Journal of
Cardiology & Cardiovascular
Surgery

Original Article

DOI: 10.51271/JCCVS-0036

The relationship between exercise-related hypertension and carotid artery intima media thickness and brachial artery endothelial function

Mustafa Ağca[1], Mesut Karataş[2], Nuri Havan[3], Mehmet Yunus Emiroğlu[2]

[1]*Department of Cardiology, Bartın Yaşam Medical Center, Bartın, Turkiye*
[2]*Department of Cardiology, Koşuyolu Yüksek İhtisas Training and Research Hospital, İstanbul, Turkiye*
[3]*Department of Cardiology, Ataşehir Florance Nightingale Hospital, İstanbul, Turkiye*

Cite this article: Ağca M, Karataş M, Havan N, Emiroğlu MY. The relationship between exercise-related hypertension and carotid artery intima media thickness and brachial artery endothelial function. *J Cardiol Cardiovasc Surg.* 2024;2(3): 48-52

Corresponding Author: Mustafa Ağca, agca87@hotmail.com

Received: 08/09/2024 ◆ **Accepted**: 29/09/2024 ◆ **Published**: 30/09/2024

ABSTRACT

Aims: Hypertension is one of the most common chronic diseases in the world. There are some non-invasive tests which are used to assess end organ damages in patients with hypertension. The purpose of this study is to show relationship between carotid artery intima media thickness (CIMT) and flow mediated dilatation (FMD) in patients with exercise induced hypertension (EIH).

Methods: 73 healthy normotensive men and women, who are between 18 and 65 years of age, participated in this study. All patients underwent electrocardiography, echocardiography, 24-hour ambulatory blood pressure monitoring and symptom-limited treadmill testing before CIMT and FMD were measured with Doppler ultrasonography. CIMT and FMD values of both groups were statistically compared with each other.

Results: Of a total of 73 individuals, 56 were evaluated as the patient group and 17 as the control group. Age, smoking rate, body mass index, resting and maximum blood pressure values, and ascending aorta diameter were significantly higher in the patient group ($p=0.02$ for smoking, $p<0.01$ for the rest). Right/left main CIMT, right/left bulbus IMT, and left ventricular diastolic dysfunction was significantly higher in the patient group ($p<0.05$ for all). In addition, the mean CIMT and mean FMD (%) values were significantly higher and lower, respectively, in the patient group compared to the control group. No difference was observed between the two groups in terms of right/left internal CIMT and passive smoking exposure. In addition, the mean values of CIMT and FMD (%) did not show a statistically significant difference according to hypertensive response stages and gender.

Conclusion: CIMT and FMD are significantly associated with EIH. EIH should be evaluated as important risk factor for future hypertension and may cause asymptomatic end-organ damage. It can be easily assessed using CIMT and FMD.

Keywords: Exercise-induced hypertension, CIMT, FMD, hypertension

INTRODUCTION

Hypertension is the leading cause of cardiovascular disease and premature death worldwide. It is associated with heart disease, stroke, kidney disease, premature death and many organ failure, and although it is a disease that burdens societies both in terms of health and economy, it is a preventable and treatable disease thanks to new developments in today's health field.[1,2] Early diagnosis and treatment of hypertension is important in terms of preventing progressive complications of hypertension. In addition to the use of methods such as office blood pressure measurement, home blood pressure and ambulatory blood pressure measurement in the diagnosis of hypertension, the detection of asymptomatic organ damage is also important in terms of the prognosis of hypertension diagnosis and treatment.[3,4] Among these, carotid artery intima-media thickness (CIMT) and endothelial function are among the important parameters.[5]

The increase in blood pressure during exercise is physiologic. Especially systolic blood pressure increases more than diastolic blood pressure. However, in some patients, blood pressure may reach relatively much higher values during exercise. This is defined as exercise-associated hypertension. Although there is no consensus on any blood pressure threshold value that fits this definition, systolic blood pressure values of ≥210 mmHg in men and ≥190 mmHg in women have been generally accepted as exercise-induced hypertension (EIH) as a result of many studies.[6] The observation of excessive hypertensive response during exercise testing in some patients who are normotensive in clinical measurements has been the subject of many studies.[7] Although there are studies that emphasize EIH and its prognostic value, this issue has not yet been adequately included in the guidelines. There are also questions about EIH that remain to be investigated and answered.[7]

Therefore, we investigated the association of EIH with CIMT and brachial artery endothelial function in healthy young adult patients without known coronary artery disease, diabetes mellitus, hypertension, heart failure, arrhythmia, chronic renal failure and chronic obstructive pulmonary disease.

