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Nocturnal hypoxemia and central apneas increase mortality, but not recurrent ischemic events after ischemic stroke☆

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ABSTRACT

Background: The aim of the study was to investigate whether findings in cardiorespiratory polygraphy had an association with stroke mortality or ischemic event recurrence after ischemic stroke.
Methods: We prospectively studied 204 ischemic stroke patients who underwent cardiorespiratory polygraphy within the first 48 h after the symptom onset. We followed all these patients for a median of 6.2 years. We evaluated mortality, time of survival, causes of death and new ischemic events.
Results: Of 204 ischemic stroke patients, 43 died and 48 had a new ischemic event during the follow-up. The lowest arterial oxyhemoglobin saturation (min SaO_2) ($P = 0.007$) was lower, the percentage of time spent below arterial oxyhemoglobin saturation less than 90% (T90) ($P = 0.005$) was higher, and central apnea index per hour (CAI/h) ($P = 0.04$) was higher among the deceased. Male gender, older age, diabetes mellitus, elevated modified Rankin scale (mRS) score, lower Glasgow Coma Scale (GCS) score and CAI/h independently predicted higher mortality. Peripheral arterial disease (PAD) and higher National Institutes of Health Stroke Scale (NIHSS) score were independent predictors for a recurrent ischemic event. Among those having respiratory event index (REI) at least 30, older age and lower GCS score independently predicted higher mortality. Only 21 stroke patients initiated continuous positive airway pressure (CPAP) treatment; of those, only one had a new ischemic event.
Conclusions: The non-survivors had more severe nocturnal hypoxemia and more central apneas than survivors. Among patients with REI at least 30/h, increased CAI predicted higher mortality, but not independently.
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1. Introduction

Sleep-disordered breathing (SDB) is very common in stroke patients and is typically obstructive, rather than central, in nature [1]. Stroke patients have four- to six-fold risk for obstructive sleep apnea (OSA) [2]. Sleep apnea is an independent risk factor for stroke [3,4], and stroke itself may predispose to sleep apnea [5]. The association between SDB and incident stroke has been discovered in multiple meta-analyses based on prospective cohort studies [5–7]. However, it is difficult to point out sleep apnea as an independent risk factor for stroke because of the shared risk factors, but untreated OSA may play a role in stroke onset [8]. Respiratory events and recurrent hypoxemia cause hemodynamic, metabolic, endothelial, coagulatory and inflammatory changes, which link sleep apnea to stroke [2,9,10].

Stroke is the second leading cause of death worldwide [11]. Risk of death after stroke has been reported to be fourfold, and those stroke patients who survived over one month had more than two-fold greater risk of death over the next five years compared to general population matched for age and sex [12]. Furthermore, the risk of death after the first year was around 10% per year. During the

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Abbreviations:

AASM	American Academy of Sleep Medicine
AHI	apnea-hypopnea index
BMI	body mass index
CAI	central apnea index
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CPAP	continuous positive airway pressure
CT	computed tomography
ESS	Epworth Sleepiness Scale
GCS	Glasgow Coma Scale
HR	hazard ratio
IQR	interquartile range
MRI	magnetic resonance imaging
mRS	modified Rankin scale
NIHSS	National Institutes of Health Stroke Scale
OSA	obstructive sleep apnea
PAD	peripheral arterial disease
PSG	polysomnography
REI	respiratory event index
SaO_2	arterial oxyhemoglobin saturation
SDB	sleep-disordered breathing
TIA	transient ischemic attack
T90	time of arterial oxyhemoglobin saturation less than 90%
WHO	World Health Organization

first thirty days after stroke, most of the deaths were due to index stroke or recurrent stroke, and after five years, the causes of death were either those mentioned above or due to other cardiovascular causes [12]. A respiratory event index (REI) $\geq$ 30 has been associated with an increased risk of death after first ischemic stroke or transient ischemic attack (TIA) [13]. Past studies have established that stroke patients with OSA have an increased risk of death [13–15].

Every year, around fifteen million people experience stroke according to the World Health Organization (WHO) [16]. Approximately 160,000 recurrent ischemic strokes occur each year, and these events are more costly than incident strokes [17]. The incidence of recurrent vascular events varies from 5.4% to 20% at one year to 11.3%–40% at five years [18–21], being significantly higher in patients with sleep apnea compared to patients without sleep apnea within two years of observation [22].

This study had two aims. First, we investigated whether unattended sleep study results associated with long-term mortality and recurrence of ischemic events in ischemic stroke patients. Second, we examined the causes of death of ischemic stroke patients. We hypothesized that mortality rates and new ischemic events would be elevated among those with more apnea events or worse nocturnal hypoxemia.

