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Stroke 2003;34:2208-2214; originally published online Jul 31, 2003;

DOI: 10.1161/01.STR.0000085087.41330.FF

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75214
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ISSN: 1524-4628

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Persistent Poststroke Hyperglycemia Is Independently Associated With Infarct Expansion and Worse Clinical Outcome

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Background and Purpose—Hyperglycemia at the time of ischemic stroke is associated with increased mortality and morbidity. Animal studies suggest that infarct expansion may be responsible. The influence of persisting hyperglycemia after stroke has not previously been examined. We measured the blood glucose profile after acute ischemic stroke and correlated it with infarct volume changes using T2- and diffusion-weighted MRI.

Methods—We recruited 25 subjects within 24 hours of ischemic stroke symptoms. Continuous glucose monitoring was performed with a glucose monitoring device (CGMS), and 4-hour capillary glucose levels (BGL) were measured for 72 hours after admission. MRI and clinical assessments were performed at acute (median, 15 hours), subacute (median, 5 days), and outcome (median, 85 days) time points.

Results—Mean CGMS glucose and mean BGL glucose correlated with infarct volume change between acute and subacute diffusion-weighted MRI ($r \geq 0.60$, $P < 0.01$), acute and outcome MRI ($r = 0.56$, $P = 0.01$), outcome National Institutes of Health Stroke Scale (NIHSS; $r \geq 0.53$, $P < 0.02$), and outcome modified Rankin Scale (mRS; $r \geq 0.53$, $P = 0.02$). Acute and final infarct volume change and outcome NIHSS and mRS were significantly higher in patients with mean CGMS or mean BGL glucose ≥ 7 mmol/L. Multiple regression analysis indicated that both mean CGMS and BGL glucose levels ≥ 7 mmol/L were independently associated with increased final infarct volume change.

Conclusions—Persistent hyperglycemia on serial glucose monitoring is an independent determinant of infarct expansion and is associated with worse functional outcome. There is an urgent need to study normalization of blood glucose after stroke. (*Stroke*. 2003;34:2208-2214.)

Key Words: brain ischemia ■ glucose ■ hyperglycemia ■ magnetic resonance imaging, diffusion-weighted ■ prospective studies

The influence of diabetes mellitus as an independent predictor of the incidence of ischemic stroke is well recognized and relates to a variety of causes.¹ However, between 20% and 40% of patients admitted with ischemic stroke are hyperglycemic, often without a pre-existing diagnosis of diabetes.² A meta-analysis by Capes et al³ suggests that the relative risk of death in hyperglycemic nondiabetic stroke patients is increased by 3.3 (95% confidence interval, 2.3 to 4.6). Recent analyses of both prospective and case-control studies have confirmed the importance of acute hyperglycemia as a predictor of outcome after stroke.^{4,5}

Multiple mechanisms contribute to the detrimental effect of acute hyperglycemia.⁶ Animal models of focal cerebral ischemia suggest that the type of vessel occlusion, presence of collateral blood flow, and occurrence of reperfusion are relevant and that hyperglycemia may influence neuronal damage through accentuated tissue acidosis and lactate gen-

eration.^{7,8} Using novel MRI techniques, including MR spectroscopy, our group has demonstrated a mechanistic link between admission hyperglycemia and stroke outcome involving infarct growth through recruitment of penumbral tissue and increased cerebral lactate production.⁹ In contrast, CT, PET, and conventional MRI techniques have yielded inconclusive results.¹⁰⁻¹²

Although there is compelling evidence that hyperglycemia has an effect on stroke outcome, debate continues as to whether the effect is independent of the influence of diabetes or initial stroke severity.¹³ Most groups have used a single time point measure of blood glucose to define glycemic control.^{2,14} However, animal models of focal ischemic stroke suggest that persistent elevation of blood glucose through the period during which the ischemic penumbra exists may yield a more robust measure of the influence of hyperglycemia on infarct evolution.¹⁵

Received November 18, 2002; final revision received March 13, 2003; accepted April 14, 2003.

