Adverse Effect of Nighttime Blood Pressure on the Outcome of Lacunar Infarct Patients

Yasumasa Yamamoto, MD; Ichiro Akiguchi, MD; Kaiyo Oiwa, MD; Masamichi Hayashi, MD; Jun Kimura, MD

Background and Purpose—Antihypertensive therapy has dramatically reduced the incidence of stroke recurrence; however, recent studies have suggested that the excessive lowering of blood pressure (BP) could cause ischemic cerebral lesions. We conducted a prospective study using MRI and ambulatory blood pressure monitoring to elucidate the appropriate BP control level for the prevention of silent and symptomatic cerebral infarction.

Methods—We studied 105 patients with symptomatic lacunar infarcts who underwent repeated MRI and 24-hour BP monitoring in the period between the two MRI examinations. The patients were divided into five groups according to their outcome as follows: group 1, those who showed neither symptomatic episodes nor the development of new silent lesions detected by repeated MRI; group 2, those who only showed the development of silent lacunae; group 3, those who showed development of diffuse white matter lesions only; group 4, those who showed the development of both silent lacunae and diffuse white matter lesions; and group 5, those who showed symptomatic cerebrovascular disease. Groups 2 through 5 were then compared with group 1 with respect to the ambulatory BP values.

Results—The average follow-up period was 3.2±2.6 years (mean±SD). In all patients in group 4 and group 5, nighttime systolic BPs were significantly higher than in group 1 (both P<.01), and the magnitude of the nocturnal systolic BP dip and diastolic BP dip in group 4 and group 5 were significantly smaller than in group 1 (all P<.01). In patients who took antihypertensive agents, the 24-hour systolic and diastolic BPs and nighttime systolic and diastolic BPs in group 4 were significantly higher than in group 1 (P<.01, P<.01, P<.001, P<.01, respectively). The magnitude of the nocturnal systolic and diastolic BP dip in group 5 was significantly smaller than in group 1 (both P<.01).

Conclusions—A high average ambulatory BP, especially nighttime BP, and a reduced nocturnal BP dip may have an adverse effect on the development of silent ischemic lesions and symptomatic stroke attack in patients with lacunar infarcts. (Stroke. 1998;29:570-576.)

Key Words: Binswanger’s disease ■ blood pressure, nocturnal ■ lacunar infarction ■ white matter

The issue of the control of blood pressure levels in stroke prevention remains unresolved. Uncontrolled hypertension has been shown to produce arteriosclerosis in small vessels and atherosclerosis in medium-sized vessels in the brains of experimental animals with hypertension.1,2 Antihypertensive medications can prevent these pathological changes in medium-sized vessels.3 Antihypertensive therapy reduces cerebrovascular and cardiovascular morbidity and mortality in humans with chronic hypertension.4-6 Nevertheless, several studies have suggested that an excessive lowering of BP can cause ischemic stroke7-11 and a decline in cognitive function.12 These studies also suggest that decreased BP might reduce cerebral blood flow, especially in chronic stroke patients in whom an upward shift of the autoregulatory range was recognized after the acute period had passed,13 even though it is widely thought that a high sustained BP may accelerate pathological changes in the cerebral vessels of the brain.14-16 Irie and his colleagues17 reported that the J-curve phenomenon, in which there is a point beyond which BP reduction in hypertensive subjects is no longer beneficial and possibly even deleterious, which has been recognized in cardiac events,18 was also found in ischemic stroke recurrences.

The studies mentioned above were conducted with casual BP values. Since the introduction of ABPM devices, many reports have demonstrated that hypertensive target organ damage can be more accurately demonstrated by the 24-hour monitored BP than by the casual BP.19-21 Most authors have reported that nondippers, patients with an absent or decreased nocturnal dip in their BP, tended to have more severe target organ damage, including cerebrovascular disease,22-24,25 than dippers with a normal nocturnal dip in BP. Verdecchia et al26 conducted a prospective study and reported that cardiovascular morbidity was higher in nondippers than in dippers among women. Conversely, recent reports have suggested that excessive falls in the nighttime BP27,28 or a lowering of nighttime BP by antihypertensive agents29 could produce cerebral ischemic....
lesions. Therefore, the issue as to what degree the nighttime BP should be controlled also remains unresolved.

