ECG-Based Clinical Indexes During Exercise Test Including Repolarization, Depolarization and HRV

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Abstract

In this work we compared ECG clinical ischemia indexes from ventricular depolarization, repolarization and heart rate variability (HRV) during exercise test. ST segment deviations, ST/HR hysteresis, Q, R and S wave amplitudes, QRS duration, and HRV indexes were automatically measured. Coronary angiography was used as gold standard to include patients in the ischemic group. Multivariate discriminant analysis was applied to classify the patients. Results based on classical ST indexes correctly classified 58% of patients. When depolarization, repolarization and HRV indexes were jointly considered the exactness improved to 91% (sens=94%, spec=89%). These results are close to those obtained by exercise echocardiography or exercise nuclear imaging.

1. Introduction

The traditional interpretation of exercise ECG for diagnosis of coronary artery disease (CAD) is based on the ST segment depression during an exercise test. However, the diagnostic accuracy of a positive criterion of 0.10 mV ST segment depression is about 70% in the detection of CAD in clinical populations [1].

Clinical indexes with information of the ST level and heart rate (HR) have been shown to improve the diagnostic accuracy compared with ST segment depression [2]. Conventional ST/HR variables consider only the exercise phase of the test. A new method, ST/HR hysteresis, which integrates exercise and recovery of ST/HR diagram, has been recently shown to be more competent [3]. Indexes measured on the depolarization period, like the Athens QRS score [4], have been proposed to improve the exercise test value. Alternative combinations of QRS amplitude variables have shown a better performance than the Athens score [5]. Heart rate variability (HRV) measurements during exercise test have not been widely analyzed. There are some studies describing the relationship between ischemia and HRV during Holter recordings focusing on the different behavior of ischemia etiology [6]. We hypothesize that HRV behavior during exercise is different in patients with CAD from non-ischemic patients, and consequently, HRV indexes may improve the diagnostic value of routine exercise test.

The aim of our study was to evaluate the diagnostic value of the described clinical indexes during exercise test.

2. Materials and methods

2.1. Study population

In the University Hospital of Zaragoza, ECGs of 811 patients undergoing treadmill (Bruce protocol) exercise test were recorded, including 66 non-ischemic volunteers. Standard leads (V1, V3-V6, I, II, III, aVR, aVL and aVF) and RV4 (substituting classical V2 to extract more information from the right part of the heart) were digitally recorded (1 KHz sampling rate, amplitude resolution of 0.6 μV).

Patients were classified into two groups: *'ischemic'* and *'non-ischemic'*. The *'ischemic'* group was composed by 73 patients with significant stenoses in at least one major coronary artery from coronary angiography. The *'non-ischemic'* group included 286 patients: 220 patients with negative clinical and electrical exercise test and reaching at least 90% of the maximal (age-related) heart rate, and 66 volunteers from Spanish Army (with negative exercise test). Some particular measurements were not included in the analysis due to power line interference, excessive baseline variations, signal loss or excessive ectopic beat rate. The remaining 452 non-classified patients were not analyzed in this study.

2.2. Measurements

ECG signal preprocessing was performed before clinical index extraction: detection and selection of *'normal beats'* labelled according to ARISTOTLE [7], cubic splines baseline wander attenuation and rejection of beats which difference in isoelectric level with respect to adjacent beats is more than 600 μV.

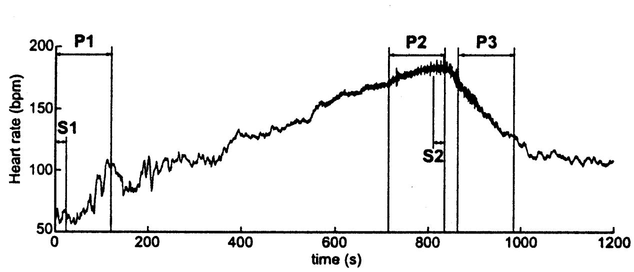

Figure 1. Time periods for the clinical indexes estimation during exercise test.

