nature publishing group

Association Between White-Coat Effect and Blunted Dipping of Nocturnal Blood Pressure

Murielle Bochud[1], Pascal Bovet[1,2], Peter Vollenweider[3], Marc Maillard[4], Fred Paccaud[1], Gilles Wandeler[1], Anne Gabriel[2] and Michel Burnier[4]

BACKGROUND
In this study, we assessed whether the white-coat effect (difference between office and daytime blood pressure (BP)) is associated with nondipping (absence of BP decrease at night).

METHODS
Data were available in 371 individuals of African descent from 74 families selected from a population-based hypertension register in the Seychelles Islands and in 295 Caucasian individuals randomly selected from a population-based study in Switzerland. We used standard multiple linear regression in the Swiss data and generalized estimating equations to account for familial correlations in the Seychelles data.

RESULTS
The prevalence of systolic and diastolic nondipping (<10% nocturnal BP decrease) and white-coat hypertension (WCH) was respectively 51, 46, and 4% in blacks and 33, 37, and 7% in whites. When white-coat effect and nocturnal dipping were taken as continuous variables (mm Hg), systolic (SBP) and diastolic BP (DBP) dipping were associated inversely and independently with white-coat effect ($P < 0.05$) in both populations. Analogously, the difference between office and daytime heart rate was inversely associated with the difference between daytime and night-time heart rate in the two populations. These results did not change after adjustment for potential confounders.

CONCLUSIONS
The white-coat effect is associated with BP nondipping. The similar associations between office–daytime values and daytime–night-time values for both BP and heart rate suggest that the sympathetic nervous system might play a role. Our findings also further stress the interest, for clinicians, of assessing the presence of a white-coat effect as a means to further identify patients at increased cardiovascular risk and guide treatment accordingly.

Am J Hypertens 2009; **22**:1054-1061

Blood pressure (BP) follows a circadian rhythm with a 10–15% fall at night. Subjects who fail to show a 10% nocturnal BP decrease are considered to be "nondippers."[1] BP nondipping is associated with target organ damage and cardiovascular mortality.[2–4] Ambulatory BP might better predict mortality than casual BP readings.[5] Also, night-time ambulatory BP might be a better predictor of mortality than daytime BP and the night–day ambulatory BP ratio appears to predict all-cause mortality, independently of 24-h BP.[5,6] Although several neurohormonal systems regulating BP have been shown to follow a circadian rhythm and may contribute to the abnormal circadian variations in BP observed in some subjects, the exact causes of the nondipping pattern have not been well identified yet. Determinants of the circadian BP variations seem to include variations in the activity of the sympathetic nervous system[7,8] and the capacity to excrete sodium during daytime.[9]

The white-coat effect is usually defined as the difference between office BP and either daytime ambulatory BP or home BP. This effect can be observed in normotensive as well as in hypertensive subjects. White-coat hypertension (WCH), also called isolated office hypertension, refers to a persistently elevated BP in the office together with a normal BP outside of the office. WCH is generally defined as office BP ≥140/90 mm Hg with daytime ambulatory BP <135/85 mm Hg. WCH can be found in 10–18% of the general population[10,11] and in 10–38% of hypertensive subjects.[11,12]

It is generally recognized that patients with WCH have a lower risk of target organ damages and cardiovascular complications than truly hypertensive patients.[13] Yet, they appear to have more target organ damage than normotensive subjects. In cross-sectional studies, WCH has been associated with carotid atherosclerosis,[14] impaired arterial distensibility,[15] higher left-ventricular mass,[14] greater proteinuria, and left-ventricular diastolic dysfunction.[15] However, a significant difference in target organ damage between white-coat hypertensive and normotensive subjects was not found in other studies.[16,17] In longitudinal studies, WCH was found to be a risk factor for sustained hypertension,[18] insulin resistance,[19] and increased all-cause

[1]Institut Universitaire de Médecine Sociale et Préventive, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland; [2]Ministry of Health and Social Development, Victoria, Republic of Seychelles; [3]Department of Internal Medicine, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland; [4]Department of Medicine, Division de Néphrologie et Consultation d'Hypertension, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland. Correspondence: Michel Burnier (michel.burnier@chuv.ch)

Received 10 April 2009; first decision 2 May 2009; accepted 31 May 2009; advance online publication 23 July 2009. doi:10.1038/ajh.2009.133

mortality.[20] The association of WCH with cardiovascular outcomes was not confirmed in other longitudinal studies.[21,22] The mechanisms of the pressor response in patients with WCH are not well understood. Psychological as well as behavioral factors linked to the stress of the medical consultation and to anxiety have been identified in these patients. These factors may activate the sympathetic nervous system and increase BP responsiveness to the medical environment.

We hypothesized that the white-coat effect and BP nondipping could share common pathophysiological mechanisms, i.e., an overactivity of the sympathetic nervous system. The possibility of an association between these two phenomena was once tested by Palatini *et al.* in 1,013 hypertensive patients, but no significant association was found.[23] In this study, we analyzed whether (i) the white-coat effect was associated with BP dipping on a continuous scale, (ii) similar associations, if any, could be found for heart rate, and (iii) WCH was associated with BP nondipping, in 371 black normotensive and hypertensive individuals in the Seychelles as well as in 295 white subjects enrolled recently in an ongoing population-based study in Switzerland.

METHODS

Seychelles. The study took place in the Seychelles islands, where the population is of predominantly African descent. The study was approved by the Ethical Committees of the Ministry of Health in the Seychelles and the University of Lausanne (Switzerland). All participants provided written informed consent. The selection criteria for the study have been described elsewhere.[24] In brief, participants were recruited between August 1999 and January 2002 along a family-based approach. Based on BP information of an ongoing national hypertension register that includes all patients with hypertension who attend primary health care centers, families with two or more first-degree members included in the register were identified. Of the 135 screened families 76 were found to be eligible. A total of 371 subjects from 74 families had data available for the present analyses.

