High Stress Hyperglycemia Ratio Predicts Poor Outcome after Mechanical Thrombectomy for Ischemic Stroke

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Objective: The present study aimed to evaluate the association between stress hyperglycemia ratio (SHR) and outcome at 3 months after mechanical thrombectomy (MT) for acute occlusion in the anterior circulation. *Methods:* Data from 160 consecutive patients with large vessel occlusion in the anterior circulation who underwent MT from May 2013 to March 2018 were retrospectively reviewed. SHR was calculated as the fasting glucose concentration divided by the estimated average glucose concentration (derived from the glycosylated hemoglobin level). Patients were dichotomized into 2 groups in accordance with the median SHR. Univariate and multivariate analyses were used to identify predictors of functional outcome. Good and poor outcomes were defined as modified Rankin Scale scores of 0-2 and 3-6, respectively. *Results:* patients with unfavorable outcome had significantly higher levels of SHR than those with favorable outcome (median in SHR = 1.02 versus .84, $P = .000$). The median SHR was .96. Univariate analysis showed that significantly more patients with a poor outcome had SHR $\geq$ .96 compared with those with a good outcome (65.2% versus 31.0%, $P = .000$). After adjusting for potential covariates, Increased SHR (odds ratio [OR] 6.97, 95% confidence intervals [CI] 1.22-39.65, $P = .029$, for continuous SHR levels) and SHR $\geq$ .96 (OR 3.12, 95% CI 1.39-6.96, $P = .006$) remained independent predictors of poor outcome. *Conclusions:* Increased SHR is strongly correlated with poor outcome at 3 months after MT for proximal artery occlusion in the anterior circulation.

Key Words: Stress hyperglycemia—ischemic stroke—outcome—mechanical thrombectomy

Introduction

Mechanical thrombectomy (MT) is the standard treatment for acute large vessel occlusion in the anterior circulation, as it results in an increased rate of recanalization and improved functional outcome.[1] However, more than half of the patients who undergo MT still have a poor clinical outcome.[2] Previous studies have demonstrated that an adverse functional outcome following endovascular treatment with MT or thrombolysis for acute occlusion of a large artery was associated with an elevated random glucose concentration at admission or an elevated fasting glucose concentration.[3-7] However, the absolute glucose concentration, including the random and fasting concentrations, cannot distinguish between chronic poor management of background glucose levels and a physiologic stress response to acute stroke.

Recently, Roberts et al.[8] introduced the stress hyperglycemia ratio (SHR) as the glucose concentration at admission

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Received October 31, 2018; revision received January 12, 2019; accepted February 16, 2019.

Financial Support: This work was supported by the Youth Fund in Fujian Province's Health System (nos. 2012-2-85, 2012-2-86) and the projects of serving people from Xiamen Science and Technology Program (no. 3502Z20144024).

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1052-3057/$ - see front matter

https://doi.org/10.1016/j.jstrokecerebrovasdis.2019.02.022

divided by the estimated average glucose concentration derived from the glycosylated hemoglobin (HbA1c) level, and established that the SHR was a better predictor of critical illness than absolute hyperglycemia. The SHR may be a more reliable method which to measure the degree of stress hyperglycemia, as it controls for background glucose levels. The SHR is reportedly related to the occurrence of major adverse cardiovascular and cerebrovascular events in patients with coronary artery disease undergoing percutaneous coronary intervention.[9] Moreover, in patients with a minor ischemic stroke or transient ischemic attack, the SHR is associated with an increased risk of recurrent stroke.[10]

It remains unclear whether the SHR can predict the clinical outcome in patients with large vessel occlusion in the anterior circulation. The aim of the present study was to explore the relationship between the SHR and the functional outcome at 3 months after MT for acute proximal vessel occlusion in the anterior circulation.

Methods

We retrospectively analyzed prospectively collected data from consecutive patients with proximal artery occlusion in the anterior circulation who underwent MT at our institution from May 2013 to March 2018. Detailed clinical information was collected for each patient, including demographic data (age and sex), risk factors, and medical history (hypertension, diabetes mellitus, dyslipidemia, current smoking status, coronary artery disease, history of stroke, or transient ischemic attack), procedure-associated characteristics, laboratory findings, and imaging data. Written informed consent was obtained from all patients. The present study was approved by the ethics committee of Zhongshan Hospital Xiamen University.

