HEART RATE VARIABILITY AND HEART RATE RECOVERY AS PROGNOSTIC FACTORS

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Abstract

Background and aim. Heart rate (HR) can appear static and regular at rest, during exercise or recovery after exercise. However, HR is constantly adjusted due to factors such as breathing, blood pressure control, thermoregulation and the renin-angiotensin system, leading to a more dynamic response that can be quantified using HRV (heart rate variability). HRV is defined as the deviation in time between successive normal heart beat and is a noninvasive method to measure the total variation in a number of HR interval. HRV can serve as measure of autonomic activity of sino-atrial node. The aim of the study was to determine the influence of certain clinical and paraclinical parameters on heart rate recovery after exercise in patients with ischemic heart disease and the relation with HRV using 24 h Holter monitoring.

Methods. The study included 46 patients who were submitted to cardiovascular exercise stress test and also to 24 h Holter EKG monitoring. Subjects had a mean age of 56.2±11.2 years, with a minimum of 25 and a maximum of 79 years. The study included 22 (47.8%) men and 24 (52.2%) women. Statistical analysis was performed using MedCalc software version 14.8.1. Multivariate analysis consisted of the construction of several multiple linear regression models. A p value of 0.05 was considered statistically significant.

Results. The HRV values (time domain) were all lower in the IHD compared with the group without coronary heart disease, even if the difference is not statistically significant. Also rest and maximal HR values were similar but during the test varies in the sense that those with IHD had higher values of rest and maximal HR and lower HRR, but not statistically significant.

Conclusions. HRV is a very easy and safe method if there is an available device and it is used for evaluation of the autonomic nervous system in many cardiovascular diseases, but also in other pathologies.

In uncomplicated ischemic heart disease HRV is depressed, but not significant. HRR, which is also considered an indicator of the parasympathetic activity after exercise termination, is also non-significantlly decreased in ischemic patients and the correlation between them is weak. Both HRV and HRR parameters can be easily measured, but the best algorithm of this issue requires further studies, conducted in larger patient populations. Although HRR and HRV are tools to measure the autonomic nervous system activity the relation between them need more studies to be able to quantify the arrhythmogenic risk.

Keywords: heart rate recovery, heart rate variability, stress test, ischemic heart disease

Background and aim

Heart rate (HR) may seem to be static and regular at a time at rest, during exercise or recovery after exercise. However, HR is constantly adjusted due to factors such as breathing, blood pressure control, thermoregulation and the renin-angiotensin system, leading to a more dynamic response [1,2,3]. This dynamic model is caused by the interaction between the SNS (sympathetic nervous system) and PNS (parasympathetic nervous system) and HR adjustment based on physiological needs [4,5,6]. The activities of SNS (sympathetic nervous system) and PNS (parasympathetic nervous system) on sinus is characterized by rhythmic mode discharges in synchronization with the cardiac cycle [2,7]. These discharges are regulated by afferent stimuli from central and peripheral components of the autonomic nervous system [8] and may cause variations in time that occurs between successive heart beats [9,10].

It was found that the discharge of PNS causes greater variations over time between consecutive heartbeats compared with discharges from SNS [3]. This is due to the rapid hydrolysis of acetylcholine by acetylcholinesterase [11]. Acetylcholinesterase rapid activity results in a rapid and transient HR response to vagal activity, which causes variation in time between consecutive heart beats [12,13].

Beat-to-beat variation in HR can be quantified using HRV [14]. HRV is defined as the deviation in time between successive normal heart beat and is a noninvasive method to measure the total variation in a number of HR data [15]. Individual variations between heartbeats are caused by modulation of SA node by PNS and SNS [16].

As a result, HRV can serve as measure of autonomic activity node SA [15,16]. However, HRV does not measure the basic tone of each branch of the autonomic nervous system as sometimes reported in the literature [4,13,17,18]. HRV measures the variation of PNS and SNS activity that modulates intrinsic HR [19]. For example, the PNS saturated tone is constant in size and reduces the difference between normal and reduced HRV heartbeat. Also, the complete withdrawal of PNS tone is constant in size and shows reduced HRV. In this case, reduced HRV reflects the change in the amount of PNS tone and it would be inappropriate to use HRV to describe the PNS tone [18]. Therefore, we can say that HRV measures the modulation SNP and SNS [13,18,19].

HRV is valued at a record electrocardiogram (ECG) in HR [15]. An ECG quantifies electric current passing through the heart during the cardiac cycle [20,21]. One heartbeat on an ECG reveals three successive peaks in the electrical activity of the heart. The first is the P wave, reflecting atrial depolarisation. P wave depolarization is followed by complex measures QRS.QRS complex ventricular depolarization and atrial depolarization masks because of high peak power during ventricular depolarization [20,22] of a single peak .The last peak of a cardiac cycle is T-wave, which reflects ventricular depolarization [22].

