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Deterioration of Heart Rate Recovery Index in Patients with Non-Alcoholic Fatty Liver Disease (NAFLD)

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Background: Non-alcoholic fatty liver disease (NAFLD) has been considered as a benign disease often associated with central obesity and insulin resistance and, in general, with factors of the metabolic syndrome. Heart rate recovery after exercise is a function of vagal reactivation, and its impairment is an independent prognostic indicator for cardiovascular and all-cause mortality. The aim of our study was to evaluate the heart rate recovery index in patients with NAFLD.

Material/Methods: The study population included 59 patients with NAFLD (mean age=42.3±9.3 years) and 22 healthy subjects as controls (mean age=40.7±6.5 years). Basal electrocardiography, echocardiography, and treadmill exercise testing were performed on all patients and controls. The heart rate recovery index was defined as the reduction in the heart rate from the rate at peak exercise to the rate at the 1st minute (HRR1), 2nd minute (HRR2), 3rd minute (HRR3), and 5th minute (HRR5) after stopping exercise stress testing.

Results: There were significant differences in HRR1 and HRR2 indices between patients with ED and the control group (19.9±8.2 *vs.* 34.1±9.6; p<0.001 and 24.3±5.4 *vs.* 40.5±9.1; p=0.006, respectively). Similarly, HRR indices after the 3rd and 5th minutes of the recovery period were significantly lower in patients with NAFLD compared with those indices in the control group (32.3±8.5 *vs.* 58.4±6.5; p=0.001 and 58±18.2 *vs.* 75.1±15.8; p<0.001). Effort capacity was markedly lower (11±1.9 *vs.* 12.5±1.5 METs; p=0.001) among the patients with NAFLD.

Conclusions: The heart rate recovery index is deteriorated in patients with NAFLD. When the prognostic significance of the heart rate recovery index is considered, these results may help explain the increased occurrence of cardiac death. It points to the importance of the heart rate recovery index in the identification of high-risk patients.

MeSH Keywords: Autonomic Nervous System • Fatty Liver • Heart Rate

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Background

Non-alcoholic fatty liver disease (NAFLD) is a benign disease often associated with central obesity and insulin resistance and, in general, with factors of metabolic syndrome [1]. NAFLD contains a spectrum of pathologic conditions, ranging from simple steatosis to nonalcoholic steatohepatitis and cirrhosis [2,3]. The effect of NAFLD on the autonomic nervous system (ANS) is still unknown. A few reports of autonomic neuropathy in this disease have been published [4]. However, previous studies showed that both sympathetic and parasympathetic pathways are impaired, either singly or together.

The autonomic nervous system plays a central role in regulating cardiovascular function, and cardiovascular autonomic nervous system dysfunction is related to significantly increased cardiovascular mortality [5,6]. Heart rate recovery (HRR) is an important measure of autonomic nervous system dysfunction and is directly correlated with parasympathetic activity [7]. The value for the HRR index is defined as the reduction in the heart rate from the rate at peak exercise to the rate at the 1st, 2nd, 3rd, and 5th minutes after the discontinuation of an exercise stress test. Autonomic dysfunction can contribute to serious arrhythmias in a patient with NAFLD. The impairment of HRR provides useful clinical information about evaluating patients with NAFLD for higher risk of serious arrhythmias [8,9].

Previous studies [4] investigated the effect of NAFLD on autonomic dysfunction but none have evaluated the heart rate recovery index. The aim of our study was to evaluate the heart rate recovery index in patients with NAFLD.

Material and Methods

Study population

The study population included 59 patients with NAFLD (mean age=42.3±9.3 years) and 22 healthy subjects as controls (mean age=40.7±6.5 years). All patients were admitted to the Gastroenterology Clinic with NAFLD and the Cardiology Department for general health examination and were evaluated with detailed history and physical examination. We recorded age, sex, and body mass index, as well as biochemical measurements (fasting blood glucose, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglyceride levels). Demographic characteristics and clinical features of the patients and the controls are given in Table 1.

In all subjects, we performed 12-lead electrocardiography (ECG) at 25 mm/sec (paper speed), and we performed transthoracic echocardiography by means of a GE-Vingmed Vivid 7 system (GE-Vingmed Ultrasound AS, Horten, Norway) using a 2.5-MHz transducer. The control subjects had no cardiovascular or any other organ system disease and presented with normal physical examination, chest roentgenogram, electrocardiogram, and 2-dimensional and Doppler echocardiogram. Patients were excluded from the study if they had <10g/dl hemoglobin; had diseases interfering with the autonomic nervous system, including diabetes mellitus, renal diseases, Parkinson's disease, porphyria, and amyloidosis; had cardiovascular diseases, including hypertension, ischemic heart disease, left ventricle (LV) ejection fraction lower than 50%, severe valvular regurgitation, moderate or severe valvular stenosis, cardiomyopathy, and cardiac arrhythmia; or had neurological diseases and chronic obstructive pulmonary disease. We excluded smokers. This study complied with the Declaration of Helsinki and was approved by the local Ethics Committee. Informed consent was obtained from each patient.

