Smoking and overweight associated with masked uncontrolled hypertension: A Hypertension Optimal Treatment (HOT) sub-study

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Abstract

Purpose: The Hypertension Optimal Treatment (HOT) Study investigated the relationship between target office diastolic blood pressure (BP) ≤ 80 , ≤ 85 or ≤ 90 mmHg and cardiovascular morbidity and mortality in 18 790 patients aged 50-80 years. The home BP sub-study enrolled 926 patients and the aim was to clarify whether the separation into the BP target groups in the office prevailed in the out-of-office setting. The present study aimed to identify variables that characterized masked uncontrolled hypertension (MUCH) and white coat uncontrolled hypertension (WUCH). **Material and Methods:** The sub-study participants took their home BP when office BP had been up titrated. The cut-off for normal or high BP was set to $\geq 135/85$ mmHg at home and $\geq 140/90$ mmHg in the office. We analyzed data by using multivariate and stepwise multivariate logistic regression with home and office BP combinations as the dependent variables. **Results:** WUCH was associated with lower body mass index (BMI) (odds ratio (OR) 0.92, 95% confident intervals (CIs) 0.88-0.96, $p < 0.001$). MUCH was associated with smoking (OR 1.89, 95% CIs 1.25-2.86, $p = 0.0025$) and weaker with lower baseline heart rate (OR 0.98, 95% CIs 0.97-0.99, $p = 0.03$) and higher BMI (OR 1.03, CIs 1.00-1.06, $p = 0.04$). MUCH remained associated with smoking (OR 2.76, 95% CIs 1.76-4.35, $p < 0.0001$) also when using $\geq 140/90$ mmHg as cut-off for both home and office BP. MUCH was also associated with higher BMI (OR 1.05, 95% CIs 1.01-1.09, $p = 0.009$) while WUCH was associated with lower BMI (OR 0.93, 95% CIs 0.90-0.97, $P = 0.0005$) when using $\geq 140/90$ mmHg as cut-off. **Conclusion:** Our data support that “reversed or masked” treated but uncontrolled hypertension (MUCH) is common and constitutes about 25% of treated hypertensive patients. This entity (MUCH) is rather strongly associated with current smoking and overweight while uncontrolled white coat (office) hypertension (WUCH) is associated with lower BMI.

KEYWORDS Blood pressure; hypertension; masked hypertension; smoking; overweight

Introduction

The Hypertension Optimal Treatment (HOT) Study included patients in 26 countries. The rationale was described in detail [1] and HOT was conducted in accordance with the Prospective Randomized Open Blinded Endpoint (PROBE) design [2]. The main aim was to evaluate the relationship between three levels of target diastolic blood pressure (BP) (≤ 80 , ≤ 85 or ≤ 90 mmHg) and cardiovascular morbidity (CV) and mortality in hypertensive patients. In addition, the study examined the effects of a low dose (75 mg daily) of acetylsalicylic acid vs. placebo. 18 790 patients between 50 and 80 years of age participated. Antihypertensive treatment commenced with a calcium antagonist. Additional antihypertensive therapy were given in accordance with a set protocol to reach target BPs. Details of the patient characteristics at randomization, cardiovascular risk profiles, early BP results and CV outcomes were published [1,3,4].

Home BP, or self-monitoring of BP, can easily be learned and it has a high reproducibility and sensitivity of measurement [5-7]. Because of limited prospective mortality/morbidity data in clinical outcome trials, home BP monitoring cannot be used alone to decide whether treatment is indicated; treatment decisions must usually be based on repeated standard clinic BP readings [8]. Taking home BP by patients was particularly feasible in the HOT Study because of the standardization of measurements of BP with a semiautomatic device and the subsequent possibility to train subjects at every office visit. Therefore, the aim of the home BP sub-study was to compare home BP with office BP in a fairly large and representative subsample of the HOT Study population after the up titration of antihypertensive treatment. The two BPs in the office and at home were on average nearly identical (9). Heart rate averaged 1.7 ± 8.6 beats/min higher in the office compared to at home ($p < 0.0001$) (9). The sub-study also aimed to clarify whether the separation of subjects into the three main groups (≤ 80 , ≤ 85 or ≤ 90 mmHg) based on office readings prevailed into the out-

