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The relationship of masked hypertension with autonomic dysfunction and cardiometabolic parameters: a case-control study

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Abstract. – OBJECTIVE: Masked hypertension (MH) is associated with cardiovascular events and mortality. Data on the association between exaggerated blood pressure response (EBPR) to exercise, heart rate recovery (HRR), which are indicators of autonomic dysfunction, and MH are lacking. This study aimed at evaluating the association between EBPR, HRR, and MH.

PATIENTS AND METHODS: Between January 2020 and January 2021, 130 MH (57 male, median age = 52.8 years) and 60 healthy (28 male, median age = 40.8 years) subjects were included in this single-center, case-control, and cross-sectional study. Office blood pressure measurement, 24-hour ambulatory blood pressure monitoring, treadmill test, echocardiography, and specific biochemical parameters were evaluated.

RESULTS: The frequency of blunted HRR (73 subjects, 56.2%) and EBPR (40 subjects, 30.8%) were significantly higher in patients with MH ($p < 0.001$). Patients with MH had higher serum uric acid levels and frequency of hyperlipidemia ($p < 0.05$). Diameters of the left atrium (LA), aortic root, and ascending aorta were significantly higher in MH patients ($p < 0.05$). Thirty-two (24.6%) patients with MH had left ventricular hypertrophy and 33 (25.4%) had diastolic dysfunction ($p < 0.001$). Multivariate analysis identified the presence of blunted HRR as an independent predictor factor of MH as well as smoking, hyperlipidemia, GFR, LA diameter, and aortic root diameter were other independent factors.

CONCLUSIONS: The frequency of blunted HRR and EBPR were significantly higher in the MH group compared to the control group, suggesting a close relationship between MH and autonomic dysfunction.

Key Words:
Masked hypertension, Autonomic dysfunction, Heart rate recovery, Exaggerated blood pressure response.

Introduction

Hypertension is the most important risk factor for cardiovascular-related morbidity and mortality and is one of the main causes leading to cerebrovascular and kidney diseases[1,2]. Since office blood pressure (BP) may mislead, out-of-office BP measurements (self-home or ambulatory BP monitoring) should be used for the diagnosis and decision of the treatment, especially in those with BP close to the hypertension cut-off range[3-5]. In some patients, while the BP measured during the examination is constantly high, the daytime or 24-hour ambulatory BP values are within the normal range, which is defined as white coat hypertension (WCH). The contrary, measuring the BP as normal in the clinic or office but high in the out-of-office is defined as masked hypertension (MH)[6].

Numerous studies[6-9] reported that MH causes aortic stiffness, end-organ damage and renal injury, leading to a significantly increased risk of the incident cardiovascular events. The frequency of MH has been reported to vary between 15% and 60%, depending on the assessment method[7,10,11]. It is vital to evaluate this clinical entity with ambulatory or home BP measurements in selected patients.

MH may be associated with an increased sympathetic system activity, decreased heart rate recovery (HRR), and impaired microcirculation[12,13]. Exaggerated BP response to exercise (EBPR), known to be associated with increased sympathetic activity, is also associated with end-organ damage and plays an important role in the development of essential HT or MH[14,15]. The decrease in HRR, evaluated non-invasively during the treadmill test, is an indicator of autonomic dysregulation, and is a strong predictor which can be used in overall mortality[16].

There are limited studies investigating the relationship between MH, EBPR and HRR[14,15,17]. We hypothesized that impaired autonomic regulation in patients with MH may be an important factor in terms of increased cardiovascular risk

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in the future. This study aimed at evaluating the autonomic function indicators, such as EBPR and HRR, in patients with MH, and also investigate their association with some specific metabolic and echocardiographic parameters.

Patients and Methods

All participants included in this single-center, case-control, and cross-sectional study were informed about the scope of the study and their informed written consent was obtained. The study was evaluated and approved by Local Ethical Committee of Kırıkkale University Hospital, Kırıkkale, Turkey in terms of compliance with the Helsinki principles (Date: 10.02.2022, Approval No. 2022.03.17). Between January 2020 and January 2021, a total of 190 patients (130 with MH and 60 healthy controls), aged between 18 and 80 years, with normal renal function tests, were included in this study. Cases with systemic disease (secondary hypertension, severe liver or kidney disease, neurological disorder, or malignant disease) that would affect the results of the study were excluded from the study.

