

Hyperglycemia, excess weight, and history of hypertension as risk factors for poor outcome and cerebral infarction after aneurysmal subarachnoid hemorrhage

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Object. Stress-induced hyperglycemia has been shown to be associated with poor outcome after aneurysmal subarachnoid hemorrhage (SAH). The authors prospectively tested whether hyperglycemia, independent of other factors, affects patient outcomes and the occurrence of cerebral infarction after SAH.

Methods. Previous diseases, health habits, medications, clinical condition, and neuroimaging variables were recorded for 175 patients with SAH who were admitted to the hospital within 48 hours after bleeding. The plasma level of glucose was measured at admission and the fasting value of glucose was measured in the morning after aneurysm occlusion. Factors found to be independently predictive of patient outcomes at 3 months after SAH onset and the appearance of cerebral infarction were tested by performing multiple logistic regression.

Plasma glucose values at admission were found to be associated with patient age, body mass index (BMI), history of hypertension, clinical condition, amount of subarachnoid or intraventricular blood, shunt-dependent hydrocephalus, outcome variables, and the appearance of cerebral infarction. When considered independently of age, clinical condition, or amount of subarachnoid, intraventricular, or intracerebral blood, the plasma glucose values at admission predicted poor outcome (per millimole/liter the odds ratio [OR] was 1.24 with a 95% confidence interval [CI] of 1.02–1.51). After an adjustment was made for the amount of subarachnoid blood, the clinical condition, and the duration of temporary artery occlusion during surgery, the BMI was found to be a significant predictor (per kilogram/square meter the OR was 1.15 with a 95% CI of 1.02–1.29) for the finding of cerebral infarction on the follow-up computerized tomography scan. Hypertension (OR 3.11, 95% CI 1.11–8.73)—but not plasma glucose (OR 1.06, 95% CI 0.87–1.29)—also predicted the occurrence of infarction when tested instead of the BMI.

Conclusions. Independent of the severity of bleeding, hyperglycemia at admission seems to impair outcome, and excess weight and hypertension appear to elevate the risk of cerebral infarction after SAH.

KEY WORDS • subarachnoid hemorrhage • cerebral infarction • hyperglycemia • hypertension • outcome

ANEURYSMAL SAH, despite improvements in surgical and medical treatment, remains a serious disease with high rates of mortality and morbidity.^{8,9,12} Although patients with SAH have a lower prevalence of diabetes mellitus and are leaner than the general adult population or patients with other types of stroke,^{13,14} plasma glucose levels have been reported to be elevated after aneurysm rupture, probably due to a stress reaction.^{1,4,15} Plasma glucose values at hospital admission (< 24–72 hours after SAH) correlate with the severity of bleeding, particularly with the clinical condition of the patient, and thus also can be used to predict or mediate the occurrence of poor outcome.^{1,4,15} In addition, stress-induced hypergly-

cemia has previously been shown to predict both death and poor functional recovery in survivors after ischemic stroke in nondiabetic but not in diabetic patients.³ In patients who experience spontaneous ICH, stress-induced hyperglycemia did not significantly predict outcome.³

In addition to the severity of stroke, the extent of stress-induced hyperglycemia may be affected by dysglycemia or insulin resistance, an important part of the metabolic syndrome in addition to hypertension, obesity, and dyslipidemia.^{3,7,18} Patients with dysglycemia or insulin resistance have an increased risk for cerebral vasculopathy, which may lead to greater ischemic damage at the time of stroke than expected.

After aneurysm rupture, elevated BP values and chronic hypertension preceding SAH, and possibly patient age, elevated BMI, and excessive alcohol consumption may lead to an increased risk of death or poor outcome.^{11,12} Furthermore, in the general population BP can be raised independently by age, BMI, pulse rate, amount of regular alcohol use, and sodium intake.^{16,20} It thus remains unclear which of these factors alone or through interaction with other variables impairs outcome after SAH. In this prospective study, we test-

Abbreviations used in this paper: BMI = body mass index; BP = blood pressure; CI = confidence interval; CT = computerized tomography; FIND = fixed ischemic neurological deficit; GOS = Glasgow Outcome Scale; ICH = intracerebral hemorrhage; IVH = intraventricular hemorrhage; MR = magnetic resonance; mRS = modified Rankin Scale; OR = odds ratio; RIND = reversible ischemic neurological deficit; SAH = subarachnoid hemorrhage; SD = standard deviation; WFNS = World Federation of Neurosurgical Societies.

