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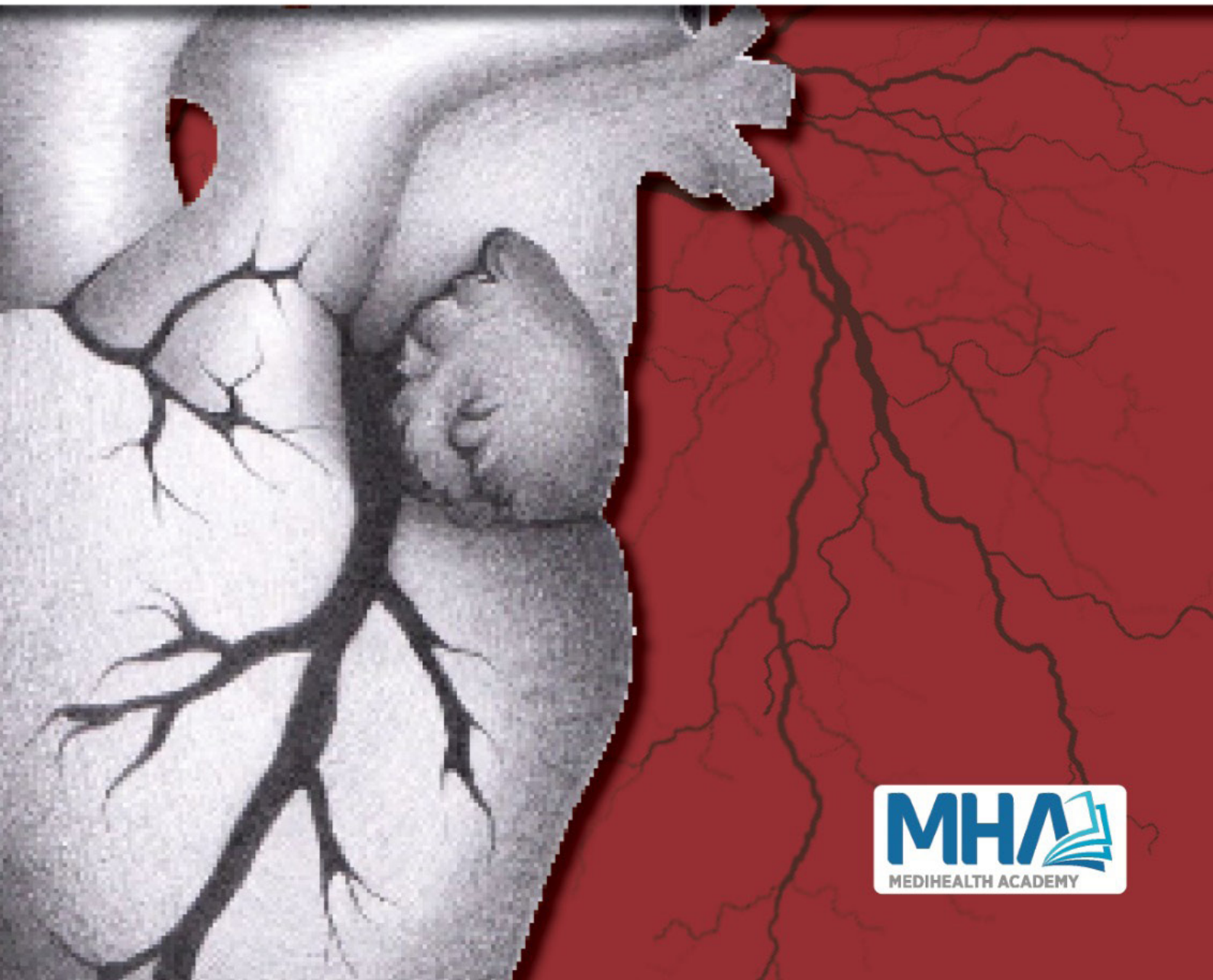

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Original Article

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The effect of anxiety on metabolic parameters in patients with primary hypertension

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ABSTRACT

Aims: Although the role of anxiety in the pathogenesis of hypertension is known, the effect of anxiety on metabolic parameters in hypertension has not been demonstrated. This study aimed to evaluate the effect of anxiety on metabolic parameters and blood pressure regulation in patients with primary hypertension.

Methods: The study was designed as a single-center, descriptive cross-sectional study. A total of 150 patients receiving antihypertensive therapy for primary hypertension were included in the study. Patients were divided into minimal, mild, moderate, and severe anxiety groups according to the Beck Anxiety Inventory. Anthropometric measurements, metabolic parameters, and blood pressure measurements were compared between groups.

Results: Significant positive correlations were found between anxiety severity and total cholesterol, LDL cholesterol, body mass index, and waist circumference ($p<0.05$). Subgroup analyses showed that total cholesterol, LDL cholesterol, body mass index, and waist circumference were higher in the severe anxiety group than in the minimal anxiety group ($p<0.05$).

Conclusion: Anxiety in patients with primary hypertension appears to have negative consequences on total cholesterol, LDL cholesterol, body mass index, and waist circumference. In hypertension, female gender and obesity are associated with increased anxiety levels.

Keywords: Hypertension, anxiety disorders, cholesterol, body mass index

INTRODUCTION

Cardiovascular diseases remain the most important cause of morbidity and mortality today.[1] Atherosclerotic disease, which is the basis of cardiovascular diseases, progresses insidiously, and combating risk factors is critical in preventing the development of cardiovascular disease.[1] Hypertension and dyslipidemia are the most important modifiable risk factors for cardiovascular disease.[2]

Findings in studies conducted in the United States population indicate that optimal total cholesterol levels are approximately 150 mg/dL (3.8 mmol/L), which corresponds to approximately 100 mg/dL (2.6 mmol/L) of low-density lipoprotein cholesterol (LDL-C). Adult populations with cholesterol concentrations in this range are accepted to be at low risk for atherosclerotic cardiovascular disease. Although LDL-C is the main causative parameter associated with atherosclerosis, other risk factors also contribute to the development of atherosclerosis, including smoking, hypertension, hyperglycemia, and other lipoprotein abnormalities.[3]

Metabolic syndrome is a complex condition that has risk factors interrelated with the development of cardiovascular diseases and diabetes. These factors include hyperglycemia, high blood pressure, high triglyceride levels, low high-density lipoprotein cholesterol (HDL-C) levels, and obesity (especially central adiposity).[4]

Anxiety disorders are associated with the onset and progression of heart disease and in many cases, are also related to adverse cardiovascular outcomes, including mortality. Both behavioral and physiological mechanisms (autonomic dysfunction, inflammation, endothelial dysfunction, changes in platelet aggregation) may help explain the associations between anxiety and cardiovascular disease. Individuals with anxiety tend to increase dietary cholesterol intake and total energy intake, adopt a sedentary lifestyle, and reduce physical activity. These are consistent with findings showing that patients with anxiety have increased rates of dyslipidemia, obesity, diabetes, and substance use.[5]

The present study aimed to reveal the effects of anxiety on metabolic parameters and blood pressure control in patients with primary hypertension under treatment.

METHODS

Between May 2018 and September 2018, 150 patients with primary hypertension who were receiving antihypertensive therapy were included in the study. Patients under 18 years of age, with secondary hypertension, diabetes mellitus (DM), chronic kidney disease (glomerular filtration rate (GFR) <60 mL/min/1.73 m^2), hyperlipidemia, coronary artery disease, smoking and alcohol use, hyperthyroidism or hypothyroidism, pregnancy, psychiatric disease, Alzheimer's disease, and those using any psychiatric drugs (antidepressant, anxiolytic, antipsychotic, etc.) or antihyperlipidemic drugs were excluded from the study. Written informed consent was obtained from all patients. The Clinical Researches Ethics Committee of the institution approved the study protocol (Date: 09.05.2018 Decision No: 2018/7-09). The study was carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The Beck Anxiety Inventory (BAI) for assessment of the severity of anxiety was applied to all patients. The BAI is a 21-item scale used to determine the severity of anxiety. Participants are asked the level of discomfort they have felt regarding each of the items (symptoms) within the past week. The degree of discomfort is scored between 0 (never) and 3 (severe – hardly bearable). The total score ranges between 0 and 63. The BAI scores classification was defined as follows: 0-7 minimal anxiety symptoms, 8-15 mild anxiety symptoms, 16-25 moderate anxiety symptoms, and 26-63 severe anxiety symptoms. The patients were divided into the respective groups (minimal, mild, moderate, and severe anxiety) according to the scores obtained from the BAI. Patients were asked to do a one-week home blood pressure monitoring under their current antihypertensive treatment.

In the morning after 12 hours of fasting, blood was taken from the patients, and fasting plasma glucose and lipid parameters (total cholesterol, LDL-C, HDL-C, triglyceride) were measured on the same day. Fasting plasma glucose and lipid parameters were measured using a Beckman Coulter AU680 device (Beckman Coulter, Miami, FL, USA) with original reagents. LDL-C level was calculated with the Friedewald formula [LDL-C = Total cholesterol – HDL-C – (Triglyceride/5)] in patients with triglyceride levels of <400 mg/dL, while LDL-C was directly measured in patients with triglyceride levels higher than 400 mg/dL. The GFR was calculated with the Modification of Diet in Renal Disease (MDRD) GFR equation [Estimated GFR (mL/min/1.73 m^2) = 186 × (Serum creatinine$^{-1.154}$) × (age$^{-0.203}$) × 0.742 (if female)]. Patients with estimated GFR <60 mL/min/1.73 m^2 were not included in the study.

Anthropometric measurements including weight, height, and waist circumference were obtained. The height of the patients was measured by portable stadiometers. Body weight was measured by trained healthcare professionals with participants standing without shoes in light indoor clothing, using a digital scale. Waist circumference was measured midway between the lowest border of the rib cage and the upper border of the iliac crest, at the end of normal expiration. Body mass index (BMI) was calculated as the ratio of body weight in kilograms to the square of height in meters. A BMI over 30 kg/m^2 is considered obese.

Statistical Analysis

It was performed using SPSS version 22.0 for Windows statistical software (IBM SPSS Statistics, Chicago, IL, USA). The data were expressed as mean±standard deviation for continuous variables and as proportions for categorical variables. The normal distributions of continuous variables were evaluated with the Shapiro-Wilk test. The One-way ANOVA test was used to compare normally distributed variables. The Kruskal-Wallis test was used for the comparison of non-normally distributed variables. Correlation analyses were performed using Pearson's correlation analysis for normally distributed variables, and Spearman's correlation analysis for non-normally distributed variables. Categorical parameters were analyzed using the Chi-square test. For all analyses, $p<0.05$ was considered statistically significant.

RESULTS

Of the 150 patients included in the study, 125 (83.3%) were women. The average age of the patients was 55±10 years, and the age range was 27-73 years. According to the BAI scores, 37 patients (22 women, 15 men) had minimal anxiety symptoms, 41 patients (33 women, 8 men) had mild anxiety symptoms, 45 patients (43 women, 2 men) had moderate anxiety symptoms, and 27 patients (all women) had severe anxiety symptoms.

