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Discrimination between Demand and Supply Ischemia Episodes in Holter Recordings

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Abstract— **ST segment changes provide a sensitive marker in the diagnosis of myocardial ischemia in Holter recordings. However not only the mechanisms of ischemia result in ST segment deviation but also heart rate related events. The very similar signature of ST modifications in ischemia and heart rate related events have driven us to look for other ECG indexes allowing to discriminate between them. Heart rate-based indexes, correlation between the absolute ST segment deviation and heart rate series, the interval between T apex and T end and changes in the upward/downward slopes of the QRS complex have been shown as significant discriminant parameters, getting a sensitivity for the ischemic events** $SE = 82.2\%$**, specificity** $SP = 88.4\%$**, positive predictivity value** $+PV = 87.6\%$ **and negative predictivity value** $-PV = 83.2\%$ **in ST events of the Long Term ST database.**

I. INTRODUCTION

Myocardial ischemia is the most common cause of death in the industrialized countries and, as a consequence, its early diagnosis and treatment is of great importance [1].

Myocardial ischemia can be defined as the imbalance between oxygen/nutrient delivery with regard to myocardial requirements. It is usually produced when a coronary artery gets slightly occluded reducing the amount of blood and then oxygen in the heart. Ischemia is a transient phenomena, then time constrained and could be missed during physical examination and routine electrocardiography (ECG) because these procedures permit only a few seconds of observation. To diagnose ischemia, longer periods of ECG recording are required while the patient is pursuing his or her normal routine. The most common method is Holter monitoring that gives a constant reading of two to three channels of ECG data over a 24-hour period.

The cellular modifications generated by acute ischemia are responsible for changes in the ST segment, which makes ST segment changes as an early marker of ischemia [2]. Electrocardiographic images of ischemia are different depending on whether the ischemic area affects mainly the sub-endocardium or the sub-epicardium. In case of sub-endocardial ischemia ST depression appears of different intensity according to the degree and in case of sub-epicardial or transmural ischemia ST elevation occurs [3].

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However, changes in the ST segment are also caused by ST events not generated by transient artery occlusions such as heart rate related events, body position changes or conduction changes. This makes ischemia detection in ambulatory recordings a difficult task.

Several techniques that automate ischemia detection have been proposed during the last decade and neatly rely on ST changes. However distinction between ST changes given by artery occlusion (*supply ischemia*) or because increased demand (*demand ischemia*) could be highly desirable in order to have a proper diagnosis of the occlude artery problem [4] [5].

For the 2003 Physionet/Computers in Cardiology Challenge [6] it was proposed to classify ST changes as ischemic or non-ischemic (heart rate- related, axis shifts or conduction changes) using a set of 43 freely available annotated records of the Long Term ST Database (LTSTDB) as training set and the remaining 43 as the test set. Only two groups ended up the challenge with a performance in terms of sensitivity/positive predictivity of 98%/83% and 64%/48%. The top scoring entry of this challenge [7] considered only the change in ST relative to a baseline ST level provided by the PhysioNet database, and based on level thresholding within specified time windows. In this challenge there was no distinction between the two different patterns: transient ST events such as heart rate related events and sudden shifts in the ST segment produced by axis shifts or conduction changes. Alternatively, in this work we do no consider axis changes but we concentrate on distinguishing between ischemic ST episodes and heart rate related events; both of them with similar ST patterns so being the more problematic to differentiate by automatic ischemia detectors.

II. MATERIALS AND METHODS

A. Long-Term ST Database

The LTSTDB [8] consists of 86, two or three leads, 21 to 24 hour, Holter ECG recordings sampled at $f_s = 250$ Hz. Complete expert annotations have been provided for the database following different annotation protocols and with the clinical history as the gold standard for episode classification. Although ST changes provide a sensitive marker of supply ischemia, there are a variety of other events that result in ST segment changes as we mentioned before. In the LTSTDB non-supply ischemic events such as heart rate related events, body position changes and conduction changes were also annotated. The dynamics of these ST changes is different in each case. Heart rate related events as well as supply ischemic events are considered transient ST segment episodes

characterised by a duration and a extremum deviation, while body position changes and conduction changes are bounded with a sudden shift in the ST level function. One ST episode, ischaemic or non-ischaemic heart-rate related, had to be significant to be annotated according to the following rules: a) episode beginning when the magnitude of the ST deviation first exceeds 50 μV, b) ending when the deviation becomes smaller than 50 μV, provided that it does not exceed 50 μV in the following 30 s and c) the deviation must reach a magnitude of V_{min} or more throughout a continuous interval of at least T_{min} s.