Antihypertensive therapy, if any, was stopped for 2 weeks before performing ambulatory BP monitoring. Two sets of triplicate office BP measurements (one on the day before and one on the day after ambulatory BP monitoring) were taken in the morning between 7.00 and 10.30 AM by trained health professionals on subjects who had been sitting quietly for at least 10 min, using a standard mercury sphygmomanometer with a triple-bladder cuff (Tricuff) that automatically adjusts bladder width to arm circumference. Ambulatory BP was monitored using validated[25] electronic Diasys devices (DIASYS Integra; Novacor, Rueil-Malmaison, France) placed on the left arm with an appropriately sized cuff. Measurements were recorded every 20 min during the day and every 30 min during the night. The actual awake and asleep periods were used, as reported by participants, to define daytime and night time. Validation criteria have been previously described.[26] For the analyses, the average of 10 randomly selected daytime and 10 randomly selected night-time BP measures was used to have the same number of measures for each participant and for each period.[26] The white-coat effect was defined as office minus daytime ambulatory BP, for systolic BP (SBP), diastolic BP (DBP), and heart rate. WCH was defined as office BP ≥140/90 mm Hg with daytime ambulatory BP <135/85 mm Hg (ref. 1). Dipping was defined as daytime minus night-time values for ambulatory BP or heart rate. Nondipping was defined as a <10% proportional nocturnal decrease for SBP, DBP, or heart rate.

Urinary and plasma sodium and potassium concentrations were measured by flame photometry (IL-943; Instrumentation Laboratory, Milan, Italy) and creatinine concentration was measured by the picric acid method (Cobas-Mira; Roche, Basel, Switzerland). Glomerular filtration rate was estimated using the abbreviated Modification of the Diet in Renal Disease (MDRD) equation [27].

Switzerland. We randomly selected participants to the CoLaus study,[28] who were a representative sample of the Caucasian population aged 35–75 years in 2003–2006 in the city of Lausanne, Switzerland. The study is ongoing and so far 295 had data available for the present analyses. We used the same method (device and criteria) to measure ambulatory BP and 24-h urine collection as in the Seychelles, and the same definitions for dipping and white-coat effect. In Switzerland, antihypertensive treatment was not stopped before conducting the ambulatory BP monitoring. Office BP was measured using a validated automatic oscillometric BP device (Omron HEM 907; Omron Healthcare Europe, Hoofddorp, the Netherlands). Office BP was defined by the mean of three measurements performed by the same research assistant just before the ambulatory BP device was installed.

Statistical analyses. We used Stata 10.0 (StataCorp, College Station, TX) to conduct all statistical analyses. Continuous variables were compared with *t*-tests and categorical variables with χ^2-tests. Spearman rank correlation coefficients were used to measure association between white-coat effect and dipping for SBP, DBP, and heart rate. We assessed trends across tertiles of white-coat effect, separately for SBP, DBP, and heart rate, using a nonparametric test for trend. We used generalized estimating equations with an exchangeable correlation structure and a Gaussian link for continuous dependent variables or a logit link for dichotomous dependent variables to account for the familial correlations in the Seychelles data. In the Swiss data, we used standard multiple linear or logistic regressions because participants were unrelated. Continuous dipping (mm Hg) was used as the dependent variable and continuous white-coat effect (mm Hg) as the predictor of interest, using separate models for SBP, DBP, and heart rate. Different sets of covariate adjustments were compared to assess the effect of potential confounders. We conducted sensitivity analyses that (i) excluded participants taking antihypertensive treatment in Switzerland and in Seychelles; (ii) added a correction for ascertainment in Seychelles as previously described[24] (correction for ascertainment aims to determine what would have been the results had the investigators not ascertained this way). We corrected the models for BP ascertainment by including as a covariate

an indicator variable whose value was 1 if the participant was hypertensive and whose value was 0 otherwise.

RESULTS

In Seychelles, the study included 167 men and 204 women from 74 pedigrees, each with at least two hypertensive siblings. Overall there were 176 normotensive and 195 hypertensive participants. Women were slightly older (mean ± s.d.: 47.5 ± 12.5 vs. 45.5 ± 11.2 years) and more overweight (28.7 ± 5.1 vs. 26.1 ± 4.6) than men. The 24-h urinary sodium and potassium excretions were 109 and 49 mmol/24-h, respectively. The 24-h urinary creatinine excretions were 0.17 mmol/kg in women and 0.21 mmol/kg in men. The prevalence of nondipping was 51% (190/371) for SBP, 46% for DBP, and 12% (45/371) for heart rate. The prevalence of WCH was 4% (15/371).

In Switzerland, the study included 143 men and 152 women, with mean ± s.d. age 56.1 ± 9.8 and 57.2 ± 10.5 years ($P = 0.36$), and mean body mass index 26.8 ± 3.4 and 24.6 ± 4.0 kg/m^2 ($P < 0.001$), respectively. The prevalence of hypertension, defined as office BP ≥140/90 mm Hg or being on antihypertensive treatment, was 29% in men and 26% in women, of which 55 and 50% were treated, respectively. By comparison, the prevalence of hypertension in the entire CoLaus study was significantly higher in men (43%, $P < 0.05$), but similar in women (31%, $P = 0.42$). The 24-h urinary sodium and potassium excretions were 134 and 64 mmol/24-h, respectively. The 24-h urinary creatinine excretions were 0.15 mmol/kg in women and 0.19 mmol/kg in men. The prevalence of nondipping was 33% (97/295) for SBP, 37% (109/295) for DBP, and 20% (60/295) for heart rate. The prevalence of WCH was 7% (22/295).

In Seychelles (**Figure 1a**), the distributions of the SBP/DBP dippings were centered at 13.3/9.0 mm Hg and those of the systolic/diastolic white-coat effects at 1.7/0 mm Hg, respectively. In Switzerland (**Figure 1b**), the distributions of the SBP/DBP dippings were centered at 16/10 mm Hg and those of the systolic/diastolic white-coat effects at 4.1/−7.3 mm Hg, respectively.

