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Association between nocturnal oxygen desaturation and ischaemic stroke outcomes

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ABSTRACT

Clinical rationale for the study. This study aimed to assess the association between nocturnal hypoxemia and early acute ischaemic stroke (AIS) outcomes in patients without oxygen supplementation.

Material and methods. One hundred and six AIS patients consecutively admitted to the stroke unit were included in this study. Baseline demographic and medical data and arterial blood saturation (SpO_2) measurements during night-sleep (from 10pm to 6am) were examined for their association with stroke outcomes, including the National Institutes of Health Stroke Scale (NIHSS) score on the 7th day or differences between the NIHSS score on the 1st day and the 7th day after stroke onset.

Measurements of SpO_2 were made using a pulse oximeter of the Spacelabs Medical Inc. (USA) monitoring system, and the number of apnoea episodes and their duration were recorded by ECG Holter with respiration monitoring (CardioMem®, Getamed, GE).

Results. The study showed that age (Spearman's r = 0.207, p = 0.033) and parameters attributable to anaemia (RBC r = –0.205, p = 0.035, Hb r = –0.225, p = 0.02 and HCT r = –0.196, p = 0.044), atrial fibrillation and ischaemic changes in both brain hemispheres (p = 0.023 and 0.01, respectively) were correlated with the study outcomes.

In terms of saturation parameters, we demonstrated that the 'total desaturation burden' (i.e. [100% minus actual measured SpO_2%] x apnoea duration) and multiple apnoeas of longer than 20 seconds were correlated with worse functional outcomes. Measures of shorter desaturation episodes (i.e. SpO_2 oxygen desaturation index (ODI) at 3% and 4%, and time-weighted desaturations below the determined thresholds (SpO_2 from 95% to 85%) demonstrated non-significant associations with the study outcomes.

Conclusions and clinical implications. This study demonstrated that long-lasting desaturation episodes during the night, depicted by the 'total desaturation burden', were correlated with worse functional outcomes in AIS, while measures of shorter desaturation episodes were not correlated. In future clinical trials, indications for oxygen supplementation should include the methodology of personalised medicine and introduce individual approaches based on specially formulated, novel multifactorial algorithms.

Key words: night-sleep, apnoea, oxygenation, hypoxia, SpO_2, ischaemic stroke, stroke outcome

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Introduction

Hypoxemia followed by brain hypoxia may significantly affect the outcomes of acute ischaemic stroke (AIS) [1–3]. Additionally, hypoxemia is frequently intermittent and undetected [4]. Technically, hypoxemia is defined as a decrease in the partial pressure of oxygen in the blood. In contrast, the more general term hypoxia indicates abnormally low oxygen content in any tissue or organ, or the body as a whole [5, 6]. Hypoxemia can cause hypoxia (hypoxemic hypoxia), but hypoxia can also occur via other mechanisms, such as anaemia [5, 6].

According to a previous study, hypoxia is likely to occur during stroke care when the control of patients' vital parameters is more challenging to observe. Challenges occur most often during diagnostics and therapeutic procedures, for example during head scanning and during and after enteral feeding tube insertion, as well as during transfer from an emergency department to a stroke unit, and particularly at night [2, 3, 7, 8].

The most convenient and commonly used tool for blood oxygen saturation assessment is pulse oximetry. Pulse oximetry is a microprocessor-based instrument that incorporates both oximetry and plethysmography to provide continuous noninvasive monitoring of the oxygen saturation of arterial blood (SpO_2) and identify hypoxemia [6, 9].

In AIS, hypoxia in the acute phase might damage the ischaemic penumbra and worsen clinical outcomes [1–3, 10, 11]. Interestingly, studies on normobaric oxygen therapy and hypoxemia measured by pulse oximetry have predicted AIS outcomes differentially [12]. A recent systematic review and meta-analysis found no effect of normobaric oxygen therapy on outcomes, including early neurological improvement, functional outcomes at 3–6 months, or the mortality rate [13].

This finding is in agreement with a previous clinical trial demonstrating that routine oxygen supplementation throughout the 24-hour period after stroke onset was not effective in improving stroke outcomes [14].

