Noninvasive Study of Endothelial Function in White Coat Hypertension

Jorge Gómez-Cerezo, Juan José Ríos Blanco, Inés Suárez García, Pilar Moreno Anaya, Pilar García Raya, Enrique Vázquez-Muñoz, Francisco Javier Barbado Hernández

Abstract—Several studies have demonstrated that endothelial dysfunction is present in patients with essential hypertension. However, the presence of endothelial dysfunction in patients with white coat hypertension has not been studied. We evaluated the variation in the diameter of the brachial artery produced by flow-mediated dilation after a mechanical stimulus in patients with recently diagnosed mild to moderate sustained essential hypertension compared with patients with white coat hypertension. A total of 29 patients fulfilled inclusion criteria; 15 healthy volunteers were also included. After 24-hour ambulatory blood pressure monitoring, 15 patients were classified with sustained essential hypertension; 14 patients with white coat hypertension. Vascular ultrasound scans were performed according to the method described by Celermajer et al, with modification for noninvasive determination of endothelial dysfunction. Basal brachial artery diameter did not differ significantly among the 3 groups. Changes in arterial diameter 60 seconds after cuff deflation were higher in the control group compared with both hypertensive groups, but no significant differences were found between the sustained essential hypertension group and the white coat hypertension group. Flow-mediated dilation was similar in white coat hypertensives and sustained essential hypertensives. The presence of endothelial dysfunction in subjects with white coat hypertension suggests that it should not be considered a harmless trait and that white coat hypertension has common features with sustained essential hypertension. (Hypertension. 2002;40:304-309.)

Key Words: endothelium ■ vasodilation ■ arteries ■ brachial ■ blood pressure

White coat hypertension (WCH) is defined as the observation of high blood pressure (BP) levels in the doctor’s office and normal BP during ambulatory monitoring. Patients with WCH can be identified by means of 24-hour ambulatory BP monitoring (ABPM). For most investigators considering WCH in a patient with high BP levels in the doctor’s office, the accepted cutoff for normal daytime ambulatory BP is 135/85 mm Hg. The prevalence of WCH has been estimated by several transversal studies between 20% and 40% among the population of mild hypertensives. Whether this group of patients has an increased cardiovascular risk similar to that of sustained essential hypertensives (SEHs), or similar to that of normotensive subjects, is an interesting and still unsolved question that could entail therapeutic implications. Only a few studies have been published about the natural history of WCH; some of them have found a higher frequency of progression to SEH compared with that of normotensive subjects.

Endothelial dysfunction (ED) is considered an early event in the development of atherosclerosis, and several studies have demonstrated that ED is present in patients with essential hypertension. However, the presence of ED in patients with WCH has not been studied. ED was first studied by measuring the increase of the diameter of coronary arteries after intravenous infusion of acetylcholine; the absence of vasodilation in response to acetylcholine was considered a marker of ED. More recent publications studied ED by measuring vasodilation in response to acetylcholine in brachial or femoral arteries with plethysmography. Nowadays, noninvasive methods based on flow-mediated dilation (FMD) after the compression of the arterial wall with a pneumatic tourniquet have been validated for the study of ED, and they are used in most recent works.

The aim of this study is to evaluate with a noninvasive method the presence of ED in patients with WCH. We intend to evaluate the variation in the diameter of the brachial artery produced by FMD after a mechanical stimulus in patients with recently diagnosed mild to moderate SEH without any previous antihypertensive treatment compared with patients with WCH and to a control group, by means of echography.

Methods

Design
Transversal observational study with patients referred to the department of internal medicine at the Hospital Universitario La Paz (Madrid, Spain), between January 1, 1999, and December 31, 2000.
The study protocol was approved by the ethics committee of the Hospital Universitario La Paz in April 7, 1998.

Subjects

Subjects were outpatients age >18 years with recent diagnosis of arterial hypertension. A control group of healthy normotensive volunteers was also included. Inclusion criteria were as follows: (1) suspected essential hypertension and no previous antihypertensive treatment, (2) diagnosis of mild to moderate hypertension according to the World Health Organization criteria,\(^1\) and (3) written informed consent. Exclusion criteria were as follows: (1) secondary hypertension; (2) personal history of cerebrovascular events, coronary artery disease, or diabetes mellitus; (3) body mass index (BMI) \(>30\); (4) smoking; (5) serum creatinine >159.12 \(\mu\)mol/L, total cholesterol >6.24 mmol/L, or triglycerides >1.97 mmol/L; and (6) target-organ damage owing to hypertension.