Both in absolute (i.e., in mm Hg) and relative (i.e., proportional dipping) terms, SBP dipping was substantially lower in subjects within the highest tertile of SBP white-coat effect as calculated by the office–ambulatory daytime SBP difference and this for

Table 1 | Blood pressure and heart rate by tertiles of systolic, diastolic, and heart rate white-coat effects, Seychelles

		White-coat effect			
	All	Tertile 1	Tertile 2	Tertile 3	*P* trend
Systolic blood pressure, *N*	371	124	124	123	
Age (years)	46.6 ± 0.6	42.1 ± 1.0	47.3 ± 1.1	50.4 ± 1.0	<0.001
Body mass index (kg/m^2)	27.0 ± 0.3	26.2 ± 0.4	27.3 ± 0.4	27.5 ± 0.5	0.03
MDRD (ml/min/1.73 m^2)	115 ± 3	118 ± 6	110 ± 3	115 ± 8	0.21
White-coat effect (mm Hg)	1.6 ± 0.7	−11.9 ± 0.7	1.7 ± 0.3	15.2 ± 0.7	<0.001
Office (mm Hg)	132.8 ± 1.0	122.0 ± 1.5	133.3 ± 1.6	143.3 ± 1.6	<0.001
Daytime (mm Hg)	131.2 ± 0.9	133.9 ± 1.7	131.5 ± 1.6	128.1 ± 1.4	0.039
Night time (mm Hg)	117.9 ± 0.9	116.3 ± 1.5	119.3 ± 1.6	118.1 ± 1.4	0.230
Absolute dipping (mm Hg)	13.3 ± 0.5	17.6 ± 0.8	12.2 ± 0.9	10.0 ± 0.8	<0.001
Proportional dipping (proportion)	0.10 ± 0.00	0.13 ± 0.01	0.09 ± 0.01	0.08 ± 0.01	<0.001
Diastolic blood pressure, *N*	371	124	124	123	
White-coat effect (mm Hg)	0.0 ± 0.4	−8.6 ± 0.4	0.3 ± 0.2	8.3 ± 0.4	<0.001
Office (mm Hg)	84.9 ± 0.6	80.0 ± 1.0	83.9 ± 0.9	90.8 ± 1.0	<0.001
Daytime (mm Hg)	84.9 ± 0.6	88.6 ± 1.1	83.6 ± 0.9	82.5 ± 1.0	<0.001
Night time (mm Hg)	75.9 ± 0.6	76.7 ± 1.2	75.1 ± 1.0	76.0 ± 1.0	0.967
Absolute dipping (mm Hg)	9.0 ± 0.4	11.9 ± 0.6	8.5 ± 0.6	6.6 ± 0.5	<0.001
Proportional dipping (proportion)	0.11 ± 0.00	0.14 ± 0.01	0.10 ± 0.01	0.08 ± 0.01	<0.001
Heart rate, *N*	371	125	123	123	
White-coat effect (beats/min)	−4.1 ± 0.4	−12.6 ± 0.4	−3.9 ± 0.2	4.5 ± 0.4	<0.001
Office (beats/min)	74.9 ± 0.5	71.1 ± 0.8	74.2 ± 0.9	79.4 ± 0.9	<0.001
Daytime (beats/min)	78.9 ± 0.5	83.7 ± 0.9	78.1 ± 0.9	75.0 ± 0.8	<0.001
Night time (beats/min)	64.0 ± 0.4	64.7 ± 0.7	63.9 ± 0.8	63.2 ± 0.7	0.172
Absolute dipping (beats/min)	15.0 ± 0.4	19.0 ± 0.6	14.1 ± 0.6	11.8 ± 0.5	<0.001
Proportional dipping (proportion)	0.19 ± 0.00	0.22 ± 0.01	0.18 ± 0.01	0.16 ± 0.01	<0.001

Data are means ± s.e. Tertiles are sex-specific, and therefore have the same proportion of men and women. The tertiles for systolic, diastolic and pulse data do not encompass the same subjects. White-coat effect is calculated as office minus daytime ambulatory values. Dipping is calculated as daytime minus night-time ambulatory values. P values are for a nonparametric test for trend across tertiles.
MDRD, Modification of the Diet in Renal Disease

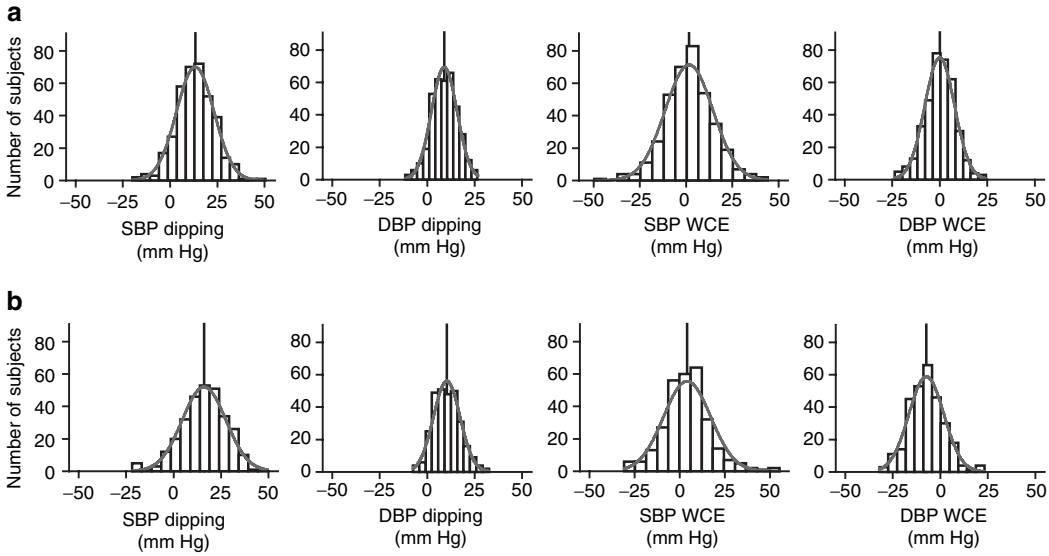

Figure 1 | Histograms of white-coat effects and dipping profiles for blood pressure. Histograms of white-coat effect and dipping for blood pressure in (**a**) Seychelles and in (**b**) Switzerland. Each vertical line represents the mean of the distribution. DBP, diastolic blood pressure; SBP, systolic blood pressure.

both populations (**Tables 1** and **2**). The same observation was made when subjects were classified into tertiles of DBP or heart rate white-coat effects.