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Stroke is available at <http://www.strokeaha.org>

DOI: 10.1161/01.STR.0000085087.41330.FF

Few studies have examined sequential blood glucose measures after stroke.^{16,17} A significant relationship between mean glucose levels and clinical outcome in nondiabetic patients was observed using by use of daily measures of blood glucose in the week after stroke. A more recent study by Christensen et al¹⁷ using 2 glucose measurements obtained in the first 12 hours after stroke showed that glucose levels were higher in those with more severe neurological deficits and furthermore that acute hyperglycemia predicted early mortality.¹⁷ The development of continuous glucose monitoring with a subcutaneous sensor device (Continuous Glucose Monitoring System [CGMS], Medtronic MiniMed, Medtronic Inc) has provided a novel tool to directly address the relationship between stroke outcome and contemporaneous glycemia.¹⁸

We therefore conducted a prospective study to clarify the effect of persisting hyperglycemia after stroke. We performed serial MRI studies and clinical assessments in subjects within 24 hours of ischemic stroke and assessed these findings in conjunction with 4 parameters of glycemic control after stroke. These parameters were admission plasma glucose, admission glycosylated hemoglobin (HbA_{1c}) levels, mean capillary glucose measured every 4 hours for 72 hours after admission, and mean CGMS sensor glucose measured every 5 minutes for 72 hours after admission.

Patients and Methods

Patients

Sequential patients presenting within 24 hours of anterior circulation ischemic symptoms and with a National Institutes of Health Stroke Scale (NIHSS) score of ≥ 4 were recruited prospectively from the Stroke Care units of the Royal Melbourne Hospital and the Austin and Repatriation Medical Centre between March 2001 and June 2002. Patients were excluded if they had a pre-existing modified Rankin Scale (mRS) score of > 2 , a history of previous stroke that would hamper interpretation of clinical or radiological data, or a contraindication for MRI scanning. In addition, those patients initially enrolled but with subsequent resolution of neurological symptoms and absence of diffusion-weighted imaging (DWI) lesion on acute and subacute MRI were excluded. The study was performed with the approval of the Human Research and Ethics committees at both centers, and written informed consent was obtained from the patient or next of kin. NIHSS and mRS scores were obtained by a neurologist or a trained research nurse who was blinded to MRI and glucose results at the time of enrollment in the study, before the subacute MRI study, and at outcome.

Glucose

Plasma venous glucose was measured on admission to hospital in all patients. In concordance with other studies, admission hyperglycemia was defined as a venous glucose ≥ 8 mmol/L.^{5,19} After acute MRI, a venous blood sample for determination of HbA_{1c} levels was obtained, and the CGMS device was inserted. This device is a minimally invasive continuous glucose monitor. The needle-delivered subcutaneous sensor detects glucose through an electrochemical reaction with glucose oxidase and records interstitial glucose levels every 5 minutes for up to 72 hours.²⁰ Concurrent, 4-hour capillary glucose measurements were obtained during the monitoring period and used to calibrate the CGMS. In keeping with current diagnostic criteria for the definition of diabetes, we defined a mean glucose level ≥ 7 mmol/L over the monitoring period as hyperglycemia, and a raised HbA_{1c} was defined as $\geq 6.2\%$.²¹

MRI Studies

Serial MRI studies were performed on all patients. Scan time windows were within 24 hours of stroke onset (acute), between days 3 and 6 (subacute), and at 3 months (outcome). Our imaging protocol has been described in detail previously.²² All MRI studies were obtained with a 1.5-T echoplanar image equipped whole-body scanner (Signa Horizon SR 120, General Electric). Acute and subacute sequences consisted of a T1-weighted sagittal localizer and a DWI sequence. DWIs were obtained with an axial, isotropic-spin echoplanar imaging sequence ($b=0, 500, \text{ and } 1000 \text{ s/mm}^2$). For outcome studies, a T1-weighted sagittal localizer, an axial DWI sequence, an axial proton density, and T2-weighted fast-spin double-echo sequence were performed.

