Diagnosis of Mild Hypertension by Ambulatory Blood Pressure Monitoring

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Background  Between 20% and 30% of patients with clinically diagnosed hypertension have normal blood pressure (BP) values during automated ambulatory 24-hour BP monitoring. It has not been clear, however, whether these patients can be regarded as normotensive or whether they should be treated in the same way as confirmed hypertensive patients.

Methods and Results  Ambulatory BP monitoring was performed in 88 normal control subjects and 171 hypertensive patients (office diastolic BP ≥90 mm Hg on three visits; never treated or off treatment for more than 6 months). Hypertensive patients were classified as nonconfirmed or white coat (n=58) if their 24-hour diastolic averages were <85 mm Hg and at least 15 mm Hg lower than their office values. For comparisons, white coat patients were pair-matched with normal subjects by 24-hour diastolic averages and sex, and by similar age and weight; there were 40 such pairs. White coat patients were likewise pair-matched with confirmed hypertensive patients by identical office BPs (51 pairs). Participants were studied by individualized treadmill testing, Doppler echocardiography, and assays of resting plasma catecholamines, upright plasma renin and aldosterone, and lipid, glucose, and insulin concentrations. Because of the matching, compared with normal subjects, patients with white coat hypertension and normal subjects had identical 24-hour BP averages. The white coat patients exhibited slightly greater variability among individual readings (obtained each 15 minutes) throughout the day [P<.05]), but there were no differences in hemodynamic responses to exercise. Plasma norepinephrine (P<.05), renin and aldosterone (P<.01 for each), and insulin and low-density lipoprotein cholesterol levels (P<.01 for each) were higher in the white coat group, as were left ventricular septal wall (P<.05) and muscle mass (P=.07) echocardiographic measurements. When compared with the confirmed hypertensive patients, the white coat patients had higher renin (P<.01) but were otherwise similar. Within the white coat group, plasma norepinephrine correlated with total cholesterol and triglycerides (P<.05 for each), and aldosterone correlated with left ventricular mass (P<.01); there were no significant correlations within the normal control subject or confirmed hypertension groups.

Conclusions  Patients with white coat hypertension differ in metabolic, neuroendocrine, and cardiac findings from normal control subjects and have greater BP variability. These changes appear to be mediated by heightened activity of the sympathetic and renin-angiotensin systems. Although these characteristics could reflect an alerting reaction in the clinic due to awareness of their diagnosis, the white coat hypertensive patients also have evidence for additional, more-sustained differences from normal subjects. Thus, this condition appears to be a true variant of hypertension. (Circulation. 1994;90:2291-2298.)

Key Words  • blood pressure  • angiotensin system  • hypertension  • catecholamines

There is increasing emphasis on the importance of treating mild forms of hypertension.1 It can be difficult, however, to separate patients with mild hypertension from those with normal blood pressure (BP). Between 20% and 30% of patients with hypertension diagnosed in the physician's office have normal BPs when measured at home2 or when evaluated by 24-hour ambulatory BP monitoring.3-5 The terms white coat,6 office,4 and nonconfirmed7 hypertension have been used to describe patients who have high BPs in the office but normal values during whole-day monitoring.

Because the 24-hour BP values correlate more strongly than conventional measurements with evidence for hypertensive target organ changes,7,9 it has been suggested that individuals with white coat hypertension and normal 24-hour readings do not require antihypertensive management.10,11 But it has not yet been clearly established that patients with white coat or nonconfirmed hypertension are, in fact, truly normal. These patients may have a tendency to increased BP variability throughout the day,12 and one study has shown that patients whose hypertensive BPs regressed to normal during follow-up office visits had greater echocardiographic left ventricular (LV) muscle mass than normotensive control subjects.13 Moreover, in the community-based Tecumseh study,2,14 patients labeled as having white coat hypertension on the basis of high BPs in the office but normal self-measured values at home were found to be overweight, to have faster heart rates, and to differ from normotensives in their plasma measurements of lipid and glucose metabolism.

