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Linking Cerebral Oximetry to Outcomes of Reperfusion Therapy in Ischemic Stroke: a *Post-Hoc* Analysis of a Randomized Controlled Trial

Alexey R. Avidzba[1,2]*, Vitaliy A. Saskin[1,2], Anton M. Nikonov[1,2], Ayyaz Hussain[1,2], Mikhail Y. Kirov[1,2]

[1] Northern State Medical University, Ministry of Health of Russia, 51 Troitsky Ave.,163069 Arkhangelsk, Arkhangelsk region, Russia
[2] Volosevich City Clinical Hospital No. 1, 1 Suvorova Str., 163001 Arkhangelsk, Arkhangelsk region, Russia

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***Correspondence to:** Alexey R. Avidzba, avidzba_a@rambler.ru

Summary

Aim. To evaluate the predictive value of cerebral oximetry for functional recovery in patients undergoing reperfusion therapy for ischemic stroke.

Materials and Methods. A post hoc analysis was performed using data from a single-center, open-label, randomized controlled trial. The study included 45 patients with ischemic stroke who received systemic thrombolysis. Primary outcomes included functional recovery as assessed by modified Rankin Scale and mortality. Serial cerebral oximetry was performed within the first 24 hours after thrombolysis. The interhemispheric difference (IHD) in cerebral oximetry was used to determine a cutoff point for predicting functional recovery using ROC curve analysis. Associations between IHD and outcomes were analyzed using univariate and multivariate logistic regression models.

Results. The IHD in cerebral oxygenation between the unaffected and affected hemispheres was 4% (3–5%) before thrombolysis and dropped to 3% (1–4%) 24 hours after thrombolysis ($P = 0.024$). An IHD of less than 4% was identified as an independent predictor of favorable functional outcome with an adjusted odds ratio of 12 (95% CI: 1.6–93.7; $P = 0.017$). However, IHD less than 4% was not predictive of mortality ($P = 0.301$).

Conclusion. Systemic thrombolysis in ischemic stroke is associated with improved cerebral oxygenation. An IHD in cerebral oxygenation of less than 4% serves as an independent predictor of favorable functional recovery in ischemic stroke patients but does not correlate with reduced mortality.

Keywords: ischemic stroke, systemic thrombolysis, cerebral oximetry, functional outcome

Conflict of interest. The authors declare no conflict of interest.

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Introduction

Ischemic stroke (IS) is a common debilitating condition with a high mortality rate and a significant economic burden on healthcare systems [1–3]. Treatment during the hyperacute phase of IS focuses on rapid recanalization of the occluded artery and restoration of cerebral blood flow [4, 5]. Both pharmacological and mechanical methods of reperfusion are used. Pharmacological approaches include systemic and local thrombolytic therapy (TLT), while mechanical methods include thrombectomy and thrombus aspiration [4, 6]. Advances in neuroimaging techniques, such as magnetic resonance imaging (MRI) and perfusion studies, have facilitated the extension of therapeutic windows for reperfusion interventions [7–9].

In recent years, the potential benefits of additional monitoring methods during the hyperacute phase of IS have been widely discussed in the scientific literature. Cerebral oximetry is one such method that offers a non-invasive, user-friendly method to assess local brain oxygenation with sufficient accuracy [10, 11]. Currently, cerebral oximetry is used as an adjunctive monitoring tool in various cardiovascular surgeries and critical illness [10, 12, 13].

Cerebral oximetry has shown utility in the diagnosis of secondary hypoperfusion, oligemia caused by intracranial hypertension, and cerebral vasospasm. It can also assess cerebral blood flow and autoregulatory integrity and help individualize hemodynamic parameters in patients with aneurysmal subarachnoid hemorrhage [10]. In addition, cerebral oximetry has been shown to accurately detect intracerebral hematomas larger than 3.5 mL located within 2.5 cm of the cortical surface of the brain [14].

The use of cerebral oximetry in intensive care for patients with focal brain injury, such as ischemic stroke or hypertensive intracerebral hemorrhage, is controversial due to potential discrepancies between the site of cerebral saturation measurement (rSO_2) and the location of the brain lesion. However, this monitoring method is particularly promising for ischemic stroke patients for several reasons.

