Outcome of critically ill hyperglycemic stroke patients admitted to the intensive care unit

Kamel Abdelaziz Mohamed[a], Ahmad Saad[b]

[a]Departments of Critical Care, [b]Internal Medicine, Faculty of Medicine, Cairo University, Cairo, Egypt

Correspondence to Kamel Abdelaziz Mohamed, MD, Department of Critical Care, Faculty of Medicine, Cairo University, 7 Manial Museum Street, Cairo, Egypt
e-mail: kamel.abdalla64@gmail.com

Received 15 July 2013
Accepted 23 July 2013

The Egyptian Journal of Internal Medicine
2013, 25:185–190

Introduction
It has been suggested that admission hyperglycemia is a marker of extensive brain damage. Despite these observations, studies that have examined the relationship between glucose levels and the outcome after stroke in diabetic and nondiabetic patients have reported conflicting results.

Aim
We evaluated data on stroke patients admitted to the intensive care department to estimate the influence of hyperglycemia on the short-term mortality in both diabetic and nondiabetic patients.

Patients and methods
A total of 100 consecutive adult patients with stroke admitted to the ICU were studied over a period of 28 months. The patients were followed up for 28 days until discharge from the hospital or until death, whichever occurred first. The patients were divided into three broad groups, on the basis of fasting blood glucose or random sugar and HbA1c to rule out undetected diabetes patients.

Results
There were no significant differences in the stroke subtype or the baseline stroke severity between diabetic (group 3) and hyperglycemic (group 2) patients. Also, there was no significant association between the stroke severity and the glycosylated hemoglobin level in group 2 and group 3 ($r = 0.26$, $P = 0.4$; $r = 0.19$, $P = 0.31$; respectively). With regard to an excellent outcome of stroke, which was measured by the modified Rankin scale (0–1), there was no significant difference between group 2 and group 3. The unadjusted risk ratio was 1.85 (95% confidence interval 0.52–4.41) for group 2, whereas it was 1.25 (95% confidence interval 0.7 6–4.3) in group 3. Nondiabetic patients with hyperglycemia had a 1.6 times higher relative risk of in-hospital 28-day mortality than diabetic patients. There were four nonsurvivors (11%) out of 36 patients in the control nondiabetic (group 1), whereas eight (26%) of 31 patients died in group 2, which was statistically significant when compared with group 1 ($P = 0.02$). However, six nonsurvivors (18%) of 33 in group 3 when compared with group 2 was statistically significant ($P = 0.04$).

Conclusion
Our current study showed that nondiabetic patients with hyperglycemia had a 1.6 times higher relative risk of in-hospital 28-day mortality than diabetic patients. Stress hyperglycemia predicts an increased risk of in-hospital mortality after ischemic stroke; thus, we should not underestimate the potential harm, as patients with the highest admission glucose levels would have most likely been treated earlier and more aggressively.

Keywords:
diabetes mellitus, hyperglycemia, stroke

Egypt J Intern Med 25:185–190

1110-7782

Introduction

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]. Similarly, several studies have indicated that patients with diabetes are more likely to die or to have substantial neurological disability after acute stroke than nondiabetic individuals [2]. A high proportion of patients suffering an acute stress such as stroke [3] or myocardial infarction [4] may develop hyperglycemia, even in the absence of a pre-existing diagnosis of diabetes. Both human and animal studies suggest that this is not a benign occurrence and that stress-induced hyperglycemia is associated with a high risk of mortality after both stroke [5] and myocardial infarction [6]. Moreover, glucose lowering with insulin reduces ischemic brain damage in animal models of stroke [7], which suggests that stress-induced hyperglycemia may be a modifiable risk factor for brain damage. Despite these observations, the relationship between glucose levels and the outcome after stroke in diabetic and nondiabetic patients has not been well characterized, and studies that have examined this relationship have reported conflicting results. However, between 20 and 40% of patients admitted with ischemic stroke are hyperglycemic, often without a pre-existing diagnosis of diabetes [8]. Recent meta-analyses of prospective