Objectives

The aim of the study was to determine the influence of certain clinical and paraclinical parameters on heart rate recovery after exercise and the relation with HRV using 24 h monitoring , in patients with ischemic heart disease.

Material and method

The study was conducted at the Rehabilitation Clinical Hospital between 2011-2013.

It was an observational, analytical, prospective cohort study. Data collection was done according to the exposed - non-exposed type.

Subjects were included in the study after meeting the inclusion criteria and after signing a consent form for enrolment. The study protocol was approved by the Ethics Committee of "Iuliu Hatieganu" University of Medicine and Pharmacy Cluj-Napoca.

The study included 46 patients who were subjected to cardiovascular stress test and also to 24 h Holter EKG monitoring. Subjects had a mean age of 56.2±11.2 years, with a minimum of 25 and a maximum of 79 years. The study included 22 (47.8%) men and 24 (52.2%) women.

The indications for the stress test included: diagnosis and risk stratification of patients with suspected ischemic heart disease, determining disease severity in patients with clear diagnosis of ischemic cardiomyopathy, monitoring patients throughout medical treatment or intervention.

Before the stress test, patients had undergone echocardiography using a Esaote MyLab X-View 50 ultrasound machine, manufactured in 2008, with a linear variable 7.5-10 MHz frequency probe, Doppler color.

No effort test was conducted in patients who had indications of one of the following diagnoses: heart attack (within the past 2 days), unstable angina not stabilized by medical therapy, symptomatic uncontrolled arrhythmia, decompensated heart failure, pulmonary thromboembolism, acute pericarditis or myocarditis, aortic dissection, severe symptomatic aortic valve stenosis, uncontrolled BP (200/100 mm Hg), hypertrophic cardiomyopathy, high-grade atrio-ventricular block.

The stress test was performed by a specialist cardiologist with experience in this department. The test was performed using a cycloergometer.

The following parameters were measured in each patient: blood pressure and pulse rate prior to exercise, during exercise and at protocol-established time intervals, as well as 1 and 3 minutes after the end of the stress test. The following were reasons for stopping the stress test: chest pain, fatigue, dyspnea, pressor response.

A series of clinical and laboratory data were assessed in patients included in the study. Patient history helped identify the presence of diabetes mellitus, essential

hypertension, ischemic heart disease.

The diagnosis of ischemic heart disease was determined by medical history, electrocardiogram (ECG), echocardiography or coronarography results. The following were clinical features: constrictive discomfort, pressure or burning, location in the chest, jaw, shoulder, back, arms, occurring during physical effort, emotional stress, or at rest. The pain may be of variable duration and it can disappear following cessation of effort or following sublingual nitroglycerin administration. The ECG monitored the presence of the following elements: changes in the ST-segment (significant elevation or depression), pathological Q wave, negative or flat T wave, bundle branch block, ventricular hypertrophy. Echocardiography determined the presence of kinetic changes in the ventricles (hypokinesia, akinesia, dyskinesia).

Statistical analysis was performed using MedCalc software version 14.8.1. Data were considered as nominal or quantitative. The normal distribution of continuous variables was examined using the Kolmogorov-Smirnov test. The frequency and percentage were reported for nominal data, and the mean and standard deviation were reported for continuous data.

Table I. Clinical characteristics of the studied patients.

Variable	Value
BMI (body mass index)	313 ± 9.4
HRrest (beats/min)	81.1 ± 16.8
HRmax (beats/min)	118.8 ± 26.2
HR1 (beats/min)	101.9 ± 26.4
HRR1 (beats/min)	17 ± 13.2
HR3 (beats/min)	85 ± 17.3
HRR3 (beats/min)	33.8 ± 18
SDNN (standard deviation of all NN intervals)	70.2 ± 40
SDANN (standard deviation of sequential 5-minute R-R interval means)	127.5 ± 39
SDNNi (mean of standard deviations of all NN intervals in all 5-minute segments)	57.1 ± 29.8
rMSSD (square root of the mean squared differences of successive NN intervals)	34.5(22; 51)
pNN50 (total number of NN intervals)	5.8 (2.7, 14)
SBP	123.9 ± 11.7 basal
TAD	77.1 ± 9.9 basal
SBP	185.9 ± 28.1 max effort
TAD	88.8 ± 9.6 max effort
SBP	128.3 ± 18.1 after effort
TAD	77.8 ± 12.3 after effort
HTA	36 (78.3%)
IHD	23 (50%)
Acom	4 (8.7%)
DM	10 (21.7%)
Treatment with beta-blocker	42 (91.3%)

The comparison between two groups of a continuous variable was performed using the independent samples t-test. The correlation between two variables was tested using Pearson's correlation. Percentage differences between two groups of nominal variables were assessed using the chi-square test.

