Jaana Huhtakangas

EVOLUTION OF OBSTRUCTIVE SLEEP APNEA AFTER ISCHEMIC STROKE
JAANA HUHTAKANGAS

EVOLUTION OF OBSTRUCTIVE SLEEP APNEA AFTER ISCHEMIC STROKE

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Abstract
In Finland, the costs of stroke are approximately 1.1 billion euros annually due to long disability and hospitalization episodes. Sleep apnea is a risk factor for stroke. The prevalence of sleep apnea among stroke patients is unknown because sleep recording is not usually performed on stroke patients. There are no previous studies investigating the association of thrombolysis on the prognosis of sleep apnea. The relation between sleep apnea and cardiovascular events is still unclear.

In this prospective, observational study, I recruited voluntary, consecutive ischemic stroke patients over the age of 18 years who were or were not eligible for thrombolysis treatment. The investigators did not affect the treatment and patients were not randomized to thrombolysis. The final analysis included 204 patients; of these, 110 underwent thrombolysis therapy and 94 were treated without thrombolysis. Cardiorespiratory polygraphy was carried out with a portable three-channel device (ApneaLinkPlus™, Resmed, Sydney, Australia) at the ward within 48 hours after the onset of stroke symptoms. The cardiorespiratory polygraphy was repeated at home after a six-month follow-up.

Both automatic scoring and manual scoring pointed out excellent agreement in arterial oxyhemoglobin decrease of > 4% (ODI4), lowest arterial oxyhemoglobin saturation (SaO2) or percentage of time spent below 90 percent saturation. The automated scoring underestimated the severity of sleep apnea, recognized poorly the type of event, and missed 18.6% of sleep apnea diagnoses.

The total prevalence of sleep apnea in this study was 91.2% on admission to hospital. The stroke patients treated with thrombolysis had more, and more severe sleep apnea in the first sleep recording compared to those without thrombolysis therapy. After follow-up, the prevalence of sleep apnea still remained high, and sleep apnea was aggravated in two thirds of the stroke patients. The study patients without thrombolysis treatment had six-fold higher risk for incident sleep apnea after the follow-up. The stroke patients with thrombolysis therapy and visible stroke on CT had more nocturnal hypoxemia and higher obstructive apnea index than the patients without stroke lesion on follow-up CT 24 hours after thrombolysis treatment. The larger the ischemic stroke volume, the greater the time spent with saturation below 90%.

Keywords: cardiorespiratory polygraphy, sleep apnea, stroke, thrombolysis, volume of ischemic stroke
Huhtakangas, Jaana, Uniapnean evoluutio aivoinfarktin jälkeen.
Oulun yliopiston tutkijakoulu; Oulun yliopisto, Lääketieteellinen tiedekunta; Oulun yliopistollinen sairaala; Turun yliopisto

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**Tiivistelmä**


Sekä automaattitulos että manuaalitesti arvioituun unirekisteröintitulos olivat erittäin yhteensä, kun arvion kohteena olivat hapikyllästeisyyden neljän prosenttiyksikön suuruiset pudotukset tuntia kohti, matalin veren hapikyllästeisyys tai alle 90 % hapikyllästeisyden osuus yössä. Automaattianalyysi aikiuniapnean vaikeuden, havaitsi huonosti hengityskatoken tyypin eikä löytänyt 18,6 prosenttia uniaipneadiagnooseista.

Uniapnean esiintyvyys koko aineistossa oli sairaalaan tullessa 91,2 %. Liuotushoidetuilla potilailta todettiin ensimmäisessä rekisteröinnissä enemmän uniapneaa ja se oli vaikeampaa kuin ei-liuotushoidetuilla. Seurannassa uniapnean määrä pysyi edelleen korkeana ja uniapnea vaikeutui kahdella potilaalla kolmesta. Liuotushoidon soveltumattomilla aivoinfarktipotilailta todettiin liuotushoidon saaneisiin verrattuna kuusinkertainen riski sairastua uniapneaan puolen vuoden aikana. Liuotushoidetuilla aivoinfarktipotilailta, joilla oli infarktimutostun kuvantamistutkimuksissa, oli yliollistat valtimoveren hapikyllästeisyyden huonomemista ja ylhäengitysteenähtävyydestä kohtuutuneita johtuvia hapikyllästeisiksi muita mitattavissa 24 tuntia liuotushoidon jälkeen. Mitä suurempi aivoinfarktin tilavuus, sitä suuremmann osuuden yöstä veren hapikyllästeisyyys oli alle 90 %.

**Asiasanat:** aivoinfarkti, aivoinfarktin koko, liuotushoito, uniapnea, yöpolygrafia
To my Family
Acknowledgements

The work was carried out at Oulu University Hospital during 2013–2016. My deepest thanks belong to my supervisor, Professor Tarja Saarersranta, MD, PhD, who discovered the ideas for my thesis and spurred me to interdisciplinary work between the departments of neurology and pulmonology. Tarja always had time to supervise my work, give me good ideas and advice, and she always encouraged me during these years and believed in my possibilities to complete my thesis. I deeply appreciate Tarja’s passion for scientific work and I wonder how terrified she was when I said “good enough is enough”. I express my gratitude to my other supervisor, Juha Huhtakangas, MD, PhD, for his constant support, endless discussions about how meaningful the research work is, and reminding me of reaching the goal. The statistical analyses would never have been ready without Risto Bloigu, M.Sc., who had the strength to teach me over and over again. Our conversations about statistics and beyond it were pleasant. I am much obliged to Professor Kari Majamaa for overseeing my work and for his support towards it. I express my gratitude to Respiratory Medicine Unit. The co-author of one original article deserves special mention. Docent Michaela K. Bode, MD, PhD, did the hard work with stroke volume measurements and gave me valuable knowledge and instructions. My follow-up group members, Professor Riitta Kaarteenaho, MD, PhD, docent Mikko Kärppä MD, PhD, and docent Ulla Anttalainen MD, PhD, gave me good advice, critical comments and encouragement throughout this process. The official reviewers, Professor Eeva Lindberg, MD, PhD, and Docent Juha Puustinen, MD, PhD, kindly appraised this thesis and offered constructive comments.

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My lovely children Teemu, Moona and Joonas asked me many times when the tables would be ready, and Joonas suspected that my writing process was a never-ending story. The wonderful memories from Finnish baseball and volleyball courts, when I have been screaming at their games, are still going on. I am proud that our children have made their own career plans, but they have also listened to their dull, caring mum telling them how important it is to have a plan B in your life.

My husband Juha has had many roles over the past years. It seems that Ostrobothnian and Karelian persons are well matched and our hearts beat as one. It is now time to move forward. Life is full of surprises and how you spend your time
shows where your heart is. Love carried us forward and I am still beloved by and in love with you.

_Oulu, October 2019_  

_Jaana Huhtakangas_
### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AASM</td>
<td>American Academy of Sleep Medicine</td>
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<tr>
<td>AHA</td>
<td>American Heart Association</td>
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<td>ASA</td>
<td>American Stroke Association</td>
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<tr>
<td>AHI</td>
<td>apnea-hypopnea index</td>
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<tr>
<td>ANOVA</td>
<td>analysis of variance</td>
</tr>
<tr>
<td>Auto-CPAP</td>
<td>autotitrating continuous positive airway pressure</td>
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<td>BI</td>
<td>Barthel Index</td>
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<tr>
<td>BMI</td>
<td>body mass index</td>
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<tr>
<td>CAI</td>
<td>central apnea index</td>
</tr>
<tr>
<td>CT</td>
<td>computed tomography</td>
</tr>
<tr>
<td>ICC</td>
<td>interclass correlation coefficient</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>CPAP</td>
<td>continuous positive airway pressure</td>
</tr>
<tr>
<td>ESS</td>
<td>Epworth Sleepiness Scale</td>
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<tr>
<td>ESUS</td>
<td>embolic strokes of undetermined source</td>
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<tr>
<td>GCS</td>
<td>Glasgow Coma Scale</td>
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<tr>
<td>MAD</td>
<td>mandibular advancement device</td>
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<tr>
<td>MAI</td>
<td>mixed apnea index</td>
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<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
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<tr>
<td>mRS</td>
<td>modified Rankin scale</td>
</tr>
<tr>
<td>NIHSS</td>
<td>National Institutes of Health Stroke Scale</td>
</tr>
<tr>
<td>OAI</td>
<td>obstructive apnea index</td>
</tr>
<tr>
<td>ODI</td>
<td>oxygen desaturation index</td>
</tr>
<tr>
<td>ODI4</td>
<td>arterial oxyhemoglobin decrease of ≥ 4%</td>
</tr>
<tr>
<td>OR</td>
<td>odds ratio</td>
</tr>
<tr>
<td>PAD</td>
<td>peripheral arterial disease</td>
</tr>
<tr>
<td>PSG</td>
<td>polysomnography</td>
</tr>
<tr>
<td>REI</td>
<td>respiratory event index</td>
</tr>
<tr>
<td>SaO$_2$</td>
<td>arterial oxyhemoglobin saturation</td>
</tr>
<tr>
<td>SD</td>
<td>standard deviation</td>
</tr>
<tr>
<td>SDB</td>
<td>sleep-disordered breathing</td>
</tr>
<tr>
<td>SIRS</td>
<td>systemic inflammatory response syndrome</td>
</tr>
<tr>
<td>SPSS</td>
<td>Statistical Package for the Social Sciences</td>
</tr>
<tr>
<td>SSS</td>
<td>Scandinavian Stroke Scale</td>
</tr>
<tr>
<td>TIA</td>
<td>transient ischemic attack</td>
</tr>
<tr>
<td>tPA</td>
<td>tissue plasminogen activator</td>
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</table>
List of original publications

The present thesis is based on the following articles, which are referred to in the text by their Roman numerals.


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1 Introduction

The prevalence of sleep apnea, encompassing both obstructive and central sleep apnea, ranges from 52.0% to 86% after stroke worldwide depending on the definition, diagnostic method, and timing of sleep study (Bassetti & Aldrich, 1999; Ifergane et al., 2016; Seiler et al., 2019; Tosun, Köktürk, Karatas, Çiftçi, & Sepici, 2008; Turkington, Bamford, Wanklyn, & Elliott, 2002; Väyrynen et al., 2014). In general population, the prevalence of sleep apnea among middle-aged men is 14% and among women, 5% (Peppard et al., 2013; Young et al., 1993). Studies investigating sleep apnea in stroke patients have not reported either the possible thrombolysis treatment of stroke or evaluated the effect of thrombolytic treatment on sleep apnea.

Stroke is the second leading cause of death worldwide (Lopez, Mathers, Ezzati, Jamison, & Murray, 2006) and the fourth in Finland (Cause of death statistics of statistics in Finland, 2018). Thrombolysis treatment attenuates the deleterious consequences of stroke (Clark et al., 1999; Hacke et al., 1995; Hacke et al., 1998; Hacke et al., 2008; Marler, 1995), but the influence on sleep apnea has been unknown. Alteplase treatment may exacerbate inflammation and neuronal death (Macrez et al., 2011). The prevalence of sleep apnea among stroke patients undergoing thrombolysis has been unknown, as have the possible differences in type and severity of sleep apnea.

Sleep apnea is a remarkable health problem worldwide, also in Finland, increasing health-care costs and absence from work already before diagnosis (AlGhanim, Comondore, Fleetham, Marra, & Ayas, 2008). The annual health-care costs of stroke are estimated to be over one billion euros in Finland (Meretoja et al., 2011). Patients with stroke and sleep apnea are at high risk for protracted hospitalization, reduced recovery, cardiovascular seizures, and death (Bassetti, Milanova, & Gugger, 2006; Parra et al., 2011; Turkington, Allgar, Bamford, Wanklyn, & Elliott, 2004). Untreated sleep apnea leads to impaired quality of sleep, daytime tiredness, reduced quality of life, increased comorbidities, and the risk of a new ischemic event and mortality (Aaronson et al., 2015; Martinez-Garcia, Galiano-Blancart, Soler-Cataluna, Cabero-Salt, & Roman-Sanchez, 2006; Turkington et al., 2004; Wolk, Kara, & Somers, 2003; Yaggi & Mohsenin, 2004). Sleep apnea is an independent risk factor for stroke (Wessendorf, Teschner, Wang, Konietzko, & Thilmann, 2000; Yaggi & Mohsenin, 2004), and stroke itself may predispose to sleep apnea (Loke, Brown, Kwok, Niruban, & Myint, 2012). Sleep apnea may elevate the risk for cardiovascular diseases by recurring upper airway
closing, which causes nocturnal hypoxia, increased sympathetic activation, and systemic inflammation (Chami et al., 2013; Leung, Comondore, Ryan, & Stevens, 2012). Respiratory events with repetitive hypoxemia produce several hemodynamic, coagulatory, endothelial, neural, metabolic, and inflammatory alterations, linking sleep apnea with stroke (Bassetti et al., 2006; T. D. Bradley & Floras, 2009; Reggiani et al., 2012). The association between sleep apnea and cardiovascular events is still unclear, but intermittent hypoxemia causes oxidative stress and systemic inflammation, which may cause progressive atherosclerosis and lead to stroke (Ifergane et al., 2016).

The influence of ischemic stroke volume on the prevalence or severity of sleep apnea in patients treated with thrombolysis has been an unexplored research area. The central regulation of respiration may be modified by the stroke lesion, resulting in sleep apnea or causing weakness in respiratory muscles (Rowat, Dennis, & Wardlaw, 2006). Desaturation of oxygen level may affect 20% of stroke patients after a few hours, and two days post stroke, almost two-thirds may develop hypoxia (Rowat et al., 2006). Sleep apnea patients with oxygen saturation below 90% for more than 10% of their sleep time were at almost twofold higher risk for stroke than those without a drop in saturation (Stone et al., 2016). The independent predictors of poor functional outcome of stroke patients were lower scores on the Scandinavian Stroke Scale (SSS), expressing stroke severity on hospital admission, and higher apnea-hypopnea index (AHI) assessed three months after stroke, but after six months, the only independent predictor for poor functional outcome was SSS score on admission (Yan-fang & Yu-ping, 2009). The stroke patients with more than ten events of oxygen hemoglobin desaturation per hour had significantly worse functional outcome evaluated by Barthel Index (BI) than those without oxygen desaturation after three months and after one year (Good, Henkle, Gelber, Welsh, & Verhulst, 1996). In the study by Bruno and coworkers (Bruno, Shah, Akinwuntan, Close, & Switzer, 2013), the simplified modified Rankin Scale questionnaire reflecting the clinical outcome among stroke patients with lacunar and non-lacunar strokes had a high correlation with stroke size three to twelve months after the stroke.

Daytime sleepiness is unusual among stroke patients with sleep apnea (Arzt et al., 2010; Kaneko et al., 2003) and the diagnosis of sleep apnea is mainly based on sleep study. The need for sleep studies is growing, and although polysomnography (PSG) is the gold standard for the diagnosis of sleep apnea (Epstein et al., 2009), it is laborious, expensive, with limited availability, and impractical in the acute care setting compared to cardiorespiratory polygraphy.

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Screening of sleep apnea is uncommon in stroke patients, and only American Heart Association (AHA) /American Stroke Association (ASA) guidelines have recommended sleep apnea screening among these patients (Kernan et al., 2014), although with PSG. Sleep apnea screening by unattended sleep study within three days after stroke or transient ischemic attack (TIA) has shown good analyzability in at least 80% of cases (Boulos et al., 2017; Broadley et al., 2007; Kepplinger et al., 2013; Martinez-Garcia et al., 2006; Parra et al., 2000). In several countries, unattended, portable devices have been validated for diagnostic use or for patients without comorbidity (Bloom et al., 2009; Launois, Pépin, & Lévy, 2007). However, AHI in cardiorespiratory polygraphy is on average 20–30% lower in comparison to PSG (Escourrou et al., 2015; Hedner et al., 2011). Furthermore, it is still unclear whether the automatic analysis of cardiorespiratory polygraphy is exact enough for the sleep apnea screening of stroke patients. In the acute phase of ischemic stroke, sleep apnea screening with cardiorespiratory polygraphy may be a useful tool to identify patients with comorbid sleep apnea, facilitating faster treatment, and possibly, better recovery. However, it remains unclear whether it would be wise to perform cardiorespiratory polygraphy in the acute phase of stroke or later, considering the spontaneous improvement of sleep apnea after stroke (Harbison, Ford, James, & Gibson, 2002; Parra et al., 2000).

This observational, prospective study provides information of the feasibility of cardiorespiratory polygraphy in the screening of sleep apnea among patients with acute ischemic stroke. Of importance, the study increases the understanding of the pathophysiology and the effect of thrombolysis on post-stroke sleep apnea, and may provide elements for phenotyping of stroke, thus enabling personalized treatment of comorbid sleep apnea in stroke patients.
2 Review of the literature

2.1 Sleep apnea

2.1.1 Definitions of obstructive and central sleep apnea

It was not until 1966 that Gastaut and coworkers (Gastaut, Tassinari, & Duron, 1966) first discovered obstructive sleep apnea (OSA) in obese people and showed periodic airway obstruction with repetitive arousals as well as a connection between sleep-related airway obstruction, sleep fragmentation, and daytime sleepiness. In OSA, the upper airway collapses during sleep, causing repetitive cessation of inspiratory airflow with the presence of respiratory effort. When recurrent obstructive apnea events produce sleep fragmentation and daytime sleepiness it is called obstructive sleep apnea syndrome (OSAS), which is the focus of my thesis. In central sleep apnea, there is absence of airflow and no breathing efforts, all this leading to insufficient ventilation and disturbances in gas exchange. Sleep-disordered breathing (SDB) includes a wide array of nocturnal breathing disorders from simple snoring, airway narrowing, and periods of hypoventilation or hypopnea to full airway closing or apnea, i.e. OSA.

2.1.2 Definition of apneas

The American Academy of Sleep Medicine scoring rules (Berry et al., 2012) are shown in Table 1. Apnea, defined as cessation of airflow accompanied by a decrease in arterial oxyhemoglobin saturation, usually ends in arousals. Obstructive apnea consists of at least ten-second-long repetitive collapses of the airway and arousals, while central sleep apnea is without airflow and breathing efforts because the breathing is abnormal due to malfunction of central regulation. Hypopnea is defined as partial decrease in airflow also lasting at least ten seconds with diminished respiratory effort. During sleep, patients with obstructive sleep apnea may have either obstructive and central apneas or hypopneas during one night. The mainly dominant type of apnea (over 50% of all apneas) determines the diagnosis of sleep apnea, i.e. obstructive or central sleep apnea. The most common type of breathing disorder is obstructive sleep apnea. The number of apneas and hypopneas per hour is expressed as apnea-hypopnea index (AHI) or as respiratory event index.
(REI). The REI is used solely when reporting the results of cardiorespiratory polygraphies.

Table 1. American Academy of Sleep Medicine (AASM 2012) scoring rules of apneas and hypopneas, when the nasal cannula connected to pressure transducer is used to monitor airflow.

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Apnea</td>
<td>Drop of signal by ≥ 90% of pre-event baseline and the drop continues ≥ 10 seconds</td>
</tr>
<tr>
<td>Obstructive apnea</td>
<td>Apnea criteria and either continued or increased inspiratory breathing effort during absent airflow</td>
</tr>
<tr>
<td>Central apnea</td>
<td>Apnea criteria and no inspiratory breathing efforts during absent airflow</td>
</tr>
<tr>
<td>Mixed apnea</td>
<td>Apnea criteria and no inspiratory breathing effort in the beginning of the event, then followed by inspiratory breathing effort again</td>
</tr>
<tr>
<td>Hypopnea</td>
<td>Drop of signal by ≥ 30 % of pre-event baseline and the drop continues ≥ 10 seconds and oxygen desaturation is ≥ 3 % from pre-event baseline or the event is connected with an arousal</td>
</tr>
<tr>
<td>Unclassified apnea</td>
<td>Oronasal thermal airflow sensor and finger probe pulse oximeter are not functioning</td>
</tr>
</tbody>
</table>

2.1.3 Pathophysiology and consequences of obstructive sleep apnea

Patients with sleep apnea have hardly any problems with their breathing or airway muscle tonus while awake. The human pharyngeal dilator muscles are not tightly adhered to skeletal structures as only the upper part of muscle is fixed to bone and the lower part to cartilage. Numerous muscles coordinate the opening and dilation of the oropharynx and when someone falls asleep, the pharyngeal muscles relax. This relaxation of the muscles may cause partial or total airway closure in anatomically narrowed upper airways. Both functional abnormalities that promote airway collapse and anatomic abnormalities affecting the pharyngeal space are reasons for upper airway obstruction. Upper airway narrowing leads to recurrent episodes of apneas and hypopneas and they end up with arousals as well as recovery of upper airway muscles tonic activity. The apnea generally ends in arousal, snoring, or deeper breathing before the upper airways close again. All these arousals and apnea episodes increase sympathetic nervous system activity, disturb sleep, and may cause daytime sleepiness. The apnea is often accompanied by a decrease in arterial oxygen level and leads to transient arousals from sleep. During apnea or hypopnea, the carbon dioxide retention increases and leads to increasing breathing efforts, which cause higher intrathoracic pressure (Dempsey, Veasey, Morgan, & O'Donnell, 2010).
The recurrent hypoxemia induces oxidative stress and hemodynamic, coagulator, endothelial, metabolic, and inflammatory consequences in sleep apnea. One important metabolic aspect is insulin resistance and dysregulation of glucose. Several studies have reported a positive association between OSA and insulin resistance (Ip et al., 2002; Kendzerska, Gershon, Hawker, Leung, Tomlinson, 2014; Mokhlesi, Ham, & Gozal, 2016; Punjabi et al., 2002). A study from Sweden pointed out that OSA is independently associated with development of insulin resistance, with oxygen desaturation index (ODI) playing a major role (Lindberg et al., 2012). In the Sleep-Heart-Health study among OSA patients with AHI ≥ 15/h, the OR was 1.46 for fasting glucose after adjustment for age, gender, waist circumference, BMI, race, and smoking (Punjabi et al., 2004). In the large European Sleep Apnoea Cohort Study, the prevalence of type 2 diabetes mellitus was higher in patients with severe OSA compared to those without OSA (28.9% versus 6.6%).

Oxidative stress and systemic inflammation have been shown to associate with sleep apnea, and increased levels of inflammatory biomarkers such as C-reactive protein, interleukin-6, tumor necrosis factor-α in blood and intracellular reactive oxygen species have been found in the patients (Dyugovskaya, Lavié, & Lavié, 2002; Ryan, Taylor, & McNicholas, 2005; Shamsuzzaman et al., 2002; Yokoe et al., 2003).

Sleep apnea promotes thrombosis by increasing platelet activation and aggregation (Eisensehr et al., 1998; Robinson, Pepperell, Segal, Davies, & Stradling, 2004; von Kanel, Loredo, Ancoli-Israel, & Dimsdale, 2006) and by raising fibrinogen levels (Dziewas et al., 2007; Wessendorf et al., 2000) by decreasing fibrinolytic activity (Rangemark, Hedner, Carlson, Gleerup, & Winther, 1995).

Endothelial cell apoptosis may enhance coagulator activity among patients suffering from sleep apnea (El Solh, Akinnusi, Baddoura, & Mankowski, 2007) and endothelial dysfunction may promote atherosclerosis (Price & Loscalzo, 1999). It has been pointed out that patients with obstructive sleep apnea experience vasoconstriction during apnea (Anand, Remsburg-Sailor, Launois, & Weiss, 2001; Imadojemu, Gleeson, Gray, Sinoway, & Leuenberger, 2002; C. P. O'Donnell, Allan, Atkinson, & Schwartz, 2002). The arousals from sleep and sleep distribution are the reasons behind increased sympathetic nerve activity and blood pressure (Morgan et al., 1996); in addition, they enhance the pressure effects of hypoxemia (Morgan et al., 1998).

As mentioned above, obstructive apnea induces intermittent hypoxia and hypercapnia leading to disturbance in autonomic and hemodynamic responses such
as sympathetic activation, oxidative stress, endothelial dysfunction and vasoconstriction, all these factors connecting obstructive sleep apnea to cardiovascular diseases (Dempsey et al., 2010; Somers, Mark, Zavala, & Abboud, 1989). The Wisconsin Sleep Cohort with a longitudinal study design reported convincing results for association between OSA and hypertension, and this study showed that OSA patients with AHI over 5 per hour had elevated odds ratios and dose response between OSA severity and hypertension (Peppard, Young, Palta, & Skatrud, 2000). Contrary to this previous study, the Sleep Heart Health Study with prospective study design and larger sample size could not find a dose-response relationship between AHI and incident hypertension (O’Connor et al., 2009).

