Frequency of Increased Blood Pressure Levels During Systemic Thrombolysis and Risk of Intracerebral Hemorrhage

Lars Kellert, MD; Andrea Rocco, PhD; Marek Sykora, PhD; Werner Hacke, PhD; Peter A. Ringleb, MD

Background and Purpose—Significantly increased blood pressure (BP) is common in patients receiving intravenous thrombolysis (IVT). We aimed to investigate frequency of pre- and post-treatment elevated BP and its relation to intracerebral hemorrhage (ICH) and symptomatic ICH (sICH), respectively.

Methods—Data for patients treated with intravenous thrombolysis in the years 2007 to 2009 were retrospectively extracted from our prospectively conducted local stroke database. All documented BP levels from admission to follow-up imaging scan were analyzed. BP protocol violations were defined as systolic BP $>185$ mm Hg and/or diastolic BP $>110$ mm Hg. sICH was defined as ICH plus worsening of the National Institute of Health Stroke Scale $\geq 4$ points.

Results—BP protocol violation before IVT emerged in 12.6% and during the course of IVT in 40.1% of 427 patients. sICH occurred in 10 (2.3%) and ICH in general occurred in 51 (11.9%) of 427 patients. Proportions of BP protocol violations were similar in patients without ICH, with any ICH, and with sICH (3.1% vs 2.8% vs 3.2%). Systolic BP levels and mean arterial pressure did not differ between patients without ICH, patients with any ICH, and patients with sICH. In the multivariate analysis, only early CT findings independently predicted ICH (OR, 2.39; 95% CI, 1.25–4.61; $P=0.009$).

Conclusions—BP protocol violations are common before and during the course of IVT, but neither the frequency of BP protocol violations nor the BP levels predicted ICH or sICH in univariate or multivariate analyses. (Stroke. 2011;42:00-00.)

Key Words: blood pressure ■ intracerebral hemorrhage ■ intravenous ■ stroke ■ thrombolysis

There is an ongoing controversy concerning the impact of blood pressure (BP) levels in patients with acute ischemic stroke treated with intravenous thrombolysis (IVT). Patients presenting with pretreatment systolic BP levels $>185$ mm Hg and diastolic BP levels $>110$ mm Hg should be excluded from IVT according to current guidelines of the European Stroke Organization1 or American Heart Association2 because early pilot studies demonstrated an increased risk of symptomatic intracerebral hemorrhage (sICH) associated with elevated BP levels.3,4 However, blood pressure levels are elevated in up to 70% of patients with acute ischemic stroke, and most guidelines only recommend treating high BP when these levels are severely increased (for example, 220/120 mm Hg).1 However, patients treated with IVT represent 1 important exception from this recommendation. Results from randomized clinical trials on this topic are lacking. Recently published studies accentuate the pretreatment systolic BP and the 2-hour and 24-hour systolic BP after IVT, respectively, as independent risk factors for sICH.5–7 This is in line with the current guidelines. Thus, it is still not known how often elevated BP levels emerge in the course of IVT and whether they are associated with ICH and sICH. Our aim was to investigate the frequency of elevated BP and its relation to development of ICH and sICH, respectively.

Patients and Methods

We retrospectively extracted data for consecutively documented patients treated with intravenous recombinant tissue plasminogen activator in the years 2007 to 2009 from our local stroke database. Based on our local standard operating procedures, IVT is offered as standard treatment to patients with acute ischemic stroke who fulfill the criteria of the European labeling, which includes an upper age limit of 80 years and, so far, an upper time limit of 3 hours between symptom onset and treatment. We also offer this treatment to patients older than 80 years and within a longer time window as off-label treatment. Patients presenting within a 4.5-hour time window are usually treated according to CT imaging findings, whereas patients with duration of symptoms longer than 4.5-hour are selected by multimodal MR imaging based on criteria established in the DIAS trials.8

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L.K. collected and analyzed the data, conducted the statistical analysis, and wrote the first draft of the manuscript. A.R. collected clinical data and reviewed the manuscript. M.S. gave advice to the statistical analysis and reviewed the manuscript. W.H. influenced the data analysis and reviewed the manuscript.

