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COMPUTER-AIDED DIAGNOSIS OF CORONARY ARTERY DISEASE BY MEANS OF STRESS ECG

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ABSTRACT

Several indexes have been reported to improve the performance of classical exercise test ECG analysis in coronary artery disease (CAD) diagnosis (based on ST depression criterion). The aim of this work was to identify the best exercise ECG indexes for CAD diagnosis. Indexes were estimated from the ECGs of 115 patients undergoing an exercise test. Since exercise test recordings are usually very noisy, a robust method to automatically estimate repolarization and depolarization indexes was used. A discriminant analysis was applied to classify patients into: *ischemic* (positive coronary angiography) and *low-risk* (Framingham risk index $< 5\,\%$). HR-corrected repolarization indexes improved the sensitivity (SE) and specificity (SP) of classical exercise test (SE=90 %, SP=79 % vs. SE=65 %, SP=66 %), as well as depolarization indexes did (SE=78 %, SP=81 %). Depolarization indexes did not add significant information to HR-corrected repolarization indexes. HRV indexes obtained the best classification results (SE=94 %, SP=92 %) by means of the very high frequency power (VHF) (0.4 to 1 Hz) at stress peak.

1. INTRODUCTION

The classical interpretation of the exercise ECG for the diagnosis of coronary artery disease (CAD), based on the ST segment depression criterium, has limited accuracy in clinical studies with reported sensitivities (SE) of 68 %±16 % (mean±standard deviation(SD)) and specificities (SP) of 77 %±17 % [8].

The study of new indexes to improve the diagnostic performance of the exercise ECG is challenging.

It has been shown that the addition of heart rate (HR) information to ST level measurements improves the CAD diagnostic accuracy of exercise testing. Several indexes can be computed from the diagram of the ST depression against the HR (referred to as ST/HR diagram), such as the HR-adjusted ST depression [5] and the so-called ST/HR hysteresis, which measures the average ST depression difference between the exercise and recovery phases relative to HR [13].

Indexes measured on the depolarization period, such as the Athens QRS score [19] and the QRS duration [18], have been also proposed to improve the exercise test CAD diagnostic value. In other works, alternative combinations of QRS amplitude indexes have shown a better performance than the Athens QRS score [7].

Finally, there is some evidence of the relation of the sympathetic and parasympathetic nervous system activity (measured by means of HRV) to the incidence of CAD. The relation of HRV and ischemic cardiomyopathy has been studied during ambulatory monitoring [3] and, much less extensively, during exercise testing [6].

Exercise ECG recordings are usually contaminated with a high noise level since the patient is constantly moving. It has been observed that repolarization and depolarization indexes are highly sensitive to exercise test noise, especially when automatically estimated. Therefore, a robust signal processing method to automatically estimate repolarization and depolarization indexes in noisy exercise ECG recordings is needed.

The aim of the work was to identify the best exercise ECG indexes to discriminate between CAD patients and low CAD-risk subjects.

2. MATERIALS AND METHODS

2.1. Study population

The ECGs of 844 patients referred to treadmill exercise test (following Bruce Protocol) were recorded in the University Hospital 'Lozano Blesa' of Zaragoza (Spain). Standard leads (V1, V3-V6, I, II, III, aVR, aVL and aVF)

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and RV4 were digitally recorded at 1-KHz sampling rate with an amplitude resolution of 0.6 μV. The classical standard lead V2 was substituted by lead RV4 to extract more information from the right part of the heart, as suggested in [17]. The investigation was conformed to the principles outlined in the Declaration of Helsinki. The procedures and protocols used in this study were approved by the Ethics Committee of the hospital. Informed consent was obtained from all subjects prior to data collection.

Patients were classified in two groups:

Ischemic: This group was composed by 79 patients with significant stenoses in at least one major coronary artery as shown by coronary angiography (gold standard).

Low-risk: The gold standard to include patients in this group was the Framingham risk index. The Framingham risk algorithm computes the 10-year predicted risk of developing manifest CAD using data of several risk factors (age, total and HDL cholesterol, blood pressure, diabetes and smoking) [4]. Information on all risk factors was not available for all patients. The score given to risk factors with missing information was zero. Only patients with information on at least 4 (out of 6) risk factors presenting an index lower than 5 % were included in the *low-risk* group. Three of the patients classified as *low-risk* by the Framingham index were indeed *ischemic*, as shown by coronary angiography, and, therefore, excluded from this group. Finally, the *low-risk* group consisted of 44 patients (22 with information on 6 risk factors, 6 on 5 and 16 on 4), all presenting negative clinical and electrical exercise test.