of-office setting [9]. The present sub-study data were presented at the 14th European Hypertension Meeting (10). For many years the HOT sub-study on home BP was the only large study of home BP in treated hypertensive patients (9). However, in light of the increasing interest in uncontrolled reversed office (“masked”) hypertension (MUCH), and the new nomenclature recently introduced (11-14), we aim to fully publish the presented data (10). The aim is to identify variables and clinical characteristics found to be associated with various combinations of home and office BP being high or normal, and in particular the combination of high home BP/normal office BP, namely uncontrolled reversed office (“masked”) hypertension (MUCH).

Material and methods

Patients:

In the main study 18 790 patients of any race of 50 to 80 years were randomized in 26 countries. Details of their characteristics at randomization were published [3]. The average mean $\pm$ SD randomization BP in patients untreated at enrollment was $169\pm14/106\pm3$ mmHg (n=8917) and in the previously treated patients, after at least 2 weeks of washout, BP averaged $170\pm14/105\pm3$ mmHg (n=9873). The three target BP groups were well-matched at the outset of the study [3].

There were no additional criteria for participation in the home BP sub-study except for investigator interest and patient willingness and 88 of the 1921 participating centers in the HOT Study participated. The sample (n=926) that participated in the sub-study contained a higher percentage of previously treated patients (66 vs. 52%); otherwise, characteristics were comparable with patients in the main study [9]. The distribution of the 926 patients between countries was as follows: Canada 72, Greece 34, Hungary 36, Israel 10, The Netherlands 19, Norway 109, Spain 124, Sweden 82 and United States 440 patients.

Data sharing:

Data sharing is not applicable to this article as the database was closed for further analyses more than 10 years ago and no new data were created.

Protocol:

The ethics committees in all participating countries approved the study. Patients gave informed consent. Blood pressure was measured at enrollment and then at two qualifying visits at least 7 days apart. The diastolic BP had to be in the range of ≥ 100 to ≤ 115 mm Hg at both qualifying visits. A number of exclusion criteria were specified [1]. All patients started active antihypertensive treatment with the calcium antagonist felodipine 5 mg once daily. Additional antihypertensive therapy was given with either an angiotensin-converting enzyme inhibitor or a β -adrenoceptor blocker if the target BP was not reached. Dosage adjustments were if needed made in accordance with a set protocol. As a final step a diuretic was added if it was needed. After 6 months [3], the percentages of patients who had achieved their randomized target clinic diastolic BP were 57, 71 and 83% for the target groups at ≤ 80 , ≤ 85 , or ≤ 90 mmHg, respectively, and after 12 months they were 57, 72 and 84%, respectively. The distributions of the drug dose steps in the three target groups were rather similar.

Blood pressure and heart rate were measured in the sitting position with a newly calibrated semiautomatic oscillometric device with a digital readout (Visomat OZ, D2 International, Hestia Pharma GmbH, Mannheim, Germany). The accuracy of this device was validated in 407 normotensive and hypertensive people against standard sphygmomanometer readings according to the recommendations of the British Hypertension Society, with the conclusion that this device could provide accurate and reliable measurements of BP [15]. Blood pressure measurements were taken in the same arm each time and with a cuff of appropriate size relative to the patient's arm. The cuffed arm was kept at the heart level, and the arm was supported at the time of the measurement. In the office, three measurements were

taken at least 15 seconds apart, after 5 minutes of rest, and the averages were calculated for statistical analysis. Visits took place at the same time of the day, usually in the morning.

Measurements were performed at the end of the dosing interval (“at trough”) and preferably by the same person.

