White-Coat and Masked Hypertension

Long-Term Risk of Sustained Hypertension in White-Coat or Masked Hypertension

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Abstract—It is debated whether white-coat (WCHT) and masked hypertension (MHT) are at greater risk of developing a sustained hypertensive state (SHT). In 1412 subjects of the Pressioni Arteriose Monitorate e Loro Associazioni Study, we measured office blood pressure (BP), 24-hour ambulatory BP, and home BP. The condition of WCHT was identified as office BP >140/90 mm Hg and 24-hour BP mean <125/79 mm Hg or home BP <132/82 mm Hg. Corresponding values for MHT diagnosis were office BP <140/90 mm Hg, 24-hour BP ≥125/79 mm Hg, and home BP ≥132/82 mm Hg. SHT was identified when both office and 24-hour BP means or home BP were over threshold values and normotension was under the threshold value. Subjects were reassessed 10 years later to evaluate the BP status of the various conditions defined previously. At the first examination, 758 (54.1%), 225 (16.1%), 124 (8.9%), and 293 (20.9%) subjects were normotensive, WCHT, MHT, and SHT subjects, respectively. At the second examination, 136 normotensives (18.2%), 95 WCHT (42.6%), and 56 MHT (47.1%) subjects became SHT. As compared with normotensives, adjusting for age and sex, the risk of becoming SHT was significantly higher for WCHT and MHT subjects (odds ratio: 2.51 and 1.78, respectively; *P*<0.0001). Similar results were obtained when the definition of the various conditions was based on home BP. Independent contributors of worsening of hypertension status were not only baseline BP, but also, although to a lesser extent, metabolic variables and age. Subjects with WCHT and MHT are at increased risk of developing SHT. This may contribute to their prognosis that appears to be worse as compared with that of normotensive subjects. (*Hypertension*. 2009;54:226-232.)

Key Words: masked hypertension ■ white-coat hypertension ■ ambulatory blood pressure monitoring ■ prognosis

No conclusive evidence exists as to whether isolated office or white-coat hypertension (HT; WCHT) and masked HT (MHT), ie, the conditions in which, respectively, only office or out-of-office blood pressure (BP) is elevated, are clinically innocent or rather associated with an increase in cardiovascular (CV) risk.[1–3] This is because in white-coat and masked hypertensive individuals, the prevalence of structural organ damage has not invariably been found to be greater than in "truly" normotensive individuals.[3–7] It is also because the longitudinal studies that have addressed this issue by assessing the incidence of morbidity and mortality have been based on a small number of CV events and/or a relatively short observation period.[8–14]

Information on the clinical significance of WCHT and MHT can also be obtained by investigating whether, compared with "true" normotension, these conditions are accompanied by a greater rate of development of a "sustained" hypertensive state, ie, HT both in and outside the clinical environment. We have addressed this issue in the Pressioni Arteriose Monitorate e Loro

Associazioni (PAMELA) population by identifying subjects with WCHT and MHT through in-office and out-of-office BP measurements and by detecting the development of sustained HT (SHT) over a 10-year time interval, ie, a long follow-up that allowed a large number of cases to occur. A peculiar aspect of the study was that out-of-office BP was measured both at home and over 24 hours, which allowed us to obtain 2 separate identifications of WCHT and MHT.

Methods

The methodology used in the PAMELA Study has been reported in detail elsewhere.[12,15] Briefly, 3200 individuals were randomly selected from the white residents of Monza (a town in the northeast outskirts of Milan), to be representative of its residents for sex, age (25 to 74 years), and socioeconomic characteristics, according to the criteria used by the World Health Organization Monitoring Diseases Project[16] conducted in the same geographic area.[6] Data were collected in 2051 subjects (64% of the original sample), and survivors were contacted 10 years later to be re-examined. All of the subjects agreed to participate in the study after explanation of its nature and purpose the study, and protocol was approved by the ethics committee of the institutions involved.