The aim of the present study was to prospectively compare individuals with white coat hypertension with both confirmed hypertensive patients and normal volunteers. White coat hypertension is defined by high clinic BPs but normal 24-hour values. Thus, comparison of white coat patients with the confirmed hypertensive patients was performed in matched pairs of patients with identical office values, whereas the comparison with normal control subjects was performed in pairs of white coat hypertensive patients and normal subjects matched for identical 24-hour BP values. The participants were selected within a narrow age and weight range, thus avoiding the effects of age and weight differences among the groups. Moreover, hypertensive

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patients in the study had either never been treated for hypertension or had been free of treatment for at least 6 months. Our findings indicate that white coat hypertension appears to be a distinct entity, differing in key respects from observations in normal individuals as well as in patients with confirmed hypertension.

Methods

Participants
The study was performed in 171 hypertensive patients (146 men, 25 women) and 88 normotensive volunteers (73 men, 15 women). Participants were between the ages of 23 and 54 years (median, 45 years) and all were within 25% of their ideal body weights. The majority of hypertensive patients were identified by screening programs. Of the 171 patients in this group, 128 had never been treated, whereas the other 43 had been without treatment for at least 6 months (mean, 16 months). None of the participants had a known history of cardiovascular events, any significant disorder of renal function or liver function, or diabetes mellitus or other metabolic disorders.

The diagnosis of hypertension was based on three outpatient measurements of BP, obtained at weekly intervals, and measured after 5 minutes in the seated position. BP was measured by using the recommendations of the American Society of Hypertension,15 and the diagnosis of hypertension required that the diastolic readings at all three preliminary visits were ≥90 mm Hg. Normal control subjects were required to have all three diastolic BP values <90 mm Hg.

Procedures
A complete history was taken and physical examination, including fundal evaluation, was performed in each patient. Each patient was subjected to 24-hour ambulatory BP monitoring by methods described previously.16 Readings were obtained with the portable automated oscillometric SpaceLabs 90207 device (SpaceLabs Inc). Readings of BP were obtained each 15 minutes throughout the 24-hour monitoring period, and for each participant the data were then edited and reduced into 24 consecutive 1-hour averages, as described previously.16 During the monitoring procedure, participants were allowed to follow their routine daily activities, although they were instructed not to engage in excessive physical activity. No other procedures were performed during the day of monitoring.

All participants were studied by Doppler echocardiography. M-mode and two-dimensional echocardiography were performed from parasternal and apical windows.17 Standard views were obtained by using a commercially available phased-array Doppler echocardiographic instrument (General Electric, Pass II or RT500). Standard M-mode echocardiograms were recorded from the parasternal window on strip-chart paper at a speed of 50 mm/s. LV mass was calculated in grams with the equation \( LV_{mass} = 1.05[(LVDD + PW + VS)^2 - (LVDD)^2] \), where VS is ventricular septal thickness, LVDD is LV diastolic dimension, and PW is LV posterior wall thickness. Transmural flow velocities were recorded at the level of the mitral orifice from the apical window in either the apical long-axis or apical four-chamber view as previously described.18 Flow velocity was maximized by angulation in the lateral and orthogonal planes. No correction for the presumed direction of flow in the imaging plane was made. Spectral blood flow velocities were recorded on strip chart at a sweep speed of 50 mm/s.

Diastolic blood flow velocities and flow times were measured by the methods previously described.19 Peak transmural flow velocities were measured in centimeters per second at the darkest point of the spectral wave forms (peak mural velocities). The peak early diastolic flow velocity, corresponding to early rapid filling (PFVE), and peak late diastolic flow velocity, corresponding to atrial systole (PFVA), were measured in three to five cardiac cycles and the results averaged. The ratio of late to early peak LV filling velocities (A/E) was derived by dividing PFVA by PFVE.

Two ramp treadmill studies were performed in each participant. The first procedure was carried out to familiarize the patient with the technique, and also to obtain a measurement of \( \dot{V}_{O2} \) that was used during the second treadmill procedure to individualize the protocol for each participant.20 BP values were obtained manually at 2-minute intervals during the treadmill testing.