and case—control studies confirmed the importance of early stress hyperglycemia as a predictor of stroke outcome, but the debate continues as to whether the effect is independent of a pre-existing diagnosis of diabetes or the initial stroke severity. It is still not clear as to what cut-off value of the mean blood glucose level should be considered safe in diabetic and nondiabetic patients [9]. New and sophisticated techniques such as MR spectroscopy, computed tomography, PET, and conventional MRI findings still yield inconclusive results [10]. Therefore, we evaluated data on stroke patients admitted to the intensive care department to estimate the influence of stress hyperglycemia on short-term mortality in both diabetic and nondiabetic patients. We sought to address this issue by studying the blood sugar level at the time of hospitalization after stroke. Second, we sought to ascertain whether a high sugar level, if seen during admission, can be explained in terms of diabetes on the basis of the history and the glycosylated hemoglobin level. Third, we tried to assess whether this blood sugar level shows any association with the outcome of stroke, that is, whether the patient survived or not.

Patients and methods

A total of 100 consecutive adult patients of both sexes with stroke admitted to the ICU of Riyadh Care Hospital, Saudi Arabia, were studied over a period of 28 months (from June 2009 to October 2011). Provided the patient reached the hospital within 6 h of suspected stroke, the time lag between the onset of first signs of suspected stroke and hospitalization was noted. Of 139 such cases, 100 patients were included in the study after confirmation using computed tomography scan and after excluding other potential differential diagnoses such as space-occupying lesion, subdural hematoma, and a history of stroke. For the purpose of this study, transient ischemic attack and subarachnoid hemorrhage were excluded. Each patient was clinically evaluated to assess their general medical status and stroke severity besides obtaining consent from the patient or a relative. To quantify the stroke severity on the basis of clinical features, the Glasgow coma scale was used to assess the stroke severity and the modified Rankin scale for the outcome. Acute physiology and chronic health evaluation II (APACHE II) scores were determined [11]. The length of stay (LOS) in the ICU as well as in the hospital was calculated in terms of the number of calendar days. The use of vasopressors and mechanical ventilation was recorded. Patients were followed up for 28 days until discharge from the hospital or until death, whichever occurred first. A sample of blood for biochemical workup after admission was collected, and blood glucose and glycosylated hemoglobin were measured. The blood glucose measured was considered to be a random sample as the fasting blood sugar cannot be practically applied in these patients. Patients who had eaten or received intravenous dextrose less than 2 h from admission were excluded. The patient's blood pressure at the time of admission was recorded with proper clinical assessment. All patents were given appropriate standard therapeutic care and were monitored during the stay in hospital (up to a maximum of 28 days). Other information collected was the demographic profile of the patient, history of diabetes, and hypertension. The primary end point of the study was in-hospital mortality. Random blood sugar was measured for each patient on the first day of stroke on admission; patients were considered hyperglycemic when the blood sugar was more than 8 mmol/l. Follow-up of blood sugar for all patients during the ICU stay and the mean levels were recorded on the third and the fifth days for all patients.

The patients were divided into three broad groups on the basis of the fasting blood glucose or random sugar and HbA1c to rule out undetected diabetes patients. Group 1: history negative, immediate glycemic status normal, and HbA1c less than 8. Group 2: history negative, immediate glycemic status abnormal, and HbA1c less than 8. Group 3: history negative or positive and HbA1c 8 or more.

Data of various categorical variables were presented as absolute numbers (expressed as mean ± SD) and percentages. A statistical analysis was performed using StatSoft (StatSoft Inc.) for Windows. Proportions were used in most tables. The unadjusted relative risk and 95% confidence interval (95% CI) for mortality were determined in all stroke patients including group 2 and group 3 patients. The χ^2-test was used to test differences in proportions. Statistically significant values were considered for P less than 0.05.

Results

A total of 100 patients were studied, including 61 male patients (61%) aged between 42 and 86 years and 39 female patients (39%) aged between 39 and 84 years. The most common indications for admission to the ICU were airway protection and treatment and follow-up of high blood pressure in 47% of the admitted patients; 9% of the total number of patients admitted also had atrial fibrillation. Patients were divided into three groups:

Group 1: number of patients, 36 (36%); range of age, 52–81 years; 21 men and 15 women.