Sleep apnea induces changes in cardiovascular structure and function by oxidative stress, inflammation, and neurohumoral activation (Dempsey et al., 2010). Sympathetic nervous system activation increases in sleep apnea patients and sympathetic nerve activity is increased during sleep, but also when patients are awake (Dempsey et al., 2010). During apneas, the nocturnal hypoxemia (saturation below 90%) induces oxidative stress and increases endothelin-1 induced vasoconstriction (Dempsey et al., 2010). Sleep apnea may reduce nitric oxide levels, and this is harmful because nitric oxide inhibits inflammation and thrombosis (Dempsey et al., 2010). The reactive oxygen species initiate an inflammatory response causing vascular dysfunction, and sleep apnea patients may have elevated levels of C-reactive protein and inflammatory cytokines (Dempsey et al., 2010). Inflammation may be the major link between activated sympathetic nervous system and vascular dysfunction in sleep apnea patients (Dempsey et al., 2010). Sympathetic activity increases inflammation in numerous organs and vascular beds (Dempsey et al., 2010). Hypoxia increases renal sympathetic nerve activity, and thereby, activity of the renin-angiotensin-aldosterone system (Dempsey et al., 2010). Both oxidative stress and inflammation increase mineralocorticoid receptor stimulation, causing endothelial dysfunction and vascular remodeling (Dempsey et al., 2010). The degree of hypoxemia is important in cerebral circulation and the changes in vascular regulation may harm brain tissue perfusion, because apnea first increases cerebral blood flow, and after apnea, hyperventilation decreases the cerebral flow to brain tissue (Balfors & Franklin, 1994). The normal reduction in blood pressure during sleep vanishes during apnea, leading to worse vascular function again (Dempsey et al., 2010).

The pathophysiological connections between OSA and stroke are related to the factors mentioned above and notably, to inflammation or possible thrombolysis treatment. Obstructive sleep apnea has been pointed out to associate with increased
levels of inflammatory and coagulation factors (Ifergane et al., 2016). Successful thrombolysis treatment may predispose or lead to systemic inflammatory response syndrome (SIRS), which is related to decreased short-time functional outcome (Boehme et al., 2013). Thrombolysis treatment of stroke by tPA may favor either excitotoxic or ischemic neuronal death (Macrez et al., 2011) and there may be reperfusion damage, large edema, or intracerebral hemorrhage (Broderick, 1997; Marler, 1995). The recovery from stroke may be reduced because of intracerebral hematoma followed by tPA (Hacke et al., 1995).

2.2 Prevalence of sleep apnea

2.2.1 Epidemiology

In general population, the prevalence of sleep apnea is estimated to be 14% for men and 5% for women (Peppard et al., 2013). It is estimated that at least 4% of men and 2% of women suffer from symptoms of sleep apnea (Bixler et al., 2001; Gislason, Almqvist, Eriksson, Taube, & Boman, 1988; Young et al., 1993). The occurrence of sleep apnea is highest in middle age, in the age group between 40 and 65 years (Partinen & Hublin, 2005), and moderate or severe sleep apnea is present in 17% of middle-aged men and in 9% of women (Peppard et al., 2013). The incidence of sleep apnea has been growing in past years, especially in Western countries where it has become a healthcare burden, but sleep apnea is still underdiagnosed, partly because patients are unaware of snoring and apneas (Young et al., 1993). The increasing overweight problem (Punjabi, 2008; Young, Peppard, & Gottlieb, 2002) and partly, awareness of sleep apnea explain the high rates of sleep apnea prevalence. Convincing data on the heredity of sleep apnea are still lacking.

A large European cohort with 6,555 OSA patients studied four clinical phenotypes (excessive daytime sleepiness, insomnia, no excessive sleepiness or insomnia, excessive daytime sleepiness and insomnia) with respect to occurrence, phenotypes’ association with comorbidity and compliance to CPAP therapy (Saaresranta et al., 2016). In that study, the researchers pointed out that more than half of the OSA patients had insomnia phenotype, which had more comorbidity than other phenotypes, while excessive daytime sleepiness phenotype had better CPAP usage than other phenotypes (Saaresranta et al., 2016). Similar findings have been reported in other cohorts as well (Eysteinsdottir et al., 2017; Pien et al.,
The phenotypes of OSA may be based on the physical appearance or living entity such as craniofacial structure, sleepiness, obesity, upper airway control, or control of ventilation (Riha, Gislason, & Diefenbach, 2009). In the study of Eckert and coworkers (Eckert, White, Jordan, Malhotra, & Wellman, 2013), the phenotypes were divided based on low genioglossus muscle activity, deviant chemoreflex response to carbon dioxide levels, and low respiratory arousal threshold. This phenotyping raises the possibility for personalized treatment of sleep apnea because oropharyngeal muscle training (Guimaraes, Drager, Genta, Marcondes, & Lorenzi-Filho, 2009) may help to increase muscle activity and oxygen therapy can improve chemoreflex response (Wellman et al., 2008), and sedatives may alter low arousal threshold (Carter et al., 2016).

### 2.2.2 Prevalence, type and severity of sleep apnea in acute phase of stroke

Stroke patients have four- to six-fold risk for OSA (Bassetti et al., 2006). The sleep apnea prevalence among stroke patients has been estimated and different AHI cut-off points have been used for the diagnosis of sleep apnea as shown in Tables 2–7. The sleep apnea criterion of AHI ≥ 5/h was widely used (Boulos et al., 2017; Bravata et al., 2017; Ifergane et al., 2016; Tosun et al., 2008), while some studies have used AHI ≥ 10/h (Bassetti & Aldrich, 1999; Iranzo, Santamaria, Berenguer, Sánchez, & Chamorro, 2002) or AHI ≥ 15/h (Patel et al., 2018) as the diagnostic cut-off point of sleep apnea. Regardless of AHI per hour, sleep apnea prevalence among stroke patients has been between 62.5 and 86% (Bassetti & Aldrich, 1999; Dyken, Somers, Yamada, Ren, & Zimmerman, 1996; Ifergane et al., 2016; Mohsenin & Valor, 1995; Seiler et al., 2019; Tosun et al., 2008), and if the sleep apnea was defined as AHI ≥ 5 per hour, the prevalence rates varied from 73.7 to 86% (Ifergane et al., 2016; Tosun et al., 2008). Obstructive sleep apnea is more common than central sleep apnea in stroke patients (Bravata et al., 2017). Central sleep apnea is more common among stroke patients than in cases without stroke (Brown, McDermott et al., 2014; Siccoli, Valko, Hermann, & Bassetti, 2008).
Table 2. Unattended sleep study within seven days after stroke.

<p>| Author          | Diagnosis          | Timing of sleep study after stroke, mean (d^\text{7}) | Unattended polygraphy, setting: ICU\textsuperscript{10}, ward, sleep laboratory, rehabilitation unit, home | Study design | Subjects (n), male (m) | Demographics: mean age (y\textsuperscript{13}), BMI\textsuperscript{19} (kg/m(^2)), neck circumference (cm) | Characteristics of SDB and stroke: mean AHI\textsuperscript{1}, ESS\textsuperscript{8}, mRS\textsuperscript{12}, BI\textsuperscript{3}, CS\textsuperscript{3}, SSS\textsuperscript{16}, NIHSS\textsuperscript{13} | Sleep apnea prevalence; CPAP\textsuperscript{2,6} initiation | Comments |
|-----------------|--------------------|------------------------------------------------------|-------------------------------------------------------------------------------------------------|-------------|------------------------|------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|------------------|
| Fisse et al., 2017 | Ischemic stroke | Within 72h Yes ICU, ward | Prospective, observational n = 142, m 65.5% mean 64 y, BMI 26.2 | n = 142, m 65.5% | 64 y, m 65.5% | mRS 3, NIHSS 5.8 | AHI ≥ 10 in 86/59% |                     |
| Ifergane et al., 2016 | Acute stroke | Within 48h No, WatchPat peripheral arterial tonometry: pulse oximetry and actigraphy ICU, ward | Prospective, consecutive n = 43, m 30.2% 66.1 y, BMI 28.2 | n = 43, m 30.2% | 66.1 y, m 30.2% | median AHI 14.3, mRS 0, NIHSS 4 | AHI ≥ 15 in 51%, AHI ≥ 30 in 32.5% |                     |
| Kepplinger et al., 2013 | Acute ischemic stroke, TIA\textsuperscript{17} | 1–3.3 d Yes ICU, ward | Prospective, consecutive n = 61, m 44% 65.6 y, BMI 27.2 | n = 61, m 44% | 65.6 y, m 44% | median AHI 20, AHI ≥ 5 in 91%; median mRS 1, CPAP 8/14.8% | Deaths 1/1.6% within 6 m\textsuperscript{11} |                     |</p>
<table>
<thead>
<tr>
<th>Author</th>
<th>Diagnosis</th>
<th>Timing of sleep study after stroke, mean h, d^T</th>
<th>Unattended polygraphy, setting: ICU^15, ward, sleep laboratory, rehabilitation unit, home</th>
<th>Study design</th>
<th>Subjects (n), mean age (y), BMI (kg/m²), neck circumference (cm)</th>
<th>Demographics: mean age (y)^16, BMI (kg/m²), neck circumference (cm)</th>
<th>Characteristics of SDB and stroke: mean AHI^1, ESS^4, mRS^7, BI^2, CS^5, SSS^10, NIHSS^3</th>
<th>Sleep apnea prevalence; CPAP^2^6 initiation</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parra et al., 2011</td>
<td>Stroke</td>
<td>48–72 h Yes ICU, ward Prospective, consecutive</td>
<td>n = 235, m 70.6%</td>
<td>AHI 38.4, ESS 7.8, mRS 2.6, BI 74.7, CS 8.2</td>
<td>AH ≤ 20 in 53.6% Deaths 4.3% within 1 y randomized CPAP in 57, no CPAP in 69</td>
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<tr>
<td>Joo et al., 2011</td>
<td>Stroke, TIA</td>
<td>Within 48 h Yes Prospective, consecutive</td>
<td>n = 63.8, m 52.7%</td>
<td>AHI 15.1, ESS 5.2, mRS 1.9, NIHSS 3.5</td>
<td>AH ≥ 10 in 60%, AH ≥ 20 in 23.9%</td>
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<tr>
<td>Chan et al., 2010</td>
<td>Minor stroke, TIA</td>
<td>Yes ICU, ward, home Prospective,</td>
<td>n = 66, m 28.9%</td>
<td>ESS &gt;10 in 22.7%</td>
<td>71% sleep apnea (RDI^10 &gt; 5), mild in 56%, moderate in 24%, severe in 20%</td>
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<tr>
<td>Author</td>
<td>Diagnosis</td>
<td>Timing of sleep study after other stroke, mean h⁰</td>
<td>Unattended polygraphy, d¹</td>
<td>Setting: ICU⁰, ward, sleep laboratory, rehabilitation unit, home</td>
<td>Study design</td>
<td>Subjects (n), male (m)</td>
<td>Demographics: mean age (y⁰), BMI⁰ (kg/m²), neck circumference (cm)</td>
<td>Characteristics of SDB and stroke: mean AHI⁰, ESS⁰, mRS⁰, BI⁰, CS⁰, SSS⁰, NIHSS³</td>
<td>Sleep apnea prevalence; CPAP²⁶ initiation</td>
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<tr>
<td>Rowat et al., 2006</td>
<td>Stroke</td>
<td>Median 4 h</td>
<td>Yes</td>
<td>ICU, ward</td>
<td>Prospective</td>
<td>n = 156, m 41%</td>
<td>79 y, NIHSS 9.5</td>
<td>33/24%</td>
<td>Deaths 13.8.3%, within 1 w⁰, 19% within 3 m</td>
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<tr>
<td>Siccoli et al., 2008</td>
<td>Ischemic stroke</td>
<td>45 h</td>
<td>Yes</td>
<td>ICU, ward</td>
<td>Prospective</td>
<td>n = 74, m 66.2%</td>
<td>63 y, BMI 28</td>
<td>AHI 20, mRS 2, NIHSS 6</td>
<td>55%</td>
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<td>Rola, 2008</td>
<td>Ischemic stroke, TIA</td>
<td>Within 7 d</td>
<td>Yes</td>
<td>ICU, ward</td>
<td>Prospective</td>
<td>n = 91, m 65.9%</td>
<td>64.5 y, BMI 27.7</td>
<td>AHI 20.8, NIHSS 5.7</td>
<td>61/67.7%</td>
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<td>Dziewas et al., 2007</td>
<td>Ischemic stroke</td>
<td>Within 72 h</td>
<td>Yes</td>
<td>Sleep laboratory, consecutive</td>
<td>Prospective</td>
<td>n = 214, m 66.4%</td>
<td>64.7 y, BMI 26.1</td>
<td>OSA 110/51% (AHI ≥ 10h)</td>
<td>53%</td>
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<tr>
<td>Broadley et al., 2007</td>
<td>Stroke</td>
<td>Median 2 d</td>
<td>Yes</td>
<td>ICU, ward</td>
<td>Prospective</td>
<td>n = 55, m 56.2%</td>
<td>71 y, BMI 26.8</td>
<td>ESS 5, BI 53</td>
<td>65.4% in stroke, in TIA 10.5; NIHSS 2.7 (AHI &gt; 5)</td>
</tr>
<tr>
<td>Rola et al., 2007</td>
<td>Ischemic stroke, hemispheric TIA</td>
<td>Within 7 d</td>
<td>Yes</td>
<td>ICU, ward</td>
<td>Prospective</td>
<td>n = 70, m 85.7%</td>
<td>66.2 y, BMI 28.8</td>
<td>AHI 14.0 in stroke, in TIA 10.5; NIHSS 2.7 (AHI &gt; 5)</td>
<td>66.6% in TIA</td>
</tr>
</tbody>
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### Table

<table>
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<tr>
<th>Author</th>
<th>Diagnosis</th>
<th>Timing of sleep study after stroke, mean h^9, d^7</th>
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<th>Study design</th>
<th>Subjects (n), mean age (y^10), BMI (kg/m²), neck circumference (cm)</th>
<th>Demographics: mean age (y^10), BMI (kg/m²), neck circumference (cm)</th>
<th>Characteristics of SDB and stroke: mean AHI^1, ESS^3, mRS^2, BI^3, CS^3, SSS^2, NIHSS^1</th>
<th>Sleep apnea prevalence; CPAP^2,6 initiation</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Martinez-Garcia, 2006</td>
<td>Stroke, TIA</td>
<td>Within 72 h</td>
<td>ICU, ward Prospective n = 59, m 61.0% 73.2 y, BMI 28.8</td>
<td>AHI 34.9, ESS &gt; 10 in 37.3%</td>
<td>Deaths 10/6.9% 1.23 d-65.9 d</td>
<td></td>
<td>AhI ≥ 5 in 62.8%, AhI 5–10 in 37%, AHI10–20 in 29.6%, AHI &gt; 20 in 33.3%</td>
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<td>Wierzbicka, 2006</td>
<td>Stroke, TIA</td>
<td>Within 1 w</td>
<td>ICU, ward Prospective n = 43, m 81.4% 68.5 y, BMI 27.8</td>
<td>AHI 13.3</td>
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<tr>
<td>Dziewas, 2005</td>
<td>Ischemic stroke</td>
<td>Within 72 h</td>
<td>ICU, ward Prospective n = 102, m 66.7% 64.5 y, BMI 26, neck 42</td>
<td>NIHSS 6.6 58.8% (RDI ≥ 10)</td>
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<td>Timing of sleep study after stroke, mean h²</td>
<td>Unattended polygraphy, stroke, mean h³</td>
<td>Setting: ICU, ward, sleep laboratory, rehabilitation unit, home</td>
<td>Study design</td>
<td>Subjects (n), male (%)</td>
<td>Study design</td>
<td>Demographics: mean age (y), BMI (kg/m²), neck circumference (cm)</td>
<td>Characteristics of SDB and stroke: mean AHI, ESS, mRS, BI, CS, SSS, NIHSS</td>
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<tr>
<td>Martinez-Garcia et al., 2004</td>
<td>Ischemic stroke</td>
<td>1.4 d, No, Autoset portable plus laboratory</td>
<td>Sleep laboratory</td>
<td>Prospective n = 139, m 59%</td>
<td>73.6y, 73.6, 40.4</td>
<td>21.6%, AHI 29.1 (AHI ≥ 10 in 65%, AHI ≥ 20 in 43%)</td>
<td>No, Autoset portable plus II Sleep laboratory</td>
<td>Prospective n = 139, m 59%</td>
<td>73.6y, 73.6, 40.4</td>
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<td>Parra et al., 2004</td>
<td>Stroke, TIA</td>
<td>48–72 h Yes ICU, ward</td>
<td>Prospective n = 161, m 50.9%</td>
<td>72 y, 72.46, 40.4</td>
<td>AHI &gt;10 in 72%, AHI &gt; 30 in 28%, AHI &gt; 40 in 11.2%, AHI &gt; 50 in 5%</td>
<td>22/13.7%</td>
<td>AHI &gt;10 in 72%, AHI &gt; 30 in 28%, AHI &gt; 40 in 11.2%, AHI &gt; 50 in 5%</td>
<td>22/13.7%</td>
<td>AHI &gt;10 in 72%, AHI &gt; 30 in 28%, AHI &gt; 40 in 11.2%, AHI &gt; 50 in 5%</td>
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<tr>
<td>Author</td>
<td>Diagnosis</td>
<td>Timing of sleep study after other stroke, mean h², d¹</td>
<td>Unattended polygraphy, mean h², d¹</td>
<td>Setting: ICU, ward, sleep laboratory, rehabilitation unit, home</td>
<td>Study design</td>
<td>Subjects (n), male (m)</td>
<td>Demographics: mean age (y), BMI (kg/m²), neck circumference (cm)</td>
<td>Characteristics of SDB and stroke: mean AHI², ESS⁸, mRS¹², BI³, CS⁵, SSS¹⁶, NIHSS¹³</td>
<td>Sleep apnea prevalence; CPAP²,⁶ initiation</td>
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<td>Szucs et al., 2002</td>
<td>Ischemic or hemorrhagic stroke</td>
<td>6 d</td>
<td>Yes</td>
<td>Home</td>
<td>Prospective</td>
<td>n = 106, m 42.5%</td>
<td>67 y</td>
<td>mean ODI⁴ 26, ODI &gt; 10 in 67%, ODI &gt; 20 in 42.5%</td>
<td>NIHSS 19</td>
</tr>
<tr>
<td>Parra et al., 2000</td>
<td>Ischemic or hemorrhagic stroke or TIA</td>
<td>2–3 d</td>
<td>Yes</td>
<td>ICU, ward</td>
<td>Prospective</td>
<td>n = 161, m 50.9%</td>
<td>71.8 y, BMI 26.6</td>
<td>AHI 21.2; BI 75.5, CS 7.9</td>
<td>AHI &gt; 10 in 72%, AHI &gt; 20 in 47.2%, AHI &gt; 30 in 28%</td>
</tr>
</tbody>
</table>

¹ apnea- hypopnea index, ² autotitrating continuous positive airway pressure, ³ Barthel Index, ⁴ body mass index (kg/m²), ⁵ Canadian Scale, ⁶ continuous positive airway pressure, ⁷ days, ⁸ Epworth sleepiness scale, ⁹ hour, ¹⁰ Intensive Care Unit, ¹¹ month, ¹² modified Rankin Scale, ¹³ National Institutes of Health Stroke Scale, ¹⁴ oxygen desaturation index, ¹⁵ RDI, respiratory disturbance index, ¹⁶ Scandinavian Stroke Scale, ¹⁷ transient ischemic attack, ¹⁸ week, ¹⁹ year
Table 3. Unattended sleep study over seven days after stroke.

<p>| Author                | Diagnosis | Timing of sleep study after stroke, mean days | Setting: ICU, ward, rehabilitation unit, home | Study design | Subjects (n), male (%) | Demographics: mean age (y), BMI (kg/m²), neck circumference (cm) | Characteristics of SDB and stroke: mean AHI, ESS, mRS, BI, CS, NIHSS, CPAP initiation | Sleep apnea prevalence; CPAP (%) initiation | Comments                        |
|-----------------------|-----------|-----------------------------------------------|----------------------------------------------|--------------|------------------------|------------------------------------------------------------------|----------------------------------------------------------------------------------|-----------------------------------------------|
| Boulos et al., 2017   | Stroke TIA | 21d Yes                                       | ICU, ward or home                              | Prospective  | n = 102, m 55.9%       | 68.7 y, BMI 27.7                                                  | AHI 13.7, ESS 7, mRS 25, NIHSS 1                                                 | 63.4%, CPAP 34/52%                    | Some had tPA, stroke size measured         |
| Lefevre-Dognin et al., 2014 | Stroke    | Within 10 d Yes                               | Rehabilitation unit                           | Prospective  | n = 45, m 66.7%        | 60.9 y, BMI 24                                                    | AHI 19.4, ESS 6.4, NIHSS 8.9                                                    | AHI ≥ 10 in                         |                                |
| Brown DL et al., 2014 | Stroke    | Median 13 d, within 30-45 d                   | Home                                          | Retrospective | n = 355, m 55.5%       | 63 y, BMI 28.5                                                   | AHI 4, NIHSS 3.5                                                                | 71.5%                               |                                |</p>
<table>
<thead>
<tr>
<th>Author</th>
<th>Diagnosis</th>
<th>Timing of sleep study after stroke, other mean d, m</th>
<th>Setting: ICU, ward, sleep laboratory, rehabilitation unit, home</th>
<th>Study design: Prospective, consecutive</th>
<th>Subjects (n), male (%)</th>
<th>Demographics: mean age (y), BMI (kg/m²), neck circumference (cm)</th>
<th>Characteristics of SDB and stroke: mean AHI, ESS, mRS, BI, CS, SSS, NIHSS</th>
<th>Sleep apnea prevalence; CPAP initiation</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Ahn et al., 2013</td>
<td>Acute ischemic stroke</td>
<td>Within 4.1–8.5 d Yes ICU, ward</td>
<td>n = 293, m 54.3%</td>
<td>68.4 y, BMI 23.6, mRS 2.2, NIHSS 6.3</td>
<td>AHI ≥ 10 in 63.1%, AHI ≥ 20 in 34.5%</td>
<td>AHI &gt; 15 in 55.9%</td>
<td></td>
<td>AHI &gt; 15 in 55.9%</td>
<td></td>
</tr>
<tr>
<td>Kotzian et al., 2012</td>
<td>Stroke</td>
<td>8–22 m Yes Rehabilitation unit</td>
<td>n = 68, m 71% (total 515 cases, Embletta for 68)</td>
<td>63 y, BMI 29 AHI 22, BI 78</td>
<td>AHI &gt; 15 in 55.9%</td>
<td></td>
<td></td>
<td>AHI &gt; 15 in 55.9%</td>
<td></td>
</tr>
<tr>
<td>Martinez-Garcia et al., 2012</td>
<td>Acute ischemic stroke</td>
<td>Over 2 m Yes Prospective</td>
<td>n = 166, m 59%</td>
<td>73.3 y, BMI 28.7 AHI 26, ESS 9.1, BI 69.1</td>
<td>AHI 10–19 in 53.6% in 23.5%, AHI ≥ 20 in 57.8%; CPAP 57.8%</td>
<td>Deaths 89/53.6% within 7 y AHI &gt; 15 in 47%; CPAP initiation</td>
<td></td>
<td>AHI &gt; 15 in 47%; CPAP initiation</td>
<td></td>
</tr>
<tr>
<td>Disler et al., 2002</td>
<td>Stroke</td>
<td>7–28 d Yes Rehabilitation unit</td>
<td>n = 38, weight 75 kg</td>
<td>65 y, AHI 15 weight 75 kg</td>
<td></td>
<td></td>
<td></td>
<td>AHI &gt; 15 in 47%; CPAP initiation</td>
<td></td>
</tr>
<tr>
<td>Author</td>
<td>Diagnosis</td>
<td>Timing of sleep study after stroke, mean d(^{1}), m(^{11})</td>
<td>Unattended polygraphy, other</td>
<td>Setting: ICU(^{10}), ward, sleep laboratory, rehabilitation unit, home</td>
<td>Study design</td>
<td>Subjects (n), male (m)</td>
<td>Demographics: mean age (y), BMI(^{4}) (kg/m(^{2})), neck circumference (cm)</td>
<td>Characteristics of SDB and stroke: mean AHI(^{1}), ESS(^{9}), mRS(^{12}), BI(^{3}), CS(^{5}), SSS(^{16}), NIHSS(^{13})</td>
<td>Sleep apnea prevalence; CPAP(^{2,6}) initiation</td>
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<tr>
<td>Harbison et al., 2002</td>
<td>Stroke</td>
<td>10 (range 7–14 d)</td>
<td>Yes, Autoset</td>
<td>ICU, ward</td>
<td>Prospective n = 68</td>
<td>73 y, BMI 25.5, neck 38</td>
<td>AHI 30, mRS 1, BI 7.1, SSS 26</td>
<td>Deaths 10 /15% within 3 m</td>
<td></td>
</tr>
</tbody>
</table>

\(^{1}\) apnea-hypopnea index, \(^{2}\) autotitrating continuous positive airway pressure, \(^{3}\) Barthel Index, \(^{4}\) body mass index (kg/m\(^{2}\)), \(^{5}\) Canadian Scale, \(^{6}\) continuous positive airway pressure, \(^{7}\) central sleep apnea, \(^{8}\) day(s), \(^{9}\) Epworth sleepiness scale, \(^{10}\) ICU, Intensive Care Unit, \(^{11}\) month, \(^{12}\) modified Rankin Scale, \(^{13}\) National Institutes of Health Stroke Scale, \(^{14}\) month, \(^{15}\) obstructive sleep apnea, \(^{16}\) Scandinavian Stroke Scale, \(^{17}\) transient ischemic attack, \(^{18}\) week, \(^{19}\) year
It is difficult to know the real correlation between stroke and sleep apnea if there is no objective data about the diagnosis of sleep apnea before stroke, although a causal connection might exist between sleep apnea and stroke (Bassetti, Aldrich, Chervin, & Quint, 1996; Martinez-Garcia et al., 2009; Sahlin et al., 2008; Yaggi et al., 2005).