Taken as a categorical variable, WCH was a significant determinant of both SBP nondipping (odds ratio ± s.e. = 4.0 ± 2.6, $P = 0.03$) and DBP nondipping (odds ratio = 5.0 ± 3.3, $P = 0.01$) in the Seychelles. These associations were similar after adjustment for potential confounding factors such as age, sex, body mass index, and daytime SBP. In Switzerland, the associations of WCH with SBP nondipping (odds ratio ± s.e. = 2.1 ± 1.0, $P = 0.11$) and DBP nondipping (odds ratio =1.6 ± 0.7, $P = 0.30$) were also positive, but not significant.

Taken as a continuous variable, the SBP white-coat effect was significantly and inversely correlated with the SBP dipping ($P < 0.001$) in the Seychelles as well as in Switzerland ($P < 0.001$) (**Figure 2**), suggesting that a large SBP white-coat effect is associated with reduced SBP dipping. Similar observations were made for DBP and heart rate.

Mean white-coat effects by selected categories of dipping are presented in **Figure 3**. In both populations, the larger SBP white-coat effect observed in SBP nondippers was independent of daytime SBP. The nonsignificant difference in tertile 2 in Switzerland may reflect low power due to a small number of nondippers in this group. Moreover, similar results were obtained in normotensive and hypertensive subjects (data not shown). For DBP and heart rate, results were analogous but less significant (data not shown).

The results of multiple linear regressions are presented in **Table 3**. In both populations, the SBP white-coat effect was significantly and inversely associated with the SBP dipping, even after adjusting for possible confounding factors. Our results indicate that, at equal daytime SBP, the higher the systolic white-coat effect, the smaller the SBP dipping, or in other words, the higher the night-time SBP. Similar results were obtained for DBP and for heart rate.

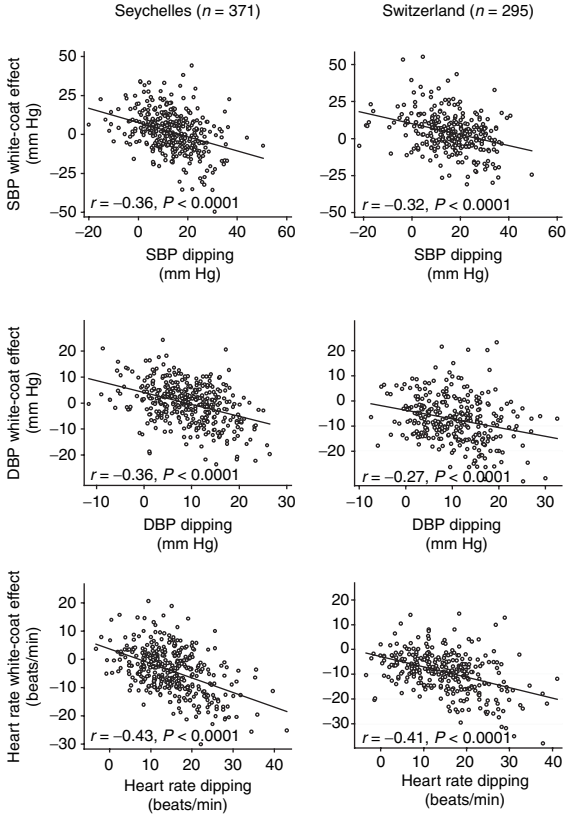

Figure 2 | Associations between white-coat effect and dipping for blood pressure and heart rate. DBP, diastolic blood pressure; *r*, Spearman rank correlation coefficient; SBP, systolic blood pressure.

We also conducted additional analyses using night-time BP as the dependent variable and office and daytime BP as independent variables of interest, to avoid the simultaneous use of daytime BP in both sides of the equation (i.e., dependent and independent variables), As shown in **Table 4**, after adjustment

Table 2 | Blood pressure and heart rate by tertiles of systolic, diastolic, and heart rate white-coat effect, Switzerland