The remaining 721 non-classified patients were not analyzed in this study.

A total of 8 ECGs (7 from *ischemic* and 1 from *low-risk*) were excluded from the analysis due to power line interference, excessive baseline variations, signal loss or excessive ectopic beat rate.

The study population characteristics are summarized in Table 1.

Characteristic	*Ischemic*	*Low-risk*
Number	72	43
Age(yr)*	59±10	41±13
Sex(male/female)	68/4	28/15
MaxHR(beats/min)*	132±19	173±14
10-year CAD risk(%)*	18±11	3±1

* Mean±Standard Deviation (SD).
MaxHR:maximum heart rate achieved.

Table 1. Study population characteristics.

2.2. ECG indexes

2.2.1. Repolarization and depolarization indexes

Two different time periods were considered: the beginning of the recording (S1) and the exercise peak (S2), defined as the instant of maximal heart rate (see Fig. 1). The duration of S1 and S2 were 11 beats.

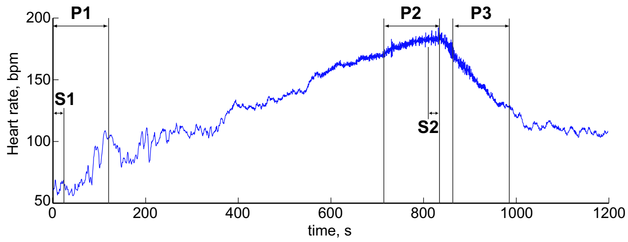

Figure 1. Time periods for the ECG indexes estimation overplotted on a HR series.

Repolarization indexes

• ST indexes (*Repo*): ST level was estimated averaging 10 ms of ECG signal at a HR-dependent distance from the QRS fiducial point [1]:

$$STpoint = QRSpoint + (40ms + 1{,}2 \cdot RR^{1/2}).$$

The QRS fiducial point was defined as the center of gravity of the whole QRS complex. The isoelectric level was obtained averaging 10 ms of signal starting 70 ms before the QRS fiducial point. ST level at exercise peak (S2) was denoted as STp. The ST difference (ΔST) was computed between S2 and S1. The absolute value of the ST difference ($|\Delta ST|$) was also considered to take into account either a depression or an elevation of ST level.

• HR-corrected repolarization indexes (*Repo/HR*): Several indexes were measured from the ST/HR diagram: the ST difference corrected by the HR increment between S2 and S1 ($\Delta STc = \Delta ST/\Delta HR$) [5], the corresponding absolute value ($|\Delta STc|$) and the ST/HR hysteresis (*STHL*), defined as the integrated difference between ST depression during exercise and recovery over HR from 3 minutes after stress peak to the maximum HR, normalized by the HR increment [13] (see Fig. 2).

Depolarization indexes (*Depo*)

Amplitude of Q, R and S waves and QRS duration were automatically measured on the corresponding beat using the system described in [7, 12]. Indexes ΔQ, ΔR, ΔS and $\Delta QRSd$ were computed as the differences between S2 and S1 values. Due to the high noise level at stress peak, QRS duration usually could not be correctly estimated on each lead. The $\Delta QRSd$ considered in this study was the averaged QRS duration among all leads, after visual inspection and rejection of outlier measures.

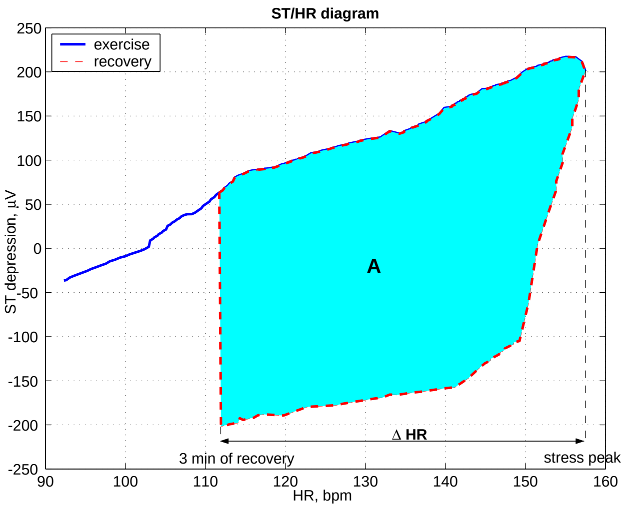

Figure 2. ST/HR diagram: ST/HR hysteresis = $\frac{A}{\Delta HR}$; A = area between the recovery and exercise ST depression values; ΔHR = HR difference between stress peak and the first 3 minutes of recovery.