Blood Pressure Measurement and 24-Hour Ambulatory Blood Pressure Monitoring

Office BP measurement was carried out by the same doctor by measuring 3 times with an interval of 5 minutes. The mean of systolic blood pressure (SBP) and diastolic blood pressure (DBP) measurements were recorded.

24-hour ambulatory blood pressure monitoring (ABPM) was performed on each participant's non-dominant arm. The accuracy of the ABPM device was confirmed with a standard mercury sphygmomanometer. The measurements between 08:00 AM and 10:00 PM were defined as daytime, and those between 10:00 PM and 08:00 AM were defined as nighttime. The device was set to measure at 20-minute intervals in the daytime and 40-minute intervals at nighttime. 24-hour mean SBP and DBP levels in the daytime, nighttime, and BP variability were calculated.

The diagnosis of MH was evaluated according to the 2018 ESC criteria[4]. Accordingly, while office BP was normal (<140/90 mmHg), MH was diagnosed if at least one of the following criteria was detected: the daytime mean BP greater than or equal to 135/85 mmHg, 24-hour mean BP greater than or equal to 130/80 mmHg.

Treadmill Test

During the procedure, SBP and DBP measurements were performed at 3-minute intervals in the non-dominant arm with an automatic device. The measurements of HR and BP were recorded at the end of each 3-min stage at peak exercise and at 1-min and 2-min intervals throughout recovery. Peak exercise SBP $\geq$ 210 mmHg in men and $\geq$ 190 mmHg in women was defined as EBPR. During the recovery phase, subjects continued walking at 1.5 mph for 1 minute, followed by 3 minutes of sitting and resting, with continuous monitoring of BP, HR, and heart rhythm. Blunted HRR was defined as a HR difference $\leq$ 12 bpm between peak HR and HR 1 minute after peak HR.

Echocardiographic Measurements

Echocardiography was performed by the same physician on all subjects using the Vivid 7 Doppler echocardiographic unit (GE Vingmed Ultrasound, Horten, Norway). Two-dimensional and M-mode echocardiography were utilized to investigate ejection fraction (EF), left ventricular mass index (LVMI), the left atrium (LA) diameter, the diameter of the aortic root, and the ascending aortic diameter. Tissue doppler imaging techniques were used to assess the following: late diastolic myocardial velocity (Am), early diastolic myocardial velocity (Em), Em/Am ratio (Em/Am). Increased Am, decreased Em and Em/Am ratios implied a decreased ventricular diastolic function. For further analyses, the average value of the measurements obtained along with three consecutive cardiac cycles was used.

Statistical Analysis

SPSS 25.0 program (IBM Corp., Armonk, NY, USA) was used in the analysis of the variables. While the normal distribution of the data was evaluated with the Shapiro-Wilk Francia test, the Levene's test was used to evaluate the homogeneity of variance. In the comparison of the quantitative data of two independent groups, Independent-Samples *t*-test with the Bootstrap results or the Mann-Whitney U test with Monte Carlo results were used. In the comparison of categorical variables, the Pearson Chi-Square test with the Monte Carlo Simulation technique was performed and column ratios were compared with each other using the Benjamini-Hochberg method. Odds ratio with 95% confidence intervals was used to determine how many times more effects were caused by those who were exposed to a risk factor compared to those who were not.

Receiver operating characteristics (ROC) curves were used to define the cut-off value of uric acid that yielded the highest sensitivity and specificity. Multiple logistic regression test (Backward Stepwise, Wald) was used to determine the cause-effect relationship between MH groups and the explanatory variables. While quantitative variables were expressed as mean±standard deviation and median [percentile 25 (q1) / percentile 75 (q3)], categorical variables were shown as numbers (%). The variables were analyzed at a 95% confidence level, and a *p*-value lower than 0.05 was considered significant.