Exercise testing

All patients in the study underwent exercise treadmill testing using the Bruce protocol. The predicted peak heart rate was calculated as (220 - age), and the aim was to reach at least 85% of the age-predicted heart rates. The end of exercise was flagged, and at least 5 min of postexercise heart rate recorded with the subject at rest. Qualified exercise physiologists and/or cardiology fellows prospectively collected physiologic and hemodynamic data during testing, including symptoms, heart rate, heart rhythm, blood pressure, and estimated functional capacity in metabolic equivalents (METs; where 1 MET=3.5 ml/kg per min of oxygen consumption). Heart rate recovery indices were defined as the reduction in heart rate from the rate at peak exercise to the rate at the 1st, 2nd, 3rd, and 5th minutes after the cessation of the exercise stress test, and these results were indicated as HRR_1, HRR_2, HRR_3 and HRR_5, respectively.

Statistical analysis

Continuous variables are given as mean ±SD and categorical variables are given as a percentage. An independent-samples t test was used to compare the study variables between NAFLD patients and control subjects. A probability value of $p<0.05$ was considered significant, and 2-tailed p values were used for all statistics. All statistical analyses were carried out using statistical software (SPSS, version 15.0 for Windows; SPSS, Chicago, IL).

Results

The baseline characteristics of the study groups are shown in Table 1. According to the basic clinical and demographic characteristics, both groups were similar with respect to age, sex, and fasting glucose levels. All subjects were normotensives,

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Table 1. Demographic and clinical futures of the patients and the controls (mean ±SD).

	NAFLD patients (n: 59)	Healthy controls (n: 22)	P value
Age, years	42.3±9.3	40.7±6.5	0.39
Gender(M/F)	38/21	10/12	0.13
Body mass index, kg/m^2	32.7±5.3	24.4±3.2	<0.001
Heart rate, beats/min	79.6±10.4	77.1±8.2	0.07
Systolic blood pressure, mmHg	128.7±15	122.1±12.8	0.06
Diastolic blood pressure, mmHg	75.6±8.6	73.7±5	0.11
Fasting glucose, mg/dl	98.2±12.3	94.5±6.4	0.08
Total cholesterol, mg/dl	217.6±49.4	197.6±33.9	0.04
HDL-cholesterol, mg/dl	45±11.6	64.6±17.5	<0.001
LDL-cholesterol, mg/dl	137.8±41.6	114.2±34.3	0.01
Plasma triglyceride, mg/dl	158.4±84.7	86.6±37.9	<0.001
AST (IU/L)	26.8±12.3	20.5±3.8	0.001
ALT (IU/L)	37.7±21.7	18.2±7.7	<0.001

Table 2. Comparison of echocardiographic and exercise stress test derived variables of patients and controls (mean ±SD).

	NAFLD patients (n: 59)	Healthy controls (n: 22)	P value
Ventricular M-mode derived variables			
Left ventricular end-diastolic diameter, mm	50.1±2.9	49.7±3.9	0.06
Left ventricular end-systolic diameter, mm	30.7±2.4	29.6±3.1	0.09
Left ventricular ejection fraction,%	67.7±3.4	68.5±2.8	0.30
LV mass	196.1±46.9	146.2±35	<0.001
Exercise Stress Test Findings			
Exercise time, min	8.5±1.5	10±21.4	<0.001
Maximal heart rate, beats/min	171.6±10.3	173.5±8.5	0.39
Maximal systolic blood pressure, mmHg	186.4±15.8	174±15.2	0.003
Maximal diastolic blood pressure, mmHg	88.6±13.2	81.8±8.4	0.009
Maximal metabolic equivalents, METs	11±1.9	12.5±1.5	0.001
HRR_1	19.9±8.2	34.1±9.6	<0.001
HRR_2	24.3±5.4	40.5±9.1	0.006
HRR_3	32.3±8.5	58.4±6.5	0.001
HRR_5	58.±18.2	75.1±15.8	<0.001

METs – metabolic equivalents (1 MET=3.5 ml/kg per min of oxygen consumption); HRR – heart rate recovery index; NAFLD – non-alcoholic fatty liver disease.

and no significant differences were observed in systolic or diastolic blood pressures and resting heart rates between the 2 groups (SBP; 128.7±15, 122.1±12.8, p: 0.06, DBP; 75.6±8.6, 73.7±5, p: 0.11; HR; 79.6±10.4, 77.1±8.2, p: 0.07, respectively).

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All patients and healthy participants had sinus rhythm and normal 12-lead ECG results at rest. All completed the exercise stress test without rhythm abnormalities, ischemic changes, or other complications.

