Predicting Stroke Using 4 Ambulatory Blood Pressure Monitoring–Derived Blood Pressure Indices

The Ohasama Study

Ryusuke Inoue, Takayoshi Ohkubo, Masahiro Kikuya, Hirohito Metoki, Kei Asayama, Taku Obara, Haruhisa Hoshi, Junichiro Hashimoto, Kazuhiro Totsune, Hiroshi Satoh, Yoshiaki Kondo, Yutaka Imai

Abstract—We investigated the association between stroke and blood pressure (BP) indices (systolic BP [SBP], diastolic BP [DBP], mean BP [MBP], and pulse pressure [PP]) determined by ambulatory BP monitoring. The predictive power for stroke of these indices was compared in the general Japanese population. We obtained ambulatory BP data in 1271 subjects (40% men) aged ≥40 (mean: 61) years. During a mean follow-up of 11 years, 113 strokes were observed. The multivariate adjusted relative hazard and likelihood ratio for a 1-SD increase for each BP index was determined by Cox proportional hazard regression. Comparison of the likelihood ratio between Cox models including 2 indices and those including 1 index indicated that PP was significantly less informative than other indices (P<0.01 when adding MBP, SBP, or DBP to the PP model; P>0.09 when adding PP to the model including another index). However, after removing age from covariates, PP became more informative than DBP and MBP (P<0.0001 when adding PP to the MBP or DBP model, whereas SBP was more informative than PP even after removing age; P<0.05 when adding SBP to the PP model).

In conclusion, PP was the weakest predictor of stroke. Exclusion of age from covariates increased the predictive power of PP, suggesting that the stroke risk associated with PP reflected the risk of aging per se. (Hypertension. 2006;48:877-882.)

Key Words: ambulatory blood pressure monitoring ■ pulse pressure ■ systolic blood pressure ■ diastolic blood pressure ■ mean blood/arterial pressure ■ stroke

It is widely accepted that hypertension is a major risk factor for cardiovascular diseases. Recently, it has been recognized that the management of systolic blood pressure ([BP] SBP) is more important than the management of other BP indices.1–4 In addition, many studies have reported that an increase in pulse pressure (PP) is associated with cardiovascular disease risk, particularly in the elderly.5–9 These findings, however, were based on data collected in Western populations and primarily reflected only coronary heart diseases or a combination of coronary heart diseases and cerebrovascular diseases.

Some studies1,2,7–11 have examined the risk of coronary heart diseases and cerebrovascular diseases separately; most of them showed that mean BP (MBP) was a stronger predictor for stroke than PP.1,2,9–11 However, these findings were also based on data collected in Western populations. Examining a Japanese population, Miura et al12 reported that MBP was the strongest predictor of stroke; PP was not a stronger predictor than other indices. However, that study was based on data obtained by casual-screening BP (CBP), which is biased and therefore unreliable.13–15 No studies have investigated the association between stroke and PP in an Asian population using data obtained from 24-hour ambulatory BP monitoring ([ABP] ABPM), which has been shown to be superior to CBP for predicting cardiovascular events.16–21

The present study compared the relationship of 4 BP indices (SBP, diastolic BP [DBP], PP, and MBP) derived from ABP and CBP data to stroke risk in a Japanese population.

Methods

Design

The background rationale, study population, and BP measurement used in the Ohasama Study have been presented in detail previously.16–18,22 The study protocol was approved by the Tohoku University School of Medicine Institutional Review Board and by the Department of Health of the Ohasama Town Government.

Study Population

The details of the strategy used to select the study population have been described previously.16,17 In brief, a total of 1552 subjects over the age of 40 years living in Ohasama gave their informed consent...
and participated in the study. Ten subjects were excluded from the present analysis, because their ambulatory BP recording included <8 hours during the waking period or 4 hours during the sleeping period. Of the 1542 remaining subjects, 78 had a previous history of stroke or transient ischemic attack (TIA); these subjects were, therefore, excluded from the present study of stroke or TIA and BP. Another 193 subjects were also excluded because of lack of CBP data. Data from the remaining 1271 subjects were analyzed. The representativeness of the study subjects has been fully reported in previous articles.\textsuperscript{16,17}

