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DIFFERENCES BETWEEN OFFICE AND AMBULATORY BLOOD PRESSURE MEASUREMENTS IN PATIENTS USING TRIPLE ANTIHYPERTENSIVE TREATMENT

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Abstract

Objectives: It has been suggested that blood pressure (BP) measurements in the office/clinic may fall short of detecting phenomena such as a white coat or masked hypertension (HT). In this cross-sectional study, we aimed to evaluate the differences in office and ambulatory BP measurements (ABPM) and investigate the secondary causes in patients using triple antihypertensive medication.

Materials and Methods: Of the included 57 patients using triple antihypertensives, 28 had high office BP measurements (HOM-HT group), whereas 29 had normal office BP values (NOM-HT group). Both groups underwent an ABPM. Also, serum biochemistry, 24-hour urine tests, Epworth Sleepiness Scale, and renal artery Doppler assessments were performed to detect secondary causes of HT. Groups were compared regarding ABPM values, tests, scale results, and secondary causes.

Results: No significant differences were found between the demographics and serum tests. According to the ABPM, white coat HT was detected in 15 patients (53.67%) in the HOM-HT group, whereas five (17.24%) in the NOM-HT group had masked HT (p=0.018). In three patients, secondary causes were detected (hyperaldosteronism, renal artery compression, and sleep apnea), all of whom were in the HOM-HT group. The groups did not differ significantly regarding the frequency of secondary causes (p=0.112). In contrast to when the ABPM is taken into account (16.66% vs. 0% p=0.028).

Conclusion: Data of the present study showed that ABPM is necessary to detect white coat and masked HT. Also, depending on ABPM rather than office/clinic measurements may save time and expenses when investigating secondary causes.

Keywords: Ambulatory blood pressure, office blood pressure, resistant hypertension, white coat, masked.

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Introduction

Hypertension (HT) is one of the most important causes of mortality and morbidity in the aging population. Although the incidence of HT may vary according to age, gender, or race, the crude prevalence was estimated to be approximately 20% in adults worldwide according to the "Seventh Joint National Committee" (JNC-7) criteria published in 2003.[1] However, the prevalence in the current reports is even higher, reaching up to 31.1% as published by the "American Heart Association" (AHA) in 2018.[2] Moreover, the "American College of Cardiology" (ACC)/(AHA) lowered the threshold values of HT from 140/90 to 130/80 mmHg in 2017, which boosted the prevalence in the American population up to 46%.[2] In Turkey, the prevalence of HT in the adult population has been reported as 31.8%, close to AHA.[3]

While most patients with primary HT respond to one or two antihypertensive drugs, in some patients, lifestyle changes and appropriate drug selection may not suffice to manage HT. These patients may constitute the resistant HT, which is defined as the blood pressure (BP) ≥ 140/90 mmHg despite three antihypertensive drugs in maximum tolerable doses, one of which is a diuretic, or can only be controlled with at least four or more antihypertensive medications.[4] Although different rates for resistant HT were reported probably due to different study designs; most studies gave a prevalence of 10-15% for resistant HT.[2,5-7] The diagnosis of resistant HT necessitates further clinical and laboratory tests and inevitably increases health care expenditures.

Although there is a well-accepted definition of resistant HT, the rationale of its threshold is not strongly evidence-based. Moreover, the values determined in single or multiple measurements in the office/clinic may be unreliable. Therefore, we sought to assess the patients who fall in the resistant HT category and those who have their BPs in target levels in office/clinic measurements using ambulatory blood pressure monitoring (ABPM) and compare the frequency of secondary hypertension.

Materials and Methods

Patients

This study is planned as a cross-sectional study. The eligibility criteria for study inclusion were as follows: Being over the age of 18, having HT and using ≥ three antihypertensive agents of different classes, at least one of which is a diuretic applied to the Internal Medicine or Cardiology outpatient clinics of Gülhane Training and Research Hospital between December 2010 and June 2011. BPs were measured between 08:00 and 11:00 in the morning, at both arms after five minutes of rest. Then, a second measurement was made on the side with a higher value, and the average of both measures was recorded. Before the measurements, we confirmed that

the patients had taken their morning antihypertensive regimens. Patients with office BP values ≥140/90 mmHg that was thought to have resistant HT were assigned to the "High Office Measurement" hypertensive (HOM-HT) group. In comparison, others (office BP <140/90 mmHg) constituted the "Normal Office Measurement" hypertensive (NOM-HT) group. Participants were excluded with chronic renal or hepatic insufficiency, malignancy, acute infection, pregnancy, and contraindication in diuretics. The local ethics committee approved the study. All procedures followed the Declaration of Helsinki, and informed consent was obtained from all participants.

