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Detection and quantification of acute myocardial ischemia by morphologic evaluation of QRS changes by an angle-based method☆

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Abstract

Objective: In acute myocardial ischemia changes within the QRS complex can add valuable information to that from the repolarization phase. This study evaluates three angles obtained from the main slopes of the R-wave within the QRS complex to assess acute myocardial ischemia.

Methods: The QRS angles, denoted by $\O_R$ (R-wave angle), $\O_U$ (up-stroke angle) and $\O_D$ (down-stroke angle), were evaluated in 12-lead electrocardiogram (ECG) recordings of 79 patients before and during coronary occlusion by elective percutaneous coronary intervention (PCI). In a subset of 38 patients, ischemia was quantified by myocardial scintigraphy.

Results: At baseline the QRS angles presented low variations. During occlusion, $\O_U$ and $\O_D$ developed a fast and abrupt change, whereas $\O_R$ showed a smaller and gradual change. There were significant correlations between both maximal and sum of positive change in $\O_R$ and ischemia: $r = 0.67$; $p < 0.001$ and $r = 0.78$; $p < 0.001$, for extent, and $r = 0.60$; $p < 0.001$ and $r = 0.73$; $p < 0.001$, for severity, respectively. Prediction of extent and severity of ischemia increased by 50% by adding $\O_R$ changes to ST-segment changes, for LCX occlusions, whereas increased by 12.1% and 24.6% for LAD and RCA occlusions, respectively. No significant correlation was seen between $\O_U$ and $\O_D$ angles and ischemia.

Conclusions: Evaluation of QRS angles from the standard 12-lead ECG represents a sensitive marker for detection of acute myocardial ischemia, whereas, $\O_R$ changes can be used for prediction of its extent and severity.

Keywords: QRS angles; PCI; Acute myocardial ischemia; Depolarization

Introduction

By convention, changes occurring in the repolarization phase (ST-T segment) of the standard 12-lead ECG are used for detection of acute myocardial ischemia in monitoring situations of patients with suspect acute coronary syndrome (ACS), or by stratifying acute myocardial infarction (AMI) patients for direct revascularization strategy (by primary percutaneous coronary intervention (pPCI) if meeting ST elevation myocardial infarction (STEMI) criteria). During severe ischemia, changes also in the depolarization phase may be seen due to slowing of conduction through the myocardium at risk (MaR), causing loss of cancellation during the ventricular activation and changes mainly in the later part of the QRS complex as well as prolongation of the depolarization phase. By these changes within the depolarization phase in addition to ST-T changes, those patients with high risk of rapid infarct evolution may be identified. However, proper quantification of QRS changes due to ischemia is more challenging than ST-segment evaluation

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since there is no general, easily available baseline reference (such as the isoelectric baseline when evaluating the ST-segment deviation) to compare with. Therefore QRS changes from a single, "snap-shot" ECG are in general less informative, why QRS methods are applicable mostly in monitoring situations or when having a prior baseline ECG from the same patient retrieved from a resting ECG database, as to make relative comparisons.

Several ECG-derived indices extracted from the QRS complex have been reported as indicators of potentially reversible myocardial ischemia, such as: QRS prolongation,[1–5] amplitude changes in the R- and S-waves,[4,6,7] distortion of the terminal part of the QRS complex,[8–12] changes in the high-frequency components of the QRS (in the frequency band 150–250 Hz),[13–15] changes in shape features of the QRS loop[16,17] as well as intra-QRS potentials.[18] In a study reported by Wong et al.[2,3] carried out in a large cohort of STEMI patients, a positive and independent relationship between QRS duration on admission ECG and 30-day mortality was found for anterior infarct location. However, prolongation of QRS duration is usually difficult to assess accurately, because the presence of ST elevation challenges the delineation between the end of the depolarization and beginning of the repolarization.

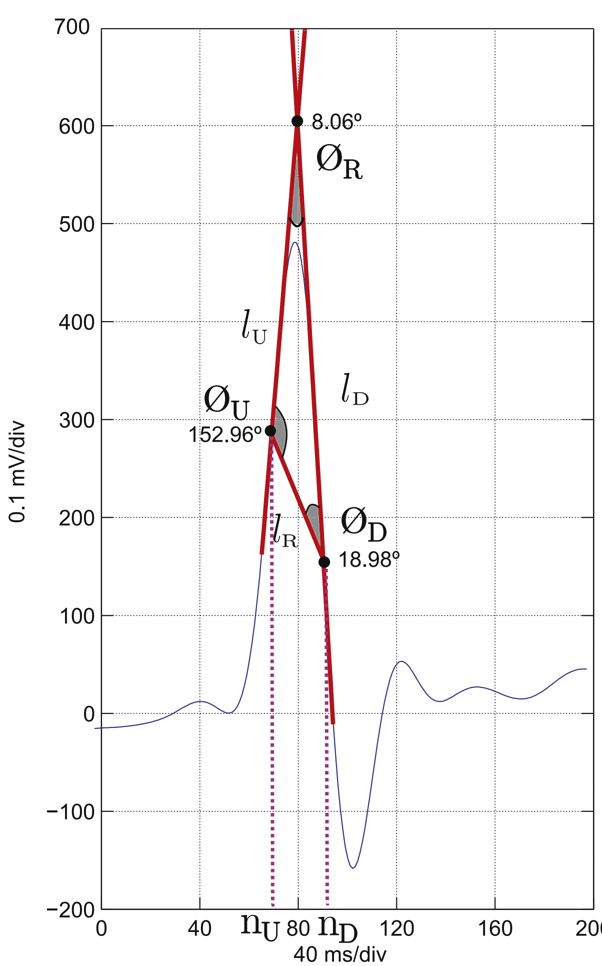

Fig. 1. Example of evaluation of QRS angles for a particular beat of a recording analyzed in this study.

In order to be able to use the changes within the QRS complex clinically, a robust, fairly noise resistant and easily applicable method is needed. Such a method was proposed by Pueyo et al. in 2008, by the QRS-slope method in which both amplitude and duration changes within the QRS complex are characterized by measuring the two main slopes of the QRS complex, i.e. the upward and downward slopes of the R wave.[19] The method was later further developed,[20] and the QRS slope changes, in particular the down-slope between R- and S-wave, was shown to correlate with both extent and severity of ischemia as quantified by single photon emission computed tomography (SPECT) in an acute ischemia model by elective PCI.[21] Moreover, changes within the QRS slopes were shown to provide information about the amount of ischemia complementary to that of the ST-segment.