\section*{ABPM}

Well-trained public health nurses visited each participant on a weekday morning to attach the ABPM device and revisit the participants to detach the device 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 arose. ABP data were included in the analysis when the monitoring period included >8 waking hours (daytime) and >4 hours in bed (nighttime). These periods were estimated from the subjects’ diaries. The mean±SD duration of monitoring was 22.6±2.4 hours; the mean±SD number of measurements was 45.2±4.9.\textsuperscript{22} Artifactual readings during ABPM were defined according to previously described criteria\textsuperscript{23} and were omitted from the analysis: SBP <60 mm Hg and MBP <40 mm Hg; MBP >200 mm Hg and/or SBP >250 mm Hg, with no similar preceding or subsequent respective value; PP of ≤10 mm Hg; and abrupt increase or decrease in PP, SBP, MBP, and/or heart rate by ≥50% from the value immediately before or after respective readings. None of the subjects were excluded because of these criteria, although 2.8 readings on average were excluded for each subject. The averages of the 24-hour, daytime, and nighttime BP values were calculated for each subject. The PP was calculated as SBP−DBP, and the MBP was calculated as DBP+PP/3.

\section*{CBP Measurements}

Annual health checkups, including ABP measurement and hemato-logic examination, are available to all Japanese citizens aged ≥40 years. During these checkups, BP is measured twice consecutively in the sitting position after a rest of ≥2 minutes by nurses or technicians using a semiautomated device. The average of the 2 readings, defined as the CBP, was used in this analysis.

\section*{BP Monitoring Devices}

ABP was monitored using the ABPM-630 (Nippon Colin), a fully automatic device that was preset to measure BP every 30 minutes.\textsuperscript{23} Although SBP and DBP were measured by both the cuff-oscillometric method and the microphone method, we only used data obtained by the cuff-oscillometric method in the analysis. CBP was measured with the USM-700F (UEDA Electronic Works Co Ltd), an automatic device based on the microphone method. Because arm circumference was <34 cm in almost all of the subjects, we used a standard arm cuff for both ambulatory and CBP measurements. Both the ABPM device and the CBP measurement device used in the present study have been validated previously\textsuperscript{22,23} and meet the criteria of the Association for the Advancement of Medical Instrumentation.\textsuperscript{24} The accuracy of the ABPM-630 was assessed against the auscultatory method in 100 patients. Simultaneous measurements with the device and auscultatory method were made, and 5 separate ABPM-630s were used randomly. For each patient, 2 to 4 measurements were made, and 297 simultaneous readings were taken. Mean differences between readings taken with the auscultatory method and those obtained by the ABPM-630 were −0.28±6.15 mm Hg for SBP and 0.96±2.62 mm Hg for DBP.\textsuperscript{22,24} Mean differences between readings taken with the auscultatory method and those taken with the USM-700F were 0.8±5.2 mm Hg for SBP and −0.5±7.3 mm Hg for DBP (321 readings).\textsuperscript{22} The accuracy of the device used to measure CBP was validated annually by the Ohasama Department of Health.

\section*{Follow-Up and Outcome}

Residence in Ohasama (as of December 31, 2001) was confirmed by the residents’ registration cards. In Japan, these cards are considered accurate and reliable, because they are used for pensions and social security benefits. The incidence of stroke and TIA until December 31, 2001, was determined by reviewing the Stroke Registration System of Iwate Prefecture, death certificates, National Health Insurance receipts, and questionnaires sent to each household at the time of ABPM. This information was then confirmed by checking the medical charts of Ohasama Hospital, which is the only hospital in the town and where >90% of the subjects have their regular checkups. Almost all of the stroke cases were admitted to Ohasama Hospital, where the diagnosis was confirmed by computed tomography and/or MRI of the brain. The diagnostic criteria of stroke subtypes were based on the Classification of Cerebrovascular Disease III of the National Institute of Neurological Disorders and Stroke.\textsuperscript{26} We defined “cerebral infarction” as ischemic stroke and defined “intracerebral hemorrhage” and “subarachnoid hemorrhage” as hemorrhagic stroke.

\section*{Data Collection}

Information on smoking status, the use of antihypertensive medication at baseline, and past history of heart disease, diabetes mellitus, and hypercholesterolemia were obtained from questionnaires sent to each household at the time of the ABPM measurements and from the medical charts of the Ohasama Hospital, which included the results of laboratory investigations performed at the time of the annual health checkups. Subjects using lipid-lowering drugs or those with serum cholesterol levels of ≥5.68 mmol/L were considered to have hypercholesterolemia. Subjects with a fasting glucose level of ≥7.0 mmol/L or nonfasting glucose level of ≥11.1 mmol/L or those using insulin or oral antihyperglycemic drugs were defined as having diabetes mellitus. A past history of heart disease included a history of myocardial infarction, angina pectoris, atrial fibrillation, or cardiac failure.

