Reference Values for 24-Hour Ambulatory Blood Pressure Monitoring Based on a Prognostic Criterion

The Ohasama Study

Takayoshi Ohkubo, Yutaka Imai, Ichiro Tsuji, Kenichi Nagai, Sadayoshi Ito, Hiroshi Satoh, Shigeru Hisamichi

Abstract—Although reference values for ambulatory blood pressure (ABP) monitoring have been investigated in several population studies, these values were derived from cross-sectional observations and were based merely on the statistical distribution of blood pressure values. Therefore, we conducted a prospective cohort study to identify reference values for 24-hour ABP in relation to prognosis. We obtained measurements of 24-hour ABP for 1542 subjects (565 men) aged 40 years and over in a general population of a rural Japanese community and then followed-up their survival status. There were 117 deaths during the follow-up period (mean, 6.2 years). The association between baseline 24-hour ABP values and mortality, examined by the Cox proportional hazards regression model adjusted for possible confounding factors, showed a better fit with a second-degree equation than with a first-degree equation. On the basis of the results of this analysis, we identified the following reference values as the optimal blood pressure ranges that predict the best prognosis: 120 to 133 mm Hg for systolic blood pressure and 65 to 78 mm Hg for diastolic blood pressure. 24-Hour ABP values $>134/79$ mm Hg and $<119/64$ mm Hg were related to increased risks for cardiovascular and noncardiovascular mortality, respectively. This is the first report to propose reference values for 24-hour ABP based on a prognostic criterion. (Hypertension. 1998;32:255-259.)

Key Words: blood pressure, ambulatory $n$ reference values $n$ mortality $n$ prospective studies $n$ Japanese population

Noninvasive techniques for measuring ABP now make it possible to monitor blood pressure during activity and sleep and provide more reproducible information than casual (screening) blood pressure measurements. Target-organ damage and cardiovascular morbidity are more strongly correlated with ABP than with casual blood pressure. However, there is no consensus on the use of ABP to diagnose and manage hypertension, in part because reference values have not been established. Proposed reference values for ABPM are based on cross-sectional observations. However, because the reference value must be the value that best predicts the risk of morbidity and mortality, a longitudinal study in a general population is needed to investigate the prognostic significance of the value.

We initiated ABPM in the general population of a rural Japanese community and have been monitoring the survival of these individuals since 1987. In brief, of the 2716 residents of Ohasama aged 40 years or older, 575 were excluded because they worked outside of town. This exclusion criterion was necessary because public health nurses visited subjects to attach the ABPM devices during the workday. We also excluded hospitalized individuals (n=121) and demented or bedridden individuals (n=31). Thus, 1989 individuals were eligible for the study. Of the eligible residents, 447 declined to participate for various reasons. Thus, the study population consisted of 1542 individuals, representing 78% of the total eligible population (565 men, mean age of 62.5 years; 977 women, mean age of 61.2 years). We previously confirmed that the study population was representative of the general population. Informed consent was obtained from all subjects.

Ambulatory Blood Pressure Monitoring

Well-trained public health nurses visited participants on a weekday morning to attach the ABPM device and returned to detach it the next morning. Participants were asked to keep a diary in which they recorded their daily activities, including the time at which they went to bed and when they got up.

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Blood Pressure Monitoring Device

ABP was monitored with the ABPM-630 (Nippon Colin), a fully automatic device, preset to measure blood pressure every 30 minutes. Although SBP and DBP were measured by both the cuff-oscillometric method and the microphone method, we used only data obtained by the cuff-oscillometric method for analysis. Because the circumference of the arm was <34 cm in most cases, we used a standard arm cuff for both blood pressure measurements. The ABPM device used in the present study has been previously validated and meets the criteria of the Association for the Advancement of Medical Instrumentation.

Data Analysis

ABP data were included in the analysis if the monitoring period included >8 waking hours (daytime) and >4 hours during the time the subject was in bed (nighttime). These periods were estimated from the subjects' diaries. If the 24-hour ABP data were not complete, the 24-hour average ABP was calculated as follows: 24-hour average ABP = (daytime average × waking hours + nighttime average × sleeping hours)/24, where sleeping hours represent the time the subjects spent in bed (waking hours + sleeping hours = 24 hours). The mean ± SD duration of monitoring was 22.6 ± 2.4 hours; the mean ± SD number of measurements was 45.2 ± 4.9 (n = 1542). Artifactual readings during ABPM were defined according to previously described criteria and were omitted from the analysis. The average 24-hour values for ABP were calculated for each subject.

