Acute Hyperglycemia State Is Associated With Lower tPA-Induced Recanalization Rates in Stroke Patients

Marc Ribo, MD, PhD; Carlos Molina, MD, PhD; Joan Montaner, MD, PhD; Marta Rubiera, MD; Raquel Delgado-Mederos, MD; Juan F. Arenillas, MD, PhD; Manuel Quintana; José Álvarez-Sabín, MD, PhD

**Background and Purpose**—Hyperglycemia (HG) has a deleterious effect in stroke patients by accelerating ischemic brain damage; moreover, its antifibrinolytic effect may also influence reperfusion. We aimed to study the effect of acute/chronic HG on tissue-type plasminogen activator (tPA)–induced recanalization.

**Methods**—We studied 139 consecutive stroke patients with documented intracranial artery occlusion treated with intravenous tissue-type plasminogen activator (tPA). Admission glucose levels were recorded (in mg/dL). The existence of previous chronic HG was determined by plasma levels of glycosylated hemoglobin (HbA1c, %) and fructosamine (in μmol/L). Transcranial Doppler monitoring assessed complete recanalization 2 hours after tPA bolus. National Institutes of Health Stroke Scale (NIHSS) scores were obtained at baseline and 48 hours.

**Results**—On admission, the median NIHSS score was 18 and mean glucose value was 140 ± 63 mg/dL. At 2 hours, 32% of patients (n = 44) achieved complete recanalization. Patients who recanalized showed lower admission glucose levels (127 vs 146 mg/dL; P = 0.039) but no differences in HbA1c (6.3% vs 6.3%; P = 0.896) or fructosamine (292 vs 293 μmol/L; P = 0.957) were observed. Other variables associated with recanalization were initial distal middle cerebral artery occlusion (P = 0.011) and platelet count (P = 0.015). Patients with an admission glucose level > 158 mg/dL had lower recanalization rates (16% vs 36.1%; P = 0.035) and a higher NIHSS score at 48 hours (7 vs 14.5; P = 0.04). After adjustment for stroke etiology, age, and risk factors, the only independent predictors on admission of no recanalization were glucose value > 158 mg/dL (odds ratio [OR], 7.3; 95% confidence interval [CI], 1.3 to 42.3; P = 0.027), proximal middle cerebral artery occlusion (OR, 2.6; 95% CI, 1.1 to 6.5; P = 0.034), and platelet count < 219 000/mL (OR, 2.6; 95% CI, 1.1 to 6.1; P = 0.029).

**Conclusions**—In tPA-treated patients, the acute but not chronic HG state may hamper the fibrinolytic process, delaying reperfusion of the ischemic penumbra. Early measures to reduce HG may favor early recanalization. *(Stroke. 2005;36:1705-1709.)*

Key Words: hyperglycemia ■ stroke, acute ■ thrombolysis ■ ultrasonography, Doppler, transcranial

In the acute phase of ischemic stroke, hyperglycemia (HG) is a frequent phenomenon that affects up to 50% of patients, often in those without a preexisting diagnosis of diabetes. HG has repeatedly shown a deleterious effect of exacerbating ischemic brain injury, accelerating the molecular processes leading to cell death, and resulting finally in larger infarct volumes and poorer outcomes. The relative risk of death in hypoglycemic nondiabetic stroke patients is increased by 3 times. HG is also a well-known inhibitor of fibrinolysis. In diabetic patients, decreased plasma fibrinolytic activity and elevated plasma levels of plasminogen activator inhibitor type 1 (PAI-1) have been observed. Furthermore, studies performed on endothelial cells and smooth muscle cell cultures have shown that elevated glucose concentrations are able to decrease the fibrinolytic potential. More recent in vivo studies have shown that not only a chronic state but also acute HG may represent a strong stimulus able to inhibit plasma fibrinolysis, increase PAI-1, and decrease tissue-type plasminogen activator (tPA) activity.

Whether the effect of hampering fibrinolysis by acute or chronic HG contributes to its detrimental effect in the acute phase of ischemic stroke by delaying reperfusion is unknown. We aimed to study the impact of a chronic HG state and admission glycemia on tPA-induced recanalization in stroke patients.