Table 1. Entry Demographic and Clinical Variables in True Normotension, WCHT, and MHT Based on Office vs 24-Hour Mean BP

Variable	True NT: Office → and 24 h →	WCHT: Office ↑ and 24 h →	MHT: Office → and 24 h ↑
N	758	225	124
Age, y	44.0±11.9*†‡	53.3±11.2†‡	47.8±12.7‡
Male, n (%)	329 (43.4)†‡	110 (48.9)†‡	88 (71.0)
BMI, kg/m²	24.1±3.6*†‡	26.8±4.1	26.0±3.8
SBP office, mm Hg	117.4±10.1*†‡	141.2±13.1†‡	126.9±7.5‡
DBP office, mm Hg	76.9±6.8*†‡	89.9±6.1†‡	82.3±5.0‡
SBP home, mm Hg	112.6±12.3*†‡	125.2±13.1‡	128.2±12.9‡
DBP home, mm Hg	70.8±8.6*†‡	78.0±8.4‡	80.3±7.1‡
SBP 24 h, mm Hg	112.8±6.5*†‡	117.0±5.2†‡	127.6±5.8‡
DBP 24 h, mm Hg	70.4±4.8*†‡	72.8±4.2†‡	80.0±5.0‡
Serum cholesterol, mg/dL	213.7±41.0*‡	233.9±40.9	224.1±43.9
Serum triglycerides, mg/dL	95.7±55.1*†‡	124.4±68.6	125.5±80.6
Serum HDL cholesterol, mg/dL	57.4±15.8‡	55.4±15.9	54.1±16.3
Serum glucose, mg/dL	85.5±12.3*†‡	93.0±19.1	92.5±27.8
SBP variability, mm Hg)	8.6±2.0*†‡	9.8±2.4‡	9.8±1.9‡
DBP variability, mm Hg	7.5±1.8*†‡	8.3±2.0‡	8.4±2.0
D day-night SBP, mm Hg	14.6±7.0‡	15.9±8.2	15.8±7.5
Δ day-night DBP, mm Hg	14.1±5.5	14.5±6.2	14.8±5.6

Data are shown as mean±SD. BMI indicates body mass index; SBP, systolic BP; DBP, diastolic BP; NT, normotension; HDL, high-density lipoprotein.

*P<0.05 vs WCHT.

†P<0.05 vs MHT.

‡P<0.05 vs true HT.

Table 2. Entry Demographic and Clinical Variables in True Normotension, WCHT, and MHT Based on Office vs Home BP

Variable	True NT: Office → and 24 h →	WCHT: Office ↑ and 24 h →	MHT: Office → and 24 h ↑
N	703	177	124
Age, y	43.1±11.3*†‡	50.3±10.4‡	50.7±12.9‡
Male, n (%)	303 (43.1)†‡	92 (52.0)†‡	87 (70.2)‡
BMI, kg/m²	23.9±3.6*†‡	26.3±4.3	26.3±3.5
SBP office, mm Hg	117.5±10.0*†‡	139.9±11.6†‡	126.0±8.1‡
DBP office, mm Hg	77.0±6.9*†‡	90.8±6.1†‡	81.2±5.0‡
SBP home, mm Hg	111.4±10.4*†‡	119.2±8.1†‡	134.1±12.5‡
DBP home, mm Hg	69.9±6.9*†‡	74.9±5.4†‡	84.8±8.9
SBP 24 h, mm Hg	113.6±7.3*†‡	120.0±7.7‡	122.6±9.0‡
DBP 24 h, mm Hg	71.0±5.3*†‡	75.6±5.9‡	76.6±6.6‡
Serum cholesterol, mg/dL	213.0±40.7*†‡	231.4±44.5	229.9±43.0
Serum triglycerides, mg/dL	94.5±53.8*†‡	123.4±78.7	126.9±83.1
Serum HDL cholesterol, mg/dL	57.7±15.6†‡	56.0±14.8	53.6±17.2
Serum glucose, mg/dL	85.5±12.1*†‡	92.0±18.8	92.6±28.6
SBP variability, mm Hg	8.5±2.0*†‡	9.3±1.9‡	9.8±2.2‡
DBP variability, mm Hg	7.4±1.7*†‡	8.0±1.9‡	8.4±2.2
Δ day-night SBP, mm Hg	14.9±6.7	16.1±7.8	15.3±7.7
Δ day-night DBP, mm Hg	14.3±5.4	14.7±6.0	14.7±5.8

Data are shown as mean±SD. BMI indicates body mass index; SBP, systolic BP; DBP, diastolic BP; NT, normotension; HDL, high-density lipoprotein.