Home BP measurements were performed through seven consecutive days with the same type of semiautomatic device after appropriate supplemental training of the participating patients. After they sat for 5 minutes, both in the morning before leaving home and in the afternoon after returning home, BPs and heart rates were taken three times, and the measurements were registered on special case record forms. Conditions for measurements were thus comparable at home and in the investigator’s office though measurements at home per protocol were less standardized related to the intake of the antihypertensive medication. The averages of all BP measurements at home, in most patients 42 measurements, were calculated for comparisons with the respective office measurements.

Assessments of BP and heart rates at home were performed at a time when the titration of antihypertensive medication in the study had been finalized, i.e., at least 6 months after randomization [9]. **Fig. 1** schematically illustrates the design of the study. An automatic device was given to the patient after a scheduled visit for the majority of patients at 6 (n=168), 12 (n=462), 18 (n=191), or 24 (n=67) months; the home measurements were then performed shortly thereafter (on average 4 days later) and in most patients (n=890) on consecutive days. The data from the home assessments in each patient was compared with BP and heart rate taken at the regular scheduled visit to the office of the investigator that was nearest in time to, and usually preceded, the home measurements. Nine patients were excluded from the home-office comparison because the exact time for home measurements had not been written on the recording form. One patient had not written the diastolic BPs on the form, and four had not registered heart rates.

The home BP data was edited by one of the investigators (S.E.K.) according to an a priori protocol for the purpose of cleaning the data for clearly erroneous recordings [9]. This was done before any statistical analysis. Approximately 3% of all recordings were considered erroneous (single numbers incompatible with life or way out of range with all others in the same patient, diastolic BP almost identical to systolic BP or higher, heart rates compatible with a paroxysmal tachycardia); the accompanying BPs and heart rates taken simultaneously were deleted. Not all patients had all measurements taken at all 14 occasions, leaving nearly 34 000 measurements of both BPs and heart rates for analysis.

Statistics:

The patients were divided into the four categories according to their average home and office BPs. This was done to investigate the patients' characteristics, and identify the variables influencing their home BP. Terms like "white coat" hypertension for isolated elevation of BP in the office and "masked hypertension" for isolated elevation of BP out of the office, were previously reserved for people without antihypertensive treatment. But these terms are now also used for people who are treated for hypertension [11-14].

We have therefore used the following corresponding terms: Controlled home and office BP (CONTROLLED BP), controlled home but not office BP (WHITE COAT UNCONTROLLED HYPERTENSION = WUCH), controlled office but not home BP (MASKED UNCONTROLLED HYPERTENSION = MUCH) and uncontrolled office and home BP (UNCONTROLLED BP). The cut-off for normal ("controlled") or high BP was set to $\geq 135/85$ mmHg for home BP and $\geq 140/90$ mmHg for office BP. The groups were compared by using multivariate logistic regression and stepwise multivariate logistic regression with the dependent variables being home BP normal/high and office BP normal/high. The analyses were carried out with all baseline variables including age, previous

diseases and treatments included in the models. Data are shown as mean $\pm$ SD or percent. P-value <0.05 (two-tailed) was considered statistically significant.

Results

Distribution of the treated home/office BP categories

The distribution of participants in the four categories (**Fig. 2**) was the following when using cut off $\geq 135/85$ mmHg for home BP and cut off $\geq 140/90$ mmHg for office BP (**Table 1**).

Normal both home and office BP (CONTROLLED) 31% (n=280), normal home and high office BP (WUCH) 11% (n=103), normal office and high home BP (MUCH) 25% (n=232) and high both office and home BP (UNCONTROLLED) 33% (n=300). Age ranged from 59.8 to 62.1 yrs. in the four categories without significant differences (Table 2).

Findings in patients with masked uncontrolled hypertension (MUCH):

MUCH had the highest mean body mass index (BMI) for males (30.1 kg/m^2) and for females (29.7 kg/m^2) and lower heart rate 79 (11) beats/min (**Table 2**). MUCH had the highest portion of current smokers (18.5%, **Table 2**). These findings were statistically significant and the logistic multivariate models showed that the MUCH patients (high home, normal office BP) were associated with more smoking (OR 1.89, CIs 1.25-2.86, $p=0.0025$), with lower baseline heart rate (OR 0.98, CIs 0.97-0.99, $p=0.03$) and higher BMI (OR 1.03, CIs 1.00-1.06, $p=0.04$).

