The Significance of Blood Pressure Variability for the Development of Hemorrhagic Transformation in Acute Ischemic Stroke

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Background and Purpose—Elevated blood pressure (BP) is commonly observed in acute ischemic stroke and is known to be associated with hemorrhagic transformation (HT). However, the effect of BP variability on the development of HT is not known well.

Methods—A consecutive series of patients with acute ischemic stroke, who were hospitalized within 24 hours of onset and showed no HT on initial gradient echo MRI, were enrolled in this study. BP measurements during the first 72 hours were obtained, and BP variability of each patient was described using various summary parameters: SD, maximum (max), minimum (min), difference between max and min (max−min), average squared difference between successive measurements (sv), and maximum sv (svmax).

Results—Of 792 patients meeting the eligibility criteria, 70 (8.8%) developed HT. Among BP variability parameters categorized into quartiles, SBPmax, SBPmin, SBPmax−min, SBPsvmax, DBPmin, DBPmax, DBPmax−min, and DBPsvmax were significantly associated with HT independent of mean SBP, age, interval from onset to arrival, initial stroke severity, diabetes mellitus, stroke subtype, thrombolysis, initial glucose, and total cholesterol (P<0.05 on likelihood ratio test of trend). The analyses about the interaction between thrombolysis and variability parameters showed that the effects of BP variability on the development of HT did not differ by whether patients received thrombolysis or not.

Conclusions—Our study suggests that we may consider not only the absolute level of BP but also its variability to prevent hemorrhagic transformation. (Stroke. 2010;41:2512-2518.)

Key Words: blood pressure ■ cerebral infarction ■ hemorrhage

Hemorrhagic transformation (HT) is a prevalent and perhaps the most critical complication related to the management of acute ischemic stroke. Rates of HT from 10% to 30% have been reported among patients treated with recombinant tissue plasminogen activator (rt-PA). There is a concern that thrombolysis-related HT might dramatically worsen the prognosis of a patient. It has been clearly shown that the increase of hematoma size is accompanied by the significant increase in the risk of deterioration during the first 24 hours and the 3-month case-fatality.

The extent of cerebral infarction on baseline CT scan, congestive heart failure, old age, and high baseline systolic blood pressure (BP) were reported to be associated with HT in patients treated with rt-PA. Among these factors, the role of high baseline systolic BP is notable in both experimental and clinical settings. The current American Heart Association/American Stroke Association guidelines for the early management of acute ischemic stroke recommend to maintain systolic BP (SBP) below 185 mm Hg and diastolic BP (DBP) below 110 mm Hg before beginning intravenous thrombolytic therapy.

HT is commonly observed even when revascularization therapy is not given. Despite the belief in the association between BP and HT, there is still uncertainty in their causal relationship. Numerous studies about the role of BP repeatedly told us that high level of BP in acute stroke is associated with a poor outcome. However, with respect to BP variability, its impact on clinical outcome has been raised quite recently.

BP variability may have an negative influence on cerebral perfusion and aggravate an ischemic injury where autoregulation is not well maintained or absent.
lotion has been already impaired because of the injury itself.\textsuperscript{14} A sudden rise of BP can contribute to the rupture of blood vessels damaged and weakened by the ischemic insult. It is therefore reasonable to hypothesize that BP variability contributes to the development of HT.

In the present study, we intended to investigate whether BP variability increases the risk of HT after acute ischemic stroke and, if it does, the extent of the relationships between HT and BP variability parameters.

### Methods

A consecutive series of patients with ischemic stroke, who were admitted to Seoul National University Bundang Hospital between January 1, 2004 and August 31, 2007, were identified using the Korean stroke registry database.\textsuperscript{16} We enrolled patients hospitalized within 24 hours of stroke onset and showing relevant lesions on an initial diffusion-weighted MRI (DWI). Those who did not undergo gradient echo T2-weighted MRI (GRE), showed HT on an initial GRE, had no follow-up brain image within the first 14 days of hospitalization, or had inadequate BP data were excluded. The study protocol was approved by the local institutional review board. The casual supine BP was measured from a nonhemiparetic arm using a standard mercury sphygmomanometer and entered manually into the electronic medical record (EMR) system as part of the clinical routine when patients were cared for on general wards. In the emergency room, stroke unit, or intensive care unit, BP was measured using a noninvasive BP monitoring system and recorded automatically into the EMR system. BP measurements within the first 72 hours were thus obtained from the EMR system electronically.

Demographics, clinical profiles that included the TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification of stroke subtype,\textsuperscript{17,treatments, and laboratory findings were obtained directly from the stroke registry or by reviewing medical records. Two neurologists (Y.K. and J.H.P.) reviewed all brain images (CT or MRI) taken within the first 14 days and determined the neuroimaging profile of each patient with regard to the presence and severity of HT (weighted profile of each patient with regard to the presence and severity of HT). The appropriateness of test was determined by visual inspection of the normality on the distribution of each continuous variable using histogram. Proportions were compared using Pearson’s $\chi^2$ test. Multiple logistic regression analysis was performed to assess the independent association of each BP parameter with the development of HT. Variables for adjustments were identified from univariate analyses when their probability values were $<0.25$. Mean SBP was chosen to represent the level of BP during the first 72 hours and was also included in multiple logistic regression models. Because BP parameters were mostly different from each other in the meaning of one unit change, they were categorized into quartiles. To avoid the risk of multicollinearity caused by including highly correlated variables in the same model, we replaced each variability parameter one by one instead of including all the BP variability parameters in one model. Resulting adjusted odds ratios (ORs) and 95\% CIs are reported. Dose-response relationships between variability parameters and the development of HT were examined using a likelihood ratio test of trend.

In line with methods used elsewhere,\textsuperscript{13,23} we examined the consistency of BP variability in its impact on HT by different BP levels. Patients were stratified according to the quartile of their mean BP during the first 72 hours, and each stratum were further divided into low variability ($\leq$median) and high variability ($>$median) groups using the median value of BP variability parameters of the stratum. The proportion of patients who developed HT was calculated in each group. The homogeneity in the association of BP variability parameters and HT across the mean BP quartiles was determined using the Breslow and Day’s test.

