Acıbadem Univ. Sağlık Bilim. Derg. 2024; 15 (2)
https://doi.org/10.31067/acusaglik.1318875

ORIGINAL ARTICLE / ARAŞTIRMA YAZISI

Infectious Diseases / Bulaşıcı Hastalıklar

Evaluation of Oxygen Consumption at Maximal Workload in Cases of Post-COVID-19 Syndrome

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Received: 23.06.2023
Accepted: 15.12.2023

ABSTRACT

Objective: Oxygen consumption at maximum workload is a physiological criterion expressing aerobic capacity. We aimed to evaluate whether aerobic capacity is affected in post-COVID-19 syndrome by comparing oxygen consumption and heart rate index values in patients whose complaints continued after the acute phase of SARS-CoV2 disease passed.

Methods: 27 patients who underwent scintigraphy to be evaluated for coronary artery disease between January and March 2021 were included in the study. Our patients underwent treadmill exercise using the Bruce Protocol procedure. Patients achieved 100% of heart rate calculated using the 220-age formula. Oxygen consumption and heart rate index values at maximum workload values were compared in the same patient group before and after COVID-19 infection.

Results: 11 of the cases (40.7%) were women. The median age of the patients was 53 (49-57) years. In our patients with post-COVID-19 syndrome, oxygen consumption and heart rate index values at the maximum workload values calculated before COVID-19 infection were higher than those calculated later. Oxygen consumption in the same patient group is as follows; It was calculated as 43 (28-44) and 37 (26-38) before and after COVID infection (p:0.0005). Heart rate index values were calculated as 2.5 (2.4-2.6) and 2.4 (2.3-2.6) (p:0.0005).

Conclusion: In the presence of post-COVID-19 syndrome, there is a decrease in aerobic capacity. Determining the cause of complaints will allow us to develop prevention and treatment methods. In the presence of maximum workload, oxygen consumption and heart rate index values can be used in the monitoring of patients with post-COVID-19 syndrome.

Key Words: heart rate, exercise test, post-acute COVID-19 syndrome, radionuclide imaging

ÖZET

Amaç: Maksimum iş yükünde oksijen tüketimi aerobik kapasiteyi ifade eder ve dayanıklılığın önemli bir fizyolojik kriteridir. Post-COVID-19 sendromunda SARS-CoV2 hastalığının akut fazı geçtikten sonra bazı şikayetler en az 12 hafta devam etmektedir. Maksimum iş yükü varlığında oksijen tüketimi ve kalp atım hızı indeks değerlerini karşılaştırarak, post-COVID-19 sendromda aerobik kapasitenin etkilenip etkilenmediğini doğrulamayı amaçladık.

Yöntemler: Çalışmaya Ocak-Mart 2021 tarihleri arasında göğüs ağrısı ve nefes darlığı şikayetleri nedeniyle koroner arter hastalığı açısından değerlendirilen ve miyokard perfüzyon sintigrafi tetkiki yapılan 27 hasta dahil edildi. Hastaların 11'i kadındı. Hastalarımıza Bruce Protokolü prosedürü kullanılarak koşu bandı egzersizi uygulandı. Hastalarımızın tamamı 220-yaş formülü kullanılarak hesaplanan kalp hızının %100'üne ulaştı. Aynı hasta grubunda COVİD-19 enfeksiyonu öncesi ve sonrasında maksimum iş yükü varlığında oksijen tüketimi ve kalp atım hızı indeksi değerleri karşılaştırıldı.

Bulgular: Olguların 11'i (%40,7) kadındı. Hastaların ortanca yaşı 53 (49-57) yıl idi. Post-COVİD-19 sendromlu hastalarımızda, COVİD-19 enfeksiyonu öncesinde hesaplanan maksimum iş yükünde oksijen tüketimi ve kalp atım hızı indeksi değerleri, daha sonra hesaplananlara göre daha yüksekti. Aynı hasta grubunda maksimum iş yükünde oksijen tüketimi sırasıyla; COVİD enfeksiyonu öncesi ve sonrası 43 (28-44) ve 37 (26-38) olarak hesaplandı (p:0,0005). Kalp atım indeksi değerleri 2,5 (2,4-2,6) ve 2,4 (2,3-2,6) olarak hesaplandı (p:0,0005).

