Classification of Blood Pressure Levels by Ambulatory Blood Pressure in Hypertension

Andreas Bur, Harald Herkner, Marianne Vlcek, Christian Woisetschläger, Ulla Derhaschnig, Michael M. Hirschl

Abstract—Whereas clinic blood pressure (CBP) above normality is divided into stages, no corresponding classifications are available for 24-hour ambulatory blood pressure (ABP). We conducted a study (1) to define stages of hypertension by ABP corresponding to CBP stages and (2) to evaluate if these stages have prognostic impact similar to CBP stages. Seven hundred thirty-six hypertensive patients were included. Mean systolic blood pressure was 149±15.2/87±8.6 mm Hg for CBP and 135±13/79±9.7 mm Hg for ABP. The mean bias between both methods was −13.3 mm Hg (95% CI, −14.3 to −12.2; 1.96×SD limits of agreement, 15.7 to −42.3) and −7.3 mm Hg (95% CI, −7.9 to −6.6; 1.96×SD limits of agreement, 9.8 to −24.3) for systolic and diastolic blood pressure (P>0.0001 for both), respectively. Classification of hypertension by ABP revealed lower cutoff values for the different stages of hypertension compared with the corresponding cutoff values for CBP (CBP versus ABP: 140/90 versus 132/81 mm Hg; 160/100 versus 140/88 mm Hg; 180/110 versus 148/94 mm Hg, P<0.001). Overall, 82 (11.1%) patients had nonfatal clinical cardiovascular events and 9 (1.2%) patients died of a cardiovascular cause during follow-up. The distribution of cardiovascular events was significantly associated with increasing ABP value (P<0.006). Staging of hypertension by ABP may facilitate the use of this method in daily clinical practice, as ABP can now be used not only to confirm the diagnosis of hypertension but also to assess the severity and prognosis of hypertensive disease. (Hypertension. 2002;40:817-822.)

Key Words: hypertension, arterial | hypertension, essential | blood pressure | diastole | blood pressure monitoring, ambulatory | systole

Ambulatory blood pressure monitoring (ABPM) has been established as a method of first choice in specific indications, for example, white coat hypertension, evaluation of antihypertensive treatment, and circadian patterns of blood pressure.1,2 Recently published studies have precisely defined the level of normal ambulatory blood pressure.3–5 Additionally, the prognostic value of ABPM was evaluated in different highly selected hypertensive populations.6–8 However, there is still a lack of data that compare ABPM and clinic blood pressure in a moderate to severe hypertensive population. Whereas clinical blood pressure above normality is divided into stages, no corresponding classifications are available for ABPM. Such a lack of corresponding stages between clinic and ambulatory blood pressures limits the use of ABPM in daily clinical practice. No studies have classified hypertension by ABPM in correspondence to the recommended classification by clinic blood pressure. We therefore conducted a study (1) to define stages of hypertension by ABPM corresponding to clinic blood pressure stages in a hypertensive population and (2) to evaluate if these stages have prognostic impact similar to clinic blood pressure stages by monitoring fatal and nonfatal cardiovascular events.

Methods

The study was performed at the Hypertension Unit of the Department of Emergency Medicine in Vienna. Overall, 736 patients were included between January 1994 and June 2001. All patients were informed about the study protocol and gave their informed consent before study inclusion. Inclusion criteria were evidence of hypertension defined as blood pressure ≥140/90 mm Hg evaluated by 3 measurements on 3 consecutive visits according American Heart Association guidelines.6 Patients with secondary hypertension were excluded. The presence of previous cardiovascular events did not constitute exclusion in subjects maintaining their normal physical and work activities. At the beginning, the study procedure included a medical visit, which took place in the morning and consisted of a comprehensive medical history, a physical examination, and assessment of antihypertensive drug treatment. Twenty-four-hour ABPM was performed at the time of entrance. The incidence of cardiovascular events during the time of follow-up was recorded. A minimal 6-month follow-up was required for being included in the analysis.

