The J-Curve Phenomenon in Stroke Recurrence

Katsumi Irie, MD; Takenori Yamaguchi, MD; Kazuo Minematsu, MD; Teruo Omae, MD

Background and Purpose: The relation of poststroke blood pressure to stroke recurrence remains underdetermined, and the optimal control of blood pressure has not been established. We performed the present study to resolve these issues.

Methods: We analyzed 368 stroke patients with a history of hypertension (mean age, 62 years) who were admitted within 3 months after stroke onset and observed for 6 months or more. We determined stroke recurrence rate in relation to baseline (or initial) blood pressure, mean values of poststroke blood pressure, stroke subtypes, age, antihypertensive treatment, and other clinical features.

Results: The recurrence rate had a J-curve relation to poststroke diastolic blood pressure but not to poststroke systolic blood pressure and baseline diastolic and systolic blood pressures. The stroke recurrence rate was 3.8% per patient-year in 94 patients who had a poststroke diastolic blood pressure of 80 to 84 mm Hg, significantly lower than the rates of 9.2% per patient-year (P<.05) and 11.4% per patient-year (P<.01) in those with a lower and higher poststroke diastolic blood pressure, respectively. The range of poststroke diastolic blood pressure accompanying the lowest stroke recurrence rate was higher in patients with atherothrombotic (85 to 89 mm Hg) than in those with lacunar infarction (80 to 84 mm Hg). Neither antihypertensive therapy nor patients’ age affected this phenomenon.

Conclusions: The present study suggests that lower blood pressure does not always result in favorable effects on stroke recurrence. The effects of poststroke blood pressure and antihypertensive therapy on stroke recurrence may be complicated by the J-curve phenomenon. (Stroke. 1993;24:1844-1849.)

Key Words • antihypertensive agents • blood pressure • cerebral infarction

Antihypertensive therapy is a general recommendation for stroke survivors with hypertension to reduce stroke recurrence.1,2 Many, but not all, studies have demonstrated that antihypertensive therapy effectively reduces cardiovascular morbidity, mortality, and stroke recurrence.3-8 A potential benefit of antihypertensive therapy is to prevent further progression of pathological changes in the brain vessels.9-12 A decrease in blood pressure (BP), however, may reduce cerebral blood flow (CBF) in patients with impaired cerebral autoregulation and with hemodynamically compromised brain tissues, potentially causing recurrent ischemic events.13-17 Recent studies in hypertensive patients with vascular complications or in elderly patients demonstrated that lowering BP reduces cardiovascular morbidity and mortality, but an excessive drop in BP may paradoxically increase cardiovascular complications.18-25 The relation of diastolic BP with the incidence of cardiac events provides a J-shaped curve with a nadir at approximately 85 mm Hg, representing a complex effect of BP on cardiovascular events.26-29 No studies have confirmed a similar relation for stroke recurrence.

In the present study, we evaluated retrospectively the effect of poststroke BP on stroke recurrence. We also determined the effects of stroke subtypes, age, and antihypertensive treatment on the BP-stroke recurrence rate curves.

Subjects and Methods

We performed the present study on 368 consecutive hypertensive patients (266 men, 102 women; mean age, 62 years) with brain infarction, transient ischemic attack (TIA), and brain hemorrhage who were admitted within 3 months after stroke onset and observed for at least 6 months at the Cerebrovascular Division, National Cardiovascular Center, Japan, during the period from 1982 to 1986. Their observation period was 6 to 96 months, with an average of 38 months.

Patients were classified into the following stroke subtypes: (1) brain hemorrhage, (2) atherothrombotic brain infarction (ATBI), (3) lacunar brain infarction (LBI), (4) embolic brain infarction (EBI), (5) brain infarction of undetermined type (BIU), and (6) TIA. Patients without a potential cardiac source of emboli were entered into EBI only when an occlusion of brain vessels by an embolus or vanishing occlusion was documented by cerebral angiography. Details of our diagnostic criteria for these stroke subtypes were described previously.30,31 Of 368 patients, 51 patients were classified as brain hemorrhage, 74 as ATBI, 149 as LBI, 30 as EBI, 22 as BIU, and 42 as TIA.