Patients were considered for study inclusion if they met the following inclusion criteria: age 18 years or older; large vessel occlusion in the anterior circulation confirmed by Computed tomography angiography (CTA), Magnetic resonance angiography (MRA), or Digital substraction angiography (DSA); National Institutes of Health Stroke Scale (NIHSS) score of $\geq$2; premorbid modified Rankin Scale (mRS) score of $\leq$1; hypodensity $<$1/3 of the middle cerebral artery territory on cranial computed tomography. We excluded patients with conditions affecting the HbA1c level, including renal failure (serum creatinine concentration greater than 180 μmol/L) and anemia (hemoglobin $<$100 g/L). In the current study, most patients underwent MT within 6 hours from the time of symptom onset. Some patients underwent MT more than 6 hours after symptom onset based on a favorable benefit-risk ratio as assessed by experienced neurointerventionists or a mismatch on perfusion imaging.

Stroke severity was assessed via the NIHSS score at admission and at 24 hours after MT. Repeated imaging (computed tomography or magnetic resonance imaging) was performed at 24 hours after the procedure or at any time at which a patient exhibited neurological deterioration. Current smokers were defined as those who smoked at least 1 cigarette every day. Symptomatic intracerebral hemorrhage was defined as any hemorrhage that occurred within 36 hours after intervention, combined with an increase in the NIHSS score of $\geq$4. Recanalization status was evaluated using the Modified Treatment in Cerebral Infarction Scale[11] as complete recanalization (2b-3) or incomplete recanalization (0-2a). Collateral flow was graded using the American society of interventional and therapeutic neuroradiology/society of interventional radiology.[12] Stroke etiology was classified in accordance with the Trial of ORG 10172 in Acute Stroke Treatment criteria.[13] Follow-up data were obtained via outpatient visits or telephone interviews. The clinical functional outcome at 3 months after MT was defined as either poor (mRS score 3-6) or good (mRS score 0-2).

Blood samples were taken within the first 48 hours after admission after overnight fasting. The fasting glucose concentration and HbA1c level were rapidly measured after venipuncture. HbA1c levels were assayed by an autoanalyzer (ADAMS A1c HA-8180, ARKRAY Factory, Inc., Japan). The HbA1c level was used to calculate the estimated average glucose concentration during the 3 months before admission using the following equation:[14] $(1.59 \times \text{HbA1c}) - 2.59$. The SHR was calculated as the fasting glucose concentration divided by the estimated average glucose concentration: [fasting glucose concentration (mmol/L)]/[$(1.59 \times \text{HbA1c}) - 2.59$]. Patients were diagnosed with diabetes mellitus on the basis of a prior history of diabetes mellitus or a HbA1c level of $>$6.5%.

Statistical Analysis

Continuous variables were expressed as the mean (SD) or median (IQR). Statistical comparisons were performed with the Student's t test or the Mann-Whitney U test. Categorical variables were presented as percentages, and analyzed using the chi-square test or Fisher's exact test. Covariates influencing the clinical outcome of the univariate analysis ($P < .10$) were entered into a forward stepwise multiple logistic regression model. Furthermore, subgroup analysis was performed based on diagnosis of diabetes mellitus. Statistical analyses were conducted using SPSS 23.0 software, and a 2-tailed P value of $< .05$ was considered statistically significant.

Results

During the study period, 187 patients who underwent MT met the inclusion criteria. Of these, 168 patients had fasting glucose and HbA1c data available. Five patients with anemia and 3 patients with renal failure were excluded. Hence, the study cohort comprised a total of 160 patients (mean age 63.2 $\pm$ 12.2 years, 67.5% male). The clinical characteristics of the included patients are summarized in Table 1. The median NIHSS score on

