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RESEARCH ARTICLES

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galenos yayınevi

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Editors

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galenos yayinevi

Publisher Contact
Address: Molla Gürani Mah. Kaçamak Sk. No: 21/1 34093 İstanbul, Turkey Phone: +90 (212) 621 99 25 Fax: +90 (212) 621 99 27
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Administration Office

Şair Eşref Bulvarı, 1402 Sk. No: 2/2 Özbaş Apt.
Alsancak / Izmir / Turkey

Phone: + 90 232 464 19 63 / **Fax:** +90 232 464 24 70

e-mail: info@oztekinoto.com | info@tksv.com

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Journal: Sawhney N, Anousheh R, Chen WC, Narayan S, Feld GK. Five-Year Outcomes After Segmental Pulmonary Vein Isolation for Paroxysmal Atrial Fibrillation. Am J Cardiol 2009; 104(3):366–72.

Book: Baue AE, Geha AS, Hammond GL, Laks H, Naunheim KS. Gleen's thoracic and cardiovascular surgery. 1st ed. London: Appleton&Lange; 1991.

Book Chapter: Weinberg PM. Aortic arch anomalies. In: Allen HD, Clark EB, Gutgesell HP, Driscoll DJ (eds). Moss and Adams' heart disease in ınfants, children, and adolescents. 1st ed. Philadelphia: Lippincott Williams & Wilkins; 2001. p. 707-735.

Conference Paper: Davis L, Lee M, Sheridan B, et al. Berlin Heart EXCOR support in the first year of life. In: 32nd EACTS Annual Meeting; 18-20 October, 2018; Milan, Italy.

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Correspondence

Heart and Health Foundation of Turkey

Address: Şair Eşref Bulvarı, 1402 Sk. No: 2/2 Özbaş Apt. Alsancak - İzmir - TÜRKİYE

Phone: +90 232 464 19 63

Fax: +90 232 464 24 70

E-mail: info@tksv.com

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Review Article

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Stuck Leaflets in Prosthetic Heart Valves with Different Etiology and Treatments

Serkan Asil[1], Murat Çelik[1], Murat Kadan[2], Uygar Çağdaş Yüksel[1], Cengiz Bolcal[2], Cem Barçın[1]

[1]University of Health Sciences Turkey, Gülhane Training and Research Hospital, Clinic of Cardiology, Ankara, Turkey
[2]University of Health Sciences Turkey, Gülhane Training and Research Hospital, Clinic of Cardiovascular Surgery, Ankara, Turkey

Abstract

A stuck leaflet in the prosthetic heart valve is a rare but severe mechanical valve replacement complication requiring prompt diagnosis and treatment. Multimodality cardiac imaging is essential in diagnosis. 2D-3D echocardiography, fluoroscopy, and cardiac computed tomography scan are important for the definition of etiopathogenesis and differential diagnosis. The treatment might vary from medical follow-up to emergency surgery, depending on the etiological cause and the patient's clinical manifestation. In this review, we shared our four cases and discussed different etiologies and treatments for stuck leaflets.

Keywords: Prosthetic heart valve, stuck and restricted leaflet, prosthetic heart valve dysfunctions

Introduction

Valve replacement with bioprosthetic or mechanical valves is widely used for the surgical treatment of valve regurgitation and stenosis. A stuck leaflet in the prosthetic heart valve (PHV) is a possible and uncommon complication after surgery, particularly during the long-term follow-up[1,2]. Although stuck leaflet is mainly known as a complication of mechanical prosthetic valves, it has also been reported in bioprosthetic heart valves[3,4]. Although cases of stuck leaflets are generally reported during surgery and the early follow-up period, the number of cases of stuck leaflets in PHVs in the late period is limited[3,4]. Echocardiography, cardiac computed tomography (CT), and fluoroscopy are used to diagnose the stuck leaflet in the PHVs. Especially fluoroscopy and 2D-3D transesophageal echocardiography (TEE) are essential for rapid and high-sensitivity diagnosis. This report presents a case series of stuck leaflets treated

Address for Correspondence: Serkan Asil, University of Health Sciences Turkey, Gülhane Training and Research Hospital, Clinic of Cardiology, Ankara, Turkey
e-mail: dr_serkanasil@hotmail.com **ORCID:** orcid.org/0000-0002-6782-4237
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differently due to different etiologies. Even though ethics committee approval is not required for case reports and review in our country, the Declaration of Helsinki was followed, and informed consent was obtained from the patient and relatives to publish this report.

Case Reports and Literature Review

Case 1

A 65-year-old female patient was admitted to our hospital with a complaint of shortness of breath. In her past medical history, she had undergone minimally invasive robotic cardiac surgery due to rheumatic mitral valve disease, and mitral valve replacement preserving the posterior leaflet (Medtronic Open-Pivot 27 mm mechanical valve) was performed in 2019 (Figure 1). Transthoracic echocardiography (TTE) showed an increased gradient in the mechanical mitral prosthesis. TEE was performed and revealed that mechanical prosthesis leaflet movements close to the posterior annulus were restricted and a pressure gradient of 29/16 mmHg through the mitral prosthetic valve (Figure 2). Even though the increase in tissue echogenicity on the mitral valve, no thrombus, vegetation, or any mass could be observed, fluoroscopy revealed that one of the mitral leaflets was stuck, and its movements were restricted. The international normalized ratio (INR) values were within the normal range over the last 6 months. The patient was recommended to re-operate. During the operation, it was observed that the atrial surface of the mitral prosthesis had tissue overgrowth, and the posterior leaflet was stuck. However, no entrapment of the sub-valvular tissue was detected, and no additional pathology was observed on the ventricular surface of the mitral prosthesis. The mitral mechanical prosthetic valve was replaced with a Medtronic Hancock II 27 mm mitral bioprosthetic valve (Figure 2).

Case 2

A 74-year-old female patient was admitted to our clinic with a complaint of dyspnea and decreased effort capacity in 2018. Her past medical history, she had a mechanical aortic prosthesis (21-mm bi-leaflet aortic valve, St Jude Medical, Inc, St Paul, Minn.) and mitral prosthesis (29-mm bi-leaflet mitral valve St Jude Medical, Inc, St Paul, Minn.) due to a rheumatic heart valve disease in 1999. TTE showed a pressure gradient of 88/55 mmHg through the aortic prosthetic valve. We performed TEE; no thrombus was observed in the aortic and mitral valves. However,

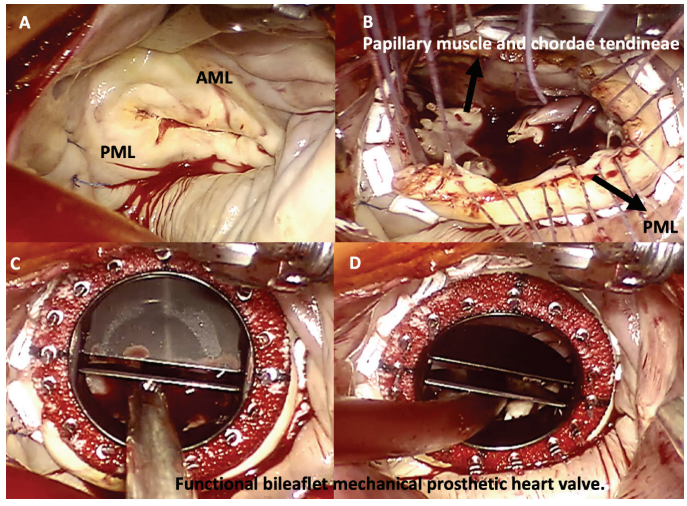

Figure 1. A-D; Images of robotic mitral valve replacement in 2019 and normal mitral valve function

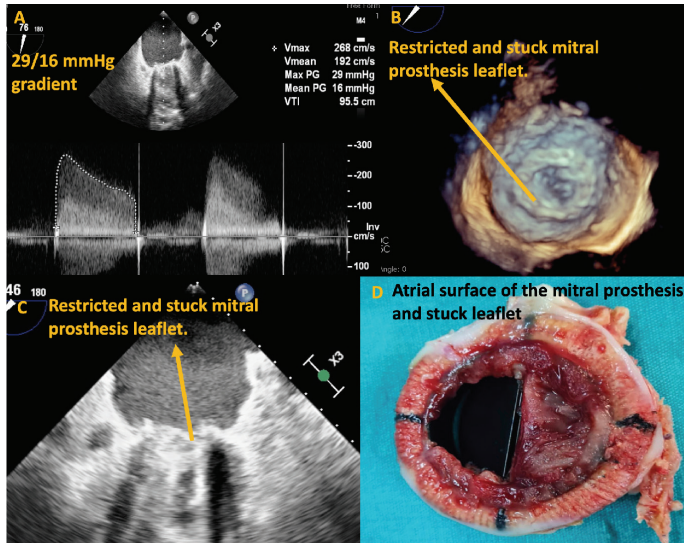

Figure 2. A-C; 2D and 3D transesophageal echocardiography images of increased mitral prosthetic heart valve gradient and restricted leaflet movements. D: Resected mitral prosthetic heart valve atrial surface images showed tissue overgrowth and stuck leaflets

it was determined that the valve tissue was thickened, particularly in the aortic prosthesis, and the mitral valve was normal. INR value was within the normal therapeutic range. During fluoroscopy, one of the aortic valve leaflets was stuck (Video 1). We diagnosed the patient with a stuck aortic prosthesis due to pannus overgrowth and recommended a re-operation, but she refused the surgery. INR values were closely monitored and kept between 3.0-3.5 to resolve the microthrombus that we could not detect in the echocardiographic examination, and acetylsalicylic acid was added.

At follow-up, the aortic gradient decreased to 57/34 mmHg in 3 years. Echocardiography and fluoroscopy revealed that bi-leaflet aortic prosthetic valve movements were nearly normal and unstuck (Figure 3, Video 1). We performed cardiac CT for the definite diagnosis of valve pathology, confirming the normal leaflet movements and pannus overgrowth (Figure 3). We believe that the primary pathophysiological mechanism is pannus overgrowth plus microclots, which are resolved with efficient anticoagulation.

Case 3

A 67-year-old male patient was admitted to the emergency unit with decompensated heart failure and low cardiac output. From his past medical history, we learned that he underwent mitral bi-leaflet metal prosthesis surgery due to rheumatic heart disease in 1999 and that he was re-operated in 2014 for pannus overgrowth. TTE revealed a pressure gradient of 39/24 mmHg through the mitral valve prosthesis, severe tricuspid regurgitation, systolic pulmonary artery pressure of 90 mmHg, right ventricular dilatation, and dysfunction (Figure 4). In the TEE, one of the leaflet movements of the mitral prosthetic valve was restricted and stuck, and a 40/21 mmHg gradient was observed (Figure 4). No thrombus

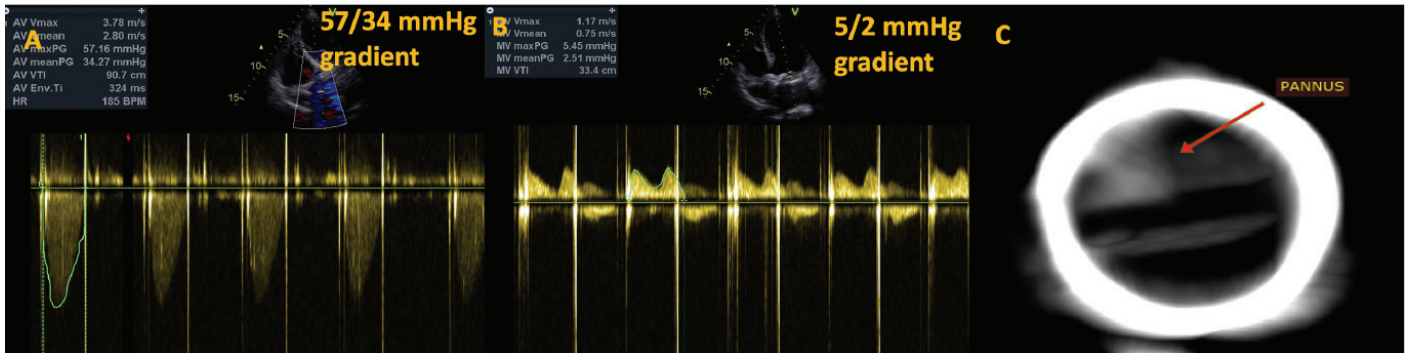

Figure 3. A-B; Transthoracic echocardiographic images of aortic and mitral valve gradient. C; Cardiac computed tomography confirmation of normal leaflet movements and pannus overgrowth

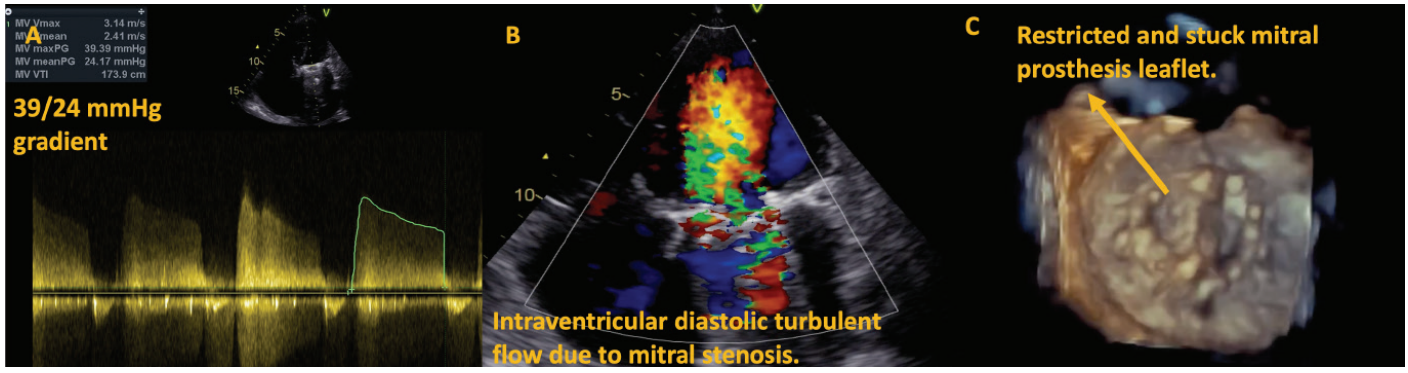

Figure 4. A-C; In 2D and 3D transesophageal echocardiography images of increased mitral prosthetic heart valves gradient, Intraventricular diastolic turbulent flow due to mitral stenosis, and restricted leaflet movements

was observed in the valve, but valve thickness increased due to pannus overgrowth, which caused stuck leaflets (Figure 4). Finally, fluoroscopy showed that one leaflet of the mitral prosthesis valve did not move and stuck (Video 2). INR values were within the normal range in the last 6 months. The primary pathophysiological mechanism was pannus overgrowth; thus, emergency surgery was planned. However, the patient's hemodynamic status could not be stabilized, and he died.

Case 4

A 57-year-old female patient presented with increased dyspnea for the last three months. to her past medical history, she had operated on a mitral valve replacement nine years ago. TTE showed an increased gradient through the mitral valve prosthesis. TEE revealed that the movements of the anterior leaflet of the bi-leaflet mitral metal prosthesis were restricted and stuck, and a gradient of 29/12 mmHg was detected (Video 3). It was observed the valve thickness increased because of pannus overgrowth, but thrombus and vegetation were not detected. Fluoroscopy confirmed that one of the mitral metal prosthesis leaflets was restricted and stuck (Video 3). INR values were within the normal range in the last 6 months. As a result, it was thought that the primary pathophysiological mechanism was pannus overgrowth, and surgery was recommended.

Discussion

In these reports, four different patients who developed stuck leaflets in mechanical PHV were discussed. The etiologies and treatments of these four patients were different. Based on these differences, stuck leaflet diagnosis and management were reviewed and discussed. PHV dysfunction is a rare but often severe complication that is caused mainly through valve thrombosis, pannus formation, vegetation, or sub-valvular tissue entrapment[5]. A detailed evaluation of mechanical PHV obstruction and stuck leaflets to understand the underlying etiology is pivotal because all they all have different management strategies.

PHV thrombosis is one of a major causes of primary valve obstruction and stuck leaflets. The PHV thrombosis incidence was reported to be 0.03% in bioprosthetic valves, 0.5-8% in mechanical valves[6]. Different therapeutic modalities for valve thrombosis include anticoagulation with heparin or warfarin, thrombolytic therapy, and surgery, and the decision is primarily influenced by a valvular obstruction, valve location, and clinical features. The management of mechanical heart valve thrombosis in non-critically ill patients depends mainly on the occurrence of a thromboembolic event and the size of the thrombus. Firstly, the optimization of the oral anticoagulation drug dosage and IV heparin administration can be considered[7,8]. After that, fibrinolytic therapy can be considered and indicated for patients with a small clot, no contraindication to fibrinolysis, first-time episode of valve thrombosis, and New York Heart Association functional classes I to II[7,8]. However, surgery should be recommended in critically ill patients with large clots and patients with recurrent valve thrombosis[7,8].