Multivariate analysis consisted of the construction of several multiple linear regression models. A p value of 0.05 was considered statistically significant [23].

Results

The study included 46 patients with mean age 56.2 $\pm$ 11.2 years, minimum 25, maximum 79 years, of which 24 (52.2%) women and 22 (47.8%) men.

Clinical and laboratory characteristics of patients can be seen in Table I.

The age of patients was not correlated with SDNN values (r=-0.036; p=0.8), SDANN (r=0.119; p=0.4), SDNN (r=-0.165; p=0.2), RMSSD (r=-0.028; p=0.8), pNN50 (r=0.021; p=0.8).

SDNN values (p=0.07), SDANN (p=0.2), SDNN (p=0.08), RMSSD (p=0.4), pNN50 (p=0.3) did not differ according to the sex of patients.

SDNN values (p=0.6), SDANN (p=0.9), SDNN (p=0.3), RMSSD (p=0.8), pNN50 (p=0.8) did not differ according to CIC presence.

SDNN values (p=0.6), SDANN (p=0.8), SDNN (p=0.3), RMSSD (p=0.06), pNN50 (p=0.2) did not differ according to HTA presence.

SDNN values (p=0.6), SDANN (p=0.9), SDNN (p=0.9), RMSSD (p=0.4), pNN50 (p=0.5) did not differ depending on DZ presence.

SDNN values (p=0.1), SDANN (p=0.3), SDNN (p=0.6), RMSSD (p=0.7), pNN50 (p=0.9) did not differ according to the presence of beta-blocker therapy.

HRmax values were correlated with the SDNN (r=0.029; p=0.8), SDANN (r=0.002; p=0.9), SDNN (r=-0.019; p=0.9), RMSSD (r=-0.088; p=0.5), pNN50 (r=-0.138; p=0.3).

HRrest values were correlated with the SDNN (r=-0.018; p=0.9), SDANN (r=-0.022; p=0.8), SDNN (r=-0.010; p=0.9), RMSSD (r=0.049; p=0.7), pNN50 (r=-0.050; p=0.7).

HR1 values were correlated with the SDNN (r=-0.015; p=0.9), SDANN (r=-0.052; p=0.7), SDNN (r=0.04; p=0.9) RMSSD (r =-0.011; p=0.9), pNN50 (r=-0.097; p=0.5).

HRR1 values were correlated with the SDNN (r=0.020; p=0.9), SDANN (r=0.074; p=0.6), SDNN (r=-0.130 p=0.3), RMSSD (r=-0.211; p=0.1), pNN50 (r=-0.181; p=0.2).

HR3 values were correlated with the SDNN (r=0.057; p=0.7), SDANN (r=-0.039; p=0.7), SDNN (r=0.000; p=1), RMSSD (r=-0.009; p=0.9), pNN50 (r=-0.121; p=0.4).

HRR3 values were correlated with the SDNN (r=-0.055; p=0.7), SDANN (r=-0.046; p=0.7), SDNN (r=-0.095; p=0.5), RMSSD (r=-0.175; p=0.2), pNN50 (r=-0.181; p=0.2).

Twenty three patients had ischemic heart disease (IHD) and the other twenty three were free of coronary

ischemia. All of the patients with IHD had also high blood pressure with treatment, ten of them had diabetes mellitus and four of them had also peripheral vascular disease. Male gender is significantly higher in the patient group with IHD. The use of betablockers is similar between groups.

There was no significant difference between the systolic and diastolic blood pressure of the groups, at the beginning of the exercise test. But systolic blood pressure increased with exercise in the group with IHD and hypertension, the difference being significant. Heart rate was also similar between groups.

The HRV values (time domain) were all lower in the IHD compared with the group without coronary heart disease, even if the difference is not statistically significant. Also rest and maximal HR values were similar but during the test varies in the sense that those with IHD had higher values of rest and maximal HR and lower HRR, but not statistically significant

Discussion

HRV is a very easy and safe method if there is an available device and it is used for evaluation of the autonomic nervous system in many cardiovascular diseases, but also in other pathologies. HRV measurements include two components - time domain and frequency domain parameters. In time domain analysis, the most used parameters is SDNN which is a general measurement of overall autonomic function. pNN50, on the other hand, reflects predominantly parasympathetic activity. Frequency domain parameters consists of low frequency value, high frequency value and the ratio between them, but we choose not to use them in this study [24,25].

Abnormal or imbalanced autonomic function is demonstrated for decades to correlate with arrhythmias and higher risk of sudden death. Increased sympathetic activity or decreased parasympathetic activity has been proved to be a predictor of mortality and morbidity in patients with myocardial infarction, heart failure or diabetes mellitus with autonomic neuropathy as a complication. Increased parasympathetic activity correlates with a better prognosis of those patients, as it has a protective effect [26,27,28,29].

