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Evaluation of heart rate recovery index in patients with coronary slow flow: preliminary results

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Abstract. – OBJECTIVE: Coronary slow flow (CSF) is an angiographic finding detected in patients presenting with chest pain and with normal coronary artery appearance on routine angiograms. Heart rate recovery index (HRRI) reflects autonomic function and independently predicts cardiovascular disease. The aim of the study was to evaluate HRRI in patients with CSF.

PATIENTS AND METHODS: The study was conducted with a total of 200 individuals including 72 (36%) females and 128 (64%) males who presented to the cardiology clinic. Coronary blood flow was calculated numerically using the TIMI frame count (TFC) method. Treadmill stress electrocardiogram (ECG) test was applied to all patients according to the Bruce protocol. HRRIs at 1, 2, 3 and 5 minutes were recorded after the stress test. HRRI was calculated by subtracting the HR at 1, 2, 3 and 5 minutes of recovery from the subject's maximal exercise HR at the end of the exercise.

RESULTS: Duration of exercise, METs, max. HR, SBP and DBP at baseline, max. SBP and DBP, and changes in SBP and DBP were similar between the groups ($p>0.05$). HRRIs at 1, 2, 3 and 5 minutes were higher in CSF patients compared to control subjects (all $p<0.001$).

CONCLUSIONS: Coronary slow flow affects HRRI values. CSF may adversely affect the neuro-cardiovascular system.

Key Words:
Coronary slow flow, Heart rate recovery index, TIMI frame count.

Introduction

Coronary slow flow (CSF) is a microvascular disease characterized by delayed progression of the opaque material to distal vascular structures in the absence of epicardial coronary artery occlusion during coronary angiography (CA). CSF manifests itself as pain in the precordial region at rest or during exercise[1]. However, this phenomenon should not be confused with coronary artery spasm, coronary artery enlargement, valvular disease, myocardial dysfunction, and coronary reperfusion therapy (such as angioplasty and thrombolysis). Although the pathophysiology of aforementioned conditions is well known, the mechanism underlying slow coronary blood flow and its clinical relevanceof have not been fully elucidated. Left and right ventricular biopsies of patients with CSF showed small vessel disease such as thickening of capillary endothelium, lumen narrowing, loss of normal nuclear morphology and sepsis[2].

Heart rate recovery index (HRRI) is defined as reduction of HR (heart rate) after exercise stress test[3]. HR recovery involves normalization of blood pressure (BP), HR, and ECG. Left ventricular dysfunction and reduced exercise capacity further aggravate delay in HR recovery[4]. This takes about 9 minutes. In healthy individuals and athletes, HR drops rapidly in the first 30 seconds after exercise and then slows down. Early administration of atropine prevents this reduction, suggesting that this rapid decline is due to vagal activation[5]. In the current study, we aimed to evaluate HRRI in patients with CSF angiographically.

Patients and Methods

Study Population

This prospective case-control study was conducted between January 2020 and June 2020. A total of 100 patients (66 males and 34 females) with coronary slow flow in at least one major epicardial coronary artery on coronary angiography were included in the CSF group. Control group consisted of 100 individuals (62 males and 38 females) with normal coronary blood flow. Patients with typical chest pain or myocardial ischemia detected by non-invasive tests underwent coronary angiographyion. Exclusion criteria were defined as coronary artery disease (CAD), severe valvular

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heart disease, hypertension, thyroid dysfunction, atrial fibrillation, chronic obstructive pulmonary disease, hemoglobin abnormality, and renal or hepatic dysfunction. Before CA, blood samples and transthoracic echocardiography images were obtained. Echocardiographic examination was performed in the left lateral decubitus position using a Vivid E9 (Bioject Medical Technologies Inc., Portland, OR, USA) device in the M-mode. All images were captured according to the American Society of Echocardiography (ASE) criteria[6].

Demographic data of the patients were recorded after physical examination. The smoking status of the participants was determined in terms of pack-years. Blood glucose, lipid profile and creatinine values were recorded for all participants.

TFC Calculation and CSF Diagnosis

Coronary angiograms were acquired using the standard Judkins technique with multi-angle images at 30 frames/s (Allura Xper FD10; Philips Healthcare, Best, The Netherlands). Angiograms were examined by two blinded cardiologists. Left anterior descending (LAD) artery, left circumflex (LCX) artery and right coronary artery (RCA) were visualized in multiple projections with caudal and cranial angulations. Iopromide was used as the contrast agent for all CA studies. Coronary angiograms were thoroughly examined to identify CSF.