*P<0.05 vs WCHT.

†P<0.05 vs MHT.

‡P<0.05 vs true HT.

Measurements

Between 1990 and 1992, participants were recruited to come to the outpatient sector of the local hospital (Ospedale San Gerardo) in the morning of a working day (Monday through Friday), after a fasting night. The data were collected by trained medical personnel. Those relevant to the present report are as follows: (1) 3 sphygmomanometric BP measurements with the subject in the sitting position; (2) a 24-hour (morning-to-morning) ambulatory BP monitoring through a validated oscillometric device (SpaceLabs 90207)[12–15] with the BP readings set at 20-minute intervals; and (3) 2 home BP measurements (at 7 AM and 7 PM) through a validated semiautomatic device (model HP 5331, Phillips), with measurements obtained from the arm contralateral to that used for ambulatory monitoring; (4) plasma glucose and lipid profile (standard glucose oxidase and enzymatic method, respectively) from venous blood; (5) body mass index (body weight in kilograms divided by the square of the height in meters); and (6) information on other CV risk factors, major diseases, and drug treatment via subjects' history and physical examination. The same data were collected from 2001 to 2002. Care was taken to keep the data collection procedure identical in the 2 occasions.

Data Analysis

In each individual office, home and 24-hour BP values were averaged separately for the 1990–1992 and 2001–2002 data collec-

tion periods. WCHT was diagnosed when, at the first (1990–1992) examination, subjects showed an office BP ≥140 mm Hg systolic or 90 mm Hg diastolic with a 24-hour average BP <125 mm Hg and 79 mm Hg diastolic or a home BP <132 mm Hg systolic and 83 mm Hg diastolic. MHT was diagnosed when, at the first examination, office BP was <140 mm Hg systolic and 90 mm Hg diastolic while the 24-hour average values were ≥125 mm Hg or 79 mm Hg diastolic or the home values were ≥132 mm Hg systolic or 83 mm Hg diastolic. The remaining subjects were classified as "true" normotensive or sustained hypertensive based on normality or elevation, respectively, of either office and ambulatory or office and home BPs. Those with SHT were not considered for further analysis. The above-mentioned cutoff ambulatory and home BP values were derived from analysis of the correspondence among the office, ambulatory, and home BP distribution in the PAMELA population.[15] They closely reflect the cutoff values dividing ambulatory or home HT from normotension indicated by the European guidelines.[2]

