ARCHIVES OF THE TURKISH SOCIETY OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

Different Cardio-Selective ß-Blockers and the Prevention of Exaggerated Blood Pressure Response During Exercise: A Retrospective Cross-Sectional Study

Farklı Kardiyoselektif ß-Blokerler ve Egzersiz Sırasında Abartılı Kan Basıncı Yanıtının Önlenmesi: Retrospektif Bir Kesitsel Çalışma

ABSTRACT

Objective: The aim of this study was to analyze the role of various ß-blockers in managing exercise-induced blood pressure escalations, referred to as exaggerated blood pressure response (eBPR). Despite the importance of this phenomenon, there is limited data on the efficacy of ß-blockers in controlling eBPR.

Method: Our retrospective cohort for this study comprised 2,803 individuals who underwent treadmill tests from January 2016 to February 2018. A further subgroup analysis of 1,258 patients receiving ß-blocker treatment was performed to evaluate the influence of different ß-blockers on eBPR.

Results: The results demonstrated that ß-blockers play a significant role in mitigating the occurrence of eBPR (P = 0.026), irrespective of the specific type of ß-blocker. Additionally, no significant variance was observed in the development of eBPR among the different ß-blocker groups (P = 0.532 for systolic blood pressure (BP); P = 0.068 for diastolic BP). This finding remained consistent even among the 992 hypertensive patients, where no notable association was found between the type of ß-blocker and the development of eBPR (P = 0.736 for systolic BP; P = 0.349 for diastolic BP). It is noteworthy that patients using ß-blockers had unique clinical and demographic attributes.

Conclusion: Our study suggests that ß-blockers can potentially deter the development of eBPR during physical activity, a benefit that is consistent across all types of ß-blockers. The study sheds light on prospective randomized studies on the use of eBPR as a new treatment target.

Keywords: Blood pressure, exaggerated blood pressure, blood pressure response to exercise, beta-blockers, atenolol, metoprolol, bisoprolol, carvedilol, nebivolol

ÖZET

Amaç: Egzersiz sırasında sempatik sinir sistemi aktivitesindeki artış dengelenemezse kan basıncında (KB), belirgin bir abartılı kan basıncı cevabı (aKBC) artışı olabilir. Bu çalışmanın amacı, egzersizle tetiklenen kan basıncı artışlarını yönetmede çeşitli ß-blokerlerin rolünü analiz etmektir. Bu fenomenin önemine rağmen, aKBC'yi kontrol etmede ß-bloker etkinliği hakkında sınırlı veri bulunmaktadır.

Yöntem: Çalışmamız, retrospektif ve kesitsel bir çalışma olup Ocak 2016-Şubat 2018 arasında koşu bandı egzersiz testi yapılan 2803 bireyi içeren verilerin alt-grup analizidir. Kardiyo-selektif farklı ß-blokerlerin aKBC üzerindeki etkisini değerlendirmek için ß-bloker tedavisi altındaki 1258 hastanın sonuçları karşılaştırmalı olarak analiz edilmiştir.

Bulgular: Sonuçlarımız, ß-blokerlerin aKBC'nin ortaya çıkmasını önlemede spesifik ß-bloker türüne bakılmaksızın önemli bir rol oynadığını (P = 0.026) göstermiştir. Ayrıca, farklı ß-bloker grupları arasında aKBC gelişiminde anlamlı bir değişiklik gözlenmemiştir (sistolik BP için P = 0.532 ve diyastolik BP için P = 0.068). Bu bulgu, 992 hipertansif hastanın arasında da tutarlıdır, ß-bloker türü ve aKBC gelişimi arasında belirgin bir ilişki bulunmamıştır (sistolik BP için P = 0.736, diyastolik BP için P = 0.349). ß-bloker kullanan hastaların farklı klinik ve demografik özelliklere sahip olduğunu belirtmek önemlidir.

Sonuç: Çalışmamız, ß-blokerlerin fiziksel aktivite sırasında aKBC gelişimini engelleyebileceğini öne sürmektedir, bu fayda tüm ß-bloker türleri arasında tutarlıdır. Bu araştırma, aKBC'yi yeni bir tedavi hedefi olarak kullanma üzerine prospektif-randomize çalışmalar için bir öncül oluşturabilir.

Anahtar Kelimeler: Kan basıncı, abartılı kan basıncı yanıtı, egzersize kan basıncı yanıtı, beta blokörler, atenolol, metoprolol, bisoprolol, karvedilol, nebivolol

ORIGINAL ARTICLE
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Received: April 13, 2023
Accepted: August 08, 2023

Cite this article as: Mert GÖ, Şener E, Yılmaz AS, et al. Different cardio-selective ß-blockers and the prevention of exaggerated blood pressure response during exercise: a retrospective cross-sectional study. *Turk Kardiyol Dern Ars.* 2024;52(1):27-35.