Fasting blood samples were obtained for measurements of clinical chemistries, including lipid profiles and glucose. Insulin was measured by radioimmunoassay.21 Plasma renin activity was measured by radioimmunoassay in blood samples obtained after 3 hours of ambulation.22 Aldosterone concentrations measured in plasma obtained at the same time as the renin samples also were measured by immunoassay.23 After the renin and aldosterone sampling, patients were recumbent for 30 minutes, and plasma samples were obtained from indwelling venous ports for measurement of norepinephrine and epinephrine concentrations; these assays used a radioenzymatic method.24

Analysis
The designation of nonconfirmed or white coat hypertension required the following criteria: an average 24-hour diastolic BP value <85 mm Hg and a mean 24-hour diastolic BP value that was at least 15 mm Hg less than the average of the three clinically measured diastolic BP values. This latter criterion was based on the observation in our normal volunteers (n=88) that the difference between their office and their 24-hour average diastolic difference was 9±6 (SD) mm Hg; thus, a difference of 15 mm Hg approximated a value based on the mean±SD. Using this approach, we judged 58 of the 171 hypertensive patients to have nonconfirmed hypertension. These individuals were then subjected to a match with normal volunteers such that each pair should have 24-hour diastolic BP averages within 2 mm Hg of each other and be of the same sex; pair numbers also were required to have less than a 10-kg weight difference or a 10-year age difference between them. This procedure provided 40 such pairs. The nonconfirmed hypertensive patients also were matched with the confirmed hypertensive patients on the basis of having averaged office diastolic BP values within 3 mm Hg of each other; the other matching criteria were identical to those used in the matching with the normal volunteers. There were 51 nonconfirmed:confirmed hypertensive pairs. Data from patients who could not be matched appropriately were not used for any comparisons between groups although they were used for within-group correlation calculations.

The principal hypothesis of the study, namely, that metabolic and cardiovascular characteristics of white coat hypertensive patients differ from those of normal subjects or confirmed hypertensive patients, was tested by comparing data between the matched nonconfirmed hypertensive patients and the normal subjects, or between the matched nonconfirmed hypertensive patients and the confirmed hypertensive patients. Unpaired t tests were employed. Because the study had been designed prospectively to specifically compare designated measurements, it was not believed appropriate to make statistical adjustments for multiple comparisons. A value of P<.05 was regarded as significant. Correlations were by the Pearson method. Data are expressed as mean±SD.

Results

Blood Pressure Values
Table 1 shows the principal clinical and BP values obtained in the matched groups of normal volunteers and nonconfirmed hypertensive patients, and true hypertensive patients and nonconfirmed hypertensive patients. There were no significant differences in age or
TABLE 1. Clinical Characteristics of Matched Groups

<table>
<thead>
<tr>
<th></th>
<th>Nonconfirmed Hypertension (N=40)</th>
<th>Normal (N=40)</th>
<th>Nonconfirmed Hypertension (N=51)</th>
<th>Hypertension (N=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>41.3±13.1</td>
<td>44.6±13.8</td>
<td>42.6±15.7</td>
<td>46.7±11.3</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>84.2±14.8</td>
<td>81.4±13.2</td>
<td>84.5±13.7</td>
<td>85.7±13.1</td>
</tr>
<tr>
<td>Office SBP, mm Hg</td>
<td>138±9*</td>
<td>128±10</td>
<td>141±11</td>
<td>141±11</td>
</tr>
<tr>
<td>Office, DBP, mm Hg</td>
<td>95.9±4.3*</td>
<td>84.5±3.6</td>
<td>96.1±4.3</td>
<td>95.8±4.4</td>
</tr>
<tr>
<td>24-Hour SBP, mm Hg</td>
<td>127±9</td>
<td>126±9</td>
<td>129±10*</td>
<td>136±9</td>
</tr>
<tr>
<td>24-Hour DBP, mm Hg</td>
<td>76.5±4.9</td>
<td>76.5±5.0</td>
<td>76.5±5.3*</td>
<td>87.8±6.0</td>
</tr>
</tbody>
</table>

SBP indicates systolic blood pressure; DBP, diastolic BP.
*P<.000; values are mean±SEM.

weight between the matched groups. By definition, the office systolic and diastolic BP values were significantly higher in the nonconfirmed hypertensive patients than in the normal subjects, but the whole-day BP values were virtually identical in the two groups. In contrast, the office BP values were closely similar in the nonconfirmed and confirmed hypertensive groups, but the 24-hour BP values were significantly greater in the confirmed hypertensive patients.

