White Coat Effect and Reactivity to Stress
Cardiovascular and Autonomic Nervous System Responses

Pierre Lantelme, Hugues Milon, Claude Gharib, Christian Gayet, Jacques-Olivier Fortrat

Abstract—The aim of this study was to elucidate further the precise nature of the so-called “white coat” (WC) effect. We enrolled 88 hypertensive (46 men, 42 women) and 18 normotensive (4 men, 14 women) subjects in whom beat-to-beat blood pressure (BP) and heart rate (HR) were measured with a Finapres device at rest (R period) and during conventional BP measurement (WC period). The WC effect was defined as WC period minus R period values of Finapres systolic BP. Using the same method, we also measured the BP and HR variations induced by mental stress (MS period) and by assuming the standing position (S period). Variability was estimated in the frequency domain for BP (BPV) and HR (HRV) and gave indices of the autonomic nervous system. Pulse wave velocity was taken as an index of arterial distensibility. In hypertensive subjects, the WC effect was significantly and positively correlated with the BP response to stress (0.51, P<.0001) and standing (0.63, P<.0001). An increased BPV was observed in the low-frequency band (0 to 0.150 Hz) during WC, MS, and S periods. In normotensive subjects, the WC effect was very slight and not correlated with the responses to stress and standing. In this group, the WC period was not accompanied with an increased BPV, unlike the stress and standing periods. HRV was similar in normotensives and in hypertensives: decreased, unchanged, and increased during MS, S, and WC periods, respectively. The PWV was significantly increased in the hypertensives relative to the normotensives, even in the quartile of those with the lowest BP (on average similar to that of the normotensives). This work shows that the WC effect is associated with an enhanced BP response to standing and mental stress; these three situations are characterized by an increased BPV in the low frequencies, suggesting a similar modification of the sympathovagal balance. The WC effect may entail an increased risk because it is associated with impaired arterial distensibility. (Hypertension. 1998;31:1021-1029.)

Key Words: hypertension, white coat, blood pressure monitoring, baroreflex, autonomic nervous system

White coat hypertension is characterized by a difference between office and ambulatory BP. It usually implies that a subject demonstrates “normal” BP levels when measured out of the physician’s office but levels in the hypertensive range when taken by a physician using arbitrary conventional criteria. This categorical definition is debatable because both office and ambulatory BP are continuously distributed. Hence, several authors used a quantitative definition requiring a particular magnitude of “WC effect” that is probably better adapted to the continuous distribution of BP in a population. Perhaps because it depends on the adopted criteria, the prognosis of WC hypertension is still a controversial issue. Some authors believe that it is a benign condition, while others argue that it might entail an increased cardiovascular risk. Whatever the definition, the lack of a sustained BP elevation suggests that if there are harmful consequences, they may be related to increased BPV. Indeed, an exaggerated BPV (1) provokes greater target organ damage in true hypertensives and has already been reported in WC hypertension. An increased responsiveness to different stressors of everyday life may account for such an increased BPV.

The purpose of the present study was to determine (1) the precise nature of WC effect and (2) whether, for a given level of ambulatory BP, the WC effect is a marker of an overall enhanced BPV. This was achieved by (1) searching a correlation between the WC effect and other types of BPV in a group of subjects referred for hypertension and (2) comparing these different types of BPV between a normotensive group and the hypertensives having the lowest ambulatory BP level. We chose lying, standing, and mental stress as experimental situations. BP was recorded by an automatic device or beat-to-beat by a Finapres device. Beat-to-beat BPV and HRV were assessed in the frequency domain as indices of the autonomic nervous system; “long-term” BPV was assessed in the time domain. PWV was taken as an index of vascular damage.