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ed the independent predictive role of hyperglycemia as a risk factor for poor outcome and for the occurrence of permanent cerebral ischemic lesions in survivors by taking into account several confounding variables such as the severity of bleeding, patient age, BMI, and hypertension—values of which are commonly available at admission.

Clinical Material and Methods

Patient Population

This prospective study included 175 patients (87 men and 88 women; age range 23.2–75.7 years [mean 50.6 years]) with aneurysmal SAH who were admitted to our hospital within 48 hours after bleeding and whose aneurysms were surgically treated or filled with coils. After admission, these patients and their family members were interviewed according to a structured questionnaire that focused on previous diseases, medication, and health habits. Of the 57 patients (33%) with a history of hypertension (patients with a pre-SAH BP > 140/90 mm Hg [systolic/diastolic] or those who were taking antihypertensive medication), 12 (7%) had BP values greater than 160/95 mm Hg. Two patients (1%) had diabetes mellitus, nine (5%) had coronary heart disease (four of whom had previously suffered a myocardial infarction), 39 (22%) had used nonsteroidal antiinflammatory drugs, and 20 (11%) had consumed more than 80 g of alcohol within 24 hours before SAH.

Clinical Monitoring, Treatment, and Outcome

The patients' clinical conditions were scored according to both the Glasgow Coma Scale and the WFNS Grading Scale.⁵ Blood samples were obtained at admission before aneurysm treatment (mean \pm SD 22 \pm 13 hours [median 19 hours] after onset of symptoms) and again after the patient had fasted, on the morning after surgery (1.9 \pm 0.7 days [median 1.7 days]) and analyzed to determine the plasma glucose values. Normal values for plasma glucose in our laboratory range from 4 to 6.4 mmol/L (72–115 mg/dl). After admission, elevated plasma glucose levels were actively treated with insulin.

The ruptured aneurysms were occluded within a mean 26 hours after bleeding (median 22 hours [range 5–84 hours]) by performing open surgery (placement of an aneurysm clip in 165 patients and proximal occlusion or trapping of the parent artery in five patients) or endovascular coil placement (five patients). During surgery, 47 patients underwent temporary occlusion of the proximal artery (lasting a mean of 9 minutes and a median of 5.6 minutes; in 13 patients > 10 minutes). A bolus administration of thiopental (5–10 mg/kg) and elevation of the patient's mean BP was used routinely before temporary artery occlusion. Mannitol was routinely used in all operations. Permanent artery occlusion was visible on angiography in 12 patients (7%): clipping of the aneurysm together with the artery (seven patients), thrombosis of either the afferent or efferent artery (two patients), or trapping or proximal clipping of a fusiform aneurysm (three patients).

Intravenous nimodipine treatment was started after admission and continued for 10 to 12 days. Thereafter, nimodipine was administered orally until 21 days post-SAH. No hypertensive, hypervolemic, or endovascular vasospasm therapy was used routinely, but these options were used if ischemic symptoms occurred (for example, during endo-

vascular treatment in four cases). Patients who underwent surgery received betamethasone routinely, 4 mg every 6 hours, starting after blood sampling just before surgery and continuing until the 6th postoperative day at diminishing doses.

Neurological examinations were performed daily after admission. Delayed cerebral ischemia (RIND or FIND) was defined as a gradual development of focal neurological signs or a deterioration in consciousness due to no known reason (for example, ICH, repeated hemorrhage, or hydrocephalus). Causes of poor clinical condition were determined by performing repeated CT studies, routine postoperative angiography, autopsy, or laboratory investigations.

Outcome was assessed 3 months after SAH according to the GOS¹⁰ and the mRS.^{2,19} A regularly scheduled follow-up CT scan was obtained 3 months after SAH to reveal permanent hypodense areas consistent with cerebral infarction; this scan was available for 155 patients (89%). Of the remaining 20 patients with a missing CT scan, 15 died before the planned CT study (one additional patient with a poor grade died between the time of the CT study and the planned outpatient department visit), and five patients each had individual reasons for missing the follow-up CT study. Two of these five patients underwent follow-up MR imaging.