During the first twenty-four hours after stroke onset the sleep apnea prevalence of stroke patients has been reported to be 52–62% (Iranzo et al., 2002; Turkington et al., 2002; Väyrynen et al., 2014). The central apnea index (CAI) is deemed to be low according to previous studies (Haba-Rubio et al., 2012; Parra et al., 2000), and the main type of apnea event is generally obstructive apnea (Bassetti et al., 1996; Iranzo et al., 2002; Parra et al., 2000).

### 2.2.3 Evolution of sleep apnea in stroke

The prevalence, and at the same time, the severity of sleep apnea tended to decrease by 9.8 to 22% in the post-stroke phase after follow-up time (Table 7) according to previous studies (Bassetti et al., 2006; Harbison et al., 2002; Hui et al., 2002; Parra et al., 2000), but this was not confirmed in the recent meta-analysis (Seiler et al., 2019). One explanation for the decrease of AHI is the decreased physical energy of stroke patients (Giebelhaus, Strohl, Lormes, Lehmann, & Netzer, 2000; Peppard & Young, 2004). After follow-up time of stroke, CAI decreased (Bassetti & Aldrich, 1999; Bassetti et al., 2006; Iranzo et al., 2002; Parra et al., 2000; Stahl et al., 2015) whereas the obstructive apnea index (OAI) remained higher than CAI (Bassetti et al., 2006; Iranzo et al., 2002; Parra et al., 2000). Only one study pointed out that OAI was the same at acute stroke and after follow-up (Parra et al., 2000) while other studies found a decline of OAI after follow-up (Bravata et al., 2017; Hui et al., 2002). The results of earlier follow-up studies are reported in Tables 6 and 7.
Table 4. Full polysomnography (PSG) within seven days after stroke.

<table>
<thead>
<tr>
<th>Author</th>
<th>Diagnosis</th>
<th>Timing of sleep study</th>
<th>PSG Setting:</th>
<th>Study design</th>
<th>Subjects</th>
<th>Demographics:</th>
<th>Characteristics of SDB and stroke:</th>
<th>Sleep apnea prevalence; CPAP initiation</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Väyrynen et al., 2014</td>
<td>Mild ischemic stroke (NIHSS &lt; 12) or TIA&lt;sup&gt;10&lt;/sup&gt;</td>
<td>1 d ICU, ward Prospective</td>
<td>ICU, ward</td>
<td>n = 42, m 31.0%</td>
<td>69 y, median BMI 26, median neck circumference 40</td>
<td>AHI ≥ 15 in 52.4%</td>
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<tr>
<td>Bravata et al., 2011</td>
<td>Stroke</td>
<td>40 h, Yes ICU, ward Prospective</td>
<td>ICU, ward</td>
<td>n = 55, m 67.3%</td>
<td>71.1 y, median BMI 28.1, neck circumference 40.4</td>
<td>AHI ≥ 5 in 86.7%, auto-CPAP intervention for 30 d in 16 cases, usage ≥ 4 h in 62.5%</td>
<td></td>
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<tr>
<td>Brown DL et al., 2008</td>
<td>Ischemic stroke</td>
<td>within 7 d Yes ward Prospective</td>
<td>ward</td>
<td>n = 30, m 67.0%</td>
<td>median AHI 23, mRS 0–2, BI 70, NIHSS 7</td>
<td>AHI ≥ 5 in 73%</td>
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<tr>
<td>Author</td>
<td>Diagnosis</td>
<td>Timing of sleep study (d)</td>
<td>PSG Setting: ICU, ward, sleep laboratory, rehabilitation unit, home</td>
<td>Study design Subjects</td>
<td>Demographics: mean age (y), BMI (kg/m²), neck circumference (cm)</td>
<td>Characteristics of SDB and stroke: mean AHI, ESS, mRS, BI, CS, SSS, GCS, NIHSS</td>
<td>Sleep apnea prevalence; CPAP initiation</td>
<td>Comments</td>
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<tr>
<td>Yan-fang et al., 2009</td>
<td>Ischemic stroke</td>
<td>6.5</td>
<td>ICU, ward</td>
<td>Prospective</td>
<td>n = 60, 57.9 y, m 68.3%, BMI 25.2</td>
<td>AHI 19.6, SSS 32.0</td>
<td>AHI ≥ 5 in 65%, AHI ≥ 15 in 50%, AHI &gt; 30 in 30%</td>
<td>Yan-fang et al., 2009 Ischemic stroke 6.5 d Yes ICU, ward Prospective n = 60, m 68.3% 57.9 y, BMI 25.2 AHI 19.6, SSS 32.0 AHI ≥ 5 in 65%, AHI ≥ 15 in 50%, AHI &gt; 30 in 30%</td>
<td></td>
</tr>
<tr>
<td>Bassetti et al., 2006</td>
<td>Acute ischemic stroke</td>
<td>3 (range 0–9)</td>
<td>ICU, ward</td>
<td>Prospective</td>
<td>n = 152, 55.8 y, m 67.8%, BMI 26.3</td>
<td>AHI 18, ESS 5.8, mRS 1.9, BI 87, SSS 35.9, NIHSS 7.0</td>
<td>AHI ≥ 15 or AHI ≥ 10 + ESS &gt; 10 in 46%, AHI ≥ 10 in 58%, AHI ≥ 20 in 31%, AHI ≥ 30 in 17%, CPAP in 51%</td>
<td>Bassetti et al., 2006 Acute ischemic stroke 3 d (range 0–9) Yes ICU, ward Prospective n = 152, m 67.8% 55.8 y, BMI 26.3 AHI 18, ESS 5.8, mRS 1.9, BI 87, SSS 35.9, NIHSS 7.0 AHI ≥ 15 or AHI ≥ 10 + ESS &gt; 10 in 46%, AHI ≥ 10 in 58%, AHI ≥ 20 in 31%, AHI ≥ 30 in 17%, CPAP in 51%</td>
<td></td>
</tr>
<tr>
<td>Hui et al., 2002</td>
<td>Stroke</td>
<td>2.7 (range 0.7–4.7)</td>
<td>ICU, ward</td>
<td>Case-control</td>
<td>n = 51, 64.2 y, m 54.9%, BMI 24.3, neck 38.1</td>
<td>AHI 23, ESS 6.8, BI 14.3, NIHSS 3.8</td>
<td>AHI ≥ 10 in 67%, AHI ≥ 15 in 61%, AHI ≥ 20 in 49%, AHI ≥ 30 in 31%, CPAP in 4 cases</td>
<td>Hui et al., 2002 Stroke 2.7 d (range 0.7–4.7) Yes ICU, ward Case-control n = 51, m 54.9% 64.2 y, BMI 24.3, neck 38.1 AHI 23, ESS 6.8, BI 14.3, NIHSS 3.8 AHI ≥ 10 in 67%, AHI ≥ 15 in 61%, AHI ≥ 20 in 49%, AHI ≥ 30 in 31%, CPAP in 4 cases</td>
<td></td>
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<tr>
<td>Turkington et al., 2002</td>
<td>Acute stroke</td>
<td>10 h</td>
<td>ICU, ward</td>
<td>Prospective</td>
<td>n = 120, 79 y, m 41.7%, BMI 26.3, neck 38.3</td>
<td>SSS 30, GCS 15</td>
<td>RDI &gt; 5 in 79%, RDI &gt; 10 in 61%, RDI &gt; 15 in 45%, CPAP in 16 cases usage 2.5 h/d</td>
<td>Turkington et al., 2002 Acute stroke 10 h Yes ICU, ward Prospective n = 120, m 41.7% 79 y, BMI 26.3, neck 38.3 SSS 30, GCS 15 RDI &gt; 5 in 79%, RDI &gt; 10 in 61%, RDI &gt; 15 in 45%, CPAP in 16 cases usage 2.5 h/d</td>
<td></td>
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<tr>
<td>Author</td>
<td>Diagnosis</td>
<td>Timing of PSG Study Setting</td>
<td>Study Design</td>
<td>Subjects Demographics</td>
<td>Characteristics of SDB and Stroke</td>
<td>Comments</td>
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<tr>
<td>Iranzo et al., 2002</td>
<td>Ischemic stroke</td>
<td>1d (11.6 h) ICU, ward</td>
<td>Prospective</td>
<td>n = 50, m 60.0%</td>
<td>AHI ≥ 10 in 62%, AHI ≥ 20 in 46%</td>
<td>AHI ≥ 25 in 40%, AHI ≥ 30 in 40%</td>
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</tbody>
</table>

Table 5. Full polysomnography (PSG) over 7 days after stroke.

<table>
<thead>
<tr>
<th>Author</th>
<th>Diagnosis</th>
<th>Timing of PSG after stroke, mean days</th>
<th>Setting: ICU, ward, sleep laboratory, rehabilitation unit, home</th>
<th>Study design</th>
<th>Subjects (n), male (%)</th>
<th>Demographics: mean age (y), BMI (kg/m²), neck circumference (cm)</th>
<th>Characteristics of SDB and stroke: mean AHI, ESS, mRS, BI, CS, SSS, NIHSS</th>
<th>Sleep apnea prevalence; CPAP initiation</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ryan et al., 2017</td>
<td>Stroke</td>
<td>49.1 d</td>
<td>ICU, ward or sleep laboratory first night, then at home</td>
<td>Prospective</td>
<td>n = 23, m 47.8%</td>
<td>66.4 y, BMI 26.1</td>
<td>AHI ≥ 5 in 78%, AHI ≥ 10 in 39.3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bravata et al., 2017</td>
<td>Stroke, TIA</td>
<td>199 d</td>
<td>Home</td>
<td>Prospective, randomized, controlled</td>
<td>n = 225, m 97.4%</td>
<td>70.0 y, BMI 39.1, neck circumference 41.5</td>
<td>AHI 14.7, ESS ≥ 10 in 28.3%, NIHSS 2.1</td>
<td>61.9%</td>
<td>Deaths 2/0.8%</td>
</tr>
<tr>
<td>Brown, DL et al 2013</td>
<td>Stroke</td>
<td>3 m</td>
<td>ICU, ward</td>
<td>Prospective, randomized, controlled</td>
<td>n = 74, m 33.0%</td>
<td>67 y, BMI 28.5</td>
<td>AHI ≥ 5 in 73%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tosun et al., 2008</td>
<td>Ischemic stroke</td>
<td>14.8 m</td>
<td>Rehabilitation unit</td>
<td>Prospective</td>
<td>n = 19, m 68.4%</td>
<td>59.6 y, BMI 25.6</td>
<td>73.7%, mild in 41.2%, moderate in 10.5%, severe in 21.1%</td>
<td></td>
<td>Mid OSA (AHI 5–15), Moderate OSA (AHI 15–30), Severe OSA (AHI &gt; 30)</td>
</tr>
</tbody>
</table>

Notes: AHI = Apnea Hypopnea Index, ESS = Epworth Sleepiness Scale, mRS = Modified Rankin Scale, BI = Barthel Index, CS = Carolina Sleepiness Scale, SSS = Sleep Severity Scale, NIHSS = National Institutes of Health Stroke Scale, CPAP = Continuous Positive Airway Pressure.
<table>
<thead>
<tr>
<th>Author</th>
<th>Diagnosis</th>
<th>Timing of sleep study</th>
<th>PSG study</th>
<th>Setting</th>
<th>Study design</th>
<th>Subjects</th>
<th>Demographics:</th>
<th>Characteristics of SDB and stroke:</th>
<th>Sleep apnea</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nopmaneej, 2005</td>
<td>Ischemic or hemorrhagic stroke</td>
<td>44 d</td>
<td>Yes</td>
<td>Rehabilitation unit</td>
<td>Prospective</td>
<td>n = 93,</td>
<td>mean age (y), BMI (kg/m²), neck circumference (cm)</td>
<td>mean AHI¹, ESS¹, mRS¹⁴, BI, CS³, SSS²¹, NIHSS¹⁰</td>
<td>AHI ≥ 10 in 63%,</td>
<td>CSA² in 19%</td>
</tr>
<tr>
<td>Bassetti et al., 1999</td>
<td>Stroke 75, TIA 53</td>
<td>9 d, range 1–71 d</td>
<td>Yes</td>
<td>ICU, ward or sleep laboratory</td>
<td>Prospective</td>
<td>n = 128,</td>
<td>mean age (y), BMI (kg/m²)</td>
<td>AHI ≥ 28, SSS 39</td>
<td>RDI ≥ 10 in 31%,</td>
<td></td>
</tr>
<tr>
<td>Bassetti et al., 1996</td>
<td>Stroke 36, TIA 23 12 d, range 1–71 d</td>
<td>Yes</td>
<td>ICU, ward or sleep laboratory</td>
<td>Prospective</td>
<td>n = 59,</td>
<td>mean age (y), BMI (kg/m²)</td>
<td>AHI ≥ 10 in 70%, ESS &gt; 10 in 34%,</td>
<td>AHI &gt; 20 in 55%</td>
<td></td>
<td></td>
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<tr>
<td>Dyken et al., 1996</td>
<td>Ischemic or hemorrhagic stroke 15.7 d, range 14–35 d</td>
<td>Yes</td>
<td>ICU, ward or sleep laboratory</td>
<td>Prospective</td>
<td>n = 51,</td>
<td>mean age (y), BMI (kg/m²)</td>
<td>AHI ≥ 31.6, SSS 37</td>
<td>m in 77%</td>
<td>Deaths 11.8% within 4 y</td>
<td></td>
</tr>
<tr>
<td>Good et al., 1996</td>
<td>Ischemic stroke median 13 d, range 4–69 d</td>
<td>Yes</td>
<td>Rehabilitation unit</td>
<td>Prospective</td>
<td>n = 47,</td>
<td>Median 69 y</td>
<td>AHI ≥ 35.6, BI 32.7</td>
<td>AHI ≥ 10 in 95%, AHI ≥ 20 in 68%, AHI ≥ 30 in 53%</td>
<td>Deaths 6.4% within 3m, 10.6% within 1 y</td>
<td></td>
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<tr>
<td>Mohsenin et al., 1995</td>
<td>Stroke 90 d</td>
<td>Yes</td>
<td>Rehabilitation Case-control unit</td>
<td>Prospective</td>
<td>n = 20,</td>
<td>mean age (y), BMI (kg/m²)</td>
<td>AHI ≥ 35.6</td>
<td>RDI ≥ 20 in 80%</td>
<td></td>
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<tr>
<td>Author</td>
<td>Diagnosis</td>
<td>Timing of sleep study</td>
<td>PSG</td>
<td>Setting:</td>
<td>Study design</td>
<td>Subjects (n)</td>
<td>Demographics:</td>
<td>Characteristics of SDB and stroke:</td>
<td>Sleep apnea prevalence;</td>
<td>Comments</td>
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<tr>
<td>Wessendorf Stroke et al., 2000</td>
<td>26–66 d Yes Rehabilitation Prospective unit</td>
<td>n = 147, m = 103</td>
<td>ICU, ward, sleep study, stroke, mean d10, m13</td>
<td></td>
<td></td>
<td></td>
<td>mean age (y12), BMI (kg/m²), neck circumference (cm),</td>
<td>RDI &gt; 5 in 61.2%,</td>
<td>CPAP7 initiation</td>
<td></td>
</tr>
</tbody>
</table>

1 apnea-hypopnea index, 2 autotitrating continuous positive airway pressure, 3Barthel Index, 4 body mass index, 5Barthel Score, 6central apnea index, 7continuous positive airway pressure, 8 Canadian Scale, 9central sleep apnea, 10day(s), 11 Epworth Sleepiness Scale, 12 Glasgow coma scale, 13 month, 14modified Rankin Scale, 15National Institutes of Health Stroke Scale, 16obstructive apnea index, 17 odds ratio, 18obstructive sleep apnea, 19polysomnography, 20respiratory disturbance index, 21 Scandinavian Stroke Scale, 22transient ischemic attack, 23 week, 24 year
Table 6. The prognosis of stroke patients in evolution of sleep apnea without follow-up sleep study.

<table>
<thead>
<tr>
<th>Author</th>
<th>Diagnosis</th>
<th>Study design</th>
<th>Subjects</th>
<th>Demographics: mean age (y), BMI (kg/m²), neck change</th>
<th>Sleep apnea diagnosis criterion</th>
<th>Results of baseline sleep study; sleep apnea prevalence, mean AHI; (baseline, change)</th>
<th>Follow-up time; CPAP initiation, compliance</th>
<th>New vascular events, n%</th>
<th>Comments</th>
<th>Death %, time to death; intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lefevre-Dognin et al., 2014</td>
<td>Stroke</td>
<td>Prospective</td>
<td>n = 45, m 66.7%</td>
<td>60.9 y, BMI24</td>
<td>AHI ≥ 10</td>
<td>62.2%, mild 37.1%, moderate 28.6%, severe 34.3%; ESS 6.4, NIHSS 8.9→5.4</td>
<td>2 m³</td>
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<tr>
<td>Ahn et al., 2013</td>
<td>Prospective, consecutive</td>
<td>n = 293, m 54.3%</td>
<td>68.4 y, BMI 23.6</td>
<td>AH ≥ 10</td>
<td>63.1%, AHI ≥ 20 in 34.5%; mRS 2.2→1.43, NIHSS 6.3</td>
<td></td>
<td>3 m</td>
<td></td>
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<tr>
<td>Parra et al., 2011</td>
<td>Stroke</td>
<td>Randomized, controlled</td>
<td>n = 140, m 70.6%</td>
<td>64.7 y, BMI 29.5, ESS 7.8, neck 42.1</td>
<td>AHI ≥ 20</td>
<td>53.6%, AHI 38.4; ESS 7.8, mRS 2.6→1.8→1.9→2, BI 74.7→94→93.4→93.7, CS 8.2→9.3→9.4→9.4</td>
<td>1 m, 12 m, 24 m</td>
<td>57.53H/d, 13/12.0%</td>
<td>54.3% within 24 m; intervention CPAP</td>
<td></td>
</tr>
<tr>
<td>Author</td>
<td>Diagnosis</td>
<td>Study design</td>
<td>Subjects</td>
<td>Demographics: mean age (y), BMI (kg/m²), neck change</td>
<td>Sleep apnea diagnosis criterion</td>
<td>Results of baseline sleep study; sleep apnea prevalence, mean AHI; (baseline, change)</td>
<td>Follow-up time</td>
<td>CPAP² insertion, compliance</td>
<td>New vascular events, n%</td>
<td>Comments</td>
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<tr>
<td>Brown DL et al., 2013</td>
<td>Stroke</td>
<td>Randomized controlled</td>
<td>n = 74, m 33.0%</td>
<td>67 y, BMI 28.5</td>
<td>AHI ≥ 5</td>
<td>73%, AHI 18.5; ESS 7.5, mRS 2, BI 97.5, NIHSS 1.5–1.4</td>
<td>3 m</td>
<td>11 CPAP active, 17 CPAP sham; usage 4 h and 6 h</td>
<td></td>
<td>2/2.7%, 1 at hospital, 1 within 3 m; intervention CPAP</td>
</tr>
<tr>
<td>Rowat et al., 2006</td>
<td>Stroke</td>
<td>Prospective</td>
<td>n = 156, m 41.0%</td>
<td>median age 79 y, nasal airflow</td>
<td>&gt; 50% jin</td>
<td>33/24% CSA; BI median 10, NIHSS 9.5–8.5–7.5</td>
<td>24 h, 7 d⁰, 3 m</td>
<td></td>
<td></td>
<td>3/1.9% within 1 d, 10/4.4% within 7 d, 19% within 3 m</td>
</tr>
<tr>
<td>Turkington 2002; 2004 study</td>
<td>Stroke</td>
<td>Prospective</td>
<td>n = 114, m 41.7%</td>
<td>median 7.9 y, RDI &gt; 10</td>
<td>61%;</td>
<td>ESS 6, BI 3–1.5, SSS 30–30, GCS 15</td>
<td>6 m</td>
<td></td>
<td></td>
<td>25% died at hospital</td>
</tr>
<tr>
<td>Iranzo et al., 2002</td>
<td>Ischemic stroke</td>
<td>Prospective</td>
<td>n = 80, m 60.0%</td>
<td>67 y, BMI 26</td>
<td>AHI &gt; 10</td>
<td>SSS 40.8→49.5</td>
<td>1 m, 3 m, 6 m</td>
<td></td>
<td></td>
<td>sleep apnea had association with early neurologic worsening in 30% OR 1.8, 95% CI 1.21–3.23</td>
</tr>
<tr>
<td>Author</td>
<td>Diagnosis</td>
<td>Study design</td>
<td>Subjects (n), male (m)</td>
<td>Demographics: mean age (y), BMI (kg/m²), neck change</td>
<td>Sleep apnea diagnosis criterion</td>
<td>Results of baseline sleep study; sleep apnea prevalence, mean AHI</td>
<td>Follow-up time CPAP initiation, compliance</td>
<td>New vascular events, n%</td>
<td>Comments</td>
<td></td>
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</tr>
<tr>
<td>Good et al., 1996</td>
<td>Stroke</td>
<td>Prospective</td>
<td>n = 47, m 55.0%</td>
<td>AHI &gt; 10</td>
<td>95%, AHI ≥ 20 in 68%, AHI ≥ 30 in 53%; BI 32.7—70.7—73.9</td>
<td>3 m, 12 m</td>
<td></td>
<td>6.4% within 3 m, 10.6% within 1 y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parra et al., 2004</td>
<td>Stroke, TIA²²</td>
<td>Prospective</td>
<td>n = 161, m 50.9% BMI 26.6, AHI &gt; 10</td>
<td>AHI 1.2, OSA in 52.2%, CSA in 38.5%, AHI &gt;10 in 72%, AHI &gt;30 in 28%; ESS 4.8, BI 75.5, CSS 7.9</td>
<td>22.8 m., range 0.4—32 m</td>
<td>vascular disease in 63.6% of deaths 22/13.7% within 24 m HR 1.05 for every increase point of AHI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

²²TIA: Transient Ischemic Attack
<table>
<thead>
<tr>
<th>Author</th>
<th>Diagnosis</th>
<th>Study design</th>
<th>Subjects</th>
<th>Demographics</th>
<th>Sleep apnea diagnosis criterion</th>
<th>Results of baseline sleep study</th>
<th>Follow-up time</th>
<th>CPAP^2,7 initiation, compliance</th>
<th>New vascular events, n%</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rola et al., 2008</td>
<td>Ischemic stroke, TIA</td>
<td>Prospective</td>
<td>n = 91, m 65.9%, 64.5 y, BMI 27.7</td>
<td>AHI &gt; 5/h 67.7%, AHI 20.8, AHI &lt; 20 in 60.7%, AHI &gt; 20 in 39.3%, NIHSS 5.7</td>
<td>Sleep disordered breathing increased risk for new stroke or TIA (OR = 1.52)</td>
<td>6/6.6%</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Martinez-Garcia et al., 2012</td>
<td>Acute ischemic stroke</td>
<td>Prospective</td>
<td>n = 223, m 59.0%, 73.3 y, BMI 28.71</td>
<td>AHI ≥ 10 26, AHI 10–19/h in 23.5%, AHI &gt; 20 in 57.8%, AHI &lt; 10 in 37.8%, ESS 9.1, BI 69.1</td>
<td>96/57.8% initiation, tolerant (&gt; 4 h) 28/16.9%</td>
<td>44/26.5%</td>
<td>34 within 2 m, 89/53.6% within 7 y, sleep study was performed in 166 cases</td>
<td></td>
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</tr>
<tr>
<td>Author</td>
<td>Diagnosis</td>
<td>Study design</td>
<td>Subjects</td>
<td>Demographics:</td>
<td>Sleep apnea diagnosis criterion</td>
<td>Results of baseline sleep study; sleep apnea prevalence, mean AHI; (baseline, change)</td>
<td>Follow-up time</td>
<td>CPAP2 initiation, compliance</td>
<td>New vascular events, n%</td>
<td>Comments</td>
</tr>
<tr>
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</tr>
<tr>
<td>Keplinger et al., 2013</td>
<td>Acute ischemic stroke, TIA</td>
<td>Prospective, consecutive</td>
<td>n = 61, m 44.0%</td>
<td>65.6 y, BMI 27.2</td>
<td>AHI ≥ 5</td>
<td>61%, median AHI 20, OSA in 86%, CSA in 4%, mild in 32%, moderate in 30%, severe in 29%; median ESS 5, mRS 1→1, median NIHSS 1</td>
<td>6 m, 12 m</td>
<td>2/0.3%</td>
<td>1/1.6% within 6 m; mild OSA (AHI 5–14/h), moderate (AHI 15–29), severe (AHI ≥ 30/h)</td>
<td></td>
</tr>
<tr>
<td>Sahlin et al., 2008</td>
<td>Stroke</td>
<td>Prospective</td>
<td>n = 132, m 41.0%</td>
<td>76.7 y, BMI 23.9</td>
<td>OAI ≥ 15</td>
<td>17.4% OSA, 21.2% CSA</td>
<td>10 y, 33 y</td>
<td>116/87.9%</td>
<td>within 10 y</td>
<td></td>
</tr>
</tbody>
</table>

1 apnea-hypopnea index, 2 autotitrating continuous positive airway pressure, 3 Barthel Index, 4 body mass index, 5 Barthel Score, 6 central apnea index, 7 continuous positive airway pressure, 8 Canadian Scale, 9 central sleep apnea, 10 days, 11 Epworth Sleepiness Scale, 12 Glasgow coma scale, 13 month, 14 modified Rankin Scale, 15 National Institutes of Health Stroke Scale, 16 obstructive apnea index, 17 odds ratio, 18 obstructive sleep apnea, 19 polysomnography, 20 respiratory disturbance index, 21 Scandinavian Stroke Scale, 22 transient ischemic attack, 23 week, 24 year.
Table 7. The prognosis of stroke patients in evolution of sleep apnea with follow-up sleep study.

