The effects of stress hyperglycemia in diabetic and nondiabetic patients with large vessel occlusions undergoing mechanical thrombectomy

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Abstract:

INTRODUCTION: Diabetes and hyperglycemia are major risk factors that can increase infarction volume and contribute to poor functional status. Our study aim was to investigate the effect of stress hyperglycemia on various safety and efficacy outcomes in patients with large vessel occlusions (LVOs) undergoing mechanical thrombectomy (MT) with or without diabetes.

METHODS: A retrospective analysis of consecutive LVO patient data treated with MT at a Comprehensive Stroke Center in the Mid-South was conducted. Adult patients with LVO on computed tomography angiography (CTA) and treated with MT within 24 h of symptom onset were included. The primary outcome was to determine if there was an association in collateral flow or infarct size in the setting of hyperglycemia. Secondary outcomes included National Institute of Health Sciences Score (NIHSS) and Modified Rankin Score (mRS).

RESULTS: A total of 450 patients underwent MT, out of which 433 had baseline hemoglobin A1c recorded: mean age: 64 ± 15 years, 47% women, pretreatment NIHSS median 15 points (interquartile range 10–19), 323 (75%) with good collaterals grades >2 on multiphasic CTA, 326 (75%) were non-diabetic, and 107 (25%) were diabetic. Nondiabetics with stress hyperglycemia had a tendency toward higher pre-treatment NIHSS scores (mean 17.5 ± 7.6, $P = 0.02$) and at 24-h (12.9 ± 9.0, $P = 0.02$), poor collaterals (multiphasic CTA score ≥2; 21.4% vs. 34.5%, $P = 0.02$), larger infarct volumes (50.7 ± 63.6 vs. 24.4 ± 33.8 cc, $P < 0.0001$), and had poorer functional outcomes (good mRS 0–2 47.7% vs. good mRS 0–2 36.8%) when compared to nondiabetics without stress hyperglycemia. For every 1 mg/dL increase in admission blood glucose, there was a 0.3 cc increase in infarct volume (95% confidence intervals for β =0.2–0.4; $P < 0.0001$) after adjusting for the final thrombolysis in cerebral infarction score.

CONCLUSIONS: LVO patients with stress hyperglycemia without previously diagnosed diabetes had more severe strokes, developed larger infarct volumes, poorer collaterals, and had worse functional outcomes at 90 days post-MT. In addition, LVO patients with diabetes and stress hyperglycemia exhibited more passes during MT and worse functional outcomes.

Keywords:

Diabetes, hyperglycemia, ischemic stroke, large vessel, thrombectomy

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Introduction

It is well-known that diabetes and hyperglycemia are major risk factors in

the development of acute ischemic strokes. In addition, they lead to the expansion of infarct volume and contribute to poor functional outcomes.[1-5] Diabetes is known to cause damage to the blood vessels by