Residence in Ohasama as of August 30, 1997, was confirmed by the residents' registration cards. These cards in Japan are accurate and reliable because they are the basis for pensions and social security benefits. Twelve subjects (0.8%) moved away and were lost to follow-up. There were 117 deaths (7.6%) identified by the residents' registration cards. Death certificates were obtained from the Ohasama Health Department, and the cause of death was classified according to the recommendations of the World Health Organization's International Classification of Diseases, 10th Revision (ICD-10), by which deaths are attributed to the underlying cause initiating the sequence of events leading to mortality. The mean ± SD duration of follow-up was 6.2 ± 2.1 years (range, 0.01 to 9.3 years). The leading cause of death was cancer (35 deaths, 30%), followed by cerebrovascular disease (25 deaths, 21%) and heart disease (15 deaths, 13%).

The association between the baseline ABP levels and mortality was examined using the Cox proportional hazards regression model adjusted for age, gender, smoking status, use of antihypertensive medication at baseline, and history of cardiovascular disease, diabetes, and hypercholesterolemia, using the SAS PHREG procedure. The dependent variable was the number of days from the date of ABPM to the date of death or withdrawal from the study. Survivors were withdrawn on August 30, 1997.

The association between the baseline ABP level and mortality was estimated parametrically. In this analysis, the ABP level was a continuous variable in the regression model. Parametric analysis using the Cox model usually assumes a linear relation in a logarithmic scale between dependent and independent variables. In the present study, we examined the association using the following formula: \( \ln(RH) = \beta_1(BP) + \alpha \), where \( \beta \) was the regression coefficient of each variable and \( \alpha \) was the intercept calculated according to the confounding factors used to adjust the association between ABP level and mortality. However, our previous nonparametric analysis indicated that there was a possibility of a nonlinear association between ABP and mortality and that this association would show a better fit to an equation of the second degree rather than of the first degree. Thus, we also analyzed the data using the following formula:

\[
\ln(RH) = \beta_1(BP) + \beta_2(BP)^2 + \alpha
\]

We performed parametric analysis of both the first-degree and second-degree models. The appropriateness of the addition of \( BP^2 \) as an independent variable was examined by comparing the log likelihood ratios of the models. The difference between the log likelihood ratios is testing the significance in contribution of \( BP^2 \) to the model. This value follows a \( \chi^2 \) distribution with 1 df.

The information on smoking status, use of antihypertensive medication at baseline, and history of cardiovascular disease, diabetes, and hypercholesterolemia was obtained both from questionnaires sent to each household at the time of ABP measurements and from medical records at Ohasama Hospital, the only hospital in the town, where >90% of the subjects go for regular checkups. Of the 1542 study subjects, 334 (22%) were classified as current or ever-smokers, and 473 (31%) were receiving antihypertensive medication. History of cardiovascular disease, diabetes, or hypercholesterolemia was identified in 69 subjects (5%), 265 subjects (17%), and 248 subjects (16%), respectively.

The estimated RH and 95% CI of variables were derived from the coefficient and its standard error, as determined by the Cox proportional hazards model. Data are mean ± SD. A value of \( P<0.05 \) was accepted as indicating statistical significance.

Results

The mean 24-hour SBP was 123.3 ± 13.0 mm Hg (range, 91 to 181) and the mean 24-hour DBP was 72.0 ± 7.7 mm Hg (range, 49 to 105).

There was a nonlinear association between crude mortality rate and 24-hour blood pressure values (Figure 1).

The 24-hour SBP was not significantly related to overall mortality based on the results of analysis using the first-degree equation (Table 1). When data were fitted to the second-degree equation, both SBP and SBP² were significantly related to overall mortality. The difference in the log likelihood ratio between the first-degree and the second-degree models was 14.6 \( (P<0.001) \), indicating that the
TABLE 1. Relation Between Overall Mortality and 24-Hour SBP Determined by Cox Proportional Hazards Model Adjusted for Age, Gender, Use of Antihypertensive Medication, Smoking Status, and History of Cardiovascular Disease, Diabetes, and Hypercholesterolemia

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient</th>
<th>SE</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-degree model</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>24-Hour SBP</td>
<td>0.00742</td>
<td>0.00735</td>
<td>0.313</td>
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<tr>
<td>−2 log likelihood = 175.784 (P &lt; 0.001)</td>
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<tr>
<td>Second-degree model</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24-Hour SBP</td>
<td>−0.30165</td>
<td>0.07037</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>24-Hour SBP²</td>
<td>0.00118</td>
<td>0.00026</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>−2 log likelihood = 190.384 (P &lt; 0.001)</td>
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The inclusion of SBP² significantly improved the fit. For the relationship between 24-hour DBP and overall mortality, the addition of DBP² also significantly improved the fit: the difference in the log likelihood ratio between the first-degree and the second-degree models was 6.6 (P < 0.02) (Table 2).

