Serum Glucose Level and Diabetes Predict Tissue Plasminogen Activator–Related Intracerebral Hemorrhage in Acute Ischemic Stroke

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Background and Purpose—Five pretreatment variables (P < 0.1 univariate analysis), including serum glucose (>300 mg/dL), predicted symptomatic intracerebral hemorrhage (ICH) in the National Institute of Neurological Disorders and Stroke rtPA trial. We retrospectively studied stroke patients treated <3 hours from onset with intravenous rtPA at 2 institutions to evaluate the role of these variables in predicting ICH.

Methods—Baseline characteristics, including 5 prespecified variables (age, baseline glucose, smoking status, National Institutes of Health Stroke Scale [NIHSS] score, and CT changes [>33% middle cerebral artery territory hypodensity]), were reviewed in 138 consecutive patients. Variables were evaluated by logistic regression as predictors of all hemorrhage (including hemorrhagic transformation) and symptomatic hemorrhage on follow-up CT scan. Variables significant at P < 0.25 level were included in a multivariate analysis. Diabetes was substituted for glucose in a repeat analysis.

Results—Symptomatic hemorrhage rate was 9% (13 of 138). Any hemorrhage rate was 30% (42 of 138). Baseline serum glucose (5.5-mmol/L increments) was the only independent predictor of both symptomatic hemorrhage [OR, 2.26 (CI, 1.05 to 4.83), P = 0.03] and all hemorrhage [OR, 2.26 (CI, 1.07 to 4.69), P = 0.04]. Serum glucose >11.1 mmol/L was associated with a 25% symptomatic hemorrhage rate. Baseline NIHSS (5-point increments) was an independent predictor of all hemorrhage only [OR, 12.42 (CI, 1.64 to 94.3), P = 0.01]. Univariate analysis demonstrated a trend for nonsmoking as a predictor of all hemorrhage [OR, 0.45 (CI, 0.19 to 1.08), P = 0.07]. Diabetes was also an independent predictor of ICH when substituted for glucose in a repeat analysis.

Conclusions—Serum glucose and diabetes were predictors of ICH in rtPA-treated patients. This novel association requires confirmation in a larger cohort. (Stroke. 1999;30:34-39.)

Key Words: cerebral hemorrhage ■ diabetes mellitus ■ glucose ■ stroke, acute ■ thrombolytic therapy

The most critical complication of intravenous recombinant tissue plasminogen activator (rtPA) therapy for acute ischemic stroke is intracerebral hemorrhage (ICH). In the National Institute of Neurological Disorders and Stroke (NINDS) rtPA trial, 6.4% of rtPA-treated patients developed neurological deterioration due to ICH compared with only 0.6% in the placebo-treated group.1 In the European Cooperative Acute Stroke Study (ECASS-I) trial, 20% of rtPA-treated patients developed parenchymal hematomas compared with 7% in the placebo arm.2

Identifying patients who are at high risk of hemorrhagic complications may lead to improved patient selection and safety of this treatment. Few factors have been identified as predictors of symptomatic hemorrhage. In the NINDS rtPA trial, only stroke severity as defined by National Institutes of Health Stroke Scale (NIHSS) and CT changes of mass effect, edema, or hypodensity were independent predictors of symptomatic hemorrhage. A statistical trend (0.1 > P > 0.05) was seen for age and the dichotomous variable blood glucose >300 mg/dL as baseline predictors of symptomatic hemorrhage. A possible protective role of recent tobacco use was observed (0.1 > P > 0.05). In the ECASS rtPA trial,4 only age was identified as an independent predictor of parenchymal hematoma.

Elevated serum glucose has been identified as an independent predictor of poor outcome in acute stroke.5 Hyperglycemia accentuates ischemic injury with reperfusion, raising particular concern for hyperglycemia in a setting of...
thrombolytic use. Recent animal studies have confirmed an increase in hemorrhagic transformation, with elevated glucose levels. However no human clinical studies to date have closely examined the role of hyperglycemia in the setting of thrombolysis. We hypothesized that serum glucose as a continuous variable was an independent predictor of rtPA-related ICH and tested this hypothesis on a cohort of open-label patients treated at 2 academic centers.