In summary, in normoxemic AIS (as well as myocardial infarction) patients, the prophylactic use of low-dose oxygen supplementation did not significantly affect all-cause mortality or rehospitalisation and early neurological recovery or functional outcome measures, such as early disability or mortality. Therefore, these findings do not support low-dose oxygen supplementation in nonhypoxic patients with AIS [4, 13–15].

For the reasons mentioned, the threshold of intervention with oxygen therapy in AIS patients is thus unclear. It has been shown that saturations equal to or below 85% are associated with worse functional outcomes, but saturations equal to or below 90% are not [12]. Current guidelines recommend close monitoring of oxygenation status and the prevention of hypoxia. As the data obtained has been limited and not entirely consistent, the optimal level of SpO_2 in the arterial blood of AIS patients has not been specified. Therefore, guidelines from both the European Stroke Organisation and the American Heart Association/American Stroke Association do not recommend the routine use of supplemental oxygen for nonhypoxic patients, i.e. those with an oxygen saturation ≥ 95% [16–18].

Clinical rationale for the study

There is limited evidence regarding the influence of blood desaturation during night-sleep on clinical outcomes in AIS patients without indications for oxygen therapy. Therefore, our study aimed to assess the correlation between hypoxemia during the first three nights after stroke onset and early stroke outcomes in normoxemic AIS patients without oxygen supplementation.

Material and methods

Study time and participants

The study was performed between 1 October 2018 and 30 July 2019 at the Stroke Unit in the Department of Neurology and Cerebrovascular Disorders, Poznan University of Medical Sciences, Poznan, Poland.

Patients were managed according to the 2018 American Heart Association/American Stroke Association and Polish Society of Neurology acute ischaemic stroke guidelines [16, 18].

We evaluated all patients with acute ischaemic stroke who were consecutively admitted to the stroke unit and fulfilled the inclusion criteria.

Data collection

Baseline demographic data, medical history, the National Institutes of Health Stroke Scale (NIHSS) score, and laboratory data were collected at admission. The oxygenation data was collected at least within the first three days and nights of a patient's stay in the stroke unit. Over 96% of patients underwent a baseline cranial CT or MRI. We performed a short Six-Minute Magnetic Resonance Imaging Protocol according to Nael et al., with in-home modifications [19]. Stroke severity was evaluated at presentation and on every day of the hospital stay during morning visits using the NIHSS (see Tab. 1 for details). When necessary, chest X-ray or chest CT was performed.

The inclusion criteria for the study were admission within 12 h after AIS onset, a previous Barthel score ≥ 85 (as signs of disability before stroke are independent risk factors for worse prognosis, especially in elderly AIS patients treated with intravenous thrombolysis [20]), and the absence of stupor or coma.

The exclusion criteria included a definite indication for oxygen supplementation (daytime oxygen saturation of less than 95%, decompensated congestive cardiac failure, pneumonia, known chronic hypoxia requiring oxygen treatment),