METHODS

Healthy young adult patients between 18 and 65 years of age without known cardiovascular disease, hypertension, arrhythmia, diabetes mellitus, chronic renal failure, and chronic obstructive pulmonary disease who were admitted to the Cardiology Clinic of Kartal Koşuyolu Yüksek İhtisas Training and Research Hospital were included in the study. All patients were informed about the study and informed consent was obtained. The study protocol was approved by the Kartal Koşuyolu Yüksek İhtisas Training and Research Hospital Ethics Committee (Date: 06.06.2018, Decision No 2018/5). All procedures were carried out in accordaance with the ethical rules and the principles of the Declaration of Helsinki.

Patients with mean blood pressure >140/90 mmHg, positive exercise test, major valvular pathology (moderate to severe stenosis or insufficiency) or left ventricular systolic dysfunction on transthoracic echocardiography were excluded. First, office blood pressures were measured manually using an endostall perfect aneroid sphygmomanometer and a 29-40 cm cuff in all volunteer patients who met the study criteria, and whose informed consent was obtained. Patients were seated in a resting position for 5 minutes before measurement. Then, the cuff was connected, and the sphygmomanometer was inflated while the arm was at the heart level and the hand was open. This procedure was repeated twice in both arms and two minutes apart.

Echocardiography was performed using a Philips Epiq 7c Cardiac Ultrasound device and S5-1 Purewave transducer probe. Ejection fraction (EF), valvular function, heart cavities, ascending aortic diameter, and presence of diastolic dysfunction were evaluated separately in each patient.

Exercise testing was performed using the cardiac science TM55 Treadmill device and in accordance with the Bruce protocol. A 12-lead ECG was recorded, and blood pressure was measured in the upright standing position in the resting state and the values were recorded. After the test started, ECG recordings were taken towards the end of each three-minute phase of the test and blood pressure values were noted. All patients who reached 14.8 METs in stage 4 without any problems during the test and whose heart rate reached 85% of the maximal heart rate were considered negative and the test was terminated. Stage 1 and stage 2 periods with mild to moderate exercise load in the exercise test were classified as the early period, while stage 3 and stage 4 with moderate to severe exercise load and recovery periods at the end of the test were classified as the late period.

Patients with normal office blood pressure values, no major valvular pathology and left ventricular systolic dysfunction on echocardiography, and negative exercise test results were subjected to 24-hour ambulatory blood pressure measurement to rule out masked hypertension and nocturnal hypertension. Patients with nocturnal or masked hypertension were considered as hypertensive patients and diet and drug treatment were started. These patients were also excluded from the study.

A total of 73 patients who met the criteria were included in the study. In the study, the threshold value for EIH was determined as 190 mmHg for both men and women. Patients with a systolic blood pressure of 190 mmHg and above were defined as the patient group and those with a systolic blood pressure below this value were defined as the control group.

CIMT and flow-mediated dilation (FMD) measurements were performed by an experienced radiologist in 73 patients. CIMT was measured in the supine position after at least 10 minutes of rest. Both common carotids, bulbus and internal carotid arteries were evaluated in detail. Measurements were performed using an ultrasonography device only on the posterior wall of the carotid artery and characteristic echogenicities of the lumen-intima and media-adventitia surfaces were utilized during the measurements. A CIMC value of 0.9 mm or more in any part of the carotid artery segments evaluated in detail was considered as focal intimal thickening. Segments with plaque or focal intimal thickening were also noted.