Assessments

The sociodemographic data of all participants were evaluated in detail, including body mass index (BMI) and waist circumference. For the detection of secondary HT causes, a whole blood count, routine biochemistry (including fasting blood glucose, urea, creatinine, electrolytes, total cholesterol, low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL), triglyceride, aldosterone, plasma renin activity, thyroid-stimulating hormone (TSH), as well as 24-hour urine analysis including microalbumin, protein, sodium, vanillylmandelic acid (VMA), 5-hydroxy indole acetic acid (5-HIAA), metanephrine, normetanephrine, adrenaline, and noradrenaline levels were investigated. Additionally, 24-hour ABPM was performed in all participants. Cut-off values of <130/80mmHg for 24 hours, <135/85mmHg for daytime, and <120/70mmHg for nighttime were taken for the ABPM. Participants with higher mean values in either of these cut-offs were considered to have an abnormal ABPM (9). Besides, electrocardiography and renal ultrasound, and renal artery Doppler imaging were performed in all patients. The "Epworth Sleepiness Scale" (ESS) was applied to screen obstructive sleep apnea (OSA). High scores in ESS were confirmed by polysomnography (PSG).

Statistical analysis

The sample size of the present study was calculated based on the previous study and preliminary data. The estimated difference between the groups regarding high BP values in the ABPM was 35%, with an estimated WCH of 50% and masked HT of 15%. With 5% type-1 error (two-tailed) and 80% power, 27 patients were needed in each arm". Visual histograms and the Kolmogorov-Smirnov test analyzed the distribution of the data. Quantitative data are given as mean/median or SD/min-max. Concerning group comparisons with continuous variables, independent samples t-test or Mann-Whitney U test was used according to the distribution of the data. Chi-square or Fisher's exact tests compared nominal data. A 2-sided p-value of <0.05 was considered significant. SPSS Statistics 22.0.0 (SPSS Ltd., Chicago IL) was used for statistics.

Results

A total of 57 patients were included in the study, 28 of whom had HOM-HT. No significant difference was found between the groups regarding age (p=0.342), sex (p=0.509), BMI (p=0.363), and waist circumference (p= 0.690) (Table 1).

As an enrollment criterion, all the patients were taking diuretics. With respect to other antihypertensive medication, the percentage of patients treated with angiotensin receptor blockers, calcium channel blockers, beta-blockers, angiotensin-converting enzyme inhibitors, alpha-blockers, aldosterone antagonists, and centrally acting antihypertensives was 82.46, 80.70, 63.16, 17.54, 3.51, 3.51, and 1.75%, respectively. No significant difference was found in terms of the evaluated serum biochemistry. 24-hour urine assessments revealed significant differences for normetanephrine, adrenaline, and noradrenaline, but these did not indicate any secondary cause such as pheochromocytoma (Table 2).

Table 1. Distribution of sociodemographic characteristics of the groups.

	HOM-HT group (n=28)	NOM-HT group (n=29)	P
	Mean±SD	Mean±SD	
Age, years	60.64±9.28	58.10±10.58	0.342
Male sex, n (%)	10 (35.71)	8 (27.59)	0.509
Antihypertensive treatment duration, years	12.73 (7.79)	11.34 (9.76)	0.572
Waist circumference, cm	96.54±8.80	97.52±9.42	0.690
BMI, kg/m^2	30.77±5.38	32.11±5.52	0.363
BMI, kg/m^2 n(%)			
≤ 24.9	3 (10.71)	1 (3.44)	0.543
25-29.9	9 (32.14)	9 (31.03)	
>30	16 (57.14)	19 (65.52)	
Smoking, n			
Non-smoker	18	20	0.921
Current smoker	7	6	
Quitted	3	3	
Accompanying chronic illness			
Hyperlipidemia	11 (39.28)	10 (34.48)	0.707
Type-II DM	9 (32.14)	11 (37.93)	0.647
Coronary artery disease	3 (10.71)	2 (6.90)	0.610

HOM-HT: high office measurement; NOM-HT: normal office measurement; BMI: body mass index; cm, centimeter; DM: Diabetes Mellitus.