Stratification

Patients underwent ABPM with Spacelabs 90207. BP was measured every 20 minutes during daytime and every 40 minutes during nighttime. According to the results of ABPM, patients were classified into a group of mild to moderate SEH or a group of WCH. Following the criteria of Report VI of the Joint National Committee,\(^14\) WCH was diagnosed if average daytime ambulatory systolic BP was <135 mm Hg and diastolic BP was <85 mm Hg. BP measurements were divided in daytime (between 10:00 AM and 8:00 PM) and nighttime (between midnight and 6:00 AM). Patients were classified as nondippers when the difference between average daytime BP and average nighttime BP was <10%.\(^15\) BMI >25 and <30 was considered overweight, and BMI <25 was considered normal. Blood samples were obtained for determinations of glucose, total cholesterol, and creatinine. Microalbuminuria was defined as albumin concentration between 20 and 200 \(\mu\)g/min in a urinary sample collected from 11:00 PM to 7:00 AM. The overall cardiovascular risk score was calculated according to the Recommendations of the Task Force of the European Society of Cardiology, European Atherosclerosis Society and European Society of Hypertension.\(^16\)

Procedure

Vascular ultrasound scans were performed according to the method described by Celermajer et al\(^17\) with modification\(^1\) for noninvasive determination of ED. Arterial diameter was measured with a SSH-140 HG Toshiba ultrasound machine. Ultrasound images were recorded on videotape. Flow increase was induced by inflation of a pneumatic tourniquet placed 10 cm above the elbow to 300 mm Hg for 4 minutes. Diameter of right brachial artery was measured basally and 60 seconds after cuff deflation. Diameter changes were expressed as the percentage change relative to the average baseline scan. Video images were analyzed separately by 2 radiologists unaware of the patients’ clinical details. Diameter changes \(\leq 5\%\) at 60 seconds were considered a deficient FMD. Interassay variability was \(<2\%\).

Statistical Analysis

Data were analyzed using the statistical program SPSS version 10.0. All data in the text are expressed as mean±SD. Univariate analysis was performed by use of parametric tests. Overall differences between groups in age, cholesterol, creatinine, glycemia, BMI, and differences in results of brachial artery studies were compared by use of ANOVA test. The variables that showed significant differences with the ANOVA test were compared afterward between each group by use of Bonferroni test for multiple comparisons. Measures of ABPM were compared between the group with WCH and the control group by Student’s \(t\) test. The correlations between variables were determined by use of the Spearman and Pearson correlation coefficient. \(P<0.05\) was considered significant.

Results

Seventy-five patients referred to our hospital fulfilled the first 2 inclusion criteria (mild to moderate hypertension without any previous antihypertensive treatment), among which 46 had \(\geq 1\) exclusion criteria. A total of 29 patients, who signed informed consent, were selected for the study. Fifteen healthy volunteers were also included. After ABPM, 15 patients were classified with SEH and 14 patients with WCH.

Characteristics of the 3 groups are shown in Table 1. No differences were found in the male/female ratio between the 3 groups. Although mean age of the normotensive group was slightly lower than that of the SEH and WCH groups, this difference had no statistical significance. The proportion of patients who were overweight was higher in the group with WCH, but this difference was not statistically significant. No significant differences were found between mean total cholesterol concentrations of the 3 groups. Average serum glucose levels were higher in the groups with SEH and WCH compared with the control group, but these differences were statistically significant only when comparing SEHs and normotensives. Average serum creatinine was significantly higher only in the WCH group compared with normotensives. Four patients had microalbuminuria (2 with SEH, 2 with WCH, none among controls). The overall cardiovascular risk scores calculated for the 3 groups are shown in Table 2.

