Association of Pretreatment Blood Pressure With Tissue Plasminogen Activator-Induced Arterial Recanalization in Acute Ischemic Stroke

Georgios Tsivgoulis, MD; Maher Saqqur, MD; Vijay K. Sharma, MD; Annabelle Y. Lao, MD; Michael D. Hill, MD; Andrei V. Alexandrov, MD; for the CLOTBUST Investigators

Background and Purpose—Elevated systolic blood pressure (SBP) and lack of early vessel recanalization are predictors of poor outcome among patients with stroke treated with systemic tissue plasminogen activator (tPA). We aimed to evaluate the potential relationship between pretreatment SBP and tPA-induced recanalization.

Methods—Consecutive patients with acute ischemic stroke resulting from intracranial artery occlusion were treated with standard intravenous tPA and assessed with 2-MHz transcranial Doppler for arterial recanalization. Early arterial recanalization was determined with previously validated Thrombolysis in Brain Ischemia flow grading system at 120 minutes after tPA bolus. Functional outcome at 3 months was evaluated using the modified Rankin Scale.

Results—A total of 351 patients received intravenous tPA (mean age: 68.7 ± 13.4 years, median National Institutes of Health Stroke Scale score 16.5). Patients with complete recanalization (n=94) had lower mean pretreatment SBP values (152 ± 23 mm Hg) than patients with incomplete or absent recanalization (n=257, 160 ± 22 mm Hg, P=0.010). Pretreatment SBP levels were inversely associated with complete recanalization (OR per 10-mm Hg increase: 0.85; 95% CI: 0.74 to 0.98, P=0.022) after adjustment for demographics, risk factors, stroke severity, pretreatment Thrombolysis in Brain Ischemia grades, and continuous versus intermittent exposure to transcranial Doppler. Although patients with poor functional 3-month outcomes (modified Rankin Scale >2) had higher pretreatment SBP values (160 ± 25 mm Hg) than functionally independent patients (154 ± 20 mm Hg, P=0.027), pretreatment SBP levels were not independently associated with functional outcome on multivariable analysis. Age, complete recanalization, baseline National Institutes of Health Stroke Scale score, and time from symptom onset to tPA bolus were independent (P<0.05) predictors of 3-month outcome.

Conclusion—Higher pretreatment SBP levels are associated with poor recanalization in patients with acute stroke treated with intravenous tPA. (Stroke. 2007;38:961-966.)

Key Words: blood pressure □ outcome □ recanalization □ stroke □ thrombolysis

Intravenous tissue plasminogen activator (tPA) is the only approved treatment for acute ischemic stroke with a number needed to treat of 8 to cure one additional stroke.1 Several factors, including stroke severity, older age, systolic hypertension, extent of hypodensity or brain swelling on pretreatment CT, and admission hyperglycemia were shown to predict poor outcome in patients with stroke treated with tPA.2-5 On the contrary, early arterial recanalization is strongly associated with early neurologic improvement, reduced infarct size, and favorable early as well as sustained long-term outcome after thrombolysis.6-9 Recently, the course of elevated systolic blood pressure (SBP) was found to be inversely associated with the degree of vessel recanalization in patients treated with intraarterial thrombolysis. SBP levels remained elevated longer when recanalization failed.10

The purpose of the present study was to determine the relationship between pretreatment blood pressure levels and early recanalization in consecutive patients with acute stroke treated with intravenous tPA using a multicenter data set based on the Combined Lysis of Thrombus in Brain Ischemia Using Transcranial Ultrasound and Systemic t-PA protocol.

Methods

The present analysis included all tPA-treated patients with symptoms of acute cerebral ischemia caused by an intracranial artery (middle cerebral artery [MCA], terminal internal cerebral artery, anterior cerebral artery [ACA], basilar artery, and vertebral artery) occlusion on pretreatment transcranial Doppler (TCD). Clinical and ultrasound
data were prospectively collected in 4 academic stroke centers (Houston, Barcelona, Edmonton, and Calgary) and entered into a multicenter database. Our multicenter database was designed using the Combined Lysis of Thrombus in Brain Ischemia Using Transcranial Ultrasound and Systemic t-PA trial methodology.11,12 On arrival in the emergency room, patients underwent standard neurologic examination, electrocardiogram, blood chemistry, and noncontrast CT before tPA administration. Clinical status at baseline was assessed with the National Institutes of Health Stroke Scale (NIHSS) by a certified neurologist. Pretreatment SBP was measured using automated cuffs. When SBP exceeded 185 mm Hg, antihypertensive agents were given (first-line agents: labetalol or nicardipine).