Magnetic resonance imaging studies were performed at 3 months post-SAH in 150 patients by using a 1-tesla MR imaging unit (Gyrosan; Philips, Eindhoven, The Netherlands). Standard axial T₁-weighted (TR 560 msec, TE 14 msec, 205 \times 256 matrix), T₂-weighted (TR 2870 msec, TE 120 msec, 238 \times 256 matrix), and fluid-attenuated inversion recovery (TR 4460 msec, TE 105 msec, 248 \times 256 matrix) sequences were obtained, as well as a coronal T₁-weighted sequence (TR 30 msec, TE 8.9 msec, 256 \times 256 matrix). In four cases (3%) the MR imaging study revealed a lesion that was not visible on the CT scan.

Computerized tomography scans (GE LightSpeed QX/i; General Electric Medical Systems, Milwaukee, WI) were routinely performed on admission, on the 1st postoperative day, at discharge, and at 3 months; scanning was repeated if the patient's clinical condition deteriorated. The amount of subarachnoid blood on the CT scan at admission was categorized according to the Fisher scale.⁶ Twenty patients (11%) had moderate-to-severe and 69 (39%) had slight (a small amount of blood in the occipital horns or in the third or fourth ventricle) IVH.

Hypodense lesions, none of which were visible on the initial CT scan, were found on follow-up CT scans in 100 (65%) of 155 patients. Causes of hypodense areas on CT scans were grouped in the following manner. A Group 1 lesion was a lesion found in the same area as a previous ICH (10 patients) or a lesion resulting from damage to a penetrating artery during surgery (11 patients), temporary or permanent occlusion of the proximal artery of a saccular aneurysm or trapping of a fusiform aneurysm (12 patients), another cause (such as spatula pressure during surgery, angiographic complication, or cardiovascular embolus; 13 patients), or multiple causes (eight patients). A Group 2 lesion presumably was caused by delayed cerebral ischemia after exclusion of other causes, and appeared on later CT scans, although it was absent on the first postoperative CT scan (46 patients). Any patient in whom CT scans revealed separate hypodense areas due both to delayed ischemia and

TABLE 1

Baseline characteristics of patients with SAH according to plasma glucose levels at admission

Characteristic	Glucose Levels		
	Normal (42 patients)	Elevated (133 patients)	All Patients (175 patients)
no. of women (%)	19 (45)	69 (52)	88 (50)
patient age (yrs) (mean ± SD)*	47.3 ± 13.3	51.6 ± 12.1	50.6 ± 12.5
BMI (kg/m ² , mean ± SD)†	24.5 ± 3.2	26.0 ± 4.6	25.6 ± 4.3
no. of patients (%)			
hypertension‡	9 (21)	48 (36)	57 (33)
antihypertensive medication	5 (12)	22 (17)	27 (15)
cigarette smoking			
ever regular	32 (76)	86 (65)	118 (67)
current§	32 (76)	69 (52)	101 (58)
excessive alcohol use	3 (7)	16 (12)	19 (11)
coronary disease	2 (5)	7 (5)	9 (5)
premonitory leak symptoms	4 (10)	5 (4)	9 (5)
use of aspirin before hemorrhage	6 (14)	18 (14)	24 (14)

* p = 0.056 for difference between groups.

† p = 0.053.

‡ p = 0.077.

§ p = 0.006.

|| Within 1 month before onset of SAH.

previous ICH (five patients) was included in Group 2. Small lesions (< 20 mm in diameter) were visible on follow-up CT scans in 66 patients and on follow-up MR images in 67 patients. Larger lesions were visible on CT scans in 34 patients and on MR images in 31 patients.

Statistical Analysis

Data were analyzed using commercially available statistical software (SPSS for Windows, version 9.0.1 [1999]; SPSS, Inc., Chicago, IL). Categorical variables were compared by performing the Fisher exact two-tailed test, the Pearson chi-square test, or the test for a linear trend. Continuous variables were compared between groups by performing the Mann-Whitney U-test, a t-test, or analysis of variance with corrected multiple pairwise comparisons based on the Dunnett method.

A univariate association of continuous variables was tested using either the Pearson (r) or Spearman rank (r_s) correlation coefficients. Univariate and multivariate ORs and 95% CIs of risk factors (including their interactions) for impaired outcome or for ischemic lesions on the follow-up CT scan were analyzed by performing an unconditional logistic regression. Maximum-likelihood forward stepwise logistic regression was used, with the selection of variables based on the magnitude of their probability values being less than 0.05. A two-tailed probability value less than 0.05 was considered significant.

