Glycemic variability after mechanical thrombectomy for anterior circulation acute ischemic stroke is associated with increased mortality

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Introduction. Morbidity remains high among patients who undergo successful mechanical thrombectomy (MT) for anterior circulation large vessel occlusion (LVO). Stress hyperglycemia worsens the prognosis after acute ischemic stroke (AIS), but aggressively treating hyperglycemia does not improve the outcome. There is no consensus on how to best manage glycemia after AIS. Glycemic variability (GV) reflects glycemic fluctuations over time and could be the culprit. We aimed to elucidate how GV impacts outcome of AIS patients treated with MT.

Patients and methods. This was a single-center retrospective study. We consecutively included AIS patients who received MT for anterior circulation LVO. We recorded discrete blood glucose measurements within the first 24 hours post thrombectomy, from which we calculated two measures of GV: standard deviation (SD) and coefficient of variation. Univariate and multivariate analyses were conducted to identify predictors of poor functional outcome (modified Ranking scale score 3-6) and mortality at 3-month follow-up.

Results. We included 657 patients. Patients with poor functional outcome (42.5%) and patients that died (14.8%) had significantly higher GV as measured by SD. In a multivariable model adjusted for confounders, higher SD was associated with mortality –adjusted odds ratio: 1.020 (95% CI 1.001-1.040)– but not with functional outcome –adjusted odds ratio for modified Ranking scale score 3-6: 1.007 (95% CI 0.990-1.025)–.

Conclusions. Our results suggest that higher GV after MT for anterior circulation AIS is an independent risk factor for 3-month mortality. Future trials should evaluate the benefit of reducing GV in this setting.

Key words. Blood glucose. Hyperglycemia. Hypoglycemia. Prognosis. Stroke. Thrombectomy.

Introduction

Acute ischemic stroke (AIS) is a leading cause of death and disability worldwide. Mechanical thrombectomy (MT) is standard of care for patients with anterior circulation large vessel occlusion. However, even in case of successful recanalization, half of patients do not regain functional independence [1]. Identifying modifiable risk factors for adverse outcomes after MT is the first step towards providing better care and improving patient outcomes.

Hyperglycemia in AIS occurs due to a generalized stress response to brain injury. It leads to faster progression of penumbra to infarct, ischemia-reperfusion injury, and hemorrhagic transformation. Hyperglycemia upon admission correlates independently with stroke size, worse functional and cognitive outcomes, and mortality, both in patients with and without diabetes, regardless of recanalization therapies [2]. Admission hyperglycemia in patients treated with MT is associated with worse 3-month functional outcome and increased 3-month mortality [3]. Hyperglycemia upon admission does not influence rate of recanalization after MT [4].

However, the SHINE trial showed that intensive treatment of hyperglycemia after AIS (maintaining blood glucose between 80 and 130 mg/dL) does not improve functional outcome nor reduce mortality, and that it increases risk of severe hypoglycemia [5]. Hypoglycemia also negatively affects outcome in AIS [6]. Consequently, ESO guidelines recommend against tight glycemic control and suggest blood glucose should be kept in the 140-180 mg/dL range, without providing a standardized protocol for glycemia management [7]. There is no evidence-based consensus on how to best manage glycemia after AIS.

Considering that both hyper- and hypoglycemia are associated with poor prognosis in AIS patients and that intensive glucose control does not improve outcomes, glycemic variability (GV), a measure of glycemic fluctuations over time, has drawn atten-

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Statement of ethics:
This study protocol was reviewed and approved by the ethics committee of our institution (Comissão de Ética para a Saúde do Centro Hospitalar de Vila Nova de Gaia/EPE), approval number 219-2022. The committee waived the need for written consent due to the study's retrospective design.

