Frequency and Temporal Profile of Poststroke Hyperglycemia Using Continuous Glucose Monitoring

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OBJECTIVE — Poststroke hyperglycemia (PSH) is common and has adverse effects on outcome. In this observational study, we aimed to describe the frequency and temporal profile of PSH using a continuous glucose monitoring system (CGMS) in patients with and without diabetes.

RESEARCH DESIGN AND METHODS — Fifty-nine patients with acute hemispheric ischemic stroke were prospectively studied with the CGMS, regardless of medication, admission plasma glucose value, and diabetes status. The CGMS records interstitial glucose every 5 min for 72 h.

RESULTS — On admission, 36% of patients had preexisting diabetes. At the earliest analyzed time point of 8 h from stroke onset, 50% of nondiabetic subjects and 100% of diabetic patients were hyperglycemic (≥7 mmol/l). This early-phase hyperglycemia was followed by a decrease in glucose 14–16 h poststroke when only 11% of nondiabetic and 27% of diabetic patients were hyperglycemic. A late hyperglycemic phase 48–88 h poststroke was observed in 27% of nondiabetic and 78% of diabetic patients. Thirty-four percent of nondiabetic and 86% of diabetic patients were hyperglycemic for at least a quarter of the monitoring period. Multivariate regression analysis demonstrated that diabetes, insular cortical ischemia, and increasing age independently predicted higher glucose values.

CONCLUSIONS — Poststroke hyperglycemia is common and prolonged despite treatment based on current guidelines. There are early and late hyperglycemic phases in nondiabetic as well as diabetic patients. Treatment protocols with frequent glucose measurement and intensive glucose-lowering therapy for a minimum of 72 h poststroke need to be evaluated.

Diabetes Care 29:1839–1844, 2006

Poststroke hyperglycemia (PSH) is an attractive physiological target for acute stroke therapies with potential application across broad time windows, stroke subtypes, and stroke severity. Despite the increasing awareness of PSH prevalence and detrimental effects upon stroke outcomes (1–3), little is known about the detailed temporal profile as previous studies have used infrequent and random time point glucose measurements (4–6).

An early and modest rise in glucose within 6–12 h of stroke onset has been observed (5). A reduction, followed by a plateau in the glucose curve over the subsequent 24–40 h, has been demonstrated (6,7). Glucose has been documented to decline progressively during the first poststroke week on the basis of daily measurements in patients with and without diabetes (4,8). However, questions regarding the duration and degree of PSH, which are fundamental to the design and potential success of glucose-lowering protocols, remain.

The frequency of glucose monitoring is critical to the determination of the temporal profile of PSH. Continuous glucose monitoring (CGM) represents a novel method of accurately defining PSH by facilitating the detection and duration of glycemic excursions. The MiniMed continuous glucose monitoring system (CGMS) is a minimally invasive subcutaneous glucose monitor currently approved for the investigation of glycemic profiles in diabetic outpatients (9). Recent data have shown that CGM can be successfully undertaken in the acute hospital setting (10,11). Our pilot data suggested that quantification of persistent PSH with the CGMS was a more robust indicator of infarct growth and clinical outcome than isolated glucose estimates in hyperglycemic acute stroke patients (10). Therefore, the aim of this observational study was to accurately describe the frequency and temporal profile of PSH using the CGMS in patients with and without diabetes.

RESEARCH DESIGN AND METHODS

— Sixty-eight patients with hemispheric ischemic stroke syndromes presenting to the Stroke Unit of the Royal Melbourne Hospital within 24 h of symptom onset were prospectively enrolled regardless of age, medication, admission venous plasma glucose level, and diabetes status. Patients with a history of previous stroke within the same hemisphere or a contraindication to magnetic resonance imaging (MRI) were excluded. MRI was performed, and a National Institutes of Health Stroke Scale score was obtained on admission (baseline).

Categorization of diabetes status was based upon an established history or treatment with glucose-lowering therapies prestroke. This study was approved by the Human Research Ethics Commit-

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Received for publication 25 January 2006 and accepted in revised form 19 April 2006.