All analyses were carried out using SPSS for Windows version 15.0 (SPSS Inc, Chicago, Ill), and a probability value of $<0.05$ was considered as statistically significant.

### Results

Among 1763 patients who were hospitalized for acute ischemic stroke during the study, 1046 (59.3\%) were admitted within 24 hours of symptom onset. DWIs were performed in almost all patients (99.2\%, 1038/1046), and 1025 had relevant lesions on initial DWI. From these 1025, a number of patients were excluded because of the following causes: 130 (12.7\%) who did not undergo GRE, 23 (2.2\%) who showed HT on an initial GRE, 71 (6.9\%) who had no follow-up images, and 9 (1.1\%) who had inadequate BP ($<$9 BP measurements during the first 72 hours). As a result, 792 patients were finally enrolled in this study. Median delay between stroke onset and the last follow-up images was 4 days (IQR, 2 to 6 days).

Follow-up images revealed HT in 8.8\% (70/792), the median interval from symptom onset to the detection of HT was 1 day (IQR, 0 to 4 days). CT was the only follow-up imaging modality in 112 (14.1\%). MRI was repeated in the remaining 680 patients (85.9\%). The frequency of HT was 12.5\% in the CT-only group and 8.2\% in the MRI group ($P=0.14$ with Pearson’s $\chi^2$ test). Among the 70 patients with HT, 17\% (12/70) were symptomatic and types of HT were as follows: HI-1 in 6 patients (8.6\%); HI-2 in 16 (22.9\%); PH-1 in 27 (38.6\%); and PH-2 in 15 (21.4\%). Clinical characteristics are presented according to the presence of HT (Table 1). Compared to patients without HT, patients with HT were more likely to have large artery atherosclerosis or cardioembolic stroke, to receive thrombolysis, to arrive at the hospital quickly, to have severe neurological deficits, and to show a high serum glucose level.

The median frequency of BP measurements per person during the first 72 hours was 18 times (IQR, 14 to 57). The HT and no-HT groups were different in the frequency of BP measurements ($P<0.001$ on the Mann–Whitney U test).
Table 1. Comparison of Baseline Characteristics Between Patients With and Without HT

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Yes (n=70, 8.6%)</th>
<th>No (n=722, 91.2%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean±SD, yr)</td>
<td>69.5±11.1</td>
<td>66.7±12.3</td>
<td>0.07*</td>
</tr>
<tr>
<td>Interval from onset to arrival (median and IQR, hours)</td>
<td>2 (0.7–3.7)</td>
<td>4.8 (1.7–10.4)</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>NIHSS at admission (median and IQR)</td>
<td>13 (7–18)</td>
<td>4 (2–6)</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>26 (37.1%)</td>
<td>192 (26.2%)</td>
<td>0.06</td>
</tr>
<tr>
<td>Hypertension</td>
<td>42 (60.0%)</td>
<td>426 (59.0%)</td>
<td>0.87</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>14 (20.0%)</td>
<td>120 (16.6%)</td>
<td>0.47</td>
</tr>
<tr>
<td>Smoker†</td>
<td>16 (22.9%)</td>
<td>212 (29.4%)</td>
<td>0.25</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>14 (20.0%)</td>
<td>151 (20.9%)</td>
<td>0.86</td>
</tr>
<tr>
<td>TOAST classification</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Large artery atherosclerosis</td>
<td>30 (42.9%)</td>
<td>282 (39.1%)</td>
<td></td>
</tr>
<tr>
<td>Small vessel occlusion</td>
<td>0 (0.0%)</td>
<td>161 (22.3%)</td>
<td></td>
</tr>
<tr>
<td>Cardioembolism</td>
<td>27 (38.6%)</td>
<td>145 (20.1%)</td>
<td></td>
</tr>
<tr>
<td>Other determined etiology</td>
<td>1 (1.4%)</td>
<td>12 (1.7%)</td>
<td></td>
</tr>
<tr>
<td>Undetermined etiology</td>
<td>12 (17.1%)</td>
<td>122 (16.9%)</td>
<td></td>
</tr>
<tr>
<td>Thrombolysis</td>
<td>45 (64.3%)</td>
<td>113 (15.7%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heparinization</td>
<td>15 (21.4%)</td>
<td>177 (24.5%)</td>
<td>0.57</td>
</tr>
<tr>
<td>Initial serum glucose (mean±SD, mmol/L)</td>
<td>8.97±3.75</td>
<td>8.16±3.28</td>
<td>0.08*</td>
</tr>
<tr>
<td>Total cholesterol (mean±SD, mmol/L)</td>
<td>4.88±1.03</td>
<td>5.05±1.06</td>
<td>0.19*</td>
</tr>
<tr>
<td>Small vessel disease§</td>
<td></td>
<td></td>
<td>0.92</td>
</tr>
<tr>
<td>Grade 0</td>
<td>18 (25.7%)</td>
<td>169 (23.4%)</td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>34 (25.7%)</td>
<td>340 (47.1%)</td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td>11 (15.7%)</td>
<td>130 (18.0%)</td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td>7 (10.0%)</td>
<td>83 (11.5%)</td>
<td></td>
</tr>
<tr>
<td>Microbleeds</td>
<td>15 (21.4%)</td>
<td>147 (20.4%)</td>
<td>0.83</td>
</tr>
<tr>
<td>No. of BP measurements (median, IQR)</td>
<td>75 (52–85)</td>
<td>17 (13–45)</td>
<td>&lt;0.001†</td>
</tr>
</tbody>
</table>

Values represent no. of patients if not otherwise indicated. Proportions were compared using Pearson’s χ² test. TOAST indicates Trial of Org 10 172 in Acute Stroke Treatment.17; NIHSS, National Institute of Health Stroke Scale.