The anthropometric and clinical characteristics of the patients according to the anxiety symptom groups are shown in Table 1. It was observed that as the anxiety severity of the groups increased, the female gender ratio also increased. BAI score was higher in female hypertensive patients than in males (18.5±11.6 vs 6.4±5.2, respectively, $p<0.001$). Significant differences were found in terms of gender, height, BMI, and waist circumference ($p<0.05$). In the subgroup analyses, BMI and waist circumference were found to be significantly higher, and height was found to be significantly lower in the severe anxiety group than in the minimal anxiety group ($p<0.05$). It was also observed that as the anxiety severity of

Table 1. Anthropometric and clinical characteristics of patients by anxiety groups

	Minimal (n=37)	Mild (n=41)	Moderate (n=45)	Severe (n=27)	p-value
Age (years)	55.2±10.9	55.4±8.9	53.7±10.7	55.5±9.7	0.867
Female gender (n, %)	22 (59.5)	33 (80.5)	43 (95.6)	27 (100)	<0.001
Weight (kg)	79.8±14.8	80±13.3	79.8±5.1	83.4±14.2	0.937
Height (cm)	162.5±9.2	157.7±8.1	157.8±6.4	154.3±6.3	0.002
Body mass index (kg/m^2)	30.27±5.62	32.16±5.02	32.07±5.1	35.08±6.07	0.013
Obesity (n, %)	16 (43.2)	25 (61%)	34 (75.6)	22 (81.5)	0.004
Waist circumference (cm)	97±11	100±12	101±11	106±11	0.039
Hypertension duration (years)	6.3±4.9	7.1±5.8	7.3±7.5	9.9±7.1	0.245
Regularity of antihypertensive medication use (n, %)					
Regular	32 (86.5)	39 (95.1)	39 (86.7)	25 (92.6)	0.483
Irregular	5 (13.5)	2 (4.9)	6 (13.3)	2 (7.4)	
Number of antihypertensive medications (n, %)					
Monotherapy	9 (24.3)	9 (22)	9 (20)	11 (40.7)	0.622
Dual combination therapy	22 (59.5)	25 (61)	28 (62.2)	13 (48.2)	
Triple or greater combination therapy	6 (16.2)	7 (17)	8 (17.8)	3 (11.1)	

Data are given as mean ± standard deviation or number with percentage

Table 2. Blood pressure and antihypertensive medications of patients by anxiety groups

	Minimal (n=37)	Mild (n=41)	Moderate (n=45)	Severe (n=27)	p-value
Systolic blood pressure (mmHg)	124.3±12.2	124±11.4	125.5±10.8	128.8±11.6	0.339
Diastolic blood pressure (mmHg)	77.5±8.9	77.8±8.9	76.9±8.6	80.5±7.1	0.366
Controlled hypertension (n, %)	19 (51.4)	27 (65.9)	24 (53.3)	13 (48.1)	0.438
Antihypertensive medication (n, %)					
Angiotensin-converting enzyme inhibitors	6 (16.2)	9 (22.0)	9 (20.0)	9 (33.3)	0.416
Angiotensin receptor blockers	24 (64.9)	25 (61.0)	30 (66.7)	12 (44.4)	0.269
Calcium channel blockers	15 (40.5)	14 (34.1)	18 (40.0)	9 (33.3)	0.882
Beta-blockers	6 (16.2)	7 (17.1)	7 (15.6)	5 (18.5)	0.990
Diuretics	21 (56.8)	24 (58.5)	28 (62.2)	11 (40.7)	0.337

Data are given as mean ± standard deviation or number with percentage

the groups increased, the obesity ratio also increased. Obese hypertensive patients had higher BAI scores than non-obese patients (18.9±11.9 vs 12.1±10.1, respectively, p<0.001). There was no significant difference between the groups in terms of the duration of hypertension (p=0.245). Additionally, the regularity of antihypertensive medication use was found to be similar in the groups (p=0.483) and the frequency of regular medication use was over 86% in all groups.

The antihypertensive treatments of the patients were evaluated under three main groups; monotherapy, double combination therapy, and triple (or greater) combination therapy. Of the 150 patients, 38 (25.3%) were using antihypertensive monotherapy, 88 (58.7%) were using a double combination, and 24 (16%) were using triple or greater combination treatments. There was no difference between the anxiety groups in terms of the number of antihypertensive medications used (p=0.622).

Blood pressure and antihypertensive medications of patients according to the anxiety groups are shown in Table 2. When the systolic and diastolic pressures were examined, no significant differences were found between the groups. The most frequently used antihypertensive drug groups by the patients were angiotensin receptor blockers (60.7%), diuretics (56%), calcium channel blockers (37.3%), angiotensin-converting enzyme inhibitors (22%), and beta-blockers (16.7%), respectively. There was no difference between the groups in terms of antihypertensive medication groups.

The laboratory values of the patients according to the anxiety groups are shown in Table 3. There was a significant difference between the groups in terms of total cholesterol (p=0.029) and LDL-C (p=0.025). Subgroup analyses revealed that total cholesterol and LDL-C levels were significantly higher in the severe anxiety group than in the minimal anxiety group (p=0.007).

In the analysis of the study population, significant relationships were found between BAI score and total cholesterol, LDL-C, BMI, and waist circumference (Figure a, b, c, d).

Table 3. Laboratory values of patients by groups

	Minimal (n=37)	Mild (n=41)	Moderate (n=45)	Severe (n=27)	p-value
eGFR (ml/min/1.73 m^2)	81.4±14.6	80.4±12.9	79.3±13.7	80.7±15.5	0.909
Fasting plasma glucose (mg/dl)	99.2±11.5	99.9±11.7	98.5±11.5	96.3±8.7	0.616
Total cholesterol (mg/dl)	183.3±33.5	191.7±31.3	193.7±39.3	209.7±31.6	0.029
HDL-C (mg/dl)	47.5±13.7	48.1±10.8	48.2±8.9	49.3±10.6	0.934
LDL-C (mg/dl)	109.9±25.7	117.9±27.2	117.5±34.5	132.8±28.4	0.025
Triglyceride (mg/dl)	132.6±68.9	135.5±70.9	142±61	129.9±50.3	0.863

Data are given as mean ± standard deviation
Abbreviations: eGFR: Estimated glomerular filtration rate, HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol

DISCUSSION

Hypertension and dyslipidemia are the most important modifiable risk factors for cardiovascular diseases. Anxiety disorder is the most common psychiatric disorder with a 12-month prevalence of 18.1%.[6] While there are many studies on hypertension and anxiety disorders separately, the number of studies investigating the relationship between these two diseases is relatively few. We found that BMI, waist circumference, total cholesterol, and LDL-C levels of patients with severe anxiety were found to be significantly higher compared to those with minimal anxiety symptoms. No significant difference was found between the other groups.

In the present study, 83.3% of the patients were women and the proportion of women was higher than that of men. In epidemiological studies, it has been shown that generalized anxiety disorder and panic disorder are approximately twice as common in women than in men.[7] In our study, as the anxiety severity of the groups increased, the women's frequency increased.

In our study, the BMI of the severe anxiety group was found to be significantly higher than the minimal anxiety group. Again, when the patients were compared in terms of obesity presence, we found that obesity was significantly more common in the severe anxiety group and the moderate anxiety group compared to the minimal anxiety group. These results are in line with the results of studies that report high obesity frequency in subjects with anxiety disorders.[8,9] In the study by Black et al.[10], it was shown that mood disorders, personality disorders, and anxiety disorders are higher in patients defined to be morbidly obese compared to their non-obese counterparts. As a result of not being able to cope with anxiety adequately, loss of control over eating occurs in those with anxiety disorders, and they have a tendency to eat more, and thus, become obese.[8]

In our study, no significant relationships were found between anxiety severity and systolic or diastolic blood pressure. In conclusion, no relationship was found between the level of anxiety and the regulation of hypertension under treatment. In a study that examined whether there was a relationship between anxiety disorders and resistant hypertension, although no direct relationship could be found between panic disorder and resistant hypertension, the prevalence of panic disorder was found to be quite high in hypertension patients.[11] The results of our study were similar to this study in terms of the lack of a relationship between the regulation

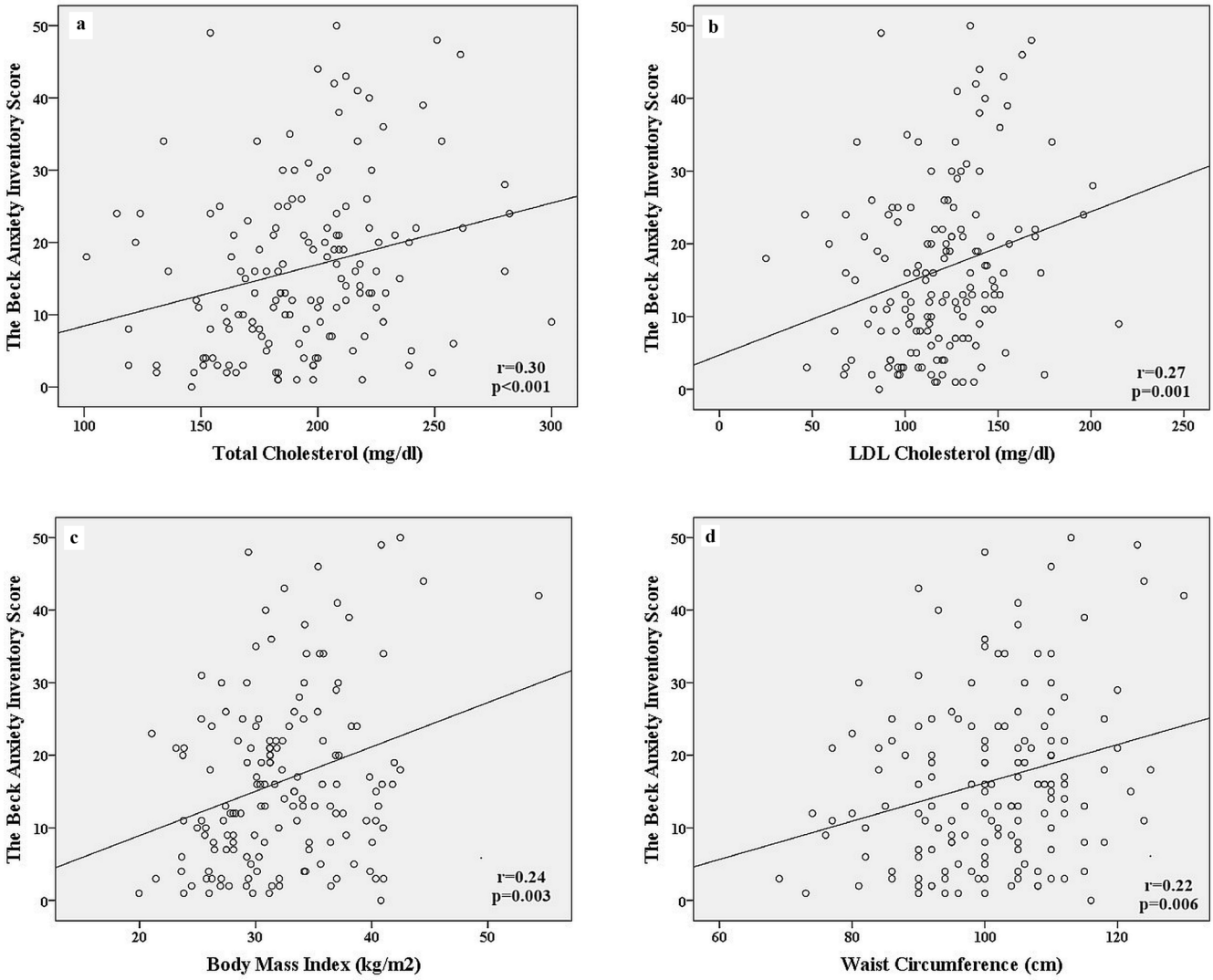

Figure. Relationships between The Beck Anxiety Inventory score and total cholesterol (**a**), low-density lipoprotein cholesterol (**b**), body mass index (**c**), and waist circumference (**d**).