Sonuç: Post-COVID-19 sendromu varlığında aerobik kapasitede azalma mevcuttur. Şikayetlerin sebebini belirlemek, önleme ve tedavi yöntemlerini geliştirmemize olanak sağlayacaktır. Maksimum iş yükü varlığında oksijen tüketimi ve kalp atım hızı indeksi değerleri, post-COVID-19 sendromlu hastaların takibinde kullanılabilir. Bu konuda ileriye dönük çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: kalp hızı, egzersiz testi, post-akut COVID-19 sendromu, radyonuklit görüntüleme

Maximal aerobic capacity is a frequently used guiding parameter when determining the ability to sustain effort. Oxygen consumption at maximal workload (VO2max) is one of the important physiological criterion of endurance that has been used for many years and expresses aerobic capacity (1). Bruce Protocol (BP) is a treadmill test protocol that allows the subject to reach VO2max in a short time due to the increase in incline and speed together (Table 1) (2). Clinical entity-defined related studies are ongoing (3). In post-COVID syndrome (PCS), some complaints persist for at least 12 weeks after the acute as PCS has approximately 200 different symptoms and the phase of SARS-CoV2 disease has passed (4-5). Patients with COVID-19 typically present with a respiratory infection, however cardiac manifestations are also common. Among the possible causes of myocardial damage in COVID-19 patients; are stress cardiomyopathy, hypoxic injury, vasculitis, endothelitis, acute cor pulmonale, myocarditis, and cytokine storm (6). Patients may present with palpitations and chest pain (7). Elevated cardiac troponin levels are a generally accepted marker for determining myocardial damage (7). Patients with mildly symptomatic COVID-19 have a lower frequency of troponin elevation (8). In a few patients with COVID-19, myocarditis has been histologically confirmed, but the viral genome has not been identified in the myocardium (9). The possibility of immune myocarditis has been suggested but unproven (10). We compared pre-pandemic and post-pandemic cardiac parameters in our patients who were investigated for coronary artery disease (CAD) and subsequently diagnosed with PCS. In our retrospective study, myocardial perfusion scintigraphy was performed on our patients and they were evaluated for CAD. This study aimed to verify whether aerobic capacity is affected in PCS by comparing VO2max values and heart rate index (HRI) values.

Material-Method

Between January and March 2021, 27 patients who underwent scintigraphy to evaluate myocardial perfusion in terms of coronary artery disease due to chest pain were included in the study. Eleven of the patients were female. Although all of our patients were previously positive for COVID-19 PCR, PCR tests became negative between June and August 2020. In our patients, who survived the COVID-19 infection with mild symptoms without being hospitalized, the complaints of significant shortness of breath and whole body and left shoulder pain developed after COVID-19 continued. Effort myocardial perfusion scintigraphy (MPS) was performed in all patients 32-35 weeks after the PCR test turned negative, in line with cardiac indications (2). All 27 patients underwent their first stress myocardial perfusion scintigraphy performed for the indication in 2019. 11 female patients had recurrent syncope with no known cause, and 16 male patients had recurrent chest pain and ST changes on the exercise ECG. Before the test, detailed anamnesis was performed on our patients. Our patients did not have bundle branch blocks or pacemakers. 27 patients included in the study had no history of chronic heart disease, chronic lung disease, or chronic disease. No history of chronic drug use. None of the 27 patients had diabetes mellitus, hypertension, hypercholesterolemia, smoking, obesity, and other cardiovascular risk factors. Some patients had a family history of coronary heart disease. The data of the patients are summarized in Table 2. None of the 27 patients had hospitalization or intensive care indications during COVID-19 infection. No elevation was found in inflammation markers for infection. MPS indication was made with these findings. Treadmill exercise was applied to our patients using the BP procedure (Table 1). All of our patients reached 100% of the cardiac rate calculated with the 220-age formula, and the test was terminated because of burnout. ECG monitoring was performed during the test and no significant ECG changes were found. Our patients had no history of chronic drug use or chronic disease. Our patients cut out foods containing methylxanthines 12 h beforehand. Imaging was performed by the guidelines (2). A dose of 8-12 mCi was administered for stress imaging and 24-36 mCi for rest imaging. The first stress images were recorded after 20-40 min. A low-energy high-resolution collimator was used. Imaging was performed in the supine position. A 64x64 matrix was used. SPECT image quality was increased by reducing noise with appropriate filtering (11). (Figure 1). Iterative reconstruction methods were used. Thus, attenuation, scattering, and blurring were corrected. MPS images were evaluated quantitatively according to the 17-segment model (12). (Figure 2). Mediso Anyscan-S dual-headed SPECT gamma camera, PC-based TEPA brand treadmill and stresswin software were used. Qualitative and quantitative data were obtained from the SPECT images. None of our 27 patients had evidence of perfusion defect in the gated MPS examination. (Figure 1). In our patients who were clinically accepted as PCS, the quantitative data calculated from two scintigraphic images and parameters showing aerobic capacity such as VO2max in patients with maximum effort according to BP were compared. The duration (T) of the patient's exertion was determined according to BP. There are some formulas for the VO2max calculation (13).