Results

Plasma glucose values at admission (mean ± SD 8.2 ± 2.3 mmol/L) significantly (r = 0.236, p = 0.002) correlated with postoperative glucose values (7.8 ± 1.2 mmol/L). De-

TABLE 2

Associations between clinical and neuroimaging characteristics and plasma glucose values in patients with SAH

Characteristic	No. of Patients	Plasma Glucose Level (mmol/L)*	
		At Admission	After Surgery
WFNS grade on admission†			
I	96	7.5 ± 1.7	7.8 ± 1.2
II or III	43	8.9 ± 3.0	7.7 ± 1.2
IV or V	36	9.3 ± 2.2	7.7 ± 1.4
Fisher grade			
on admission CT scan‡			
thin layer or diffuse deposition	48	7.2 ± 2.0	7.7 ± 1.1
thick layer or localized clots	127	8.6 ± 2.4	7.8 ± 1.3
ICH diameter >10 mm	17	8.3 ± 1.6	7.5 ± 0.9
IVH§			
none	86	7.3 ± 1.8	7.6 ± 1.1
slight	69	8.9 ± 2.3	7.8 ± 1.2
moderate or severe	20	9.6 ± 3.1	8.1 ± 1.7
delayed cerebral ischemia			
none	128	8.2 ± 2.4	7.7 ± 1.2
RIND	17	8.4 ± 2.0	7.7 ± 1.4
FIND	29	8.1 ± 2.5	8.1 ± 1.5
shunt-dependent hydrocephalus‡			
none	143	7.9 ± 2.2	7.7 ± 1.2
present	32	9.5 ± 3.1	8.1 ± 1.4
GOS score at 3 mos			
good recovery or minimal disability	95	7.6 ± 1.7	7.7 ± 1.0
moderate disability	26	8.5 ± 2.3	7.4 ± 1.3
severe disability or vegetative state	38	9.7 ± 3.2	8.0 ± 1.4
death**	16	8.0 ± 1.5	8.3 ± 1.7
mRS score at 3 mos			
no symptoms	29	7.5 ± 1.6	7.7 ± 0.9
minor symptoms	50	7.3 ± 1.7	7.5 ± 1.1
slight disability	32	8.4 ± 1.9	7.6 ± 1.3
moderate disability	33	9.6 ± 2.8	7.8 ± 1.2
moderately severe disability	10	8.9 ± 3.8	8.1 ± 0.8
severe disability	5	10.1 ± 3.9	7.9 ± 3.1
death**	16	8.0 ± 1.5	8.3 ± 1.7
hypodense areas on follow-up CT scan‡‡			
none	55	7.6 ± 2.1§§	7.7 ± 1.2
Group 1	54	8.4 ± 2.1	7.6 ± 1.0
Group 2	46	8.8 ± 2.9§§	7.9 ± 1.4

*Values are expressed as means ± SDs.

** Causes of death: primary bleeding (two patients), early rebleeding (three patients), delayed ischemia (one patient), pneumonia (six patients), pulmonary embolus (one patient), or surgical complications (three patients).

‡‡ For grouping of hypodense areas, see *Clinical Material and Methods*.

† r_s = 0.344, p < 0.001.

‡ p < 0.01.

§ r_s = 0.397, p < 0.001.

|| r_s = 0.249, p = 0.001.

†† r_s = 0.265, p < 0.001.

§§ p = 0.033 for differences between characteristics and plasma glucose values at admission.

spite the initiation of betamethasone treatment after the first blood sampling, this decline in glucose values was also significant (p = 0.011) because insulin was used to treat high glucose levels. A comparison of elevated plasma glucose levels (> 6.4 mmol/L) and normal levels at admission as

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TABLE 3
Risk factors for poor or impaired outcome after SAH*

Characteristic	Multivariate Analysis					
	Univariate Analysis		Model I		Model II	
	OR	95% CI	OR	95% CI	OR	95% CI
patient age (per yr)	1.05	1.02–1.08†	1.09	1.04–1.14†	1.02	0.99–1.05
plasma glucose level (per mmol/L)						
at admission	1.31	1.13–1.53†	1.24	1.02–1.51‡	1.20	1.00–1.44‡
after surgery	1.36	1.04–1.78‡	—	—	—	—
WFNS grade						
II or III	2.68	1.17–6.11‡	1.50	0.51–4.42	2.03	0.87–4.74
IV or V	8.84	3.72–21.04†	3.23	1.01–10.37‡	3.84	1.36–10.87‡
Fisher grade on admission, thick layer or localized clots	2.84	1.22–6.58‡	1.27	0.37–4.40	1.25	0.51–3.03
IVH bleeding	10.43	4.51–24.11†	6.13	2.10–17.87†	2.07	0.95–4.49
ICH diameter >10 mm	2.83	1.03–7.78‡	5.40	1.34–21.71‡	1.50	0.46–4.87
permanent artery occlusion	30.70	3.85–244.85†	231.10	18.93–2821.82†	23.16	2.58–207.75†