Results

Between January 2020 and January 2021, 130 MH (57 male, median age = 52.8 years) and 60 healthy (28 male, median age = 40.8 years) subjects were included in the study. The median age of the patients with MH was significantly higher than the control group's ($p < 0.001$). Both groups were similar in terms of gender, BMI, and the diabetes mellitus rate ($p = 0.755$, $p = 0.058$, $p = 0.067$, respectively). The frequency of smoking habits was significantly higher in the MH group ($p < 0.001$). In laboratory data, patients with MH had lower hemoglobin and glomerular filtration rate (GFR), higher serum uric acid levels, and frequency of hyperlipidemia ($p < 0.05$). According to echocardiographic measurements, EF was lower in patients with MH, but LA diameter, aortic root diameter, and ascending aorta diameter were significantly higher in the MH group ($p < 0.05$). In addition, 32 (24.6%) patients with MH had left ventricular hypertrophy (LVH) and 33 (25.4%) had diastolic dysfunction ($p < 0.001$) (Table I).

HR (basal, maximum, and mean), SBP (daytime, nighttime, and during exercise), DBP (daytime, nighttime, and during exercise) and mean BP (daytime and nighttime) values were found to be significantly higher in patients with MH ($p < 0.05$) (Table II). The frequency of blunted HRR (73 subjects, 56.2%) and EBPR (40 subjects, 30.8%) were significantly higher in MH group ($p < 0.001$) (Table II, Figure 1).

Multivariate logistic regression analysis revealed that the presence of blunted HRR, smoking, hyperlipidemia, lower GFR, increased LA diameter, and aortic root diameter were found to be associated with MH ($p < 0.05$) (Table III).

Discussion

The most important finding of this study was that the frequency of blunted HRR and EBPR, which are indicators of autonomic dysfunction,

Table I. Comparison of the demographic, clinical, echocardiographic, and laboratory characteristics of the two groups.

	Total (n = 190)	Control (n = 60)	Masked hypertension (n = 130)	Odds Ratio (95% CI)	p
Age, years	49 ± 9.5	40.8 ± 5.6	52.8 ± 8.4	1.3 (1.2-1.4)*	< **0.001**[a]
Gender, male, n (%)	85 (44.7)	28 (46.7)	57 (43.8)	-	0.75[c]
Body mass index, kg/m^2	22.4 (21.5/23.1)	22.3 (21.55/22.9)	22.5 (21.4/23.4)	-	0.06[b]
Smoke, n (%)	100 (52.6)	8 (13.3)	92 (70.8)	15.7 (6.8-36.3)	< **0.001**[c]
Diabetes mellitus, n (%)	34 (17.9)	6 (10.0)	28 (21.5)	-	**0.06**[c]
Hyperlipidemia, n (%)	65 (34.2)	8 (13.3)	57 (43.8)	5.1 (2.2-11.5)	< **0.001**[c]
Uric acid, mg/dL	5.1 (4.22/6)	4.4 (4/4.95)	5.5 (4.5/6.36)	2.4 (1.7-3.4)*	< **0.001**[b]
Hemoglobin, gr/dL	14.3 (13.4/15.2)	14.7 (13.9/15.2)	14.1 (13.3/15.2)	0.8 (0.6-0.9)*	0.**033**[b]
Glomerular filtration rate, mL/min	103.3 (95/115)	118 (113/122.5)	98.5 (84.74/106)	0.8 (0.8-0.9)*	< **0.001**[b]
Resting heart rate, beats/minute	80.5 (74/91)	78.5 (73/89.5)	81 (75/92)	-	0.36[b]
Ejection fraction, %	63 (60/65)	65 (60/65)	62 (5 /65)	0.9 (0.80.9)*	< **0.001**[b]
Left atrium diameter, mm	34 (32/36)	33 (31.5/35)	34 (33/36)	1.2 (1.05-1.3)*	**0.005**[b]
Aortic root diameter, mm	33 (31/34)	31 (30/33)	34 (32/35)	1.4 (1.2-1.6)*	< **0.001**[b]
Ascending aorta diameter, mm	32 (30/34)	30 (29/32)	33 (31/35)	1.5 (1.3-1.8)*	< **0.001**[b]
Left ventricular hypertrophy, n (%)	32 (16.8)	0 (0)	32 (24.6)	-	< **0.001**[c]
Diastolic dysfunction, n (%)	33 (17.4)	0 (0)	33 (25.4)	-	< **0.001**[c]