Table 1. *Comparison of clinical characteristics between good and poor outcome*

Variables	Total (n = 160)	mRS 0-2 (n = 71)	mRS 3-6 (n = 89)	*P* value
Age (years), mean (SD)	63.2 (12.2)	58.8 (12.5)	66.8 (10.8)	.000
Male, n (%)	108 (67.5)	50 (70.4)	58 (65.1)	.481
Risk factors and medical history, n (%)				
Hypertension	86 (53.1)	33 (46.5)	53 (59.6)	.099
Diabetes mellitus	29 (18.1)	12 (16.9)	17 (19.1)	.720
Dyslipidemia	7 (4.4)	4 (5.6)	3 (3.4)	.701
Coronary artery disease	21 (13.1)	5 (7.0)	16 (17.9)	.048
Stroke/TIA	20 (12.5)	8 (11.2)	12 (13.5)	.674
Current smoking	36 (22.5)	19 (26.8)	17 (19.1)	.249
Stroke characteristics				
Initial NIHSS score, median (IQR)	15.0 (12.0-20)	13.0 (10.0-15.0)	17.0 (14.0-21.0)	.000
SBP (mmHg), median (IQR)	139.0 (125.0-160.0)	135.0 (124.0-146.0)	147.0 (130.0-162.0)	.005
DBP (mmHg), mean (SD)	83.5 (13.9)	81.6 (10.6)	84.9 (16.0)	.121
ASITN/SIR < 2, n (%)	65 (40.6)	18 (25.4)	47 (52.8)	.000
Vessel occlusion site, n (%)				
LCA	64 (40.0)	26 (36.6)	38 (42.7)	.436
M1	75 (46.9)	32 (45.1)	43 (48.3)	.683
M2	18 (11.3)	12 (16.9)	6 (6.7)	.043
Stroke etiology, n (%)				
Large-artery atherosclerosis	79 (49.4)	38 (52.5)	41 (46.1)	.349
Cardioembolic	60 (37.5)	25 (35.2)	35 (39.3)	.593
Other or undetermined	21 (13.1)	8 (11.3)	13 (14.6)	.534
Stroke management				
Intravenous thrombolysis, n (%)	50 (31.3)	22 (30.9)	28 (31.4)	.949
Onset to groin puncture (min), median (IQR)	280.0 (227.0-332.0)	278.0 (220.0-333.0)	289.0 (230.0-335.0)	.670
Total time of operation (min), median (IQR)	106.0 (80.0-147.0)	99.0 (75.0-130.0)	115.0 (85.0-172.0)	.018
Complete recanalization, n (%)	104 (65.0)	61 (85.9)	43 (48.3)	.000
sICH, n (%)	12 (7.5)	2 (2.8)	10 (11.2)	.067
Laboratory values				
Hemoglobin (g/L), mean (SD)	136.5 (16.9)	139.4 (17.2)	134.2 (16.4)	.054
Creatinine (μmol/L), mean (SD)	73.9 (19.6)	70.6 (15.9)	76.7 (21.8)	.049
Admission glucose (mmol/L), median (IQR)	7.4 (6.2-8.6)	7.2 (6.1-8.3)	7.5 (6.3-9.3)	.106
Fasting glucose (mmol/L), median (IQR)	6.6 (5.5-8.1)	5.9 (5.1-6.8)	7.3 (6.3-9.1)	.000
Hemoglobin A1c	6.0 (5.6-6.5)	5.8 (5.6-6.5)	6.0 (5.7-6.6)	.150
SHR (IQR)	0.96 (.80-1.10)	0.84 (.73-.98)	1.02 (.91-1.17)	.000
SHR ≥ .96, n (%)	80 (50.0)	22 (31.0)	58 (65.2)	.000

ASITN/SIR, American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology; DBP, diastolic blood pressure; ICA, internal carotid artery; IQR, interquartile range; M1/M2, middle cerebral artery first segment/second segment; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale; SBP, systolic blood pressure; SHR, stress hyperglycemia ratio; sICH, symptomatic intracerebral hemorrhage; TIA, transient ischemic attack.

admission was 15.0 (12.0-20.0), and the median SHR was .96 (.80-1.10). Complete recanalization was achieved in 104 (65.0%) patients, and the outcome after MT was poor in 89 (55.6%) patients. As the median SHR was .96, the patients were dichotomized into a high-SHR group (SHR ≥ .96) and a low-SHR group (SHR < .96).