Postprocessing of raw images was performed with customized software developed in Interactive Data Language with MEDx medical imaging processing version 3.2 (Sensor Systems Inc). Volumetric analyses of DWI and T2-weighted lesions were performed by 1 investigator blinded to clinical and glucose data using a semiautomated pixelwise thresholding technique. DWI volumes were measured with the maximum diffusion sensitivity isotropic image because it demonstrated greatest contrast between the hyperintense infarct and surrounding tissue. Acute infarct volume change was defined as the difference between acute and subacute DWI lesion volumes with similar slice locations viewed concurrently. Final infarct volume change was defined as the difference between acute DWI lesion and outcome T2 lesion volume with similar slice locations viewed concurrently.

Statistical Analysis

Stata statistical software (Stata Corp, release 6.0, 1999) was used for analysis. Dependent variables were compared by use of nonparametric techniques, except when normality of data could be proved. Demographic and glucose monitoring data are presented as median and interquartile range. The Spearman rank correlation coefficient and multiple linear regression analysis using the ordinary least-squares regression for > 1 variable were used to compare the strength of association between variables. The Mann-Whitney test was used to compare lesion volume change and clinical outcome scores between the normoglycemic and hyperglycemic groups. Results were considered statistically significant at the 5% level.

Outcome Measures and Hypotheses

Four outcome measures were identified prospectively: acute infarct volume change, final infarct volume change, outcome NIHSS score, and outcome mRS score. We had 4 hypotheses: (1) Hyperglycemia at the time of admission and persistent hyperglycemia on serial monitoring after admission would be associated with greater infarct growth and worse clinical outcome; (2) accurate assessment of glycemia with continuous monitoring would provide a more robust predictor of outcome than a single measure of glucose on admission; (3) this effect would be independent of premorbid glycemic control and stroke severity; and (4) clinical outcome measures would parallel MRI-defined outcome measures.

Results

Twenty-five patients were enrolled in the study. Five subjects were subsequently excluded from analysis because of resolution of neurological symptoms in association with absence of visible DWI lesion on acute and subacute imaging ($n=2$), posterior circulation stroke ($n=1$), a second stroke during the monitoring period ($n=1$), and death before subacute MRI ($n=1$). Of the 20 patients, 6 had a premorbid diagnosis of type 2 diabetes mellitus. Demographic, infarct volume, and overall glycemic monitoring data are shown in Table 1. Treatment with intravenous recombinant tissue plasminogen activator (rtPA) was performed in 4 patients according to established guidelines before enrollment in the study.²³

TABLE 1. Demographic and Overall Glycemic Data

Number of patients	20 (6 with diagnosed diabetes)
Age, y	71.5 (65–75)
NIHSS on admission	14 (6–18)
Time from stroke to MRI	
Acute, h	15 (6–19)
Subacute, d	5 (3–6)
Outcome, d	85 (77–100)
Duration of glucose monitoring, h	70.7 (65.2–72.6)
CGMS sensor readings per patient over monitoring period, n	614 (434–773)
Capillary glucose readings per patient over monitoring period, n	18 (15–20)
Admission venous plasma glucose, mmol/L	7.1 (6.0–8.4)
Admission HbA _{1c} , %	5.8 (5.1–7.2)
Mean capillary glucose over 72 h, mmol/L	6.8 (6.0–7.4)
Mean CGMS sensor glucose over 72 h, mmol/L	5.6 (4.8–7.4)
Acute DWI infarct volume, cm ³	16.5 (10.5–23.5)
Subacute DWI infarct volume, cm ³	47.4 (13.6–66.8)
Final T2 infarct volume, cm ³	25.2 (11.7–60.4)
Acute infarct volume change, cm ³	18.0 (0.6–43.8)
Final infarct volume change, cm ³	6.3 (0.8–37)

Results are expressed as median (interquartile range).

All patients had acute MRI; 1 patient refused subacute MRI; 3 patients died before outcome MRI and clinical assessment; and 2 patients were unable to tolerate outcome MRI but attended clinical follow-up. In accordance with standard practice, imaging data from these patients were carried forward from prior studies, and deceased patients were accorded NIHSS scores of 42 and mRS scores of 6.^{24,25}

Glucose Monitoring

Admission plasma venous glucose, HbA_{1c}, and 4-hour capillary glucose readings were obtained on all subjects. CGMS monitoring was unsuccessful in 1 subject. Individual CGMS sensor glucose readings were strongly correlated with ($r=0.72$, $P<0.005$) but significantly lower than concurrent capillary glucose readings (mean capillary glucose over 72 hours, 6.8 mmol/L; mean CGMS sensor glucose over 72 hours, 5.6 mmol/L; $P<0.005$) (Figure 1). The regression equation linking time concordant capillary and CGMS sensor glucose readings was $BGL=3.2+(0.6\times CGMS)$. Median mean absolute error between paired capillary and sensor glucose readings was 19% (interquartile range, 17% to 26%).