Methods

Subjects
Eighty-eight patients were included who constituted the “hypertensive group.” They fulfilled the following criteria: (1) referral to the hospital for hypertension, as judged by their private doctors, and (2) no antihypertensive treatment in the 8 days preceding their study.
Selected Abbreviations and Acronyms
BP = blood pressure
BPV = blood pressure variability
DBP = diastolic blood pressure
HF = high frequency
HR = heart rate
HRV = heart rate variability
LF = low frequency
MS = mental stress
PWV = pulse wave velocity
R = rest
S = standing position
SBP = systolic blood pressure
SBR = spontaneous baroreflex
WC = white coat

participation. This mode of selection was thought to provide patients with widely different levels of ambulatory BP, WC effect, and variability. Eighteen subjects constituted the “normotensive group.” They were selected from the spouses of our patients if these spouses were known to have a normal BP. None of these subjects had a known history of cardiovascular events, diabetes mellitus, or renal or other metabolic disorders. The protocol was approved by a committee on ethics in human investigations (CCPPRB Lyon). All subjects gave informed consent to enter the study.

Ambulatory BP Recordings
All recordings were performed with a Diasys monitor (model 200 RS, Novacor) or a SpaceLab device (model 90207, SpaceLab). The cuff was placed on the nondominant arm, and conventional auscultatory measures were taken by a physician at the other arm. The monitor was programmed to measure BP every 15 minutes during daytime (6 AM to 10 PM) and every 30 minutes during nighttime (10 PM to 6 AM). Recordings were taken during the patient’s ordinary daily activity. Means of 24-hour, daytime, and nighttime SBP and DBP were calculated. Patients of the hypertensive group were separated into quartiles according to their 24-hour ambulatory SBP level. Standard deviations of the 24-hour SBP and daytime/nighttime SBP difference were considered as indices of long-term BPV.

Beat-to-Beat Recordings
We obtained beat-to-beat BP from the middle phalanx of the middle finger of the right hand with a Finapres device (model 2300, Ohmeda) and R-peaks from a standard bipolar electrocardiograph. The procedures for data collection and analysis have already been described.13 Briefly, the analog output of the ECG was processed to detect the QRS complex of each heart beat, converted by an analog-to-digital converter (12 bits), and sampled at 1000 Hz by a personal computer. Waves were detected automatically with pressure-sensitive transducers (model XCX01DNC, Sensymtronic), one at the base of the neck for carotid artery and one over the femoral artery. At least 15 cycles were considered, sampled at 1000 Hz, and stored for off-line blinded processing with personal software. The transit time between the two waves was measured between the feet of the waves; at least seven measurements were averaged. The distance traveled by the pulse was measured between the orthogonal projections of the two recording sites on the examination table. The PWV was obtained from the ratio of the distance (meters) divided by the transit time (seconds).

Protocol
Under standardized conditions of temperature (20°C to 23°C), lighting, and noise, brachial arterial pressure was measured with an oscillometric device (Dinamap, Critikon) during 30 minutes with one measure every 5 minutes while the subject was lying alone in the room. Under the same conditions, BP and HR were measured beat to beat during a 30-minute rest period in the supine position (R period). For the three following periods, BP and HR were recorded during a sufficient time to provide at least 300 beats (4 to 5 minutes generally): (1) during at least five consecutive clinical BP measurements made by the physician to quantify the WC effect (WC period), (2) during a period of active standing (S period), and (3) during a period of mental stress (MS period) induced by using a computer version derived from the Stroop Word Color Conflict test.16 This version has been recently shown to produce a significant BP elevation (at least 25 mm Hg in normotensive subjects).13 During this third period, the recording began after a period of minimal training, and the investigator continuously encouraged the subjects to do their best on the test. The WC effect, the response to stress, and the response to standing were defined as the WC, MS, and S periods, respectively, minus the R period values of Finapres SBP. This protocol was followed by a measurement of PWV and an ambulatory BP measurement.

