HEART RATE VARIABILITY MEASUREMENTS DURING EXERCISE TEST MAY IMPROVE THE DIAGNOSIS OF ISCHEMIC HEART DISEASE

J. Mateo[1], P. Serrano[2], R. Bailón[1], J. García[1], A. Ferreira[2], A. Del Río[2], I. J. Ferreira[2], P. Laguna[1]
[1]Communications Technology Group, CPS, University of Zaragoza, Zaragoza, Spain.
[2]Department of Cardiology, University Hospital "Lozano Blesa", Zaragoza, Spain.

Abstract – **In this work we have analyzed changes in the heart rate variability (HRV) during exercise test comparing them with the ST deviation criteria to improve the diagnostic value of the exercise test. Coronary angiography was considered as gold standard to establish the classification of patients in two groups (ischemic and non-ischemic). ST deviations and HRV indexes were automatically measured and used as independent factors in discriminant analysis to find those more useful to classify both groups. Several approaches were performed starting with different sets of variables. Results showed that by using only the ST indexes it is possible to correctly classify 76% of patients. The inclusion of HRV indexes improves the exactness up to 84%. The very high frequency (0.4 to 1 Hz) at the stress peak has shown to have diagnostic value. Adding the age and the maximum heart rate the exactness goes up to 87.4% (sens. 85.5%, spec. 89.1%), close to that obtained by exercise echocardiography or exercise nuclear imaging.**
Keywords – **Heart rate variability, exercise test, ischemia.**

I. INTRODUCTION

Heart rate variability (HRV) measurements during exercise test have not been widely studied, due to e.g. the impossibility to evaluate these measurements for long periods of time. There are some studies describing the relationship between ischemia and HRV during 24 hours ECG recordings focusing the different behavior of HRV indexes depending on the ischemia ethiology [1].

We hypothesize that the HRV behavior during exercise is different in patients with ischemic coronary disease from non-ischemic patients. The aim of our study was to analyze the changes in HRV during exercise test and to investigate whether these changes may improve the diagnostic value of routine exercise test, as compared with the information provided from changes in the ST segment.

II. METHODOLOGY

A. Study population

The ECG of 838 patients were recorded undergoing exercise test in the Department of Cardiology of the University Hospital "Lozano Blesa" of Zaragoza (Spain). We also recorded the exercise test of 74 non-ischemic volunteers. Standard leads (V1, V3-6, I, II, III, aVR, aVL, aVF) and RV4, substituting V2, were digitally recorded using equipment by Siemens-Elema AB (Solna, Sweden), sampling at 1 KHz with amplitude resolution of 0.6 μV. The investigation was conformed to the principles outlined in the Declaration of Helsinki.

The patients were classified into two groups labeled as '*ischemic*' or '*non-ischemic*'. The gold standard for comparison of exercise test-based results was coronary angiography performed after the exercise test. The '*ischemic*' group was composed by 80 patients with significant stenoses in at least one major coronary artery. The '*non-ischemic*' group was composed by 288 patients: 214 '*non-ischemic patients*', for whom clinical and electrical exercise test results for ischemia were negative and reached at least 90% of the maximal (age-related) heart rate (HR) and 74 '*non-ischemic volunteers*' from Spanish army, who underwent an exercise test with negative results for ischemia. The remaining 470 non-classified patients were not analyzed in this study.

B. Measurements

For each exercise test recording we considered three different periods of two minutes of duration, which were measured at beginning of the exercise (P1), just before the peak of maximal stress (P2) and during the recovery period (P3), starting 30 s after the maximal stress peak. Fig. 1 shows these periods during an exercise test recording case.