Three different protocols A, B and C are set depending on V_{min} and T_{min}.

- Protocol A: $V_{\mathrm{min}} = 75\ \mu V$ and $T_{\mathrm{min}} = 30$ s.
- Protocol B: $V_{\mathrm{min}} = 100\ \mu V$ and $T_{\mathrm{min}} = 30$ s.
- Protocol C: $V_{\mathrm{min}} = 100\ \mu V$ and $T_{\mathrm{min}} = 60$ s.

In this work we have used protocol B for the classification analysis. Annotations are attached to the lead or leads where the episode is significant, so all the study will consider the lead at which the annotated episodes are linked to.

We select the set of ST episodes from the annotated LTSTDB, removing manually those with mistakes in the T wave delineation process, and resulting in 735 ST episodes evaluated in the performance analysis. From those, 623 are ischemic and 112 heart rate related events.

B. Classification between heart rate related and ischemic events

Different ECG features (F) measured from repolarization, depolarization and heart rate indexes have been used in a discriminant analysis. These features have been computed in three different intervals ($I1$, $I2$ and $I3$) of 30 s each, located around each ST episode as described in Fig. 1. Changes between them ($\Delta\mathrm{F}$) across the three intervals ($\Delta\mathrm{F}_{12}$, $\Delta\mathrm{F}_{13}$ and $\Delta\mathrm{F}_{23}$) have been evaluated (Fig. 1). All the indexes are computed over the ECG after removal of the baseline wander with a cubic splines technique. The same preprocessing was applied to all recordings and should affect similarly all of them.

$\Delta\mathrm{F}_{\mathrm{jk}}$ is defined as the difference across intervals of the mean feature value in every interval, equation 1.

$$\Delta\mathrm{F}_{\mathrm{jk}} = \frac{\sum_{\mathrm{i}\in\mathrm{I_k}} \mathrm{F}\,(i)}{N_{\mathrm{I_k}}} - \frac{\sum_{\mathrm{i}\in\mathrm{I_j}} \mathrm{F}\,(i)}{N_{\mathrm{I_j}}} \qquad (1)$$

where i is an integer denoting the i^{th} beat order in interval I and $N_{\mathrm{I_k}}$ and $N_{\mathrm{I_j}}$ are the number of beats at interval I_{k} and I_{j} respectively.

1) Repolarization indexes (Fig. 2):

- The ST level series are estimated in each i^{th} beat and lead by averaging the first 8 ms of the ECG signal from a heart rate related position ($n_{\mathrm{ST}}(i)$) from the QRS fiducial point defined as the center of gravity of the whole QRS complex ($n_{\mathrm{QRS}}(i)$):

$$\mathrm{n_{ST}\,(i)} = \mathrm{n_{QRS}\,(i)} + \left(40 + 1.3\sqrt{\mathrm{RR\,(i)}\frac{1000}{\mathrm{fs}}}\right)\frac{\mathrm{fs}}{1000} \qquad (2)$$

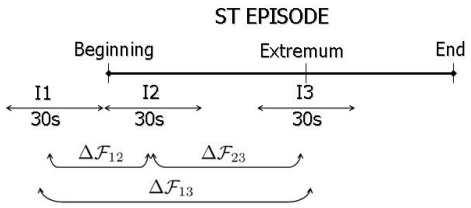

Fig. 1. The three different intervals $I1$, $I2$ and $I3$ used to compute $\Delta\mathrm{F}_{12}$, $\Delta\mathrm{F}_{13}$ and $\Delta\mathrm{F}_{23}$ are shown.

where $RR(i) = n_{\mathrm{QRS}}(i) - n_{\mathrm{QRS}}(i-1)$.

Changes in the deviation of the ST level are denoted as ΔST_{12}, ΔST_{13} and ΔST_{23}. The absolute value of these changes in the ST level series are also considered for the classification analysis and denoted as $|\Delta ST_{12}|$, $|\Delta ST_{13}|$ and $|\Delta ST_{23}|$.

