation, respectively, for the analysis of QRS slopes during ischemia. The duration of the occlusion ranged from 1 min 30 s to 7 min 17 s (mean 4 min 26 s). The occlusion sites of the PCI procedures were: left anterior descending coronary artery (LAD) in 25 patients, right coronary artery (RCA) in 38 patients, and left circumflex artery (LCX) in 16 patients.

B. Preprocessing

All ECG signals involved in the study were preprocessed before the evaluation of the analyzed indices as follows: 1) QRS complex detection; 2) selection of normal beats according to [14]; 3) baseline drift attenuation via cubic spline interpolation; and 4) wave delineation using a wavelet-based technique [15].

C. QRS Slopes in a Single ECG Lead

To quantify the ischemic QRS changes, the following indices were evaluated for each beat and lead:

1) $\mathcal{I}_{\rm US}$: Upward slope of the R wave.
2) $\mathcal{I}_{\rm DS}$: Downward slope of the R wave.
3) $\mathcal{I}_{\rm TS}$: Upward slope of the S wave (in leads V1–V3).

A three-step procedure was applied to compute the earlier indices. First, the time locations of the Q, R, and S peaks were determined, denoted by $n_{\rm Q}$, $n_{\rm R}$, and $n_{\rm S}$, respectively. Beats for which $n_{\rm R}$ could not be successfully determined were rejected from further analysis. Beats for which the delineator determined a valid $n_{\rm R}$, but was unable to determine $n_{\rm Q}$ or $n_{\rm S}$ due to the absence of the Q or the S waves, a second search was performed to delimit the reference points used in the QRS slopes calculation. For the Q wave, the interval ranging from 2 ms after QRS onset $n_{\rm ON}$, until 2 ms before $n_{\rm R}$ was examined and the time instant associated with the lowest signal amplitude was identified as $n_{\rm Q}$. Analogously, $n_{\rm S}$ was determined from the interval 2 ms after $n_{\rm R}$ until 2 ms prior to QRS offset $n_{\rm OFF}$. It should be noted that the determination of $n_{\rm Q}$, $n_{\rm R}$, and $n_{\rm S}$ is not critical, since they just delimit the interval over which the slope is calculated [11]. Importantly, the $\mathcal{I}_{\rm TS}$ corresponding to the upslope of the S wave, was only computed for leads V1–V3, where the S wave is usually more pronounced. In addition, during more pronounced ischemia, the final part of the QRS complex might get highly distorted, thus making it difficult to delineate the S wave, or it might disappear. In these cases, the measure of the $\mathcal{I}_{\rm TS}$ was discarded.

The second step consisted of determining the time instant of: $n_{\rm U}$ associated with maximum slope of the ECG signal between $n_{\rm Q}$ and $n_{\rm R}$ (global maximum of the ECG signal derivative between $n_{\rm Q}$ and $n_{\rm R}$); $n_{\rm D}$ associated with the minimum slope between $n_{\rm R}$ and $n_{\rm S}$ (global minimum of the ECG signal derivative between $n_{\rm R}$ and $n_{\rm S}$); and finally $n_{\rm T}$, corresponding to the

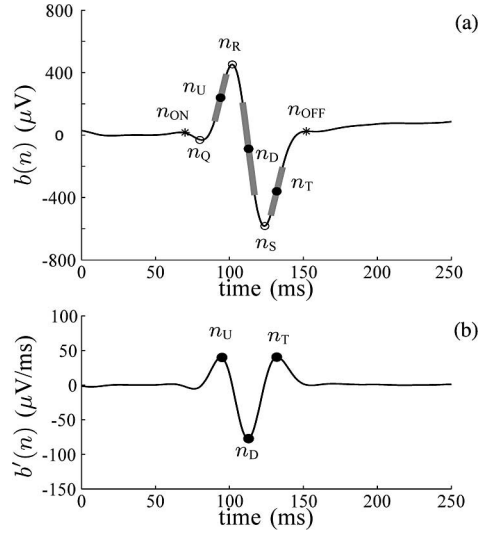

Fig. 1. (a) Beat example with the delineation marks used to evaluate the QRS slopes. (b) ECG derivative with the marks of maximum and minimum slopes within the QRS complex.

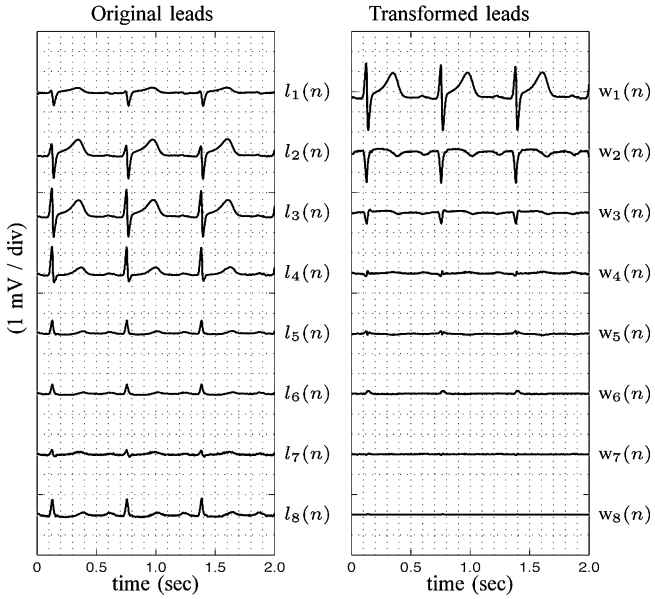

Fig. 2. (a) Standard 12-lead ECG signal (only $l_1(n), \ldots, l_8(n)$ are displayed). (b) Transformed orthogonal ECG leads obtained from the PCA technique.

maximum slope between $n_{\rm S}$ and the QRS complex offset $n_{\rm OFF}$ (see Fig. 1).

Finally, three lines were fitted in the least-squares sense to the ECG signal in 8-ms windows centered around $n_{\rm U}$, $n_{\rm D}$, and $n_{\rm T}$, respectively; the resulting slopes of these three lines were denoted by $\mathcal{I}_{\rm US}$, $\mathcal{I}_{\rm DS}$, and $\mathcal{I}_{\rm TS}$ [see thick lines in Fig. 1(a)].