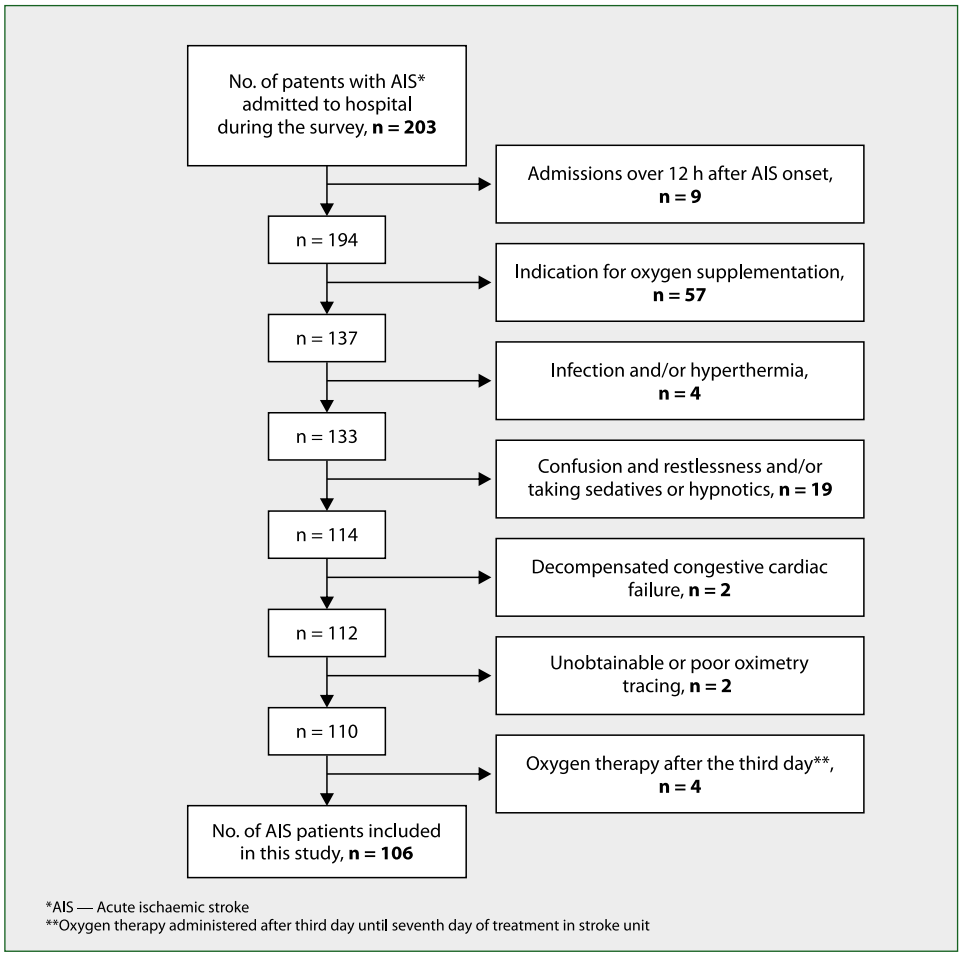

Figure 1. Pathway of patient selection

and any airway support. Other reasons for study exclusion were body hyperthermia (temperatures > 38°C) [16], confusion and restlessness making pulse oximetry probes or ECG electrodes placement difficult, reduced peripheral perfusion leading to unobtainable or poor oximetry tracing, and taking sedatives or hypnotics. Patients were also excluded from the study if oxygen therapy was provided during the first seven days in the stroke unit. The pathway of patient selection is set out in Figure 1.

Oxygenation data

We used 21% as the fraction of inspired oxygen (FiO_2), and none of the patients in the study were provided oxygen by an oxygen mask or nasal cannula; therefore, we could only assess SpO_2, which was proportional to the SpO_2/FiO_2 ratio. Night-time was defined as 10pm to 6am. The nurses were asked to record on an observation chart whether the patient was awake or asleep during the night of the study period. Patients were also inspected to ensure that their fingers were warm and well perfused. The sensory probe was normally fitted to the index finger.

In patients who were aroused or awakened for longer than 30 minutes during the night, the study measurements were performed the next night. Patients were excluded from the study if the measurements were also unsuccessful on the second and third nights after AIS onset.

Measurements of SpO_2 were made using a pulse oximeter of an Ultraview SL2600 monitoring system (Spacelabs Medical Inc., USA), which met and exceeded ANSI/AAMI standard SP-10. Apnoea episodes and their duration were recorded by ECG Holter monitoring (CardioMem® CM 4000 B 3-channel, ECG and respiration recorder, Getamed, GE Healthcare, Germany). The time on the Spacelabs monitoring system and ECG recorder were coordinated at 10pm each night during the study. The time-weighted SpO_2 desaturation was assessed according to the methodology used by Akca et al. [21], and oxygen saturation variability (SpO_2 fluctuations) was assessed according to Zhang et al. [22].

Outcome measures

The outcomes were: NIHSS ranges (or scores) on the seventh day after stroke onset; and differences between

Table 1. Distribution of seven ranges (levels) according to categorical scores on NIHSS or death at 1st and 7th day

Categorical scores (ranges) (1 to 7) and NIHSS scores (from 0 to 42 points)	No. of cases [total no./(%)] n = 106	
	1st day	7th day
1 — scores 0–4	32 (30.2)	49 (46.2)
2 — scores 5–9	34 (32.1)	25 (23.6)
3 — scores 10–14	20 (18.9)	9 (8.5)
4 — scores 15–19	12 (11.3)	11 (10.4)
5 — scores 20–24	4 (3.8)	5 (4.7)
6 — scores ≥ 25	4 (3.8)	3 (2.8)
7 — death	0 (0.0)	4 (3.8)

NIHSS ranges (or scores) on the first and seventh days of hospitalisation [the first-day NIHSS range (or score) minus the seventh-day range (or score)]. The study endpoint assessment was conducted by a neurologist dedicated to the study. The functional assessment was preceded by an intraobserver reliability check comprising neurologists involved in prior studies (RK) [23].