First, cerebral oximetry may aid in the early detection of large vessel occlusion in the prehospital setting, thereby improving triage. It allows determination of appropriate patient routing — either to a center equipped with endovascular reperfusion techniques or to the nearest facility capable of administering systemic thrombolysis [15]. Second, this method can be used to comprehensively monitor the recanalization status during mechanical thrombectomy (MT) under general anesthesia [16]. Third, cerebral oximetry has the potential to predict functional and social recovery in patients undergoing reperfusion therapy for ischemic stroke [17, 18].

In addition, preliminary evidence suggests that cerebral oximetry is useful in assessing the safety of early mobilization in stroke patients [19].

All of the applications of rSO_2 monitoring discussed are in patients with large intracranial vessel occlusions and subsequent use of MT for recanalization. However, the scientific literature lacks data on the extent to which rSO_2 measurements can predict functional recovery in patients who have undergone TLT alone or in mixed groups receiving both TLT and MT.

Therefore, the aim of our study is to evaluate the predictive ability of cerebral oximetry for functional recovery in patients after reperfusion interventions for ischemic stroke.

Materials and Methods

A post hoc analysis was performed using data from a single-center, open-label, randomized controlled trial (RCT) conducted at the Department of Anesthesiology and Intensive Care of the Regional Vascular Center (RVC) of the First City Clinical Hospital named after E. E. Volosevich in Arkhangelsk, Russia.

The RCT protocol was approved by the Ethics Committee of the Northern State Medical University (Arkhangelsk) on January 26, 2022 (Protocol No. 01/01-22) and registered at ClinicalTrials.gov (NCT05517109). Written informed consent was obtained from all participants. For patients who were unable to provide informed consent, a medical consilium was convened to determine the feasibility of enrolling them in the study.

Patients over 18 years of age diagnosed with IS and scheduled for TLT or MT were included in the study. All enrolled participants were required to have a systolic blood pressure (SBP) of at least 140 mmHg at enrollment. For post hoc analysis, only patients with IS in the anterior cerebral circulation and rSO_2 measurements taken within the first 24 hours after TLT were included.

Randomization was performed using a sealed envelope method. Upon admission to the ICU of the RVC, patients were randomized into two groups: the control group with a target SBP of 161–185 mmHg during the first 24 hours and the intensive hypotensive therapy group with a target SBP of < 160 mmHg. Randomized SBP targets were maintained during reperfusion and for the first 24 hours after TLT. If SBP exceeded the target range, TLT was stopped temporarily for SBP correction; once target SBP was achieved, reperfusion was resumed.

Exclusion criteria were as follows:

- Lack of informed consent or a medical consilium decision.
- Patient refusal to participate in the study.
- Pregnancy.
- Participation in another clinical trial within the previous 90 days.
- Off-label use of TLT, except in cases where patient selection was based on DWI/FLAIR mismatch assessment using brain MRI.
- Failure to achieve target SBP within 20 minutes prior to initiation of TLT.
- SBP above target range for more than 60 minutes during the first 24 hours after TLT.
- SBP less than 100 mmHg for more than 60 minutes after reperfusion therapy.

Hemodynamic parameters were monitored with GE PROCARE B40 (USA) or Comen WQ-002 (China) devices. Blood pressure was controlled according to the randomization protocol with intravenous azamethonium bromide and urapidil as needed.

Thrombolytic therapy was administered with alteplase at a dose of 0.9 mg/kg. For patients over 80 years of age, the attending intensivist could reduce the dose to 0.6 mg/kg. Ten percent of the dose was given as an intravenous bolus, with the remainder infused continuously over the next hour using a syringe pump.

For all patients, biometric parameters, primary and comorbid conditions, IS subtype according to the TOAST classification [20], and stroke severity according to the National Institutes of Health Stroke Scale (NIHSS) [21] were recorded.

Cerebral oxygen saturation (rSO_2) was monitored using the Masimo Root device (USA). Two sensors were placed in standard positions on the forehead, right and left of the midline. Data from both sensors were collected, reflecting rSO_2 values for the intact and affected hemispheres during the first 24 hours post-TLT. Studies suggest that the ratio of arterial to venous blood oxygenation in the cerebral cortex is highly individual, which can significantly influence absolute rSO_2 values and define an individual normal range [22]. With this in mind, the degree of damage to the affected hemisphere was assessed by calculating the difference in rSO_2 values between the intact and affected hemispheres ($\triangle rSO_2$).