Abbreviations: cFPG, capillary finger-prick glucose; CGM, continuous glucose monitoring; CGMS, continuous glucose monitoring system; MRI, magnetic resonance imaging; NGF, nasogastric tube feeding; PSH, poststroke hyperglycemia.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

DOI: 10.2337/dc06-0204

Table 1—*Patient data*

	Nondiabetic group	Diabetic group
n	38	21
Age (years)	75 (50–89)	72 (51–87)
Male sex (%)	51	38
Admission blood glucose (mmol/l)	6.0 (4.5–10.4)	9.2 (3.2–19.5)
Time to admission glucose (h)*	7 (1–23)	6 (1–21)
Admission hyperglycemia (≥7.0 mmol/l) (%)	32	81
Admission A1C (%)	5.6 (3.9–7.0)	7.5 (5.1–12.9)
Stroke onset to start CGMS (h)	18 (5–44)	15 (6–41)
Feeding (%)		
Oral	68	67
Nasogastric	29	33
Glucose-lowering treatment (%)		
Oral	0	14
Subcutaneous insulin	3	29
Combined	0	14
Admission NIHSS score	9 (1–26)	11 (3–23)
Insular cortical involvement (%)	42	47
Baseline DWI lesion volume (ml)	14 (0.0–128)	13 (0.0–117)

Data are median (range) unless otherwise indicated. *Time from stroke onset to measurement of admission blood glucose in hours. DWI, diffusion-weighted imaging; NIHSS, National Institutes of Health Stroke Scale.

tee, and informed consent was obtained for all patients.

Glucose measurements

A random venous plasma glucose measurement was performed upon admission, before administration of intravenous solutions or glucose-lowering therapies, and between 8:00 and 11:00 A.M. on day 1. Capillary finger-prick glucose (cFPG) measurements were obtained four to six times per day for the purpose of guiding treatment, using a MediSense precision glucose meter calibrated every 24 h.

CGM was performed using the MiniMed CGMS (Medtronic MiniMed, Northridge, CA) according to the manufacturer's instructions. The CGMS is a minimally invasive subcutaneous glucose sensing system inserted into the anterior abdominal wall that records interstitial fluid glucose values (2.2–22.0 mmol/l) every 5 min for up to 72 h (9). The CGMS requires a minimum of four cFPG values to be entered daily for calibration purposes. CGMS software retrospectively calibrates sensor data using entered cFPG readings during download at the completion of monitoring.

In keeping with our pilot study and in accordance with current American Diabetes Association criteria for the diagnosis of diabetes, hyperglycemia was defined as a glucose level ≥7 mmol/l (10,12).

Glucose-lowering therapies

Glucose-lowering therapy consisted of oral hypoglycemic agents and/or titrated subcutaneous insulin administered every 4–6 h, at the discretion of the treating physician in accordance with current stroke management guidelines (13,14). Patients either continued with preadmission oral treatment ($n = 3$), had additional insulin ($n = 5$), or had oral agents discontinued with ($n = 4$) or without ($n = 3$) ancillary insulin. No patient received dextrose-containing solutions.

Feeding

Maintenance intravenous fluids consisted of 0.9% normal saline, which was commenced acutely and continued until a feeding regimen was established. Feeding was classified broadly into oral or continuous nasogastric tube feeding (NGF), and the poststroke day of commencement (day 1, 2, or 3) was noted. Assignment to either feeding modality was in accordance with published guidelines (14).

Imaging

MRI studies were performed using a 1.5-T echo planer imaging-equipped whole-body scanner (Signa Horizon SR120; General Electric, Milwaukee, WI). Our MRI protocol, volumetric analysis, and anatomical definition of insular cortical involvement have been previously described (15,16).

