Coronary artery disease diagnosis by means of heart rate variability analysis using respiratory information

D. Hernando[1], M. Kähönen[2,3], J. Lázaro[4], R. Lehtinen[5], T. Nieminen[6], K. Nikus[7,3], T. Lehtimäki[8,3], R. Bailón[1] and J. Viik[9]

[1] BSICoS group, I3A, IIS Aragón, University of Zaragoza, Zaragoza, and CIBER, Madrid, Spain
[2] Department of Clinical Physiology, Tampere University Hospital, Tampere, Finland
[3] Faculty of Medicine and Life Sciences, University of Tampere, Tampere, Finland
[4] STADIUS, ESAT, KU Leuven, Leuven, Belgium, and IMEC, Leuven, Belgium
[5] Tampere University of Applied Sciences, Tampere, Finland
[6] Department of Internal Medicine, University of Helsinki, Helsinki, Finland
[7] Heart Center, Tampere University Hospital, Tampere, Finland
[8] Department of Clinical Chemistry, Fimlab Laboratories, University of Tampere, Tampere, Finland
[9] BioMediTech Institute and Faculty of Biomedical Science and Engineering, Tampere University of Technology, Tampere, Finland

Abstract— **Heart rate variability (HRV) analysis during exercise has been used to evaluate cardiovascular response to the stress of exercise, which may offer additional value than in rest condition. To properly analyze HRV during exercise, several challenges need to be addressed, such as including respiratory information and removing the dependance with the mean heart rate (HR) level. The objective of this work is to extract parameters from HRV analysis and respiratory information during exercise to evaluate their capability of diagnose coronary artery disease (CAD). Significant differences in mean HR were found due to medication effect in patients with CAD. By correcting the HRV parameters by mean HR, this effect is minimized. Power related to high frequency, when guided by respiration, results to have the best diagnosis capability (AUC $>$ 0.7).**

Keywords— **Exercise test, respiratory rate, CAD diagnosis.**

I. Introduction

Heart rate variability (HRV) is a well known tool to non-invasively assess the autonomic nervous system (ANS) regulation over the heart at rest. Spectral analysis of HRV at rest unveils two main components: one at low frequency (LF) [0.04, 0.15] Hz, and another at high frequency (HF) [0.15, 0.4] Hz. The LF component largely reflects sympathetic modulation when normalized with respect to LF and HF components [1]. The HF component mainly reflects parasympathetic activity, being influenced by respiration. The ratio between LF and HF components has been proposed to assess the sympathovagal balance controlling the heart rate (HR).

Coronary artery disease (CAD) is defined as the narrowing of one or more coronary arteries, which leads to a decrease of the oxygen supply to the heart. This lack of oxygen supply to the myocardium (myocardial ischemia) may cause angina pectoris or even lead to myocardial infarction. Traditional non-invasive techniques for CAD diagnosis are based on exercise ECG tests. Several studies have used HRV analysis during exercise, since impairment of autonomic cardiovascular regulation has been observed in ischemic CAD [2]. However, controversial results have been reported regarding HRV parameters during exercise, and the lack of a standard methodology for HRV analysis during exercise hinders a direct comparison of the results. In the study by Bailón et al. [3], HRV parameters during exercise showed accuracy values ranging from 76% to 95%, but the authors claimed that mean HR and respiratory frequency need to be taken into account. On the other hand, HRV parameters corrected by mean HR from exercise and recovery phase were reported by Virtanen et al. [4] to be inadequate for CAD detection.

The purpose of this study is to apply the methodologies described in [3], which include respiratory information, to an expanded version of the data set studied in [4] with the aim of determining the diagnostic performance of HRV analysis during exercise in the detection of CAD. Respiratory rate was estimated from the ECG using an algorithm based on the QRS slopes, which has been validated in stress tests [5]. Then, HRV parameters were extracted and their CAD diagnosis capability were evaluated in different phases of the exercise test.

II. Methods

A. Database and protocol

A subset of the FINCAVAS database [6] consisting of 457 ECG recordings was analyzed. Patients underwent a maximal exercise test at Tampere University Hospital using a bicycle

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ergometer with electrical brakes. The initial workload varied from 20 to 30 W, and the load was increased stepwise by 10-30 W each minute. The recovery phase after the exercise was at least five minutes. Continuous ECG was recorded at 500 Hz with CardioSoft exercise ECG system (Version 4.14, GE Healthcare, Freiburg, Germany) using the Mason-Likar modification of the standard 12-lead system. The study protocol was approved by the Ethical Committee of the Hospital District of Pirkanmaa, Finland, and all patients gave informed consent prior to the interview and measurements as stipulated in the Declaration of Helsinki.