\section*{Statistical Analysis}

Primary analyses assessed the relation of individual BP indices to stroke. The association between baseline BP levels and the incidence of the first stroke or TIA was examined using Cox proportional hazard regression,\textsuperscript{27} adjusted for age, sex, smoking status, the use of antihypertensive medication, and history of heart disease, diabetes mellitus, or hypercholesterolemia. The dependent variable in these analyses was the number of days from the date of the ABPM to the date of stroke/TIA or censoring. Stroke/TIA-free survivors were censored as of December 31, 2001. When examining the incidence of stroke/TIA, we treated death from causes other than fatal stroke events as censoring. The analysis included only the first event in those subjects who had multiple nonfatal events.

To compare the association of different BP indices with stroke, relative hazard (RH) and 95% CI were estimated for a 1-SD difference in each index. This is a “standardized” comparison of RH and is necessary because each BP index is measured on a different scale. The likelihood ratio (LR) \(\chi^2\) value was used as a measure of the improvement of goodness of fit,\textsuperscript{28} or “informativeness” between a model containing each BP index (and the confounders) compared with a model that only contained the confounders but no BP index (the “base model”).

Secondary analyses consisted of including 2 BP indices in the Cox model to assess the relation simultaneously with adjustment for each other. The LR \(\chi^2\) test between the model containing a single BP index and the model containing >1 index was used to assess whether the additional index significantly improved the adequacy of the model. A significant LR \(\chi^2\) indicates that regression coefficient of the additional index is significant compared with 0;\textsuperscript{29} that is, the index provides significantly more information.

\section*{Results}

\subsection*{Characteristics of Subjects}

The overall mean age of the subjects was 61 years, and the male:female ratio was 40:60. At baseline, of the 1271 study...
subjects, 245 (19%) were classified as current or ex-smokers, 350 (28%) were treated with antihypertensive medication, 14 (1.1%) were classified as having a history of heart disease, 220 (17%) had a history of diabetes mellitus, and 202 (16%) had a history of hypercholesterolemia.

**Follow-Up and Outcome**
The mean duration of follow-up was 11.1±2.7 years. Of the 1271 subjects, 192 died, and 25 moved out of the region during the follow-up period. A first stroke or TIA occurred in 127 subjects, 192 died, and 25 moved out of the region.

**Profiles of BP Indices**
All of the ABP and CBP indices during follow-up were significantly higher in the subjects who developed stroke than in those who did not (Table 1; *P*<0.001). There were no differences between the BP values of ischemic stroke patients and hemorrhagic stroke patients; however, hemorrhagic stroke subjects had a trend toward having higher daytime BP indices than ischemic stroke subjects.

**Predictive Powers of BP Indices**
Adjusted RHs are shown in the Figure. LR *χ*² values compared with the base model are also shown in the Figure. With the exception of casual PP (*P*=0.16), all of the indices produced positive and significant changes for predicting the risk of total stroke when compared with the base model (all *P*<0.05).

In all of the analyses, the predictive power of CBP was lower than that of ABP for all of the BP indices. These associations were similar for the risks of various stroke subtypes (data not shown).

**Comparison of Predictive Power of PP With Those of SBP, DBP, and MBP**
In further analyses, 24-hour MBP and PP were simultaneously included in the Cox model to assess whether there was additional information provided for stroke compared with a model including either MBP or PP alone. There was no change in the LR *χ*² statistic for the MBP and PP model compared with the MBP-alone model (“adding PP to a model with MBP”; *P*=0.58). In contrast, comparison of the combined MBP and PP model to the PP-alone model (“adding MBP to a model with PP”) produced significant changes in the LR *χ*² statistic (*P*<0.01; Table 2, model a). These indicate that PP provided no significant incremental contribution over and above the information provided by MBP alone and indicate a significant contribution of MBP over and above that for PP.