*Means were compared using Student’s t test.
†Means were compared using Mann–Whitney U test.
‡Current smoker or had quit smoking within the past 5 years.
§Fazekas grading.18

(Tables 1 and 2) but were not in the average of either SBP or DBP (SBPmean and DBPmean) (Table 2). The SDs and maximum values (SBPstd, SBPmax, DBPstd, and DBPmax) were higher in the HT group than the no-HT group, but the minimum values (SBPmin and DBPmin) were lower in the HT group (P<0.001). Consequently, the differences between the maximum and minimum (SBPmax−min and DBPmax−min) were higher in the HT group than the no-HT group (P<0.001). The successive variation for SBP (SBPsv) did not differ by the presence of HT (P=0.37), but the successive variation for DBP (DBPsv) did (12.9±4.5 in the HT group and 11.4±3.5 in the no-HT group, P=0.002). The maximum successive variation (SBPsvmax

Table 2. Comparison of BP Profiles Between Patients With and Without HT

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Yes (n=70)</th>
<th>No (n=722)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBPinitial</td>
<td>164.4±27.3</td>
<td>162.6±28.9</td>
<td>0.60</td>
</tr>
<tr>
<td>SBPmean</td>
<td>145.2±18.1</td>
<td>145.5±18.0</td>
<td>0.87</td>
</tr>
<tr>
<td>SBPmax</td>
<td>16.5±6.2</td>
<td>14.8±4.6</td>
<td>0.03</td>
</tr>
<tr>
<td>SBPstd</td>
<td>188.6±24.5</td>
<td>176.8±24.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SBPmin</td>
<td>109.2±20.5</td>
<td>118.3±17.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SBPmax−min</td>
<td>79.4±29.6</td>
<td>58.6±22.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SBPsv</td>
<td>15.9±5.5</td>
<td>16.5±5.2</td>
<td>0.37</td>
</tr>
<tr>
<td>SBPsvmax</td>
<td>50.5±24.3</td>
<td>38.6±13.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DBPinitial</td>
<td>88.1±19.8</td>
<td>87.7±16.8</td>
<td>0.83</td>
</tr>
<tr>
<td>DBPmean</td>
<td>77.8±11.5</td>
<td>80.3±10.5</td>
<td>0.06</td>
</tr>
<tr>
<td>DBPstd</td>
<td>11.2±3.5</td>
<td>9.5±3.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DBPmax</td>
<td>113.7±21.4</td>
<td>101.0±15.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DBPmin</td>
<td>50.7±14.8</td>
<td>61.4±12.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DBPmax−min</td>
<td>63.2±27.6</td>
<td>39.6±16.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DBPsv</td>
<td>12.9±4.5</td>
<td>11.4±3.5</td>
<td>0.002</td>
</tr>
<tr>
<td>DBPsvmax</td>
<td>44.7±23.7</td>
<td>27.7±12.6</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are means±SD. *Student’s t test. 

Cutoff values of quartiles for BP variability parameters and the rate of HT in each quartile were shown in Table 3. Using a Mantel–Haenszel χ² test, significant linear associations were noted in the rate of HT with quartiles except SBPmean, SBPstd, SBPsv, and DBPmean. Simple comparisons between the HT and no-HT groups yielded P<0.25 for age, interval from symptom onset to arrival, National Institute of Health Stroke Scale (NIHSS), diabetes mellitus, TOAST (Trial of Org 10 172 in Acute Stroke Treatment) classification, thrombolysis, serum glucose, and total cholesterol (Table 1). With adjustments for these variables and mean SBP during the first 72 hours, the ORs and 95% CIs were calculated for each quartile of BP variability parameters. SBPmax, SBPmin, SBPmax−min, SBPsvmax, DBPstd, DBPmax, DBPmin, DBPmax−min, and DBPsvmax showed a significant association with the development of HT (Table 4). To determine whether the effect of BP variability on the risk of HT differs according to thrombolysis, interaction terms between BP variability parameters and thrombolysis were added to logistic models presented in Table 4. There was no significant interaction except SBPsv (see the Supplemental Table, available at http://stroke.ahajournals.org). Furthermore, as a sensitivity analysis, we included mean DBP instead of mean SBP in multivariable logistic regression models, but there was also no significant change in results (not presented here).

Analyses comparing high and low variability groups within each mean SBP and DBP quartile showed that the development of HT was more frequent in the high variability groups than the low variability groups consistently for some of SBP variability parameters (SBPmax−min, SBPsvmax) and most of
DBP variability parameters (DBP_SD, DBP_max−min, DBP_sv, and DBP_svmax; Figure, B and D through H) (P<0.05 on the Breslow and Day’s test).

**Discussion**

To the best of our knowledge, this is the first study to report an association between BP variability and the development of HT after acute ischemic stroke independent of BP level and thrombolysis. BP is generally very dynamic; it fluctuates considerably during the first several hours of stroke.\(^{22}\) When brain is attacked by ischemic stroke, a failure of cerebral autoregulation occurs, and blood flow is mainly determined by the systemic arterial pressure in ischemic brain regions. As a result, even minor fluctuations in BP may lead to under- or overperfusion of ischemic brain.\(^{22,23}\) Although several studies have shown that HT is associated with the absolute level of BP, an association between the development of HT and BP variability has not yet been established.\(^{6,24,25}\) We examined various measures of BP variability, including extreme values (max and min), the maximal difference

| Table 3. Rate of HT According to Quartiles of BP Variability Parameters |
|---------------------------------|-------------------------------|------------------|
| Cutoff Values (mm Hg)           | 25th Percentile | 50th Percentile | 75th Percentile |
| SBP<sub>mean</sub>              | 133.19          | 144.92          | 157.01          |
| SBP<sub>SD</sub>                | 11.46           | 13.91           | 17.52           |
| SBP<sub>max</sub>               | 161             | 175             | 193             |
| SBP<sub>min</sub>               | 107             | 117             | 130             |
| SBP<sub>max−min</sub>           | 44              | 56              | 71              |
| SBP<sub>sv</sub>                | 12.75           | 15.46           | 19.49           |
| SBP<sub>svmax</sub>             | 29              | 37              | 47              |
| DBP<sub>mean</sub>              | 72.96           | 79.54           | 87.28           |
| DBP<sub>SD</sub>                | 7.47            | 9.27            | 11.42           |
| DBP<sub>max</sub>               | 91              | 99              | 110             |
| DBP<sub>min</sub>               | 52              | 61              | 69              |
| DBP<sub>max−min</sub>           | 29              | 38              | 49              |
| DBP<sub>sv</sub>                | 9               | 10.99           | 13.5            |
| DBP<sub>svmax</sub>             | 20              | 26              | 35              |
| Hemorrhagic Transformation (%)  |                 |                 |                 |
| 1Q                             | 11.1            | 7.6             | 7.6             |
| 2Q                             | 8.6             | 5.6             | 8.1             |
| 3Q                             | 4.1             | 6.6             | 10.4            |
| 4Q                             | 13.7            | 11.2            | 4.5             |
| P*                             | 0.05            | 0.73            | <0.001          |

