Initial Body Temperature in Ischemic Stroke
Nonpotentiation of Tissue-Type Plasminogen Activator Benefit and Inverse Association With Severity

Seo Hyun Kim, MD; Jeffrey L. Saver, MD

Background and Purpose—Body temperature (BT) is an important physiological factor in acute ischemic stroke. However, the relationship of initial BT to stroke severity and degree of benefit from thrombolytic therapy has been delineated incompletely.

Methods—We analyzed the public data set of the 2 National Institute of Neurological Disorders and Stroke Tissue-Type Plasminogen Activator (tPA) stroke trials, comparing patients with lower (<37.0°C) and higher (≥37.0°C) presenting BT.

Results—Among 595 patients (297 placebo and 298 tPA treated) with documented initial BT, 77.1% had initial BT <37.0°C and 22.9% ≥37.0°C. Patients with higher initial BT had lower baseline stroke severity in both tPA-treated patients (the National Institute of Health Stroke Scale median, 11 versus 15; P=0.05) and placebo-treated patients (median, 13 versus 16; P<0.01). Patients with higher initial BT also had lower infarction volume on computed tomography at 3 months in both tPA-treated patients (median, 9.6 versus 16.7 cm³; P=0.08) and placebo-treated patients (median, 13.1 versus 28.1 cm³; P=0.02), but no clinical outcome differences. Analysis of lytic treatment effect found no heterogeneity in the degree of tPA benefit in both higher and lower BT groups (≥37.0°C: odds ratio for the modified Rankin Scale 0–1 outcome, 2.55; 95% confidence interval, 1.05–6.21 and <37.0°C: odds ratio, 2.30; 95% confidence interval, 1.38–3.84; heterogeneity P=0.83).

Conclusions—In patients with hyperacute stroke, higher presenting temperatures are associated with less severe neurological deficits and reduced final infarct volumes. Presenting temperature does not modify the benefit of tPA on 3-month favorable outcome. (Stroke. 2015;46:132-136. DOI: 10.1161/STROKEAHA.114.006107.)

Key Words: body temperature ■ outcome measures ■ stroke ■ tissue-type plasminogen activator

Body temperature (BT) is an important index and modifier of pathophysiological events in acute ischemic stroke. Two unresolved issues in the understanding of the role of BT in acute stroke are the relationship of initial BT to stroke severity and whether initial BT modifies the effect of intravenous thrombolytic therapy.

With regard to ischemic stroke severity, multiple studies have found that a rise in BT 4 to 12 hours after ischemic stroke onset is associated with increased stroke severity and worse final outcome.1-4 However, in the hyperacute stage, during the first 1 to 6 hours after onset, studies have not uniformly supported an association of presenting hyperthermia with increased severity.1-10 Indeed, a few studies have suggested a reverse relationship: increased initial BT associated with less severe neurological deficits and more neurological improvement within 24 hours.9,11 However, these studies were generally single center investigations without the rigorous follow-up attained in multicenter clinical trials.

With regard to the relationship of BT to response to intravenous thrombolysis, a few studies have suggested that higher presenting BT is associated with increased benefit from therapy with intravenous tissue-type plasminogen activator (tPA).7,9 The promotion of clot lysis by higher temperature was suggested as the mechanism of improved outcome.12 However, the reports linking higher BT to potentiation of tPA benefit were not randomized trials of lytic therapy and therefore are subject to measured and unmeasured confounders. Thus, detailed analysis of randomized lytic trial data is needed.