Table 1: Patient baseline characteristics

Variable	Nondiabetic patients (HbA1c <6.4%), *n* (%)	Diabetic patients (HbA1c ≥6.4%), *n* (%)
Age (years), mean±SD	64±15.1	63±12.2
Female	156 (47.9)	48 (44.9)
Race		
African American	188 (57.7)	66 (61.7)
Caucasian	136 (41.7)	39 (36.4)
Hispanic	0	1 (0.9)
Asian	0	0
Other	1 (0.3)	0
Concurrent medical conditions		
Hypertension	244 (74.8)	94 (87.9)
Hyperlipidemia	120 (36.8)	59 (55.1)
Atrial fibrillation	87 (26.7)	24 (22.4)
Congestive heart failure	128 (39.3)	47 (43.9)
Smoker	89 (27.3)	26 (24.3)
Coronary disease	74 (22.7)	33 (30.8)
Medications		
tPA given on admission	226 (69.3)	67 (62.6)
Statin use	95 (29.1)	49 (45.8)
Anticoagulation	46 (14.1)	19 (17.8)
Antiplatelet	97 (29.8)	45 (42.5)
Thrombolysis given	227 (69.6)	68 (63.6)
Laboratory values		
HbA1c level, median (IQR)	5.7 (5.3–6)	8.1 (7.1–9.7)
Location of occlusion		
Anterior circulation	291 (89.2)	93 (86.9)
Posterior circulation	35 (10.7)	14 (13.1)
ASPECT score, median (IQR)	10 (8–10)	10 (8–10)
Collateral status		
Poor (Grade 0–1)	81 (24.8)	29 (27.1)
Good (Grade 2–3)	245 (75.2)	78 (72.9)
TICI score		
TICI 0	35 (10.7)	11 (10.3)
TICI 1	10 (3.1)	2 (1.9)
TICI 2[a]	41 (12.6)	14 (13.1)
TICI 2[b]	75 (23.0)	22 (20.6)
TICI 2[c]	9 (2.8)	2 (1.9)
TICI 3	144 (44.2)	47 (43.9)
TICI critical stenosis	0	1 (0.9)
Infarct volume (mm^3), mean±SD	31.0±44.8	28.1±34.6
Admission NIHSS, median (IQR)	16 (11–20)	15 (9–18)
NIHSS at 24 h, median (IQR)	11 (5–16)	8 (5–15)
NIHSS at discharge, median (IQR)	7 (3–16)	7 (3–20)
Discharge mRS		
Good mRS (0–2)	107 (32.8)	37 (34.6)
Bad mRS (3–6)	214 (65.6)	70 (65.4)

SD: Standard deviation, mRS: Modified Rankin Score, IQR: Interquartile range, HbA1c: Hemoglobin A1c, TICI: Thrombolysis in cerebral infarction, NIHSS: National Institute of Health Sciences Score

inducing endothelial dysfunction through various glyco-oxidative products, releasing chemokines, and interfering with vascular endothelial growth factor, leading to inhibition of angiogenesis.[6] It is also known that poor collaterals harm stroke recovery.[4] The relationship between hyperglycemia and cerebral collateral blood flow is poorly understood. Based on current literature, there are two theories from prior retrospective studies and animal models regarding the effect of hyperglycemia in acute ischemic strokes. Some studies suggest that hyperglycemia or uncontrolled diabetes may potentially affect collaterals' recruitment, resulting in higher infarct volume. However, others suggest that in the hyperacute phase, stress hyperglycemia might help prevent the expansion of infarcted brain tissue.[1-7]

Significant variability in these theories mirrors the complicated pathophysiology that hyperglycemia exhibits on the body's vasculature. There remains a need to further study the dynamics of stress hyperglycemia in diabetics and nondiabetics and how it affects collaterals, infarct volume, and outcomes for ischemic stroke patients.

Methods

Study population

Data were collected through an institutional review board-approved database. The patients included in the database were adults from one tertiary care hospital in the Mid-South United States that underwent mechanical thrombectomy (MT) for computed tomography angiography (CTA) diagnosed with large vessel occlusion (LVO) within 24 h. Data collection dates ranged from January 1, 2013, to December 31, 2019.

Table 2: Baseline admission blood glucose and its effect on collateral circulation and interventional outcomes in nondiabetic patients (hemoglobin A1c <6.4%)

Variable	BG ≤140	BG >140	P
Overall (%)	238	87	
Mean HbA1c±SD	5.6±0.4	5.7±0.5	0.3
Admission NIHSS (mean±SD)	15.5±6.6	17.5±7.6	0.02
NIHSS score at 24 h (mean±SD)	10.6±7.7	12.9±9.0	0.02
Collaterals, *n* (%)			
Poor collaterals	51 (21.4)	30 (34.5)	0.02
ASPECT score, *n* (%)			
Good (ASPECT >6)	222 (94.5)	83 (96.5)	
Bad (ASPECT ≤6)	13 (5.5)	3 (3.5)	0.7
Complete recanalization	148 (64.6)	59 (67.8)	0.3
Number of passes during MT (mean±SD)	1.3±1.2	1.2±1.0	0.8
Time to recanalization (mean±SD)	58.9±33.9	58.3±42.2	0.9
Infarct volume (mean±SD)	24.4±33.7	50.7±63.6	<0.0001
Good mRS (mRS 0–2) at 90 days, *n* (%)	113 (47.7)	32 (36.8)	0.04
Mortality at 90 days, *n* (%)	39 (16.4)	20 (22.9)	0.17