Statistical Analysis
Values are mean±SE. The correlations between WC effect and other types of variability were examined in each quartile of this group and with coarse-graining spectral analysis). This method has the advantage of separating harmonic and nonharmonic variations. We used linear regression as a detrending procedure for HRV and BPV. The total spectral power (Ptot) was determined, and the harmonic components were used to assess the low-frequency (LF band, 0 to 0.150 Hz) power (P LF) and the high-frequency (HF band, 0.150 to 0.500 Hz) power (PHF) densities. These bands have been defined for BPV and HRV according to previous studies using coarse-graining spectral analysis.11,12 To evaluate the contribution of each band to the overall variability, a normalization was performed by dividing P LF and PHF by Ptot. Data point series were too short to permit analysis of the fractal component.13

These recordings also allowed the calculation of the sensitivity of the SBR. For each recording, sequences of at least three beats in which the R-R interval and SBP varied in the same direction were considered to be SBR events, and the averaged slope of all sequences was considered an index of SBR sensitivity.14

Pulse Wave Velocity
We used a method similar to that of Asmar et al15 to calculate the PWV. Two different pressure waveforms were obtained simultaneously with pressure-sensitive transducers (model XCX01DNC, Sensymtronic), one at the base of the neck for carotid artery and one over the femoral artery. At least 15 cycles were considered, sampled at 1000 Hz, and stored for off-line blinded processing with personal software. The transit time between the two waves was measured between the feet of the waves; at least seven measurements were averaged. The distance traveled by the pulse was measured between the orthogonal projections of the two recording sites on the examination table. The PWV was obtained from the ratio of the distance (meters) divided by the transit time (seconds).

TABLE 1. Age, Sex, Smoking, and Ambulatory BP in Hypertensive and Normotensive Subjects

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Sex, M/F</th>
<th>Smoking, n (%)</th>
<th>24-h SBP, mm Hg</th>
<th>24-h DBP, mm Hg</th>
<th>24-h HR, bpm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertensive (n=88)</td>
<td>50±1</td>
<td>46/42</td>
<td>23 (26)</td>
<td>139±2</td>
<td>89±2</td>
</tr>
<tr>
<td>1st quartile (n=23)</td>
<td>46±3</td>
<td>10/13</td>
<td>4 (17)</td>
<td>116±2</td>
<td>76±2</td>
</tr>
<tr>
<td>Normotensive (n=18)</td>
<td>52±2</td>
<td>4/14</td>
<td>2 (11)</td>
<td>113±3</td>
<td>72±2</td>
</tr>
</tbody>
</table>

1st quartile indicates first quartile of the hypertensive subjects according to 24-hour ambulatory SBP, 24-h SBP, DBP, and HR, 24-hour ambulatory SBP, DBP, and HR. Values are mean±SE except for sex and smoking.
in the total hypertensive group by Pearson’s *r* coefficient. The comparison within each group between the different periods used a paired *t* test. The comparison between the first quartile of the hypertensive group (having the lowest ambulatory SBP level) and the normotensive group used a *t* test.

**Results**

The main characteristics of the hypertensive and normotensive groups are given in Table 1. As we hoped, the mode of selection provided a large distribution of BP in the hypertensive group, which allowed its separation into four quartiles according to level of ambulatory SBP (quartile 1, <124 mm Hg; quartile 2, 124 to 136 mm Hg; quartile 3, 136 to 149 mm Hg; quartile 4, >149 mm Hg). It is noteworthy that the first quartile had the same average ambulatory SBP level as the normotensive group. Considering a classic definition of WC hypertension, ie, an office BP of >140/90 mm Hg, an ambulatory BP of <140/90, and a WC SBP effect ≥10 mm Hg, 56% of the hypertensive subjects would have fulfilled these criteria.

**WC Effect and Reactivity to Other Stimuli**

In all subjects taken together, the beat-to-beat SBP was strongly correlated with the other modes of BP measurements (*r* = .70, *P* < .0001 with the oscillometric method and *r* = .85, *P* < .0001 with the auscultatory method), allowing us to quantify the WC effect as the difference of Finapres SBP recordings during the WC period minus those during the R period. These values are given in Table 2. In the hypertensive group, each of the three periods, WC, MS, and S, was characterized by an increased SBP level; however, as shown in Table 3, a significant increase in HR was observed only during the latter two periods. Fig 1 gives an example of one individual beat-to-beat recording showing an increase of SBP that was especially marked during the MS period but also present during the WC and S periods compared with the R period. A significant correlation was found between the WC effect and the response to mental stress in the hypertensive subjects (Fig 2A). To allow for any possible confounding effect of the average BP level, the same correlation has been calculated in each quartile of this hypertensive group and found statistically significant, except in the fourth quartile (Fig 2B). Similar results were found for the response to standing (Fig 2A and 2B).