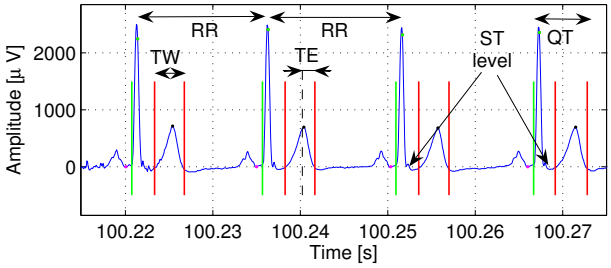

Fig. 2. In this figure it is shown the different intervals used for obtaining the series of T width (TW), T apex to T end (TE), the QT interval (QT) and the RR interval used for the HR series. The ST level series is calculated by averaging the first 8 ms of the ST.

- As a potential feature related to repolarization dispersion and eventually related also to ischemia [9], the width of the T wave was measured in each lead of the ECG using a wavelet-based ECG delineator [10]. Changes of the T wave width across the three intervals are denoted as ΔTW_{12}, ΔTW_{13} and ΔTW_{23}.
- Analogously, changes in the interval from the peak to the end of the T wave are measured in each lead as dispersion markers. These changes measured in each ST episode are denoted as ΔTE_{12}, ΔTE_{13} and ΔTE_{23}.
- Differences of the QT interval have been also measured in the lead of each annotated ST episode over the same intervals (ΔQT_{12}, ΔQT_{13} and ΔQT_{23})
- The correlation between the heart rate series (HR) and the deviation of the ST level series within an interval (I) from 20 s before the beginning of the ST episode to the expert annotated extremum of it has also been evaluated and referred to as ρ. It has been calculated after resampling the series to an evenly sampling frequency of 1 Hz in the following way:

$$\rho = \sum_{\mathrm{k}\in\mathrm{I}} \frac{(ST(k) - \mu_{\mathrm{ST}})(HR(k) - \mu_{\mathrm{HR}})}{N\sigma_{\mathrm{ST}}\sigma_{\mathrm{HR}}} \qquad (3)$$

where μ_{ST} and μ_{HR} are the mean in each vector series, σ_{ST} and σ_{HR} are the standard deviation of the ST vector and heart rate vector series, and N the number of elements of the vector.

TABLE I

THIS TABLE SHOWS THE SUMMARY OF THE MEANS AND STANDARD DEVIATION IN ISCHEMIC AND HEART RATE RELATED EVENTS, PERFORMANCE AND P-VALUE OF THE DIFFERENT VARIABLES USED IN THE CLASSIFICATION ANALYSIS.

VARIABLES	ISCHEMIC EVENTS		HR RELATED EVENTS		PERFORMANCE					P-VALUE
	MEAN	STD. DEV.	MEAN	STD. DEV.	SE	SP	+PV	-PV	EX	
$\lvert\Delta HR_{13}\rvert$ (bpm)	9.93	9.40	18.86	11.46	76	60.7	65.9	71.6	73.7	$5.8\ E-18$
$\lvert\Delta ST_{13}\rvert\ (\mu V)$	144.07	82.98	93.76	47.48	55.2	78.6	72.0	63.7	58.8	$1.1\ E-09$
$\Delta ST_{13}\ (\mu V)$	– 71.07	150.4	– 26.25	102.13	77.9	42.9	57.7	66	72.6	$2.7\ E-03$
$HR_{\mathtt{ext}}$ (bpm)	85.25	19.48	101.74	19.91	65.3	63.4	64.1	64.6	65	$1.5\ E-15$
ΔSl_{23}	6.61	154.36	50.98	155.56	58.7	50.9	54.5	55.2	57.6	$5.6\ E-03$
ΔQT_{13} (ms)	– 4.55	27.3	– 27.8	31.64	74.2	57.1	63.4	68.9	71.6	$3.4\ E-15$
ΔTE_{12} (ms)	– 2.34	7.29	– 1.60	9.86	49.3	58.0	54.0	53.4	50.6	0.35
$\lvert\Delta HR_{12}\rvert$ (bpm)	5.05	5.33	9.89	7.53	77.0	58.0	76.0	71.6	74.1	$1.3\ E-15$
$TW_{13}(ms)$	– 18.1	25.6	– 30.4	36.5	65.9	53.6	58.7	61.1	64.0	$4.6\ E-05$
ρ	– 0.04	0.55	– 0.32	0.57	55.4	65.2	61.4	59.4	56.9	$3.9\ E-06$
ΔSe_{23}	– 16.4	122.5	27.0	116.3	60.8	54.5	57.2	58.2	59.9	$5.8\ E-04$