DOI:10.5543/tkda.2023.73480

During exercise, an increase in blood pressure (BP) is a normal response, stemming from heightened sympathetic nerve activity (SNA). This increase in SNA boosts cardiac output to meet the demand of active muscles for oxygen-rich blood. The rise in cardiac output is more pronounced than the decrease in vascular resistance, resulting in a either a slight decrease or no change in diastolic BP, while systolic BP is expected to increase with the intensity of exercise on a treadmill.[1] The increase in cardiac output during exercise can be counterbalanced through peripheral vasodilatation. Without this compensation, a sharp rise in systolic BP may occur, leading to an exaggerated blood pressure response to exercise (eBPR).

Stiffening of the large arteries, due to aging or disease, is a major causative factor of eBPR, although the underlying mechanisms are not yet well understood.[2] Despite its uncertain progression, eBPR has been identified as a prognostic factor for end-organ damage,[3,4] cardiovascular disease,[5-8] stroke,[7,9] and overall mortality[8,10] in patients with hypertension.

ß-blockers have demonstrated superior efficacy in controlling blood pressure better during exercise compared to other antihypertensive drugs.[11,12] Previously, ß-blockers were identified as the only medication significantly associated with the prevention of eBPR in a subgroup of our cohort, which included hypertensive patients.[13] However, there is a lack of data regarding whether different types of ß-blockers have different effects on the management of eBPR. The current study aims to assess and compare the effects of cardio-selective ß-blockers on the development of eBPR.

Materials and Methods

The study was conducted with the approval of the Research Ethics Committee of Eskişehir Osmangazi University (Approval Number: 07.05.2019/18, Date: 07.05.2019), and the data of 2,970 individuals who underwent a treadmill exercise test between January 2016 and February 2018 were collected retrospectively as previously described elsewhere.[13] Briefly, exercise stress tests were performed using a computer-based stress test system equipped with a treadmill and an integrated electrocardiogram (ECG) recorder (Norav 1200HR Stress Test and T2000/T2100 Treadmill Complete System, NORAV Medical GmbH, Wiesbaden, Germany). All individuals underwent either the Naughton or Bruce protocol.[14] Subjects were encouraged to continue until they attained 85% of their age-adjusted target heart rate (HR). A 12-lead ECG was recorded during the exercise. We also recorder their demographics and treadmill exercise test (TET) parameters, including age, gender, body mass index (BMI), indication for TET, TET protocol, total distance, total duration, target HR, max-HR, max-systolic BP, max-diastolic BP, heart rate recovery, peak metabolic equivalents, and estimated peak volume of oxygen inspired. Systolic and diastolic BP were measured non-invasively before and during each exercise stage, as well as during the recovery phase. Concomitant diseases and medications were obtained from the clinical data system.

To define exaggerated blood pressure response (eBPR), the working group employed a previously established definition, which included criteria of a systolic blood pressure exceeding the 90th percentile (> 210 mmHg in males and > 190 mmHg in females) or a difference of at least 50 mmHg in females and 60 mmHg in males between peak and baseline systolic blood pressure throughout the treadmill exercise test.[15-17] After excluding 167 individuals due to insufficient data, 2,803 participants were included in the study for analysis. In these subgroup analyses, 1,258 patients under ß-blocker treatment were evaluated to assess the impact of the type of ß-blocker on eBPR.

Statistical Analysis

The investigation utilized the Statistical Package for the Social Sciences (SPSS) version 25.0 (SPSS, Chicago, IL) for statistical analysis. Continuous variables were presented as mean ± standard deviation. The Shapiro-Wilk test was used to determine the distribution of these variables. Variables following a normal distribution were compared using the independent Student's t-test, while the Mann-Whitney U and Kruskal-Wallis tests were applied to variables with skewed distributions. Categorical variables were presented as frequencies and percentages and were analyzed using the chi-square or Fisher's exact test. A p-value of less than 0.05 was considered statistically significant across all tests.

Results

Among the 2,803 individuals included in the study, 355 (12.7%) developed eBPR. The frequency of eBPR was significantly higher in men and hypertensive patients, whereas it was lower in those on ß-blocker therapy. The eBPR group had higher BMI and age and was more frequently associated with the Bruce protocol, but less frequently associated with heart failure (Figure 1A). Except for ß-blockers, there was no significant difference in medication use between the eBPR and non-eBPR groups. Table 1 demonstrates the association between eBPR development and demographic, clinical characteristics, concomitant diseases, and medications.

Of the 1,258 patients under ß-blocker treatment, those receiving treatment were more likely to be male (60.7% vs. 66.9%; P = 0.001) and older (49.6 ± 11.8 vs. 56.4 ± 10.1; P < 0.001), with more concomitant diseases such as hypertension (HT) (27.0% vs. 47.7%; P < 0.001), diabetes mellitus (22.3% vs. 36.4%; P < 0.001), coronary heart disease (11.4% vs. 55.3%; P < 0.001), heart failure (2.1% vs. 12.6%; P < 0001), and arrhythmias (4.9% vs. 8.3%; P < 0.001). Despite higher comorbidities and medication use in the ß-blocker treatment group, the development of eBPR was significantly lower than in the non-ß-blocker treatment group (13.6% vs. 11.1%; P = 0.026) (Figure 1A).