Since 1990, we have been pursuing a prospective study to clarify the appropriate BP for the prevention of silent and symptomatic infarctions and to test whether the J-curve phenomenon exists for the daytime BP or nighttime BP.

Because both lacunar infarcts and diffuse white matter lesions are related to small artery disease (in which hypertension may play a major role), we restricted the subjects to lacunar infarct patients. We then followed them by tracking the progression of silent lesions, which consisted of lacunar infarcts and diffuse white matter lesions, as well as the recurrence of cerebrovascular disease by using MR1 and ABPM.

**Subjects and Methods**

**Subjects**

We studied 105 patients with symptomatic lacunar infarcts that were located in the supratentorial region; those patients were followed up with MRI and 24-hour BP monitoring. The patients were selected in the following manner. Two hundred eighty-five patients with symptomatic lacunar infarcts for the first time were treated in our clinic at Kyoto Second Red Cross Hospital between January 1991 and December 1996. Of these 285 patients, 182 who had undergone 24-hour BP monitoring for over 4 weeks after ictus were registered in this study and were informed that follow-up MRI scans would be conducted in the future. All of the patients consented to participate in this study. Excluded were 28 patients in whom the dosage and kinds of antihypertensive agents had been changed after 24-hour BP monitoring, 22 patients who had not undergone a repeat MR1 during the follow-up period, 23 patients who had dropped out, and 4 patients who had died. Thus a total of 105 patients who underwent repeat MRI as well as 24-hour BP monitoring, 22 patients who had not undergone a repeat MR1 during the follow-up period, 23 patients who had dropped out, and 4 patients who had died. Thus a total of 105 patients who underwent repeat MR1 as well as 24-hour BP monitoring in the period between the two MR1 examinations were enrolled in this study. Patients who had embolicogenic cardiac disease and obvious atheromatous stenotic lesions as detected by MRA were excluded. Antiplalet drugs were administered to all of the patients.

**Twenty-Four-Hour Blood Pressure Monitoring**

We monitored the 24-hour BP by using a portable automatic recorder (ABPM–630, Nippon Corin Co) after the patients had undergone their first MR1 examination. The accuracy of the equipment had been established and the pattern of circadian BP change were thought to be reproduced well in same person. The 24-hour BP monitoring was carried out in an outpatient office and was managed by the authors of this study during a period in which each patient’s BP appeared to be appropriately controlled as detected by the casual BP, with and without antihypertensive drugs. The goals of the casual BP control were determined as follows: SBPs were controlled below the level of 160 mm Hg in patients who were 69 years old or younger; 170 mm Hg in patients who were 70 to 79 years old; and 180 mm Hg in patients who were 80 to 89 years old; DBPs were controlled below the level of 95 mm Hg in all age groups. Blood pressure was recorded at 30-minute intervals over 24 hours from 1 PM to 1 PM next day. ABP values, including the average 24-hour BP, daytime BP, and nighttime BP, were calculated as follows. SBP and DBP were averaged over successive 30-minute periods throughout the 24-hour period. The mean daytime (6 AM to 10 PM) and nighttime (10:30 PM to 5:30 AM) BP values were also calculated. The magnitude of the nocturnal BP dip was calculated as [(mean daytime BP–mean nighttime BP)/average BP for the entire 24 hours]×100.

**Statistical Analysis**

Statistical comparisons among the five groups were performed with a one-way ANOVA for parametric values and with a Kruskal-Wallis test for nonparametric categories. When there were differences among the five groups, groups 2 through 5 were each compared by Bonferroni’s method with group 1, which had the best prognosis. In analyzing the distribution of sex and risk factors among the groups, a χ² test was used. The values were expressed as mean±SD. A value of P<.05 was considered statistically significant, but a value of P<.0125 was considered to be statistically significant by Bonferroni’s method.