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Diagnosis</th>
<th>Study design</th>
<th>Subjects (n), male (%)</th>
<th>Demographics</th>
<th>Sleep apnea diagnosis criterion</th>
<th>Characteristics of SDB and stroke: (baseline, change)</th>
<th>Timing of follow-up sleep study after sleep study or change (n), mean, from</th>
<th>Results of follow-up sleep study or change from baseline: sleep apnea prevalence</th>
<th>CPAP intervention, compliance</th>
<th>New vascular events, death %, time to death; intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bravata et al., 2017</td>
<td>Stroke, TIA</td>
<td>Randomized controlled</td>
<td>n = 225, m 97.4%</td>
<td>70.9 y, BMI 39.1, neck 41.5</td>
<td>AHI ≥ 5</td>
<td>Baseline</td>
<td>61.9%</td>
<td>58 cases, CPAP ≥ 4 h, mean usage 2.5 h/d</td>
<td>86.7% — 68.6%</td>
<td>2/0.8%, intervention full unattended polysomnography, auto-CPAP (AHI ≥ 5) for 1 y, controls unattended polysomnography after 1 y</td>
</tr>
<tr>
<td>Bravata et al., 2011</td>
<td>Stroke</td>
<td>Prospective</td>
<td>n = 55, m 67.3%</td>
<td>71.7 y, BMI 28.1, neck 40.4</td>
<td>AHI ≥ 5</td>
<td>31 cases in 1 m, median NIHSS (n=30)</td>
<td>31 cases in 1 m, median NIHSS (n=30)</td>
<td>3 — 0, controls 3 — 2</td>
<td>33.3% — 22.9%</td>
<td>Deaths 0, intervention auto-CPAP^2</td>
</tr>
</tbody>
</table>

Legend:
- AHI: Apnea-Hypopnea Index
- OAI: Oxygen-Arrest Index
- CAI: Central Apnea Index
- ESS: Epworth Sleepiness Scale
- mRS: Modified Rankin Scale
- BI: Barthel Index
- SSS: Stroke Specific Scale
- NIHSS: National Institute of Health Stroke Scale
- PSG: Polysomnography
- AHI ≥ 5: Apnea-Hypopnea Index ≥ 5
- CPAP: Continuous Positive Airway Pressure
<table>
<thead>
<tr>
<th>Author</th>
<th>Diagnosis Study design</th>
<th>Subjects (n), male (m)</th>
<th>Demographics</th>
<th>Sleep apnea diagnosis (mean age (y), BMI (kg/m²), neck circumference (cm); change)</th>
<th>Characteristics of SDB and stroke: (baseline, change) (mean, n), mean, d, w</th>
<th>Timing of follow-up sleep study after follow-up (n), mean, from baseline:</th>
<th>Results of follow-up sleep study or change from baseline:</th>
<th>CPAP initiation, compliance</th>
<th>New vascular events, n/%</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harbison et al., 2002</td>
<td>Stroke Prospective n = 68</td>
<td>73 y, BMI 25.5→ neck 38 →</td>
<td>AHl ≥ 10</td>
<td>AHI 31→24, OAI10, CAI6, ESS11; mRS13, BI3, CS9, SSS19, NIHSS14</td>
<td>96%→74%, AHI ≥ 15 in 84%→62%, AHI ≥ 20 in 86%→54%, AHI ≥ 30 in 42%→34%</td>
<td>50 cases in 6→9 w, Autoreset</td>
<td>3/6% 10/15% within 3 m</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parra et al., 2000</td>
<td>Ischemic or hemorrhagic stroke, TIA</td>
<td>n = 161, m 50.9%</td>
<td>AHI 10</td>
<td>AHI 21.2→16.9, ESS 4.8→4.5, BI 80.0→81.9, CS 8.3→9.5</td>
<td>96%→74%, AHI ≥ 15 in 84%→62%, AHI ≥ 20 in 86%→54%, AHI ≥ 30 in 42%→34%</td>
<td>86 cases in 3 m</td>
<td>3/6% 10/15% within 3 m</td>
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<table>
<thead>
<tr>
<th>Author</th>
<th>Diagnosis</th>
<th>Study design</th>
<th>Subjects (n), male (%)</th>
<th>Demographics</th>
<th>Subjects</th>
<th>Sleep apnea diagnosis</th>
<th>Characteristics</th>
<th>Timing of sleep study after follow-up (n), mean, d</th>
<th>Results of follow-up sleep study or change from baseline: sleep apnea prevalence</th>
<th>CPAP initiation, compliance</th>
<th>New vascular events, n/%</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Szucs et al., 2002</td>
<td>Ischemic or hemorrhagic stroke</td>
<td>Prospective n = 106, m 66.0%</td>
<td>ODI &gt; 10</td>
<td>ODI 26→17 (hemorrhagic group ODI 26→10, ischemic group ODI 24→22), NIHSS 19–8</td>
<td>51 cases in 3 m portable device</td>
<td>ODI &gt; 10 in 67%, ODI &gt; 20 in 42.5%</td>
<td>10/9% within 3 m</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bassetti et al., 2006</td>
<td>Stroke</td>
<td>Prospective n = 152, m 68.4%</td>
<td>AHI &gt;10</td>
<td>AHI 17.5, in 28/33 cases AHI ≥10 in 33 cases in 6m, AHI &lt; 10 in 58%→46%, CPAP in 16/12%</td>
<td>Auto-CPAP, AHI ≥ 10 in 58%, AHI ≥ 20 in 132 cases 58%, AHI ≥ 30 in assessed 31%, by NIHSS 7</td>
<td>18/14% within 6 m</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

**Note:**
- **Author:** The authors’ names are listed.
- **Diagnosis:** The type of diagnosis is specified.
- **Study design:** Indicates whether the study was prospective or not.
- **Subjects:** Specifies the number of subjects and the gender distribution.
- **Demographics:** Includes mean age, BMI, neck circumference, and change.
- **Subjects:** Describes the mean age, BMI, and neck circumference.
- **Sleep apnea diagnosis:** Includes AH1, OAI, CAI, ESS, mRS, BI, SSS, NIHSS.
- **Characteristics:** Details the mean age, BMI, neck circumference, and change.
- **Timing of sleep study after follow-up (n), mean, d:** Specifies the timing of the follow-up study.
- **Results of follow-up sleep study or change from baseline:** Describes the results of the follow-up study.
- **CPAP initiation, compliance:** Details the CPAP initiation and compliance.
- **New vascular events, n/%:** Specifies the new vascular events and their percentage.
- **Comments:** Provides additional comments or notes.
<table>
<thead>
<tr>
<th>Author</th>
<th>Diagnosis</th>
<th>Study design</th>
<th>Subjects (n), male (m)</th>
<th>Demographics (y), BMI, neck circumference (cm); change</th>
<th>Characteristics of SDB and stroke: (baseline, change) mean</th>
<th>Timing of follow-up sleep study after follow-up or change</th>
<th>Results of follow-up sleep study or change from baseline: sleep apnea prevalence</th>
<th>CPAP initiation, compliance</th>
<th>New vascular events, n/%</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hui et al., 2002</td>
<td>Stroke case-control</td>
<td>n = 51, m 54.9%</td>
<td>64.2 y, BMI 24.3, neck 38.1</td>
<td>AHI ≥ 10, OSA AH1 ≥ 20</td>
<td>AH1 ≥ 10 in 20 cases in 1 m, PSG, AHI ≥ 15 in 3 m Auto-CPAP (n=4)</td>
<td>AHI ≥ 10 in 67%, AHI ≥ 15 in 61%, AHI ≥ 20 in 49%; 1 m (n=20), OAI 27.3 → 20.5, CAI 5 → 2.5, AHI ≥ 20 in 80% → 45%, auto-CPAP in 4 cases, 3 m CPAP 2.5 h/d</td>
<td>1/2.0% at hospital</td>
<td></td>
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</tr>
</tbody>
</table>

Hui et al., 2002

Stroke case-control

n = 51, m 54.9%

64.2 y, BMI 24.3, neck 38.1

OSA AH1 ≥ 20

AH1 ≥ 10 in 20 cases in 1 m, PSG, AHI ≥ 15 in 3 m Auto-CPAP (n=4)

AHI ≥ 10 in 67%, AHI ≥ 15 in 61%, AHI ≥ 20 in 49%; 1 m (n=20), OAI 27.3 → 20.5, CAI 5 → 2.5, AHI ≥ 20 in 80% → 45%, auto-CPAP in 4 cases, 3 m CPAP 2.5 h/d

1/2.0% at hospital
<p>| Author                  | Diagnosis Study design | Subjects (n), male (m) | Demographics | Sleep apnea diagnosis criterion (mean age (y), BMI (kg/m²), neck circumference (cm); change) | Characteristics of SDB and stroke: (baseline, change) meaningful difference | Timing of sleep study after follow-up (n), mean, difference in baseline: | Results of follow-up sleep study or change from baseline: | CPAP (initiation, compliance) | New vascular events, n/% | Comments | Death %, time to death; intervention |
|------------------------|------------------------|------------------------|--------------|--------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|------------------------------------------------------------------------|------------------------------------------------------------------------|-------------------------------|-----------------------------|---------------------------|
| Broadley et al., 2007  | Prospective case-control | n = 55, m 58.0%        | median 71 y, BMI 26.8 | AHI ≥ 10 ESS&gt;9 in 18%, CAI 7-4 in 11/11 cases, BI 5 | 11 cases in 6 w (CPAP group), CPAP group 11/11 cases with AHt 10 | 53% CPAP (AHI ≥ 15) in 13 cases | 11.8%, 4 y | AutoSet Portable Plus | 10/16.9% during 1.23–5.9 d; | Broadley et al., 2007 |
| Dyken et al., 1996     | Prospective            | n = 51, m 51.0%        | 64.6 y, AHI 10 | 3-5 m (4), 4y (all) | 77% 1 | 11.8%, 4 y | AutoSet Portable Plus | 10/16.9% during 1.23–5.9 d; | Broadley et al., 2007 |
| Martinez-Garcia et al., 2006 | Prospective            | n = 107, m 33.6%       | 73.2 y, BMI 28.8–28.1, neck 40.7 | AHI 34.9–20.1, OAI 26.3–12.4, CAI 3.1–2.8, BS 61, CS 7.4 | 59 cases in 60–90 d, AutoSet Portable Plus | 10/16.9% during 1.23–5.9 d; mean 65.9 d | 10/16.9% during 1.23–5.9 d; | AutoSet Portable Plus | 10/16.9% during 1.23–5.9 d; | Broadley et al., 2007 |</p>
<table>
<thead>
<tr>
<th>Author</th>
<th>Diagnosis</th>
<th>Study design</th>
<th>Subjects (n), male (m)</th>
<th>Demographics</th>
<th>Sleep apnea diagnosis (y²), BMI (kg/m²), neck circumference (cm); change</th>
<th>Characteristics of SDB and stroke: (baseline, change) mean (n), mean, from</th>
<th>Timing of sleep study after follow-up or change</th>
<th>Results of follow-up sleep study or change from baseline: sleep apnea prevalence</th>
<th>CPAP initiation, compliance</th>
<th>New vascular events, time to death; intervention</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yan-fang et al., 2009</td>
<td>Ischemic stroke</td>
<td>Prospective n = 60, m 68.3%</td>
<td>57.9 y, BMI 25.2</td>
<td>AHI ≥ 5/h</td>
<td>AHI 19.6→ 57.9 (3m)→ 31.0 (6m), SSS 32.0</td>
<td>65%→26.3% →19.3</td>
<td>2/3.3%</td>
<td>57 cases</td>
<td>65%→26.3% →19.3</td>
<td>2/3.3%</td>
<td>Death %, time to death; intervention</td>
</tr>
</tbody>
</table>

1 apnea-hypopnea index, 2 autotitrating continuous positive airway pressure, 3 Barthel Index, 4 body mass index, 5 Barthel Score, 6 central apnea index, 7 central sleep apnea, 8 continuous positive airway pressure, 9 Canadian Scale, 10 day(s), 11 Epworth Sleepiness Scale, 12 month, 13 modified Rankin Scale, 14 National Institutes of Health Stroke Scale, 15 obstructive apnea index, 16 oxygen desaturation index, 17 obstructive sleep apnea, 18 polysomnography, 19 Scandinavian Stroke Scale, 20 transient ischemic attack, 21 week, 22 year
2.3 Diagnosis of sleep apnea

2.3.1 Symptoms, clinical features and diagnosis

The most typical symptom of sleep apnea is daytime sleepiness. The sleepiness is frequently assessed with Epworth Sleepiness Scale (ESS, scale 0–24) (Johns, 1991). Sleep apnea patients may feel sleepy, but they may also suffer from insomnia symptoms (Lavie, 2007). In a population-based sample, excessive daytime sleepiness occurred in 18% – of these 14% were men and 22% women – and the significant daytime sleepiness did not necessarily associate with OSA (Duran Joaquin, Santiago Esnaola, ramon Rubio, Angeles Iztueta, 2001).

Typical clinical features such as obesity (BMI > 30), daytime sleepiness (ESS scores over ten), male gender, snoring and witnessed apneas suggest the diagnosis of sleep apnea. Stroke patients lack the classic characteristics such as obesity and daytime tiredness (Chan, Coutts, & Hanly, 2010). In a recent study from Denmark, the investigators did not find a correlation between ESS and AHI, but AHI correlated with BMI, age, and male gender (Fuglsang, Lilja-Fischer, Petersen, & Bille, 2019). The sleep apnea diagnosis has been estimated among stroke patients and different AHI cut-off points have been used for the diagnosis of sleep apnea as shown in Tables 2–7. The sleep apnea criterion of AHI ≥ 5/h has been widely used (Boulos et al., 2017; Bravata et al., 2017; Ifergane et al., 2016; Tosun et al., 2018), while some studies have used AHI ≥ 10/h (Bassetti & Aldrich, 1999; Iranzo et al., 2002) or AHI ≥ 15/h (Patel et al., 2018) as the diagnostic cut-off point of sleep apnea. Sleep apnea is usually classified into mild (AHI 5–15/h), moderate (15–30), or severe sleep apnea (AHI ≥ 30/h).

Significant daytime sleepiness (ESS > 10) is uncommon among stroke patients with sleep apnea (Chan et al., 2010). The daytime sleepiness may be stable, but cognitive capacity tends to decrease (Engleman & Douglas, 2004; Van Dongen, Maislin, Mullington, & Dinges, 2003). Snoring and apneas are typical symptoms of sleep apnea disturbing nighttime sleep and causing sleepiness and reduced quality of life (Bassari & Guilleminault, 2000; Engleman & Douglas, 2004). In clinical practice, disturbed sleep, night sweating, nocturnal diuresis, and headache in the morning (Loh, Dinner, Foldvary, Skobieranda, & Yew, 1999; Neau et al., 2002) are common, and some sleep apnea patients may have memory disorder, difficulty in concentrating, and even mental disorder (Saunamaki & Jehkonen,
Sleep apnea diagnosis is based on symptoms, clinical features, and the results of nocturnal cardiorespiratory polygraphy or polysomnography.

### 2.3.2 Unattended portable monitors in sleep apnea diagnostics

Even though PSG is the gold standard of sleep apnea diagnosis (Epstein et al., 2009), unattended portable polygraphy may be a more feasible and convenient way to screen for sleep apnea than PSG, especially among hospitalized stroke patients (Brown et al., 2013; Collop et al., 2007). The availability of PSG is limited, requires specialized staff, and is laborious. The analyzability of unattended portable monitors in sleep apnea screening was 80.3–96.5% among stroke patients evaluated one to three days after hospitalization (Boulos et al., 2017; Broadley et al., 2007; Ifergane et al., 2016; Joo et al., 2011; Kepplinger et al., 2013; Parra et al., 2000). An unattended portable monitor, such as ApneaLinkPLus™ Version 9.30 (Resmed, Sydney, Australia) has been validated against full polysomnography for screening of obstructive sleep apnea, but without convincing data for diagnosing central sleep apnea (Lesser, Haddad, Bush, & Pian, 2012), and has not been validated but is nevertheless used with stroke patients (Brown et al., 2014; Lesser et al., 2012). A nocturnal cardiorespiratory polygraphy can be performed in the stroke unit or at home and it is technically easy to perform. The three channels in ApneaLinkPLus™ (Resmed, Sydney, Australia) give information about breathing efforts (thoracic belt), SaO2 (finger probe pulse oximeter), and nasal airflow (nasal cannula).

A nocturnal polygraphy reports 20–30% lower AHI than PSG (Escourrou et al., 2015; Hedner et al., 2011), but the agreement between PSG and cardiorespiratory polygraphy is good (Masa et al., 2011; Santos-Silva et al., 2009; Zou, Grote, Peker, Lindblad, & Hedner, 2006). The gold standard of sleep apnea diagnosis is PSG (Epstein et al., 2009) and it is mainly carried out in the recovery phase of stroke (Bassetti & Aldrich, 1999; Dyken et al., 1996; Iranzo et al., 2002; Mohsenin & Valor, 1995; Tosun et al., 2008). The American Academy of Sleep Medicine suggests considering PSG among stroke patients for diagnosis of sleep apnea in laboratory settings or at home (Epstein et al., 2009). Unattended portable polygraphy is both secure and bearable (Broadley et al., 2007), as well as reliable for finding sleep apnea among patients without considerable comorbidities (Collop et al., 2007; Masa et al., 2011).

Manual scoring of cardiorespiratory polygraphy is easier and quicker than scoring PSG by a technologist or experienced clinician. The manual scoring rules of the American Academy of Sleep Medicine are different for PSG and unattended
portable recording (Berry et al., 2012). The software of ApneaLinkPlus™ analyzes the nocturnal recording data automatically. In the acute phase of stroke, sleep apnea screening has mainly been done with PSG from an epidemiological point of view, but not from the perspective of practical aspects (Bassetti et al., 2006; Broadley et al., 2007; Iranzo et al., 2002). Kepplinger and coworkers (Kepplinger et al., 2013) evaluated 61 stroke or TIA patients in the acute phase of stroke by cardiorespiratory polygraphy and compared the findings to follow-up full PSG, showing 94.7% sensitivity for moderate to severe sleep apnea when compared to acute phase cardiorespiratory polygraphy. The diagnosis of sleep apnea among stroke patients and comparisons between automatic and manual scoring results by ApneaLinkPlus™ after stroke are scarce (Brown, Chervin et al., 2014).

The automatic and manual scoring data of 327 stroke patients showed no differences concerning CAI, hypopnea index, and ODI, but there was a significant difference in AHI (automatic data AHI 9 and manual data AHI 13) in a study from the United States (Brown et al., 2014). In that study, the diagnosis of sleep apnea was missed in only 81 to 82% of patients. So far, only AHA/ASA guidelines advise giving consideration to sleep study of stroke patients (Kernan et al., 2014)). Significant daytime sleepiness (ESS > 10) is uncommon among stroke patients with sleep apnea (Chan et al., 2010). Daytime sleepiness may be stable, but cognitive capacity tends to decrease (Engleman & Douglas, 2004; Van Dongen et al., 2003).

### 2.3.3 Differential diagnosis, pre-screening and comorbidities

It is important to exclude other reasons for sleepiness, such as depression, hypothyroidism, high plasma glucose level, post-menopause, and burnout. A widely used screening method of SDB is the Basic Nordic Sleep Questionnaire (Partinen & Gislason, 1995). The likelihood of OSA may be evaluated with questionnaires such as STOP-bang (Chung, Yang, Brown, & Liao, 2014) or the BERLIN questionnaire (Netzer, Strohs, Netzer, Clark, & Strohl, 1999). Questionnaires such as STOP BANG and the BERLIN questionnaire have been reported to be superior to ESS (Chiu et al., 2017; Luo, Huang, Zhong, Xiao, & Zhou, 2014; Prasad et al., 2017). One recent study from Sweden evaluated whether STOP-Bang and pulse oximetry together may find cases with undiagnosed OSA (Christensson et al., 2018). The authors reported that 91% of the cases with a STOP-Bang score over six had OSA, and for cases with scores 2–5 they suggested nocturnal pulse oximetry for screening of sleep apnea before surgery (Christensson et al., 2018).
et al., 2018). It has been pointed out that the questionnaires evaluating sleepiness are in most cases insensitive and unspecific in diagnosing OSA in primary care (Miller & Berger, 2016). The pre-screening of sleep apnea in stroke patients with questionnaires showed sensitivities between 52 and 100% and specificities ranging from 14.0 to 100% in a recent systematic review from Finland, but the investigators did not recommend using questionnaires as a screening method for sleep apnea after stroke (Takala, Puustinen, Rauhala, & Holm, 2018). In that same review (Takala et al., 2018), nocturnal oximetry had a sensitivity of 77% and a specificity of 100%, while capnography had the best power to predict sleep apnea with a sensitivity of 87% and a specificity of 100%, although it is not convenient in the acute phase of stroke.

Sleep apnea is related to other diseases such as hypertension, type II diabetes, cardiovascular diseases, and stroke. As many as 48% of the patients with hypertension suffer from sleep apnea (Williams et al., 1985), and patients with cardiovascular diseases have two to three times more sleep apnea than healthy people (Somers et al., 2008). In a large study from Denmark including 19,438 patients with OSA, the prevalence of atrial fibrillation was 1.46% of cases three years prior to an OSA diagnosis and atrial fibrillation had an OR of 1.47 (95% CI 1.27–1.70, p < 0.001) for OSA. A prospective study by Javaheri (Javaheri, 2006) included 100 middle-aged overweight male patients with heart failure, and 49% of the patients were reported to have sleep apnea. Patients with coronary artery disease also have elevated risk for OSA, and a recent study by the Tehran Heart Center observed that among 337 included patients undergoing coronary angiography, three-vessel disease was more prevalent in the OSA group compared to the non-OSA group (68% versus 32.0%) (Vasheghani-Farahani et al., 2018). A recent study from the United Kingdom (Feher, Hinton, Munro, & de Lusignan, 2019) investigated obstructive sleep apnea prevalence in 1,275,461 people with type 2 or type 1 diabetes in primary care setting, showing 0.7% overall prevalence of obstructive sleep apnea; among type 2 diabetes patients, the prevalence was 0.5% in those with normal weight and 9.6% in obese people, while the prevalence was lower among those with type 1 diabetes (0.3% and 4.3%). Of importance, OSA in men and women is associated with twofold risk of disability pension and nearly twofold risk of sick leaves (Sjosten et al., 2009).
2.4 Risk factors for sleep apnea and stroke

In a Spanish population-based study, over one third of the population without sleep apnea experienced snoring and 6% of the studied people had witnessed apneas in PSG, but snoring (46% men versus 25% women) as well as apneas (10% versus 2.5%) were more common among men than among women, and both increased with age (Duran Joaquin, Santiago Esnaola, Ramon Rubio, Angeles Iztueta, 2001). In the same study, the prevalence of OSA increased with age in both genders, the OR was 2.2 for every 10-year increase, and OSA was more prevalent in women only in age group 50–59 years (35.0% versus 27.9%) (Duran Joaquin, Santiago Esnaola, Ramon Rubio, Angeles Iztueta, 2001).

The prevalence of sleep apnea among men and women differs due to differences in hormonal factors, upper airway anatomy, and respiratory control mechanisms (Mohsenin, 2003). In males, obstructive sleep apnea is related to a combination of higher BMI and increasing age (Anttalainen et al., 2007). Men may have even fourfold probability of sleep apnea but the probability was only twofold in those over 52 years of age (Martinez-Rivera, Abad, Fiz, Rios, & Morera, 2008).