of hypertension and the severity of anxiety. However, the conclusion in Kaplan's study that panic symptoms complicate the treatment of hypertension should also be kept in mind.[12] Symptoms frequently described by these patients are palpitations, dizziness, paresthesia, and headache. It should be noted that situations such as failure to detect panic symptoms by patients and physicians or linking symptoms to antihypertensive treatment may lead to inappropriate discontinuation and modification of antihypertensive treatments. In another study, the prevalence of hypertension in patients with panic disorder was found to be higher than in the normal population.[13] In another study, the prevalence of panic disorder in hypertension patients was found to have an approximately threefold increase.[14] To summarize, although anxiety disorders are a risk factor for hypertension, there is no direct relationship between these conditions in terms of resistance to treatment. More comprehensive studies are needed on this subject. It should be kept in mind that anxiety disorders and hypertension are two intertwined diseases.

In our study, the total cholesterol and LDL-C values have shown positive correlations with the severity of anxiety. In terms of other metabolic parameters (fasting plasma glucose, HDL-C, triglyceride), there was no relationship between the severity of anxiety and these parameters. The results of studies on this subject are quite different from each other. Many previous studies have shown that natural or induced stress and anxiety disorders may cause an increase in cholesterol levels.[15-19] In our study, the LDL-C and total cholesterol levels were found to be significantly higher in patients with severe anxiety compared to those with minimal anxiety, which supports previous studies. From this, it can be concluded that stress leads to an increase in cholesterol levels. It may be erroneous to try and treat high cholesterol levels by ignoring anxiety in patients with untreated anxiety. It is a well-established fact that stress increases the risk of cardiovascular events.[16] As shown in our study, anxiety can cause an increase in cholesterol levels, which may lead to an increase in cardiovascular risk. Although most of the relevant studies focused on panic disorder, a study examining generalized anxiety disorder also found a relationship with elevated cholesterol levels.[19] Based on these findings, it can be concluded that stress and anxiety disorders may increase cholesterol levels.

Generalized anxiety disorder often begins at an early age, has a chronic course, and is often associated with other mood disorders, as well as being comorbid with other diagnoses.[20] Those who used any psychiatric medication were not included in our study. It has been shown that many psychiatric drug groups (antipsychotics, antidepressants, anxiolytics, etc.) have positive or (mostly) negative effects on

metabolic parameters.[21-23] For example, many antipsychotic drugs can cause hyperglycemia, dyslipidemia, insulin resistance, and metabolic syndrome.[21] Although the exact mechanism has not been clarified, it is believed that various mechanisms may contribute to this outcome, including the inhibition of glucose uptake receptors in peripheral tissue, increased insulin secretion, and increased catecholamine levels.[21-24] Again, the central effect of antipsychotics and the increase in food intake are thought to be important factors in the development of these results.[21,25] It has been reported that selective serotonin reuptake inhibitors, which are frequently used in the treatment of anxiety, may also have positive or negative effects on metabolic parameters in a few studies, although the findings are different.[22,26] In light of this information, we excluded all parameters other than anxiety severity that could influence metabolic parameters positively or negatively, such as additional variables or drug use, to ensure the integrity of our data and to increase the accuracy of our findings.

Although there are many studies on hypertension, anxiety disorder, and hyperlipidemia, our literature review did not yield any studies examining these three issues in concert. Examining these three issues together can be considered as one of the strong aspects of our study. The most important limitation of the present study is the significantly high frequency of women in the study group.

CONCLUSION

Anxiety levels are higher in female hypertensive patients than in males. Anxiety levels are also higher in obese patients with hypertension than non-obese. The BMI, waist circumference, total cholesterol, and LDL-C levels are related to the severity of anxiety symptoms in patients with primary hypertension. Total cholesterol and LDL-C levels are increased in patients with severe anxiety. Severe anxiety in hypertension patients may increase the risk of cardiovascular disease by causing an increase in BMI, waist circumference, total cholesterol, and LDL-C levels. There is no relationship between the severity of anxiety and the regulation of blood pressure in hypertension patients receiving antihypertensive treatment. There is a need for more comprehensive studies exploring the effects of anxiety disorders on the increased risk of cardiovascular disease in patients with hypertension.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was initiated with the approval of the Kütahya Dumlupınar University Medical Faculty Clinical Researches Ethics Committee (Date: 09.05.2018, Decision No: 2018/7-09).

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.

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

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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/m^2), 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.

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Current approach to resistant hypertension

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ABSTRACT

Resistant hypertension is the inability to achieve target blood pressure (<130/80 mmHg) despite using the maximum tolerated doses of three antihypertensive drugs, including a diuretic, or the need for four or more medications. It is linked to aging, obesity, obstructive sleep apnea, and chronic kidney disease, with contributing factors such as high sodium intake and sympathetic nervous system overactivity. Treatment includes optimizing diuretic use, with spironolactone proving highly effective. Lifestyle modifications, including sodium reduction and exercise, are critical. Emerging therapies like renal denervation offer promising long-term blood pressure control.

Keywords: Resistant hypertension, sympathetic nervous system, diuretic, renal denervation

INTRODUCTION

Hypertension is a significant modifiable risk factor for coronary artery disease (CAD), heart failure (HF), stroke, chronic kidney disease (CKD), and dementia.[1]

According to 2017 American College of Cardiology/ American Heart Association (ACC/AHA) Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults; hypertension stage 1 is systolic blood pressure (SBP) 130-139 or DBP 80-89 mm Hg, and hypertension stage 2 is SBP ≥140 or diastolic blood pressure DBP ≥90 mm Hg[2]. The 2024 ESC Guidelines define non elevated blood pressures as SBP <120 mmHg and DBP <70, elevated blood pressures as SBP 120-139 mmHg or DBP 70-90 mmHg hypertension as a confirmed office SBP of ≥140 mmHg or DBP of ≥90 mmHg.[1]

Resistant hypertension (RH) is characterized by the inability to reach target blood pressure levels (<130/80 mmHg (average of two readings at a healthcare clinic on two different or consecutive days) or average BP of <125/75 mmHg on a 24-hour ambulatory BP monitor (ABPM)) when a patient is prescribed the highest or most tolerable doses of three antihypertensive medications from different classes, including a diuretic.[3] RH also encompasses patients whose blood pressure remains at target levels despite the use of four or more antihypertensive medications.

ETIOLOGY

RH is a prevalent issue encountered by both primary care providers and specialists. Although the precise prevalence is not well-established, clinical trials indicate that it affects an estimated 20% to 30% of participants.[4] The prevalence of RH is expected to rise due to factors such as an aging population and increasing rates of obesity, sleep apnea, and CKD.[5]

The diagnosis of RH requires ruling out "pseudo resistance" due to medication non-adherence, improper blood pressure measurement, and the white-coat effect. Measuring blood pressure accurately requires proper technique, proper cuff size, and use of validated devices.[6]

An often reason for pseudo-resistant hypertension is the insufficient dosage of antihypertensive medications or the use of inappropriate drug combinations. According to data from a specialized hypertension clinic, the most common adjustment that helped patients reach their blood pressure goals was either increasing the dosage of their medication or starting or switching to the correct diuretic.[5]

After confirming adherence to antihypertensive medications and ruling out a white-coat effect through out-of-office blood pressure measurements, the evaluation of RH involves identifying lifestyle factors contributing to the condition, detecting any drugs that might affect antihypertensive efficacy, screening for secondary causes of hypertension, and assessing for target organ damage.

Contributing factors as considered as volume expansion, overweight/obesity, exogenous substances, physical inactivity, excess daily dietary sodium, excess habitual alcohol consumption.[1] Secondary hypertension is more prevalent in individuals with RH compared to those with general hypertension. The most frequent causes of RH are hyperaldosteronism, CKD, renal artery stenosis, and

obstructive sleep apnea (OSA). The likelihood of secondary hypertension also increases with age, primarily due to higher rates of CKD, OSA, and renal artery stenosis.[7]

In one study, it was observed that younger patients with RH presented with a significantly higher prevalence of the condition compared to older individuals. These younger patients were diagnosed with hypertension at an earlier age and exhibited a greater prevalence of obesity, OSA, elevated aldosterone levels, and higher dietary sodium intake. This distinct phenotype in younger patients underscores a more severe form of RH, driven by a combination of these risk factors, which contributes to their elevated cardiovascular risk compared to older patients.[8]

PATHOPHYSIOLOGY

Normal blood pressure is maintained through various physiological mechanisms, and disruptions in these mechanisms can lead to hypertension. RH is primarily associated with two key processes: the renin-angiotensin-aldosterone system and increased activity of the sympathetic nervous system.[9]

In patients with RH, elevated sympathetic nerve activity is thought to be the primary contributing factor.[10]

Secondary hypertension is often categorized by plasma renin activity levels, with low-renin cases involving sodium handling issues in the distal nephron, including mineralocorticoid receptor dysfunction or problems with tubular pathways like the epithelial sodium channel or sodium chloride co-transporter. Rare causes such as glucocorticoid-remediable aldosteronism and Liddle's syndrome are well-documented, primary aldosteronism is a common secondary cause, affecting 20% to 23% of patients with RH.[11] These factors cause an overload of volume and sodium, resulting in increased peripheral vascular resistance, arterial stiffness, and subsequent damage to organs due to hypertension.[12]

Several conditions contribute to these mechanisms. The most frequent causes of RH are hyperaldosteronism, CKD, renal artery stenosis, and OSA.[12]

TREATMENT

The ACC/AHA guideline suggests aiming for a blood pressure target of less than 130/80 mm Hg for all of the age groups.[2] Both the ACC/AHA and ESC guidelines recommend starting antihypertensive treatment for patients with established cardiovascular disease (CVD) and a blood pressure of 130/80 mm Hg or higher. The ACC/AHA guidelines also specify that treatment should begin for those with a 10-year risk of atherosclerotic CVD exceeding 10%.[13]