Subjects and Methods
Consecutive patients treated with intravenous rtPA therapy for ischemic stroke within 3 hours of symptom onset between December 1995 and July 1998 were included. Patients were treated either by the University of Texas–Houston Stroke Team at 1 of 4 Houston-area hospitals (Hermann Hospital, St. Luke’s Episcopal Hospital, Southwest Memorial Hospital, Northwest Memorial Hospital) or by the University of Calgary neurology staff at Foothills Hospital in Calgary, Alberta. Hermann Hospital is the main teaching hospital for the University of Texas–Houston Medical School and an active stroke referral center. St. Luke’s Episcopal Hospital (979 beds), Southwest Memorial Hospital (565 beds), and Northwest Memorial Hospital (504 beds) are all private, nonprofit community hospitals with academic affiliations. Foothills Hospital is an 850-bed tertiary referral center for the city of Calgary, Alberta, and surrounding communities, servicing a population of 1 million residents. It is the main teaching hospital for the University of Calgary. All acutely ill neurological patients are directly referred to this institution from the Calgary, Alberta, region.

Medical charts were reviewed retrospectively and information collected for the 4 predetermined variables (age, smoking status, pretreatment NIHSS, and pretreatment serum glucose) in 138 consecutive patients. These were chosen for the initial analysis because the NINDS rtPA trial identified these variables as the only pretreatment factors (P<0.1) predictive of symptomatic hemorrhage on univariate analysis. The pretreatment serum glucose level was performed at baseline in all patients. When the NIHSS was not documented in the chart, it was extrapolated from the recorded neurological examination.

Other demographics collected included gender, history of risk factors, dosage of rtPA, and pretreatment platelet count. Patients were considered diabetic if their medical record stated a prior history of diabetes mellitus. Patients with elevated glucose levels or increased HbA1c levels without a history of diabetes were not considered diabetics for the purpose of this study.

Each initial pretreatment head CT scan was reevaluated by a stroke neurologist or neuroradiologist at each institution. CT reviewers were blinded to individual patient clinical information except for side of motor weakness. The initial CT scan was evaluated for any early acute changes. We classified major CT changes as evidence of hypodensity involving >33% of the middle cerebral artery (MCA) territory and were included in this variable in the intended univariate analysis.

The follow-up CT or MRI scan was also reevaluated by a stroke neurologist or neuroradiologist blinded to individual patient clinical information. The follow-up CT or MRI was performed within 24 to 36 hours in most cases. The standard practice of both institutions was to obtain these follow-up scans within the first 24 to 36 hours in order to decide whether antplatelet or anticoagulant therapies should be initiated. Hemorrhage was classified as any area of increased HbA1c within the infarcted area, without space-occupying effect. Demographic characteristics of the patient population included in the study were compared with the rtPA treatment group in the NINDS rtPA trial with use of χ² and Student t test statistical methods. Logistic regression analysis was performed with all 5 variables to determine predictors of symptomatic hemorrhage and all hemorrhage. All variables were first tested in a univariate model. Covariates significant at the P<0.25 critical level were included in a multivariate model.

The identification of serum glucose as an independent predictor of ICH compelled us to also evaluate the history of diabetes mellitus. A logistic regression analysis was performed with diabetes included as a variable and serum glucose excluded. Both variables were not included together in a multivariate analysis owing to the limitations of a small sample size and the inherent close association between diabetes and baseline glucose levels.

Results
One hundred thirty-eight consecutive ischemic stroke patients received intravenous rtPA within 3 hours of symptom onset and were included in this analysis (Hermann Hospital, n=67; St. Luke’s Episcopal Hospital, n=13; Southwest Memorial Hospital, n=13; Northwest Memorial Hospital, n=8; and Foothills Hospital, n=37). The baseline characteristics in this patient cohort (Table 1) resembled the rtPA-treated study population, with the exception of a higher incidence of atrial fibrillation in the Calgary/Houston cohort.