Group 2: number of patients, 31 (31%); range of age, 46–86 years; 21 men and 10 women.

Group 3: number of patients, 33 (33%); range of age, 39–79 years; 19 men and 14 women.

Blood sugar

In group 1, the blood sugar remained within the normal range from the 1st to the last day.

Whereas all the patients included in group (2 had elevated blood sugar on the 1st day, five of 31 (16%) patients had normal blood sugar on the 3rd day and 19 (61%) returned to normal blood sugar before ICU discharge, and all of them were treated with insulin.

Patients in group 3 showed an elevated blood sugar on the 1st day, which then decreased gradually on subsequent days; 18 of 33 patients returned to normal blood sugar before ICU discharge; all of them were treated with insulin. A total of 31% of the patients had high fasting or random blood sugar during admission without being known as diabetic and had normal HbA1c level, and these patients were included in group 2.

Computed tomography scan

In group 1, 24 patients (67%) had infarction, whereas 12 (33%) had hemorrhagic stroke.

In group 2, 22 patients (71%) had infarction and nine (29%) had hemorrhagic stroke.

In group 3, 23 patients (70%) had infarction and 10 (30%) had hemorrhagic stroke.

There were no statistically significant differences between the type of stroke whether infarction or hemorrhagic stroke in group 2 when compared with group 1 or group 3.

There were no significant difference between group 2 and group 3 with regard to the severity of the condition according to APACHE II scores or the LOS in the ICU and the hospital. Moreover, there was no significant association between the stroke severity and the glycosylated hemoglobin level in group 2 and also in group 3 (r = 0.26, P = 0.4; r = 0.19, P = 0.31; respectively). Regarding excellent outcome of stroke, which was measured by the modified Rankin scale (0–1), there was no significant difference between group 2 and group 3.

The unadjusted risk ratio was 1.85 (95% CI 0.52–4.41) for group 2, whereas it was 1.25 (95% CI 0.7 6–4.3) in group 3. Nondiabetic patients with hyperglycemia had a 1.6 times higher relative risk of in-hospital 28-day mortality than diabetic patients.

Diabetic patients (group 3) were older, but there was no significant difference when compared with group 2; there was also no significant difference between both groups regarding hypertension, congestive heart failure, and coronary artery disease; however, patients with diabetes mellitus were less likely to be current smokers, but the percentage of patients with atrial fibrillation was higher. There were no differences in the stroke subtype or the baseline stroke severity between both groups. Fourteen patients died during ICU stay, another four died in the hospital after ICU discharge, and 77 survived to hospital discharge in the 28-day follow-up of the study. A comparison of survivors and nonsurvivors in all groups revealed a significant difference in APACHE II scores [11], in ICU and hospital LOS, and also the use of supportive measures such as mechanical ventilators and inotropics were significantly higher in nonsurvivors. However, there were no significant differences in the age or admission due to hypertensive emergency.

Hemorrhage infarction was significantly higher in nonsurvivors. There were four nonsurvivors (11%) out of 36 patients in group 1, whereas eight (26%) of 31 patients died in group 2, which was statistically significant when compared with group 1 (P = 0.02). However, six nonsurvivors (18%) out of 33 in group 3 when compared with group 2 was statistically significant (P = 0.04) (Tables 1–5).

Table 1 Baseline patient characteristics in group 2 and group 3

Clinical variables at baseline	Group 2	Group 3	*P* value
Age (mean±SD) (years)	70.7 ± 12.9)	71.6 ± 11.6)	0.06
Male : female	21 : 10	19 : 14	0.03
Vascular risk factors [*N* (%)]			
Hypertension	17 (54.8)	18 (54.5)	0.75
Atrial fibrillation	4 (12.9)	5 (15.1)	0.045
Dyslipidemia	8 (25.8)	9 (27.2)	0.25
Current cigarette use	5 (16.1)	3 (9)	0.014
Ischemic heart disease	7 (22.5)	8 (24.2)	0.2
Congestive heart failure	1 (3.2)	1 (3)	0.7
Systolic BP (mean ± SD)	156 ± 28.6	155 ± 29.8	0.1
GCS on admission (mean ± SD)	8 ± 3	8 ± 4	0.8
Excellent outcome Modified Rankin scale (0–1)	9 (29)	10 (28)	0.09
APACHE II scores	25 ± 4	24 ± 5	0.07
ICU LOS (days)	5.7 ± 0.9	5.9 ± 0.8	0.2
Hospital LOS (days)	16.2 ± 5.9	17 ± 6.3	0.08
Nonsurvivors [*N* (%)]	8 (26)	6 (18)	0.03

APACHE II, acute physiology and chronic health evaluation II; BP, blood pressure; LOS, length of stay.