Lifestyle Modifications

Patients with RH should be advised on lifestyle changes to help reduce their blood pressure. A key factor in RH is high sodium intake. Sodium restriction has a particularly significant impact on lowering blood pressure in patients with RH. In one study, reducing sodium intake to 1.1 g/day led to a 23/9 mm Hg decrease in 24-hour ambulatory blood pressure among patients whose hypertension was not well controlled despite being on a three-drug regimen that included a diuretic.[14]

The Dietary Approaches to Stop Hypertension (DASH) diet promotes the consumption of whole grains, vegetables, fruits, and low-fat dairy products, while reducing intake of saturated fats, processed foods, and added sugars. Research has consistently shown that this dietary strategy effectively lowers blood pressure in individuals with RH. Additionally, the Mediterranean diet has been found to offer comparable benefits in managing blood pressure levels.[12,15]

For patients with hypertension, engaging in physical activity is linked to a reduced risk of CVD mortality compared to those who are sedentary. The ESC 2024 guidelines recommend at least 150 minutes of moderate-intensity aerobic exercise per week (about 30 minutes on most days, 5-7 days per week), or 75 minutes of vigorous-intensity exercise per week spread over at least 3 days. Additional benefits are observed with 300 minutes of moderate-intensity or 150 minutes of vigorous-intensity aerobic exercise per week.[1]

Medical Treatment

Pharmacological treatment for patients with RH despite a three anti-hypertensive medicine should begin with optimization of diuretic use.[14] Researches indicate that adjusting diuretic therapy—whether by introducing a new diuretic, increasing its dose, or switching types based on kidney function—can help more than 60% of patients achieve their blood pressure goals.[5,16,17]

A study revealed that chlorthalidone, a thiazide like diuretic, is at least twice as potent as hydrochlorothiazide.[18]

Spironolactone, a potent aldosterone antagonist, has shown significant efficacy in treating RH, particularly in cases where sodium retention is a primary factor. The PATHWAY-2 study demonstrated that spironolactone, when added to a three-drug regimen, reduced SBP more effectively than placebo, bisoprolol, or doxazosin. Its effectiveness is linked to its ability to counteract aldosterone's effects, and renin profiling can predict responsiveness to the drug. Despite its advantages, careful monitoring is required due to risks like hyperkalemia, especially in patients with kidney disease.[19] In a recent network meta-analysis involving 24 studies and approximately 3,000 participants, spironolactone emerged as the most effective treatment for lowering office SBP compared to other interventions.[20]

For patients who qualify for sodium-glucose cotransporter 2 inhibitors (SGLT2Is), adding these medications to existing antihypertensive therapy can provide a moderate additional reduction in blood pressure.[21]

Invasive Strategies

Sympathetic nervous system overactivity contributes to the development and progression of hypertension.[1,22,23]

Increased renal norepinephrine (NE) spillover in numerous patients with primary and RH supports the idea that renal nerves are crucial in linking heightened central sympathetic activity to impaired renal function, which contributes to chronic hypertension.[23] 2024 ESC guidelines advise considering renal denervation therapy as a supplementary or alternative treatment for patients with RH that remains uncontrolled or who suffer from side effects of medications.[1]

Long-term follow-up studies show that these BP-lowering effects can be sustained for up to 3 years, with some data suggesting benefits may last up to 10 years. This suggests a notable advantage of renal denervation: its potentially enduring impact on BP, which may appeal to patients who struggle with adherence to daily medication and prefer a single, long-lasting intervention.[24,25]

CONCLUSION

Because patients with resistant hypertension are at higher risk of complications, including cardiovascular disease, stroke, renal failure, and death, lifestyle changes, use of antihypertensive drugs with different mechanisms of action, and a stepwise approach to management should be targeted to achieve blood pressure control, as should the search for secondary causes.

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Hypertensive emergency: diagnostic and therapeutic strategies

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ABSTRACT

Hypertensive emergencies are life-threatening conditions with end-organ damage caused by sudden increases in blood pressure that exceed 180/110-120 mmHg. Clinical conditions affecting the brain, arteries, retina, kidney and heart are encountered. The brain and cardiovascular system are most commonly affected. Ischemic stroke and acute pulmonary edema are the most common conditions. Some patients may experience end-organ damage independent of blood pressure values. This condition develops due to microangiopathy and deterioration of autoregulation that provides organ blood flow by damaging the vascular endothelium due to increased blood pressure. High blood pressure also increases end-organ damage in a vicious cycle by activating the renin-angiotensin-aldosterone system. This pathophysiology is important in treatment. As a general approach, rapid blood pressure reduction is not desired. Perfusion in end-organs that cannot adapt to autoregulation is impaired, and organ dysfunction deepens with ischemia and necrosis. In the general approach, a 10-20% decrease is targeted in the first hour, while a 5-15% decrease in blood pressure in the remaining 23 hours is sufficient. However, in ischemic stroke, blood pressure control is reduced according to both the treatment and the degree of pressure. If thrombolytic therapy is not to be given, if the blood pressure is not above 220/120 mmHg, no intervention is made. In aortic dissection, the aim is to reduce systolic blood pressure to 100-120 mmHg in a period of 20 minutes. In short, according to the target organ damage, short-acting intravenous antihypertensive drugs that can be treated stepwise and are selected according to the selected target values. In the selection of these drugs, options that may cause secondary damage to organ damage are avoided. Nitroprusside and nitroglycerin, which can increase central pressure, are not preferred primarily in ischemic stroke. Or, in adrenergic crisis, beta blockers can worsen blood pressure without sufficient alpha blockade. It should also be well known that such drugs have important side effects such as severe hypotension and cardiogenic shock.

Keywords: End organ damage, hypertensive emergency, treatment

INTRODUCTION

Hypertension (HT) is the most important risk factor that can be controlled to reduce adverse outcomes related to cardiovascular disease.[1] In addition, hypertensive emergency (HE) causes end-organ damage (EOD) within hours, causing serious morbidity and mortality. The brain, arteries, retina, kidney and heart (BARKH) are the end organs damaged by high blood pressure. The critical threshold value is systolic blood pressure (SBP) above 180 mmHg and diastolic blood pressure above 110-120 mmHg. HE may develop after pre-existing HT or may result from a newly developing clinical condition. There is no critical threshold value in a young person who develops acute kidney injury such as eclampsia or glomerulonephritis, where the life-threatening blood pressure level suddenly increases rapidly. In this case, the acceleration of the increase rather than the patient's blood pressure value brings about EOD. In short, HE can develop even at lower blood pressure (BP) values.[1-3] It has been determined that the rate of patients presenting to the emergency department with an SBP value over 180 mmHg is 13.8%, and that one in 200 patients presents with HE. The rate of HE among patients presenting to the emergency department due to hypertension worldwide varies between 1-3%. More than 95% of patients presenting to the emergency department with HE have cerebral and cardiac EOD. The most common conditions are hypertensive pulmonary edema and heart failure. This is followed by myocardial infarction, ischemic and hemorrhagic stroke. Other end-organ damages are encountered less frequently. The in-hospital mortality rate of these patients is around 2.5-4%.[4-7]

PATHOPHYSIOLOGY

The factors that trigger HE are generally the hypertensive patient's skipping medication doses or suddenly stopping taking them, difficulties in reaching a health institution, increased salt consumption, increased use of non-steroidal anti-inflammatory drugs, glucocorticoid consumption, pseudoephedrine, cocaine and amphetamine-like stimulants.[8-9]

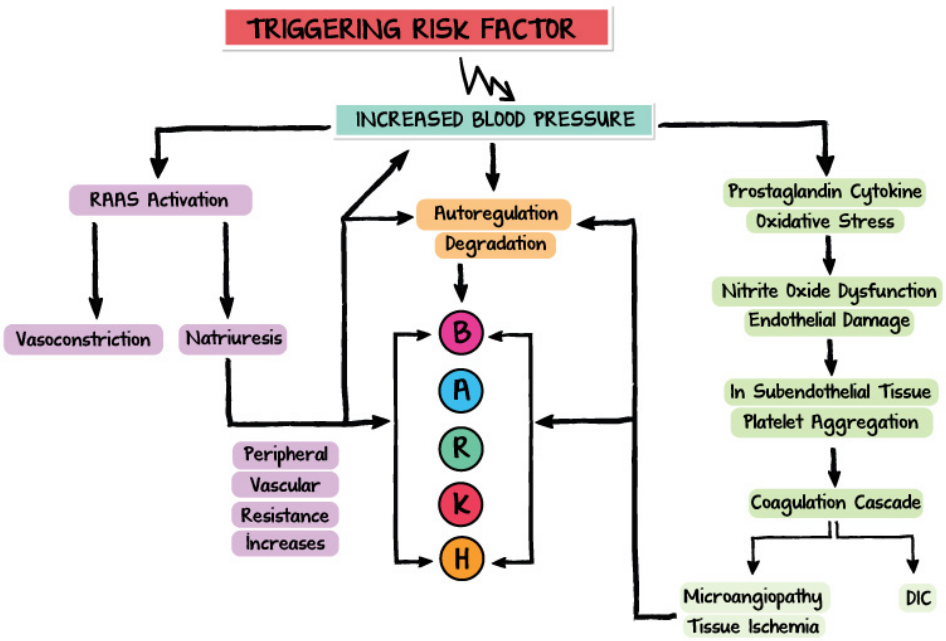

Figure 1. Hypertensive emergency pathophysiology
RAAS: Renin Angiotensin-Aldosterone System, BARKH: Brain, Arteries, Retina, Kidney, Heart
DIC: Disseminated Intravascular Coagulation

There is an autoregulation mechanism that provides perfusion of organs. This balance correlates with systemic blood pressure. While the mean arterial pressure for cerebral perfusion is 70-90 mmHg in individuals with normal blood pressure values, this value increases to 110-150 mmHg in individuals who have been hypertensive for a long time. Autoregulation, especially in brain tissue, may not respond sufficiently to sudden and rapidly increasing blood pressure. Vasogenic edema develops in the brain, leading to increased intracranial pressure (ICP). Clinical symptoms such as headache, nausea and vomiting occur. In addition, hypertensive damage develops in other tissues containing BARKH. In sudden decreases, it leads to ischemia, namely optic nerve ischemia, coronary ischemia or necrosis of penumbra tissue, together with hypoperfusion. This situation constitutes the basic strategy of emergency treatment of HE. The organs of patients who have been hypertensive for a long time establish a balance to continue blood circulation. This process increases permeability in the capillary area and leads to hyperperfusion. Increased systemic blood pressure activates the renin angiotensin-aldosterone system (RAAS). RAAS increases vasoconstriction, and fluid loss develops with pressure natriuresis. This increases peripheral resistance in organs containing BARKH. Autoregulation is disrupted and a vicious circle is entered. Thus, systemic blood pressure continues to increase. Increased pressure leads to the release of prostaglandins, cytokines and oxidative stress factors. Nitric oxide loses its function and the vascular endothelium is damaged. Subendothelial tissue is exposed and the coagulation cascade begins with platelet aggregation. Thus, microangiopathy and tissue ischemia or necrosis occur in the arterioles. We encounter hematuria, bleeding and exudate in the fundus. If the pressure continues, disseminated intravascular coagulation may develop (Figure 1).[6,10-12]