Table 2. Comparison of the serum and 24-hour urine assessments of the groups.

	HOM-HT group (n=28)	NOM-HT group (n=29)	P†
	Mean±SD	Mean±SD	
Serum parameters			
Fasting glucose, mg/dL	128±58.66	105.66±15.28	0.522
Urea, mg/dL	31.90±10.64	31.79±7.62	0.960
Creatinine, mg/dL	0.96±0.215	0.88±0.14	0.052
Na, mmol/L	137.95±10.44	140.80±2.81	0.114
K, mmol/L	4.36±0.46	4.28±0.32	0.454
Total cholesterol, mg/dL	211.13±51.19	202.52±32	0.461
LDL cholesterol, mg/dL	132.58±43.94	124.82±28.50	0.439
Triglycerides, mg/dL	180.85±117.72	158.07±105.45	0.447
HDL cholesterol, mg/dL	49.69±109.90	48.48±10.10	0.654
TSH, mikroIU/mL	1.20±1	1.59±1.37	0.251
Urine parameters			
Microalbuminuria, mg/day	7. 29 (3.60-6678)‡	9.60 (4.40-80.40) ‡	0.237
Proteinuria, mg/day	105 (44-8260)‡	105 (48-180) ‡	0.260
Urine Na, mmol/day	161.96 ±68.53	188.69 ±82.91	0.242
VMA, mg/day	3.28 ±1.40	4.18 ±2.29	0.109
5-HIAA, mg/day	2.96 ±1.77	3.52 ±1.83	0.288
Homovalinic acid, mg/day	4.18 ±2.45	3.32 ±1.54	0.174
Metanephrine, mcg/day	118.83 ±146.19	84.85 ±50.15	0.992
Normetanephrine, mcg/day	289.85 ±342.05	405.91 ±496.94	0.047*
Adrenaline, mcg/day	2.88 ±1.54	5.26 ±4.29	0.042*
Noradrenaline, mcg/day	34.10 ±15.90	51 ±28.64	0.021*

HOM-HT: high office measurement; NOM-HT: normal office measurement; Na: sodium; K: potassium; LDL: low-density lipoprotein; TG: triglyceride; HDL: high-density lipoprotein; TSH: thyroid-stimulating hormone; VMA: Vanilla mandelic acid; 5-HIAA: 5-Hydroxy indole acetic acid.

† Independent samples t-test

‡ Median (min-max)

*p<0.05

Secondary causes of HT were identified in three patients, all of whom were in the HOM-HT group (10.71%). They were diagnosed with hyperaldosteronism, OSA, and a mass compressing the renal artery, respectively. Of note, the patient with a mass pressuring renal artery was operated on and subsequently became normotensive without medication. None in the NOM-HT group had secondary causes, but this difference was not significant (10.71% vs. 0%, Fisher's exact test p=0.112). However, when the patients were re-grouped according to the ABPM, patients with accurate resistant HT (n=18) differed significantly in the frequency of secondary causes (16.66% vs. 0%, Fisher's exact test p=0.028).

In total, 18 (31.58%) of all patients (n=57) were detected to have true resistant HT according to the ABPM values. Significant differences were found between the groups regarding ABPM (Table 3). Within the HOM-HT group, only 13 (46.43%) had ABPM values consistent with the definition of resistant HT; the remaining 15

(53.67%) failed to fulfill the definition of resistant HT. In the NOM-HT group, 5 (17.24%) were had resistant HT assessed by ABPM (p=0.018). There was no significant difference in circadian BP measurements between the groups (systolic BP, p=0.109; diastolic BP, p=0.104, Table 3).