Another common cause of mechanical valve obstruction and stuck leaflets is pannus overgrowth, particularly in the late period of the disease. Pannus is a non-immune inflammatory reaction of the body to the valve prosthesis, a proliferation of fibroelastic tissue and collagen, with a starting point in the suture[9]. It usually proliferates on the ventricular side of the prostheses. It is associated with certain risk factors such as operative technique, small valve ring, prosthesis characteristics, young age, female sex, low cardiac output, turbulent flow, infection, and inadequate anticoagulation[9]. Surgery or palliative care are treatment options for patients with clinical and imaging features consistent with PHV pannus overgrowth with moderate to severely symptomatic obstruction. It is essential to distinguish between thrombus and pannus as the leading causes of PHV obstruction. Some clinical and imaging features favor pannus. In echocardiographic imaging, dense, non-mobile, and often not visualized mass by TTE and TEE favors the pannus[10]. In a patient with new

mechanical valve obstruction, if a leaflet motion is well visualized and normal by TEE, then pannus is likely[10]. In cardiac CT, high attenuation mass, which is greater than the interventricular septum and HU ≥145 units as considered pannus[11]. Fluoroscopy provides the most reliable assessment of mechanical leaflet motion but does not enable the assessment and differentiation of soft tissue associated with the valve. Surgery is the primary treatment for pannus overgrowth, but palliative follow-up can be performed in patients who are prohibited at high risk of surgery due to advanced age and additional comorbidities or refused surgery.

Infective endocarditis is a rare cause of PHV obstruction. PHV endocarditis is usually seen with valve dehiscence, paravalvular abscess, and regurgitation. PHV obstruction and stuck leaflets are extremely rare and are mainly the result of large vegetation that limits valve movements[12]. Surgery is recommended for PHV endocarditis complicated by a heart block, annular or aortic abscess, dehiscence, or obstruction[12].

Entrapment of the sub-valvular tissue is another important reason for PHV obstruction and dysfunction[13]. The preservation of sub-valvular tissue, especially the posterior leaflet, has become the recommended surgical method in mitral valve replacement. This procedure has advantages such as preserving left ventricular geometry and function and improving early and long-term survival[14]. Nevertheless, preservation of the sub-valvular apparatus also has potential complications. One is left ventricular outflow tract obstruction caused by the anterior leaflet[15,16]. Additionally, intermittent PHV obstructions due to entrapment of chordal tissue between the disk of the valve and housing have been reported [16]. To avoid these complications and to maintain left ventricular performance and geometry, preserving the posterior leaflet, resection of the unsupported portion of the anterior leaflet, or chordal transfer have been recommended[14,15].

No case of stuck leaflets due to tissue hyperproliferation on the atrial surface of the valves has been reported, particularly in the early period after surgery. Pannus overgrowth develops more frequently in the late period after surgery because of fibroelastic tissue and collagen hyperproliferation on the ventricular surface with the effect of flow dynamics. We do not think that the development of tissue hyperproliferation on the atrial surface in case 1 in the early period can be explained by the dynamics and pathophysiology of pannus formation. We think that this is the result of other inflammatory reactions. Inflammation at least occurs at every heart valve implantation site[17]. Removing the native valves damage tissues. After that, the implantation of a PHV leads to trauma and the presence of new foreign material, leading to thrombosis and inflammatory cell exudation[17].

For diagnosis, multimodality imaging is essential. TTE is recommended as an initial test to suspect the diagnosis. A 2D or 3D TEE is a commonly used imaging modality to identify the cause of PHV malfunction[10,18]. Fluoroscopy is an essential imaging technique for assessing mechanical PHV movements and identifying the type of implanted prosthesis and its function[19]. Additionally, it can evaluate valve leaflet mobility and valvular ring motion. At cine fluoroscopy, the normal-opening angle is usually less than 30° typically less than 20°, and the closing angle is usually greater than 120°-130°. With a stuck leaflet, there is a limited range or absence of motion of the PHV leaflet[18,20]. Cardiac CT is another crucial imaging modality that can provide additional information on valvular mobility, thrombus and pannus distinction, as well as valvular and paravalvular pathologies[11]. A specific opening and closing angle for each valve are provided by the manufacturer, which also varies with the position (ie, mitral vs aortic). At CT, the normal-opening angle is 73°-90° for bi-leaflet valves and 60°-80° for mono-leaflet valves[20].

Conclusion

The stuck leaflet is a rare but potentially severe complication of PHV. TEE, fluoroscopy, and cardiac CT

are feasible and highly effective imaging modalities that can detect and make the differential diagnosis of etiology. Furthermore, the treatment might vary from medical follow-up to emergency surgery, depending on the etiological cause and the patient's clinical manifestation.

Ethics

Informed Consent: Informed consent was obtained from the patient and relatives to publish this case report.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Kadan M, Bolcal C, Concept: Asil S, Design: Asil S, Data Collection and/or Processing: Çelik M, Analysis and/or Interpretation: Çelik M, Yüksel UÇ, Bolcal C, Barçın C, Literature Search: Asil S, Yüksel UÇ, Writing: Asil S, Barçın C.

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Video 1. Stuck leaflet image on fluoroscopy and resumption of leaflet movements with medical treatment three years later

http://glns.co/3bq2e

Video 2. Fluoroscopy images of stuck and restricted mitral leaflet movements

http://glns.co/if9v6

Video 3. In 2D and 3D transesophageal echocardiography and fluoroscopy, images of mitral prosthetic valve restricted leaflet movements and stuck leaflets

http://glns.co/hiqag

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Research Article

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Relationship of Ascending Aortic Aneurysm with Serum Uric Acid and Blood Inflammatory Parameters

Mehmet Atay[1], Serhat Çalışkan[2], Fatih Güngören[3]

[1]Bahçelievler State Hospital, Clinic of Cardiovascular Surgery, İstanbul, Turkey
[2]Bahçelievler State Hospital, Clinic of Cardiology, İstanbul, Turkey
[3]Harran University Faculty of Medicine, Department of Cardiology, Şanlıurfa, Turkey

Abstract

Objectives: Ascending aortic aneurysm (AAA) is defined as the enlargement of the aorta at the point where it exits the heart, and many pathophysiological processes play a role in its development. Studies have shown that the inflammatory process and blood uric acid levels play a role in many cardiovascular diseases. In our study, we investigated the effects of uric acid and blood inflammation parameters on the development of AAA by comparing them with the control group.

Materials and Methods: The study included 97 patients who were found to have AAA in echocardiographic examination and 100 patients without AAA. Patients with AAA were determined as group 1, and those without aneurysm were determined as group 2. The clinical and laboratory data of the patients were evaluated retrospectively through the hospital information system.

Results: In the AAA group, compared to the control group, uric acid levels (5.7±1.4 vs 3.9±0.8, p=0.001), systemic immune inflammation index (SII) [538 (330-854) vs 440 (324-578), p=0.007] and neutrophil-lymphocyte ratio (NLR) [4.7 (3.7-5.9) vs 4.1 (3.2-4.9), p=0.001] were found to be significantly higher, while the platelet-lymphocyte ratio [110 (84-170) vs 105 (82-135) p=0.186] was found to be similar. In multivariate logistic regression analysis, uric acid (p=0.001) was found to be an independent predictor of AAA.

Conclusion: In our study, we found that inflammatory parameters such as NLR and SII, and serum uric acid level were higher in patients with AAA compared in the control group. We showed that increased serum uric acid level is an independent predictor of AAA.

Keywords: Ascending aortic aneurysm, uric acid, systemic immune inflammatory index, neutrophil/lymphocyte ratio

Address for Correspondence: Mehmet Atay, Bahçelievler State Hospital, Clinic of Cardiovascular Surgery, İstanbul, Turkey
Phone: +90 542 723 61 11 **e-mail:** drataym@gmail.com **ORCID:** orcid.org/0000-0003-0011-190
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Introduction

Ascending aortic aneurysm (AAA) is one of the most common diseases of the aorta after atherosclerosis[1]. AAA, which is usually asymptomatic, is detected incidentally by imaging methods. In patients with Marfan syndrome, bicuspid aortic valve, or patients with a wide aorta on pleurography, the definitive diagnosis can be made with contrast-enhanced computed tomographic angiography (CTA) or magnetic resonance angiography[1].

Many studies have been conducted to prevent mortality and morbidity in AAA and to understand the underlying pathophysiology. Among the mechanisms suggested for the pathophysiology of AAA, it is stated that the effect of hemodynamic strength due to hypertension (HT), the chronic inflammatory process formed in the vessel wall, oxidative stress and the role of genetic predisposition[2,3]. The disruption of the balance between matrix metalloproteinases and their inhibitors plays a role in aortic wall degeneration. The increase in inflammatory cells in the aortic wall causes this imbalance to become more pronounced[2]. Another pathophysiological process is that increased oxidative stress causes damage to the vessel wall. Studies have shown that uric acid, which affects oxidative stress, plays a role in cardiovascular diseases[4].

Blood inflammation markers are increased in many diseases and are used in determining prognosis. Neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) are frequently used as indicators of inflammation. Additionally, current studies indicate that the systemic immune inflammatory index (SII), which is a new parameter, is a good indicator of inflammation[5,6]. SII, which is an index obtained by multiplying the NLR with the platelet count, provide important prognostic information in chronic diseases. Considering the chronic inflammatory process of AAA in the vascular wall, whether there is a relationship between SII and AAA is an issue that needs to be investigated. In our study, we investigated the relationship between serum uric acid levels and NLR and PLR, which are indicators of inflammation, and between SII, a relatively new indicator and AAA.

Materials and Methods

Patient Population

Patients admitted to Bahçelievler State Hospital between January 2015 and January 2021 and diagnosed with AAA were included in the study. In the echocardiographic examination, 97 patients with an ascending aortic diameter greater than 38 mm were determined as group 1. One hundred patients with normal AAA diameters were taken as group 2 (control group). The demographic characteristics and laboratory data of the patients were retrospectively reviewed through the hospital registry system. Patients using antihypertensive medicines and patients with blood pressure values >140/90 mmHg in the last three follow-ups were considered hypertensive. We have followed up in patients using echocardiography and routine laboratory values at the time of the examination.

Patients with known liver disease, chronic renal failure (creatinine >1.5 mg/dL), hematological disease, those using thiazide diuretics, those with bicuspid aortic valve, previous cardiac and aortic surgery history, and gout disease diagnosis were excluded from the study.

Ethics committee approval was received for the study from the Ethics Committee of Bakırköy Dr. Sadi Konuk Training and Research Hospital (protocol number: 2021/331).

Laboratory Analysis

Hemoglobin (Hb), white blood cell (WBC), red cell distribution width (RDW), mean platelet volume (MPV), and platelet counts were measured using an automatic complete blood count device (Coulter LH 750 Hematology Analyzer, Beckman Coulter, Miami, Florida). The NLR was calculated by dividing the neutrophil count by the lymphocyte count and the PLR was calculated by dividing the platelet count by the lymphocyte count. The SII index was calculated by multiplying the NLR by the platelet count. The reference ranges for uric acid were taken as 3.5-7.2 mg/dL in male patients and 2.6-6 mg/dL in female patients.

Echocardiography

Echocardiographic measurements were performed according to recommendations of the guidelines of the American echocardiography society[7]. The ascending aortic diameter was measured in 2 dimensions using an Echocardiography device (EPIQ 7, Philips Medical Systems, Andover, MA). The diameter measured perpendicular to the aorta in the parasternal long axis view was recorded as the largest aortic diameter. Patients with an ascending aortic diameter greater than 38 mm were considered aneurysmal. 2D and M-mode were used for heart cavities and aortic diameter measurements.

Statistical Analysis

SPSS (Statistical Package for the Social Sciences) 24.0 program was used for statistical analysis. While evaluating the study data, independent sample t-test was used in the comparison of two groups of normally distributed parameters as well as descriptive statistical methods (mean, standard deviation, median, frequency, ratio, minimum, maximum). Pearson chi-square test was used in the analysis of qualitative data. Receiver operating characteristic (ROC) curve test was used to calculate the sensitivity and specificity values according to the groups (cut-off). Logistic regression analysis was used to examine the effects of NLR, PLR, SII Index and uric acid value on the groups. A p-value of <0.05 was considered statistically significant.

Results

The basic demographic characteristics and laboratory parameters of the groups included in the study are presented in Table 1. The mean age of group 1 was 67.9±14 and group 2 was 65.1±12.8 (p=0.137). There was no significant difference between the two groups in terms of the presence of comorbidities such as diabetes mellitus (DM), HT, hyperlipidemia (HL), and coronary artery disease (CAD) (p>0.05). Low density lipoprotein (LDL), triglyceride, aspartate aminotransferase, alanine aminotransferase, WBC, platelet count, MPV and RDW values were similar between groups 1 and group 2 (p>0.05). High density lipoprotein (HDL) was significantly higher in group 1 [45 (37-52) vs 38 (39-75), p=0.015], while Hb value was lower (13.0±1.8 vs 13.5±1.5, p=0.034). Uric acid level (5.7±1.4 vs 3.9±0.8, p=0.001), SII index [538 (330-854) vs 440 (324-578), p=0.007] and NLR [4.7 (3.7-5.9) vs 4.1 (3.2-4.9), p=0.001] were found to be higher in the AAA group than in the control group. PLR [110 (84-170) vs 105 (82-135) p=0.186] values were similar between the two groups.

Multivariate logistic regression analysis was performed to identify the independent predictors of AAA. A model was created by including HDL, uric acid, SII index, NLR, presence of HT, presence of diabetes, presence of HL,

Table 1. Demographic and laboratory data of the patient and control groups

	Group 1	Group 2	
Male gender, n (%)	50 (51.5)	47 (47)	[a]**0.523**
Age, years	67.9±14.0	65.1±12.8	[b]**0.137**
Diabetes, n (%)	21 (21.6)	22 (22)	[a]**0.953**
Hypertension, n (%)	42 (43.3)	40 (40)	[a]**0.639**
Hyperlipidemia, n (%)	19 (19.6)	21 (21)	[a]**0.805**
CAD, n (%)	16 (16.5)	16 (16)	[a]**0.925**
LDL cholesterol, g/dL	118 (93-145)	121 (93-145.5)	[c]**0.648**
HDL cholesterol, mg/dL	45 (37-52)	38 (39-57)	[c]**0.015***
Triglyceride, mg/dL	133 (93-168)	119 (93-168)	[c]**0.412**
AST, m/L	20 (16-25)	19 (16-22)	[c]**0.223**
ALT, m/L	17 (12-24)	16 (12-21)	[c]**0.273**
WBC, x10^9/L	8.1±2.3	7.5±1.9	[b]**0.580**
Hemoglobin, g/dL	13.0±1.8	13.5±1.5	[b]**0.034***
Platelet, 10^9/L	243±78	256±65	[b]**0.200**
MPV, fL	9.7±1.4	9.9±1.1	[b]**0.666**
Uric acid, mg/dL	5.7±1.4	3.9±0.8	[b]**0.001****
RDW	13.9±1.7	13.4±1.3	[b]**0.070**
SII index	538 (330-864)	440 (324-578)	[c]**0.007****
NLR	4.7 (3.7-5.9)	4.1 (3.2-4.9)	[c]**0.001****
PLR	110 (84-170)	105 (82-135)	[c]**0.186**

*[a]Pearson chi-square, [b]Independent sample t-test, [c]Mann-Whitney U test. **p<0.01, *p<0.05*
CAD: Coronary artery disease, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, WBC: White blood cell, MPV: Mean platelet volume, RDW: Red cell distribution width, SII: Systemic immune inflammatory index, NLR: Neutrophil-lymphocyte ratio, PLR: Platelet-lymphocyte ratio, LDL: Low density lipoprotein, HDL: High density lipoprotein

gender, presence of CAD and Hb level in the multivariate analysis. When the table containing the coefficients in the regression model and the significance of these coefficients were examined, it was observed that uric acid and NLR were independent predictors of AAA (Table 2).

ROC curve analysis was performed to determine a cutoff value for uric acid, which was determined as an independent predictor in multivariate regression analysis. In the ROC curve analysis, the sensitivity of uric acid above 4.56 mg/dL in predicting AAA was 77.3%, and the specificity was 77% (area under the curve 0.881) (Figure 1).

Discussion

The main finding of our study is that serum uric acid level, NLR and SII are higher in patients with AAA than in the control group. Also, serum uric acid level and NLR are independent predictors of AAA development.

