ORIGINAL ARTICLE

Evaluation of heart rate recovery in patients with primary nephrotic syndrome

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Abstract

Background/aim: Abnormal heart rate recovery after an exercise stress test is a strong predictor of cardiovascular death in healthy subjects and various patient groups. The aim of the present study was to investigate heart rate recovery (HRR), a cardiovascular risk factor, in patients with primary nephrotic syndrome (NS).

Material and Methods: Forty patients with primary NS (mean age 39.6 ± 9.3 years) and 42 healthy subjects (mean age 36.0 ± 7.9) were included in the study. HRR was calculated by subtracting the heart rates in the first, second, and third minutes of the recovery period from the maximum heart rate, reached during the exercise stress test.

Results: The HRR in the first minute was significantly slower in the NS group compared with the control group (25.5 ± 10.1 and 32.4 ± 11.1, respectively; p =0.004). The HRR in the second and third minutes was also slower in the NS group, but the difference was not statistically significant. When a comparative analysis of HRR and the etiology of NS was carried out, no difference was found at any time point.

Conclusions: Impaired first minute HRR was identified in patients with NS. This suggests that primary NS patients should be monitored due to the potential increased risk of cardiovascular disease. Hippokratia 2015; 19 (2):109-113.

Keywords: Exercise stress test, heart rate recovery, nephrotic syndrome

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Introduction

Premature atherosclerosis could lead to coronary artery disease (CAD) in patients with primary nephrotic syndrome (NS), resulting in increased morbidity and mortality. Many defined risk factors for the development of atherosclerotic heart disease could be associated with NS, including increased total cholesterol, low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL)-cholesterol, decreased high-density lipoprotein (HDL)-cholesterol, tendency for thrombosis, and endothelial dysfunction[1].

In patients with NS, hypertension and hyperlipidemia develop frequently due to steroid use. In addition, impaired glucose tolerance and the presence of hyperlipidemia with hypercoagulability could increase the risk of developing CAD[1-3]. As well, premature atherosclerosis, coronary thrombus and acute coronary syndrome can occur without atherosclerotic plaque rupture due to hypercoagulability and an impaired fibrinolytic system[4,5]. Since many CAD patients are asymptomatic, early diagnosis and the evaluation of modifiable risk factors are important[6].

Heart rate recovery (HRR) is the reduction of the heart rate after a period of exercise[7]. Recovery continues until the heart rate, blood pressure, and electrocardiographic changes all return to baseline values. Heart rate recovery is calculated by subtracting the heart rate at the first, second, and third minutes of recovery from the maximum heart rate during exercise. During exercise, sympathetic activity increases whereas vagal activity decreases. After exercise, the heart rate slows as a consequence of the increased parasympathetic and decreased sympathetic activity[8,9]. HRR is an indicator of vagal activity, and many studies suggest that slow HRR is an important predictor of death from all causes and cardiovascular mortality[10-12]. However, HRR in patients with primary NS has not been investigated thoroughly yet. In the present study, we investigated the changes in HRR in patients with primary NS.

Material and Methods

Study design and patient population

Forty patients with NS and 42 healthy subjects were enrolled in the study. Nephrotic syndrome was defined

by the presence of proteinuria in excess of 3.5 g/24 hours along with hypoalbuminemia, edema, hyperlipidemia (hypertriglyceridemia and hypercholesterolemia), and lipiduria[2]. In patients with previously diagnosed NS, presence of proteinuria <0.3 g/d and normal serum albumin concentration was considered remission of disease[13].

The NS group comprised patients aged 18-75 years, who had been followed for at least three months after the diagnosis of primary NS. Exclusion criteria were as follows: secondary NS (due to collagen vascular disease, vasculitis, diabetes mellitus, amyloidosis, or drug-induced glomerulonephritis), coronary artery disease, heart valve disorders, rhythm disorders, acute pericarditis, myocarditis, endocarditis, liver disease, malignancy, current smoking and alcohol use, the use of drugs that could affect the autonomous system, a glomerular filtration rate (GFR) of <90 ml/min/1.73m^2, and pregnancy. All patients (n=40) were administered 100 mg/day aspirin, and lipid-lowering drugs (if necessary) for at least 2 months before the study. Patients were on a protein (0.6-0.8 g/kg/day) and salt (4-6 g/day sodium) restricted diet throughout the study. The control group was chosen from healthy volunteers with no known drug use and disease, and whose GFR was >90 ml/min/1.73m^2 with normal urine protein excretion (<150 mg/day).