ABBREVIATIONS

BMI	Body Mass Index
BP	Blood Pressure
eBPR	Exaggerated Blood Pressure Response to Exercise
ECG	Electrocardiogram
GMP	Guanosine Monophosphate
HR	Heart Rate
HT	Hypertension
LV	Left Ventricular
NO	Nitric Oxide
SNA	Sympathetic Nerve Activity
TET	Treadmill Exercise Test

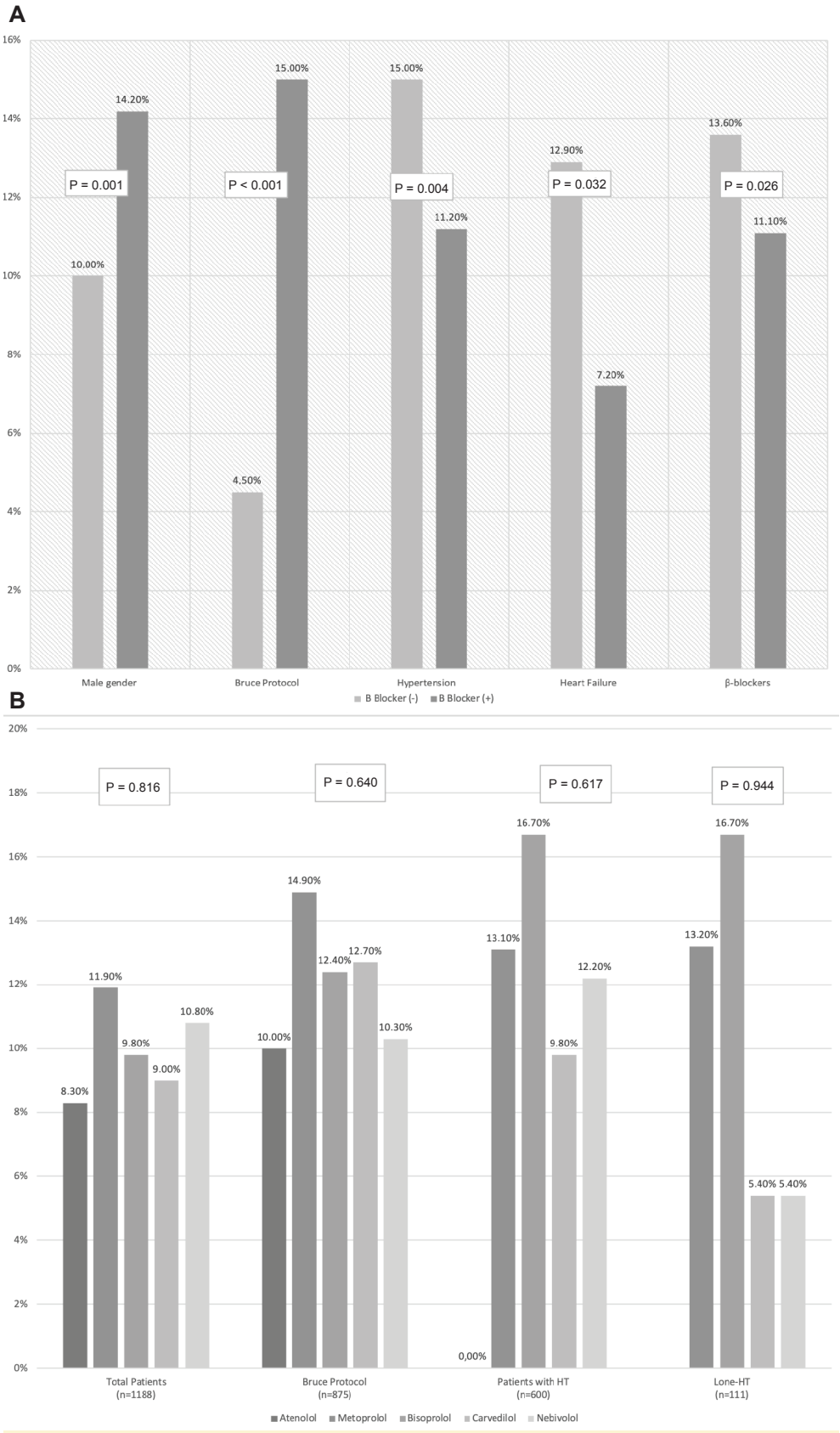

Figure 1. Effect of cardio-selective ß-blockers on exercise-induced blood pressure response. (A) Among patients with varying clinical and demographic characteristics. (B) Among patients undergoing different ß-blocker therapies.