Clinic Blood Pressure Measurements

During the physician’s visit (8 to 11 AM), blood pressure was measured in a quiet environment with a mercury sphygmomanometer with the patient in a sitting position after 5 minutes of rest, following the recommendations of the British Hypertension Society. 10 Systolic and diastolic blood pressure values (Korotkoff phase I and phase V, respectively) represented in each visit the mean of 3
different readings measured at 5-minute intervals. In any patient, sphygmomanometric measurements were obtained by the same medical doctor.

**Ambulatory Blood Pressure Monitoring**

Ambulatory blood pressure monitoring was performed with oscillometric Meditech ABPM-04 devices, which had previously been validated and recommended for clinical use. The monitoring equipment was applied at the end of the medical visit. The cuff was fixed to the nondominant arm, and 3 blood pressure readings were taken concomitantly with sphygmomanometric measurements to ensure that the average of the 2 sets of values did not differ by >5 mm Hg. The device was set to measure blood pressure at 15-minute intervals during the daytime (6 AM to 10 PM) and at 30-minute intervals during the nighttime (10 PM to 6 AM). The patient was sent home with instructions to hold the arm immobile at the time of measurements, to keep a diary of daily activities and quality of night rest, and to return to the hospital 24 hours later. The monitoring was always done on a working day and for treated patients during the normal intake of the usual antihypertensive treatment. The patients had no access to the ambulatory blood pressure values. Each of the 6 ambulatory blood pressure devices available for the study was checked monthly as described previously.

**Data Analysis**

In each participant, the blood pressure values obtained by the sphygmomanometer (before and after 24-hour ABPM) were averaged to calculate a single systolic and diastolic clinic blood pressure value. Ambulatory blood pressure data were edited for artifacts according to the following criteria.

Measurements recorded during the ambulatory period were stored on a personal computer and screened for editing of artificial values by applying previously described criteria. A 24-hour record was rejected for analysis if more than one third of potential daytime and nighttime measurements were absent (daytime minimum, 18; nighttime minimum, 8). The editing criteria that were considered removed <1.0% of the readings without any effect on the findings. The ambulatory blood pressure values are expressed as 24-hour average systolic and diastolic pressures. Each patient was then classified according to ambulatory blood pressure values (normal stage <132/81 mm Hg; stage I <140/88 mm Hg; stage II <148/94 mm Hg; and stage III >148/94 mm Hg). When systolic and diastolic pressures fall into different categories, the higher category was selected to classify the individual’s blood pressure status.

**Patient Follow-Up**

After the initial evaluation, at intervals a physical examination was performed. A comparison of the incidence of new cardiovascular events, fatal and nonfatal, between blood pressure groups was made during the follow-up. Patients who died of a noncardiovascular cause were considered to have been event-free until death. In subjects with multiple nonfatal events, the analysis included only the first event. Cardiovascular events included myocardial infarction, angina pectoris, coronary revascularization, arrhythmia (eg, atrial fibrillation), stroke, transient ischemic attack, peripheral artery disease, acute left ventricular failure, hypertensive crisis requiring hospitalization, and recurrence of aortic aneurysm.