\(^{*}\)Calculated by Mantel–Haenszel \(\chi^2\) test.

| Table 4. Independent Associations Between BP Variability Parameters and the Development of HT After Adjustment for Mean SBP During the First Seventy-Two Hours |
|---------------------------------|-------------------------------|------------------|------------------|
| Adjusted OR* (95% CI)           | First Quartile | Second Quartile | Third Quartile | Fourth Quartile | P for Trend† |
| SBP<sub>SD</sub>                | 1               | 0.85 (0.55–2.06) | 1.21 (0.53–2.80) | 1.62 (0.74–3.52) | 0.15         |
| SBP<sub>max</sub>               | 1               | 2.76 (1.00–7.63) | 3.54 (1.25–10.04) | 5.37 (1.70–17.01) | <0.01        |
| SBP<sub>min</sub>               | 1               | 0.76 (0.35–1.64) | 0.32 (0.12–0.88) | 0.28 (0.09–0.91) | 0.01         |
| SBP<sub>max−min</sub>           | 1               | 1.65 (0.47–5.80) | 3.55 (1.11–11.33) | 4.36 (1.39–13.69) | 0.001        |
| SBP<sub>sv</sub>                | 1               | 1.95 (0.93–4.10) | 1.27 (0.55–2.93) | 1.31 (0.55–3.21) | 0.7          |
| SBP<sub>svmax</sub>             | 1               | 1.63 (0.58–4.58) | 2.23 (0.84–5.93) | 3.30 (1.27–8.57) | <0.01        |
| DBP<sub>SD</sub>                | 1               | 2.44 (0.91–6.59) | 2.43 (0.90–6.53) | 3.09 (1.19–8.07) | 0.03         |
| DBP<sub>max</sub>               | 1               | 1.20 (0.43–3.35) | 1.00 (0.34–2.96) | 3.05 (1.14–8.14) | <0.01        |
| DBP<sub>min</sub>               | 1               | 0.48 (0.23–1.03) | 0.49 (0.21–1.15) | 0.24 (0.08–0.70) | 0.001        |
| DBP<sub>max−min</sub>           | 1               | 1.88 (0.36–9.78) | 3.97 (0.86–18.30) | 7.70 (1.69–35.04) | <0.001        |
| DBP<sub>sv</sub>                | 1               | 0.64 (0.26–1.60) | 1.10 (0.47–2.58) | 1.60 (0.70–3.62) | 0.11         |
| DBP<sub>svmax</sub>             | 1               | 1.04 (0.23–4.69) | 4.16 (1.16–14.86) | 4.96 (1.40–17.61) | <0.001        |

*First quartile indicates ≤25th percentile; second quartile, >25th and ≤50th; third quartile, >50th and ≤75th; fourth quartile, >75th.

*Variables adjusted for are mean SBP, age, interval from onset to arrival, initial National Institute of Health Stroke Scale, diabetes mellitus, Trial of Org 10 172 in Acute Stroke Treatment\(^{17}\) (TOAST) classification, thrombolysis, initial serum glucose, and total cholesterol.

†Likelihood ratio test of trend.
(labeled as max−min), SD, and sv, and most of those variability parameters showed an independent association with the development of HT. Furthermore these findings were supported by the simple stratified analyses; when dividing patients into mean BP quartiles and further splitting the members of each quartile into high and low variability groups (Figure 1),\textsuperscript{13} most variability parameters for DBP (SD, max−min, sv, svmx) and some for SBP (max−min, svmx) were consistently associated with HT across all the mean BP quartiles.

Recently, Yong and Kaste reported that SBP profiles, such as baseline (initial), mean, max, and sv of SBP, during the first 24 hours were independent predictors of parenchymal hemorrhage in tPA-treated patients.\textsuperscript{15} There were some differences between our results and the results of Yong and Kaste. All the associations of SBP profiles and HT were not
significant in patients not receiving thrombolysis in the study by Yong and Kaste. However, in our study, there was no interaction between most of BP parameters and thrombolysis, which means that the effects of BP profiles on HT are independent of whether patients were given thrombolysis or not. Although differences in study design and methods, such as clinical trial versus retrospective observational study, gathering SBP during the first 24 hours versus during the first 72 hours, and adjustment for mean SBP versus no adjustment, may partly explain those discrepancies, they do not seem to offer a complete explanation. Further studies are warranted.

It is noteworthy in the present study that the variability parameters for DBP were more closely related to HT than those for SBP. Previous studies about BP variability and stroke outcome have also reported that DBP variability might be more closely correlated with stroke outcome than either mean BP or SBP variability, although the reasons are not known.\textsuperscript{13,14}

When excluding studies based on thrombolysis trials or restricting their subjects to patients receiving thrombolysis, it is not easy to find reports concerning the effects of BP parameters on the development of HT. One study reported that BP was not related to the incidence of HT in patients with acute cerebral embolism.\textsuperscript{10} However, rather than various parameters representing the dynamics of BP, the only measure used in that study was a mean BP during hospitalization. Using a time-invariant parameter only could have led to an influence of BP on clinical outcome being missed.\textsuperscript{14}

Despite the evidence supporting the association of high BP level and poor outcome, some researchers maintain that BP is of little prognostic value.\textsuperscript{26} Others even argue that constantly high BP can contribute to good outcome.\textsuperscript{27} This controversy may be attributable to the parallel harmful and beneficial effects associated with high BP. On one hand, high BP increases the risk of cerebral edema and HT in an infarcted area. On the other hand, high BP helps to preserve perfusion at an ischemic penumbra.\textsuperscript{28} Maintaining high BP could be beneficial if perfusion of an ischemic area is inadequate because of incomplete recanalization or poor collaterals. Low BP or BP fluctuation could increase infarct size and, as a result, lead to poor outcome.\textsuperscript{29} In contrast, if an occluded vessel is recanalized, high BP may provoke edema or HT. Under these circumstances, there is no doubt that it would be beneficial to maintain BP relatively low and constant within a reasonable range.\textsuperscript{14}

Some limitations of the present study need to be addressed. These include the study being performed in a single university hospital and the retrospective design, which mean that the modality and timing of brain images used to detect HT, as clinical trial versus retrospective observational study, gathering SBP during the first 24 hours versus during the first 72 hours, and adjustment for mean SBP versus no adjustment, may partly explain those discrepancies, they do not seem to offer a complete explanation. Further studies are warranted.