When cut-off was set to $\geq 140/90$ mmHg, for both home and office BP (n=137, 59% males, 41% females), the portion of current smokers was 24.8% (n=34, **Fig. 3**) and smoking remained highly significantly associated with MUCH (OR 2.76, CIs 1.76-4.35, $p<0.0001$). Higher BMI (OR 1.05, CIs 1.01-1.09, $p=0.009$) was also associated with MUCH while there

was a borderline significant association for baseline heart rate (OR 0.98, CIs 0.97-1.00, $p=0.049$).

Findings in patients with uncontrolled white coat hypertension (WUCH):

With cut-off set to $\geq 135/85$ mmHg for home BP and $\geq 140/90$ mmHg for office BP, the group with normal home and uncontrolled high office BP (WUCH) had the lowest mean BMI for females (27.3 kg/m^2) (**Table 2**). In multivariate models this group was associated with lower BMI (OR 0.92, CIs 0.88-0.96, $p<0.001$). When cut-off was set to $\geq 140/90$ mmHg for both home and office BP ($n=165$, 53% males, 47% females, $n=18$ smokers, 10.9%), this group (WUCH) remained associated with lower BMI (OR 0.93, CIs 0.90-0.97, $p=0.0005$). Chronic pulmonary disease was also associated with WUCH at the same cut-off ($\geq 140/90$ for both home and office BP) (OR 3.26, CIs 1.23-8.65, $p=0.0125$, $n=7$) but with this low n (4.2%) we consider this results as a likely chance finding.

Discussion

We investigated variables that characterized various combinations of home and office BP being high or normal in patients with treated hypertension and in particular the combination of high home BP/normal (controlled) office BP. Our data support that such “reversed or masked” treated but uncontrolled hypertension (MUCH) is common and constitutes about 25% of treated hypertensive patients. Heart rate may be involved, but firstly MUCH is rather strongly associated with current smoking and overweight. These findings in MUCH were confirmed and extended by applying a more conservative approach using $\geq 140/90$ mmHg as cut off for both home and office BP. Patients with normal home and uncontrolled high office BP (WUCH) was associated with lower body weight whether using ≥ 135 or ≥ 140 mmHg as cut off for home BP.

When evaluating the distribution of participants, it is important to note that the size of the four fractions may depend on several conditions. The majority of the HOT Study patients (66%) was previously treated while approximately one third was previously untreated. The choice of using diastolic BP as target, as well as separating the patients into target groups of ≤ 80 , ≤ 85 or ≤ 90 mmHg, without attention to systolic BP might also have had impact on our results of fraction size. That is to say, the distribution and the high MUCH of 25% and WUCH of 11% may not necessarily correspond with findings in other studies. A more recent publication from the large ELSA study [11] aiming to evaluate the long-term reproducibility of MUCH and WUCH assessed by average 24-h ambulatory BP, found that after 1 year of antihypertensive treatment 21.1% and 17.8% of patients were classified as MUCH and WUCH, respectively. Although these numbers are fairly comparable to ours, the study also uncovered that despite the prevalence for both conditions being similar in the following years, there was a large change in patient composition, and only 4.5% and 6.2% of the patients remained in MUCH and WUCH throughout the treatment period of 4 years. Thus, by 24-hour ambulatory BP monitoring the fraction findings for MUCH demonstrated poor reproducibility [11-12]. However, it appears that when analyzing the presence of antihypertensive drugs or drug metabolites in urine samples, poor medication adherence did not explain the existence of MUCH [13-14]. It is more likely that MUCH is representing a form of hypertension that is worsening with time, and if no further intervention (adding more medication to gain BP control), there is transition from MUCH to established uncontrolled hypertension [11].