The most optimal method for evaluation of depolarization changes, however, is not yet determined. The QRS slope measurements mentioned above seem to be a robust way to quantify QRS changes taking into consideration both amplitude and QRS duration changes, i.e. changes affected by slowing of the activation wavefront. Another way to quantify morphologic changes within the QRS complex is to evaluate the angles within the complex. In this study we evaluate if the angles of the triangle formed by the lines of the QRS complex could be used in quantification of depolarization changes induced by acute ischemia. These angles are illustrated in Fig. 1. We hypothesize that the angles, non-linearly related to the slopes of the triangle, may represent the ischemia-induced changes within the QRS complex. In particular we hypothesize that the R-wave angle can be a robust surrogate of QRS width as well as being a composite estimate of both the QRS slope changes described above. The main objectives of the present study are to:

a) Assess the dynamic evolution of the QRS angles during acute myocardial ischemia and characterize the spatial distribution of their changes in relation to the coronary occlusion site.
b) Compare the sensitivity of the QRS angles to ischemia-induced alterations with that shown by other depolarization indices such as the R-wave amplitude and the QRS slopes as well as ST-segment deviation.
c) In a subset of patients assess the association between QRS-angle changes and extent and severity of ischemia as quantified by SPECT imaging.

Materials and methods

Study population

The study population comprised 79 patients from the STAFF III dataset, described previously.[5] All these patients were admitted to the Charleston Area Medical Center in West Virginia, USA, for prolonged, elective PCI due to stable angina pectoris. The study was approved by the local Investigational Review Board and informed consent was obtained from each patient prior to enrolment. All patients were clinically stable during the study protocol. Patients who presented any signal loss during acquisition were not included. The exclusion criteria for the selected patients were: evidence of an acute or recent myocardial infarction, intraventricular conduction delay with a QRS duration of 120 milliseconds or longer (including right bundle-branch block (RBBB) and left bundle-branch block (LBBB)), low voltage, pacemaker rhythm, atrial fibrillation/flutter, or any ventricular rhythm at inclusion or during the PCI procedure. The duration of the occlusion procedure ranged from 1.5 to 7.3 min (mean: 4.4). The distribution of occluded coronary arteries and their respective mean occlusion times were: left anterior descending coronary artery (LAD) in 25 pts (3.9 min), right coronary artery (RCA) in 38 pts (4.6 min), and left circumflex artery (LCX) in 16 pts (4.8 min).

ECG acquisition

The ECGs were recorded using 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 1000 Hz with an amplitude resolution of 0.6 μV. The three augmented leads aVL, −aVR and aVF were generated from the limb leads to yield the complete standard 12-lead ECG. Prior to the PCI procedure, a baseline recording was acquired continuously during 5 min at rest, in the supine position. Another continuous ECG was acquired during the PCI procedure, starting before balloon inflation and ending after balloon deflation.

Myocardial perfusion imaging

The extent and severity of myocardial ischemia were defined for each patient by performing two imaging studies, the PCI study and the control study the day after the procedure. In 38 patients of the total population (8 LAD, 21 RCA and 9 LCX) approximately 30 mCi (1100 MBq) of ^{99m}Tc-sestamibi was intravenously injected after angiographic confirmation of total coronary artery occlusion by the balloon. The scintigraphic imaging for the PCI study was obtained within 3 hours after completion of the PCI procedure using a single-head rotating gamma camera (Elscint, Haifa, Israel). Image acquisition was made with a high-resolution collimator in a 64 × 64 matrix, 6.9-mm pixel size, using 30 projections (25 seconds/projection) at 180° (from 45° right anterior oblique to 45° left posterior oblique). Using filtered back projection with a Butterworth filter, transverse sections were reconstructed without attenuation correction. Short-axis sections were reconstructed for further analysis.[22]

For the control study the day after the PCI procedure, a second injection of approximately 30 mCi (1100 MBq) ^{99m}Tc-sestamibi was administered, and image acquisition was performed between 2 and 3 hours later with the same gamma camera and protocol used for the PCI study.

To process the scintigraphic images, the Cedars-Sinai and Emory quantitative analysis program (CEqual; ADAC Laboratories, Milpitas, CA)[23,24] was used to make volume-weighted bull's eye plots from the short-axis slices. Comparison of the bull's eye plots of the 2 studies for each patient was performed by an automatic procedure and was expressed as both extent and severity of the myocardial ischemia, as described in Ringborn et al.[14] In brief, any loss of perfusion during the PCI study compared with the control study was determined for each patient.[22] A reduction in the perfusion by 25% or more was used as the threshold for indicating significantly hypoperfused myocardium.[22] The area above this threshold in the bull's eye plot was delineated as an "extent map" and expressed as a percentage of the left ventricle, thus the "extent" of ischemia. The total pixel count difference (or local perfusion loss) between the control and occlusion study within that area in the "extent map" was defined as the "severity" of the ischemia and was expressed as a percentage of the total pixel count in the control situation within that area.[22]

ECG pre-processing

All ECG signals involved in the study were pre-processed as follows: (a) QRS detection, (b) normal beats selection as previously described,[25] (b) baseline drift attenuation via cubic spline interpolation, (b) delineation using a wavelet-based technique[26] and (e) ECG normalization.[20]

Calculation of QRS angles

The QRS angles measured in this study are illustrated in Fig. 1:

- Ø_R: the R-wave angle (the angle opposite to the R line l_R).
- Ø_U: the up-stroke (U) angle (the angle opposite to the down line l_D).
- Ø_D: the down-stroke (D) angle (the angle opposite to the up line l_U).