Temperature and temperature management is a topic of substantial continued interest in current stroke care, as evidenced not only by ongoing hypothermia trials but also by trials examining temperature control within the normothermic range, including the ongoing Paracetamol In Stroke 2 trial of acetaminophen in acute stroke and the recently completed Quality in Acute Stroke Care cluster randomized trial.13,14 The aims of our study were to investigate the relationship of initial BT to stroke severity and tPA benefit in the 2 pivotal National Institute of Neurological Disorders and Stroke (NINDS) tPA stroke trials.
Methods
The public data set of the 2 NINDS tPA stroke trials was analyzed.\textsuperscript{15} Relationship of BT to outcome was analyzed treating BT both as a continuous variable and dichotomized. In the continuous variable analysis, relationship of BT to initial stroke severity and 3-month infarction volume was analyzed by correlation coefficients. In the dichotomous analysis, subjects were classified into 4 groups by treatment assignment (tPA versus placebo) and by initial BT using a cutoff value of 37.0°C (higher BT [≥37.0°C] versus lower BT [<37.0°C]). The 37.0°C cutoff value was selected as it is commonly accepted as the average human BT and was the cutoff value used in several prior studies.\textsuperscript{3,10,11} The 4 groups were compared on the following baseline variables: demographics (age, sex), comorbidities (hypertension, diabetes mellitus, atrial fibrillation, previous stroke, current smoking, and preexisting disability), mean arterial pressure, laboratory blood tests (glucose level and white blood cell count), initial stroke deficit severity assessed with the National Institute of Health Stroke Scale (NIHSS), abnormal findings on initial computed tomography (CT; hypodensity, intravascular thrombus, or mass effect), stroke subtype, and time from onset to treatment. Preexisting disability was defined as a modified Rankin Scale score of 2 to 5. Outcome variables analyzed included early improvement or deterioration at 24 hours, symptomatic intracerebral hemorrhage within 36 hours, 3-month CT infarct volume, global functional outcome assessed with the modified Rankin Scale at 3 months, and mortality at 3 months. Early improvement was defined as complete resolution of the neurological deficit or a ≥4-point decrease in the baseline NIHSS 24 hours after stroke onset. Deterioration at 24 hours after stroke was defined as a ≥4-point increase from the baseline NIHSS. The 3-month infarct volume was based on an intention-to-treatment algorithm.\textsuperscript{18} Infarct volumes were measured from unenhanced CT scans at 3 months after stroke onset using volumetric analysis as described in detail in previous studies.\textsuperscript{15} Symptomatic intracerebral hemorrhage was defined as a CT-documented hemorrhage with any neurological decline. A favorable outcome was defined as a 3-month modified Rankin Scale of 0 to 1.

Statistical Analysis
The \( \chi^2 \) test was used for analysis of categorical variables between BT groups, and the nonparametric Mann–Whitney \( U \) test was performed for comparison of continuous variables. Relationship of BT to presenting severity and 3-month infarct volume was analyzed using Spearman rank correlation coefficient. Relationship of dichotomized BT groups to tPA treatment effect was analyzed using logistic regression with adjustment for the following 13 variables identified as important to prognosis in previous studies\textsuperscript{15}: age, sex, hypertension, diabetes mellitus, current smoking, preexisting disability, mean arterial pressure, serum glucose, baseline NIHSS, stroke subtype, baseline CT hypodensity, baseline CT intravascular thrombus, and baseline CT mass effect. \( P \) values <0.05 were considered significant. All statistical analyses were performed using PASW 22.0 (SPSS Inc).

Results
Among the 624 patients enrolled in the 2 NINDS tPA stroke trials, 595 patients (297 placebo and 298 tPA treated) had documented initial BT and were included in this study. Among these 595 patients, median time from last known to randomization was 109 minutes (interquartile range, 89–155). The median initial