The incidence of AAA increases with advancing age, and it mostly shows an asymptomatic course[8,9]. The asymptomatic course of this disease, the results of which can be fatal when symptomatic, causes a delay in diagnosis[10]. Early recognition and treatment of modifiable risk factors are important in AAA, where acquired factors and genetic factors play a role in its etiology[9,10]. There is a genetic transmission in 20% of the patients, and autosomal dominant transmission is observed[10].

Oxidative stress is another mechanism implicated in the pathogenesis of AAA. Several mechanisms are proposed for the damage of oxidative stress to the vessel wall in AAA. Inflammatory cells in the aortic wall, mechanical distension, smooth muscle cells, growth factors and lipid mediators increase oxidative stress by producing reactive oxygen derivatives[11]. It has been determined that uric acid is central to oxidative stress-related cardiovascular diseases, mostly from the data obtained from epidemiological studies. The protective effects of allopurinol, which lowers serum uric acid levels, have been demonstrated in cardiovascular diseases such as ischemia-reperfusion injury, in which oxidative stress plays an important role[12].

Factors such as smooth muscle cells, mechanical distension, growth factors, and most importantly,

Table 2. Multivariate regression analysis for AAA risk factors

	Odd's ratio	95% CI For EXP(B)		Multivariate p-value
		Lower	Upper	
HDL	1,006	0.966	1,047	0.787
Uric acid	0.187	0.113	0.311	**0.000**
SII index	1,002	0.999	1,004	0.269
NLR	0.414	0.174	0.985	**0.046**
Hypertension	1,108	0.458	2,680	0.820
Diabetes	1,083	0.375	3,127	0.883
Gender	0.853	0.318	2,289	0.752
Coronary artery disease	0.888	0.226	3,495	0.866
Hyperlipidemia	0.842	0.278	2,550	0.761
Hemoglobin	1,272	0.944	1,714	0.114

NLR: Neutrophil-lymphocyte ratio, SII Systemic immune inflammatory index, LDL: Low density lipoprotein, HDL: High density lipoprotein, AAA: Ascending aortic aneurysm, CI: Confidence interval

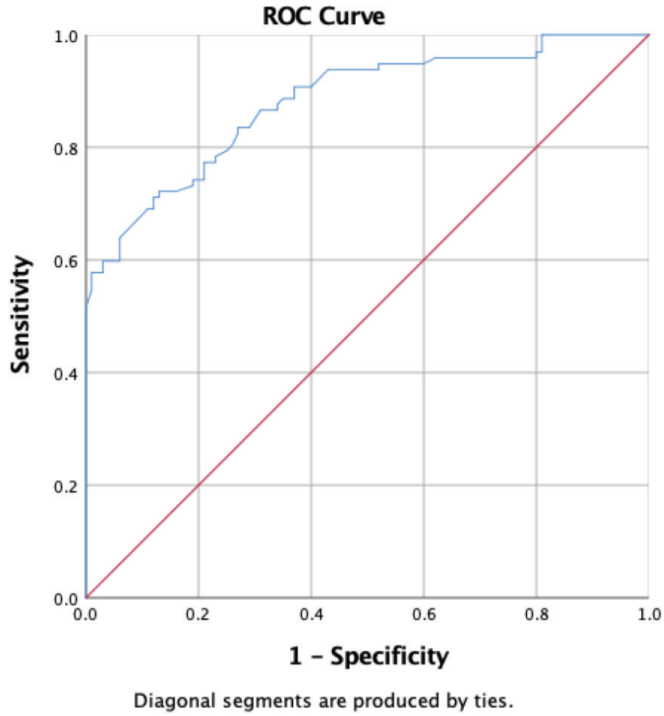

Figure 1. Evaluation of uric acid by ROC analysis
ROC: Receiver operating characteristic

inflammatory cells are thought to affect the balance between aortic wall regeneration and destruction, and AAA develops because of this imbalance[13]. Especially, recently, it has been stated that an increase in uric acid may cause vascular endothelial dysfunction by increasing oxidative stress[2,14]. Uric acid is a product of purine metabolism and is indicated as a strong indicator of cardiovascular risk and poor outcome[15]. Uric acid causes the conversion of nitric oxide (NO) to glutathione and reduces the amount of NO[16]. Considering the vasodilator effects of NO on vascular smooth muscle cells, the negative effects of increased uric acid levels in the pathogenesis of aortic aneurysms can be understood more easily. Additionally, some studies have also shown that increased serum uric acid levels result in the proliferation of vascular smooth muscle cells and have proinflammatory effects on vascular smooth muscle cells[17]. However, studies have not clearly demonstrated the relationship between AAA sensitivity and severity and uric acid increase[14]. In our study, we found that the uric acid levels were significantly higher in the group with aortic aneurysm than in the healthy group. In a study by Cai et al.[14] in patients with Behçet's disease, it was stated that serum uric acid level could be used as an independent marker for the risk and severity of AAA. Our study is consistent with the literature in this respect. Additionally, in our study, we found that a serum uric acid level above 4.56 mg/dL had a sensitivity of 77.3% and a specificity of 77% in predicting AAA. Şerefli et al.[18] found that homosyctein levels higher in coronary artery bypass patients with infrarenal AAA. In another study, the AAA diameter was found to be higher in patients with increased homocysteine values[19].

In a study by Uluganyan[10], it was observed that although male gender was found to be high in the AAA group, it did not reach statistical significance. In the same study, age, presence of DM, presence of HL, presence of CAD, HDL level, LDL level, and TG level was found to be similar between the AAA group and the healthy groups[10]. In our study, when the AAA group and the control groups were compared, age and gender were similar between the two groups. In our study, comorbid conditions such as DM, HT, and CAD, were found to be similar in both groups. In a study by Esen et al.[2], unlike our study, HT was found to be significantly higher in the AAA group. HT plays a role in the development of AAA by applying a continuous radial force to the aortic vessel wall by weakening and expanding the vessel wall[10]. The similarity found in both groups in our study may be due to the small number of patients included in the study.

HDL modulate oxidative stress as an anti-inflammatory and antioxidant, as well as regulates cholesterol flow from tissues. It shows its anti-inflammatory effect on monocytes through apolipoprotein A1, which is its main component[15]. Additionally, HDL molecules increase the release of NO synthase. In a study conducted in patients with bicuspid aortic valve, it was shown that patients with AAA had lower HDL levels than patients without aortic dilatation[20]. Also in our study, HDL level was found to be higher in the control group than in the AAA group, similar to other studies.

Inflammatory cells increase infiltration in the aortic wall and the cytokines secreted by these cells trigger the development of AAA[21,22]. NLR is increased based on increased neutrophil counts due to acute inflammation. In our study, we found the NLR value to be significantly higher in the AAA group than in the control group. Similar to our study, in a study by Güngör et al.[9], NLR value was found to be significantly higher in the AAA group. In another study, it was stated that NLR could be an important indicator of rupture in symptomatic AAA[23]. In a study by Cem et al.[22], NLR level was stated as an independent and strong predictor of AAA in newly diagnosed hypertensive patients. We believe that the effect of high NLR on the development of AAA is due to increased inflammation-related wall degeneration and thinning of the aortic wall. SII value is a combination of NLR and PLR values and is a new marker of inflammation and the immune system. In our study, the SII value was found to be higher in the AAA group than in the control group. Su et al.[6] stated that SII can be used in risk stratification to determine long-term

outcomes after hospitalization and discharge in patients with Type B aortic dissection treated with endovascular methods.

Despite an increasing number of studies, it is still controversial whether elevated serum uric acid levels are an independent risk factor for cardiovascular diseases[24,25].

Study Limitations

There were some limitations to our study. A prominent limitation was that it was a single-center and a retrospective study with a low number of patients. Another limitation may be counted as making the diagnosis of AAA only by echocardiography. The use of advanced imaging techniques, such as CTA and magnetic resonance, could provide a more detailed evaluation of the aneurysm. Extensive prospective studies are needed to reveal the pathophysiology of AAA more clearly.

Conclusion

As a result, in our study, we found that inflammatory parameters such as NLR and SII, and serum uric acid level were increased in patients with AAA compared with the control group. We also found that uric acid is an independent predictor of AAA development. Considering that serum uric acid levels and inflammatory parameters are increased in patients with AAA, we think that controlling these parameters in these patient groups may be effective in controlling the disease.

Ethics

Ethics Committee Approval: This study was received for the study from the Ethics Committee of Bakırköy Dr. Sadi Konuk Training and Research Hospital (protocol number: 2021/331).

Informed Consent: Patient data were retrospectively collected.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Atay M, Çalışkan S, Concept: Atay M, Çalışkan S, Güngören F, Design: Atay M, Çalışkan S, Güngören F, Data Collection and/or processing: Atay M, Çalışkan S, Analysis and/or Interpretation: Atay M, Çalışkan S, Güngören F, Literature Search: Atay M, Çalışkan S, Güngören F, Writing: Atay M, Çalışkan S, Güngören F.

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Relationship Between CHA_2DS_2-VASc Score, Coronary Tortuosity and Atrial Fibrillation in Patients with Coronary Artery Disease

Uğur Küçük, Bahadır Kırılmaz

Çanakkale Onsekiz Mart University Faculty of Medicine, Department of Cardiology, Çanakkale, Turkey

Abstract

Objectives: Coronary tortuosity (CT) is a common coronary angiography result and the clinical significance of CT is not clearly understood. In this study, the relationship between the presence of CT with CHA_2DS_2-VASc score and atrial fibrillation (AF) was analyzed.

Materials and Methods: Our study included 511 patients who underwent coronary angiography with evidence of coronary artery ischemia. All patients were assessed for the presence and severity of CT. Three or more bends that caused at least 45° changes in the main body of the coronary artery in both systole and diastole were defined as CT. The study patients were divided into groups according to the presence and severity of CT.

Results: CHA_2DS_2-VASc score was higher in the significant (SCT) group (p=0.001). Increased CHA_2DS_2-VASc score, regardless of age and female gender, was statistically SCT only for the presence of LAD SCT [p=0.003, adjusted odds ratio (OR): 1.95, 95% confidence interval (CI): 1.69-2.20]. Left anterior descending (LAD) SCT (p=0.014, OR: 3.11, 95% CI: 1.25-7.69) was reported to be a possible predictor of AF.

Conclusion: Patients who have LAD SCT observed on coronary angiography should be considered for periodic verification with electrocardiography in terms of AF development.

Keywords: CHA2DS2-VASc score, atrial fibrillation, coronary artery disease, coronary tortuosity

Address for Correspondence: Uğur Küçük, Çanakkale Onsekiz Mart University Faculty of Medicine, Department of Cardiology, Çanakkale, Turkey
e-mail: drugurkucuk@hotmail.com **ORCID:** orcid.org/0000-0003-4669-7387
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Introduction

Coronary arteries lie directly on the pericardium surface and meet the requirements for sustaining the functions of the heart and vital organs[1]. Curving or bending of these arteries is sometimes called ectasia, aneurysmal, and tortuosity in terminology[2]. Coronary tortuosity (CT), which has various names such as curved, bent, and angled vessels, is not a rare condition while its incidence is not known because the reporting frequency is inconsistent in clinical practice[3]. Although CT was demonstrated to be related to traditional risk factors such as senility, left ventricular diastolic dysfunction, hypertension (HT), and diabetes mellitus (DM), the effect on prognosis is unknown[4-6]. Advanced age, female gender, and the presence of comorbid conditions are often associated with clinical conditions such as atrial fibrillation (AF), which can have serious cardiac outcomes[7]. AF not only causes palpitations but can result in thromboembolic events that seriously affect life[8].

The CHA_2DS_2-VASc score, the utility of which was proven by clinical studies, is a useful score in predicting the risk of stroke in patients with AF[9]. Additionally, the correlation of the score with the severity of coronary artery disease (CAD) was demonstrated, and its utility outside its routine use has become a possibility[10]. The relationship between AF and coronary ischemia has been shown in previous studies[11,12]. In addition to all this, CT has shown that the coronary arteries' curved point can lead to ischemia, causing the coronary perfusion pressure decreasing[13].

Despite all this information, the benefit of CHA_2DS_2-VASc score in the relationship between the presence of CT was unknown. This study aimed to investigate the presence of CT with AF occurrence and to determine the effects of CHA_2DS_2-VASc score among CT.

Materials and Methods

Patient Population and Inclusion Criteria

Our retrospective cohort study comprised 511 consecutive patients who underwent coronary angiography between January 2013 and January 2021 with evidence of coronary artery ischemia (patients with newly-diagnosed left ventricular wall motion defects, myocardial perfusion scintigraphy, and evidence of ischemia on treadmill exercise test).

Our study population was divided into three groups according to the presence of CT significant CT (SCT), non-significant (non-SCT), and non-CT. CT patients included in the study had coronary tortuosity in at least one coronary artery. Our study consisted of patients with permanent AF. AF was defined as irregular RR intervals and no discernible P waves on ECG. Permanent AF was defined as patients with AF for more than 12 months who were not considered for intervention for rhythm control based on history and electrocardiography[14].

Patients who underwent interventions at the hospital because of the newly-diagnosed acute coronary syndrome, patients with malignant diseases, active infections, acute cerebrovascular disease, moderate and severe valvular disease, those receiving immunosuppressive therapy, those with known connective tissue diseases, chronic renal failure, patients under the age of 18, with history of the coronary artery bypass graft, chronic occlusion patients were excluded from the study.

Laboratory results were analyzed in peripheral venous blood samples at the time of admission, and demographic and clinical characteristics were recorded. Echocardiography of all patients was performed during admission, and the CHA_2DS_2-VASc score was calculated from the clinical and demographic characteristics at the time of admission.

After approval by the Çanakkale Onsekiz Mart University Ethics Committee, the study was performed under the rules of the Declaration of Helsinki.

Calculation of CHA_2DS_2-VASc Score

Scoring was made for each item specified in the calculation of the CHA_2DS_2-VASc risk score. Two points were given for age ≥75 years and stroke and one point each was given for congestive heart failure (ejection fraction <40%), HT, DM, vascular disease (peripheral

artery disease, prior occurrence of myocardial infarction, or an aortic plaque), age 65-74 years and gender (female).

Coronary Angiography and Coronary Tortuosity

Coronary imaging (GE Healthcare Innova 2100, New Jersey, USA) was performed by an experienced cardiologist using the standard Judkins technique and iopromide (Ultravist-370, Bayer Schering Pharma, Germany) with the femoral or radial approach. Angiographic images were evaluated by two experienced cardiologists. Stenosis was defined as the observation of more than 50% stenosis in the coronary arteries.

While defining coronary tortuosity, coronary arteries were evaluated from different angles. The presence of CT was determined by evaluating the images obtained from the right anterior oblique cranial angle for the left anterior descending (LAD) coronary artery, the caudal and left anterior oblique angles for the left circumflex coronary artery (LCX), and the right anterior oblique angle for the right coronary artery (RCA).

Three or more bends that caused at least 45° change in the main body of the coronary artery in both systole and diastole were defined as CT (Figure 1). While mild CT was defined as the presence of three or more bends in the epicardial coronary artery with 45°-90° curvature measured at the end of the diastole; in coronary arteries with a diameter of <2 mm, it was accepted as the presence of 90°-180° bends[15]. Moderate CT was defined as the presence of ≥3 consecutive bends with 90°-180° curvature measured at the end of diastole in the epicardial coronary artery and bends with ≥2 mm diameter, while severe CT was defined as the presence of ≥2 consecutive bends with ≥180° curvature in a major epicardial coronary artery[16,17].

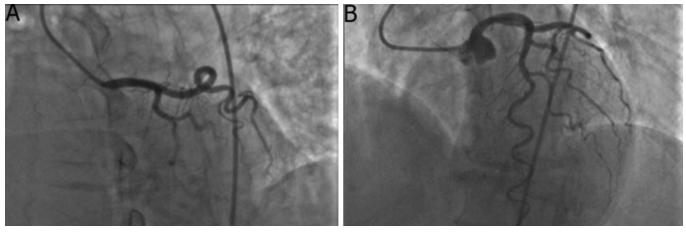

Figure 1. Coronary tortuosity (CT)
A: Significant coronary tortuosity (SCT) B: Non-significant coronary tortuosity (Non-SCT)

While CTs of mild severity were defined as insignificant; moderate and severe CTs were defined as significant . Weighted kappa statistics were performed for interobserver agreement (k=0.95, p=0.001).

Transthoracic Echocardiographic Evaluation

Transthoracic echocardiographic were examined by simultaneous electrocardiography using a 2.5 MHz probe with a Vivid 7 Pro device (GE, Vingmed, Horten, Norway). Left ventricular ejection fraction (LVEF) values were calculated using the modified Simpson method[18].

Risk Factors

HT was defined as systolic blood pressure above 140 mmHg and/or diastolic blood pressure above 90 mmHg or the use of antihypertensive drugs. DM was defined as fasting blood glucose above 126 mg/dL or the use of anti-diabetic medication. Hyperlipidemia was defined as using lipid-lowering medication or fasting total cholesterol ≥200 mg/dL or triglyceride ≥150 mg/dL. Smoking was defined as smoking for longer than the last six months.