The three proposed angles were calculated from the URD triangle, which was built by joining the three lines l_R, l_U and l_D shown in Fig. 1. The angles inside the URD triangle, Ø_R, Ø_U and Ø_D were calculated following the methodology described below:

a) the lines l_U and l_D were obtained by least square fitting the ECG signal, $x(n)$, in 8-ms windows centered at points of maximal inflection n_U (global maximum of the ECG derivative between the Q and R wave peaks) and n_D (global minimum of the ECG derivative between the R and S wave peaks), respectively.[20] The slopes of the fitted lines l_U and l_D were calculated and denoted by s_U and s_D, respectively.
b) the line l_R was obtained by joining the points $U = [n_U, x(n_U)]$ and $D = [n_D, x(n_D)]$. The slope s_R of the line l_R was calculated as:

$$s_R = \frac{x(n_D) - x(n_U)}{n_D - n_U}. \quad (1)$$

c) The angles Ø_R, Ø_U and Ø_D were calculated in the following order. First, Ø_R was assumed to be an acute angle (i.e., $Ø_R < 90º$) and was calculated using the angular expression:

$$Ø = \arctan\left(\left|\frac{s_U - s_D}{1 + s_U s_D}\right|\right). \quad (2)$$

The above expression is the general equation assuming a two-dimensional (2D) euclidean space coordinate system. In this study, the units of the horizontal axis (time) and vertical axis (voltage) were rescaled to match the particular case of conventional ECG tracings in clinical printouts, where a speed of 25 mm/s and a gain of 10 mm/mV are used. Equivalently, in clinical printouts 1 mm represents 40 ms in the horizontal direction and 0.1 mV in the vertical one. Thus, the equation for $Ø_R$, when the slopes s_U and s_D are expressed in μV/ms, is given by:

$$Ø_R = \arctan\left(\left|\frac{s_U - s_D}{0.4(6.25 + s_U s_D)}\right|\right). \quad (3)$$

Second, depending on the sign of the slope s_R, $Ø_U$ or $Ø_D$ was first computed:
If $s_R > 0$,

$$Ø_R = \arctan\left(\left|\frac{s_U - s_R}{0.4(6.25 + s_U s_R)}\right|\right), \quad (4)$$
$$Ø_D = 180° - (Ø_U + Ø_R).$$

else,

$$Ø_D = \arctan\left(\left|\frac{s_D - s_R}{0.4(6.25 + s_D s_R)}\right|\right), \quad (5)$$
$$Ø_U = 180° - (Ø_D + Ø_R).$$

The above distinction was made to guarantee that the angles $Ø_U$ and $Ø_D$ were correctly evaluated, as the equation (2) that uses arctan is only valid for the smallest of the two angles generated by the interception of two lines (l_U and l_R or l_D and l_R, respectively).

Quantification of absolute and relative changes

Absolute Δ_I and relative R_I changes during the PCI procedure were tracked for each angle $I = \{Ø_R, Ø_U, Ø_D\}$. $\Delta_I(t)$ was calculated every 10 s from the start of occlusion ($t = 0$) by subtracting from the value of I at time t, $I(t)$, the initial reference I_{REF}, which is defined as the averaged value of the index I during the first 5 seconds of occlusion, $\Delta_I(t) = I(t) - I_{REF}$. $R_I(t)$ was calculated as the ratio between the absolute change observed during PCI, $\Delta_I(t)$, and the normal fluctuations of I observed during the baseline recording prior to the PCI, defined by the standard deviation (SD) σ_I of I[5]: $R_I(t) = |\Delta_I(t)|/\sigma_I$.

R-wave amplitude and QRS slope analysis

To assess the sensitivity of the QRS angles to the ischemia-induced changes in comparison to other depolarization indices, the following indices were also computed: R-wave amplitude (R_a), upward slope of the QRS complex (s_U) and downward slope of the QRS complex (s_D) as previously described.[20]

ST-segment analysis

ST-segment deviation (at the ST-J point) was determined in all patients. This index, denoted by (ST_J), was measured automatically in each of the 12 leads in the control recording before, as well as during the entire PCI procedure, using the PR segment as the isoelectric level.

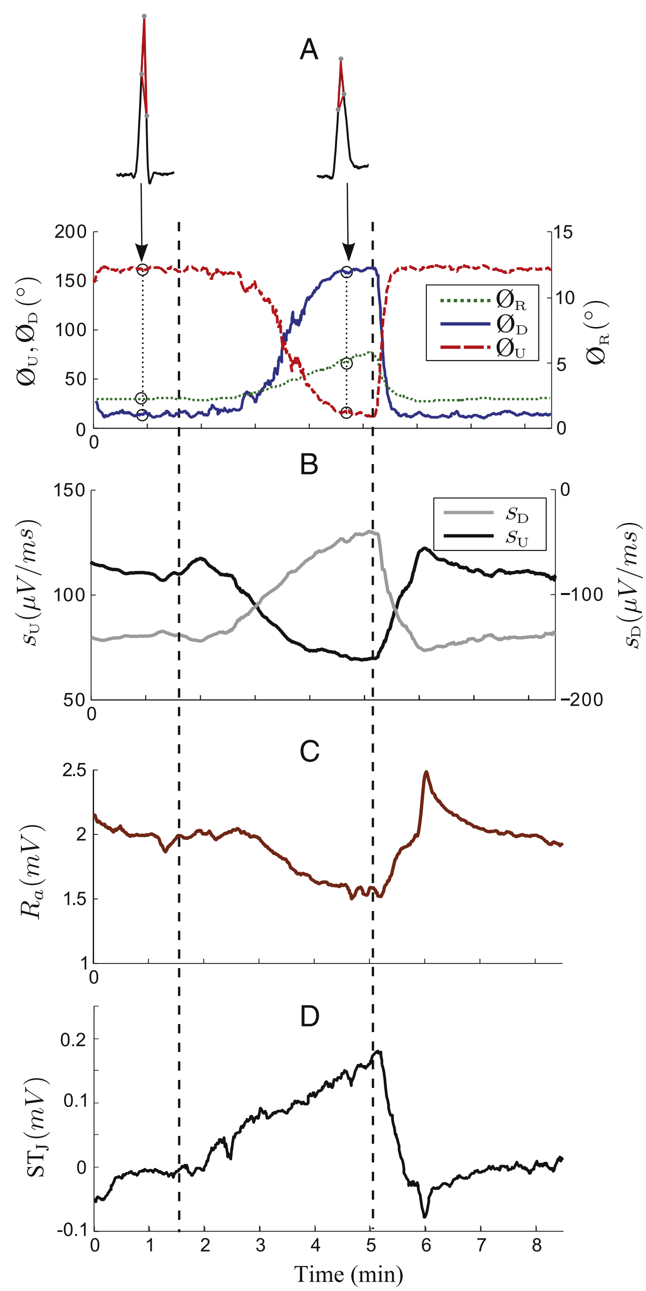

Fig. 2. (A) Temporal evolution of QRS angles and illustrative beats taken at specific time instants representative of pre-occlusion and occlusion periods. (Note different scales on the right and left y-axis.) (B) Temporal evolution of upward and downward QRS slopes. (C) Temporal evolution of R-wave amplitude and (D) temporal evolution of ST level. All represented indices are evaluated for a particular patient in lead V4. Dashed lines mark the occlusion period during the recording. Arrows indicate the position in time corresponding to the illustrated beats.