Statistical analysis

For each patient, median glucose values for sequential 2-h time intervals from stroke onset were derived from the CGMS measurements recorded every 5 min. The percentage of time spent hyperglycemic (≥7 mmol/l) was calculated as (number hyperglycemic 2-h time intervals/total 2-h time intervals) × 100. Univariate relationships were assessed using parametric or nonparametric tests as appropriate. For the purpose of descriptive profiling, data were analyzed according to diabetes status. However, patient groups were pooled for the hierarchical generalized linear model used to assess relationships between potential prognostic variables and natural log-transformed glucose. The final model was devised stepwise, including all variables that appeared to be significant explanatory factors ($P < 0.05$) or potential confounders (diabetes, age, time, and insular cortical ischemia, a cortical autonomic center previously found to be independently associated with stress hyperglycemia) (16). The estimates shown were adjusted for these variables. The first graphical representation of raw data suggested the possibility of an initial fall in glucose followed by a subsequent increase; hence, separate analyses were performed for the periods 8–24 and 24–88 h. Estimates shown represent the proportional change in glucose per unit increase in each explanatory variable. Statistical analysis was performed using the GLLAMM program in Stata 7.0 (StataCorp) and GraphPad Prism version 4.02 (GraphPad Software).

RESULTS — Fifty-nine patients were included in the final analysis (Table 1) after exclusion of nine patients with technically inadequate CGMS data: absent data at the time of download ($n = 3$), persistent sensor malfunction ($n = 5$), or study withdrawal ($n = 1$). At presentation, 36% of patients had preexisting diabetes. Six patients without known diabetes but with elevated HbA_{1c} (A1C) (≥6.2%) on admission (two hyperglycemic and four normoglycemic) were included in the nondiabetic group. Admission hyperglycemia was documented in 81% of patients with and 32% without diabetes. Systemic thrombolysis with recombinant tissue plasminogen activator was administered to 12 patients.

The CGMS sensor was well tolerated with no patient-reported adverse events. Insertion site bleeding was noted in all recombinant tissue plasminogen activa-

tor–treated patients, with sensor replacement required in three. CGM was commenced 5–44 h after stroke onset and performed for a median of 69 h, yielding 719 (range 260–965) glucose readings per patient. CGMS glucose per patient was significantly higher in those with (median 7.9 [range 5.5–16.1 mmol/l]) compared with those without known diabetes (5.6 [3.5–8.4 mmol/l]; $P < 0.001$).

CGMS glucose profiles

CGMS profiling demonstrated early and late hyperglycemic phases in patients with and without diabetes.

Nondiabetic group. At the earliest analyzed time point of 8 h from stroke onset, mean glucose was 6.5 mmol/l when 50% of patients were hyperglycemic (Fig. 1*A*). After this, mean glucose decreased sequentially until 16 h from stroke onset, reaching a minimum of 5.3 mmol/l when 11% of patients were hyperglycemic. Mean glucose remained relatively stable until 66 h when a moderate increase to ~6.0 mmol/l was observed for the duration of monitoring. For the period 24–48 h poststroke, a median of 19% of patients were hyperglycemic, increasing to 27% for the period 48–88 h poststroke. Thirty-four percent of patients were hyperglycemic for at least a quarter and 13% for at least half of the monitoring period. There was a direct correlation between admission blood glucose and time spent hyperglycemic (Spearman $\rho = 0.47$, $P = 0.003$).

Diabetic group. At the earliest analyzed time point of 8 h from stroke onset, mean glucose was 8.4 mmol/l when 100% of patients were hyperglycemic (Fig. 1*B*). Similar to that in patients without diabetes, mean glucose decreased sequentially until ~14 h from stroke onset to reach the minimum of 6.1 mmol/l when only 27% of patients were hyperglycemic. Mean glucose subsequently increased to >8.0 mmol/l at ~18 h from stroke onset, heralding persistent hyperglycemia with frequent glycemic excursions for the remainder of the monitoring period. With increasing time from stroke onset, the proportion of hyperglycemic patients increased from 58% between 24 and 48 h to 78% between 48 and 88 h poststroke. Eighty-six percent of patients were hyperglycemic for at least a quarter and 71% for at least half of the monitoring period. There was a weak association between admission blood glucose and time spent hyperglycemic (Spearman $\rho = 0.37$, $P = 0.098$).