Statistical Analysis

Kolmogorov-Smirnov test was used to determine the distribution of the study data. Variables are expressed as mean ± standard deviation, median, interquartile range (25^{th} and 75^{th} percentiles), and percentages ad numbers are used to express category variables. To compare continuous variables between groups, Student's t-test, Kruskal-Wallis tests, or One-Way ANOVA were used. Afterward, Bonferroni's post-hoc test was used. Chi-square or Fisher's exact tests were used to compare the probability ratios of categorical data. Multivariate logistic regression analysis was performed to adjust demographic parameters (age and female gender) that directly affect severe coronary tortuosity. Variables with p-values <0.05 in univariate analysis were considered for inclusion in the multivariable model. To examine the effect of

variables on atrial fibrillation, multivariate logistic regression analysis was performed, and odds ratios and 95% confidence intervals (CI) were calculated. The SPSS 20.0 (SPSS Inc, Chicago, IL, USA) program was used for statistical analyzes. P-values below 0.05 were considered statistically significant.

Results

Our study included 511 (234 women and 277 men) patients. Table 1 shows the primary characteristics of the groups. There were no statistical differences observed between the groups in terms of DM (p=0.265),

Table 1. Baseline characteristics of study group on the presence or absence of significant coronary tortuosity

Parameters	Total (n=511)	Non-CT (n=309)	Non-SCT (n=97)	SCT (n=105)	p-value
Age (years)					
Mean ± SD	56.9±13	53.1±12.4	57.6±9.6**	67.4±11.6**††	<0.001
Female gender n (%)	234 (45.8)	123 (39.8)	40 (41.2)	71 (67.6)	0.001
Smoking n (%)	119 (23.3)	70 (58.8)	25 (25.8)	24 (22.9)	0.813
Co-morbidities n (%)					
Hypertension	107 (20.9)	65 (21)	14 (14.4)	28 (26.7)	0.072
Diabetes mellitus	101 (19.8)	54 (17.5)	19 (19.6)	28 (26.7)	0.265
Dyslipidemia	112 (21.9)	71 (23)	15 (15.5)	26 (24.8)	0.216
Drugs n (%)					
ACEi or ARBs	108 (21.1)	60 (19.4)	18 (18.6)	30 (28.6)	0.110
Beta blocker	86 (16.8)	45 (14.6)	17 (17.5)	24 (22.9)	0.143
Calcium Channel Blocker	57 (11.2)	28 (9.1)	13 (13.4)	16 (15.2)	0.164
Statins	64 (12.5)	33 (10.7)	13 (13.4)	18 (17.1)	0.216
LVEF (%)	57.62±5.99	57.76±6.21	58.32±5.729	56.53±5.41	0.084
LA (mm)	36.91±5.89	36.76±6.21	36.98±5.88	37.26±4.84	0.744
Glucose (mg/dL)	90 (74-101)	88 (70-100)	90 (80-100)	91 (81-120)	0.134
TSH (uIU/mL)	1.6 (1-1.8)	1.6 (1-1.7)	1.5 (1-1.8)	1.6 (0.9-2)	0.934
HbA1C (%)	7.29±0.31	7.25±0.24	7.29±0.40	7.39±0.24	0.149
TIMI frame count					
LAD CT			17.27±0.82	18.51±2.37	<0.001
LCX CT			17.25±0.89	18.60±2.31	<0.001
RCA CT			17.18±0.79	17.11±0.88	0.548
Atrial fibrillation n (%)	55 (10.7)	23 (7.4)	9 (9.2)	23 (21.9)	0.002
LAD CT			2 (2)	10 (9.5)	
LCX CT			5 (5.1)	11 (10)	
RCA CT			2 (2)	0 (0)	
LAD & LCX			0 (0)	2 (1.9)	
CHA2DS2-VASc score	1.29±1.12	1.09±0.99	0.96±0.94	2.17±1.22**††	0.001
LAD CT			1.48±1.20	2.25±1.35	0.003
LCX CT			1.42±1.20	2.15±1.22	<0.001
RCA CT			1.64±1.24	0.63±0.92	0.008

**P<0.05 and **P<0.01 vs. Non-CT group, †P<0.05 and ††P<0.01 vs. Non-SCT group*
Hypertension, age ≥75 years (doubled), diabetes mellitus, prior stroke or transient ischemic attack (doubled), and vascular disease, age 65-74 years, and sex category (female)
ACEI: Angiotensinogen converting enzyme inhibitor, ARB: Angiotensin receptor blocker, LVEF: Left ventricle ejection fraction, LA: Left atrium, TSH: Thyroid stimulating hormone, HbA1C: Glycated haemoglobin, TIMI: Thrombolysis in myocardial infarction, CT: Coronary tortuosity, SCT: Significant coronary tortuosity, LAD: Left anterior descending coronary artery, LCX: Left circumflex coronary artery, RCA: Right coronary artery, CHA2DS2-VASc: Congestive heart failure, SD: Standard deviation

HT (p=0.072), and dyslipidemia (p=0.216). Similarly, there were no statistical differences between the groups in terms of the use of angiotensin-converting enzyme inhibitor or angiotensin receptor blockers (p=0.110), beta-blockers (p=0.143), calcium channel blockers (p=0.164) and statins (p=0.216). While there were no differences observed between the groups in terms of LVEF (p=0.084), HbA_1C (p=0.149), Thyroid-stimulating hormone (TSH) (p=0.934), and left atrium (LA) diameter (p=0.744), statistical significance was observed in the SCT group compared to the non-CT group for atrial fibrillation (p=0.002). For the CHA_2DS_2-VASc score, statistical significance was observed in the SCT group compared with both the non-CT and non-SCT groups (p<0.001). No statistical differences were observed between the groups in terms of heart rates (p=0.347) (Table 1). CT was observed in 202 patients; it was most prevalently observed in the LCX artery. Similarly, the most frequent frequency of LCX was seen in the SCT group (Table 2).

When the distribution of CT patients was examined according to the CHADS-VASC score, most patients in the SCT group were in the higher score group than the non-SCT patients, and patients in the LAD SCT group were especially distributed in the high - scoring group (p<0.001, for both all) (Table 3).

AF was reported to be associated with LAD SCT and CHA_2DS_2-VASc score (p=0.014 and p<0.001 respectively (Table 4). Statistical significance for the CHA_2DS_2-VASc score, independent of age and female gender, was observed in the LAD SCT (p=0.003) (Table 5).

Discussion

Important results were obtained in our study. Firstly, AF was observed more frequently among SCT patients

Table 2. Distribution of tortuosity in coronary arteries

Artery n (%)	All patients with CT (n=202)	Non-SCT (n=97)	SCT (n=105)
LAD	54 (26.7%)	27 (27.8%)	27 (25.7%)
LCX	103 (51%)	58 (59.8%)	45 (42.9%)
RCA	7 (3.5%)	5 (5.2%)	2 (1.9%)
LAD & LCX	32 (15.8%)	6 (6.2%)	26 (24.8%)
LAD & RCA	0 (0%)	0 (0%)	0 (0%)
LCX & RCA	2 (1%)	1 (1%)	1 (1%)
LAD & LCX & RCA	4 (2%)	0 (0%)	4 (3.8%)

LAD: Left anterior descending coronary artery, LCX: Left circumflex coronary artery, RCA: Right coronary artery, CT: Coronary tortuosity, SCT: Significant coronary tortuosity

Table 3. Distribution of CT patients by CHADS-VASc score

		CHA_2DS_2-VASc score					p-value
Score point		0	1	2	3	4	
SCT (n) (n=105)		12	20	25	33	15	<0.001
Non-SCT (n) (n=97)		34	40	17	4	2	
LAD (n) (n=54)	SCT,	2	2	3	11	9	<0.001
	Non -SCT	5	9	9	1	3	
CX (n) (n=103)	SCT	5	8	12	15	5	0.116
	Non-SCT	9	19	13	8	9	
RCA (n) (n=7)	SCT	0	0	1	1	0	0.314
	Non-SCT	1	1	2	1	0	

LAD: Left anterior descending coronary artery, SCT: Significant coronary tortuosity, RCA: Right coronary artery, CT: Coronary tortuosity, SCT: Significant coronary tortuosity

compared to non-SCT and non-CT patients. Secondly, CHA_2DS_2-VASc score was associated with LAD SCT, independent of age and female gender. Thirdly, LAD SCT has been reported to be a possible predictor of AF.

In animal models, artery enlargement and increased pressure were reported to be associated with CT; however, the absence of a relationship in patients with HT is an indication of the complexity of the CT etiology[19,20]. Another recent study showed a relationship between CT and HT[21]. In accordance with the study by Chiha et al.[22], there was no relationship observed between SCT and HT in our study. When studies were examined, CT definitions differed between studies. CT definitions may have played an active role in obtaining different results related to HT. Age and sex affect heart size. The prevalence of CT increases as the heart size and mass decreases, especially in elderly and female patients. In our study, observation of more CT among cases of female gender and older age supports the literature. Although the results of our study and literature reviews show the relationship between demographic variables and CT, a definitive statement about pathogenesis is not possible[23].

The CHA_2DS_2-VASc score, which is calculated using similar demographic features in CT etiology, is useful in deciding on the use of oral anticoagulant drugs to protect against stroke in routine AF patients[24]. In the current studies, its utility outside the ordinary area of use was investigated. The relationship between coronary artery severity and the score was studied in patients with acute coronary syndrome, and the utility of the CHA_2DS_2-VASc score was shown in the risk classification of saphenous vein graft disease in another study[25,26]. In our study, the increased CHA_2DS_2-VASc score was higher, especially in the SCT group.

Moreover, because of regression analysis, examined the effect of variables on atrial fibrillation, significance was obtained especially in the LAD SCT group, and we believe that it will be possible to add SCT to the CHA_2DS_2-VASc score because of future multi-center studies. In the literature, it has been shown that the

Table 4. Multivariate logistic regression analysis of parameters for atrial fibrillation

Parameters	B	SE	χ^2 value	p-value	OR	95% CI
Hyperlipidemia	0.021	0.429	0.002	0.962	1.021	0.441-2.365
TSH	-0.238	0.237	1.006	0.316	0.788	0.495-1.255
HbA_1C	1.252	1.011	1.532	0.216	3.496	0.482-25.376
RCA SCT	0.739	0.706	1.096	0.295	2.095	0.525-8.364
LCX SCT	0.561	0.426	1.738	0.187	1.753	0.761-4.040
LAD SCT	1.135	0.462	6.020	0.014	3.110	1.256-7.698
CHA_2DS_2-VASc score	0.663	0.122	29.693	<0.001	1.942	1.529-2.465
LA	0.079	0.067	1.418	0.234	1.083	0.950-1.234
LVEF	-0.098	0.065	2.267	0.132	0.907	0.799-1.030

RCA: Right coronary artery, SCT: Significant coronary tortuosity, LAD: Left anterior descending coronary artery, LCX: Left circumflex coronary artery, LVEF: Left ventricle ejection fraction, LA: Left atrium, TSH: Thyroid stimulating hormone, HbA1C: Glycated haemoglobin, OR: Odds ratio, CI: Confidence interval

Table 5. Corrected significant coronary tortuosity

	LAD SCT		LCX SCT		RCA SCT	
Parameter	AOR (95% CI)*	p-value	AOR (95% CI)*	p-value	AOR (95% CI)*	p-value
CHA_2DS_2-VASc score	1.950 (1.699-2.201)	0.003	1.736 (1.534-1.938)	0.119	1.169 (0.764-1.574)	0.035

**Adjusted odds ratio for age and female gender.*
AOR: Adjusted odds ratio, CI: Confidence interval, RCA: Right coronary artery, SCT: Significant coronary tortuosity, LAD: Left anterior descending coronary artery, LCX: Left circumflex coronary artery,

incidence of lacunar infarction is higher in patients with hypertensive CT than in patients without CT, which supports our recommendation[27]. The relationship between a high CHA_2DS_2-VASc score and LAD SCT is one of the important results of our study. Although the CHA_2DS_2-VASc score depends on female gender and age, statistical significance for the CHA_2DS_2-VASc score was observed in the LAD SCT, regardless of age and female gender, because of our analysis.

In animal experiments, AF was triggered because of increased spontaneous atrial ectopic activity and decreased atrial conduction because of atrial ischemia[28]. In acute coronary syndrome patients, vascular occlusion is effective in the development of AF, and studies have reported different prevalences of LAD, LCX, and RCA-induced ischemia with new-onset AF[29]. Various factors such as traditional risk factors, coronary ischemia, and ventricular remodeling have been blamed for AF development; however, the primary pathogenesis is impaired microcirculation and atrial ischemia because of decreased coronary blood flow[30]. We consider that SCT can affect the development of AF.

In the literature, including our study, the extent to which CT with fractional flow reserve can affect hemodynamics and cause atrial ischemia was not studied. However, it was suggested in studies that coronary blood flow encounters varying degrees of resistance during exercise depending on the severity of tortuosity and that ischemia may occur because of a decrease in filling pressures in the distal coronary circulation[31]. Moreover, the number of thrombolysis in myocardial infarction (TIMI) squared, a useful coronary perfusion indicator, was statistically and numerically higher in the SCT group compared to the non-SCT group, which supports our theory[32].

Study Limitations

Our study has some limitations. Firstly, although TIMI provided information about blood flow between groups, the degree to which coronary tortuosity affected hemodynamic change was not evaluated with intravascular ultrasound. Secondly, because of the design of the study, the time until atrial fibrillation may develop in patients with SCT in sinus rhythm is not known. Thirdly, the frequency of thromboembolic events developing in patients is unknown for SCT to be added to the CHA_2DS_2-VASc score.

Conclusion

In patients with LAD SCT observed during coronary angiography, periodic checks, at least with electrocardiography, for AF development can be considered. Increased CHA_2DS_2-VASc score is associated with stroke and similar embolic events, and with the combination of atrial fibrillation and SCT, paying attention to coronary tortuosity may be considered in the calculation of the score.

Ethics

Ethics Committee Approval: The study was approved Çanakkale Onsekiz Mart University Ethics Committee and was conducted in accordance with the Declaration of Helsinki (date: 03.03.2021, decision no: 2011-KAEK-27/2020-E.2100017038).

Informed Consent: Patient consent is not required due to study design.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: Küçük U, Kırılmaz B, Design: Küçük U, Kırılmaz B, Data Collaection and/or processing: Küçük U, Kırılmaz B, Analysis and/or Interpretation: Küçük U, Kırılmaz B, Literature Search: Küçük U, Kırılmaz B, Writing: Küçük U, Kırılmaz B.

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The Relationship Between Dual Antiplatelet Treatment Score and Thrombus Burden in Patients with Acute Myocardial Infarction

Özge Çakmak Karaaslan, Cem Çöteli, Murat Oğuz Özilhan, Mehmet Timur Selçuk, Hatice Selçuk, Orhan Maden

Ankara City Hospital, Clinic of Cardiology, Ankara, Turkey

Abstract

Objectives: High thrombus burden (HTB) was an independent predictor of death, repeat myocardial infarction, and infarct-related artery intervention and stent thrombus in patients with acute myocardial infarction (AMI). This study aimed to evaluate the predictive role of the dual antiplatelet therapy (DAPT) score in the estimation of intracoronary thrombus burden in patients with AMI.

Materials and Methods: Between March 2020 and May 2020, 360 consecutive patients admitted with AMI who underwent coronary angiography at the cardiology department of our institution were retrospectively evaluated. The DAPT score has been defined as previously in the DAPT study. The thrombolysis in myocardial infarction (TIMI) thrombus grade was calculated for each patient from the diagnostic angiographic images taken before percutaneous coronary interventions. HTB was defined as TIMI thrombus grades 4 and 5 calculated according to the TIMI thrombus grading scale. The study population was divided into two groups according to their TIMI thrombus grade: low thrombus burden (LTB) (TIMI 0-3) and HTB (TIMI 4 and 5).

Results: There were 133 patients (36.9%) in the LT group and 227 patients (63.1%) in the HTB group. Patients with HTB had significantly a higher DAPT score (p=0.010) compared with LTB patients. The ability of the DAPT score to predict the

Address for Correspondence: Özge Çakmak Karaaslan, Ankara City Hospital, Clinic of Cardiology, Ankara, Turkey
Phone: +90 537 739 56 70 **e-mail:** ozgecakmak2323@gmail.com **ORCID:** orcid.org/0000-0003-0173-4017
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Abstract

HTB was evaluated by receiver operating characteristic curve analysis. The cut-off value of the DAPT score for predicting the HTB was 2 (with a sensitivity of 67.8%, specificity=69.4%) according to the Youden index. Univariate regression analysis demonstrated that the DAPT score was significantly associated with the HTB. On multivariate analysis, the DAPT score (Odds ratio: 1,245, 95% confidence interval: 1,009-1,537; p=0.041) was found as an independent predictor of the HTB when the DAPT score was analyzed as a continuous variable.