D. QRS Slopes From the Spatial QRS Loops

1) QRS Loop From the Vectorcardiogram: From the standard 12-lead ECG $l_1(n), \ldots, l_{12}(n)$, it is possible to generate the three orthogonal leads $x(n)$, $y(n)$, and $z(n)$ by applying the Dower inverse matrix over leads V1–V6, I, and II [16]. These new orthogonal leads can be represented in a 3-D space, so that one can observe the variations of the electrical heart vector-cardiogram (VCG), given by $\mathbf{v}_{\rm VCG}(n) = [x(n), y(n), z(n)]^T$. During depolarization, the dominant direction $\mathbf{u}$ of the QRS loop ($\rm QRS_{VCG}$) points to the QRS loop tip, called the *mean electrical axis*. Thus, determining the main direction of the $\rm QRS_{VCG}$ loop, a new lead was obtained by projecting the loop onto that vector. For this analysis, we first searched for the main direction $\mathbf{u}$ by maximizing the following equation:

$$\mathbf{u} = [u_x, u_y, u_z]^T = [x(n_0), y(n_0), z(n_0)]^T$$

with

$$n_0 = \arg\max_n [x^2(n) + y^2(n) + z^2(n)] \tag{1}$$

where n spans over the samples of the running beat from 10 ms before $n_{\rm ON}$ to 130 ms after $n_{\rm ON}$. Then, the new projected lead $g(n)$ was calculated by projecting the points of the $\rm QRS_{VCG}$ loop onto the $\mathbf{u}$ axis

$$g(n) = \frac{\mathbf{v}_{\rm VCG}^T(n)\,\mathbf{u}}{\|\mathbf{u}\|}. \tag{2}$$

The indices described in the previous section were then evaluated on this new lead.

2) QRS Loop Using Principal Component Analysis: Principal component analysis (PCA) is a technique employed in signal processing. One way to implement PCA is by applying singular value decomposition (SVD) on the standard 12-lead ECG to generate a new lead system that concentrates the most energy of the signal in a small set of leads [17]. Specifically, the SVD was applied over leads V1–V6, I, and II to obtain eight transformed leads $\rm w_k(n)$, $k = 1, 2, \ldots, 8$, by using the following transformation:

$$\mathbf{w}(n) = \mathbf{U}^T\,\mathbf{l}(n) \tag{3}$$

where the vector $\mathbf{l}(n) = [l_1(n), l_2(n), \ldots, l_8(n)]^T$ contains the original leads (only V1–V6, I, and II) and $\mathbf{U}$ is the matrix containing the right singular vectors of a training set obtained from $\mathbf{L} = [\mathbf{l}_1, \ldots, \mathbf{l}_8]$, with $\mathbf{l}_k = [l_k(1), l_k(2), \ldots, l_k(N)]^T$, and N is the number of samples in the recording. Fig. 2 shows this lead-reducing transformation. It is evident that the energy of the original leads is mostly concentrated in the first three of the eight transformed leads $\rm w_k(n)$. The new lead system given by the orthogonal transformed leads $\rm w_1(n)$, $\rm w_2(n)$, and $\rm w_3(n)$ was subsequently used to represent the QRS loop in a different way, called the $\rm QRS_{PCA}$ loop. Analogously to the process described in Section II-D1, the same methodology was applied here to compute a new lead by projecting the $\rm QRS_{PCA}$ loop onto its dominant direction using (1) and (2). The only difference with respect to Section II-D1 is that $\mathbf{v}_{\rm VCG}(n)$ was replaced with $\mathbf{v}_{\rm PCA}(n)$ defined as follows:

$$\mathbf{v}_{\rm PCA}(n) = [\rm w_1(n), w_2(n), w_3(n)]^T. \tag{4}$$

Examples of the two approaches described earlier are presented in Fig. 3, where three consecutive beats in three orthogonal leads are shown, corresponding to each of the two vectorial techniques (VCG or PCA) used in this study. Corresponding

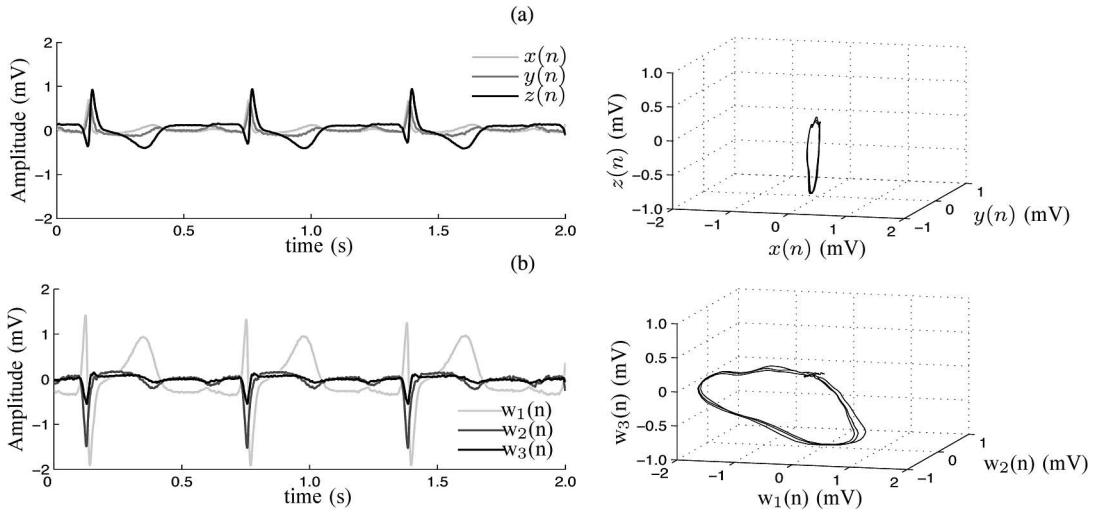

Fig. 3. (a) Orthogonal X, Y, and Z leads derived from Dower inverse matrix in a time segment, and their corresponding loops. (b) Transformed orthogonal ECG leads obtained from the PCA technique, and their corresponding loops.

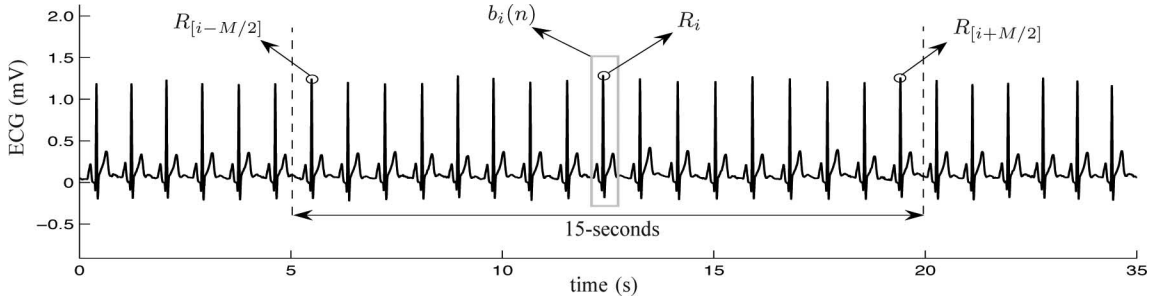

Fig. 4. ECG normalization used to compensate for low-frequency oscillations. The gray rectangle represents the analyzed beat and the dashed lines the boundaries of the 15-s window.

QRS loops are shown as well. Finally, we evaluated the QRS slopes in the new leads obtained by projection of QRS loops in order to compare these results with those obtained from individual leads of the standard 12-lead ECG system.