Results of ABPM are shown in Table 3. Average systolic daytime BP and average systolic nighttime BP measured during ABPM was higher in the group with WCH compared with the control group. No significant differences were found in average diastolic BP. Results of ABPM were not compared between the SEH group and the WCH group because these are different by definition. Seven out of 29 (24%) patients

### TABLE 1. Characteristics of Study Subjects

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>SEH ((n = 15))</th>
<th>WCH ((n = 14))</th>
<th>Normotensives ((n = 15))</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>55.0±16.2</td>
<td>53.9±14.9</td>
<td>45.8±14.1</td>
<td>0.207</td>
</tr>
<tr>
<td>Age range, y</td>
<td>25–74</td>
<td>24–76</td>
<td>26–71</td>
<td></td>
</tr>
<tr>
<td>Gender, m/f</td>
<td>4/11</td>
<td>6/8</td>
<td>10/5</td>
<td>0.086</td>
</tr>
<tr>
<td>Cholesterol, mg/dL</td>
<td>5.31±0.85</td>
<td>5.21±0.64</td>
<td>4.51±0.99</td>
<td>0.064</td>
</tr>
<tr>
<td>Glycemia, mmol/L</td>
<td>5.28±0.50</td>
<td>5.15±0.39</td>
<td>4.63±0.35</td>
<td>0.019*</td>
</tr>
<tr>
<td>Creatinine, (\mu)mol/L</td>
<td>77.7±22.9</td>
<td>90.1±13.2</td>
<td>68.9±15.9</td>
<td>0.014†</td>
</tr>
<tr>
<td>Overweight patients, %</td>
<td>23.1</td>
<td>57.13</td>
<td>35.7</td>
<td>0.184</td>
</tr>
</tbody>
</table>

Values are mean±SD.

\*Significant differences between SEH and normotensives; †significant differences between WCH and normotensives.
with mild to moderate hypertension were classified as nondippers. Six patients (40%) of the SEH group followed the nondipper pattern, whereas in the WCH group only 1 subject (7%) was classified as nondipper.

Brachial artery studies are shown in Table 4. Basal brachial artery diameter and diameter at 60 seconds after cuff deflation (FMD) did not differ significantly between the 3 groups. Diameter increase at 60 seconds after cuff deflation was higher in the control group compared with both hypertensive groups, but no significant differences were found between SEH and WCH groups (Figure). The simple correlation analysis showed a negative correlation between basal brachial artery diameter and FMD ($r=−0.534; \ P=0.001$). This correlation was not observed in the results per groups. Neither the differences between serum glucose and creatinine levels nor the percentage of nondippers had any effect on FMD. Deficient FMD was found in both hypertensive groups, with no significant differences between both groups. None of the patients in the control group had deficient FMD.

**Discussion**

Since the definition of WCH was established,1 several studies have been made to estimate the prevalence and clinical significance of these patients and to find out whether or not they have an increased cardiovascular risk.7–18,19 Because left ventricular hypertrophy predicts coronary events independently of BP levels, echocardiography has been used as a noninvasive method to evaluate target-organ damage in WCH measuring changes in left ventricular mass; most investigators found an increased left ventricular mass,20 even though other reports could not confirm these findings.21 Recently, Muldoon et al19 demonstrated by ultrasound study the presence of carotid artery atherosclerosis in subjects with WCH, and they found that the prevalence in this group was similar to that among patients with SEH. Even though the natural history of WCH is still not completely understood, Strandberg et al7 found during a 21-year follow-up period a higher total and cardiovascular mortality in subjects with WCH compared with normotensive subjects. Verdecchia22 described a cardiovascular mortality in subjects with WCH, which was similar to that among patients with moderate hypertension, and he also found that 37% of the subjects with WCH progressed eventually to SEH. On the other hand, Khattar et al18 found a lower incidence of cardiovascular events in subjects with WCH compared with patients with mild SEH over a 10-year follow-up period. Altogether, studies on WCH suggest that it should not be considered a benign trait but rather a cardiovascular risk factor, which is at least intermediate between normotensives and patients with SEH.

The discovery of endothelial function as a regulator of cardiovascular tone and structure, and the description of mediators such as NO originated many research works over the past decade.23 ED is defined by the production of vasospasm, vasoconstriction, platelet aggregation, thrombosis, inflammation, and increased vascular proliferation. Several studies found that ED is a marker of the development of atherosclerosis;6 this finding is probably related to the unbalance of endothelial factors, caused by a predominance of proatherosclerotic endothelial factors over the ones that promote antiatherosclerotic phenomena. Many reports have also demonstrated that the presence of ED is associated to cardiovascular risk factors such as diabetes mellitus,24 hypertriglyceridemia,25 smoking,26 hyperhomocysteinemia,27 and even alcoholism28 and mental stress.29 ED has been also demonstrated both in coronary and peripheral circulation of patients with SEH.9,30 Our study found that subjects with SEH and WCH showed similar FMD 60 seconds after stimulus, and these were lower than FMD of healthy controls; ie, patients with SEH and WCH showed more intense ED than did the control group.

