Variability Between Current Definitions of 'Normal' Ambulatory Blood Pressure
Implications in the Assessment of White Coat Hypertension

Paolo Verdecchia, Giuseppe Schillaci, Francesca Boldrini, Ivano Zampi, and Carlo Porcellati

The assessment of white coat hypertension is complicated by the lack of generally agreed-on normal limits of ambulatory blood pressure. To assess the influence of four of these limits on the prevalence of white coat hypertension and the corresponding distribution of left ventricular hypertrophy, we performed 24-hour ambulatory blood pressure monitoring and echocardiographic studies in 346 untreated patients with essential hypertension and 47 age-matched normotensive control subjects. The upper limits of normal daytime ambulatory blood pressure were lower using standards drawn from clinically normotensive populations than using standards drawn, partly or entirely, from general populations. The prevalence of white coat hypertension differed markedly using the different standards, being 12.1%, 16.5%, 28.9%, and 53.2% (x^2=346.0, p<0.0001). Left ventricular mass index averaged 77 g/m^2 in the control group, 85 g/m^2 in the two groups with white coat hypertension defined by using standards drawn from normotensive populations (both comparisons not significant versus control group), and 90 and 98 g/m^2 in the two groups with white coat hypertension defined by using the other two standards (both p<0.01 versus control group). The prevalence of echocardiographic left ventricular hypertrophy was 0% in the control group, 2.4% and 3.5% in the two groups with white coat hypertension defined by using standards drawn from normotensive populations, and 9.0% and 14.7% in the other two groups with white coat hypertension (p<0.05 and p<0.01, respectively, versus control group). Late diastolic transmitral peak blood flow velocity and its ratio to early peak blood flow velocity were abnormally increased only in the group with white coat hypertension defined by using standards drawn from general populations. These data indicate that until generally agreed-on criteria of ambulatory blood pressure normalcy are available, it is advisable to rely on conservative values to avoid extending the definition of white coat hypertension to subjects at increased risk of left ventricular hypertrophy. (Hypertension 1992;20:555-562)

KEY WORDS • hypertension, essential • blood pressure monitoring, ambulatory • echocardiography • hypertrophy

Some patients with arterial hypertension defined on the basis of blood pressure (BP) measured in a clinic setting have normal ambulatory or self-measured BP outside of the physician's office. These patients are referred to as having office or "white coat" hypertension. It is known that the measurement of BP in the clinic environment is associated with an alarm reaction that triggers a mean rise in BP of 27/14 mm Hg, maximal during the first 4 minutes of the visit, disappearing within about 10 minutes, and persisting over several visits despite increasing familiarity with the clinic environment. In some normotensive individuals, the persistence of this alerting reaction during the clinic measurements of BP may thus lead to misclassification of hypertension.

Pickering et al found that 21% of 292 untreated patients with mild hypertension had awake systolic/diastolic ambulatory BP below 134/90 mm Hg, i.e., the 90th percentile of their distribution in a clinically normotensive population. Using lower limits to define normalcy of daytime ambulatory BP (130/80 mm Hg), White et al found that left ventricular structure and function were not dissimilar in patients with white coat hypertension compared with a group of normotensive subjects. In two studies using different upper limits of normalcy of ambulatory BP (130/85 mm Hg in one study and 135/85 mm Hg in the other), the prevalence of white coat hypertension was 38% and 22%, respectively. In a third study, more than 60% of patients with borderline hypertension showed ambulatory BP levels of <134/90 mm Hg. Unfortunately, there is no general agreement concerning the normal limits of ambulatory BP on which clinicians should base their decisions. A recent meta-analysis of 23 studies indicated upper limits of normal mean daytime BP of 146/91 mm Hg regardless of age and sex. Higher upper limits, up to 155/103 and 177/97 mm Hg, respectively, in men and women aged 50-79 years were suggested from a large general population study. These upper limits differ markedly from those used in the aforementioned investigations of white coat hypertension. Therefore, standardization of the diagnosis of white coat hyperten-
sion, which should be primarily aimed at identifying a low-risk subgroup of subjects with clinical hypertension, is greatly complicated by the different definitions of the upper limits of "normal" ambulatory BP in the different studies, with important implications in the clinical assessment of hypertensive patients.