**Statistical Analysis**

Data are presented as mean and standard deviation or 95% CI or number and percentage. The 24-hour mean values of ABPM measurements and the mean of 6 clinic blood pressure measurements either before or after 24-hour ABPM from each patient were used for the calculations. Systolic and diastolic blood pressure values were analyzed separately. To assess the association between ABPM and clinic blood pressure values, we used Pearson’s linear correlation. Linear regression analysis was used to quantify the association between clinic blood pressure and ABPM and the difference of the two methods. To assess the influence of the absolute blood pressure level on the difference between ambulatory blood pressure and clinic blood pressure, we plotted the difference between ambulatory blood pressure and clinic blood pressure against clinic blood pressure. According to the visual aspect of the data distribution, we calculated linear regressions of this association. The regression equations were used to calculate the cutoff values of ABPM corresponding to the clinic blood pressure values as defined by the JNC-VI and WHO guidelines. We calculated the mean difference (ie, the bias) between ABPM and clinic blood pressure measurements. The limits of agreement were calculated as 1.96×SD of the mean bias. For statistical comparison of ABPM and clinic blood pressure values, the paired t test was used. Additionally, we used the χ² test for trend to assess linear association between ambulatory blood pressure stages and proportion of cardiovascular events. Kaplan-Meier estimates were used to assess the probability of cardiovascular events for the different ambulatory blood pressure groups. Differences in probability of cardiovascular events were calculated by use of the log rank test. Data processing was performed with Microsoft Excel 97 for Windows and SPSS 7.5 for Windows. A 2-sided probability value <0.05 was considered statistically significant.

**Results**

**General Data**

Overall, 736 (362 male) patients could be enrolled into the study. The average age of the patients was 55±14 years. Initially, 557 (75%; 270 male) of the enrolled patients were treated. The treatment consisted of commonly available drugs including β-adrenergic–blocking drugs, calcium channel antagonists, ACE inhibitors, α-adrenergic–blocking drugs, and thiazide diuretics alone or combined. The average duration of hypertension was 6.4±8.4 years. Laboratory values concerning renal function and serum electrolytes were within the normal range in all patients (serum creatinine, 1.01±0.21 mg/100 mL; blood urea nitrogen, 15.6±4.9 U/L; serum sodium, 140.5±5.8; serum potassium, 4.2±1.6). During follow-up in 442 (60%) patients, treatment was modified.

<table>
<thead>
<tr>
<th>Stages</th>
<th>Δ Systolic CBP, mm Hg</th>
<th>Δ Diastolic CBP, mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>−10(7)</td>
<td>−5(3)</td>
</tr>
<tr>
<td>Stage I</td>
<td>−12(8)</td>
<td>−6(4)</td>
</tr>
<tr>
<td>Stage II</td>
<td>−13(7)</td>
<td>−8(6)</td>
</tr>
<tr>
<td>Stage III</td>
<td>−20(8)</td>
<td>−9(4)</td>
</tr>
</tbody>
</table>

Values are mean (±SD). CBP indicates clinical blood pressure.

**Clinic and Ambulatory Average Blood Pressures**

A total of 528 patients (72%) had systolic clinic blood pressure values ≥140 mm Hg, and 308 patients (42%) had diastolic clinic blood pressure values ≥90 mm Hg. The mean systolic as well as diastolic blood pressure values were similar before and after the 24-hour ABPM (148±14 versus 149±16 mm Hg; 87±9 versus 86±8 mm Hg). Mean ambulatory blood pressure values were 135±13 mm Hg and 79±10 mm Hg for systolic and diastolic blood pressure, respectively.

Twenty-four-hour ambulatory blood pressure and clinic blood pressure were associated with a correlation coefficient
of 0.46 and 0.61 for systolic and diastolic blood pressure, respectively \((P<0.0001\) for both; Figures 1A and 1B). The linear regression coefficients were 0.405 and 0.307 and the intercepts 75.2 and 25.4 for systolic and diastolic blood pressure, respectively.

The mean bias between ABPM and clinic blood pressure was \(-13.3\) mm Hg (95% CI, \(-14.3\) to \(-12.2\); 1.96×SD limits of agreement, 15.7 to \(-42.3\)) and \(-7.3\) mm Hg (95% CI, \(-7.9\) to \(-6.6\); 1.96×SD limits of agreement, 9.8 to \(-24.3\)) for systolic and diastolic blood pressure \((P>0.0001\) for both), respectively. The 95% CI at the cut-point of the regression line (ambulatory blood pressure, 132/82 mm Hg; clinic blood pressure, 140/90 mm Hg) was 116 to 148 mm Hg for systolic blood pressure and 70 to 94 mm Hg for diastolic blood pressure.

