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Evaluation of Heart Rate Recovery Index in Patients with Coronavirus Disease

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Abstract

Objectives: In coronavirus disease-2019 (COVID-19), autonomic dysfunction may ensue. The heart rate recovery index (HRRI) measures autonomic function and predicts cardiovascular disease (CVD). The research assessed HRRI in patients with COVID-19.

Materials and Methods: The research group included 160 verified COVID-19 cases, and the control group had 160 healthy participants without a history of immunization. All patients underwent treadmill stress electrocardiogram according to the Bruce protocol. After the stress test, HRRIs were taken at 1, 2, 3, and 5 min. HRRI is computed by subtracting the subject's maximum exercise heart rate (HR) at the end of the exercise from HR after 1, 2, 3, and 5 min of recovery.

Results: Both groups had equal exercise duration, metabolic equivalents, maximum (max.) HR, systolic blood pressure (SBP) and diastolic blood pressure (DBP) at baseline, max. SBP and DBP, and changes in SBP and DBP ($p>0.05$). HRRIs were greater in COVID-19 patients than in controls at 1, 2, 3, and 5 min ($p<0.001$).

Conclusion: COVID-19 impacts HRRI. COVID-19 may affect neural-cardiovascular systems.

Keywords: Cardiovascular disease, coronavirus disease-2019, heart rate recovery index

Introduction

In February 2020, World Health Organization (WHO) identified coronavirus disease-2019 (COVID-19), the 2019 coronavirus illness. COVID-19 is caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2). Coughing, sneezing, and hand contact with contaminated surfaces can spread the virus. Asymptomatic individuals can also transmit. The normal incubation time is 5 days

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(2-14 days); however, recent cases include people who had no interaction with the infected people. Fever, cough, and dyspnea are common infection symptoms. Severe cases may cause pneumonia, severe acute respiratory tract infections, renal failure, and death. Mortality is approximately 2% and varies with virus genetics[1].

The heart rate (HR) drop after exercise is called the HR recovery index (HRRI)[2]. Recovery takes approximately 9 min until the patient's HR, blood pressure (BP), and ECG are near baseline. Impairment of left ventricular (LV) function and inadequate exercise ability impede this reduction[3]. In normal, asymptomatic people and athletes, the HR drops rapidly in the first 30 s after activity, then slowly. Atropine prevents this fast drop early on, indicating vagal effects[4]. Post-exercise HRRI depends on the chronotropic response. An aberrant HRRI after exercise is usually caused by chronotropic insufficiency[5]. We know of no investigation on the HRRI in COVID-19 patients without complications. The primary objective of this study was to assess HRRI in individuals diagnosed with COVID-19.

Materials and Methods

Study Population

We recruited participants from our cardiology outpatient clinic from May 2020 to September 2021. Ethical committee approval was obtained from the Ethics Committee of Adıyaman University (approval no.: 2021/03-14, date: 16.03.2021) and it complied with the Declaration of Helsinki. Written informed consent was obtained from all patients. A total of 160 consecutive COVID-19 patients who did not need hospitalization, home oxygen, or significant organ involvement were included in the study. A total of 160 healthy individuals without COVID-19 infection or immunization comprised the control group. We tested all healthy controls for asymptomatic COVID-19 using a nasal swab. To prevent reoccurrence, the research group was tested for SARS-CoV-2. Our study includes data on patients who had COVID-19 in the last 6 months and presented to the outpatient clinic with chest discomfort and a mild to moderate risk score. Outpatient clinic exertion tests of these patients were analyzed. Exertional test results were also recorded for patients without COVID-19 who experienced chest discomfort. System records revealed further patient demographic and analytical data. Following the exercise stress test, the HRR index was computed by comparing the peak exercise rate to the 1st, 2nd, 3rd, and 5th minute records.

Participants were excluded if they presented with an active COVID-19 infection, a previous history of COVID-19 infection that necessitated hospitalization, home oxygen treatment or severe respiratory complications, moderate-to-severe valvular heart disease, prosthetic heart valves, coronary artery disease (CAD), LV dysfunction, chronic obstructive pulmonary disease, asthma, obstructive sleep apnea, body mass index (BMI) exceeding 30 kg/m^2, renal failure, cerebrovascular disease or thyroid disease, chronic liver disease, or inflammatory and autoimmune disorders. Blood samples and transthoracic echocardiogram images were acquired. Echocardiographic examination was conducted with the subject in the left lateral decubitus position using a Vivid E9 device (Bioject Medical Technologies Inc., Portland, OR, USA) in M mode. The acquisition of all images adhered to the guidelines set out by the American Society of Echocardiography[6]. Demographic information of the patients was documented after physical examination. The individuals' smoking status was assessed on the basis of their pack-year history. The individuals' blood glucose, lipid profile, and creatinine levels were documented.