		White-coat effect			
	All	Tertile 1	Tertile 2	Tertile 3	*P* trend
Systolic blood pressure, *N*	295	99	99	97	
Age (years)	56.6 ± 0.6	53.7 ± 1.0	56.7 ± 1.0	59.5 ± 1.0	<0.001
Body mass index (kg/m^2)	25.7 ± 0.2	25.0 ± 0.4	25.6 ± 0.4	26.5 ± 0.4	0.01
MDRD (ml/min/1.73 m^2)	80 ± 1	81 ± 1	79 ± 2	80 ± 2	0.48
White-coat effect (mm Hg)	4.1 ± 0.8	−9.2 ± 0.7	4.2 ± 0.3	17.6 ± 1	<0.001
Office (mm Hg)	125.8 ± 1	116.9 ± 1.3	123.7 ± 1.4	137 ± 1.8	<0.001
Daytime (mm Hg)	121.7 ± 0.9	126.1 ± 1.5	119.5 ± 1.3	119.4 ± 1.5	0.0028
Night time (mm Hg)	105.7 ± 0.9	106.7 ± 1.5	102.6 ± 1.4	107.8 ± 1.6	0.7842
Absolute dipping (mm Hg)	16 ± 0.7	19.5 ± 1.1	16.9 ± 1	11.7 ± 1.2	<0.001
Proportional dipping (proportion)	0.13 ± 0.01	0.15 ± 0.01	0.14 ± 0.01	0.10 ± 0.01	<0.001
Diastolic blood pressure, *N*	295	99	99	97	
White-coat effect (mm Hg)	−7.3 ± 0.5	−16.7 ± 0.5	−7.7 ± 0.3	2.7 ± 0.6	<0.001
Office (mm Hg)	71.9 ± 0.6	66 ± 0.9	69.7 ± 0.8	80.2 ± 1	<0.001
Daytime (mm Hg)	79.2 ± 0.5	82.7 ± 1	77.4 ± 0.8	77.5 ± 0.9	0.0001
Night time (mm Hg)	68.9 ± 0.5	70 ± 0.8	67.4 ± 0.8	69.2 ± 0.9	0.4774
Absolute dipping (mm Hg)	10.3 ± 0.4	12.7 ± 0.7	10 ± 0.7	8.2 ± 0.6	<0.001
Proportional dipping (proportion)	0.13 ± 0.01	0.15 ± 0.01	0.13 ± 0.01	0.10 ± 0.01	0.0001
Heart rate, *N*	295	99	100	96	
White-coat effect (beats/min)	−9.1 ± 0.5	−18.3 ± 0.5	−8.2 ± 0.2	−0.6 ± 0.5	<0.001
Office (beats/min)	70.6 ± 0.6	65.4 ± 1	70.9 ± 0.9	75.7 ± 1.1	<0.001
Daytime (beats/min)	79.8 ± 0.6	83.7 ± 1	79.1 ± 0.9	76.4 ± 0.9	<0.001
Night time (beats/min)	64.9 ± 0.5	64 ± 0.9	65.4 ± 0.9	65.2 ± 0.8	0.4332
Absolute dipping (beats/min)	14.9 ± 0.5	19.7 ± 0.9	13.7 ± 0.7	11.2 ± 0.7	<0.001
Proportional dipping (proportion)	0.18 ± 0.01	0.23 ± 0.01	0.17 ± 0.01	0.14 ± 0.01	<0.001

Data are means ± s.e. Tertiles are sex-specific, and therefore have the same proportion of men and women. The tertiles for systolic, diastolic and pulse data do not encompass the same subjects. White-coat effect is calculated as office minus daytime ambulatory values. Dipping is calculated as daytime minus night-time ambulatory values. *P* values are for a nonparametric test for trend across tertiles.

for age, sex, body mass index, antihypertensive treatment, urinary sodium and potassium excretion, for a given daytime BP and heart rate, night-time BP was higher when office BP measured in the morning was higher confirming that the greater the white-coat effect the smaller the dipping at night. This was true for both populations, for SBP as well for DBP and heart rate. Sensitivity analyses provided very similar results (i.e., that differed by <1 standard error from the main analyses) and did not change our conclusions.

DISCUSSION

We found an inverse association between the white-coat effect—as assessed by the difference between several office BP readings and ambulatory daytime BP—and BP dipping—as assessed by the difference between daytime and night-time ambulatory BP—in two widely different populations. This association was independent of daytime BP levels and other possible confounding factors. A similar association was also found with heart rate (i.e., inverse association between the daytime–office difference in heart rate and the daytime–night-time difference in heart rate). These common associations for BP and heart rate are consistent with the hypothesis that the white-coat effect and the absence of physiological nocturnal BP dipping are mediated by a common pathway, e.g., overactivity of the sympathetic nervous system.

The basis of our hypothesis was supported by several previous observations. The white-coat effect was initially described as a defense reaction against the person measuring BP, which included an increase in both BP and heart rate, and was believed to be an alert reaction mediated essentially by the sympathetic nervous system.[29] Although this description was done >20 years ago, there has been little evidence to either support or refute this hypothesis. Nonetheless, WCH has been associated with increased muscle sympathetic nerve activity when compared to normotension.[30] Moreover, additional indirect evidence for sympathetic overactivity is supported by the findings that the

Table 3 | Associations between the white-coat effect[a] and dipping for blood pressure[b] and heart rate, based on multiple linear regression

Country	Dependent variable	Covariates	Coefficient (s.e.) (mm Hg dipping/ 10 mm Hg white-coat effect)	*P* value
Seychelles	SBP dipping (mm Hg)	None	−2.70 (0.38)	<0.001
		Full model[c]	−1.86 (0.40)	<0.001
	DBP white-coat effect (mm Hg)	None	−3.41 (0.41)	<0.001
		Full model[c]	−2.45 (0.43)	<0.001
	Heart rate white-coat effect (beats/min)	None	−4.30 (0.42)	<0.001
		Full model[c]	−2.51 (0.40)	<0.001
Switzerland	SBP dipping (mm Hg)	None	−2.90 (0.49)	<0.001
		Full model[c]	−1.40 (0.55)	0.011
	DBP white-coat effect (mm Hg)	None	−1.99 (0.43)	<0.001
		Full model[c]	−1.22 (0.44)	0.006
	Heart rate white-coat effect (beats/min)	None	−4.22 (0.53)	<0.001
		Full model[c]	−2.71 (0.55)	<0.001

In Seychelles, models were also adjusted for persons who measured office BP and for being taken off antihypertensive treatment. In Switzerland, models were also adjusted for being on current antihypertensive treatment.
DBP, diastolic blood pressure; SBP, systolic blood pressure.
[a]White-coat effect is calculated as office minus daytime ambulatory values. [b]Dipping is calculated as daytime minus night-time ambulatory values. [c]Full models are adjusted for age, sex, body mass index, daytime SBP (or DBP or heart rate), urinary sodium excretion, and urinary potassium excretion.