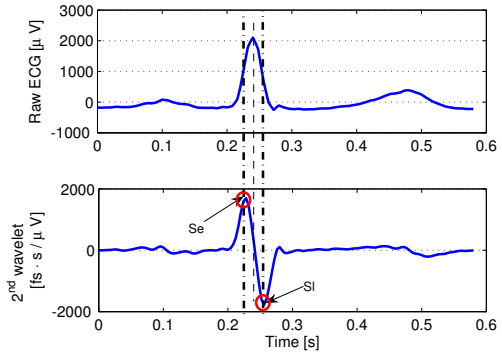

Fig. 3. In this figure it is shown the QRS complex of the raw ECG signal in the upper figure and its second scale wavelet transform in the lower figure. The maximum and minimum of the wavelet transform corresponds to the two steepest slopes. Note that zero crossing of the wavelet transform corresponds with the peak of the QRS complex.

2) Depolarization indexes: Changes in the steepest slopes of the QRS complex that will be referred to as the early (Se) and late (Sl) slopes, are considered in the classification analysis. Se and Sl can be sequenced either upward/downward or downward/upward depending of the QRS morphology. The QRS slope series are computed by taking, from the processing in the QRS detection [10], the second scale-wavelet transform maximum (minimum) that correspond to the maximum (minimum) derivative of the QRS complex (see Fig. 3). Changes in the absolute values of these series (early and late QRS slopes) across the three intervals are taking into account and denoted as ΔSe_{12}, ΔSe_{13}, ΔSe_{23}, ΔSl_{12}, ΔSl_{13} and ΔSl_{23}.

3) Heart rate indexes: Changes in the heart rate corresponding to the three intervals were also measured (ΔHR_{12}, ΔHR_{13} and ΔHR_{23}). The absolute value of these changes are also analysed and referred to as $\lvert\Delta HR_{12}\rvert$, $\lvert\Delta HR_{13}\rvert$ and $\lvert\Delta HR_{23}\rvert$. The absolute value averaging 40 s before the beginning the ST episode and 40 s around the extrema were computed and denoted as $HR_{\mathtt{bef}}$ and $HR_{\mathtt{ext}}$ respectively.

C. Statistical Analysis

First monovariate ANOVA discriminant analysis is performed to each variable so to establish the individual significance for classification performance. The multivariate discriminant analysis has been used to pick out the most significant indexes that distinguish ischemic from heart rate related events. The stepwise approach is applied, using the Wilk's Lambda minimization as the criteria for entry and removal of variables [11]. F statistic is set to 3.84 for entry and 2.71 for removal.

The cross-validated estimation (leave-one-out) is applied for the classification results. As the name suggests, leave-one-out cross-validation (LOOCV) uses a single observation from the original sample as the validation data, and the remaining observations as the training data. This is repeated such that each observation in the sample is used once as the validation data.

The performance analysis was calculated in terms of sensitivity (SE), specificity (SP), positive predictivity value ($+PV$), negative predictivity value ($-PV$) and exactness (EX).

III. RESULTS

The mean and the standard deviation of several variables evaluated in the discriminant analysis for the two different groups (ischemic and heart rate related) are presented in Table I. The performance analysis and the p value of the discrimination between groups are also evaluated for each variable individually (Table I).

For the multivariate analysis, the stepwise method based on the minimization of the Wilk's Lambda has picked out as the most significant variables entering in the classification analysis $\lvert\Delta HR_{13}\rvert$, $\lvert\Delta ST_{13}\rvert$, ΔST_{13}, $HR_{\mathtt{ext}}$, ΔSl_{23}, ΔQT_{13}, ΔTE_{12}, $\lvert\Delta HR_{12}\rvert$ and ΔTW_{13}. Table II shows the classification performance in terms of SE, SP, $+PV$ and $-PV$, obtained when adding new significant variables in the stepwise approach.

IV. DISCUSSION AND CONCLUSIONS

Although some indexes show a poor performance individually (Table I), they may have complementary information or minimize the variance of the groups so that increasing the combined performance and being included in the multivariate analysis (Table II).