Consequently, we analyzed a large group of patients with essential hypertension according to the limits proposed by 1) our internal standards, 2) Pickering et al,1 3) Staessen et al,12 and 4) O'Brien et al13 to examine the prevalence of white coat hypertension and the corresponding distribution of left ventricular hypertrophy should those limits be accepted as standard.

Methods

Patient Population

From June 12, 1986, to June 15, 1991, we performed 24-hour noninvasive ambulatory BP monitoring in 1,297 white subjects. Among these, 346 hypertensive patients fulfilled all of the following inclusion criteria: 1) no previous treatment for hypertension or anti-hypertensive drug therapy withdrawn for at least 4 weeks; 2) diastolic BP of ≥90 mm Hg (Korotkoff phase V) on at least three visits in the previous 3 weeks; 3) agreement within 5 mm Hg between mercury column and pressure recorder on at least three consecutive measurements taken simultaneously on the same arm before beginning the ambulatory monitoring session; 4) at least one valid ambulatory BP reading (see below) per hour; 5) good-quality echocardiographic tracings (see below); 6) no clinical or laboratory evidence of heart or renal failure, secondary causes of hypertension, valvular defects, or coronary artery disease; and 7) no use of sedative or hypnotic drugs during ambulatory BP monitoring. Hypertensive patients were identified in a rural area of 18,500 inhabitants by a group of general practitioners who referred all their patients with clinic systolic/diastolic BP consistently >140/90 mm Hg and fulfilling the above points from 3 to 7 were included as a control group. All subjects gave informed consent to the study, which was conducted in accordance with the Declarations of Helsinki and Tokyo in the absence of a local ethics committee.

Blood Pressure Measurements

Clinic BP was measured in the morning between 8 AM and noon with a mercury sphygmomanometer. All subjects had been previously asked not to smoke or ingest caffeine during the previous 2 hours. Measurements were made by a physician with the subject seated for at least 5 minutes and holding his nondominant arm at the heart level, relaxed and supported. The mean of at least three consecutive readings taken at 1-minute intervals was used for analysis.

Ambulatory BP was recorded using the fully automatic units SpaceLabs 5200, 90020, and 90027 (SpaceLabs, Redmond, Wash.) set to take a measurement every 15 minutes throughout 24 hours. The reading, editing, and analysis of data provided by the recorders was done by the ABP5600 and ABP90204 interfaces (SpaceLabs) installed on an IBM personal computer, according to procedures previously described.14,15 Systolic readings of >260 or <70 mm Hg, diastolic readings of >150 or <40 mm Hg, and pulse pressure readings of >150 or <20 mm Hg were automatically discarded.

The daytime interval was arbitrarily defined as that between 6 AM and 10 PM, in line with recent guidelines.16

Reference Standards for Ambulatory Blood Pressure

Because the original definition of white coat hypertension is based on the normal values of mean awake ambulatory BP,1 we selected from the literature three studies that formally reported the upper limits for noninvasively measured awake, or daytime, ambulatory BP in reference populations, with a description of the statistical method of calculation. One study1 was performed in clinically normotensive healthy subjects, one12 is a meta-analysis of 23 investigations using an invasive or noninvasive technique of recording ambulatory BP in clinically normotensive subjects or in general populations, and one13 is the largest single-center study published so far on the reference values of noninvasively monitored ambulatory BP carried out in a general population including normotensive and untreated hypertensive subjects. Owing to its large patient population, this latter study could provide age- and sex-specific reference limits.

We also analyzed a population of 146 healthy subjects (68 women and 78 men), mean±SD age 45.5±15 years, with clinic sphygmomanometric BP of <140 mm Hg systolic and <90 mm Hg diastolic on three consecutive visits, who performed 24-hour noninvasive ambulatory BP monitoring (see above for methodology) in our center. For administrative reasons, echocardiographic tracings of the left ventricle could be obtained in 47 of these healthy subjects, who served as the control group (see above). None of these subjects had a personal or family history of hypertension or was taking drugs. Average daytime systolic/diastolic BP was higher in the men than in the women (124±79 versus 118±76 mm Hg, p=0.0006 and 0.04, respectively), whereas nighttime BP did not differ between the sexes (112±69 versus 109±67 mm Hg). Because the Shapiro-Wilk W test17 disclosed a non-Gaussian distribution of average 24-hour diastolic BP (p=0.0002), average daytime diastolic BP (p=0.0001), and average nighttime systolic BP (p=0.045) in men and of average nighttime systolic (p=0.023) and diastolic (p=0.005) BP in women as a result of skewness toward low values, we used the 90th percentile, and not the mean ±2 SD, to define the upper limits of normal mean daytime BP.