**Results**

**Classification by Outcomes**

We obtained complete tracking data from 105 of the 182 patients who entered the study from January 1991 through
December 1997. The mean duration of tracking was 3.2 years (range, 6 to 74 months). The 105 patients studied for the entire period were divided into five groups: group 1, 50 patients in whom the MRI findings had not changed; group 2, 16 patients in whom a silent lacuna or lacunae had developed; group 3, 14 patients in whom white matter hyperintensities had developed; group 4, 11 patients in whom both silent lacunae and white matter hyperintensities had developed; and group 5, 15 patients in whom symptomatic cerebral infarctions had developed. (Symptomatic cerebral infarctions consisted of 13 lacunar infarcts and 2 cortical infarcts.) The patient characteristics for each group, including age, sex, complications from diabetes mellitus and hypercholesterolemia, smokers, and the degree of lacunar and white matter lesions on baseline MRI findings, are given in Table 1. Groups 2 through 5 were then compared with group 1 with respect to these items.

There were no significant differences among the five groups in age, sex, complications from diabetes mellitus, hypercholesterolemia, smokers, and the degree of lacunar and white matter lesions, although the percentages of diabetes mellitus and hypercholesterolemia tended to be higher in groups 4 and 5. There were significant differences among the five groups in the degree of diffuse white matter lesions ($P=.0015$) (ANOVA). However, when groups 2 through 5 were each compared with group 1, there were no significant differences.

**Casual and ABP Values Between Groups**

The mean values and standard deviations at which the casual BPs were controlled, the average 24-hour BP, daytime BP, nighttime BP, and the magnitude of the nocturnal BP dip are given in Table 2. The patients whose casual BPs were not controlled within the range that we had described in the “Methods” section were as follows: three patients in group 1, three in group 2, two in group 3, two in group 4, and two in group 5. Compared with group 1, groups 2 through 5 had significantly higher systolic nighttime BPs (group 4, $P=.002$, and group 5, $P=.002$), smaller magnitude of the nocturnal SBP dip (group 4, $P=.001$, and group 5, $P=.01$), higher nighttime BP (group 4, $P=.003$), and smaller magnitude of the nocturnal DBP dip (group 4, $P=.001$, and group 5, $P=.005$) (Table 2).

**Table 1. Characteristics of Patients in Five Groups Divided by Outcome**

<table>
<thead>
<tr>
<th>Total No.</th>
<th>Age, y</th>
<th>Men</th>
<th>Women</th>
<th>Diabetes Mellitus</th>
<th>Hyperlipidemia</th>
<th>Smoker</th>
<th>Degree of Lacunae</th>
<th>Degree of White Matter Lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>50</td>
<td>68.3±7.5</td>
<td>33</td>
<td>17</td>
<td>8 (16)</td>
<td>12 (24)</td>
<td>14 (28)</td>
<td>1.6±0.8</td>
</tr>
<tr>
<td>Group 2</td>
<td>16</td>
<td>67.6±9.6</td>
<td>14</td>
<td>2</td>
<td>2 (12.5)</td>
<td>4 (25)</td>
<td>3 (18.7)</td>
<td>1.7±0.8</td>
</tr>
<tr>
<td>Group 3</td>
<td>14</td>
<td>67.4±8.4</td>
<td>7</td>
<td>7</td>
<td>4 (28.5)</td>
<td>5 (35.7)</td>
<td>2 (14.2)</td>
<td>1.7±0.9</td>
</tr>
<tr>
<td>Group 4</td>
<td>10</td>
<td>68.5±10.8</td>
<td>8</td>
<td>2</td>
<td>4 (40)</td>
<td>4 (40)</td>
<td>3 (30)</td>
<td>2.5±0.7</td>
</tr>
<tr>
<td>Group 5</td>
<td>15</td>
<td>65.7±8.2</td>
<td>10</td>
<td>5</td>
<td>7 (46.6)</td>
<td>8 (53.3)</td>
<td>5 (33.3)</td>
<td>1.6±0.8</td>
</tr>
</tbody>
</table>

Values in parentheses are percentages.