Table 3. Ambulatory/office BP values and circadian patterns of the groups.

		HOM-HT group (n=28)	NOM-HT group (n=29)	P
		Mean±SD	Mean±SD	
ABPM and office measurements				
Average 24-hour, mmHg	SBP	126.43 ±15.39	114.90 ±10.00	0.001†**
	DBP	74.75 ±11.90	69.21 ±7.00	0.036†*
Average daytime, mmHg	SBP	128.43 ±15.50	117.90 ±10.03	0.003†**
	DBP	77.07 ± 12.62	71.71 ±7.30	0.054†
Average nighttime, mmHg	SBP	122.46 ±17.34	108.90 ±10.20	0.001†**
	DBP	70.04 ±11.39	63.72 ±6.27	0.012†*
Office BP, mmHg	SBP	153.63 ±17.33	124.48 ±12.50	<0.001†**
	DBP	88.59 ±11.58	75.60 ±5.90	<0.001†**
Circadian SBP, n (%)				
Extreme dipper		0 (0)	0 (0)	0.109‡
Dipper		3 (10.71)	6 (20.69)	
Non-dipper		16 (57.14)	20 (68.96)	
Raiser		9 (32.14)	3 (10.34)	
Circadian DBP, n (%)				
Extreme dipper		0 (0)	0 (0)	0.104‡
Dipper		14 (50.00)	7 (24.14)	
Non-dipper		8 (28.57)	15 (51.72)	
Raiser		6 (21.43)	7 (24.14)	

HOM-HT: high office measurement; NOM-HT: normal office measurement; SBP: systolic blood pressure; DBP: diastolic blood pressure: BP: blood pressure.
† independent samples t-test
‡ Chi-square test
*p<0.05
**p<0.01

Discussion

Patients using at least three antihypertensive medications in this study were assessed using an ABPM. Our results revealed a significant disagreement between office/clinic and ABPM measurements, indicating the existence of white coats and masked HT within the groups.

Whitecoat hypertension (WCH)

The (WCH) is a fundamental cause for false resistance defined as >20 / 10 mmHg increase in SBP/DBP values measured in the doctor's office compared to home or ABPM.[4,8] The white coat effect is more common in patients

with resistant HT than in the general hypertensive population.[5] The prevalence of false resistance is 20-45% in all hypertensive patients[5,9], including WCH in the hypertensive population. In Turkey, the reported rates vary in a wide range of 17-72%.[10,11]

The incidence of conversion of WCH to permanent HT is between 1-5% per year with ABPM.[12] Concerning the WCH, studies have found that these individuals have a higher cardiovascular risk than normotensive people but lower than those with persistent and masked HT.[13-15] In our study, the result that at least half of the HOM-HT group (53.67%) supposed to have resistant HT were found to have normal values measured by ABPM. This striking result is attributed to WCH, considering that our study design controlled other causes of false resistance such as inappropriate measurement and office settings, lack of rest, failure of taking the morning pill, etc. Moreover, the physician effect may inflict an additional contribution on this high rate since a physician performed the measurements, but not a nurse, in agreement with the studies that the white coat effect created by physicians is higher than that of nurses.[13] Detecting WCH is crucial to avoid unwanted adverse effects caused by excessive treatment and avoid unnecessary, expensive, and sometimes invasive approaches to investigate secondary causes of HT. Thus, the diagnosis of resistant HT is supposed to be confirmed with ABPM before further steps for the treatment and therapy are taken.[4,12]

Masked hypertension

Another finding of our study is that 17.24% of the NOM-HT group had masked resistant HT. While the prevalence of masked HT is between 10-26% in community studies, it may range from 14% to 30% in studies among normotensives,[16-18], according to the frequency obtained in our study. Unlike WCH, individuals with masked HT have similar cardiovascular risk and all-cause mortality rates as those with permanent HT. Secondary causes may also be found in patients with masked HT. However, in our study, none of the patients with masked HT had a secondary reason, probably due to the small sample size. On this basis, ABPM may be employed in routine clinical assessments not to miss the masked HT.