Data availability statement:
The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participants but are available from the corresponding author upon reasonable request. →

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tion as a candidate treatable prognostic factor [6]. No agreement exists regarding the optimal method for measuring GV, but standard deviation (SD) and coefficient of variation are frequently used parameters [8,9]. Among critically ill patients, including those receiving percutaneous coronary interventions, GV has been associated with increased mortality [10,11]. In the setting of AIS treated with MT, studies have yielded conflicting data regarding the impact of GV on outcome, and so its prognostic role remains to be elucidated [12-14].

We aimed to clarify if GV in the first 24 hours after MT for anterior circulation AIS affects functional outcome and mortality at 3-month follow-up. We hypothesized that greater GV could be associated with worse functional outcome and increased mortality.

Patients and methods

Study population

This study was approved by our institution's ethics committee and the need for written consent was waived due to its retrospective design. This was a single-center study. We consecutively included AIS patients with anterior circulation large vessel occlusion who underwent MT (with or without thrombolysis) at our stroke center between January 2015 and December 2019. Decision to treat with reperfusion therapies was in accordance with ESO guidelines [15,16]. Exclusion criteria were age under 18 years, simultaneous anterior and posterior circulation large vessel occlusion, less than 4 blood glucose measurements available regarding the first 24 hours after AIS, lack of information on outcome at 3 months of follow-up.

Demographic, clinical and paraclinical data were recorded. Patients were considered to have diabetes mellitus based on past medical records and medication, and whenever HbA1c at admission was ≥6,5% [17]. Reperfusion was graded according to the modified thrombolysis in cerebral infarction scale.

Glycemia and measures of glycemic variability

Blood glucose at admission was obtained before any treatment. After MT and during hospital stay, blood glucose was measured approximately every 4 hours using Accu-Chek Performa (Roche Diagnostics GmbH, Mannheim, Germany) blood glucose meter. Values concerning the first 24 hours after MT were recorded. Mean, median, maximum, and minimum blood glucose values were determined. Two measures of GV were calculated: SD of the mean and coefficient of variation. SD is defined as the square root of the average squared difference between each individual value and the mean of the multiple blood glucose values obtained [14]. Coefficient of variation is corrected for the mean and equals SD/mean blood glucose level. GV parameters were calculated according to Suh et al [9].

Subcutaneous insulin therapy according to a sliding scale was used to keep blood glucose in the range of 140-180 mg/dL. Hypoglycemia was defined as blood glucose below 70 mg/dL and was treated with intravenous dextrose 50%.

Statistical analysis

Data are presented as frequencies (percentages) for categorical variables, median (interquartile range, IQR) for non-normally distributed continuous variables and mean ± SD for normally distributed continuous variables. GV was treated as a continuous variable. Univariate analyses were performed with Student's *t*-tests and Chi-squared tests as appropriate. Variables that yielded a *p*-value of <0.10 in univariate analyses were included in a multivariate model to identify independent predictors of outcome. Collinear parameters were excluded. Crude and adjusted odds ratios and 95% confidence intervals were calculated. In multivariate regression analysis, a model was created for each parameter related to glycemia. Data analyses were performed in IBM SPSS Statistics version 27 (SPSS, INC., Chicago, IL, USA). A *p*-value of <0.05 was considered statistically significant.

Results

The primary outcomes of this study were functional outcome and mortality at 3-month follow-up. Poor functional outcome was defined as a modified Rankin scale score of 3-6.

Study population

A total of 657 patients were included. Their baseline characteristics are shown in table I. 43.5% were male and median age (IQR) was 77 (66-83) years. Diabetes mellitus, hypertension and dyslipidemia were found in 32.4%, 71.2% and 52.4% respectively. On admission, median blood glucose was 124 (108-157) mg/dL. Approximately half of patients re-

ceived thrombolysis (51.9%). MT yielded a successful recanalization in 92.5%. Median time from onset of symptoms to recanalization (ORT) was 295 (232-397) minutes. Patients had a median of 7 (6-9) blood glucose measurements. Median SD and coefficient of variation were 16.68 (10.43-28.27) mg/dL and 13.75 (9.31-20.99) mg/dL respectively. At 3-month follow-up, 57.5% of patients had achieved functional independence (mRS score 0-2) and 14.8% had died.