<table>
<thead>
<tr>
<th>Table 1. Patient Baseline Characteristics</th>
<th>Placebo</th>
<th>( &lt;37^\circ C \text{ (n=226)} )</th>
<th>( ≥37^\circ C \text{ (n=71)} )</th>
<th>( P ) Value</th>
<th>tPA</th>
<th>( &lt;37^\circ C \text{ (n=229)} )</th>
<th>( ≥37^\circ C \text{ (n=69)} )</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, mean (SD)</td>
<td>66.3 (11.6)</td>
<td>64.2 (13.0)</td>
<td>0.22</td>
<td>68.4 (11.2)</td>
<td>66.6 (11.7)</td>
<td>0.32</td>
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<td></td>
</tr>
<tr>
<td>Female</td>
<td>96 (42.5)</td>
<td>27 (38.0)</td>
<td>0.58</td>
<td>99 (43.2)</td>
<td>30 (43.5)</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>92 (40.9)*</td>
<td>14 (20.0)*</td>
<td>&lt;0.01</td>
<td>73 (32.6)†</td>
<td>26 (38.2)*</td>
<td>0.39</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>141 (63.2)‡</td>
<td>53 (74.6)</td>
<td>0.09</td>
<td>150 (66.4)‡</td>
<td>42 (61.8)*</td>
<td>0.56</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>44 (19.6)§</td>
<td>14 (19.7)</td>
<td>1.00</td>
<td>47 (20.7)§</td>
<td>16 (23.2)</td>
<td>0.74</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>44 (19.6)*</td>
<td>10 (14.1)</td>
<td>0.38</td>
<td>46 (20.4)‡</td>
<td>9 (13.2)*</td>
<td>0.22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preexisting disability</td>
<td>22 (9.7)</td>
<td>1 (1.4)</td>
<td>0.02</td>
<td>19 (8.3)</td>
<td>5 (7.2)</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous stroke</td>
<td>64 (28.3)</td>
<td>25 (35.2)</td>
<td>0.30</td>
<td>78 (34.1)</td>
<td>21 (30.4)</td>
<td>0.66</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean arterial pressure, mm Hg, mean (SD)</td>
<td>111.5 (16.7)</td>
<td>112.7 (20.5)</td>
<td>0.78</td>
<td>112.0 (16.6)</td>
<td>115.3 (19.5)</td>
<td>0.28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body temperature, °C</td>
<td>36.4 (36.1–36.7)</td>
<td>37.2 (37.1–37.4)</td>
<td>&lt;0.01</td>
<td>36.4 (36.1–36.7)</td>
<td>37.2 (37.1–37.4)</td>
<td>&lt;0.01</td>
<td></td>
<td></td>
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<tr>
<td>NIHSS</td>
<td>16 (10–22)</td>
<td>13 (9–17)</td>
<td>&lt;0.01</td>
<td>15 (10–19)</td>
<td>11 (6–17)</td>
<td>0.05</td>
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<tr>
<td>Presumed stroke subtype</td>
<td>...</td>
<td>...</td>
<td>0.42</td>
<td>...</td>
<td>...</td>
<td>0.36</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small-vessel occlusive</td>
<td>18 (8.0)</td>
<td>10 (14.1)</td>
<td>...</td>
<td>35 (15.3)</td>
<td>14 (20.3)</td>
<td>...</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardioembolic</td>
<td>103 (45.6)</td>
<td>30 (42.3)</td>
<td>...</td>
<td>99 (43.2)</td>
<td>31 (44.9)</td>
<td>...</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large-vessel occlusive</td>
<td>98 (43.4)</td>
<td>28 (39.4)</td>
<td>...</td>
<td>90 (39.3)</td>
<td>21 (30.4)</td>
<td>...</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>7 (3.1)</td>
<td>3 (4.2)</td>
<td>...</td>
<td>5 (2.2)</td>
<td>3 (4.3)</td>
<td>...</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline CT hypodensity</td>
<td>19 (8.5)§</td>
<td>7 (10.0)*</td>
<td>0.64</td>
<td>18 (7.9)§</td>
<td>5 (7.4)*</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline CT intravascular thrombus</td>
<td>37 (16.5)§</td>
<td>16 (22.9)*</td>
<td>0.28</td>
<td>29 (12.8)§</td>
<td>5 (7.4)*</td>
<td>0.28</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are n (%) or median (interquartile range) unless otherwise stated. All analyses are univariate. CT indicates computed tomographic; NIHSS, National Institute of Health Stroke Scale; tPA, tissue-type plasminogen activator; and WBC, white blood cell.

*One missing value; †5 missing values; ‡3 missing values; and §2 missing values.
BT did not differ between tPA and placebo patients (36.6°C [interquartile range 36.2–36.9] versus 36.6°C [interquartile range 36.2–36.9]; $P=0.71$). Categorically, 77.1% (226 placebo- and 229 tPA-treated patients) had lower initial BT and 22.9% (71 placebo- and 69 tPA-treated patients) had higher initial BT.

The baseline characteristics of the patients are shown in Table 1. The only variable consistently different among the 4 groups was presenting stroke severity. In the placebo-treated patients, but not in the tPA-treated patients, current smoking and preexisting disability were less prevalent in the higher BT group. All other baseline characteristics showed no statistical difference between the BT groups. Patients with a higher initial BT had lower presenting NIHSS in both tPA-treated patients (median, 11 versus 15; $P=0.05$) and placebo-treated patients (median, 13 versus 16; $P<0.01$; Figure 1A). Among all 595 patients, patients with higher BT had lower baseline NIHSS (median, 12 versus 15; $P<0.01$; Figure 1B). BT as a continuous variable correlated inversely with presenting NIHSS ($r=−0.20$; $P=0.01$).

Patient outcomes are shown in Table 2. Point estimates for disability and mortality outcomes were nominally better in the higher BT groups, but these differences did not reach statistical significance. Infarction volume on CT at 3 months was measured in 589 patients (295 tPA and 294 placebo treated). Patients with higher BT tended to have lower infarction volume in tPA-treated patients (median, 9.6 versus 16.7 cm$^3$; $P=0.08$) and had lower infarction volume in placebo-treated patients (median, 13.1 versus 28.1 cm$^3$; $P=0.02$; Figure 1C).