All patients received intravenous tPA according to standard criteria.13 The patients received either continuous or intermittent 2-MHz TCD assessment of recanalization within 2 hours of tPA bolus. All patients had evidence of obstructive residual flow signals in proximal intracranial arteries on baseline TCD assessment before tPA bolus. An experienced physician–sonographer diagnosed these occlusions using previously validated criteria, including the Thrombolysis in Brain Ischemia (TIBI) flow-grading system, if grades 0 to 3 were present.14,15 Concomitant and persisting severe stenosis or occlusion of the proximal internal carotid artery was established by carotid duplex ultrasonography or by angiography. In all patients with anterior circulation occlusions, transducers were positioned over the temporal bone with a standard head frame (M arc series; Spencer Technologies). The depth with the worst residual flow signal as measured on the TIBI scale was selected for display. An insolation depth of 45 mm or more was used for the identification of proximal (ie, M1) MCA occlusion and depths of 30 to 45 mm for presumed distal occlusions (ie, M2). Contralateral ACA (if available) or ipsilateral MCA were used as comparison vessels in case of ACA occlusions. In patients with evidence of posterior circulation occlusions (vertebral or basilar artery), TIBI flow grade was determined through the transfeninal window after analyzing the worst flow signal detected at the presumed occlusion site. Normal vertebral artery (if available) was used as the comparison vessel in cases of basilar artery occlusion. TIBI grade was compared with the contralateral vertebral or the basilar artery in patients with suspected vertebral artery occlusions.

Early arterial recanalization was determined using the TIBI system by the site investigators who gave t-PA and monitored residual blood flow signals. Recanalization was determined 2 hours after t-PA bolus. Complete recanalization was diagnosed if flow improved to TIBI grades 4 to 5 and partial recanalization was identified if flow improved by one grade or more from the baseline but not to grades 4 to 5 on the TIBI scale. Patients with reocclusion within 2 hours were diagnosed as having persisting occlusion 2 hours after tPA bolus if patients with concomitant and persisting severe stenosis or occlusion of the proximal internal carotid artery, complete recanalization of the MCA was considered to have been achieved if TCD showed low-resistance waveforms (TIBI 2 or greater) over both M1 and M2 segments with an improvement in mean flow velocity to more than 20 cm/sec.12,13 Ischemic stroke subtypes were classified according to the Trial of Org 10172 in Acute Stroke Treatment subtypes, baseline TIBI grade, NIHSS score, pretreatment SBP and serum glucose, continuous versus intermittent exposure to TCD ultrasonography) were performed. To maximize sensitivity, those variables with a univariable association of P<0.2 were included as candidates into a multivariable logistic regression model and then removed by the backward stepwise selection procedure. To confirm the robustness of multivariable models, we repeated all multivariable analyses using a forward selection procedure. Predictor variables that were significant at P<0.05 were retained in the multivariable model. Associations are presented as OR with corresponding 95% CIs. Because the absence of symmetric counterpart vessels in patients with vertebral artery, basilar artery, and ACA occlusions might be a source of discrepancies in the calculation of a valid TIBI score, all analyses were repeated after excluding the former patient subgroups. The Statistical Package for Social Science (version 11.5 for Windows; SPSS Inc., Chicago, IL) was used for statistical analyses.