DIAGNOSTIC APPROACH TO HYPERTENSIVE EMERGENCY

HE includes many clinical conditions that develop as a result of BARKH injury, along with increased systolic and diastolic blood pressure values, along with history and physical examination. The most common symptoms are angina, visual disturbances, dyspnea and headache. Physical examination of patients, including all systems, is very important in early diagnosis and treatment. When HE develops in patients with brain damage, ischemic or hemorrhagic stroke, transischemic attack, increased intracranial pressure syndrome (ICP), posterior reversible encephalopathy syndrome (PRES), hypertensive encephalopathy and intracranial hemorrhage due to head trauma are seen. Patients develop symptoms such as sudden changes in consciousness, agitation, nausea, vomiting, seizures, delirium, visual disturbances and loss of strength in the extremities. Chest pain, back pain and dyspnea suggest acute coronary syndrome or aortic dissection and aneurysm. Sudden onset of dyspnea and pretibial edema suggest pulmonary edema and heart failure, while hematuria, pretibial and periorbital edema suggest acute kidney injury. Retinal hemorrhage, exudate and papilledema on fundoscopic examination are important in terms of retinopathy and ICP. Hypertension developing after the 20th week of pregnancy or an increase in preexisting blood pressure suggests preeclampsia and eclampsia. High liver enzymes and thrombocytopenia indicate HELLP syndrome in pregnant women. Sudden discontinuation of antihypertensive agents such as clonidine may lead to HE. Increased consumption of cocaine, amphetamine, monoamine oxidase inhibitors and tyramine-containing foods and pheochromocytoma may cause HE by causing adrenergic crisis. Postoperative bleeding from vascular anastomosis sites or patients scheduled for emergency surgery may enter the HE state. Blood tests and radiological imaging to be performed on patients are decided according to the patient's clinical picture (Table 1).[9,13,14]

MANAGEMENT OF HYPERTENSIVE EMERGENCY TREATMENT

The most important goal of treatment is not to reduce the numbers but to prevent hypoperfusion and reduce the damage

Table 1. Tests requested for specific conditions in hypertensive emergencies

Causes of hypertensive emergencies	Recommended tests
Acute coronary syndrome	ECG, high sensitive troponin I/T, echocardiography
Acute pulmonary edema	ECG, Chest X-ray, echocardiography,
Heart failure (Decompensated)	Blood urea nitrogen /creatinine, electrolyte (Na, K, Cl, Ca) Arterial blood gas, high sensitive troponin I/T B-type natriuretic peptide
Aortic dissection	D-dimer, ECG Chest CT angiography, Transthoracic echocardiography
Acute kidney injury	Creatinine, blood urea nitrogen electrolytes Arterial blood gas Urinalysis (proteinuria, hematuria) Renal ultrasound
Stroke	ECG (for arrhythmia, atrial fibrillation) INR, aPTT (coagulation tests) Brain CT (to differentiate between hemorrhagic and ischemic stroke) Diffusion MRI
Preeclampsia/ eclampsia	Complete blood count Creatinine, liver function tests (AST, ALT) 24-hour urine analysis or spot urine test for proteinuria Obstetric ultrasound (to assess pregnancy status)
Hypertensive encephalopathy	Complete blood count Blood urea nitrogen /creatinine, electrolyte ECG Fundoscopy (to assess for papilledema) Brain CT or MRI
Pheochromocytoma crisis	Serum and urine electrolytes Abdominal CT or MRI Plasma free metanephrines 24-hour urinary catecholamines

ECG: Electrocardiogram. CT: Computed Tomography; MRI: Magnetic Resonance Imaging; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase

that may occur in EOD. While doing this, aggressive approaches may lead to secondary damage. Intravenous antihypertensive drugs are used first. Their short duration of action and gradual treatment features help to control HE.[15] The most important part to be careful about is that if the arterial blood pressure value is reduced, the hypotension that may develop due to these drugs may lead to cardiogenic shock and even death. In addition, organ autoregulation cannot adapt to the rapid blood pressure decrease and may lead to worsening ischemia in the end organ.[2] For this, close arterial blood pressure monitoring is required. While extremity measurements can be made at the beginning of treatment, intraarterial blood pressure monitoring is important in the ongoing process. It is also important to make measurements from both arms and even the lower extremity. A difference of 10-20 mmHg between the arms is within acceptable limits, while more than this suggests aortic coarctation or another vascular anomaly going to the lower extremity. If there is HE here, treatment is planned according to the extremity where the high blood pressure measurement is made.[3,4,15]

In the general treatment approach, the aim is to reduce the initial measurement by 10-20% within the first hour. The target value here is calculated to be below 180/120 mmHg. A 5-15% decrease is achieved within the next 23 hours. This means reaching values below 160/110 mmHg on average. It is planned to bring the blood pressure to normal limits in the following 24-48 hours. In rare cases such as aortic dissection, preeclampsia and pheochromocytoma, the target value is below 130 mmHg for systolic pressure and below 80 mmHg for diastolic pressure. However, this general approach includes differences according to the affected organ as a result of EOD. Again, the antihypertensive drug selected varies accordingly (Table 2).[2,16,17]

ACUTE ISCHEMIC STROKE

In ischemic stroke, vasodilation and a decrease in perfusion pressure occur distal to the occluded vessel. The blood circulation of this distal tissue depends on systemic tension. In fact, increased blood pressure is thought to be a kind of protective mechanism. The brain's autoregulation cannot respond to sudden drops in blood pressure and may cause necrosis of the healthy penumbra tissue. Therefore, blood pressure regulation is provided according to the treatment to be applied to the patient in ischemic stroke.18 If thrombolysis or thrombectomy is not to be applied, no intervention is made unless the blood pressure rises above 220/120 mmHg. A 15% decrease is targeted after 24 hours from the moment the stroke begins.[18-19]

If thrombolysis or thrombectomy is to be performed, the blood pressure is reduced below 185/110 mmHg before the procedure. This value is kept below 180/105 mmHg during the procedure and for the following 24 hours. Antihypertensive treatment is started in stable patients who have been above 140/90 mmHg for more than 3 days. 18-19 Blood pressure is measured every 15 minutes for the first 2 hours. Measurements are made every 30 minutes for the next 6 hours. Blood pressure is monitored every hour for the remaining 16 hours.[18]

Labetolol, nicardipine and clevidipine are the primary agents in treatment. Nitroprusside is a secondary agent that can be preferred because it increases ICP and impairs platelet functions. It is an alternative to other agents in uncontrolled HE. Drugs that can reduce blood pressure suddenly and have long-term effects, such as nifedipine, should be avoided.[18]

ACUTE HEMORRHAGIC STROKE

Lowering blood pressure by more than 70 mmHg from the initial value increases the likelihood of renal function and neurological deterioration. Studies have shown that rapid reduction of blood pressure reduces the growth of bleeding.[19] If the patient's SBP value at the time of admission is above 220 mmHg, this value is reduced to below 220 mmHg within the first hour. It is aimed to keep it between 140-160 mmHg within the next few hours. If the patient's clinical condition is unstable, the dose of the antihypertensive drug is reduced. If the patient's SBP value at the time of admission is between 150-220 mmHg, it is reduced to below 140 mmHg within 1 hour. Nicardipine and labetolol are the drugs of choice for this. Nicardipine is more preferred above the initial SBP value of 160 mmHg. If it is below, labetolol is more preferred. Nitroprusside and nitroglycerin are not preferred due to their potential to increase intracranial pressure.[20]

HYPERTENSIVE ENCEPHALOPATHY

Arterioles respond to increased systemic blood pressure with vasoconstriction to maintain central perfusion at a constant flow. This is autoregulation of the brain. However, in sudden and rapid increases, this response cannot occur

Table 2. Characteristics of drugs used in hypertensive emergencies

Drugs	Minimum dose	Maximum dose	Indication	Side effects	Warning
Nitroglycerin	5 mcg/minute	100 mcg/minute	ACS Pulmonary edema	Headache, tachycardia, methemoglobinemia	Hypotension, Bradycardia, Azotemia, Tolerance with long-term use, Right-sided AMI, Caution in those using phosphodiesterase inhibitors.
Nicardipine	5 mg/hour (Increase by 2.5 mg/hour every 15 minutes)	15 mg/hour	Stroke	Headache, hypotension, tachycardia, angina	Half-life of 3-6 hours Do not use in ACS and severe aortic stenosis.
Esmolol	Loading dose: 500-1000 mcg/kg over per minute. Maintenance dose: 50 mcg/kg /minutes infusion	200 mcg/kg/minute	Aortic Dissection, stroke, Intraoperative postoperative	Excessive sweating, Shock, Altered consciousness, Dizziness	Do not use in pulmonary edema. Avoid in asthma, adrenergic crisis, heart block, heart rate <50 bpm, if Verapamil was used, metabolic acidosis, pulmonary hypertension.
Nitroprusside	0.25-0.5 mcg/kg/minute	8-10 mcg/kg/minute	Aortic dissection	Cyanide intoxication (starts at doses >2 mcg/kg/min) |	Do not administer the maximum dose for more than 10 minutes, Avoid use in subarachnoid hemorrhage, azotemia and optic atrophy. Discontinue the drug if lactic acidosis or bicarbonate depletion occurs.
Labetalol	Starting dose: 20 mg, 20-80 mg administered every 10 minutes. Infusion dose: 0.5-2 mg/minute	200 mg	Preeclampsia, Eclampsia (Max dose: 160 mg), ACS: (Max dose 120 mg)	Rash Elevated liver enzymes, Thrombocytopenia, Hyperkalemia, Worsening of Raynaud's syndrome	Do not use in pulmonary edema. Avoid use in asthma, COPD, heart failure, 1st-degree heart block, bradycardia, and hyperadrenergic conditions.
Hydralazine	10 mg	20 mg	Preeclampsi Eclampsia	Increases cardiac workload, may reduce placental blood flow	Avoid in pulmonary edema.
Urapidil	Starting dose: 10-50 mg Initial infusion dose: 2 mg/minute Maintenance dose: 9 mg/hour		Severe hypertensive heart disease uncontrolled by other agents. Intraoperative Postoperative	Dizziness, headache, angina, priapism, tachycardia, bradycardia.	Contraindicated in aortic coarctation and active arteriovenous shunt disease. Avoid in patients on phosphodiesterase inhibitors. Reduce dose in hepatic or renal impairment, and in elderly patients.