The analysis of the effect of BT on response to tPA, incorporating adjustment for 13 prognostic factors, is shown in Figure 2. The benefit of tPA was homogenous across the lower and higher BT groups ($P$ for heterogeneity=0.83).

**Discussion**

In this study, patients with hyperacute stroke with higher initial BT had less severe presenting neurological deficits and smaller final infarction volumes. The effect of tPA on
favorable outcome at 3 months, however, was similar across BT subgroups.

The findings in this study that higher BT in both the placebo group and the tPA group was associated with reduced baseline stroke severity confirm and extend the findings of a study of Norwegian cohort. In their report, Kvistad et al suggested 2 possible mechanisms: (1) an imbalance between coagulation and lysis in favor of coagulation at lower BT might cause larger clot formation at lower BT; (2) slower spontaneous lysis at low temperature might be related to higher stroke severity. In vitro studies have shown a 5% decrease in lytic activity per degree Celsius decrease in temperature. Recent research showing that permanent arterial occlusion is associated with lower baseline BT supports these mechanisms. However, the range of BT in the in vitro studies might not apply to the in vivo situation, as the data do not show any change in lytic activity in the range of 36°C to 38°C, which corresponds to the BT of most patients in the present and previous studies. Moreover, an association between higher baseline BT and lower presenting severity has also been reported in traumatic brain injury and subarachnoid hemorrhage, which are not associated with thrombotic occlusions and their lysis. Accordingly, additional mechanisms must be considered to explain the inverse relationship between early BT measures and presenting stroke severity.

An important alternative set of mechanisms is suggested by observations in traumatic brain injury literature of mechanisms that likely apply to acute ischemic stroke. Autonomic dysfunction, such as sympathetic hyperactivity immediately after stroke onset, may lower the hypothalamic thermoregulatory set-point through increased catecholamine activity in the hypothalamus. Like other physiological variables, BT is apt to change according to alterations in physical conditions and the environment. To maintain BT within the range that is thermostatically set by the hypothalamus, heat dissipation and production should be balanced. Immobilization as a result of altered consciousness and motor weakness might prevent heat production from muscle activity or proper physiological behaviors for heat preservation, especially under cold exposure during transport to hospital, disrobing for examination, and intravenous infusion of cold fluid. Finally, coexisting disorders such as cardiac dysfunction or sedative drugs might prevent heat production.

Various clinical studies of the effects of initial BT on stroke severity, long-term outcome, and thrombolytic treatment have yielded superficially divergent results, but likely much of the differences are because of variations across studies in the duration from stroke onset to temperature measurement. BT has been reported to rise 4 to 6 hours after stroke onset through a systemic response to brain insult and this elevation reaches a peak between 1 and 2 days after stroke. Accordingly, BTs measured in the subacute period, 4 to 48 hours after onset, are likely to be directly related to stroke severity, whereas BTs measured in the acute period, within the first 4 hours, seem to be inversely related to stroke severity.

In this study, initial BT did not modify the benefit of tPA on favorable outcome. Although a few prior uncontrolled series raised the possibility that higher BT might potentiate tPA benefit, the absence of control arms rendered these studies subject to measured and unmeasured confounders. Notably, better outcomes comparing higher BT with lower BT tPA patients may be a prognostic variable effect, not a treatment interaction variable effect. Presenting higher BT in hyperacute stroke might not have a positive impact on thrombolytic therapy but imply less severe neurological deficits and smaller infarction volume.
The randomized trial data analyzed in this study provides a much stronger assessment for interaction effects and did not demonstrate that BT modifies the benefit of tPA.

There are several limitations to this study. First, BT measurement methods including thermometer type and sites for measuring were not standardized; the temperature data reflect pragmatic measurement in practice, rather than more formal methodology. Second, factors affecting BT such as circadian cycle and ambient temperature were not considered. Although these factors might have only a small effect on BT, they are important because the initial BTs were mostly within the normal range, and the temperature differences between the groups were small. Third, actual durations from stroke onset to BT measurement and BT values other than the initial BT were not documented. Fourth, the modest sample sizes of the 2 NINDS trials constrained statistical power; potential improved outcomes with initial higher BT suggested by point estimates could not be definitely confirmed or disconfirmed. Pooling of BT data collected in additional tPA randomized trials is desirable.

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Disclosures

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