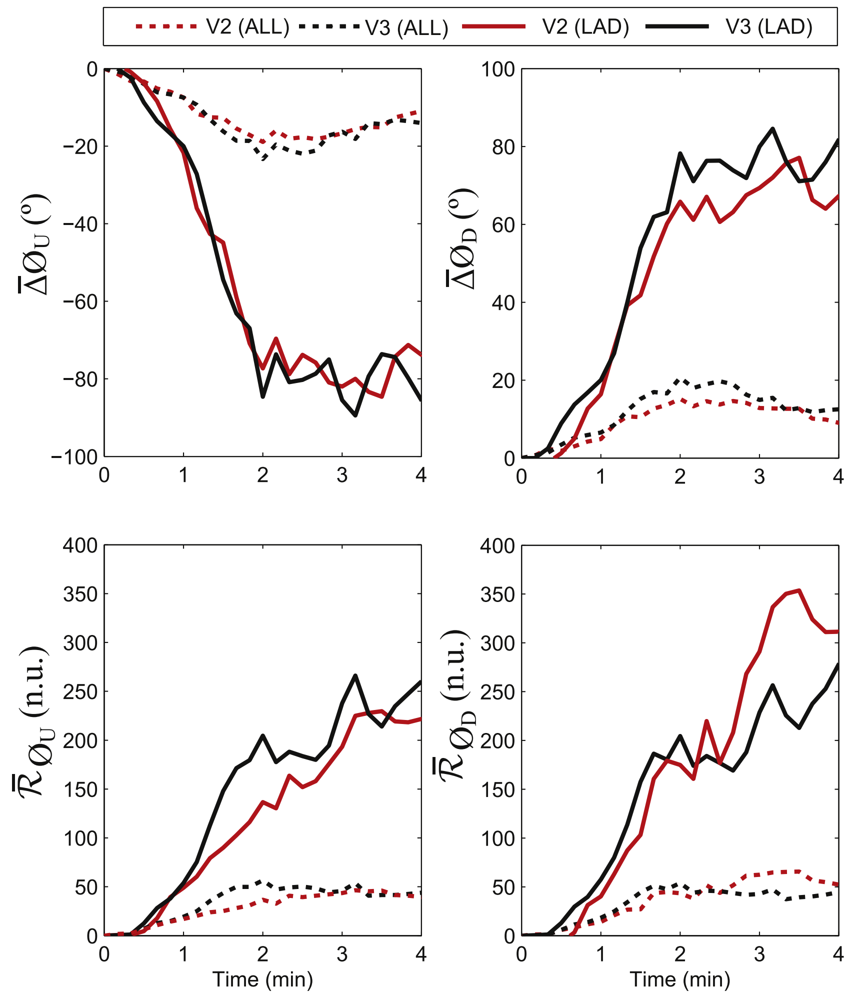

Fig. 3. Absolute $\Delta_I(t)$ (top panels) and relative $R_I(t)$ (bottom panels) changes ($I = \O_U, \O_D$) during occlusion averaged for patients in the LAD subgroup (solid lines) and the whole study population (dashed lines) in leads V2 and V3.

Statistical analysis

Results for absolute and relative changes are presented as mean ± SD.

For the correlation analysis between the ECG indices and measures of ischemia, the Spearman rank correlation coefficient (r) was used because of the small number of patients. Statistical tests were 2-sided, and significance was defined as $p < 0.05$. Multiple linear regression (MLR) analysis was used to evaluate the additional value of QRS-angle changes to ST-segment changes when predicting the extent/severity of ischemia. Statistical analysis was performed using SPSS, version 19.0 (SPSS, Chicago, IL, USA).

Results

QRS angles

Fig. 2 (A) shows an example of the QRS angles $\O_R$, $\O_U$ and $\O_D$ evaluated for a particular patient in lead V4. Fig. 2 (B) and (C) display the QRS slopes s_U and s_D and the R-wave amplitude *Ra*, used here for comparison. As can be observed from Fig. 2, the QRS angles are stable at baseline. In the beginning of the occlusion, $\O_U$ and $\O_D$ in particular show an abrupt change with an almost complementary behavior. The angle $\O_R$, on the other hand presents a more gradual change compared to $\O_U$ and $\O_D$ during the occlusion period. From Fig. 2 it is possible to appreciate that the absolute variation of $\O_R$ is approximately 3.5º whereas 155º for $\O_U$ and $\O_D$. The QRS slopes and R-wave amplitude, evaluated for the same patient and lead, show notable changes during occlusion as well, with their evolution being similar to that of $\O_R$, however slower as compared to the angles $\O_U$ and $\O_D$.

Mean values of $\O_R$ of all patients at baseline, $\overline{\O}_R(l)$ were computed in each lead *l*. The lowest values were found in lead V4 (3.6º ± 1.7º) and highest in lead III (20.3º ± 13.3º), respectively. Normal variations given by the SD of $\O_R$ at baseline, averaged for all patients $\overline{\sigma}_R(l)$, ranged between 0.17º and 2.74º, depending on the lead.

Regarding $\O_U$ and $\O_D$, mean values $\overline{\O}_U(l)$ and $\overline{\O}_D(l)$ and normal variations $\overline{\sigma}_U(l)$ and $\overline{\sigma}_D(l)$ at baseline were considerably higher: $\overline{\O}_U(l)$ varied between 66º (lead V6) and 163º (lead V3), while $\overline{\sigma}_U(l)$ ranged between 3.29º and 10.01º. $\overline{\O}_D(l)$ varied between 7º (lead V2) and 105º (lead V6), while $\overline{\sigma}_D(l)$ ranged between 3.51º and 8.70º.