Univariate regression analysis

Patients with good functional outcome were younger –73 (62-81) vs. 80 (74-85) years, $p < 0.001$– and less likely to have diabetes mellitus (25.9% vs. 36.6%, $p = 0.003$). On admission, they had lower blood glucose –120 (105-143) vs. 136 (112-178) mg/dL, $p < 0.001$–, lower NIHSS (13.4 ± 5.7 vs. 16.6 ± 4.9, $p < 0.001$) and higher ASPECTS (8.4 ± 1.4 vs. 7.8 ± 1.5, $p < 0.001$). Thrombolysis was more frequent (56.3% vs. 45.9%, $p = 0.008$), onset to recanalization time was shorter –285 (215-389) vs. 320 (250-421) minutes, $p = 0.003$–, and thrombectomy was more often successful (97.6% vs. 85.7%, $p < 0.001$). Regarding glycemic variability, patients who achieved functional independence had a lower median SD –15.11 (9.26-25.15) vs. 17.91 (11.94-30.37) mg/dL, $p < 0.001$–. We found no significant difference in coefficient of variation –13.45 (8.59-20.13) vs. 14.09 (10.14-22.04) mg/dL, $p = 0.134$–. They had lower mean blood glucose –112 (101-126) vs. 128 (151-113) mg/dL, $p < 0.001$–, median blood glucose –109 (98-123) vs. 126 (110-148) mg/dL, $p < 0.001$–, minimum blood glucose –96 (87-106) vs. 108 (95-121) mg/dL, $p < 0.001$–, and maximum blood glucose –134 (116-163) vs. 157 (131-187) mg/dL, $p < 0.001$–.

Conversely, patients who died were older –81 (74-86) vs. 76 (65-82) years, $p < 0.001$– and had a higher prevalence of diabetes mellitus (40.2% vs. 28.7%, $p = 0.024$). On admission, they had higher blood glucose –146 (118-180) vs. 122 (108-153) mg/dL, $p < 0.001$–. They were less likely to receive thrombolysis (33% vs. 55.2%, $p < 0.001$), had longer onset to recanalization times –332 (266-448) vs. 292 (226-394) minutes, $p = 0.016$–, and less successful thrombectomy (81.4% vs. 94.5%, $p < 0.001$). They had higher GV both SD –23.96 (12.94-37.83) vs. 16.00 (10.02-25.40) mg/dL, $p < 0.001$– and coefficient of variation –16.15 (11.34-26.25) vs. 13.32 (8.96-20.01) mg/dL, $p = 0.002$–. They also had higher mean blood glucose –134 (117-160) vs. 117 (103-135) mg/dL, $p < 0.001$–, median blood glu-

Table I. Baseline characteristics of study population.

Demographics	Age (years), median (IQR)	77 (66-83)
	Male sex, *n* (%)	286 (43.5%)
Comorbidities	Smoking, *n* (%)	93 (14.2%)
	Diabetes mellitus, *n* (%)	200 (32.4%)
	Hypertension, *n* (%)	468 (71.2%)
	Dyslipidemia, *n* (%)	344 (52.4%)
Stroke parameters	NIHSS on admission, mean ± SD	14.7 ± 5.6
	ASPECTS, mean ± SD	8.1 ± 1.5
Occlusion site	ICA, *n* (%)	154 (23.4%)
	M1, *n* (%)	357 (54.3%)
	M2, *n* (%)	146 (22.2%)
Parameters at hospital admission	Blood glucose on admission, mg/dL, median (IQR)	124 (108-157)
	SBP, mmHg, median (IQR)	147 (128-162)
	DBP, mmHg, median (IQR)	79 (67-89)
Stroke etiology	Cardioembolic source, *n* (%)	367 (55.9%)
	Large vessel disease, *n* (%)	91 (13.9%)
	Unknown, *n* (%)	174 (26.5%)
	Other determined, *n* (%)	25 (3.8%)
Parameters related to treatment	IVT, *n* (%)	341 (51.9%)
	ORT, minutes, median (IQR)	295 (232-397)
	mTICI ≥ 2b, *n* (%)	608 (92.5%)
Parameters related to glycemia	HbA1c, %, median (IQR)	5.8 (5.5-6.3)
	Number of blood glucose measurements, median (IQR)	7 (6-9)
	Mean blood glucose, mg/dL, median (IQR)	119 (105-139)
	Median blood glucose, mg/dL, median (IQR)	114 (102-135)
	GV, SD, mg/dL, median (IQR)	16.68 (10.43-28.27)
	GV, coefficient of variation, mg/dL, median (IQR)	13.75 (9.31-20.99)
Outcomes	NIHSS 24 hours post MT, median (IQR)	6 (3-14)
	sICH, *n* (%)	17 (2.6%)
	3-month mRS 0-2, *n* (%)	378 (57.5%)
	3-month mortality, *n* (%)	97 (14.8%)