E. Quantification of Ischemic Changes

The ability of a certain index $\mathcal{I}$ to track PCI-induced ischemic changes in relative terms with respect to the normal variation measured at resting state was characterized by the parameter $\mathcal{R}_{\mathcal{I}}$ [5]. This parameter, evaluated at time instant t_ϕ taken in increments of 10 s from $t = 0$ (occlusion start) until the end of the occlusion, was defined as the ratio between the change observed during PCI up to time t_ϕ, denoted by $\Delta_{\mathcal{I}}(t_\phi)$, and the normal fluctuations observed during the control recording immediately prior to the PCI, as defined by the standard deviation (SD) of $\mathcal{I}$ in this control recording denoted by $\sigma^{\mathcal{I}}$

$$\mathcal{R}_{\mathcal{I}}(t_\phi) = \frac{\Delta_{\mathcal{I}}(t_\phi)}{\sigma^{\mathcal{I}}}. \tag{5}$$

F. ECG normalization

When large physiological variations occur in the ECG signal at resting state, the potential value of $\mathcal{R}_{\mathcal{I}}$ as a marker of ischemia is highly reduced because of the increase of $\sigma^{\mathcal{I}}$ in the denominator of $\mathcal{R}_{\mathcal{I}}$ (5). This occurs when respiration or other low-frequency modulations of the ECG affect the QRS complex amplitude and the slope estimates. To compensate for this, an ECG signal normalization procedure was employed [18]. In brief, the normalization uses a running window of 15 s duration centered around the R wave of each processed beat $b_i(n)$ with i denoting beat index. The median of the R wave amplitudes corresponding to the M (or $M + 1$) beats within the 15-s window was computed: $R_{m_i} = \text{median}\{R_{[i-M/2]}, \ldots, R_{[i+M/2]}\}$, and the normalized beat $\hat{b}_i(n)$ was defined as follows:

$$\hat{b}_i(n) = \frac{R_{m_i}}{R_i} b_i(n). \tag{6}$$

Fig. 4 shows this ECG normalization procedure. This procedure was applied to both the control and PCI recordings in all the processed leads, either standard ones or derived from the QRS_{VCG} and QRS_{PCA} loops.

G. Normal Variations of the QRS Slopes

1) Intraindividual Variability Analysis: To assess the intraindividual variability of QRS-slope variations, $\mathcal{I}_{\text{US}}$ and $\mathcal{I}_{\text{DS}}$ were measured on the normalized beats of each of the two control recordings analyzed per patient. The SD of $\mathcal{I}$ ($\mathcal{I}_{\text{US}}$ or $\mathcal{I}_{\text{DS}}$), denoted by $\sigma^{\mathcal{I}}_{k,c}(j)$, was computed for each patient $j = 1, \ldots, J$,

and lead $k = 1, \ldots, 12$ in each of the two control recordings ($c = 1, 2$). The difference between the SDs of the two control recordings was quantified: $d_k^{\mathcal{I}}(j) = \sigma_{k,1}^{\mathcal{I}}(j) - \sigma_{k,2}^{\mathcal{I}}(j)$.

A statistical test (one-sample t-test) was applied to the difference $d_k^{\mathcal{I}}(j)$ evaluated for the whole set of patients, and each lead k and index $\mathcal{I}$, with the purpose of contrasting the following hypothesis:

1) H0: intraindividual change ($\overline{d_k^{\mathcal{I}}}$) is $= 0$;
2) H1: intraindividual change ($\overline{d_k^{\mathcal{I}}}$) is $\neq 0$;

where

$$\overline{d_k^{\mathcal{I}}} = \frac{1}{J} \sum_{j=1}^{J} d_k^{\mathcal{I}}(j). \tag{7}$$

2) Interindividual Variability Analysis: To assess the interindividual variability of QRS-slope variations, the mean of the two SDs $\sigma_{k,c}^{\mathcal{I}}(j)$, $c = 1, 2$, was computed for each patient j, lead k, and index $\mathcal{I}$: $\sigma_k^{\mathcal{I}}(j) = 1/2\{\sigma_{k,1}^{\mathcal{I}}(j) + \sigma_{k,2}^{\mathcal{I}}(j)\}$. Then, the SD of $\sigma_k^{\mathcal{I}}(j)$ over patients was quantified, and denoted by $s_k^{\mathcal{I},\updownarrow}$. Additionally, the SD of the $\sigma_{k,c}^{\mathcal{I}}(j)$, $c = 1, 2$, for each patient j was also computed and denoted by $s_k^{\mathcal{I},\leftrightarrow}(j) = 1/\sqrt{2}|\sigma_{k,1}^{\mathcal{I}}(j) - \sigma_{k,2}^{\mathcal{I}}(j)| = 1/\sqrt{2}\left|d_k^{\mathcal{I}}(j)\right|$.

A statistical test (one-sample t-test) was applied to compare the intraindividual variability $s_k^{\mathcal{I},\leftrightarrow}(j)$, $j = 1, \ldots, J$, with the interindividual variability of the whole population $s_k^{\mathcal{I},\updownarrow}$.

H. Time Course of QRS Slope Changes During Ischemia

Absolute $\Delta_{\mathcal{I}}(t)$ and relative $\mathcal{R}_{\mathcal{I}}(t)$ ischemia-induced changes during occlusion were computed for each patient j and lead k. These values were averaged over the whole population as well as over each of the three groups defined according to the occlusion site. In addition, determination of significant changes in the QRS slopes due to the induced ischemia during PCI, and their timing, was performed by applying a statistical test of the type described in Section II-G. In this case, differences were computed between the mean $\mathcal{I}_{\mathrm{REF}}$ of the analyzed index $\mathcal{I}$ ($\mathcal{I}_{\mathrm{US}}$ or $\mathcal{I}_{\mathrm{DS}}$) during the first 5 s of the PCI recording (taken as a reference) and the current values of $\mathcal{I}$ in the PCI recording $\mathcal{I}(t)$ evaluated at time instants t taken in increments of 3 s from the onset of occlusion ($t = 0$), in each lead k.

I. Calculation of ST-Segment Change

The ST level measured at J point $\mathcal{I}_{\mathrm{ST}}$ was also quantified in all of the analyzed recordings. Subsequently, the corresponding absolute $\Delta_{\mathcal{I}_{\mathrm{ST}}}$ and relative $\mathcal{R}_{\mathcal{I}_{\mathrm{ST}}}$ changes during PCI were calculated, and compared with those corresponding to QRS slope indices.

III. Results

A. Methodological Analysis

An example of the effect of the normalization technique described in Section II-F is presented in Fig. 5, which shows sequences of $\mathcal{I}_{\mathrm{DS}}$ values measured before and after application of the ECG normalization. It is clear from Fig. 5 that normalization attenuates the low-frequency oscillations, most likely generated by respiration or other very low-frequency components of uncertain origin, which affect the slope measurements through modulation of the QRS amplitude. In these patients presenting this low-frequency oscillatory behavior (31 out of a total of 152), the mean of the oscillation frequency was 0.04 $\pm$ 0.01 Hz. As a consequence, the variability observed in $\mathcal{I}_{\mathrm{US}}$, $\mathcal{I}_{\mathrm{DS}}$, and $\mathcal{I}_{\mathrm{TS}}$ in any recording at rest becomes substantially lower after applying the normalization procedure (e.g., for $\mathcal{I}_{\mathrm{DS}}$ a reduction of 20.3% was observed among the 12 leads in the STAFF III dataset, with maximum of 33.4% in lead II), thus making these measurements in normalized ECG suitable for assessing ischemia-induced changes through evaluation of the relative ratio $\mathcal{R}_{\mathcal{I}}$.