Radiological evaluation of the baseline CT scan revealed >33% hypodensity within the MCA territory in 18% of patients (24 of 134). Evaluation of follow-up CT scan revealed any hemorrhage (including hemorrhagic transformation) in 30% of patients (42 of 138) and symptomatic hemorrhage in 9% of patients (13 of 138). The parenchymal hematoma rate was 14% (20 of 138), and the hemorrhagic transformation rate was 16% (22 of 138). The symptomatic hemorrhage in-hospital mortality rate was 54% (7 of 13), and the 6 symptomatic ICH survivors had severe neurological deficits (Rankin Index score of 4 to 5) at hospital discharge.

Two univariate logistic regression analyses were performed for the 5 predetermined variables, with the dichotomous dependent variable being all hemorrhage in one analysis and symptomatic hemorrhage in the other. The ORs and CIs are shown in Table 2. In the all-hemorrhage analysis, which included any hemorrhagic transformation or parenchymal hematoma, all 5 variables were considered covariates (P<0.25) and included in the final multivariate logistic regression model. Only serum glucose and NIHSS were independent predictors of all hemorrhage on multivariate analysis (Table 3).

A similar logistic regression analysis was also performed for symptomatic hemorrhage. Current smoking, NIHSS score, >33% MCA territory hypodensity, and serum glucose were found to be covariates (P<0.25) and were evaluated in a multivariate model. Only serum glucose was an independent predictor of symptomatic hemorrhage in multivariate analysis (Table 3).

Because of the close association between diabetes mellitus and hyperglycemia, diabetes mellitus was tested in a separate analysis excluding glucose level. Diabetes mellitus also was determined to be a significant predictor of all hemorrhage and symptomatic hemorrhage (Table 3). A history of diabetes...
mellitus was associated with a 25% (8 of 32) symptomatic hemorrhage rate and 50% all-hemorrhage rate (16 of 32) compared with a 5% symptomatic hemorrhage rate (5 of 106) and 25% all-hemorrhage rate (26 of 106) for nondiabetics.

The relationship between serum glucose and symptomatic hemorrhage is illustrated in Figure 1. The rate of symptomatic hemorrhage increased gradually with increasing glucose levels. The rate of all hemorrhage appeared to increase substantially above the 8.4 mmol/L level. Fourteen of 16 subjects with serum glucose levels >11.1 mmol/L were diabetics in this study.

Discussion

This study demonstrates a definite relationship between baseline serum glucose/diabetes history and intracerebral hemorrhage after rtPA treatment. Animal studies would suggest that hyperglycemia is the more significant abnormality.\textsuperscript{13} However, marked hyperglycemia may be a marker of diabetes mellitus, which is known to produce damaging effects on the microvasculature that may result in increased bleeding risk.\textsuperscript{14} Hyperglycemia may also be an epiphenome-

non indicating increased stress due to a neuroendocrine response.\textsuperscript{15} Serum glucose levels do tend to be higher in patients with larger infarcts, which should be more prone to hemorrhagic conversion.\textsuperscript{16}

Animal models have demonstrated an important association between hyperglycemia and ischemic injury. Both increased\textsuperscript{17,18} and reduced\textsuperscript{19–21} injury have been demonstrated with hyperglycemia in permanent focal ischemia models. Initially, hyperglycemia may be neuroprotective\textsuperscript{22} by reducing ischemic depolarizations through delayed breakdown of transmembrane ion gradients with extended anaerobic glycolysis.\textsuperscript{23,24} With persistent ischemia, however, hyperglycemia produces a profound cellular acidosis due to the excessive substrate for the predominant anaerobic glycolysis occurring in hypoxic/ ischemic tissue.\textsuperscript{25} Once a critical threshold of acidosis is reached, hyperglycemia becomes detrimental.\textsuperscript{26} Proposed mechanisms for the deleterious effects of hyperglycemia and the resultant cellular acidosis include enzymatic dysfunction, enhanced free radical production (lipid peroxidation) through increased iron-catalyzed hydroxyl radical production,\textsuperscript{27} depressed mitochondrial function by inhibited