The fact that no significant differences were found between the ages of the 3 groups in our study is important because several studies have demonstrated that the impairment of endothelial-dependent arterial vasodilation increases with age.31 This impairment is specially evident in subjects >65 years of age,32 but it can be detected from 40 years of age both in healthy subjects and patients with SEH.33 The proportion of patients who were overweight was lower among the SHE group than among the WCH group, although this difference was not statistically significant. This may probably be because patients with SEH who were overweight also had other associated cardiovascular risk factors, and therefore, they were excluded from the study. However, a previous work found no association between BMI and FMD in the brachial artery.34 The 3 groups had similar cholesterol levels and BMI. Although creatinine was different between the WCH group and normotensives, and serum glucose was different between the SEH group and normotensives, no significant relation was found between diameter changes at 60 seconds and glucose or creatinine levels. No differences in the overall cardiovascular risk scores could be studied between the groups.

### Table 2. Overall Cardiovascular Risk Scores

<table>
<thead>
<tr>
<th>10-Year Risk</th>
<th>SEH</th>
<th>WCH</th>
<th>Normotensives</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5%</td>
<td>4 (26.6)</td>
<td>5 (35.7)</td>
<td>7 (46.6)</td>
</tr>
<tr>
<td>5%–10%</td>
<td>4 (26.6)</td>
<td>4 (28.5)</td>
<td>6 (40)</td>
</tr>
<tr>
<td>10%–20%</td>
<td>5 (33.3)</td>
<td>5 (35.7)</td>
<td>2 (13.3)</td>
</tr>
<tr>
<td>20%–40%</td>
<td>2 (13.3)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Values are n (%).

### Table 3. Results of Ambulatory Blood Pressure Monitoring

<table>
<thead>
<tr>
<th>ABPM Measurements</th>
<th>SEH</th>
<th>WCH</th>
<th>Normotensives</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ASDBP, mm Hg</strong></td>
<td>150.9±11.1</td>
<td>125.7±4.9</td>
<td>112.7±8.2</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td><strong>ADDBP, mm Hg</strong></td>
<td>89.5±7.0</td>
<td>75.8±6.0</td>
<td>71.4±7.6</td>
<td>0.100</td>
</tr>
<tr>
<td><strong>ASNBP, mm Hg</strong></td>
<td>134.6±14.9</td>
<td>109.2±6.7</td>
<td>92.3±11.7</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td><strong>ADNB P, mm Hg</strong></td>
<td>74.9±9.5</td>
<td>60.2±7.2</td>
<td>57.2±7.5</td>
<td>0.281</td>
</tr>
</tbody>
</table>

*Nondippers, n (%).

*Values are mean±SD.

ASDBP indicates average systolic daytime blood pressure; ADDBP, average diastolic daytime blood pressure; ASNB P, average systolic night-time blood pressure; and ADNB P, average diastolic night-time blood pressure.

*WCH and normotensives.
The percentage of nondippers in both hypertensive groups was similar to the prevalence of nondippers among the hypertensive population. Although the percentage of nondippers was higher in the SHE group than in the WCH group, this difference did not have any effect in the FMD. The fact that ABPM results were different between the WCH group and healthy controls is noteworthy (average daytime and nighttime measures being higher in the WCH group than in healthy controls), and this finding highlights that both populations should be considered separately. Patients with WCH are probably closer to patients with SEH than to normotensives, even though by definition average daytime ABPM readings in WCH are different than those in SEH.

Our study shows that subjects with WCH have ED that is similar to that of patients with SEH and higher than that of the control group by means of the noninvasive method described by Celermajer et al. This method, based on FMD, has been developed over the past decade as a reproducible noninvasive technique for the study of ED, and it is nowadays the most widely used. In our study, the cuff was placed above the transducer, which induces more hyperemia and vasodilation. This method has been used in recent reports. When the interpretation of hyperemic response is performed by experimented radiologists, the interobserver variability coefficient is small, and the results are correlated with invasive tests bases on acetylcholine infusion. This method has also been used as a screening test for coronary artery disease, and to evaluate improvement on ED in recent studies over therapeutic interventions in patients with SEH.