The study was conducted in accordance with the Declaration of Helsinki, and the study protocol was approved by the Ankara Numune Education and Research Ethics Committee. All subjects provided written informed consent prior to participating in the study.

Laboratory procedures

Blood sampling was performed from 8-10 a.m. after an overnight fast. Laboratory values were also determined, including complete blood counts, kidney function tests, calcium, potassium, total protein, albumin, fasting glucose, lipid profiles, and 24-hour protein excretion.

Sysmex XE 2100 hematology auto-analyzer (Roche Diagnostics Corp., Indiana, USA), was used for photometric analysis of hemoglobin; 24-hour urine protein was measured by microalbumin turbidimetric method; creatinine total protein was measured by albumin colorimetric method; fasting glucose, total cholesterol and triglycerides (TG) were measured by enzymatic colorimetric method; HDL-cholesterol was measured by homojen enzymatic colorimetric method using Hitachi Modular P800 auto-analyzer (Roche Diagnostics Corp., Indiana, USA). LDL-cholesterol was calculated by Friedewald method. In patients with LDL-cholesterol >130 mg/dl, TG >150 g/dl was considered dyslipidemia. The GFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation: GFR = 141 × min (Scr/κ,1)$^{\alpha}$ × max(Scr/κ,1)$^{-1.209}$ × 0.993^{Age} × 1.018 [if female] × 1.159 [if African American][14].

Exercise stress tests

All subjects included in the study underwent routine 12-lead electrocardiography (ECG) with ECG analysis before exercise. Exercise stress tests (EST) were then performed according to the Bruce protocol, targeting the maximal heart rate according to age to calculate HRR[15]. The patients were instructed to fast for at least two hours before assessment, but to take their regular medicines except for angiotensin converting enzyme inhibitors and nitrates, which were stopped for at least 48 hours before the test. At the end of each stage of the EST, heart rate, blood pressure, and ECG findings were recorded. For the target heart rate, the formula [Maximum heart rate (beat/minute) = 220 - age (years)] was used[10]. To calculate HRR, all patients underwent an EST without a cool-down period (in accordance with the Bruce protocol, in cool-down period patients remain upright and walk at a very slow pace for two minutes after EST[16]) with the aim of reaching at least 85% of the age-predicted heart rates. Heart rates at the first, second, and third minutes were subtracted from the maximal heart rate, and HRR was calculated at each minute. Heart rate (HR) response during exercise was evaluated by the chronotropic reserve (CR), as follows: [CR = (peak HR – resting HR/220 – age – resting HR) x 100][10].

Statistical analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 17 software (SPSS Inc., Chicago IL, USA). The Kolmogorov-Smirnov test was used to determine the distribution characteristics, and the Levene test was used to assess the homogeneity of variances. Continuous variables are expressed as means ± standard deviation (SD) or medians with interquartile ranges, according to the distribution characteristics. Categorical variables are expressed as numbers and percentages. Continuous variables were compared using Student's *t*-test or the Mann-Whitney U-test, as appropriate. Categorical variables were compared by chi-squared test, and were reported as percentages. Student's *t*-test was used for comparisons between the primary NS and control groups for the HRR at the first, second and third minutes. p values <0.05 were considered to indicate statistical significance.

Results

The demographic and basal clinical characteristics of the patients and control group are shown in Table 1. No differences in age or gender were found between groups.

The mean fasting glucose levels of the patients were 80.2 ± 6.7 mg/dL, triglyceride 162.3 ± 9.2 mg/dL and total cholesterol 206 ± 53.8 mg/dL. Dyslipidemia was found in 12 (30%) patients. There was no difference between patients with and without dyslipidemia in terms of HRR in the first minute (24.8 ± 13.7 vs 25.2 ± 8.4, respectively; p =0.826).