Results

We evaluated 351 patients (mean age 69±13 years; 188 men, 163 women) with acute ischemic stroke resulting from intracranial artery occlusions. The median baseline NIHSS score was 16.5 (interquartile range: 7 points). The median time from symptom onset to tPA bolus was 136 minutes (interquartile range: 60 minutes). A total of 275 patients received continuous 2-MHz TCD ultrasonography, whereas 76 patients received intermittent TCD assessments. Baseline TCD revealed proximal MCA (n=178), distal MCA (n=97), tandem internal carotid artery/MCA (n=56), terminal internal cerebral artery (n=11), basilar (n=4), vertebral (n=3), and ACA (n=2) occlusions. The distribution of ischemic stroke subtypes was large artery atherosclerotic stroke (n=87 [25%]), cardioembolic stroke (n=165 [47%]), infarct of undetermined cause (n=87 [25%]), and infarct of other determined cause (n=12 [3%]).

Complete recanalization at 2 hours after t-PA bolus was seen in 94 patients (26.8%). Partial recanalization was identified in 98 patients, whereas persisting occlusion was documented in 159 cases. Arterial reocclusion was present in 51 patients (15%). Pretreatment SBP values were different among patients with complete recanalization (152±23 mm Hg), reocclusion (157±20 mm Hg), and persisting occlusion (161±22 mm Hg; F=3.989, df=2, P=0.019). The pretreatment SBP levels of patients with atrial fibrillation (157±23 mm Hg) were similar (P>0.5) to patients without any history or electrocardiographic evidence of atrial fibrillation (159±22 mm Hg). SBP values did not differ among patients with large artery atherosclerotic stroke (157±25 mm Hg), cardioembolic stroke (158±23 mm Hg), infarct of undetermined cause (157±19 mm Hg), and infarct of other determined cause (156±26 mm Hg; F=0.054, df=3, P>0.9). Although there was no difference (P>0.2) in pretreatment SBP levels by various TIBI grades before tPA bolus, higher pretreatment mean SBP levels were documented in patients with persisting high resistance occlusions (TIBI grade 0 to 1; 161±21 mm Hg) 2 hours after the t-PA bolus compared with patients with normal or low resistance residual flow (TIBI grade 2 to 5; 154±22 mm Hg; P=0.009) 2 hours after the initiation of thrombolytic treatment.
The following factors were associated with complete recanalization on univariable analyses (P<0.2, Table 1): hypertension, diabetes mellitus, exposure to 2-hour TCD monitoring, pretreatment SBP and serum glucose levels, baseline TIBI grades, and baseline NIHSS scores. The distribution of Trial of Org 10172 in Acute Stroke Treatment subtypes in patients with complete recanalization was similar to patients with persisting occlusion or incomplete recanalization (Table 1). In a multivariable logistic regression model (Table 2) complete recanalization was more likely in patients exposed to continuous TCD monitoring (OR: 3.54; 95% CI: 1.68 to 7.46) and less likely among patients with baseline TIBI grade <2 (OR: 0.47; 95% CI: 0.25 to 0.87), higher baseline serum glucose levels (OR per additional 10 mg/dL: 0.94; 95% CI: 0.90 to 0.99), higher SBP (OR per additional 10 mm Hg: 0.85; 95% CI: 0.74 to 0.98), and higher NIHSS (OR per one-point increase: 0.94; 95% CI: 0.88 to 0.99). The multivariable model’s internal validity was assessed using the Hosmer-Lemeshow goodness-of-fit test (χ² statistic=10.433, df=8, P=0.236) that indicated the model was internally valid.

All analyses were repeated after excluding the patients with basilar artery, ACA, and vertebral artery occlusions (n=9). Higher pretreatment SBP levels were documented in patients with persisting occlusion or incomplete recanalization (160±23 mm Hg, n=251) than in patients with complete comparison (151±22 mm Hg, n=91, P=0.016). In the former subgroup of patients (including only MCA or terminal internal cerebral artery occlusions), the following factors were independently (P<0.05) associated with vessel recanalization on the multivariate analyses: continuous TCD monitoring (OR: 3.81; 95% CI: 1.76 to 8.23), baseline TIBI grade