Two groups were formed: a low likelihood of CAD group (LLC) and a CAD group. Patients for first group were chosen by detailed patient information and from symptoms from the exercise test: all patients who underwent angiography or if they reported chest pain during the exercise test were excluded from the LLC group. Patients in the CAD group underwent selective coronary angiography within 180 days of exercise testing, and they presented at least 50% luminal narrowing of the diameter of at least one major epicardial coronary artery or main branches. Table 1 shows the population characteristics. Some of the patients in the CAD group were on medication (number of patients in brackets): ACE inhibitors (61), beta blockers (169), calcium channel blockers (38), glyceryl trinitrate (86), long-acting nitrate (90) and diuretics (34). Also several CAD patients reported chest pain during the exercise test, leading to a shorter exercise phase.

Table 1: Population characteristics (BMI=body mass index, MI=myocardial infarction). [a] denotes median ± median absolute deviation (MAD) values, * denotes significant differences between groups (Mann-Whitney test, p<0.001).

	LLC ($n = 214$)	CAD ($n = 195$)
Age (years) [a]	48 ± 9	62 ± 7 *
Gender (male/female)	124/90	149/46
BMI ($kg \cdot m^{-2}$) [a]	26 ± 3	27 ± 2 *
MI (patients)	0	57 *
Diabetes (patients)	12	34
Chest pain (patients)	0	67 *
Exercise length (min) [a]	7.4 ± 1.4	5.8 ± 1.2 *

B. Preprocessing

ECG waveforms were delineated by a multi-lead wavelet-based detector optimized to stress test recordings [7]. The beat time occurrences creates the RR series. Due to a high level of arrhythmic events in this database, several rules are imposed on the RR series as in [4]: beat intervals must be higher than 0.3s and lower than 1.5s, and the relative change between successive intervals must be lower than 20%. If the recording has more than 20% abnormal beats, the recording is removed from the study. In total, 48 recordings were discarded, remaining 409 recordings.

C. HRV and respiratory rate estimation

The HRV signal is obtained using the Time-Varying Integral Pulse Frequency Modulation model (TVIPFM) [8], which assumes that the activity of the ANS can be modelled by a modulating signal $m(t)$. From beat time occurrences t_k, the instantaneous HR is obtained $d_{\mathrm{HR}}(n)$, sampled at 4Hz. Since the very low frequency components can mask the low frequency band, a low-pass filter with a cut-off frequency of 0.03 Hz is used to obtain the filtered signal $d_{\mathrm{HRM}}(n)$. The variability signal $d_{\mathrm{HRV}}(n)$ is calculated as $d_{\mathrm{HRV}}(n) = d_{\mathrm{HR}}(n) - d_{\mathrm{HRM}}(n)$. The modulating signal is estimated as $\hat{m}(n) = d_{\mathrm{HRV}}(n)/d_{\mathrm{HRM}}(n)$. This method also deals with ectopic and misdetected beats, assuming a low number of incidences [9].

Respiratory rate is estimated from an algorithm which exploits the respiration-induced beat morphology variations on the QRS slopes of each one of the 12 Mason-Likar ECG leads. A spectral-based fusion technique is subsequently applied in order to get an estimation of the respiratory rate $F_r(n)$ every 5 s. Further details are given in Lázaro et al. [5].

D. Interval selection and physiological parameters

To deal with the nonstationary nature of $\hat{m}(n)$ during exercise, the analysis is performed in short intervals of the signal. Four 2-min windows are selected for each patient: at the beginning of the recording (resting phase), 30 s after the exercise phase begins, just prior to the end of the exercise and 30 s after the exercise ends (recovery phase). Within these windows, a 1-min segment is searched with less than 5% abnormal beats. These segments, if found, are considered the intervals of analysis: I_{rest}, I_{exe1}, I_{exe2} and I_{rec}. Figure 1 shows an example of $d_{\mathrm{HRM}}(n)$ for one patient, and the windows where each interval is located. Vertical continuous lines indicates the beginning and the end of the exercise.