A high prevalence of MUCH was also recently described in the Spanish Registry [16]; of 14 840 patients with treated and controlled office BP, as many as 4608 patients (31%) had MUCH according to 24-hour ambulatory BP criteria. The prevalence of MUCH was higher in

patients at high CV risk (smokers, diabetes and obesity). However, MUCH appeared most often because of poor control of nocturnal BP. Approximately 14% of their patients had MUCH if assessed with daytime ambulatory BP. Their fraction of 14% is lower than our finding of 25% in the HOT Home BP sub-study and the finding of 21% in the ELSA study [11]. The explanation is most likely that the Spanish Registry data had been collected and analyzed during years with generally more aggressive BP lowering therapy (after 2010). The HOT Home BP and the ELSA Study data were collected approximately 20 years ago [10, 11] though the ELSA study data on reproducibility was analyzed more recently [11].

Other studies have compared the characteristics of hypertensive patients and found that variables such as obesity, relatively higher office systolic BP, habitual drinking, and the use of two or more antihypertensive drugs are associated with MUCH [17, 18]. Another study has shown that passive smoking in a dose-related manner is associated with masked hypertension [19] and a study using ambulatory BP measurements showed already in 1997 that smokers, and in particular elderly men, had less white coat effect [20]. Smoking may also raise ambulatory BP [21, 22].

The detailed effects of smoking on BP are unknown though it is likely that hemodynamic effects of tobacco may contribute. It has since long been known that blood pressure and heart rate increase during smoking [23]. These effects are specifically associated with nicotine while the other components of tobacco, of which more than a thousand have been isolated, seem to be of minor importance [24, 25]. The rise in blood pressure is due both to an increase in cardiac output and total peripheral vascular resistance. The blood pressure rise appears immediately and occurs before any increase in circulating plasma catecholamines.

It is a paradox that while smoking acutely increases blood pressure a slightly lower blood pressure level has been found among smokers than nonsmokers in larger

epidemiological and cross-sectional studies [26, 27]. The mechanisms have been unknown though development of chronic pulmonary disease and weight loss could be possible mechanisms [24, 25]. Longitudinal studies have been scarce; however, in the Oslo Ischemia Study 7 years of follow up of 1393 apparently healthy middle-aged men showed that smoking predicted a highly significant rise of 4.3 mmHg ($p < 0.001$) in the prognostic important peak systolic BP on 600 kpm/min for 6 min during ergometer exercise [28]. These findings rather strongly suggest that smoking is a causative factor for high blood pressure when concomitant diseases are not involved or adjusted for in statistical multivariate analysis [24, 25].

High fraction of previous treatment for hypertension may potentially have influenced our results in the HOT Home BP sub-study. It is however unknown why patients participated in the sub-study beyond willingness. Our data are contradictory to the notion that smokers have normal or even low BP. On the contrary, our results add to a body of evidence that smoking is associated with higher BP. Possibly MUCH represents a clustering of CV risk factors [29] and that the BP component in this “metabolic syndrome” develops with time with transition to uncontrolled BP as shown in the ELSA study [11]. We cannot distinguish whether our findings of smoking associated with MUCH is just an expression of chronic smoking or whether the patients are smoking prior to or during BP measurements at home. Smoking could potentially directly increase the participants’ home BP and contribute to the MUCH status of the patients.

Overweight and obesity were significant determinants of masked hypertension in the general hypertension as well as in people with high normal BP [30]. Our analysis suggests that MUCH is associated with higher BMI. This is compatible with the findings of other investigators [31]. A review of literature stated that studies have found patients with masked hypertension to be associated with higher BMI or waist to hip ratio comparable to normotensives [32]. As mentioned another large study suggested an association with obesity,

compared to controlled hypertension [16]. In contrast to MUCH, we found WUCH to be associated with less body weight, which remains unexplained but supported in the literature [18, 33].

In the general population age may be a significant determinant of masked and white coat hypertension [30]. However, this is not necessarily a finding in drug treated hypertensive patients, neither in the ELSA study [11] nor in the present HOT sub-study.