Table 1 shows the upper limits of normal mean daytime ambulatory BP reported in the three studies selected from the literature and in the reference population examined in our laboratory. Several valuable studies on ambulatory BP in reference populations18-21 could not be included in the present analysis, which required a formal definition of the upper limits of normal noninvasively monitored daytime ambulatory BP.

As shown in Table 1, the upper limits of daytime ambulatory BP differed among the studies, being lower in those carried out in clinically normotensive populations and higher in those including general populations. There were also some differences among the studies in the statistical definition of the upper limit of normal (90th percentile, 95th percentile, mean ±2 SD).
Echocardiographic Measurements

The M-mode echocardiographic study was performed under cross-sectional control using ATL Ultramark 8 and 9 Systems (Advanced Technology Laboratories, Bellevue, Wash.). End-systolic and end-diastolic measurements were taken with the patient in the partial left lateral decubitus position according to American Society of Echocardiography recommendations. Only frames with optimal visualization of interfaces and showing simultaneous visualization of the septum, left ventricular internal diameter, and posterior wall were read.

Using the formula introduced by Devereux et al.[23] on the basis of necropsy validation studies, left ventricular mass in grams was calculated as 0.80×\(1.04\times\left[\text{septal thickness+left ventricular internal diameter+posterior wall thickness}\right]-\left[\text{left ventricular internal diameter}\right]\)+0.6 g.

Cross-sectional area was calculated using the formula reported by Ditchey et al.[24] and relative wall thickness was calculated as \(2\times\left[\text{posterior wall thickness}\right]/\left[\text{left ventricular internal diameter}\right]\).

According to the standard formula, mean velocity of circumferential fiber shortening was calculated as (end-diastolic left ventricular internal diameter−end-systolic left ventricular internal diameter)/(end-diastolic left ventricular internal diameter×ejection time).

Pulsed Doppler study of transmitral blood flow was performed from the apical four-chamber view on subjects in the partial left lateral decubitus position, with the sample volume positioned at the level of the tips of the mitral valve leaflets. The interrogating beam was carefully adjusted to obtain the signals demonstrating the highest velocities. Parameters of transmitral flow were calculated according to standard techniques.[25] Peak E velocity and peak A velocity were the first and second peak velocities in the mitral flow waveform, respectively.

All echocardiographic examinations were performed by the same physician, and tracings were read by two investigators. The mean value from at least five measurements of the left ventricle per observer was computed. Because it has been shown that even small changes in heart rate may markedly affect the transmirtal flow pattern,[26] Doppler measurements were made from at least 10 R-R intervals.

At the time of the echocardiographic examination, all involved investigators were unaware of the patients' casual and ambulatory BP levels.

Statistical Analysis

Data were handled and stored using the DBASE IV package (Ashton-Tate Corp., Torrance, Calif.) and analyzed with SAS (SAS Institute, Inc., Cary, N.C.). Standard descriptive statistics, one-way analysis of variance, and multiple comparisons (Tukey's test) between the groups were performed when appropriate. For each of the four standards of ambulatory BP normalcy, the \(\chi^2\) test was performed to test the null hypothesis that the frequency of left ventricular hypertrophy was the same in the control group, the white coat hypertension group, and the ambulatory hypertension group. Values are reported as mean±SD. The \(p<0.05\) level of significance was adopted for all tests.

Results

Table 2 shows some clinical characteristics, including the clinic and ambulatory BP values, in the hypertensive patients diagnosed as having white coat hypertension or daytime ambulatory hypertension according to each of the four different standards of normalcy of daytime ambulatory BP. The same variables are reported in the control group.

Regardless of the standard of normalcy used to classify the patients into groups with white coat hypertension and ambulatory hypertension, the age, sex ratio, height, weight, and body surface area did not differ between the two groups, while the known duration of hypertension was shorter in those with white coat hypertension (all \(p<0.05\)).