Temporal evolution of ischemia-induced depolarization changes

The evolution of changes observed for the QRS angles $\O_U$ and $\O_D$ is shown in Fig. 3. Absolute $\Delta_I(t)$ and relative

Table 1
The maximum relative change and their corresponding lead, achieved for each QRS angle ($I = \O_R, \O_U, \O_D$) during the occlusion in the total study population and within the three occluded artery subgroups (LAD, LCX and RCA).

Index	Total population	LAD	LCX	RCA
$\O_U$	Lead V2: 56	Lead V3: 266	Lead V5: 11	Lead III: 17
$\O_D$	Lead V3: 65	Lead V2: 354	Lead V5: 10	Lead III: 38
$\O_R$	Lead V3:18	Lead V3: 63	Lead V6: 18	Lead II: 19

$R_I(t)$ changes ($I = \O_U, \O_D$), averaged in the total population as well as the LAD subgroup, are displayed along 4 min of occlusion in leads V2 and V3. Maximum, relative changes of the three angles are shown in Table 1. In the LAD subgroup, maximum relative change of $\O_U$ and $\O_D$ was substantially larger than for the total population and for the other two subgroups RCA and LCX. Regarding absolute changes $\Delta_I(t)$ for these two indices along the coronary occlusion, it can be observed from Fig. 3 that the angles varied, in mean, around 75–90º in the LAD subgroup, whereas for the whole study population the variation caused by the induced ischemia was approximately 15–23º. The variations observed for $\O_R$ were considerably smaller as compared to $\O_U$ and $\O_D$, which can be explained by the lower changes observed in the slopes of the lines l_U and l_D as compared to the line l_R.

The results obtained for the QRS angles, especially for $\O_U$ and $\O_D$, far exceeded those obtained for other QRS-derived indices like QRS slopes, s_U and s_D, and the R-wave amplitude R_a, Maximum relative changes reached up to 9.3 (lead V3) for s_D and 6.01 (lead V2) for s_U, as previously reported.[20] In the case of R_a, the maximum relative change was achieved in lead II and was of 7.7 times its normal variation at baseline.

Spatial distribution of ischemia-induced ECG changes

QRS angles

Fig. 4 shows mean ± standard error of the mean (SEM) for $\Delta\O_U$ and $\Delta\ \O_D$ computed for each of the three subgroups in the 12 standard leads, both considering the total study population and the subset (n = 38) of patients with SPECT imaging data. The spatial distributions obtained for $\Delta\O_U$ and $\Delta\O_D$ were very closely related, as the behavior of the two angles during occlusion was almost complementary. Lead V1 is not represented in Fig. 4, as in several patients the QRS angles could not be measured in that lead due to the QRS morphology (usually QS complex). Those leads showing remarkable negative delta values (as leads V2-V4 in the LAD subgroup, Fig. 4-A) indicate that the angle $\O_U$ goes from higher values at baseline to lower values during occlusion. The opposite behavior was found for $\O_D$ in those cases.

According to the QRS-angle results shown in Fig. 4 the LAD subgroup could be separated from the LCX and RCA subgroups by evaluating $\O_U$ and $\O_D$ changes in most of the leads except for V5, aVL and −aVR. The three subgroups could be separated using the same two angles in leads aVF and III. These results suggest that identification of the occluded artery should be easier when distinguishing between the LAD subgroup and the other two subgroups (LCX and RCA) than when separating LCX from RCA.

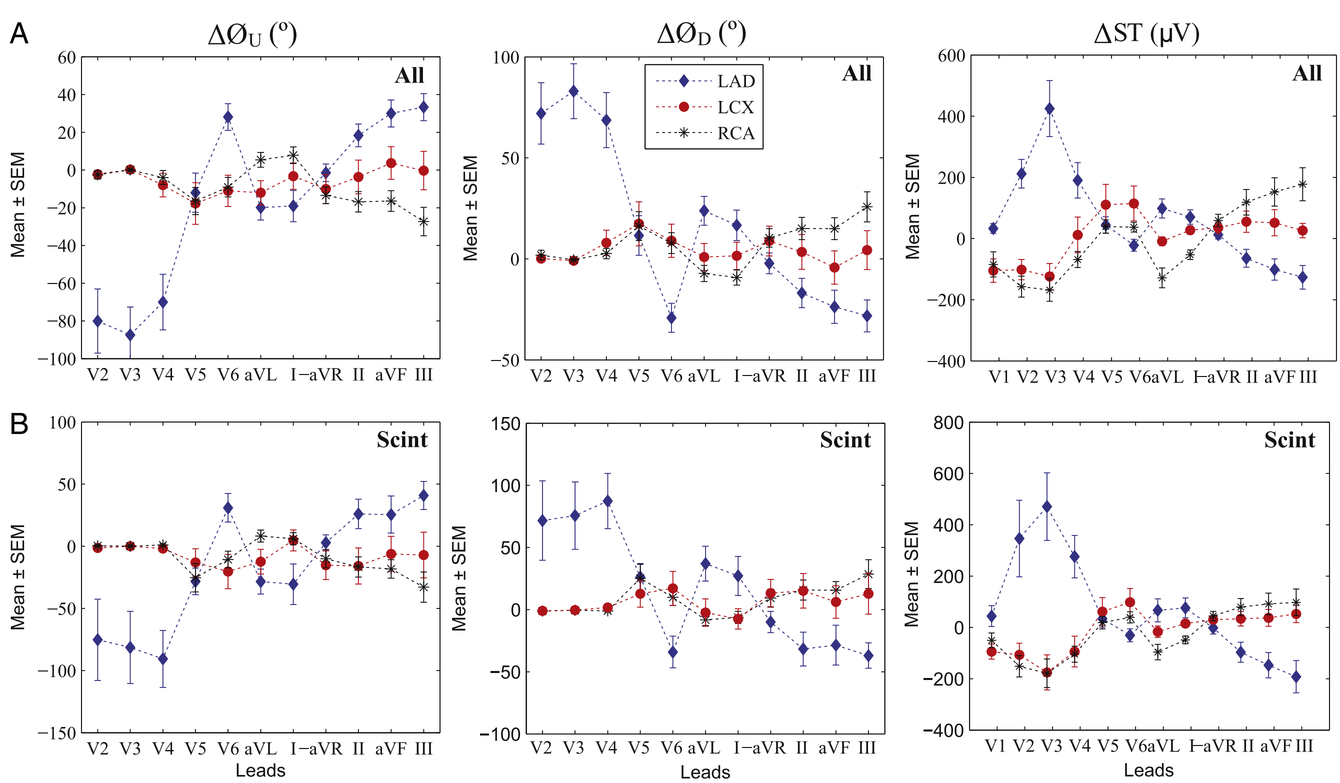

Fig. 4. Lead-by-lead spatial profile of the averaged absolute changes for $\O_U$, $\O_D$ and ST in A) the whole study population and B) the subset of patients with available scintigraphic data.