Patients were placed in resting and sitting position for FMD measurement. The arm of the dominant extremity was brought to the level of the heart. The procedure was started by measuring the basal brachial artery diameters. During the measurement, the moment when the artery was widest in the post-systolic pulse wave was taken into consideration ultrasonographically. Careful attention was paid to the presence of anatomical early segmentation in the area of measurement, and in patients with early segmentation, measurements were performed from the proximal part of the brachial artery. The diameter of the brachial artery was measured between the anterior and posterior adventitia walls (outside to outside). After baseline brachial artery diameters were measured, the cuff of the endostall perfect aneroid sphygmomanometer, which was previously used for office blood pressure measurement, was placed on the forearm of the dominant limb of the patients and the sphygmomanometer was inflated to approximately 250 mmHg. A stopwatch was used for 5 minutes, and the sphygmomanometer was deflated at the end of the time. After waiting 60 seconds, the brachial artery diameter was measured again on the same spot where the basal diameter of the brachial artery was measured. This value was recorded as the diameter after hyperemia. At the end of the procedure, the FMD values of all patients were calculated and recorded as percentages using the formula [FMD=(post-hyperemia diameter-basal diameter)/basal diameterX100].

Statistical Analysis

Before analyzing the data, the presence or absence of outliers in the CIMT and FMD values among patients was examined by creating box plots. In the next step, the distribution of CIMT and FMD data was analyzed by Kolmogorov-Smirnov and Shapiro-Wilk normality tests. It was found that the data had a normal distribution. Accordingly, parametric analysis techniques were used to compare the measurements obtained from the participants according to the patient and control groups. The relationship between the groups and Plaque or focal intimal thickening status and smoking exposure status was analyzed by chi-square analysis. Data were analyzed at 95% confidence level using SPSS 25.0 software (IBM SPSS, Chicago, IL).

RESULTS

Out of a total of 73 participants, 56 were considered as the patient group and 17 as the control group. Of the participants, 74% were male and 26% were female.

Age, smoking rate, body mass index, resting and maximum blood pressure values, and ascending aorta diameter were significantly higher in the patient group (p=0.02 for smoking, p<0.01 for the rest). Similarly, the ratio of right/left main CIMT, right/left bulbus IMT, and left ventricular diastolic dysfunction was significantly higher in the patient group compared to the healthy group (p<0.05 for all). In addition, the mean CIMT and mean FMD (%) values of the patient group were significantly higher and lower, respectively, than those of the control group. No difference was observed between the two groups in terms of right/left internal CIMT and passive smoking exposure. When the groups were compared in terms of carotid plaque or focal intimal thickening, carotid artery disease was detected in 50% of the patient group and 17.6% of the control group and this difference was statistically significant (p=0.02) (Table 1).

Table 1. Demographic, imaging characteristics of the patients

	Patient group (n=56)	Control group (n=17)	p value
Age (year), mean +SD	44.8+9.8	34.4+9.3	<0.01*
BMI (kg/m²), mean +SD	29.4+4.4	24+4.3	<0.01*
Active smoking (packet/year), mean +SD	17.8+13.8	5.3+6	0.02*
Smoking exposure, n (%)	35(62.5%)	7(41.2%)	0.12
Mean CIMT, mean +SD	0.59+0.12	0.49+0.10	<0.01*
FMD (%), mean +SD	5.13+3.34	7.37+4.34	0.03*
Resting BP, mean +SD	132.3+10.6	120.5+19.8	<0.01*
Maximum BP, mean +SD	208+14.5	155.5+22.2	<0.01*
Ascendan aorta diameter, mean+SD	3.3+0.37	3+0.27	<0.01*
Right main CIMT, mean +SD	0.55+0.13	0.45+0.1	<0.01*
Left main CIMT, mean +SD	0.58+0.13	0.45+0.11	<0.01*
Right bulbus IMK, mean +SD	0.68+0.17	0.58+0.13	0.02*
Left bulbus IMK, mean +SD	0.69+0.15	0.55+0.14	<0.01*
Right internal CIMT, mean +SD	0.55+0.17	0.47+0.12	0.07
Left internal CIMT, mean +SD	0.51+0.13	0.47+0.18	0.35
Right mean CIMT, mean +SD	0.59+0.13	0.49+0.09	0.01*
Left mean CIMT, mean +SD	0.59+0.12	0.49+0.13	<0.01*
LV diastolic dysfunction, n (%)	44 (78.6%)	2 (11.8)	<0.01*
Plaque/focal intimal thickening, n(%)	28 (50%)	3 (17.6%)	0.02*