Cardiac Stress Testing

The subjects underwent treadmill stress electrocardiogram (ECG) in accordance with the Bruce protocol. The administration of potentially influential substances was discontinued for 48 h prior to the administration of the test. To ensure accurate recording and high-quality results, the chest region was meticulously shaved and thoroughly washed with alcohol to minimize artifacts. The stress test was conducted using a Schiller

CS-200 apparatus manufactured by Schiller AG in Baar, Switzerland. Following the first measurements of baseline ECG and BP, further assessments of BP and ECG were conducted at regular intervals of every 3 min throughout the stress test. Additionally, measurements were taken during the 1st, 2nd, 3rd, and 5th minutes of the recovery phase. The criteria for discontinuing treadmill stress testing were based on the guidelines established by the American Heart Association, which determined that achieving 85% of the maximum HR was considered satisfactory[7].

HR, systolic BP (SBP), and diastolic BP (DBP) at rest, exercise duration, exercise capacity, maximum HR, maximum SBP, and DBP, as well as HRRI at 1, 2, 3, and 5 min after recovery from the stress test, were all recorded. HRRI was determined by subtracting the HR at 1, 2, 3, and 5 min after the subject's maximum exertion from their HR at the end of the exercise.

Statistical Analysis

Statistical Package for the Social Sciences version 25.0 (Armonk, NY, USA) was used for statistical analysis. A Kolmogorov-Smirnov test was conducted to verify data distribution normality. The means and medians of the study groups were compared using Mann-Whitney U and Student's t-tests. Chi-square tested categorical variables were displayed as percentages. Significance was defined at $p<0.05$.

Results

Table 1 display the study population laboratory and demographic data. The cardiology clinic saw 360 patients, 106 (29%) females and 214 (59%) males. CAD risk variables [diabetes mellitus (DM), dyslipidemia, and family history] and demographics (age, sex) were similar between the groups ($p>0.05$), whereas smoking was

Table 1. Characteristics of the study population

	COVID-19 group (n=160)	Normal group (n=160)	p-value
Age, years	55.4±0.3	54.2±0.2	0.612
Gender, male, n, (%)	110	104	0.458
BMI, kg/m^2	27.5±0.2	26.7±0.3	0.356
Smoking, n (%)	96	74	**<0.001**
Diabetes mellitus, n (%)	62	58	0.316
Hypertension, n (%)	98	93	0.438
Dyslipidemia, n (%)	68	64	0.772
Family history of CAD, n, (%)	58	55	0.352
Clinical findings			
Resting HR, beats/min	87.1±1.2	85.2±1.0	0.662
Resting Systolic BP, mmHg	123.4±7.3	121.1±6.8	0.409
Resting Diastolic BP, mmHg	76.3±5.5	75.1±4.3	0.752
LVEF, %	55.1±0.5	54.7±0.8	0.696
Glucose, mg/dL	90.8±5.4	87.5±4.7	0.752
eGFR, mL/min	92.4 (67.2-108.8)	92.2 (64.5-102.1)	0.874
TG, mg/dL	176.1±4.8	168.5±4.2	0.256
HDL-C, mg/dL	38.3±1.2	41.1±1.3	**0.042**
LDL-C, mg/dL	141.8±4.4	118.3±7.7	**0.032**
TC (mg/dL)	184.6±9.0	178.6±8.8	0.522

**Student's t-test, Mann-Whitney U test. p-value <0.05.*
BP: Blood pressure, BMI: Body mass index, CAD: Coronary artery disease, COVID-19: Coronavirus disease-2019, DBP: Diastolic blood pressure, HDL-C: High-density lipoprotein cholesterol, HR: Heart rate, LDL-C: Low-density lipoprotein cholesterol, LVEF: Left ventricular ejection fraction, SBP: Systolic blood pressure, TC: Total cholesterol, TG: Triglyceride

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considerably higher in the COVID-19 group (p<0.001). Both groups had equivalent HR, SBP, DBP at rest, LV ejection fraction, BMI, and laboratory tests (fasting blood glucose, estimated glomerular filtration rate, total cholesterol, and triglyceride). Table 1 shows that patients with COVID-19 had greater low-density lipoprotein cholesterol (LDL-C) and lower high-density lipoprotein (HDL) than controls (p=0.032 and 0.042, respectively). Between groups, exercise duration, metabolic equivalents, maximum HR, baseline, maximal, and changes in SBP and DBP were similar (p>0.05). HRRIs increased in the COVID-19 group at 1, 2, 3, and 5 min (p<0.001) (Table 2).

Discussion

We found higher HRRIs at 1, 2, 3, and 5 min in COVID-19 patients than in controls. We believe this is the first study to examine HRRI in COVID-19 survivors.

The COVID-19 pandemic affected Lombardy the worst, with 40% of cases and 50% of deaths. The hospital in Cremona has one of the highest COVID-19 case rates in the country. Since early observations, COVID-19 individuals have had poor prognoses with CAD and cardiovascular (CV) risk factors. CAD is associated with COVID-19 mortality in several observational studies, including larger ones. CV disease also increased the risk of poor outcomes in Middle East respiratory syndrome patients. The extent of CAD's elevated mortality risk compared with age, male sex, and other CV risk factors is unknown. Mechanisms of COVID-19 severity in patients with CAD include systemic inflammation, platelet activation, endothelial dysfunction, and prothrombosis[8,9].