The TIMI frame count (TFC) is the number of cineangiographic frames required for the opaque contrast material to reach distal LAD. The first frame is the time when contrast material enters the LAD. The last frame is the time when the contrast agent reaches the distal end of the LAD. The TIMI frame count is calculated by taking the difference between the last and first frames. With this method, quantitative assessment of coronary flow becomes more reliable and acceptable[2]. On average, LAD is 1.7 times longer than RCA and Cx and therefore, the calculated LAD frame counts were divided by 1.7 to derive the corrected TFC. Reference values are 36.2 ± 2.6 frames/s for LAD, 22.2 ± 4.1 frames/s for LCx and 20.4 ± 3.0 frames/s for RCA.

Cardiac Stress Testing

Treadmill stress electrocardiogram (ECG) test was performed for all participants according to the Bruce protocol. Drugs that might affect the test results were stopped for 48 hours before the test. The chest area was shaved and cleansed with alcohol to avoid artifacts and to obtain good quality recording. Schiller CS-200 device (Schiller AG, Baar, Switzerland) was used for the stress test. After the baseline ECG and BP recordings, BP and ECG were performed periodically every 3 minutes during the stress test and at the 1st, 2nd, 3rd, and 5th minutes of recovery. The indications for termination of treadmill stress testing were those published by the American Heart Association and reaching 85% of the maximal HR was deemed sufficient[7].

Hear rate, and systolic and diastolic BP (SBP, DBP) at rest, exercise duration, exercise capacity, maximum HR, maximum SBP and DBP, and HRRIs at 1, 2, 3 and 5 minutes of recovery were recorded after the stress test. HRRI was calculated by subtracting the HR at 1, 2, 3 and 5 minutes of recovery from the subject's maximal exercise HR at the end of the exercise.

Statistical Analysis

Statistical Package for the Social Sciences (SPSS), version 24.0 (Armonk, NY, USA) software package was used for statistical analysis. Kolmogorov-Smirnov test were used to check the normality of the data distribution. Mann-Whitney U test and Student's *t*-test were used to compare the means and medians between the study groups tests. Categorical variables which were analyzed using the chi-square test were shown as percentage (%). Significance was set at $p < 0.05$.

Results

Table I shows the laboratory and demographic data of the study population. The study was conducted with a total of 200 individuals including 72 (36%) females and 128 (64%) males presenting to the cardiology clinic. Demographic characteristics (age, sex) and CAD risk factors (DM, hyperlipidemia, and family history) were similar between groups ($p > 0.05$), whereas smoking was significantly more common in the CSF group ($p< 0.001$).

HR, SBP and DBP at rest, left ventricular ejection fraction (LVEF), BMI, and laboratory investigations (fasting blood glucose, creatinine, eGFR, total cholesterol, and triglyceride) were similar between groups. LDL-C was significantly higher ($p= 0.04$ and $p= 0.012$, respectively) and HDL level was significantly lower in the CSF group compared to control group ($p= 0.016$) (Table I).

Duration of exercise, METS, maximal HR, SBP and DBP at baseline, maximal SBP and DBP, and changes in SBP and DBP were similar between groups ($p > 0.05$). HRRIs at 1, 2, 3 and 5 minutes were greater in CSF groups (all $p < 0.001$) (Table II, Figure 1).

Table I. Study population characteristics.