**Table 2. Comparison of Blood Pressure Values Among the Five Groups**

<table>
<thead>
<tr>
<th>Group</th>
<th>No.</th>
<th>Casual SBP (mm Hg)</th>
<th>Casual DBP (mm Hg)</th>
<th>24-h SBP (mm Hg)</th>
<th>24-h DBP (mm Hg)</th>
<th>Daytime SBP (mm Hg)</th>
<th>Daytime DBP (mm Hg)</th>
<th>Nighttime SBP (mm Hg)</th>
<th>Nighttime DBP (mm Hg)</th>
<th>Degree of SBP Dip</th>
<th>Degree of DBP Dip</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>50</td>
<td>147.0±12.1</td>
<td>96.7±92.8</td>
<td>141.2±12.1</td>
<td>145.0±12.6</td>
<td>134.2±13.6</td>
<td>7.2±7.8</td>
<td>78.5±9.3</td>
<td>94.3±9.1</td>
<td>73.4±9.7</td>
<td>10.4±7.2</td>
</tr>
<tr>
<td>Group 2</td>
<td>16</td>
<td>140.0±17.3</td>
<td>85.1±10.8</td>
<td>141.8±15.7</td>
<td>145.3±17.0</td>
<td>135.4±15.2</td>
<td>8.8±6.4</td>
<td>80.3±10.1</td>
<td>83.0±9.8</td>
<td>75.5±12.1</td>
<td>9.3±9.4</td>
</tr>
<tr>
<td>Group 3</td>
<td>14</td>
<td>149.8±16.2</td>
<td>86.2±11.6</td>
<td>146.3±15.2</td>
<td>148.4±15.7</td>
<td>141.8±18.6</td>
<td>4.6±9.9</td>
<td>81.3±9.6</td>
<td>84.0±10.1</td>
<td>76.1±11.8</td>
<td>9.9±12.8</td>
</tr>
<tr>
<td>Group 4</td>
<td>10</td>
<td>147.8±21.7</td>
<td>86.1±12.4</td>
<td>149.2±19.0</td>
<td>148.1±20.0</td>
<td>151.1±19.0</td>
<td>−2.1±9.2</td>
<td>85.1±10.7</td>
<td>85.3±11.9</td>
<td>84.6±10.5</td>
<td>0.5±8.8†</td>
</tr>
<tr>
<td>Group 5</td>
<td>15</td>
<td>149.6±13.0</td>
<td>81.6±11.6</td>
<td>149.2±13.1</td>
<td>148.9±11.7</td>
<td>148.4±14.6</td>
<td>1.3±7.9†</td>
<td>79.6±10.3</td>
<td>80.6±10.7</td>
<td>77.9±11.0</td>
<td>3.3±8.1†</td>
</tr>
</tbody>
</table>

Values are expressed in mm Hg (mean±SD). Groups 2 through 5 were compared with group 1.

†$P<.01$, ‡$P<.001$. 

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Sex Differences
All of the patients in each group were divided into male (72 patients) and female (33 patients) subgroups. The ABP values were then compared across severity groups including both D(1) and D(2) within each sex. In both men and women, there were no significant differences among the five groups in any of the ABP values (ANOVA).

Antihypertensive Treatment
All of the patients studied were then divided into two groups: group D(2), 35 patients who did not take antihypertensive agents, and group D(1), 70 patients who took antihypertensive agents. Their mean casual BP, average 24-hour BP, daytime BP, nocturnal BP, and the magnitude of their nocturnal BP dip in group D(2) and group D(1) are given in Table 2.

Patients Without Antihypertensive Treatment
Compared with group D(1), groups D(2) through D(5) had significantly smaller magnitude of the nocturnal DBP dip [group D(2)4 (P = .002)]. The daytime and nighttime BPs for the five groups are plotted in Fig 1.