From these intervals, two parameters are extracted:

- $\bar{d}_{\mathrm{HRM}}$: Mean heart rate, obtained as the median value of $d_{\mathrm{HRM}}(n)$ in the interval of interest.
- $\bar{F}_r$: Respiratory rate, obtained as the median value of $F_r(n)$ in the interval of interest.

Subsequently, the power spectral density of $\hat{m}(n)$ within these 1-min-length intervals ($S_{\hat{m}}(f)$) was obtained based on Welch periodogram, using windows of 30 s and 20s of overlapping. Powers related to the two main componetns, P_{HF} and

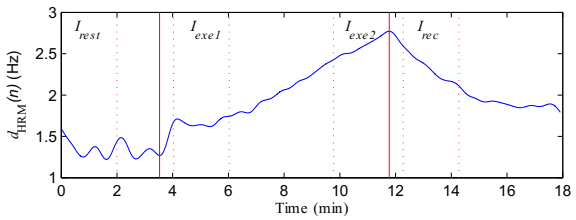

Fig. 1: Example of $d_{\mathrm{HRM}}(n)$ for one patient. Vertical lines delimite the exercise phase, while dashed lines show the windows where the intervals I_{rest}, I_{exe1}, I_{exe2} and I_{rec} are located.

P_{LF} were obtained from $S_{\hat{m}}(f)$. Classical LF band [0.04 Hz, 0.15 Hz] was used, while an alternative HF band centred at $\bar{F}_r$ with a bandwidth of 0.15 Hz was used: [max(0.15 Hz, $\bar{F}_r$ - 0.075 Hz), $\bar{F}_r$ + 0.075 Hz]. An additional HF parameter, P_{HFe}, was obtained within an extended band (from 0.15 Hz to half the mean HR) to compare with P_{HF}.

The following spectral parameters were extracted for each one of the intervals:

- P_{LFn}: LF power normalized by the total power in LF and HF bands.
- P_{HF}: HF power obtained around the respiratory frequency.
- R: Ratio between LF and HF powers.
- P_{HFe}: Extended HF power.

E. Statistical analysis

Assumption of normal distribution was rejected using a Kolmogorov-Smirnov test in all parameters. The Mann-Whitney test was used to test equality of population medians ($p<0.001$) among LLC and CAD groups. A Wilcoxon signed-rank test between P_{HF} and P_{HFe} was also performed to compare these parameters ($p<0.001$). Additionally, the area under the receiver operating characteristic curve (AUC) was obtained for each studied parameter.

III. Results

Statistical analysis between LLC and CAD group is shown in Table 2. $\bar{d}_{\mathrm{HRM}}$ and P_{HF} are significantly different in all intervals, with $\bar{d}_{\mathrm{HRM}}$ being always higher in LLC group, and P_{HF} being higher in LLC group in I_{rest} and I_{exe1}, while higher in CAD group in I_{exe2} and I_{rec}. P_{HFe} behaves similarly than P_{HF} throughout the test, but the differences are lost in I_{exe2}. Overall, P_{HFe} values are always higher than P_{HF} ones, and a paired Wilcoxon analysis between both HF parameters reveals that they are significantly different in I_{exe2} and I_{rec}. Both P_{LFn} and R are very similar (only P_{LFn} is shown), with significantly higher values for LCC group during I_{rest} and I_{exe1}. $\bar{F}_r$ values are significantly higher in the LCC groups during I_{exe2} and I_{rec}, but they do not differ during I_{rest} and I_{exe1}. Figure 2 shows the AUCs for each parameter in each interval.

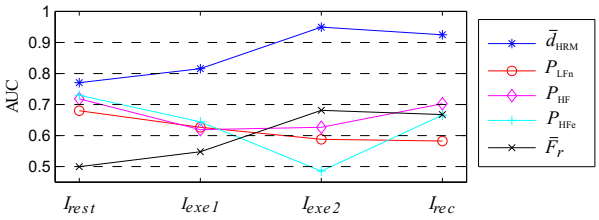

Fig. 2: AUCs for each parameter in the different intervals.