Moreover, regardless of the standard used, clinic systolic and diastolic BP were higher in the patients with ambulatory hypertension than in those with white coat hypertension and in the patients with white coat hypertension than in the control group (all \(p<0.01\)).

### Table 1. Clinical Studies Formally Reporting Upper Limits for Normal Noninvasive Measurements of Daytime Ambulatory Blood Pressure in Reference Populations

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
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<td>Subjects (No.)</td>
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<td>3,476</td>
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<td>Average clinic BP (mm Hg)</td>
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<td></td>
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<tr>
<td>Systolic</td>
<td>125</td>
<td>117</td>
<td>...</td>
<td>119</td>
</tr>
<tr>
<td>Diastolic</td>
<td>79</td>
<td>77</td>
<td>...</td>
<td>76</td>
</tr>
<tr>
<td>Upper limit for average daytime BP</td>
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</tr>
<tr>
<td>Statistical method</td>
<td>90th percentile</td>
<td>90th percentile</td>
<td>Mean+2 SD</td>
<td>95th percentile</td>
</tr>
<tr>
<td>Systolic (mm Hg)</td>
<td>136 (men), 131 (women)</td>
<td>134</td>
<td>146</td>
<td>By age and sex*</td>
</tr>
<tr>
<td>Diastolic (mm Hg)</td>
<td>87 (men), 86 (women)</td>
<td>90</td>
<td>91</td>
<td>By age and sex*</td>
</tr>
</tbody>
</table>

BP, blood pressure; SD, standard deviation.

*Age ranges: 17–29 years (men: 144/88 mm Hg, women: 131/83 mm Hg), 30–39 years (men: 143/91 mm Hg, women: 132/85 mm Hg), 40–49 years (men: 150/98 mm Hg, women: 150/94 mm Hg), and 50–79 years (men: 155/103 mm Hg, women: 177/97 mm Hg).
TABLE 2. Demographic Variables and Clinic and Ambulatory Blood Pressure in 346 Hypertensive Patients and 47 Normotensive Subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control group (normotensive subjects)</th>
<th>Internal standards</th>
<th>Pickering et al</th>
<th>Staessen et al</th>
<th>O'Brien et al</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Subjects (No.)</td>
<td>White coat</td>
<td>Ambulatory</td>
<td>White coat</td>
<td>Ambulatory</td>
</tr>
<tr>
<td>Subjects (No.)</td>
<td>47</td>
<td>42</td>
<td>304</td>
<td>57</td>
<td>289</td>
</tr>
<tr>
<td>Age (years)</td>
<td>49±9</td>
<td>49±10</td>
<td>52±11</td>
<td>50±10</td>
<td>52±11</td>
</tr>
<tr>
<td>Sex ratio (male/female)</td>
<td>27/20</td>
<td>19/23</td>
<td>158/146</td>
<td>24/33</td>
<td>153/136</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>167±8</td>
<td>166±9</td>
<td>167±8</td>
<td>165±9</td>
<td>167±8</td>
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<tr>
<td>Weight (kg)</td>
<td>75±12</td>
<td>73±13</td>
<td>76±14</td>
<td>72±12</td>
<td>76±14</td>
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<tr>
<td>Body surface area (cm²)</td>
<td>1.83±0.2</td>
<td>1.84±0.3</td>
<td>1.84±0.2</td>
<td>1.83±0.2</td>
<td>1.84±0.2</td>
</tr>
<tr>
<td>Duration of hypertension (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinic BP (mm Hg)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Systolic</td>
<td>127±8</td>
<td>144±11*</td>
<td>160±18†</td>
<td>144±12*</td>
<td>160±18†</td>
</tr>
<tr>
<td>Diastolic</td>
<td>79±7</td>
<td>93±4*</td>
<td>99±7†</td>
<td>93±4*</td>
<td>98±7†</td>
</tr>
<tr>
<td>Average daytime BP (mm Hg)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>123±10</td>
<td>124±5</td>
<td>148±14†</td>
<td>125±5</td>
<td>149±13†</td>
</tr>
<tr>
<td>Diastolic</td>
<td>81±7</td>
<td>81±5</td>
<td>96±8†</td>
<td>82±5</td>
<td>97±8†</td>
</tr>
<tr>
<td>Average 24-hour BP (mm Hg)</td>
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<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>118±9</td>
<td>120±6</td>
<td>143±14†</td>
<td>121±6</td>
<td>144±14†</td>
</tr>
<tr>
<td>Diastolic</td>
<td>77±6</td>
<td>77±5</td>
<td>92±8†</td>
<td>78±5</td>
<td>92±8†</td>
</tr>
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</table>

BP, blood pressure. Hypertensive patients were divided into a white coat hypertensive group and a daytime ambulatory hypertensive group on basis of reported upper limits for normal daytime ambulatory blood pressure (groups 1-4). See text and Table 1 for explanations. Data expressed as mean±SD.