Abbreviations: * statistically significant, BMI: Body-mass index, BP: Blood pressure, CIMT: Carotid artery intima media thickness, FMD: Flow mediated dilatation, LV:Left ventricle

Table 2. Comparison of mean CIMT and FMD values of the patient group according to hypertensive response stage

Group	Parameter	Hypertensive response stage	N	Mean	SD	p
Patient	Mean CIMT, mean +SD	Early	16	0,61	0,11	0,37
		Late	40	0,58	0,12	
	FMD (%), mean +SD	Early	16	4,95	2,96	0,80
		Late	40	5,20	3,51	

CIMT: Carotid artery intima media thickness, FMD: Flow mediated dilatation, SD: Standart deviation

Table 3. Comparison of mean CIMT and FMD values of the patient group according to hypertensive response stage

Group	Parameter	Gender	N		SD	*p*
Patient	Mean CIMT, mean +SD	Male	47	0360	0,11	041
		Female	9	0,56	0,12	
	FMD (%), mean +SD	Male	47	5,27	3,38	0,47
		Female	9	4,39	3,15	

CIMT: Carotid artery intima media thickness, FMD: Flow mediated dilatation, SD: Standart deviation

When Table 2 was analyzed, it was determined that mean CIMT and FMD (%) values in the patient group did not show a statistically significant difference according to hypertensive response stages (p=0.37, p=0.8).

Likewise in Table 3, it was determined that the mean values of CIMT and FMD (%) in the patient group did not show a statistically significant difference according to gender (p>0.05).

DISCUSSION

In this study, it was shown that I CIMT was significantly increased and FMD was significantly decreased in individuals with EIH compared to healthy individuals. II The impairment of these two parameters is an indication that vascular endothelial function is impaired in patients with EIH and that the risk for future cardiovascular diseases may be significantly increased.

Although there is not yet a consensus on the threshold value for EIH, in some studies, the threshold value for exercise hypertension (≥90th percentile and above in a group of healthy adults classified according to age and sex who have exercised) has been set as ≥210 mmHg in men and ≥190 mmHg in women. Although an increase in diastolic blood pressure during exercise is not a very expected condition, an increase of ≥110 mmHg or more in diastole in men and women was added to the definition.[8] Although the prevalence of EIH varies in studies, it was found to be 3-4% on average when healthy adult groups of various ages, genders and ethnicities were examined.[9]

Since EIH is considered a precursor of essential hypertension, the factors involved in its etiology and mechanism of occurrence are similar. Although advanced age, male gender, lack of fitness and seasonal factors are known to increase the incidence of EIH, the risk of EIH as an indicator of baroreceptor dysfunction is quite high in conditions such as smoking, hyperlipidemia, obesity, insulin resistance, diabetes mellitus, and metabolic syndrome.[9,10] In studies investigating diabetic patients, it is interestingly observed that this rate increases up to 50% in patients diagnosed with diabetes.[11,12] According to recent studies, autonomic dysfunction and EIH have been detected in some patients diagnosed with masked hypertension.[13,14] Martin et al.[15] showed that traumatic stress causes peripheral and systemic vasoconstriction in the body, in other words, impaired vascular tone in individuals with post-traumatic stress disorder. Inanc et al.[16] examined the relationship of COVID-19 with endothelial dysfunction and EIH in a study including 122 patients in total and showed that COVID-19 may increase cardiovascular risk in the future by causing autonomic sequelae.