Our study has some limitations worthwhile mentioning. The HOT Study and the home BP sub-study took place more than 20 years ago at a time when the evidence in support of aggressive BP lowering was less obvious. This was evident in the protocol [1], which instructed investigators to treat patients to modest target diastolic BPs such as ≤ 80 , ≤ 85 or ≤ 90 mmHg without emphasis on systolic BP control. The sub-study patients participated based on willingness, only, and potentially they are not ideally representative for the HOT Study population though their characteristics were similar [9]. As mentioned above, our data cannot discriminate between effects on home BP of acute and chronic smoking.

In conclusion, our data support that “reversed or masked” treated but uncontrolled hypertension (MUCH) is common and constitutes about 25% of treated hypertensive patients. This entity (MUCH) is rather strongly associated with current smoking and overweight while uncontrolled white coat (office) hypertension (WUCH) is associated with lower BMI. It is obvious to us that the phenomenon of “reversed or masked” treated but uncontrolled hypertension (MUCH) affects a major fraction of the general population. Consequently, MUCH must be the target for future research.

Disclosures statement

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Figure legends

Figure 1. Design of the HOT study with embedded the design of the sub-study on home BP measurements

Figure 2. Distribution of the home BP sub-study population in categories depending on control of home BP $\leq 135/85$ mmHg and office BP ≤ 140 mmHg

Figure 3. Fractions of smokers in the various HOT study home BP sub-study categories when using $\geq 135/85$ mmHg and $\geq 140/90$ mmHg as cut-offs for elevated home BP, respectively

Table 1. Distribution of HOT sub-study participants (n=915) according to their home and office BPs during treatment

Variables	CONTROLLED Normal Home and Office BP (n=280)	WUCH Normal Home and High Office BP (n=103)	MUCH High Home and Normal Office BP (n=232)	UNCONTROLLED High Home and Office BP (n=300)
Home systolic BP, mmHg	124 (7)	127 (6)	143 (10)	148 (11)
Home diastolic BP, mmHg	77 (5)	77 (5)	86 (7)	87 (7)
Home heart rate, beats/min	74 (19)	76 (11)	76 (10)	75 (11)
Office systolic BP, mmHg	126 (9)	148 (9)	129 (8)	152 (11)
Office diastolic BP, mmHg	79 (6)	88 (7)	79 (6)	87 (8)
Office heart rate, beats/min	75 (12)	79 (13)	77 (11)	77 (13)

Data shown as Mean (SD)

BP = blood pressure; WUCH and MUCH, see text

Table 2. Characteristics of participants in the HOT home BP sub-study (n=915)

Variables	CONTROLLED Normal Home and Office BP (n=280)	WUCH Normal Home and High Office BP (n=103)	MUCH High Home and Normal Office BP (n=232)	UNCONTROLLED High Home and Office BP (n=300)
Age, yrs.	59.8 (6.6)	62.1 (7.6)	61.1 (7.3)	62.1 (7.4)
Females, %	48.9	52.4	56.5	57.7
Female BMI, kg/m ²	29.7 (3.3)	27.3* (2.4)	29.7* (4.0)	29.7 (3.2)
Male BMI, kg/m ²	29.1 (2.3)	28.4 (3.7)	30.1* (1.2)	29.7 (2.8)
Baseline systolic BP, mmHg	163 (12)	169 (15)	168 (15)	175 (15)
Baseline diastolic BP, mmHg	105 (4)	105 (4)	105 (4)	106 (4)
Baseline heart rate, beats/min	81 (12)	81 (13)	79 (11)*	80 (13)
Previously treated for hypertension, %	66.1	69.9	65.5	65.7
Diabetes, %	4.6	8.7	6.0	10.7
Smoking, %	10.7	11.7	18.5*	12.3
Serum creatinine, μmol/L	94 (24)	91 (20)	96 (22)	95 (23)
Serum cholesterol, mmol/L	6.0 (1.1)	6.1 (1.3)	5.8 (1.0)	5.9 (1.2)

Data shown as % or Mean (SD)

BP = blood pressure; BMI = body mass index; WUCH and MUCH, see text

**Baseline BMI, heart rate and smoking status significantly different in logistic multivariate models*

Fig. 1

Fig. 2

Fig. 3