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Local standard operating procedures recommend that BP be measured by using an automatic monitoring system (Infinity Delta; Draeger Medical Systems) before IVT, every 15 minutes for the first 2 hours after the start of IVT, and at least hourly thereafter until the follow-up imaging examination.

Before the start of recombinant tissue plasminogen activator treatment, a BP level of $\leq 185/110$ mm Hg is mandatory. If the BP is higher, then pretreatment with antihypertensives, usually urapidil (5–50 mg intravenous), is recommended in the standard operating procedures. Last measured BP before the start of IVT was defined as pretreatment BP. BP protocol violations were defined as systolic BP $> 185$ mm Hg and/or diastolic BP $> 110$ mm Hg. Mean arterial pressure was calculated as (systolic BP + 2 x diastolic BP)/3.

Baseline and demographic characteristics, cardiovascular risk factors, time intervals, admission and follow-up imaging scans, and stroke severity (using NIHSS) were prospectively collected. All patients were reassessed after 3 months either during an outpatient visit or by a telephone interview using the modified Rankin scale by an investigator not blinded to the IVT treatment but unaware of any protocol violations. Early infarct signs were defined as parenchymal hypodensity or loss of gray–white differentiation in the cortical ribbon or the basal ganglia and/or mass effect in the baseline CT attributable to an ischemic lesion.

A control CT (in rare cases a MRI) was performed 20 to 36 hours after IVT or immediately after clinical deterioration. If clinical deterioration developed later, then another scan was performed; thus, later clinically relevant bleedings were also detected. Occurrence of new hyperdense brain lesions were counted as intracerebral hemorrhage (ICH), irrespective of the clinical consequences. According to the definition in the ECASS trials, the ICH were grouped according to radiological appearance. sICH was defined according to the ECASS 2 definition (detection of blood plus clinical deterioration reflecting by NIHSS worsening of $\geq 4$ points).

Realization of this study and management of our local stroke database were performed according to the STROBE statement for reporting case control studies. Because of the retrospective character of this study, the lack of treatment influence, and the clinical data having been collected as part of national and international quality-control programs, we did not apply for the vote of an ethic committee.

**Statistical Analysis**

Distribution of the data were tested using histograms and the 1-sample Kolmogorov-Smirnov test. For normally distributed data, the results are presented as mean and standard deviation and for non-normally distributed data results are presented as median and interquartile range or counts and percentages, respectively. Univariate analysis for comparison between patients with or without ICH was performed by using 1-way ANOVA as indicated. All parameters showing significance in the univariate analysis were tested in a multivariate logistic regression model to explore predictors for ICH and main outcome parameters. Because of the possible collinearity of tested variables, we applied a stepwise logistic regression model. The results were considered statistically significant when $P<0.05$. For all statistical testing, we used the Statistical Package for Social Science (SPSS 16.0 for Windows).

**Results**

For 451 patients treated with IVT in the years 2007 to 2009, complete BP data sets were available for 427 patients. Among them, 203 (47.5%) patients were treated according the European Summary of Product Characteristics criteria. Frequent off-label administration included patients with age older 80 years ($n=126$; 29.5%), a time window of 3.0 to 4.5 hours ($n=58$; 13.6%), time window $> 4.5$ hours ($n=43$; 10.1%), NIHSS $< 4$ or $> 25$ ($n=38$; 8.9%), and elevated BP ($n=54$; 12.6%). Overall, 51 (11.9%) patients experienced any ICH and 10 (2.3%) patients experienced sICH (Figure 1). Table 1 shows baseline characteristics, risk factors for ICH and sICH, radiological ICH types, and BP protocol violations for patients with and without ICH.

Time to follow-up imaging scan was 20.6 hours (7.3) for patients without ICH, 21.3 hours (7.6; $P=0.42$) for patients with any ICH, and 9.7 hours (18.7; $P<0.001$) for patients with sICH. Median (Interquartile Range) frequency of BP measurements was 21.0 (9) for patients without ICH, 20.0 (9) for patients with any ICH, and 11.0 (15) for patients with sICH.

Pretreatment BP protocol violations were identified in 54 patients (12.6%); however, no significant differences were observed between patients without ICH (47; 12.5%), with any ICH (7; 13.7%; $P=0.81$), and with sICH (2; 20.0%; $P=0.48$). During and after IVT until follow-up imaging scan, BP protocol violations had occurred in 175 (40.1%) patients, in 155 (41.2%) patients without ICH, in 20 (39.2%) patients with any ICH ($P=0.99$), and in 5 (50%) patients with sICH ($P=0.58$).

