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Sleep Apnea in Stroke. Diagnosis, Consequences & Treatment

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SLEEP APNEA IN STROKE: SUMMARY

The overall objective of this thesis was to improve our understanding of the effects of obstructive sleep apnea (OSA) and its treatment with continuous positive airway pressure (CPAP) on the recovery of stroke patients. Specifically, the aims of our studies were to 1) improve early recognition of sleep apnea in stroke patients during inpatient rehabilitation, 2) determine the effects of OSA on daily functioning, more specific on cognitive and functional status of stroke patients at admission to stroke rehabilitation, and 3) investigate whether CPAP treatment can improve the recovery of cognitive and functional outcome after stroke. In this chapter we will summarize and discuss the results of the studies described in this thesis. We will address methodological considerations of our studies and discuss the clinical implications of this thesis. Finally, we will conclude with some recommendations for future research.

Chapter 1 provided a general introduction to the topic of this thesis, and started with the definition, incidence, consequences and treatment options of both stroke and sleep apnea. Subsequently, the relationship between stroke and sleep apnea was outlined and the current literature on this subject was briefly summarized.

CPAP treatment in the general OSA population

In preparation of our study on the effect of CPAP treatment on cognitive functioning in stroke patients, we first carried out a meta-analysis of CPAP treatment in the general OSA population. Earlier reviews suggested that CPAP would improve cognitive functioning in several domains such as vigilance, attention and memory, but due to the qualitative nature of these reviews the magnitude of these effects was unclear.[1-3] In **Chapter 2** the results of our meta-analysis of thirteen randomized controlled trials (RCT's) on the effect of CPAP treatment on neuropsychological functioning were presented. The main finding of this meta-analysis was a small, positive effect of CPAP in the domain of attention, while no significant improvement was seen in the other cognitive domains. More specifically, the improvement was observed on tasks for divided attention, with the more demanding tasks revealing larger improvements. Additionally, in our selected studies, we found improvement on measures of sleepiness and mood, which is in line with prior research.[4] Although this meta-analysis indicated that, contrary to earlier views, only slight improvement of cognitive functioning after CPAP treatment can be expected, additional RCT's are needed to further quantify the influence of OSA severity, treatment duration and compliance on this effect.

Early recognition of sleep apnea in stroke patients during inpatient rehabilitation

Sleep apnea is a highly prevalent sleep disorder in stroke patients with reported prevalence ranging from 38% to 78% compared to 3-17% in the general population.[5,6] Moreover, sleep apnea has been found to contribute to poor functional recovery, increased risk of recurrent stroke, and post-stroke mortality.[7-10] Despite its high prevalence and serious consequences, standard evaluation of sleep apnea in stroke rehabilitation settings is limited.[11] The standard diagnostic test for sleep apnea is overnight polysomnography or multichannel polygraphy.[12] In stroke rehabilitation, however, these approaches are often not feasible due to limited access, high costs, and practical constraints. To overcome these limitations and to improve sleep apnea screening in stroke rehabilitation, we proposed a step-by-step diagnostic approach to sleep apnea in which stroke patients only receive the level of sleep apnea screening they need. This approach asks for easily administered and reliable screening instruments. In **Chapter 3** and **Chapter 4** we therefore investigated the validity of two different screening methods for the detection of sleep apnea in stroke patients.

The aim of the study described in **Chapter 3** was to validate the use of nocturnal oximetry for screening of sleep apnea and to identify possible clinical predictors of sleep apnea in stroke rehabilitation. Oximetry is a method that monitors the number of oxygen desaturations per hour (ODI) and the heart rate through an infrared sensor usually placed on the fingertip. Although the use of oximetry as a screening instrument for sleep apnea in sleep laboratories is widespread, the sensitivity and specificity of the instrument in the stroke population had not yet been subject of investigation.[13] In our study 56 stroke patients underwent both nocturnal polygraphy and oximetry. We found that forty-six percent of the patients were diagnosed with sleep apnea (AHI≥15). The majority of stroke patients with sleep apnea was male, older and had a higher body mass index than the stroke patients without sleep apnea. Nocturnal oximetry accurately discriminated between patients with and without a sleep apnea, with a 93% diagnostic accuracy. The sensitivity of nocturnal oximetry (ODI≥15) was 77% with a specificity of 100%. Given the high prevalence of sleep apnea in the studied population, a positive oximetry result increased the likelihood of sleep apnea to 100% (positive predictive value), while a negative result lowered the probability to 17% (negative predictive value of 83%). Other clinical variables did not add to the predictive value of oximetry. Our findings showed that nocturnal oximetry is an adequate screening instrument for sleep apnea in the stroke population.