[a]Independent Sample *t*-test (Bootstrap), [b]Mann-Whitney U test (Monte Carlo), [c]Pearson Chi-Square Test (Monte Carlo), [rc]Roc Curve Analysis (Youden index J-Honley&Mc Nell), AUC: Area under the ROC curve, SE: Standard Error, *Odds Ratio data were obtained by Logistic Regression Analysis, [ss]Sensitivity, [sp]Specificity, CI: Confidence Interval. Data are given as mead ± SD, median [IQR 25 (q1)-75(q3)] percentiles or numbers (%).

Table II. Parameters of treadmill test and 24-hour ambulatory blood pressure monitoring.

	Total (n = 190)	Control (n = 60)	Masked hypertension (n = 130)	p
Heart Rate, bpm				
Rest heart rate	91.1 ± 14.8	78.9 ± 9.4	96.72 ± 13.5	**0.001**[a]
Max heart rate	153 (142 161)	151 (143.5/ 160.5)	154 (141/161)	0.43[b]
HR at recovery 1st min	142 (130/150)	135 (128.5/145)	144.5 (130/151)	**0.008**[b]
HR at recovery 2nd min	126 (115/137)	118 (10 /131)	131 (121/141)	< **0.001**[b]
Mean heart rate	108.5 (100/119)	101 (94.5/110)	111 (102/122)	< **0.001**[b]
Blunted HRR, n (%)	80 (42.1)	7 (11.7)	73 (56.2)	< **0.001**[c]
Systolic BP, mmHg				
During exercise	167.5 (150/ 85)	140 (135/145)	175 (165 190)	< **0.001**[b]
Daytime	151 (118 / 173)	110 (105/117.5)	164 (150/184)	< **0.001**[b]
Nighttime	130.9 ± 27.2	97.0 ± 8.8	146.5 ± 16.4	**0.001**[a]
Nondippers, n (%)	10 (6 12)	11 (11/13)	8 (4/11)	< 0.001[b]
Office blood pressure	120 (110/130)	120 (110/130)	120 (110/130)	0.96[b]
EBPR, n (%)	41 (21.6)	1 (1.7)	40 (30.8)	< **0.001**[c]
Diastolic BP, mmHg				
During exercise	100 (90 105)	90 (85/92.5)	105 (95/110)	< **0.001**[b]
Daytime	97 (76/109)	72.5 (70/75)	105.5 (96/116)	< **0.001**[b]
Nighttime	81 (65/96)	61 (60 / 65)	89.5 (81 99)	< **0.001**[b]
Non-dippers, n (%)	13 (10/ 6)	14 (12.5/ 5)	12.5 (7/16)	**0.008**[b]
Office blood pressure	70 (65/80)	70 (65/80)	70 (65 80)	0.97[b]
Mean BP, mmHg				
Daytime	112.5 ± 22.4	84.5 (80 / 89)	123 (114/137)	**0.001**[a]
Nighttime	100.5 (78 / 114)	74.43 (5.33)	108.85 (13.25)	< **0.001**[b]

[a]Independent Sample *t*-test (Bootstrap), [b]Mann-Whitney U test (Monte Carlo), [c]Pearson Chi-Square Test (Monte Carlo). Data are given as mead ± SD, median [IQR 25 (q1)-75(q3)] percentiles or numbers (%), Non-dippers, < 10% reduction in blood pressure during nighttime. BP, blood pressure; EBPR, exaggerated blood pressure response; HRR, heart rate recovery.