Obesity is a remarkable risk for sleep apnea and of those with BMI over 40 kg/m², more than half have sleep apnea, and two thirds of sleep apnea patients are obese or overweight (Marshall et al., 2009). Neck circumference expresses obesity and increases the risk of OSA twofold, and even mild central obesity is another notable risk factor for OSA (Martinez-Rivera et al., 2008; Newman et al., 2001).

Lifestyle habits such as alcohol consumption and smoking are risk factors for sleep apnea. It is common that the occurrence and duration of apneas increase after alcohol consumption, and this may exacerbate sleep apnea particularly in men (Peppard, Austin, & Brown, 2007; Roehrs & Roth, 2001). Smoking increases the risk for sleep apnea (Deleanu et al., 2016), and smoking cessation tends to have positive effects on OSA and cardiovascular morbidity.

Sleep apnea and snoring are independent risk factors for stroke, the risk being one to threefold (Yaggi & Mohsenin, 2004). Ischemic stroke and sleep apnea share the risk factors concerning aging, male gender, smoking, excessive alcohol consumption, atrial fibrillation, coronary artery disease, and diabetes mellitus. Sometimes 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 (Dyken & Im, 2009). The ten most important risk factors explain 90% of the risk for all strokes and they are: hypertension (OR 2.64), cardiac causes (OR 2.38; including atrial fibrillation, flutter, myocardial infarction, rheumatic valve
disease, prosthetic heart valve), current smoking (OR 2.09), increasing waist-to-hip ratio (OR 1.65), alcohol consumption (OR 1.51, over 30 drinks per month OR 1.18–1.92), diabetes mellitus (OR 1.36), depression (OR 1.35), psychosocial stress (OR 1.30), ratio of apolipoproteins B to A1, i.e. problems with blood fat levels (OR 1.89), and reduced physical activity (OR 0.69) (O'Donnell et al., 2010). Of all cardiac risk factors, atrial fibrillation is the most common cardioembolic risk for stroke. The risk for stroke increases with aging, and men under 75 years have twofold risk compared to women because women get stroke at older age (Hyvärinen et al., 2010; Seshadri et al., 2006). Smoking increases the risk for stroke, and the risk grows with the amount of cigarettes (O'Donnell et al., 2010). Heavy alcohol consumption (more than three drinks per day) increases both the risk for stroke and mortality, the risk being higher in women than in men (Patra et al., 2010).

2.5 Stroke

2.5.1 Definition, etiology, and location of stroke

Ischemic stroke occurs when cerebral blood flow is reduced, and thromboembolism arises from intracranial or extracranial arteries (artery-to-artery embolism), emboli of cardiac origin, hypercoagulable states, occlusion of small penetrating arteries of the brain, or non-atherosclerotic vasculopathies (Bradley, Daroff, Fenichel, & Marsden, 1995). A hemorrhagic infarction is the result of multifocal extravasation, and parenchymal hematoma results from bleeding due to blood vessel damage caused by ischemia and reperfusion (Immediate anticoagulation of embolic stroke: Brain hemorrhage and management options. Cerebral Embolism Study Group 1984). Transient ischemic attack is defined as temporary disruption in cerebral blood flow without permanent damage to the brain, usually lasting some minutes or less than one hour (Ischemic stroke and TIA. Current care guidelines. Working group set up by the Finnish Medical Society Duodecim and the Finnish Neurological Society. Helsinki: The Finnish Medical Society Duodecim, 2016). The etiology of stroke has an influence on patients’ treatment and outcome (Ischemic stroke and TIA. Current care guidelines. Working group set up by the Finnish Medical Society Duodecim and the Finnish Neurological Society. Helsinki: The Finnish Medical Society Duodecim, 2016). Based on the symptoms of stroke and acute phase imaging, stroke or TIA may be divided into anterior and posterior circulation region, depending on the anatomical region areas of cerebral blood

The widely used subdivision of stroke etiology is based on the Trial of Org Acute Stroke Treatment (TOAST) classification: large-artery atherosclerosis, cardioembolism, small-vessel occlusion, stroke of other determined etiology, and stroke of undetermined etiology (Adams et al., 1993). The term embolic stroke of undetermined source, or ESUS, is used when the etiology of the stroke is unknown (Hart et al., 2014). Large-artery atherosclerosis is the most common (20.9%) cause of stroke among stroke patients aged 45 to 70 years, although cardioembolism is the reason in a quarter of the cases (Grau et al., 2001). Hypertension, diabetes mellitus, hypercholesterolemia, and overweight are most prevalent in small-vessel disease (20.5%), which is associated to the lowest stroke severity and mortality rates (Grau et al., 2001). Atherosclerosis increases the risk for new ischemic stroke by 15 to 20% (Purroy et al., 2007).

Strokes in the brainstem region (10% of strokes) may cause Cheyne-Stokes respiration (Lee, Klassen, Heaney, & Resch, 1976; Nachtmann, Siebler, Rose, Sitzer, & Steinmetz, 1995) or a high proportion of central sleep apneas (Lee et al., 1976). Brainstem stroke has three times higher odds for SDB, central sleep apnea, and higher nocturnal desaturations compared to cortical strokes (Brown et al., 2014). Strokes in the brainstem and cerebellum regions also result in greater AHI as compared to cortical strokes (Bassetti, Aldrich, & Quint, 1997; Manconi et al., 2014). Many studies have pointed out that stroke lesion location and sleep apnea severity and sleep apnea type had no correlation (Fisse et al., 2017; Nopmaneejumruslers, Kaneko, Hajek, Zivanovic, & Bradley, 2005; Parra et al., 2000; Stahl et al., 2015; Szucs et al., 2002). The highest AHI was in the anterior circulation region and the second highest value of AHI existed in pons in a study by Siccoli and coworkers (Siccoli et al., 2008).

### 2.5.2 Epidemiology of stroke

The incidence of stroke has decreased from the year 2000 to 2010 both in Finland and other welfare states worldwide, (Feigin et al., 2014), with the exception of Finnish men under 45 years whose morbidity has increased (Statistics of Finland). In Finland, the mean age of stroke patients was 72.7 years; of those, 51.2% were men and one fifth were still working in 2010. In Finland, 1.5% of the population were stricken with stroke ten years ago (Meretoja et al., 2010); globally, 46–
72/1,000 people in the age group over 65 years are affected by stroke every year (Feigin, Lawes, Bennett, & Anderson, 2003).

Stroke, which is among the four leading causes of mortality, increases morbidity and healthcare costs, and the costs during the first three months depend strongly on the ability to function at hospital discharge as assessed by mRS (Dawson et al., 2007; Luengo-Fernandez, Gray, & Rothwell, 2009a; Meretoja et al., 2011). The stroke patients treated with thrombolysis were self-employed (MRS scores 0–2) in 68% of the cases three months after stroke and were most likely to have better ability to act and lower mortality in the future (Magalhaes et al., 2014; Ovbiagele & Saver, 2010). The stroke patients who underwent thrombolysis and in whom the etiology of stroke was small-vessel occlusion had better recovery than those with other etiologies (Mustanoja et al., 2011). It has been pointed out that fast diagnosis and treatment of stroke reduce significantly the 90-day risk of fatal or disabling stroke, overall days in hospital, hospital admissions for recurrent stroke, hospital admissions due to vascular events, and healthcare costs after stroke (Luengo-Fernandez, Gray, & Rothwell, 2009b).

2.5.3 Symptoms, imaging, clinical evaluation and thrombolysis treatment of stroke

The symptoms of ischemic stroke appear quickly, within minutes or hours (Ischemic stroke and TIA. Current care guidelines. Working group set up by the Finnish Medical Society Duodecim and the Finnish Neurological Society. Helsinki: The Finnish Medical Society Duodecim, 2016). Clinical evaluation must be done fast and diagnosis of stroke should be confirmed with computed tomography (CT) or magnetic resonance imaging (MRI) (Ischemic stroke and TIA. Current care guidelines. Working group set up by the Finnish Medical Society Duodecim and the Finnish Neurological Society. Helsinki: The Finnish Medical Society Duodecim, 2016). In the case of acute stroke, the stroke lesion size was evaluated by CT and the ischemic stroke volume measurements were correlated with the neurologic examination scores on admission (Brott et al., 1989). The NIHSS is a 15-item scale developed in 1989 used to assess stroke severity in different domains: level of consciousness, eye and facial movements, visual fields, arm and leg strength, coordination, sensation, speech and neglect (Brott et al., 1989). The original NIHSS scale ranges from 0 to 42, but different variations have been modified from the primary version; in any case, the interpretation of NIHSS scores is that the higher the scores, the more severe the stroke (Ischemic stroke and TIA.
Stroke patients’ primary imaging with head CT or MRI reveals the ischemic stroke lesion or hemorrhagic infarction on hospital admission (Ischemic stroke and TIA. Current care guidelines. Working group set up by the Finnish Medical Society Duodecim and the Finnish Neurological Society. Helsinki: The Finnish Medical Society Duodecim, 2016). A study from Hungary showed that three months after stroke, the number of apneas decreased in hemorrhagic stroke patients but remained unchanged in ischemic stroke patients (Szucs et al., 2002). A parenchymal hematoma in imaging predicts worse neurological outcome and increased mortality (Sussman & Connolly, 2013). The clinical decision of thrombolytic treatment is difficult if the patient does not know the time of symptom onset; in that case, brain MRI is more sensitive for showing the ischemic lesion (Ischemic stroke and TIA. Current care guidelines. Working group set up by the Finnish Medical Society Duodecim and the Finnish Neurological Society. Helsinki: The Finnish Medical Society Duodecim, 2016). In most cases, brain CT (native CT) is performed before the decision of intravenous thrombolysis therapy (Ischemic stroke and TIA. Current care guidelines. Working group set up by the Finnish Medical Society Duodecim and the Finnish Neurological Society. Helsinki: The Finnish Medical Society Duodecim, 2016).

Intravenous thrombolysis treatment with alteplase, tissue plasminogen activator, is possible if stroke patients have less than 4.5 hours from symptom onset, NIHSS scores are two or more, the patient is self-dependent (modified Rankin scale score 0–3), and there is no contraindication for tPA treatment (Ischemic stroke and TIA. Current care guidelines. Working group set up by the Finnish Medical Society Duodecim and the Finnish Neurological Society. Helsinki: The Finnish Medical Society Duodecim, 2016). Common contraindications for intravenous thrombolytic treatment are bleeding in the brain tissue, unawareness of stroke symptom onset, or anticoagulation medication for atrial fibrillation. The thrombolytic treatment aims to dissolve the thrombus, restrict the stroke lesion, ensure better outcome, and decrease possible complications. Register-based studies reported 1.7–2.4% prevalence rates in symptomatic hemorrhage among stroke patients treated with thrombolysis within 4.5 hours of symptom onset (Wahlgren et al., 2008)). The focus of conservative treatment is on restricting the stroke size, preventing new ischemic events, and taking care of blood pressure, glucose level, comorbidities and healthy lifestyle (Ischemic stroke and TIA. Current care guidelines. Working group set up
2.6 Sleep apnea and stroke size

The medulla oblongata guides respiratory control. The stroke lesion may change the central regulation of breathing and reduce respiratory muscle activity or produce sleep apnea (Rowat et al., 2006). The size of stroke has been pointed out to associate with sleep apnea severity; for example, total anterior circulation region stroke and bilateral stroke lesions caused more severe sleep apnea than stroke in a single region (Ahn et al., 2013; Siccoli et al., 2008). Contrary to the study of Siccoli and coworkers (Siccoli et al., 2008), another study found that sleep apnea has no correlation to stroke size (Iranzo et al., 2002). Also, opposite research results have been reported, i.e., that stroke size did not affect the severity of sleep apnea, but sleep apnea was more severe and prevalent in brainstem infarction than in cortical strokes (Brown et al., 2014).

2.7 Treatment of sleep apnea

2.7.1 Continuous positive airway pressure (CPAP)

Untreated sleep apnea among stroke patients may decrease recovery from stroke and increase mortality (Bassetti et al., 2006; Dyken et al., 1996; Good et al., 1996; Kaneko et al., 2003; Turkington et al., 2004). Individual consideration is important in the treatment of sleep apnea. Compliant long-time CPAP users had reduced risk of both fatal and nonfatal cardiovascular events compared to those without CPAP treatment (Myllylä et al., 2019). It is wise to treat stroke patients’ obstructive sleep apnea with CPAP (Sleep apnea syndrome. Current care guidelines. Working group appointed by the Finnish Medical Society Duodecim and the Finnish Respiratory Society. Helsinki: The Finnish Medical Society Duodecim, 2017.), although we still do not know which stroke patients benefit the most from CPAP therapy.

The most common treatment of sleep apnea is CPAP therapy, which pushes air with pressure toward the airways, keeps the airway open, and prevents airway collapse. CPAP devices may have a certain pressure, or the machine may detect the pressure required if autotitrating continuous positive airway pressure (auto-CPAP) is used to treat apneas and prevent airway collapse. The positive effects of CPAP
therapy seen in randomized, controlled trials include improvement of endothelial function (Schwarz, Puhan, Schlatter, Stradling, & Kohler, 2015) and decreased systolic blood pressure in normotensive obstructive sleep apnea (2 to 3 mm Hg) (Montesi, Edwards, Malhotra, & Bakker, 2012) and in resistant hypertension cases (6 to 7 mm Hg) (Iftikhar et al., 2014) as well as improved insulin sensitivity (Iftikhar, Hoyos, Phillips, & Magalang, 2015). Also clinical studies with observational design have reported reduced rates of cardiovascular complications and mortality due to cardiovascular causes, particularly among compliant patients (Campos-Rodriguez et al., 2012; Marin, Carrizo, Vicente, & Agusti, 2005). The Sleep Heart Health Study reported a connection between obstructive sleep apnea and risk of stroke (Redline et al., 2010) and there had been many expectations of the effect of CPAP to reduce the risk of stroke.

An extensive randomized control trial of 2,717 adult patients pointed out that patients with coronary or cerebrovascular disease and moderate or severe OSA treated with CPAP did not have a reduced risk for recurrent stroke, and only patients who were extremely committed to use CPAP (≥ 4 h per night) might achieve a slight protective effect (McEvoy et al., 2016). However, this study has been criticized for some limitations, such as low compliance and the fact that the most severe OSA patients were excluded, and the negative results in the study were likely caused by these two reasons (Javaheri et al., 2017). Some studies have pointed out improvements in functional recovery (assessed by NIHSS), reduced hospitalization time, lower numbers of re-hospitalization, and one third decrease in mortality rates among stroke patients when sleep apnea was treated with CPAP (Bravata et al., 2011; Martinez-Garcia et al., 2009; Minnerup et al., 2012). Compliance is good if CPAP is used longer than four hours per night, but as many as half of sleep apnea patients discontinue the use of CPAP (Marin et al., 2005; McEvoy et al., 2016). The main problem is lack of CPAP compliance due to mask problems, anxiety, and difficulties in adapting to CPAP in general population. CPAP compliance is even poorer among stroke patients, being under four hours per night, and less than 50% use CPAP (Aaronson et al., 2016; Bassetti et al., 2006; Hsu et al., 2006; Hui et al., 2002). When compliance with CPAP is poor, it is advisable to consider other treatment options as well among stroke patients, such as weight reduction, supine avoidance therapy, e.g. mandibular advancement device (MAD), and in certain cases, oxygen therapy.
2.7.2 Other treatment options

Many sleep apnea patients are overweight, and dieting as well as physical exercise may decrease the severity of sleep apnea (Foster et al., 2009; Kuna et al., 2013); in the case of mild sleep apnea, weight loss can be the only treatment (Effect of weight loss on upper airway collapsibility in obstructive sleep apnea (Schwartz et al., 1991). A Finnish study reported sufficient weight reduction with a cognitive-behavioral program among OSA patients with or without CPAP treatment after two years’ follow-up, and the decrease in weight was not significantly better in those on CPAP therapy (Kajaste, Brander, Telakivi, Partinen, & Mustajoki, 2004). Stroke patients often lose muscle mass and at the same time, gain more fat mass during stroke recovery (Jorgensen & Jacobsen, 2001).

The American Academy of Sleep Medicine has given recommendations on the importance of weight reduction and physical exercise in everyday life in the treatment of OSA and to decrease the OSA-linked cardiovascular morbidity (Dobrosielski, Papandreou, Patil, & Salas-Salvado, 2017). Physical exercise alone can improve the severity of sleep apnea, as has been shown in empirical studies (Araghi et al., 2013).

Supine avoidance devices have shown good compliance and reduction in severity of OSA (Eijsvogel et al., 2015; van Maanen & de Vries, 2014) as well as significant reduction in AHI in a randomized controlled trial among stroke patients treated with a supine avoidance pillow (Svatikova et al., 2011). The avoidance of supine position is not possible if the stroke patient has hemiplegia. Oral appliance therapy, or MAD therapy, moves the mandible forward and opens the airway, leading to 30–50% reduction of apneas, especially in mild sleep apnea cases (Edwards et al., 2016). Although MAD treatment is feasible, well-tolerated, and more comfortable than CPAP, there are no previous studies concerning MAD therapy among stroke patients. Oxygen therapy may be one possibility in the case of significant oxygen desaturation, bearing in mind the possibility that oxygen therapy may prolong apneas (Mehta, Vasu, Phillips, & Chung, 2013). Surgical operations may reduce the severity of sleep apnea in general population with sleep apnea, but there are no studies concerning stroke patients (Kotecha & Hall, 2014).

2.7.3 Untreated sleep apnea and stroke

Shortly after stroke, the coexistence of stroke and OSA decrease the functional outcome and increase mortality compared to stroke patients without OSA in the
acute phase of stroke (Good et al., 1996). The underlying mechanisms of how sleep apnea is associated with stroke outcome are still unclear. Untreated obstructive sleep apnea among stroke patients reduces patients’ quality of sleep and quality of life. Stroke patients with sleep apnea also experience higher risk for cardiovascular events, mortality, re-strokes, reduced functional recovery, and prolonged hospitalization (Bassetti et al., 2006; Brown et al., 2019; Dyken et al., 1996; Good et al., 1996; Kaneko et al., 2003; Mansukhani et al., 2011; Redline et al., 2010; Rola et al., 2008; Turkington et al., 2004; Yaggi et al., 2005).
3  **Aims of the study**

There is no consensus as to whether and how sleep apnea should be screened in patients with acute ischemic stroke. The present series of studies focused on the feasibility of type 4 cardiorespiratory polygraphy device in screening for sleep apnea, the prevalence, type, and severity of sleep apnea in ischemic stroke patients who underwent thrombolysis or not, as well as the natural evolution of sleep apnea during six months post stroke. This study also addressed whether ischemic stroke volume or presence of stroke lesion would predict severity of sleep apnea among patients with thrombolysis treatment.

The aims of the present study were:

1. to evaluate the feasibility of cardiorespiratory polygraphy in screening of sleep apnea in the acute phase of ischemic stroke, and to compare agreement between automatically and manually scored results in the acute phase of stroke (I),
2. to investigate the prevalence, type, and severity of sleep apnea among ischemic stroke patients in Northern Finland with or without treatment with thrombolysis (II),
3. to explore the association between ischemic stroke volume or the presence of ischemic stroke lesion on CT and sleep apnea among stroke patients undergoing thrombolysis (III),
4. to find out the evolution of the prevalence, type, and severity of sleep apnea among ischemic stroke patients in Northern Ostrobothnia treated with or without thrombolysis after six-month follow-up (IV).
4 Subjects and methods

4.1 Patients

The cohort of this prospective, observational cohort consisted of 254 ischemic stroke patients (122 consecutive patients with thrombolysis therapy and 132 consecutive patients without thrombolysis) aged 18 years or over admitted to the Stroke Unit at the Department of Neurology of the Oulu University Hospital from April 22, 2013 to January 22, 2015 (Figure 1).

Fig. 1. Flow chart of the study.
The aim of this study was to include at least 100 stroke patients in both groups, i.e. stroke patients with or without thrombolysis treatment. The screening of stroke patients treated without thrombolysis ended on May 9, 2014, when 204 patients had been recruited as reported in Figure 1.

The inclusion criterion was an ischemic stroke, which was confirmed by an on-call neurologist on admission to hospital, based on clinical evaluation and head CT or MRI imaging. The exclusion criterion was inability to co-operate, i.e. confusion or inability to understand the study protocol. Of the entire cohort, 204 ischemic stroke patients were eligible for the final analyses; of those, 110 received thrombolysis treatment and 94 did not (Studies I, II) (Table 8). Study III (Table 9) comprised those undergoing thrombolysis treatment (n = 110). After the six-month follow-up, there were 177 eligible patients (Study IV) (Table 10). The drop-outs are depicted in Figure 1.

4.2 Implementation of the study

Self-contained stroke patients with NIHSS scores > 2 and no contraindication for treatment received thrombolysis treatment within 4.5 hours from stroke symptom onset. The exclusion criteria for thrombolysis therapy were determined in accordance with the Finnish Current Care Guideline for Ischemic Stroke (Lindsberg, 2011). Cardiorespiratory polygraphy was performed within the first 48 hours after symptom onset at the stroke unit, and repeated after six months' follow-up at home. The diagnosis of sleep apnea was based on the cardiorespiratory sleep study, defined as an REI ≥ 5/h. An in-house data collection form was used for collection of clinical data on admission to the hospital.

4.3 Methods

4.3.1 Demographics, medical history and questionnaires

In-house data collection form was used on admission to hospital; thereafter, the data was transferred to Statistical Package for the Social Sciences (SPSS, version 22.0, IBM Corp., Armonk, New York, United States) for statistical analyses.

On admission, age, gender, and history of snoring or witnessed apneas as well as previous comorbidities and current medication were documented. All comorbidities were recorded but the focus was on hypertension,
hypercholesterolemia, diabetes mellitus, coronary artery disease, atrial fibrillation, and peripheral arterial disease (PAD). Neck and waist circumference and BMI in the acute phase of stroke and after follow-up were measured. 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.

On admission to hospital and after six months, daytime sleepiness was assessed by the ESS (Johns, 1991), and stroke outcome, signifying the ability to act, was evaluated with the Modified Rankin Scale (mRS; scale 0–5) (van Swieten, Koudstaal, Visser, Schouten, & van Gijn, 1988). ESS score over 10 is usually considered to reflect increased sleepiness. The degree of handicap is severe when mRS score is over three. The severity of stroke was evaluated with the National Institutes of Health Stroke Scale (NIHSS; scale 0–35) (Goldstein, Bertels, & Davis, 1989) and the level of consciousness with the Glasgow Coma Scale (GCS; scale 3–15) (Teasdale & Jennett, 1976) on admission.

### 4.3.2 Cardiorespiratory polygraphy (Figure 2)

Cardiorespiratory polygraphy was performed within the first 48 hours after symptom onset of ischemic stroke on all study patients at hospital (Studies I-IV) and after a six month follow-up period at home (Study IV). At follow-up, we asked all CPAP users to interrupt the CPAP treatment for one night before the cardiorespiratory polygraphy. The unattended sleep study was done with a three-channel portable, type 4 device as illustrated in Figure 2 (ApneaLinkPlus, ApneaLink™ Plus (Resmed, Sydney, Australia), which is S0C401xP0E2R2 according to the SCOPER OCST classification by Dr. Nancy Collop (Collop et al., 2011). The portable device was battery-powered and consisted of a nasal cannula, finger probe pulse oximeter and thoracic belt which were attached to the patient. The sleep study was put into operation in the evening by nurses or the investigator JKH. Nasal prongs were used to measure nasal airflow connected to a pressure transducer. The finger probe pulse oximeter recorded data on SaO₂ and the thoracic belt measured respiratory efforts. For analysis, we accepted polygraphy recordings with a duration of four hours or more, which was a criterion for successful and technically correct recording.
JKH scored manually all cardiorespiratory recordings according to the AASM criterion (Berry et al., 2012) (Table 1) and was not blinded to the results of the ApneaLink™ Plus autoscore. To confirm objectivity and quality of scoring, JKH randomly reassessed 10% of the follow-up sleep recordings (Study II); the results did not change. An apnea was defined as a drop in peak signal excursion by 90% of pre-event baseline lasting over 10 seconds. An apneic event was scored as obstructive if it met the apnea criterion and was associated with increased or continued inspiratory effort. ApneaLink calculates all flow-limited breaths from the recording and the percentage of flow-limited breathing of the total breaths found and divides that percentage by ten. That number, the adjusted Risk Indicator, is the estimated value added to the scored REI. Hypopnea was determined by a drop in the peak signal excursion of more than 30% of pre-event baseline of more than 10 seconds’ duration and in oxygen desaturation, of more than 3% from pre-event baseline. Apnea was defined as central if it met the apnea criterion and was
associated with absence of inspiratory effort. Mixed apneas had to meet the apnea criterion and be associated with absence of inspiratory effort in the first part of the event, and followed by inspiratory effort in the second part. Apnea was scored as unclassified if nasal cannula and finger probe pulse oximeter measurements were not noticeable during the apnea. Threshold for ODI4 was used to define disordered breathing events. Sleep apnea (REI \geq 5/h) was divided into three categories: mild (REI 5–15), moderate (REI 15–29) and severe (REI \geq 30 per hour) sleep apnea. Obstructive sleep apnea existed when > 50% of events were obstructive, and central sleep apnea when > 50% of events were central. CPAP treatment was recommended for all those stroke patients who had sleep apnea, and CPAP usage was evaluated at follow-up.