Glucose-lowering therapy, diabetes, and the CGMS profile

During the monitoring period, 57% of patients with diabetes received glucose-lowering therapy (Table 1). The remaining patients with diabetes received no in-hospital glucose-lowering treatment. Not surprisingly, patients who received glucose-lowering therapy had evidence of poorer previous glycemic control than those not receiving such treatment with median A1C values of 7.9 and 6.6%, respectively ($P = 0.008$) and higher day 1 venous plasma glucose levels (12.4 vs. 7.8 mmol/l; $P = 0.004$). The median proportion of total monitoring time that individuals spent within the hyperglycemic range was 57% in those who received no in-hospital glucose-lowering therapy and 81% in those who received stroke unit glucose-lowering treatment.

Feeding and CGMS profiles

Feeding was initiated on day 1 in 36%, on day 2 in 53%, and on day 3 in 10% of patients. An exploratory assessment of feeding and glycemic profiles was undertaken. Median CGMS glucose per patient was similar in nondiabetic patients fed orally (5.5 [range 3.5–7.5 mmol/l]) or by NGF (5.4 [4.3–8.4 mmol/l]; $P = 0.814$). Median glucose in patients with diabetes was also similar in oral (7.8 [5.5–16.1 mmol/l]) or NGF groups (9.3 [5.7–13.6 mmol/l]; $P = 0.710$). Stratification according to the mode of feeding had little quantifiable effect upon time spent hyperglycemic in those with (70% NGF and 65% oral; $P = 0.628$) or without (12% NGF and 15% oral; $P = 0.894$) diabetes.

Predictors of early and late PSH

Early hyperglycemia. Over the first 24 h poststroke, patients with diabetes had glucose values 1.22 times higher than those without diabetes ($P < 0.001$) (Table 2). Patients with insular cortical ischemia had glucose values 1.13 times higher than those without ($P = 0.007$). Increasing age was associated with a modest increase in glucose level ($P = 0.013$).

Late hyperglycemia. During the period 24–88 h poststroke, individuals with diabetes had glucose levels 1.43 times higher than those without diabetes ($P < 0.001$), and patients with insular cortical ischemia had glucose levels 1.10 times higher than those without insular ischemia ($P < 0.001$). Age was again associated with a modest increase in glucose ($P = 0.002$). There was no strong evidence for an effect of sex, baseline stroke severity (National Institutes of Health Stroke Scale score), or infarct volume upon the genesis of early or late hyperglycemia.

Among patients with diabetes, the relationship between administration of glucose-lowering therapy and glucose level was assessed. Over the first 24 h poststroke, patients who received standard glucose-lowering therapy had glucose values similar to those who did not (ratio 0.91 [95% CI 0.63–1.31]; $P = 0.600$). During the period 24–88 h, patients given glucose-lowering therapy had glu-

Table 2—*Multivariate regression analysis exploring predictors of early and late PSH*

Prognostic variables	Ratio*	95% CI	*P* value
Early hyperglycemia: 8–24 h poststroke ($n = 49$)			
Diabetes	1.22	1.13–1.33	<0.001
IC+	1.13	1.03–1.23	0.007
Age (per 10 years)	1.05	1.01–1.09	0.013
Baseline DWI volume (ml)	0.96	0.91–1.01	0.141
Baseline NIHSS score	1.00	0.99–1.01	0.838
Sex	0.97	0.86–1.08	0.613
Late hyperglycemia: 24–88 h poststroke ($n = 53$)			
Diabetes	1.43	1.35–1.51	<0.001
IC+	1.10	1.05–1.15	<0.001
Age (per 10 years)	1.04	1.02–1.07	0.002
Baseline DWI volume (ml)	1.01	0.97–1.03	0.411
Baseline NIHSS score	1.00	0.99–1.00	0.318
Sex	1.01	0.98–1.05	0.437

Pooled data include patients with and without diabetes.*Proportional change in glucose per unit increase in each explanatory variable. DWI, diffusion-weighted imaging; IC+, insular cortical ischemia; NIHSS, National Institutes of Health Stroke Scale.