It is noteworthy in the present study that the variability parameters for DBP were more closely related to HT than those for SBP. Previous studies about BP variability and stroke outcome have also reported that DBP variability might be more closely correlated with stroke outcome than either mean BP or SBP variability, although the reasons are not known.\textsuperscript{13,14}

When excluding studies based on thrombolysis trials or restricting their subjects to patients receiving thrombolysis, it is not easy to find reports concerning the effects of BP parameters on the development of HT. One study reported that BP was not related to the incidence of HT in patients with acute cerebral embolism.\textsuperscript{10} However, rather than various parameters representing the dynamics of BP, the only measure used in that study was a mean BP during hospitalization. Using a time-invariant parameter only could have led to an influence of BP on clinical outcome being missed.\textsuperscript{14}

Despite the evidence supporting the association of high BP level and poor outcome, some researchers maintain that BP is of little prognostic value.\textsuperscript{26} Others even argue that constantly high BP can contribute to good outcome.\textsuperscript{27} This controversy may be attributable to the parallel harmful and beneficial effects associated with high BP. On one hand, high BP increases the risk of cerebral edema and HT in an infarcted area. On the other hand, high BP helps to preserve perfusion at an ischemic penumbra.\textsuperscript{28} Maintaining high BP could be beneficial if perfusion of an ischemic area is inadequate because of incomplete recanalization or poor collaterals. Low BP or BP fluctuation could increase infarct size and, as a result, lead to poor outcome.\textsuperscript{29} In contrast, if an occluded vessel is recanalized, high BP may provoke edema or HT. Under these circumstances, there is no doubt that it would be beneficial to maintain BP relatively low and constant within a reasonable range.\textsuperscript{14}

Some limitations of the present study need to be addressed. These include the study being performed in a single university hospital and the retrospective design, which mean that the modality and timing of brain images used to detect HT, as well as the frequency of BP measurements, were variable. Nevertheless, our results strongly suggest that BP variability contributes to the development of HT following acute ischemic stroke. This implies that an effort to maintain BP constantly during the acute stage of ischemic stroke may prevent HT and improve clinical outcome. However, further studies are required to confirm if BP variability does indeed cause HT and to identify the mechanism by which this might occur.

Sources of Funding
This study was supported by grants of the Korea Health 21 Research and Development project, Ministry of Health and Welfare, Korea (A060171).

Disclosures
None.

References

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*Stroke*. 2010;41:2512-2518; originally published online October 14, 2010;
doi: 10.1161/STROKEAHA.110.595561
*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

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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Supplement Table. Interaction analysis between BP variability parameters and thrombolysis

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</table>

* Each variability parameter and its interaction term with thrombolysis were put into the logistic model one by one with mean SBP, age, interval from onset to arrival, initial NIHSS, diabetes mellitus, TOAST classification, thrombolysis, initial serum glucose, and total cholesterol.
급성 허혈뇌졸중의 출혈변환 발생에 대한 혈압 변동성의 의미

The Significance of Blood Pressure Variability for the Development of Hemorrhagic Transformation in Acute Ischemic Stroke

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(Stroke. 2010; 41: 2512-2518)

Key Words: 
- cerebral infarction 
- hemorrhage

배경과 목적: 급성 허혈뇌졸중(ischemic stroke)에서 혈압(blood pressure, BP) 상승은 혼란 관찰되고, 출혈변환(hemorrhagic transformation, HT)과 관련된다고 알려져 있다. 그러나 HT 발생에서의 BP 변동성의 효과는 잘 알려져 있지 않다.

방법: 증상 발생 24시간 이내에 입원하고 첫 기울기에서 자기공명영상(gradient echo MRI)에서 HT가 없었던 급성 허혈뇌졸중 환자들의 272시간 동안의 BP 측정 기록을 확인하였고, 다양한 요약 메개변수를 사용하여 각 환자의 BP 변동성을 기술하였다: 표준편차(SD), 최대값(max), 최소값(min), 최대값과 최소값의 차(max-min), 연속 측정 간 차별 평균(sv)과 최대 sv (smax).

결과: 각기 기준을 만족시키는 환자 792명 중 70명(8.8%)에서 HT가 발생하였다. 사분위수로 분류된 BP 변동성 매개변수들 중 수축기 혈압(SBP)의 최대값(SBPmax), SBP의 최소값(SBPmin), SBP 최대값과 최소값의 차(SBPmax-min), SBP 차별 평균의의 최대값(SBPmax), 이완기 혈압(DBP)의 표준편차(DBPstd), DBP의 최대값(DBPmax), DBP의 최소값(DBPmin), DBP의 최대값과 최소값의 차(DBPmax-min), DBP 차별 평균의의 최대값(DBPmax)에서 평균 SBP, 연령, 증상 발생부터 병원 도착까지 경과 시간, 첫 뇌졸중 중 증상, 당뇨병, 뇌졸중 약, 혈전용해, 첫 포도당고 혈관위험군에 등급한 HT와 통계적으로 의미 있게 연관이 있었다(우도비(likelihood ratio) 경향 분석법에서 P<0.05).

결론: 저자들의 연구는 HT를 예방하기 위해 재해의 BP 수준뿐만 아니라 변동성 또한 고려하여 할지라도 모른다는 것을 나타낸다.