Conclusion: The DAPT score is a practical score system to guide DAPT duration, accounting for both ischemic risk and bleeding risk factors. Considering the increasing number of patients with acute coronary syndromes, prediction of thrombus burden through a simple and practical scoring system may be of benefit.

Keywords: Acute myocardial infarction, DAPT score, percutaneous coronary intervention, thrombus burden

Introduction

In spite of the incidence of acute myocardial infarction (AMI) declining recently, patients with AMI still have a higher mortality than that of the general population[1,2]. The preferred treatment approach of patients with AMI is percutaneous coronary intervention (PCI). Patients with AMI are at a high risk of recurrent ischemia after PCI, and current guidelines recommend that their treatment includes individual risk factor modification and long-term dual antiplatelet therapy (DAPT)[3]. In previous reports, the association of the presence of intracoronary thrombi with procedural complications such as stent thrombosis, no-reflow, or distal embolization was shown in patients with acute AMI undergoing PCI[4].

The DAPT score is a new decision tool recently developed to identify patients most likely to provide benefit from long-term dual antiplatelet therapy[5]. The DAPT score includes the following parameters: age, diabetes mellitus (DM), myocardial infarction (MI) at presentation, prior PCI or MI, cigarette smoking, congestive heart failure (CHF) or left ventricular ejection fraction (LVEF) <30%, paclitaxel-eluting stents, stent diameter <3 mm and vein graft stent[5].

The present study evaluated the predictive role of the DAPT score in the estimation of intracoronary thrombus burden in patients with AMI.

Materials and Methods

Between March 2020 and May 2020, 426 consecutive patients admitted with AMI at the cardiology department of our institution were retrospectively evaluated. Hospital records and patient files were reviewed. AMI was determined by the appropriate guidelines[6]. AMI was defined as the presence of cardiomyocyte necrosis detected by abnormal cardiac biomarkers in a clinical setting consistent with acute myocardial ischemia and persistent ST-segment elevation or without persistent ST-segment elevation.

Patients with MI and non-obstructive coronary artery disease (n=19), a known hematological disease (n=2), a history of chronic inflammatory disease (n=1), a history of autoimmune diseases (n=1), malignancy (n=3), those using oral anticoagulants (n=5), or patients with missing clinical data (n=3) were excluded from the study. Additionally, we excluded patients (n=32) who did not undergo coronary angiography (CAG). The final study population consisted of 360 AMI patients who underwent CAG.

The retrospective observational study protocol was approved by the local ethics committee of our hospital (E1-22-2362).

Baseline clinical and demographic parameters, laboratory measurements, and angiographic images of patients were gathered from the hospital's medical database.

The DAPT score was defined as previously in the DAPT study[5]. The DAPT score was calculated by assigning -2 points for age ≥75 years, -1 points for age between 65 and 75 years, 0 points for age <65 years, 1 point each for cigarette smoking, DM, MI at presentation, prior PCI or prior MI, paclitaxel-eluting stent and stent diameter <3 mm, and 2 points for vein graft stent and CHF or LVEF <30%, respectively.

The CAG was performed via the transradial or transfemoral approach using the Seldinger technique according to the operator's discretion. According to the European Society of Cardiology guidelines, an immediate invasive strategy was performed on patients with at least one very-high-risk non-ST elevation MI (NSTEMI) criterion or with ST-elevation MI (STEMI); all the remaining patients underwent CAG within 48 h after admission with a diagnosis of NSTEMI[7,8]. All the patients in the study received a loading dose of aspirin and depending on the discretion of the operator, a loading dose of clopidogrel 600 mg, or ticagrelor 180 mg, or prasugrel 60 mg on admission or after the decision to proceed with PCI were taken. Procedural decisions, including device selection and adjunctive pharmacotherapy, such as glycoprotein IIb/IIIa inhibitors, were made by the operator. All patients received 70-100 U/kg of intravenous unfractionated heparin before the PCI procedure.

Two experienced interventional cardiologists who were unaware of the DAPT score of patients reviewed the angiographic images of the study patients. In the case of inconsistency between the two cardiologists, a third interventional cardiologist's assessment was wanted. The Thrombolysis in MI (TIMI) thrombus grade was calculated for each patient from the diagnostic angiographic images taken before PCI. Thrombus burden was quantified into five grades based on the classification of Gibson et al.[9]. High thrombus burden (HTB) was defined as TIMI thrombus grades 4 and 5 calculated according to the TIMI thrombus grading scale.

The study population was divided into two groups according to their TIMI thrombus grade: low thrombus burden (LTB) (TIMI 0-3, n=113) and HTB (TIMI 4 and 5, n=227).

Statistical Analysis

All the data were analyzed using the SPSS 22.0 Statistical Package Program for Windows (SPSS; IBM, Armonk, New York, USA). A Kolmogorov-Smirnov test was used for assessing the normality of distribution. Continuous variables were presented as mean ± standard deviation and median (interquartile ranges) and categorical variables as the number of patients and percentages. A comparison between groups was made with a Student's t-test for normally distributed variables and a Mann-Whitney U test for variables without normal distribution. Categorical data from both groups were compared using the χ^2 or Fisher's exact test.

The ability of the DAPT score to predict HTB was evaluated by receiver operating characteristic (ROC) curve analysis and area under the curve (AUC) values. The cut-off value was calculated according to the Youden index. A value of $p<0.05$ (using a two-sided test) was set as statistically significant.

Univariate and multivariate logistic regression analyses were used to evaluate the independent predictors of HTB. Variables displaying $p<0.05$ in the univariate analysis were used in a multivariate logistic regression analysis.

Results

A total of 360 patients admitted with AMI who underwent CAG constituted the final study population. There were 133 patients (36.9%) in the LTB group and 227 patients (63.1%) in the HTB group. The baseline demographic and clinical characteristics of the study groups are shown in Table 1. The mean age was 61 (29-92) years, and most study group patients (78%) were male. There were no differences between the two groups concerning age and gender. Patients with HTB had significantly a higher DAPT score (p=0.010), smoking (p=0.020) and lower LVEF (p=0.015) compared with LTB patients. There were no significant differences between

the study groups in terms of the systolic blood pressure and heart rate.

There were no significant differences between the study groups with respect to the history of DM, hypertension, hyperlipidemia, CHF, peripheral arterial disease and previous cerebrovascular accident. However, compared to the patients with HTB, those with LTB had a higher prevalence of known coronary artery disease (p=0.002).

There were 141 (39.2%) patients with STEMI and 219 (60.8%) patients with NSTEMI. Patients with HTB had a significantly higher STEMI proportion (p<0.001) and lower NSTEMI proportion (p<0.001) compared with LTB patients.

There were no significant differences between the study groups in medications at discharge, except for aspirin + tikagrelor and aspirin + clopidogrel. The ratio of aspirin + clopidogrel therapy prescribed at discharge was higher in the patients with LTB (p<0.001) (Table 1). In the patients with HTB, aspirin + ticagrelor was prescribed more frequently compared to the patients with LTB (p=0.001).

The fasting blood glucose (FBG) (p=0.002), aspartate transaminase (p<0.001), alanine aminotransferase

Table 1. Comparison of low thrombus burden and high thrombus burden groups according to the baseline demographics, clinical characteristics, and medications

	All groups (n=360)	LTB (n=133)	HTB (n=227)	p-value
Age (years)	61 (29-92)	62 (33-92)	60 (29-91)	0.162
Male, n (%)	284 (78.9)	99 (74.4)	185 (81.5)	0.113
DAPT score	2 (-1-6)	2 (-1-5)	2 (-1-6)	**0.010**
Smoking, n (%)	93 (25.8)	25 (18.8)	68 (30)	**0.020**
LVEF, %	45 (15-65)	46 (20-65)	45 (15-65)	**0.015**
SBP, mmHg	130 (65-180)	130 (70-170)	130 (65-180)	0.072
Heart rate, BPM	76 (38-140)	76 (43-140)	76 (38-132)	0.871
Diabetes mellitus, n (%)	179 (49.7)	61 (45.9)	118 (52)	0.262
Hypertension, n (%)	201 (55.8)	72 (54.1)	129 (56.8)	0.619
Hyperlipidemia, n (%)	146 (40.6)	53 (39.8)	93 (41)	0.835
Previous CVA, n (%)	20 (5.6)	10 (7.5)	10 (4.4)	0.813
Known CAD, n (%)	148 (41.1)	69 (51.9)	79 (34.8)	**0.002**
History of CHF, n (%)	102 (28.3)	31 (23.3)	71 (31.3)	0.105
History of PAD, n (%)	21 (16.9)	7 (15.2)	14 (17.9)	0.695
Admission diagnosis, n (%)				
STEMI	141 (39.2)	25 (18.8)	116 (51.1)	**<0.001**
NSTEMI	219 (60.8)	108 (81.2)	111 (48.9)	**<0.001**
Medications at discharge, n (%)				
Aspirin + Clopidogrel	137 (38.1)	67 (50.4)	70 (30.8)	**<0.001**
Aspirin + Ticagrelor	200 (55.6)	59 (44.4)	141 (52.1)	**0.001**
Aspirin + Prasugrel	14 (3.9)	4 (3.0)	10 (4.4)	0.585
Beta-blocker	330 (91.7)	124 (93.2)	206 (90.7)	0.410
ACEIs or ARBs	319 (88.6)	123 (92.5)	196 (86.3)	0.077
Spironolactone	87 (24,2)	31 (23,3)	56 (24,7)	0.771
Statins	335 (93,1)	124 (93,2)	211 (93)	0.919
Diuretics	83 (23,1)	28 (21,1)	55 (24,2)	0.490

LTB: Low thrombus burden, HTB: High thrombus burden, DAPT: Dual antiplatelet treatment, LVEF: Left ventricular ejection fraction, SBP: Systolic blood pressure, CVA: Cerebral vascular accident, CAD: Coronary artery disease, CHF: Chronic heart failure, PAD: Peripheral arterial disease, STEMI: ST elevation myocardial infarction, NSTEMI: Non-ST elevation myocardial infarction, ACEI: Angiotensin-converting enzyme inhibitors, ARBs: Angiotensin receptor blockers

(p=0.029), low-density lipoprotein-cholesterol (LDL-C) (p=0.013), white blood cell (WBC) counts (p<0.001), neutrophil counts (p<0.001) and hemoglobin levels (p=0.012) were significantly higher in patients with HTB as shown in Table 2.

There were no significant differences between the study groups regarding the proportions of stent diameter <3 mm, proportions of 1 vessel disease and 3 vessel disease and proportions of by-pass graft disease. However, the patients with HTB had significantly higher proportions of 2 vessel disease (p=0.021) compared with LTB patients (Table 3).

The ability of the DAPT score to predict the HTB was evaluated by ROC curve analysis. The AUC value of this analysis is presented in Figure 1 [AUC=0.579, 95% confidence interval (CI)=0.520-0.638, p=0.012]. The cut-off value of the DAPT score for predicting the HTB was 2 (with a sensitivity of 67.8%, specificity =69.4%) according to the Youden index.

Univariate regression analysis demonstrated that the DAPT score, smoking, STEMI, increased FBG levels, reduced LVEF, increased LDL-C levels, increased WBC levels and increased neutrophil levels were significantly associated with the HTB, as shown in Table 4.

Table 2. Comparison of low thrombus burden and high thrombus burden groups according to the laboratory characteristics

	All groups (n=360)	LTB (n=133)	HTB (n=227)	p-value
FBG (mg/dL)	119 (48-576)	109.5 (66-576)	129 (48-371)	**0.002**
Creatinine (mg/dL)	0.8 (0-6.91)	0.8 (0.4-2.9)	0.86 (0-6.91)	0.139
eGFR (mL/min/1.73 m^2)	91 (7-137)	89 (27-137)	92 (7-127)	0.973
Albumin (g/dL)	41 (3.7-55)	41 (3.9-55)	42 (3.7-54)	0.213
AST	32 (2-627)	27 (8-627)	36 (2-553)	**<0.001**
ALT	26 (6-326)	23.5 (6-326)	27 (8-128)	**0.029**
Total cholesterol (mg/dL)	176 (75-412)	168 (75-374)	180 (84-412)	0.108
Triglycerides (mg/dL)	118 (34-2179)	120.5 (34-968)	116 (37-2179)	0.601
HDL-C (mg/dL)	35 (10-72)	36 (21-72)	34 (10-67)	0.142
LDL-C (mg/dL)	112 (15-277)	104 (15-188)	116 (16-277)	**0.013**
WBC (×10^3/μL)	9.96 (1-31)	9,305 (1-31)	10.6 (4.69-24.18)	**<0.001**
Neutrophil (×10^3/μL)	7 (0.51-76.4)	6,265 (0.51-29)	7.58 (1.24-76.4)	**<0.001**
Lymphocyte (×10^3/μL)	1,88 (1.85-2.04)	1.85 (1.75-2.04)	1.89 (1.85-2.09)	0.745
Hemoglobin (mg/dL)	14.2 (7.9-21)	13.8 (8.5-17.8)	14.4 (7.9-21)	**0.012**
Platelet (×10^3/μL)	255 (71-660)	251.5 (71-611)	256 (109-660)	0.503
CRP	15.33 (10.2)	17.14 (10.9)	14.20 (10.5)	0.995

LTB: Low thrombus burden, HTB: High thrombus burden, FBG: Fasting blood glucose, eGFR: Estimated glomerular filtration rate, AST: Aspartate transaminase, ALT: Alanine transaminase, HDL-C: High density lipoprotein cholesterol, LDL-C: Low density lipoprotein cholesterol, WBC: White blood cell, CRP: C-reactive protein

Table 3. Comparison of angiographic data characteristics of low thrombus burden and high thrombus burden groups

	All groups (n=360)	LTB (n=133)	HTB (n=227)	p-value
Stent diameter <3 cm	114 (31.7)	41 (30.8)	73 (32.2)	0.793
Extension of CAD				
1 Vessel disease	249 (69.7)	96 (73.3)	153 (67.7)	0.268
2 Vessel disease	69 (19.3)	17 (13)	52 (23)	0.021
3 Vessel disease	24 (6.7)	10 (7.6)	14 (6.2)	0.663
By-pass graft disease	18 (11.2)	5 (8.8)	13 (12.5)	0.473

LTB: Low thrombus burden, HTB: High thrombus burden, CAD: Coronary artery disease

On multivariate analysis, the DAPT score [Odds ratio (OR): 1,245, 95% CI: 1,009-1,537; p=0.041], STEMI (OR: 4,412, 95% CI: 2,497-7,795; p<0.001), increased FBG (OR: 1,005, 95% CI: 1,001-1,008; p=0.015) and increased LDL-C levels (OR: 1,007, 95% CI: 1,000-1,014; p=0.039) were found as independent predictors of the HTB when DAPT score was analyzed as a continuous variable (Table 5).

Discussion

The main findings of this study were as follows: the patients with HTB had a higher DAPT score compared to with patients with LTB. DAPT score ≥2 had a sensitivity of 67.8%, a specificity of 69.4% and an AUC of 0.579 for predicting HTB. The DAPT score, STEMI, increased FBG levels and increased LDL-C levels were found to be significant independent predictors of HTB.