Fig. 6 shows the QRS-slope series evaluated in two control recordings and the PCI recording for a particular patient in lead V2 (LAD occlusion). It can be observed from the first two

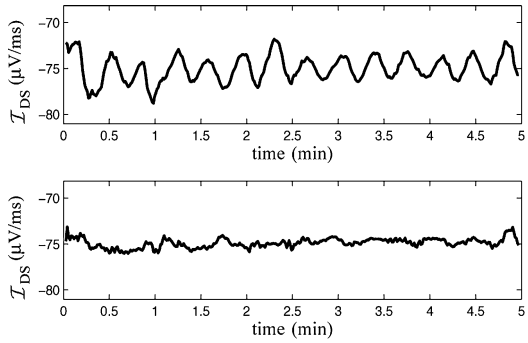

Fig. 5. $\mathcal{I}_{\mathrm{DS}}$ values measured in lead II in a control recording of a patient from the STAFF III dataset before (top) and after (bottom) applying ECG normalization.

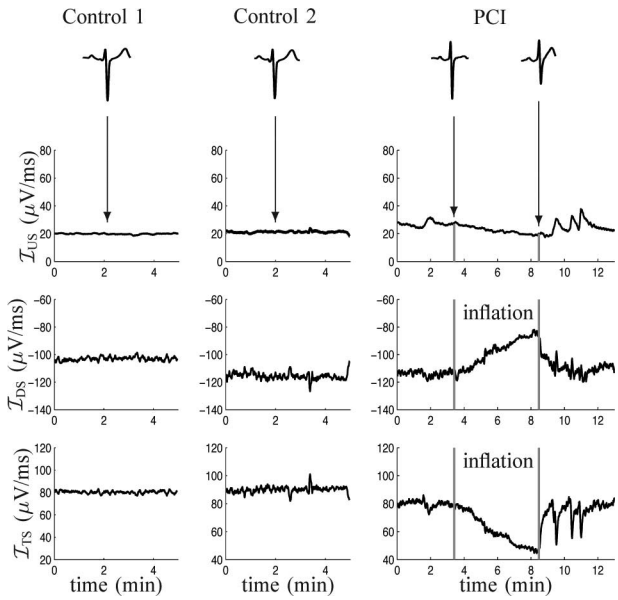

Fig. 6. QRS slopes in normalized ECGs of a patient in lead V2. On top, representative beats during control and PCI (LAD occlusion) are shown. Each row corresponds to an evaluated index ($\mathcal{I}_{\mathrm{US}}$, $\mathcal{I}_{\mathrm{DS}}$, and $\mathcal{I}_{\mathrm{TS}}$), whereas each column represents a different recording. Gray vertical lines in the right column mark the beginning and end of the occlusion.

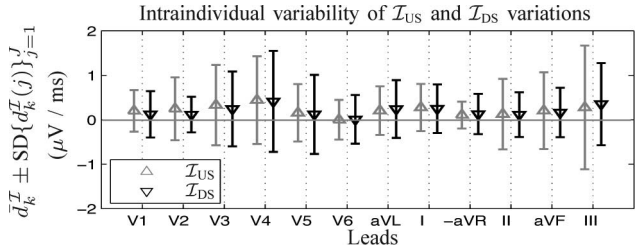

Fig. 7. Mean ± SD over patients of the intraindividual variations $d_k^{\mathcal{I}}(j)$ for $\mathcal{I}_{\rm US}$ and $\mathcal{I}_{\rm DS}$.

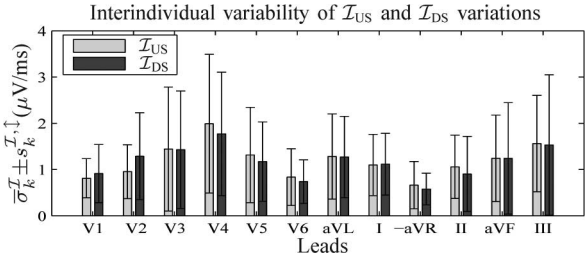

Fig. 8. Mean ± SD over patients of the variations $\sigma_k^{\mathcal{I}}(j)$ for $\mathcal{I}_{\rm US}$ and $\mathcal{I}_{\rm DS}$.

columns (control recordings) that the three QRS slopes show high stability. More importantly, their degree of variation in the two control recordings is very similar between them. However, the amount of change in $\mathcal{I}_{\rm US}$ during PCI was much lower than in $\mathcal{I}_{\rm DS}$ or $\mathcal{I}_{\rm TS}$.

B. Intraindividual Variability of the QRS-Slope Variations

The low-intraindividual variability of the QRS-slope variations is confirmed by the results of the statistical test described in Section II-G. In all the leads, except for V3, I, -aVR, and II, the p-value is <0.05 and the hypothesis H0 of the intraindividual variability of QRS-slope variations being negligible is accepted. In leads V3, I, -aVR, and II, despite the p-value being >0.05, the differences between the two control recordings were very close to 0. To illustrate this, Fig. 7 presents averaged results and dispersion of $d_k^{\mathcal{I}}(j)$.

C. Interindividual Variability of QRS-Slopes Variations

The interindividual variability of the QRS-slope variations as a representation of how the SDs of $\mathcal{I}_{\rm US}$ and $\mathcal{I}_{\rm DS}$ at resting state vary within the whole population is presented in Fig. 8.

The statistical test described in Section II-G2 confirms that, in all leads, the differences between intraindividual variations $s_k^{\mathcal{I},\leftrightarrow}(j)$ and the SD $s_k^{\mathcal{I},\updownarrow}$ of the whole dataset are highly significant ($p < 0.05$), being $s_k^{\mathcal{I},\updownarrow} > \bar{s}_k^{\mathcal{I},\leftrightarrow}$ in all cases, with $\bar{s}_k^{\mathcal{I},\leftrightarrow} = \frac{1}{J}\sum_{j=1}^{J} s_k^{\mathcal{I},\leftrightarrow}(j)$.