2. Participants and methods

2.1. Participants and data collection

The cohort of this prospective, observational study consisted of 204 ischemic stroke patients aged 18 years or older admitted to the Stroke Unit at the Department of Neurology of the Oulu University Hospital from April 22, 2013, to January 22, 2015. Written informed consent was obtained from all patients or their relatives. The Northern Ostrobothnia Hospital District ethics committee approved the study protocol. Our inclusion criterion was ischemic stroke confirmed by an on-call neurologist on admission to hospital, based on clinical evaluation and head computed tomography (CT) or magnetic resonance imaging (MRI). The exclusion criterion was inability to co-operate, i.e. confusion or inability to understand the study protocol. An unattended sleep study was performed within the first 48 h after symptom onset at the stroke unit. The diagnosis of sleep apnea was based on the cardiorespiratory polygraphy, defined as REI $\geq$5/h. We collected information about age, gender, and history of snoring or witnessed apneas as well as previous comorbidities and current medication on admission. We measured the neck and waist circumference and body mass index (BMI) in the acute phase of stroke. Alcohol consumption was documented as daily units of 10 g ethanol and patients were categorized as users or non-users. Heavy use was defined as daily ethanol consumption over 30 g (three units). Smoking was documented as pack-years and patients categorized as smokers or nonsmokers. Daytime sleepiness was assessed by the Epworth Sleepiness Scale (ESS) [23]. Stroke outcome was evaluated with the Modified Rankin Scale (mRS, scale 0–5) [24]. The severity of stroke was evaluated with the National Institutes of Health Stroke Scale (NIHSS, scale 0–35) [25] and the level of consciousness with the Glasgow Coma Scale (GCS, scale 3–15) [26].

We collected data about new diseases and causes of death until June 10, 2020, from the case records of the Oulu University Hospital, which is the only hospital treating patients with suspected acute stroke in the area. A new or recurrent ischemic event was confirmed by an independent on-call neurologist on admission to the hospital, based on clinical examination and head computed tomography or magnetic resonance imaging. Furthermore, we collected data from the Causes of Death Register kept by Statistics Finland according to the WHO guidelines and with telephone interviews.

2.2. Cardiorespiratory polygraphy

We performed the unattended sleep study with a three-channel portable type 4 device, ApneaLink™ Plus (ResMed, Sydney, Australia). The sleep recordings were scored manually (American Academy of Sleep Medicine [AASM] criterion) [27]. The criteria of obstructive, central, and mixed apnea as well as hypopnea and ODI4/h have been described in detail previously [28]. In brief, hypopnea was defined as both a decrease of the peak signal excursion of over 30% from the pre-event baseline with a duration of more than 10 s and oxygen desaturation greater than 3% from the pre-event baseline, but obstructive and central hypopneas were not scored separately. A respiratory event was scored as a central apnea if it met the apnea criteria and was associated with an absence of inspiratory effort. Mixed apneas were required to meet the apnea criteria and to be associated with an absent inspiratory effort initially, subsequently followed by an inspiratory effort in the second part of the event. Sleep apnea (REI $\geq$5/h) was divided into three categories: mild (REI 5–15), moderate (REI 15.1–29) and severe (REI $\geq$30 per hour) sleep apnea. We offered CPAP treatment for all stroke patients who had moderate or severe sleep apnea [29].

2.3. Statistical analysis

We performed all statistical data analyses by using IBM SPSS Statistics version 25.0.0 for Windows. The categorical variables

were compared using Fisher's exact two-tailed test and the Pearson Chi-square test, and continuous variables were compared using Spearman's rank correlation coefficients (rs), t-tests or Mann-Whitney U tests for comparisons between baseline characteristics and our primary dependent variable (death) and secondary dependent variable (a new ischemic event). Year-by-year mortality was analyzed with life-table analysis and Kaplan-Meier survival curves. We chose the Cox proportional hazards regression model to evaluate the risk factors for mortality. We used the forward LR method for multivariate analysis. The validity of the proportional hazards assumption was assessed using Kaplan-Meier survival curves. We used the Cox proportional hazards model to determine hazard ratios (HR) and 95% confidence intervals (CI) of variables that predict death. The variables mentioned in Tables 3–5 were included in the final model. The test for significance was based on changes in log (partial) likelihood. A two-tailed p value less than 0.05 was considered statistically significant.

3. Results

In total, 43 (21.1%) of the 204 patients with ischemic stroke had died before June 10, 2020. The median duration from stroke to death was 2.7 years (IQR 0.4; 4.2). The total follow-up time was 1115.4 person-years. The median follow-up time of all patients was 6.2 years (range 0.01 to 7.1 years). Sleep apnea was found in 147 (91.3%) survivors and in 39 (90.7%) non-survivors. Of those who met the criteria of sleep apnea diagnosis, 80.9% had obstructive sleep apnea and 19.2% had central sleep apnea (more than 50% of events were central). The mean central apnea index (CAI) was 3.9/h and that of mixed apneas/h and unclassified apneas was 0.1. The mean REI was 30.5/h and mean ODI4/h 19.9. The underlying causes of death in patients with and without sleep apnea are presented in Table 1.