### Table 1. Univariable Analysis of Factors Associated With Complete Recanalization at 2 Hours After tPA Bolus

<table>
<thead>
<tr>
<th>Variable</th>
<th>Persistent Occlusion or Partial Recanalization</th>
<th>Complete Recanalization</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>69±14</td>
<td>68±13</td>
<td>0.224</td>
</tr>
<tr>
<td>Male sex</td>
<td>53%</td>
<td>54%</td>
<td>0.875</td>
</tr>
<tr>
<td>Hypertension</td>
<td>67%</td>
<td>60%</td>
<td>0.196</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>37%</td>
<td>20%</td>
<td>0.009</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>35%</td>
<td>27%</td>
<td>0.242</td>
</tr>
<tr>
<td>Median baseline NIHSS (interquartile range)</td>
<td>17 (6)</td>
<td>15 (6)</td>
<td>0.020</td>
</tr>
<tr>
<td>Pretreatment blood glucose</td>
<td>156±79</td>
<td>131±49</td>
<td>0.011</td>
</tr>
<tr>
<td>Pretreatment SBP</td>
<td>160±22</td>
<td>152±23</td>
<td>0.001</td>
</tr>
<tr>
<td>Baseline TIBI score &lt;2</td>
<td>68%</td>
<td>50%</td>
<td>0.001</td>
</tr>
<tr>
<td>Median time from symptom onset to tPA bolus</td>
<td>142 (43)</td>
<td>145 (48)</td>
<td>0.209</td>
</tr>
<tr>
<td>Continuous ultrasound exposure for 2 hours</td>
<td></td>
<td></td>
<td>0.019</td>
</tr>
<tr>
<td>Trial of Org 10172 in Acute Stroke Treatment subtype</td>
<td></td>
<td></td>
<td>0.222*</td>
</tr>
<tr>
<td>Large artery atherosclerotic stroke</td>
<td>28%</td>
<td>17%</td>
<td></td>
</tr>
<tr>
<td>Cardioembolic stroke</td>
<td>46%</td>
<td>51%</td>
<td></td>
</tr>
<tr>
<td>Infarct of undetermined cause</td>
<td>23%</td>
<td>29%</td>
<td></td>
</tr>
<tr>
<td>Infarct of other determined cause</td>
<td>3%</td>
<td>3%</td>
<td></td>
</tr>
</tbody>
</table>

Table continued...

Continuous values are presented as mean±SD or median (interquartile range). Noncontinuous variables are presented as percentages.

*χ² statistic=4.394, df=3.

### Table 2. Independent Predictors of Complete Recanalization 2 Hours After tPA Bolus in the Multivariable Logistic Regression Analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient (SE)</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline NIHSS (per one-point increase)</td>
<td>−0.067 (0.031)</td>
<td>0.94 (0.88 to 0.99)</td>
<td>0.031</td>
</tr>
<tr>
<td>Pretreatment blood glucose (per 10-mg/dL increase)</td>
<td>−0.057 (0.026)</td>
<td>0.94 (0.90 to 0.99)</td>
<td>0.027</td>
</tr>
<tr>
<td>Pretreatment SBP (per 10-mm Hg increase)</td>
<td>−0.159 (0.069)</td>
<td>0.85 (0.74 to 0.98)</td>
<td>0.022</td>
</tr>
<tr>
<td>Continuous ultrasound exposure for 2 hours after tPA bolus</td>
<td>1.264 (0.380)</td>
<td>3.54 (1.68 to 7.46)</td>
<td>0.001</td>
</tr>
<tr>
<td>Baseline TIBI grade (0 to 1 vs 2 to 3)</td>
<td>−0.762 (0.316)</td>
<td>0.47 (0.25 to 0.87)</td>
<td>0.016</td>
</tr>
</tbody>
</table>
TABLE 4. Independent Predictors of Good Functional Outcome at 3 Months in Multivariable Logistic Regression Analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient (SE)</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per 1-year increase)</td>
<td>-0.068 (0.018)</td>
<td>0.93 (0.90 to 0.97)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline NIHSS</td>
<td>-0.142 (0.044)</td>
<td>0.87 (0.80 to 0.94)</td>
<td>0.001</td>
</tr>
<tr>
<td>Complete recanalization</td>
<td>1.788 (0.428)</td>
<td>5.98 (2.58 to 13.84)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time from onset of symptoms to tPA bolus (per 1-minute increase)</td>
<td>-0.011 (0.005)</td>
<td>0.99 (0.98 to 1.00)</td>
<td>0.039</td>
</tr>
</tbody>
</table>