D. Dynamic Changes of the QRS Slopes During Ischemia in Standard Leads

1) Global Analysis: Relative changes of the QRS slopes measured during PCI, and averaged over patients, were computed for the standard 12-lead ECG. First, the performances of the three QRS slopes ($\mathcal{I}_{\rm US}$, $\mathcal{I}_{\rm DS}$, and $\mathcal{I}_{\rm TS}$) were analyzed for the precordial leads V1–V3. In these leads, we found that the two last slopes within the QRS complex (i.e., $\mathcal{I}_{\rm DS}$ and $\mathcal{I}_{\rm TS}$) present a similar behavior along time, but not so for $\mathcal{I}_{\rm US}$. Fig. 9 shows the relative factor of change ($\mathcal{R}_{\mathcal{I}}$) for the three slopes during 5 min of coronary occlusion in leads V2 and V3. It is clear that there is a strong relationship between the slopes. In all the other leads, where the $\mathcal{I}_{\rm TS}$ index was not evaluated, the $\mathcal{I}_{\rm DS}$ slope presented higher sensitivity to the ischemia-induced changes, with maximum values reached in leads V3 and V5. In lead V3, the maximum averaged factors of change of $\mathcal{I}_{\rm DS}$ and $\mathcal{I}_{\rm US}$, quantified by the parameter $\mathcal{R}_{\mathcal{I}}$, were found to be 9.31 and 5.11, respectively. In lead V5, the maximum factors of change were 8.06 and 6.01.

This means that QRS slopes are very sensitive to the ischemia-induced changes, and their values during PCI change by at least a factor of 5 (in leads V3 and V5) with respect to their normal variations during control.

The amount of relative change $\mathcal{R}_{\mathcal{I}}$ averaged for all patients and leads was found to increase by 27.3% when the ECG normalization described in Section II-F was applied prior to measuring $\mathcal{I}_{\rm US}$ and $\mathcal{I}_{\rm DS}$.

2) Analysis Restricted to the Occlusion Site: The results described in Section III-D1 were obtained from the total population without separating into groups according to the occlusion site. In order to see whether changes in the slopes vary as a function of the occlusion site, the same analysis described in III-D1 was performed, but clustering patients in three different groups according to the occluded artery. Fig. 10 presents the three leads with the largest sensitivity to the ischemia-induced changes for each group, both in absolute and relative terms. For the LAD group, the greatest changes were found in the anterior leads V2–V4, V3 being the most sensitive one with maximum values of $\bar{\Delta}_{\mathcal{I}_{\rm DS}} = 47.11$ μV/ms and $\bar{\mathcal{R}}_{\mathcal{I}_{\rm DS}} = 28.7$ times their normal variation in the control recordings. For the LCX group, leads V4–V6 presented the largest changes, with $\bar{\Delta}_{\mathcal{I}_{\rm DS}} = 10.41$ μV/ms and $\bar{\mathcal{R}}_{\mathcal{I}_{\rm DS}} = 8.05$ in lead V5. Finally, in the RCA group the largest changes were found in leads II, aVF, and III. Although lead III showed the largest absolute change $\bar{\Delta}_{\mathcal{I}_{\rm DS}} = 7.02$ μV/ms, the greatest relative change $\bar{\mathcal{R}}_{\mathcal{I}_{\rm DS}} = 8.61$ was seen in lead II.

E. Dynamic Changes of QRS Slopes During Ischemia in Loop-Projected Leads

1) Slopes Evaluated From QRS Loops: Fig. 11 shows averaged QRS loops ($\mathrm{QRS}_{\rm VCG}$ and $\mathrm{QRS}_{\rm PCA}$) for the control recording of a particular patient as well as their evolution during PCI. For the control recording, the loops corresponding to all beats contained within the last minute of the recording were averaged and shown in the left panel of top and middle rows (see Fig. 11(a) for $\mathrm{QRS}_{\rm VCG}$, and Fig. 11(b) for $\mathrm{QRS}_{\rm PCA}$). The evolution of the loops along the occlusion time using both approaches is presented in the remaining panels of Fig. 11(a) and (b). Fig. 11(c) shows the beats obtained by projecting $\mathrm{QRS}_{\rm VCG}$ and $\mathrm{QRS}_{\rm PCA}$ onto their dominant directions. It can be observed how the magnitude of the loop varies, while increasing the degree of ischemia, and how it looks very similar to the control loop in the first 30 s of the PCI process.

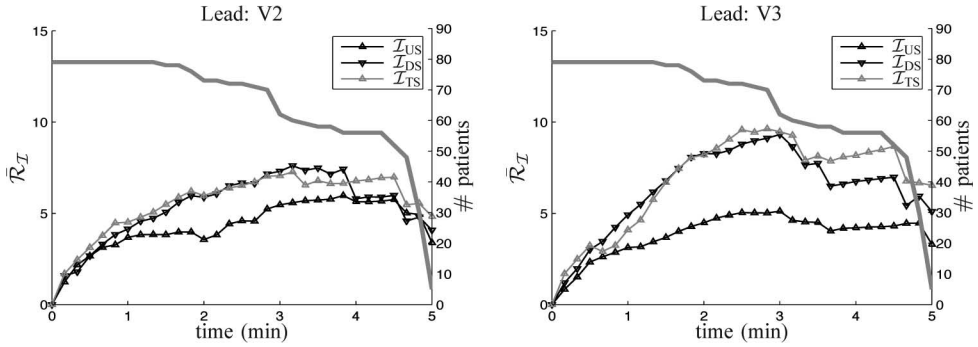

Fig. 9. Relative changes $\mathcal{R}_{\mathcal{I}}$ of the three QRS slopes ($\mathcal{I}_{\rm US}$, $\mathcal{I}_{\rm DS}$, and $\mathcal{I}_{\rm TS}$) in leads V2 and V3. The gray lines represent the number of patients that remain under occlusion at each time instant.