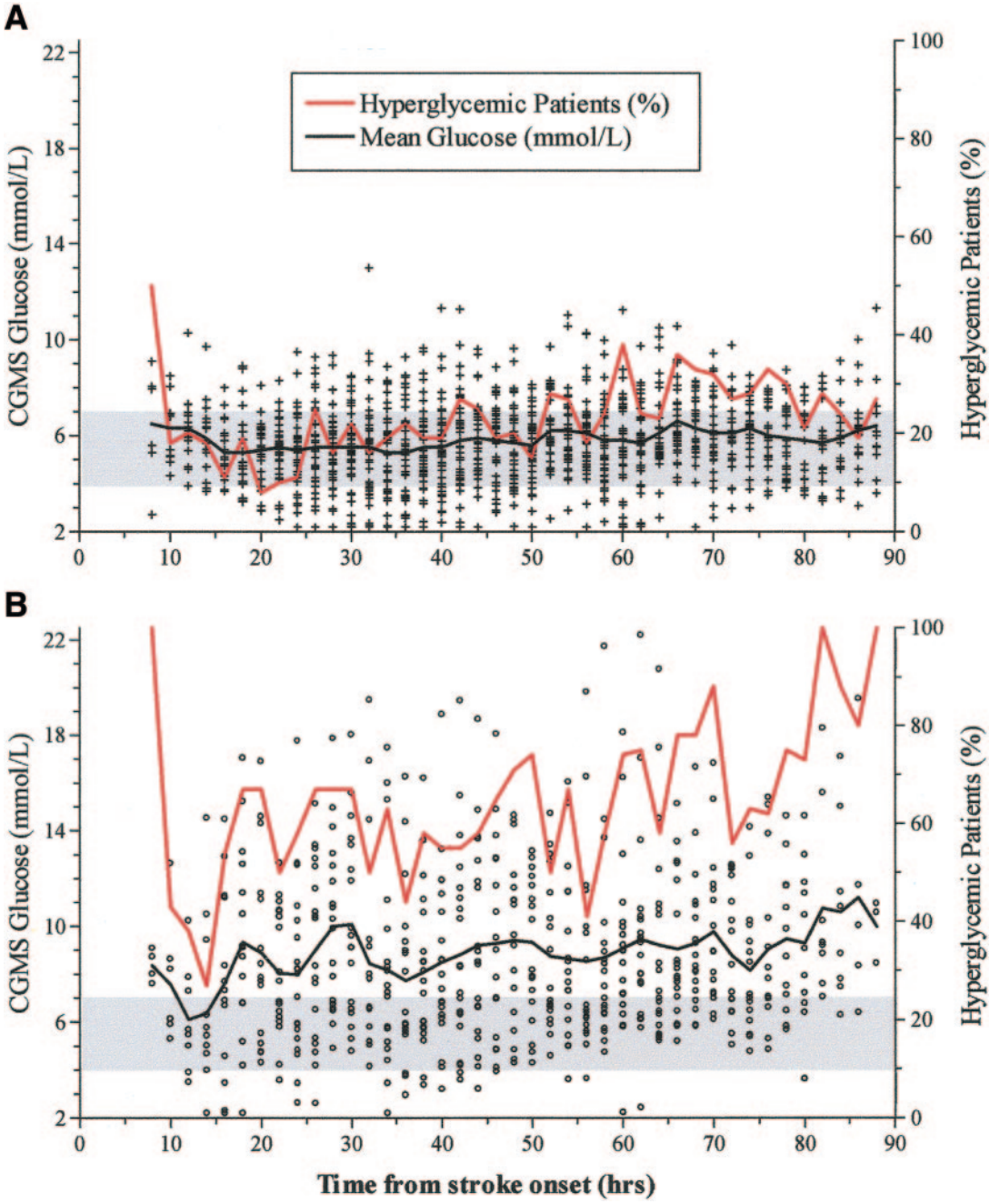

Figure 1—*CGMS glucose values for patients without* (A) *and with* (B) *diabetes in sequential 2-h time epochs illustrating an early and late hyperglycemic phase in both groups. The gray box represents the euglycemic range (4–7 mmol/l), the black line is the mean glucose value (left axis), and the red line is the proportion of patients with hyperglycemia (right axis) across sequential time points from stroke onset.*

cose values 1.67 times higher than those not administered such therapy (95% CI 1.57–1.77; $P < 0.001$).