The development of SHT was determined by the percentage of subjects with true normotension, WCTH, or MHT at the first examination (1990–1992) who, at the second examination (2001–2002), showed both office and 24-hour or home BP values in the hypertensive range. The χ^2 test was used to compare the percentage data. The odds ratio of developing SHT was assessed by a logistic regression model, with the true normotensive condition as
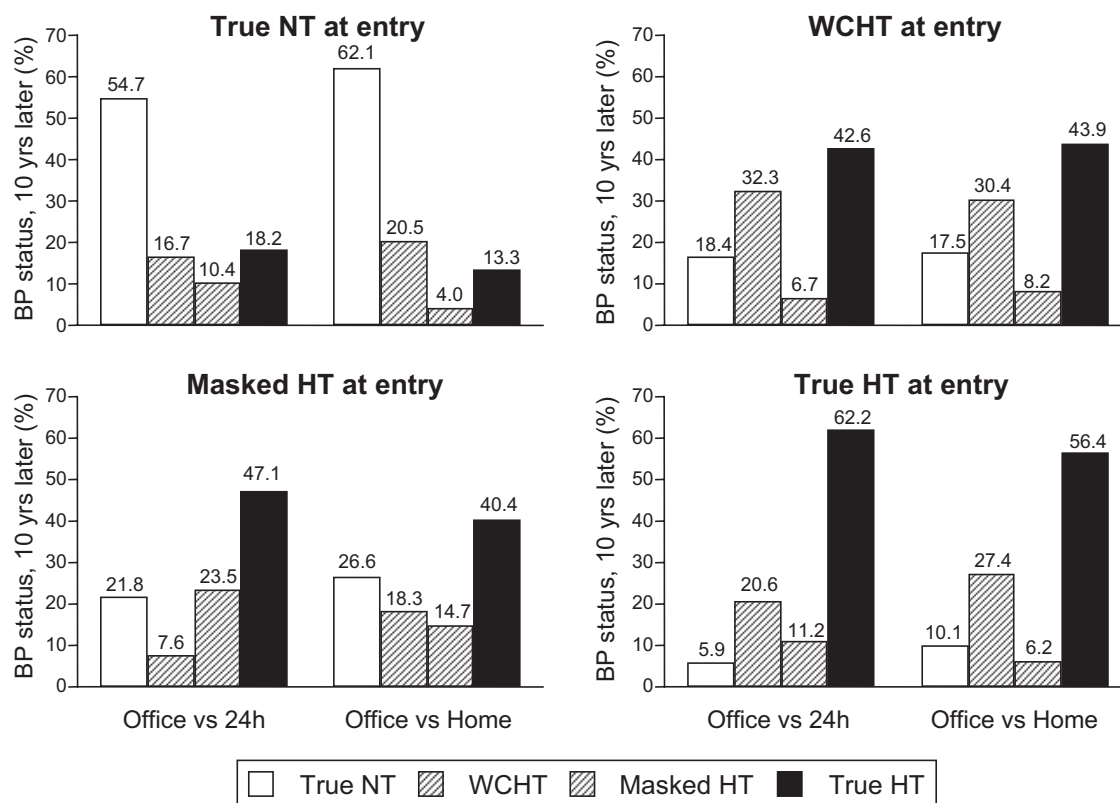
Figure 1. Mean percentage changes in BP status among normotension (NT), WCHT, and MHT over the 10-year period of the study. Data referring to true HT are shown for comparison.

a reference, and adjusting data for between-group differences in age and sex.

A multivariate analysis was used to identify the variables independently predictive of the development of SHT. Independent variables were entered into the model using a stepwise selection procedure and ranked by using χ^2 score to determine their level of significance in the model. In addition to age and sex, the variables considered were smoking; use of antihypertensive drugs at the first visit (n=216); use of antihypertensive drugs at the second visit (n=481); baseline values of office, 24-hour, and home systolic and diastolic BPs; serum glucose and lipid variables (total serum cholesterol and triglycerides); day-night systolic and diastolic BP difference (calculated by subtracting the mean nighttime [midnight to 6 AM] from the mean daytime [6 AM to midnight] values); and 24-hour systolic and diastolic BP variability (calculated by quantifying the erratic BP variations that occurred throughout the day and night via Fourier analysis of the 24-hour BP tracing). This was done because both the day-night BP difference and the erratic BP variability have been shown to independently predict the risk of CV mortality.[17] We also considered one additional variable, ie, for WCHT the presence of only one or both out-of-office BP normalities and for MHT the presence of only 1 or 2 out-of-office BP elevations. The age- and sex-adjusted risks of new-onset SHT were also calculated in subjects without antihypertensive treatment or those reporting the use of antihypertensive drugs at the first or second examination (n=497). Mean values (±SD or SE) were calculated for the baseline data, as well as for the BP changes (systolic, diastolic, and pulse pressures) between the first and the second examination, the comparison being made via ANOVA. A $P<0.05$ was taken as the level of statistical significance.

