Effects of Admission Hyperglycemia on Stroke Outcome in Reperfused Tissue Plasminogen Activator–Treated Patients

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**Background and Purpose**—We sought to investigate the impact of hyperglycemia before reperfusion on long-term outcome in patients treated with intravenous tissue plasminogen activator (tPA).

**Methods**—Of 268 consecutive patients with a nonlacunar middle cerebral artery (MCA) stroke evaluated at <3 hours after onset, 73 (27.2%) received intravenous tPA. Serum glucose was determined at baseline before tPA administration. Hyperglycemia was defined as a glucose level >140 mg/dL. National Institutes of Health Stroke Scale (NIHSS) scores were obtained at baseline and 24 hours. Transcranial Doppler monitoring of recanalization and reocclusion was conducted during the first 24 hours. Total infarct volume was measured on CT at day 5 to 7. Modified Rankin Scale was used to assess outcome at 3 months.

**Results**—Median NIHSS score was 17. At baseline, 31 patients (42.5%) were hyperglycemic and 42 (57.5%) normoglycemic. Early reperfusion (<6 hours) occurred in 43 patients (58.9%). Admission blood glucose correlated negatively with the degree of neurological improvement at 24 hours in reperfused \( r = -0.37; P = 0.019 \) but not in nonreperfused \( r = -0.20; P = 0.21 \) tPA-treated patients. Increased age \( P = 0.014 \), history of diabetes mellitus \( P = 0.043 \), admission glucose >140 mg/dL \( P = 0.002 \), and early reocclusion \( P = 0.004 \) were factors associated with poor outcome among reperfused patients. A logistic regression modeling revealed that only admission glucose value >140 mg/dL \( (\text{odds ratio, } 8.4; 95\% \text{ CI, } 1.76 \text{ to } 40.02; P = 0.005) \) emerged as an independent predictor of poor outcome despite tPA-induced recanalization. In patients with 6-hour persistent MCA occlusion, baseline NIHSS score >15 points \( P = 0.011 \) and proximal MCA occlusion \( P = 0.039 \) were variables associated with poor outcome on univariate analysis. In a logistic regression model, only NIHSS score >15 points \( (\text{odds ratio, } 11.9; 95\% \text{ CI, } 1.48 \text{ to } 97.1; P = 0.032) \) remained as an independent predictor of poor outcome and functional dependence at 3 months in nonreperfused tPA-treated patients.

**Conclusions**—Hyperglycemia before reperfusion may in part counterbalance the beneficial effect of early restoration of blood flow, which translates into a worse outcome in hyperglycemic patients despite tPA-induced recanalization. *(Stroke. 2003;34:1235-1241.)*

**Key Words:** disease progression ■ hyperglycemia ■ outcome ■ thrombolysis ■ ultrasonography

Up to 20% to 50% of acute stroke patients have hyperglycemia at presentation.\(^1\)\(^-\)\(^3\) Several studies have demonstrated a detrimental effect of acute hyperglycemia on outcome from ischemic stroke.\(^4\)\(^-\)\(^6\) Increased admission glucose levels in acute stroke have also been associated with longer in-hospital stay, increased cost, and mortality.\(^6\)

Hyperglycemia has been widely shown to exacerbate brain injury in a variety of animal models of focal cerebral ischemia by enhancement of intracellular acidosis in the ischemic penumbra, which leads to loss of ion homeostasis, mitochondrial dysfunction, and bioenergetic failure. These deleterious effects of hyperglycemia appear to depend on whether the acutely ischemic brain tissue is reperfused. Hyperglycemia has consistently increased infarct size in models of brief transient cerebral ischemia, but it either had no effect or decreased infarct size in models of severely prolonged or persistent ischemia without reperfusion.\(^7\)\(^-\)\(^10\) In humans, hyperglycemia has been shown to be detrimental in nonlacunar strokes, in which reperfusion may eventually occur, but not in lacunar strokes with little or no reperfusion.\(^4\) However, the relationship between increased blood glucose, reperfusion, and outcome in human stroke has not been established.