In patients whose metabolic equivalent (MET) was determined according to BP, this value was multiplied by 3.5 to obtain VO2max (13). HRI value is the ratio of exercise heart rate to resting heart rate (13). Information and consent forms were obtained from the patients. Our retrospective study was approved by Gaziosmanpasa Training and Research Hospital Ethics Committee with 72 numbers on 08.06.2022.

Table -1: Bruce Protocol

Stage	Duration (min)	Speed (MPH)	Grade (%)
1	3	1.7	10
2	3	2.5	12
3	3	3.4	14
4	3	4.2	16
5	3	5	18
6	3	5.5	20
7	3	6	22

Table-2: Data from patients with no chronic disease and no known coronary artery disease

no	gender	age	Daily routine	Recurring complaints	Marital status	Time between two stress test(months)	Family history of coronary artery disease
1	male	57	sporty	Left shoulder pain	married	40	yes
2	male	55	sporty	Chest pain	married	42	yes
3	female	52	sedentary	syncope	married	39	no
4	male	53	sedentary	Chest pain	single	41	yes
5	male	57	sporty	Left shoulder pain	single	40	yes
6	female	50	sporty	syncope	married	40	no
7	female	49	sporty	ECG changes		41	no
8	female	53	sedentary	syncope	married	39	yes
9	male	49	sedentary	Chest pain	single	38	no
10	male	50	sedentary	Chest pain	single	38	no
11	female	51	sedentary	Left shoulder pain, syncope	married	40	yes
12	male	51	sporty	Chest pain	married	41	yes
13	male	57	sedentary	Chest pain	married	40	yes
14	female	55	sporty	ECG changes	married	40	no
15	female	56	sporty	syncope	married	39	no
16	male	57	sporty	Chest pain	married	39	no
17	male	57	sporty	Chest pain	single	41	yes
18	male	49	sedentary	ECG changes	married	42	yes
19	female	51	sedentary	syncope	married	42	no
20	male	52	sporty	Left shoulder pain	married	40	yes
21	male	55	sporty	Chest pain	married	41	no
22	male	57	sedentary	Chest pain	single	41	no
23	female	49	sedentary	ECG changes, syncope	married	40	no
24	female	52	sporty	syncope	married	39	yes
25	female	53	sporty	Chest pain, syncope	single	39	yes
26	male	55	sporty	Chest pain	single	38	no
27	male	57	sporty	Chest pain	married	38	yes

Table-3: Changes in maximal oxygen consumption, heart rate index, ejection fraction, and body mass index values in patients diagnosed with post-Covid-19 syndrome.

	before Covid-19 infection	post Covid-19 infection	p
Maximal oxygen consumption (kg/ml/min)	43 (28-44)	37 (26-38)	0,0005
heart rate index	2,5 (2,4-2,6)	2,4 (2,3-2,6)	0,0005
Ejection fraction	57 (55-59)	56 (55-59)	0,459
Body mass index	22,9 (19,7-24,9)	23,2 (19,6-24,8)	0,684

Statistics

Continuous variables that were not normally distributed are expressed as medians (minimum and maximum). Categorical variables are expressed as case numbers and percentages. The Wilcoxon test was used to compare continuous variables before and after COVID-19 infection. A p-value of <0.05 was considered statistically significant.

Results

11 (40.7%) of the cases were female. The median age of the patients was 53 (49-57) years. VO2max and HRI values calculated before COVID-19 infection in our patients with PCS were higher than those calculated later. VO2max value in the same patient group, respectively, before and after COVID infection, calculated as 43 (28-44) and 37 (26-38) (p:0.0005). The HRI value is, respectively; calculated as 2.5 (2.4-2.6) and 2.4 (2.3-2.6) (p:0.0005). A significant decrease was observed in VO2max and HRI values in patients with COVID-19 infection and whose complaints persisted at the end of the acute phase. According to our findings, the aerobic capacity was reduced in our PCS patients. The findings are summarized in Table 3.