The outcomes were assessed using the distribution of seven ranges (levels) of increasing neurological impairment, according to the categorical scores ranging from 1 to 7 on the NIHSS, or death according to the HeadPoST trial by Anderson et al. (2017) [24] (Tab. 1).

Statistical methods

Continuous variables were summarised with the number of items, mean, median, standard deviation (SD), and interquartile range (IQR) defined as the difference between the third and first quartiles of our data. In the case of ordinal variables, the number of items and corresponding percentages are presented. Spearman's rank correlation coefficient was used to investigate monotonic relationships between two variables: this coefficient takes values from –1 to 1. A statistically significant ($H0 : \rho \neq 0$) result concerning Spearman's correlation coefficient proves the existence of monotonic interdependencies between these variables. If the coefficient is positive, it indicates that as one variable increases, the value of the other variable increases as well. However, if the correlation is negative, as the value of one parameter increases, the value of the other parameter decreases. The following standard classification of the correlation strength was used in this study:

- $|r| = 0$ — no correlation,
- $0 < |r| \leq 0.3$ — very weak correlation,
- $0.3 < |r| \leq 0.5$ — weak correlation,
- $0.5 < |r| \leq 0.7$ — moderate correlation,
- $0.7 < |r| \leq 0.9$ — high correlation,
- $0.9 < |r| < 1.0$ — very high correlation,
- $|r| = 1$ — full correlation.

To compare two independent groups of patients, an unpaired two-sample Wilcoxon test was used. Where applicable, a multiple linear regression model was used to examine the relationship between the dependent and explanatory variables. In each case, we checked the feasibility of the multiple linear regression model, as well as the model fit described by the coefficient of determination (R-squared), which always takes values from the interval [0.1] (greater values of this coefficient suggest that our model explained more variability of the dependent variable, and hence, in such cases, that the fit was better). The values of the coefficients in this model estimated the size of the effect that the respective independent variables had on the dependent variable. The choice of the best set of explanatory variables was made in this study, with stepwise regression based on the well-known Akaike information criterion (AIC), which can select a model that minimises information loss.

In this study, the level of statistical significance was set at $p = 0.05$. All statistical calculations were performed using standard RStudio distribution (version 4.02).

Results

Table 1 presents the distribution of seven ranges of increasing neurological impairment according to the categorical scores on the NIHSS or death at the 1st and 7th days after stroke onset.

The median SpO_2 during night-sleep for all patients was 93% (IQR 91–95%). The median duration of a single apnoea was 23.8 seconds (IQR 8.8–42.2 s). The median number of apnoeas was 67, and the total duration was 1.594 s per night (indicating 7.75 apnoeas and a duration of 3.32 minutes per hour, and 26.6 minutes of apnoea per eight hours of night-sleep).

In terms of the outcomes, according to the distribution of categorical scores (for the NIHSS ranges between the 1st and 7th days), the median of the results equalled 5 [IQR 3–6] on the first day and 2 [IQR 1–3] from the 2nd to the 7th day after stroke onset, and the differences were significant (Friedman test, p value < 0.001).

Our study (Tab. 2) showed that age (Spearman's $r = 0.207$, $p = 0.033$) and parameters attributable to anaemia (RBC Spearman's $r = -0.205$, $p = 0.035$; Hb $r = -0.225$, $p = 0.02$; and HCT $r = -0.196$, $p = 0.044$) significantly correlated with the study outcome (i.e. NIHSS range, 1st day minus 7th day). Additionally, we revealed an association between persistent atrial fibrillation (AF) (*vs.* absence of AF, Wilcoxon test, $p = 0.023$) and ischaemic changes in both brain hemispheres (*vs.* left or right hemisphere only, $p = 0.018$ and $p = 0.01$, respectively) and stroke outcome (NIHSS range, 1st day minus 7th day). Additionally, we did not find any difference between outcomes in patients with first-ever and recurrent stroke for NIHSS ranges on the seventh day, or between NIHSS ranges on the first and seventh days (U Mann-Whitney test, $p = 0.08$, and $p = 0.13$, respectively).