Table 1. Comparison of Demographic Characteristics, Stress Test Parameters, and Medications in Individuals With and Without Exaggerated Blood Pressure Response

	eBPR (-) n = 2,448	eBPR (+) n = 355	*P*
Demographics			
Age (years)	52.2 ± 11.7	54.4 ± 10.6	<0.001
Male, n (%)	1,527 (62.5)	253 (71.3)	0.001
BMI	27.9 ± 4.5	29.5 ± 4.7	<0.001
Smoking, n (%)	465 (19.0)	82 (23.3)	0.057
HT, n (%)	843 (34.4)	149 (42.3)	0.004
DM, n (%)	689 (28.1)	93 (26.4)	0.503
CHD, n (%)	727 (29.7)	108 (30.7)	0.702
Heart Failure, n (%)	154 (6.3)	13 (3.4)	0.032
CVD/TIA, n (%)	59 (2.4)	5 (1.4)	0.246
Total Distance (m)	300.2 ± 123.0	345.1 ± 120.7	<0.001
Stress Test Parameters			
Protocol (Bruce), n (%)	1,852 (75.7)	327 (92.1)	<0.001
Target HR (bpm)	162.8 ± 12.8	161.7 ± 11.9	0.245
Max HR (bpm)	146.4 ± 32.6	156.3 ± 19.6	<0.001
Max SBP (mmHg)	151.0 ± 18.1	188.7 ± 18.8	<0.001
Max DBP (mmHg)	81.4 ± 7.2	92.5 ± 49.8	<0.001
HRR	29.7 ± 16.63	28.8 ± 11.5	0.440
Time	484.2 ± 156.4	518.7 ± 171.4	0.001
METs	10.2 ± 3.5	10.9 ± 2.7	<0.001
VO_2	33.2 ± 18.5	38.9 ± 18.5	<0.001
Total Distance (m)	300.2 ± 123.0	345.1 ± 120.7	<0.001
Medications			
ASA, n (%)	861 (35.2)	127 (12.9)	0.735
Beta blockers, n (%)	1,056 (43.1)	132 (37.5)	0.026
Diuretics, n (%)	685 (28.0)	110 (31.3)	0.202
Doxazosin, n (%)	68 (2.8)	15 (4.3)	0.125
Ca channel blockers, n (%)	472 (17.3)	36 (16.3)	0.693
ACE-I/ARBs, n (%)	534 (21.8)	87 (24.7)	0.222

ACE-I, Angiotensin-converting enzyme inhibitors; ARB, Angiotensin II receptor blockers; ASA, acetylsalicylic acid; BMI, body mass index; Ca, calcium; CHD, coronary heart disease; CVD, cerebrovascular disease; DBP, diastolic blood pressure; DM, diabetes mellitus; eBPR, exaggerated blood pressure response to exercise; HR, heart rate; HRR, heart rate recovery; HT, hypertension; METs, metabolic equivalents; SBP, systolic blood pressure; TIA, transient ischemic attack; VO_2, volume of oxygen consumed.

The study also analyzed the effects of different ß-blockers on eBPR in the 1,258 patients under ß-blocker treatment. Atenolol, metoprolol, bisoprolol, carvedilol, and nebivolol were used, but no statistically significant difference was found between the ß-blocker groups in terms of eBPR development (*P* = 0.816). Although nebivolol and atenolol were less preferred agents in patients with coronary heart disease and heart failure, nebivolol was more preferred in patients with hypertension. Demographic characteristics, stress test parameters, and medications used by patients under ß-blocker treatment are shown in Table 2.

Among the 992 patients with hypertension, 600 (60.4%) were receiving treatment with ß-blockers, including 9 on atenolol, 325 on metoprolol, 58 on bisoprolol, 170 on carvedilol, and 119 on nebivolol. The analysis did not reveal any statistically significant association between the type of ß-blocker and the development of eBPR. The demographics, stress test parameters, and medication of hypertensive subjects among the ß-blocker treatment are demonstrated in Table 3.

A total of 2,140 individuals underwent the Bruce protocol, with 812 (37.9%) of them being under ß-blocker treatment. Among those without ß-blocker treatment, 226 (17.0%) individuals developed eBPR compared to 104 (12.8%) with ß-blocker treatment (*P* = 0.009). However, there was no statistically significant difference in the development of eBPR between patients on different ß-blocker treatments, with 76 (13.8%) on metoprolol, 10 (11.4%) on bisoprolol, and 16 (10.1%) on nebivolol developing eBPR (*P* = 0.422) (Figure 1B).