*p<0.01 different from normotensive subjects.

**p<0.01 different from both normotensive subjects and patients with white coat hypertension.

Prevalence of White Coat Hypertension

As expected, the prevalence of clinically hypertensive patients diagnosed as having white coat hypertension showed important differences ($\chi^2=346.0, p<0.0001$) among the four standards of noninvasive measurements of ambulatory BP (Figure 1). In fact, prevalence ranged between 12.1% according to our internal standards to 53.2% according to the age- and sex-specific limits reported by O'Brien et al, with intermediate values of 16.5% using the limits reported by Pickering et al, and 29.8% using the limits calculated by Staessen et al.

In a subgroup of 285 patients (82% of the hypertensive population) with mild hypertension (clinic diastolic BP between 90 and 104 mm Hg), the prevalence of subjects with white coat hypertension ranged from 14.7% using our internal standards to 59.6% using the age- and sex-specific limits reported by O'Brien et al, with intermediate values of 19.3% using the limits reported by Pickering et al and 34.4% using the limits reported by Staessen et al.

Ambulatory Blood Pressure

As shown in Table 2, average 24-hour BP and daytime BP did not differ from values in the control group in those patients with white coat hypertension defined by upper limits of normal ambulatory BP drawn from normotensive populations. By contrast, BP was increased in persons with white coat hypertension defined by standards drawn partly or entirely from general populations when compared with the control group (all $p<0.01$). Regardless of the BP reference standard, all groups of patients with white coat hypertension showed lower values of average 24-hour and daytime BP than the patients with daytime ambulatory hypertension (all $p<0.01$).
### Table 4. Prevalence of Echocardiographic Left Ventricular Hypertrophy (Left Ventricular Mass Index >110 g/m² in Women or 134 g/m² in Men) in Patients with White Coat Hypertension or Daytime Ambulatory Hypertension Defined by Four Reference Standards

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Hypertensive patients</th>
<th>Internal standards</th>
<th>Pickering et al¹</th>
<th>Staessen et al¹²</th>
<th>O'Brien et al¹³</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control group (normotensive subjects)</td>
<td>White coat</td>
<td>Ambulatory</td>
<td>White coat</td>
<td>Ambulatory</td>
</tr>
<tr>
<td>At end-diastole</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interventricular septum thickness (cm)</td>
<td>0.85±0.2</td>
<td>0.93±0.2</td>
<td>1.08±0.3*</td>
<td>0.92±0.2</td>
<td>1.08±0.3*</td>
</tr>
<tr>
<td>Posterior wall thickness (cm)</td>
<td>0.75±0.2</td>
<td>0.80±0.1</td>
<td>0.93±0.2*</td>
<td>0.81±0.2</td>
<td>0.93±0.2*</td>
</tr>
<tr>
<td>Left ventricular internal diameter (cm)</td>
<td>5.11±0.6</td>
<td>5.05±0.6</td>
<td>5.18±0.6</td>
<td>5.01±0.5</td>
<td>5.20±0.6</td>
</tr>
<tr>
<td>Left ventricular mass index (g/m²)</td>
<td>77±19</td>
<td>85±20</td>
<td>108±34*</td>
<td>85±25</td>
<td>109±34*</td>
</tr>
<tr>
<td>Relative wall thickness</td>
<td>0.30±0.1</td>
<td>0.32±0.1</td>
<td>0.37±0.1*</td>
<td>0.33±0.1</td>
<td>0.37±0.1*</td>
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<tr>
<td>Cross-sectional area index (cm²/m²)</td>
<td>8.1±2</td>
<td>8.8±2</td>
<td>10.7±3*</td>
<td>8.9±2</td>
<td>10.8±3*</td>
</tr>
<tr>
<td>Shortening fraction (%)</td>
<td>39.5±7</td>
<td>38.0±7</td>
<td>38.1±7</td>
<td>37.8±7</td>
<td>38.2±7</td>
</tr>
<tr>
<td>Mean velocity of circumferential fiber shortening (circ/sec)</td>
<td>1.23±0.3</td>
<td>1.17±0.3</td>
<td>1.23±0.3</td>
<td>1.19±0.3</td>
<td>1.23±0.3</td>
</tr>
<tr>
<td>Peak A velocity (m/sec)</td>
<td>0.57±0.1</td>
<td>0.60±0.2</td>
<td>0.66±0.2†</td>
<td>0.62±0.2</td>
<td>0.66±0.2†</td>
</tr>
<tr>
<td>Peak E velocity (m/sec)</td>
<td>0.61±0.1</td>
<td>0.65±0.2</td>
<td>0.59±0.2</td>
<td>0.65±0.2</td>
<td>0.59±0.2</td>
</tr>
<tr>
<td>Peak A/peak E ratio</td>
<td>0.99±0.3</td>
<td>1.02±0.4</td>
<td>1.21±0.4*</td>
<td>1.02±0.4</td>
<td>1.22±0.4*</td>
</tr>
</tbody>
</table>