We found a linear relation between clinic blood pressure and the difference between the methods for systolic and diastolic blood pressure (Figures 2A and 2B). Using the above regression equations, we calculated the ambulatory blood pressure cutoff values corresponding to the recent recommended guidelines for clinic blood pressure, which are presented in Table 2. According to these calculations, stage 1 hypertension is defined from 132 to 140 mm Hg systolic and from 82 to 87 mm Hg diastolic ambulatory blood pressure and stage 2 hypertension from 140/88 to 148/94 mm Hg, respectively.

**Frequency Distribution of Age and Average Blood Pressure Values in Different Ages**

The distribution of age in the different blood pressure groups are demonstrated in Figure 3. No significant difference in the distribution of age are noted. In patients <65 years of age, the upper normal limit of ambulatory blood pressure was 132 mm Hg and 82 mm Hg for systolic and diastolic blood pressure, respectively. The cutoff values in patients >65 years of age were 132 mm Hg for systolic and 81 mm Hg for diastolic ambulatory blood pressure.

**Frequency of Cardiovascular Events**

The mean time of observation was 52 months, ranging from 6 to 96 months (median, 48 months). Overall, 82 (11.1%) patients had nonfatal clinical cardiovascular events and 9 (1.2%) patients died of cardiovascular causes. Death was caused in 4 patients by acute myocardial infarction, in 3 patients by cerebral infarction, and in 2 patients by cerebral hemorrhage. In 26 patients, causes for nonfatal clinical cardiovascular events were coronary heart disease, myocardial infarction, angina pectoris, and atrial fibrillation; in 15 patients, cerebrovascular disease, stroke, or transient ischemic attack; in 11 patients peripheral artery disease; in 28 patients, acute left ventricular failure and hypertensive crisis requiring hospitalization; and in 2 patients, recurrence of aortic aneurysm.

**TABLE 2. Corresponding Values of Clinic and Ambulatory Blood Pressure**

<table>
<thead>
<tr>
<th></th>
<th>Systolic CBP, mm Hg</th>
<th>Systolic ABP, mm Hg</th>
<th>Diastolic CBP, mm Hg</th>
<th>Diastolic ABP, mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>135</td>
<td>130</td>
<td>85</td>
<td>78</td>
<td></td>
</tr>
<tr>
<td>140†</td>
<td>132</td>
<td>90†</td>
<td>81</td>
<td></td>
</tr>
<tr>
<td>159</td>
<td>140</td>
<td>99</td>
<td>87</td>
<td></td>
</tr>
<tr>
<td>160‡</td>
<td>140</td>
<td>100‡</td>
<td>88</td>
<td></td>
</tr>
<tr>
<td>179</td>
<td>148</td>
<td>109</td>
<td>93</td>
<td></td>
</tr>
<tr>
<td>180‡</td>
<td>148</td>
<td>110‡</td>
<td>94</td>
<td></td>
</tr>
</tbody>
</table>

*Stage 1, JNC-VI; †Stage 2, JNC-VI; ‡Stage 3, JNC-VI.
Ambulatory Blood Pressure Stages and Cardiovascular Events

According to the ABPM values 260 (35%), patients were assigned in normal (132/81 mm Hg), 216 (29%) patients in stage I (140/88 mm Hg), 131 (18%) patients in stage II (148/94 mm Hg), and 129 (18%) patients were assigned in stage III (148/94 mm Hg). The distribution of the nonfatal and fatal clinical cardiovascular events are demonstrated in Table 3. We found a linear association of increasing ABPM value and the number of cardiovascular events (P<0.006) (Figure 4). The Kaplan-Meier plot demonstrating the survival probability of the different ambulatory blood pressure groups is presented in Figure 5. We found a statistical trend toward a difference in survival probability between the ambulatory blood pressure groups within a mean observational period of 52 months (P=0.07).