Comparisons also were made of indexes of BP variability throughout the day. Within each individual patient, the SD of the mean of all the BP readings throughout the day was used as a measure of short-term variability. For the nonconfirmed hypertensive group, the mean±SD of the standard deviation of the systolic BP mean value (12.1±3.5) was greater (P<.05) than the value in the normal control subjects (10.9±3.0). There was no difference in their respective diastolic values (10.4±2.6 and 9.7±2.5). Within each patient, the difference in the mean BP values for daytime (6 AM to 10 PM) and nighttime (10 PM to 6 AM) were used as a measure of long-term variability. In comparing the nonconfirmed hypertensive patients with the normal control subjects, we found no difference in the systolic day/night differences, 14.5±7.7 and 13.5±7.7 mm Hg, nor in the diastolic day/night differences, 12.5±5.5 and 12.6±6.5 mm Hg. As a further index of variability, within each patient we measured the difference between the 1-hour period with a highest BP value during the whole day and the 1-hour period with the lowest BP value during the whole day. For the systolic difference, the value of 67±16 mm Hg in the nonconfirmed hypertensive patients was slightly but not significantly (P=.1) greater than the difference in the normal control subjects of 63±12 mm Hg; however, there was a significant difference (P<.01) between the diastolic values of 57±12 and 50±12 mm Hg. Comparing the nonconfirmed hypertensive patients with the confirmed hypertensive patients showed no significant differences for either the systolic or diastolic indexes of variability.

Heart Rate

There were no significant differences among the study groups in office heart rate. The values in the nonconfirmed hypertensive patients and the normal control subjects were 71.0±8.5 and 68.2±8.0 beats per minute (bpm), and for the nonconfirmed and confirmed hypertensive patients they were 70.0±8.4 and 70.6±9.1 bpm. The respective 24-hour averages were 72.4±10.9 and 69.4±9.9 bpm, and 71.9±10.5 and 74.4±9.4 bpm. These differences were not significant. The indexes of variability during the 24-hour monitoring period were as follows: the means of the maximum hourly differences (difference between highest and lowest hourly heart rate averages during the 24-hour period) were 65±26 and 56±21 bpm in the nonconfirmed groups (NS). The mean±SDs of heart rates within each of the groups were, respectively, 11.0±3.9 and 9.7±2.7 (P<.05), and 10.6±3.0 and 9.8±3.1 (NS). There were no significant differences among the groups for other historical or physical examination findings. A family history of hypertension (as reported in a first-degree relative) occurred in 27 of the 40 white coat hypertensive patients and in 18 of the 40 normal control subjects. In the comparison between the nonconfirmed and confirmed hypertensive patients, positive family histories were reported in 34 of 51, and 27 of 51, respectively. Changes in the optic fundi, defined as Keith-Wagner-Barker grade I or higher, were observed in 16 of 40 nonconfirmed hypertensive patients and 9 of 40 normal control subjects; in the nonconfirmed and confirmed hypertensive patient comparison, fundal changes were observed in 19 of 51 and 28 of 51 patients, respectively.

Cardiac Measurements

Fig 1 shows the principal measurements obtained with Doppler echocardiography in the matched pairs of normal control subjects and nonconfirmed hypertensive patients, and the nonconfirmed hypertensive patients and true hypertensive patients. LV septal thickness was significantly greater in the nonconfirmed hypertensive patients than in the normal control subjects, but there was no difference between the nonconfirmed and true hypertension groups. Posterior wall thickness (not shown in Fig 1) was not different within either of the two matched pairs. LV muscle mass indexed for body surface area tended to be higher in the nonconfirmed hypertensive patients than in the normal control subjects (P=.1). There were no differences in LV mass when the nonconfirmed and true hypertensive patients were compared. The ratio of late to early atrial filling (A/E ratio), as measured by Doppler flow, was not different between the nonconfirmed hypertensive patients and the control subjects; however, it was significantly greater in the patients with true hypertension than in the nonconfirmed group, indicating a greater dependency of diastolic filling on the late atrial phase.
Non-Control Confirmed 1.1 - 1.0

NON TRUE CONFIRMED HYPERTENSION

Fig 1. Graphs show comparisons of left ventricular (LV) septal thickness, muscle mass index, and late to early atrial filling Doppler (A/E) ratios in matched groups of nonconfirmed hypertensive patients and normal control subjects (n=40), and nonconfirmed hypertensive patients and confirmed hypertensive patients (n=51). Values are mean±SEM.