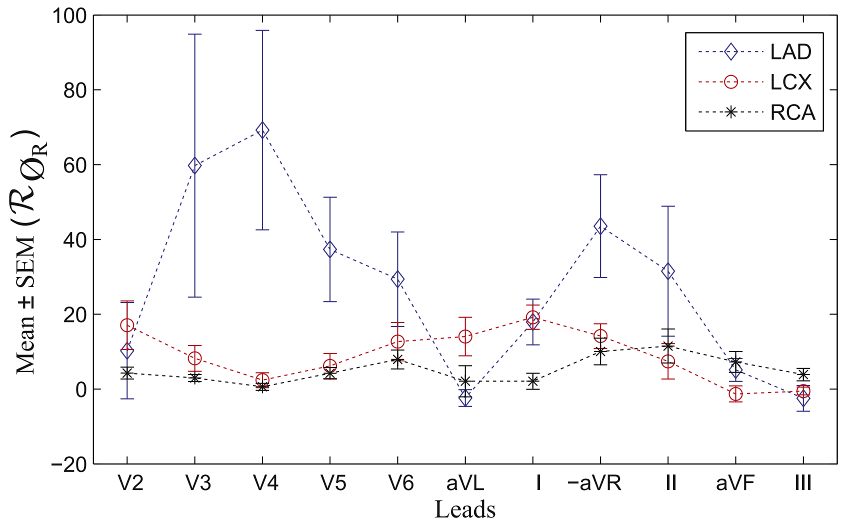

Fig. 5. Lead-by-lead spatial profile of the averaged relative changes for the angle $Ø_R$.

Regarding changes of the angle $Ø_R$, a less remarkable spatial lead profile was observed when absolute changes at the end of the occlusion were averaged. This could be due to the smaller range of variation presented by $Ø_R$. However, when relative changes were analyzed for $Ø_R$, the spatial lead profile showed more specific patterns, as illustrated in Fig. 5. Also in this case the LAD subgroup could be easily distinguished from the other two subgroups, while separation of LCX and RCA subgroups was less clear.

ST-segment changes

The spatial lead profile of the ST-segment deviation measured at the end of occlusion is also shown in Fig. 4 (right column). In this case lead V1 is also included. Both for the total study population and the subset of patients with SPECT imaging data, the spatial ST deviation profiles are similar to those observed for the angle $Ø_D$. The largest ST elevation within the LAD group was seen in leads V2-V4, whereas patients with RCA occlusions had most marked ST elevation in leads II, aVF and III. In the LCX cases the most pronounced ST deviations were depression in leads V2–V4.

Association between QRS angles and ischemia by SPECT

The ischemia during PCI quantified by SPECT as extent and severity for the subset of patients (n = 38) as well as subsets according to occluded coronary vessel is shown in Table 2. Absolute and relative changes of the QRS angles measured at the end of the occlusion were correlated with the extent and severity of ischemia, respectively, in the total population and in each of the three subgroups (LAD, LCX and RCA).

The correlation between $Ø_R$ changes (max change in any lead and sum of changes among all leads) and the two measures of ischemia is illustrated in Table 3. The highest overall correlation coefficient was seen between relative sum $Ø_R$ and ischemia ($r = 0.78$, $p < 0.001$ for extent and $r = 0.73$, $p < 0.001$ for severity). For both relative $Ø_R$ measures (max and sum) significant correlations regarding extent were seen within all 3 subgroups, with the highest correlation coefficients for the LAD group. When considering absolute $Ø_R$ changes, however, the correlation coefficients were considerably lower for the total population ($r = 0.45$, $p = 0.005$ for extent and $r = 0.39$, $p = 0.015$ for severity). Only the LAD subgroup showed a significant correlation for extent of ischemia, however not for severity. None of the other subgroups showed any significant correlation regarding the absolute $Ø_R$ changes (Table 3). The other two QRS angles, $Ø_U$ and $Ø_D$, which absolute and relative changes far exceeded those obtained for $Ø_R$ during coronary occlusion did not show any significant correlation with ischemia, either by absolute or relative changes.

Regression analysis involving both QRS-angle changes and ST-segment elevation

The sum of ST elevation among all leads and maximal single lead ST elevation were also considered for correlation with extent and severity of ischemia. Moreover, these two ST measures were used together with the same combinations in $Ø_R$ to evaluate their complementariness by multiple linear regression analysis. Table 4 summarizes the results of the regression analysis and shows the improvement in the prediction of ischemia when $Ø_R$ changes are added to the ST changes in each artery subgroup. In the LAD subgroup, no significant additive effect was seen as regards severity of ischemia either by absolute or relative $Ø_R$ changes. However a slightly higher additive effect by the 11–12% was noted for extent as the dependent variable when adding sum of relative $Ø_R$ changes to the respective ST measures. Furthermore, no

Table 2
Myocardial ischemia during occlusion expressed as extent and severity in patients with available scintigraphic data and subgroups according to the occluded coronary artery.

Occluded artery	Extent (% of LV)	Severity (%)
Total (n = 38)	20 ± 17 (0–65)	38 ± 8 (26–63)
LAD (n = 8)	43 ± 15 (15–65)	47 ± 9 (33–63)
LCX (n = 9)	19 ± 14 (4–45)	35 ± 5 (29–43)
RCA (n = 21)	12 ± 10 (0.1-32)	35 ± 7 (26–51)

Values are shown as mean ± SD (range). LV = left ventricle.

Table 3
Spearman rank correlation coefficients between the ischemia measures and both maximal, positive single-lead change in $Ø_R$, as well as the sum of positive changes in $Ø_R$, among all leads.