The proportion of BP protocol violations in relation to the overall number of measurements per patient was 3.1% for patients without ICH, 2.8% for patients with any ICH, and 3.2% for patients with sICH (Figure 2).

There were no significant differences in maximum systolic BP (median; interquartile range) between patients without ICH (180 mm Hg: 30), with any ICH (180 mm Hg: 20; $P=0.81$), and with sICH (178 mm Hg: 35; $P=0.71$), or in mean systolic BP between patients without ICH (148 mm Hg: 22.3), with any ICH (152 mm Hg: 25.3; $P=0.39$), and with sICH (156 mm Hg: 16.5; $P=0.44$). The maximum mean arterial pressure did not differ between patient without ICH (122 mm Hg: 20), with any ICH (125 mm Hg: 16.6; $P=0.67$), and with sICH (126 mm Hg: 26.6; $P=0.79$), and the mean of the mean arterial pressure between patients without ICH (99 mm Hg: 13.2), with any ICH (103 mm Hg: 13.7; $P=0.12$), and sICH (104 mm Hg: 12.5; $P=0.64$) were within the same range from admission to follow-up imaging scan (Figure 3).

Multivariate analysis of risk factors for any ICH after IVT, including atrial fibrillation, NIHSS on admission, early in-
farct signs, and platelets only found early infarct signs (OR, 2.39; 95% CI, 1.25–4.61) to be an independent risk factor (Table 2). In univariate analysis, only early infarct signs were a significant risk factor for sICH (Table 1). Thus, no multivariate analysis for sICH was performed. Stepwise logistic regression model found age (OR, 1.08; 95% CI, 1.05–1.11), NIHSS on admission (OR, 1.11; 95% CI, 1.07–1.15), and sICH (OR, 10.55; 95% CI, 1.64–68.09) as independently associated with 3-month mortality.

**Discussion**

BP monitoring and treatment are still the subjects of discussion in acute stroke management. Before, during, and 24 hours after administration of IVT, an upper limit of 185/110 mm Hg is recommended. The suggestion to withhold recombinant-tissue plasminogen activator in patients with markedly elevated BP levels is based on potential safety risks, particularly the risk of intracerebral bleeding. We demonstrate the incidence of BP protocol violations before and during IVT administration and show the impact of these violations on clinical outcomes.