Neuroendocrine Measurements

Comparisons of plasma renin activity, plasma aldosterone concentrations, and plasma norepinephrine concentrations are shown in Fig 2. Plasma renin activity in the nonconfirmed hypertensive patients was significantly higher than in either the control group or the true hypertensive patients. Plasma aldosterone and plasma norepinephrine concentrations were each significantly higher in the nonconfirmed hypertensive patients than in the control subjects; however, the values in the nonconfirmed patients were closely similar to those in the true hypertensive patients. Plasma epinephrine concentrations, not shown in the Figure, were similar in the nonconfirmed hypertensives and the controls (54.3±19.1 and 50.9±18.0 pg/mL) and in the nonconfirmed and true hypertensive patients (53.1±16.3 and 51.4±18.2 pg/mL), respectively.

Metabolic Measurements

Comparisons of measurements of total and LDL cholesterol and triglyceride levels between the matched study groups are shown in Fig 3. Both total cholesterol and LDL cholesterol were higher in the nonconfirmed hypertensive patients than in the normal control sub-

Fig 2. Graphs show comparisons of plasma renin activity, plasma aldosterone, and plasma norepinephrine concentrations in matched groups of nonconfirmed hypertensive patients and normal control subjects (n=40), and nonconfirmed hypertensive patients and confirmed hypertensive patients (n=51). Values are mean±SEM.
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Fig 3. Graphs show comparisons of plasma total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglyceride concentrations in matched groups of nonconfirmed hypertensive patients and normal control subjects (n=40), and nonconfirmed hypertensive patients and confirmed hypertensive patients (n=51). Values are mean±SEM.

Fig 4. Graphs show comparisons of blood glucose and insulin concentrations in matched groups of nonconfirmed hypertensive patients and normal control subjects (n=40), and nonconfirmed hypertensive patients and confirmed hypertensive patients (n=51). Values are mean±SEM.

jects; triglycerides also tended to be higher, but the difference did not reach statistical significance. There were no differences in any of these measurements between the nonconfirmed and the confirmed hypertensive patients. There were no differences in high-density lipoprotein cholesterol levels (not shown in the Figure) between the nonconfirmed hypertensive patients and normal subjects (48±11 and 53±16 mg/dL) or between the nonconfirmed and confirmed hypertensive patients (50±11 and 50±16 mg/dL). Values for glucose and insulin are shown in Fig 4. There were no differences between the groups in their glucose measurements, but plasma insulin concentrations were significantly higher in the nonconfirmed hypertensive patients than in the control subjects; there were no differences in insulin between the nonconfirmed and confirmed hypertensive patients. There were no differences between the comparison groups in renal function or urinary protein excretion.

Treadmill Studies

There were no significant differences among the comparison groups in their BP responses to treadmill testing. In the nonconfirmed hypertensive and normal

<table>
<thead>
<tr>
<th></th>
<th>CONTROL</th>
<th>NON CONFIRMED</th>
<th>TRUE HYPERTENSION</th>
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</thead>
<tbody>
<tr>
<td>TOTAL CHOLESTEROL mg/dl</td>
<td>220</td>
<td>200</td>
<td>180</td>
</tr>
<tr>
<td>LDL CHOLESTEROL mg/dl</td>
<td>160</td>
<td>140</td>
<td>120</td>
</tr>
<tr>
<td>TRIGLYCERIDES mg/dl</td>
<td>130</td>
<td>110</td>
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</tr>
</tbody>
</table>

\*P<0.05
\**P<0.01

Treadmill Studies

There were no significant differences among the comparison groups in their BP responses to treadmill testing. In the nonconfirmed hypertensive and normal

<table>
<thead>
<tr>
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<th>CONTROL</th>
<th>NON CONFIRMED</th>
<th>TRUE HYPERTENSION</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLUCOSE mg/dl</td>
<td>100</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>INSULIN uU/ml</td>
<td>20</td>
<td>15</td>
<td>15</td>
</tr>
</tbody>
</table>