Results

Baseline Data
Of the 2051 subjects seen at the first examination, 157 died in the subsequent 10 years. A total of 482 subjects refused to participate or could not be selected. Thus, a full set of data was obtained in 1412 subjects, including individuals with SHT. As shown in Tables 1 and 2, in this population, entry age, male prevalence, and body mass index were greater in individuals with WCHT or MHT than in those with true normotension (ie, with normal in-office and out-of-office BP values), both when these conditions were identified by office versus ambulatory and by office versus home BP. This was also the case for total serum cholesterol, serum triglycerides, plasma glucose, and BP variability, whereas serum high-density lipoprotein cholesterol and the day-night BP difference were similar or only slightly different among the 3 groups.

New-Onset SHT
Figure 1 shows that, over the 10 years between the first and the second examination, a substantial proportion of subjects remained in the BP category that they were in at the study entry. A noticeable percentage of subjects, however, changed from one category to another, including progression to SHT. As shown in Figure 2, the incidence of new-onset SHT was markedly greater in subjects with WCHT and MHT than in true normotensive individuals both when the groups were identified by office versus ambulatory and by office versus home BP. Compared with true normotension, the age- and sex-adjusted risks of developing SHT were usually significantly increased in subjects with WCHT and MHT (Figure 3), with no significant difference in the increased risk between these 2 conditions ($P=0.372$ for office versus ambulatory BP and $P=0.398$ for office versus home BP). This was usually
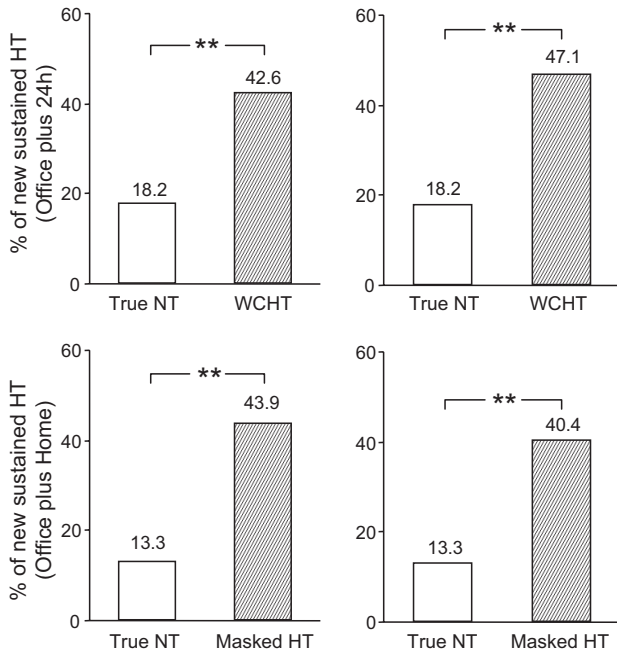
Figure 2. Mean percentage of individuals developing sustained HT, ie, a combined office and ambulatory HT (top) or office and home HT (bottom) in subjects with WCHT, MHT, and true normotension (NT) at entry. **P<0.0001 refers to the statistical significance between groups.

also the case when separate calculations were made of the subgroups without any antihypertensive treatment (Figure 4) or those reporting use of antihypertensive drugs at the first or the second examination (WCHT based on office versus 24-hour BP: 1.30, P=0.370; WCHT based on office versus home BP: 2.26, P=0.009; MHT based on office versus 24-hour BP: 1.73, P=0.005; MHT based on office versus home BP: 1.63, P=0.020). Similar findings were obtained when the cutoff 24-hour mean and home BP values dividing normotension from HT were precisely those indicated by the European Guidelines on Hypertension,[2] ie, <125/80 mm Hg and <135/85 mm Hg for 24-hour mean and home BPs, respectively. Compared with true normotension, the age- and sex-adjusted odd ratios of developing SHT were 2.54 and 3.15 in WCHT (P<0.0001 and <0.0001, office versus 24-hour or home BP, respectively). The corresponding odd ratios for MHT ere 1.66 and

1.68 (P<0.0001 and 0.0003, office versus 24-hour or home BP, respectively).