Comparisons of the baseline echocardiographic values among NAFLD patients and healthy controls are summarized in Table 2. There was no difference regarding left ventricular diameters and ejection fraction.

Comparisons of the maximal heart rate, maximal systolic and diastolic blood pressure, exercise duration, and metabolic equivalents attained during the exercise stress test values among NAFLD patients and healthy subjects are also summarized in Table 2. According to these results, the 1st- and 2nd-minute HRR indices of patients with NAFLD were significantly lower than those of the healthy control group (19.9±8.2 *vs.* 34.1±9.6; p<0.001 and 24.3±5.4 *vs.* 40.5±9.1; p=0.006, respectively). Similarly, HRR indices after the 3rd and 5th minutes of the recovery period were significantly lower in patients with NAFLD compared with those indices in the control group (32.3±8.5 *vs.* 58.4±6.5; p=0.001 and 58±18.2 *vs.* 75.1±15.8; p<0.001) (Table 2). However, we found that metabolic equivalents attained during the exercise stress test of patients with NAFLD were significantly lower than those of the healthy control group (11±1.9 *vs.* 12.5±1.5 METs; p=0.001) (Table 2).

Discussion

In this study we have demonstrated that heart rate recovery indices impaired in the 1st, 2nd, 3rd, and 5th minutes of the recovery period after maximal exercise testing in patients with non-alcoholic fatty liver disease compare to healthy control subjects. We also showed that effort capacity was significantly higher in patients with NAFLD.

NAFLD might be considered as a manifestation of metabolic syndrome, and insulin resistance plays a role in both conditions [10]. The components of metabolic syndrome perform sympathetic activation [11], and several studies have demonstrated the association between metabolic syndrome and decreased heart rate variability [12,13].

The autonomic dysfunction responsible for NAFLD is difficult to determine. The autonomic nervous system plays a central role in regulating cardiovascular function in both disease and health. The rise in heart rate during exercise is considered to be due to activation of the sympathetic nervous system and the simultaneous suppression of the parasympathetic nervous system [14]. On the other hand, the fall in heart rate immediately after exercise is considered to be the parasympathetic reactivation together with sympathetic withdrawal [15].

Previous studies showed that heart rate recovery is a marker of autonomic system function and is directly associated with parasympathetic nervous system activity [16,17]. Another study found that an increment in vagal activation as well as a decrement in sympathetic activation was detected during the first minutes of the recovery soon after exercise cessation [17]. Imai et al. showed that short- and mid-term HRR indices (30 s to 2 min) are mediated primarily by vagal reactivation [15]. Kannankeril et al. demonstrated that parasympathetic effect on heart rate was defined by the difference in heart rate with and without atropine [18]. These data showed that parasympathetic system effects continued during high-intensity exercise, and a large parasympathetic system effect on heart rate was noted at 1 min, increased at 4 min, and then stayed stable until 10 min in the recovery period. Heart rate recovery has been studied in various diseases such as heart failure [19], coronary artery disease [14], diabetes mellitus [20], obstructive sleep apnea [21], systemic lupus erythematosus [22], and psoriasis [23]. In the present study, we excluded subjects with coronary artery disease, neurologic diseases, prior cardiovascular event presence, and current smoking to avoid the effects of these variables on heart rate recovery index.

Several studies have reported that impaired heart rate recovery index after exercise is a powerful and independent predictor of cardiovascular and all-cause mortality [24]. Additionally, previous studies reported that a delayed decrease in heart rate during the 1st minute after exercise is a potent predictor of overall mortality, of the presence or absence of myocardial perfusion defects, and of changes in heart rate during exercise [25,26]. Jouven et al. reported that an HRR of less than 25 beats/min after the 1st min of the recovery period increased the relative risk for sudden cardiac death by 2.2-fold compared with the HRR group rate of more than 40 beats/min [27].

Various laboratory methods to assess autonomic nervous system function may help. However, they often require special equipment and training, and are not easily used in routine evaluation. Heart rate recovery provides a useful method to measure autonomic activity. Our results show that NAFLD patients have decreased heart rate recovery index compared with healthy controls. Hence, autonomic dysfunction might be a risk factor for cardiac death in patients with NAFLD, and heart rate recovery index analysis might be used for risk stratification.

Conclusions

The heart rate recovery index is impaired in patients with non-alcoholic fatty liver disease. When the prognostic significance of the heart rate recovery index is considered, these results may explain the increased occurrence of cardiac death in patients with NAFLD. This study calls attention to the importance of

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the heart rate recovery index, which is simple to use and may be clinically useful in the identification of high-risk patients.

Limitations

The major limitations of the present study are that it is based on a single-center experience and may be limited by the small number of patients. However, our population contained a homogeneous mix of unselected patients with NAFLD, therefore mirroring the real-world situation.

Conflict of interest

None.

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