### Table 1. Univariate Analyses of Baseline Characteristics and Risk Factors for Intracerebral Hemorrhage

<table>
<thead>
<tr>
<th>Parameter</th>
<th>No ICH, n=376 (88.1%)</th>
<th>Any ICH, n=51 (11.9%)</th>
<th>P*</th>
<th>sICH‡, n=10 (2.3%)</th>
<th>P§</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>72.7 (12.8)</td>
<td>73.2 (11)</td>
<td>0.83</td>
<td>74.9 (14.6)</td>
<td>0.59</td>
</tr>
<tr>
<td>Female</td>
<td>195 (51.8%)</td>
<td>25 (49.0%)</td>
<td>0.70</td>
<td>8 (80%)</td>
<td>0.08</td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>303 (80.6%)</td>
<td>41 (80.4%)</td>
<td>0.99</td>
<td>10 (100%)</td>
<td>0.13</td>
</tr>
<tr>
<td>Diabetes</td>
<td>91 (24.2%)</td>
<td>10 (19.6%)</td>
<td>0.50</td>
<td>3 (30%)</td>
<td>0.66</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>92 (24.5%)</td>
<td>13 (25.5%)</td>
<td>0.85</td>
<td>3 (30%)</td>
<td>0.68</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>123 (32.7%)</td>
<td>24 (47.1%)</td>
<td>0.041</td>
<td>5 (50%)</td>
<td>0.25</td>
</tr>
<tr>
<td>Nicotine use</td>
<td>66 (17.6%)</td>
<td>8 (15.7%)</td>
<td>0.77</td>
<td>1 (10%)</td>
<td>0.55</td>
</tr>
<tr>
<td>Antiplatelet use</td>
<td>163 (43.4%)</td>
<td>24 (47.1%)</td>
<td>0.64</td>
<td>5 (50%)</td>
<td>0.48</td>
</tr>
<tr>
<td>Anticoagulant use</td>
<td>21 (5.6%)</td>
<td>4 (7.8%)</td>
<td>0.52</td>
<td>0 (0%)</td>
<td>0.47</td>
</tr>
<tr>
<td>Previous cardiovascular event</td>
<td>61 (16.2%)</td>
<td>10 (19.6%)</td>
<td>0.52</td>
<td>4 (40%)</td>
<td>0.05</td>
</tr>
<tr>
<td>Risk factors for ICH and sICH</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early infarct signs on CT,† n=394</td>
<td>99 (n=348; 28.4%)</td>
<td>24 (n=46; 52.2%)</td>
<td>0.0011</td>
<td>6 (n=10; 60%)</td>
<td>0.018</td>
</tr>
<tr>
<td>Time window, min</td>
<td>168.4 (102.8)</td>
<td>170.5 (94.4)</td>
<td>0.89</td>
<td>179.7 (55.5)</td>
<td>0.73</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>87 (23.1%)</td>
<td>18 (35.3%)</td>
<td>0.06</td>
<td>5 (50%)</td>
<td>0.05</td>
</tr>
<tr>
<td>Platelets</td>
<td>263.5 (95.6)</td>
<td>233.3 (62.4)</td>
<td>0.028</td>
<td>246.7 (73.3)</td>
<td>0.58</td>
</tr>
<tr>
<td>Platelets count, &lt;100/nL</td>
<td>3 (0.7%)</td>
<td>0</td>
<td>0.52</td>
<td>0</td>
<td>0.78</td>
</tr>
<tr>
<td>Serum glucose, mg/dL</td>
<td>134.7 (47.7)</td>
<td>139.5 (44.4)</td>
<td>0.45</td>
<td>127.6 (29.9)</td>
<td>0.64</td>
</tr>
<tr>
<td>NIHSS on admission</td>
<td>10.5 (9)</td>
<td>14 (8)</td>
<td>0.015</td>
<td>15.5 (12)</td>
<td>0.47</td>
</tr>
<tr>
<td>Pretreatment BP protocol violations</td>
<td>47 (12.5%)</td>
<td>7 (13.7%)</td>
<td>0.81</td>
<td>2 (20%)</td>
<td>0.48</td>
</tr>
<tr>
<td>Posttreatment BP protocol violations</td>
<td>155 (41.2%)</td>
<td>20 (39.2%)</td>
<td>0.99</td>
<td>5 (50%)</td>
<td>0.58</td>
</tr>
<tr>
<td>Proportion of BP protocol violations (N of measured BP per patient)</td>
<td>3.1% (21, 9)</td>
<td>2.8% (20, 9)</td>
<td>0.70</td>
<td>3.2% (11, 15)</td>
<td>0.97</td>
</tr>
<tr>
<td>BP intervention</td>
<td>131 (34.8%)</td>
<td>21 (41.2%)</td>
<td>0.37</td>
<td>2 (20%)</td>
<td>0.33</td>
</tr>
<tr>
<td>Latency to follow-up imaging scan, h</td>
<td>20.6 (7.3)</td>
<td>21.3 (7.8)</td>
<td>0.42</td>
<td>9.7 (18.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Off-label treatment</td>
<td>202 (53.7%)</td>
<td>22 (43.1%)</td>
<td>0.16</td>
<td>7 (70%)</td>
<td>0.31</td>
</tr>
</tbody>
</table>

**ICH types**

- HI1 14 (3.3%)
- HI2 10 (2.3%)
- PH1 16 (3.7%)
- PH2 10 (2.3%)
- SAH † 1 (0.3%)
- sICH 10 (2.3%)‡

Numbers are mean (SD) or median (IQR) or counts (percentages).

BP indicates blood pressure; CT, computed tomography; ICH, intracerebral hemorrhage; HI, hemorrhagic infarction; NIHSS, National Institutes of Health Stroke scale; PH, parenchymal hematoma; SAH, subarachnoid hemorrhage; sICH, symptomatic intracerebral hemorrhage.