* A poor outcome (for the univariate analysis and for Model I of the multivariate analysis) was defined as a severe disability or worse, and impaired outcome (for Model II) was defined as moderate disability or worse according to the GOS. The ORs represent comparisons with patients with no risk factor, those with WFNS Grade I, or those with a thin layer of blood in the Fisher scale (reference categories of independent variables).

† $p < 0.01$.

‡ $p < 0.05$.

they related to patients' baseline characteristics is shown in Table 1. The BMIs (calculated as weight/height squared [kg/m^2]) correlated with the plasma glucose values at admission ($r_s = 0.194$, $p = 0.012$) and postoperatively ($r_s = 0.161$, $p = 0.038$). Furthermore, patients with a history of hypertension had higher plasma glucose levels (9.1 ± 2.7 mmol/L compared with 7.8 ± 2 mmol/L, $p < 0.001$) and BMIs (27 ± 5.5 compared with 25 ± 3.5 , $p = 0.004$), were older (54.3 ± 11 years compared with 48.8 ± 12.8 years, $p = 0.006$), and were less likely to be current cigarette smokers (42% compared with 66%, $p = 0.003$) than patients without hypertension. Current smokers were younger (48.3 ± 11 years compared with 53.4 ± 13.8 years; $p = 0.01$) and had somewhat lower BMIs (25.3 ± 3.5 compared with 26.1 ± 5.2) and lower plasma glucose values (7.8 ± 2.4 mmol/L compared with 8.7 ± 2.1 mmol/L, $p = 0.011$) than patients who were not current smokers.

Associations between clinical and neuroimaging variables and plasma glucose values are shown in Table 2. The clinical and neuroimaging grades highly correlated with the plasma glucose levels at admission but did not postoperatively. The Glasgow Coma Scale scores also correlated with plasma glucose values at admission ($r_s = -0.355$, $p < 0.001$). Shunt-dependent hydrocephalus correlated with the WFNS ($p < 0.001$), Fisher ($p = 0.011$), and IVH ($p < 0.001$) grades as well as with both outcome scales ($p < 0.001$), and thus also with plasma glucose values. Patients with poor grades who had increased intracranial pressure were frequently treated with ventriculostomy and later with a permanent shunt to improve cerebral perfusion pressure, although the sizes of the ventricles were not significantly increased.

Plasma glucose values at admission or postoperatively did not appear to be significantly associated with repeated bleeding (12 patients), location of the ruptured aneurysm,

number of aneurysms, mode of aneurysm treatment (surgery or coil embolization), betamethasone treatment, duration or number of episodes of temporary proximal artery occlusion, permanent artery occlusion, or number of blood transfusion units.

Plasma glucose values at admission did not predict the symptoms of delayed cerebral ischemia, although those patients with severe ischemic symptoms, such as unconsciousness or neurological deficits leading to a severe disability, had a somewhat higher plasma glucose level (8.6 ± 2.9 mmol/L).

The presence of hypodense areas on follow-up CT scans was significantly ($p = 0.002$) associated with symptoms of delayed ischemia. Of the 24 patients with delayed ischemia who had an FIND, 22 (92%) had such a lesion, and of the 15 patients with ischemia who had an RIND, 12 (80%) had such a lesion; of the remaining 116 patients, 66 (57%) had a lesion. The occurrence and sizes of these lesions as well as the symptoms of delayed ischemia were significantly ($p < 0.01$) associated with both patients' GOS and mRS scores. Patients with lesions had significantly ($p = 0.022$) higher plasma glucose levels at admission (8.6 ± 2.5 mmol/L) than those without lesions (7.6 ± 2.1 mmol/L). Particularly, patients with lesions caused by delayed ischemia had elevated values (Table 2). Patients whose lesion was visible on follow-up MR imaging also had significantly ($p = 0.009$) higher plasma glucose levels at admission (98 patients, 8.5 ± 2.3 mmol/L) than did those with no lesion (52 patients; 7.5 ± 2.1 mmol/L). In addition, the sizes of lesions that were visible on both CT and MR images correlated significantly with glucose values ($r_s = 0.180$, $p = 0.025$; and $r_s = 0.198$, $p = 0.015$, respectively).