The National Institute of Neurological Disorders and Stroke (NINDS) trial clearly demonstrated a beneficial effect of intravenous tissue plasminogen activator (tPA) when given at <3 hours of symptom onset.\(^11\) In this setting, hyperglycemia has been shown to increase the risk of symptomatic
intracranial hemorrhage (ICH).\textsuperscript{12,13} Although a recent analysis of the NINDS trial demonstrated that admission blood glucose is associated with poor outcome and increased risk of symptomatic ICH, this analysis did not indicate a need to withhold tPA in stroke patients because of hyperglycemia.\textsuperscript{6} Furthermore, given that the aforementioned studies did not systematically evaluate recanalization after thrombolysis, whether the detrimental effects of hyperglycemia on outcomes is linked to the occurrence of reperfusion remains uncertain.

In the present study we sought to explore the effects of admission hyperglycemia on early clinical course, infarct size, and long-term outcome among reperfused and nonreperfused tPA-treated patients.

**Subjects and Methods**

Our target group consisted of patients with acute ischemic stroke admitted within the first 3 hours after symptom onset. Stroke onset was defined as the last time the patient was known to be without any neurological deficit. A total of 268 consecutive patients with a nonlacunar stroke involving the vascular territory of the middle cerebral artery (MCA) were evaluated between March 2000 and June 2002. Of these, 152 (56.7\%) underwent urgent carotid ultrasound and transcranial Doppler (TCD) examinations. One hundred forty-one patients (52.6\%) with a documented MCA occlusion on TCD were initially included in the study. We excluded patients who were taking anticoagulants (n=15), were older than 88 years (n=17), showed mild (National Institutes of Health Stroke Scale [NIHSS] score \(<4\)) neurological deficit (n=11), experienced dramatic spontaneous neurological improvement (n=9), or showed early signs of infarction \(>33\%\) of the MCA territory on baseline CT (n=16). Finally, 73 patients (27.2\%) with an acute stroke due to MCA occlusion received intravenous tPA in a standard 0.9-mg/kg dose at \(<3\) hours of symptom onset and were included in the study.

On arrival in the emergency department, patients underwent standard neurological and cardiological examinations, ECG, blood chemistry, and contrast CT before enrollment in the study. Serum glucose was determined in all patients before tPA administration. Hyperglycemia was defined as admission random blood glucose value \(\geq140\) mg/dL.\textsuperscript{4} Blood pressure, temperature, and glucose levels were managed following the European Stroke Initiative recommendations.\textsuperscript{14} In patients with suspected cardioembolic stroke, anticoagulant therapy was started in the absence of hemorrhagic transformation. The presence and type of hemorrhagic transformation were defined according to previously published criteria.\textsuperscript{15,17} Hemorrhagic infarction was defined as a petechial infarction without space-occupying effect, and parenchymal hematoma was defined as hemorrhage with mass effect. Total infarct volume was measured on CT at day 5 to 7. We measured the ischemic lesion with and without hemorrhagic transformation using the formula for irregular volumes. In patients who died before day 5 to 7, the last available CT was used for the measurement of infarct volume. CT scans were reviewed by a neuroradiologist with extensive experience in acute stroke who was blinded to the clinical and TCD details.

**TCD Assessment**

A standard TCD examination was performed in the emergency department on admission before tPA administration (\(<3\) hours). To assess recanalization, TCD was repeated at 6 hours of stroke onset. To assess reocclusion, an additional TCD examination was performed in case of neurological worsening after documented recanalization. Baseline and follow-up studies were conducted by the same neurologist. Systolic blood pressure, diastolic blood pressure, and heart rate were measured at the time of each TCD recording. The TCD examination was performed with Multidop\textsuperscript{\textregistered}4 equipment with a hand-held probe in a range-gated, pulsed-wave mode at a frequency of 2 MHz. Flow velocity of the MCAs, the anterior cerebral arteries, and the posterior cerebral arteries was bilaterally recorded by the transtemporal approach. The MCA was identified as a flow signal directed toward the probe at an insonation depth of 55 mm and traced up and down to 35 and 65 mm, respectively. The anterior cerebral artery was identified as a flow signal directed away from the probe at a depth of 65 mm and traced down to 80 mm. The flow signal from the posterior cerebral artery was detected at 65 mm as a signal directed toward the probe and traced from a 60- to 70-mm depth. Doppler shifts from all arteries were recorded each 2-mm step. Proximal MCA occlusion was defined as the absence of flow or the presence of minimal flow signal throughout the MCA at an insonation depth between 45 and 65 mm, accompanied by flow diversion in the ipsilateral anterior cerebral arteries and posterior cerebral arteries. Distal MCA occlusion was defined as a diffuse dampening of the mean flow velocity in the affected MCA >21\% compared with the unaffected MCA.\textsuperscript{16} Recanalization was diagnosed when a dampened flow appeared in a previously demonstrated proximal MCA occlusion (partial recanalization) or when a previous absent, minimal, or dampened flow came within the normal range (complete recanalization).\textsuperscript{16} The appearance of a low-resistance stenotic signal on follow-up was also considered complete recanalization.\textsuperscript{16} No change in the abnormal waveforms indicated that no recanalization had occurred. Reocclusion was defined as a worsening in waveforms on TCD performed at the time of neurological deterioration after documented recanalization.