ASPECTS: Alberta Stroke Program Early CT Score; DBP: diastolic blood pressure; GV: glycemic variability; HbA1c: glycated hemoglobin A1c; ICA: internal carotid artery; IQR: interquartile range; IVT: intravenous thrombolysis; MT: mechanical thrombectomy; mTICI: modified thrombolysis in cerebral infarction scale; NIHSS: National Institutes of Health Stroke Scale; ORT: onset to recanalization time; SBP: systolic blood pressure; SD: standard deviation; sICH: symptomatic ICH.

cose –130 (112-158) vs. 113 (101-132) mg/dL, $p < 0.001$–, minimum blood glucose –106 (95-122) vs. 98 (88-112) mg/dL, $p < 0.001$–, and maximum blood glucose –166 [138-204] vs. 140 (121-169) mg/dL, $p < 0.001$– (Table II).

Multivariate regression analysis

After adjusting for confounding variables, SD was no longer significantly associated with poor functional outcome –aOR 1.007 (95% CI 0.990-1.025), $p = 0.391$–, but remained independently associated with mortality –aOR 1.020 (95% CI 1.001-1.040), $p = 0.035$–. Parameters reflecting hyperglycemia (blood glucose on admission, mean and median blood glucose) remained independently associated with poor functional outcome and mortality (Table III).

Discussion

In this study, we aimed to assess how GV in the first 24 hours after MT impacts prognosis of patients with anterior circulation AIS. Our results suggest that GV measured through SD is an independent risk factor for mortality at 3-month follow-up.

Additionally, admission hyperglycemia and mean and median blood glucose in the first 24 hours after MT were independently associated with poor functional outcome and mortality at 3-month follow-up, which agrees with the literature [3].

Other groups have previously tried to understand how GV and outcome after MT correlate. Our findings are in line with those by Deng et al's follow-up study, which included 70 AIS patients with anterior circulation large vessel occlusion treated with MT [12]. They assessed blood glucose through continuous glucose monitoring for an average of 3.5 days and found that SD was independently associated with in-hospital and 3-month mortality rates. There was no significant association between GV and 3-month functional outcome.

Baudu et al retrospectively assessed GV 24 hours after anterior or posterior circulation AIS treated with MT and thrombolysis [13]. 93 patients were included. GV was calculated from a minimum of 6 blood glucose measurements and treated as a dichotomous variable (high vs. low) according to receiver operating characteristic (ROC) curve analysis. They found a correlation between high GV and worse functional outcome. Contrary to the literature, there was no significant correlation between high admission and mean blood glucose and worse functional outcome at 3-month follow-up. Results were not adjusted for diabetes mellitus or glycated hemoglobin, and mortality rate was not assessed.

Lastly, Gordon et al did a retrospective two-center study with 79 patients and analyzed GV for 24 hours after MT, with 4 to 6 blood glucose measurements per patient [14]. They found SD to correlate independently with poor functional outcome at 3-month follow-up but did not assess mortality.