Accuracy of CGMS glucose estimates

CGMS glucose values were strongly correlated with concurrent cFPG readings (Spearman $\rho = 0.81$, $P < 0.0001$). Accuracy of the CGMS glucose data were determined using 95% limits of agreement (mean difference ± 2 SD) between 857 paired CGMS and cFPG glucose estimates (17). CGMS glucose values were, on average, 0.12 mmol/l lower than the corresponding cFPG value (95% limits of agreement of −2.80 to +2.56 mmol/l).

CONCLUSIONS — This study of the temporal profile of PSH has shown that many patients remain hyperglycemic for at least 88 h poststroke. In addition to the well-documented early phase of PSH, CGMS profiling has demonstrated a late hyperglycemic phase that exists in stroke patients with and without diabetes. Time spent hyperglycemic is a useful parameter enabling the quantitative assessment of time spent in marked glycemic excursions. Not surprisingly, the temporal profile of PSH was substantially different in patients with and without diabetes, suggesting that future treatment protocols may need to be diabetes specific. The duration of PSH documented in this study suggests that glucose-lowering therapies, although their value is currently un-

proven, should be tried for a minimum of 72 h poststroke.

Higher admission glucose levels have been shown to dramatically reduce penumbral salvage, increase final infarct volume, and worsen clinical outcome (3,18). In addition, persistence of hyperglycemia (≥7 mmol/l) has been documented to independently predict infarct growth and worse outcome (10). In our study, the CGMS has shown that a substantial proportion of individuals without diabetes and the majority of those with diabetes have glucose values persistently above this threshold level for poor outcome throughout the subacute phase of stroke.

Consistent with the glucose profile demonstrated by the control arm of the Glucose Insulin in Stroke Trial (GIST) in the U.K. (6,7), we have also documented an early hyperglycemic phase followed by a decline over the first 14 h poststroke (Fig. 1), potentially reflecting delayed early feeding. At the earliest analyzed time point, 50% of those without and 100% of those with diabetes were hyperglycemic, highlighting the need to implement glucose-lowering therapies as close to stroke onset as possible. Increasing time from stroke onset heralded a late hyperglycemic phase (48 h onward) in both patient groups (78% with and 27% without diabetes). This degree of persistent and late hyperglycemia has not been previously documented in acute stroke patients. Although persistent PSH may not be surprising in those with diabetes, the utilization of a CGMS has shown that the magnitude continues to increase with time from stroke onset (Fig. 1). Our data contrast with the findings of previous studies in which glucose determinations were performed less frequently and declining glucose values over the 1st poststroke week were documented (4,8). As illustrated by our study, a higher frequency of glucose measurement, regardless of modality, is likely to facilitate the identification of glycemic excursions.

In nondiabetic patients, stratification according to admission hyperglycemia was useful in identifying individuals at risk of persistent PSH, and this value may represent an appropriate glucose threshold for the early introduction of glucose-lowering therapy. In contrast, the presence of admission hyperglycemia in patients with diabetes had less prognostic value for time spent hyperglycemic. A meta-analysis addressing the impact of acute hyperglycemia on stroke outcomes failed to demonstrate an association between admission hyperglycemia and increased mortality in those with diabetes (2). Our findings suggest that in people with diabetes, clinicians should not rely upon a single-point glucose estimate when assessing the independent impact of hyperglycemia on stroke outcome because this value grossly underestimates the true glycemic profile. Future researchers may need to consider quantitative measures of PSH, such as time spent hyperglycemic, when exploring stroke outcomes.

As anticipated, the presence of diabetes was a potent predictor of higher glucose levels across the monitoring period despite some glycemic modification by glucose-lowering treatment. The presence of insular cortical ischemia in patients with and without diabetes was associated with significantly higher glucose values. We found no strong evidence for an effect of baseline stroke severity or infarct volume on the genesis of early or late hyperglycemia, suggesting that PSH is not simply an epiphenomenon of a more severe stroke. Other factors may have contributed to the presence of sustained or late hyperglycemia, including discontinuation of preadmission therapies and ineffective treatment protocols, early enteral feeding that we could not adequately assess is this study, and late stroke complications (e.g., pneumonia) that may contribute to an enhanced or prolonged stress response.