BG: Blood glucose, SD: Standard deviation, HbA1c: Hemoglobin A1c, mRS: Modified Rankin Score, NIHSS: National Institute of Health Sciences Score, MT: Mechanical thrombectomy, ASPECT: Albert stroke program early CT score

Baseline characteristics and outcomes

Patient baseline demographics, admission blood glucose, and hemoglobin A1c (HbA1c) were collected. In addition, CTA collateral score (calculated based on multiphasic CTA), infarct volume (measured on MRI obtained 24 h after presentation), thrombolysis in cerebral infarction (TICI) score, number of passes during MT procedure, admission and discharge National Institute of Health Stroke Scale (NIHSS), and discharge Modified Rankin Score (mRS) were collected.[8] A good mRS was defined as an mRS of 0–2 and a poor mRS as 3–6. mRS was collected on the date of discharge and at 90 days. Diabetic individuals were defined with HbA1c ≥6.4%. Stress hyperglycemia was defined as blood glucose of >140 mg/dl in nondiabetic patients and >180 mg/dl in diabetic patients on admission. These values were derived from cardiology literature that assessed similar outcomes in patients with myocardial infarctions.[9,10] Data were collected retrospectively and throughout the patient's admission.

Statistical analyses

All data were descriptively presented using mean ± standard deviation for continuous data and frequencies for categorical data. Chi-squared and analysis of variance were used for categorical and continuous variables, respectively. A multivariate analysis was performed using binary logistic regression model for odds ratio after adjusting for all possible confounders (age, race [including American Indian, Asian, African American, and Caucasian], hypertension, and smoking), binary variables, as well as linear regression models for continuous variables with 95% confidence intervals including admission Glasgow Coma Scale score and discharge NIHSS score. Those patients with missing consecutive blood glucose measurements and missing hemoglobin A1c levels were excluded from the final analysis. The level of statistical significance was set at $P < 0.05$. All statistical analyses were performed using SPSS Statistics for Windows, Version 23.00, 64-bit edition (IBM, Armonk, New York). The goal of this study was to determine if there was an association between hyperglycemia and collaterals as well as infarct volume in

Table 3: Multivariate analysis for nondiabetics and outcomes

Nondiabetics with stress hyperglycemia	Unadjusted OR (95% CI)	P	Multivariate-adjusted OR (95% CI)†	P
Poor collaterals				
BG ≤140	Reference	Reference	Reference	Reference
BG >140	1.93 (1.1–3.3)	0.017	1.87 (1.1–3.3)	0.032
Unfavorable outcome at 90 days (mRS 3–6)				
BG ≤140	Reference	Reference	Reference	Reference
BG >140	1.7 (1.0–2.8)	0.045	1.7 (1.0–3.0)	0.060
Mortality at 90 days				
BG ≤140	Reference	Reference	Reference	Reference
BG >140	1.5 (0.8–2.8)	0.17	1.4 (0.7–2.7)	0.28

†Adjusted for: Age, Gender, Race, Hypertension, Hyperlipidemia, and Smoking. BG: Blood glucose, OR: Odds ratio, CI: Confidence interval

diabetics and nondiabetics with admission hyperglycemia. Secondary measures that were studied included NIHSS and functional outcome (discharge mRS).

Clinical trial registry

This work is a retrospective analytical study. No clinical trials were involved.