Robust estimation of repolarization and depolarization indexes

The estimation of repolarization and depolarization indexes is highly sensitive to the high noise content of exercise ECG recordings, specially around the stress peak when the muscular activity of the patient is high. A robust signal processing method described in [2] was used to automatically estimate repolarization and depolarization indexes. The method is divided in three stages: first, a *preprocessing* step, where QRS detection, filtering and baseline beat rejection were applied to the raw ECG, prior to a running weighted averaging; then, a postprocessing step, where potentially noisy averaged beats were identified and discarded based on their noise variance; finally, the measurement step, where repolarization and depolarization indexes were computed from the averaged beats.

This method was previously evaluated by means of simulated exercise test records [2].

*2.2.2. HRV indexes (*HRV*)*

HRV was measured from the ECG after QRS detection and selection of *normal* beats [20]. Three different two-minute duration intervals were considered: the beginning of the exercise (P1), just before the peak of maximal exercise (P2) and during the recovery period (P3), starting 30 s after the maximal exercise peak (see Fig. 1).

• Time domain HRV indexes (*HRV time*): *SDNN* (standard deviation of the normal-to-normal (NN) QRS intervals) and *RMSSD* (root mean squared of successive NN differences) were calculated after linear detrending of the HR series in the P1, P2 and P3 periods. The slopes *SLP* from linear detrending in each period were also included in the analysis.

• Frequency domain HRV indexes (*HRV frequency*): Power spectral density (PSD) of HRV was estimated from the linearly detrended and interpolated heart timing signal [14], resampled at 2 Hz, reducing the effect of ectopic beats by the method proposed in [15]. The Fast Fourier Transform (FFT) was applied over two-minute duration episodes in P1, P2 and P3 (see Fig. 1). ECG indexes were defined as the spectral power in the following frequency bands: *VLF* (0 to 0.04 Hz), *LF* (0.04 to 0.15 Hz), *HF* (0.15 to 0.4 Hz) and very high frequency band (*VHF*) (0.4 to 1 Hz). Also the total power, *AF*, was considered. The power in the *VHF* band can not be evaluated in resting conditions because of the low HR, leading to a low HR series sampling rate. However, the power in the *VHF* band becomes significant during P2 and P3 periods, when the mean HR is above 120 bpm (HR series sampling rate above 2 Hz). Fig. 3 shows the PSD of the HR trend of Fig. 1 during the three intervals considered.

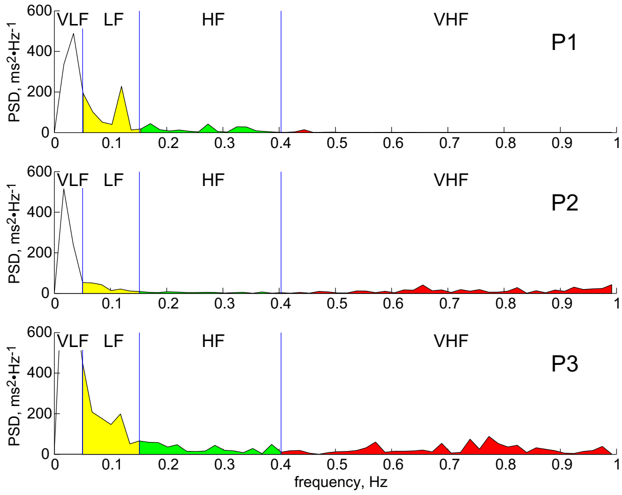

Figure 3. Distribution of the PSD in VLF, LF, HF and VHF bands during the P1, P2 and P3 periods.