Discussion

Comparison of Clinic and Ambulatory Blood Pressure

Our study of 736 participants provides new information on the relation between clinic and ambulatory blood pressure obtained from a moderate to severe hypertensive population. First, the mean difference between ambulatory blood pressure and blood pressure assessed by a doctor in the clinic environment was significant at all blood pressure levels. Second, the mean difference between ambulatory blood pressure and clinic blood pressure increases with increasing blood pressure values. Whereas the mean difference of systolic blood pressure between both methods was 7 mm at the level of 135 mm Hg, this difference increases to 32 mm Hg at a level of 180 mm Hg. A similar pattern of increasing disparity between both methods was observed for diastolic blood pressure. Our findings extend previous findings that ambulatory blood pressure is significantly lower than clinic blood pressure even in patients above the normal values of 140/90 mm Hg. These results are in line with the data provided by the PAMELA study, which also reported an increasing difference between both methods, dependent on the actual clinic blood pressure in a normotensive population.3,4

Because of the increasing difference between clinic blood pressure and ambulatory blood pressure, a direct conversion of ABPM results into clinical stages would be an incorrect procedure that may result in a lower staging of patients with severely elevated ambulatory blood pressure.

Comparison of Our Data With Previously Published Data

As our study population consisted of a high percentage of hypertensive individuals, our mean systolic and diastolic blood pressure was significantly higher compared with three other population studies. Whereas our mean ambulatory blood pressure was 135/79 mm Hg, the mean values of the

![Figure 3. Distribution of age (mean±SD) in different blood pressure groups. Normal, 55±1 years; stage I, 58±1 years; stage II, 57±1 years; stage III, 57±1 years.](http://hyper.ahajournals.org/)

**TABLE 3. Distribution of Cardiovascular Events in Different ABP Stages**

<table>
<thead>
<tr>
<th>ABP Stages</th>
<th>Cardiovascular Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>No 237 (91) Yes 23 (9)</td>
</tr>
<tr>
<td>Stage I</td>
<td>191 (88) Yes 25 (12)</td>
</tr>
<tr>
<td>Stage II</td>
<td>111 (85) No 20 (15)</td>
</tr>
<tr>
<td>Stage III</td>
<td>106 (82) No 23 (18)</td>
</tr>
</tbody>
</table>

Values are n (%).
previous studies were 118/74, 119/71, and 119/70 mm Hg, respectively. Similar differences were observed concerning the clinic blood pressure. Despite these differences between our mean blood pressure values and the previously reported results, the normal value of the 24-hour ABPM assessed in our study population was similar to the PAMELA study and the results published by Staessen et al. Our upper limit of normality for 24-hour ambulatory blood pressure is 132/81 mm Hg, which is similar to the data of a Belgian population (129/80 mm Hg) of the PAMELA study (128/82 mm Hg), and of an international database (133/82 mm Hg). In contrast to these previous studies, our study population consists of normotensive as well as hypertensive subjects of all stages.

Definition of Corresponding Stages Between Ambulatory and Clinic Blood Pressure
Because >70% of our patients had a systolic value >140 mm Hg and >40% had a diastolic value >90 mm Hg, corresponding stages between clinic and ambulatory blood pressure over a wide range of blood pressure values above normality were assessed. The definition of corresponding stages between both methods provides some clinically relevant advantages:

First, patients classified as severely hypertensive by 24-hour ambulatory blood pressure measurement (>148/94 mm Hg) will no longer be classified as mild or moderately hypertensive, according to clinic blood pressure stages. Second, ambulatory blood pressure values can be used for treatment decision according to the recently published guidelines because the cutoff values obtained in this study correspond with the cutoff values recommended for the clinic blood pressure.