Similarly, when 24-hour SBP and PP were simultaneously included in the same Cox model, PP had no additional

| TABLE 1. Baseline BP Values and Age for All Subjects, for Those Who Developed Stroke, and for Those Who Did Not Develop Stroke |
| --- | --- | --- | --- |
| Variables | Overall | Did Not Develop | Developed |
| | | | Type of Stroke |
| | | Ischemic | Hemorrhagic |
| N | 1271 | 1158 | 113 | 74 | 34 |
| Age | 61.4±9.8 | 60.8±9.7 | 67.7±9.1* | 67.5±8.6 | 67.2±9.1 |
| 24-h SBP | 123.1±13.1 | 122.2±12.7 | 131.7±13.4* | 130.7±12.5 | 133.9±14.6 |
| DBP | 72.0±7.8 | 71.6±7.7 | 76.0±7.7* | 75.6±7.5 | 77.1±8.3 |
| MBP | 89.0±9.2 | 88.5±9.1 | 94.6±9.2* | 94.0±8.7 | 96.1±10.0 |
| PP | 51.1±7.2 | 50.6±7.0 | 55.8±8.2* | 55.1±7.4 | 56.8±8.9 |
| Daytime SBP | 128.7±13.9 | 127.8±13.5 | 137.4±14.6* | 135.6±13.2 | 140.8±16.5 |
| | 76.1±8.4 | 75.6±8.3 | 80.3±8.6* | 79.5±8.2 | 82.1±9.5 |
| | 93.6±10.0 | 93.0±9.8 | 99.3±10.2* | 98.2±9.6 | 101.7±11.4 |
| | 52.6±7.5 | 52.2±7.3 | 57.2±8.5* | 56.1±7.3 | 58.8±9.5 |
| Nighttime SBP | 112.0±14.4 | 111.1±14.0 | 121.1±15.4* | 121.2±15.5 | 121.4±15.5 |
| | 63.9±8.1 | 63.5±8.0 | 67.9±8.4* | 68.2±8.2 | 68.1±8.8 |
| | 80.0±9.9 | 78.4±9.7 | 85.6±10.3* | 85.8±10.2 | 85.9±10.6 |
| | 48.1±8.1 | 47.6±7.8 | 53.2±9.5* | 53.0±9.5 | 53.3±9.3 |
| CBP SBP | 130.9±18.5 | 130.0±18.2 | 139.6±19.6* | 139.7±18.7 | 138.4±22.2 |
| | 74.0±11.2 | 73.6±11.2 | 77.3±11.1* | 77.5±10.6 | 76.7±12.3 |
| | 92.9±12.4 | 92.4±12.2 | 98.1±12.6* | 98.2±12.0 | 97.3±14.0 |
| | 57.0±14.2 | 56.5±14.0 | 62.3±15.3* | 62.2±14.4 | 61.7±17.7 |

Data are presented as mean±SD. Hemorrhagic stroke included intracerebral hemorrhage and subarachnoid hemorrhage.

*P*<0.001.
information for predicting stroke, and SBP was more informative ($P=0.02$ when PP was added to the SBP-alone model and $P<0.01$ when PP was added to the DBP-alone model; Table 2, model a). This indicates a significant contribution of SBP over and above that for PP. The same relation was observed Between 24-hour DBP and PP ($P=0.10$ when PP was added to the DBP-alone model and $P<0.01$ when DBP was added to the PP-alone model; Table 2, model a). SBP, DBP, or MBP produced no significant change when added to the model including another index (data not shown).

**Comparison of Predictive Powers of BP Indices Removing Age From Confounding Factors in the Cox Model**

It is well known that SBP tends to increase and that DBP tends to decrease with aging, resulting in a tendency toward an elevated PP with increased age. Because aging is also one of the strongest risk factors for stroke, we removed age as a confounding factor in the Cox model and compared predictive power of PP with those of other 3 indices (Table 2, model b).

When 24-hour MBP and PP were simultaneously included in the same multivariate Cox model, the MBP and PP model compared with the MBP-alone model produced significant changes in the LR $\chi^2$ statistic ($P<0.0001$). Comparison of the combined MBP and PP model to the PP-alone model also produced significant changes in the LR $\chi^2$ statistic ($P<0.05$). Both indices were informative; however, magnitude of changes in the LR $\chi^2$ statistic of PP was greater than MBP. The same relation was observed Between 24-hour DBP and PP ($P<0.0001$ when PP was added to the DBP-alone model and $P<0.05$ when DBP was added to the PP-alone model).

However, when 24-hour SBP and PP were simultaneously included in the same Cox model, PP had no additional information, and SBP was more informative ($P=0.06$ when PP was added to the SBP-alone model and $P<0.05$ when SBP was added to the PP-alone model). These indicate that PP provided no significant incremental contribution over and above the information provided by SBP alone and indicate a significant contribution of SBP over and above that for PP, even after removing age from covariates.

**Discussion**

The present study was based on longitudinal observation of a representative sample of the general population living in a rural Japanese community. The main findings from this study are: (1) of the BP measurements, SBP and MBP were the strongest predictors of stroke risk; (2) DBP was also a strong predictor for stroke risk; and (3) PP was weaker predictor for stroke incidence than the other 3 BP indices.