Association Between Glycemic Parameters and Outcome Measures

Correlations between glycemic parameters and MRI-defined and clinical outcomes are detailed in Table 2. Both mean capillary glucose levels and mean CGMS sensor glucose levels over 72 hours after admission showed significant correlations with acute infarct volume change, final infarct volume change, and clinical outcomes. In contrast, neither admission glucose levels nor admission HbA_{1c} showed a

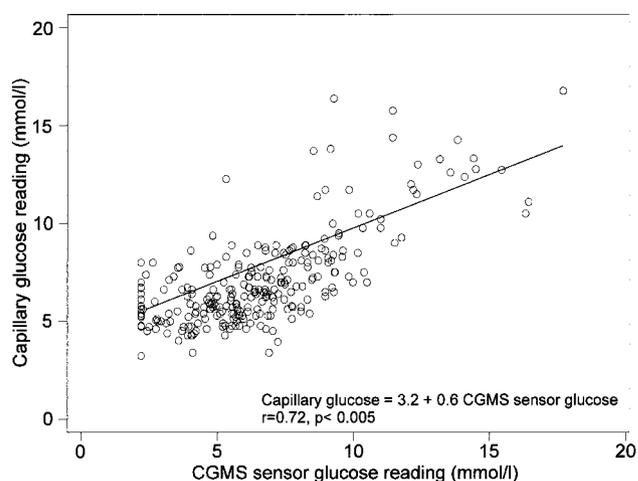


Figure 1. Correlation between time-concordant capillary and CGMS sensor glucose readings.

statistically significant association with surrogate or clinical outcomes.

Hyperglycemia Versus Normoglycemia Group Data

Hyperglycemic groups were defined and compared by the use of 4 criteria: admission glucose level ≥ 8 mmol/L, mean capillary or mean CGMS sensor glucose level ≥ 7 mmol/L over the 72-hour monitoring period, and admission HbA_{1c} level $\geq 6.2\%$. Of the 20 subjects, 7 had admission plasma glucose levels ≥ 8 mmol/L. Three of these 7 subjects (43%) subsequently had mean capillary or CGMS sensor glucose levels ≥ 7 mmol/L. Thirteen subjects had admission glucose levels < 8 mmol/L; 6 of these 13 (46%) developed mean capillary glucose levels ≥ 7 mmol/L. Admission NIHSS scores were not significantly different in subjects with either admission plasma glucose levels ≥ 8 mmol/L (12 versus 16, $P=0.3$) or mean capillary glucose levels ≥ 7 mmol/L (11 versus 16, $P=0.08$).

Univariate analyses comparing acute infarct volume change, final infarct volume change, outcome NIHSS, and mRS between hyperglycemia and normoglycemia groups for each of the glycemic parameters are illustrated in Figure 2. In summary, significantly greater acute and final infarct volume changes were observed in subjects with either a mean capillary or mean CGMS sensor glucose ≥ 7 mmol/L. In addition, clinical outcome scores were worse in subjects with

TABLE 2. Correlations Between Glycemic Parameters and Outcome Measures

	<i>r</i>			
	Acute Volume Change	Final Volume Change	Outcome NIHSS	Outcome mRS
Admission glucose	0.19	0.38	0.25	0.24
Admission HbA _{1c}	0.26	0.25	0.15	0.16
Mean capillary glucose over 72 h	0.54*	0.56*	0.58*	0.64*
Mean sensor glucose over 72 h	0.60*	0.56*	0.53*	0.53*

* $P<0.05$.