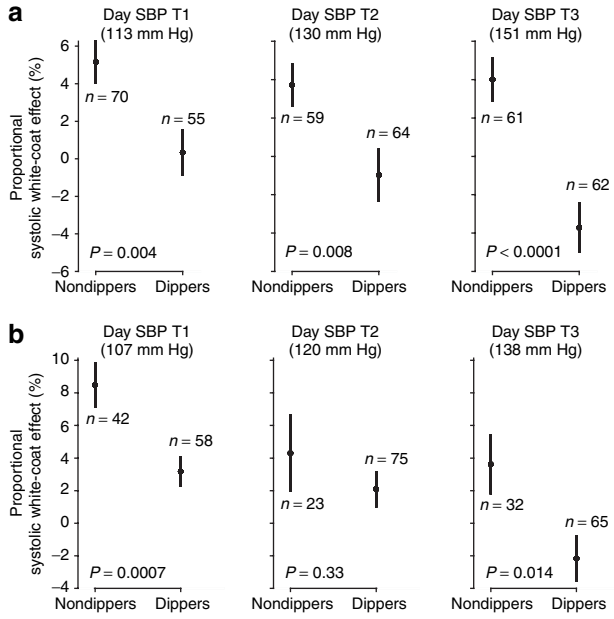

Figure 3 | Proportional white-coat effect vs. dipping status of (**a**) Seychelles and (**b**) Switzerland, by tertiles of daytime ambulatory systolic blood pressure. Dippers were defined as subjects having at least 10% nocturnal systolic blood pressure decrease. All the other subjects were classified as nondippers. *P* values are from *t*-tests comparing white-coat effect (i.e., office-day BP difference) by dipping status.

white-coat effect is associated with increased BP reactivity to (i) stress,[31,32] although this was not confirmed in all studies,[33] (ii) standing,[32,34] or (iii) anxiety.[35]

There is also substantial experimental evidence that the sympathetic activity contributes to the circadian rhythm of BP. In rats, sympathectomy abolishes the circadian rhythm of BP.[36,37] Dopamine β-hydroxylase knockout mice, which completely lack epinephrine and norepinephrine, have an attenuated circadian rhythm of BP.[38] Few data exist in humans probably because of the difficulty to measure the sympathetic activity overnight. However, nondippers, in particular African Americans, tend to have smaller daytime–night-time difference in urinary excretion of catecholamines and higher α1-adrenergic responsiveness than dippers.[7] Palatini *et al.*[23] did not find a statistically significant association between white-coat effect and BP dipping in hypertensive patients, but the trend observed in their study was consistent with our findings. In a recent study, patients with WCH and increased number of metabolic syndrome components had higher night-time SBP levels.[39] As the metabolic syndrome is associated with sympathetic overactivity, this latter observation is also consistent with our hypothesis.

One potential limitation in our study is that daytime SBP is included in both sides of the equation (i.e., dependent and independent variables). Therefore, we performed additional statistical analysis in which daytime SBP was used only as independent variable (see **Table 4**). In these analyses, for a given daytime BP, night-time BP was positively associated with office BP. These analyses confirmed that, for any given daytime BP, high white-coat effect is associated with reduced dipping pattern. Another limitation relates to the fact that the Seychelles study included families enriched in hypertensive individuals, which may limit the external validity of our findings. However, similar results were obtained in all BP tertiles in the Seychelles (the lowest including mostly normotensive persons) as well as in unrelated subjects from the general population of a Swiss city. Dietary salt intake was low in both study populations and our results may therefore not apply to other groups with higher

Table 4 | Regression of office blood pressure, or heart rate, on night-time ambulatory blood pressure or heart rate

Study	Dependent variable	Covariates of interest	Coefficient (s.e.) (1 unit of depvar/ 10 units of covariate)	*P* value
Seychelles	Night-time SBP	Office SBP	1.82 (0.39)	<0.0001
		Daytime SBP	6.17 (0.41)	<0.0001
	Night-time DBP	Office DBP	2.42 (0.43)	<0.0001
		Daytime DBP	6.20 (0.42)	<0.0001
	Night-time heart rate	Office heart rate	2.55 (0.39)	<0.0001
		Daytime heart rate	4.08 (0.39)	<0.0001
Switzerland	Night-time SBP	Office SBP	1.40 (0.55)	0.011
		Daytime SBP	5.78 (0.59)	<0.0001
	Night-time DBP	Office DBP	1.22 (0.44)	0.006
		Daytime DBP	5.90 (0.53)	<0.0001
	Night-time heart rate	Office heart rate	2.56 (0.49)	<0.0001
		Daytime heart rate	3.46 (0.52)	<0.0001

DBP, diastolic blood pressure; SBP, systolic blood pressure.
Units are mm Hg for blood pressure and beats/min for heart rate. In Seychelles, models are adjusted for age, sex, body mass index, being taken off antihypertensive treatment, urinary sodium excretion, urinary potassium excretion, person who measured the office BP. In Switzerland, models are adjusted for age, (age squared for DBP), sex, body mass index, antihypertensive treatment, urinary sodium, and potassium excretion.

dietary salt intakes. As previously discussed,[24] even in participants with urinary creatinine excretion above the sex-specific 20th percentile (0.154 mmol/kg/24 h for men and 0.112 mmol/kg/24 h for women), urinary sodium excretion was as low as 114 mmol/24 h. We consider that these results reflect low dietary salt intake in Seychelles. The urinary sodium excretion obtained in the Swiss sample is in line with previous reports.[40]

Does the observed inverse association between the white-coat effect and the nocturnal dipping pattern have any clinical implication for physicians? Night-time BP is still not measured on a regular basis by physicians, although it might represent a better predictor of cardiovascular risk and mortality than daytime BP.[5,6] By contrast, it is easier to identify a white-coat effect or WCH with home BP measurements. A message for physicians is that when they identify patients with white-coat effect, these patients may also present a nondipping BP at night time. Subsequently, these patients might be at higher risk of developing target organ damage. Further studies are needed to determine whether specific interventions on night-time BP can improve the prognosis of these patients.

Perspectives

We found that the white-coat effect occurring in the physician's office is associated with reduced nocturnal BP dipping in two genetically and environmentally different populations. The similar associations between office–ambulatory and daytime–night-time differences observed for both BP and heart rate suggest similar underlying mechanisms, which may be mediated by the sympathetic nervous system. Considering the high disease burden of hypertension and, in particular, the potential impact of nocturnal hypertension,[6] our findings also further stress the interest, for clinicians, of assessing the presence of a white-coat effect as a means to further identify patients at increased cardiovascular risk and guide treatment accordingly.