As shown in Table 3, office, home, and 24-hour BP values all independently predicted the development of SHT, together with an independent and usually less important contribution of age and metabolic variables, eg, serum glucose and body mass index. There was, on the other hand, no independent predictive value for BP variability and the day-night BP difference or the use of antihypertensive drugs, lipid profile, smoking habit, and sex in the development of SHT. This was the case also for the presence of 1 or 2 out-of-office BP normalities in WCHT or 1 of 2 out-of-office BP elevations in MHT.

10-Year BP Changes

As shown in Figure 5, in all 3 of the groups, BP showed an overall increase over the 10-year time interval. In subjects with WCHT, the increase in systolic BP was always significantly greater than that seen in subjects with true normotension, this also almost being the case for office systolic BP in subjects with MHT. In contrast, compared with true normotensives, subjects with WCHT or MHT showed a smaller (and not significant) increase in diastolic BP (data not shown), which resulted into an almost invariably significant and markedly greater increase in pulse pressure in both groups (Figure 5).

Discussion

Our study shows that the percentage of subjects who develop a sustained hypertensive state over a relatively long time interval (10 years) is greater in individuals who originally had WCHT or MHT than in true normotensive individuals, ie, individuals in whom both in-office and out-of-office BPs are within the normal range. It further shows that this is the case regardless of whether the definitions of these different BP states are based on office versus ambulatory or on office versus home BP values. It finally shows that, compared with a true normotensive condition, the greater choice of new-onset SHT exhibited by WCHT and MHT is by no means marginal, because the age- and sex-adjusted risks were almost doubled and more than tripled when these conditions were diagnosed, respectively, by office versus home and office versus ambulatory BP. Because the incidence of CV fatal and nonfatal events and mortality is greater in the presence of SHT than when only the in-office or out-of-office BP value is
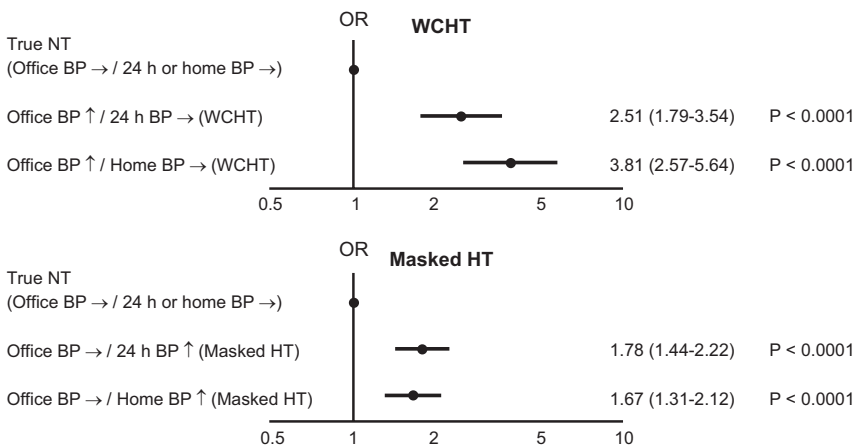

Figure 3. Ten-year age- and sex-adjusted odds ratios (ORs) of new-onset SHT in WCHT and MHT vs true normotension (NT) at entry. Symbols are as in preceding figures and tables.
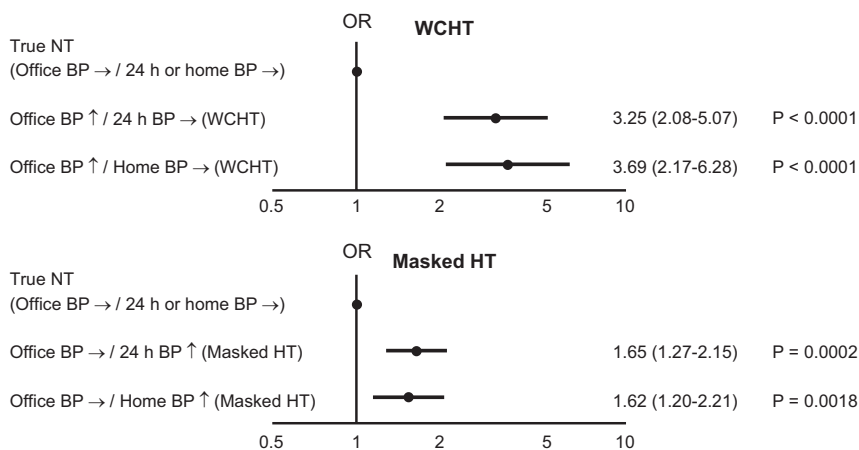
Figure 4. Ten-year age- and sex-adjusted risk (odds ratio [OR]) of new-onset SHT in WCHT and MHT vs true normotension (NT) at entry after exclusion of patients reporting use of antihypertensive drugs at the first or second examination. Symbols as in preceding figures and tables.