No patient was prescribed calcium channel or beta-blockers. Immunosuppressive treatments were as follows: 21 patients (52.5%) did not use any immunosuppressive treatment, seven (17.5%) used steroids, five (12.5%) were treated with cyclosporine, four (10%) used a combination

Table 1: Demographics of the 40 patients with nephrotic syndrome and the 42 subjects of the control group.

	Nephrotic syndrome	Control group	p
Number (n)	40	42	
Gender: n (%)			
Female	20 (50%)	21 (50%)	
Male	20 (50%)	21 (50%)	
Age (years)	39.6 ± 9.3	36.0 ± 7.9	0.064
Presentation of NS: n (%)			
MN	18 (45%)	0	–
FSGS	12 (30%)	0	
MPGN	6 (15%)	0	
Mez PGN	4 (10%)	0	
Duration of NS (months)	49.2 (9-112)	0	–
Hypertension: n (%)	7 (17.5%)	0	
Dyslipidemia: n (%)	12 (30 %)	7 (16%)	–

Age is presented as mean ± standard deviation while duration of nephrotic syndrome as median (min-max), n: number, NS: nephrotic syndrome, MN: membranous nephropathy, FSGS: focal segmental glomerulosclerosis, MPGN: membranoproliferative glomerulonephritis, MezPGN: mesangioproliferative glomerulonephritis.

of steroids and cyclosporine, and three (7.5%) steroids and cyclophosphamide. A total of 23 patients (57.5%) were in remission.

When the heart rate recovery of patients and controls was evaluated, the HRR in the first minute was significantly slower in the primary NS group compared with control (25.5 ± 10.1 and 32.4 ± 11.1, respectively; p =0.004) (Figure 1). Although the HRR in the second and third minutes was faster in the control group compared with primary NS, the difference was not statistically significant (p =0.092 and p =0.145, respectively). When the patients were stratified according to presentation of primary NS, no difference in HRR was found between these subgroups. When primary NS patients were divided into two groups based on their remission status, no difference was found in HRR between those who were in remission (n=33, 77.5%), and those who were not (p =0.638). Steroid use was also not correlated with HRR.

During cardiological evaluation of subjects, no difference was found in ECG-measured ejection fractions between groups. Based on the results of the EST, basal heart rate, metabolic equivalents and chronotropic reserve values were similar in the patient and control groups. All EST findings are shown in Table 2.

Discussion

In the present study, first minute HRR after EST was slower in patients with primary NS compared with healthy controls. No difference in HRR was also found when NS patients were divided into subgroups based on

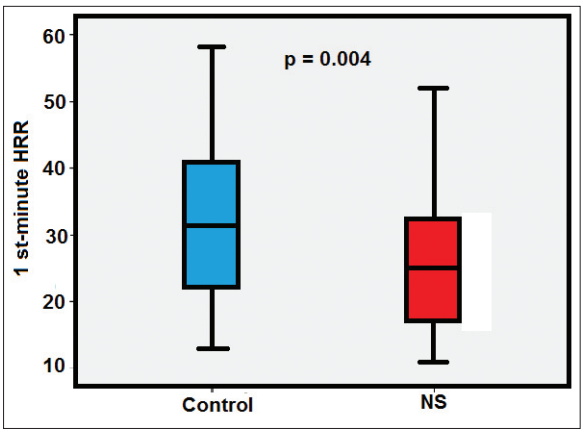

Figure 1: First minute heart rate recovery of the 40 patients with nephrotic syndrome and the 42 subjects of the control group.
NS: nephrotic syndrome, HRR: heart rate recovery.

Table 2: Comparison of cardiac autonomic function parameters between the 40 patients with nephrotic syndrome and the 42 subjects of the control group.