**Predictive Power of PP for Stroke**

Using CBP data, recent large-scale cohort studies have reported that PP is less useful in predicting long-term stroke risk than SBP and MBP. In the present study, we used both ABP and CBP data, because ABP has been shown to be

**TABLE 2. Increases in Goodness-of-Fit Adding 24-Hour BP Indices to the Cox Model**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Model a</th>
<th>Model b</th>
</tr>
</thead>
<tbody>
<tr>
<td>LR $\chi^2$</td>
<td>$P$</td>
<td>LR $\chi^2$</td>
</tr>
<tr>
<td>Adding MBP to a model with PP</td>
<td>10.5</td>
<td>$&lt;0.01$</td>
</tr>
<tr>
<td>Adding PP to a model with MBP</td>
<td>0.3</td>
<td>0.58</td>
</tr>
<tr>
<td>Adding SBP to a model with PP</td>
<td>10.5</td>
<td>$&lt;0.01$</td>
</tr>
<tr>
<td>Adding PP to a model with SBP</td>
<td>0.6</td>
<td>0.42</td>
</tr>
<tr>
<td>Adding DBP to a model with PP</td>
<td>10.5</td>
<td>$&lt;0.01$</td>
</tr>
<tr>
<td>Adding PP to a model with DBP</td>
<td>2.7</td>
<td>0.10</td>
</tr>
</tbody>
</table>

This table shows increases in goodness-of-fit from adding 1 BP index to a model including another index (and confounding variables) and vice versa. The greater LR $\chi^2$, the greater the increase in goodness-of-fit or “informativeness” with the additional BP index. The $P$ value tests the statistical significance of change. Model a: model adjusted for all confounding variables (age, sex, smoking status, use of antihypertensive medication, and history of heart disease, diabetes mellitus, or hypercholesterolemia). Model b: model adjusted for confounding variables without age.
superior to CBP in predicting cardiovascular diseases. We also observed that PP obtained from ABP was a relatively weak predictor for stroke, whereas SBP and MBP derived from ABP were strong predictors. The Cox model containing PP and MBP, SBP, or DBP showed that PP is less informative than the other 3 indices.

Increasing the Predictive Power of the PP by Excluding Age

After removing age from the Cox model, 24-hour PP became more informative than for the 24-hour DBP and MBP. The tendency for the SBP to increase and the DBP to decrease with age has been demonstrated. Thus, PP consists of 2 components that are both influenced by aging, resulting in an increase of PP with advancing age. MBP also tends to increase with age, but this increase is gradual compared with the increase in PP, because of the age-dependent decrease in DBP. It is, therefore, possible that PP may be more influenced by aging than the other BP indices. Exclusion of age from the multivariate Cox model produced a greater increase in the predictive power of PP for stroke risk; this suggests that the risk associated with an increased PP is a reflection of the risk associated with age per se. In addition, we also demonstrated the importance of age by presenting both the results adjusted for age and those not adjusted for age.

Predictive Power of SBP

SBP was more informative than PP even after excluding age from confounding factors. DBP was also strong when adjusted for confounding factors including age but became weaker when age was removed from covariates. It, therefore, seems that, of the 4 BP indices, SBP is affected least by age. It is widely recognized that SBP control is the most important factor for preventing cardiovascular diseases. Thus, SBP, rather than the other BP indices, may be the most useful index to follow in daily medical practice.

Comparison of ABP and CBP

Our study also compared the predictive powers for stroke of BP indices based on ABP and those based on CBP. It is widely recognized that ABP has a much stronger predictive power for stroke risk than CBP. In the present study, predictive powers of CBP-derived BP indices were typically lower than those of ABP-derived BP indices. These results show that even PP based on ABP measurement, which was the weakest predictor of the ABP-derived BP indices, is superior to any CBP-derived BP indices in predicting stroke.

Perspectives

In the Japanese population, ABP-derived SBP has a very strong predictive power for stroke, whereas ABP-derived PP is a relatively weak predictor of stroke. Because exclusion of age as a confounding factor from the Cox model increased the predictive power of PP, the stroke risk associated with PP seems to reflect the risk of age per se. The predictive power of ABP- and CBP-derived BP indices for the other cardiovascular diseases, particularly coronary heart disease, should be investigated in future population-based studies.


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Hypertension. 2006;48:877-882; originally published online September 18, 2006; doi: 10.1161/01.HYP.0000242285.83728.ee

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2006 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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