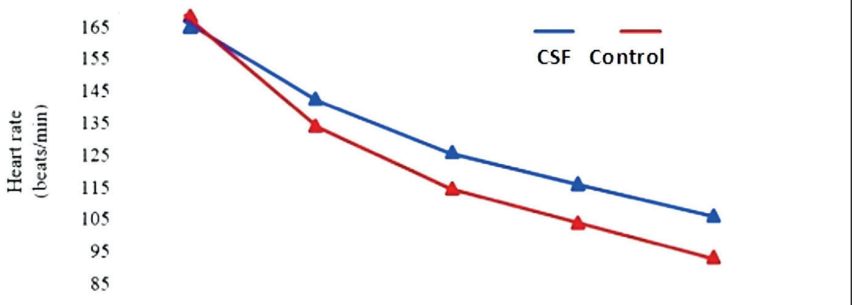
Variables	Control group (100)	CSF group (100)	*p*-values
Age, years	56.8±2.6	57.7±1.6	0.540
Sex, male, n, (%)	62 (62)	66 (66)	0.464
Diabetes mellitus, n (%)	22 (26)	26 (26)	0.256
Smoking, n, (%)	45(45)	56 (56)	**<0.001**
Hyperlipidemia, n (%)	38 (38)	39 (39)	0.756
Family history of CAD, n, (%)	25 (25)	28 (28)	0.112
LVEF, (%)	55.2±1.9	55.0±1.1	0.840
BMI, kg/m^2	25.6±1.6	26.2±2.1	0.344
Resting SBP, mmHg	118.1±5.3	122.8±4.8	0.322
Resting DBP, mmHg	76.3±4.8	76.2±5.4	0.802
Resting HR, beats/min	84.1± 1.2	86.2±2.0	0.762
Glucose, mg/dL	87.5±4.7	93.8±7.4	0.152
Creatinine, mg/dL	0.41±0.04	0.59±0.03	0.452
eGFR, mL/min	93.8 (67.2-108.8)	92.2 (64.5-102.1)	0.774
TG, mg/dL	168.0±4.5	175.1±5.8	0.242
HDL-C, mg/dL	49.9±3.4	41.1±3.7	**0.016**
LDL-C, mg/dL	115.4±9.7	138.8±9.4	**0.012**
TC (mg/dL)	178.0±14.8	182.6±19.0	0.516
TIMI frame count (frame/s)			
Cx	25.2±2.4	42.3±4.4	**<0.001**
LADc	27.5±3.8	46.3±5.9	
RCA	20.5±2.4	32.8±3.15	
Mean TFC	24.9±3.1	39.2±3.7	

*Student's *t*-test, Mann-Whitney U test. *p*-value <0.05.
BMI, body mass index; Cx, circumflex artery; DBP diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; HR, heart rate; LAD, left anterior descending; LDL-C, low-density lipoprotein cholesterol; LVEF, Left ventricular ejection fraction; RCA, right coronary artery; SBP, systolic blood pressure; TC, total cholesterol; TIMI, Thrombolysis in Myocardial Infarction; TG, triglyceride; WBC, white blood cell; TFC, TIMI frame count.

Table II. Exercise testing results among groups.

Variables	Control group (100)	CSF group (100)	*p*-values
Duration of exercise, min	11.2±2.2	12.5±1.8	0.187
METs	11.7±1.6	12.9±2.1	0.122
Max. HR, beats/min	169.8±8.6	167.3±8.3	0.654
Baseline SBP, mmHg	112.3±11.8	118.5±11.7	0.116
Baseline DBP, mmHg	70.8±3.7	72.1±4.3	0.525
Max. SBP, mmHg	163.1±12.2	165.5±10.0	0.612
Max. DBP, mmHg	82.1±9.5	84.2±9.9	0.722
SBP changes, mmHg	40.8 (5–113)	41.7 (15–88)	0.900
DBP changes, mmHg	7 (-19–68)	10 (-9–45)	0.659
HRRI1	33.8±10.3	26.1±7.3	**<0.001**
HRRI2	50.6±10.8	44.1±9.1	**<0.001**
HRRI3	60.2±10.5	51.7±8.5	**<0.001**
HRRI5	68.3±11.0	57.3±10.1	**<0.001**

*Student's *t*-test, Mann-Whitney U test.
p-value <0.05.
HRRI, heart rate recovery index; Max. DBP, maximum diastolic blood pressure; Max. HR, maximum heart rate; Max. SBP, maximum systolic blood pressure; MET, metabolic equivalent.



	MAX HR	HRR 1.MİN	HRR 2.MİN	HRR 3.MİN	HRR 5 MİN
CSF	167.3±8.3	143.7	128.6	117.6	107.7
Control	169.8±8.6	130.1	112.3	102.5	91.8
P value	0.654	**<0.001**	**<0.001**	**<0.001**	**<0.001**

Figure 1. Heterogeneity of TILs and its role in TNBC.

Discussion

In the present study, we observed greater HRRIs at 1, 2, 3 and 5 minutes in patients with CSF when compared with control subjects.