2.3. Statistical Analysis

A multivariate discriminant analysis (SPSS 11.0) was applied to the ECG indexes to classify patients into their constituent groups: *ischemic* and *low-risk*. Discriminant analysis assumes that the implied variables are Gaussian. However, the statistical distribution of the HRV indexes is highly asymmetric and not Gaussian. Therefore, HRV indexes were logarithmically transformed to reduce their skewness (mean skewness of HRV indexes was reduced from 2.80 to 0.003 by the logarithmic transformation). The discriminant analysis used the *stepwise* approach and the *Wilk's Lambda* minimization criterion for the variable inclusion/rejection (F=3.84 for inclusion and F=2.71 for rejection). Classification results were calculated with cross-validated estimation (*leave-one-out*). Multivariate discriminant analysis was independently applied to different sets of indexes. Since multivariate discriminant procedures requires that all observation have complete data and not all the ECG indexes could be estimated for all the patients (outlier QRS widths, unmeasurable wave amplitudes in some leads), the number of cases included in each discriminant analysis is not the same. The number of *stepwise* selected variables used in each set was truncated, when necessary, to follow the criterium of *number of variables* $<$ *(smallest group size)*$^{1/2}$.

Classification performance was assessed by means of five variables: sensitivity (SE), specificity (SP), positive predictive value (P+), negative predictive value (P-) and exactness (EX).

3. RESULTS

The goal of our study was to identify those ECG indexes which best discriminate between the *ischemic* and *low-risk* groups.

Multivariate discriminant analysis was independently applied to different sets of indexes. Classification results in terms of SE, SP, P+, P- and Ex are summarized in Table 3. The discriminant variables in each case are listed in the same order as selected by the *stepwise* method.

The addition of HR information to ST level measurements improved the diagnostic performance of repolarization indexes (SE=90 %, SP=79 % vs. SE=65 %, SP=66 %). It can be appreciated that ST/HR hysteresis alone obtained classification results (SE=89 %, SP=75 %) similar to all HR-corrected repolarization indexes. Depolarization indexes also improved the diagnostic accuracy (SE=78 %, SP=81 %) of classical repolarization indexes. Note that the addition of depolarization indexes to HR-corrected indexes did not add classification capability (SE=90 %, SP=76 % vs. SE=90 %, SP=79 %). HRV indexes achieved the best classification results (SE=94 %, SP=92 %) in our study population. When all ECG indexes were jointly considered, the set of *stepwise* selected discriminant variables obtained an EX of 82 %. A new set including the most significant variables of depolarization, repolarization and HRV was defined, achieving an EX of 85 % (see last row of Table 3). The VHF power at stress peak exhibited a potential value in this case, accounting for a 9 % of the total EX.

4. DISCUSSION

In this work several ECG indexes reported in the clinical literature have been studied. In our study population the diagnostic performance of ST level (SE=54 %, SP=71 %) was in the range of those reported in other publications (SE=68±16 %, SP=77±17 %) [8]. Depolarization indexes outperformed the diagnostic performance of repolarization indexes (SE=78 %, SP=81 % vs. SE=65 % SP=66 %), which agrees with previous works [19, 21, 7]. HR-adjusted ST-based indexes improved the EX in approximately 20 % over ST indexes in our study population (86 % vs. 65 %), which is in concordance with previous works [5, 13]. The ST/HR hysteresis was reported to be the most competent among all HR-corrected ST-based indexes [13], which was corroborated in our study population (SE=89 %, SP=75 %). Note that ST/HR hysteresis obtained similar classification results to all repolarization indexes together. In [21], QRS score was found to be unrelated and, therefore, complementary to exercise-induced ST depression. However, in our study population depolarization indexes did not add diagnostic accuracy to HR-corrected repolarization indexes (SE=90 %, SP=76 %), suggesting that depolarization information might be redundant with repolarization indexes, at least when HR information is considered. In the present work, HRV indexes obtained the best diagnostic performance of all variable sets, which is in concordance with previous works reporting the relationship between ischemia and HRV [16]. Frequency domain indexes obtained higher diagnostic accuracy than time domain indexes (SE=89 %, SP=87 % vs. SE=74 %, SP=77 %). The combination of time and frequency domain indexes achieved classification results (SE=94 %, SP=92 %) similar to that obtained by exercise echocardiography (SE=85 %, SP=84 %, [22]) or nuclear imaging (SE=90 %, SP=90 %, [11]).

In Table 3 it can be appreciated that the EX obtained with all ECG indexes (82 %) is lower than the achieved with only HRV indexes (93 %). The reason is that some repolarization and/or depolarization indexes could not be measured on all patients, reducing the number of cases included in the discriminant analysis in comparison with the HRV index analysis. We should be cautious when analysing classification results from varying-size data sets since diagnostic performance from the smaller ones could be optimistically biased. Not only diagnostic performance but also the number of cases for which a variable set could be determined should be taken into account when judging the practical clinical value of an index set. In our study HRV presented the best compromise *diagnostic perfomance/availabe number of cases*.