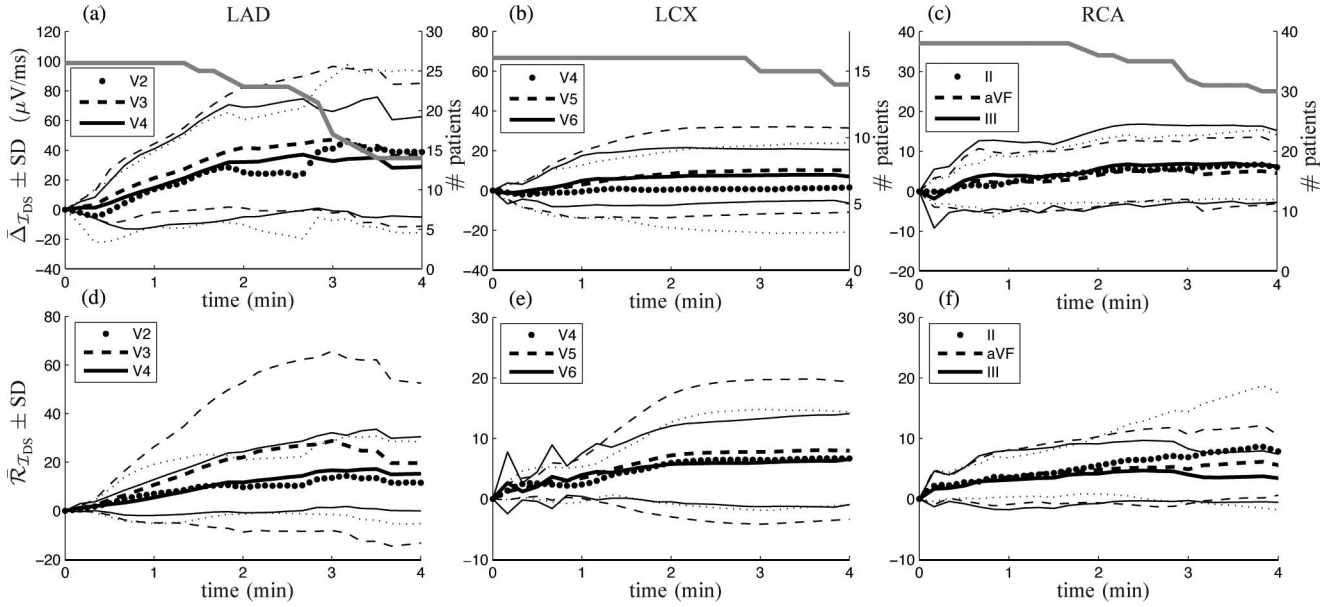

Fig. 10. Leads with the highest ischemia-induced changes according to the occluded artery. (a)–(c) Mean (thick lines) $\pm$ SD (thin lines) over patients of $\Delta_{\mathcal{I}_{\rm DS}}$ in groups LAD, LCX, and RCA, respectively. (d)–(f): Mean $\pm$ SD of $\mathcal{R}_{\mathcal{I}_{\rm DS}}$ for the same leads and groups showed in (a), (b), and (c), respectively. Gray lines represent the number of patients under occlusion.

In the same way that the shape of the loop varies, so does its dominant direction and, consequently, the morphology, duration, and amplitude of the projected beats. In Fig. 11(c), a reduction in the QRS amplitude and a prolongation of the QRS duration can be observed at the different stages of the PCI as compared to the control.

Sequences of the slope values ($\mathcal{I}_{\rm US}$ and $\mathcal{I}_{\rm DS}$) evaluated on the projected leads during PCI are shown in Fig. 12 for a representative patient of the STAFF III dataset. As can be observed, the magnitude of the slope changes as measured in leads projected from $\rm QRS_{PCA}$ are greater in absolute values than those obtained from the $\rm QRS_{VCG}$, which can be confirmed by looking at the heartbeats shown in Fig. 11(c). However, the variability ($\sigma^{\mathcal{I}}$) of the slopes during control recording is smaller for VCG-projected leads than for PCA ones (see numbers at the top of Fig. 12), thus compensating somehow the quantification of the relative change ($\mathcal{R}_{\mathcal{I}}$) during PCI.

2) Standard 12-Lead ECG Versus QRS-Loop Methods: In order to corroborate whether the new approaches based on the QRS loop provide QRS-slope measurements that perform better than those directly measured on the standard 12-lead ECG system, we compared the relative slope changes averaged over the whole population in lead V3 and the two leads obtained by projection of the QRS loops ($\rm QRS_{VCG}$ and $\rm QRS_{PCA}$). As can be observed in Fig. 13(a) and (b), the methods based on the QRS loop seem superior.

Regarding $\mathcal{I}_{\rm US}$, the PCA-derived lead was more sensitive to the ischemia-induced relative changes ($\mathcal{R}_{\mathcal{I}}$) than the VCG-derived lead, with their maximum values being 10.5 (103% higher than in V3) and 7.87 (54% higher than in V3), respectively. In the case of $\mathcal{I}_{\rm DS}$, the two loop methods showed very similar behavior, with maximum relative factors of 12.4 and 13.7 for PCA- and VCG-derived leads, which were 36% and 47% higher, respectively, compared to lead V3. Despite the fact

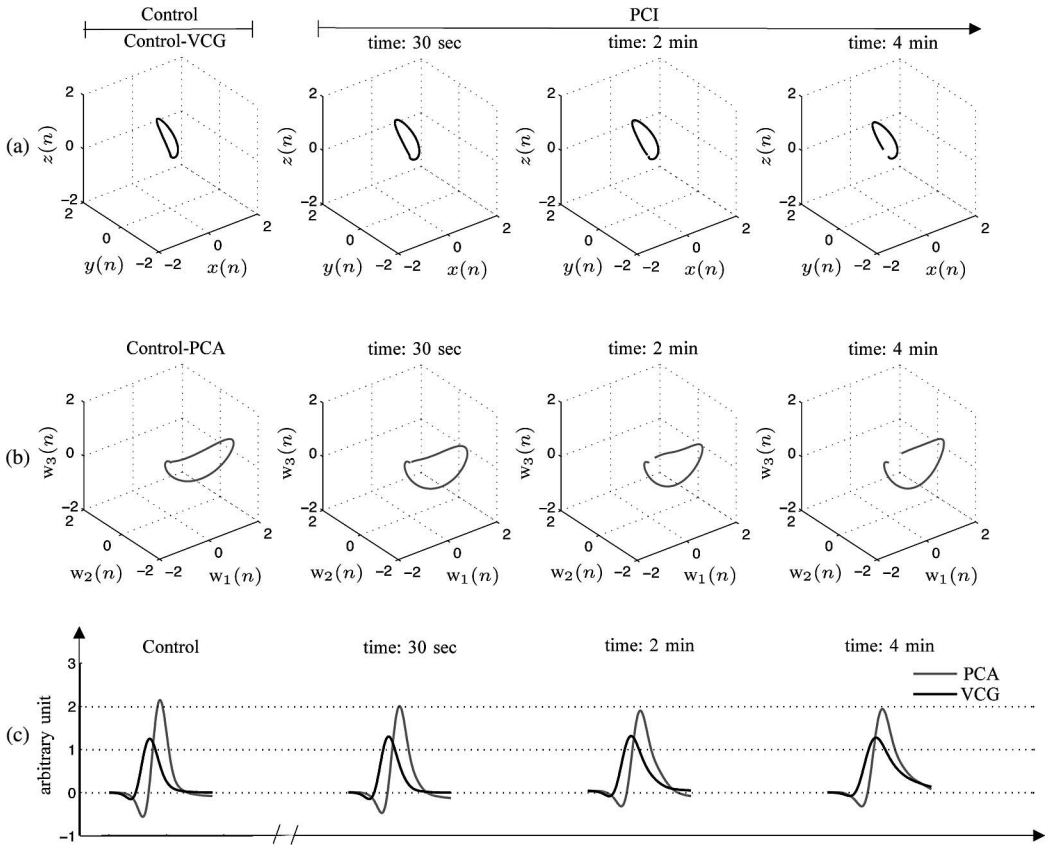

Fig. 11. Averaged loops in control (average over the last minute) and at different times during the PCI procedure (in each case, the average corresponds to the previous 30 s) using: (a) the VCG technique, (b) the PCA technique, and (c) beats obtained by projection onto the dominant direction of each loop.