2.2.1 Repolarization and depolarization indexes

Repolarization and depolarization clinical indexes were obtained on each lead from measurements in two time periods: the beginning of the recording (S1) and the exercise peak (S2), defined as the instant of maximal heart rate (see Fig. 1). To identify the exercise peak, a median filtering (5 beats) and moving-average filtering (10 beats) were applied to the HR trend of normal beats. Clinical indexes were measured on a weighted average of 10 heartbeats during both periods, S1 and S2, due to the highly non-stationary noise.

- ST level: The ST level was measured at a HR-dependent distance from the QRS fiducial point estimated as the QRS gravity center according to the expression used in [5]. ST level at exercise peak is denoted as STp. The ST difference (ΔST) was computed between the exercise peak and rest period. The absolute value of the ST differences ($|\Delta ST|$) was also considered.

- ST/HR indexes: The ST/HR diagram is the plot of ST depression against HR during both exercise and recovery phases. Several indexes measured on this diagram have been proposed [3]. The ST difference corrected by the HR increment ($\Delta STc = \Delta ST/\Delta HR$) [2] and the corresponding absolute value ($|\Delta STc|$) were included in the study. Also the ST/HR hysteresis (*STHL*) was measured as the signed area (clockwise considered negative) of the hysteresis loop during exercise and the first 3 minutes of recovery divided by ΔHR [3].

- QRS wave amplitudes and QRS duration: Amplitude of Q, R and S waves and QRS width were automatically measured on the averaged beat using the detector described in [5, 8]. Clinical indexes ΔQ, ΔR, ΔS and $\Delta QRSd$ were computed as the differences between the exercise peak and rest values.

2.2.2 HRV indexes

HRV was measured on three different two minute intervals: 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).

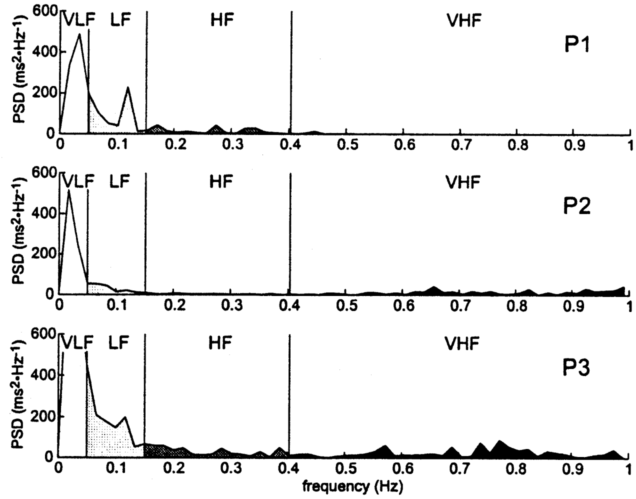

Figure 2. Distribution of the PSD in VLF, LF, HF and VHF bands during the P1, P2 and P3 periods.

- Time domain HRV indexes: *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 from linear detrending in each period were also included in the analysis.

- Frequency domain HRV indexes: Power spectral density (PSD) of HRV from the linearly detrended heart timing signal [9] was estimated reducing the effect of ectopic beats [10]. Clinical 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 Hz to 1 Hz). The *VHF* band is proposed in this study for exercise test recordings. The power in the *VHF* band can not be evaluated in resting conditions because of the low HR that results in a low HR series sampling rate. However, this parameter becomes significant during P2 and P3 periods, when the mean HR is above 120 bpm (HR series sampling rate above 2 Hz). Fig. 2 shows the PSD of the HR trend given in Fig. 1 during the three analyzed periods. Note the presence of spectral power in the *VHF* band during P2 and P3 periods.

2.3. Statistical analysis

Significance test and linear discriminant analysis assume that the variables are Gaussian. However, the statistical distribution of the main HRV variables is highly asymmetric and not Gaussian (skewness>1). Thus, all HRV indexes were logarithmically transformed to reduce their skewness. Multivariate discriminant analysis was used to classify the patients in two groups. The ischemic group was weighted by a factor of four to avoid inclusion of *a priori* information, due to the different group sizes. We used in the analysis the *stepwise* method that permits the reduction in the number of variables included in the discrimination, identifying those that have better prediction capability for the classification. The criterion followed in the variable inclusion/rejection was the *Wilks' lambda* minimization ($F = 3.84$ for inclusion and $F = 2.71$ for rejection). The classification results were calculated with cross-validated estimation (*leave-one-out*).