On the basis of these findings, we illustrated the association between ABP values and the RHs as the second-degree equation curves (Figure 2). RH was determined relative to the RH of the preceding 1 mm Hg of blood pressure and was calculated according to the following formula: \( \ln(RH) = (\beta \text{ of } BP) \times [BP - (BP - 1)] + (\beta \text{ of } BP²) \times [BP² - (BP - 1)²] \). The 95% CI was calculated according to the following formula: \( \ln(95\% \text{ CI}) = \ln(RH) \pm 1.96 \times SE \text{ of } \ln(RH) \). The standard error of \( \ln(RH) \) was calculated from the standard errors of BP and BP² and from the covariance between BP and BP². The standard errors of BP and BP² and the covariance between BP and BP² was determined by the Cox proportional hazards model adjusted for age, gender, smoking status, use of antihypertensive medication at baseline, and history of cardiovascular disease, diabetes, and hypercholesterolemia. The standard errors of BP and BP² are shown in Table 1 for 24-hour SBP and in Table 2 for 24-hour DBP. The covariance between 24-hour SBP and 24-hour SBP² was \( -1.85 \times 10^{-5} \), and the covariance between 24-hour DBP and 24-hour DBP² was \( -1.09 \times 10^{-4} \).

An RH < 1.0 indicates that the mortality risk decreases as blood pressure increases; an RH > 1.0 indicates that the risk increases as blood pressure increases. Thus, the lowest mortality risk was associated with an RH of 1.0, which corresponded to SBP of 128 mm Hg and DBP of 74 mm Hg. We defined the ranges for optimal blood pressures as the values between the upper and lower 95% CIs for an RH of 1.0, corresponding to 120 to 133 mm Hg for SBP and 65 to 78 mm Hg for DBP (Figure 2). Hypertension was defined as 24-hour blood pressure > 134 mm Hg for SBP and > 79 mm Hg for DBP; low blood pressure was defined as SBP < 119 mm Hg and DBP < 64 mm Hg. SBP of 134 mm Hg and DBP of 79 mm Hg corresponded to the 82nd and 80th percentiles of the study population, respectively.

When we examined the relation between these blood pressure categories and mortality with the Cox proportional hazards model for 24-hour SBP and DBP using the normotensive group as the reference category, we found that the mortality risk increased significantly for 24-hour SBP in the hypertensive group (RH = 1.95, P = 0.0056) and the low blood pressure group (RH = 1.80, P = 0.0139) (Table 3). The RH for mortality increased significantly for 24-hour DBP in the hypertensive group (RH = 1.59, P = 0.0454) but did not significantly increase for 24-hour DBP in the low blood pressure group (RH = 1.48, P = 0.1264).

The excess mortality risk in the hypertensive group was largely attributable to cardiovascular mortality (SBP: RH = 1.96, P = 0.0441; DBP: RH = 2.22, P = 0.0235; compared with the low blood pressure and normotensive groups) (Table 4), and the excess mortality risk in subjects with low blood pressure was largely attributable to noncardiovascular mortality (SBP: RH = 1.55, P = 0.0636; DBP: RH = 1.50, P = 0.1728; compared with the normotensive and hypertensive groups).

TABLE 2. Relation Between Overall Mortality and 24-Hour DBP Determined by Cox Proportional Hazards Model Adjusted for Age, Gender, Use of Antihypertensive Medication, Smoking Status, and History of Cardiovascular Disease, Diabetes, and Hypercholesterolemia

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient</th>
<th>SE</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-degree model</td>
<td></td>
<td></td>
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<tr>
<td>24-Hour DBP</td>
<td>0.00405</td>
<td>0.01289</td>
<td>0.754</td>
</tr>
<tr>
<td>−2 log likelihood = 174.872 (P &lt; 0.001)</td>
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<tr>
<td>Second-degree model</td>
<td></td>
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<tr>
<td>24-Hour DBP</td>
<td>−0.36265</td>
<td>0.12841</td>
<td>0.005</td>
</tr>
<tr>
<td>24-Hour DBP²</td>
<td>0.00246</td>
<td>0.00085</td>
<td>0.004</td>
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<tr>
<td>−2 log likelihood = 181.503 (P &lt; 0.001)</td>
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</table>

Figure 2. RH (solid line) and 95% CIs (broken lines) of 24-hour SBP (a) and DBP (b) values for overall mortality, approximated as the curves fitted to the second-degree equation determined by the Cox proportional hazards model adjusted for age, gender, smoking status, use of antihypertensive medication at baseline, and history of cardiovascular disease, diabetes, and hypercholesterolemia.
TABLE 3. RH and 95% CI of Reference Values for 24-Hour ABP for Overall Mortality Adjusted for Age, Gender, Use of Antihypertensive Medication, Smoking Status, and History of Cardiovascular Disease, Diabetes, and Hypercholesterolemia