Group	Relative changes				Absolute changes			
	Extent (% of LV)		Severity (%)		Extent (% of LV)		Severity (%)	
	r	P	r	P	r	P	r	P
A) Total (n = 38)								
Max pos $Ø_R$	0.67	<0.001*	0.60	<0.001*	0.25	=0.128	0.20	=0.231
Sum pos $Ø_R$	0.78	<0.001*	0.73	<0.001*	0.45	=0.005*	0.39	=0.015*
B) LAD (n = 8)								
Max pos $Ø_R$	0.88	=0.004*	0.57	=0.139	0.88	=0.004*	0.38	=0.352
Sum pos $Ø_R$	0.95	<0.001*	0.71	=0.047*	0.81	=0.015*	0.50	=0.207
C) LCX (n = 9)								
Max pos $Ø_R$	0.72	=0.030*	0.50	=0.168	0.13	=0.732	0.09	=0.814
Sum pos $Ø_R$	0.87	=0.002*	0.66	=0.053	0.42	=0.265	0.20	=0.604
D) RCA (n = 21)								
Max pos $Ø_R$	0.51	=0.018*	0.37	=0.108	0.11	=0.642	0.24	=0.298
Sum pos $Ø_R$	0.66	=0.001*	0.58	=0.006*	0.22	=0.348	0.31	=0.166

Results are shown for both relative and absolute changes in $Ø_R$. The asterisk (*) indicates significant correlation.

increased extra value in the RCA subgroup was seen adding absolute $Ø_R$ changes, however between 22.6% and 24.6% adding sum of relative $Ø_R$ changes (Table 4). The most striking add-on effect by $Ø_R$ to the ST measures was noted for the LCX subgroup, in which the increase was up to 42.2% (absolute change) and 50.0 % (relative change) for extent, whereas at the most 15.8% for severity (relative change). When considering all occlusions together, regardless of location, the added value of $Ø_R$ is less noticeable, with corresponding percentages of improvement of 4.3% for the extent and 2.3% for the severity when adding absolute changes. When adding relative changes the percentages of improvement were of 16.7% for the extent and 7.9% for the severity.

Discussion

In the present study three new indices, $Ø_R$, $Ø_U$, and $Ø_D$, quantifying angles within the QRS complex, are proposed and evaluated in 12-lead ECG recordings during acute myocardial ischemia produced by prolonged, elective PCI. The computation of these angles is straightforward and robust as to measure alterations within the QRS complex during ischemia. The three angles showed high stability at baseline, as assessed by their standard deviations measured in the recording prior to the PCI. If absolute changes during the coronary occlusion are made relative to fluctuations at baseline, the QRS angles turn out to be very sensitive indices to the ischemia-induced changes as compared with other QRS-derived indices like QRS slopes and R-wave amplitude.[20] Regarding the temporal evolution of the QRS angles during ischemia, an important difference was noted between the angle $Ø_R$ and the other two angles, $Ø_U$ and $Ø_D$. While $Ø_R$ presented a gradual change, $Ø_U$ and $Ø_D$ developed a larger and very abrupt change some time after the start of the occlusion, which reaches a maximal value at a given time and remains stable from that time on. The differences observed between the three angles can be attributed to the fact that ischemia-induced changes in QRS amplitudes and/or QRS width have larger effects on the l_R line (which determines $Ø_U$ and $Ø_D$) than on the l_U or l_D lines (defining $Ø_R$). Results obtained in most of the analyzed leads suggest a widening of the QRS complex, due to the induced ischemia.

The spatial distribution of changes in the QRS angles suggests that their lead profiles could distinguish between the LAD subgroup and the other two subgroups (LCX and RCA), particularly considering the notable differences found in leads V2–V4. Discrimination between the LCX and RCA subgroups was more challenging, with the largest differences found in lead III. Similar results regarding the distinction between artery groups were reported by García et al. using ECG indices derived from the Karhunen-Loève transform in the same study population.[27] These results suggest that ischemia-induced depolarization changes may be tracked by leads overlying the ischemic region, however they do not seem to be more accurate than ST-segment changes in terms of localization of ischemia.

Despite larger changes within the angles $Ø_U$ and $Ø_D$ along the PCI, no significant correlations with ischemia were observed. A possible explanation for that may be that changes within $Ø_U$ (and $Ø_D$, respectively) were clustered into two groups of either very low or very high values, depending on the patient and lead, showing a clear non-linear relation with the ischemia measures, which are more evenly distributed along their respective range.

By presenting changes in the QRS angle $Ø_R$ as maximal positive, single lead change, or sum of positive changes among all leads at the end of occlusion, relative changes proved to be better predictors of the ischemia as compared to absolute values. The significant association between $Ø_R$ and the amount of ischemia by SPECT in the present study is interesting in comparison to our earlier findings regarding correlation between ischemia and QRS slope as well as R-wave amplitude changes, using the same dataset.[21] In the previous study, the maximal correlation with the extent and severity of the ischemia was found when considering changes in the downward slope of the R-wave, by the highest correlation coefficient (Spearman) of $r = 0.71$ ($p < 0.001$) and $r = 0.73$ ($p < 0.001$) for extent and severity, respectively. In the present study, relative changes in the

Table 4
Results of the multiple regression analysis for prediction of the extent and severity of ischemia by combining maximal positive, or sum of changes across leads in the angle $Ø_R$ and the ST level.