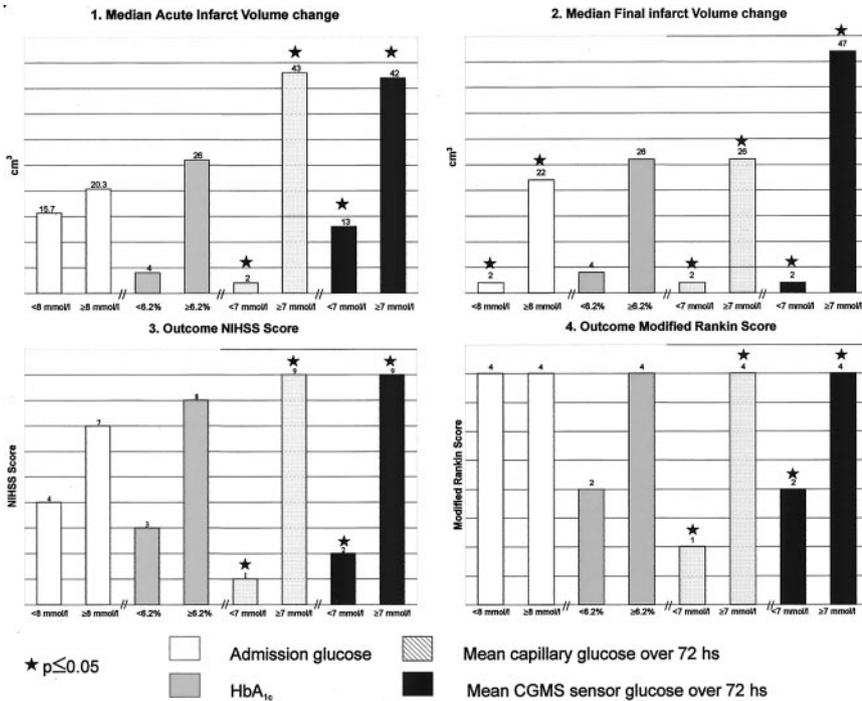


Figure 2. Univariate analysis of acute infarct volume change (1), final infarct volume change (2), outcome NIHSS (3), and outcome mRS (4) in patients with dichotomized glycemic parameters.

raised glucose levels over the monitoring period. However, only a modest increase in final infarct volume change was associated with admission glucose levels ≥ 8 mmol/L, and HbA_{1c} levels $\geq 6.2\%$ were not associated with statistically significant differences in any outcome measure. Figure 3 shows an example of a 24-hour CGMS glucose profile and MRI from a patient with persistent poststroke hyperglycemia.

Multiple Regression Analysis

Multiple regression analysis was performed for final infarct volume change as a continuous variable. The regression model included mean capillary and mean CGMS

sensor glucose ≥ 7 mmol/L as independent variables, in addition to other potentially predictive variables that might have influenced lesion growth. These included initial NIHSS score dichotomized to 13, prior glycemic control (HbA_{1c} $\geq 6.2\%$), treatment with rtPA, and time to first MRI study.²⁶ This analysis demonstrated that mean glucose levels ≥ 7 mmol/L over the monitoring period (measured by either 4-hour capillary or CGMS sensor glucose) correlated with MRI outcome. Furthermore, this relationship was independent of initial stroke severity, pre-existing glycemic status, treatment with rtPA, and time to initial MRI study (Table 3).