A new ischemic event occurred in 48 patients (23.5%) during the follow-up. The median duration from stroke to a recurrent ischemic event was 1.1 years (IQR 0.1;3.9). Of those 48 patients, 28 (58.3%) had a new ischemic stroke, 5 (10.4%) had a transient ischemic attack, and 15 (31.3%) a myocardial infarction.

The baseline characteristics according to survival for all the patients are shown in Table 2. Those who died during follow-up were older (P<0.001) and smoked (P = 0.009) less frequently. Non-survivors had higher prestroke mRS score (P<0.001), higher NIHSS score (P = 0.03), and lower GCS score (P = 0.002) on admission than the survivors. Hypercholesterolemia (P = 0.03), diabetes mellitus (<0.001), coronary artery disease (P = 0.007), atrial fibrillation (P = 0.001), and prior myocardial infarction (P = 0.006) were more common among the deceased. The min SaO_2 (P = 0.007) was lower, T90 (P = 0.005) higher, and CAI higher (P = 0.04) among non-survivors than survivors.

The baseline characteristics according to a new ischemic event are shown in Table 3. Those who had a new ischemic event had peripheral arterial disease (PAD) (P = 0.03) more often than others. None of the findings in the cardiorespiratory polygraphy differed between these two groups. CPAP treatment was initiated more often (P = 0.03) for those who did not suffer a new ischemic event during the observation period.

Fig. 1 shows the survival time of sleep apnea patients having REI under 30 and patients having REI at least 30. Twenty-four of the 91 sleep apnea patients having REI at least 30 and 15 patients of the 95 sleep apnea patients having REI under 30 died during the follow-up. Mean survival times were 5.81 years (95%CI 5.32–6.30) and 6.46 (6.13–6.80). The difference is not statistically significant (P = 0.061).

In the univariate models, older age, non-smoking, higher prestroke mRS, GCS and NIHSS score, hypercholesterolemia, diabetes mellitus, coronary artery disease, and atrial fibrillation predicted higher mortality. In the univariate models, the predictors for mortality were higher REI/h, ODI4/h, CAI/h and T90, and lower mean saturation. In the final multivariate model, male gender, older age, higher prestroke mRS score, lower GCS score, and diabetes mellitus independently predicted higher mortality (Table 4).

Of all the variables tested, higher pack-years, higher NIHSS score, coronary artery disease and PAD predicted recurrent ischemic event in the univariate models. None of the findings in the cardiorespiratory polygraphy predicted recurrent ischemic event. Only higher NIHSS score and PAD independently predicted higher recurrence of a new ischemic event in the final multivariate model (Table 5).

Among patients with REI at least 30, of all the variables tested, older age, higher prestroke mRS score, higher NIHSS score, lower GCS score, diabetes mellitus, atrial fibrillation, and CAI predicted higher mortality in the univariate models. In the final multivariate model, higher age and lower GCS score independently predicted higher mortality (Table 6).

4. Discussion

The main findings of this 6-year follow-up study were that nocturnal hypoxemia and higher CAI were associated with stroke mortality. In our study, T90 was one and a half times greater and the mean min SaO_2 was lower among non-survivors. The mean CAI was over twofold higher in the deceased patients and CAI also predicted mortality in patients with REI over 30 per hour. Furthermore, the most common underlying cause of death was ischemic heart disease.

Our deceased patients spent more time below saturation of 90% and had lower lowest saturation compared to survivors. In line with our study, a previous study by Good et al. [30] showed that death within one year correlated with T90 and with mean SaO_2 whereas no significant difference in T90 was found in two other studies

Table 1
Underlying causes of death in patients with or without sleep apnea.

Cause of death	Deceased patients n (%), (n = 43)	Patients with sleep apnea n (%), (n = 39)	Patients without sleep apnea n (%), (n = 4)
Ischemic heart disease	12 (27.9)	11 (28.2)	1 (25.0)
Late effects of ischemic stroke	7 (16.3)	5 (12.8)	2 (50.0)
Ischemic stroke	6 (14.0)	6 (15.4)	0 (0.0)
Cancer	6 (14.0)	5 (12.8)	1 (25.0)
Alzheimer's disease	3 (7.0)	3 (7.7)	0 (0.0)
Falling	3 (7.0)	3 (7.7)	0 (0.0)
Intracerebral hemorrhage	2 (4.7)	2 (5.1)	0 (0.0)
Hypertension	1 (2.3)	1 (2.6)	0 (0.0)
Parkinson's disease	1 (2.3)	1 (2.6)	0 (0.0)
Diabetes mellitus	1 (2.3)	1 (2.6)	0 (0.0)
Aneurysm of abdominal aorta	1 (2.3)	1 (2.6)	0 (0.0)

Table 2
Baseline characteristics according to survival.