Secondary causes

Studies show that there may be underlying secondary causes of HT in 10-20% of hypertensive patients.[19] In our study, secondary causes of HT were detected in three patients, which constituted 10.71% of the HOM-HT group and was not significantly different from the NOM-HT, which had no such patients. The low rate of above threshold BP levels with ABPM, i.e., high rate of WCH in the HOM-HT group, is a potential explanation of this result. Indeed, this percentage increased to 16.66% (3 out of 18) within the true resistant patients (according to ABPM) and was significantly higher compared to patients with normal ABPM values (p=0.028). Of those three patients, one had primary hyperaldosteronism, which was reported to be found in 5-10% of HT patients, and around 20% in resistant HT.[20] We detected OSA in another patient who had a high score in the ESS and

confirmed by PSG. OSA prevalence in resistant HT is relatively high (>80%)[21,22], unlike our finding with one patient. This may be due to the low sensitivity of the ESS, which we used as a screening test.[23,24] In another patient, renal Doppler imaging revealed a mass was compressing the renal artery. The association between renal masses and hypertension is known with a frequency of 1-2%, which aligns with our finding.[25] This patient became free from HT after the removal of the mass. The BP values of these three patients with secondary HT were 164/107 mmHg, 161/103 mmHg, and 155/102 mmHg. Although it is not universally accepted, the threshold for HT was determined as >130/80 mmHg in the latest guideline published by the ACC/AHA in 2018.[26] Our study applied the threshold of ≥140/90 mmHg recommended by the European Society of Cardiology and Hypertension (ESC/ESH) in-office measurements. In our patients with detected secondary causes, BP values were well above the threshold given in both guidelines (systolic 20-30 mmHg more). This allows the conclusion that it may be helpful to investigate secondary causes in individuals with values far above the threshold.

Another issue considered in our study was the differences in circadian BP patterns between the groups. SBP "dipper" rate was two times higher in the NOM-HT group than the HOM-HT group, whereas the SBP "raiser" rate was three times higher in the HOM-HT group than the NOM-HT group. However, these differences were non-significant, probably due to the small sample size (type-2 error). Determining the dipping / non-dipping profile in ABPM is valuable because it predicts the prognosis associated with organ damage that may result in consequences such as cardiovascular mortality, microalbuminuria, left ventricular hypertrophy, and arterial stiffness.[27]

Study limitations

The limitations of our study that may be potential sources of bias should also be mentioned. The most important limitation is the small sample size. As mentioned before, the insignificant difference between the groups regarding the secondary causes may also be influenced by the power of the study and the presence of WCH in HOM-HT. Also, it is generally recommended to repeat ABPM within three to six months to confirm the diagnosis in individuals with WCH, which was not done in our study.[28] Given that HT is a progressive disease, it is possible for patients evaluated as WCH to convert to true resistant HT in the future. However, the opposite may also be likely.[29] Therefore, the study's cross-sectional design and the lack of confirmation with follow-up ABPMs are shortcomings. Also, as stated above, the ESS used for sleep apnea screening may be insufficient to detect OSA patients. Moreover, it has been shown that the patients' plasma renin and aldosterone levels may have been affected by antihypertensive usage.[30] Thus, renin and aldosterone levels should be interpreted with caution. On the other hand, obtaining information in standardized face-to-face interviews and investigating secondary HT causes in all patients are the strengths of our study.

In conclusion, in this study, around half (53.67%) of the patients supposed to have resistant HT in-office measurements had WCH, and 17.24% of the patients who were thought to be under control with treatment had masked HT as measured by ABPM. Our findings add to a growing corpus of research showing that ABPM predicts cardiovascular risks better than office measurements, can detect WCH, masked HT, non-typical circadian changes in BP, prevents unnecessary tests for the secondary causes, and should be performed before the diagnosis of resistant HT. Future research with a larger sample size in the Turkish population is needed to validate our findings.

Ethical considerations: All research procedures were evaluated and accepted by the Research Ethics Committee of Gülhane Military Medical Faculty Hospital, (date: 22.07.2010, decision number: 1491-957-10/1539) and were conducted in agreement with the ethical standards specified in the Declaration of Helsinki. Written informed consent was obtained from patients before they participated in this study.

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