Table 2 The glycemic status of the patients at the time of admission

Groups	Mean ± SD		
	1st day	3rd day	5th day
Group 1	5.7 ± 1.9	5.5 ± 1.6	5.0 ± 1.7
Group 2	13.1 ± 2.4	11.8 ± 2.1	9.6 ± 0.9
Group 3	14.4 ± 4.3	13 ± 2.3	10.8 ± 1.1

Table 3 Mortality risk in the three groups

Glucose (mmol/l)	Mortality (95% CI)	*P* value
Group 1	1.06 (1.02–2.1)	0.35
Group 2	1.85 (0.52–4.41)	0.02
Group 3	1.25 (0.76–4.3)	0.01

CI, confidence interval.

Table 4 Survivors and nonsurvivors in all groups

Risk factor	Nonsurvivors	Survivors	Total
Group 1	4	32	36
Group 2	8	23	31
Group 3	6	27	33

Table 5 Comparison of demographic and clinical features between the two outcome groups

Patients	Survivors	Nonsurvivors	*P* value
Age (years)	66.9 ± 10.3	64.5 ± 14.5	0.2
Mean BP	143 ± 29	161 ± 35	0.1
Mean admission blood sugar	12.3 ± 4.1	15.6 ± 4.5	0.02
APACHE II scores	21 ± 3	28 ± 5	0.03
Predicted LOS	5.5 ± 0.8	6.4 ± 0.8	0.02
ICU LOS (days)	5.3 ± 0.8	8.7 ± 0.24	0.01
Hospital LOS	16 ± 6	19 ± 8	0.03
Mechanical ventilation *n* (%)	3 (4)	14 (77)	0.01
Need of inotropic *n* (%)	4 (5)	14 (77)	0.01
Type of CVA [*n* (%)]			
Infarct	59 (72)	10 (66)	0.06
Hemorrhage infarction	23 (28)	8 (44)	0.01
Hypertensive emergency	39 (47)	8 (44)	0.3

APACHE II, acute physiology and chronic health evaluation II; BP, blood pressure; LOS, length of stay.

Discussion

It has been suggested that admission hyperglycemia is a marker of extensive brain damage leading to a greater increase in stress hormones resulting in hyperglycemia [12–15]. However, Van Kooten *et al.* [16], who also found a significant association between hyperglycemia on admission and the stroke outcome, did not find a correlation between catecholamine and glucose levels, implying that increased stress was not responsible for the hyperglycemia. If hyperglycemia is proven to be an independent predictor of poor outcome, a policy for early detection and glucose control may be warranted. However, animal studies showing that administration of insulin reduces the size of the infarct and improves prognosis after stroke strongly support the view that stress hyperglycemia is of pathophysiological significance in patients with stroke and is not simply an epiphenomenon of the stress response to stroke [7,17].

Whereas many studies have shown that diabetes increases the risk of mortality after stroke, few have explored the relationship between admission hyperglycemia and the prognosis after stroke in nondiabetic patients. The main aim of this study was to find evidence that admission hyperglycemia in nondiabetic patients increases the risk of mortality within a short-term follow-up of ischemic stroke. In this study, diabetic patients (group 3) were older, but there was no significant difference when compared with group 2. There was also a significant difference in sex distribution, wherein a higher percentage of male patients was found in group 2; however, patients with diabetes mellitus were less likely to be current smokers, but the percentage of patients with atrial fibrillation was higher. There were no differences in the stroke subtype between both groups. Our study found that there were no significant difference between group 2 and group 3 with regard to the baseline severity of the condition according to APACHE II scores or the ICU and hospital LOS. Moreover, there was no significant difference between both groups regarding the distribution of vascular risk diseases such as hypertension, coronary artery disease, or congestive heart failure. However, the unadjusted risk ratio was 1.85 (95% CI 0.52–4.41) for group 2, whereas it was 1.25 (95% CI 0.7 6–4.3) in group 3. Our current study showed that nondiabetic patients with hyperglycemia had a 1.6 times higher relative risk of in-hospital 28-day mortality than diabetic patients, which correlates with previous studies showing a relative risk about 2.0 times higher in nondiabetic patients than in diabetic patients [12,15].