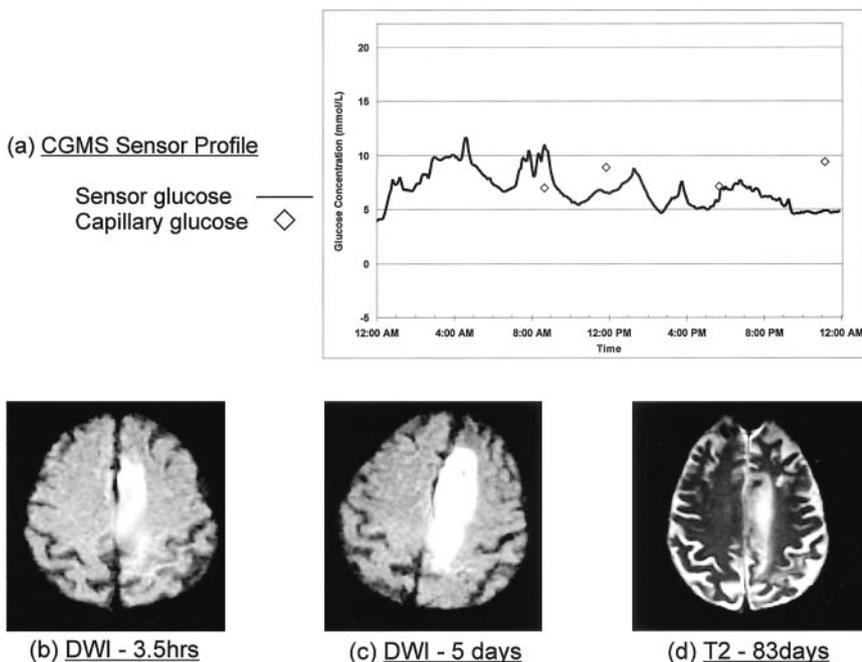


Figure 3. The 24-hour CGMS glucose profile (a) and corresponding MRI studies (b, c, d) in a patient with anterior cerebral artery infarction and persistent hyperglycemia.

TABLE 3. Multiple Regression Analysis of Final Infarct Volume Change

	R^2	Final Infarct Volume Change P
MCG ≥ 7 mmol/L alone	0.21	<0.05
MCG ≥ 7 mmol and HbA _{1c} $\geq 7\%$ (yes/no)	0.53	<0.05
Day 1 NIHSS ≥ 13 (yes/no)		NS
tPA treatment (yes/no)		NS
Time to first MRI (h)		NS
CGMS SG ≥ 7 mmol/L alone	0.35	<0.01
CGMS SG ≥ 7 mmol and HbA _{1c} $\geq 7\%$ (yes/no)	0.55	<0.05
Day 1 NIHSS ≥ 13 (yes/no)		NS
tPA treatment (yes/no)		NS
Time to first MRI (h)		NS

MCG indicates mean capillary glucose over 72 h after admission; SG, sensor glucose over 72 h after admission.

Discussion

This is the first clinical study to examine continuous physiological glucose monitoring early after stroke onset and to demonstrate that persisting hyperglycemia after ischemic stroke is an independent determinant of infarct expansion that is associated with worse clinical outcome. This study clearly shows that persisting hyperglycemia influences stroke evolution. This effect on infarct volume change is independent of baseline stroke severity using a NIHSS score dichotomized to ≥ 13 and premonitory glycemic control defined by HbA_{1c} > 2 SD above the population normal. Furthermore, a novel finding is that the serial profile of glycemic status is a more robust indicator of infarct evolution and clinical outcome than an isolated measure of glucose on admission to hospital. Indeed, we failed to show an expected association between admission hyperglycemia and outcome. However, it is notable that similar findings have occurred in other studies of small sample size, so this may reflect a type 2 statistical error.²⁷

Hyperglycemia after stroke is common and associated with a poorer outcome.^{2,28,29} In animal models of focal cerebral ischemia, controlled hyperglycemia at the time of cerebral insult consistently but not exclusively results in greater infarct size.^{8,30,31} Normalization of glycemia with insulin has ameliorated these effects, although whether this effect is through maintenance of euglycemia or relates to additional neuroprotective benefits from insulin remains to be shown.^{32,33}

Unlike animal models, the cause of human stroke is heterogeneous. The timing of hyperglycemia cannot be readily controlled for, and the definition of hyperglycemia with a single measure of blood glucose at a variable time period after the ictus is problematic. Most previous studies in this field have been limited by the use of a single time point measure of glucose, the inclusion of subjects with cerebral hemorrhage, and poorly defined stroke severity and outcome measures.