TABLE 3. Rates of Complete Recanalization 2 Hours After tPA Bolus Stratified by Pretreatment SBP Levels

<table>
<thead>
<tr>
<th>SBP Subgroups</th>
<th>Persistent Occlusion or Partial Recanalization</th>
<th>Complete Recanalization</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n, %)</td>
<td>(n, %)</td>
</tr>
<tr>
<td>&gt;185 mm Hg</td>
<td>24 (86%)</td>
<td>4 (14%)</td>
</tr>
<tr>
<td>140 to 185 mm Hg</td>
<td>180 (75%)</td>
<td>60 (25%)</td>
</tr>
<tr>
<td>&lt;140 mm Hg</td>
<td>53 (64%)</td>
<td>30 (36%)</td>
</tr>
</tbody>
</table>

χ² = 6.329, df = 2, P = 0.042.

<2 (OR: 0.49; 95% CI: 0.26 to 0.95), baseline serum glucose levels (OR per additional 10 mg/dL: 0.94; 95% CI: 0.89 to 0.99), pretreatment SBP (OR per additional 10 mm Hg: 0.85; 95% CI: 0.73 to 0.98), baseline NIHSS (OR per one-point increase: 0.93; 95% CI: 0.87 to 0.99), and tandem internal carotid artery/MCA lesions (OR: 0.16; 95% CI: 0.05 to 0.49).

Finally, exclusion of patients with reocclusion from the multivariable model did not affect the independent relationship between pretreatment SBP and recanalization (OR per additional 10 mm Hg: 0.85; 95% CI: 0.74 to 0.96; P = 0.010).

The rate of complete recanalization 2 hours after the tPA bolus was 14% in patients with higher pretreatment SBP (>185 mm Hg), 25% in cases with SBP of 140 to 185 mm Hg, and 36% in patients with SBP <140 mm Hg (P = 0.042, Table 3). No significant (P>0.4) differences were documented concerning pretreatment SBP values between patients with proximal (157±22 mm Hg) and distal (159±23 mm Hg) MCA occlusion as well as between patients with tandem MCA/internal carotid artery (158±23 mm Hg) occlusion and isolated MCA (158±22 mm Hg) occlusion. sICH occurred in 28 patients (8.0%). The rate of sICH was similar in patients with continuous (n=23 [8%]) and intermittent TCD monitoring (n=5 [7%], P>0.6). The baseline SBP levels in the subgroup of sICH (157±27 mm Hg) were similar to patients without sICH (158±22 mm Hg; P>0.8).

At 3 months, mRS scores were available for 292 patients (83%). Pretreatment SBP levels did not differ (P>0.5) between patients with complete (157±20 mm Hg) and incomplete 3-month (159±23 mm Hg) follow up. A total of 137 (47%) patients became functionally independent (mRS score ≤2), whereas 61 (21%) patients had died during the follow-up period. Functionally dependent (mRS score 3 to 5) or dead patients had higher pretreatment mean SBP levels (160±25 mm Hg) and lower complete recanalization rates (13%) 2 hours after t-PA bolus in comparison to subjects with good functional outcome (154±20 mm Hg and 47%, respectively; P<0.05). The multivariable logistic regression model (Table 4) showed age, complete recanalization, baseline NIHSS, and elapsed time from symptom onset to t-PA bolus infusion were independent (P<0.05) predictors of good outcome at 3 months. Pretreatment SBP was not independently associated with outcome on multivariable logistic regression analyses (P>0.5) both for the whole study group and after exclusion of patients with vertebral artery, MCA, and ACA occlusions.

**Discussion**

Our study showed that higher pretreatment SBP levels were associated with lower rate of complete recanalization 2 hours after tPA bolus among patients with acute stroke treated with intravenous tPA. Pretreatment SBP values turned out to be higher in patients with persisting high-resistance occlusions that had the worst residual flow 2 hours after tPA bolus. However, only the recanalization rate and not pretreatment SBP was an independent predictor of 3-month outcome in the multivariable logistic regression analysis.