Univariate analysis showed that the factors that significantly differed between patients with a poor outcome versus those with a good outcome were SHR ≥ .96 (P = .000), age (P = .000), initial NIHSS score (P = .000), coronary artery disease (P = .048), baseline systolic blood pressure (P = .005), collateral flow (P = .000), occlusion of the second segment of the middle cerebral artery (P = .043), total operation time (P =.018), complete recanalization (P = .000), plasma creatinine concentration (P = .049), fasting glucose concentration (P = .000), and SHR level (P = .000; Table 1). The multivariate analysis results are presented in Table 2. Multivariate analysis identified increased SHR level (odds ratio [OR] 6.97, 95% confidence intervals [CI] 1.22-39.65, P = .029 for continuous variable) and SHR ≥ .96 (OR 3.12, 95% CI 1.39-6.96, P = .006) as independent predictors of poor outcome. Figure 1 illustrates the distribution of the mRS score in patients with a SHR ≥ .96 and those with a SHR < .96. Moreover, advanced age and higher initial NIHSS score were also strong risk factors for poor outcome, whereas complete recanalization was a protective factor against poor outcome.

In the current cohort, 39 patients were diagnosed with diabetes mellitus. SHR ≥ .96 (OR 5.11, 95% CI 2.36-11.09, P = .000) were associated with unfavorable outcome in

Table 2. *The association between stress hyperglycemia ratio and poor outcome by multiple logistic regression analyses*

	Continuous SHR levels		SHR ≥ .96	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age, years	1.05 (1.02-1.09)	.005	1.05 (1.02-1.09)	.005
Initial NIHSS score	1.16 (1.07-1.26)	.001	1.16 (1.06-1.26)	.001
Complete recanalization	.17 (.07-.43)	.000	.15 (.06-.39)	.000
SHR	6.97 (1.22-39.65)	.029	3.12 (1.39-6.96)	.006

Adjusted for fasting glucose level, hypertension, coronary artery disease, systolic blood pressure, ASITN/SIR, middle cerebral artery second segment, total time of operation, symptomatic intracerebral hemorrhage, hemoglobin level, creatinine level.

NIHSS, National Institutes of Health Stroke Scale; SHR, stress hyperglycemia ratio.

patients without diabetes mellitus by univariate analyses. When the same analysis was conducted in the diabetic patients, the association was not significant (OR 2.75, 95% CI .68-11.11, $P = .156$). After adjusting for potential covariates, there remained a clear relationship between SHR ≥ .96 and adverse outcome (OR 4.08, 95% CI 1.57-10.63, $P = .004$) in nondiabetic patients.

Discussion

The present study found that increased SHR was a strong predictor of poor clinical outcome (mRS score 3-6) at 3 months after MT in patients with acute anterior circulation stroke caused by large artery occlusion independent of fasting glucose level. The predictive power of SHR ≥ .96 for adverse outcome was significant in nondiabetic patients, but not in patients with diabetes mellitus.

In patients with ischemic stroke, the association of stress hyperglycemia (defined in accordance with the absolute glucose concentration) with adverse functional outcome is controversial due to variations in research methods and study populations.[15-18] Moreover, absolute glucose concentration cannot discriminate between stress hyperglycemia and chronic high background glucose concentration. In contrast, the SHR is a relative indicator of hyperglycemia that represents a quantitative assessment of acute stress-induced hyperglycemia by adjusting for the background glucose concentration. Emerging evidence suggests that the SHR is strongly related to the occurrence of major adverse cardiovascular and cerebrovascular events in patients with coronary artery disease receiving percutaneous coronary intervention, and an increased risk of recurrent stroke in patients with a minor ischemic stroke or transient ischemic attack.[9,10] Our findings further extend the results of this previous research.