Discussion

COVID-19 coronavirus disease causes a severe acute respiratory disease called SARS-Cov-2. This disease is difficult to control. In 10-20% of patients who experience the acute symptomatic phase, the effects of the disease may continue after 12 weeks. Available evidence regarding PCS is increasing day by day (14). PCR was negative in all 27 patients included in our study after acute infection between June and August 2021. The coronavirus responsible for SARS-Cov-2 infection causes acute respiratory infection and atypical pneumonia, which can potentially develop into a serious illness. In the infection that emerged in Wuhan city on December 31, 2019, and spread all over the world, clinical findings after COVID treatment lasted longer than 1 month in 10-20% of patients (15). In PCS; headache, confusion, inability to perform daily physical tasks, stress, depression and insomnia. Additionally, as in our patients, fatigue and pain may be prominent throughout the body. Although some medications have been tried, these long-standing complaints have not disappeared (14). Anamneses such as decreased exercise capacity and shortness of breath revealed the need to test patients for CAD.

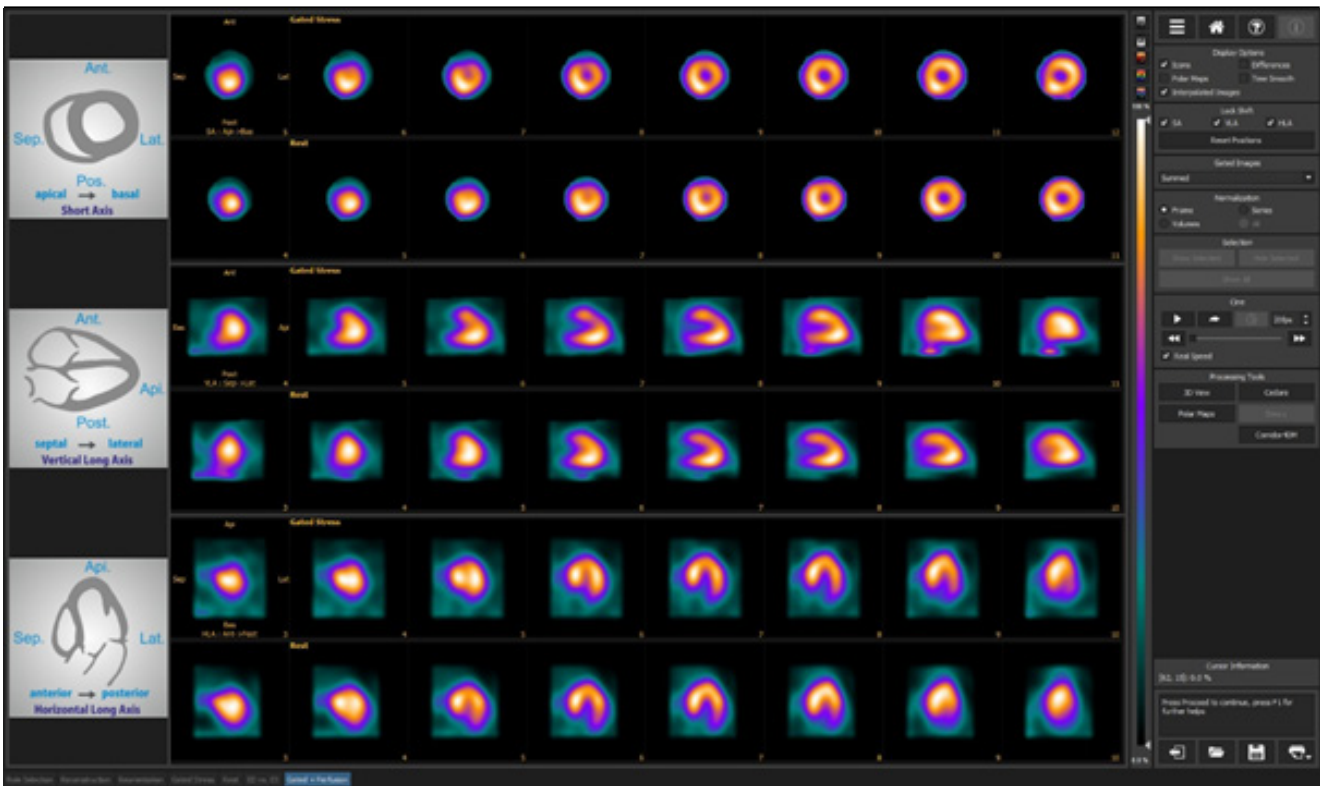

Figure 1: *Sections of left ventricular walls in myocardial perfusion scintigraphy.*