	Nephrotic syndrome	Control group	p
Basal Heart Rate (bpm)	93.6 ± 17.0	92.7 ± 15.7	0.801
Chronotropic reserve	86.1 ± 15.0	91.2 ± 15.7	0.133
Exercise tolerance, METs (mL/kg/min)	12.4 ± 2.3	12.3 ± 2.2	0.978
HRR1 (bpm)	25.5 ± 10.1	32.4 ± 11.1	0.004
HRR2 (bpm)	47.4 ± 13.0	52.2 ± 12.6	0.092
HRR3 (bpm)	54.1 ± 13.0	58.7 ± 15.1	0.145

Numerical variables with a normal distribution are presented as means ± standard deviation. bpm: beats per minute; METs: metabolic equivalents, HRR1: first minute heart rate recovery, HRR2: second minute heart rate recovery, HRR3: third minute heart rate recovery.

primary NS etiology and remission status. To our knowledge, the present study is the first to investigate HRR in patients with primary NS.

HRR was evaluated previously in various patient groups, including chronic kidney disease, heart failure, coronary artery disease, diabetes mellitus, Behçet's disease, and systemic lupus erythematosus[17-20]. Although the relationship between slow HRR and cardiovascular mortality remains incompletely understood, it was proposed that a slow HRR increases susceptibility to atherosclerosis. In the Framingham heart study, a slow HRR implied the presence of autonomic dysfunction, which has prognostic significance[21]. Several studies described a relationship between impaired parasympathetic function and atherosclerosis. For example, impaired parasympathetic activity in response to physiological stress was associated with subclinical calcifications of the aorta and coronary arteries[22]. A correlation between HRR and GFR was reported, where lower glomerular filtration rates accompanied a slower HRR. It was suggested that this is the result of sympathetic hyperactivity common in chronic renal failure[17].

Increased parasympathetic activity decreases heart rate and blood pressure, and is protective in ischemia-associated dysrhythmia[23]. In a study of 2,428 patients without CAD by Cole et al, a lack of the expected fall in heart rate in the first minute after exercise was an indication of decreased vagal activity, and was a strong predictor of general mortality independent of basal heart rate or changes in heart rate during exercise[24]. Consistent with this, a study following 5,234 patients without any significant cardiovascular disease for 12 years established that the rate of mortality was significantly higher in patients with slow HRR, independent of exercise, basal heart rate, and other cardiac risk factors[10].

In the Lipid Research Clinics Prevalence Study, 2,994 female subjects with no known cardiovascular disease underwent EST. During long-term follow up, it was determined that slow HRR was associated with all-cause and cardiovascular mortality[12]. Cheng et al, performed a study on male diabetic patients and found that the risk of cardiac mortality was 1.5-2 times higher in patients with the slowest HRR compared to those with the fastest after matching for several variables, including age and basal heart rate[25].

A study of 12,712 male patients without angina symptoms identified impaired HRR that correlated with increased coronary artery intima-media thickness[26]. Although the relationship between slowed HRR and atherosclerosis is not completely understood, it was suggested that impaired HRR was associated with endothelial dysfunction, which facilitated vessel wall inflammation and accelerated the development of atherosclerosis. Therefore, HRR could be an independent predictor of endothelial dysfunction[27]. Previous studies revealed that proteinuria could be associated with endothelial dysfunction[28]. Therefore, the proteinuria that occurs during NS could be associated with endothelial dysfunction and atherosclerosis.

In the present study, significant differences in total cholesterol, LDL and HDL levels, and proteinuria were found between NS patients and controls. The presence of dyslipidemia and uremia in patients could have contributed to the impaired HRR. NS patients also had an increased risk of atherosclerotic CAD. Destructive coronary artery narrowing can occur after infections that are associated with immunosuppression and the use of dyslipidemic drugs such as steroids[1].

Conclusions

In the present study, HRR was slower in patients with primary NS. However, no significant difference was found between primary NS patients in remission and not in remission. The small sample size and short duration of remission could explain this, although further studies are needed. Therefore, it could be useful to investigate HRR in primary NS patients and monitor them for cardiac risk.

Conflict of interest

Authors report no conflicts of interest.

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