Compared to previous similar studies, our study group GV was lower: SD of 16.68 mg/dL vs. 19.35 mg/dL in Baudu et al [13] and 30.80 mg/dL in Gordon et al [14]. While blood glucose upon admission, mean blood glucose and HbA1c were similar. Differences in GV between studies could be due to distinct blood glucose management protocols.

GV is believed to be more deleterious than hyperglycemia alone as it aggravates the effects of hyperglycemia on brain tissue [18-20]. GV promotes a pro-inflammatory and pro-thrombotic environment, leading to increased risk of infectious and thrombotic complications, which contribute to increased mortality [12]. Even in non-critically ill patients, GV is associated with longer hospital stays and greater 3-month mortality [21].

Candidate therapeutic agents for treating GV include glucose-like peptide-1 (GLP-1) receptor agonists, namely exenatide. GLP-1 is a peptide hormone that maintains normoglycemia and is practically devoid of hypoglycemic risk, thus reducing GV [22]. On the pre-clinical level, GLP-1 receptor agonists have been shown to have neuroprotective properties, and in animal models of ischemic stroke they seem to reduce inflammation and oxidative stress, and to favor angiogenesis [23].

The TEXAIS trial (Trial of EXenatide in Acute Ischaemic Stroke) was a phase II trial that randomized AIS patients to standard care and to treatment with exenatide begun within nine hours of symptom onset [24]. Exenatide was well tolerated and significantly reduced frequency of hyperglycemic events, without causing any hypoglycemic episodes [25]. Regarding functional outcomes, no significant benefit was noted. However, recruitment was terminated early due to COVID-19 related constraints, which may have limited power to show statistically significant results. Exenatide's favorable safety profile and success in managing blood glucose in AIS is promising and larger randomized clinical trials are warranted.

Altogether, data point towards a need to treat dysglycemia in a patient-tailored manner, considering factors such as diabetes mellitus, collateral status, and stroke subtype.

Table II. Univariate analyses comparing patients with according to functional outcome mortality at 3-month follow-up.

		mRS 0-2 (*n* = 378)	mRS 3-6 (*n* = 279)	*p*-value
Demographic and clinical characteristics	Age (years), median (IQR)	73 (62-81)	80 (74-85)	**<0.001**
	Male sex, *n* (%)	176 (46.6%)	110 (39.4%)	0.068
	Smoking, *n* (%)	69 (18.3%)	24 (8.6%)	**<0.001**
	Diabetes mellitus, *n* (%)	98 (25.9%)	102 (36.6%)	**0.003**
	Hypertension, *n* (%)	261 (69%)	207 (74.2%)	0.15
	Dyslipidemia, *n* (%)	193 (51.1%)	151 (54.1%)	0.437
	HbA1c, %, median (IQR)	5.8 (5.4-6.2)	5.9 (5.6-6.6)	**<0.001**
	NIHSS on admission, mean ± SD	13.4 ± 5.7	16.6 ± 4.9	**<0.001**
	ASPECTS, mean ± SD	8.4 ± 1.4	7.8 ± 1.5	**<0.001**
Occlusion site	ICA, *n* (%)	75 (19.8%)	79 (28.3%)	**0.011**
	M1, *n* (%)	214 (56.6%)	143 (51.3%)	0.173
	M2, *n* (%)	89 (23.5%)	57 (20.4%)	0.342
Parameters at hospital admission	Blood glucose on admission, mg/dL, median (IQR)	120 (105-143)	136 (112-178)	**<0.001**
	SBP, mmHg, median (IQR)	145 (127-160)	149 (128-168)	0.073
	DBP, mmHg, median (IQR)	78 (66-86)	80 (70-93)	**0.015**
Parameters related to treatment	IVT, *n* (%)	213 (56.3%)	128 (45.9%)	**0.008**
	ORT, minutes, median (IQR)	285 (215-389)	320 (250-421)	**0.003**
	mTICI ≥ 2b. *n* (%)	369 (97.6%)	239 (85.7%)	**<0.001**
Outcomes	NIHSS 24 hours post MT, median (IQR)	4 (2-7)	14 (8-18)	**<0.001**
	sICH, *n* (%)	1 (0.3%)	16 (5.7%)	**<0.001**
Stroke etiology	Cardioembolic source, *n* (%)	189 (50.0%)	178 (63.8%)	**<0.001**
	Large vessel disease, *n* (%)	63 (16.7%)	28 (10%)	**0.015**
	Unknown, *n* (%)	106 (28%)	68 (24.4%)	0.292
	Other determined, *n* (%)	20 (5.3%)	5 (1.8%)	**0.021**
Parameters related to glycemia	Number of blood glucose measurements, median (IQR)	6 (6-9)	7 (6-9)	0.171
	GV, SD, mg/dL, median (IQR)	15.11 (9.26-25.15)	17.91 (11.94-30.37)	**<0.001**
	GV, coefficient of variation, mg/dL, median (IQR)	13.45 (8.59-20.13)	14.09 (10.14-22.04)	0.134
	Mean blood glucose, mg/dL, median (IQR)	112 (101-126)	128 (151-113)	**<0.001**
	Median blood glucose, mg/dL, median (IQR)	109 (98-123)	126 (110-148)	**<0.001**
	Minimum blood glucose, mg/dL, median (IQR)	96 (87-106)	108 (95-121)	**<0.001**
	Maximum blood glucose, mg/dL, median (IQR)	134 (116-163)	157 (131-187)	**<0.001**