It is very difficult to determine whether the patients had high sugar before the stroke. However, certain findings from the study seem to go against this and support our view that the sugar level increased after the stroke. The blood glucose level showed a strong association with higher mortality, which was significantly higher in group 2 when compared with group 3. In contrast, glycosylated hemoglobin was not found to show an association with stroke severity, a matter that could not relate the hyperglycemia seen in our study to the stroke event. These results are comparable to that mentioned by Murros *et al.* [18]. However, the issue of stress-induced hyperglycemia is far more difficult to address. Indeed researchers like Christensen and Boysen [19] suggested that hyperglycemia in acute stroke is primarily an epiphenomenon related to stroke severity. This finding is supported by studies showing higher mean admission glucose level in nonsurvivors of stroke compared with

survivors [20–22]. It is also supported by multivariate analyses of data from two large studies, in which the admission glucose level was a significant predictor of mortality [23] or poor functional recovery [24] after stroke independent of other prognostic factors. Several explanations may account for the observed association between hyperglycemia and poor prognosis after ischemic stroke. First, hyperglycemia may be directly toxic to the ischemic brain. Although the mechanism is not fully understood, accumulation of lactate and intracellular acidosis in the ischemic brain (produced through anaerobic cerebral glucose metabolism) may be a contributor [25]. Intracellular acidosis may promote and accelerate ischemic injury by enhancing lipid peroxidation and free radical formation, allowing accumulation of intracellular calcium (a key component of the glutamate-dependent excitotoxicity seen in ischemic neurons), and impairing mitochondrial function. These neurotoxic effects may be particularly important in the ischemic penumbra (the region of brain tissue surrounding the core of infarcted tissue where neurons are injured but still viable) [26–28]. However, Uyttenboogaart *et al*. [29] found that moderate hyperglycemia is associated with a favorable outcome in acute lacunar stroke. In contrast, our results go hand by hand with Yong and Kaste [30], when he studied the dynamics of hyperglycemia as a predictor of stroke outcome. Other studies showed the effect of hyperglycemia in patients who suffered stoke only on the long term [31,32]. In contrast to our results, Ntaios *et al*. [33] found that there was no association between persistent hyperglycemia at 24–28 h and outcome in either diabetic or nondiabetic patients.

The discrepancy between this finding and the strong association between stress hyperglycemia and mortality in nondiabetic patients with ischemic stroke may be due to the number of diabetic patients in the studies. Our study showed a nearly equal number of hyperglycemic and diabetics patients. Also, the threshold values that defined hyperglycemia in the individual studies may be variable as the definition of stress hyperglycemia is intrinsically problematic. Again, diabetic patients are more likely to receive therapy for hyperglycemia even before stoke occurred, which would reduce the amount of glucose available to diffuse into the brain and might reduce cerebral lactic acidosis and other harmful metabolic changes in the brain. Our study has shown that hyperglycemia in general at admission was correlated with a worsened clinical outcome including a longer ICU LOS, use of inotropics, mechanical ventilation, and also the type of infarction as the hemorrhage infarction, which was significantly higher in nonsurvivors. Our results once again demonstrate the need for systematic clinical studies to encourage the restoration of normoglycemia in the acute phase of stroke, with or without applying thrombolysis and/or neuroprotectives in both nondiabetic and diabetic patients. The results of this study are limited because the relative risk was not adjusted for other risk factors, but despite that, a strong and consistent association between admission hyperglycemia and an increased 28-day stroke mortality, especially in nondiabetic hyperglycemic patients, suggests that hyperglycemia even without a history of diabetes is an important risk factor affecting the stroke outcome. Further multicenter studies are needed to clarify that acute hyperglycemia predicts an increased risk of in-hospital mortality after ischemic stroke in nondiabetic patients and an increased risk of poor functional recovery in nondiabetic stroke survivors. In conclusion, our current study showed that stress hyperglycemia is a commonly encountered condition. It is important to distinguish between diabetes mellitus and stress hyperglycemia for proper management of the patient. Inability to do so may result in overenthusiastic diagnosis of diabetes mellitus and use of glucose-lowering medication, which may be harmful to the patient. However, at the same time, the presence of stress hyperglycemia should not be overlooked because of its prognostic implications in many clinical settings. Thus, close monitoring by plasma glucose estimation and guarded management of hyperglycemia is recommended in such patients.