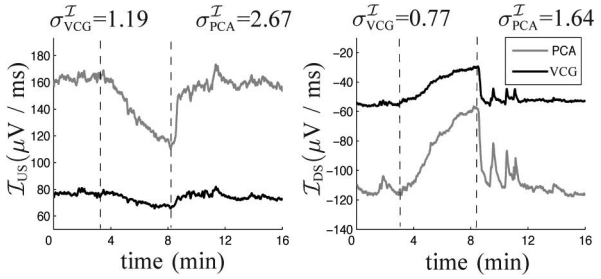

Fig. 12. Sequences of $\mathcal{I}_{\rm US}$ and $\mathcal{I}_{\rm DS}$ during the PCI recording of a representative patient evaluated on the new leads obtained by projecting QRS loops (PCA and VCG). Dash lines mark the beginning and end of the occlusion.

that the maximum absolute change for $\mathcal{I}_{\rm DS}$ in the VCG-derived lead was slightly inferior to that of the PCA-derived lead, its variation in the control is substantially smaller, thus explaining the slightly superior relative factor of change found for $\mathcal{I}_{\rm DS}$ in the VCG-derived lead.

F. Comparison With ST Level

Relative changes of the ST level ($\mathcal{R}_{\mathcal{I}_{\rm ST}}$) were found to be greater than those of the QRS slopes ($\mathcal{R}_{\mathcal{I}_{\rm US}}$ and $\mathcal{R}_{\mathcal{I}_{\rm DS}}$) in most of the standard leads, and more notably, so for leads with large projection of the ST-T complex. This was applicable both to the analysis performed over the whole study population, and also to the analysis over the different occlusion groups. Specifically, $\mathcal{R}_{\mathcal{I}_{\rm ST}}$ was around three times greater than $\mathcal{R}_{\mathcal{I}_{\rm DS}}$ in lead V3 for the LAD group, and in lead II for the RCA group. However, in leads with low projection of the ST-T complex, like V6, I, and -aVR, $\mathcal{R}_{\mathcal{I}_{\rm DS}}$ was found to be of the same magnitude than $\mathcal{R}_{\mathcal{I}_{\rm ST}}$. Moreover, $\mathcal{R}_{\mathcal{I}_{\rm DS}}$ values computed over loop-derived leads were larger than $\mathcal{R}_{\mathcal{I}_{\rm ST}}$ values computed in V6, I, and -aVR, as shown in Fig. 13(c).

A correlation analysis of the absolute changes of $\mathcal{I}_{\rm DS}$ ($\Delta_{\mathcal{I}_{\rm DS}}$) and those of $\mathcal{I}_{\rm ST}$ ($\Delta_{\mathcal{I}_{\rm ST}}$) confirmed that $\mathcal{I}_{\rm DS}$ adds complementary information to that provided by $\mathcal{I}_{\rm ST}$. Specifically, in the LAD group, the Spearman correlation coefficient (r^2) between $\Delta_{\mathcal{I}_{\rm DS}}$ and $\Delta_{\mathcal{I}_{\rm ST}}$ computed in lead V3 at the end of the coronary occlusion was 0.40. In the RCA group, the corresponding correlation coefficient computed in lead II was 0.22.

G. Timing of Significant QRS Slope Change During PCI

Fig. 14 shows examples of the time course during PCI of the p-values computed for the statistical test described in Section II-H. A p-value < 0.05 implies that significant changes in the QRS slopes occur due to the induced ischemia. In leads V4 and V5 significant changes in $\mathcal{I}_{\rm US}$ and $\mathcal{I}_{\rm DS}$ were found to occur between 1 and 2 min after initiation of the coronary occlusion. In lead V3, significant changes were already seen at around 30 s. In leads V3 and V4, significant changes occurred in $\mathcal{I}_{\rm DS}$ earlier than in $\mathcal{I}_{\rm US}$. This performance was representative of most of the other leads. Notice that, as time progresses, there is

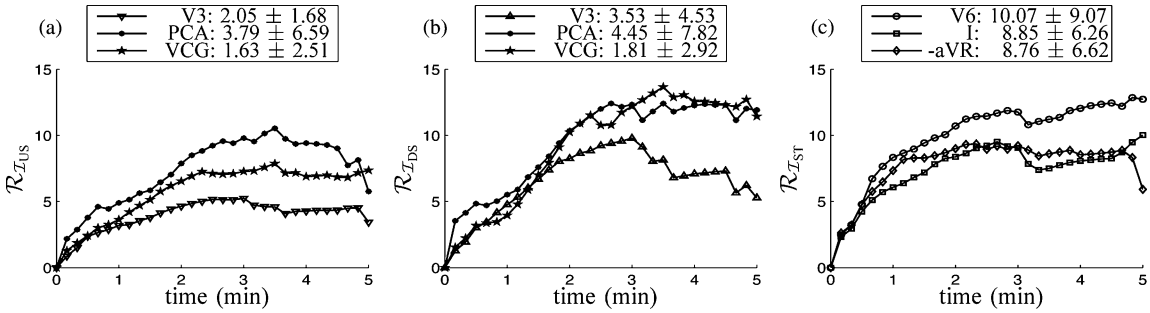

Fig. 13. Evolution of the relative factor of change $\mathcal{R}_{\mathcal{I}}$ for $\mathcal{I}_{\mathrm{US}}$, $\mathcal{I}_{\mathrm{DS}}$, and $\mathcal{I}_{\mathrm{ST}}$ during PCI. Mean ± SD of $\sigma^{\mathcal{I}}$ over patients in the control recordings are displayed on top of each graph.

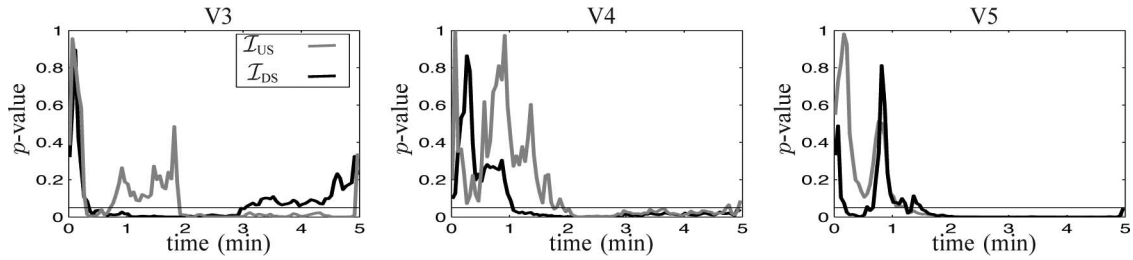

Fig. 14. Significance of changes in $\mathcal{I}_{\mathrm{US}}$ and $\mathcal{I}_{\mathrm{DS}}$ along time during PCI as evaluated by the p-value of the statistical test described in Section II-H. The threshold for significance $p = 0.05$ is shown in black solid line.

a decline in the number of patients that remain under occlusion and, consequently, the p-values shown in Fig. 14 are computed for a different number of patients at each time instant.