Hypertensive patients were divided into a white coat hypertensive group and a daytime ambulatory hypertensive group on basis of reported upper limits for normal daytime ambulatory blood pressure (groups 1-4). See text and Table 1 for explanations. Data expressed as mean±SD.

*p<0.01 different from both normotensive subjects and patients with white coat hypertension.

†p<0.01 different from normotensive subjects.

*Echocardiographic Parameters of Left Ventricle

Data are reported in Table 3. Left ventricular mass index did not differ from that in the control group in the group with white coat hypertension defined by upper limits of normal ambulatory BP drawn from normotensive populations, but it did in the other two groups of patients with white coat hypertension defined by standards obtained, partly or entirely, from general populations.¹²,¹³

Interventricular septum thickness, posterior wall thickness, relative wall thickness, and cross-sectional area index differed among the groups, as did left ventricular mass index. Left ventricular internal diameter, shortening fraction, and the mean velocity of circumferential fiber shortening did not differ among the groups.

Table 4 shows that, compared with the control group, the prevalence of echocardiographic left ventricular hypertrophy (left ventricular mass index of >110 g/m² in women or 134 g/m² in men) was increased in the patients with white coat hypertension defined by the two standards drawn, partly or entirely, from general populations, but not in the other two groups with white coat hypertension. In all four groups of patients with white coat hypertension the prevalence of left ventricular hypertrophy was significantly lower than that in the patients with daytime ambulatory hypertension (all p<0.01).

Compared with the control group, peak A velocity and the peak A/peak E ratio were increased in the group with white coat hypertension defined by standards drawn, partly or entirely, from general populations.
The original definition of white coat hypertension was essential hypertension with a clinic diastolic BP of ≥90 mm Hg on at least two visits and awake ambulatory BP within the normotensive range. White coat hypertension has also been defined as a normal self-measured BP at home in subjects with clinic hypertension. Regardless of the use of ambulatory or self-measured BP to identify subjects with white coat hypertension, the comparability of different studies and the clinical management of an individual patient are likely to be affected by the different definitions of BP normalcy with either technique. So far, the upper limits of normal ambulatory BP used to define white coat hypertension ranged between 130 and 135 mm Hg systolic and between 80 and 90 mm Hg diastolic, but very different values (up to 155/103 mm Hg in men and 177/97 mm Hg in women aged >50 years) have been suggested as temporary reference limits for noninvasive measurements of daytime ambulatory BP. Generally agreed-on normative values for noninvasive measurements of ambulatory BP are therefore needed.

**Definition of White Coat Hypertension**

The prevalence and clinical characteristics of patients with white coat hypertension have been investigated in some studies in which the dividing line between normal and abnormal ambulatory BP was defined empirically, not from the analysis of a reference population.