increased,[12] these results provide a strong argument against the clinical "innocence" of these conditions, supporting their adverse long-term prognostic significance instead.

Several other results deserve to be mentioned. First, in our study, a number of subjects were on antihypertensive drug treatment, which could have made it more difficult to reach the BP value defining office or out-of-office BP elevation and prevented a precise determination of the "natural" progression to SHT. It should be emphasized, however, that antihypertensive drugs were more likely to be administered in subjects with WCHT or MHT, which means that, if anything, drug treatment might have led to an underestimation of the actual increase in the risk of developing SHT in these 2 conditions. Furthermore, and more importantly, antihypertensive drug treatment was not found to be an independent predictor of new-onset SHT in the multivariate analysis that explored the determinants of this phenomenon. Finally, the increment in the risk of developing SHT in WCHT and MHT remained substantially unaltered when calculations excluded subjects reporting an antihypertensive drug assumption, and its size was similar in untreated and treated individuals. Thus, antihypertensive drug treatment did not play any major role, presumably because, in the Italian clinical practice, implementation of effective antihypertensive treatment is limited.[18]

This was also shown, years ago, for hypertensive patients included in the PAMELA population.[19]

Second, the most significant predictors of new-onset SHT were the BP values at entry, an expected finding because it is obvious that the higher the initial BP the greater the chance over the years to reach the cutoff BP value separating normotension from HT. However, this does not entirely explain our results, because the independent determinants of new-onset SHT included metabolic variables. Furthermore, compared with truly normotensive subjects, subjects with WCHT and MHT showed over the 10-year time interval a greater increase in both in-office and out-of-office systolic BPs, indicating that, in these 2 conditions, there was not just a reduced distance to the cutoff values defining SHT but also a more pronounced increase in BP. Interestingly, because subjects with WCHT and MHT showed a somewhat attenuated rise in diastolic BP, the more pronounced increase was even more evident for pulse pressure. This could mean that their greater rate of progression to SHT depends at least in part to a more pronounced stiffening of the large arteries.[4,20]

Finally, previous studies have shown that the size of nocturnal hypotension independently predicts the incidence of CV morbid and fatal events[17,21,22] and that this is the case also for BP variability.[17,23] However, in our subjects, these

Table 3. Independent Predictors of New-Onset SHT in WCHT and MHT

	Office vs 24-h BP			Office vs Home BP	
Variable	χ^2 Score	P	Variable	χ^2 Score	P
WCHT			WCHT		
SBP office, mm Hg	110.90	<0.0001	SBP office, mm Hg	116.08	<0.0001
DBP 24 h, mm Hg	35.65	<0.0001	SBP home, mm Hg	19.38	0.001
SBP home, mm Hg	19.60	<0.0001	Serum glucose, mg/dL	7.50	0.0062
Serum glucose, mg/dL	7.61	0.0058	DBP 24 h, mm Hg	6.76	0.0093
			Age, y	4.18	0.0409
MHT			MHT		
SBP office, mm Hg	36.09	<0.0001	SBP home, mm Hg	89.05	<0.0001
Age, y	12.26	0.0189	SBP office, mm Hg	34.00	<0.0001
DBP 24 h, mm Hg	9.79	<0.0001	DBP 24 h, mm Hg	8.90	0.0029
SBP home, mm Hg	4.30	<0.003	BMI, kg/m^2	7.54	0.0060