Table II. Univariate analyses comparing patients with according to functional outcome mortality at 3-month follow-up. *(cont.)*.

		Alive (*n* = 560)	Dead (*n* = 97)	Valor de *p*
Demographic and clinical characteristics	Age (years), median (IQR)	76 (65-82)	81 (74-86)	**<0.001**
	Male sex, *n* (%)	242 (43.2%)	44 (45.4%)	0.694
	Smoking, *n* (%)	83 (14.8%)	10 (10.3%)	0.239
	Diabetes mellitus, *n* (%)	161 (28.7%)	39 (40.2%)	**0.024**
	Hypertension, *n* (%)	401 (71.6%)	67 (69.1%)	0.611
	Dyslipidemia, *n* (%)	295 (52.7%)	49 (50.5%)	0.694
	HbA1c, %, median (IQR)	5.8 (5.5-6.3)	6.1 (5.6-6.8)	**0.005**
	NIHSS on admission, mean ± SD	14.3 ± 5.6	17.1 ± 5.2	**<0.001**
	ASPECTS, mean ± SD	8.2 ± 1.4	7.8 ± 1.6	0.054
Occlusion site	ICA, *n* (%)	125 (22.3%)	29 (29.9%)	0.104
	M1, *n* (%)	306 (54.6%)	51 (52.6%)	0.706
	M2, *n* (%)	129 (23%)	17 (17.5%)	0.228
Parameters at hospital admission	Blood glucose on admission, mg/dL, median (IQR)	122 (108-153)	146 (118-180)	**<0.001**
	SBP, mmHg, median (IQR)	147 (128-162)	141.5 (127-175)	0.624
	DBP, mmHg, median (IQR)	79 (67-90)	80.5 (69-86)	0.978
Parameters related to treatment	IVT, *n* (%)	309 (55.2%)	32 (33%)	**<0.001**
	ORT, minutes, median (IQR)	292 (226-394)	332 (266-448)	**0.016**
	mTICI ≥ 2b. *n* (%)	529 (94.5%)	79 (81.4%)	**<0.001**
Outcomes	NIHSS 24 hours post MT, median (IQR)	6 (2-11)	16 (9-19.75)	**<0.001**
	sICH, *n* (%)	5 (0.9%)	12 (12.4%)	**<0.001**
Stroke etiology	Cardioembolic source, *n* (%)	305 (54.5%)	62 (63.9%)	0.083
	Large vessel disease, *n* (%)	83 (14.8%)	8 (8.2%)	0.084
	Unknown, *n* (%)	148 (26.4%)	26 (26.8%)	0.938
	Other determined, *n* (%)	24 (4.3%)	1 (1%)	0.155
Parameters related to glycemia	Number of blood glucose measurements, median (IQR)	7 (6-9)	7 (6-9)	0.997
	GV, SD, mg/dL, median (IQR)	16 (10.02-25.4)	23.96 (12.94-37.83)	**<0.001**
	GV, coefficient of variation, mg/dL, median (IQR)	13.32 (8.96-20.01)	16.15 (11.34-26.25)	**0.002**
	Mean blood glucose, mg/dL, median (IQR)	117 (103-135)	134 (117-160)	**<0.001**
	Median blood glucose, mg/dL, median (IQR)	113 (101-132)	130 (112-158)	**<0.001**
	Minimum blood glucose, mg/dL, median (IQR)	98 (88-112)	106 (95-122)	**<0.001**
	Maximum blood glucose, mg/dL, median (IQR)	140 (121-169)	166 (138-204)	**<0.001**