Characteristic	Survivors (n = 161)	Nonsurvivors (n = 43)	Total (n = 204)	P-value
Men, n (%)	97 (60.2)	31 (72.1)	128 (62.7)	0.15
Mean age, years (SD)	65.3 (13.2)	77.0 (9.3)	67.7 (13,4)	**<0.001**
Mean BMI (SD)	27.4 (4.4)	26.7 (5.6)	27.3 (4.7)	0.22
Current smoking n (%)	41 (25.5)	3 (7.0)	44 (21.6)	**0.009**
Mean pack years (SD)	11.0 (16.7)	11.7 (17.3)	11.1 (16.8)	0.91
Alcohol consumption daily n (%)	19 (11.8)	4 (9.3)	23 (11.3)	0.79
Snoring n (%)	105 (65.2)	22 (51.2)	127 (62.3)	0.09
Prior sleep apnea (%)	7 (4.3)	2 (4.7)	9 (4.4)	0.93
Mean neck circumference, cm (SD)	42.6 (8.3)	43.4 (6.9)	42.8 (8.0)	0.43
Mean waist circumference, cm (SD)	103.5 (15.2)	101.8 (13.6)	103.1 (14.9)	0.46
Mean ESS (SD)	4.7 (2.9)	4.8 (2.4)	4.7 (2.8)	0.75
Median prestroke mRS (SD) (scale 0–5)	0.0 (1.0)	1,0 (1.5)	0.76 (1,16)	**<0.001**
Median NIHSS score (SD) (0-35)	5.0 (4.4)	7.3 (6.0)	4.0 (4.9)	**0.03**
Median GCS score (SD) (3-15)	14.6 (1.0)	13.8 (2.1)	15.0 (1.3)	**0.002**
Hypertension n (%)	92 (57.1)	31 (72.1)	123 (60.3)	0.08
Hypercholesterolemia n (%)	67 (41.6)	26 (60.5)	93 (45.6)	**0.03**
Diabetes mellitus n (%)	23 (14.3)	17 (39.5)	40 (19.6)	**<0.001**
Coronary artery disease n (%)	23 (19.9)	17 (39.5)	49 (24.0)	**0.007**
Myocardial infarction n (%)	18 (11.2)	12 (27.9)	30 (14.7)	**0.006**
Atrial fibrillation n (%)	18 (11.2)	14 (32.6)	32 (15.7)	**0.001**
PAD n (%)	4 (2.5)	3 (7.0)	7 (3.5)	0.15
Thrombolysis treatment n (%)	89 (55.3)	21 (48.8)	110 (53.9)	0.45
Sleep apnea (REI ≥5/h) n (%)	147 (91.3)	39 (90.7)	186 (91.2)	0.90
Mean REI/h (SD)	28.4 (21.3)	38.5 (27.9)	30.5 (23.1)	**0.05**
Mean ODI4/h (SD)	17.8 (16.1)	25.3 (25.1)	19.9 (18.7)	0.21
Mean OAI/h (SD)	4.9 (7.8)	6.7 (9.3)	5.3 (8.1)	0.34
Mean CAI/h (SD)	2.9 (5.7)	7.5 (12.9)	3.9 (8.0)	**0.04**
Mean MAI/h (SD)	0.1 (0.3)	0.1 (0.4)	0.1 (0.3)	0.82
Mean hypopneas/h (SD)	20.5 (16.5)	24.3 (20.7)	21.3 (17.5)	0.56
Mean average oxygen saturation (SD)	92.7 (2.0)	92.0 (3.0)	92.6 (2.3)	0.10
Mean lowest oxygen saturation (SD)	80.9 (8.0)	78.5 (7.4)	80.4 (7.9)	**0.007**
Saturation<90%, % (SD)	16.6 (23.8)	25.2 (25.0)	18.4 (24.2)	**0.005**
CPAP treatment initiated n (%)	17 (10.6)	4 (9.3)	21 (10.3)	0.81

BMI, body mass index; ESS, Epworth sleepiness scale; mRS, modified Rankin Scale; NIHSS, National institutes of health stroke scale; GCS, Glasgow coma scale; PAD, peripheral arterial disease; REI/h, Respiratory event index per hour; ODI4/h, arterial oxyhemoglobin saturation decreases of ≥4%; OAI/h, obstructive apnea index per hour; CAI/h, central apnea index per hour; MAI/h, mixed apnea index per hour.

[2,13]. The min SaO_2 was a risk factor for death after stroke in our study, confirming previous findings [31]. The desaturation events may exacerbate brain damage due to reduced oxygen delivery to penumbral brain tissue [32–34]. Prior researchers demonstrated that a fifth of acute stroke patients may suffer from intermittent hypoxia within the first hours after stroke onset and nearly two thirds within two days [32–34]. Moreover, Kendzerska et al. [35] pointed out that T90 was the most powerful predictor for cardiovascular attack in OSA patients. An earlier study of Sulter et al. [33] showed that oxygen desaturation developed in stroke patients with more severe strokes and older age. Intermittent hypoxia and respiratory events cause hemodynamic, neural, metabolic, coagulatory, endothelial, and inflammatory alterations; these factors link sleep apnea and stroke [4]. Hypoxemia causes oxidative stress and systemic inflammation, which can promote the progress of atherosclerosis; furthermore, serious hypoxemia may cause cerebral ischemia and add to the risk of stroke [36]. In addition, untreated sleep apnea produces hypoxia, sympathetic activation, systemic inflammation, oxidative stress and endothelial dysfunction, which may initiate atherogenesis [37]. T90 at least 10% per night is a risk factor for the emergence of stroke in sleep apnea patients [38].