**Patients and Methods**

From February 2002 to December 2004, all patients with an acute (<3 hours from symptoms onset) nonlacunar stroke admitted to...
the Emergency Department of a university hospital were prospectively studied. Seven hundred sixty patients were evaluated and underwent urgent extracranial and transcranial Doppler (TCD) ultrasound examinations. Patients with an inadequate temporal bone window were excluded. One hundred thirty-nine patients had a TCD-documented middle cerebral artery (MCA) occlusion and fulfilled established criteria for tPA treatment (0.9 mg/kg).11

Clinical Protocol
A detailed history of vascular risk factors was obtained from each patient. To identify potential mechanism of cerebral infarction, a set of diagnostic tests was performed: when indicated, patients also underwent special coagulation tests, transthoracic/transesophageal echocardiography, and Holter monitoring. With this information and the neuroimaging data, previously defined etiologic subgroups were determined.12 Glucose levels were determined by blood analyses performed before tPA administration; HG was defined as an admission glucose value >140 mg/dL.13 To assess the existence of a previous hyperglycemic state, we determined plasma glycosylated hemoglobin (HbA1c) and fructosamine values in a fasting blood sample on the first day after admission (≤48 hours from symptoms onset). Clinical examination was performed every hour during the first 3 hours and at 12, 24, and 48 hours after tPA bolus. Stroke severity as well as neurologic improvement or worsening was assessed by using the National institutes of Health Stroke Scale (NIHSS).14

TCD Protocol
A standard TCD examination was performed in the emergency room on admission before tPA administration with 1-channel, 2-MHz equipment (TCD 100M, Spencer Technologies, Multidop DWL). A standard set of diagnostic criteria was applied to diagnose arterial occlusion. 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 and posterior communicating arteries, according to the Thrombolysis in Brain Ischemia grading system.15 To assess recanalization, continuous TCD monitoring was performed during 2 hours after tPA administration. Recanalization on TCD was diagnosed as partial when blunted or dampened signals appeared in previously demonstrated absent or minimal flow. Complete recanalization on TCD was diagnosed when the end-diastolic flow velocity improved to normal or elevated values (normal or stenotic signals).16 No change in the abnormal waveforms indicated that no recanalization had occurred. We defined the recanalization end point as complete at 2 hours after tPA bolus administration.

Statistical Analyses
Descriptive and frequency statistical analyses were obtained, and comparisons were made with use of the SPSS 10.0 statistical package. Statistical significance for intergroup differences was assessed by Pearson χ² or the Fisher exact test for categorical variables and Student t test and ANOVA for continuous variables. Pearson’s correlation coefficient was used to determine correlations between biomarker levels and other continuous variables. When indicated, Mann–Whitney U and Spearman tests were used. To determine the glucose cut point that better predicted no recanalization, a receiver operating characteristic curve was configured. Logistic regression analysis was performed to determine factors that could be considered independent predictors of MCA recanalization. For this purpose, we assessed recanalization rates 2 hours after tPA bolus administration. A probability value <0.05 was considered significant.

Results
We included in the study 139 patients (43% women), with a mean age of 71±11.4 years (range, 26 to 92) with an acute MCA occlusion. Baseline characteristics of the patients are shown in the Table. Median NIHSS score on admission was 18 (range, 4 to 23), and mean time to treatment was 169 minutes. The mean plasma glucose level on admission was 140±63 mg/dL; 44 (32%) patients had HG, and of those, only 57% had a history of diabetes mellitus. The mean HbA1c was 6.3±0.8%, and the mean fructosamine 293±29.3 μmol/L. According to TOAST criteria, stroke etiologies were cardioembolic 48%, atherothrombotic 30%, undetermined 19%, and dissection 3%.

Predictors of Recanalization
Two hours after tPA bolus, 32% of patients (n=44) achieved complete recanalization. Patients with complete recanalization presented with lower admission glucose
levels (127 vs 146 mg/dL; \( P = 0.039 \)), but no differences in HbA1c (6.3% vs 6.3%; \( P = 0.896 \)) or fructosamine (292 vs 293 \( \mu \)mol/L; \( P = 0.957 \); Figure 1) were observed. Other variables associated with recanalization were initial distal MCA occlusion (\( P = 0.011 \)) and platelet count (\( P = 0.015 \)). No statistically significant differences were observed in recanalization rates according to etiologic stroke subtypes (Table 1), although cardioembolic occlusions seemed to be more prone to recanalize than atherothrombotic (38% vs 22%; \( P = 0.085 \)). A receiver operating characteristic curve determined the cut point on admission glucose levels that better predicted further recanalization at 158 mg/dL. Patients with an admission glucose level \( > 158 \) mg/dL had lower recanalization rates (16% vs 36.1%; \( P = 0.035 \); Figure 2) and higher NIHSS scores at 48 hour (7 vs 14.5, \( P = 0.04 \)). After adjustment for etiology, age, and risk factors, the only independent predictors on admission of no recanalization were admission glucose \( > 158 \) mg/dL (odds ratio [OR], 7.3; 95% confidence interval [CI], 1.3 to 42.3; \( P = 0.027 \)), initial proximal MCA occlusion (OR, 2.6; 95% CI, 1.1 to 6.5; \( P = 0.034 \)), and platelet count \( > 219,000 / \mu \)L (OR, 2.6; 95% CI, 1.1 to 6.1; \( P = 0.029 \)).