### 4.3.3 Thrombolysis therapy and radiological imaging

All self-contained patients received thrombolysis treatment in the emergency room on admission if they had NIHSS scores > 2 and had no contraindications for thrombolysis therapy (Hacke et al., 2008). Thrombolysis treatment was given intravenously within 4.5 hours from stroke symptom onset. The maximum dose of recombinant tissue plasminogen activator (alteplase) was 100 mg and the dose depended on patient’s weight. The Finnish Current Care Guideline for Ischemic stroke defined the exclusion criteria for thrombolysis treatment (Lindsberg, 2011).

An independent on-call radiologist verified ischemic stroke diagnosis with brain CT or MRI imaging on admission in all subjects (Study II, III). The location of stroke was divided into three categories: middle artery syndrome, lacunar syndrome, and other location (Study III, I). Stroke location was further classified into six groups: middle cerebral artery territory, anterior cerebral artery territory, posterior cerebral artery territory, lacunar syndrome, cerebellum, vertebrobasilar territory, brainstem, and basilar artery thrombosis.

The follow-up brain CT was done 24 hours after thrombolysis therapy and an experienced neuroradiologist measured stroke volume without blinding to the clinical outcomes (Study III). Multiple infarctions were summed into one volume. Depending on the CT machine, sequential technique with 5 mm axial slices or helical acquisition provided volumetric data, later formatted to 3–5 mm thick slices on the axial plane. Infarction area was determined by tracing its boundaries on each slice on a clinical workstation, after which the area was multiplied with the slice thickness and the volume of each slice was summed. One patient had only MRI images available; in this case, stroke volume was measured from diffusion
weighted images in a similar manner as in CT. Stroke volume was divided into two groups: ischemic stroke volume maximum 1.69 mL, and stroke volume over 1.69 mL (Study III). Study III evaluated whether stroke lesion was visible or not on follow-up CT and whether stroke volume or visible stroke associated with sleep apnea. Also, the presence of hemorrhage was recorded (Study III). In accordance with previous definitions (Pessin, Del Zoppo, & Estol, 1990; Wolpert et al., 1993), hemorrhagic infarctions were divided into two types, types I and II, and parenchymal hematoma into types I and II.

4.4 Ethical considerations

Patients participated entirely voluntarily and written informed consent was obtained from all patients or their relatives. Patients who were unable to co-operate were excluded. At follow-up study, patients with CPAP treatment discontinued their treatment for one night before the follow-up sleep study. One night without CPAP was considered to be an ethically appropriate time, although it might be too short to eliminate the influence of CPAP on REI or ODI. The Northern Ostrobothnia Hospital District ethics committee approved the study protocol.

4.5 Statistical analyses

All statistical analyses were performed with IBM SPSS (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, version 22.0. Armonk, NY: IBM Corp.). P values < 0.05 were considered statistically significant.

In studies I-IV, patients’ demographic as well as sleep data were reported as means and standard deviations (SD).

In studies II-IV, the chi-square test or Fischer exact test was applied for categorical variables. Normally distributed variables were assessed by Student’s t-tests. Group comparisons were performed with Mann-Whitney U test when the data was not normally distributed. The two-sample test of proportion was used to evaluate both the mRS scores and sleep apnea severity.

In study II, the NIHSS and GCS scores were reported as medians and SDs. Logistic regression analyses were performed to evaluate the predictors for sleep apnea after stroke and to determine odds ratios (ORs) and 95% confidence intervals (CIs) of variables with univariate and multivariate models. The variables that predicted sleep apnea in univariate analysis were included in the multivariate model to assess independent predictors.
In study IV, both correlations between continuous positive airway pressure (CPAP) and REI or ODI4 changes were estimated and multiple comparisons were made using analysis of variance (ANOVA). The McNemar-Bowker test was used to assess changes in the mRS scores from baseline to the six-month follow-up. Logistic regression analyses were performed to assess the predictors of new sleep apnea after stroke by using univariate model.

In study III, Spearman correlation coefficient was applied to estimate correlations between stroke volume and REI, ODI4 and the percentage of time spent with saturation below 90%.

In study I, two-way mixed effect model was used to compare automatically and manually scored REI, ODI4, OAI, CAI, mixed apnea index (MAI), mean saturation, lowest saturation, and percentage of time spent with saturation below 90%. Interclass correlation coefficient (ICC) was based on the 95% CI of the ICC estimate. ICC contains 10 forms of ICCs (Koo & Li, 2016). Values higher than 0.9 indicated excellent and values between 0.75 and 0.9 good agreement. Values between 0.5 and 0.75 indicated moderate and values under 0.5 poor agreement.

The Kappa test was determined to evaluate agreement for sleep apnea prevalence and severity. Kappa test values from 0.81 to 1.00 indicated nearly perfect agreement, while substantial agreement was indicated by values between 0.61 and 0.80. Kappa values from 0.41 to 0.60 pointed to moderate and values between 0.21 and 0.40 to fair agreement, while values ranging from 0.00 to 0.20 indicated slight agreement.
5 Results

5.1 Feasibility and reliability of unattended cardiorespiratory polygraphy in screening of sleep apnea in acute phase of ischemic stroke (Study I)

The main finding of study I was the excellent agreement in cardiorespiratory polygraphy between automated and manual scoring results in ODI4, lowest saturation, and the percentage of time spent with saturation below 90% among acute stroke patients.

The screening of patients is described in Figure 1 and patients’ characteristics are summed up in Table 8. Unattended sleep study, performed in the acute phase of ischemic stroke, was feasible for screening sleep apnea at the stroke unit. Unattended cardiorespiratory polygraphy was performed within 28.7 (SD 16.8) vs. 31.6 (SD 13.7) hours from the time of admission in the THR and the NTHR groups (p = 0.023), respectively. It was repeated in 12 (6%) cases due to poor quality of the sleep recording, and in only seven stroke patients (thrombolysis group 6, non-thrombolysis group 1), a successful recording was performed 48 hours after hospitalization. The time range for successful cardiorespiratory polygraphy ranged from 3.7 to 95.4 hours.

Automatic scoring detected sleep apnea (defined as REI ≥ 5/h) in 72.5% of the cohort, while manual scoring found 91.2%. Automated analysis did not observe 18.6% of sleep apnea cases. The agreement was moderate (Kappa value 0.407) regarding sleep apnea diagnosis as well as mean saturation. Automated scoring was poor in recognizing the type of nocturnal respiratory events, resulting in poor agreement in central apneas (ICC value 0.440, 95% CI 0.262–0.575) and mixed apneas per hour (ICC value 0.139, 95% CI -0.135–0.346). However, OAI (ICC value 0.848, 95% CI 0.800–0.885) showed good agreement.

Most of our stroke patients had obstructive sleep apnea (80.9%) and minority of them experienced central sleep apnea (more than 50% of events were central) (19.2%). Sleep apnea severity, assessed by REI, showed fair agreement (Kappa value 0.297) and automatic scoring underrated the severity of sleep apnea. Both scoring methods estimated correctly mild sleep apnea in 42.0%, moderate sleep apnea in 28.9%, and severe sleep apnea in 47.3% of the cases. Automated scoring reported mild sleep apnea in 31.9% of the cases, while manual scoring found 24.5%. Moderate sleep apnea was detected in 19.6% of patients with automated scoring.
and in 22.1% by manual scoring. Severe sleep apnea was diagnosed in 21.1% of cases by automatic scoring, while manual scoring found 44.6% of patients to have severe sleep apnea. In our study, automated scoring missed 38 sleep apnea diagnoses found by manual scoring, and of those 38 patients, 26 had mild, 7 had moderate, and 5 had severe sleep apnea.

**Table 8. Characteristics of patients (Study I, II).**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients with thrombolysis (n = 110)</th>
<th>Patients without thrombolysis (n = 94)</th>
<th>Total (n = 204)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men, n (%)</td>
<td>72 (65.6)</td>
<td>56 (59.6)</td>
<td>128 (62.7)</td>
<td>0.387</td>
</tr>
<tr>
<td>Mean age, years (SD)</td>
<td>65.8 (14.6)</td>
<td>70.0 (11.5)</td>
<td>67.7 (13.4)</td>
<td>0.027</td>
</tr>
<tr>
<td>Mean BMI(^1) (SD)</td>
<td>27.5 (4.9)</td>
<td>27.1 (4.4)</td>
<td>27.3 (4.7)</td>
<td>0.474</td>
</tr>
<tr>
<td>Current smoking n (%)</td>
<td>20 (18.2)</td>
<td>24 (25.5)</td>
<td>44 (21.6)</td>
<td>0.234</td>
</tr>
<tr>
<td>Mean pack years (SD)</td>
<td>8.7 (14.4)</td>
<td>14.0 (19.0)</td>
<td>11.1 (16.8)</td>
<td>0.026</td>
</tr>
<tr>
<td>Alcohol consumption daily n (%)</td>
<td>19 (17.3)</td>
<td>4 (4.3)</td>
<td>23 (11.3)</td>
<td>0.003</td>
</tr>
<tr>
<td>Heavy drinkers n (%)</td>
<td>3 (2.7)</td>
<td>4 (4.3)</td>
<td>7 (3.4)</td>
<td>0.706</td>
</tr>
<tr>
<td>Snoring n (%)</td>
<td>79 (71.8)</td>
<td>48 (51.1)</td>
<td>127 (62.3)</td>
<td>0.002</td>
</tr>
<tr>
<td>Prior sleep apnea</td>
<td>5</td>
<td>4</td>
<td>9</td>
<td>0.920</td>
</tr>
<tr>
<td>Mean neck circumference, cm (SD)</td>
<td>42.2 (6.6)</td>
<td>43.6 (10.2)</td>
<td>42.8 (8.0)</td>
<td>0.214</td>
</tr>
<tr>
<td>Mean waist circumference, cm (SD)</td>
<td>103.3 (15.3)</td>
<td>102.9 (14.5)</td>
<td>103.1 (14.9)</td>
<td>0.821</td>
</tr>
<tr>
<td>Mean ESS(^2) (SD)</td>
<td>4.7 (3.0)</td>
<td>4.7 (2.6)</td>
<td>4.7 (2.8)</td>
<td>0.880</td>
</tr>
<tr>
<td>Rankin scale (scale 0–5)</td>
<td></td>
<td></td>
<td></td>
<td>0.064</td>
</tr>
<tr>
<td>Rankin scale 0 n (%)</td>
<td>80 (72.7)</td>
<td>59 (62.8)</td>
<td>139 (68.1)</td>
<td>0.130</td>
</tr>
<tr>
<td>Rankin scale 1 n (%)</td>
<td>15 (13.6)</td>
<td>13 (13.8)</td>
<td>28 (13.7)</td>
<td>0.967</td>
</tr>
<tr>
<td>Rankin scale 2 n (%)</td>
<td>3 (2.7)</td>
<td>9 (9.6)</td>
<td>12 (5.9)</td>
<td>0.037</td>
</tr>
<tr>
<td>Rankin scale 3 n (%)</td>
<td>10 (9.1)</td>
<td>6 (6.4)</td>
<td>16 (7.8)</td>
<td>0.475</td>
</tr>
<tr>
<td>Rankin scale 4 n (%)</td>
<td>2 (1.8)</td>
<td>7 (7.4)</td>
<td>9 (4.4)</td>
<td>0.051</td>
</tr>
<tr>
<td>Rankin scale 5 n (%)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Median NIHSS(^3) score (SD) (0–35)</td>
<td>5.5 (6.0)</td>
<td>2.0 (4.0)</td>
<td>4.0 (4.9)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Median GCS(^4) score (SD) (3–15)</td>
<td>15.0 (1.3)</td>
<td>15.0 (1.3)</td>
<td>15.0 (1.3)</td>
<td>0.027</td>
</tr>
<tr>
<td>Hypertension n (%)</td>
<td>65 (59.1)</td>
<td>58 (61.7)</td>
<td>123 (60.3)</td>
<td>0.704</td>
</tr>
<tr>
<td>Hypercholesterolemia n (%)</td>
<td>46 (41.8)</td>
<td>47 (50.0)</td>
<td>93 (45.6)</td>
<td>0.242</td>
</tr>
<tr>
<td>Diabetes mellitus n (%)</td>
<td>21 (19.1)</td>
<td>19 (20.2)</td>
<td>40 (19.6)</td>
<td>0.841</td>
</tr>
<tr>
<td>Coronary artery disease n (%)</td>
<td>22 (20.0)</td>
<td>27 (28.7)</td>
<td>49 (24.0)</td>
<td>0.146</td>
</tr>
<tr>
<td>Myocardial infarction n (%)</td>
<td>13 (11.8)</td>
<td>17 (18.1)</td>
<td>30 (14.7)</td>
<td>0.208</td>
</tr>
<tr>
<td>Atrial fibrillation n (%)</td>
<td>5 (4.5)</td>
<td>27 (28.7)</td>
<td>32 (15.7)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>PAD(^5) n (%)</td>
<td>3 (2.7)</td>
<td>4 (4.5)</td>
<td>7 (3.5)</td>
<td>0.501</td>
</tr>
</tbody>
</table>

\(^1\) body mass index, \(^2\) Epworth Sleepiness Scale, \(^3\) National Institutes of Health Stroke Scale, \(^4\) Glasgow Coma Scale, \(^5\) peripheral arterial disease
The agreement in ODI4/h, (ICC value 0.993, 95% CI 0.990–0.994), lowest saturation (ICC value 0.989, 95% CI 0.985–0.991) and percentage of time spent with saturation below 90% (ICC value 0.987, 95% CI 0.982–0.990) was excellent in the current study. The mean automatically scored REI was 17.0/h and the mean manually scored REI was 30.5/h, and there was good agreement for REI (ICC value 0.869, 95% CI 0.828–0.901). Automatically and manually analyzed results were equivalent concerning mean ODI4/h (19.3 vs. 19.9), mean lowest oxygen saturation (80.3 vs. 80.4), and time spent with saturation below 90% (18.9 vs. 18.4).

5.2 Prevalence of sleep apnea among ischemic stroke patients (Study II)

The most important finding of this prospective study indicated that in the acute phase of stroke, sleep apnea was markedly high, 91.2% vs. 83.3%, when using cutoff REI 5/h and REI 10, respectively.

The baseline characteristics of the study patients are shown in Table 8. Moreover, sleep apnea (REI ≥ 5/h) was more common in the thrombolysis group (96.4% vs. 85.1%, p < 0.007). Obstructive sleep apnea was found in 80.9% of study patients while central sleep apnea existed in only 19.1% of those who met the criteria of sleep apnea diagnosis. In the thrombolysis group, the mean baseline REI was higher (33.7 vs. 26.8, p = 0.017). The differences between the thrombolysis and non-thrombolysis groups in REI, ODI4, OAI, CAI, and hypopnea index are shown in Figure 3. Sleep apnea severity did not differ significantly between the study groups, although severe sleep apnea was more prevalent in the thrombolysis group (47.3% vs. 41.5%, p = 0.036). The severity of stroke, assessed by NIHSS, at the time of admission was associated with sleep apnea severity both in terms of REI (r = 0.30, p < 0.001) and ODI4 (r = 0.27, p < 0.001). In this study, no between-group differences emerged in mean ODI4 (thrombolysis group 21 vs. non-thrombolysis group 18), average oxygen saturation (thrombolysis group 92.7 vs. non-thrombolysis 92.4, p = 0.244), lowest oxygen saturation (thrombolysis group 80.76 vs. non-thrombolysis group 79.93, p = 0.402), or time spent with oxygen saturation below 90% (thrombolysis group 16.25% vs. non-thrombolysis group 20.40%, p = 0.928).
The distribution of stroke location differed between the study groups. Stroke patients in the thrombolysis group experienced less lacunar syndrome (17.3% vs. 36.2%, p < 0.002) and cerebellar and posterior cerebral artery syndrome, while the incidence of middle cerebral artery syndrome (60.9% vs. 33.0%, p < 0.001), anterior cerebral artery syndrome, basilar artery thrombosis, and brainstem infarction was higher (60.9% vs. 33.0%, p < 0.001). The prevalence of sleep apnea was similar in patients diagnosed with lacunar syndrome and middle cerebral artery syndrome (90.6% vs. 90.8%), although patients with lacunar syndrome showed a tendency toward experiencing more severe sleep apnea relative to those with middle cerebral artery syndrome.

Thrombolysis was the strongest predictor for previously undiagnosed sleep apnea after stroke (OR 8.068, 95% CI 21.09–30.896), with waist circumference (OR 1.057, 95% CI 1.015–1.102) as well as age (OR 1.052, 95% CI 1.014–1.091)
as other predictors. Diabetes mellitus and heavy drinking predicted sleep apnea, but statistical analysis was not performed because all those patients had sleep apnea.

5.3 **Impact of ischemic stroke volume or visible stroke on sleep apnea (Study III)**

Ischemic stroke patients \( (n = 110) \) who underwent intravenous thrombolysis treatment were classified into two groups depending on whether they had a visible stroke lesion or not in the control CT scan 24 hours after thrombolysis. The patients were also divided according to brain infarct volume into those with infarct volume 1.69 mL or below and those with stroke volume exceeding 1.69 mL.

The main finding was that acute ischemic stroke patients with stroke volume over 1.69 mL after thrombolysis had significantly deeper nocturnal hypoxemia and spent almost twice as much time with saturation below 90% than others. Furthermore, stroke patients with a visible lesion on neuroimaging after thrombolysis had significantly higher ODI4 and more obstructive apneas per hour than those without a visible lesion.

The characteristics of patients and main results are summarized in Table 9. There was a positive correlation between ischemic stroke volumes and time spent below 90% saturation \( (p = 0.025) \). Study patients with stroke volume over 1.69 mL spent 23.3% of successful sleep recording time below 90% saturation while the other group spent 12.5%, \( p = 0.016 \). Time spent below 90% saturation seemed to be a more important factor than REI. Sleep apnea was present in 106 (96.4%) of patients if diagnosis criterion was \( \text{REI} \geq 5/\text{h} \) and in 80 (72.8%) with \( \text{REI} > 15/\text{h} \). It was not possible to analyze the correlation between stroke volume (mean 15.9 mL) and diagnosis of sleep apnea and its severity or perform logistic regression analysis for predictors of sleep apnea after stroke, because 106 patients had sleep apnea and only 4 patients were without diagnosis, and the CI was too wide. In addition, the small number of patients with hemorrhage did not allow analysis of the correlation between hemorrhage as a complication and sleep apnea severity. There was no correlation between Rankin scale score, ODI4, REI, and stroke volume.
Table 9. Characteristics of patients (study III).

<table>
<thead>
<tr>
<th>Characteristics of patients</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 110</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>72 (65.5)</td>
</tr>
<tr>
<td>Mean age, years (SD)</td>
<td>65.8 (14.6)</td>
</tr>
<tr>
<td>Mean BMI1 kg/m² (SD)</td>
<td>27.5 (4.9)</td>
</tr>
<tr>
<td>Current smoking, n (%)</td>
<td>20 (18.2)</td>
</tr>
<tr>
<td>Mean pack years, years (SD)</td>
<td>8.7 (14.4)</td>
</tr>
<tr>
<td>Alcohol users, n (%)</td>
<td>19 (17.3)</td>
</tr>
<tr>
<td>Heavy alcohol users, ≥ 30 g/d, n (%)</td>
<td>3 (2.7)</td>
</tr>
<tr>
<td>Mean neck circumference, cm (SD)</td>
<td>42.2 (5.6)</td>
</tr>
<tr>
<td>Mean waist circumference, cm (SD)</td>
<td>103.3 (15.3)</td>
</tr>
<tr>
<td>Snoring, n (%)</td>
<td>79 (71.8)</td>
</tr>
<tr>
<td>Mean ESS2 score (SD)</td>
<td>4.7 (3.0)</td>
</tr>
<tr>
<td>Mean NIHSS3 (scale 0–30) (SD)</td>
<td>7.1 (5.0)</td>
</tr>
<tr>
<td>Rankin scale (scale 0–5) n (%)</td>
<td></td>
</tr>
<tr>
<td>Rankin scale 0</td>
<td>80 (72.7)</td>
</tr>
<tr>
<td>Rankin scale 1</td>
<td>15 (13.6)</td>
</tr>
<tr>
<td>Rankin scale 2</td>
<td>3 (2.7)</td>
</tr>
<tr>
<td>Rankin scale 3</td>
<td>10 (9.1)</td>
</tr>
<tr>
<td>Rankin scale 4</td>
<td>2 (1.8)</td>
</tr>
<tr>
<td>Rankin scale 5</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Hypertension n (%)</td>
<td>65 (59.1)</td>
</tr>
<tr>
<td>Hypercholesterolemia n (%)</td>
<td>46 (41.8)</td>
</tr>
<tr>
<td>Diabetes mellitus n (%)</td>
<td>21 (19.1)</td>
</tr>
<tr>
<td>Coronary artery disease n (%)</td>
<td>22 (20.0)</td>
</tr>
<tr>
<td>Atrial fibrillation n (%)</td>
<td>5 (4.5)</td>
</tr>
<tr>
<td>PAD4 n (%)</td>
<td>5 (4.5)</td>
</tr>
<tr>
<td>Mean stroke volume (mL)</td>
<td>15</td>
</tr>
<tr>
<td>Hemorrhage as complication, n (%)</td>
<td>8 (7.3)</td>
</tr>
<tr>
<td>Death n %</td>
<td>4 (3.6)</td>
</tr>
</tbody>
</table>

1 body mass index, 2 Epworth sleepiness scale, 3 National Institutes of Health Stroke Scale, 4 peripheral arterial disease

The stroke patients with a visible lesion on neuroimaging after thrombolysis had significantly higher ODI4 (23.9 vs. 16.5, p = 0.028) and significantly more obstructive apneas per hour (6.2 vs. 2.7, p = 0.007) than those without a visible lesion. Stroke patients with a visible stroke lesion also had more serious strokes assessed with NIHSS score than those without a visible lesion. In this study, REI, CAI, hypopneas per hour, average saturation, lowest saturation, percentage of time with SaO2 below 90%, and sleep apnea severity did not differ between patients with
or without visible stroke lesion. This is the first study investigating the connection between brain infarct volume and sleep apnea-related hypoxia among ischemic stroke patients treated with thrombolysis.

5.4 Evolution of sleep apnea within six months post stroke (Study IV)

After a six-month follow-up, the overall prevalence of sleep apnea did not change. A novel finding in our study was that thrombolysis was an independent protective factor for developing sleep apnea within six months post stroke, while patients without thrombolysis treatment had a 6.1-fold risk for developing new sleep apnea ($p = 0.024$) independent of age, daytime sleepiness, and atrial fibrillation. However, there was a selection bias between groups and the difference was confounding by indication.

After a six-month follow-up, there were 177 (86.8%) ischemic stroke patients who participated in the follow-up and 27 drop-outs (Figure 1). The changes in the characteristics of the thrombolysis and non-thrombolysis groups are presented in Table 10. New ischemic stroke was experienced by 8 (8.2%) thrombolysis patients and 4 (5.1%) non-thrombolysis patients ($p = 0.415$), and only two patients (2%) in the thrombolysis group suffered a new TIA. Of the 11 deceased patients, eight had severe sleep apnea, one had moderate disease, and two had mild sleep apnea. The time to death was 68.3 (SD 51.0) days in the thrombolysis group and 23.3 (SD 19.8) days in the non-thrombolysis group.

Sleep apnea prevalence declined from 95.9% to 93.9% in the thrombolysis group, while there was an increase from 82.3% to 91.1% in the non-thrombolysis group, $p = 0.488$. Sleep apnea severity worsened in the mild sleep apnea group because 69.2% of the patients proceeded to moderate to severe sleep apnea; however, at the same time, 20.2% of the patients with previous moderate or severe sleep apnea moved on to have mild sleep apnea. There was no difference in the prevalence of either severe (46.9% vs. 36.7%, $p = 0.172$) or mild sleep apnea (20.4% vs. 27.8%, $p = 0.249$). Two thirds of the patients had obstructive sleep apnea and the remaining one third had central sleep apnea. CPAP therapy was offered if the patient was diagnosed with sleep apnea, but only 20 were willing to start CPAP. CPAP treatment was initiated one to five months after stroke, and at follow-up time, all those 20 CPAP patients, except for one, were willing to continue with the treatment. Thrombolysis and nasal CPAP treatment together predicted the decline
of REI (p = 0.005) in the whole group, but this effect was not seen for ODI4 (p = 0.828).

During follow-up, ODI4 declined more in the thrombolysis group (6.1%, p < 0.001 vs. -4.2, p = 0.001), and the same decline was seen in the lowest oxygen saturation (2.4%, p = 0.046 vs. -2.2, p = 0.043). At six months, the thrombolysis group had more hypopneas (22.9/h vs. 16.0/h, p = 0.005) than the non-thrombolysis group. After follow-up, central apneas per hour increased in the whole group by 2.2% (p = 0.002), and the increase was lower in the thrombolysis group (2.0%, p = 0.024) than in the other group (2.5%, p = 0.029). The change in REI was not significant (Figure 2.). Both obstructive apneas per hour (1.7%, p = 0.014) and mixed apneas per hour (0.07%, p = 0.010) decreased in the whole study group.
Table 10 Characteristics of patients at baseline and six months post-stroke (Study IV).