Stepwise selected variables showed that aVL appeared the most relevant lead to measure ST level at exercise peak. Significant ST based indexes collected information from *pseudo-orthogonal* leads. Information from lead $RV4$ may be recovering those cases with occlusion in the right coronary artery, as suggested by [17]. Significant depolarization indexes represented information mainly from the frontal plane of the body. QRS width was selected as a discriminant variable, supporting the findings in [18]. The most relevant HRV index was the *V*HF at exercise peak. This index was first analyzed in exercise test recordings in [16] and might be related to the sympathetic tone, as it is only significant at high HR and during exercise.

The main limitation of this work is the referral bias, that is, the conventional interpretation of exercise ECG af-

Variable set	N	Cases	SE (%)	SP (%)	P+ (%)	P- (%)	EX (%)
(ST peak)							
STp_{aVL}	1	72/42	54	71	76	48	61
(Repo)							
$STp_{aVL}, STp_{V1}, \|\Delta ST_{RV4}\|, \|\Delta ST_{V6}\|, STp_{III}, STp_{aVF}$	6	71/41	65	66	77	52	65
(ST/HR hysteresis)							
$STHL_{II}, STHL_{V3}, STHL_{aVR}, STHL_{I}, STHL_{V1}$	5	61/36	89	75	86	79	84
(Repo,Repo/HR)							
$STHL_{V5}, \Delta ST_{V6}, \|\Delta ST_{V1}\|, STp_{I}, STHL_{II}$	5	59/34	90	79	88	82	86
(Depo)							
$\Delta Q_{II}, \Delta QRS_{d}, \Delta Q_{aVL}, \Delta S_{aVR}, \Delta S_{V1}$	5	58/27	78	81	90	63	79
(Depo,Repo,Repo/HR)							
$\Delta Q_{V6}, \Delta S_{V4}, \|\Delta ST_{RV4}\|, STHL_{V3}, STHL_{II}$	5	58/29	90	76	88	79	85
(HRV time)							
$RMSSD_{P2}, SDNN_{P1}, SDNN_{P2}, RMSSD_{P3}, SDNN_{P3}$	5	72/43	74	77	84	63	75
(HRV frequency)							
$LF_{P1}, VHF_{P2}, HF_{P3}, SLP_{P3}, VLF_{P2}, HF_{P2}$	6	64/39	89	87	92	83	88
(HRV)							
$VHF_{P2}, VLF_{P2}, SDNN_{P1}, HF_{P3}, SLP_{P3}, SDNN_{P2}$	6	65/40	94	92	95	90	93
(Depo,Repo,Repo/HR,HRV)							
$\Delta Q_{V6}, STHL_{II}, STHL_{V3}, \|\Delta ST_{V1}\|$	4	59/30	85	77	88	72	82
§ $VHF_{P2}, STHL_{V5}, VLF_{P2}, \Delta Q_{II}, \Delta QRS_{d}, \Delta ST_{V6}$	6	54/28	85	86	92	75	85

N: number of variables. Cases: Ischemic/Low-risk. Depo: depolarization indexes. Repo: repolarization indexes. Repo/HR: HR-adjusted repolarization indexes. HRV: HRV indexes. § Most significant variables from depolarization, repolarization and HRV to discriminate between Ischemic and Low-risk.

Table 2. Classification results: *Ischemic* vs *Low-risk*.

fected the decision to proceed with coronary angiography. It is impractical in clinical routine to investigate all patients with coronary angiography regardless of the results of the preceding exercise test.

5. CONCLUSIONS

The CAD diagnostic performance of several exercise ECG indexes was analyzed: ST/HR hysteresis improved the diagnostic accuracy of the classical exercise test, based only on ST level measurements; depolarization indexes did not add significant information to HR-corrected repolarization indexes, suggesting they are redundant; finally, HRV indexes showed a potential value in CAD diagnosis, specially by means of the VHF power at stress peak.

Due to the high noise levels in exercise ECG recordings, mainly at stress peak, the application of a robust method to automatically estimate repolarization and depolarization indexes was needed prior to ECG index diagnostic performance analysis.

The improvement achieved in stress test diagnostic performance would reduce the number of uncomfortable and expensive unnecessary interventions such as coronary angiography and other techniques and would permit to focalize clinical efforts in CAD-risk patients. Nevertheless, the inclusion of these ECG indexes in routine exercise test trials still needs further studies in prospective populations.

6. BIBLIOGRAPHY

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