The primary endpoints were 90-day mortality and functional recovery as assessed by the modified Rankin Scale (mRS) at 90 days after stroke onset [23]. Data were collected via telephone interviews with

the patient or their next of kin. Functional recovery was categorized as favorable (mRS score 0–2) or unfavorable (mRS score 3–5) [24].

Statistical data analysis. Continuous data were presented according to their distribution, either as mean *(M)* ± standard deviation *(SD)* or as median *(Me)* with interquartile range *(IQR: Q1; Q3)*. Categorical data were described as absolute numbers *(N)* and percentages (%). Normality of distribution was assessed using the Shapiro–Wilk test.

For comparisons of continuous variables between groups, independent samples were analyzed using either the Student's t-test (for normally distributed data) or the Mann–Whitney *U* test (for non-normally distributed data). For paired samples, the Wilcoxon signed-rank test was used. Comparisons of categorical variables were made using Fisher's exact test.

The cutoff point for predicting favorable functional recovery based on $\triangle rSO_2$ values was determined using receiver operating characteristic (ROC) curve analysis, which evaluates the proportion of correctly classified values. The association between rSO_2 measurements and functional recovery was evaluated using univariate and multivariate logistic regression models.

For multivariate logistic regression models, confounders significant in published studies (such as age and NIHSS score on admission) were selected and simultaneously included in the model. Statistical analyses were performed with STATA 14 MP software (StataCorp, USA).

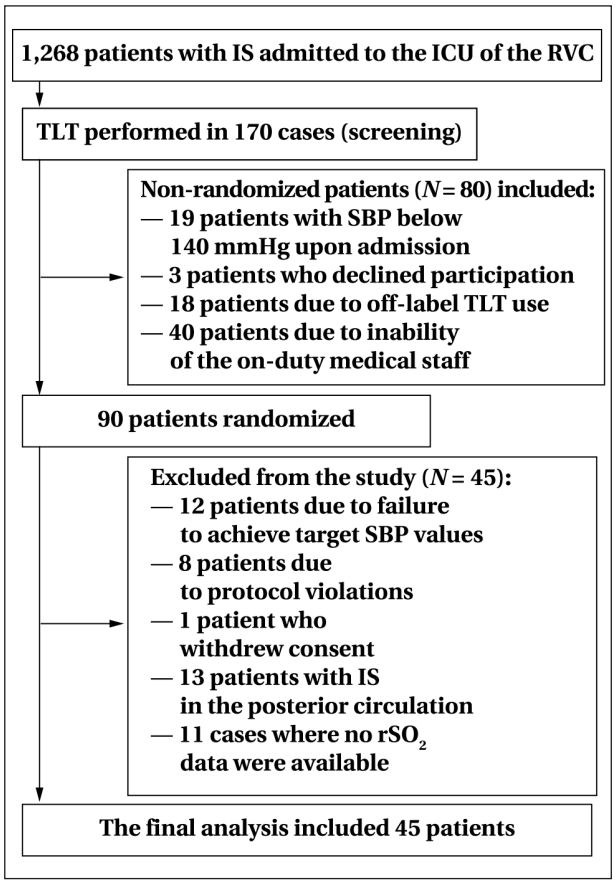

Fig. 1. Study flowchart.
Note. IS — ischemic stroke; TLT — thrombolytic therapy; SBP — systolic blood pressure.

Results and Discussion

During the study period, 1,268 patients with IS were admitted to the ICU of the RVC. Screening was performed in 170 patients who underwent TLT, of whom 90 were randomized. The final analysis included 45 patients with carotid territory strokes and recorded rSO_2 measurements (Fig. 1).

Of the participants, 27 (60%) were men with a mean age of 70.9±10.9 years and a median NIHSS score of 9 (IQR: 6; 16) (Table 1). The distribution of IS subtypes was as follows:

- Atherothrombotic stroke: 17 patients (37.8%)
- Cardioembolic stroke: 14 patients (31.1%)
- Lacunar stroke: 3 patients (6.7%)
- Cryptogenic stroke: 11 patients (24.4%).

The $\triangle rSO_2$ before TLT was 4 (3; 5). Twenty-four hours after TLT, $\triangle rSO_2 24$ was 3 (1; 4), which was significantly different ($P = 0.024$).