Acknowledgments: We thank the Ministry of Health of the Republic of Seychelles for its support to this epidemiological research, and Air Seychelles and SkyChef for their logistic support in transporting equipment and samples. We thank the study nurses of both studies for data collection and we are grateful to all participants. The study benefited from a grant from the Swiss National Science Foundation (TANDEM No 31-51115.97). M.Bo. is supported by a grant from the Swiss National Science Foundation (PROSPER 3200BO-111362/1 and 111361/1). M. Bu. is supported by the Swiss National Science Foundation (Project No 3100A0-103629). M. Bu., P.B., and F.P. conceived and designed the study and developed the protocol. M. Bo., G.W., and M.M. collected the data. M.Bo. analyzed the data and carried out the statistical analyses. M.Bo., P.B., A.G., and M.Bu. interpreted the data and prepared the manuscript. M.Bo., P.B., M.M., F.P., A.G., P.V., G.W., and M.Bu. revised the article for critical intellectual content and approved the final version. Part of this work was presented in an abstract at the meeting of the European Society of Hypertension, Milan, Italy, 15–19 June 2007.

Disclosure: The authors declared no conflict of interest.

1. Pickering TG, Hall JE, Appel LJ, Falkner BE, Graves J, Hill MN, Jones DW, Kurtz T, Sheps SG, Roccella EJ. Recommendations for blood pressure measurement in humans and experimental animals: part 1: blood pressure measurement in humans: a statement for professionals from the Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research. *Hypertension* 2005; 45:142–161.
2. Cuspidi C, Meani S, Salerno M, Valerio C, Fusi V, Severgnini B, Lonati L, Magrini F, Zanchetti A. Cardiovascular target organ damage in essential hypertensives with or without reproducible nocturnal fall in blood pressure. *J Hypertens* 2004; 22:273–280.
3. Hoshide S, Kario K, Hoshide Y, Umeda Y, Hashimoto T, Kunii O, Ojima T, Shimada K. Associations between nondipping of nocturnal blood pressure decrease and cardiovascular target organ damage in strictly selected community-dwelling normotensives. *Am J Hypertens* 2003; 16:434–438.
4. Ohkubo T, Imai Y, Tsuji I, Nagai K, Watanabe N, Minami N, Kato J, Kikuchi N, Nishiyama A, Aihara A, Sekino M, Satoh H, Hisamichi S. Relation between nocturnal decline in blood pressure and mortality. The Ohasama Study. *Am J Hypertens* 1997; 10:1201–1207.
5. Sega R, Facchetti R, Bombelli M, Cesana G, Corrao G, Grassi G, Mancia G. Prognostic value of ambulatory and home blood pressures compared with office blood pressure in the general population: follow-up results from the Pressioni Arteriose Monitorate e Loro Associazioni (PAMELA) study. *Circulation* 2005; 111:1777–1783.