In the normotensive group, SBP rose significantly during the MS and S periods. However, contrary to the hypertensive

<table>
<thead>
<tr>
<th>TABLE 2. Beat-to-Beat BP Level and Variability Evaluated in Frequency Domain in Hypertensive and Normotensive Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Hypertensive (n=88)</td>
</tr>
<tr>
<td>Rest</td>
</tr>
<tr>
<td>White coat</td>
</tr>
<tr>
<td>Mental stress</td>
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<tr>
<td>Standing</td>
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<tr>
<td>Normotensive (n=18)</td>
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<tr>
<td>Rest</td>
</tr>
<tr>
<td>White coat</td>
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<tr>
<td>Mental stress</td>
</tr>
<tr>
<td>Standing</td>
</tr>
</tbody>
</table>

*P* indicates total spectral power; *P*(SBP), power in LF band; *P*(HF), power in HF band. Values are mean±SE.

**TABLE 3. Beat-to-Beat HR Level and Variability Evaluated in Frequency Domain in Hypertensive and Normotensive Subjects**

<table>
<thead>
<tr>
<th></th>
<th>HR, bpm</th>
<th><em>P</em>(HR)</th>
<th><em>P</em>(LF)</th>
<th><em>P</em>(HF)</th>
<th><em>P</em>(Ptot/Ptot)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertensive (n=88)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>73.4±1.3</td>
<td>672±91</td>
<td>225±38</td>
<td>84±18</td>
<td>0.3±0.01</td>
</tr>
<tr>
<td>White coat</td>
<td>73.4±1.1</td>
<td>918±115</td>
<td>349±56</td>
<td>66±12</td>
<td>0.34±0.01</td>
</tr>
<tr>
<td>Mental stress</td>
<td>83.8±1.4</td>
<td>463±47</td>
<td>153±21</td>
<td>28±5</td>
<td>0.30±0.01</td>
</tr>
<tr>
<td>Standing</td>
<td>85.5±1.5</td>
<td>628±81</td>
<td>258±42</td>
<td>30±8</td>
<td>0.36±0.01</td>
</tr>
<tr>
<td>Normotensive (n=18)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>71.8±2.0</td>
<td>745±261</td>
<td>221±64</td>
<td>198±141</td>
<td>0.32±0.04</td>
</tr>
<tr>
<td>White coat</td>
<td>71.4±2.1</td>
<td>1433±713</td>
<td>407±151</td>
<td>285±227</td>
<td>0.37±0.03</td>
</tr>
<tr>
<td>Mental stress</td>
<td>83.5±2.8</td>
<td>416±93</td>
<td>112±19</td>
<td>72±54</td>
<td>0.31±0.03</td>
</tr>
<tr>
<td>Standing</td>
<td>82.3±2.6</td>
<td>466±68</td>
<td>177±31</td>
<td>16±5</td>
<td>0.32±0.03</td>
</tr>
</tbody>
</table>

*P*(HR) indicates total spectral power; *P*(LF), power in LF band; *P*(HF), power in HF band. Values are mean±SE.

*P* < .05; †*P* < .01; ‡*P* < .001, vs rest period.
Figure 1. Example of beat-to-beat recordings of SBP and HR obtained in the same subject; the right graphs show the corresponding spectra obtained by coarse-graining spectral analysis.
group, the WC effect was very weak and not significantly correlated with the responses to stress ($r=.36$, NS) and to standing ($r=-.06$, NS).