were significantly higher in patients with MH than in healthy controls, suggesting the relationship between MH and autonomic dysregulation. The mechanism of MH has not been elucidated yet. In a small number of studies[12,13,18,19], it has been shown that MH may be associated with the predominance of the sympathetic system, autonomic dysregulation due to deterioration in the parasympathetic system, or impaired microcirculation. In addition, various studies[20-22] have reported that the frequency of MH is increased in various conditions, such as intense and stressful lifestyle, advanced age, male gender, smoking, microalbuminuria, increased sodium intake, diabetes mellitus, sedentary lifestyle, and sleep apnea syndrome. In our study, both groups were similar in terms of gender, BMI, and the frequency of diabetes mellitus, unlike the literature data. However, the median age, hyperlipidemia, and the frequency of smoking status were significantly higher in patients with MH.

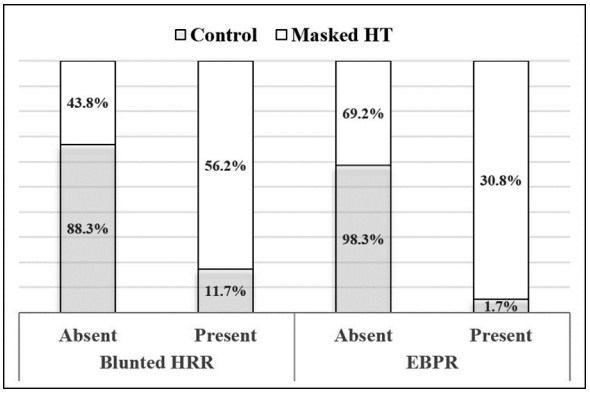

Figure 1. Distribution of exaggerated blood pressure response (EBPR) to exercise and blunted heart rate recovery (HRR) percentages in masked hypertension and control groups.

In our study, serum uric acid levels were significantly higher in the MH group. Similarly, Çalişkan et al[23] reported significantly higher serum uric acid levels in MH subjects. Some studies[24,25] suggested that elevated uric acid levels may predispose to the risk of endothelial dysfunction, development of hypertension, and cardiovascular diseases. High uric acid levels may cause hypertension by many mechanisms, such as activation

Table III. Risk factors associated with the masked hypertension according to multivariate logistic regression analysis.

Reference group: masked hypertension (+)	p	Odds ratio	95% Confidence interval for odds ratiol	
			Lower bound	Upper bound
Smoking (Present)	0.001	48.810	5.201	458.097
Hyperlipidemia, (Present)	0.015	14.820	1.689	130.069
Blunted HRR (Present)	0.003	16.,826	5.873	4,625.566
Glomerular filtration rate (mL/min) ↓	0.001	1.282	1.113	1.478
Ejection fraction (%) ↓	0.09	1.228	0.967	1.560
Left atrium diameter (mm) ↑	0.006	4.402	1.531	12.653
Aortic root diameter (mm) ↑	0.001	14.408	2.796	74.256
Constant	0.217	-	-	-

Predicted Masked hypertension (+) = 97.7; Predicted Control = 95. Predicted overall: 96.8; p-value < 0.001. Multiple Logistic Regression (Backward Stepwise, Wald). HRR, heart rate recovery.

of the renin-angiotensin system, causing renal afferent arteriopathy and tubulointerstitial disease, or inhibition of nitric oxide production, leading to endothelial dysfunction[26,27]. Based on that evidence, our study suggested that higher uric acid levels may contribute to the development of MH.