Table 2. Comparison of Demographics, Stress Test Parameters, and Medications Across Different ß-Blocker Therapies in the Study Population

	Atenolol n = 13	Metoprolol n = 740	Bisoprolol n = 133	Carvedilol n = 170	Nebivolol n = 199	*P*
Demographics						
Age (years)	61.3 ± 10.1	56.4 ± 10.3	56.3 ± 10.5	58.1 ± 9.4	55.0 ± 9.7	0.021
Male, n (%)	5 (38.5)	527 (71.2)	85 (63.9)	114 (67.1)	108 (54.3)	<0.001
BMI	29.9 ± 5.7	28.7 ± 4.35	28.0 ± 4.3	29.3 ± 5.0	28.8 ± 4.3	0.110
Smoking, n (%)	1 (7.7)	143 (19.3)	23 (17.3)	33 (19.3)	25 (12.4)	0.179
HT, n (%)	9 (69.2)	325 (43.9)	58 (43.6)	89 (52)	119 (59.2)	0.001
DM, n (%)	6 (46.2)	257 (34.7)	48 (36.1)	66 (38.6)	81 (40.3)	0.540
CHD, n (%)	6 (46.2)	457 (61.8)	72 (54.1)	103 (60.2)	58 (28.9)	<0.001
Arrhythmias, n (%)	0 (0)	67 (9.1)	13 (9.8)	12 (7.0)	12 (6.0)	0.416
Heart Failure, n (%)	0 (0)	101 (13.6)	10 (7.5)	43 (25.1)	5 (2.5)	<0.001
CVD/TIA, n (%)	0 (0)	27 (3.6)	2 (1.5)	9 (5.3)	4 (2.0)	0.272
Stress Test Parameters						
Protocol (Bruce), n (%)	10 (76.9)	523 (70.7)	96 (72.7)	115 (67.3)	160 (79.6)	0.075
Target HR (bpm)	151.8 ± 8.8	159.5 ± 11.0	158.9 ± 11.6	157.6 ± 11.1	159.3 ± 11.3	0.56
Max HR (bpm)	128.6 ± 17.0	142.1 ± 46.5	138.1 ± 28.2	133.8 ± 23.4	140.6 ± 23.2	0.076
Max SBP (mmHg)	155.8 ± 24.3	155.1 ± 21.8	153.6 ± 20.7	153.4 ± 23.9	156.4 ± 22.1	0.532
Max DBP (mmHg)	80.8 ± 2.9	83.3 ± 35.0	82.0 ± 7.11	82.6 ± 7.43	83.5 ± 9.5	0.068
eBPR, n (%)	1 (8.3)	84 (11.9)	12 (9.8)	14 (9.0)	21 (10.8)	0.816
HRR	25.3 ± 6.6	28.2 ± 12.3	29.4 ± 22.1	28.6 ± 12.0	27.8 ± 10.9	0.808
Time	386.3 ± 139.6	464.1 ± 187.2	476.9 ± 181.6	424.5 ± 169.8	465.7 ± 162.9	0.003
METs	8.7 ± 2.8	9.0 ± 6.2	9.1 ± 4.8	7.8 ± 3.4	9.1 ± 2.9	0.003
VO_2	30.5 ± 9.9	31.4 ± 20.1	30.6 ± 12.3	27.1 ± 12.0	31.5 ± 10.3	0.004
Total Distance (m)	229.2 ± 107.9	275.8 ± 122.1	285.3 ± 133.7	243.2 ± 123.3	282.0 ± 116.5	0.002
Medications						
ASA, n (%)	5 (38.5)	478 (64.6)	74 (55.6)	106 (62)	95 (47.3)	<0.001
Antiaggregants, n (%)	7 (53.8)	574 (77.6)	93 (69.9)	133 (77.8)	110 (54.7)	<0.001
Diuretics, n (%)	9 (69.2)	315 (42.6)	45 (33.8)	95 (55.6)	91 (45.3)	0.001
Doxazosin, n (%)	0 (0)	27 (3.6)	6 (4.5)	10 (5.8)	18 (9.0)	0.052
Ca-channel blockers, n (%)	3 (23.1)	127 (17.2)	20 (15.0)	41 (24.0)	62 (30.8)	<0.001
ACE-I, n (%)	4 (30.8)	277 (37.4)	37 (28.0)	62 (36.3)	63 (31.3)	0.192
ARB, n (%)	3 (23.1)	168 (22.7)	31 (23.3)	54 (31.6)	62 (30.8)	0.286

ACE-I, Angiotensin-converting enzyme inhibitors; ARB, Angiotensin II receptor blockers; ASA, acetylsalicylic acid; BMI, body mass index; Ca, calcium; CHD, coronary heart disease; CVD, cerebrovascular disease; DBP, diastolic blood pressure; DM, diabetes mellitus; eBPR, exaggerated blood pressure response to exercise; HR, heart rate; HRR, heart rate recovery; HT, hypertension; METs, metabolic equivalents; SBP, systolic blood pressure; TIA, transient ischemic attack; VO_2, volume of oxygen consumed.