Mattle et al have recently investigated the potential association between the course of blood pressure values and the grades of recanalization determined using Thrombolysis in Myocardial Infarction criteria in a series of patients treated with intraarterial thrombolysis. Interestingly, larger SBP decreases were documented in subjects with successful recanalization, whereas a persistent elevation of SBP values inversely correlated to the degree of recanalization. However, it should be noted that the blood pressure levels before thrombolysis did not differ between patients with adequate and inadequate recanalization. This discrepancy with our results may be associated with the longer time window used for intraarterial thrombolytic treatment, different methods of blood pressure recording (automatically versus manually), and the different criteria for determination of vessel recanalization (Thrombolysis in Myocardial Infarction grades versus TIBI grades) between the 2 studies.

We hypothesize that the inverse relationship between increased pretreatment SBP levels and vessel patency might be attributable to the following different pathophysiological mechanisms.

**Association of Increased Pretreatment Systolic Blood Pressure Levels With Cerebral Edema**

In experimental studies, poststroke hypertension increased blood–brain barrier permeability and exacerbated cerebral edema during the first hours of focal brain ischemia. SBP >180 mm Hg was an independent predictor of cerebral edema in the placebo arm of the Lubezulole-International-9 trial. Furthermore, elevated 24-hour SBP levels documented by means of oscillometric blood pressure-monitoring devices were also associated with subsequent cerebral edema formation in a series of hyperacute patients with stroke. Interestingly, in the present study, higher pretreatment SBP values were observed in patients with persisting high-resistance occlusions. Because brain swelling is associated with increased resistance to residual blood flow, it may be assumed that high pretreatment blood pressure values by exacerbating early brain swelling could have a possible detrimental effect on vessel recanalization. In addition, cyto-
toxic edema can impede microcirculation in the core of infarction during the first 3 hours of ictus as seen in animal models of the MCA occlusion. In our study, the baseline stroke severity was high (median NIHSS score 16 points). Thus, patients with future malignant MCA infarction in which mass effect and extreme elevations of intracranial pressure could develop within the first hours of brain ischemia were included in the present analyses. On the other hand, it can be argued that at the time of thrombolysis, it is too early for mass effect to develop and thus is unlikely that early brain swelling might have increased intracranial pressure and impeded residual cerebral blood flow at such a narrow time window from stroke onset.

Elevated Pretreatment Blood Pressure and Increased Baseline Thrombus Burden
Although it is plausible that larger thrombi may lead to higher systemic blood pressure values, in our study, there was no association between proximity or tandem nature of occlusions and pretreatment SBP. Even if such correlation exists, it may be overshadowed by successful recanalization that was a stronger outcome predictor in our analyses.

Association of Elevated Pretreatment Systolic Blood Pressure Levels With Impaired Endogenous Capacity for Fibrinolysis
Increased SBP values have been correlated with higher fibrinogen levels, whereas the activation of the endogenous fibrinolytic system by acute release of t-PA is markedly impaired in hypertensive patients. Moreover, in animal studies, increased intraluminal pressure decreased t-PA expression and release in human umbilical veins or cultured endothelial cells. Furthermore, recent evidence have shown that antihypertensive treatment with either an angiotensin-converting enzyme inhibitor or a calcium channel blocker endothelial fibrinolytic function and enhanced endogenous fibrinolysis. Although fibrinogen levels and fibrinolytic activity were not measured in our population, it may be hypothesized that higher pretreatment SBP levels may have some detrimental effect on vessel recanalization by hampering the endogenous capacity for fibrinolysis.

Certain limitations of the present report should be acknowledged. First, diastolic blood pressure was not recorded and consequently the association between certain blood pressure components (diastolic blood pressure, pulse pressure, mean arterial pressure) and vessel recanalization could not be evaluated. Second, we did not obtain details as to how mass effect to develop and thus is unlikely that early brain swelling might have increased intracranial pressure and impeded residual cerebral blood flow at such a narrow time window from stroke onset.

References


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