<table>
<thead>
<tr>
<th>Variable</th>
<th>Any Hemorrhage</th>
<th>Symptomatic Hemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;33% MCA hypodensity</td>
<td>1.82 (0.73, 4.53)</td>
<td>0.20</td>
</tr>
<tr>
<td>Age (10-y intervals)</td>
<td>1.21 (0.92, 1.59)</td>
<td>0.18</td>
</tr>
<tr>
<td>Current smoker</td>
<td>0.45 (0.19, 1.08)</td>
<td>0.07</td>
</tr>
<tr>
<td>Serum glucose (per 5.5 mmol/L)</td>
<td>2.01 (1.08, 3.77)</td>
<td>0.03</td>
</tr>
<tr>
<td>Diabetes mellitus*</td>
<td>3.07 (1.35, 7.00)</td>
<td>0.007</td>
</tr>
<tr>
<td>NIHSS (5-pt intervals)</td>
<td>1.71 (1.20, 2.45)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

\*Diabetes analyzed in repeated analyses.
ADP-stimulated respiratory activity, \(^{28}\) induction of endonucleases that may initiate programmed cell death, \(^{29}\) increased intracellular Ca\(^{2+}\) accumulation, \(^{30}\) and cellular swelling. \(^{31}\)

In reversible focal ischemia, hyperglycemia consistently aggravates ischemic damage. \(^{6,7,8,32}\) Restoration of blood flow after 8 hours of occlusion is associated with a higher mortality than permanent occlusion. \(^{18}\) Hyperglycemia increases damage to the blood-brain interface, \(^{33}\) resulting in increased edema \(^{34}\) and hemorrhagic transformation with reperfusion. Very high tissue lactate concentrations in hyperglycemic cats increased the hemorrhagic conversion rate 5-fold and hemorrhage size 25-fold. \(^{9}\) A glucose infusion resulted in a 75% hemorrhagic transformation rate compared with 9% in the normoglycemic group in another study. \(^{10}\) Hyperglycemia may increase hemorrhagic transformation by accelerating microvascular injury. Neuropathological studies have demonstrated reduced flow in the microcirculation, \(^{29}\) which may be due to increased capillary endothelial cell swelling that reduces luminal diameter. \(^{35}\) A severe perfusion deficit has been demonstrated with hyperglycemia, which may further aggravate injury. \(^{10,36,37}\)

Therapeutic interventions aimed at lowering glucose levels or neutralizing the effects of the acidosis have recently been studied. Insulin therapy, \(^{18,32,38}\) tirilazad \(^{39,40}\) (a free radical scavenger), deferoxamine, \(^{41}\) and hypothermia \(^{33}\) have all shown promising neuroprotection in hyperglycemic animal models.

Experimental studies fully support previous clinical studies identifying the detrimental effects of hyperglycemia. Berger and Hakim \(^{42}\) demonstrated that hyperglycemia is frequently associated with cerebral edema in stroke patients, while other stroke studies have consistently shown hyperglycemia to be associated with increased morbidity and mortality. \(^{42–44}\) This association appears independent of stroke severity. \(^{5}\) Early pilot studies are now being planned for a trial of glucose-insulin treatment in acute stroke. \(^{45,46}\)

In this study, clinical stroke severity measured by NIHSS was also an independent predictor of all hemorrhage but not symptomatic hemorrhage. The importance of NIHSS only in all hemorrhage may be explained by the definition of symptomatic hemorrhage, which requires a clinical deterioration attributable to hemorrhage. The severe clinical neurological deficit may mask any deterioration, even in the presence of large hemorrhages. One limitation of this study is the extrapolation of NIHSS score based on recorded neurological examination required in some cases. This may have led to inaccurate estimation of the NIHSS score, therefore minimizing the importance of this variable in the univariate and multivariate models.