Table 2. Baseline characteristics of acute ischaemic stroke patients

Variable	Parameter	Total (n = 106)
Sex, no. (%)	Female	52 (49.1)
	Male	54 (50.9)
Age (years) *	Median (IQR)	71 (64–79)
	Mean (SD)	72 (11)
I.V. thrombolytics therapy*, no. (%)	Yes	31 (29.2)
	No	75 (70.8)
Brain imaging mode, no. (%)	MR — magnetic resonance imaging	10 (9.4)
	MR + A — magnetic resonance imaging plus angiography MR	68 (64.1)
	CT — computed tomography	21 (19.8)
	CT + CTA — computed tomography plus angiography CT	3 (2.7)
	Lack of data	4 (3.8)
Stroke type (according to TOAST Study) [25] no. (%)	Large artery atherosclerosis	37 (34.9)
	Small vessels occlusion	24 (22.6)
	Cardioembolic	29 (27.4)
	Stroke of other determined and undetermined aetiologies	16 (15.1)
Previous stroke, no. (%)	Yes	17 (16)
	No	89 (84)
Peripheral vascular diseases, no. (%)	Yes	9 (8.5)
	No	97 (91.5)
Diabetes, no. (%)	Type 2	15 (14.2)
	Type 2 insulin dependent	17 (16)
	No	74 (69.8)
Hypertension, no. (%)	Yes	97 (91.5)
	No	9 (8.5)
History of myocardial infarction, no. (%)	Yes	14 (13.2)
	No	92 (86.8)
Heart failure (NYHA 1 and 2), no. (%)	Yes	12 (11.3)
	No	94 (88.7)
History of atrial fibrillation*, no. (%)	Persistent	21 (19.8)
	Paroxysmal	15 (14.2)
	No	70 (66)
History of any cancer, no. (%)	Yes	10 (9.4)
	No	96 (90.6)
Smoking, no. (%)	Current smoker	18 (17)
	Never smoked	9 (8.5)
	Previous smoker	41 (38.7)
	No data	38 (35.8)
Obesity, no. (%)	Waist-hip circumference (female)	48 (45.3)
	Abdominal type (male)	29 (27.4)
	No	29 (27.4)
Cholesterol (mg/dL), no. = 104**	Mean (SD)	182.52 (57.05)
LDL (mg/dL), no. = 104**	Mean (SD)	104.2 (46.48)
HDL (mg/dL), no. = 104**	Mean (SD)	50.79 (15.69)
Triglycerides (mg/dL), no. = 104**	Mean (SD)	137.94 (132.72)
WBC (10^3/μL)	Mean (SD)	8.64 (3.57)
RBC * (10^6/μL)	Mean (SD)	4.5 (0.58)
HB * (g/dL)	Mean (SD)	13.66 (1.76)
HCT * (%)	Mean (SD)	40.07 (4.72)
MCV (fL)	Mean (SD)	89.52 (6.34)
PLT (tys./μL)	Mean (SD)	229.72 (75.88)
CRP (mg/L)	Mean (SD)	8.73 (7.96)
Creatinine (μmol/L)	Mean (SD)	86.12 (23.86)
GFR (ml/min/m^2), no (%)	30–59	30 (28.3)
	> 60	76 (71.7)
Troponin T (pg/mL), no = 102**	Mean (SD)	22.54 (23.94)
ALAT (U/L)	Mean (SD)	18.94 (11.78)
ASPAT (U/L)	Mean (SD)	24.32 (14.3)
Death in hospital, no. (%)	Yes	4 (3.8)
	No	102 (96.2)
SpO_2 (%) in patients with acute ischaemic stroke	Median (IQR)	93.0 (91.0–95.0)
Number of apnoeas per night *	Median (IQR)	67 (30.25–120.5)
Total duration of apnoeas * (s)	Median (IQR)	1,594 (587.25––2,826.25)
Night of SpO_2 assessment, no. (%)	First	60 (56.6)
	Second	34 (32.1)
	Third	12 (11.3)

*Variables significantly correlated with study outcome
** Number of patients, if different from 106

The correlation between the outcome measures and saturation parameters is set out in Table 3.