The mechanisms of the association between an increased SHR and poor outcome following MT in patients with acute stroke are incompletely understood. There are several possible explanations for this phenomenon. First, the stress-induced inflammatory response and neurohormonal derangements result in a cycle of excessive hepatic glucose production, increasing insulin resistance, and exacerbation of the inflammatory and oxidative stress responses; these components promote endothelial dysfunction, platelet aggregation, and mitochondrial dysfunction.[19] Second, stress hyperglycemia may lead to reperfusion injury due to increased oxidative stress and inflammation.[20] Third, hyperglycemia may cause direct toxic injury to ischemic brain tissue via

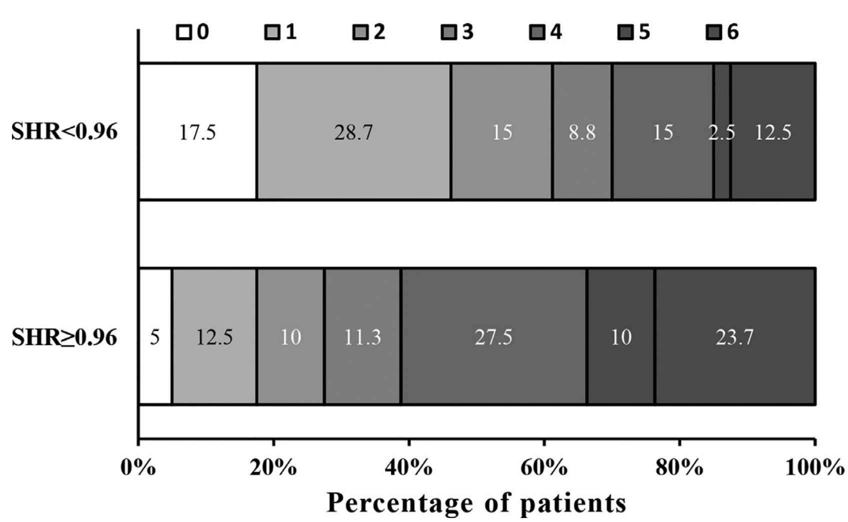

Figure 1. *Modified Rankin Scale (mRS) at 3 months among patient with SHR ≥ .96 and SHR < .96. SHR, stress hyperglycemia ratio.*

intracellular acidosis derived from anaerobic cerebral glucose metabolism at the site of ischemic brain tissue.[15]

The result of subanalysis showed the predictive power of SHR ≥ .96 for unfavorable outcome in nondiabetic patients, but not in patients with diabetes mellitus. This could be explained by cellular adaptation to hyperglycemia due to physiologic readjustments to higher glucose concentration in diabetic patients occur over time.[21,22] Moreover, patients with diabetes mellitus may be more tolerant to degrees of glycemic variability than those without diabetes mellitus in the setting of stress response.[22,23]

Our study indicated that advanced age was closely associated with poor outcome at 3 months after MT, which is consistent with previous studies.[7,24] A recent review reported that only 27% of octogenarian patients have a good outcome at 3 months after MT, and that the mortality rate in this population at 3 months after MT is 34%.[25] Various factors have been identified as predictors of age-related poor outcome after MT, including pre-existing disability, prestroke leukoaraiosis, reduced neuronal plasticity, increased tortuosity of the cerebral vasculature, and a greater proportion of post-procedure comorbidities and complications.[26,27] Our analysis also found that a higher initial NIHSS score was a risk factor for poor outcome, while complete recanalization was a protective factor against poor outcome; these findings are in agreement with previous research.[7]

The present study had several limitations that should be considered. First, the present study had a retrospective and single-center design, which inevitably produced selection bias. Second, the relatively small sample size limited the statistical power. Further investigation in a multicenter trial with a large sample size is warranted. Third, we did not monitor change in glucose level and record the use of hypoglycemic agents.

In conclusion, the present study demonstrated that higher SHR (calculated as the fasting glucose concentration divided by the estimated average glucose concentration) is independently related to poor outcome at 3 months after MT in patients with acute anterior circulation stroke.

Author Contributions

F.P., X.Y.C., and Z.J.L. conceived and designed the study, and manuscript drafting. J.Y.M. and X.W.Y. contributed to data collection, analysis, and interpretation of the data. Q.W.Y. participated in statistical analysis. W.H.Z. performed the data collection and critical revision of manuscript. X.R.Z. contributed to review and correction of the manuscript.

Conflict of Interest

The authors declare no conflict of interest.

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