출처: 출혈변환(hemorrhagic transformation, HT)은 급성 허혈뇌졸중(ischemic stroke) 치료와 관계된 보편적이고, 아마도 가장 치명적인 합병증일 것이다.1 제조형 조직플라스마 노렌활성체(recombinant tissue plasminogen activator, rt-PA)로 치료받은 환자들 중에서 10~30%의 HT가 발생하였다고 보고되어 왔다.2,3 혈전용해 관련 HT는 환자의 애로를 극적으로 악화시키기도 모른다는 우려가 있다.4 혈중 크기가 증가하면 첫 24시간 동안 약화 위험과 3개월째 치사율(case-fatality)이 통계적으로 의미 있게 올라간다고 명백히 보여져 왔다.5

첫 전산화단층촬영(CT) 영상에서의 뇌경색증(cerebral infarction) 범위, 유혈심부전(congestive heart failure), 고혈, 첫 고수축기 혈압(high baseline systolic blood pressure)이 rt-PA로 치료받은 환자들에서 HT와 연관된다고 보
고되었다.14 이 요소들 중 첫 고수축기 혈압의 역할은 실험 및 임상에서 모두 유명하다.15 급성 혈관뇌졸중의 조기 치료를 위한 현재 American Heart Association/American Stroke Association 가이드라인은, 정맥내 혈전용해술을 시작하기 전에 수축기 혈압(systolic BP, SBP)을 185 mm Hg, 이완기 혈압(diastolic BP, DBP)을 110 mm Hg 미만으로 유지하도록 권고하고 있다.15

HT는 혈관재장성(revascularization) 치료가 시행되지 않았을 때도 합리적 관찰된다.10,11 BP와 HT의 관계에 대한 많은 연구에

도 불구하고 그들의 원인 관계에 대하여서는 여전히 불분명하다. 급성 뇌졸중에서 높은 BP는 나쁜 결과와 연관이 있다고, 혈압의 역할에 대한 많은 연구들에서 반복적으로 이야기하고 있다.15 임상적 결과에 대한 BP 변동의 영향은 최근 많이 연구되어 왔다.15-17 BP 변동성은 혈관 자체로 인하여 가이자 동조절 작용(autoregulation) 장애가 있는 고혈관(cerebral perfusion)에 부정적인 영향을 끼치고 혈압은 혈관을 약화시킬 수도 있다.15 BP의 감각순환은 혈관 손상으로 피해를 입고 약화된 혈관의 관을 얻을 수 있다. 그러므로 BP 변동성이 HT 발생에 기여할 수 있다는 가설을 세우는 것은 타당하다.

본 연구에서 저자들은 BP 변동성이 급성 혈관뇌졸중 후에 HT의 위험을 증가시키는지, 만약 그러한다면 HT와 BP 변동성 매개변수들의 관계를 규명할 수 있는 가설을 세우는 것은 타당하다.

방법

2004년 1월 1일~2007년 8월 31일에 부산서울대학교병원에 입원한 연속된 혈관뇌졸중 환자를 한국 뇌졸중 등록(Korean stroke registry) 자료를 통해 확인하였다.16 저자들은 뇌졸중 발생 24시간 이내에 입원하고 첫 확장장고 자기공명영상(dif-

fusion-weighted MRI, DWI)에서 상용화를 받은 환자들은 등록하였다. 첫 기울기에 T2 강조 자기공명영상 (gradient echo T2-weighted MRI, GRE)을 촬영하지 않았
저나 씨의 GRE에서 HT를 보였으나, 입원 씨의 14일 이내에 추적
된 영역을 활용하지 않았거나 적절한 BP 자료가 없는 환자들
은 배제하였다. 연구 프로토콜은 지역 연구 윤리 심의 위원회
(institutional review board, IRB)의 승인을 받았다. 환자들
이 일반 병동에서 치료를 받을 때 일상적인 임상의 일부로서
표준 수은 혈압계로 바이어지 않은 판에서 평상시 양의 BP
가 측정되었고, 전자 의료 기록(electronic medical record,
EMR)에 수동으로 입력되었다. 응급실, 혈압측 전문 병동
(stroke unit), 중환자실에서의 BP는 비침습 혈압 감시 체계
로 측정되었다. 자동화된 EMR 시스템에 기록되었다. 콜 72시
간 이내의 BP 측정 기록은 이처럼 EMR 체계로부터 얻었다.

연구학적 프로파일과 뇨증성 이형의 TOAST (Trial of Org
10 172 in Acute Stroke Treatment) 분류, 17 치료와 검사 결
과를 포함한 입원 경로 프로파일을 뇨증성 등록 사업에 의무 기록
검토를 통하여 얻었다. 두 명의 신경과 의사(호흡기, 박정현가)
체14일 이내에 시행된 모든 뇨 영역(전산화단층촬영[CT] 또는
자기공명영상[MRI])을 검토하였고, HT의 존재와 증상도
(weighted κ=0.89; 95% 신뢰구간[CI], 0.82~0.96), 백혈 변
화 등급(0.59; 0.51~0.68), 미세 출혈의 존재와 계수(0.74; 0.64~0.83)에 관한 각 환자의 신경영상 프로파일을 반
단하였다. EUROPEAN Cooperative Acute Stroke Study
(ECASS)에서 제안한 기준에 따라 HT를 방사선학적 차이에
기초하여 4개 범주로 분류하였다: (1) 출혈성사구형(1형hemor-
rhagic infarction type 1, HI-1); (2) 출혈성사구형 2형(HI-2);
(3) 뇨실질내출혈 1형(parenchymal hematoma type 1,
PH-1)과 (4) 뇨실질내출혈 2형(PH-2).

첫 72시간 동안의 BP 프로파일을 각 SBP와 DBP의 다양한
매개변수를 사용하여 표현하였다: 평균(mean), 최대값(max),
최소값(min), 최대값과 최소값의 차이(max~min), 표준편차
(SD), 그리고 BP 변동성을 나타내는 연속 변화(successive
variation, sv)와 최대 sv (svmax)를 사용하였다. SV는 연속
측정된 BP의 평균 차를 계급한 것이고, 다음 등식에 의하여
계산된다.

\[ SV = \sqrt{\frac{1}{n-1} \sum (x_n-x_1)} \]

n은 측 BP 측정 횟수이다. svmax는 연속적인 BP 측정들 간
차 계급의 최대값이다. SD가 변동(variation) 측정에 평범위
하게 사용되고 있지만, sv와 svmax는 변동의 시간 순서를 나
타낼 수 있다. 18 저자들은 이처럼 각 SBP와 DBP의 BP 변동성을
나타내는 6개의 매개변수로 표현하였다: max, min, max~
min, SD, sv, svmax.