In this study, CAI was over twofold higher in non-survivors compared to survivors, which is in line with a prior study [13]. In contrast, Sahlin et al. [14] have reported that obstructive sleep apnea, but not central sleep apnea, remained a significant risk for death from any cause. The previous observation that instead of a decline in the blood flow of the middle cerebral artery during central apneas, there was a decline during hypopneas and obstructive apneas, supports the notion that obstructive apnea may be a risk factor in acute cerebrovascular disease [39].

In this study, those who died tended to have higher REI than survivors, and, REI predicted death in the univariate analysis. Our finding is in line with a prior study of stroke patients where AHI associated independently with mortality, which meant a 5% increase in mortality risk for each unit of increase in AHI [13]. Moreover, Sahlin et al. [14] showed that an obstructive apnea-hypopnea index greater than 10 per hour was independently related to death. There was no significant difference in the mortality in our patients with REI below or above 30, contrary to the study by Parra et al. [13].

Our non-survivors were older and had worse prestroke mRS, NIHSS and GCS scores, which is in line with previous studies [2,12–14,40]. In our study, male gender, diabetes mellitus, prestroke mRS score, GCS score and older age were independent predictors of mortality, male gender being the strongest predictor in multivariate model. Furthermore, we pointed out that hypercholesterolemia was not associated with the mortality in stroke patients, which is in line with the study by Zhang et al. [41] but contrary to two other previous studies [2,13]. In this study, we demonstrated that ischemic heart disease, atrial fibrillation and diabetes mellitus were predictors of death after stroke, confirming previous findings [2,14]. In the previous study of Vernino et al. [42], the well-identified predictive factors of mortality in cerebrovascular disease were older age, male gender, current or previous smoking, increased NIHSS or higher mRS scores, lower GCS scores,

Table 3
Baseline characteristics according to a new ischemic event.

Characteristic	Ischemic event (n = 48)	No new events (n = 156)	Total (n = 204)	P-value
Men n (%)	30 (62.5)	98 (62.8)	128 (62.7)	0.97
Mean age, years (SD)	68.7 (11.9)	67.5 (13.8)	67.7 (13,4)	0.95
Mean BMI (SD)	26.7 (4.2)	27.4 (4.8)	27.3 (4.7)	0.59
Current smoking n (%)	12 (25.0)	32 (20.5)	44 (21.6)	0.51
Mean pack-years (SD)	15.7 (18.9)	9.7 (15.9)	11.1 (16.8)	0.18
Alcohol consumption daily n (%)	4 (8.3)	19 (12.2)	23 (11.3)	0.46
Snoring n (%)	27 (56.3)	100 (64.1)	127 (62.3)	0.33
Prior sleep apnea (%)	4 (8.3)	5 (3.2)	9 (4.4)	0.22
Mean neck circumference, cm (SD)	41.8 (4.8)	43.1 (8.8)	42.8 (8.0)	0.67
Mean waist circumference, cm (SD)	102.3 (12.7)	103.4 (15.5)	103.1 (14.9)	0.68
Mean ESS (SD)	4.2 (2.8)	4.9 (2.8)	4.7 (2.8)	0.12
Median prestroke mRS (SD) (scale 0–5)	0.0 (1.1)	0.0 (1.2)	0.76 (1,16)	0.63
Median NIHSS score (SD) (0-35)	5.9 (6.1)	5.3 (4.4)	4.0 (4.9)	0.58
Median GCS score (SD) (3-15)	14.3 (1.4)	14.5 (1.3)	15.0 (1.3)	0.64
Hypertension n (%)	32 (66.7)	91 (58.3)	123 (60.3)	0.30
Hypercholesterolemia n (%)	25 (52.1)	68 (43.6)	93 (45.6)	0.30
Diabetes mellitus n (%)	13 (27.1)	27 (17.3)	40 (19.6)	0.14
Coronary artery disease n (%)	16 (33.3)	33 (21.2)	49 (24.0)	0.08
Myocardial infarction n (%)	10 (20.8)	20 (12.8)	30 (14.7)	0.17
Atrial fibrillation n (%)	6 (12.5)	26 (16.7)	32 (15.7)	0.48
PAD n (%)	4 (8.3)	3 (1.9)	7 (3.5)	**0.03**
Thrombolysis treatment n (%)	25 (52.1)	85 (54.5)	110 (53.9)	0.77
Sleep apnea n (%)	43 (81.6)	143 (91.7)	186 (91.2)	0.66
Mean REI/h (SD)	29.6 (24.2)	30.8 (22.9)	30.5 (23.1)	0.61
Mean ODI4/h (SD)	17.5 (18.3)	20.0 (18.7)	19.9 (18.7)	0.41
Mean OAI/h (SD)	4.9 (6.9)	5.4 (8.5)	5.3 (8.1)	0.81
Mean CAI/h (SD)	2.3 (5.0)	4.4 (8.6)	3.9 (8.0)	0.14
Mean MAI/h (SD)	0.1 (0.4)	0.1 (0.3)	0.1 (0.3)	0.86
Mean hypopneas/h (SD)	22.5 (19.6)	20.9 (16.8)	21.3 (17.5)	0.85
Mean average oxygen saturation (SD)	92.7 (2.9)	92.5 (2.1)	92.6 (2.3)	0.44
Mean lowest oxygen saturation (SD)	80.4 (7.5)	80.4 (8.1)	80.4 (7.9)	0.69
Saturation <90%, % (SD)	19.0 (26.5)	18.3 (23.6)	18.4 (24.2)	0.83
CPAP treatment initiated n (%)	1 (2.1)	20 (12.8)	21 (10.3)	**0.03**