ACS: Acute coronary syndrome

and hyperperfusion occurs. As a result, vasogenic edema and increased ICP develop.[21] Headache, drowsiness, seizures, changes in consciousness and visual disturbances occur. Hypertensive retinopathy and microangiopathic hemolytic anemia may often accompany. With the regulation of blood pressure, the patient's symptoms begin to improve. However, rapid pressure reduction can lead to organ hypoperfusion. For this, blood pressure is reduced by 10-20% in the first hour. This decrease should be maintained for 2-6 hours. A decrease of more than 25% is not desired within 24 hours. When the initial blood pressure decrease is tolerated by the patient, it is appropriate to reduce it gradually to 160/110 mmHg over 48 hours.2,21 Nicardipine and labetalol are primarily preferred. Nitroglycerin is not used due to its venodilator effect and potential to increase ICP.[2,22]

SUBARACHNOID HEMORRHAGE

The target value for uncontrolled aneurysm hemorrhage is below 160 mmHg. However, in patients with a good level of consciousness, below 140 mmHg may be beneficial. When blood pressure control is required, intravenous labetalol, nicardipine or clevidipine are preferred. The use of vasodilators such as nitroprusside or nitroglycerin should be avoided because of their tendency to increase cerebral blood volume and ICP.[23]

ACUTE HEAD TRAUMA

To control increased ICP due to trauma, intervention is performed when systemic blood pressure increases when cerebral perfusion pressure exceeds 120 mmHg and ICP exceeds 20 mmHg. Rapid blood pressure regulation has been associated with poor outcomes. It is beneficial for patients to have their heads 30 degrees above heart level. Valsalva maneuvers that increase ICP should be avoided.[2]

PREECLAMPSIA-ECLAMPSIA

The main treatment for this condition, which occurs after the 20th week of pregnancy, is delivery. However, in patients who develop HE, the goal is to reduce blood pressure control to below 160/105 mmHg within 150-180 minutes. Labetalol and nicardipine may be preferred in treatment. If eclampsia or proteinuria, severe hypertension (blood pressure above 160/110 mmHg) and preeclampsia accompanied by neurological findings are treated with magnesium sulfate. 4 g magnesium is given intravenously as a 5-minute infusion. Then, treatment is continued by infusing 1 g per hour. If magnesium is given with nifedipine, there is a risk of hypotension. Emergency delivery is considered in patients whose blood pressure cannot be controlled within 6 hours. Diuretic treatment is avoided.[19]

ACUTE PERIOPERATIVE HYPERTENSION AND POSTOPERATIVE SURGICAL HYPERTENSION

HE may progress with fear, pain, adrenargic stimulation and intravascular volume variability. Blood pressure above 180/100 mmHg increases the risk of bleeding. Surgery may need to be postponed or blood pressure may need to be regulated. Nicardipine, nitroglycerin, and esmolol are drugs that have been successfully used. Esmolol has an important role in cardiac surgery because it reduces the potential for supraventricular or ventricular tachycardia. Routine perioperative use of beta blockers is not recommended in non-cardiac surgeries. Preoperative use of angiotensin converting enzyme inhibitors carries the risk of perioperative hypotension, and discontinuation may lead to postoperative hypertension. Calcium channel blockers may be preferred in the preoperative period. There is no harm in routine loop diuretic use in patients with heart failure.[19,22]

ACUTE SYMPATHETIC CRISIS

Pheochromocytoma, paraganglioma, sudden discontinuation of clonidine or short-acting beta blocker antihypertensive drugs, cocaine, amphetamine, LSD, etc. use, consumption of monoamine oxidase inhibitors and tyramine-containing foods (cheese, vinegar, alcohol, etc.) and autonomic dysfunction (Gullian Barre, acute spinal cord injury) may cause sympathetic overactivity and cause HE. Changes in consciousness, palpitations, angina, seizures and agitation may be observed.[2,16]

Phentolamine and doxazosin are used to reduce the increased blood pressure in pheochromocytoma. Nicardipine is preferred as an alternative treatment. In patients without sufficient alpha receptor blockade, the use of beta blockers leads to an increase in blood pressure.[16]

When antihypertensive drugs, especially clonidine, are administered to a person using the drug, the blood pressure is brought under control in a short time, while this period may be longer with other drugs.[2]

In autonomic dysfunction, phentolamine, nitroprusside or labetolol may be preferred.[2]

Benzodiazepine is initially used to control hypertension due to narcotic consumption. Nitroglycerin or nicardipine may be preferred as additional agents for blood pressure regulation. The use of beta blockers in the control of high blood pressure caused by these sympathomimetic drugs carries the concern of myocardial ischemia.[2,16]

CARDIAC EMERGENCIES

Acute coronary syndrome (ACS) and acute pulmonary edema are important end-organ damages for HE. The main purpose in ACS is to reduce afterload without reducing left ventricular diastolic filling and to reduce myocardial oxygen consumption. Because in HE, the deteriorated endothelium and underlying atherosclerosis trigger type 1 myocardial infarction (MI). Or, it disrupts the oxygen supply-demand balance and leads to type 2 MI. In the presence of HE with ACS, it is recommended to reduce SBP below 140 mmHg within 1 hour. Nitroglycerin is primarily recommended here. It can reduce ischemia by increasing coronary blood flow. Use with beta blockers such as labetalol reduces reflex tachycardia and indirectly myocardial workload. However, when using it, it should be determined that patients have right MI, use of phosphodiesterase (in the last 24-48 hours), pulse is not below 50 and above 100 per minute and SBP is not below 90 mmHg. Patients can quickly go into prolonged hypotension and cardiogenic shock. Agents that can lead to poor outcomes such as nifedipine should be avoided. It can cause uncontrolled hypotension and impair organ perfusion.[24-25]

Acute hypertensive pulmonary edema is the most common cardiac complication of HE. These patients often have known HT, as well as left ventricular hypertrophy and diastolic dysfunction. Increased systemic pressure increases left ventricular filling pressure, paving the way for pulmonary congestion. Patients may present with cough, pink frothy sputum, dyspnea, inability to lie on their backs, fear of death and palpitations. Congestion, cardiomegaly or mediastinal expansion may be seen in the form of cotton wool on lung imaging. Nitroprusside and nitroglycerin are effective in treatment by reducing preload and afterload. The first step is to reduce blood pressure by 15-25% and basically to gradually reduce SBP below 140 mmHg. Unless contraindicated, beta blockers reduce reflex tachycardia. Loop diuretics are important in reducing symptoms by adding them to the treatment. However, excessive diuresis is not a desired condition. In both pulmonary congestion and ACS, urapidil reduces peripheral vascular resistance and provides an alternative treatment.[25-26]

AORTIC SYNDROMES

Although it can be seen most frequently as aortic dissection, aortic aneurysm rupture, intramural hematoma and aortic ulcer constitute this syndrome. It is the least common cardiac complication of HE. Although aortic dissection is the most common symptom of tearing pain in the chest and back, it can also present with syncope, abdominal pain, flank pain or stroke findings. As the vascular tissue is dissected, the clinical condition of the patients becomes more severe. Progressive clinical conditions such as pericardial tamponade, MI and acute kidney injury may be added. For this reason, SBP should be reduced to 100-120 mmHg and pulse rate should be reduced to less than 60 beats per minute within the first 20 minutes of treatment. Nitroprusside and nitroglycerin are primarily preferred for blood pressure control. Nicardipine is used as an alternative. In addition, beta blockers (esmolol, labetolol) are preferred to control the pulse.[25,27]

RENAL EMERGENCIES

Patients present with newly developed, mostly microscopic hematuria and increased creatinine values. It is recommended that patients' blood pressures be reduced by 20-25% within 3-24 hours. Nicardipine and labetolol are among the drugs that can be preferred.[22,28]

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Case Report

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Mitral annular disjunction as the cause of malignant ventricular arrhythmia in a young adult: a case report

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ABSTRACT

Mitral annular disjunction (MAD) is associated with ventricular arrhythmias and sudden cardiac death (VA/SCD). Risk prediction for VA/SCD in individuals with MAD includes clinical, ECG and imaging markers. Imaging assessment for MAD includes transthoracic echocardiography (TTE) and cardiac magnetic resonance imaging (CMRI) and there are certain features in each modality to aid both diagnosis and risk assessment. A 23-year-old female with no medical history presented to hospital following out of hospital cardiac arrest. Effective bystander CPR and successful cardioversion from ventricular fibrillation to sinus rhythm by paramedics achieved return of spontaneous circulation. Focused transthoracic echocardiography and cardiac magnetic resonance imaging identified MAD. Notably, there were no specific high risk clinical or imaging features. The patient recovered completely and was discharged with implantable defibrillator for secondary prevention. MAD is a rare cause of VA/SCD. Arrhythmias secondary to MAD are more likely with abnormalities on cardiac imaging, including late gadolinium enhancement, fibrosis of the mitral annulus or papillary muscles, mitral valve pathology and ventricular ectopic beats. In this case, none of the traditional risk factors for VA/SCD were present. Thus, MAD remains an important differential in all patients with an otherwise unexplained cardiac arrest, even if high risk features are not present.

Keywords: Primary cardiac tumor, rhabdomyosarcoma, cardiooncology

INTRODUCTION

Mitral annular disjunction (MAD) is a structural cardiac defect that is identified by separation of the mitral annulus and ventricular myocardium in systole. It is commonly associated with mitral valve prolapse (MVP) and resultant mitral regurgitation (MR).[1] The prevalence of MVP in the general population is 2-3%, and a sizeable minority (estimated 30%) of these have associated MAD. Conversely, most but not all patients with MAD (78%) can have concurrent MVP.[2,3]

MAD is associated with ventricular arrhythmias and sudden cardiac death (VA/SCD),[2] and these can occur irrespective of whether MVP is present or absent.[3] Changes in mechanical function of the valvular and annular apparatus, and subsequent tissue changes including regional fibrosis are thought to be the source of VA/SCD.[1] Features associated with higher risk of VA/SCD in MAD include recurrent palpitations, ECG and telemetry changes, longer disjunction distance, and presence of papillary muscle fibrosis on cardiac magnetic resonance (CMR).[2-4]

We present a case of a young adult whose sentinel presentation was aborted cardiac arrest, with hallmark features for MAD on multimodality imaging. Of interest, our case lacked high risk clinical and imaging features for VA/SCD. This case highlights both the heterogeneity of presentation, and the utility of multimodality imaging in conjunction with exclusion of alternative causes for SCD.

CASE

A 23-year-old Caucasian female with no known medical history presented to our hospital following cardiac arrest at work while cleaning windows. A colleague commenced effective bystander cardiopulmonary resuscitation for approximately 10 minutes prior to arrival of paramedics. Initial rhythm was ventricular fibrillation and a single 200 joule shock resulted in successful reversion to sinus rhythm.

A detailed history revealed 2 previous episodes of syncope without presentation to a medical care provider and infrequent, brief palpitations in the preceding 5 years. There was no known family history of cardiomyopathy or SCD. She denied any recreational drug use or excessive exercise. Physical examination was normal.