By means of automated algorithms developed by our group, we measured:

- ST deviation at the maximal stress with respect to the beginning of the exercise (dST) and ST deviation adjusted by the HR deviation (STc = dST/dHR), both estimated for each lead. ST segment level was automatically measured on the ECG after signal pre-processing: QRS complexes detection and selection of normal beats, baseline wander attenuation using cubic splines and rejection of beats presenting differences in their mean isoelectric level with respect to adjacent beats of more than 600μV. The ST segment level was measured at a distance dependent on the HR and the amplitude was beat-by-beat estimated with respect to the isoelectric level applying a weighted-average filter [2].
- Time domain HRV indexes: SDNN (standard deviation of the normal-to-normal (NN) QRS intervals), RMSSD (square root of the mean squared differences of successive NN intervals), pNN50 (proportion derived by dividing the number of interval differences of successive NN intervals greater than 50 ms by the total number of NN intervals) [3]. SDNN and RMSSD were calculated after detrending the heart rate series.
- Frequency domain HRV indexes: We estimate the power spectral density (PSD) of HRV from the heart timing signal [4], reducing the effect of ectopic beats presence by the

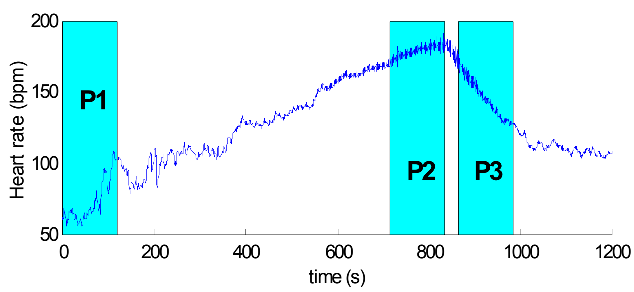

Fig. 1. Time periods for the HRV indexes estimation during exercise test.

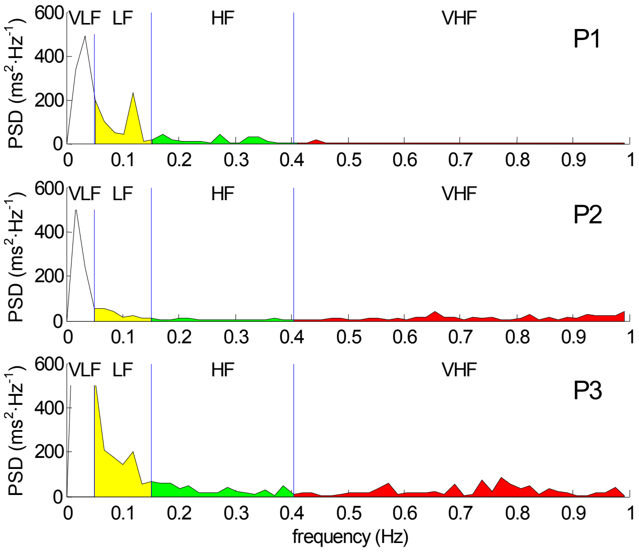

Fig. 2. Distribution of the PSD in VLF, LF, HF and VHF bands during the P1, P2 and P3 periods.

proposed method in [5]. Then, we calculate the clinical indexes as the spectral power in the frequency bands: VLF from frequency greater than 0 to 0.04 Hz, LF from 0.04 to 0.15 Hz, HF from 0.15 to 0.4 Hz and very high frequency band (VHF) from 0.4 Hz to 1 Hz. Also the LF/HF ratio and total power, AF, are estimated. The VHF band is proposed in this study for exercise test recordings. Although the power at VHF band is very low in resting conditions, we analyzed this parameter because it significantly increases when the HR is above 120 beats per minute (P2 and P3 periods). Fig. 2 shows the distribution of the PSD for the same patient of Fig. 1 into the four bands during the three analyzed periods.

C. Statistical analysis

Significance test and discriminant analysis assume that the implied variables are gaussian. However, the statistical distribution of the main HRV variables is highly asymmetric and not gaussian (skewness > 1). Thus, we transformed logarithmically all HRV indexes to reduce their skewness, except pNN50 and LF/HF which are defined as ratios.

For all the studied HRV indexes, we compared by means of the *t*-test if there were significant differences among the *'ischemic patients'*, *'non-ischemic patients'* and *'non-ischemic volunteers'* groups and also between the whole *'ischemic'* and *'non-ischemic'* groups.