\**P<0.01
volunteer groups, respectively, baseline systolic BP was 141±17 and 128±15 mm Hg, and the maximum changes during exercise were 56±18 and 60±17 mm Hg. For diastolic BP, baselines were 91±8 and 81±8 mm Hg, and the increases during exercise were 5.9±8.4 and 3.2±7.7 mm Hg. For the matched comparison between the nonconfirmed and confirmed hypertensive patients, the baseline systolic BPs were 143±15 and 143±18 mm Hg, and the exercise-induced increases were 55±18 and 61±17 mm Hg. For diastolic BP, the baselines were 91±8 and 93±10 mm Hg, and the maximum changes during exercise were 6.3±8.7 and 3.0±9.4 mm Hg.

Correlations

To determine whether neuroendocrine factors, specifically, the renin-angiotensin-aldosterone system (plasma renin activity or aldosterone) or the sympathetic nervous system (norepinephrine) might have contributed to the differences in metabolic and cardiac measurements observed between nonconfirmed hypertensive patients and the other groups, correlations were calculated for the relations between plasma renin activity, plasma aldosterone, or plasma norepinephrine with measurements of cholesterol, triglycerides, LV wall thickness, and LV muscle mass. There were no significant correlations between plasma renin activity and any of the other metabolic or cardiac variables. However, as shown in Table 2, plasma aldosterone concentrations correlated significantly with LV muscle mass within the nonconfirmed hypertension group, although not in any of the other groups. Similarly, plasma norepinephrine concentrations correlated with both total cholesterol and triglyceride concentrations within the nonconfirmed hypertension group but not within either of the other study groups.

Discussion

Previous reports that have characterized nonconfirmed or white coat hypertension have concluded that patients with this condition can be regarded as normotensive.4,5,10,11 In the present study, however, patients with white coat hypertension were found to differ from normal control subjects in some key respects. Specifically, patients with this condition were found to have increased activity of both the renin-angiotensin and sympathetic systems and to have higher plasma lipid and insulin levels than normal control subjects. Moreover, there were trends toward increased wall thickness and muscle mass of the left ventricle. Thus, despite their normal 24-hour BP values, these patients appeared to have the spectrum of clinical features typically associated with established hypertension.25

It has been suggested that patients with white coat hypertension might have increased BP responsiveness to stress or other stimuli during their routine daily activity.12 In this study, we also noted a tendency for both short-term and long-term BP variability throughout the day to be greater in the white coat hypertensive patients than in the normal control subjects. Increased BP variability previously has been linked to high renin levels,26 a finding consistent with our present observation that plasma renin activity was higher in the white coat patients than in the other groups. Although the actual increase in variability in these patients was not very striking, it could be argued that even modest changes over the course of a lifetime could produce cardiovascular effects. Indeed, long-term follow-up of patients with heightened BP reactivity in the clinical environment has shown an increased susceptibility to coronary events,27 perhaps reflecting the metabolic and cardiovascular changes we have observed in nonconfirmed hypertensive patients.

Other investigators have suggested that awareness by patients of a recent diagnosis of hypertension can produce an alerting reaction associated with increased resting heart rate and enhanced responses of heart rate and plasma catecholamines to mental stress stimuli in the clinic setting.28 Such a mechanism could partly explain the differences in the present study between the white coat hypertensive patients and the normal control subjects. Office heart rates in the white coat group were identical to those in the established hypertensive patients and were slightly higher than in the normal subjects. This difference, however, was also observed for the full 24-hour monitoring period, and there was evidence for a greater variability in heart rate as well as in BP throughout the day. This indicates a sustained tendency to a heightened hemodynamic responsiveness in the white coat hypertensive patients that is additional to the effects of an awareness-alerting reaction. Short-term BP responses to treadmill exercise in white coat hypertensive patients were not different from those in either normal control subjects or established hypertensive patients. Other investigators, using different forms of physical and physiological stimuli, have also concluded that heightened BP reactivity to physical stress is not a primary characteristic of patients with white coat hypertension.29