**WC Effect and BPV in the Frequency Domain**

In the hypertensive subjects, the WC, MS, and S periods were associated with an increased overall BPV as indicated by a higher total spectral power density (Table 2). Oscillations were mostly augmented in the LF band as shown by the enhanced LF power and $P_{LF}/P_{tot}$ ratio during these three periods. Some variations of moderate amplitude were also observed in the high frequencies: $P_{HF}$ was increased during the S period, whereas $P_{HF}/P_{tot}$ ratio was decreased during the WC, MS, and S periods. In the particular case in Fig 1, BPV at rest was important but increased, especially during the WC and S periods in the LF band.

Conversely, the normotensive subjects, although exhibiting a similar trend to an increased BPV during the MS and S periods, did not present such spectral variations during the WC period.

**WC Effect and HRV in the Frequency Domain**

In the hypertensive subjects, contrary to what was observed for BP, the HRV was decreased during the MS period (Table 3). This was true globally and in each band. Despite total power remaining constant during the S period, the contribution of the low frequencies to the total HRV was augmented as indicated by the rise of the $P_{LF}/P_{tot}$ ratio. During the WC period, both the absolute and the normalized power in the LF band tended to be augmented ($P=.06$). This is also illustrated in Fig 1, showing an increase of HRV in the LF band during the WC and S periods and conversely a decrease during the MS period.

In the normotensive subjects, similar trends were observed even for the WC effect on HRV, but they did not reach statistical significance.

**WC Effect and Long-term BPV**

In the hypertensive subjects, no correlation was found between the WC effect and the indices of long-term SBP variability, whether the standard deviation ($r=.02$, NS) or the
daytime/nighttime difference ($r = .12$, NS). Compared with the normotensive group, the bottom hypertensive quartile exhibited a nonsignificantly greater standard deviation (16±1 versus 14±1 mm Hg, respectively).

WC Effect and Arterial Distensibility
A correlation was observed between PWV and ambulatory SBP level in hypertensive subjects ($r = -.32$, $P < .01$). Accordingly, the mean level of PWV in quartiles 1, 2, 3, and 4 was 11.8±0.5, 12.6±0.5, 13.5±0.7, and 15.2±0.8 m/s, respectively. It is noteworthy that, associated with their higher average WC response, the subjects of the bottom quartile of the hypertensive group exhibited a greater PWV than the normotensives (11.8±0.5 versus 10.5±0.2 m/s, respectively; $P < .05$).

WC Effect and Baroreflex Sensitivity
The number of sequences significantly decreased during WC and MS and increased during S periods in hypertensive subjects (Fig 4). In the normotensive group, no significant change was observed even if a trend toward an increased number of sequences was observed during the S period. The mean SBR sensitivity was nonsignificantly lower in the hypertensives than in normotensives (7.4±0.6 versus 9.6±1.5 bpm/mm Hg) during the R period. However, in hypertensives, this sensitivity was significantly correlated with ambulatory SBP ($r = -.28$, $P < .05$). Accordingly, the SBR sensitivity in quartiles 1, 2, 3, and 4 was 9.4±1.8, 8.8±1.4, 6.4±0.6, and 4.9±0.7 bpm/mm Hg, respectively. As shown in Fig 4, no significant change of SBR sensitivity was observed in either group during the WC when compared with the R period. On the contrary, during the MS and S periods, the SBR sensitivity was markedly decreased (Fig 4).

Discussion
The main results of this study are that the WC effect (1) parallels the reactivity to mental stress and standing in hypertensive subjects, (2) likely results from a sympathetic nervous activation via a vasoconstrictor response rather than
It has been shown that the WC effect may have a negative prognostic value, even in the absence of sustained hypertension. The mechanisms of such a prognostic effect may be questioned.