**CT Studies**

On admission, all patients underwent a CT within the first 3 hours after stroke onset, which was repeated after 36 to 48 hours (or earlier when rapid neurological deterioration occurred) and again between days 5 and 7. The presence of a hyperdense MCA sign, early focal hypodensity, or swelling due to developing infarction on baseline CT was assessed according to European Cooperative Acute Stroke Study (ECASS) criteria.\textsuperscript{17,18} The extent of hypodensity or swelling due to acute ischemic edema on baseline CT was categorized as normal, <33\% of the MCA territory, and >33\% of the MCA territory.

The presence and type of hemorrhagic transformation were defined according to previously published criteria.\textsuperscript{17,19,20} Hemorrhagic infarction was defined as a petechial infarction without space-occupying effect, and parenchymal hematoma was defined as hemorrhage with mass effect. Total infarct volume was measured on CT at day 5 to 7. We measured the ischemic lesion with and without hemorrhagic transformation using the formula for irregular volumes. In patients who died before day 5 to 7, the last available CT was used for the measurement of infarct volume. CT scans were reviewed by a neuroradiologist with extensive experience in acute stroke who was blinded to the clinical and TCD details.

**Clinical Assessment**

We assessed clinical status at baseline and 6 and 24 hours after symptom onset by means of the NIHSS, which was conducted by a neurologist or a senior neurology resident who was video-trained and certified for application of the NIHSS.\textsuperscript{21} Early neurological deterioration or improvement was defined as an increase or decrease of \(\geq4\) points on the NIHSS score after 24 hours from baseline assessment.\textsuperscript{11} An ICH was considered symptomatic if the patient had clinical deterioration causing an increase of \(\geq4\) points on the NIHSS and if the hemorrhage was likely to be the cause of neurological deterioration. The modified Rankin Scale\textsuperscript{22} (mRS) was used to assess clinical outcome at 90 days. We defined poor outcome as mRS score \(\geq3\).

**Statistical Analysis**

The analysis was performed with the use of SPSS 9.0 software (SPSS Inc). Statistical significance for intergroup differences was assessed by 2-tailed Fisher exact test and Pearson chi\(^2\) test for categorical variables and Student t test and Mann-Whitney U test for continuous variables. The Spearman coefficient was applied to verify correlation between examined variables. A receiver operating characteristic curve was applied to determine a cut-point of admission blood glucose that better distinguishes between favorable and unfavorable outcome. The probability of poor outcome, dependence, and death at 3 months was assessed by forward stepwise logistic regression analysis on the basis of the maximum likelihood ratio. Variables with a value of P\(<0.1\) on univariate testing were included. A level of P\(<0.05\) was accepted as statistically significant.
Results

We studied a total of 73 patients (36 men and 37 women) with an acute stroke due to MCA occlusion treated with intravenous tPA at <3 hours of stroke onset. Demographic data, risk factor profile, and baseline clinical findings are shown in Table 1. Mean age was 70.4±9.8 years (range, 31 to 86 years). Median NIHSS score of the series on admission was 17 points, and interquartile range was 12.5 to 19 points. The time elapsed between symptom onset and drug administration was 143.2±34.2 minutes, ranging from 82 to 182 minutes. The door-to-needle time was 67.6±24.7 minutes, ranging from 51 to 123 minutes. Mean admission glucose value was 154.1±59 mg/dL (range, 92 to 345 mg/dL). Fourteen patients (19.1%) had glucose value >200 mg/dL. Thirty-one patients (42.5%) were hyperglycemic and 42 (57.5%) normoglycemic. Recanalization was considered complete in 28 and partial in 15 patients. In 30 patients (41.1%) the MCA remained occluded at 6 hours. Recoiling was seen in 6 patients (8.2%), of whom 4 were partial and 2 were complete recanalizations. Baseline glucose was 148.3±48 mg/dL in reoccluded and 154.6±60 mg/dL in non-reoccluded patients (P=0.75).