Patients were diagnosed as having hypertension if they had evidence of systolic BP (SBP) above 160 mm Hg or diastolic BP (DBP) above 95 mm Hg before and/or 4 weeks after stroke onset or if they had received antihypertensive medications. Baseline SBP and DBP were determined after 4 weeks of stroke (n=283) or just before the initiation of antihypertensive treatment if the treatment was needed within 4 weeks of stroke (n=25).
We could not get a baseline BP for 60 patients who had continuously received antihypertensive medications. Mean values of poststroke SBP and DBP during the observation period were determined by averaging all the values recorded in the outpatient clinic at regular intervals. Antihypertensive agents were given to 254 patients, but not to 114 during the poststroke observation period. The agents were classified into the following subgroups: calcium-channel blockers (n=194), angiotensin converting enzyme inhibitors (n=31), β-blockers (n=90), thiazide derivatives (n=23), and others (n=57). Multiple antihypertensive agents were given in 131 patients. Antiplatelet or anticoagulant medication was given to 133 patients with brain infarction or TIA.

We prescribed the end point of observation as the first stroke recurrence or death from any cause. The type of recurrent stroke was diagnosed according to the subtypes defined above. Causes of death were divided into either cardiovascular death or other causes of death. The former includes death from myocardial infarction, ruptured aortic aneurysm, renal failure, and sudden death of unknown cause. The annual stroke recurrence rate was calculated in percentage per patient-year and then analyzed in relation to baseline SBP, baseline DBP, poststroke SBP, poststroke DBP, stroke subtypes at entry, age, and antithrombosis and antithrombotic therapies. Recurrence-free rate curves were obtained by using the Kaplan-Meier method.

Statistical comparisons among the groups were performed with a one-way analysis of variance for parametric variables and with a Kruskal-Wallis test for nonparametric categories. Intergroup comparisons were performed with Scheffé’s method for parametric variables and with Duncan’s method for nonparametric categories. Recurrence-free rate was compared between the groups with the log-rank method. A two-tailed probability value of less than 0.05 was considered significant.

### Results

Eighteen patients died during the study period: cardiovascular death in 11 and noncardiovascular cause in 7. Seven cardiovascular deaths occurred in patients with antihypertensive treatment, which was not different in frequency from those without such treatment. Stroke recurrence was observed in 77 patients, among whom 51 had received antihypertensive agents. Type of recurrent stroke was not the same as the stroke type at entry in approximately half of the patients. Among 67 ischemic stroke patients with recurrence, 62 (93%) recurrences were ischemic. The recurrent stroke type in 7 brain hemorrhage patients receiving antihypertensive agents was characteristic: only one recurrence was hemorrhagic, but the other six were ischemic.

Annual stroke recurrence rate was 7.5% per patient-year for all patients. It was 6.9% per patient-year for patients treated with antihypertensive agents, which was not significantly different from the rate of 8.8% per patient-year for patients without antihypertensive treatment. Baseline SBP and DBP had no relation to stroke recurrence rate, except in patients with SBP of 160 to 169 mm Hg, who had a significantly higher stroke recurrence rate compared with those with SBP of 150 to 159 mm Hg (Table 1). The stroke recurrence rate was almost the same among the five patient subgroups classified by the baseline DBP.

Patients with poststroke SBP of 150 mm Hg or greater had a significantly higher stroke recurrence rate than those with poststroke SBP of 140 to 149 mm Hg. The stroke recurrence rate in patients with poststroke SBP of less than 140 mm Hg was not significantly different from that in those with poststroke SBP of 140 to 149 mm Hg (Fig 1A). Patients with poststroke DBP of 80 to 84 mm Hg had the lowest stroke recurrence rate compared with those with poststroke DBP of less than 80 mm Hg (P<.05), 90 to 94 mm Hg (P<.01), and 95 mm Hg or greater (P<.05) (Fig 2), demonstrating a so-called J-shaped curve with the nadir, or J point, at

### Table 1. Effect of Baseline and Poststroke Blood Pressure on Stroke Recurrence

<table>
<thead>
<tr>
<th>SBP, mm Hg</th>
<th>Baseline BP</th>
<th>Poststroke BP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Recurrence Rate, %/patient-year</td>
</tr>
<tr>
<td>&lt;140</td>
<td>56</td>
<td>5.11</td>
</tr>
<tr>
<td>140-149</td>
<td>58</td>
<td>5.07</td>
</tr>
<tr>
<td>150-159</td>
<td>78</td>
<td>4.32</td>
</tr>
<tr>
<td>160-169</td>
<td>58</td>
<td>12.32*</td>
</tr>
<tr>
<td>≥170</td>
<td>58</td>
<td>8.13</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;80</td>
<td>62</td>
<td>6.93</td>
</tr>
<tr>
<td>80-84</td>
<td>54</td>
<td>5.77</td>
</tr>
<tr>
<td>85-89</td>
<td>57</td>
<td>6.70</td>
</tr>
<tr>
<td>90-94</td>
<td>47</td>
<td>6.32</td>
</tr>
<tr>
<td>≥95</td>
<td>86</td>
<td>7.26</td>
</tr>
</tbody>
</table>

BP indicates blood pressure; S, systolic; and D, diastolic.