Electrocardiography (ECG) showed an incomplete right bundle branch block (RBBB) with QRS interval of 112ms. Corrected QT interval was 410 milliseconds. Continuous

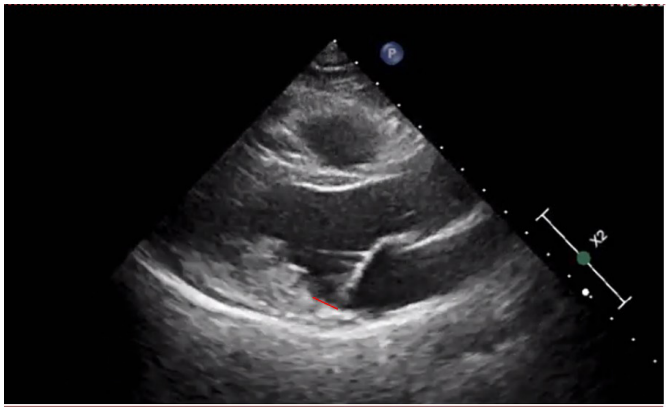

Figure 1. Parasternal long axis window at end systole with MAD distance of 8 mm.

telemetry monitoring did not reveal arrhythmia or significant pauses and intravenous flecainide challenge and high precordial lead ECG did not elicit Bragada pattern ECG changes. Initial bloods were unremarkable apart from mild hypokalaemia (3.1mmol/L) and hyperlactatemia (4.0mmol/L).

Initial transthoracic echocardiography (TTE) showed normal left ventricular size, systolic function and ejection fraction. No valvular or annular pathology was identified apart from trivial MR, and no leaflet thickening. A subsequent focused TTE at a tertiary institution demonstrated MAD, with end systolic distance of 8mm in the posterolateral window.[5] There was minimal leaflet prolapse and trivial MR with slightly posteriorly directed jet (Figure 1).

CMR at our hospital demonstrated 6.6 mm annular disjunction in 3 chamber sequence on the posterior wall (red line; figure 2), with 4mm atrial excursion of the mitral valve leaflets at end systole (blue lines; figure 2). Disjunction was also evident at the inferior wall. There was no myocardial or papillary late gadolinium enhancement (LGE) evident. Posterior wall myocardial 'curling motion' was seen. No other structural deficits were evident, and chamber size and function were in normal ranges. Coronary computed

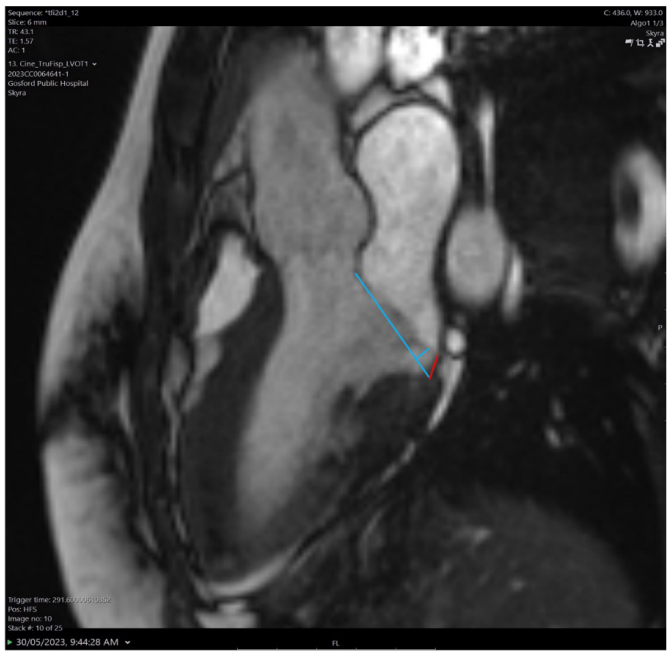

Figure 2. Parasternal long axis sequence, cardiac MRI. Longitudinal MAD distance of 6 mm (red line), with 5 mm atrial excursion of mitral annulus (blue lines).

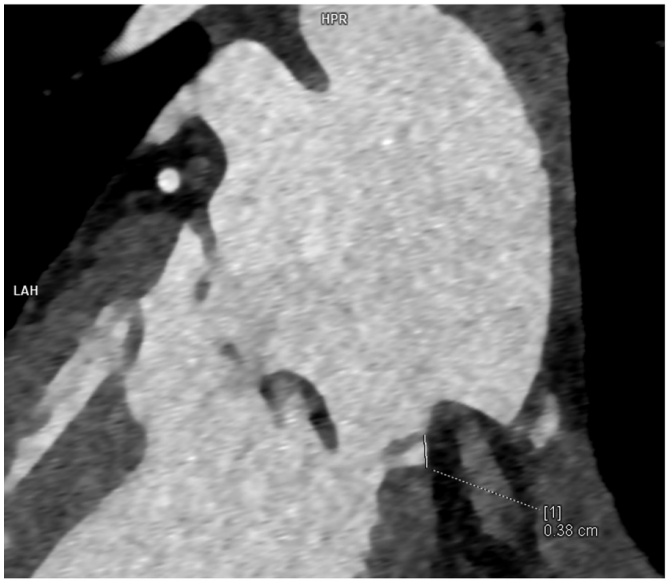

Figure 3. CCTA
Mid diastolic images, with disjunction noted at inferior wall between P1 and P2 scallops of posterior mitral valve leaflet.

tomography angiography (CCTA) acquired in mid diastole demonstrated normal coronary vessels with normal origins. Annular disjunction was again evident (Figure 3).

The patient was transferred to a tertiary institution where exercise stress testing and screening for metanephros's and catecholamines were unremarkable. Implantable cardioverter-defibrillator was inserted for secondary prevention. Genetic testing was not performed as testing to elicit changes consistent with Bragada syndrome and other channelopathies were unremarkable, and an alternative cause for SCD was found.[6]

The patient was discharged home, and at 3 month follow up remained well with no further events or recorded arrhythmias.

DISCUSSION

We present a case of aborted cardiac arrest in a young adult with characteristic imaging features for MAD, and no alternative causes for VA/SCD. In comparison to known high risk features in MAD, our case lacked a number of these. Our patient was significantly younger, with first presentation as cardiac arrest. There were concerning features in the history preceding this admission which were only attained in retrospect, and there was no pre-hospital evidence of arrhythmia or structural heart disease. In addition, there were no high-risk features on the subsequent imaging. Regardless, our case reflects recent studies,[3,4] where the presence of MAD alone can be a high-risk marker for arrhythmic events.

Our case demonstrates some of the utility and limitations of different imaging modalities to diagnose and risk stratify MAD. Firstly, initial TTE at our institution did not identify MAD, and this may have been due to the lack of associated features including MV prolapse or MR to highlight suspicion. Though an initial screening tool, the sensitivity of TTE for MAD is modest, with estimates of approximately 65%,[7] which reflects our experience and highlights the value of integrated imaging to improve diagnostic accuracy. Second, CMR which is considered to have higher sensitivity[4] identified MAD and associated annular displacement and myocardial curling.

This reflects the utility of CMR for the diagnosis of MAD as a gold standard.[1] Papillary fibrosis was not present in our case, however in a high-risk cohort it was only evident in 36% of cases,[3] and this may reflect our patient's young age and lack of time to develop fibrotic changes and other features of mitral dysfunction. The presence of disjunction on the inferolateral wall, only seen in approximately 5% of cases of MAD,[8] may suggest that this feature is associated with VA/SCD. Thirdly, MDCT and subsequent TTE helped confirm the diagnosis, and these reflect both the high specificity of TTE[7] and the potential use of CCTA.[9] Finally, advanced imaging markers including tissue tracking and extracellular volume may have greater predictive utility for diagnosis and stratifying risk,[10] though were not available for this case and remain the subject of ongoing investigation.

A 2022 European heart rhythm association consensus guideline acknowledged that, based on available literature, MAD in the absence of MVP has an unclear association with significant outcomes.[1]

CONCLUSION

This report reinforces the notion that the presentation of MAD is widely heterogenous and should be considered in all individuals with unexplained cardiac arrest, regardless of the presence of MVP. Additionally, risk prediction in these individuals remains unrefined and would otherwise not have predicted VA/SCD in this patient. Ongoing utilization of cardiac imaging markers may further stratify risk in these patients.

ETHICAL DECLARATIONS

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.

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Case Report

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Concomitant pulmonary thromboendarterectomy and supracoronary ascending aorta replacement: a case report

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ABSTRACT

Pulmonary thromboendarterectomy (PTE) is the treatment of choice for patients with operable chronic thromboembolic pulmonary hypertension (CTEPH). PTE can be performed safely with additional cardiac procedures. However, there are not enough publications in the literature regarding the treatment strategy of CTEPH patients with ascending aortic aneurysms. In this case report, we present a successful case of concomitant PTE and supracoronary ascending aorta replacement.

Keywords: Pulmonary thromboendarterectomy, chronic thromboembolic pulmonary hypertension, ascending aorta replacement

INTRODUCTION

Chronic thromboembolic pulmonary hypertension (CTEPH) is a form of the pulmonary hypertensive disease characterized by incomplete or abnormal resolution of acute pulmonary embolism (PE) causing residual emboli.[1] Pulmonary thromboendarterectomy (PTE) is the treatment of choice in patients with operable CTEPH because of its potential to be curative.[2] PTE can be performed safely with other heart surgeries.[3] However, there are not enough publications in the literature regarding the treatment strategy of CTEPH patients with ascending aortic aneurysms (AAA). In this case report, we present a successful case of concomitant PTE and supracoronary ascending aorta replacement (SCAAR) after the development of CTEPH who was previously treated with thrombolytic therapy for acute pulmonary embolism two years ago.

CASE

A 55-year-old (87 kg) male patient was admitted to our clinic with a complaint of progressive dyspnea. Two years ago, there was a thrombus that started from the proximal part of the right pulmonary artery and extended into the segmental and subsegmental branches of the middle and lower lobes (Figure 1). A catheter was placed in the right pulmonary artery and alteplase (5 mg+0.5 mg/h infusion) was administered. In addition, there was deep vein thrombosis (DVT) in the bilateral popliteal vein and right superficial femoral vein. Transthoracic echocardiography (TTE) showed spontaneous echo contrast (SEC) in the left ventricle and patent foramen ovale (PFO) with marked contrast transition from the right atrium to the left atrium. Systolic pulmonary artery pressure (sPAP) was 55 mmHg, left ventricular ejection fraction (LVEF) was 25%, tricuspid annular plane systolic excursion (TAPSE) was 14 mm, and ascending aorta diameter was 41mm. Afterward, he applied to our clinic again due to the progression of dyspnea in the last 6 months. In TTE, LVEF was 60%, sPAP was 73 mmHg, right heart chambers were dilated, and TAPSE was 19 mm. Pulmonary computed tomographic angiography (CTA) revealed a 16mm thrombus at its widest point extending from the main pulmonary artery to both pulmonary arteries (Figure 1). No critical lesion was detected in coronary angiography (CAG), but a lesion was seen in the left main coronary artery (LMCA) (Figure 2), which was thought to be due to pulmonary bifurcation and right pulmonary artery compression. Intravascular ultrasonography (IVUS) (Figure 2) and coronary CTA (Figure 3) revealed external compression. In addition, the ascending aorta was 47 mm in CTA. As a result of right heart catheterization (RHC); mean pulmonary artery pressure (mPAP) was 78 mmHg, pulmonary vascular resistance (PVR) was 22 W, cardiac output (CO) was 2.8 L/min, and cardiac index (CI) was 1.4 L/min/m^2. On the right lower extremity color doppler ultrasound, no thrombus was observed in deep veins. There were no additional features in his history and laboratory parameters. The patient was evaluated multidisciplinary and it was decided to perform PTE and SCAAR.