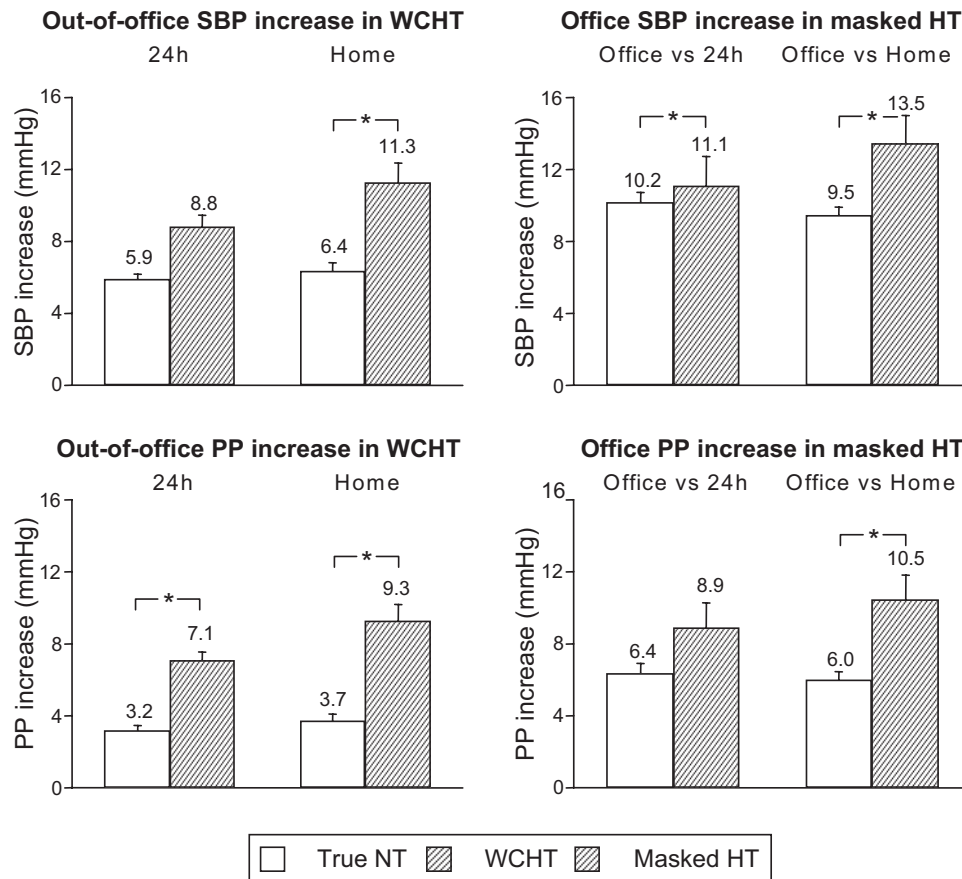SBP indicates systolic BP; DBP, diastolic BP; BMI, body mass index.

Figure 5. Increase (mean±SE) in systolic (S) BP (top), and pulse pressure (PP; bottom) over 10 years in subjects with true normotension (NT), WCHT, and MHT. Symbols as in preceding figures. *P<0.05 refers to the statistical significance between groups.

measures did not independently predict new-onset SHT, which means that their adverse prognostic significance is because of factors other than a more frequent worsening of the initial BP values. The finding has a special interest for BP variability because of the previous suggestion, derived by our study, that BP variability may be a precursor of a steady hypertensive state.[23]

Perspectives

The results of the present study provide evidence that the risk of developing a sustained hypertensive state is increased in patients with WCHT and MHT. This indicates that the 2 above-mentioned conditions cannot be regarded as innocent phenomena but as clinical states that require accurate diagnosis and follow-up.

Disclosures

None.

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