Stress hyperglycemia predicts increased risk of in-hospital mortality after ischemic stroke; thus, we should not underestimate the potential harm, as patients with the highest admission glucose levels would have most likely been treated earlier and more aggressively with glucose-lowering therapies.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

References

1 Jorgensen H, Nakayama H, Raaschou HO, Olsen TS. Stroke in patients with diabetes: the Copenhagen Stroke Study. Stroke 1994; 25:1977–1984.

2 Candelise L, Landi G, Orazio EN, Boccardi E. Prognostic significance of hyperglycemia in acute stroke. Arch Neurol 1985; 42:661–663.

3 Melamed E. Reactive hyperglycaemia in patients with acute stroke. J Neurol Sci 1976; 29:267–275.

4 Sewdarsen M, Jialal I, Vythilingum S, Govender G, Rajput MC. Stress hyperglycaemia is a predictor of abnormal glucose tolerance in Indian patients with acute myocardial infarction. Diabetes Res 1987; 6:47–49.

5 Mankovsky BN, Metzger BE, Molitch ME, Biller J. Cerebrovascular disorders in patients with diabetes mellitus. J Diabetes Complications 1996; 10:228–242.

6 Capes SE, Hunt D, Malmberg K, Gerstein HC. Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: a systematic overview. Lancet 2000; 355:773–778.

7 Hamilton MG, Tranmer BI, Auer RN. Insulin reduction of cerebral infarction due to transient focal ischemia. J Neurosurg 1995; 82:262–268.

8 Kiers L, Davis SM, Larkins R, Hopper J, Tress B, Rossiter SC, *et al.* Stroke topography and outcome in relation to hyperglycemia and diabetes. J Neurol Neurosurg Psychiatry 1992; 55:263–270.

9 Baird TA, Parsons MW, Phanh T, Butcher KS, Desmond PM, Tress BM, *et al.* Persistent poststroke hyperglycemia is independently associated with infarct volume expansion and worse clinical outcome. Stroke 2003; 34:2208–2214.

10 Parsons MW, Barber PA, Desmond PM, Baird TA, Darby DG, Byrnes G, *et al.* Acute hyperglycemia adversely affects stroke outcome: a magnetic resonance imaging and spectroscopy study. Ann Neurol 2002; 52:20–28.

11 Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med 1985; 13:818–829.

12 Capes SE, Hunt D, Malmberg K, Pathak P, Gersstein Hc. Stress hyperglycemia and prognosis of stroke in diabetic and nondiabetic patients – a systematic review. Stroke 2001; 32:2426–2432.

13 Scott JF, Robinson GM, French JM, O'Connell JE, Alberti KG, Gray CS. Glucose potassium insulin infusions in the treatment of acute stroke patients with mild or moderate hyperglycemia: the Glucose Insulin in Stroke Trial (GIST). Stroke 1999; 30:793–799.

14 Jorgensen H, Nakayama H, Raaschou HO, Olssen TS Stroke in patients with diabetes in Copenhagen Stroke Study. Stroke 1994; 25:1977–1984.

15 Bruno A, Biller J, Adams HP, Clark WR, Woolsson RF, Wiliams LS, Hansen MD. Acute blood glucose level and outcome from ischemic stroke: Trial of ORG 10172 in Acute Stroke Treatment (TOAST) investigators. Neurology 1999; 52:280–284.