3. Results and discussion

Significance test on clinical indexes showed significant differences, but the interest lies in whether these differences permit to classify the two groups of patients. Multivariate discriminant analysis was independently applied to different sets of indexes. The *stepwise* selected variable subsets and their corresponding discriminant functions are presented and discussed in this section.

A summary of the results is shown in Table 1 in terms of sensitivity (Se), specificity (Sp), positive and negative predictive values (+P and -P, respectively) and exactness (Ex), as well as the number of variables (n) selected by the discriminant classification procedure.

First, we studied the classification performance of ST level. The ST level at exercise peak (STp) achieved an exactness of 56%, lower than those reported in other works [1]. When including ST difference (ΔST) and its absolute value ($|\Delta ST|$) not significant improvement was reached (Table 1). In a second step, we included the HR information by using ΔSTc, its absolute value and the hysteresis loop area index (*STHL*). This combination obtained an exactness of 85% (Se=91%, Sp=79%) giving a notable increase over the ST indexes. Thirdly, we analyzed the classification value of depolarization indexes, ΔQ, ΔR, ΔS and $\Delta QRSd$ measured on all leads. Wave amplitudes appear more relevant than QRS width (Table 1). When $\Delta QRSd$ is added, no extra improvement is reached (Table 1). This combination corroborates the classification value in [4] but proposes a different discriminant function (Table 2) which achieves the best clinical classification in our patient set. Addition of depolarization indexes to the ST and ST/HR variable set did not improve the diagnostic value significantly, suggesting that depolarization information may be redundant when HR is considered in repolarization indexes. In a fourth analysis we studied time and frequency HRV indexes obtaining an exactness of 83% (Se=83%, Sp=83%), just slightly lower than with all depolarization and repolarization indexes. Note that frequency indexes reach slightly better results than time domain indexes, as they better stratify the HRV information. Combination of time and frequency HRV indexes added only a slight improvement (Table 1). Finally, all indexes jointly combined obtained an exactness of 91% (Se=94%, Sp=89%). This result represents an improvement at the expense of increasing the number of variables to eleven. In terms of information we can think in a spatial phenomenon (three dimensions) with two analyzed areas (depolarization and repolarization) plus four HRV bands in three time periods. This represents a total number of 18 potentially independent variables. The number of eleven variables included in the multivariate analysis appears then reasonable when all indexes are jointly considered. Also the patient group is large enough to avoid overestimation of the data.

Table 1. Classification results: number of variables selected, sensitivity, specificity, positive and negative predictive values and exactness for each variable set.

Variable set	n	Se	Sp	+P	-P	Ex
STp	1	58	53	56	55	56
STp, ΔST, $\|\Delta ST\|$	6	54	63	60	57	58
All-ST-ST/HR	9	91	79	82	89	85
ΔQ,ΔR,ΔS	3	75	62	67	71	69
ΔQRS_d	3	63	52	54	61	57
All-QRS	5	73	67	70	71	70
All-QRS-ST-ST/HR	10	90	82	84	89	86
HRVtime	4	73	72	73	72	73
HRVfrequency	6	81	78	79	79	79
All-HRV	7	83	83	84	82	83
All-combined	11	94	89	90	93	91