The present study aimed at determining the nature of the WC effect and its relations with other mental or physical stressors. We studied the whole range of the WC effect values because any arbitrary cutoff level would be debatable with regard to the continuous distribution of BP in a population. Indeed, if we used a categorical definition of WC hypertension, only some of these subjects would meet the requirements. In addition, it would restrict the range of variation of the WC effect, which could prevent the disclosure of possible correlations with other variables. Consequently, subjects referred for high BP were included regardless of their levels of office and ambulatory BP. This yielded a great range of variation of the WC effect but also of ambulatory BP levels. To avoid a confounding effect of BP level, the hypertensive group was separated into four quartiles according to ambulatory BP. To avoid a confounding effect of the stressors used. In contrast to the hypertensive subjects, the WC effect was virtually absent in the normotensives. No significant correlation was found between the WC effect and the response to both standing and mental stress, even if a trend toward a positive relation with the WC effect was noted. This trend was probably related to three subjects having a marked response to both WC and mental stress despite their usual normal office BP.

BPV and HRV provide indices of autonomic nervous system activity and thus may give an insight into the mechanisms of BP variations. Coarse-graining spectral analysis, by subtracting the fractal component that constitutes most of the very low frequencies, allows the observer to distinguish only two regions of interest in HRV and BPV spectra. During the MS period, the most obvious changes were an increased overall BPV, especially in the LF band, and a decreased HRV at all frequencies, both in hypertensive and normotensive subjects. The increased BPV in the LF band is in keeping with previous results but at variance with a report by Tulen et al showing an opposite variation during the Stroop Word Conflict test. This may have several explanations: (1) by being a computer version, our test may have induced an additive stress and a greater SBP response (>40 mm Hg versus only 25 mm Hg in Tulen’s study) and (2) we included only the plateau of the MS response whereas Tulen considered the totality of the stress period. The lack of increase in HRV has been reported by Mulder et al. and more recently by Hoshikawa et al. using the same mental stress. The origin of LF oscillations remains a matter of discussion. For HR, they likely reflect the cardiac baroreflex function. For BP, LF oscillations may represent an index of sympathetic activity or baroreflex function. In
the present study, mental stress was associated with a decreased SBR sensitivity, a previously reported finding\textsuperscript{17} that possibly results from a central inhibitory effect on the nucleus tractus solitarius\textsuperscript{26} and may explain the decreased HRV in the low frequencies. Conversely, it has also been shown that the arterial baroreceptor reflex that controls vascular resistances operates normally during stress.\textsuperscript{27,28} Thus, the augmented BPV in the LF band may either result from the activation of the sympathetic system or from the normal function of the arterial baroreceptor reflex. HF oscillations are more difficult to interpret in the absence of monitoring of respiratory rate.

During the S as well as the MS period, BPV was increased globally and in the LF band in accordance with previous reports\textsuperscript{29}. HRV remained unchanged except for the \( \frac{P_{25}/P_{tot}}{} \) ratio, which increased. This was similar in hypertensive and normotensive subjects. SBR sensitivity, which was diminished during orthostatism as previously reported,\textsuperscript{29} may explain the lack of increased HRV. The \( \frac{P_{25}/P_{tot}}{} \) ratio was not augmented during MS periods, which possibly reflects a slightly different sympathovagal balance in the two situations.

Concerning the WC period, a similar increase in HRV was found in hypertensive and normotensive subjects. Conversely, an increased BPV was observed only in the hypertensive group, in which the average WC effect was marked. In this group, BP oscillations mimicked the response to mental stress or standing while HRV did the opposite, showing that these reactions are partly different in nature. It has been put forward that HRV is an index of mental effort: the higher the invested effort, the lower the HRV.\textsuperscript{22} Because no mental effort was required during the WC period, our findings about HRV are consistent with this hypothesis. Since HRV in the LF band may be an index of the cardiac baroreflex function as mentioned above, a lack of baroreflex desensitization is an alternative explanation. Hence, the WC effect appears to be mainly related to a vasoconstrictive response, a conclusion that is in accordance with the stable HR level seen during that period.

The second aim of this study was to examine the correlation between the WC effect and indices of long-term BPV obtained from the ambulatory BP monitoring. No correlation was found between WC effect and these indices in the hypertensive group compared with the normotensive group, except for the SBR sensitivity, which was dimin-

References


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