Table 3. Comparison of Demographics, Stress Test Parameters, and Medications by Type of ß-Blocker in the Hypertensive Population

	Atenolol n = 9	Metoprolol n = 325	Bisoprolol n = 58	Carvedilol n = 89	Nebivolol n = 119	*P*
Demographics						
Age (years)	62.8 ± 11.7	58.2 ± 9.2	58.5 ± 10.4	58.8 ± 9.4	56.1 ± 9.5	0.089
Male, n (%)	3 (33.3)	217 (66.8)	34 (58.6)	56 (62.9)	54 (46.2)	0.001
BMI	28.0 ± 4.9	29.0 ± 4.4	29.3 ± 4.2	29.8 ± 5.8	29.6 ± 4.4	0.566
Smoking, n (%)	1 (11.1)	63 (19.4)	11 (19.0)	23 (25.8)	17 (14.3)	0.311
DM, n (%)	3 (33.3)	162 (49.8)	30 (51.7)	45 (50.6)	52 (43.7)	0.636
CHD, n (%)	3 (33.3)	213 (65.5)	37 (63.8)	53 (59.6)	29 (24.4)	<0.001
Arrhythmias, n (%)	0 (0)	26 (8.0)	5 (8.6)	5 (5.6)	10 (8.4)	0.828
Heart Failure, n (%)	0 (0)	41 (12.6)	3 (5.2)	11 (12.4)	2 (1.7)	0.004
CVD/TIA, n (%)	0 (0)	11 (3.4)	1 (1.7)	6 (6.7)	3 (2.5)	0.408
Stress Test Parameters						
Protocol (Bruce), n (%)	7 (77.8)	242 (74.5)	44 (77.2)	65 (73)	91 (76.5)	0.968
Target HR (bpm)	149.8 ± 8.9	157.2 ± 10.1	156.0 ± 12.4	156.3 ± 11.2	157.3 ± 11.2	0.254
Max HR (bpm)	125.6 ± 17.2	137.9 ± 23.3	136.5 ± 30.9	134.6 ± 23.7	139.0 ± 23.8	0.079
Max SBP (mmHg)	153.8 ± 14.1	158.1 ± 20.2	158.8 ± 23.3	154.5 ± 25.5	157.2 ± 23.1	0.736
Max DBP (mmHg)	81.3 ± 3.5	82.7 ± 8.0	83.2 ± 8.6	82.4 ± 7.5	84.6 ± 8.3	0.349
eBPR, n (%)	0 (0)	40 (13.1)	9 (16.7)	8 (9.8)	14 (12.2)	0.617
HRR	24.8 ± 7.9	27.3 ± 12.5	29.9 ± 2.9	27.9 ± 12.3	28.3 ± 11.0	0.662
Time	341.3 ± 125.6	429.8 ± 165.1	472.5 ± 184.7	404.3 ± 155.8	456.5 ± 170.4	0.054
METs	8.4 ± 2.8	9.1 ± 8.1	9.2 ± 5.8	7.8 ± 3.1	8.7 ± 2.8	0.171
VO_2	29.5 ± 9.8	32.0 ± 27.2	29.5 ± 10.0	27.2 ± 10.8	30.3 ± 9.9	0.222
Total Distance (m)	200.0 ± 103.5	254.6 ± 119.1	274.1 ± 115.2	233.1 ± 116.1	244.9 ± 116.3	0.055
Medications						
ASA, n (%)	3 (33.3)	209 (64.3)	34 (58.6)	58 (65.2)	49 (41.2)	<0.001
Antiaggregants, n (%)	4 (44.4)	260 (80.0)	42 (72.4)	72 (80.9)	58 (48.7)	<0.001
Diuretics, n (%)	7 (77.8)	170 (52.3)	29 (50.0)	55 (61.8)	66 (55.5)	0.285
Doxazosin, n (%)	0 (0)	14 (4.3)	4 (6.9)	6 (6.7)	15 (12.6)	0.052
Ca-channel blockers, n (%)	2 (22.2)	78 (24.0)	16 (27.6)	33 (37.1)	44 (37.0)	0.053
ACE-I, n (%)	3 (33.3)	141 (43.4)	18 (31.6)	29 (32.6)	41 (34.5)	0.156
ARB, n (%)	1 (11.1)	112 (34.5)	22 (37.9)	37 (41.6)	46 (20.2)	0.082
Statins, n (%)	2 (22.2)	191 (58.8)	30 (51.7)	46 (51.7)	40 (33.6)	<0.001

ACE-I, Angiotensin-converting enzyme inhibitors; ARB, Angiotensin II receptor blockers; ASA, acetylsalicylic acid; BMI, body mass index; Ca, calcium; CHD, coronary heart disease; CVD, cerebrovascular disease; DBP, diastolic blood pressure; DM, diabetes mellitus; eBPR, exaggerated blood pressure response to exercise; HR, heart rate; HRR, heart rate recovery; METs, metabolic equivalents; SBP, systolic blood pressure; TIA, transient ischemic attack; VO_2, volume of oxygen consumed.