Table 3 shows that several variables predicted poor or impaired outcome. In the multivariate Model I, the significance of the WFNS and Fisher grades decreased, compared

TABLE 4

*Risk factors for ischemic lesions visible on follow-up CT scan**

Characteristic	Univariate Analysis OR (95% CI)	Multivariate Analysis OR (95% CI)
patient age (per yr)	1.04 (1.01–1.07)†	—
BMI (per kg/m ²)	1.10 (1.00–1.20)‡	1.15 (1.02–1.29)‡
hypertension	2.71 (1.25–5.91)‡	—
plasma glucose level (per mmol/L)		
at admission	1.22 (1.03–1.44)‡	—
after surgery	1.09 (0.81–1.45)	—
WFNS grade	3.33 (1.60–6.90)†	2.89 (1.21–6.95)‡
>I on admission		
Fisher grade on admission, thick layer or localized clots	8.20 (3.66–18.35)†	10.50 (3.82–28.86)†
IVH bleeding	1.63 (0.83–3.21)	—
ICH diameter	7.90 (1.00–62.53)‡	—
>10 mm		
temporary artery occlusion (per min)	1.37 (1.09–1.72)†	1.58 (1.18–2.13)†

* — = not applicable.

† $p < 0.01$.‡ $p < 0.05$.

with the statistics provided by the univariate analysis because these variables correlated with patient age and plasma glucose values. Model II shows significant risk factors for impaired outcome (moderate disability or worse outcome). Compared with the results in Model I, the significance of IVH, ICH, and age decreased, but both WFNS grade and plasma glucose level remained significant predictors. After we excluded 12 patients with permanent artery occlusion from the models, the results remained similar; for example, the OR for the plasma glucose level per millimole per liter at admission was 1.22 (95% CI 1–1.49, $p = 0.05$) for Model I and 1.19 (95% CI 0.99–1.42) for Model II. When additional adjustments were made for the BMI or history of hypertension in the models in Table 3, the significance of plasma glucose levels fell only slightly ($p = 0.06$ – 0.09).

Table 4 shows risk factors for permanent ischemic lesions visible on follow-up CT scans. Of 155 patients, six were excluded because of a permanent artery occlusion during surgery, which in all cases caused a lesion. Risk was best predicted by a thick layer of subarachnoid blood, a WFNS grade greater than I, the duration of temporary artery occlusion, and the BMI. The BMI remained significant also after an additional adjustment for age (OR 1.14, 95% CI 1.01–1.28, $p = 0.030$). Because the BMI was correlated with plasma glucose and a history of hypertension, additional multivariate models were made in which the BMI was replaced by these factors. Hypertension (OR 3.11, 95% CI 1.11–8.73, $p = 0.031$) was also a risk factor, and after an additional adjustment for age, its significance slightly decreased (OR 2.73, 95% CI 0.95–7.81, $p = 0.061$). On the other hand, the plasma glucose level at admission did not reach significance (OR 1.06, 95% CI 0.87–1.29). When the analysis was restricted to those lesions caused by delayed ischemia (46 patients) compared with absence of any lesion (55 patients), risk factors included a thick layer of subarachnoid blood (OR 14.39, 95% CI 3.78–54.72, $p < 0.001$) and almost a WFNS grade greater than I (OR 2.55, 95% CI 0.97–6.74, $p = 0.059$) and hypertension (OR 2.81, 95% CI 0.93–8.48, $p = 0.066$). The plasma glucose level at admission was sig-

nificant (OR 1.21, 95% CI 1.02–1.43, $p = 0.033$) only in the univariate analysis.

Discussion

On the basis of this study, the plasma glucose value at admission, independent of the severity of bleeding and other confounding factors, seems to predict poor outcome after SAH. On the other hand, this glucose value does not independently predict the occurrence of either delayed cerebral ischemia or permanent ischemic lesions, which, however, can be predicted by the preictal factors BMI and history of hypertension, in addition to the severity of bleeding.