The discriminant function variables (clinical indexes) and coefficients for each subset are given in Table 2. In ST based indexes, leads aV_L, V_3 and RV_4 are the most relevant, representing information from *pseudo orthogonal* leads. Note the inclusion of RV_4, probably recovering those cases with occlusion in the right coronary artery. When adding the HR information V_3 remains being the most relevant and RV_4 and aV_F are replaced by V_1 and *II* still representing *pseudo orthogonal* information. When only considering depolarization indexes aV_F, V_6, I and *III* appear to be relevant suggesting that the frontal, not the transversal, plane contains the relevant depolarization information. QRS width seems to have marginal classification value since it is the least significant variable (Table 2). When de/repolarization are jointly considered variable and lead reordering comes up with similar analysis than in repolarization but with no extra classification power. The introduced *VHF* index at exercise peak gets the highest discriminant power of all HRV indexes. Moreover, VLF_{P2} and LF_{P2} appear relevant suggesting the neural control system at exercise peak clearly affected by ischemia and consequently relevant to classify patients. HRV information

Table 2. Variables, *stepwise* inclusion ordered, and discriminant functions coefficients when variables are standardized.

Variable set	Variables and Coefficients (Subindexes refer to lead or time periods in HRV variables)										
STp, ΔST, $\|\Delta ST\|$	ΔST_{aVL} 0.55	$\|\Delta ST_{V3}\|$ -0.72	ΔST_{RV4} -0.68	$\|\Delta ST_{II}\|$ 0.32	STp_{V5} 0.59	$\|\Delta ST_{V6}\|$ 0.53					
All-ST-ST/HR	$\|\Delta STc_{V3}\|$ 0.77	$STHL_{V3}$ 0.77	$STHL_{V1}$ -0.71	$STHL_{II}$ 0.59	$\|\Delta ST_{V6}\|$ -0.84	$\|\Delta STc_{V6}\|$ 0.68	STc_{V3} 0.38	STc_{V1} 0.30	$\|\Delta STc_{aVF}\|$ -0.23		
All-QRS	ΔR_{aVF} -0.63	ΔS_{V6} 0.48	ΔQ_{V6} 0.34	ΔR_{I} -0.34	ΔQRS_{III} 0.29						
All-QRS-ST-ST/HR	$\|\Delta STc_{V3}\|$ 0.72	ΔS_{V6} -0.28	$STHL_{aVR}$ 1.00	$STHL_{V1}$ -0.76	ΔS_{aVL} 0.42	$\|\Delta ST_{V6}\|$ -0.66	STc_{V1} 0.38	STc_{V6} -0.49	ΔR_{I} 0.31	ΔQRS_{V4} -0.27	
All-HRV	VHF_{P2} 1.65	$RMSSD_{P2}$ -1.28	VLF_{P2} 0.51	LF_{P2} -0.27	$SDNN_{P1}$ 0.51	LF_{P1} -0.42	HF_{P3} -0.17				
All-combined	$STHL_{V6}$ 0.32	VHF_{P2} -1.44	$RMSSD_{P2}$ 1.07	$\|\Delta STc_{V3}\|$ 0.31	LF_{P2} 0.50	VLF_{P2} -0.46	ΔR_{aVF} 0.18	ΔR_{I} 0.13	LF_{P1} 0.55	$SDNN_{P1}$ -0.32	HF_{P3} -0.23

and depo/repolarization indexes are not redundant, as corroborated when considering all indexes together. In this case, ST/HR at V_6 and V_3, and ΔR_{aVF} *(pseudo orthogonal)* plus HRV at exercise peak (P2) appear the most relevant information.

Discrimination between occluded arteries is not introduced in this study. The set of variables and discriminant functions may vary when restricting to particular occluded arteries and may improve the value of the exercise test. Interpretation of the clinical information provided by *VHF* band becomes an open question. It can be hypothesized that *VHF* represents the same phenomenon than *HF* at lower HR. Moreover this index may be correlated with respiration rate and HR.

4. Conclusions

HRV indexes during exercise test, according to this study, add new diagnostic information to the classical ST and QRS measurements. Our data suggest that combination of this information might reach a diagnostic accuracy similar to exercise echocardiography or exercise test with nuclear imaging. The exercise test peak is found to give the most relevant information from its HRV indexes, especially the *VHF* band power that is meaningful at HR over 120 bpm. The added value given by depolarization indexes is similar to that introduced when HR is considered in the repolarization (ST) indexes. Further research is needed to confirm our findings in larger prospective populations.

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