Patients With Antihypertensive Treatment
Compared with group D(1), groups D(2) through D(5) had significantly higher 24-hour SBP [group D(2)4 (P = .001)], higher nighttime SBP [groups D(2)4 (P = .0003) and D(2)5 (P = .005)], lower magnitude of nocturnal SBP dip [group D(2)5 (P = .003)], higher 24-hour DBP [group D(2)4 (P = .002)], higher daytime DBP [group D(2)4 (P = .008)], higher nighttime DBP [group D(2)4 (P = .001)], and lower magnitude of the nocturnal DBP dip [group D(2)5 (P = .006)] (Table 2). The daytime and nighttime BPs for the five groups are plotted in Fig 2. There were no patients who showed an excessively low BP in the daytime or at night in groups D(2) through D(5).

Discussion
This study demonstrated that a high ambulatory BP, especially at night, and a reduced nocturnal BP dip were both associated with the development of silent ischemic lesions (both lacunar and diffuse white matter lesion) and symptomatic ischemic stroke recurrences in lacunar infarct patients. No patients showed the development of new lesions caused by an excessive lowering of their daytime or nighttime BP. Unlike other studies, our study did not find that the J-curve phenomenon was present or that an excessive fall in the nighttime BP caused cerebral ischemic lesions.

Over the past few decades, a considerable number of longitudinal studies have been performed on the relationship between BP and stroke, and most have demonstrated that a high BP is strongly related to stroke occurrence. Most of these studies, however, were based on the casual BP and symptomatic cerebrovascular disease. The introduction of the ABPM and MRI have now made it possible for us to study the relation of BP to the development of cerebrovascular lesions more precisely, including silent cerebrovascular lesions. This study is the first that was performed prospectively with ABPM and MRI. We restricted the subjects to patients with lacunar infarcts, which are believed to be directly related to hypertension, and excluded those patients with atherothrombotic oc-
clusion and stenosis, so that we could explore the relation between BP and ischemic cerebrovascular lesions more precisely by studying a homogeneous patient group.

A high average ambulatory BP, especially at night, had a high correlation with the development of both lacunar and white matter lesions in the group that did not take antihypertensive agents [group D(−)] and in the group that took antihypertensive agents [group D(+)]. This correlation was demonstrated more clearly in group D(+) than in group D(−). These results have much in common with the previous cross-sectional studies that suggested that the nocturnal BP had a higher correlation with target organ damage than the casual or daytime BP. It has been assumed that persistent pressure overload would increase the progression of hypertensive organ damage.21–23,26,34,35 We conclude that the findings in this longitudinal study have directly supported these assumptions.

Both lacunar and white matter lesions have been believed to be strongly associated with hypertension.36–39 In this study, lacunae were identified only when they were located in the basal ganglia, subcortical white matter, and pons. This appears to be compatible with Fisher’s definition,36 in which lacunae are infarcts caused by the occlusion of branches of perforating arteries. Lesions that measured less than 3 mm were not counted as lacunae, so as to exclude état criblé. We identified diffuse white matter lesions when they were located in the deep subcortical white matter, which might correspond to characteristic pathological findings, including a focal area with the prominent loss of myelin and axons, small ischemic, microcystic infarcts, and associated gliosis. These kinds of lesions are considered to reflect ischemic tissue damages.33 We excluded periventricular caps and smooth halos, which consist of decreased myelin content, the loss of the ependymal cell layer, and reactive gliosis,40 from diffuse white matter lesions.

In group D(+2) and D(+3), lacunar and diffuse white matter lesions developed, respectively. The nighttime BP tended to be higher in these two groups, although not significantly when compared with group D(+1). It seems possible that a high nighttime BP might produce either lacunar or diffuse white matter lesions. Moreover, it is clear that a higher nighttime BP causes both lacunar and diffuse white matter lesions to occur at the same time. In patients in whom both lacunar and diffuse white matter lesions have developed, a progression to Binswanger’s disease41,42 is likely. In actual fact, the severity of diffuse white matter lesions on the first MRI tended to be greater in group 4 than in the other groups. Some of the patients in these groups could have been classified as having Binswanger’s disease from the beginning, and the other patients in these groups are likely to develop Binswanger’s disease. Thus a sustained high BP overnight may accelerate the development of Binswanger’s disease.