The role of the plasma glucose level as a predictor for poor outcome after SAH has been studied prospectively in two studies (one comprising 337 patients⁴ and another that was part of a multicenter nicardipine trial, including 616 of a total of 906 patients¹⁵) and retrospectively among 99 patients.¹ Irrespective of the dichotomous or continuous variables that have been used for the severity of bleeding, plasma glucose values have correlated better with the patient's clinical condition than with the amount of subarachnoid blood.^{4,15} Two of these studies showed that an elevated plasma glucose level at admission, independent of the severity of bleeding, predicted poor outcome.^{1,15} In one study,⁴ plasma glucose, due to its high correlation with the patient's clinical condition, did not, after simultaneous adjustment for the clinical condition and the amount of subarachnoid blood, reach significance as a predictor. Authors of that study thought that hyperglycemia may be a link in the pathway from poor condition to poor outcome.⁴

In addition to the severity of bleeding, we performed simultaneous adjustments for the BMI and hypertension, which are elements of the metabolic syndrome^{7,18} and found that the significance of the admission glucose level as a predictor of poor or impaired outcome decreased only slightly. This indicates that dysglycemia or insulin resistance accompanied by a possible underlying vasculopathy could explain, only to a slight extent, why admission glucose levels predict outcome although vasculopathy might predict the occurrence of ischemic lesions on follow-up CT scans in survivors.

Aneurysm rupture causes a marked sympathetic nervous system activation, leading to the elevation of circulating catecholamines (measured as total-body norepinephrine spillover into plasma), which persists for at least 10 days.¹⁷ By elevating glucagon and decreasing insulin secretion as well as corticosteroids and somatotropin, the catecholamine directly and indirectly causes stress-induced hyperglycemia, likely through hypothalamic involvement.^{1,3,15} A high correlation between glucose values and the severity of bleeding indicates that hyperglycemia, to a great extent, is caused by stress.^{1,4,15} High glucose values, however, seem to predict poor outcome independent of the severity of bleeding or the metabolic syndrome according to our study and previous ones.^{1,15} This supports the notion that hyperglycemia may have a direct independent deleterious effect on outcome, although it may also be either a marker or mediator of poor condition and outcome.

The harmful effect of hyperglycemia on cerebral ischemia has been demonstrated in experimental studies.^{1,3,15} In cases of incomplete cerebral ischemia, as in cases of SAH, with cerebral ischemia occurring with impaired cerebral

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blood flow but without an artery occlusion, hyperglycemia may lead to an increase in the availability of glucose in the brain, providing an abundant substrate for anaerobic glycolysis, which ultimately causes lactate accumulation and acidosis, and subsequently, through several final intracellular pathways, results in a larger area of ischemia than expected.^{1,3,15}

According to our study and a previous one,¹⁵ hyperglycemia at admission may cause impaired outcome but does not seem to elevate the risk for delayed symptomatic or angiographic vasospasm or for post-SAH cerebral infarction alone, which is commonly caused by vasospasm or surgical complications. Among patients with vasospasm, the appearance of high plasma glucose levels 3 to 7 days after SAH, however, were associated with poor outcome.¹⁵ Because hyperglycemia was actively treated with insulin after admission, we were not able to test this association.

The risk for infarction was raised by the high BMI and hypertension, which are components of the metabolic syndrome. The metabolic syndrome (insulin resistance, obesity, hypertension, hypertriglyceridemia, a low level of high-density lipoprotein cholesterol, and possibly increased inflammatory or coagulation activity)^{7,18} elevates the risk for ischemic cardio- and cerebrovascular events and later also for Type 2 diabetes mellitus through several mechanisms (vasculopathy, endothelial dysfunction, inflammation, and so on).^{3,7,18} Furthermore, patients with elevated BMIs, which are known to correlate with BP values,^{16,20} may also recover less well from aneurysm surgery.¹¹ Chronic hypertension induces hypertrophy of the arteriolar smooth-muscle cells and shifts the cerebral autoregulation curve to the right.¹² This shift, together with the narrowing of small arteries, may render hypertensive patients more vulnerable to cerebral ischemia after SAH. This may well be the mechanism by which hypertension or high BMIs through elevated BP may predict infarction after aneurysm rupture.

Conclusions

Independent of the severity of bleeding, hyperglycemia at admission seems to impair outcome, and excess weight and a history of hypertension elevate the risk of cerebral infarction after SAH. Given that preoperative hyperglycemia observed at admission seems to impair long-term outcome, it may be worthwhile to investigate ultra-early insulin treatment for hyperglycemia.

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