ASPECTS: Alberta Stroke Program Early CT Score; DBP: diastolic blood pressure; GV: glycemic variability; HbA1c: glycated hemoglobin A1c; ICA: internal carotid artery; IQR: interquartile range; IVT: intravenous thrombolysis; mRS: modified Ranking scale; mTICI: modified thrombolysis in cerebral infarction scale; NIHSS: National Institutes of Health Stroke Scale; ORT: onset to recanalization time; SBP: systolic blood pressure; SD: standard deviation; sICH: symptomatic ICH.

Table III. Multivariate analysis showing adjusted odds ratios of poor functional outcome and of mortality.

	Adjusted OR of poor functional outcome[a]	*p*-value	Adjusted OR of mortality[b]	*p*-value
GV, SD, mg/dL, median (IQR)	1.007 (0.99-1.025)	0.391	1.02 (1.001-1.04)	**0.035**
GV, coefficient of variation, mg/dL, median (IQR)	1.002 (0.975-1.03)	0.882	1.03 (0.997-1.064)	0.079
Mean blood glucose, mg/dL, median (IQR)	1.01 (1-1.019)	**0.042**	1.01 (1-1.021)	**0.046**
Median blood glucose, mg/dL, median (IQR)	1.009 (1-1.018)	**0.045**	1.01 (1.001-1.02)	**0.031**
Blood glucose at admission, mg/dL, median (IQR)	1.01 (1.003-1.017)	**0.003**	1.012 (1.006-1.018)	**<0.001**

GV: glycemic variability; IQR: interquartile range; OR: odds ratio; SD: stardard deviation. [a] Adjusted for: age, smoking, diabetes, NIHSS at admission, ASPECTS, ICA occlusion, blood glucose at admission, DBP at admission, time from symptom onset to recanalization, IVT, successful recanalization, TOAST etiology. [b] Adjusted for: age, diabetes, NIHSS at admission, blood glucose at admission, time from symptom onset to recanalization, IVT, successful recanalization.

Our study has several merits. Our study population (657 subjects) is significantly larger than what has been published previously (less than 100 subjects), which lends robustness to our results. We obtained a median of 7 blood glucose measurements per patient, and we treated GV as a continuous variable instead of dichotomizing it, which preserves information, allows increased statistical power, and avoids bias that could lead to incorrect conclusions. We evaluated functional outcome as well as mortality. Contrary to other studies, in the multivariate regression analysis we corrected our results for the presence of diabetes mellitus, which is very important as patients with and without prior diabetes mellitus seem to have different tolerability to glycemic fluctuations [10]. Our results align with the literature considering the effect of hyperglycemia, and with the only study that used continuous glucose monitoring regarding the impact of glycemic variability [12]; this reinforces the validity of our results. Lastly, our study addresses a clinically relevant topic, as glucose management in stroke is still a matter of debate.