*P<.01 vs baseline SBP 150-159 mm Hg.
†P<.01 vs poststroke SBP 140-149 mm Hg.
‡P<.05, §P<.01 vs poststroke DBP 80-84 mm Hg, by log-rank test.
the range of 80 to 84 mm Hg (Fig 1B). The quartile analysis, in which patients were subdivided almost equally into four groups according to poststroke DBP (n = 91 to 93 in each group), demonstrated that patients in the second quartile (patients with DBP of 78.9 to 84.4 mm Hg) had the lowest recurrence rate. Patients in the first (56.7 to 78.6 mm Hg) and the last (89.9 to 120.0 mm Hg) quartile had significantly higher recurrence rates than those in the second quartile, again demonstrating the J-curve phenomenon.

The J-curve phenomenon in poststroke DBP was not obvious in patients with brain hemorrhage (Fig 3A). Brain hemorrhage patients with lower poststroke DBP had less frequent recurrence. In subset analysis of patients with ATBI and LBI, the J point in poststroke DBP was higher in the former than in the latter (Fig 3B).

Comparisons of baseline clinical features among the four patient subgroups classified by poststroke DBP revealed that patients’ age was not the same among the four subgroups (P < .01, one-way analysis of variance; Table 2). Patients aged older than 65 years had a higher stroke recurrence rate than the younger patients (11.4% per patient-year and 4.8% per patient-year, P < .05). A trend of the J curve was noted in both groups (Table 3).

When the patients were fractionated into four groups according to age, ie, 45 to 54, 55 to 64, 65 to 74, and 75 to 84 years, the stroke recurrence rate was consistently the least frequent in patients with poststroke DBP of 80 to 84 mm Hg throughout all age groups, although the result was not statistically significant because of a small number of patients in each patient subgroup (data not shown).

The frequency of treatment with antihypertensive agents was different among the patient subgroups determined by the level of poststroke DBP (P < .01, Kruskal-Wallis test; Table 2). The stroke recurrence rates were not significantly different between patients with and without antihypertensive agents. Subgroup analysis of the relation between stroke recurrence rate and poststroke DBP levels demonstrated that the J-curve phenomenon was noted both in patients with and without antihypertensive treatment (Table 3).

Other baseline characteristics, including stroke subtype at entry, male-to-female ratio, other major risk factors of stroke (diabetes mellitus, hyperlipidemia, ischemic heart disease, arrhythmia, prior stroke, etc), and frequency of antiplatelet and anticoagulant treatment were almost the same among the subgroups. History of ischemic heart disease, including myocardial infarction and angina pectoris, did not increase stroke recurrence rate (9.1% per patient-year in 49 patients with ischemic heart disease versus 7.2% in 319 without ischemic heart disease; P = NS) or affect the J-curve phenomenon. Both groups experienced the lowest stroke recurrence rate at the DBP range of 80 to 84 mm Hg.

To clarify the interaction between SBP and DBP, we classified patients into three groups according to poststroke SBP, then determined the relations of poststroke DBP to stroke recurrence rate in each group. In every group, stroke recurrence rate was the lowest in patients with poststroke DBP of 80 to 84 mm Hg and demonstrated a J-shaped curve (Table 3). Stroke recurrence rate increased with elevation of poststroke SBP in the groups with poststroke DBP of 85 mm Hg or greater.
The J-curve phenomenon with DBP was likely to exist even in patients with isolated systolic hypertension, with SBP of 160 mm Hg or greater and DBP of less than 90 mm Hg.

**Discussion**

The present study demonstrates that the relation of stroke recurrence rate to poststroke DBP is consistent with a J-shaped curve. The nadir of the curve, or J point, existed at the DBP range of 80 to 84 mm Hg. Because our object was to determine the optimal range of BP control, we did not select the DBP range by quartile or quintile method but used an arbitrary ranging of DBP, which may be more appropriate from a clinical point of view. Baseline SBP and DBP had no relation to stroke recurrence, except for a high stroke recurrence rate in patients with baseline SBP of 160 to 169 mm Hg. Poststroke SBP had a positive and linear correlation with stroke recurrence. Isolated systolic hypertension had no specific effect on the J-curve phenomenon with poststroke DBP.