<table>
<thead>
<tr>
<th>Characteristics of patients</th>
<th>Baseline Patients with thrombolysis (n = 98)</th>
<th>Patients without thrombolysis (n = 79)</th>
<th>P value</th>
<th>Six months Patients with thrombolysis (n = 98)</th>
<th>Patients without thrombolysis (n = 79)</th>
<th>Total (n = 177)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men, n (%)</td>
<td>66 (67.3)</td>
<td>46 (58.2)</td>
<td>0.211</td>
<td>66 (67.3)</td>
<td>46 (58.2)</td>
<td>112 (63.3)</td>
<td>0.211</td>
</tr>
<tr>
<td>Mean age, years (SD)</td>
<td>65.0 (14.5)</td>
<td>69.1 (11.4)</td>
<td>0.039</td>
<td>65.6 (14.5)</td>
<td>69.6 (11.4)</td>
<td>67.4 (13.7)</td>
<td>0.039</td>
</tr>
<tr>
<td>Mean weight, kg (SD)</td>
<td>80.3 (16.4)</td>
<td>78.2 (16.5)</td>
<td>0.395</td>
<td>79.6 (18.2)</td>
<td>76.5 (15.2)</td>
<td>78.2 (17.0)</td>
<td>0.218</td>
</tr>
<tr>
<td>Mean ESS1 (SD)</td>
<td>4.7 (3.0)</td>
<td>4.7 (2.6)</td>
<td>0.915</td>
<td>3.0 (2.8)</td>
<td>3.8 (2.4)</td>
<td>3.3 (2.7)</td>
<td>0.045</td>
</tr>
<tr>
<td>Hypercholesterolemia n (%)</td>
<td>39 (39.8)</td>
<td>41 (51.9)</td>
<td>0.108</td>
<td>39 (39.8)</td>
<td>42 (53.2)</td>
<td>81 (45.8)</td>
<td>0.076</td>
</tr>
<tr>
<td>Atrial fibrillation n (%)</td>
<td>4 (4.1)</td>
<td>22 (27.8)</td>
<td>&lt; 0.001</td>
<td>7 (7.1)</td>
<td>22 (27.8)</td>
<td>29 (16.4)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

1 Epworth Sleepiness Scale
6 Discussion

This is the first study comparing differences in sleep apnea prevalence in patients with ischemic stroke treated with or without thrombolysis therapy. Cardiorespiratory polygraphy turned to be a feasible tool for diagnosing sleep apnea within the first two days post stroke and the agreement between automatic and manual scoring was good, especially in terms of ODI4. The screening of sleep apnea was simple to perform at the stroke unit during two days after stroke and at home; in the future, doctors will hopefully be more eager to screen for sleep apnea with portable cardiorespiratory monitors. Analyzability was good in the present study, and cardiorespiratory polygraphy with automated scoring results was useful in screening for sleep apnea in stroke patients even though twenty percent of sleep apnea diagnoses were missed when using automated scoring. It is very likely that automated scoring would find nearly all the stroke patients who have undiagnosed sleep apnea and need CPAP therapy. A novel finding was that sleep apnea was highly prevalent among the entire cohort, in the acute phase of stroke as well as after six months post stroke. The prevalence of sleep apnea was higher among those treated with thrombolysis compared to those who were treated conservatively. However, thrombolysis treatment was associated with lower incidence of sleep apnea cases within the six-month follow-up period compared to patients who had not undergone thrombolysis treatment. Larger stroke volume or a visible stroke lesion on CT scan after thrombolysis was associated with more severe measures of desaturation and sleep apnea severity.

6.1 Unattended sleep study in screening of sleep apnea in acute stroke (Study I)

Cardiorespiratory polygraphy with a portable three-channel type 4 device (ApneaLink™ Plus Version 9.30, Resmed, Sydney, Australia) was feasible and showed good analyzability for sleep apnea screening at the stroke unit in the first two days after stroke symptom onset in the present study. Automatic and manual scoring detected sleep apnea with moderate agreement. It was not surprising that automatic scoring tended to underestimate the severity of sleep apnea, was incapable of typing the events, as well as failed to diagnose sleep apnea in one fifth of the cases. Sleep apnea screening with an unattended portable monitor at the stroke unit is an appealing thought and would be an inexpensive, cost-effective, quick way to ensure sleep apnea treatment as well as better outcome for stroke
patients with undiagnosed sleep apnea. To date, only two previous studies have investigated the agreement between automatic analysis and manually scored results of ApneaLink™ Plus in diagnostic use for sleep apnea in stroke patients, but in those studies, the time from stroke onset to cardiorespiratory polygraphy was longer, and additionally, the severity of stroke was milder than in the current study (Brown et al., 2014; Patel et al., 2018).

According to earlier research, unattended sleep recording missed a few recordings, and the analyzability of sleep recordings was assumed to be over eighty percent (Boulos et al., 2017; Broadley et al., 2007; Kepplinger et al., 2013; Martinez-Garcia et al., 2006; Parra et al., 2000). Four out of five stroke patients in the present study had analyzable unattended cardiorespiratory polygraphy, as reported earlier. The portable three-channel recording device (ApneaLink™ Plus) was well-tolerated, safe, inexpensive, the recording was performed quickly, and it did not disturb normal stroke unit care as expected; on the whole, it was feasible during the first days of stroke.

In the current study, successful sleep polygraphy was achieved within 29 hours. In the present study, repeated recordings were needed due to the unsatisfactory nature of the sleep recording in only 6% of the cases, although repeated nocturnal polygraphy was performed quickly, within 33 hours. Investigators from Michigan used the same device as in the current study; in their study, the sleep recording was performed 13 days after stroke in hospital room, at home or in nursing home (Brown et al., 2014). An even longer period of time passed in a recent study from Toronto, where the sleep study was conducted with the same device as in the current study and performed at home 26 days after stroke (Patel et al., 2018). The criterion for successful sleep study in the present study was a minimum of four hours of technically correct recording, in contrast to the two other studies which required only sleep recordings of two hours minimum for evaluation (Brown et al., 2014; Patel et al., 2018). The scorer in the present study was unblinded autoscoring, contrary to that in some other studies (Brown et al., 2014; Patel et al., 2018). The Toronto group (Patel et al., 2018) and the present study used AASM 2012 guidelines for manual scoring and downloaded as well as used automatic analysis by ApneaLink™ Plus software, unlike the other group, which used modified AASM 2007 guidelines (Brown et al., 2014).

The focus of this study was on obstructive sleep apnea, but evaluation of central sleep apnea was also done. The current study had a sample size of over two hundred ischemic stroke patients, which was smaller than in the study by Brown et al (Brown et al., 2014) with over three hundred patients, but larger than in the study
of Patel et al. (Patel et al., 2018) with around one hundred stroke patients. In the current study, the mean age was 67 years and the mean BMI was 27, which are in line with the two earlier studies (Brown et al., 2014; Patel et al., 2018), but the amount of females (37%) was higher in the present study. The severity of stroke was more serious in this study (mean total NIHSS 4.0) compared to the studies from Germany and Canada (median total NIHSS 1.0) (Kepplinger et al., 2013; Patel et al., 2018).

Manually scored REI was almost double compared to automatic scoring in the present study, an observation which is in line with the past study (Brown et al., 2014). The difference in REI between automatic and manual scoring was wide in this study, and it would therefore be wise to perform manual scoring in the case of mild sleep apnea or a normal recording result obtained by automated scoring. One recent study showed substantial agreement in AHI (Patel et al., 2018) while one previous study found a small difference between edited and unedited recordings (Brown et al., 2014). In this study, automatic scoring missed one fifth of the sleep apnea diagnoses, a result also found by Brown and coworkers (Brown et al., 2014). The agreement of sleep apnea diagnosis was moderate, with diagnostic accuracy of 72% by automated scoring and 91% by manual scoring. Automated scoring underestimated sleep apnea severity and missed over half of sleep apnea diagnoses with REI ≥ 15, which was disappointing in the current study, these results being opposite to the earlier study where there was only 10% difference for every AHI cut-off between unedited and edited data (Brown et al., 2014). Altogether, manual scoring diagnosed sleep apnea severity better than automatic scoring. The study from Germany (Kepplinger et al., 2013) made comparisons between cardiorespiratory polygraphy and PSG and found that unattended sleep study detected two thirds of moderate sleep apnea and missed only twenty percent of severe sleep apnea in the acute phase of stroke, and disappointingly, the results of sleep apnea severity showed only fair agreement in the present study.

One former study showed no difference in CAI between unedited and edited data, whereas the current study found poor agreement between automatic analysis and manual scoring results in central apneas, a difference that was greater than expected on the grounds of the previous study (Brown et al., 2014). In the present study, OAI was only one unit higher in manually edited data than in automatically edited data, confirming that the agreement was good between automatically and manually scored results, also supporting the result found in one previous study (Brown et al., 2014). Automated scoring missed half of the hypopneas, as was expected on the grounds of this same study (Brown et al., 2014). The similarity of
ODI4 between scoring methods was seen in this same previous study (Brown et al., 2014) and showed excellent agreement in the present study. It was not surprising that the lowest oxygen saturation and time spent below 90% saturation matched between automatic and manual scoring results in the current study.

The current study confirmed the earlier study (Brown et al., 2014) in that manual and automated scoring had excellent agreement in ODI4 and good agreement in REI. Contrary to the previous study (Brown et al., 2014), this study did not confirm that CAI scoring results were equal in manual and automated scoring. The present study showed that one fifth of sleep apnea cases were missed, which was pointed out previously (Brown et al., 2014). This study showed only fair agreement between manual and automated scoring to verify sleep apnea severity, contrary to the past study which showed mild difference in AHI (Brown et al., 2014).

The disturbance in transportation of oxygen to brain tissue may enlarge brain injury due to oxygen desaturation (Rowat et al., 2006; Siccoli et al., 2008; Sulter, Elting, Stewart, den Arend, & De Keyser, 2000), and an earlier study has shown sleep time spent below 90% saturation to be the main predictor (HR 1.50) for cardiovascular events in patients with sleep apnea (Kendzerska et al., 2014). Measurements of oxygenation add an important feature when we think about feasible and relevant parameters for determining sleep apnea with automated scoring among stroke patients in the acute phase to improve outcome. Although sleep apnea screening with PSG in the acute phase of stroke has improved post-stroke life (Kepplinger et al., 2013), we are still unaware of the correct timing of sleep recording because sleep apnea tends to improve within 6 to 12 weeks after stroke (Harbison et al., 2002; Parra et al., 2000).

6.2 Prevalence of sleep apnea among ischemic stroke patients treated with or without thrombolysis at the acute phase of stroke (Study II) and after follow-up (Study IV)

The literature search did not identify any studies comparing the prevalence or severity of sleep apnea in stroke patients treated with or without thrombolysis treatment at the acute phase and at follow-up. The current study confirmed the high prevalence of sleep apnea among stroke patients.

In the present study, the overall prevalence of sleep apnea among stroke patients was higher (91.2%) than in the previous studies (62.5% to 86%) (Bassetti & Aldrich, 1999; Dyken et al., 1996; Ifergane et al., 2016; Mohsenin & Valor, 1995;
The novel, main finding was that sleep apnea prevalence was significantly higher among stroke patients treated with thrombolysis (96.4%) than in stroke patients without thrombolysis therapy (85.1%). Previous studies have reported sleep apnea prevalence rates from 24% to 62% during the first 24 hours after stroke (Iranzo et al., 2002; Rowat et al., 2006; Väyrynen et al., 2014). The current study pointed out that the prevalence of severe (47.3% versus 41.5%) and moderate (25.5% versus 18.1%) sleep apnea was higher among stroke patients with thrombolysis therapy than in the other group, and the total prevalence of severe sleep apnea was 44.6%. In the current study, CAI was low, a finding also reported by two other studies (Haba-Rubio et al., 2012; Parra et al., 2000).

The reason for higher sleep apnea prevalence among tPA-treated patients remains unclear in this study. Thrombolysis with intravenous tPA treatment may predispose to sleep apnea since tPA treatment may advance neuronal death (Macrez et al., 2011) and cause complications such as intracerebral hematoma, reperfusion injury, or edema, decreasing recovery from stroke (Broderick, 1997; Hacke et al., 1995; Marler, 1995), and possibly indirectly affecting areas responsible for control of breathing. Inflammatory markers are higher in patients with sleep-disordered breathing (Ifergane et al., 2016) and after success of tPA, the possible presence of systemic inflammatory response syndrome (SIRS) has been pointed out to associate with poor short-term functional outcome (Boehme et al., 2013). However, SIRS was rare in the present cohort as only three stroke patients in the thrombolysis group with sleep apnea and two (only one with sleep apnea) in the other group fulfilled the criterion of SIRS. In the present study, there were only a few hemorrhage complications, which did not explain the higher prevalence in the thrombolysis group; reperfusion injury or tPA-associated inflammation might thus be a better explanation.

Stroke patients treated without thrombolysis had contraindications to thrombolysis therapy, of which the most common reason in the current study was anticoagulation medication, and this might cause bias. The age difference between the two study groups was partially due to anticoagulation medication of atrial fibrillation in the non-thrombolysis group and on the other hand, we excluded stroke patients with milder strokes. Stroke patients in the thrombolysis group were younger (mean 65.8 vs. 70.0), snored less, needed less constant help with everyday duties assessed by modified Rankin scale, and had almost twofold fewer pack years. We found that in multivariate analysis, independent predictors for sleep apnea after stroke were thrombolysis (OR = 8.068, 95% CI 2.109–30.896), which was the strongest predictor, age (OR = 1.052, 95% CI 1.014–1.091), and waist
circumference (OR = 1.057, 95% CI 1.015–1.102). However, the investigators did not influence on the treatment and patients were not randomized to thrombolysis. Further there was a selection bias between groups and the difference was confounding by indication. The patients’ younger age in the thrombolysis group may in part explain the higher prevalence of sleep apnea in this group. This assumption is supported by the finding that sleep apnea is associated with increased risk of ischemic stroke especially under the age of fifty (Lamberts et al., 2014). In previous studies, the study population usually consisted of middle-aged patients, while in the present study the patients were older and with a wider age range. Larger waist circumference in the thrombolysis group may partly explain the greater sleep apnea prevalence in the thrombolysis group. The patients in the thrombolysis group were younger than those in the non-thrombolysis group. Gender distribution, BMI, neck circumference, ESS score, and current smoking did not differ between the study groups. Only three earlier studies have recruited more women compared to the present study (Dyken et al., 1996; Iranzo et al., 2002; Turkington et al., 2002). The results of BMIs in previous studies are comparable with the present study, but one study has reported lower BMI than other studies (Turkington et al., 2002). The neck circumference measure in this study was comparable with past studies. Neck circumference has been reported to be an independent predictor for upper airway obstruction in the first day after stroke (Turkington et al., 2002). Snoring was significantly more frequent among thrombolysis group patients in this study.

All the patients with diabetes or with daily alcohol consumption had sleep apnea in this study (diabetes predicted sleep apnea) and we were unable to assess them statistically. Sleep apnea may be present prior to the stroke and in this study, five patients in the thrombolysis group and four patients in the non-thrombolysis group had diagnosis of sleep apnea before entering the study; however, the sample size was too small for statistical analysis. Patients in the thrombolysis group experienced nearly six times less atrial fibrillation than non-thrombolysis group patients. Undiagnosed paroxysmal atrial fibrillation may be a reason for cryptogenic stroke (Putaala et al., 2015). Nocturnal atrial fibrillation and sleep apnea may be associated with each other or with ischemic stroke.

In the thrombolysis group, stroke was more severe as assessed by NIHSS score, middle cerebral artery syndrome was more common, and lacunar syndrome was less common compared with the non-thrombolysis group. In the current study, NIHSS was associated with sleep apnea severity as assessed by REI and ODI4, and thrombolysis group patients experienced more severe sleep apnea. Two previous reports showed no correlation between stroke location and sleep-related breathing
disorders, contrary to the finding in the present study that ischemic stroke patients with middle cerebral artery syndrome and without thrombolysis had less severe sleep apnea than those with lacunar syndrome (Fisse et al., 2017; Parra et al., 2000). In one earlier study, eight patients with lacunar stroke had more severe sleep apnea than those patients without lacunar stroke (Harbison et al., 2002). In the current study, the number of patients was too low for evaluation of other stroke locations. When the SSS was used to assess stroke severity Turkington and coworkers (Turkington et al., 2002) did not find an independent correlation between stroke severity, type of stroke, and upper airway obstruction.

Another possible reason for the higher prevalence or severity of sleep apnea compared to previous reports was the timing of cardiorespiratory polygraphy after stroke. One recent study (Väyrynen et al., 2014) among Finnish stroke and TIA patients in stroke unit reported forty percent lower prevalence of sleep apnea (52.4%) albeit full polysomnography or limited polygraphy was done during the first night, but the median NIHSS was lower compared to the present study. The present study showed five percent higher total prevalence of sleep apnea among stroke patients within the first 48 hours of stroke onset than the study by Bravata et al 2011 (Bravata et al., 2011). Two recent studies (Boulos et al., 2017; Bravata et al., 2017) had tighter exclusion criteria and later timing of sleep study, which may explain the higher sleep apnea prevalence compared to the present study. Some of the earlier studies were done with polysomnography with thermistors (Bassetti & Aldrich, 1999; Dyken et al., 1996; Iranzo et al., 2002; Mohsenin & Valor, 1995; Tosun et al., 2008). However, this is unlikely to explain the differences in sleep apnea prevalence since polysomnography levels of AHI are almost one third higher than polygraphy results (Escourrou et al., 2015; Hedner et al., 2011). The different criterion of sleep apnea, i.e. different AHI cut-off point of sleep apnea diagnosis, might partly explain the higher sleep apnea prevalence and severity of sleep apnea in the studies. In the current study, REI ≥ 5 was a diagnostic criterion for sleep apnea, and two other studies which used the same diagnostic criterion had twenty and thirty percent lower prevalence of sleep apnea than the current study (Bravata et al., 2017; Tosun et al., 2008). The stroke patients included in the current study had more comorbidities and severe strokes, which were probably the reasons for the higher prevalence of sleep apnea compared to previous studies. In past studies, the diagnostic criterion for sleep apnea has varied from AHI over 10 (Bassetti & Aldrich, 1999; Iranzo et al., 2002) or 15, which partly explains the higher total prevalence of sleep apnea in the present study compared to the two previously
mentioned studies that reported a prevalence between 46% and 62% (Bassetti et al., 2006; Iranzo et al., 2002).

Hypopneas were the main type of apneas and obstructive apneas were more frequent than central apneas in the acute phase (Figure 3), confirming results from previous studies (Haba-Rubio et al., 2012; Parra et al., 2000). The proportion of obstructive apneas has been higher and that of hypopnea events lower in previous studies than in the current study (Bravata et al., 2017). After follow-up, both hypopneas and obstructive apneas decreased, as we had postulated, and a decrease in obstructive apneas was seen in other studies, too (Hui et al., 2002). One previous study found that obstructive apneas may remain unchanged after follow-up (Parra et al., 2000). The previous studies showed that obstructive apneas were more frequent than hypopneas (Bravata et al., 2017; Hui et al., 2002), contrary to the finding in this study where hypopneas were the most common type of apneas. Contrary to other studies, the current study pointed out higher CAI than OAI after follow-up (Bassetti et al., 2006; Hui et al., 2002; Iranzo et al., 2002; Parra et al., 2000). Unexpectedly, an increase in CAI was seen in both groups in this study, which may partly be due to severe strokes in the thrombolysis group with higher mRS scores after follow-up (Bassetti & Aldrich, 1999; Bassetti et al., 2006; Haba-Rubio et al., 2012). The same high level of CAI among stroke patients after follow-up was pointed out in one previous study (Bravata et al., 2017).

Unlike expected, the total sleep apnea prevalence remained high after follow-up in ischemic stroke patients, and the prevalence decreased in the thrombolysis group and increased in the non-thrombolysis group. The current study is the only one evaluating sleep apnea evolution in stroke patients treated with thrombolysis. The main new finding in the present study was that thrombolysis was the most powerful, independent protective factor for sleep apnea six months after stroke. Two thirds of sleep apnea diagnoses evolved into more severe disease and central events increased slightly, contrary to all expectations.

According to earlier studies, the prevalence of sleep apnea after stroke declined by one tenth to almost one fourth over six to twelve weeks, but we were not able to confirm the previous results of a decrease in sleep apnea prevalence (Harbison et al., 2002; Parra et al., 2000). There were no significant changes in REI after the six-month follow-up in this study, but earlier reports pointed out that after one to six months, AHI declined by 23% to 40% (Bassetti et al., 2006; Harbison et al., 2002; Hui et al., 2002; Parra et al., 2000). After follow-up, REI was higher and the prevalence of severe sleep apnea was higher in stroke patients treated with thrombolysis compared to stroke patients without thrombolysis therapy. The high
prevalence of sleep apnea might arise from the cut-off point of REI ≥ 5/h for sleep apnea diagnosis and lead to situation where a small increase in REI might cause a higher amount of sleep apnea diagnosis after stroke. In the present study, almost seven out of ten patients with mild sleep apnea proceeded to moderate or severe sleep apnea after follow-up.

In this study, ODI4 decreased significantly in the thrombolysis group but showed only a modest drop in the non-thrombolysis group. Hypoxemia is a significant mechanism in the pathophysiology of sleep apnea and it connects sleep apnea to stroke. Hypoxemia initiates oxidative stress, which leads to systemic inflammation, induces atherosclerosis, and may result in brain ischemia or even stroke (Ifergane et al., 2016). Sleep apnea patients who have below 90-percent oxygen saturation, i.e. nocturnal hypoxemia, for more than ten percent of their night sleep time are at risk for stroke (Stone et al., 2016). Past studies have reported that in stroke patients with sleep apnea, a drop in oxygen level is independently associated with functional impairment and longer hospital stays (Good et al., 1996; Kaneko et al., 2003).

Sleep apnea is a risk factor for repetitive vascular episodes and mortality after stroke (Birkbak, Clark, & Rod, 2014). In this study, after six months had passed, two patients were diagnosed with coronary artery disease, one experienced a myocardial infarction, three had diagnosis of atrial fibrillations, two had new TIA, and re-stroke was diagnosed in eight study patients in the thrombolysis group. The patients in the thrombolysis group experienced more vascular events and new diseases than those without thrombolysis because the only new event was ischemic stroke in four patients. During the six-month follow-up, 11 of the study patients died in the current study. Eight of the deceased patients had severe sleep apnea, one experienced moderate disease, and two had mild sleep apnea. After six months’ follow-up, 86.8% of the stroke patients still participated in this study.

At follow-up, the patients in the thrombolysis group had male predominance and were younger than in the non-thrombolysis group. Daytime sleepiness expressed as ESS scores declined significantly, but had hardly any clinical relevance on either of the groups in this study and the decrease in ESS scores reported previously by other investigators (Bassetti et al., 2006; Parra et al., 2000). Compared to the situation before stroke, the mRS scores worsened in all except one stroke patient, reflecting deterioration of patients’ overall condition six months post stroke. The thrombolysis group patients had more severe stroke as assessed by the mRS scores, which might be one explanation for the higher sleep apnea prevalence in patients who underwent thrombolysis. The cardiorespiratory polygraphy was
done at the stroke unit, but the follow-up cardiorespiratory polygraphy was performed at home, which might explain the high prevalence of sleep apnea at follow-up in this study. In a past study (Turkington et al., 2002), stroke severity had no correlation with progression of upper airway obstruction. An elderly study cohort and reduction in physical activity along increasing mRS scores may have contributed to worsening of sleep apnea in the present study. This is supported by former studies pointing out that reduced physical activity leads to increased REI (Giebelhaus et al., 2000; Peppard & Young, 2004). However, in the present study the mRS scores dropped in both groups and the prevalence of sleep apnea increased only in the non-thrombolysis group. Earlier studies did not give information about the number of stroke patients treated with thrombolysis, which might in part explain the discrepancy between the current study and previous studies. Moreover, we cannot rule out that the results may for some reason or another be specific only for Finland. The association between oxygen desaturation and sleep apnea was found to correlate with functional disability and longer hospital stays a year after stroke in an earlier study by Good et al (Good et al., 1996), contrary to other studies which could not prove a significant connection between functional outcome and AHI (Bassetti et al., 2006; Iranzo et al., 2002; Turkington et al., 2004).