In many studies on EIH, it has been shown that this excessive increase in blood pressure during exercise predicts the development of hypertension in normotensive individuals independently of resting blood pressure values.[17,18] In addition, target organ damage, cardiovascular events and increased mortality have been observed more in patients with EIH, again independently of resting blood pressure values. Because of the association between EIH and masked (isolated ambulatory) hypertension, the detection of EIH in patients is considered an indication for ambulatory blood pressure measurement.[19]

Increased carotid intima-media thickness and endothelial dysfunction, which are among the main target organ damages of hypertension, are widely used in the clinic as parameters that can be easily demonstrated and quantitatively measured by non-invasive methods.[20] It is clearly known that CIMT is an indicator of subclinical atherosclerosis and increases future cardiovascular risk in hypertensive patients.[20-22] Similarly, it has been shown in many studies that endothelial cells play an important role in blood pressure regulation and even a 1% increase in FMD in hypertensive patients can reduce cardiovascular mortality by approximately 13%.[23] Based on this evidence, the finding of impaired FMD and increased CIMT in patients with EIH compared to the normal population may be considered as a precursor or even equivalent of hypertension in EIH. The results of our study support many previous studies.[24,25] The higher rate of diastolic dysfunction in the EIH group in our study is also an important marker of the onset of subclinical end organ damage even before EIH progresses to the stage of systemic hypertension.

In our study, not only the patient and control groups were compared, but also the patient groups were evaluated within themselves. One of these evaluations was the relationship between the stage of hypertensive response during exercise testing in the patient group (early or late stage) and the CIMT and FMD values. In one of the previous studies, it was observed that cardiovascular mortality and morbidity were higher in patients with hypertensive response during exercise testing in the early stages of the test (especially those with a response ≥175 mmHg at light to moderate workload).[26] In our subgroup analysis inspired by this study, stage 1 and stage 2 periods in which hypertensive response (systolic blood pressure ≥190 mmHg) was observed were classified as the early period, while the other stages and the recovery period at the end of the test were classified as the late period. Sixteen patients with hypertensive response in the early phase of exercise were compared with 40 patients with hypertensive response in the late phase. However, no statistically significant difference was found between both PIMC values (p=0.37) and FMD values (p=0.80).

Limitations

The main limitations of our study were the limited population and the single center. In addition, smoking and age factors may have contributed to the significant findings of CIMT, FMD, and diastolic dysfunction in the patient group.

CONCLUSION

As in hypertensive patients, the risk of asymptomatic target organ damage may be higher in patients with EIH than in normotensive patients. Therefore, patients with EIH should be under close clinical follow-up both because of the risk of developing hypertension in the future and possible complications of hypertension. Since CIMT and FMD are non-invasive, convenient, rapid, and inexpensive, they can provide early assessment of end-organ damage in this patient group, allowing earlier elimination of modifiable risk factors and prevention of end-organ damage.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Kartal Koşuyolu Yüksek İhtisas Training and Research Hospital Ethics Committee (Date: 06.06.2018, Decision No 2018/5).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Zhou B, Perel P, Mensah GA, Ezzati M. Global epidemiology, health burden and effective interventions for elevated blood pressure and hypertension. *Nat Rev Cardiol*. 2021;18(11):785-802.
2. Arıcı M, Birdane A, Güler K, et al. Turkish hypertension consensus report. *Turk Kardiyol Dern Ars*. 2015;43(4):402-409.
3. Huang QF, Yang WY, Asayama K, et al. Ambulatory blood pressure monitoring to diagnose and manage hypertension. *Hypertension*. 2021;77(2):254-264.

4. Inanc IH, Sabanoglu C. Systemic immune-inflammation index as a predictor of asymptomatic organ damage in patients with newly diagnosed treatment-naive hypertension. *Rev Invest Clin*. 2022;74(5):258-267.

5. Vasan RS, Song RJ, Xanthakis V, et al. Hypertension-mediated organ damage: prevalence, correlates, and prognosis in the community. *Hypertension*. 2022;79(3):505-515.

6. Schultz MG, Otahal P, Cleland VJ, Blizzard L, Marwick TH, Sharman JE. Exercise-induced hypertension, cardiovascular events, and mortality in patients undergoing exercise stress testing: a systematic review and meta-analysis. *Am J Hypertens*. 2013; 26(3):357-366.