Results

A total of 450 patients had undergone MT. Patients had a mean age of 64, 47% were women, and patients' pretreatment median NIHSS was 15 points (interquartile range: 10–19). There were 323 patients (75%) with good collateral grades >2 on multiphasic CTA (mCTA). Of the 433 patients with admission HbA1c levels, 326 had A1c of ≤6.4% (nondiabetics) versus 107 who had an A1c of ≥6.5% (diabetics). Details of patient characteristics between diabetic and nondiabetic patients are in Table 1. In a univariate analysis, nondiabetics without stress hyperglycemia (BG <140) on admission had significantly

lower NIHSS scores on admission (15.5 ± 6.6 vs. 17.5 ± 7.6, $P = 0.02$) and at 24 h (10.6 ± 7.7 vs. 12.9 ± 9.0, $P = 0.02$) and had smaller infarct volumes (24.4 ± 33.8 vs. 50.7 ± 63.6, $P < 0.001$). In a multivariate analysis, nondiabetics with stress hyperglycemia had poor collaterals on CTA (mCTA score <2; 34.5% vs. 21.4%, $P = 0.032$) and had worse functional status at 90 days (good mRS 47.7% vs. good mRS 36.8%, $P = 0.06$) when compared to nondiabetics without stress hyperglycemia (BG >140) on admission [Table 2]. In addition, for patients who were nondiabetic with stress hyperglycemia, for every 1 mg/dL increase in admission blood glucose, there was a 0.3 cc increase in infarct volume (95% CI for β 0.2–0.4; $P < 0.0001$) after adjusting for the final TICI score [Table 3].

Conversely, for the diabetic patients without stress hyperglycemia (BG <180), there was no significant difference in NIHSS scores (14.1 ± 8.6 vs. 15.0 ± 7.6), collaterals (70.6% vs. 75%), or infarct volume (25.5 ± 31.2 vs. 30.4 ± 37.3) [Table 4]. Notably, however, in the diabetes patients with stress hyperglycemia, there was a significant reduction in the number of passes (0.94 ± 0.86 vs. 1.4 ± 1.1, $P = 0.018$) during MT, and they had worse functional status at 90 days (good mRS 53.6% vs. 39.2%, $P = 0.0015$) [Table 5].

Discussion

Our study found that stress hyperglycemia in nondiabetic patients is more likely to be associated with poor collaterals, larger infarct volumes, higher NIHSS, and worse functional outcomes at 90 days. However, diabetic patients with stress hyperglycemia exhibited slightly different associations, as they had more passes during MT and worse functional outcomes at 90 days. Our study is the first to examine the relationship between stress hyperglycemia in diabetics and nondiabetics for LVO strokes undergoing MT.

The first studies that aimed to investigate the effect of hyperglycemia on ischemic strokes were primarily animal studies. Some of these studies suggest that uncontrolled diabetes leads to poor collaterals,

Table 4: Baseline admission blood glucose and its effect on collateral circulation and interventional outcomes in diabetic patients (HbA1c ≥6.4%)

Variable	BG ≤180	BG >180	P
Overall (%)	51	56	
Mean HbA1c±SD	8.7±8.5	9.7±2.4	0.4
Admission NIHSS (mean±SD)	14.1±8.6	15.0±7.6	0.6
NIHSS score at 24 h (mean±SD)	9.7±9.1	12.3±10.0	0.2
Collaterals, *n* (%)			
Poor collaterals	15 (29.4)	14 (25.0)	0.6
ASPECT score			
Good (ASPECT >6)	2 (3.9)	4 (7.1)	
Bad (ASPECT ≤6)	49 (96.1)	52 (92.9)	0.5
Complete recanalization, *n* (%)	32 (65.3)	37 (66.1)	0.9
Number of passes during MT (mean±SD)	0.94±0.86	1.4±1.1	0.018
Time to recanalization (mean±SD)	63.4±42.2	58.8±39.7	0.6
Infarct volume (mean±SD)	25.5±31.2	30.4±37.3	0.5
Good mRS (mRS 0–2) at 90 days, *n* (%)	30 (53.6)	20 (39.2)	0.035
Mortality at 90 days, *n* (%)	12 (21.4)	14 (27.5)	0.86

BG: Blood glucose, SD: Standard deviation, HbA1c: Hemoglobin A1c, mRS: Modified Rankin Score, NIHSS: National Institute of Health Sciences Score, MT: Mechanical thrombectomy, ASPECT: Albert stroke program early CT score