BMI, body mass index; ESS, Epworth sleepiness scale; mRS, modified Rankin Scale; NIHSS, National institutes of health stroke scale; GCS, Glasgow coma scale; PAD, peripheral arterial disease; REI/h, Respiratory event index per hour; ODI4/h, arterial oxyhemoglobin saturation decreases of ≥4%; OAI/h, obstructive apnea index per hour; CAI/h, central apnea index per hour; MAI/h, mixed apnea index per hour.

Table 4
Univariable and multivariable Cox proportional hazard models for death.

Variables at stroke onset	Univariable			Multivariable (Regression Method = Forward Stepwise)		
	HR	95% CI	P-value	HR	95% CI	P-value
Male	1.593	0.818–3.102	0.171	3.150	1.504–6.596	0.002
Age	1.091	1.056–1.128	<0.001	1.081	1.044–1.120	<0.001
Current smoking	0.248	0.077–0.803	0.020			
Pack- years	1.003	0.986–1.021	0.718			
Snoring	0.623	0.343–1.133	0.121			
Prestroke mRS score	1.580	1.296–1.927	<0.001	1.290	1.029–1.616	0.027
NIHSS score	1.083	1.028–1.141	0.003			
GCS score	0.698	0.586–0.830	<0.001	0.757	0.630–0.910	0.003
Hypertension	1.790	0.919–3.485	0.087			
Hypercholesterolemia	1.928	1.046–3.553	0.035			
Diabetes mellitus	3.272	1.775–6.034	<0.001	2.627	1.402- 4.925	0.003
Coronary artery disease	2.369	1.285–4.369	0.006			
Atrial fibrillation	3.078	1.625–5.830	0.001			
PAD	2.414	0.746–7.811	0.141			
REI/h	1.017	1.005–1.029	0.005			
ODI4/h	1.019	1.005–1.034	0.008			
OAI/h	1.021	0.990–1.052	0.183			
CAI/h	1.050	1.023–1.078	<0.001			
Lowest oxygen saturation	0.971	0.941–1.002	0.067			
Saturation <90%, %	1.011	1.000–1.021	0.040			
Mean saturation	0.883	0.786–0.992	0.036			

mRS, modified Rankin Scale; NIHSS, National institutes of health stroke scale; GCS, Glasgow coma scale; PAD, peripheral arterial disease; REI/h, Respiratory event index per hour; ODI4/h, arterial oxyhemoglobin saturation decreases of ≥4%; OAI/h, obstructive apnea index per hour; CAI/h, central apnea index per hour.

diabetes mellitus, cardiac insufficiency, chronic obstructive pulmonary disease (COPD), dyslipidemia, hypertension, atrial fibrillation, and ischemic heart disease. An earlier study of Parra et al. [13] showed that age was an independent factor related to

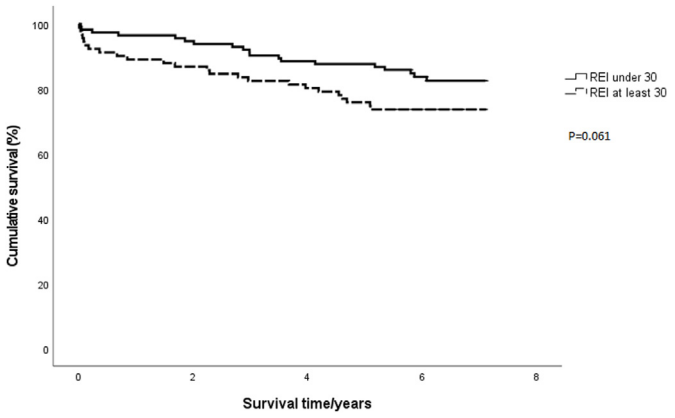

Fig. 1. Survival of sleep apnea patients having REI under 30 (n = 113) and patients having REI at least 30 (n = 91). Twenty-four of those 91 sleep apnea patients having REI at least 30 and 15 patients of those 95 sleep apnea patients having REI under 30 died during the follow-up. The difference is not significant (P = 0.061, log-rank test).

death and pointed out a 14% annual increase in mortality in patients with a first ever stroke or transient ischemic attack and sleep apnea. A previous study of Magdic et al. [43] was in line with our finding that the risk of dying after stroke was higher among men.