Several studies[8-10] have shown that the incidence of cardiovascular events in MH patients is higher than in normotensive healthy people, as in sustained hypertension, suggesting the malignant nature of MH. In a recent systematic review that evaluated 14,729 participants, cardiovascular morbidity and all-cause mortality were reported to be significantly higher in MH subjects than in those with WCH or normotension[28]. Moreover, after antihypertensive treatment, the risk of cardiovascular events and mortality continued to be significantly higher in patients with MH than in normotensive patients[28]. It was revealed that MH may increase aortic stiffness, carotid intima/media thickness, and pulse wave velocity causing left ventricular hypertrophy and renal damage[8,9]. Liu et al[29] showed that left ventricular mass indexes in patients with MH were similar to patients with sustained hypertension and higher than those in normotensive patients, suggesting that MH may cause end-organ damage similar to sustained hypertension. In a study, it was reported that coronary microvascular damage began to occur even before left ventricular hypertrophy in patients with MH, and the risk of end-organ damage was comparable to sustained hypertension[30]. In our study, similar to literature, LA diameter, aortic root diameter, ascending aorta diameter, and the frequency of left ventricular hypertrophy and diastolic dysfunction were significantly higher in the MH group.

HRR is an easy, non-invasive and cheap method to interpret, used in the analysis of autonomic nervous function (especially parasympathetic reactivation) and is evaluated according to the HR variability obtained during the treadmill test. The HR, which increases with the combination of sympathetic nervous system activation and parasympathetic nerve inhibition during exercise, is expected to decrease during the early resting phase, led by the parasympathetic nervous system, regardless of age and exercise intensity[31,32]. If the parasympathetic nervous system diminishes, the expected decrease in HR cannot occur during the resting phase, which is defined as blunted HRR[16,31,32]. Blunted HRR has been considered a strong predictor of overall mortality independent of coronary heart disease or heart failure[32]. To the best of our knowledge, this is the first study investigating the relationship between MH and HRR. We detected blunted HRR in more than half (56.2%) of patients with MH, suggesting the adverse cardiovascular effect of MH.

BP response during exercise is an important predictor of sustained hypertension and was reported[33] to be associated with cardiovascular disease risk and mortality. For the first time, Nazar et al[34] showed that young normotensive men with EBPR to exercise are predisposed to the development of MH and then, similar findings were reported in the study of Kayrak et al[14]. The EBPR during exercise was explained with an increased sympathetic nervous system activation and decreased baroreflex sensitivity which also may contribute to the progression of the metabolic syndrome[35]. In our study, the frequency of EBPR was 30.8% in the MH patients and 1.7% in the control group, suggesting the association between MH and EBPR.

Limitations

This study has several limitations. First, considering the high prevalence of MH in the community, the number of subjects included in the study was relatively low. Second, the subjects in the MH and control groups included in the study were different in terms of age, smoking, and hyperlipidemia. The age, smoking frequency, and hyperlipidemia rate of MH subjects were significantly higher. This may have affected the results of the study. Third, because sustained hypertension or the WCH group was not included in this study, we could not compare MH with those groups in terms of adverse cardiovascular effects. Finally, since it was a cross-sectional study, our findings prevented us from establishing a cause-effect relationship in terms of long-term cardiovascular disease risk.

Conclusions

The frequency of blunted HRR and EBPR in patients with MH was found to be significantly higher than in the control group suggesting a close relationship between MH and autonomic dysregulation. As secondary outcomes, we demonstrated that serum uric acid level, LA diameter, aortic root diameter, ascending aorta diameter, and the frequency of left ventricular hypertrophy and diastolic dysfunction were significantly higher in patients with MH. Since MH has a malignant nature, like sustained hypertension, it is important to evaluate people at risk for MH with out-of-office BP measurements and to treat patients with MH appropriately in terms of reducing cardiovascular risk.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Authors' Contribution

Concept – İ.H.İ, C.Ş; Design – İ.H.İ, C.Ş; Supervision – İ.H.İ. Materials – İ.H.İ.; Data Collection and/or Processing – İ.H.İ, C.Ş; Analysis and/or Interpretation – İ.H.İ, C.Ş; Literature Review – İ.H.İ., C.Ş.; Writing – İ.H.İ; Critical Review – İ.H.İ, C.Ş.

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Ethics Approval

The study was evaluated and approved by the local ethics committee in terms of compliance with the Helsinki principles (Date: 10.02.2022, Approval No. 2022.03.17).

Informed Consent

All participants were informed about the scope of the study and their informed written consent was obtained.

Availability of Data and Materials

Available.

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