Discussion

The administration of ß-blockers can reduce the occurrence of eBPR during exercise, irrespective of the specific type of ß-blocker utilized. This holds true even when considering that the cohort receiving ß-blocker treatment typically presents with a higher prevalence of comorbid conditions. Previous studies have underscored the positive impact of ß-blockers on reducing eBPR,[18,19] with our own previous studies also affirming that ß-blocker-based antihypertensive treatments, whether administered as monotherapy or as part of a combination regimen, are associated with lower eBPR.[13] In this study, we aimed to investigate whether different types of ß-blockers have varying effects on eBPR control. However, our findings suggest that the beneficial effects of cardio-selective ß-blockers are not dependent on the type used and can similarly prevent the occurrence of abnormal BP responses during exercise.

Arterial stiffness and endothelial dysfunction are considered possible causes of eBPR. Arterial stiffness reduces arterial compliance, leading to a decreased buffering capacity of BP and an excessive increase in BP during exercise.[20,21] Endothelial dysfunction also contributes to eBPR, potentially through a decrease in endothelium-dependent vasodilation.[8]

In healthy individuals, the effects of increased sympathetic nervous system activity during exercise are balanced by locally produced vasodilator metabolites.[22-24] However, in patients with HT, impaired nitric oxide (NO) signaling may lead to poor endothelium-dependent vasodilation.[22,25] Patients with exercise-induced hypertension were found to have poor endothelium-dependent vasodilation resulting from an impaired pathway involving NO and cyclic guanosine monophosphate (GMP).[26,27] Nebivolol, unlike metoprolol, improves endothelial function by increasing NO discharge.[28,29] In an experimental model, nebivolol was found to have favorable effects during exercise due to its vasodilating properties in addition to its conventional ß-blocking and BP-lowering effects.[22] However, in a study of 60 mild HT patients, metoprolol and nebivolol provided comparable control of BP during exercise.[30] Our large cohort study found that nebivolol had a similar effect as other ß-blockers in clinical practice in blunting the development of eBPR, regardless of whether HT was present or not.

Endothelial dysfunction leads to a decrease in nitric oxide (NO) bioavailability, resulting in arterial stiffening and an increase in resting systolic blood pressure.[31,32] However, during exercise, other factors may have a greater influence on blood pressure regulation, and alternative mechanisms may predominate when the NO/GMP pathway is blocked by nebivolol.[33-35] Moreover, the accumulation of metabolites is detected by chemoreceptors within the active musculature, while a central-feedback mechanism relating to the required frequency and amplitude of muscular contraction is provided by peripheral mechanoreceptors during dynamic exercise. Both sets of receptors may play a role in modulating the vasoactive state and blood pressure during exercise by increasing sympathetic outflow.[24,36] Our clinical results suggest that sympathetic nerve activity (SNA) due to stiffness, rather than the NO/GMP pathway, is the predominant cause of eBPR. This may explain the lack of eBPR prevention by nebivolol, despite its additional influence on the NO/GMP pathway during exercise. Hence, the advantageous effects of ß-blockers during exercise may stem from their competitive antagonism of SNA, which orchestrates the fight-or-flight response.

In our study, we examined the impact of two different exercise protocols, Naughton and Bruce, on eBPR. Our findings indicate a higher likelihood of eBPR development in patients subjected to the Bruce protocol compared to those who followed the Naughton protocol. This discrepancy could be attributed to the more substantial workload increments in the Bruce protocol, which may pose a challenge for certain demographic groups, including the elderly, individuals with obesity, or those experiencing musculoskeletal discomfort. Conversely, the Naughton protocol, characterized by gradual increases in workload, emerges as a more suitable alternative for these particular patients.[14] Intriguingly, our data revealed that 75% of patients adhering to the Bruce protocol did not develop eBPR, underscoring the potential influence of other unidentified and complex factors on blood pressure responses during exercise.

Compared to normotensive individuals, eBPR is more common in patients diagnosed with HT.[37-39] The Framingham Heart Study previously established a high occurrence of left ventricular (LV) hypertrophy in subjects with eBPR,[40] a condition indicative of target organ damage and associated with increased mortality rates in HT patients.[41,42] Furthermore, endothelial dysfunction, a major cause of eBPR, has been identified in patients with atherosclerosis, constituting a risk factor for coronary artery disease.[26] Recognizing eBPR holds substantial value beyond resting blood pressure measurement, as excessive BP elevations during exercise can impair target organs and increase mortality risks.[43,44] Elevated BP levels, both during exercise and at rest, are associated with alterations in LV structure and poorer outcomes, highlighting the need for dynamic BP management as an emerging treatment focus. Our findings align with previous studies, demonstrating the superiority of ß-blockers over other antihypertensive medications in managing exercise-induced BP. Furthermore, individuals receiving ß-blocker-based treatments exhibited a reduced likelihood of developing eBPR in routine clinical settings.[11,30]