A statistical trend for the unique protective role of current smoking initially suggested in the NINDS rtPA trial hemorrhage analysis \(^{3}\) was also observed in the univariate analysis of all hemorrhage. Similar results of reduced intracranial hemorrhage have been obtained for smoking in myocardial infarction thrombolytic studies. \(^{47,48}\) Animal studies provide a biological basis for this protection. Nicotine administration leads to an upregulation of endothelial expression of plasminogen activator inhibitor-1 (PAI-1), a potent inhibitor of rtPA. \(^{49}\) This increase in PAI-1 may reduce the serine protease effect of rtPA that may produce increased endothelial damage and blood-brain barrier breakdown, leading to hemorrhagic complications. \(^{50}\) This curious role for smoking should be explored further.

A positive but insignificant effect was seen (Table 1) between major CT changes and symptomatic hemorrhage in

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**TABLE 3. Multivariate Analysis**

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Hemorrhage</th>
<th>Symptomatic Hemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
<td>OR (CI)</td>
<td>P</td>
</tr>
<tr>
<td>NIHSS (5-pt intervals)</td>
<td>1.62 (1.09, 2.40)</td>
<td>0.02</td>
</tr>
<tr>
<td>Serum glucose (per 5.5 mmol/L)</td>
<td>2.26 (1.07, 4.69)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Hemorrhage</th>
<th>Symptomatic Hemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current smoking</td>
<td>0.43 (0.16, 1.16)</td>
<td>0.097</td>
</tr>
<tr>
<td>NIHSS (5-pt intervals)</td>
<td>12.42 (1.64, 94.3)</td>
<td>0.01</td>
</tr>
<tr>
<td>&gt;33% MCA hypodensity</td>
<td>&gt;0.1</td>
<td>3.22 (0.78, 13.3)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>3.61 (1.43, 9.14)</td>
<td>0.007</td>
</tr>
</tbody>
</table>

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Figure illustrates the relationship between serum glucose increments and rate of symptomatic hemorrhage (black) and asymptomatic hemorrhage (gray).
Serum Glucose and Diabetes Predict rtPA-Related ICH

our cohort. This finding requires explanation, considering the importance of these changes in predicting ICH in the NINDS rtPA trial. One explanation is the difference in definitions of CT changes used in the 2 studies. Major CT changes were defined as >33% MCA territory involvement in this study, whereas major CT changes were defined as edema or mass effect in the NINDS rtPA trial. Another explanation is the limitations of a small sample size. Both analyses did demonstrate a positive effect that was not statistically significant and may indicate a type 2 error. Alternatively, another consideration may be poor recanalization frequencies in patients with involvement of large regions of the MCA territory. Hypodensities >33% of the MCA territory are frequently due to terminal ICA or MCA stem occlusions, which are known to have a lower frequency of recanalization in previous intravenous rtPA angiographic studies.51,52 If recanalization is essential to the development of hemorrhagic complications, an association between major CT changes and hemorrhage may be modest and not clearly demonstrated in a smaller cohort.

This study suggests glucose level predicts hemorrhage with intravenous rtPA treatment in acute ischemic stroke, a finding at least partially explained by the high symptomatic hemorrhage rate among diabetics in this cohort. The results of this study should be interpreted with caution and should not at present affect clinical decision making, given the limited sample size and retrospective nature of this work. However, the association of glucose with ICH may have important implications for future stroke treatment and requires further prospective evaluation. Until such further studies have been performed we do not feel this study provides enough conclusive evidence to change currently FDA approved guidelines for thrombolytic therapy.

Acknowledgments

The University of Texas–Houston Stroke Fellowship is supported by an NIH Fellowship Training Grant. Dr L.B. Morgenstern is supported by an American Heart Association Clinician-Scientist Award. Dr A.M. Buchan is supported by Heart and Stroke Foundation of Alberta and Alberta Heritage Medical Foundation. We would like to thank P.S. Kochanski, RN, for her assistance in data collection for this study and Dr A.V. Alexandrov for his advice and helpful suggestions in manuscript preparation.

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*Stroke*. 1999;30:34-39
doi: 10.1161/01.STR.30.1.34

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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