Multivariate discriminant analysis was used to classify the patients in the two main groups. Given that the size of the *'ischemic'* group was four times smaller than *'non-ischemic'* group, it was weighted by a factor of four to compensate for the group size. We used in the analysis the stepwise method that permits the reduction in the number of variables included in the discrimination, identifying those that are good predictors for classification. The criterion followed in the variables inclusion/rejection was the *Wilks'lambda* minimization. The classification results were calculated with cross-validated estimation (leave-one-out). The cross-validated method is more realistic because each case to be classified is not used in the model derivation.

III. Results

A. Bivariate analysis

Fig. 3 shows the boxplots of SDNN, RMSSD, pNN50, VLF, LF, HF, VHF, AF and LF/HF indexes in the three analyzed periods for the three studied populations.

We have found three different types of behavior for the studied variables in the three periods:

- As compared to resting period (P1), SDNN, RMSSD and LF/HF significantly decreased in the maximum exercise period (P2) and later increased in the recovery period (P3), being in P3 significantly smaller than in P1.
- VLF, LF and AF decreased from P1 to P2 too and in P3 they increased again.
- HF and VHF significantly increased from P1 to P2 and from P2 to P3.

Regarding to the comparison among the three study populations, differences among the patient groups tended to appear in periods P1 and P3, but not in P2, except for HF and VHF, that presented significant differences among the three populations in P2 and P3, but not in P1. In most cases we have found a gradual increase or decrease when comparing the 'ischemic patients' with the 'non-ischemic patients' and these with the 'non-ischemic volunteers' with respect to any index of HRV during the same period.

B. Multivariate analysis

All the studied variables were compared in terms of ischemic/non-ischemic discrimination results applying linear discriminant analysis using leave-one-out cross-validation.

Several approaches were performed starting with different sets of variables to compare the discriminant value of each method. Then, we put the variables together to obtain a better classification and to determine which variables were selected by the model.

Table I shows the different discriminant analysis models obtained in this study. In this table we can observe that using only the ST related variables we reached a sensitivity of 72.1% and a specificity of 79.9%. Using only the HRV variables we reached a sensitivity of 73.8% and a specificity of 84.3%. When we included together ST and HRV variables, the sensitivity was increased to 80% and the specificity to 88%. Finally, including in this model the age and maximum HR at the exercise test, we got a sensitivity of 85.5% and a specificity of 89.1%. The ROC curves for the four described models are presented in Fig. 4, showing an increase in the area under the curve from 0.84, 0.92, 0.94 and 0.97, respectively.

IV. Discussion

Most studies on HRV measurements have been performed on 24 hours ECG recordings and a small proportion in 5 minutes stationary recordings. However, we deal with non-stationary recordings and we decided to measure all the variables during two minutes periods to increase time resolution. We considered that frequency resolution is enough since then we integrate the spectral power on large bands. The pNN50 index was designed to be measured during long