The cut-off point for the $\triangle rSO_2 24$ parameter was set at 4%, with a sensitivity of 50%, specificity of 88%, and overall classification accuracy of 73.2% (Fig. 2). Based on this threshold, the cohort was divided into two groups: $\triangle rSO_2 24 < 4\%$ and $\triangle rSO_2 24 \geqslant 4\%$.

Fatal outcome was observed in 4 patients (8.9%). Among surviving patients, good functional recovery was documented in 25 cases (61%) with the following distribution between groups: in the $\triangle rSO_2 24 < 4\%$ group, favorable outcomes were observed in 22 cases (73%) compared to 3 cases (27%) in the $\triangle rSO_2 24 \geqslant 4\%$ group ($P = 0.012$).

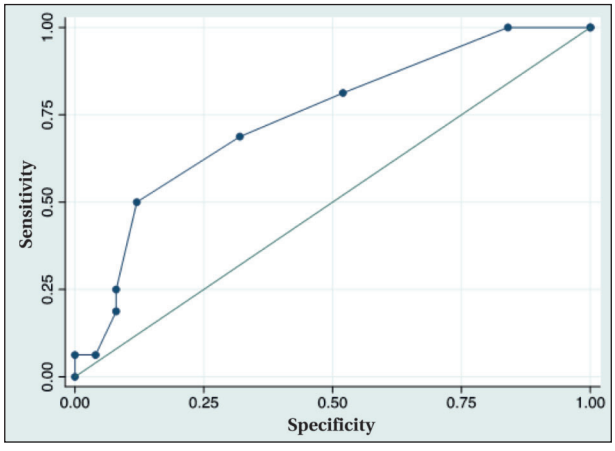

Fig. 2. ROC curve: sensitivity and specificity of interhemispheric difference in cerebral oximetry values 24 hours after systemic thrombolysis for predicting good functional recovery.
Note. The area under the curve (AUC) is 0.741 [95% CI, 0.570 to 0.857].

Table 1. Clinical and demographic characteristics of the sample and outcomes.

	Entire sample, *N* = 45	△rSO$_2$24 < 4%, *N* = 31	△rSO$_2$24 ⩾ 4%, *N* = 14	*P*-value
Age, years	70.9±10.9	71.1±10.4	70.4±12.4	0.570
Sex, male, *N* (%)	27 (60)	20 (64.5)	7 (50)	0.357
NIHSS on admission, points, *Me (Q1; Q3)*	9 (6; 16)	7 (6; 13)	14.5 (9; 20)	0.002
Comorbidities				
Hypertension, *N* (%)	38 (84.4)	26 (83.9)	12 (85.7)	0.874
Atrial fibrillation, *N* (%)	16 (35.6)	10 (32.3)	6 (42.9)	0.492
Diabetes mellitus, *N* (%)	11 (24.4)	7 (22.6)	4 (28.6)	0.717
Coronary heart disease, *N* (%)	15 (33.3)	11 (35.5)	4 (28.6)	0.743
Chronic heart failure, *N* (%)	6 (13.3)	5 (16.1)	1 (7.1)	0.648
Outcomes				
Death, *N* (%)	4 (8.9)	1 (3.2)	3 (21.4)	0.082
mRS score on day 90, points, *Me (Q1; Q3)*	2 (1; 3)	2 (1; 3)	3.5 (3; 5)	0.01

Note. mRS — modified Rankin score.

Table 2. Predictors of favorable functional recovery after thrombolytic therapy.

Predictor	Preliminary analysis			Adjusted analysis		
	OR	95 % CI	*P*-value	aOR	95 % CI	*P*-value
△rSO$_2$24 < 4 %	7.3	1.5–34.7	0.012	12	1.6–93.7	0.017
Age, years	0.9	0.8–0.9	0.029	0.9	0.8–0.9	0.016
NIHSS on admission, points	0.9	0.8–1.1	0.093	0.9	0.8–1.1	0.551

Note. Here and Tables 2, 3: △rSO$_2$24 — interhemispheric difference in cerebral oximetry; aOR — adjusted odds ratio.

Table 3. Predictors of mortality after thrombolytic therapy.