Although some have criticized the use of MRI measures as a surrogate outcome measure, we and others have demonstrated that clinical outcome measures parallel infarct volume changes.³⁴ In addition, MRI has the capacity to provide insight into the mechanisms through which hyperglycemia influences clinical outcome.^{34–36} This and other studies have demonstrated the usefulness of MRI as a surrogate outcome measure in clinical stroke research.^{24,37}

What are the limitations of this study? The problems of defining hyperglycemia have been mentioned already. We have tried to resolve with this issue through the use of a variety of measures of glycemic status. The use of any cutoff threshold to define hyperglycemia is arbitrary; however, we have attempted to maintain consistency with similar research groups in our definition of significant acute and persistent hyperglycemia.³⁸ Use of HbA_{1c} to define pre-existing glycemic status is supported by an increase in vascular risk seen with even modest elevations in glycohemoglobin levels.³⁹ Issues of stroke heterogeneity influence most stroke trials. We limited inclusion to subjects early after onset of ischemic stroke and obtained a predominant population of moderately severe anterior circulation syndrome stroke. Four of the subjects in this study, 3 of whom had pre-existing diabetes, were treated with rtPA. In the National Institute of Neurological Disorders and Stroke (NINDS) trial, admission glucose level was not associated with altered effectiveness of rtPA, although hyperglycemia did predict lower odds for good clinical outcomes and a higher risk of ICH.⁴⁰ Although we found that rtPA treatment had no significant effect in a multiple regression analysis, this could reflect the small number of patients receiving thrombolysis. In our small sample, neither acute infarct volume change or final infarct volume change was significantly different between the rtPA-treated and the untreated groups. Like many current imaging-based studies, the number of subjects in the present study is limited, and outcome MRI data in 5 subjects were extrapolated from subacute imaging studies. We recognize the limitation of this approach, which we and others have used in serial MRI studies in stroke.^{24,25}

This is one of the few imaging studies examining the relationship between acute stroke and hyperglycemia. Using CT, Horowitz et al⁴¹ previously found that admission glucose levels correlated with infarct size and hemorrhagic transformation. Analysis of a large cohort by Toni et al⁴² initially indicated no association between admission glucose within 12 hours of hemispheric stroke and outcome CT lesion size.⁴² However, when patients with angiographically demonstrated intracranial occlusion were examined, the presence or absence of collateral blood flow influenced the effect of hyperglycemia on lesion size.¹² Other groups using conventional MRI did not show an association between the presence of diabetes and the size of ischemic lesion but excluded patients with stress hyperglycemia and looked specifically at subcortical infarction.¹⁰ We have used 2 measures of volume change—acute DWI lesion volume change and final overall lesion volume change—to demonstrate the robustness of our imaging data. We have specifically excluded patients in whom neurological deficit resolved rapidly and no DWI

lesion was visible on either acute or subacute DWI imaging despite a clinical history compatible with acute stroke or transient ischemic attack. There is evidence that most ischemic lesions follow a consistent pattern of growth, with maximal volume change at day 3 to 5 and a subsequent decrease in size. The finding that poststroke glucose levels continue to correlate with final infarct volume change suggests that the effect is not mediated solely by an association with cerebral edema.⁴³

There are important parallels between stroke and acute myocardial infarction. Attenuation of hyperglycemia with intravenous insulin has been shown to substantially reduce mortality and morbidity in diabetic patients with acute myocardial infarction.⁴⁴ Similar impressive benefits of insulin-induced normoglycemia have also been seen in an intensive care population.⁴⁵ Given the wealth of evidence of an association between poststroke hyperglycemia and outcome, a clinical trial of intensive normalization of glucose is needed. The Glucose Insulin in Acute Stroke Trial (GIST) is currently ongoing but will require a large number of participants to demonstrate effect using clinical outcome measures.³⁸ We have begun a pilot study (Glucose Reduction in Acute Cerebral Events [GRACE]) using intensive insulin therapy to maintain normoglycemia after anterior circulation ischemic stroke. This trial randomizes patients to either intravenous insulin or standard therapy, uses MRI-defined surrogate outcome measures, and may provide firm evidence for both the effect of and mechanism behind the treatment of hyperglycemia.

Acknowledgments

The National Health and Medical Council of Australia and Scottish Hospital Endowment Research Trust (T.A.B.) supported this study. Invaluable assistance was provided by the radiographers and stroke research nurses at both hospitals. We would like to thank Medtronic MiniMed Inc CA for their assistance in the provision of the CGMS.

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