We demonstrated correlations between the number and total duration of apnoeas and both outcomes, as well as between 'hypoxemia measure' and NIHSS results on the 7th day; additionally, 'trend' (p = 0.052) was demonstrated in a correlation between 'hypoxemia measure' and differences in NIHSS ranges (i.e. 1st day range minus 7th day range) (Tab. 3).

Table 3. Correlation of outcome measures and total duration and number of apnoeas, hypoxemia measures, fluctuations of SpO_2, and drops in time-weighted SpO_2 below determined thresholds (%), and oxygen desaturation index (ODI), and sum of duration of apnoeas

Variables	Outcomes			
	Difference between 1st and 7th day NIHSS ranges		NIHSS score on 7th day (in NIHSS ranges)	
	Spearman's correlations (r)	P-value	Spearman's correlations (r)	P-value
Number of apnoeas per night	0.252	**0.009***	0.261	**0.007**
Total duration of apnoeas per night [s]	0.232	**0.017**	0.241	**0.013**
Hypoxemia measure [(100% — measured actual SpO_2%) x apnoea duration]	0.189	0.052	0.193	**0.048**
Variability (fluctuations) of SpO_2 (according to Zhang et al. [22])	0.063	0.524	0.121	0.218
SpO_2 threshold < 95%; n (%), 106 (100)	0.124	0.204	0.104	0.201
SpO_2 threshold < 93%; n (%), 99 (93.4)	0.042	0.672	0.032	0.782
SpO_2 threshold < 91%; n (%), 91 (85.8)	0.094	0.334	0.089	0.306
SpO_2 threshold < 89%; n (%), 75 (70.7)	0.02	0.83	0.024	0.87
SpO_2 threshold < 87%; n (%), 64 (60.4)	0.004	0.96	0.003	0.971
SpO_2 threshold < 85%; n (%), 43 (40.5)	0.07	0.447	0.054	0.566
ODI**3%	0.071	0.33	0.105	0.288
ODI 4%	0.123	0.185	0.071	0.469
Sum of 10% of longest apnoeas	0.263	**0.007**	0.261	**0.007**
Sum of 20% of longest apnoeas	0.267	**0.006**	0.241	**0.013**
Total number of apnoeas over 20 s	0.274	**0.005**	0.263	**0.007**
Total number of apnoeas over 25 s	0.256	**0.008**	0.267	**0.006**

*Significant values are in bold
**Oxygen desaturation index (ODI) was defined as a 4% (or 3%) decrease in saturation from baseline (ODI 4%) just before desaturation (according to Ali et al. [10])

There were no associations between variability (fluctuations) in SpO_2 and outcomes.

We did not find correlations between time-weighted determined thresholds of desaturation and Oxygen desaturation indexes of 3% and 4%, and with any outcome measure (NIHSS scores and NIHSS ranges). However, we found a weak, but significant, correlation between a sum of 10% and 20% of the longest apnoeas as well as the total number of apnoeas over 20 (or 25) seconds and the outcome (Tab. 3). We also found an association between IV thrombolysis therapy (with alteplase) and two SpO_2 measures. The first was called the 'hypoxemia measure' (Mann–Whitney U test, p = 0.016) and the second was the total apnoea duration during night-sleep for AIS patents who underwent thrombolysis and those who did not [median 1,028 s (IQR 439–1,819 s) *vs.* 1,862 s (IQR 855–4,082 s), p = 0.008 (see also Tab. 2)]. However, these desaturation measures did not show a correlation with the outcome. We also did not find differences among the first, second and third nights in terms of correlations of hypoxia measures and outcomes.

Additionally, stepwise forward multiple linear regression analysis of the associations between the outcomes and obtained parameters showed a weak association for two parameters. We found an association between persistent atrial fibrillation and bilateral (visible in both hemispheres, on head CT or MRI scans) ischaemic changes (p = 0.037 and p = 0.021) and 7th-day NIHSS outcomes. However, with respect to the saturation parameters in this regression analysis, no correlations were demonstrated.