Predictor variables	Extent as dependent variable		Severity as dependent variable	
	Adding absolute $Ø_R$ change	Adding relative $Ø_R$ change	Adding absolute $Ø_R$ change	Adding relative $Ø_R$ change
	R^2, (p-value), increase in %		R^2, (p-value), increase in %	
LAD (n = 8)				
Max ST + Max pos $Ø_R$	0.767 (.026) ↑3.2%	0.768 (.026) ↑3.3%	0.738 (.035) ↑0.0%	0.759 (.028) ↑ 2.1%
Max ST + Sum pos $Ø_R$	0.777 (.023) ↑4.2%	0.848 (.009) ↑11.3%	0.759 (.028) ↑2.1%	0.759 (.029) ↑ 2.1%
Max ST	*0.735 (.006)*		*0.738 (.006)*	
Sum ST + Max pos $Ø_R$	0.727 (.039) ↑ 0.3%	0.807 (.016) ↑8.3%	0.760 (.023) ↑2.5%	0.735 (.036) ↑ 0.0%
Sum ST + Sum pos $Ø_R$	0.728 (.039) ↑ 0.4%	0.845 (.009) ↑12.1%	0.735 (.036) ↑0.0%	0.759 (.029) ↑ 2.4%
Sum ST	*0.724 (.007)*		*0.735 (.007)*	
LCX (n = 9)				
Max ST + Max pos $Ø_R$	0.617 (.056; NS) ↑24.0%	0.691 (.029) ↑31.4%	0.389 (.229; NS) ↑ 6.7%	0.435 (.180; NS) ↑11.3%
Max ST + Sum pos $Ø_R$	0.799 (.032) ↑42.2%	0.877 (.002) ↑50.0%	0.504 (.122; NS) ↑18.2%	0.596 (.066; NS) ↑27.4%
Max ST	*0.377 (.078; NS)*		*0.322 (.111; NS)*	
Sum ST + Max pos $Ø_R$	0.729 (.020) ↑22.4%	0.771 (.012) ↑26.6%	0.541 (.097; NS) ↑6.5%	0.555 (.088; NS) ↑7.9%
Sum ST + Sum pos $Ø_R$	0.768 (.013) ↑26.3%	0.873 (.002) ↑36.8%	0.555 (.088; NS) ↑7.9%	0.634 (.049) ↑15.8%
Sum ST	*0.505 (.032)*		*0.476 (.040)*	
RCA (n = 21)				
Max ST + Max pos $Ø_R$	0.324 (.029) ↑0.6%	0.449 (.005) ↑13.1%	0.300 (.041) ↑0.1%	0.465 (.001) ↑16.6%
Max ST + Sum pos $Ø_R$	0.318 (.032) ↑0.0%	0.550 (.001) ↑23.2%	0.311 (.035) ↑1.2%	0.525 (.001) ↑22.6%
Max ST	*0.318 (.004)*		*0.299 (.010)*	
Sum ST + Max pos $Ø_R$	0.371 (.015) ↑0.5%	0.531 (.001) ↑16.7%	0.335 (.025) ↑0.1%	0.539 (.001) ↑20.5%
Sum ST + Sum pos $Ø_R$	0.364 (.017) ↑0.0%	0.610 (<.001) ↑24.6%	0.342 (.023), ↑0.8%	0.576 (<.001) ↑24.2%
Sum ST	*0.364 (.004)*		*0.334 (.006)*	

The increases, expressed as %, are referred to the value obtained using just the ST change (Sum ST or Max ST). NS indicates non-significant correlation. Max ST = maximal ST elevation in any lead; Sum ST = summed ST elevation among all 12 leads; Max pos $Ø_R$ = maximal $Ø_R$ in any lead; Sum $Ø_R$ = summed $Ø_R$ among all 12 leads.

angle $Ø_R$ led to maximal correlation coefficients of r = 0.78 ($p < 0.001$) and r = 0.73 ($p < 0.001$), respectively. This suggests that the more simple evaluation of the R-wave angle seems to be at least as good predictor of ischemia as compared to the down-slope of the R wave. The improvement with respect to other depolarization indices is especially true for LAD occlusions both regarding extent and severity of the ischemia. In LCX and RCA subgroups there was either no correlation or lower correlation to severity if considering either the maximum or the sum of $Ø_R$ values among all leads, although significant relation to extent was seen. More severe ischemia in the LAD occlusions and thus more evident slowing of the regional depolarization wavefront through the ischemic region could possibly explain this difference between artery subgroups.

By regression analysis relative changes in the angle $Ø_R$ used in conjunction with ST changes led to highly variable performance in the additional prediction of extent and severity of the ischemia as compared to the ST changes alone. The additive effect was modest in the LAD group, but more evident in the patients with RCA occlusion. However, the largest and most striking improvement was seen in the LCX subgroup. In this group also the additional value of absolute $Ø_R$ changes was high. In general, by the 12-lead standard ECG there are difficulties regarding the evaluation of ischemia produced by LCX occlusions as far as ST-segment deviation. The present finding of the additive value of QRS changes by the $Ø_R$ to that of ST changes, concerning particularly the LCX occlusions, raises interesting questions whether this may have important clinical implications for prediction of ischemia within this region.

The results corroborate the importance of using several indices corresponding to different phases of the ECG to better describe the amount of acute ischemia. Comparing the results of the present study with those reported in Ringborn et al,[21] which considered the depolarization indices QRS slopes and the R-wave amplitude in *absolute* terms, the added value of $Ø_R$ changes was found to be slightly overall lower to that of the downward QRS slope when combined with ST changes.

The results of this study suggest that changes in the angles $Ø_U$ and $Ø_D$ could be potentially useful in the detection of acute ischemia episodes, as they present very abrupt changes after the start of ischemia, as well as in the identification of the occluded artery, particularly in distinguishing the LAD subgroup from the LCX and RCA subgroups. On the other hand, changes in the angle $Ø_R$, which may be seen as a robust surrogate measure of particularly QRS duration, could be used for prediction of the extent and severity of the ischemia.

Limitations

This particular database represents a unique human model of about 5-min duration of controlled ischemia by PCI, which also provides myocardial scintigraphy as the gold standard for the amount of ischemia in a subset of patients (n = 38). The latter subset is small, in particular when considering occluded vessel-specific results. Therefore, the statistical findings regarding multiple correlation analyses between ECG changes and the ischemia must be interpreted with this in mind. Besides, generalization of the present results to other clinical scenarios is not straightforward, as there is not usually a baseline ECG recorded immediately before ischemia followed by another ECG recorded throughout ischemia, and thus relative ECG changes are not often possible to assess, and only absolute changes can be measured. Therefore gradual QRS changes may be most likely evaluated in monitoring situations, such as during pre-hospital transport of STEMI patients to pPCI, general in-hospital evaluation of patients with acute coronary syndrome including post-revascularization evaluation of recurrent ischemia as well as in stress test situations. However, further analysis is required to assess the effect of additional factors such as movement artifacts, among others.

Conclusions

In this study QRS angles have been proposed for evaluation of ischemia-induced changes during coronary occlusion. Relative changes of the QRS angles are suggested as an adjunct tool to conventional ST-T analysis for detecting and quantifying acute ischemia. Furthermore, changes in the R-wave angle, seen as a surrogate marker of QRS duration, could be used as predictors of the extent and severity of the ischemia, both by themselves and in conjunction to ST changes. However, further studies are needed to expand this to a more clinical acute ischemia situation and in larger study samples.

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