Therefore our patients were referred to the Nuclear Medicine clinic for MPS imaging. Imaging areas in nuclear cardiology include assessments of myocardial perfusion and global ventricular function. Exercise stress is preferred in patients who can exercise adequately. One of the most critical aspects of MPS examination is the ability to visualize myocardial perfusion under maximum stress. In patients with CAD, a homogeneous distribution of resting myocardial blood flow can be observed, up to a degree of coronary artery stenosis of up to 90% (16). Therefore, performing the stress test with optimum quality is crucial for visualizing myocardial ischemia (2). In our nuclear medicine clinic, our patients were subjected to a stress test by an experienced team. During exercise testing, the heart rate and contractility increase to meet the increased peripheral oxygen demand. The maximum physiological oxygen limit that the muscles in the body can reach is 15-17 ml/100 ml. This is also called aerobic capacity and is expressed as VO2max. With gradually increasing exercise, the VO2max curve reaches a plateau toward the end of exercise (3). All patients reached 100% of their maximum heart rate (HRmax), calculated according to the 220-age formula. ECG monitoring was performed during the test. VO2max, or maximum oxygen consumption, refers to the use of oxygen that reaches a certain maximum level as the workload or active muscle mass involved in exercise increases. The unit of VO2max is ml/kg/min. The metabolic equivalent (MET) value was obtained by dividing VO2max by 3.5. VO2max was calculated based on the time (T) to reach the maximum heart rate according to the Bruce protocol (Table 1). These calculation methods are reliable (3). In our study, VO2max was obtained using the calculation method. The same calculation method was used in both the compared studies. No significant difference was found between measurement studies performed using analyzers and indirect calculation methods. The calculation method using formulas is preferred because it is easier to implement, practical, and has low cost. All of our patients reached 100% of the maximum heart rate calculated according to the 220-age formula by exercising at an adequate level between 8 and 10 METs, with the speed and incline increasing every 3 min according to blood pressure. Treadmill testing was terminated because of burnout. It is very important to be able to adequately stress the patient in MPS imaging. The pharmacological stress method is used in patients who cannot reach 85% of the maximum heart rate or cannot reach a sufficient METS value (17). VO2max; It is the highest amount of oxygen that an individual can use during an exercise that involves large muscle groups and increases in intensity. After a certain point, oxygen use remains the same even though the workload increases. It is the amount of oxygen that the body can use in 1 min during exercise at maximum intensity. The amount of oxygen that the muscle can take from the blood and use depends on the blood coming to it and the oxygen content of the blood. VO2max is determined by the maximum amount of oxygen reaching the tissue. The higher the running speed, the higher the oxygen consumption. According to the results of our study, the prominent complaint of fatigue in our PCS patients was evaluated as compatible with the decrease in aerobic capacity. HR and breathing accelerate. VO2max is determined by expressing the amount of O2 expended per minute in volume (L) or by measuring the amount of oxygen taken in 1 min per kilogram of body weight in milliliters. Normally, the VO2max value in women is slightly lower than that in men. There were similar results in our study. Although VO2max values were within normal limits in our study, there was a significant difference between the two studies. The higher the VO2max value, the higher the aerobic capacity. VO2max is a feature that improves with training. Sedentary living during the pandemic may have decreased aerobic capacity. Our patients those who lead sedentary lives. Patients above 7 METS are generally asymptomatic in their daily activities. To exclude coronary artery disease in our patients, it is important to be able to evaluate heart wall perfusion, EDV, ESV, and EF by performing MPS imaging in our patients who underwent the Bruce protocol (3). There were no findings consistent with CAD in our patients' MPS results and ECG follow-ups. Tc-99m-MIBI is a radiopharmaceutical used for intravenous stress and rest imaging in MPS. Iterative reconstruction methods were used. Thus, attenuation, scattering, and blurriness were corrected. Stress testing is used in many clinics to evaluate cardiovascular risk (18). Exercise capacity is a proven prognostic marker of cardiovascular events and mortality (19). There is a linear relationship between oxygen consumption and HR (20). Body morphology is important for maximum performance (21). Unlike fat mass, increasing muscle mass increases performance (22). There was no significant difference between the two studies in terms of the body mass index (BMI) of our patients. VO2max is the maximum amount of oxygen that the body can use per kilogram in liters/minute against increasing workload. A linear relationship exists between workload and oxygen consumption. As exercise intensity increases, oxygen consumption also increases after reaching a plateau and being unable to consume more oxygen, and this point is VO2max. VO2max measurements are also used to determine aerobic capacity and fitness in athletes. Calculating VO2max with the formula. Laboratory tests require expensive teams and equipment (23). METS can be