Coronary slow flow is an angiographic finding detected in patients presenting with chest pain and with normal appearance of coronary arteries on routine angiograms. This phenomenon is characterized by slow filling of contrast medium distal to the non-stenotic coronary artery, and the debate continues about its clinical significance[2]. A few studies[8,9] in the literature have reported that the CSF may cause myocardial ischemia.

Chen et al[10] showed that HRR1 to HRR5 values and heart rate variability (HRV) parameters were lower in patients with stable CAD. Stable CAD (SCAD) is known to impair autonomic function and delayed HRRI correlates with the severity of CAD. Consistently, we also observed higher HRRI values in the CSF group. These findings show that CAD impairs parasympathetic function in proportion to the severity of the lesion.

Ghaffari et al[11] found a significant link between abnormal HRRI and the severity of CAD. Another study[12] also reported that abnormal HRRI was associated with CAD, but the authors argued that HRRI failed to reflect the severity of coronary lesions. Many studies have defined abnormal HRRI as the inability of the HR to fall 12 beats within the first minute after exercise. Abnormal HRRI is an independent predictor of mortality in both sexes[13,14]. There is an inverse relation between the apparent decrease in the first minute and the mortality rate[15]. While the decreased HR observed in the early rest period is related to the activation of the parasympathetic nervous system, the decrease in the late period is related to the suppression of the sympathetic nervous system[16].

Impaired lipid profile, inadequately controlled diabetes mellitus (DM), endothelial dysfunction, and a history of MI are associated with a low HRRI[17]. In our study, while coronary risk factors were similar, lipid profile (LDL-C, HDL-C) differed between the groups. However, no correlation test was performed in this study between these variables and the HRRI index.

Sympathetic hyperactivity increases cardiovascular preload and hemodynamic stress and renders the patient susceptible to cardiovascular events[4]. Parasympathetic activity prevents the development of ischemic arrhythmia by decreasing HR and BP[18]. The autonomic nervous system plays an integral role in regulating cardiovascular function in both health and disease. In a study by Nishime et al[19], 9,500 individuals who were unable to reduce their HR by more than 12 beats in the first minute after exercise (HRRI at 1 minute in 20% of healthy middle-aged individuals is 12 beats per minute) had 4 times higher mortality over the next 5 years. In a study involving 5200 healthy adults, it was found that the mortality risk in individuals with abnormal HRRI was 2.58 times higher than in individuals with normal HRRI.

In type 2 DM patients, low HRRI after exercise may indicate a clinically silent autonomic imbalance. Autonomic dysfunction is an important reversible complication of type 2 DM[20]. In our study, the groups were similar in terms of DM control.

In one study, a cohort of 2333 DM patients was followed for a duration of 15 years. During the follow-up period, patients were divided into 4 groups according to the HRR values at 5 minutes after exercise: HRR <55 bpm (group 1), 55-66 bpm (group 2), 67-75 bpm (group 3) and >75 bpm (group 4). At the end of 15 years, the groups were compared among themselves. As a result, those with a low HRR were found to have a 1.5-2 times higher all-cause mortality rate in compared to those with a higher HRR[21]. Lipinski et al[22] reported a significant increase in mortality in patients with HRR <22 beats/min during the second minute of recovery compared to those with ≥22 beats/min. HRRI may predict cardiac adverse events, regardless of the prevalence of atherosclerosis, LV function and exercise capacity[23].

Study Limitations

This study included a relatively limited number of patients and controls. Long-term follow-up is required to corroborate our findings. HRV and baroreceptor sensitivity, which are other indicators of autonomic response, were not assessed during the stress test. Larger studies are warranted for the widespread use of HRRI in clinical setting.

Conclusions

HRRI was lower in patients with CSF at 1, 2, 3 and 5 minutes of recovery. The current results suggest that CSF can adversely affect the neuro-cardiovascular system. However, further research is needed to elucidate the relationship between CSF and HRRI.

Authors' Contribution

Study concept and design: L.A.; statistical analysis: L.A.; analysis and interpretation of data: L.A.; drafting of the manuscript: L.A.; critical revision of the manuscript for important intellectual content: L.A.

Conflict of Interest

The authors declare they have no conflict of interest.

Ethical Statement

The Ethics Committee for Clinical Research of Adiyaman University approved the study protocol. The study procedures were carried out in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants.

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