Several epidemiologic and clinical studies have found that hypertension or elevated baseline SBP and DBP entails a risk of stroke recurrence. Hier et al reported that diastolic hypertension (greater than 100 mm Hg) at the time of the initial examination was a significant risk factor for stroke recurrence. The relative risk ratio, however, was quite modest (95% confidence interval, 1.003 to 1.021). In a community study in Rochester, Minn, neither level of BP before the first stroke nor management of hypertension had any effect on mortality and stroke recurrence rates throughout the follow-up period. Acute lowering of BP may cause ischemic stroke in elderly hypertensive patients and some stroke survivors. However, there is no definite evidence that sustained reduction in BP enhances stroke recurrence. Most recent studies in hypertensive patients without stroke demonstrated that overall car-

<table>
<thead>
<tr>
<th>Stroke type at entry</th>
<th>Poststroke DBP, mm Hg</th>
<th>80-84 (n=94)</th>
<th>85-89 (n=85)</th>
<th>≥90 (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATBI</td>
<td>22</td>
<td>22</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>LBI</td>
<td>35</td>
<td>34</td>
<td>37</td>
<td>43</td>
</tr>
<tr>
<td>EBI</td>
<td>9</td>
<td>9</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>BIU</td>
<td>6</td>
<td>7</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>TIA</td>
<td>17</td>
<td>8</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>HEM</td>
<td>9</td>
<td>14</td>
<td>16</td>
<td>12</td>
</tr>
<tr>
<td>Male/female</td>
<td>69/29</td>
<td>69/25</td>
<td>60/25</td>
<td>69/22</td>
</tr>
<tr>
<td>Mean age, y</td>
<td>68.0</td>
<td>61.7*</td>
<td>61.9*</td>
<td>59.7*</td>
</tr>
<tr>
<td>Risk factors except for hypertension</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>35</td>
<td>22</td>
<td>32</td>
<td>28</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>24</td>
<td>24</td>
<td>22</td>
<td>19</td>
</tr>
<tr>
<td>Obesity</td>
<td>7</td>
<td>7</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>19</td>
<td>10</td>
<td>8</td>
<td>12</td>
</tr>
<tr>
<td>Rheumatic heart disease</td>
<td>6</td>
<td>5</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>15</td>
<td>11</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>History of BI</td>
<td>28</td>
<td>21</td>
<td>18</td>
<td>26</td>
</tr>
<tr>
<td>History of HEM</td>
<td>4</td>
<td>2</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Baseline SBP, mm Hg</td>
<td>146.8</td>
<td>152.5</td>
<td>153.8</td>
<td>161.2</td>
</tr>
<tr>
<td>Baseline DBP, mm Hg</td>
<td>77.8</td>
<td>86.3</td>
<td>90.2</td>
<td>96.5</td>
</tr>
<tr>
<td>Poststroke SBP, mm Hg</td>
<td>140.6</td>
<td>145.4</td>
<td>147.2</td>
<td>159.6</td>
</tr>
<tr>
<td>Poststroke DBP, mm Hg</td>
<td>75.9</td>
<td>82.2</td>
<td>87.3</td>
<td>96.6</td>
</tr>
</tbody>
</table>

DBP indicates diastolic blood pressure; ATBI, atherothrombotic brain infarction; LBI, lacunar brain infarction; EBI, embolic brain infarction; BIU, brain infarction of unknown etiology; TIA, transient ischemic attack; HEM, brain hemorrhage; BI, brain infarction; and SBP, systolic blood pressure.

*P<.01 vs poststroke DBP <80 mm Hg by Scheffé's method.
†P<.05 vs poststroke DBP ≥90 mm Hg by Duncan's method.
Table 3. Stroke Recurrence Rate by Poststroke Diastolic Blood Pressure Range in Relation to Stroke Type, Age, Antihypertensive Treatment, and Poststroke Systolic Blood Pressure

<table>
<thead>
<tr>
<th>Poststroke DBP, mm Hg</th>
<th>Stroke Type</th>
<th>Age, y</th>
<th>Antihypertensive Treatment</th>
<th>Poststroke SBP, mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HEM</td>
<td>BI</td>
<td>ATBI</td>
<td>LBI</td>
</tr>
<tr>
<td>&lt;80</td>
<td>3.74</td>
<td>9.62**</td>
<td>9.47</td>
<td>8.11*</td>
</tr>
<tr>
<td>80-84</td>
<td>4.12</td>
<td>2.67</td>
<td>5.68</td>
<td>0.89</td>
</tr>
<tr>
<td>85-89</td>
<td>7.44</td>
<td>6.03</td>
<td>1.98</td>
<td>5.60</td>
</tr>
<tr>
<td>≥90</td>
<td>13.04</td>
<td>12.03**</td>
<td>18.00†</td>
<td>11.01**</td>
</tr>
</tbody>
</table>

Stroke recurrence rate values are percentage per patient-year. DBP indicates diastolic blood pressure; SBP, systolic blood pressure; HEM, brain hemorrhage; BI, brain infarction (except for transient ischemic attack); ATBI, atherothrombotic BI; and LBI, lacunar BI.