Guidelines from European and U.S. stroke associations for the management of PSH mandate intervention with insulin only at extreme degrees of hyperglycemia (>10 and >16.6 mmol/l, respectively) with no standardized approach to treatment duration, mode or type of insulin delivery, target glycemic range, or diabetes status (13,14). These guidelines reflect the unproven efficacy of early and aggressive induction of euglycemia on outcome. Although our study was not a randomized treatment trial and many treatment-related biases may be operative, patients with diabetes receiving glucose-lowering treatment in accordance with these guidelines did not achieve sustained euglycemia, spending 81% of the monitoring period within our hyperglycemic range. This hyperglycemia was particularly evident at later time periods when patients with diabetes receiving glucose-lowering treatment had glucose values 67% higher than those who did not have diabetes. This finding suggests that current stroke guidelines are inadequate and discordant with contemporary management of hyperglycemia in the critically ill (19).

Under physiological conditions, there is a strong positive correlation between interstitial fluid glucose dynamics and blood glucose (20). The CGMS has been shown to accurately track rapid changes over a range of interstitial fluid glucose concentrations with an acceptable time lag (21,22). In outpatients, the CGMS has been documented to be an accurate and reliable tool for assessing glycemic stability (23,24). However, concerns exist about the accuracy of the CGMS during periods of rapid glucose fluctuation and hypoglycemia (21,25). Data on the use of the CGMS in a small heterogeneous group of intensive care patients have demonstrated clinical accuracy comparable with that for outpatients (11), and we found no systematic discrepancy in glucose values measured by the CGMS. Therefore, the accuracy of data obtained in our acute stroke study compares favorably with that of data acquired in outpatients (23), further extending the validity of use of the CGMS in the acute in-hospital setting.

As this study did not stipulate strict feeding protocols or quantify caloric intake, the impact of feeding upon PSH was assessed in an exploratory fashion only. The apparent similarity in overall glycemic profiles between the feeding modalities may be explained by the simplistic feeding categorization used. Alternatively, the magnitude of expected glycemic excursions after meals may be reduced due to inadequate caloric intake (26) or modified by the catabolic stress response to stroke. In view of the lack of caloric data, our study results do not negate a role for feeding in the genesis of late hyperglycemia. Future studies with standardized nutritional protocols are warranted.

The classification of diabetes used may have led to an underestimation of the prevalence of preexisting diabetes and could potentially explain some of the persistent PSH in the nondiabetic group. Elevated A1C (≥6.2%) at admission has been suggested to predict the presence of unrecognized diabetes among hyperglycemic acute stroke patients (1). However, current diagnostic criteria for diabetes do not recommend the use of A1C (12,27). Furthermore, steady-state conditions are required for accepted diagnostic procedures (fasting plasma glucose or an oral glucose tolerance test) and the presence of a catabolic stress response after acute stroke renders results of such testing ob-

tained under these conditions unreliable (1,27). Six patients with an elevated A1C were included in our nondiabetic group. Patient reclassification to "diabetic" was not undertaken on the basis of hyperglycemia or elevated A1C. However, such patients do require future diagnostic testing for diabetes.

The effective treatment of PSH is one of the most attractive targets for acute stroke therapies. Our study indicates that persistent PSH is virtually universal in patients with diabetes and common in those without diabetes after acute ischemic stroke. Although we do not advocate CGM as a routine, frequent glucose measurements are essential to the delineation of glycemic status and administration of safe and effective treatment protocols. A multicenter randomized controlled trial exploring the potential clinical benefit of early and aggressive glucose lowering using an intensive insulin infusion protocol is currently underway (7). The results of our study suggest that intensive glucose-lowering therapies should be tried for a minimum of 72 h after acute ischemic stroke.

Acknowledgments— We thank Medtronic MiniMed for assistance in the provision of the CGMS.

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