*One-way analysis of variance.

†Thirty-three patients were treated based on magnetic resonance imaging.

‡ECASS 2 definition.

§Comparison between no ICH and sICH.
during the course of IVT. Our rate of 12.6% pretreatment BP protocol violations is similar to the rate of 12.4% reported in a recently published study. In addition, we found a significant increase in BP protocol violations in the course of IVT of up to 40.1% during the first few hours. Similar rates of BP protocol violations before and after treatment emerged in patients with and without ICH. Although BP protocol violations seem to be common, we found no increased risk for sICH. In fact, the sICH rate of 2.3% in our cohort is somewhat lower than the risks for sICH reported, for example, in SITS-MOST (4.6%) and in the ECASS 3 trial (5.3%) using the same definition. This is even more notable because more than half of our patients were treated off-label. This observation is in agreement with a recently published study demonstrating that off-label thrombolysis was not associated with poor outcome and ICH.

In contrast to other reports, we found no difference in BP levels between patients without and with ICH, and BP levels did not seem to be a predictor of ICH or sICH, respectively. The most likely reason for this surprising observation is that the proportion of BP protocol violations in ratio to no BP protocol violations is only approximately 3%, again within the same range in patients with and without ICH. This might indicate that our BP management standard during thrombolysis is sufficient in preventing long-lasting elevated BP. However, the authors are still concerned about the impact of elevated BP levels in IVT in acute ischemic stroke as a risk factor for sICH. We purport that if BP protocol violations arise in isolated cases and adequate treatment is directly introduced, then the risk for sICH does not seem to be increased and thus there is no need to withhold or interrupt thrombolysis in those patients.

Both low and high BP levels are associated with poor outcome after ischemic stroke. Several studies reported that a U-shape relationship between systolic BP and outcome parameters with different ranges of systolic BP, eg, 141 to 150 mm Hg or a plateau between 140 and 179 mm Hg, was related to most favorable outcome. With regard to the controversy about optimal BP levels in acute stroke, our data suggest that the bleeding rate after IVT in a cohort with a moderate number of BP violations is not increased. Aggressively lowering BP to prevent ICH may not be required. On the contrary, adverse consequences of lowering BP for the ischemic penumbra could be more relevant. Rapid and adequate treatment of BP protocol violations might be more essential for reducing sICH risk during the course of IVT than therapeutically lowering BP in general. We further demonstrated that the incidence of BP protocol violations was not related to a poor outcome in our patients.

Certain limitations of this study must be acknowledged. First, this is a retrospective single-center analysis of prospec-

Table 2. Multivariate Logistic Regression Model to Predict Any Intracerebral Hemorrhage

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial fibrillation</td>
<td>1.7 (0.92–3.23)</td>
<td>0.09</td>
</tr>
<tr>
<td>NIHSS on admission</td>
<td>1.02 (0.98–1.07)</td>
<td>0.27</td>
</tr>
<tr>
<td>Early infarct signs</td>
<td>2.39 (1.25–4.61)</td>
<td>0.009</td>
</tr>
<tr>
<td>Platelets</td>
<td>0.99 (0.99–1.00)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; NIHSS, National Institutes of Health Stroke scale.
tively collected data. Because of the retrospective character of this study, we cannot refer to patients who were not treated with IVT of any reason, especially because of BP violations. Second, our collective is smaller than those in similar studies. However, as compared to the publication of the SITS registry data on this topic, much more BP values and, thus, also, short-term abnormalities could be analyzed. Third, we did not know the duration of BP protocol violations exactly. Therefore, we cannot indicate the duration of BP protocol violation that would be critical for the risk of sICH. Fourth, we did not focus on optimal BP levels for favorable outcome.

Conclusions
We demonstrate a relevant incidence before IVT and a substantial increase in BP protocol violations during the course of IVT. Neither the frequency of BP protocol violations nor BP levels predicted ICH or sICH in univariate or multivariate analyses in our patients.

Disclosures
Peter Ringleb has received honoraria for lectures from Boehringer Ingelheim and was an investigator in ECASS 2 and ECASS 3. Werner Hacke has received honoraria and compensations for membership of trials steering committee from Boehringer Ingelheim and was principal investigator of the ECASS 1 to 3 trials.

References
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