Patients with stable CAD (SCAD) had lower HRR1 and HRR5 values, according to Chen et al.[10] SCAD impairs autonomic function, and delayed HRRI increases with CAD severity. The COVID-19 group HRRI scores were consistently higher in our study. These data demonstrate that the mechanisms of COVID-19 severity inhibit parasympathetic function.

Ghaffari et al.[11] found a substantial link between abnormal HRRI and CAD severity. Abnormal HRRI was linked to CAD in another study; however, it did not suggest coronary lesion severity[12]. Many studies define abnormal HRRI as failure to decrease 12 beats in the first minute after exercise. HRRI abnormalities predict mortality in both sexes separately[13,14]. Mortality is inversely affected by the first-minute drop[15]. Early rest period HR decrease is related to parasympathetic nervous system activation,

Table 2. Exercise testing results among groups

	COVID-19 group (n=160)	Normal group (n=160)	p-value
Duration of exercise, min	12.4±1.3	11.6±1.8	0.712
METs	11.4±1.2	12.3±1.7	0.558
Max. HR, beats/min	166.5±6.3	170.3±5.6	0.256
Baseline SBP, mmHg	119.4±8.7	111.6±9.8	0.114
Baseline DBP, mmHg	73.2±2.3	71.2±2.7	0.216
Max. SBP, mmHg	166.4±9.0	164.2±9.2	0.538
Max. DBP, mmHg	85.1±7.9	82.9±7.5	0.778
SBP changes, mmHg	41.2 (15-88)	40.2 (5-113)	0.856
DBP changes, mmHg	11 (-9-45)	8 (-19-68)	0.574
HRRI1	25.1±6.3	33.8±8.3	**<0.001**
HRRI2	43.1±7.1	50.2±8.8	**<0.001**
HRRI3	51.2±7.5	60.1±8.5	**<0.001**
HRRI5	55.4±7.1	67.6±9.0	**<0.001**

**Student's t-test, Mann-Whitney U test. p-value <0.05.*
COVID-19: Coronavirus disease-2019, 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

whereas late period HR decrease is due to sympathetic nervous system suppression[16].

A low HRRI is associated with an impaired lipid profile, poorly managed DM, endothelial dysfunction, and a history of myocardial infarction[17]. In our study, it was observed that while the coronary risk factors were similar, there were notable variations in the lipid profile, specifically in the levels of LDL-C and HDL-C, among the groups. However, this study did not include a correlation test to examine the relationship between these factors and the HRRI score.

Sympathetic hyperactivity increases circulatory preload and hemodynamic stress, increasing CV risk[3]. Parasympathetic action reduces HR and BP, thereby preventing ischemia and arrhythmia[18]. The autonomic nervous system controls CV function during health and illness. Nishime et al.[19] found that 9,500 people who were unable to lower their HR by more than 12 beats in the first minute after exercise (HRRI at 1 minute in 20% of healthy middle-aged persons is 12 beats per minute) had 4 times greater mortality over the following 5 years. A study of 5200 healthy people indicated that people with abnormal HRRI had a 2.58 times greater death risk than those with normal HRRI.

Type 2 DM patients with low HRRI after exercise may have a latent autonomic imbalance. The major reversible consequence of type 2 DM is autonomic dysfunction[20]. Our research found equal rates of diabetes in both groups.

At least 2333 DM patients were tracked for 15 years in one study. After exercise, patients were separated into four groups based on HRR values at 5 minutes: <55 bpm (group 1), 55-66 bpm (group 2), 67-75 bpm (group 3), and >75 bpm (group 4). The groups were compared after 15 years. A low HRR was associated with a 1.5-2 times higher all-cause death rate than greater HRR[21]. A study by Lipinski et al.[22] found that individuals with HRR <22 beats/min had a higher mortality rate in the second minute of recovery compared with those with ≥22 beats. HRRI may predict cardiac events independent of atherosclerosis, LV function, or exercise capability[23].

Study Limitations

Some limitations exist in this investigation. The research sample was limited. Long-term follow-up is required to confirm our results. HRV and baroreceptor sensitivity, which are additional autonomic markers, were not tested during the stress test. According to a recent WHO report, 80% of infections are mild or asymptomatic with no mortality, 15% are severe diseases with no mortality, and 5% are critical diseases[24]. We excluded those who healed after being critically ill during the acute phase to better represent the majority of the post-COVID-19 population. The broad use of HRRI in clinical settings requires more extensive investigations.

Conclusion

COVID-19 patients had reduced HRRI after 1, 2, 3, and 5 min of recovery. The data imply that COVID-19 may affect the neuro-cardiovascular system. However, further studies are required to understand COVID-19 and HRRI.

Ethics

Ethics Committee Approval: Ethical committee approval was obtained from the Ethics Committee of Adıyaman University (approval no.: 2021/03-14, date: 16.03.2021).

Informed Consent: Written informed consent was obtained from all participants.

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