16 Van Kooten F, Hoogerbrugge N, Naarding P, Koudstaal PJ. Hyperglycemia in the acute phase of stroke is not caused by stress. Stroke 1993; 24:1129–1132.

17 Masharani U, Karam JH. Diabetes mellitus and hypoglycemia. In: Tierney LM, McPhee SJ, Papadakis MA, editors. *Current medical diagnosis and treatment*. New York: Lange Medical Books; 2002. p. 1209.

18 Murros K, Fogelholm R, Kettunen S, Vuorela AL, Valve J. Blood glucose, glycosylated haemoglobin, and outcome of ischemic brain infarction. J Neurol Sci 1992; 111:59–64.

19 Christensen H, Boysen G. Blood glucose increases early after stroke onset: a study on serial measurements of blood glucose in acute stroke. Eur J Neurol 2002; 9:297–301.

20 Woo E, Chan YW, Yu YL, Huang CY. Admission glucose level in relation to mortality and morbidity outcome in 252 stroke patients. Stroke 1988; 19:185–191.

21 Czlonkowska A, Ryglewicz D, Lechowicz W. Basic analytical parameters as the predictive factors for 30-day case fatality rate in stroke. Acta Neurol Scand 1997; 95:121–124.

22 M'Buyamba-Kabangu J-R, Longo-Mbenza B, Tambwe MJ, Dikassa LN, Mbala-Mukendi M. J-shaped relationship between mortality and admission blood pressure in black patients with acute stroke. J Hypertens 1995; 13:1863–1868.

23 Levine SR, Welch KM, Helpern JA, Chopp M, Bruce R, Selwa J, Smith MB. Prolonged deterioration of ischemic brain energy metabolism and acidosis associated with hyperglycemia: human cerebral infarction studied by serial 31P NMR spectroscopy. Ann Neurol 1988; 23:416–418.

24 Siesjö BK, Bendek G, Koide T, Westerberg E, Wieloch T. Influence of acidosis on lipid peroxidation in brain tissues in vitro. J Cereb Blood Flow Metab 1985; 5:253–258.

25 Ou Yang YB, Mellergård P, Kristián T, Kristiánova V, Siesjö BK. Influence of acid–base changes on the intracellular calcium concentration of neurons in primary culture. Exp Brain Res 1994; 101:265–271.

26 Anderson RE, Tan WK, Martin HS, Meyer FB. Effects of glucose and Pao2 modulation on cortical intracellular acidosis, NADH redox state, and infarction in the ischemic penumbra. Stroke 1999; 30:160–170.

27 Choi DW, Rothman SM. The role of glutamate neurotoxicity in hypoxic ischemic neuronal death. Ann Rev Neurosci 1990; 13:171–182.

28 Olsen TS, Larsen B, Herning M, Skriver EB, Lassen NA. Blood flow and vascular reactivity in collaterally perfused brain tissue: evidence of an ischemic penumbra in patients with acute stroke. Stroke 1983; 14:332–341.

29 Uyttenboogaart M, Koch MW, Stewart RE, Vroomen PC, Luijckx GJ, Keyser JD. Moderate hyperglycaemia is associated with favourable outcome in acute lacunar stroke. Brain 2007; 130:1626–1630.

30 Yong M, Kaste M. Dynamic of hyperglycemia as a predictor of stroke outcome in the ECASS-II trial. Stroke 2008; 39:2749–2755.

31 Sacco RL, Shi T, Zamanillo MC, Kargman DE. Predictors of mortality and recurrence after hospitalized cerebral infarction in an urban community: the Northern Manhattan Stroke Study. Neurology 1994; 44:626–634.

32 Lee T-H, Ryu S-J, Chen S-T. The prognostic value of blood glucose in patients with acute stroke. J Formos Med Assoc 1991; 90:456–470.

33 Ntaios G, Abatzi C, Alexandrou M, Lambrou D, Chatzopoulos S, Egli M, *et al.* Persistent hyperglycemia at 24–48 h in acute hyperglycemic stroke patients is not associated with a worse functional outcome. Cerebrovasc Dis 2011; 32:561–566.