IV. Discussion

In this study, we measured the slopes of the QRS complex ($\mathcal{I}_{\mathrm{US}}$, $\mathcal{I}_{\mathrm{DS}}$, and $\mathcal{I}_{\mathrm{TS}}$) and assessed their performances for evaluation of myocardial ischemia induced by coronary occlusion during prolonged PCI. QRS slopes were first introduced in [10] and [11] as a method for characterizing ECG alterations due to myocardial ischemia on the standard 12-lead ECG system. We propose an improvement for the quantification of QRS slope changes with the purpose of providing more sensitive and reliable estimates of the occurrence of significant changes in the depolarization phase during ischemia. Our proposal is to dynamically normalize the QRS-signal amplitude so as to avoid low- and very low-frequency oscillations that directly influence the variability of the estimated slopes. Results obtained after applying normalization provide measurements of relative QRS slope changes $\mathcal{R}_{\mathcal{I}}$, during PCI that are 27.3% larger than those measured without normalization in the standard 12-lead ECG. The reason for this improvement is that the SD of the QRS slopes in normalized control recordings is substantially reduced, while absolute changes during PCI are of the same magnitude, thus leading to an increase in the relative ratio $\mathcal{R}_{\mathcal{I}}$ and, the sensitivity. In this study, the QRS slopes were also evaluated in leads derived from the QRS loops. The results obtained using the methods based on the QRS loop far exceeded those obtained in the standard 12-lead ECG system, reaching up to a 103% improvement for $\mathcal{I}_{\mathrm{US}}$ and a 46% for $\mathcal{I}_{\mathrm{DS}}$ measured in $\mathcal{R}_{\mathcal{I}}$ with respect to lead V3. The superiority of the QRS slopes evaluation using loop-derived leads as compared to standard leads holds also true when the analysis is separately performed in each of the three patient subgroups. That superiority is justified by the fact that the slopes measured from the QRS loop show higher absolute values, since the loop-derived leads result from the projection onto a dominant vector with maximized amplitude, either generated from the VCG or the PCA loop. In addition, by definition of the loop-derived leads, the timing of the $\mathcal{I}_{\mathrm{US}}$ and $\mathcal{I}_{\mathrm{DS}}$ will always be in the first and the second half, respectively, of the QRS complex; therefore, this potential drawback when dealing with single (and interchanged) leads will not appear when dealing with loop derived ones.

Regarding the dynamic analysis for the different groups according to the occluded artery, the LAD group showed the most pronounced changes, reaching a relative factor of change three times higher than that of the other two groups, particularly when analyzing lead V3 (see Fig. 10), a finding suggestive of a correlation to the amount of ischemia. In any case, the index $\mathcal{I}_{\mathrm{DS}}$ proved to be the most sensitive of the slope indices, as evaluated either using absolute or relative change. It also presents the advantage of being possible to be evaluated for any possible QRS morphology regardless of the analyzed lead or occlusion site. Analysis of S wave slope $\mathcal{I}_{\mathrm{TS}}$ change in lead V1–V3 in LAD occlusions showed a similar pattern and amount of change compared to $\mathcal{I}_{\mathrm{DS}}$.

Analysis of the intraindividual slope variability in different control recordings showed that the QRS slopes present high stability for each patient, thus providing reliable reference for the evaluation of ischemia-induced changes in the QRS complex. However, the interindividual variability is significantly larger, thereby supporting the proposal of having a patient-dependent normalization of the $\mathcal{R}_{\mathcal{I}}$ index $\mathcal{R}_{\mathcal{I}} = \Delta_{\mathcal{I}}/\sigma^{\mathcal{I}}$, provided the

reference $\sigma^{\mathcal{I}}$ used in the proposed method is taken from the same patient so as to be able to assess ischemia variations. The same observations have been corroborated from the loop-derived leads.

Significant changes in QRS slopes during PCI-induced ischemia were found to occur around 30 s after initiation of the artery occlusion in some of the analyzed leads and up to 2 min in other leads. The $\mathcal{I}_{\mathrm{DS}}$ index showed earlier reaction than $\mathcal{I}_{\mathrm{US}}$ to the induced changes in most leads. In both cases, it can be observed a kind of rebound or backwards behavior (see Fig. 14) between 30 s and 2 min after the start of the occlusion that can be justified by a remarkable R wave amplitude increase during this period that compensates the QRS widening [19].

Analysis of the time evolution of $\mathcal{I}_{\mathrm{DS}}$ showed an oscillatory behavior after balloon release (see Fig. 12). This behavior was observed in several recordings resulting from oscillatory QRS amplitudes, which are very similar to those one reported for the ST-T segment, where, in most cases, have been associated with unfavorable outcome [20]–[22]. According to Laguna *et al.* [20, Fig. 5], similar oscillations can be observed when analyzing the shape of ECG waveforms on the same data used in this study.

The applicability of the slope indices for ischemia detection is limited by the fact that the QRS slopes present high-interindividual variability, which implies the need of a reference baseline measurement to be used for computation of relative ischemia-induced slope changes. However, the fact that intraindividual variability of QRS slopes is minor suggests that the slope indices could potentially be used for monitoring ischemia over time in chest pain units, intensive care units, and as monitoring in a prehospital setting. This applicability, however, needs to be tested in future studies, since issues like the sensitivity of the slope indices to body postural changes deserve further analysis. The use of slope indices evaluated in leads derived from spatial QRS loops could not only lead to higher sensitivity to the ischemia-induced changes, as reported in this study, but also to a minor dependence on other factors, such as body postural changes. Another limitation to this study is the fact that PCI-induced, short-time ischemia of 5 min might not produce severe enough ischemia to give rise to more pronounced changes of the QRS slopes. The additive information clinically within the QRS complex to that of the ST-T changes could be risk stratification of ST segment elevation myocardial infarction (STEMI) patients with more severe ischemia and evolving infarction that could guide treatment and give prognostic information. The modest correlation, r^2 obtained between the two indices, specifically with $\mathcal{I}_{\mathrm{DS}}$, suggests that they possibly quantify different pathophysiological expressions in the ischemic myocardium. Future studies are planned to further evaluate this.

V. Conclusion

In this study, we show that QRS slopes and their variations at resting state after normalization present a high-intraindividual stability, thus being suitable for characterizing dynamic changes due to ischemia. The downward slope of the R wave ($\mathcal{I}_{\mathrm{DS}}$) was the one with the most marked changes due to ischemia, however with a similar behavior to that of the S-wave slope, confirming that the effects of ischemia are most likely to be found in the later part of the depolarization phase. Results based on the QRS-loop approaches seem to be more sensitive to the induced ischemia than evaluation of the QRS slopes from the standard leads. Temporal analysis during PCI showed that significant changes in QRS slopes occur between 30 s and 2 min after initiation of the coronary occlusion, depending on the analyzed lead. Changes in the downward slope ($\mathcal{I}_{\mathrm{DS}}$) usually occurred earlier than in the upward slope ($\mathcal{I}_{\mathrm{US}}$). QRS-slope analysis could act as a robust method of depolarization evaluation in addition to repolarization changes in risk stratification during monitoring of patients with acute ischemia.

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