**Discussion**

Our study suggests that acute rather than chronic HG delays reperfusion of the ischemic penumbra in stroke patients treated with tPA. Thus, the antifibrinolytic effect is added to the multiple detrimental mechanisms by which HG leads to poorer outcomes in stroke patients.

Hyperglycemia in acute stroke patients is common: between 30% and 50% of patients are hyperglycemic on admission, often without a preexisting diagnosis of diabetes.\(^1\) Several studies have demonstrated the deleterious effect of HG on final outcome, exacerbating neuron damage and determining larger final infarct volumes.\(^2\)–\(^5\) However, HG may also induce a hypercoagulable state. Up to 80% of patients with diabetes mellitus die of thrombotic causes, giving clear evidence that diabetes promotes a hypercoagulable state.\(^17\) However, not only the chronically increased glycometabolic state produces this change: a recent study demonstrated that acute induced HG in rats decreased plasma fibrinolytic activity, increasing PAI-1 and decreasing plasma tPA activity.\(^10\)

A recent study reported that the admission fibrinolytic profile plays an important role in tPA-treated patients and predicts early recanalization and favorable clinical outcome.\(^18\) To establish the impact of the antifibrinolytic effect of either acute or chronic HG on tPA-induced artery recanalization, we designed this study in which the severity of the previous glycometabolic state was determined by HbA1c and fructosamine. Although the existence of a previous chronic HG state appeared to be unrelated to achievement of early reperfusion, we observed that patients in whom tPA-induced early recanalization presented with significantly lower glycemia on admission. HG may be related to atherosclerotic disease, which has been shown to be more resistant to recanalization after tPA treatment.\(^19\)

When looking for independent predictors of recanalization,
to avoid possible bias, we adjusted the logistic regression model for stroke etiology, age, and vascular risk factors. Among all studied baseline variables, the only independent predictors of no recanalization after tPA treatment were admission glucose, platelet count, and initial proximal MCA occlusion.

In humans, epidemiologic and prospective intervention data link HG to vascular complications. Glycation of proteins is one favored molecular basis to explain this fact.20,21 Cell surface receptors, like annexin II, may support fibrinolytic surveillance in both intravascular and extravascular locations by stimulating plasmin generation and by protecting plasmin from its inhibitors.22–24 Annexin II is an extremely vulnerable target for glycation but in counterpart quickly responds to restoration of normoglycemia.25 Glycation of annexin II impairs the appropriate formation of the plasminogen/tPA/annexin II complex, disrupting a key regulatory mechanism in fibrinolytic vigilance.26 Glycation of key regulatory proteins like annexin II can produce decreased fibrinolytic activity and indirectly promote a thrombophilic state in acute HG states. Other mechanisms of impaired fibrinolysis may be abnormal clot structures that are more resistant to degradation or increased PAI-1 endothelial production.27,28

In our cohort of patients, we did not observe a graded response in recanalization rates according to admission glyemia (Figure 2), suggesting that the antifibrinolytic effect is triggered when blood glucose reaches values of ≈160 mg/dL; this could be the point at which glycation of key proteins is initiated.

In tPA-treated patients, HG has previously been shown to accelerate ischemic brain damage.13 The antifibrinolytic affect of HG leads to delayed reperfusion of increased damaged tissue, thus establishing the reported link between HG, late recanalization, and increased hemorrhagic damage. Thus, increased HGMarkers of post-stroke ischemic brain damage: a systematic overview. Stro- 1. Kiers L, Davis SM, Larkins R, Hopper J, Tress B, Rossiter SC, Carlin J, Ratnaike S. Stroke topography and outcome in relation to hyperglycaemia and diabetes. J Neurol Neurosurg Psychiatry. 1992;55:263–270.


Acute Hyperglycemia State Is Associated With Lower tPA-Induced Recanalization Rates in Stroke Patients
Marc Ribo, Carlos Molina, Joan Montaner, Marta Rubiera, Raquel Delgado-Mederos, Juan F. Arenillas, Manuel Quintana and José Alvarez-Sabín

*Stroke*. 2005;36:1705-1709; originally published online July 7, 2005; doi: 10.1161/01.STR.0000173161.05453.90f

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2005 American Heart Association, Inc. All rights reserved.
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:
http://stroke.ahajournals.org/content/36/8/1705

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Stroke* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Stroke* is online at:
http://stroke.ahajournals.org//subscriptions/