TABLE II

THIS TABLE SHOWS THE IMPROVEMENT IN CLASSIFATION PERFORMANCE BETWEEN SUPPLY ISCHEMIC EVENTS AND HEART RATE RELATED EVENTS IN TERMS OF SE, SP, $+PV$, $-PV$ AND EX, IN EACH STEP OF THE METHOD

VARIABLES (ORDERED BY CLASSIFICATION RELEVANCE)	SE	SP	+PV	-PV	EX
$\lvert\Delta HR_{13}\rvert$	76.0	60.7	65.9	71.7	73.7
$\lvert\Delta HR_{13}\rvert$, $\lvert\Delta ST_{13}\rvert$	78.7	77.7	77.9	78.5	78.6
$\lvert\Delta HR_{13}\rvert$, $\lvert\Delta ST_{13}\rvert$, ΔST_{13}	79.8	80.4	80.3	79.9	79.9
$\lvert\Delta HR_{13}\rvert$, $\lvert\Delta ST_{13}\rvert$, ΔST_{13}, HR_{ext}	79.5	84.8	84.0	80.5	80.3
$\lvert\Delta HR_{13}\rvert$, $\lvert\Delta ST_{13}\rvert$, ΔST_{13}, HR_{ext}, ΔSl_{23}	80.1	88.4	87.3	81.6	81.4
$\lvert\Delta HR_{13}\rvert$, $\lvert\Delta ST_{13}\rvert$, ΔST_{13}, HR_{ext}, ΔSl_{23}, ΔQT_{13}	80.7	85.7	85.0	81.6	81.5
$\lvert\Delta HR_{13}\rvert$, $\lvert\Delta ST_{13}\rvert$, ΔST_{13}, HR_{ext}, ΔSl_{23}, ΔQT_{13}, ΔTE_{12}	80.6	88.4	87.4	82.0	81.8
$\lvert\Delta HR_{13}\rvert$, $\lvert\Delta ST_{13}\rvert$, ΔST_{13}, HR_{ext}, ΔSl_{23}, ΔQT_{13}, ΔTE_{12}, $\lvert\Delta HR_{12}\rvert$	81.7	90.2	89.3	83.1	83.0
$\lvert\Delta HR_{13}\rvert$, $\lvert\Delta ST_{13}\rvert$, ΔST_{13}, HR_{ext}, ΔSl_{23}, ΔQT_{13}, ΔTE_{12}, $\lvert\Delta HR_{12}\rvert$, ΔTW_{13}	82.2	88.4	87.6	83.2	83.1

As it was expected, heart rate related events, associated to demand ischemia, have a direct relation to a higher increment of the heart rate as opposed to supply ischemic events. The absolute heart rate in demand ischemia is about 15 bpm higher than in supply ischemia, Table I. This is reflected also by changes in the QT interval, that is adapted to the RR interval. In ischemic events QT interval is hardly shortening (about 4 ms) while in heart rate related events QT interval is reduced about 28 ms.

Alterations in the late steepest slope is proposed as an index to quantify ECG changes in supply ischemia, resulting that QRS slopes were considerably less steep during prolonged ($\backsimeq$ 4 minutes) artery occlusion [12]. However, in short term ($\backsimeq$ 1 minute) angioplasty episodes, discrepant slope variations were found [13]. Our results show no concluding changes.

A greater shortening in the T width is observed in heart rate related (– 30 ms) than in ischemic events (– 18 ms) although the interval between T apex to T end does not seem to be correlated with that, so the QRS to T apex should be the responsible for the T wave shortening.

In both types of episodes appears ST level depression. In the ischemic events the ST level decrease about 71 μV and heart rate related events about 26 μV. The absolute deviation of the ST segment is also included in the significant parameters, being the ischemic events the ones that shows a higher amplitude of 144 μV in mean and heart rate related events about 93 μV.

Transmural ischemia is reflected in ST elevation while subendocardial ischemia shows ST depression. However, in Holter recordings it is very difficult to differentiate between subendocardial and transmural ischemia; indeed most of the cases are in between. Our results are compatible with this ST depression tendency, being the ischemic events the ones with higher absolute deviation.

We noticed variables with a very high p-value such as ΔTE_{12}, entering in the classification results while other parameters such as ρ did not enter, meaning that the classification information given by ρ was already supplied by the earlier parameters included in the analysis.

In relation with the Physionet/Computers in Cardiology Challenge, our results are compatible with [7] since changes in the ST level is a very important parameter for distinguishing between ischemic and non-ischemic ST events (heart rate related events, body position changes and conduction changes). However it is not enough when comparing two types of episodes with a very similar signature as ischemic and heart rate related events. We need further information as combining heart rate and repolarization indexes with a greater discriminant power.

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