변수들의 유의성에 따라 환자들의 기본 특성을 숫자(%, 평균
±SD, 또는 중앙값[사분위수 간 범위(interquartile range,
[IQR])으로 표현하였다. HT가 있는 군과 HT가 없는 군의 비교
에 Student t test 또는 Mann–Whitney U-test를 적절히
사용하였다. 히스토그램으로 각 연속 변수들 분포의 정규성을
눈으로 보아 검사의 적합성을 판단하였다. 비율(proportion)
은 Pearson’s χ² test로 비교하였다. HT의 발생과 각 BP 매
개변수들의 독립적인 관계를 평가하기 위하여 다중 로지스틱
회귀 분석을 사용하였다. 보정(adjustment)을 위하여 단변
된 분석에서 P<0.25인 변수들을 선택하였다. 평균 SBP는 콜 72
시간 동안 BP 수준을 나타내기 위하여 선택하였고, 다중 로지
스틱 회귀 모델에 또한 포함시켰다. BP 매개변수들이 대개 한
단위 변화의 의미를 서로 달았기 때문에 사분위수로 분류하였
다. 같은 모델에서 밀집하게 연관된 변수들의 다중 공선성의
위험을 피하기 위하여 한 모델에 모든 변동성 매개변수들을 포
함시키지 않고 한 번에 하나씩 각 매개변수들을 대체하였다. 결
과로 보정 교차비(odds ratio, OR)와 95% 신뢰구간(CI)을 보
고하였다. 우도비 성격 범위(likelihood ratio test of
trend)로 변동성 매개변수들과 HT 발생의 유방 반응 관계
(dose–response relationship)을 조사하였다.

다른 연구에서 사용된 방법에 따라 15, 16, 17 다른 BP 수준에서도
BP 변동성이 HT에 미치는 영향이 같지 않다고 조사하였다. 환자들은
첫 72시간 동안 평균 BP의 변화가 4cmHg 이하면 2회 측정하여
각 중(stratum)은 다시 그 중의 BP 변동성 매개변수의 중심값 기
준에 의해 나누어 부울 변동성 (≤median)과 높은 변동성 (>median)
으로 나누었다. 각 군에서 HT의 발생 비율을 계산하였다.

Breslow and Day’s test를 사용하여 각 평균 BP 사분위수들
에서 BP 변동성 매개변수들과 HT의 관계의 동질성(homo-
genicity)을 판단하였다.

원도우버전 SPSS 15.0 (SPSS Inc, Chicago, III)로 모든
분석을 하였고, P<0.05가 통계적으로 의미 있는 것으로 간주
하였다.

결과

연구 기간 동안 급성 혈뇨증으로 응원된 1,763명의 환
자들 중 1,046명(59.3%)이 중상 발생 24시간 이내에 응원하였
다. 거의 모든 환자(99.2%, 1,038/1,046)에서 DWI를 활성화
하였고, 1,025명에서 콜 DWI에서 상응하는 빈발이 있었다. 이들
1,025명 중 많은 환자들이 다음의 이유로 배제되었다: 130명
(12.7%)에서 GRE를 활성화하지 않았고 23명(2.2%)은 콜 GRE
에서 이미 HT가 있었으며, 71명(6.9%)은 추적 영역이 없었고
9명(0.9%)에서는 부적절한 BP 기록이 있었다(첫 72시간 동안 9
회 이상의 BP 측정). 결과적으로 792명의 환자들은 이 연구에
참여자로 등록하였다. 평균 환자군과 마지막 추적 영상 간 중앙값
기간은 4일(IQR, 2~6일)이었다.

추적 영상 결과 8.8% (70/792)의 환자에서 HT가 있었는데, 중상
발생과 HT 발견의 중앙값 간격(median interval)은 하
루(IQR, 0~4일)이었다. 단 112명(14.1%)의 환자에서 CT가 추적
영상 수단이었다. 남은 680명(85.9%)에서 MRI를 반복 촬영하 였다. HT 빈도는 CT만 촬영한 군에서 12.5%였고, MRI를 촬영 한 군에서는 8.2%였다(Pearson의 χ² test에서 P<0.14). HT가 있는 70명의 환자들 중 17%(12/70)에서 증상이 있었 고, HT의 유형은 다음과 같았다: HI-1, 6명(8.6%); HI-2, 16 명(22.9%); PH-1, 27명(38.6%); PH-2, 15명(21.4%), HT의 유무에 따른 임상적 특징은 Table 1에 나타난다. HT가 없는 환자들에 비해 HT가 있는 환자들에게 콧맥 혈관상세증 (large artery atherosclerosis)이나 심장성 근환족증(car dioembolic stroke)이 더 많았고 혈전형태를 더 많이 받았으 며, 병원 도착이 조금 더 빨랐고 더 심한 신경학적 결손이 있었 으며, 혈청 포도당치가 더 높았다.

환자당 총 72시간 동안 BP 측정 중간값은 18회(IQR, 14~57)였다. HT가 있는 군은 군의 BP 측정 빈도가 달랐 지만(Mann–Whitney U test에서 P<0.001)(Table 1), 평균 SBP나 DBP는 다르지 않았다(SBPmax와 DBPmax)(Table 2). SD값과 최대값(SBP, SBPmin, DBP, DBPmax)은 HT가 없는 군보다 있는 군에서 더 높았지만, 최소값(SBP, DBPmin)은 HT가 있는 군에서 낮았다(P<0.001), 결과적으로 최대값과 최소값의 차(SBPmax–min, DBPmax–min)는 HT가 없는 군보다 있는 군에서 더 높았다(P<0.001). SBP의 연속 변동성(SBP)은 HT의 존재 유무에 따라 다르지 않았으나(P=0.37), DBP의 연속 변동성(DBP)는 달랐다(HLT 군의 경우, 12.9±4.5: 있는 군, 11.4±3.5, P=0.002). 최대 연속 변동성(SBPmax와 DBPmax)은 HT가 없는 군보다 있는 군에서 더 높았다(P<0.001).