Hear rate variability has been proven to be modified among patients with stable ischemic heart disease, and HRV parameters can be reduced even before the development of symptoms, which is an important discovery also for primary prevention. In 1987, Airaksinen et al. reported for the first time the reduced vagal activity among patients with coronary heart disease. Parasympathetic activity is reduced and sympathetic activity is higher than in healthy subjects in uncomplicated coronary heart disease, particularly during sleep; the reduction in HRV is correlated with the angiographic severity of the coronary heart disease [30,31].

The patients from our study had no history of myocardial infarction and all of them had left ventricular ejection fraction within normal limits. The ratio of diabetes

mellitus, which is known to affect autonomic functions, is rather high in coronary ischemic disease group (almost half of them had DM), as compared with patients without coronary artery disease - in which there is no case of DM. This could be a study limitation, although all the cases with DM are on oral treatment and without major complications of the disease.

In our study, we observed reductions in all the time-domain parameters in the ischemic group, and also in heart rate recovery values at one minute and three minutes, but none of the values that we obtained were statistically significant reduced, as compared with the group of patients without ischemic heart disease. The time-domain HRV parameters were obtained from long (24 hours) recordings in our study, during which all patients performed daily activities, and all of them were under treatment. Previous studies have pointed out that frequency-domain analysis obtained from short recordings are more useful in the prediction of mortality and that time-domain analysis should be reserved for longer recording [32,33]. This is why we chose to analyze only time domain parameters in our study.

Although it has been shown that time-domain HRV parameters are decreased in ischemic heart disease, the mechanism is not fully explained.

The clinical significance of post-exercise heart rate recovery(HRR) and its value as an indicator of parasympathetic activity in the recovery phase has also been observed in many studies [34,35]. Cole et al. have identified reduced heart rate recovery as a strong and independent predictor of mortality, while Imai et al. have found increased heart rate recovery in athletes, but decreased HRR in heart failure [36,37]. HRR values are also a strong indicator of mortality and morbidity risk in asymptomatic and symptomatic ischemic patients, and it seems to be independent from the severity of the disease, and left ventricular function [38,39]. In our study, HRR, like HRV, was reduced but not significantly in ischemic population, similar to the findings of other studies. Ischemic heart disease could be responsible for this reduction, because clinical properties and left ventricular function were similar in both groups, but there is a subgroup of diabetes patients which could alter the results (although, as we already said, they had no insulin therapy). Also, the risk factors are similar, with one exception - high blood pressure with higher prevalence in ischemic group.

In healthy persons, the parasympathetic system is dominant at rest; exercise is associated with parasympathetic reduction and, as the intensity of exercise is increased, with sympathetic activity (40). The autonomic changes associated with exercise termination are not fully understood. It seems that the parasympathetic system is responsible for the reduced heart rates during the early stages of the recovery phase. Similar results have been found in studies on the relationship between the HRV and

the HRR [41,42]; but there are few studies that investigate the relationship between HRR and HRV at rest, with conflicting results [34,35,36]. Some studies have reported that reduced post-exercise HRR is not related to pre-exercise HRV, but is strongly and significantly correlated with the HRV in the early recovery phase [36]. Other study found that HRR was correlated with the HRV parameters measured at rest and during early recovery [35]. Other studies have found no relationship between HRR and the HRVafter maximal exercise, but showed a significant correlation measured after submaximal exercise [34].

This may be the reason why in our study, although all the parameters of HRV and HRR were altered in ischemic group, the correlations between HRV and HRR parameters are weak or even absent. The reasons may be the small number of the patients included in the study and the comorbidities. The purpose of our study was to establish the relationship between HRR and the HRV parameters measured in ischemic patients as compared with non-ischemic patients. We found that HRR and HRV were non-significantly reduced in uncomplicated ischemic disease and that post exercise HRR was not correlated with the basal HRV parameters measured before exercise.

The number of our patients is limited and it is in fact a subgroup of a larger study group, which were tested for HRR values. Although our patient population is rather homogeneous, it represents a very small percentage of patients with ischemic heart disease; thus, its conversion to clinical practice is limited. Another limitation of our study is in not having evaluated the VO2 cardiovascular conditions of our patients. In our study, HRR was measured one and three minutes after exercise; for this reason, the effects of the exercise intensity on HRR can be excluded.

Conclusion

In uncomplicated ischemic heart disease HRV is depressed, but not significantly. HRR, which is also considered an indicator of the parasympathetic activity after exercise termination, is also non-significantlly decreased in ischemic patients and the correlation between them is weak. Both HRV and HRR parameters can be easily measured, and therefore can be used to quantify the arrhythmogenic risk but the best algorithm of this issue requires further studies, conducted in larger patient populations.

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