*P<.05, **P<.01 vs poststroke DBP 60-84 mm Hg.
†P<.05 vs poststroke DBP 85-89 mm Hg, by log-rank test.

Diovascular events occurred in a J-shaped manner with DBP,20,25,28 although this is not fully confirmed.36 The main cardiovascular event in these studies was myocardial infarction, and the J point was usually present at DBP of 84 to 90 mm Hg. Reduced coronary perfusion due to excessive diastolic hypotension may not only cancel benefits of antihypertensive therapy but also cause a paradoxical increase in ischemic events. We can also apply a similar scenario to the relation of poststroke BP to stroke recurrence.

In the present study, the J-curve phenomenon was observed in patients with brain infarction but not in those with brain hemorrhage. The J point was higher in patients with ATBI than in patients with LBI. These results suggest that hypertensive patients with ATBI were particularly vulnerable to low poststroke DBP. The lower limit of autoregulation of CBF shifts to a higher level of BP in hypertensive than in normotensive subjects, so that only mild hypotension or normalization of BP may induce a decrease in CBF.11 Hemodynamically compromised brain tissues in some patients with ATBI are theoretically vulnerable to a decrease in systemic BP, although effects of chronic hemodynamic failure on stroke recurrence remain unknown.14,37,38 These pathophysiological mechanisms may be responsible for a paradoxical increase in stroke recurrence rate at the lower poststroke DBP.

Dependency of coronary circulation on DBP but not on SBP is the most likely explanation for the presence of the J-curve phenomenon only for DBP in ischemic heart disease. In contrast, both SBP and DBP have a relation to tissue perfusion in the brain. In the Framingham Study, the probability of occurrence of a brain infarction was predicted by SBP and DBP level.39 Therefore, not only DBP but also SBP may have a J-curve relation to stroke recurrence, although our data did not support this speculation. DBP may be more important than SBP in determining perfusion pressure and blood flow in the brain. This concept is supported by recent observations with ultrasonography demonstrating that the diastolic intravascular blood flow and velocity to the brain were kept at a higher level than those to other organs.40-42

Because of the retrospective nature of the study, we could not adjust patients’ age and control the use of antihypertensive agents. We found that patients with a poststroke DBP of less than 80 mm Hg were the oldest among the patient subgroups classified by ranges of poststroke DBP, which is in common with a hypertensive population.43,44 Stroke recurrence rate was higher in patients older than 65 years than in the younger patients over all ranges of poststroke DBP. Marquardt13 suggested that advancing age is accompanied by an increase in stroke recurrence, but this aging effect was absent in other studies.35 Previous studies demonstrated that the J-curve phenomenon for myocardial infarction was consistently observed even in elderly hypertensive patients.24,25,45 We could not determine the net effects of poststroke DBP, independent of aging, on stroke recurrence, although similar J-curve trends in both the younger (younger than 65 years) and older (65 years or older) patient subgroups were observed, even in age subgroups classified by 10-year intervals, suggesting that the J-curve phenomenon is independent of an aging effect.

Patients treated with antihypertensive drugs were most frequently in the highest poststroke DBP range. In some patients, DBP dropped spontaneously without medication. Both patients with antihypertensive medication and those without medication exhibited the J-curve phenomenon. A previous study reported that the J-curve phenomenon for myocardial infarction was dependent on DBP level but not on antihypertensive medication.27 In ischemic heart disease, subclinical myocardial damage may cause hypotension that precedes symptomatic events. However, we cannot apply this possibility to stroke occurrence. Sutton-Tyrrell et al46 reported recently that among patients with isolated systolic hypertension, low DBP is a marker for carotid stenosis. This observation may in part explain the relation between the low poststroke DBP and an increase in stroke recurrence rate in the present study, although we could not find an inverse correlation of DBP with stroke recurrence rate among the isolated systolic hypertension group but did confirm the J-curve even in patients with LBI.

Prior intervention studies have consistently confirmed the beneficial effects of antihypertensive treatment on stroke occurrence in young patients with severe arterial hypertension but not in older patients or patients with milder hypertension.3,8 Many factors, including stroke subtypes, hemodynamic state in the brain, age, baseline BP level, and degree and speed of decrease in BP, may influence recurrence in hypertensive stroke patients. Well-controlled prospective studies are needed to determine the optimal control levels of poststroke BP in each stroke subtype for preventing recurrent stroke.”
Acknowledgments

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