Stroke patients who were treated with thrombolysis and who started CPAP therapy showed a greater drop in REI in the follow-up cardiorespiratory polygraphy compared to patients without thrombolysis, but the difference was not significant. The patients in the current study interrupted the use of CPAP for one night, which might be too short a time to remove the effect of CPAP on REI or ODI4. As mentioned before, it would be unethical to interrupt the use of CPAP for more than one night, although previous studies have pointed out that the patients who discontinued the use of CPAP for two or more nights had an increase in ODI4, a phenomenon that was not seen after one night’s interruption (Stoberl et al., 2017). Only 10% of the stroke patients started nasal CPAP treatment in the present study, whereas 51% of stroke patients initiated CPAP in a Swiss study (Bassetti et al., 2006), and a lower rate (6%) than in this study was seen in a study from Hong Kong (Hui et al., 2002). In the present study, the stroke patients had a lot of other diseases and lacked motivation for CPAP therapy, whereas sleep apnea patients are usually eager to start CPAP in Finland. We tried to motivate the stroke patients in this study by, for example, convincing them that stroke patients with sleep apnea might recover better from stroke with auto-CPAP treatment (Bravata et al., 2011). An earlier study reported that stroke patients tolerate auto-CPAP well in the acute phase of stroke (Bravata et al., 2011). Overall, the results regarding CPAP therapy are
ambivalent (Bravata et al., 2011; Brill et al., 2018; Parra et al., 2011; Parra et al., 2015) and additional studies are required to confirm the benefits of treatment.

6.3 Stroke volume and visible stroke matter among ischemic stroke patients with thrombolysis (Study III)

To date, this is the first study investigating the connection of both stroke volume and visible stroke lesion to sleep apnea among ischemic stroke patients after thrombolysis treatment. Studies evaluating the connection between stroke size and hypoxia of sleep apnea are scarce. The mean stroke volume was associated with the amount of time slept with oxygen saturation below 90% in this study. Ischemic stroke patients with a visible stroke lesion on follow-up CT had higher oxygen desaturation index (ODI4) and a greater number of obstructive apneas per hour than those without an ischemic stroke lesion. Eight stroke patients with a visible lesion on CT after thrombolysis had hemorrhage while those without a visible lesion had none.

The main result in the present study was the positive correlation between ischemic stroke volume and time spent with saturation below 90% within the first two days, and this was a new observation. However, stroke volume did not associate with either diagnosis and severity of sleep apnea or disability in daily activities, but it seems that time slept with saturation below 90% is likely to be more significant than apneas. In one Spanish study, stroke volume was without correlation concerning AHI below ten (Iranzo et al., 2002). Stroke severity in terms of NIHSS and sleep apnea severity in terms of REI or ODI4 were associated in the entire cohort in the present study. Elderly stroke patients and those with severe strokes as assessed by NIHSS scores are more in danger of suffering from hypoxia (Sulter et al., 2000).

Normal oxygen level is important for stroke patients as hypoxemia may exacerbate the injury to the brain when oxygen supply to brain tissue is diminished (Rowat et al., 2006; Siccoli et al., 2008; Sulter et al., 2000). Nearly a fifth of acute stroke patients may experience fluctuating hypoxia within the first hours after stroke and up to two thirds during the first two days (Rowat et al., 2006; Siccoli et al., 2008; Sulter et al., 2000). In a recent study (Kendzerska et al., 2014), the time slept with oxygen saturation below 90% was the most powerful predictor (HR 1.50) for cardiovascular episodes among obstructive sleep apnea patients. In one recent study with almost two hundred stroke patients, oxygen saturation below 94% during 10 minutes on hospital admission predicted mortality (Mittal & Goel, 2017).
Sleep apnea without treatment induces hypoxia, oxidative stress, activation of sympathetic nervous system, and causes systemic inflammation as well as dysfunction of the endothelium and thus, the onset of atherogenesis (Wolk et al., 2003). The undesirable outcomes of hypoxia are cardiovascular events and mortality among both sleep apnea and stroke patients.

Desaturation was more severe in terms of ODI4 or mean lowest saturation among stroke patients with a visible stroke lesion on CT after thrombolysis compared to those who had no visible lesion. Turkington and coworkers (Turkington et al., 2004) reported even higher ODI4, pointing out that severity of stroke and minimum saturation had an independent connection to disablement after six months’ observation. Unexpectedly, the sleep apnea severity was not different between those with or without a visible lesion on CT. However, the stroke patients with a visible stroke lesion had more obstructive apneas per hour compared to those without a visible stroke lesion, and obstructive apneas have been investigated to be the most common type of apneas in stroke patients in two previous studies (Bravata et al., 2017; Turkington et al., 2004). The role of sleep apnea in inducing vascular diseases in the early stage is still uncertain (Gottlieb et al., 2010); however, obstructive sleep apnea has been associated with increased risk of cardiovascular illness in observational studies (Gottlieb et al., 2010; Somers et al., 2008). In a large study with over six thousand patients, the investigators reported a link between obstructive sleep apnea and subclinical coronary artery disease (Somers et al., 2008). On the whole, fluctuating hypoxia may be the most important factor, especially when considering the results of Punjabi and coworkers (Punjabi, 2008), who pointed out an association between obstructive apneas with a drop in saturation and cardiovascular disease of no less than four percent.

In the current study, we found hemorrhage only in ischemic stroke patients with a visible lesion on post-thrombolysis CT scans, and previous studies have shown identical results (Bang et al., 2011; Jaillard et al., 1999). The hemorrhage causes a disruption in the blood-brain-barrier, which is due to reperfusion in the ischemic region, leading to a fault in brain autoregulation and to blood extravasation as well as proceeding inflammation (Khatri, McKinney, Swenson, & Janardhan, 2012). The inflammatory response smashes the stable cerebrovascular anatomy and physiology, and ischemia is due to inflammation (Komotar et al., 2008). Due to the small number of patients, the hypothesis that sleep apnea could be more severe among those who experienced hemorrhage as a complication could not be verified by statistical analysis. A hemorrhagic transformation with dense blood clot(s) including thirty percent of stroke volume and space-occupying
influence is specified as parenchymal hematoma (Pessin et al., 1990; Wolpert et al., 1993), which is pointed out to be a strong predictor for greater mortality and neurological worsening (Sussman & Connolly, 2013); in the present study, only three study patients experienced hemorrhage of parenchymal hematoma type 2.

Stroke patients are at high risk for sleep apnea (Loke et al., 2012) and it is important to diagnose sleep apnea among this patient group because untreated sleep apnea in stroke patients associates with recurrent stroke (Brown et al., 2019; Rola et al., 2008), poorer outcome, impaired recovery from stroke, and increased mortality (Campos-Rodriguez et al., 2012; Martinez-Garcia et al., 2005; Martinez-Garcia et al., 2012; Sahlin et al., 2008; Turkington et al., 2004; Yaggi et al., 2005). Common clinical features related to sleep apnea, such as daytime sleepiness and obesity, were without predictive value in assessing sleep apnea risk among stroke patients (Chan et al., 2010), a phenomenon shown to be true in the present study as well. Screening of sleep apnea with questionnaires before nocturnal recording is easy, cheap and time-saving, but it was not recommended after stroke due to the complex results in a recent Finnish systematic review (Takala et al., 2018). The standard diagnostic device for sleep apnea is PSG, and past studies concerning early sleep apnea screening with PSG in stroke patients were performed from the perspective of epidemiological aims rather than suitability aspects (Bassetti et al., 2006; Broadley et al., 2007; Iranzo et al., 2002). Sleep recordings with unattended portable monitors have been validated for diagnosis of sleep apnea in several countries (Bloom et al., 2009; Launois et al., 2007). The portable monitor (ApneaLink™ Plus) used in this study has not been validated for sleep apnea screening in stroke patients, although it has been utilized among stroke patients (Brown et al., 2014; Patel et al., 2018); however, it has been validated against PSG (Lesser et al., 2012).

Companies should still develop cardiorespiratory polygraphy devices that are smaller in size, cheaper, and more accurate for stroke patients.

Stroke patients’ and their relatives’ knowledge of sleep apnea helps them to request sleep study to ensure better recovery from stroke. Doctors, the scientific community, and society benefit from early diagnosis of sleep apnea, and this study showed that unattended portable monitors are easier to handle at the stroke unit, thus enabling faster diagnosis and CPAP initiation. The results of this study indicated that thrombolysis was a protective factor for sleep apnea after stroke, the prevalence of sleep apnea among stroke patients was high at baseline and after follow-up, and there was no decline after follow-up in the prevalence of sleep apnea, contrary to previous studies shown in Table 7. Sleep apnea is still underdiagnosed
among stroke patients and among general population, and in this respect, increasing awareness of sleep apnea would give people better health and quality of life. The results of the present study pointed out that stroke volume predicts nocturnal hypoxemia, and time spent with saturation below 90% was shown to be a more meaningful factor than REI; these results are useful for the improvement of treatment. The observation that nocturnal hypoxemia proved to be more prognostic than REI could provide new research ideas for investigators and companies manufacturing devices. The prevalence of sleep apnea was high in the visible stroke group, the prevalence being even higher in patients without visible stroke in the current study.

The limited health care services and increasing needs for sleep apnea diagnosis require evaluation and new strategies to manage the growing queues for sleep apnea diagnosis and treatment. We are not aware of the best timing of nocturnal sleep recording among stroke patients, although quick diagnosis and treatment in the acute phase would reduce costs, outpatient clinic visits, hospital stays, and additional morbidity. In stroke patients, the STOP-BANG questionnaire together with nocturnal oximetry might be one possible prescreening method of sleep apnea, and nocturnal hypoxemia with abnormal result in STOP-BANG should be evaluated by cardiorespiratory polygraphy. The questionnaire and nocturnal oximetry could be easily conducted by nurses. We do not know which stroke patients benefit the most from sleep apnea screening, but according to the present study, stroke patients treated with thrombolysis or affected by hemorrhage as a complication should be screened by cardiorespiratory polygraphy. Undiagnosed sleep apnea causes hypoxemia and hypercapnia and may retard the recovery from stroke or cause more health hazards, and in the acute phase of stroke, hypoxemia and hypercapnia should be treated to avoid extra burden to patients.
7  Strengths and Limitations

The series of current studies has several strengths. First, the recruitment of the study population was consecutive for both groups and prospective real-life study in nature. Second, as compared to majority of previous studies, the sample size of study patients was relatively large: only some studies, conducted in the acute phase of stroke with PSG or cardiorespiratory polygraphy, had a larger sample size than this study, as shown in Tables 2 and 4. In the present study, the proportion of women was almost forty percent, which is decent proportion compared to previous studies performed with cardiorespiratory polygraphy or PSG during one week after stroke (Tables 2, 4). This study had a wide age distribution, from 22 to 95 years, wider than in most past studies as shown in Tables 2–5. The stroke patients in this study had more severe strokes than in most previous studies. The cardiorespiratory polygraphy was done within two days after stroke and it was feasible to carry out in the stroke unit. This present study is the first to evaluate both sleep apnea prevalence, type, and severity on admission and six months post stroke, and stroke volume or visibility among acute phase stroke patients receiving thrombolysis.

First, the main limitation of the study was the selection bias between groups, because the thrombolysis group and non-thrombolysis group were different due to the criteria for thrombolysis. In the current study, study III (Table 9) included only those stroke patients who were treated with thrombolysis, so the sample was homogeneous, but in the other studies the patients were grouped based on whether they received thrombolysis therapy or not. The NIHSS score was used as the sole index to evaluate the severity of stroke and was evaluated only on admission. The recovery from stroke after a six-month follow-up was assessed only by mRS. The cross-sectional nature of the study does not allow to draw any conclusions of sleep apnea severity prior to the ischemic stroke together with its impact on the type or location of stroke. One-night cardiorespiratory polygraphy was performed successfully at baseline and after half-year follow-up and these results may be influenced by night-to-night-variability, although the variety effect is the same in both groups. PSG was not performed, and automatically and manually scored results were not compared to PSG in this study. An assessment of the evolution of the inflammatory response after thrombolysis was scarcely carried out. One limitation of this study was the lack of quality of life questionnaire at baseline and after six months. The stroke volume measurements may not be accurate since they are affected by many factors such as timing of imaging, image quality, shape of the lesion, and the amount of edema, which are sources of error. The brain edema was
supposed to be the same in all patients, because we measured infarct volume roughly 24 hours after thrombolysis and only one patient’s stroke volume was evaluated with MRI in the same manner from diffusion weighted images.

In this study, the stroke patients with verified sleep apnea discontinued their CPAP treatment for one night prior to the follow-up sleep study, which may not be an adequate time period to abolish the CPAP effect on REI or ODI4. The withdrawal of nasal CPAP is found to increase ODI4 after two or more consecutive nights; however, this effect is not seen after one night of withdrawal (Stoberl et al., 2017). It was ethically dubious to request patients to have a break from their treatment for longer than just one night. The current study pointed out some novel findings, may be valid only in Finland, and needs to be confirmed in other countries.

7.1 Future aspects

There is certainly a need for randomized, controlled trials evaluating sleep apnea and its severity among stroke patients in the acute phase with or without thrombolysis treatment. Studies investigating sleep apnea severity and its effects on the type and location of stroke would also give us valuable information to estimate the need for screening of sleep apnea among certain subgroups of stroke patients. Companies should develop cardiorespiratory polygraphy devices that are smaller in size, cheaper, and more accurate for stroke patients.

In the future, we need multicenter, prospective, randomized studies assessing the long-term effects of sleep apnea screening in the acute or recovery phase among stroke patients treated with or without thrombolysis and evaluated with unattended portable monitors. It is also necessary to evaluate which subgroup of stroke patients profits the most from early screening and treatment of sleep apnea. The results of this study should be confirmed in the future. If the outcomes confirm the higher prevalence of sleep apnea among stroke patients with thrombolysis treatment, additional studies will clarify why tPA treatment increases the prevalence of sleep apnea and severe sleep apnea and how we could prevent this. We need new studies to confirm the novel finding of the present study that thrombolysis was a protective factor for incident sleep apnea after stroke.

For now, CPAP treatment of stroke patients has shown conflicting results, which is why we need larger, multi-center, randomized trials to evaluate the efficacy of CPAP. We also need studies assessing whether stroke patients with thrombolysis would profit more from auto-CPAP than other stroke patients. The queues to diagnostic tests of sleep apnea are long and healthcare resources should
be allocated reasonably; that is why we need new strategies to handle the need for nocturnal recording of sleep apnea. As nocturnal hypoxemia seems to be more significant than REI, future randomized studies could evaluate whether hypoxemia, assessed solely by nocturnal oximetry, could be sufficient for sleep apnea screening compared to cardiorespiratory polygraphy among stroke patients, which would be a better option in view of the limited resources. Future studies are needed to clarify whether the STOP-BANG questionnaire together with nocturnal oximetry could be as good as cardiorespiratory polygraphy for sleep apnea screening among stroke patients.
8 Conclusions

1. The cardiorespiratory polygraphy with a three-channel device within two days after stroke symptom onset was feasible and easy to use for screening of sleep apnea among co-operative, in-hospital stroke patients in the acute period. Analyzability was as good as the previously reported rates.

Automatically and manually scored cardiorespiratory polygraphy results showed moderate agreement and as expected, manual scoring was preferable, as automated scoring found two thirds of sleep apnea cases while manual scoring recognized nine out of ten sleep apnea cases. Arterial oxyhemoglobin reductions of over four percent per hour (excellent agreement) were more useful than REI (good agreement), and both nocturnal hypoxemia (percent of time spent with saturation below 90%) and lowest saturation demonstrated excellent agreement. Obstructive sleep apnea was present in eight out of ten cases; the rest of the study population had central sleep apnea. The agreement was poor in central apneas. Automated scoring diagnosed sleep apnea severity incorrectly, especially in mild sleep apnea cases. Therefore, to prevent underdiagnosis as well as undertreatment, it is of great importance to score manually particularly recordings that are classified as normal or mild sleep apnea by autoscoring. Automated scoring underrated the severity of sleep apnea and could not find one fifth of cases. However, automatic analysis might be cost-effective for screening of acute stroke patients, thus enabling fast diagnosis and treatment of sleep apnea in most cases.

2. The ischemic stroke patients with thrombolysis treatment experienced more, and more severe sleep apnea compared to the non-thrombolysis group, and the total sleep apnea prevalence was even higher than previously reported.

Two thirds of all stroke patients had moderate or severe sleep apnea, and the most common apnea event was obstructive apnea. Thrombolysis therapy was the strongest predictor for sleep apnea after stroke; other independent predictors were older age and larger waist circumference. The stroke patients treated with thrombolysis therapy may be one subgroup of patients who could benefit from sleep apnea screening in the acute phase of stroke.

3. The ischemic stroke patients who underwent thrombolysis treatment and had a visible stroke lesion on follow-up brain CT experienced more oxyhemoglobin reductions of over four percent per hour and obstructive apneas per hour than
those without a visible lesion on follow-up imaging. The larger the stroke size, the longer the amount of time slept with saturation below 90%.

The stroke was more severe among stroke patients with a visible stroke lesion, and hemorrhage as a complication was only found in this group. Moreover, all the stroke patients with hemorrhagic transformation had sleep apnea, which ought to be taken into account when drawing up strategies on which subgroup of stroke patients would benefit the most for sleep apnea screening. Contrary to expectations, stroke volume did not correlate with Rankin scale score, REI or ODI4. Stroke volume and visible stroke did not correlate with sleep apnea diagnosis. The sleep apnea screening of stroke patients is recommended by AHA, ASA and AASM; at the same time, the queues of patients waiting for diagnostic evaluation or treatment initiation are long. Screening of sleep apnea seems to be especially important among stroke patients with a visible lesion and thrombolysis therapy, also suggesting fast initiation of sleep apnea treatment with either well tolerated auto-CPAP or CPAP, which may ensure better rehabilitation and cardiovascular survival. This subgroup of stroke patients might be the one that benefits the most from quick screening and treatment of sleep apnea, although we need more studies to evaluate the benefit of this recommendation for stroke outcome.

4. The prevalence of sleep apnea was still high after six months’ follow-up and the risk for sleep apnea was greater among those stroke patients treated without thrombolysis therapy.

The recovery of stroke measured by Rankin scale score, measured before getting sick, declined in all patients except one. The central apnea index increased in both study groups; this result was opposite to previous studies, although as was expected, OAI decreased in both groups. ODI4 declined more in the thrombolysis group. Total sleep apnea severity became more severe in seven out of ten cases, while two out of ten patients with moderate or severe sleep apnea moved to mild sleep apnea category. Nocturnal hypoxemia is one important factor which should be taken into account when creating strategies for screening of sleep apnea among stroke patients. Studies investigating sleep apnea prevalence and its severity among stroke patients with or without thrombolysis treatment with longer follow-up time are warranted.
References


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Appendices

*Epworth Sleepiness Scale (Johns, 1991)*

Sitting and reading
- No chance of dozing (0 points)
- Slight chance of dozing (1 point)
- Moderate chance of dozing (2 points)
- High chance of dozing (3 points)

Watching television
- No chance of dozing (0 points)
- Slight chance of dozing (1 point)
- Moderate chance of dozing (2 points)
- High chance of dozing (3 points)

Sitting inactive in a public place
- No chance of dozing (0 points)
- Slight chance of dozing (1 point)
- Moderate chance of dozing (2 points)
- High chance of dozing (3 points)

Sitting for an hour as a passenger in a car
- No chance of dozing (0 points)
- Slight chance of dozing (1 point)
- Moderate chance of dozing (2 points)
- High chance of dozing (3 points)

Lying down in the afternoon to rest
- No chance of dozing (0 points)
- Slight chance of dozing (1 point)
- Moderate chance of dozing (2 points)
- High chance of dozing (3 points)
Sitting and talking to another person
   No chance of dozing (0 points)
   Slight chance of dozing (1 point)
   Moderate chance of dozing (2 points)
   High chance of dozing (3 points)

Sitting quietly after a lunch (no alcohol at lunch)
   No chance of dozing (0 points)
   Slight chance of dozing (1 point)
   Moderate chance of dozing (2 points)
   High chance of dozing (3 points)

Sitting in a car, stopped for a few minutes due to traffic
   No chance of dozing (0 points)
   Slight chance of dozing (1 point)
   Moderate chance of dozing (2 points)
   High chance of dozing (3 points)

**Modified Rankin Scale**

0. No symptoms at all
1. No significant disability despite symptoms: able to carry out all usual duties and activities
2. Slight disability: unable to carry out all previous activities but able to look after own affairs without assistance
3. Moderate disability: requiring some help, but able to walk without assistance
4. Moderately severe disability: unable to walk without assistance, and unable to attend to own bodily needs without assistance
5. Severe disability: bedridden, incontinent, and requiring
6. constant nursing care and attention
NIH Stroke Scale/Score

1A: Level of consciousness
May be assessed casually while taking history
Alert; keenly responsive 0
Arouses to minor stimulation +1
Requires repeated stimulation to arouse +2
Movements to pain +2
Postures or unresponsive +3

1B: Ask month and age
Both questions right 0
1 question right +1
0 questions right +2
Dysarthric/intubated/trauma/language barrier +1
Aphasic +2

1C: 'Blink eyes' & 'squeeze hands'
Pantomime commands if communication barrier
Performs both tasks 0
Performs 1 task +1
Performs 0 tasks +2

2: Horizontal extraocular movements
Only assess horizontal gaze
Normal 0
Partial gaze palsy: can be overcome +1
Partial gaze palsy: corrects with oculocephalic reflex +1
Forced gaze palsy: cannot be overcome +2

3: Visual fields
No visual loss 0
Partial hemianopia +1
Complete hemianopia +2
Patient is bilaterally blind +3
Bilateral hemianopia +3
4: *Facial palsy*
   Use grimace if obtunded
   - Normal symmetry: 0
   - Minor paralysis (flat nasolabial fold, smile asymmetry): +1
   - Partial paralysis (lower face): +2
   - Unilateral complete paralysis (upper/lower face): +3
   - Bilateral complete paralysis (upper/lower face): +3

5A: *Left arm motor drift*
   Count out loud and use your fingers to show the patient your count
   - No drift for 10 seconds: 0
   - Drift, but doesn’t hit bed: +1
   - Drift, hits bed: +2
   - Some effort against gravity: +2
   - No effort against gravity: +3
   - No movement: +4
   - Amputation/joint fusion: 0

5B: *Right arm motor drift*
   Count out loud and use your fingers to show the patient your count
   - No drift for 10 seconds: 0
   - Drift, but doesn’t hit bed: +1
   - Drift, hits bed: +2
   - Some effort against gravity: +2
   - No effort against gravity: +3
   - No movement: +4
   - Amputation/joint fusion: 0

6A: *Left leg motor drift*
   Count out loud and use your fingers to show the patient your count
   - No drift for 5 seconds: 0
   - Drift, but doesn’t hit bed: +1
   - Drift, hits bed: +2
   - Some effort against gravity: +2
   - No effort against gravity: +3
   - No movement: +4
   - Amputation/joint fusion: 0
6B: Right leg motor drift

Count out loud and use your fingers to show the patient your count

- No drift for 5 seconds 0
- Drift, but doesn't hit bed +1
- Drift, hits bed +2
- Some effort against gravity +2
- No effort against gravity +3
- No movement +4
- Amputation/joint fusion 0

7: Limb Ataxia

- FNF/heel-shin
  - No ataxia 0
  - Ataxia in 1 Limb +1
  - Ataxia in 2 Limbs +2
- Does not understand 0
- Paralyzed 0
- Amputation/joint fusion 0

8: Sensation

- Normal; no sensory loss 0
- Mild-moderate loss: less sharp/more dull +1
- Mild-moderate loss: can sense being touched +1
- Complete loss: cannot sense being touched at all +2
- No response and quadriplegic +2
- Coma/unresponsive +2

9: Language/aphasia

- Describe the scene; name the items; read the sentences
- Normal; no aphasia 0
- Mild-moderate aphasia: some obvious changes, without significant limitation +1
- Severe aphasia: fragmentary expression, inference needed, cannot identify materials +2
- Mute/global aphasia: no usable speech/auditory comprehension +3
- Coma/unresponsive +3
10: Dysarthria
Read the words
Normal 0
Mild-moderate dysarthria: slurring but can be understood +1
Severe dysarthria: unintelligible slurring or out of proportion to dysphasia +2
Mute/anarthric +2
Intubated/unable to test 0

11: Extinction/inattention
No abnormality 0
Visual/tactile/auditory/spatial/personal inattention +1
Extinction to bilateral simultaneous stimulation +1
Profound hemi-inattention (ex: does not recognize own hand) +2
Extinction to > 1 modality +2
Original publications

The present thesis is based on the following articles, which are referred to in the text by their Roman numerals.


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Original articles are not included in the electronic version of the dissertation.
1536. Terho, Henri (2019) Electrocardiographic risk markers for cardiac events in middle-aged population
1538. Ylönen, Susanna (2019) Genetic risk factors for movement disorders in Finland
1541. Tiri, Hannu (2019) Comorbidities and mortality of hidradenitis suppurativa in Finland
1542. Hynynen, Johanna (2019) Status epilepticus in mitochondrial diseases and the role of POLG1 variants in the valproic-acid induced hepatotoxicity
1543. Urpilainen, Elina (2019) The role of metformin and statins in ovarian and breast cancer in women with type 2 diabetes
Jaana Huhtakangas

EVOLUTION OF OBSTRUCTIVE SLEEP APNEA AFTER ISCHEMIC STROKE