Symptomatic ICH within 48 hours of stroke onset occurred in 7 patients (9.6%). There was a trend toward higher baseline glucose level (P=0.076) in patients with symptomatic ICH (169.3±28 mg/dL) than in those without symptomatic ICH (152.2±61 mg/dL). Moreover, symptomatic ICH tended (P=0.084) to be more frequent in nonreperfused (5 of 30; 17%) than in reperfused (2 of 43; 4.6%) tPA-treated patients.

On baseline TCD assessment, proximal MCA occlusion was detected in 44 patients (60.3%) and distal occlusion in 29 (39.7%). In 5 patients, carotid ultrasound also revealed a severe cervical carotid artery stenosis or carotid occlusion. Early recanalization (<6 hours) was identified in 43 patients (58.9%) (in 29 [69%] normoglycemic and 14 [45%] hyperglycemic patients). Recanalization was considered complete in 28 and partial in 15 patients. In 30 patients (41.1%) the MCA remained occluded at 6 hours. Recoiling was seen in 6 patients (8.2%), of whom 4 were partial and 2 were complete recanalizations. Baseline glucose was 148.3±48 mg/dL in reoccluded and 154.6±60 mg/dL in non-reoccluded patients (P=0.75).
Discussion

The present study demonstrates that admission hyperglycemia independently predicts poor outcome in reperfused but
not in nonreperfused tPA-treated patients. Baseline blood glucose \(>140\) mg/dL is associated with a lesser degree of neurological improvement, greater infarct size, and a worse clinical outcome after tPA-induced recanalization. These observations parallel findings in animal models of transient cerebral ischemia, suggesting that the deleterious effect of hyperglycemia on infarct growth is related to the occurrence of reperfusion.

Previous studies have demonstrated that initial stroke severity, older age, high blood pressure, early CT abnormalities, history of diabetes mellitus, and serum glucose on admission predict poor outcome and symptomatic ICH in patients receiving tPA.\(^6\),\(^13\),\(^23\),\(^24\) However, these studies did not evaluate the impact of different factors in predicting outcome in relation to the status of recanalization.

In our study admission hyperglycemia emerged as a powerful predictor of poor outcome in reperfused patients independently of possible confounders such as age, stroke severity, and diabetes mellitus. This observation suggests that an elevated blood glucose before reperfusion may counterbalance, in part, the beneficial effect of early restoration of blood flow, which translates into a lesser degree of neurological improvement, greater infarct size, and worse outcome in hyperglycemic than in normoglycemic patients despite tPA-induced recanalization. On the other hand, in patients with a persistent arterial occlusion, stroke severity on admission independently predicted poor outcome. This observation is in consonance with previous MRI studies,\(^23\),\(^26\) which observed an association between stroke severity, extent of brain hypoperfusion, and poor clinical outcome. This may indicate that in the absence of recanalization, the extent of irreversible brain injury grows progressively over time until it covers the initial hypoperfused area. In this setting, we hypothesize that blood glucose supply via collaterals may only accelerate this process, but it has little or no impact on final infarct size and long-term outcome in the absence of recanalization.

Hyperglycemia facilitates development of cortical acidosis in the ischemic penumbra. Both moderate and severe hyperglycemia have been shown to be associated with worsening of mitochondrial function in the ischemic penumbra.\(^27\) A recent MRI study\(^28\) demonstrated that elevated blood glucose levels are associated with an increased progression of hypoperfused at-risk tissue to infarction and poor stroke outcome. Moreover, hyperglycemia-induced brain lactate production, as measured by photon MR spectroscopy, was correlated with reduced penumbra salvage in stroke patients.\(^28\) Recently, admission hyperglycemia has been demonstrated to be associated with a greater degree of diffusion-weighted imaging lesion growth and larger infarct volume in patients receiving intravenous tPA.\(^29\) However, this study did not allow any conclusion about whether the effects of hyperglycemia on infarct size are linked to the occurrence of recanalization.