The reduced nocturnal BP dip also tended to be smaller in groups 4 and 5 (Table 2). It is likely that a reduced nocturnal BP dip may have a high correlation with the high nighttime BP. Verdecchia et al26 reported that ambulatory hypertension and an absent nocturnal BP dip were independent predictors of cardiovascular morbidity. Verdecchia and colleagues’ report may be the first longitudinal study to have demonstrated that cardiovascular morbidity was higher in nondippers than in dippers. However, Verdecchia and colleagues’ study was performed on the basis of baseline, off-therapy, ambulatory BP. It appears that nondippers have a worse prognosis, as detected by their ABPs during therapeutic intervention, which

![Figure 2. ABPs (upper: daytime; bottom: nighttime; left: SBP; right: DBP) in patients who took antihypertensive agents [D(+)]. Groups 2 through 5 are compared with group 1. †P<.01, ‡P<.001.](http://stroke.ahajournals.org/)
we have demonstrated in this study, as well as by their baseline, off-therapy, ambulatory BP.

Over the last several years, two questions have been the subject of controversy: whether a diminished nocturnal BP dip is the cause or the consequence of hypertensive organ damage and whether this condition has a beneficial or a harmful effect on organ damage. Traditionally, there have been two different views: one was that sustained high BP overnight might have adverse effects on end-organ damage, and the other was that a diminished nocturnal BP dip might protect against end-organ damage caused by a decrease in the blood flow during sleep. This study demonstrated that nondippers tended to have a worse prognosis than dippers in longitudinal studies. As Table 2 indicates, a reduced nocturnal BP and/or high ABPs appeared to be responsible for the new lesions and events observed in groups 4 and 5.

There are reports attributing nondipper mechanisms to autonomic disturbance. We showed that autonomic disturbances play a role as one of the mechanisms associated with a diminished nocturnal BP decline. Kohara et al. showed that the non-dipper phenomenon was due to the failure of withdrawal of sympathetic tone at night, and Ebata et al. pointed out that increased α-adrenergic receptor stimulation might be one of the primary causes of a high nighttime BP in nondippers. Thus it may be safely assumed that central autonomic disturbances, which are present in nondippers, might impair their ability to control their BP and cerebral blood flow and thus might accelerate end-organ damage. Therefore a reduced nocturnal BP dip, with or without high average ambulatory BP, may have adverse effects on end organ damage.

In this study, it appears that there were no patients in whom an excessively low BP, in either their daytime or nighttime BP, might have accelerated ischemic lesions (Fig 2). Our results differ from those in which the J-curve phenomenon was recognized and in which an excessive nocturnal BP dip was thought to cause new lesions. One of the reasons for this difference may be the fact that the patient BP was controlled at a relatively high level in this study. The high BP levels in our study were due to control, based on the theory of cerebral autoregulation, and we also had some patients in whom BP was unresponsive to medication. Another reason our results differ from those in which the J-curve phenomenon was recognized is that we restricted our subjects to patients with lacunar infarcts and excluded those with atherothrombotic lesions. Kario et al. and Watanabe et al. hypothesized that in their cross-sectional studies, an excessive nocturnal BP dip might have caused silent cerebrovascular lesions. Our longitudinal study did not support this view. It is likely that a high daytime BP in those patients with an excessive nocturnal BP dip, rather than the nocturnal BP dip itself, accelerates silent cerebrovascular lesions.

A high average ABP and a reduced nocturnal BP dip may have adverse effects on the prognosis of patients with lacunar infarcts. Although multiple factors contribute to the development of new lesions, we can expect to attenuate the development of silent cerebrovascular lesions and the recurrence of stroke by controlling BP more carefully. The mechanisms by which new lesions develop might go beyond these results. Further investigation is necessary to clarify these issues.

References


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*Stroke*. 1998;29:570-576
doi: 10.1161/01.STR.29.3.570

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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