<table>
<thead>
<tr>
<th>Variable</th>
<th>RH (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP, mm Hg</td>
<td></td>
</tr>
<tr>
<td>≤119 (low blood pressure)</td>
<td>1.80 (1.13–2.87)</td>
</tr>
<tr>
<td>120–133 (normotension)</td>
<td>1.0</td>
</tr>
<tr>
<td>≥134 (hypertension)</td>
<td>1.95 (1.22–3.12)</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td></td>
</tr>
<tr>
<td>≤64 (low blood pressure)</td>
<td>1.48 (0.90–2.43)</td>
</tr>
<tr>
<td>65–78 (normotension)</td>
<td>1.0</td>
</tr>
<tr>
<td>≥79 (hypertension)</td>
<td>1.59 (1.01–2.51)</td>
</tr>
</tbody>
</table>

Discussion

The present study was based on a longitudinal observation of a representative sample of the general population in a rural Japanese community. The association between ABP values and overall mortality fit better to a second-degree equation than to a first-degree equation. On the basis of the results of this analysis, we identified the following reference values as the optimal blood pressure ranges that predict the best prognosis: 120 to 133 mm Hg for SBP and 65 to 78 mm Hg for DBP. ABP values >134/79 mm Hg and <119/64 mm Hg were related to an increased risk for cardiovascular and noncardiovascular mortality, respectively.

Several studies have examined the association between ABP levels and morbidity and mortality among hypertensive subjects.10–12 Perloff et al10 reported that patients whose average daytime ABP exceeded their casual blood pressure had an increased risk of serious cardiovascular complications. Verdecchia et al12 reported that the cardiovascular morbidity rate was significantly higher in subjects with ambulatory hypertension than in the subjects with white coat hypertension. These studies indicated that ABP was a stronger predictor of morbidity than casual blood pressure, but reference values for ABP could not be identified because these study populations included only hypertensive subjects and did not include normotensive subjects. In the present study, we proposed reference values for ABP based on a longitudinal observation of a general population that included both normotensive and hypertensive subjects.

Reference values for ABP have been proposed in a number of studies based on cross-sectional analysis of subjects with normal casual blood pressures.18–22 In these studies, the upper limit of ABP was determined according to the statistical distribution of ABPs such as the mean + SD, the mean + 2SD, and the 95th percentile. Using data from an international database, Staessen et al19 reported that the 95th percentile of 24-hour ABP in clinically normotensive subjects was 134/82 mm Hg. The mean + 2SD of 24-hour ABP in normotensive subjects was 134/84 mm Hg in the Allied Irish Bank study.20 130/81 mm Hg in the PAMELA study.21 and 131/81 mm Hg in a Belgian population study.22 In our previous cross-sectional analysis of the first cohort of Ohasama,18 the 95th percentile of 24-hour ABP in clinically normotensive subjects was 134/79 mm Hg.

Several national organizations have also recommended an upper limit of 24-hour ABP: the American Society of Hypertension recommends 130 to 135/80 to 85 mm Hg14 and the German Hypertension League recommends 130/80 mm Hg.15

However, there is no evidence that these recommended and statistically derived values predict mortality or morbidity. Reference values are important factors in deciding on the diagnosis and treatment of hypertension and thus should be related to prognosis. In the present study, we identified the reference values for ABP in relation to prognosis and confirmed that the proposed reference values predicted the mortality risk in the general population well.

The reference values for hypertension in the present study (134/79 mm Hg) are consistent with the values derived from our previous cross-sectional study18 and with the mean + SD of 24-hour ABP for the present subjects (136/80 mm Hg). The reference values in the present study are also similar to those proposed in cross-sectional studies and recommended by national organizations. It is of interest that our mortality-based values coincided remarkably with these recommended and statistically derived values, although these values were calculated independently.

Because the present reference values were derived from a population-based study in a rural Japanese community, applicability of the findings to the whole Japanese population should be discussed. The average casual blood pressure values in this population (131.1/74.3 mm Hg for males and 129.1/72.7 mm Hg for females)19 were consistent with the national average (132.4/79.8 mm Hg for males and 127.2/76.0 mm Hg for females),22 which was derived from the national survey of all Japan.32 Although the national average of ABP values is not available, the consistency of casual blood pressure values between the present population and the whole Japanese population suggests that the present reference values could be extrapolated to the majority of Japanese persons.

Although ABPM is the focus of clinical interest, its usefulness has yet to be established, in part because the prognostic value of ABPM has not been fully evaluated and because there are no established reference values. The reference value should accurately predict the risks of mortality and morbidity. In the present study, we identified the following reference values as the optimal blood pressure ranges that predict the best prognosis: 120 to 133 mm Hg for SBP and 65 to 78 mm Hg for DBP. A 24-hour ABP value >134/79 mm Hg was the best predic-
tor of cardiovascular mortality. Additional population-based prospective studies in other countries and studies using different prognostic parameters are needed to confirm the reference values proposed in the present study. Several population-based studies in western countries may provide useful prognostic information in future.

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