Other pathophysiological mechanisms may explain the adverse effect of hyperglycemia after arterial recanalization. Hyperglycemia has been demonstrated to impair cerebrovascular reactivity in the microvasculature, which may hamper reperfusion after recanalization by contributing to the no-reflow phenomenon.\(^30\),\(^31\) Moreover, acute hyperglycemia has been shown to facilitate excitatory amino acid release. Extracellular glutamate concentrations after forebrain ischemia in rats have been observed to be higher in hyperglycemic than in normoglycemic animals.\(^32\) Furthermore, hyperglycemia affects cortical spreading depression–induced gene expression, which may trigger massive \(Ca^{2+}\) influx and initiate cell death cascade.\(^33\) In addition, hyperglycemia may alter blood-barrier permeability and promote blood-barrier disruption, which, in turn, exacerbates brain edema formation and leads to hemorrhagic transformation, respectively.\(^34\),\(^35\)

The present study has certain limitations. The analysis is based on case series, and the possibility of bias cannot be excluded; therefore, the present study does not allow the efficacy of tPA based on admission glucose levels to be determined. Moreover, the relatively small sample size limited the power for multivariate analysis, which calls for larger studies to confirm our observations. Furthermore, given that glycosylated hemoglobin was not determined in our patients, we cannot rule out that the negative effect observed in reperfused patients may be related to both diagnosed and undiagnosed diabetes rather than hyperglycemia per se. In the present study blood glucose was measured on admission before tPA administration. However, it may not accurately indicate the glucose burden that reaches the ischemic tissue at the time of reperfusion. A combined approach by continuous glucose (subcutaneous device) and TCD monitoring in the acute stroke setting may provide valuable information regarding the effects of blood glucose at different times of recanalization on stroke outcomes.

In conclusion, admission hyperglycemia is associated with a lesser degree of neurological improvement, greater infarct size, and worse outcome after tPA-induced recanalization. These findings underscore the importance of increased oxidative stress on reperfusion injury in humans. Further studies are needed to elucidate whether aggressive glycemic control before reperfusion may counteract the deleterious effects of hyperglycemia in patients receiving thrombolytic therapy.

References
Hyperglycemia and Early Reperfusion Therapy

Clinical studies of acute ischemic stroke support the conclusions of most experimental studies of focal cerebral ischemia in suggesting that admission hyperglycemia is associated with a worse clinical outcome.1 This association is more consistent in nonlacunar strokes2 and in experimental models of reversible focal cerebral ischemia.3 The acute ischemic penumbra might be preferentially susceptible to injury in hyperglycemic ischemia. Indeed, by use of MR methods, hyperglycemia in acute ischemic stroke was shown to promote the evolution of hypoperfused tissue to infarction and to do so by increased brain lactate production.4 This role of hyperglycemia may be of particular importance in patients treated with early reperfusion therapy. Elevated admission blood glucose has emerged as a probable risk factor for thrombolysis-related ICH and for poor outcome in patients with acute ischemic stroke.5-7 A recent post hoc analysis from the NINDS rtPA Stroke Trial has shown that in patients with acute ischemic stroke, higher admission glucose levels are associated with significantly lower odds for desirable clinical outcomes and significantly higher odds for symptomatic ICH, regardless of whether recombinant tPA (rtPA) treatment is given.8

In the accompanying article, Alvarez-Sabín et al demonstrate, in a case series of patients with acute ischemic stroke treated with rtPA and assessed serially by TCD, that admission hyperglycemia independently predicts poor outcome in
reperfused but not in nonreperfused rtPA-treated patients. These intriguing findings suggest that the deleterious effect of hyperglycemia on infarct growth may be related to whether or not reperfusion occurs. While the study provides useful data that extend previous observations, there are also apparent inherent caveats from the retrospective and uncontrolled nature of these analyses, which are based on a relatively small series of patients from a single center.

Hyperglycemia can be rapidly and relatively easily corrected and controlled. Better glycemic control by intravenous insulin and glucose infusion has been shown to improve clinical outcomes from acute myocardial infarction, in particular when it was added to acute reperfusion therapy. Randomized controlled trials are currently under way, designed to determine whether insulin-induced and maintained euglycemia in acute stroke patients is effective. On the basis of the current state of knowledge, including the accompanying article, it is reasonable to hypothesize that metabolic support may be of particular value, in combination with reperfusion therapy for acute ischemic stroke, in minimizing reperfusion injury related to hyperglycemia. This possibility is especially important in light of the growing use of new strategies for early reperfusion therapy in acute ischemic stroke. Aggressive insulin treatment may exert important metabolic effects beyond maintaining euglycemia, but such treatment is not without potential risks. Therefore, the optimal and safe protocol of administering insulin should be sought and rigorously tested in carefully designed prospective clinical trials utilizing reperfusion therapy.

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