Discussion

The desaturation in AIS during the night seemed to be of particular importance. Hypoxemia is a relatively frequent phenomenon in AIS; however, different methods and definitions of hypoxemia measurements have been published [4, 26–28]. In one study, 63% of patients with AIS and hemiparesis developed hypoxemia (defined as oxygen saturation < 96% for a period > 5 minutes) within 48 hours of stroke onset. Twenty-three per cent of patients with acute stroke who have normal oxygen saturation during the day spend more than 30 minutes with an oxygen saturation < 90% at night [28]. Roffe et al. showed that oxygen saturation was 94.5% while patients were awake, and was 1% lower while they were asleep (between 11pm and 6am). Additionally, oxygen saturation while awake and while asleep was approximately 1% higher in the group of patients without stroke than in the group of patients with stroke [4].

Similarly, in the present study, we found that only three of the study patients (2.83%) did not suffer any apnoea during the night. Surprisingly, we did not find a correlation between

ODI levels of 3% and 4% and the outcomes. In the following analysis, we assessed different threshold limits from 95% to 85%, and again using this approach, even using time-weighted desaturation assessments, we did not find correlations with the outcomes (Tab. 3).

Generally, in our study, factors related to short-term periodic SpO_2 decreases showed no associations with the outcomes. However, we should consider that together with a more severely decreasing SpO_2 threshold, we observed a decreasing incidence of cases; therefore, the lower number of such patients could hamper the statistical significance (Tab. 3). A second explanation is that multifactorial interplay, including haematology, vascular (including collaterals), haemodynamic and anatomical (grey *vs.* white matter ischaemia) factors, and different combinations of comorbidities make the outcomes more individually specific.

In contrast to these results, measures of global desaturation during the night showed a weak but consequently significant correlation with stroke outcomes. Notably, we found a correlation of outcomes and a variable called 'hypoxia measure' that could also be expressed as 'total hypoxia burden' during the night (Tab. 3).

Therefore, it seems that longer desaturation periods could influence the outcomes.

Our results are in agreement with those of other recent studies. Azarbarzin et al. showed that the 'hypoxic burden', an easily derived signal from an overnight sleep study, predicts cardiovascular mortality across populations [26]. Chen et al. evaluated the impact of obstructive sleep apnoea (OSA) on hypoxemia, and found that the duration and severity of total desaturation hypoxemia during sleep (SpO_2 of below 90%) were significant risk factors for cardiovascular diseases in OSA syndrome patients [27].

There are some methodological differences in our study compared to others [1, 26, 27]: in our study, the time of observation was fixed, i.e. the total observed sleep time was eight hours (10pm to 6am) for all patients, and we defined desaturation as the SpO_2 difference from 100% at baseline, i.e. 100% – X%, where X% depicted the real result of the measurement of SpO_2 below 100% in the given time.

Such discrepancies could also result from different characteristics of patients treated in different studies (IV thrombolysis frequency and effectiveness, mechanical thrombectomy or conservative treatment, etc.). Interestingly, we found a significant negative association between the two main long-term hypoxemia measures ('total desaturation burden' and total apnoea duration) and IV thrombolysis, but thrombolysis therapy did not show a significant association with the outcomes.

Theoretically, oxygen supplementation given at night, when the patients seem to be the most vulnerable, might prevent hypoxia. Surprisingly, there is minimal evidence that such an intervention is in fact effective in clinical practice. The effect of supplementation should be dependent on the extent and duration of hypoxia. According to recent guidelines, supplemental oxygen is not recommended in nonhypoxic patients with AIS [16, 18]. Additional support for these findings was provided by a randomised clinical trial of 8,003 participants randomised within 24 hours of admission.

The trial showed that there was no benefit on functional outcomes for AIS patients at 90 days, after the administration of oxygen by nasal cannula continuously for 72 hours or nocturnally for three nights (the oxygen was given at 3 L/min if the baseline SpO_2 was 93% or less and at 2 L/min if the baseline SpO_2 was > 93%) [4].

In our study, we excluded patients who required oxygen; these patients usually comprise a large group in other studies. In one study, as many as 30% of patients needed oxygen supplementation with a threshold of SpO_2 < 93%, and 6% had an SpO_2 of < 90% [26]. In our study, these numbers were similar, as we excluded also 30.05% (n = 61, 57 plus 4) of the patients with oxygen requirements at the time of participation in the study (Fig. 1). Such an approach was important from a methodological point of view. Because we aimed to determine the influence of night-sleep desaturation on AIS outcomes, the obtained results could help to make appropriate modifications to future indications for interventions with oxygen in patients with AIS and a normal range SpO_2 during the day.