IV. Discussion

Parameter $\bar{d}_{\mathrm{HRM}}$ shows values significantly higher in the LLC group than in the CAD group, even in the resting phase. This is probably due to the fact that in the latter group, 80% of the patients took beta blocker medication. Moreover, patients in CAD group were likely affected by diminished physical capacity due to myocardial ischemia. With shorter exercise sessions (5.8 min vs 7.4 min), both $\bar{d}_{\mathrm{HRM}}$ and $\bar{F}_r$ are expected to be lower in the CAD group. Similar conclusions can be extracted with the AUC values during I_{exe2}.

By correcting HRV by the mean HR, we try to minimize the effect of the beta blocker medication. The fact that there is a change of trend in P_{HF} during exercies supports our hypothesis that it is reflecting differential changes in ANS response to exercise in LCC and CAD patients rather than the effect of medication.

When analyzing HRV during exercise, there is a need to redefine HF band since respiratory rate usually increases above 0.4 Hz. In this work, we analyze two different bands: extended up to half the mean HR and centered at $\bar{F}_r$. The differences between P_{HF} and P_{HFe} are more evident near the peak of exercise. By extending the frequency band to measure the HF component, there is a risk to measure other undesirable spectral components which can mislead the measures. Previous works [10] have identified in HRV spectrum a component which is synchronous to the stride or pedalling frequency. This component increases with the intensity of the exercise and can reach up to 30% of the total power. This may explain that in I_{exe2}, P_{HFe} values greatly increase and become similar in both groups, since the origin of this component is purely mechanic.

Parameters P_{LFn} and R presented very similar trends and AUCs values. While they were not able to separate LLC and

Table 2: Median ± median absolute deviation (MAD) values and results for the statistical analysis between LLC and CAD groups. * indicates significant differences ($p<0.001$).

		I_{rest}	I_{exe1}	I_{exe2}	I_{rec}
$\bar{d}_{\text{HRM}}$ (Hz)	LLC	1.35 ± 0.17	1.65 ± 0.19	2.72 ± 0.16	2.16 ± 0.21
	CAD	1.10 ± 0.12 *	1.35 ± 0.11 *	1.94 ± 0.25 *	1.48 ± 0.18 *
P_{LFn} (n.u.)	LLC	0.81 ± 0.08	0.79 ± 0.12	0.17 ± 0.12	0.82 ± 0.08
	CAD	0.70 ± 0.13 *	0.69 ± 0.16 *	0.23 ± 0.14	0.77 ± 0.12
P_{HF} (a.u., $x10^{-5}$)	LLC	30.4 ± 19.5	6.9 ± 5.03	1.23 ± 8.9	2.57 ± 1.8
	CAD	11.7 ± 7.6 *	3.6 ± 2.4 *	2.23 ± 1.3 *	7.9 ± 5.6 *
P_{HFe} (a.u., $x10^{-5}$)	LLC	38.3 ± 23.2	15.4 ± 10.4	6.4 ± 3.6	9.5 ± 5.8
	CAD	14.3 ± 9.3 *	8.4 ± 4.6 *	7.4 ± 4.6	20.3 ± 12.5 *
$\bar{F}_r$ (Hz)	LLC	0.20 ± 0.04	0.28 ± 0.04	0.53 ± 0.06	0.42 ± 0.05
	CAD	0.20 ± 0.05	0.27 ± 0.03	0.46 ± 0.06 *	0.38 ± 0.04 *

CAD groups in some of the intervals, P_{HF} when measured guided by respiratory rate was significantly different in all intervals. Looking at the AUCs, P_{HF} values are higher, with an AUC above 0.7 at rest and recovery. Note that differences in age between the groups may have influenced the results. Some studies also claim that parameters like myocardial infarction or diabetes could influence to the decreased HRV in the CAD group [11, 12]. We repeated the analysis removing the 57 patients with MI and 46 diabetic patients, but no significant differences were found with respect to using all patients. However, they are very few patients, only representing 14% and 11% of the whole database, respectively.

V. Conclusion

The CAD diagnosis capability of some HRV parameters has been studied. Respiratory rate has been estimated from the ECG and it has been included in the analysis to correctly measure the HF component. Parameters have been corrected to remove the effect of changes in mean HR in HRV. Due to the effect of medications and differences in exercise duration in this database, mean HR cannot be reliably used to diagnose CAD. HF power, when guided by respiration, achieves the highest AUC, above 0.7 both in rest and in recovery.

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