Current guidelines for the management of HT recommend the use of ß-blockers solely for patients with comorbidities such as previous myocardial infarction, coronary heart disease, heart failure, or arrhythmias. In our study, the group of patients using ß-blockers presented diverse baseline clinical and demographic characteristics. Nonetheless, we believe this discrepancy provides a more accurate reflection of clinical practice and plays a crucial role in demonstrating the effectiveness of ß-blockers through real-life data. Although the ß-blocker group included a larger number of concurrent diseases, resulting in an elderly and high-risk population, we contend that this may have enhanced rather than limited the study's power. It is vital to emphasize that ß-blockers are not the recommended first-line therapy for HT; however, certain aspects require further consideration. Physicians often base their decisions regarding the initiation of antihypertensive drugs and the scheduling of outpatient follow-ups on BP measurements taken at rest in the clinic. This practice could account for the persistent higher risk of cardiovascular events and mortality in HT patients, despite achieving BP targets with optimal treatment, compared to normotensive individuals.[45-47] Further research is needed to ascertain whether an abnormally excessive hypertensive response during exercise could represent a new treatment target and to determine if ß-blockers should be the priority in treating this patient group. Our study has demonstrated that the use of ß-blockers, whether for concomitant conditions or for HT alone, prevents the development of eBPR to exercise. This benefit was observed consistently, regardless of the specific type of ß-blocker used.

Limitations

eBPR can manifest at any level of exercise intensity, whether during or immediately after physical activity, and is associated with a low level of fitness.[48,49] However, our study is significantly limited by the absence of data on cardiorespiratory fitness levels, and the lack of follow-up due to its retrospective design. Additionally, our results may vary according to the exercise stress test protocol used; the Naughton protocol, which allows for a more gradual increase with shorter stages, is preferred for elderly or deconditioned patients.[14] A major limitation of our study is also the lack of information on the doses of ß-blockers and the levels of treatment goals achieved, which may have influenced the results and potentially explain the absence of observed differences between the various ß-blockers. Furthermore, our study faced challenges due to missing data

regarding why patients were prescribed ß-blockers and why they underwent treadmill exercise tests. Given the study's design, the only clear groups we could identify in terms of indications for ß-blocker use were patients with a history of myocardial infarction and cardiovascular disease.

Conclusion

Our study suggests that ß-blockers can potentially prevent the development of an eBPR during physical activity, with this benefit being consistent across all types of ß-blockers. The importance of eBPR is underscored by its correlation with LV hypertrophy, a key indicator of target organ damage, and a heightened risk of mortality. This lays the groundwork for future prospective-randomized studies to consider eBPR as a novel treatment target. As we look towards future strategies, it is possible that observing exercise BP might become an essential component in the prevention and management of cardiovascular diseases.

Ethics Committee Approval: The study was conducted with the approval of the Research Ethics Committee of Eskişehir Osmangazi University (Approval Number: 07.05.2019/18, Date: 07.05.2019),

Informed consent: Informed consent was deemed unnecessary due to the retrospective nature of the study.

Author Contribution: Concept - G.Ö.M., E.Ş., A.S.Y., F.Y., E.Ç., F.E.D., M.D., Y.Ç., S.M., B.G., K.U.M.; Design - G.Ö.M., E.Ş., A.S.Y., F.Y., E.Ç., F.E.D., M.D., Y.Ç., S.M., B.G., K.U.M.; Supervision - G.Ö.M., E.Ş., A.S.Y., F.Y., E.Ç., K.U.M.; Resource - G.Ö.M., E.Ş., A.S.Y., F.Y., E.Ç., F.E.D.; Materials - G.Ö.M., E.Ş., A.S.Y., F.Y., E.Ç., F.E.D.; Data Collection and/or Processing - G.Ö.M., E.Ş., A.S.Y., F.Y., E.Ç., F.E.D., M.D., Y.Ç., S.M., B.G., K.U.M.; Analysis and/or Interpretation - G.Ö.M., E.Ş., A.S.Y., F.Y., E.Ç., F.E.D., M.D., Y.Ç., S.M., B.G., K.U.M.; Literature Review - G.Ö.M., E.Ş., A.S.Y., F.Y., E.Ç., F.E.D., M.D., Y.Ç., S.M., B.G., K.U.M.; Writing - G.Ö.M., K.U.M.; Critical Review - G.Ö.M., E.Ş., A.S.Y., F.Y., E.Ç., F.E.D., M.D., Y.Ç., S.M., B.G., K.U.M.

Peer-review: Externally Peer-reviewed.

Conflict of Interest: No conflicts of interest have been declared by the authors.

Funding: The authors declared that this study received no financial support.

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