Table 4. Univariate logistic regression analysis for prediction of high thrombus burden

	Odds ratio (95% CI)	p-value
DAPT	1,302 (1,099-1,543)	**<0.002**
Smoking	1,848 (1,099-3,106)	**0.021**
STEMI	4,515 (2,719-7,495)	**<0.001**
Glucose	1,004 (1,001-1,007)	**0.011**
LVEF	0.978 (0.951-0.994)	**0.011**
CRP	1,024 (0.986-1,063)	0.390
Albumin	0.997 (0.989-1,004)	0.485
Urea	1,002 (0.989-1,015)	0.766
Creatinine	1,087 (0.654-1,805)	0.749
TC	1,003 (0.998-1,009)	0.189
TG	1,000 (0.999-1,001)	0.989
HDL-C	0.981 (0.956-1,005)	0.123
LDL-C	1,007 (1,001-1,014)	**0.016**
WBC	1,122 (1,047-1.202)	**0.001**
Neutrophil	1,212 (1,045-1,203)	**0.001**
Lymphocyte	1,101 (0.866-1,401)	0.432

STEMI: ST-segment elevation myocardial ınfarction, LVEF: Left ventricular ejection fraction, CRP: C-reactive protein, TC: Total cholesterol, TG: Triglyceride, HDL-C: High density lipoprotein cholesterol, LDL-C: Low density lipoprotein cholesterol, WBC: White blood cell

Coronary atherosclerotic plaque rupture or erosion provokes thrombocyte aggregation and activation of coagulation, causing the formation of thrombus that leads to AMI[10]. A HTB has been connected with increased

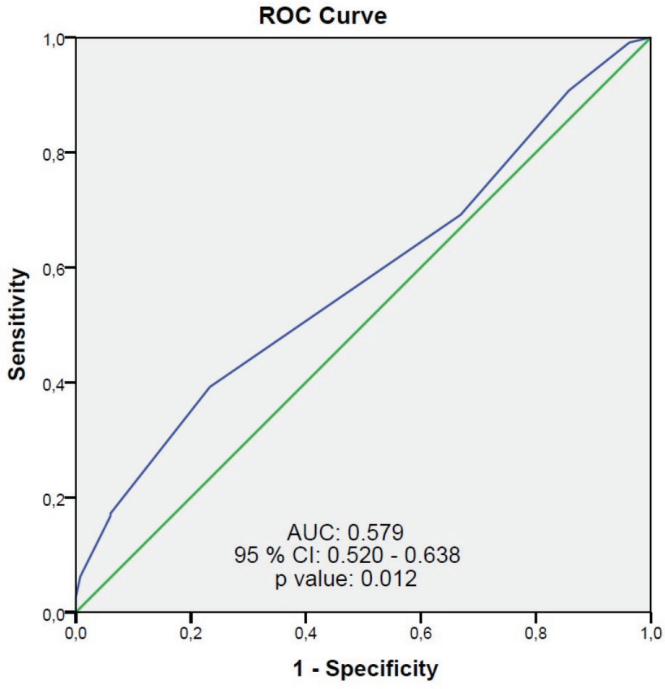

Figure 1. Receiver operating characteristics curve analysis of DAPT score in predicting high thrombus burden

DAPT: Dual antiplatelet treatment, AUC: Area under the curve, CI: Confidence interval

Table 5. Multivariate logistic regression analysis for prediction of high TIMI thrombus burden

	Odds ratio (95% CI)	p-value
DAPT	1,245 (1,009-1,537)	**0.041**
Smoking	1,759 (0.927-3.338)	0.084
STEMI	4,412 (2,497-7,795)	**<0.001**
Glucose	1,005 (1,001-1,008)	**0.015**
LVEF	0.996 (0.970-,1,023)	0.763
CRP	1,024 (0.986-1,063)	0.390
LDL-C	1,007 (1,000-1,014)	**0.039**
WBC	0.987 (0.784-1,243)	0.912
Neutrophil	1,086 (0.861-1,371)	0.486

CI: Confidence interval, DAPT: Dual antiplatelet therapy, STEMI: ST-segment elevation myocardial infarction, LVEF: Left ventricular ejection fraction, CRP: C-reactive protein, LDL-C: Low density lipoprotein cholesterol, WBC: White blood cell

1-month mortality and high rates of stent thrombosis in patients with STEMI who underwent PCI[11]. It was previously reported that the HTB was associated with impaired epicardial and myocardial perfusion, coronary micro and distal embolization, and no-reflow[12]. Distal embolization increases the risk of procedural complications, such as microvascular obstruction, no-reflow, and increased infarct size[13]. The HTB in patients with NSTEMI was an independent predictor of the 30-day adverse events and early-late stent thrombosis[14]. It is been known that a large thrombus burden is an independent predictor of death, repeat MI, and infarct-related artery intervention and stent thrombus[13-15]. Therefore, the early assessment of indicators of intracoronary thrombus burden is crucial and might lead to receiving appropriate therapy for reducing thrombus grade before and during the procedure. Previous studies have shown that C-reactive protein (CRP) levels, albumin levels, CRP to albumin ratio, neutrophil-lymphocyte ratio and baseline troponin I levels are independent predictors of HTB in patients with AMI[12,13,16].

Other recent studies have reported that the CHA_2DS_2-VASc score and PRECISE-DAPT score were established to be independently associated with intracoronary thrombus burden[13,17]. The DAPT score is a simple and practical scoring system that includes risk factors for ischemic cardiac events. The DAPT score was developed to determine the DAPT duration according to ischemia risk after PCI[18]. Besides its ability to predict ischemic risk, the association of the DAPT score with adverse cardiac events was previously demonstrated in the literature[19]. Previous studies have reported that the coronary disease severity and ischemic events are associated with a high DAPT score[20,21]. According to the DAPT study, patients with a high DAPT score had a highly calculated ischemic risk and were found to benefit from extended time DAPT[22]. It was observed in our study that the DAPT score was found to be a significant independent predictor of HTB. The DAPT score may be associated with thrombus burden, as it includes ischemic risk factors such as DM, prior MI or PCI, cigarette smoking, CHF and renal insufficiency. Compared with non-diabetic patients, erythrocyte aggregation is higher than in patients with diabetes.

Hyperglycemia stimulates thrombosis and raises the releasing of pro-inflammatory mediators by activating the inflammatory pathway[23]. It is known that DM disrupts normal endothelial function[24]. It has been reported that endothelial dysfunction is associated with HTB[25]. In our study, in patients with HTB, FBG was higher compared to patients with LTB. Additionally, in our study, increased glucose levels were demonstrated to be an independent predictor of HTB in patients with AMI. Previously, oxidized LDL-C has been shown to be associated with a HTB[26]. In our study, LDL-C levels were higher in patients with HTB and increased LDL-C levels were an independent predictor of thrombus burden.

Large intracoronary thrombus has been demonstrated in 16.4% of patients with AMI[27]. It is known that even though the existence of effective antiplatelet, the intracoronary thrombus is a risk factor for adverse cardiovascular events[12]. The duration of dual antiplatelet therapy requires a careful evaluation of the balancing between ischemia risks and bleeding risk for individual patients.

Study Limitations

Our study has several limitations. The study was designed retrospective, single-centre and the sample size was small. The absence of intravascular medical imaging modalities restricted our information on the thrombus burden size.

Conclusion

The DAPT score is a practical score system to guide DAPT duration, accounting for both ischemic risk and bleeding risk factors. Considering the increasing number of patients with acute coronary syndromes, prediction of thrombus burden through a simple and practical scoring system may be of benefit.

Ethics

Ethics Committee Approval: This study was approved by the Ankara City Hospital Ethics Committee (approval number: E1-22-2362).

Informed Consent: Informed consent was obtained from all individual participants included in the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Çakmak Karaaslan Ö, Design: Çakmak Karaaslan Ö, Data Collection or Processing: Çakmak Karaaslan Ö, Özilhan MO, Çöteli C, Analysis or Interpretation: Çakmak Karaaslan Ö, Özilhan MO, Çöteli C, Literature Search: Çakmak Karaaslan Ö, Maden O, Selçuk H, Selçuk MT, Writing: Çakmak Karaaslan Ö, Özilhan MO, Çöteli C.

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Research Article

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Are the Treadmill Test Results Reliable in Terms of Diagnosis when Performed Using a Surgical Mask?

Fatih Aydın

Eskişehir City Hospital, Clinic of Cardiology, Eskişehir, Turkey

Abstract

Objectives: Mask use plays a substantial role in reducing the spread of coronavirus disease-2019 in confined spaces. However, the use of masks is controversial in cases where intense effort is required, such as in the treadmill exercise test. In this study, the diagnostic reliability of the treadmill exercise test performed using a mask was questioned.

Materials and Methods: Two groups (with and without mask) were compared concerning various characteristics to assess diagnostic reliability and safety.

Results: The diagnostic reliability test performed using a mask was found to be similar to that of tests performed without a mask.

Conclusion: The treadmill exercise test performed by wearing surgical masks results is reliable for diagnosis.

Keywords: COVID-19, exercise treadmill testing, masks, sport

Introduction

The World Health Organization (WHO) declared coronavirus disease-2019 (COVID-19) as a pandemic on March 11, 2020, which was coincidentally also the date on which the first confirmed COVID-19 case was reported in Turkey[1,2]. Since this new type of Severe Acute Respiratory Syndrome virus is transmitted by droplets, the importance of covering the mouth/nose with masks was emphasized[2-4]. Using a mask while exercising, particularly during intense exercise, may cause some problems and WHO currently recommends that a mask should not be worn while exercising[5]. However, there are situations where exercise is necessary even during the pandemic period, such as in the treadmill exercise test.

Address for Correspondence: Fatih Aydın, Eskişehir City Hospital, Clinic of Cardiology, Eskişehir, Turkey
e-mail: drfatihaydin@hotmail.com **ORCID:** orcid.org/0000-0002-1017-1917
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In young individuals and athletes, various studies have shown that it is quite safe to exercise while wearing surgical masks covering the mouth and nose. However, this issue is still controversial, especially in subjects with advanced age-who represent most population in whom the treadmill exercise test is performed[6,7]. The safety of exercise has not been confirmed in this patient group when masks are used. The predicted risks include carbon dioxide retention and slight reduction in oxygen saturation with intense exercise[8].

This study was therefore conducted to answer this question: Are effort tests in patients wearing masks reliable in terms of the accuracy of test results?

Materials and Methods

The study was approved by the Eskişehir Osmangazi University Non-Interventional Clinical Research Ethics Committee Presidency (approval number: 2020-441, date: 03.11.2020).

Study Design and Subjects

Patients older than 18 years who were admitted to the cardiology outpatient clinic of a tertiary healthcare institution between February 2020 and March 2020 and were scheduled for a treadmill exercise test due to a suspicion of ischemic heart disease were enrolled in the study consecutively. All patients who underwent a treadmill exercise test during this period were included in the study. Patients whose complaints were not recorded in the outpatient files after the effort test, and those with artefacts that prevented the accurate evaluation of the treadmill exercise test were excluded from the study. Since the first cases of confirmed COVID-19 were seen in our country (Turkey) on March 11, 2020, it was decided by the cardiology department of our hospital that both the patient and the healthcare professionals who performed the test would use a surgical mask while treadmill exercise tests were performed. As of this date, all 169 patients who underwent the treadmill exercise test and healthcare professionals who performed the test used surgical masks throughout the procedure. In the tests conducted before this date, no masks were used.

The patients were divided into two groups concerning mask wearing. The complaints and complications of the patients during the effort test and their test results were examined, and the two groups were compared in terms of clinical characteristics. The demographic information, chronic diseases and complaints of the patients during the effort test were taken from the digital database of the hospital and clinical files. Additionally, coronary angiography data of patients who underwent the procedure due to having a positive effort test result was obtained from patients' file records.

Treadmill Exercise Test

Patients were informed not to eat and smoke for at least three hours before the examination, and they were instructed to stop any drug that would affect the test result, such as beta blockers, calcium channel blockers, digoxin, s anti-arrhythmic drugs and nitrate, for at least three days before the examination. Treadmill exercise testing was performed in a regular fashion in the routine laboratory; all tests were supervised by a trained member of the healthcare staff. Heart rate and blood pressure were monitored throughout the exercise and patient was monitored for any symptoms, such as chest pain, shortness of breath, fatigue, dizziness or nausea. We applied the Bruce protocol for treadmill exercise test. Duke Treadmill Score (DTS) was performed to assist the risk assessment of patients who had undergone a treadmill exercise test. Scores may vary from +15 to -25. A score ≥5 means low risk, while a score less than or equal to 11 means high risk[9]. Patients with a low-risk estimation were referred for additional risk stratification with imaging methods. Chest pain that developed during the exercise test was classified with the Diamont chest pain classification[10].

Coronary Angiography

Coronary angiography was performed in patients with moderate and high DTS risk if the suspicion of coronary artery disease persisted clinically. The patients

were divided into 3 groups according to the coronary angiography results. Lesions that would cause more than 50% stenosis in the LMCA in coronary arteries of 2 mm or greater, or more than 70% in other vessels, were defined as having critical stenosis of the coronary artery. Those with relatively less-severe lesions with slow coronary flow were considered to have non-critical coronary artery stenosis. Finally, those with no lesions or plaques were considered to have normal coronary arteries. Patients with a positive effort test and those with critical and non-critical coronary stenosis were considered to have coronary artery disease.

Statistical Analysis

All analyses were performed on SPSS v21 (SPSS Inc., Chicago, IL, USA). Histograms and Q-Q plots were used to determine whether variables were normally distributed. Data are given as mean ± standard deviation or median (minimum-maximum) for continuous variables according to the normality of distribution, and as frequency (percentage) for categorical variables. Normally distributed variables were analyzed with the independent samples t-test. Non-normally distributed variables were analyzed with the Mann-Whitney U test. Categorical distributions were analyzed chi-square tests, including the Fisher's exact test when necessary. The between-group comparisons of the diagnostic performance of the treadmill effort test were performed using the two-proportions Z-test. Two-tailed p-values of less than 0.05 were considered statistically significant.

Results

We included 314 patients (128 females and 186 males) into our study, mean age was 48.67±12.66 (range 18-82) years. There were no significant differences between the groups concerning age, gender, height, weight, body mass index, smoking, alcohol usage, comorbidities and ejection fraction (Table 1).

One hundred and sixty-three (96.45%) patients reached the target heart rate in the mask-wearing group and 139 (95.86%) patients reached the target heart rate in the non-mask group (p=1.000). There were no significant differences between the groups concerning stage, MET, time, systolic blood pressure and diastolic blood pressures (Table 2).

Table 1. Summary of patients characteristics with regard to groups

	Mask during test		
	Present (n=169)	**Absent (n=145)**	**p-value**
Age	49.11±13.13	48.14±12.11	0.500
Gender			
Female	67 (39.64%)	61 (42.07%)	0.663
Male	102 (60.36%)	84 (57.93%)	
Height	167.29±8.87	166.79±9.17	0.622
Weight	77.60±12.10	75.66±12.01	0.157
Body mass index	27.75±4.07	27.22±3.96	0.241
Smoking status	71 (42.01%)	68 (46.90%)	0.385
Alcohol usage	21 (12.43%)	17 (11.72%)	0.849
Hypertension	66 (39.05%)	50 (34.48%)	0.403
Diabetes mellitus	15 (8.88%)	9 (6.21%)	0.500
Coronary artery disease	24 (14.20%)	20 (13.79%)	1.000
Cerebrovascular disease	2 (1.18%)	3 (2.07%)	0.665
Ejection fraction	60 (55-66)	60 (55-66)	0.351

Data are given as mean ± standard deviation or median (minimum-maximum) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables

Thirty-eight patients underwent coronary angiography in the mask-wearing group, 22 (57.89%) patients had normal results, 8 (21.05%) patients were defined to have non-critical stenosis and 8 (21.05%) patients had critical stenosis. In the non-mask group, 31 patients underwent coronary angiography, which revealed that 19 (61.29%) patients had normal results, 3 (9.68%) patients had non-critical and 9 (29.03%) patients had critical stenosis (p=0.395). The positive predictive value of the treadmill exercise test was 42.11% [95% confidence interval (CI): 26.41% -57.80%] in the mask-wearing group, while it was 38.71% (95% CI: 21.56% -55.86%) in the non-mask group (p=0.775). The false positive rate was 14.38% (95% CI: 8.82% -19.94%) in the mask-wearing group and 14.29% (95% CI: 8.34% - 20.23%) in the non-mask group (Table 2).

Concerning symptoms during the test, we found that 59 (34.91%) patients in the mask-wearing group and 31

Table 2. Summary of the treadmill stress test and coronary angiography results and treadmill stress test performance according to coronary angiography results

	Mask during test		
	Present (n=169)	**Absent (n=145)**	**p-value**
Target heart rate			
Not reached	6 (3.55%)	6 (4.14%)	1.000
Reached	163 (96.45%)	139 (95.86%)	
Stage			
2	21 (12.43%)	15 (10.34%)	0.683
3	58 (34.32%)	56 (38.62%)	
4	55 (32.54%)	50 (34.48%)	
5	35 (20.71%)	24 (16.55%)	
Treadmill stress test results			
Not evaluated	2 (1.18%)	2 (1.38%)	0.966
Negative	128 (75.74%)	110 (75.86%)	
Low risk	1 (0.59%)	2 (1.38%)	
Medium risk	27 (15.98%)	22 (15.17%)	
High risk	11 (6.51%)	9 (6.21%)	
MET	13.4 (4.8-16.9)	13.4 (4.8-16.9)	0.712
Time	9.10±2.16	9.39±2.13	0.240
Systolic blood pressure (i)	129.08±13.27	128.11±13.34	0.519
Diastolic blood pressure (i)	78.85±8.61	78.89±8.77	0.965
Systolic blood pressure (f)	156.04±21.72	152.27±19.99	0.113
Diastolic blood pressure (f)	88.62±11.88	87.28±11.48	0.310
Coronary angiography			
Normal	22 (57.89%)	19 (61.29%)	0.395
Non-critical	8 (21.05%)	3 (9.68%)	
Critical	8 (21.05%)	9 (29.03%)	
Treadmill stress test performance			
Positive predictive value	42.11%	38.71%	0.775
False positive rate	14.38%	14.29%	0.982

Data are given as mean ± standard deviation or median (minimum-maximum) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables

(21.38%) patients in the non-mask group had shortness of breath during the treadmill exercise test, indicating a significant difference between the groups in this respect (p=0.008). However, there were no significant differences between the groups concerning the presence of dizziness, nausea, syncope and chest pain during the test (Table 3).