In one of these studies, White et al. showed that left ventricular structure and function did not differ in healthy normotensive subjects and clinically hypertensive patients with office, or white-coat, hypertension defined as a mean daytime ambulatory BP of <130/80 mm Hg. We confirmed these findings in our subjects with white coat hypertension defined as a mean daytime BP of <130/80 mm Hg showed a mean left ventricular mass index of 82 g/m² and a prevalence of left ventricular hypertrophy of 0% (all differences not significant compared with control group). In our study, the prevalence of left ventricular hypertrophy was 0% in the control group, and prevalence did not change significantly in patients with white coat hypertension defined by the upper limits of normal daytime ambulatory BP drawn from normotensive populations (2.4% and 3.5%). In contrast, the prevalence of left ventricular hypertrophy was raised clinically and statistically in the other two groups with white coat hypertension (9.0% and 14.1%), with a consequent increase in the cardiovascular risk in these subjects.

Doppler echocardiography has been shown to be accurate in the assessment of left ventricular diastolic filling, although caution is needed in interpreting the results because of the confounding effects of age, heart rate, and the atrioventricular pressure difference. In essential hypertension, the ratio of late to early transmitral peak blood flow velocity (peak A/peak E ratio) is abnormally increased and more closely related to ambulatory than clinic BP. In the present study, the peak A/peak E ratio did not differ between the control subjects and those with white coat hypertension defined by the two more restrictive standards of ambulatory BP normalcy, while the ratio was significantly increased in the other two groups with white coat hypertension. Again, these findings are in keeping with those of White et al. who showed that the rapid left ventricular filling rate detected with radionuclide ventriculography was not dissimilar in normotensive subjects and those with white coat hypertension, while the rate was abnormally increased only in subjects with elevated ambulatory BP levels.

Taken together, our findings suggest that the hypothesis of white coat hypertension as a condition of low risk of cardiac organ damage can be either demonstrated or rejected solely on the basis of the reference standard for normal ambulatory BP drawn from the current literature.

**Definition of Ambulatory Blood Pressure Normalcy and White Coat Hypertension**

Until the relevance of ambulatory BP to cardiovascular morbidity and mortality is clearly established, a clinic BP value in the normotensive or hypertensive range will continue to have an important role in the prediction of cardiovascular risk. Therefore, an ambulatory BP value, the prognostic importance of which is still uncertain, should be considered "normal" (i.e., associated with a low cardiovascular risk) if it falls within a range of normal values drawn from a clinically normotensive population free from cardiovascular disorders. The use of a general unselected sample including normotensive and hypertensive subjects to calculate reference values for normal ambulatory BP has the great advantage of estimating its distribution across the whole population but also the possible disadvantage of providing excessively high upper limits of normal because of the unpredictable influence of those subjects with a high clinic BP.

The findings of the present study support the view that the prevalence of white coat hypertension within a given hypertensive population is related to the prevalence of individuals with a high BP included in the reference population. If the upper limits for normal ambulatory BP are drawn from a clinically normotensive population, these limits will be relatively low, as will the prevalence of white coat hypertension (about 12–20%). The upper limits for normal ambulatory BP will progressively increase as the reference population becomes more representative of the general population, which will result in an increase in the prevalence of white coat hypertension to >50%. 
Because of its important clinical implications, the hypothesis that individuals with hypertension in the physician’s office and a normal BP during everyday life may represent a group at low risk of organ damage and future cardiovascular complications and not requiring antihypertensive drugs needs to be tested further in cross-sectional and longitudinal studies. In this context, the definition of the upper limits of normal ambulatory BP is of the utmost importance, and the findings reported herein may help in the planning and interpretation of these studies.

Conclusions

The upper limits of normal daytime ambulatory BP obtained from studies carried out in clinically normotensive subjects allowed the diagnosis of white coat hypertension in 12.1–16.5% of 346 unselected patients with essential hypertension (up to 19% of patients in mild hypertension), and the risk of left ventricular hypertrophy in these subjects was not dissimilar from that in normotensive individuals. The use of less restrictive limits of ambulatory BP normality resulted in a remarkable increase in the prevalence of white coat hypertension (up to 53.2% of patients, and up to about 60% of those with mild hypertension) and the associated frequency of left ventricular hypertrophy (up to 14.7%). From these data we suggest that the hypothesis of white coat hypertension as a benign condition should be tested using restrictive upper limits of normal daytime ambulatory BP, possibly not higher than 136 mm Hg systolic and 90 mm Hg diastolic.

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