Prognostic Value of the Newly Defined Stages of Ambulatory Blood Pressure
The calculation of corresponding stages between ABPM and clinic blood pressure without the evaluation of the prognostic value is only of limited clinical relevance. Our data clearly demonstrate a significant association between the frequency of cardiovascular events and height of initial ambulatory blood pressure. Patients belonging to stage III assessed by ambulatory blood pressure had the highest frequency of cardiovascular events. The difference between patients with different stages of hypertension remained unchanged over the observation period of 5 years, as demonstrated by Kaplan-Meier curves. The risk for a patient belonging to the highest blood pressure group to have a cardiovascular event showed a trend to be elevated compared with patients with an ambulatory blood pressure below the upper normal limit.

These findings are in line with recently published data which demonstrated a correlation between ABPM and the extent of left ventricular hypertrophy or microalbuminuria. Both conditions are associated with an increased risk for cardiovascular events. A former published study has demonstrated the prognostic value of ABPM. The patients belonging to the highest tertile of 24-hour ambulatory pressure had the highest rate of cardiovascular events. However, in this former study, the stages for ambulatory blood pressure did not correspond to clinic blood pressure stages. Therefore, it seems rather difficult to use these cutoffs in daily clinical practice and to estimate risk for an individual patient.

Influence of Age
It must be mentioned that age is an independent prognostic parameter for subsequent cardiovascular events in all stages of hypertension. However, the distribution of age was similar in all four groups, indicating a similar effect of age on prognosis in each group. Moreover, average blood pressure as well as the upper normal limit do not differ between patients >65 years of age and younger people. Our data are in line with the report of O’Brien et al. who demonstrated similar blood pressure values in patients 50 to 79 years of age. We therefore conclude that age contributes equally to the frequency of cardiovascular events in all four groups.

Limitations
Some limitations of the study must be emphasized. First, ABPM is influenced by the diurnal rhythm, which may contribute to the discrepancy between clinic and ABPM. The reduction of blood pressure during the night may contribute to the lower level of ambulatory blood pressure compared with clinic blood pressure values, which were assessed in the morning. However, even home blood pressure measurements taken at different times of the day remained higher than ABPM. We therefore assume that the diurnal rhythm of blood pressure is only a minor contributor to the discrepancy between clinic and ambulatory blood pressure. Second, most of the patients included in this study were receiving active treatment. Drug treatment influences the course of blood pressure, dependent on the pharmacodynamic and pharmacokinetic properties of the drug. Antihypertensive drugs with a marked peak-to-through ratio may contribute to lower mean ambulatory blood pressure values compared with clinic blood pressure values obtained in the morning. However, this discrepancy between both methods was also observed in normotensive as well as nontreated hypertensive patients. Third, the modification of antihypertensive drug treatment after the initial evaluation has influenced the frequency of subsequent cardiovascular events. A point of criticism may be that the initial ambulatory blood pressure may have only limited prognostic value. However, by analyzing the event rate over time, a significant disparity between the groups remained despite the most pronounced decrease of clinic blood pressure in stage III patients. We therefore assume that initial ambulatory blood pressure remained an independent prognostic parameter. Our data are in line with the results of the MRFIT study, which also demonstrated a prognostic impact of the initially measured clinic blood pressure on cardiovascular events despite subsequent therapeutic interventions.

In conclusion, ambulatory blood pressure is significantly lower than clinic blood pressure, even in patients with moderate and severe hypertension. The disparity between both methods increased with increasing clinic blood pressure values. Nevertheless, with ABPM, different stages of hypertension according the recent guidelines of clinic blood pressure could be identified.
Perspectives
The staging of hypertension by ABPM may facilitate the use of this method in daily clinical practice, as the 24-hour ambulatory blood pressure values can now be used not only to confirm the diagnosis of hypertension but to assess the severity and prognostic value of hypertensive disease.

References
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Hypertension. 2002;40:817-822; originally published online October 28, 2002;
doi: 10.1161/01.HYP.0000038731.19106.D1
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2002 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

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