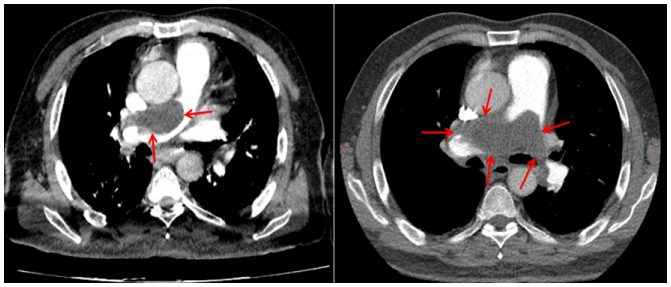

Figure 1. In the left figure, the red arrows indicate the thrombus extending from the proximal right pulmonary artery to the segmental and subsegmental branches of the middle and lower lobes. In the right figure, the red arrows indicate a thrombus extending from the main pulmonary artery to both pulmonary arteries.

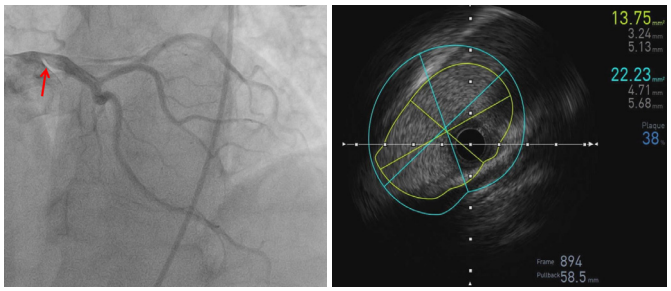

Figure 2. In the left figure, the red arrow shows the lesion at the origin and proximal of the left main coronary artery on coronary angiography. The figure on the right shows an intravascular ultrasonography image consistent with external compression in the left main coronary artery.

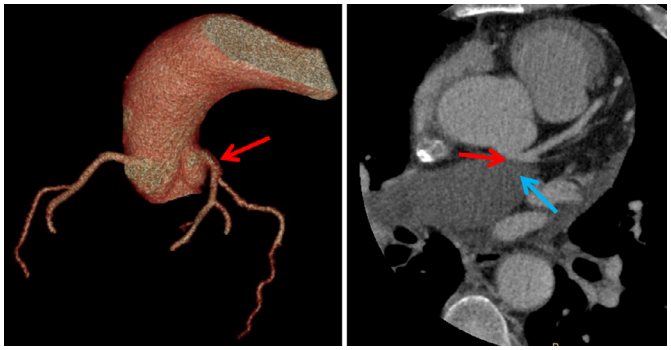

Figure 3. In coronary computed tomographic angiography images, the red arrow in the left figure shows the left main coronary artery. In the right figure, the red arrow indicates external compression by the pulmonary artery to the left main coronary, and the blue arrow indicates the compressing pulmonary artery.

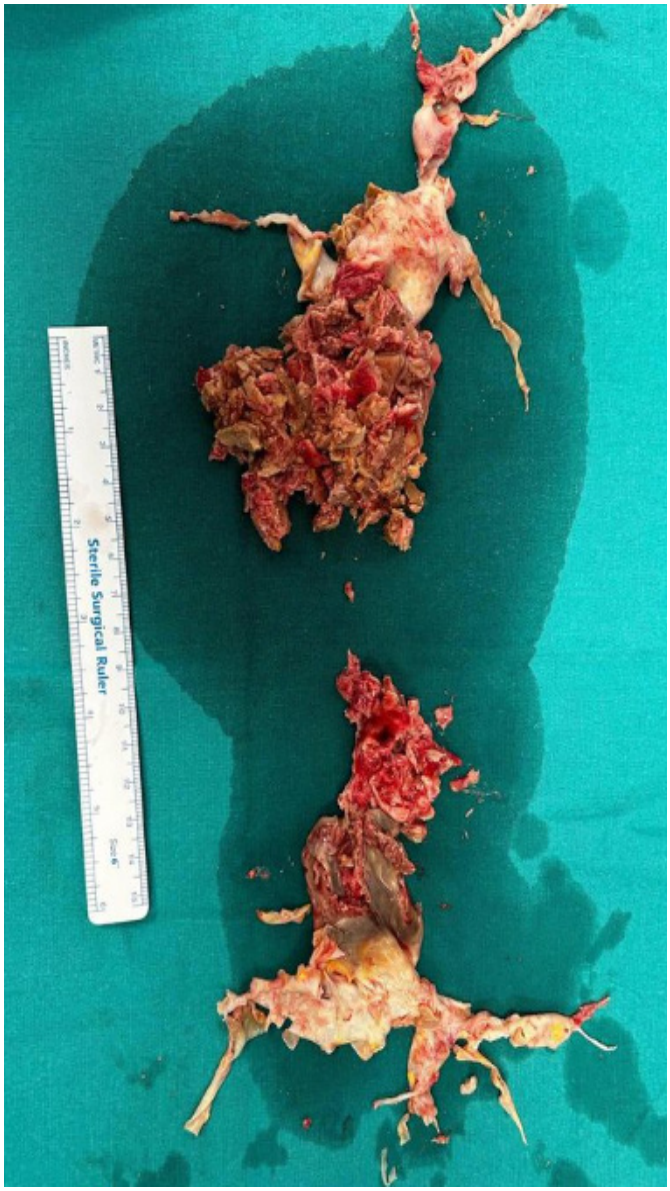

Figure 4. Thrombus removed by endarterectomy from the upper, middle, and lower lobe arteries on the right and from the upper and lower lobe arteries on the left.

After the median sternotomy, aortic and bicaval venous cannulation was performed. Venting cannulas were placed in the pulmonary artery and right superior pulmonary vein. The patient was cooled to 20^{0}C and an arteriotomy was performed on the right pulmonary artery. Level 1 and level 2 lesions were seen at the surgery. After total circulatory arrest (TCA), an endarterectomy was performed on the upper, middle, and lower lobe arteries, respectively, and the arteriotomy was closed (Figure 4). Then, an arteriotomy was performed on the left pulmonary artery. Level 1 and level 2 lesions were seen starting at the pulmonary artery lobe level. Endarterectomy was performed towards the upper and lower lobe arteries at TCA and then the arteriotomy was closed (Figure 4). In the warming phase, the aneurysmatic aorta segment was resected and SCAAR was performed with a 32 mm Intergard graft (Maquet Holding GmbH & Co. KG., Rastatt, Germany). Cross-clamp (XCL) time was 117 min, cardiopulmonary bypass (CPB) time was 335 min, and TCA time was 33 min. He was transferred to the intensive care unit with dobutamine (5 mcg/kg/min). After the operation, there was a total drainage of 575 ml and 1 unit of fresh frozen plasma (FFP) was given. The patient was extubated on the 2nd postoperative day and was discharged on the 7th day with warfarin. As a result of TTE at the postoperative 1st week, LVEF was 40%, sPAP was 20 mmHg, and TAPSE 12 mm. The postoperative PVR could not be seen because the Swan-Ganz catheter could not be placed. He was followed without any complications in the 3 months. Consent form was taken from the patient.

DISCUSSION

It has been reported that PTE may be an option for all patients with CTEPH, including high-risk patients, regardless of the degree of pulmonary hypertension (PH) or right ventricular failure when there is evidence of thromboembolic disease.[4] There are few studies on CTEPH and concomitant cardiac surgeries in the literatüre.[3,5] Although operations such as coronary artery bypass graft (CABG) and heart valve are

frequently reported in these studies, there is no published study on SCAAR to the best of our knowledge. In our case, we present a patient who was given thrombolytic therapy after the development of PE 2 years ago, but subsequently developed CTEPH and additionally underwent SCAAR due to the progression of AAA.

According to the ACC/AHA guideline for aortic diseases published in 2022,[6] there have been some updates in surgical indications compared to previous years. An increase of 3 mm per year in 2 years was determined as the intervention limit, and the intervention limit for the ascending aorta was reduced from 5.5 cm to 5 cm in centers with a multidisciplinary aortic team. In our patient, we decided to replace the ascending aorta because of the 47 mm diameter of the ascending aorta, its enlargement of 6 mm in 2 years, and the need for surgery due to CTEPH.

Additional cardiac interventions during CTEPH surgery increase mortality. It has also been reported that perioperative complication rates are high in patients with high PVR.[3] In our case, the preoperative PVR was 22 W. In addition, the bilateral large amount of thrombus was removed, SCAAR was performed, and the XCL and CPB times were slightly longer than the studies in the literatüre.[3,5] However, there were no complications in the postoperative period, no clinically significant bleeding was observed, and very few blood products were used.

Since our patient is 55 years old, we planned CAG before the operation and we saw a suspicious LMCA lesion. Due to compression of the enlarged pulmonary artery in patients with CTEPH, lesions that appear as stenosis may be seen in LMCA. In the study of Akbal et al.,[7] LMCA compression has been shown to be one of the most important complications of severe pulmonary arterial hypertension. It should be kept in mind that these lesions can be seen in this way due to external compression. IVUS and CTA provide important information in the differential diagnosis.

It has been reported that systemic thrombolytic therapy is the first choice in patients with high-risk PE, and catheter-guided thrombolysis (CDT) may be an alternative in patients who are not suitable for this.[8] However, thrombus may recur over years after thrombolytic therapy, as in our case. Therefore, close follow-up of these patients is extremely important.

In conclusion, patients requiring surgery for CTEPH should be evaluated for other possible cardiac pathologies. For patients requiring additional surgical intervention, this intervention may be appropriately performed during the warm-up period during CTEPH surgery.

CONCLUSION

To the best of our knowledge, our case is the first successful simultaneous PTE and SCAAR operation reported in the literature. These surgeries can be performed concomitantly, safely, and effectively in CTEPH patients with AAA. Cardiac evaluation should be performed in patients with DVT. Close follow-up is important in terms of recurrences after thrombolytic therapy in PE. CTEPH patients may have a stenosis-like appearance in the coronary arteries due to pulmonary artery compression which should be kept in mind in the differential diagnosis.

ETHICAL DECLARATIONS

Informed Consent

The patient signed the 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

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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.

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