Supraventricular tachycardia, ventricular tachycardia and bradyarrhythmia were not observed in either group during exercise or recovery phases. Three patients aged 82 years old who underwent a treadmill exercise test with a mask did not have syncope, shortness of breath, dizziness and chest pain to end the test. In the mask-wearing group, there were 68 patients who ran more than 14 mets and the test was completed safely (Figures 1-3).

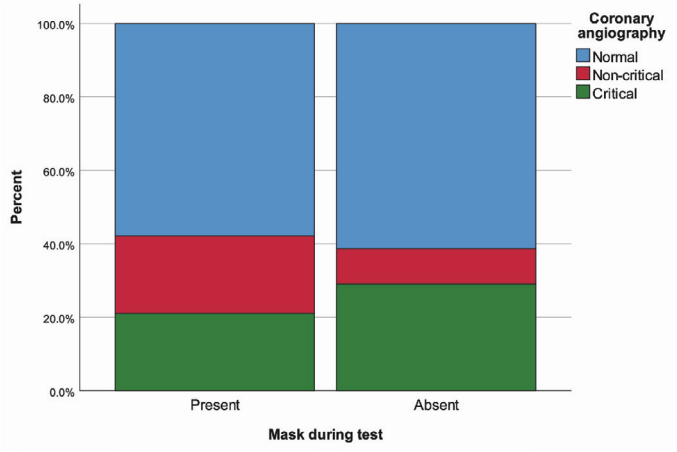

Figure 1. Coronary angiography results

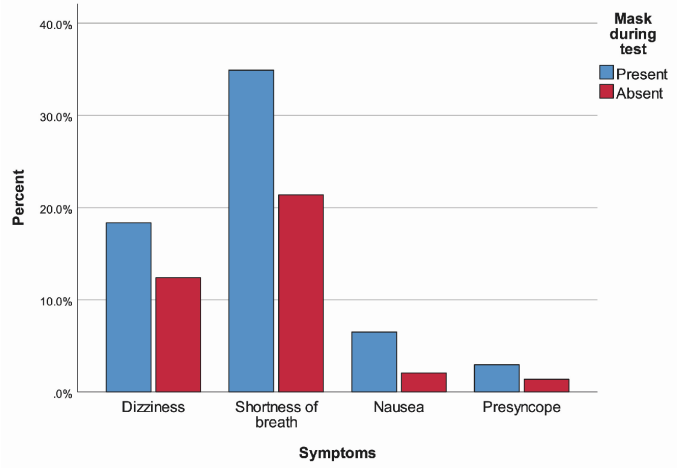

Figure 2. Symptoms during the treadmill stress test

Discussion

This study showed that the treadmill exercise test performed results with a surgical mask are reliable in the evaluation of ischemic heart disease compared with non-mask treadmill exercise tests, as demonstrated by similar outcomes in diagnostic results. Although we observed that the mask-wearing group had significantly higher frequency of shortness of breath, and some insignificant but appreciable increases in other symptoms, it appears that performing the treadmill exercise test with a mask remains a viable option because of similar safety and reliability with the usual, non-mask test. However, since the number of patients included in the study was small, it was not correct to conclude about the safety of performing the treadmill effort test with a mask.

Although there are reports in the media about deaths after intense exercise with masks[11], studies conducted on young athletes discussing the effects and safety of exercising with masks have not reproduced such findings[6,7]. Due to the lack of evidence about the reliability of the treadmill exercise test performed using a mask, the guidelines published by the Cardiovascular Imaging Council of the American College of Cardiology suggested that stress tests should be performed via pharmacological means if possible; however, if impossible, patients may undergo the effort test while wearing a mask[12]. In nuclear medicine practices, it is recommended to avoid effort testing and

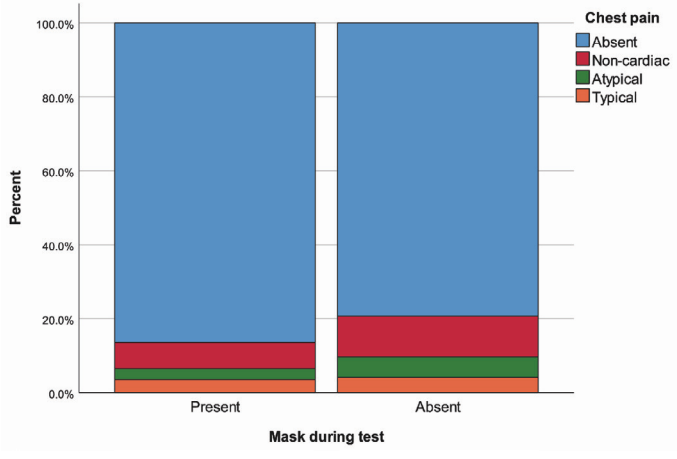

Figure 3. Chest pain during the treadmill stress test

Table 3. Summary of symptoms during the treadmill stress test

	Mask during test		
	Present (n=169)	**Absent (n=145)**	**p-value**
Dizziness	31 (18.34%)	18 (12.41%)	0.198
Shortness of breath	59 (34.91%)	31 (21.38%)	0.008
Nausea	11 (6.51%)	3 (2.07%)	0.104
Syncope			
Presyncope	5 (2.96%)	2 (1.38%)	0.458
Syncope	0 (0.00%)	0 (0.00%)	
Chest pain			
Non-cardiac	12 (7.10%)	16 (11.03%)	0.372
Atypical	5 (2.96%)	8 (5.52%)	
Typical	6 (3.55%)	6 (4.14%)	

Data are given as frequency (percentage) for categorical variables

to use protective equipment if it is necessary[13]. In this study, it was observed that mask-wearing individuals had no major differences from non-mask individuals in terms of the results, test-related symptoms.

The use of masks may cause various complaints, such as headache, fatigue, difficulty in concentration, decreased exercise tolerance, nausea, and increased heart rate[14,15]. In our study, it was found that the shortness of breath was more common in those that underwent the test while wearing masks. The shortness of breath was not severe enough to end the test, and all individuals with shortness of breath could continue the test until the target heart rate and MET value were reached or the test was completed. Non-cardiac chest pain was not severe and the two groups were again similar. The pain felt by patients after the treadmill test was almost always identified as muscle ache. Even if not statistically significant, dizziness and nausea were seen a little more in mask-wearing individuals compared to the non-mask group. We thought this situation might result from carbon dioxide retention and the possibility that increased moisture in the mask (due to sweating and strong inspiration).

One of the most important concerns with the treadmill exercise test is the possible problems in the reliability of the test. Using a mask during a short workout at an intensity of 6-8 METS reduces SO_2 by 3.7% and increases the CO_2 concentration by 20%. CO_2 increases to a greater degree in some mask models during exercise, and this may be uncomfortable and symptomatic for some subjects[16]. These symptoms may be mistakenly considered angina or dyspnea equivalent to angina and could cause erroneous DTS characterization. The treadmill exercise test is based on the principle of vasodilatation of coronary vessels and insufficient blood supply to ischemic vessels. Therefore, naturally, another question at this point arises does this clinically insignificant hypoxia and hypercarbia affect the test result? In our study, coronary artery disease was detected in only 12 of 31 patients in the non-mask, and 16 of the 38 patients in the mask-wearing group. There was no significant difference between the two groups in terms of the accuracy of the effort test in correctly detecting ischemia. This led us to the conclusion that the reliability of the stress test did not change with the use of a mask.

Study Limitations

Our study had some limitations. Since the study was retrospective, the researchers could not question whether the symptoms occurring during the test were directly associated with mask use or not. Since the number of patients included in the study was not enough, it does not give us certain information about the safety of treadmill effort, although it gives us some ideas about exercising with a mask[17].

Significant findings have shown that all patient groups can continue these activities by using masks in places such as physical therapy centers and gyms. Since there is evidence that cloth masks also reduce virus spread[18-20], the risk of COVID transmission can be reduced using a cloth mask in patients who cannot tolerate the surgical mask.

Conclusion

With this study, it has been shown that the treadmill exercise test results are reliable in patients wearing a mask.

Ethics

Ethics Committee Approval: The study was approved by the Eskişehir Osmangazi University Non-Interventional Clinical Research Ethics Committee Presidency (approval number: 2020-441, date: 03.11.2020).

Informed Consent: Since this is a retrospective study, informed consent was not obtained from the patients.

Peer-review: Externally peer-reviewed.

Financial Disclosure: The author declared that this study received no financial support.

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Research Article
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Post-COVID-19 Exercise Stress Test

Şahbender Koç

Ankara Atatürk Sanatorium Training and Research Hospital, Clinic of Cardiology, Ankara, Turkey

Abstract

Objectives: Atypical chest pain, fatigue, and palpitations can be seen in post-coronavirus disease-2019 (COVID-19) period. With the hypothesis of explaining these complaints, we evaluated the exercise stress test (EST) parameters in COVID-19 patients with mild disease.

Materials and Methods: Between the ages of 30-50 years, who had mild COVID-19 in the last 3-9 months, were taken as the COVID-19 group [n=80, male/female (M/F): 40/40]. A total of 160 patients were included, of which age and gender matched 80 patients (M/F: 40/40) without COVID-19 were the control group. During the EST, baseline heart rate HR1(beats/min), baseline systolic, diastolic blood pressure (mmHg) (SBP_1, DBP_1), maximum blood pressures (SBP_{max}, DBP_{max}), and blood pressure changes (ΔSBP, ΔDBP) were recorded. As EST parameters, Duke score, exercise time (min), ST change (mm), exercise capacity (METs), maximum reached HR (% beats/min), distance walked (m), maximum oxygen consumption amount ($VO2_{max}$ mL/kg/min), rate pressure product (RPP mmHg/min/1000), and heart HR recovery 1 (HRR_1 beats/min) was used.

Results: In the COVID-19 group, baseline HR_1, SBP_1, DBP_1, SBP_{max}, DBP_{max}, ΔSBP, ΔDBP, $VO2_{max}$, and RPP were higher, while distance walked and HRR_1 were less. There was no difference between the two groups in terms of Duke score, exercise duration, ST change and exercise capacity.

Conclusion: The fact that the exercise capacities in the COVID-19 group were similar to those in the control group, but there was a difference in the changes in heart rate and blood pressure, RPP, HRR1 suggested that the autonomic system might be affected.

Keywords: Post-COVID-19, exercise stress test, heart rate, blood pressure, heart rate recovery

Address for Correspondence: Şahbender Koç, Ankara Atatürk Sanatorium Training and Research Hospital, Clinic of Cardiology, Ankara, Turkey
e-mail: sahbenderkoc@hotmail.com **ORCID:** orcid.org/0000-0002-6437-0903
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Introduction

Atypical chest pain, fatigue, and palpitations can be found in patients who have had coronavirus disease-2019 (COVID-19)[1]. These complaints resemble those in patients with suspected coronary artery disease. Exercise stress testing (EST) is mainly used to estimate the probability of coronary artery disease in the presence of chest pain and to determine exercise capacity or to monitor for palpitations upon exertion[2].

Exercise is associated with an increase in sympathetic tone and skeletal blood flow, but a corresponding decrease in peripheral resistance is found. With exercise, an increase in systolic blood pressure up to a maximum of 230 mm high is expected, while diastolic blood pressure increases or decreases by 10 mm high. When activated, the sympathetic nervous system simulates an increase in energy expenditure and controls cardiovascular responses during exercise. Additionally, norepinephrine and epinephrine have effects on metabolism and hormone secretion, which are important during exercise[3,4]. Changes in the autonomic system during exercise are regulated by neural mechanisms, including central brain command, exercise pressure reflex, a negative feedback mechanism originating from the carotid sinus and aortic arch, cardiopulmonary baroreceptors, and arterial baroreflex, all working together[5].

It has been shown that coronaviruses can travel in a retrograde manner from mechanoreceptors and chemoreceptors in the lungs and lower airways to the autonomic center in the brainstem via synaptic connections, potentially contributing to respiratory failure[6].

Post COVID-19 syndrome has been defined relatively recently and includes a wide spectrum of signs and symptoms. Symptoms, including functional limitations, orthostatic and exercise intolerance, may persist for more than several months in more than 50% of patients[7]. In this study, EST parameters in COVID-19 patients with mild disease were evaluated according to the hypothesis that the described complaints can be explained.

Materials and Methods

Inclusion Criteria

In the study, those who presented to the hospital with at least one of the above-described complaints, did not have a known systemic disease and cardiac family history, did not smoke, did not drink alcohol, did not take any medication, were aged 30-50 years, and had mild COVID-19 in the last 3-9 months, were taken as a COVID-19 group [(n=80, M/F)=40/40]. Including a control group (n=80, M/FM=40/40) without COVID-19, 160 subjects were recruited.

These subjects who had similar mean ages, body mass index (BMI), and ideal physical activities for the last six months were included in both groups. The ideal physical activity was classified as greater than or equal to 150 min of moderate-intensity, ≥75 min of vigorous physical activity per week, or greater than or equal to 150 min of moderate-to-vigorous physical activity per week[8].

Exclusion Criteria from the Study

Patients with known systemic disease, hospitalized for inpatient treatment, suspicious findings on chest X-ray, laboratory values out of normal limits, smoking, taking alcohol or any medication, not undertaking an ideal physical activity, and who were not in the same age group were excluded from the study.

During the disease in the COVID-19 group, chest computed tomography (CT) scans were normal, and laboratory values were within the definition of the mild disease group[9]. During the study, no cardiac and pulmonary pathologies were detectable based on echocardiography, electrocardiography (ECG), troponin, and chest X-ray in both groups. Echocardiography (GE Vivid n70, Horten, Norway) was performed using a standard 2D probe. Image interpretation was based on the right and left cardiac chamber structure, size and function and evaluated in accordance with current European Association of Cardiovascular Imaging guidelines[10].

Systolic and diastolic functions were normal.Laboratory data were within normal limits. .

Laboratory Parameters

In the COVID-19 group during illness and in the control group during the study, glucose, hemoglobin, creatinine, leukocyte, lymphocyte, sedimentation, dimer, fibrinogen, ferritin, C-reactive protein (CRP), and troponin levels were recorded.

COVID-19 had not been categorised as a variant of concern or a variant under investigation. The study duration was 6 months.

Ethical approval was obtained from the Ankara Keçiören Training and Research Hospital was received before starting the study (23.9.2020/2172). After receiving informed consent forms from the participants, a treadmill EST was applied according to the protocol described below.

Treadmill Exercise Stress Test

Tests were performed according to the Bruce protocol using the full vision 3017-TMX425 device. An estimated peak heart rate was 220-patient age. Even if 85% of the estimated maximum heart rate was reached, exercise was continued until symptoms appeared. The patient's symptoms, exercise workload in metabolic equivalents (Mets) were recorded during each phase and recovery phase. Heart rate was measured at each minute of exercise, at maximum exercise, and at 1-5 min (in 1 min increment) while standing after the start of the recovery period. Criteria for completion were fatigue, chest pain, severe palpitations, and/or an increase in heart rate above the maximum predicted for patient age. After peak exercise, participants walked during a two-minute cool-down period. At the end of exercise, heart rate recovery (HRR) was defined as maximum heart rate minus heart rate within the specified period, which represented the decrease in heart rate.

Exercise testing was performed, analyzed, and reported using a computerized database and a standard protocol. In this study, all tests were terminated due to fatigue.

During the exercise test, baseline resting heart rate (HR_1 ,expressed as beats/min), systolic and diastolic baseline blood pressure [SBP_1 and DBP_1(mmHg) respectively], maximum blood pressures [SBP_{max} and DBP_{max}(mmHg) respectively], and blood pressure changes (ΔSBP, ΔDBP) were recorded.

Exercise Stress Test Parameters

Duke score: [exercise time (min)-5ST change (mm)-4^{th} angina index], exercise time (min), ST change (mm), exercise capacity or workload (Mets), maximum reached the heart rate (MrHR) expressed as (% beats/min), distance walked (m), maximum oxygen consumption amount (VO_{2max}) expressed as mL/kg/min=15 x (HR_{max}/HR_{rest}), double product or rate pressure product (RPP) expressed as mmHg/min/1000=max HR x max SBP/1000, and HRR_1 expressed as beat/min=heart rate decreasing in 1 min (normal: >12) during the recovery period were used.