7. Mohammed LLM, Dhavale M, Abdelaal MK, et al. Exercise-induced hypertension in healthy individuals and athletes: is it an alarming sign?. *Cureus*. 2020;12(12):e11988.

8. Ghidoni C, Kruzik M, Rossi VA, Caselli S, Schmied CM, Niederseer D. Definitions for hypertensive response to exercise. *Cardiol Rev.* 2024;32 (3):273-278.

9. Tokushige A, Ohishi M. Pathophysiology of the exaggerated blood pressure response to exercise. *Hypertens Res*. 2022;45(12):2028-2029.

10. Dutra-Marques AC, Rodrigues S, Cepeda FX, et al. Exaggerated exercise blood pressure as a marker of baroreflex dysfunction in normotensive metabolic syndrome patients. *Front Neurosci*. 2021;15:680195.

11. Schultz MG, Otahal P, Kovacevic AM, et al. Type-2 diabetes and the clinical importance of exaggerated exercise blood pressure. *Hypertension*. 2022;79(10):2346-2354.

12. Grotle AK, Stone AJ. Exaggerated exercise pressor reflex in type 2 diabetes: potential role of oxidative stress. *Auton Neurosci*. 2019;222:102591.

13. Cuspidi C, Gherbesi E, Faggiano A, et al. Masked hypertension and exaggerated blood pressure response to exercise: a review and meta-analysis. *Diagnostics (Basel).* 2023; 13(6):1005.

14. Inanc IH, Sabanoglu C. The relationship of masked hypertension with autonomic dysfunction and cardiometabolic parameters: a case-control study. *Eur Rev Med Pharmacol Sci*. 2022;26(17):6265-6272.

15. Martin ZT, Shah AJ, Ko YA, et al. Exaggerated peripheral and systemic vasoconstriction during trauma recall in posttraumatic stress disorder: a co-twin control study. *Biol Psychiatry*. 2024;96(4):278-286.

16. Inanc IH, Sabanoglu C. Autonomic dysfunction and metabolic disorders as the possible sequelae of COVID-19 infection. *Eur Rev Med Pharmacol Sci*. 2022;26(15):5587-5595.

17. Laukkanen JA, Kurl S. Blood pressure responses during exercise testing-is up best for prognosis? *Ann Med*. 2012;44(3):218-224.

18. Holmqvist L, Mortensen L, Kanckos C, Ljungman C, Mehlig K, Manhem K. Exercise blood pressure and the risk of future hypertension. *J Hum Hypertens*. 2012;26(12):691-695.

19. Zafrir B, Aker A, Asaf Y, Saliba W. Blood pressure response during treadmill exercise testing and the risk for future cardiovascular events and new-onset hypertension. *J Hypertens*. 2022;40(1):143-152.

20. Sun P, Liu L, Liu C, et al. Carotid intima-media thickness and the risk of first stroke in patients with hypertension. *Stroke*. 2020;51(2):379-386.

21. Magnussen CG. Carotid artery intima-media thickness and hypertensive heart disease: a short review. *Clin Hypertens*. 2017;23(1):1-4.

22. Lee J, Vasan RS, Xanthakis V. Association of blood pressure responses to submaximal exercise in midlife with the incidence of cardiovascular outcomes and all-cause mortality: the framingham heart study. *J Am Heart Assoc*. 2020;9(11):e015554.

23. Pearson MJ, Smart NA. Effect of exercise training on endothelial function in heart failure patients: a systematic review meta-analysis. *Int J Cardiol*. 2017;231:234-243.

24. Keller K, Stelzer K, Ostad MA, Post F. Impact of exaggerated blood pressure response in normotensive individuals on future hypertension and prognosis: systematic review according to PRISMA guideline. *Adv Med Sci*. 2017;62(2):317-329.

25. Baycan ÖF, Çelik FB, Güvenç TS, et al. Coronary flow velocity reserve is reduced in patients with an exaggerated blood pressure response to exercise. *Hypertens Res*. 2022;45(10):1653-1663.

26. Schultz MG, Sharman JE. Exercise Hypertension. *Pulse (Basel).* 2014;1(3-4):161-176.