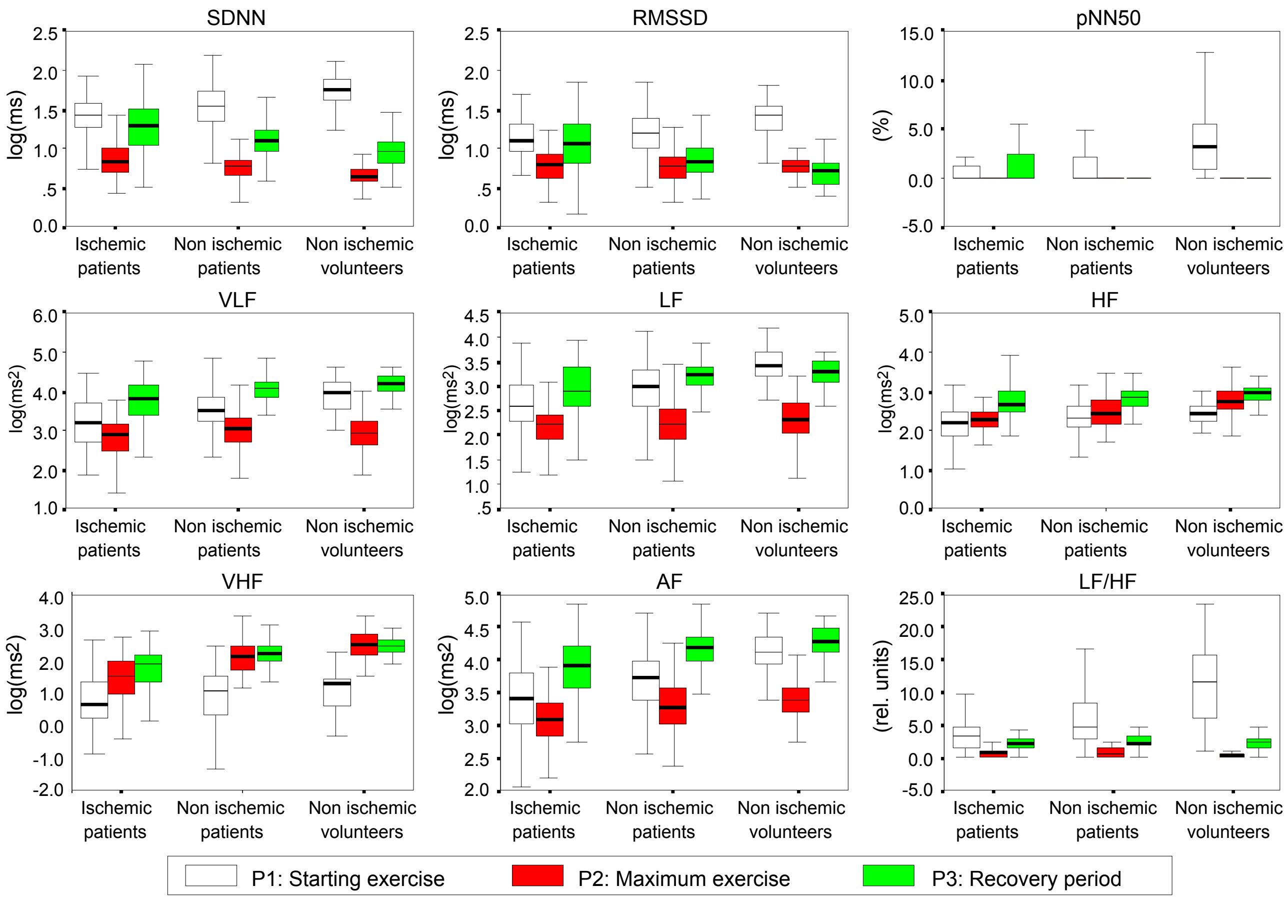

Fig. 3. Boxplots of the main HRV variables calculated on each activity period.

time periods in resting conditions. In our short recordings the pNN50 index results useless, especially during P2 and P3.

A. HRV before exercise (P1)

HRV indexes in P1 were significantly lower in the ‘ischemic’ group, suggesting a lower vagal tone. This agrees with the findings in patients after a myocardial infarction [6] or in patients with stable angina previously to the ischemic episode [7]. However, LF/HF was significantly higher in the ‘non-ischemic’ patients, suggesting a higher sympathetic tone and lower vagal tone as compared to the ‘ischemic’ population.

B. HRV during maximum stress (P2)

Exercise increases the sympathetic activity and inhibits the vagal tone [8]. A decrease in HRV indexes during exercise has been described. As it was expected, time domain indexes decreased during P2 as compared to P1. This decrease was similar in the ischemic and non-ischemic subjects. Furthermore VLF and LF decreased. On the other hand, HF and VHF increased in all the groups, but significantly less in the ‘ischemic’ patients. This result seems paradoxical, given that HF has been related to the vagal tone, which decreases with exercise, whereas LF has been related to the sympathetic