Surprisingly, smokers had lower mortality rate in our study. This may be explained by their younger age and lower prevalence of atrial fibrillation. Current smoking predicted death but was not an independent predictor. Nevertheless, those who suffered from a new ischemic event had more pack-years compared to those without a recurrent ischemic event.

The main causes of death in this study were cardiovascular or cerebrovascular, which accounted for two thirds of the deaths; this finding is in line with prior studies [2,13,14]. Almost one third of our patients died of ischemic heart disease. In accordance with the previous studies, our stroke patients' ischemic heart disease increased the risk for death [44–46]. Cancer was the second most common cause of death (14%) and every fifth of our patients died from other causes, which is in line with a Swedish study [14]. We had exact data about dates and underlying causes of death for all the deceased patients, similarly to the study by Sahlin et al. [14], where the causes of death were based on the Causes of Death Register at the Swedish National Board of Health and Welfare. The cardiovascular mortality was in line in a previous Spanish study where vascular disease accounted for 63.6% of deaths, cerebrovascular for 50%, other causes for 27%, and unknown cause for 9% of deaths in stroke or TIA patients [13].

In this study, every fifth of our patients died, and nine out of ten deceased patients had sleep apnea. Previous studies have reported similar [47], lower [2,13,22,30,40] or higher [14,31,48] mortality rates of stroke patients. This discrepancy could be due to differences in age, exclusion criteria, timing of sleep recordings and follow-up times. The quite good survival in our study may be partly due to intensive acute care of stroke patients and improvements in preventive treatment. Moreover, our low mortality rate is partly explained by effective secondary prevention and successful rehabilitation.

In this study, almost every fourth patient experienced a new ischemic event; of those, almost two thirds had a new ischemic stroke, one third had a myocardial infarction, and one fifth had a transient ischemic attack. We could not find a correlation between findings in cardiorespiratory polygraphy and new ischemic events, which is in line with one prior study [49]. Previous studies have shown recurrent ischemic event rates varying between 11.0 and 12.1% [2,40]. The median duration of time to a new ischemic event was 1.1 years in our study. Of those 21 patients who had CPAP -treatment, only one experienced a new ischemic event during the follow-up. In this study, sleep apnea was not a risk factor for recurrent vascular event after stroke, contrary to the prior studies which reported that after stroke or TIA, sleep apnea significantly increased the risk for recurrent stroke or TIA [22,50]. In addition, some studies pointed out that higher REI was associated with recurrent ischemic stroke [40,50].

In our study, those with PAD experienced more often a new ischemic event. PAD and NIHSS score were independent predictors of a recurrent ischemic event, PAD being the most powerful predictor in multivariate models. Our patients with PAD had over fourfold risk for the development of a new ischemic event, in line

Table 5
Univariable and multivariable Cox proportional hazard models for a recurrent ischemic event.

Variables at stroke onset	Univariable			Multivariable (Regression Method = Forward Stepwise)		
	HR	95% CI	P-value	HR	95% CI	P-value
Male	1.060	0.590–1.903	0.846			
Age	1.016	0.992–1.041	0.184			
Current smoking	0.873	0.451–1.689	0.687			
Pack years	1.015	1.000–1.030	0.047			
Snoring	1.003	0.561–1.793	0.991			
Rankin scale score	1.113	0.876–1.413	0.381			
NIHSS score	1.061	1.005–1.121	0.033	1.069	1.012–1.129	0.018
GCS score	0.825	0.652–1.046	0.112			
Hypertension	1.186	0.649–2.166	0.580			
Hypercholesterolemia	1,043	0.588–1.850	0.887			
Diabetes mellitus	1.788	0.944–3.386	0.074			
Coronary artery disease	1.868	1.023–3.410	0.042			
Atrial fibrillation	1.197	0.507–2.852	0.684			
PAD	3.914	1.391–11.010	0.010	4.624	1.620–13.198	0.004
REI/h	1.004	0.991–1.016	0.585			
ODI4/h	1.010	0.992–1.028	0.268			
OAI/h	0.984	0.947–1.024	0.431			
CAI/h	0.965	0.905–1.030	0.285			
Lowest oxygen saturation	0.984	0.949–1.021	0.400			
Saturation <90%, %	1.004	0.993–1.015	0.459			
Mean saturation	0.971	0.861–1.095	0.631			

mRS, modified Rankin Scale; NIHSS, National institutes of health stroke scale; GCS, Glasgow coma scale; PAD, peripheral arterial disease; REI/h, Respiratory event index per hour; ODI4/h, arterial oxyhemoglobin saturation decreases of ≥4%; OAI/h, obstructive apnea index per hour; CAI/h, central apnea index per hour.