Several studies have found a negative correlation between basal arterial diameter and FMD: subjects with higher basal arterial diameter have lower FMD. Our patients with WCH had lower basal arterial diameters compared with those of the other 2 groups, but this difference was not statistically significant. The overall analysis of our patients showed also that patients with higher brachial artery diameter at rest had lower FMD. However, this correlation was not observed when each group was analyzed separately. Moreover, the proportion of deficient vasodilatory responses defined as diameter increases ≤5% at 60 seconds was noteworthy both in the SEH (26.7%) and WCH (42.9%) groups. None of the subjects from the control group had diameter changes ≤5%. We have found a high variability of the results of the diameter increase at 60 seconds; this variability is similar to that found in other studies, which showed high SDs in the distribution of this variable.

A limitation of our study is the possibility that the subjects studied might not be representative of the populations with mild to moderate SEH and WCH. Because of the exclusion criteria, our subjects might only be representative of a group of nonsmoking, nondiabetic, normocholesterolemic patients with no history of cardiovascular complications and not of the whole population. Besides, our series is small because patients who fulfill the inclusion criteria (recent diagnosis of mild to moderate hypertension without previous antihypertensive treatment and without other cardiovascular risk factors) are usually evaluated by primary care doctors and are less frequently referred to a tertiary hospital. The fact that patients with WCH have a similar ED to that of patients with SEH suggests that this group of patients have an increased probability of developing atherosclerosis and also a greater cardiovascular risk compared with normotensive subjects, and supports previous works that questioned whether WCH be considered a innocent trait and that made it comparable to SEH. ED in WCH group also explains the high incidence of progression to SEH over the years in this group of patients. Two recent works have demonstrated that subjects with BP levels that are considered normal (120 to 129/80 to 84 mm Hg) or high-normal (130 to 139/85 to 89 mm Hg) have a high rate of progression to SEH over a 4-year period, and also that patients with high-normal BP have an increased cardiovascular risk which is greater than subjects with optimal BP. Because there is an inverse relation between BP levels and NO vascular action, it is probable that ED might be

### Table 4. Brachial Artery Studies

<table>
<thead>
<tr>
<th>Brachial Artery Measurements</th>
<th>SEH</th>
<th>WCH</th>
<th>Normotensives</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal diameter, mm</td>
<td>3.72±0.57</td>
<td>4.15±0.75</td>
<td>3.66±0.62</td>
<td>0.108</td>
</tr>
<tr>
<td>Diameter at 60 seconds, mm</td>
<td>4.19±0.52</td>
<td>4.55±0.85</td>
<td>4.56±0.53</td>
<td>0.236</td>
</tr>
<tr>
<td>Diameter increase at 60 seconds, %</td>
<td>13.28±8.81</td>
<td>9.76±9.25</td>
<td>26.21±16.35</td>
<td>0.002*</td>
</tr>
<tr>
<td>Patients with deficient FMD, n</td>
<td>4</td>
<td>6</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Values are mean±SD or n.

*Significant differences between the 2 groups of hypertensives (SEH and WCH) and the normotensives.

Diameter increase at 60 seconds. SEH indicates sustained essential hypertension; WCH, white coat hypertension.
present in subjects with normal-high BP, and this would explain the increased cardiovascular risk among this group.\textsuperscript{44} We may as well assume that because ED is present in patients with WCH, they have an increased cardiovascular risk, which would be similar to that of patients with SHE. Whether subjects with WCH, as well as the ones with high-normal BP, could have a benefit if they received similar therapeutic approaches as those with SHE is still an unsolved question that must be demonstrated in future works, even though recent data support this hypothesis. In conclusion, our study shows that FMD is similar in WCH patients and mild to moderate hypertensives.

**Perspectives**

The presence of ED among WCH subjects, in the same degree as in SHE subjects, suggests that this group of patients has early atherosclerosis and therefore higher cardiovascular morbidity and progression to SHE that have been found in this group of patients. Because several pharmacological therapies have been shown to improve ED in SHE patients, patients with WCH might benefit from pharmacological treatment to improve ED and therefore prevent early atherosclerosis. More studies are needed to find out whether antihypertensive treatment would decrease cardiovascular morbidity and mortality in WCH patients, and to investigate the potential role of the different antihypertensive drugs in improving ED in this group of patients.

**Acknowledgment**

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**References**


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