TABLE I

DIAGNOSTIC VALUE ACCORDING TO EACH DISCRIMINANT FUNCTION

Variables in the analysis	Discriminant function[a]	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Exactness	Area under the ROC curve
ST	+ 1.681·STc(V6) + 1.028·STc(V3) + 0.721·STc(RV4) – 1.577·dST(V6) – 0.745·dST(V3) – 0.668·dST(RV4)	72.1%	79.9%	78.4%	73.8%	75.9%	0.84
HRV	+ 0.353·SDNN(1) – 0.402·SDNN(3) – 0.573·RMSSD(3) – 0.177·VLF(1) + 0.644·VLF(3) + 0.256·VHF(2) + 0.311·VHF(3)	73.8%	84.3%	82.9%	75.7%	79.0%	0.92
ST & HRV	– 0.384·SDNN(3) – 0.471·RMSSD(3) + 0.242·VHF(2) + 0.854·AF(3) – 0.572·dST(V6) + 0.81·STc(V6) + 0.178·STc(AVL)	80.0%	88.0%	87.3%	81.1%	84.0%	0.94
All	+ 0.360·SDNN(1) + 0.334·SDNN(2) – 0.375·SDNN(3) + 0.443·VLF(3) – 0.382LF(1) – 0.375·dST(I) + 0.537·STc(I) + 0.300·Age + 1.171·maxHR	85.5%	89.1%	87.9%	86.9%	87.4%	0.97

[a] Standardized Coefficients and variables. (Variables are zero-meaned and with normalized standard deviation).

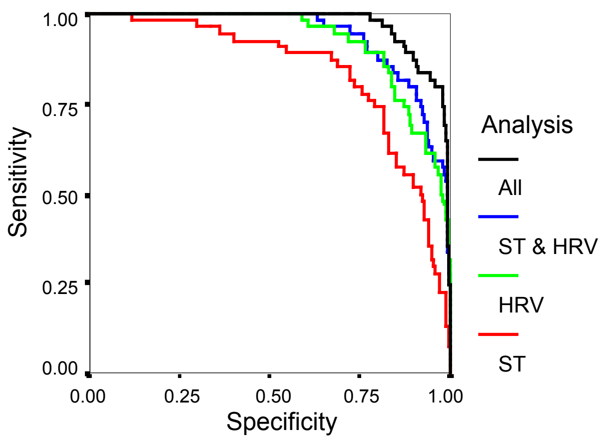

Fig. 4. *ROC* curves of the analysis with ST, ST&HRV and All variables included.

tone, which increases with exercise. Our results agree with a study in elderly population, which found a significant increase in HF, linear to the metabolic demand increase [9]. Although in resting conditions the VHF index usually is negligible, during exercise, the HR increases and also the power in this band. In fact, VHF reaches significantly higher values in the 'non-ischemic' population. We hypothesize that VHF index might be linked to the sympathetic tone, given that it only appears at high HR and increases with exercise. The influence of HR on HF and VHF bands should be further investigated, since it seems to have diagnostic value for detecting ischemia.

C. HRV during recovery (P3)

Time domain HRV indexes increase during P3 as compared to P2. This increase is significantly higher in the 'ischemic' group. The explanation could be that the 'ischemic' patients would have a more intense vagal inhibition during exercise. During P3, VLF and LF increase significantly from P2, reaching higher values than in the P1 and P2. Our findings agree with a study that demonstrated a predominant increase in LF during the 15 minutes of recovery after exercise [10]. During P3, VLF and LF were significantly lower in the 'ischemic' group. Since VLF include the power related to the HR slope, the higher VLF in P3 indicates higher descending slope in the hear rate, which has been associated with a lower risk of mortality [11]. On the other hand, the increase of these indexes from the values in the P1 was significantly higher in the 'ischemic' group.

D. Discriminant analysis

The proposed VHF index appears to be relevant in the discriminant analysis (see Table I) were VHF in P2 seems to be useful to detect ischemic patients.

The inclusion of HRV indexes in the discriminant analysis improved significantly the specificity of ST indexes and together reached a noticeable exactness of 84.0% (sens. 80.0%, spec. 88.0%). It may be argued whether age and the maximum HR should be included in the discriminant models or not, since the patient group may be biased by the age of those that typically undertake exercise test respect to the non-ischemic volunteers. By including these two variables in the model, the diagnostic accuracy increased up to 87,4% (sens. 85,5%, spec. 89,1%).

V. Conclusion

The measurements of HRV indexes during exercise test, according to this study, add new diagnostic information to the classical ST measurements. Our preliminary data suggest that the combination of this information might reach a diagnostic precision similar to the exercise echocardiography or the exercise test with nuclear imaging. The influence of HRV in the ischemic patients seems to be related to the VHF band when the HR is over 120 bpm. Further research is needed to confirm our findings in larger prospective populations.

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