Increased LV wall thickness and muscle mass measured by echocardiography are used as indexes of

| Table 2. Correlation Coefficients Within the Study Groups |
|----------------------------------|----------------|----------------|----------------|
|                                | All Subjects  | Normal Control | Nonconfirmed   | True Hypertension |
|                                | (N=259)       | Subjects (N=88)| (N=58)         | (N=113)          |
| Plasma norepinephrine with      |               |                |                |                 |
| Total cholesterol               | .158*         | .155           | .291*          | .079            |
| Triglycerides                   | .112          | .119           | .324*          | .149            |
| Plasma aldosterone with         |               |                |                |                 |
| LV muscle mass                  | .114          | .042           | .330†          | .136            |

LV indicates left ventricular.  
*P < .05; †P = .01.
hypertensive cardiac changes. Previous studies that divided hypertensive patients into confirmed and white coat hypertensive subgroups reported that echocardiographic measurements in the white coat patients were essentially normal and thereby different from those in patients with confirmed hypertension. But in the present study, LV wall measurements in the white coat group tended to be different from those in the normal control subjects, and to be more similar to those in the confirmed hypertensive patients. A factor in providing the sensitivity to observe these differences might have been our selection of hypertensive patients who, for the most part, had not previously received antihypertensive drugs that could have affected LV wall thickness and mass. Doppler measurements of LV diastolic function in the white coat group were similar to those in the normal subjects but were different from those in the confirmed hypertensive patients. Thus, the cardiac findings in the white coat patients differentiate them both from normal subjects and from confirmed hypertensive patients.

The mechanisms underlying the metabolic and cardiovascular changes in the white coat hypertension group have not been defined, but increased activity of the sympathetic and renin-angiotensin-aldosterone systems might play a part in mediating these findings. Plasma norepinephrine concentrations correlated significantly with cholesterol and triglyceride levels within the white coat hypertensive patients but not in either the normal control subjects or established hypertensive patients, suggesting that sympathetic activity plays a key role in defining features of white coat hypertension. Other investigators previously have shown a link between sympathetic drive and increased lipid and insulin levels in hypertension, especially in patients with borderline hypertension. Further, we noted a correlation between plasma aldosterone levels and LV muscle mass in the white coat hypertension group. As with earlier observations, aldosterone correlated more closely with LV mass than did plasma renin activity. This suggests either that aldosterone directly stimulates remodeling of the left ventricle in these patients or, alternatively, that aldosterone levels might reflect overall activity of the renin-angiotensin-aldosterone system more closely than measurements of renin itself.

A feature of the present work that differentiates it from previous studies of white coat hypertension has been the use of precisely matched comparisons of patients with white coat hypertension with normal control subjects and with confirmed hypertensive patients. Specifically, the process of individually matching the white coat hypertensive patients with normal control subjects on the basis of 24-hour BP averages, and of separately matching the white coat hypertensive patients with confirmed hypertensive patients on the basis of office BPs, enabled us to compare findings in white coat hypertensive patients conforming to the rigorous criteria of having clearly normal 24-hour BP averages but hypertensive office readings.

To further sharpen our evaluation of white coat hypertension, this study used a more demanding basis for making this diagnosis than those in earlier reports. Previously, patients whose office diastolic BPs were 90 or 95 mm Hg and whose 24-hour averages were considered normal at 85 mm Hg or below were labeled as white coat hypertensive patients. But since 24-hour averages, which include low nighttime readings, typically are 7 to 10 mm Hg below formal office readings, some patients with true mild hypertension can be misclassified as white coat hypertensive patients. Thus, our approach, which additionally required that the 24-hour average and the office value differ by at least 15 mm Hg—based on exceeding the mean + SD of this difference in normal volunteers—provided a more stringent and realistic diagnosis. Interestingly, even with the use of these more-exacting criteria, one third of our patients with carefully diagnosed hypertension in the office were judged to have white coat hypertension.

Several authors have demonstrated that clinical hypertension is a familial syndrome that includes metabolic abnormalities, heightened neuroendocrine activity, and early cardiovascular changes. Our present findings indicate that patients with nonconfirmed or white coat hypertension might represent an early form of the syndrome or possibly a variant form of hypertension. It should be stressed that the present study was cross-sectional in design, and careful longitudinal observations will be required to characterize the natural history of patients with nonconfirmed or white coat hypertension.

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