Table 5: Multivariate analysis for diabetics and outcomes

Diabetics with stress hyperglycemia	Unadjusted OR (95% CI)	P	Multivariate-adjusted OR (95% CI)†	P
Poor collaterals				
BG ≤180	Reference	Reference	Reference	Reference
BG >180	0.8 (0.3–1.9)	0.61	0.6 (0.2–1.7)	0.63
Unfavorable outcome at 90 days (mRS 3–6)				
BG ≤180	Reference	Reference	Reference	Reference
BG >180	2.3 (1.0–5.3)	0.05	4.3 (1.6–11.6)	0.005
Mortality at 90 days				
BG ≤180	Reference	Reference	Reference	Reference
BG >180	1.1 (0.4–2.6)	0.86	1.4 (0.5–3.7)	0.54

†Adjusted for: Age, Gender, Race, Hypertension, Hyperlipidemia, and Smoking. BG: Blood glucose, OR: Odds ratio, CI: Confidence interval, mRS: Modified Rankin Score

causing worse functional outcomes and potentially enlarging areas of infarction.[1-5] In comparison, another phenomenon described in rat models is hypermetabolism within the penumbra of an ischemic stroke requiring acutely elevated levels of glucose in the brain. This study suggests that patients may benefit from acute hyperglycemia during a stroke to prevent enlargement of the ischemic core.[7] Other studies indicate that stress hyperglycemia in diabetic patients LVOs may have worse outcomes, but are protective in nondiabetic patients.[11-14] Suissa *et al*. showed that hyperglycemia could benefit LVO patients with a clinical-Albert Stroke Program Early CT Score (ASPECTS) mismatch and complete recanalization after MT.[15] Another rat model study reports that hyperglycemia could be beneficial or harmful depending on the degree of collateral vasculature in different brain areas.[16] Our study showed that in fact there may be a trend toward a protective effect of hyperglycemia in patients who have diabetes with stress hyperglycemia compared to their nondiabetic counterparts. Perhaps, this is due to the fact that hyperglycemia in diabetics promotes collateral formation and a degree of compensation compared to nondiabetics, whose blood vessels have not been exposed to prolonged hyperglycemia enough to mount a compensatory response.

There are a few studies that answered a parallel question to ours. First, a subanalysis of the DEFUSE 3 trial found that hyperglycemia was correlated with core infarct growth in recanalized LVO patients.[17] Second, a retrospective study from the MR CLEAN database showed that patients with hyperglycemia undergoing MT had worsening functional outcomes.[18] Finally, a third study showed that initial stress hyperglycemia is associated with malignant cerebral edema, hemorrhagic conversion, and poor functional outcomes post-MT. About 50% of those patients also received tPA, however, the patients who had stress hyperglycemia were not analyzed with respect to those with diabetics and nondiabetics.[19]

The SHINE trial was the hallmark study looking to intervene in those with hyperglycemia with acute ischemic stroke. While the treatment arm had a lower mean glucose level, intensive glucose control was not associated with better outcomes. The SHINE trial studied all patients with acute ischemic stroke and did not only look at those with LVO undergoing MT.[20] Further randomized control trials with this patient population still need to be pursued.

Study strengths and limitations
Our study's strengths include the ability to analyze patient data by diabetics and nondiabetics both with and without hyperglycemia. We also were able to calculate a correlation between the increase in blood glucose with a resulting proportional increase in infarct volume in nondiabetic patients with hyperglycemia. However, our study also has several limitations. The main limitation is that our study was designed retrospectively. We also were unable to identify glucose levels after MT nor were we able to evaluate for hyperglycemia intervention or specifics of medications given for hyperglycemia given the retrospective nature of data collection and the limits of our electronic health record.

Conclusions

Stress hyperglycemia on admission may be used to predict poor collateral circulation, worse NIHSS, and worse functional outcomes in patients with ischemic strokes due to LVO undergoing MT in nondiabetics. In diabetics with stress hyperglycemia, there is an association with an increased number of passes during MT and worse functional outcomes.

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