Predictor	Preliminary analysis			Adjusted analysis		
	OR	95 % CI	*P*-value	aOR	95 % CI	*P*-value
△rSO$_2$24 < 4 %	0.12	0.1–1.3	0.082	0.25	0.01–3.9	0.301
Age, years	1	0.9–1.1	0.902	1	0.9–1.1	0.964
NIHSS on admission, points	1.2	1–1.4	0.049	1.2	0.9–1.4	0.163

△rSO$_2$24 as a predictor of favorable functional outcome. △rSO$_2$24 < 4% was associated with favorable functional recovery in univariate analysis (OR, 7.3 [95% CI, 1.5 to 34.7], *P* = 0.012). In multivariate analysis, △rSO$_2$24 < 4% also was an independent predictor of favorable functional outcome (adjusted OR, 12 [95% CI, 1.6 to 93.7], *P* = 0.017). Variables included in the model are listed in Table 2.

△rSO$_2$24 as a predictor of mortality. △rSO$_2$24 < 4% was not a predictor of mortality in either univariate analysis (OR, 0.13 [95% CI, 0.01 to 1.3]; *P* = 0.082) or multivariate analysis (adjusted OR, 0.25 [95% CI, 0.01 to 3.9]; *P* = 0.301) (Table 3).

In this post hoc analysis of an RCT investigating the optimization of blood pressure during the first 24 hours after TLT for IS, it was demonstrated that △rSO$_2$ values significantly decreased after TLT. This reduction illustrates the effectiveness of reperfusion techniques in restoring blood flow to the affected cerebral hemisphere. However, the observed decrease in △rSO$_2$ was modest in absolute terms, limiting its utility as a marker of reperfusion. These findings are consistent with those reported by Hametner et al. in which △rSO$_2$ increased in the affected hemisphere in only 2 of 25 patients after successful recanalization by MT. Therefore, the applicability of △rSO$_2$ monitoring to assess reperfusion during the hyperacute phase of acute IS remains uncertain.

To date, several studies have investigated the prognostic ability of △rSO$_2$ levels in predicting functional recovery and mortality in patients with IS. According to S. E. Eroğlu et al. [25], △rSO$_2$ values were not associated with stroke severity in acute cerebrovascular events. This lack of association may be due to the inclusion of both ischemic and hemorrhagic stroke patients in their cohort. This is partially supported by Flint et al. who demonstrated that △rSO$_2$ values did not differ between hemispheres in patients with ICH [15]. In contrast, for IS specifically, △rSO$_2$ values of 3% or greater have been identified as a potential predictor of large intracranial vessel occlusions, such as in the intracranial internal carotid artery, M1 segment of the middle cerebral artery, and A1 segment of the anterior cerebral artery [15]. Our results further suggest that △rSO$_2$24 values of 4% or greater serve as an independent predictor of poor functional recovery in IS. This observation may reflect a higher prevalence of patients with large-vessel occlusion in the cohort, resulting in larger ischemic volumes and consequently worse outcomes.

The 90-day mortality rate in our cohort was 8.9%, which is consistent with published data [26]. Our results suggest that △rSO$_2$24 is not a predictor of mortality in patients after thrombolysis. However, C. Hametner et al. reported △rSO$_2$24 as a predictor of mortality, which may be attributed to the higher mortality rate of their cohort (32.6%) and the inclusion of patients undergoing MT for large intracranial vessel occlusions. In addition, the baseline

severity of illness was significantly higher in the C. Hametner et al. study, with a median NIHSS score of 19 on admission compared to 9 in our cohort [18]. This difference likely contributed to the worse functional outcome in cases of unsuccessful recanalization in their study.

To our knowledge, this study is among the first to investigate the prognostic value of rSO_2 values in patients after TLT for IS. Nevertheless, several limitations must be acknowledged. These include the modest sample size and single-center design, which limit the generalizability of the findings. In addition, we did not assess the prevalence of large intracranial vessel occlusion, which could be a significant confounding factor influencing our results.

Conclusion

Thrombolytic therapy in IS is associated with a reduction in the interhemispheric difference in rSO_2 between the intact and affected hemispheres. A $\triangle rSO_2 24$ of 4% or greater is an independent predictor of poor functional recovery in patients after IS, but is not associated with increased mortality. Further research is needed to elucidate the role of rSO_2 monitoring in the hyperacute phase of IS.

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