Table 6
Univariable and multivariable Cox proportional hazard models of patients having REI/h >30 for death.

Variables at stroke onset	Univariable			Multivariable (Regression Method = Forward Stepwise)		
	HR	95% CI	P-value	HR	95% CI	P-value
Male	0.915	0.400–2.091	0.833			
Age	1.078	1.032–1.127	0.001	1.072	1.024–1.121	0.003
Current smoking	0.265	0.062–1.126	0.072			
Pack years	0.998	0.975–1.022	0.893			
Snoring	0.933	0.414–2.101	0.867			
Prestroke mRS score	1.385	1.036–1.852	0.028			
NIHSS score	1.073	1.005–1.145	0.035			
GCS score	0.674	0.549–0.826	<0.001	0.660	0.531–0.822	<0.001
Hypercholesterolemia	2.119	0.906–4.955	0.083			
Diabetes mellitus	3.171	1.418–7.087	0.005			
Coronary artery disease	1.659	0.736–3.736	0.222			
Atrial fibrillation	2.513	1.074–5.880	0.034			
PAD	1.626	0.382–6.925	0.511			
ODI4/h	1.019	0.999–1.039	0.066			
OAI/h	0.996	0.957–1.037	0.852			
CAI/h	1.043	1.011–1.075	0.007			
Lowest oxygen saturation	0.975	0.924–1.028	0.343			
Saturation <90%, %	0.999	0.984–1.014	0.875			
Mean saturation	0.996	0.845–1.174	0.961			

mRS, modified Rankin Scale; NIHSS, National institutes of health stroke scale; GCS, Glasgow coma scale; PAD, peripheral arterial disease; REI/h, Respiratory event index per hour; ODI4/h, arterial oxyhemoglobin saturation decreases of ≥4%; OAI/h, obstructive apnea index per hour; CAI/h, central apnea index per hour.

with most previous studies [51,52] but contradictory to some [53]. Additionally, in this study, those with higher NIHSS scores were at risk for recurrent ischemic event. Contrary to this study, previous studies could not show a correlation between functional outcomes and recurrent ischemia [22,40,50].

We had a median follow-up time of six years, similarly to Bassetti et al. [2]. Sahlin et al. [14] reported the longest follow-up time (10 years) among stroke patients who also underwent evaluation of sleep apnea. Other prospective studies have investigated the relationship between stroke and mortality after a mean of 6 to 24 months [13,22,30,31,40,47]. Similarly to our study, no patients were lost to follow-up in four previous studies [13,14,30,48] contrary to three prior studies [2,31,47], where the loss to follow-up was 6–13% of the study patients.

In our study, CPAP treatment seemed to protect from a new ischemic event, but due to the low number of CPAP users, it needs to be confirmed in future larger studies. Prior studies have reported controversial results of the ability of CPAP treatment to lower the burden of serious outcomes after stroke [2,54–56]. Improved long-term survival with CPAP in moderate to severe OSA has been demonstrated in a prior study by Parra et al. [57]. In a Spanish study, stroke patients with AHI ≥20/h and non-compliant to CPAP showed an increased risk of death and incidence of nonfatal cardiovascular events, especially new ischemic strokes [48]. On the other hand, in two previous studies there was no significant effect of CPAP-treatment on all-cause mortality after stroke [2,54].

4.1. Limitations and strengths

The strengths of our study were the prospective real-life design, wide age range from 22 to 95 years, high proportion of females, and fairly large sample size compared to other studies [2,13,14,31,40]. To the best of our knowledge, this is the largest sample size of European acute ischemic stroke patients, who underwent cardiorespiratory polygraphy on admission and were followed over five years. In this study, no one was lost to follow-up. All deceased patients had verified causes of death. Our analyses of causes of death were based on official death statistics and Oulu University Hospital records. Official death statistics are unique in Nordic countries.

This study was cross-sectional in nature, and we are unable to draw any conclusions concerning sleep apnea severity before stroke onset. Our study results may only represent the situation in Finland. We evaluated stroke severity on admission only by using the NIHSS score. We used a portable device to screen for sleep apnea, even though polysomnography is the standard diagnostic test for sleep apnea. The most common cause of death was ischemic heart disease, and higher CAI predicted higher mortality rate. Unfortunately, we did not have any information on left ventricular ejection fraction. It would be of interest since decreased ejection fraction could predispose to central apneas irrespective of stroke.

4.2. Conclusions

After ischemic stroke, every fifth patient died during the six-year follow-up. The deceased patients were older, had more often atrial fibrillation, ischemic heart disease, hypercholesterolemia, or diabetes mellitus. One third of our patients died of ischemic heart disease. Those who died had higher CAI and T90 and lower min SaO_2. Every fourth of our patients had a new ischemic event during the follow-up time.

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