In continuation of this study we wanted to investigate, as part of the stepped diagnostic approach, if even easier to administer screening instruments such as self-report

questionnaires would be useful in the detection of sleep apnea in the stroke population. A number of previous studies had found that the well-validated sleep apnea screening questionnaire, the Berlin questionnaire, could not adequately discriminate between stroke patients with and without sleep apnea.[11,14,15] Thus, in **Chapter 4** we sought to develop a predictive model based on a sleep apnea questionnaire consisting of self-reported symptoms, socio-demographic variables and clinical parameters that could serve as a first reliable screening method for sleep apnea in the stepped diagnostic approach. We administered our self-designed sleep apnea questionnaire to 438 stroke patients and used nocturnal oximetry to identify the patients with a high likelihood of sleep apnea (ODI≥15). The following variables of the sleep questionnaire were included in our final prediction model: sex, age, BMI, and self-reported symptoms of apneas and falling asleep during daytime. We found that this prediction model had an acceptable diagnostic accuracy of 76%. Using a moderate probability cut-off, the sensitivity and specificity were 72% and 69%, respectively. The corresponding positive predictive value was 50%, while the negative predictive value was 83%. We therefore concluded that a questionnaire including the variables of our prediction model seems to be a reasonable first screening tool in stepped detection of sleep apnea in stroke patients, as it significantly reduces the number of patients who need more elaborate sleep apnea screening.

The effect of OSA and CPAP treatment on rehabilitation outcome

As has been mentioned above, OSA is a common sleep disorder in stroke patients and associated with poor functional outcome and increased mortality.[7-10] However, research on the effect of OSA on cognitive functioning following stroke is scarce. Moreover, a number of studies suggest that CPAP improves functional recovery of stroke patients, but the effect on cognitive functioning has not been thoroughly investigated.[16] **Chapter 5** provided a detailed description of the rationale, design and methods of our study protocol "Treatment of Obstructive sleep apnea on Rehabilitation Outcome in Stroke" (TOROS). The primary objective of the TOROS study was to investigate the effectiveness of CPAP on both cognitive and functional outcomes in stroke patients with obstructive sleep apnea with a randomized controlled trial (RCT). Supplementary to this RCT, the protocol encompassed a case-control study that aimed to examine the association between OSA and cognitive and functional status in stroke patients. With the publication of the study protocol, including the main clinical endpoints before the results were known, we aimed to augment the transparency of our research.

In **Chapter 6** the results of this case-control study are presented. In total, 80 stroke patients with OSA (AHI≥15) and 67 stroke patients without OSA (AHI<5) participated. All these patients were compared on cognitive and functional status during early admission to the inpatient stroke rehabilitation unit of Heliomare. Our main finding was that OSA patients were significantly more impaired on both cognitive and functional status than stroke patients without OSA. More specifically, OSA patients were more impaired in the cognitive domains of attention, executive functioning, visuoperception, psychomotor ability and intelligence, and had poorer neurological status and a lower level of functional independence. Further, OSA patients on average spent eleven days longer on the inpatient stroke rehabilitation unit than patients without OSA. Finally, contrary to findings in the general OSA population, we did not find that stroke patients with OSA differed from patients without OSA on reported levels of sleepiness, fatigue, and sleep quality or on reported symptoms of depression and anxiety.

The focus of **Chapter 7** was on the effect of CPAP treatment on the rehabilitation outcome of stroke patients with OSA. Sixteen stroke patients with OSA (AHI≥15) were assigned to four weeks of rehabilitation treatment as usual, while twenty patients received four weeks of CPAP treatment. After this four-week intervention period patients receiving CPAP treatment showed greater improvement of cognitive functioning in the domains of attention and executive functioning than patients who received treatment as usual. These effects were moderate to large, implying that they were not only statistically significant, but also clinically relevant. CPAP was not associated with improvement of functional status, or of sleepiness, fatigue, sleep quality or mood. Even though no significant effect on functional status was found, our findings did indicate a trend in the expected direction. The average CPAP compliance was 2.5 hours per night, which is considered low. The low compliance may have led to an underestimation of the true effect of CPAP on stroke rehabilitation. This hypothesis is supported by the results of a subsequent per-protocol analysis, which suggests that if CPAP compliance can be increased, even greater improvement may be expected. We concluded that the beneficial effects of CPAP on stroke outcome found in our study offer a preliminary evidence base for the use of this treatment as part of a rehabilitation program for stroke patients.

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