BP 변동성 매개변수의 사분위수 임계값과 각 사분위수에서의 HT 발생률은 Table 3에 나타내고 있다. Mantel–Haenszel χ² test로 SBPmax, SBPmin, SBPmax, SBPmin은 제외한 나머지 매개 변수의 사분위수와 HT 발생률의 의미 있는 선형 관계가 언급 되었다. HT가 없는 군과 있는 군의 유의미 비교에서, 증상을 발생 후 병원 도착까지 걸린 시간, NIHSS (National Institute of Health Stroke Scale), 단노병, TOAST (Trial of Org 172 in Acute Stroke Treatment) 분류, 혈전유해, 혈청 포도 당, 총 클러스테롤이 P<0.25였다(Table 1). 이 변수들과 총 72시간 동안의 평균 SBP를 보정하여 BP 변동성 매개변수들 의 각 사분위수에서 OR값들과 95% CI를 구하였다. SBPmax, SBPmin, SBPmax–min, DBP, DBPmax, DBPmin, DBPmax–min, BPmax–min는 HT 발생과 통계적으로 유의한 관계에 있었다(Table 4). BP 변동성이 혈전유해에 관계 여부에 따라 HT 발생 위험에 까지는 영향이 다른지를 알아보기 위 해 BP 변동성 매개변수와 혈전유해의 상호작용 항목(interaction term)을 로지스틱 모델에 추가하였다(Table 4). BP, SBP를 제외 하고 통계적으로 의미 있는 상호작용은 없었다(부록 Table에서 볼 수 있다. http://stroke.ahajournals.org)."
명할 수 있음지도 모른다. 하지만 그들이 완전한 설명을 제공하는 것 같지는 않다. 이와 관련하여 더 많은 연구가 필요하다.

이 연구에서 SBP의 매개변수보다 DBP의 매개변수가 HT와 더 밀접히 관계되었다는 것은 주목할 만하다. BP 변동성과 뇌졸중 예후에 관한 이전 연구들에서, 원인이 알려져 있는지 않으나 평균 BP나 SBP 변동성보다는 DBP 변동성이 뇌졸중 예후와 더 밀접하게 관계될지도 모른다고 또한 보고하였다.1,11

혈전응해에 기초하거나 혈전응해를 받은 환자들로 대상을 재한한 연구들은 매개변수가 HT 발생에 끼치는 영향에 대한 보고를 찾기 어렵다는 연구. 한 연구에서 BP가 급성 뇌졸중 환자의 HT 발생과 관계가 없다고 보고하였다.10 그러나 BP의 동역학을 나타내는 다양한 매개변수들에 비하여 그 연구에서는 유일하게 입원 기간 중 평균 BP만을 사용하였 다. 하나의 시간 불변(time-invariant) 매개변수를 사용하는

<table>
<thead>
<tr>
<th>Table 3. Rate of HT According to Quartiles of BP Variability Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cutoff Values (mm Hg)</strong></td>
</tr>
<tr>
<td>SBP</td>
</tr>
<tr>
<td>SBP</td>
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<tr>
<td>DBP</td>
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<td>DBP</td>
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<td>DBP</td>
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<tr>
<td>DBP</td>
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<tr>
<td>Hemorrhagic Transformation (%)</td>
</tr>
<tr>
<td>10 (1st quartile) indicates ≤25th percentile: 2Q &gt; 25% and ≤50%; 3Q &gt; 50% and ≤75%; 4Q &gt; 75%.</td>
</tr>
<tr>
<td>Calculated by Mantel-Haenszel χ² test.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 4. Independent Associations Between BP Variability Parameters and the Development of HT After Adjustment for Mean SBP During the First Seventy-Two Hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>First Quartile</td>
</tr>
<tr>
<td>SBP</td>
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<td>SBP</td>
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<tr>
<td>DBP</td>
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<td>DBP</td>
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<td>DBP</td>
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</tbody>
</table>

*Variables adjusted for mean SBP, age, interval from onset to arrival, initial National Institute of Health Stroke Scale, diabetes mellitus, and trial of india 10172 in acute stroke treatment (TOAST) classification, initial serum glucose, and total cholesterol.

†Likelihood ratio test of trend.
건강에 미치는 영향을 높이게 할 수도 있다.

높은 BP 수준은 예후의 관계를 저지하는 증거가 있지만, 몇몇 연구자들은 BP가 예후에 영향을 끼치지 않는다는 결론을 내렸다. 지속적으로 높은 BP가 좋은 예후에 기여할 수 있다는 다른 주장들도 있다. 이 논란은 높은 BP와 연관된 해충과 이로운 효과가 복합된 것일지도 모른다. 한편으로는 높은 BP가 경색된 부위에서 뇌 부중과 HT의 위험을 증가시킨다. 다른 한편으로는 높은 BP는 혈류 운영(ischemic penumbra)에서 관류를 유지하는 데 도움을 준다. 블러인한 재관형성(recanalization)이나 부족한 혈관 막막(collateral)으로 인하여 혈류 부위의 관류가 높출분하면 BP를 높게 유지하는 것이 이론적이다. 낮은 BP나 BP 변동은 경색 크기를 확대시키고 결과적으로 나쁜 결과에 이르게 할 수 있었다.
도 있다. 반대로 폐색된 혈관이 재관형성되면 높은 BP는 부
중이나 HT를 유발할지도 모른다. 이러한 환경에서는 BP를 적
정한 범위 내에서 상대적으로 낮고 일정하게 유지하는 것이 이
모를 수도 있다는 의심의 여지가 없다. 
몇 가지 본 연구의 제한점을 다음과 같다. 이 연구가 한
대학병원에서 후향적 계획으로 수행되었고, 이는 HT를 감지
해낸 반 영상 방법과 시기 뿐만 아니라 BP 측정 횟수도 다양
하다는 것을 의미한다. 그럼에도 불구하고 저자의 결과는
BP 변동성이 급성 혈혈뇌졸중에 있어 생기는 HT 발생에 기여
한다는 것을 강력히 시사한다. 이는 혈혈뇌졸중의 급성기 동안
BP를 일정하게 유지하는 노력이 HT를 예방하고 임상적 결과
를 개선시킬지도 모른다는 것을 암시한다. 하지만 BP 변동성
이 정말 HT를 야기하는지의 여부와 발생 메커니즘을 확인하는
추가 연구가 필요하다.