6. Fagard RH, Celis H, Thijs L, Staessen JA, Clement DL, De Buyzere ML, De Bacquer DA. Daytime and nighttime blood pressure as predictors of death and cause-specific cardiovascular events in hypertension. *Hypertension* 2008; 51:55–61.
7. Sherwood A, Steffen PR, Blumenthal JA, Kuhn C, Hinderliter AL. Nighttime blood pressure dipping: the role of the sympathetic nervous system. *Am J Hypertens* 2002; 15:111–118.
8. Nakano Y, Oshima T, Ozono R, Higashi Y, Sasaki S, Matsumoto T, Matsuura H, Chayama K, Kambe M. Non-dipper phenomenon in essential hypertension is related to blunted nocturnal rise and fall of sympatho-vagal nervous activity and progress in retinopathy. *Auton Neurosci* 2001; 88:181–186.
9. Bankir L, Bochud M, Maillard M, Bovet P, Gabriel A, Burnier M. Nighttime blood pressure and nocturnal dipping are associated with daytime urinary sodium excretion in African subjects. *Hypertension* 2008; 51:891–898.
10. Muscholl MW, Hense HW, Bröckel U, Döring A, Riegger GA, Schunkert H. Changes in left ventricular structure and function in patients with white coat hypertension: cross sectional survey. *BMJ* 1998; 317:565–570.
11. Niiranen TJ, Jula AM, Kantola IM, Reunanen A. Prevalence and determinants of isolated clinic hypertension in the Finnish population: the Finn-HOME study. *J Hypertens* 2006; 24:463–470.
12. Verdecchia P, Palatini P, Schillaci G, Mormino P, Porcellati C, Pessina AC. Independent predictors of isolated clinic ('white-coat') hypertension. *J Hypertens* 2001; 19:1015–1020.
13. Khattar RS, Senior R, Lahiri A. Cardiovascular outcome in white-coat versus sustained mild hypertension: a 10-year follow-up study. *Circulation* 1998; 98:1892–1897.
14. Kamel N, Gursoy A, Koseoglulari O, Dincer I, Gullu S. Isolated office hypertension: association with target organ damage and cardiovascular risk indices. *J Natl Med Assoc* 2006; 98:601–606.
15. Glen SK, Elliott HL, Curzio JL, Lees KR, Reid JL. White-coat hypertension as a cause of cardiovascular dysfunction. *Lancet* 1996; 348:654–657.
16. Hara A, Ohkubo T, Kikuya M, Shintani Y, Obara T, Metoki H, Inoue R, Asayama K, Hashimoto T, Harasawa T, Aono Y, Otani H, Tanaka K, Hashimoto J, Totsune K, Hoshi H, Satoh H, Imai Y. Detection of carotid atherosclerosis in individuals with masked hypertension and white-coat hypertension by self-measured blood pressure at home: the Ohasama study. *J Hypertens* 2007; 25:321–327.
17. Ohkubo T, Kikuya M, Metoki H, Asayama K, Obara T, Hashimoto J, Totsune K, Hoshi H, Satoh H, Imai Y. Prognosis of "masked" hypertension and "white-coat" hypertension detected by 24-h ambulatory blood pressure monitoring 10-year follow-up from the Ohasama study. *J Am Coll Cardiol* 2005; 46:508–515.
18. Ugajin T, Hozawa A, Ohkubo T, Asayama K, Kikuya M, Obara T, Metoki H, Hoshi H, Hashimoto J, Totsune K, Satoh H, Tsuji I, Imai Y. White-coat hypertension as a risk factor for the development of home hypertension: the Ohasama study. *Arch Intern Med* 2005; 165:1541–1546.
19. Björklund K, Lind L, Vessby B, Andrén B, Lithell H. Different metabolic predictors of white-coat and sustained hypertension over a 20-year follow-up period: a population-based study of elderly men. *Circulation* 2002; 106:63–68.
20. Mancia G, Facchetti R, Bombelli M, Grassi G, Sega R. Long-term risk of mortality associated with selective and combined elevation in office, home, and ambulatory blood pressure. *Hypertension* 2006; 47:846–853.
21. Verdecchia P, Reboldi GP, Angeli F, Schillaci G, Schwartz JE, Pickering TG, Imai Y, Ohkubo T, Kario K. Short- and long-term incidence of stroke in white-coat hypertension. *Hypertension* 2005; 45:203–208.
22. Kario K, Shimada K, Schwartz JE, Matsuo T, Hoshide S, Pickering TG. Silent and clinically overt stroke in older Japanese subjects with white-coat and sustained hypertension. *J Am Coll Cardiol* 2001; 38:238–245.
23. Palatini P, Penzo M, Canali C, Dorigatti F, Pessina AC. Interactive action of the white-coat effect and the blood pressure levels on cardiovascular complications in hypertension. *Am J Med* 1997; 103:208–216.
24. Bochud M, Elston RC, Maillard M, Bovet P, Schild L, Shamlaye C, Burnier M. Heritability of renal function in hypertensive families of African descent in the Seychelles (Indian Ocean). *Kidney Int* 2005; 67:61–69.
25. O'Brien E, Coats A, Owens P, Petrie J, Padfield PL, Littler WA, de Swiet M, Mee F. Use and interpretation of ambulatory blood pressure monitoring: recommendations of the British hypertension society. *BMJ* 2000; 320:1128–1134.
26. Bochud M, Bovet P, Elston RC, Paccaud F, Falconnet C, Maillard M, Shamlaye C, Burnier M. High heritability of ambulatory blood pressure in families of East African descent. *Hypertension* 2005; 45:445–450.
27. Levey AS, Coresh J, Balk E, Kausz AT, Levin A, Steffes MW, Hogg RJ, Perrone RD, Lau J, Eknoyan G. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Ann Intern Med* 2003; 139:137–147.
28. Firmann M, Mayor V, Vidal PM, Bochud M, Pécoud A, Hayoz D, Paccaud F, Preisig M, Song KS, Yuan X, Danoff TM, Stirnadel HA, Waterworth D, Mooser V, Waeber G, Vollenweider P. The CoLaus study: a population-based study to investigate the epidemiology and genetic determinants of cardiovascular risk factors and metabolic syndrome. *BMC Cardiovasc Disord* 2008; 8: 6.
29. Mancia G, Bertinieri G, Grassi G, Parati G, Pomidossi G, Ferrari A, Gregorini L, Zanchetti A. Effects of blood-pressure measurement by the doctor on patient's blood pressure and heart rate. *Lancet* 1983; 2:695–698.
30. Smith PA, Graham LN, Mackintosh AF, Stoker JB, Mary DA. Sympathetic neural mechanisms in white-coat hypertension. *J Am Coll Cardiol* 2002; 40:126–132.
31. Leary AC, Donnan PT, MacDonald TM, Murphy MB. The white-coat effect is associated with increased blood pressure reactivity to physical activity. *Blood Press Monit* 2002; 7:209–213.
32. Lantelme P, Milon H, Gharib C, Gayet C, Fortrat JO. White coat effect and reactivity to stress: cardiovascular and autonomic nervous system responses. *Hypertension* 1998; 31:1021–1029.
33. Tsai PS. Determinants of the white-coat effect in normotensives and never-treated mild hypertensives. *Clin Exp Hypertens* 2003; 25:443–454.
34. Narkiewicz K, Piccolo D, Borella P, Businaro R, Zonzin P, Palatini P. Response to orthostatic stress predicts office-daytime blood pressure difference, but not nocturnal blood pressure fall in mild essential hypertensives: results of the harvest trial. *Clin Exp Pharmacol Physiol* 1995; 22:743–747.
35. Jhalani J, Goyal T, Clemow L, Schwartz JE, Pickering TG, Gerin W. Anxiety and outcome expectations predict the white-coat effect. *Blood Press Monit* 2005; 10:317–319.
36. Briaud SA, Zhang BL, Sannajust F. Continuous light exposure and sympathectomy suppress circadian rhythm of blood pressure in rats. *J Cardiovasc Pharmacol Ther* 2004; 9:97–105.
37. Makino M, Hayashi H, Takezawa H, Hirai M, Saito H, Ebihara S. Circadian rhythms of cardiovascular functions are modulated by the baroreflex and the autonomic nervous system in the rat. *Circulation* 1997; 96:1667–1674.
38. Swoap SJ, Weinshenker D, Palmiter RD, Garber G. Dbh(–/–) mice are hypotensive, have altered circadian rhythms, and have abnormal responses to dieting and stress. *Am J Physiol Regul Integr Comp Physiol* 2004; 286:R108–R113.
39. Vyssoulis G, Karpanou E, Adamopoulos D, Kyvelou SM, Gymnopoulou E, Cokkinos D, Stefanadis C. Nocturnal blood pressure fall and metabolic syndrome score in patients with white coat hypertension. *Blood Press Monit* 2008; 13:251–256.
40. Beer-Borst S, Costanza MC, Pechère-Bertschi A, Morabia A. Twelve-year trends and correlates of dietary salt intakes for the general adult population of Geneva, Switzerland. *Eur J Clin Nutr* 2009; 63:155–164.