calculated using HRI. VO2max can be obtained by multiplying METS by 3.5 (13). None of our patients were hospitalized during or after the acute infection. 200 different symptoms have been described in PCS (3). COVID-19 can have many clinical findings due to multiple organ involvement. Meta-analysis studies have shown the long-term effects of COVID-19 infection (24-25). Shortness of breath, smell and taste disorders, fatigue, neuropsychological symptoms, headache, memory loss, slow thinking, anxiety, depression, and sleep disturbance are the most common symptoms. Musculoskeletal complaints are also common. Few studies prospectively evaluate the long-term effects of COVID-19 infection (26-27). 80% of patients have more than one There are symptoms (25). Fatigue, myalgia, sleep disorder, and memory impairment are more common (3,28). These findings were also observed in our patients. The factor that most reduces the quality of life of people with PCS is fatigue. According to the results of our study, this may be due to a decrease in the aerobic capacity. This fatigue also has a neurocognitive aspect (3,28). Patients say that this limits their normal work activities. There are multiple mechanisms underlying PCS. Because of diseases accompanied by genetic factors, COVID-19 may increase existing lesions in target organs or acute COVID-19 organ failure may occur. There may be changes in the immune response to viruses or viral mechanisms (29). Cytokine storm, i.e., innate pathological and exaggerated immune response, causes a serious clinical picture. Persistent autoantibodies may have formed in self-limiting forms. Thromboembolic complications occur because of alterations in the function of the vascular endothelium (30). The continuation of endothelial inflammatory mechanisms may cause chronic symptoms. Our patients were diagnosed with PCS after long clinical evaluations. The duration of the acute phase is important for defining PCS. However, although the existing psychological and other changes are due to COVID-19, atypical findings in patients may prevent the diagnosis of PCS by thinking that it is another disease or bacterial infection. COVID-19 symptoms such as fatigue, headache, myalgia, and chills can be stimulated after mRNA-based vaccines. Patients usually improve over time. Some may get worse. There is no specific treatment for PCS. Acute phase treatment and prevention are performed. Montelukast, naltrexone, hyperbaric oxygen, and supervised exercise were administered. There is no current evidence regarding the role of a nutritional approach or physical exercise in relieving symptoms. Physical exercise can reduce not only acute symptoms but also long-term symptoms. It aims to alleviate symptoms, provide hope, and provide faster recovery (14).

Conclusion

Data on the cardiac effects of COVID-19 infection are very limited. CAD, existing or probably present before infection in patients, is confusing to determine the cause of cardiac effects. It is meaningful to evaluate the prolonged effects of COVID-19 in patient groups that were evaluated for cardiac aspects before infection. PCS complaints are accompanied by a decrease in the aerobic capacity. Identifying the cause of symptoms will enable us to develop new prevention and treatment methods. VO2max and HRI values can be used in patient follow-up in PCS. Prospective studies are required in this regard.

Abbreviations

PCS: post-COVID-19 syndrome

VO2max: oxygen consumption at maximum workload

HR: Heart rate

HRI: Heart rate index

MPS: myocardial perfusion scintigraphy

BP: Bruce Protocol

EDV: end-diastolic volume

ESV: end-systolic volume

EF: ejection fraction

CAD: coronary artery disease

BMI: body mass index

MET: metabolic equivalent

Ethics Approval And Consent To Participate

Our retrospective study was approved by Gaziosmanpaşa Training and Research Hospital Ethics Committee with 72 numbers on 08.06.2022.

Human And Animal Rights

No animals were used for studies that are the basis of this research. All human procedures followed were in accordance with the guidelines of the Helsinki Declaration of 1975.

Consent For Publication

Informed consent was obtained from all participants of this study.

Availability Of Data And Materials

Not applicable.

Funding

None.

Conflict Of Interest

The authors declare no conflicts of interest, financial or otherwise.

Acknowledgements

Declared none.

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