Our study has significant limitations as well. As this was a retrospective single-center study, generalizability of the results is limited. We used discrete values of blood glucose, which means that some fluctuations in blood glucose may have gone undetected. This could be solved by using continuous glucose monitoring, which however is more expensive and less accessible. GV was recorded for 24 hours only, which is a relatively short time span. Studies using continuous glucose monitoring have demonstrated that post-stroke hyperglycemia is probably biphasic, with an early phase hyperglycemia peaking at 8 hours post-stroke, and a delayed phase 48-88 hours post-stroke [26]. Nonetheless, as mentioned, our results were similar to Deng et al's [12], who used continuous glucose monitoring for 3.5 days. We analyzed mortality rate only, not cause of death. Such information could be in establishing a relationship between GV and thrombotic and infectious complications, thus shedding light on the mechanism through which GV increases mortality.

Lastly, caution should be exercised when inferring causality from observational studies as ours. Although we have found a significant association between hyperglycemia and GV and outcomes, causality is not necessarily implied. A causal relationship could be demonstrated by interventional studies, but both the SHINE trial [5] and the TEXAIS trial [24] failed to do so, highlighting the complexity of glycemic management in AIS. Thus, while hyperglycemia and GV may serve as important prognostic indicators, it remains unclear whether they are modifiable prognostic factors or merely markers of stroke severity. Further interventional studies are necessary to assess the benefits of treating GV and to clarify the causal relationship between GV and outcomes.

Conclusions

Our results suggest that higher GV after MT for anterior circulation AIS is an independent risk factor for 3-month mortality. Future trials should focus on assessing the benefits of treating GV and clarifying the causal relationship between GV and outcomes.

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Variabilidad glucémica tras trombectomía mecánica en el ictus isquémico agudo de la circulación anterior

Introducción. La morbilidad de los pacientes con ictus isquémico agudo (IIA) sometidos a trombectomía mecánica (TM) exitosa permanece alta. La hiperglucemia empeora el pronóstico tras un IIA, pero tratarla agresivamente no mejora los resultados. No existe consenso sobre el tratamiento óptimo de la glucemia después de un IIA. La variabilidad glucémica (VG), que refleja las fluctuaciones glucémicas a lo largo del tiempo, puede ser un factor importante. Nuestro objetivo fue investigar cómo la VG afecta el resultado de pacientes con IIA tratados con TM.

Pacientes y métodos. Realizamos un estudio retrospectivo unicéntrico que incluyó a pacientes con IIA que recibieron TM para la oclusión de un gran vaso de la circulación anterior. Se registraron mediciones discretas de glucemia en las primeras 24 horas postrombectomía, a partir de las cuales se calcularon dos medidas de VG: desviación estándar y coeficiente de variación. Se realizó un análisis univariado y multivariado para identificar predictores de resultado funcional desfavorable (escala de Rankin modificada: 3-6) y mortalidad a los tres meses.

Resultados. Se incluyó a 657 pacientes. Los que tenían una puntuación en la escala de Rankin modificada ≥ 3 (42,5%) y los fallecidos (14,8%) tuvieron una VG significativamente mayor medida por desviación estándar. En un modelo multivariado, una mayor desviación estándar se asoció de forma independiente con la mortalidad –*odds ratio* ajustada: 1,02 (intervalo de confianza al 95%: 1,001-1,04)– pero no con el resultado funcional –*odds ratio* ajustada de la escala de Rankin modificada ≥ 3: 1,007 (intervalo de confianza al 95%: 0,99-1,025)–.

Conclusiones. Nuestros resultados sugieren que una mayor VG tras la TM para el IIA de la circulación anterior es un factor de riesgo independiente de mortalidad a los tres meses. Los futuros ensayos deben evaluar el beneficio de reducir la VG en este contexto.

Palabras clave. Glucemia. Hiperglucemia. Hipoglucemia. Ictus. Pronóstico. Trombectomía.