Statistical Analysis

Data analysis was performed using the IBM SPSS Statistics version 17.0 software (IBM Corporation, Armonk, NY, USA). Whether the distributions of continuous variables were normal or not was determined by Kolmogorov-Smirnov test. Categorical data were given as number (n) and percentage (%), while quantitative data were given as mean ± standard deviation and median (25^{th}-75^{th}) percentile. Pearson's chi-square test was used for the analysis of categorical data unless otherwise stated. A Student's t-test was used when the mean differences between groups were compared, and the Mann-Whitney U test was used to compare continuous variables for which otherwise parametric test assumptions were not met.

The effects of independent variables that may affect the ETS parameters that differ between the COVID-19 and control groups were examined using the "Linear regression and General Linear Model Analysis methods". The ETS parameters are defined as the dependent variables. Independent variables for which we observed

significant effects in different groups were determined. The direction and magnitude of the relationship between each independent variable and the dependent variable within groups were determined by B (Constant), and beta (coefficient of variation). The degree of influence of the independent variable within the group was determined by F (analysis of variance value) and R^2 (Partial Eta Sq) values. P-values were considered significant at the 0.05 level.

Results

Baseline Characteristics

The COVID-19 group was not hospitalized, had the disease of a median of six months [interquartile range (IQR): 5-7 months] before the study period started, and recovery from illness was a median of 13.5 (IQR: 12-14) days. Equally, in both groups, one-half of the patients (n=80) had atypical chest pain, one-quarter (n=40) had fatigue, and one-quarter (n=40) had palpitations. The main characteristics of the groups are shown in Table 1.

Between the two groups, mean baseline HR_1 was higher in the COVID-19 group. Differences between baseline SBP_1, DBP_1 and SBP_{max}, DBP_{max} in the COVID-19 and control groups, respectively, were found. The amount of blood pressure change (Δ) was higher in the COVID-19 group.

No differences between the two groups in terms of Duke score, exercise duration, ST change, and exercise capacity were found.

Differences between the groups in terms of MrHR, distance walked, VO_{2max}, RPP, and HRR_1 were found as shown in Table 2.

Gender Differences

In men (COVID-19 versus control), differences, such as ΔSBP (mmHg): (35.3±12 versus 28±15.8; p=0.022), DBP_{max} (mmHg: 80.7±9.8 versus 73.2±8; p=0.000), ΔDBP [mmHg: 4 (1-6.7) versus 0 (-3-5); p=0.004], no difference in terms of EST parameters were observed.

In women, differences were determined as HR_1 (beats/min) 85.9±11.6 versus 79.4±10.1 p=0.009, SBP_{max} (mmHg): 147 (142.7-154) versus 141 (135.5-151); p=0.018, DBP_1 (mmHg): 77.3±5.8 versus 72.6±7.9; p=0.003, DBP_{max} (mmHg): 78.4±6.6 versus 72.1±7.8;

Table 1. Comparison of baseline characteristics in coronavirus disease-2019 (COVID-19) and control groups

Variables	COVID-19 group (n=80)*	Control group (n=80)	p-value
Age (years) median (IQR)	37,5 (34-40)	35 (32-41)	0.502†
Female/male (n,%)	40/40 (50%)	40/40 (50%)	1‡
BMI (kg/m²)	27 (25.6-28.6)	26.5 (24.6-28.8)	0.152†
Glucose (mg/dL)	88.5 (83-95)	86.5 (83-94)	0.623†
Hemoglobin (gm/dL)	12.6 (11.7-13.5)	13.05 (11.7-13.5)	0.597†
Creatinine (gm/dL)	0.84 (0.68-0.87)	0.82 (0.71-0.88)	0.882†
Leukocytes (μL)	9.4 (8.5-9.8)	5.6 (4.8-6.3)	0.000†
Lymphocyte (μL)	1.2 (0.8-1.3)	1.3 (1.2-1.4)	0.000†
Sedimentation (mm/h)	16 (13.2-24)	5.3 (4.5-6.3)	0.000†
D-dimer (ng/mL)	321 (256-420)	180 (140-217)	0.000†
Fibrinogen (mg/dL)	323.5 (250-387)	230 (210-286)	0.000†
Ferritin (ng/mL)	269.5 (212-335)	123.5 (110-132)	0.000†
CRP (mg/L)	12.4 (9.5-13.5)	5.4 (3.4-6.5)	0.000†
hsTroponin (ng/mL)	7.6 (5.8-9.4)	3.2 (2.3-5.3)	0.000†

**COVID group blood was taken during the infection,*
BMI: Body mass index, IOR: Interquartile range, †Mann-Whitney U test, ‡Chi-square test, CRP: C-reactive protein

p=0.000, MrHR (% beats/min): 89.5 (86.2-92) versus 87 (85-90); p=0.009, exercise capacity (Mets): 13.5 (10.2-13.5) versus 13.2 (10.2-13.5); p=0.307, distance walked (m): 694±130 versus 817±166; p=0.000, RPP (mmHg/min/1000): 17.800 (14.525-20.625) versus 12.400 (11.340-18.300); p=0.01, HRR_1 (beats/min): 25.8±5.29 versus 28.9±5.19; p=0.009.

Regression and General Linear Model Analyses

In the regression and general linear model analyses, troponin in men and sedimentation in women was shown to have negative effects on walking distance in the COVID-19 group, while initial SBP had a positive effect in women in the control group.

It was determined that troponin in the COVID-19 group and especially creatinine in the control group, had a negative effect on HRR_1.

CRP and maximum SBP were found to have a negative effect on HR_{max} in women with COVID-19.

The independent variables that had a significant effect on the EST parameters and their explanation rates on the dependent variable are given in Table 3. In both groups, chest pain, positivity test, and insufficient test efforts were not detected during EST.

Ventricular extrasystole [8 (10%) versus 6 (7.5)] and atrial extrasystole [10 (12.5%) versus 8 (10%)] were detected in both the COVID-19 and control groups. Exercise test positivity was not detected, so we could not make the decision of coronary angiography.

Discussion

In this study, in patients aged 30-50 years with no known systemic disease and who had recovered from a mild COVID-19 infection, the mean HR at the beginning

Table 2. Comparison of heart rate, blood pressure, exercise stress testing parameters of COVID-19 and control groups

Heart rate-blood pressure parameters	COVID-19 group (n=80)	Control group (n=80)	p-value
HR_1 (beat/min)	86.3±12	82.4±11.7	**0.04***
SBP_1 (mmHg)	120 (114-125)	117 (110-124)	**0.045†**
SBP_{max}	150 (145-154)	145 (138-152)	**0.008†**
ΔSBP	33.5±11.9	28.2±14.6	**0.013†**
DBP_1 (mmHg)	77.5 (72-80)	73 (68-80)	**0.003†**
DBP_{max}	79.5±8.4	73.2±8	**0.000***
ΔDBP	2 (-1-6)	0 (-3-5)	**0.019†**
EST parameters			
Duke score	7.6 (6.4-8.7)	8.1 (6.5-8.8)	0.527†
Exercise time(min)	9.1±1.5	9.1±1.7	0.816*
ST change (mm)	0.3 (0.2-0.4)	0.3 (0.2-0.4)	0.336†
Exercise capacity (METs)	10.2 (10.2-13.5)	13.5 (10.2-13.5)	0.171†
Mr. heart rate (%)	89.2±3.5	87.8±3.2	**0.012***
Distance walked (m)	672±148	731±192	**0.031***
$VO2_{max}$ (mL/kg/min)	36 (35.7-47.3)	35.7 (35.7-47.3)	**0.013†**
RPP (mmHg/min/1000)	18.250 (14.570-21.225)	15.800 (11.550-19.500)	**0.027†**
HRR (beat/min)	27.3±5.5	29.5±6.3	**0.024***

**Mean ± standard deviation *Student's t-test (Std), †Mann-Whitney U test, Δ: Change*
†median (interquartile range)
HR_1: Initial heart rate, max: Maximum, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, METs: Metabolic equivalents, MrHR: Maximum reached heart rate, Mr: Maximum reached $VO2_{max}$: Maximum oxygen consumption, RPP: Rate pressure product HRR1: Heart rate recovery, COVID-19: Coronavirus disease-2019

of the exercise test, the MrHR, the SBP/DBP and their changes upon effort, VO_{2max}, and RPP were higher than in the control group.

No differences between the two groups in terms of exercise duration, exercise capacity, and ST change were detected. The distance walked and the amount of HRR_1 were found to be less in the COVID-19 group. When compared with the control group, women in the COVID-19 group had greater MrHR, greater RPP, less distance walked, and less HRR_1. It was determined that women had more effective changes in EST parameters.

The fact that the lung CTs during the disease and radiographs during the study were normal in the COVID-19 group, thus caused us to move away from lung damage. When the absence of EST-positive patients due to ECG changes but with normal troponin values, absence of chest pain during exertion, and similar exercise durations are considered together, coronary and myocardial involvement that could explain the aforementioned complaints was not considered.

In the Bruce[11] protocol, exercise duration was associated with ventricular function. In these studies, the frequency of coronary disease decreased as the exercise duration increased in the ECG-positive test group[12]. In our study, the duration of exercise was found to be the same in both groups regardless of gender. The fact that the exercise capacity in the COVID-19 group was similar to that of the control group and that the heart rate increased with exercise are good indicators of cardiovascular disease[13-15]. However, the differences in heart rate and blood pressure changes suggest that there may be autonomic system involvement. An HRR_1 over 25 in the COVID-19 group may indicate that no significant autonomic imbalance exists; however, a lower HRR_1 decrease compared to the control group may indicate that this group does not have a good cardiovascular prognosis[16,17].

Table 3. Effects of independent variables on EST parameters

EST parameters	Group	n	Independent variables*	B†	95 CI%		Beta†	p-value	$R^{2‡}$
Distance walked (m)	**COVID-19, M**	40	Troponin	-21.79	-43.692	0.092	-0.303	**0.05**	0.186
	COVID-19, F	40	Sedimentation	-8.003	-15.081	-0.925	-0.390	**0.029**	0.228
			Ddimer	-0.495	-1.011	0.021	-0.347	**0.05**	0.175
	Control, F	40	Ddimer	-0.799	-1.568	-0.031	-0.430	**0.042**	0.175
			SBP_1	9.741	3.277	16.205	0.551	**0.005**	0.319
HRR1 (beat/min)	**COVID-19**	80	Troponin	-0.649	-1.151	-0.147	-0.304	**0.012**	0.100
	Control	80	Sedimentation	-0.696	-1.420	0.028	-0.249	**0.05**	0.058
			Creatinine	-14.42	-27.185	-1.669	-0.272	**0.027**	0.079
			HR_1	-0.131	-0.264	0.002	-0.243	**0.05**	0.061
MrHR (% beat/min)	**COVID-19, F**	40	CRP	-0.854	-1.535	-0.173	-0.597	**0.017**	0.264
			SBP_{max}	-0.199	-0.405	0.008	-0.456	**0.058**	0.233
	Control, F	40	Age	-0.223	-0.451	0.005	-0.358	**0.05**	0.164
			Fibrinogen	-0.018	-0.032	-0.003	-0.439	**0.017**	0.241
			SBP_{max}	0.122	-0.004	0.248	0.380	**0.05**	0.162
$VO2_{max}$ (mL/kg/min)	**COVID-19, M**	40	SBP_{max}	0.474	0.065	0.883	0.698	**0.026**	0.224
			DBP_{max}	0.559	-5.912	2.345	2.345	**0.046**	0.176
			HR_1	-0.289	-0.548	-0.036	-0.484	**0.021**	0.228
	Control, F	40	CRP	-1.54	-3.038	-0.051	-0.477	**0.043**	0.181

**CRP: C-reactive protein, SBP1: Baseline systolic blood pressure, HR1: Baseline heart rate, DBP1: Baseline diastolic blood pressure, SKB_{max}, DKB_{max}: Maximum systolic, diastolic blood pressure, COVID-19: Coronavirus disease-2019, M: Male, F: Female, MrHR: Maximum reached heart rate, CI: Confidence interval, †Linear regression, B: Constant, Beta: Coefficient of variation between dependent variable and independent variable, ‡General linear model, R^2 partial eta squared: Independent variable (within group) variance explanation rate (0.162:16.2%)*

COVID-19 can cause prolonged fatigue[1,18]. The decrease in the response of the heart muscle, which sometimes occurs after prolonged fatigue, may be manifested by a decrease in blood volume and accumulation of blood in the legs even after the situation returns to normal conditions. This phenomenon is called deconditioning[19]. Additionally, gender differences in the adaptation of innate and immune responses that influence the immunological response to pathogens can be found[20].

HRR_1 is defined as a reduction in heart rate, usually 1 min after cessation of exercise, and is an important indicator of all-cause mortality. HRR_1 is thought to indicate a reactivation of the parasympathetic nervous system with a reduction in the action of the sympathetic nervous system and possibly reduced circulating catecholamines[21]. It has been suggested that women have more parasympathetic impulses, less systolic volume, and lower cardiorespiratory condition than men. In one study, HRR was faster in women after exercise than in men. (4±1.1 beats per min, $p<0.001$)[22]. In our study, a decrease in heart rate was found in the normal range (>12) but less (25.8±5.29 versus 28.9±5.19; $p=0.009$) in women in the COVID-19 than in the control group.

RPP is the product of SBP and HR and is an indicator of myocardial oxygen consumption. SBP and HR have also been shown to be predictors of in-hospital mortality and long-term mortality[23,24]. HR and SBP are indicators of autonomic nervous system (ONS) functioning. An increase in RPP during stress indicates that ONS functions as normal buffering and good coronary perfusion[25]. However, conflicting studies on the efficacy of RPP[26,27]. Gender-related differences in RPP between the ages 35 and 54 were found to be low[28]. In our study, RPP was found to be higher in women with corona compared with the control group, and no change was found in men (18.690±4606 versus 17.963±4584; $p=0.481$).

The autonomic nervous system regulates functions that we do unconsciously control, such as HR, BP, sweating, and body temperature. COVID-19 may also increase sympathetic activity through changes in blood gases, angiotensin-converting enzyme imbalance, immune/inflammatory factors, or emotional distress apart from the contribution of comorbid diseases[29]. The potential immune/inflammatory effects of a sympathetic/parasympathetic imbalance may also play a role in the pathophysiology of COVID-19[30].

It has been found that prolonged or chronic COVID-19 affects women more than men, particularly in autonomic cardiovascular areas, such as orthostatic intolerance and inappropriate tachycardia. Most females have up to one-third less skeletal muscle mass than males and therefore have a less powerful "muscle pump" when standing have smaller hearts and are more prone to pelvic venous pooling[31,32]. Autoimmunity disorders, which are more common in women, may affect post-COVID-19 autonomic dysfunction and gender preference[33]. These probable reasons and increased sympathetic activity may partly explain the low distance traveled in women, high RPP, and low HRR.

Linear correlations were found between some parameters of heart rate variability (HRV) and laboratory indices in COVID-19 patients. It has been reported that in severe patients without improvement in HRV parameters, a longer time is needed to clear the virus and recovery[34]. In our study, the effects of troponin, sedimentation, and CRP on some parameters of the EST were found in some subgroups, as shown in Table 3.

Ten minutes after standing up, an increase in heart rate of more than 30 beats per minute for more than three months without orthostatic hypotension is defined as another sign of autonomic dysfunction under the name of long COVID-19 postural orthostatic tachycardia in those who have had COVID-19[35].

One year post-COVID, a study conducted in 22 patients with complaints similar to our study concluded that cardiac functions were not affected and complaints could not be attributed to underlying COVID-19 related cardiac disease[36].

In our study, it is possible that the higher blood pressure and heart HR values upon exertion in the COVID-19 group

were due to more increased sympathetic tone and less decrease in peripheral resistance. An abnormal elevation in blood BP during EST and recovery has been shown to be associated with an increased risk of developing hypertension in both men and women[37]. The reason for the relationship between hypertension and COVID-19 is still unclear[38].

Study Limitations

It is difficult to say whether the pre-test exercise capacities would be similar even if the participants' age ranges, BMI values, and weekly effort levels are the same. Chest radiographs were evaluated as normal. The sensitivity of chest radiographs in the diagnosis of COVID-19 (>11 days) has been reported as 79%[39].

Conclusion

As a result, after an average of six months, the effort capacity of those who had mild COVID-19 was similar to that of the control group. However, it was thought that the effect of exertion on HR and BP might be greater, and therefore, the autonomic system might be affected for a long time recovering from COVID-19. More comprehensive studies are needed for the reproducibility and clear analysis of the results.

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Ethics

Ethics Committee Approval: Ethical approval was received before starting the study from the Ankara Keçiören Training and Research Hospital Ministry of Health (approval no: 23.09.2020/2172, date: 11.06.2020).

Informed Consent: Informed consent form was obtained from the patients.

Peer-review: Externally peer-reviewed.

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Adem adar
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İsmail Yürekli
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Marko I. Turina
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