In contrast, Akca et al. showed that lower mean SpO_2/FiO_2 levels (and age and initial NIHSS score) were correlated with increased mortality within the first few hours after AIS onset (although for the record, the authors analysed only the mortality rate and did not assess patients' functional status as an outcome) [21].

In the abovementioned study, time-weighted mean SpO_2 levels between 93% and 98% were associated with the lowest mortality rates. Patients with a time-weighted mean SpO_2 of less than 92% had the highest mortality rate, but this difference in mortality was not statistically significant [21].

It is worth noting that we found a moderately increasing C-reactive protein (CRP) level in AIS patients (Tab. 2). This increased CRP was most likely due to brain ischaemia, as described before, and could even be a predictor of stroke outcome [29–32].

In summary, the lack of consistency among different studies and the failure of interventional studies [4, 16] may be explained by the multifactorial character of brain ischaemia in AIS. A number of factors can influence brain ischaemia, such as the dynamics of increasing or persisting brain penumbra, the effectiveness of collateral blood flow, atherosclerosis of the carotid, vertebral and cerebral arteries, small vessel status, heart insufficiency, lung status, brain microembolism, and coexisting diseases. For example, we demonstrated that anaemia could also be a risk factor correlated with desaturation and worse AIS outcomes, which is in agreement with other authors [5, 6]. Moreover, as opposed to the recent results by Danish and Polish (Pomerania) groups [33, 34], we did not find associations between outcomes in patients with first-ever and recurrent stroke. However, we could not exclude that the

relatively low number of recurrent strokes compared to the number of all AIS patients hampers the test significance.

Limitations of the study

Ours was a study with a selected population (i.e. patients who needed oxygen therapy were excluded). On the other hand, this made it possible to examine the association between desaturation episodes and outcomes in a normoxemic population of stroke patients. We did not perform polysomnography, and we did not analyse the nature of the apnoea (obstructive sleep apnoea, central sleep apnoea, or complex apnoea). We also did not assess collateral blood flow or extend both stroke and penumbra volumes; however, in our opinion, this is not crucial in emergency decision-making algorithms, and makes our study as similar to everyday clinical practice as possible. Additionally, for the simplicity of our paper's message, we avoided introducing SpO_2/FiO_2 ratios.

We only assumed early (on the 7th day) outcomes expressed by NIHSS ranges (or scores). We avoided long-term outcomes because we believe that desaturation could influence the earlier phases of AIS. Many factors could interfere with longer, i.e. 90--day or 12-month, outcomes. Additionally, it has been demonstrated that the NIHSS score on the 7^{th} day after stroke onset correlates with longer outcomes [35, 36]. The MR CLEAN trial investigators stated that such an approach "could reduce the stroke-outcome assessment to its essentials (i.e. neurological deficit), and reduce trial duration and costs" [35]. Ours was a preliminary study, and further study in this field is needed.

Clinical implications and future directions

This study demonstrated that among the many assessed blood saturation parameters in AIS, the 'total desaturation burden' was correlated with functional outcomes in AIS. Measures of shorter desaturation episodes demonstrated weaker and nonsignificant associations with the outcomes.

Regarding future therapeutic approaches, in light of the ambiguous results obtained by both our team and other groups, we can assume that there are probably no universal standard methods of delivering oxygen for AIS patients.

In future clinical trials, for multifactorial, dynamically changed, and complex disorders such as AIS, indications for oxygen therapy should include the methodology of personalised medicine and introduce individual approaches based on specially formulated, novel multifactorial algorithms.

Ethical approval: *The study data was collected retrospectively from the Department's records. Before the beginning of the study, the protocol was presented to the Bioethics Committee of Poznan University of Medical Sciences, and the Committee determined that the study did not require the approval of the Committee, as the study included retrospective data analyses. There were no features of an interventional study. Nevertheless, apart from the first and senior authors (IW, RK), no other persons had access to identifiable health information. After the data had been obtained, it was anonymised (names, surnames, personal identification numbers, and addresses of participants were removed) and subjected to statistical analysis with only information stored about a participant's sex and age. The data was stored on electronic media (a back-up hard drive) without network access.*

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