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The effect of continuous positive airway pressure on spectral encephalogram characteristics in stroke patients with obstructive sleep apnea

Hisham Alshaer[a], Aditya Pandya[b], Igor Zivanovic[a], Carolina Gonzaga Carvalho[a,c], Clodagh M. Ryan[a,d,*]

[a] Sleep Research Laboratory, Toronto Rehabilitation Institute, University Health Network, Toronto, ON, Canada
[b] Department of Physics, Ryerson University, Toronto, ON, Canada
[c] Sleep Laboratory, Insituto Dante Pazzanese de Cardiologia, Sao Paulo, SP, Brazil
[d] Department of Medicine, University of Toronto, Toronto, ON, Canada

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ABSTRACT

Objectives: To evaluate if treatment with continuous positive airway pressure (CPAP) compared to usual care in stroke patients with obstructive sleep apnea (OSA) over one month reduces delta and alpha oscillations on quantitative electroencephalography (EEG) in association with improvements in cognitive or functional outcomes.

Methods: Spectral EEG analysis was performed in patients with subacute stroke and OSA randomized to usual care or CPAP treatment from a previous study.

Results: A total of 23 subjects were included. Compared to CPAP (n = 14), those in the control (n = 9) group demonstrated a significant increase in alpha power (p = 0.042). There was no between group differences for delta, theta or beta power. No significant correlation was demonstrated between the change in alpha power and indices of OSA severity or sleepiness. The increase in alpha power did not correlate with improvements in outcomes.

Conclusion: Contrary to expectations CPAP treatment of OSA did not significantly decrease alpha and delta oscillations in stroke subjects.

1. Introduction

Stroke is a significant cause of morbidity and the second leading cause of death worldwide. It leads to cognitive impairment and the loss of functional independence. Recovery from stroke is dependent on neuroplasticity of the brain. Sleep plays a key role in the modulation of brain injury recovery and neuroplasticity. Obstructive sleep apnea, which results from the narrowing and collapse of the pharyngeal upper airway (OSA) may precede or be a consequence of stroke (Sanchez-de-la-Torre et al., 2013) and is known to have a high prevalence of between 30 and 70% in post-stroke patients. The significance of OSA relates to the recurrent hypoxia and carbon-dioxide retention and exaggerated negative intrathoracic pressure generation which cause alterations in cerebral blood flow and elevated blood pressure during, and frequent awakenings from sleep (Bradley and Floras, 2009). In the post-stroke period, the adverse impact of OSA may be heightened, resulting in post-stroke sleep disturbance, excessive daytime sleepiness and low mood. This is confirmed by lower functional independence capacity and longer hospital stays and increased mortality in observational studies of stroke patients with OSA compared to those without OSA (Martinez-Garcia et al., 2012; Martinez-Garcia et al., 2009; Ryan et al., 2011; Sahlin et al., 2008). Treatment with continuous positive airway pressure (CPAP) in stroke patients with OSA reduces daytime sleepiness and improves mood, motor and some neurocognitive outcomes (Parra et al., 2011; Ryan et al., 2011).

Conventional measures of sleep architecture and sleep disruption are derived from visual inspection of the sleep electroencephalogram (EEG). However, subtle alterations in the sleep or wake EEG cannot be detected with visual scoring. Spectral EEG analysis allows in-depth and temporal analysis of sleep quality during the night and provides a more sensitive analysis of sleep disruption and potentially neurobehavioral function, then either sleep architecture or arousals (Borbely et al., 1981; Svanborg and Guilleminault, 1996). During sleep, greater alpha oscillations on EEG spectral analysis are thought to be related to poorer sleep quality(Asyali et al., 2007). However, in stroke changes in delta, theta and spindle frequency range have been demonstrated to be

* Corresponding author at: 9N-967, Toronto General Hospital, Toronto, ON, M5G 2N2, Canada.
E-mail address: clodagh.ryan@uhn.ca (C.M. Ryan).

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related to both acute cerebral ischemia and neuroplasticity related to stroke recovery (Foreman and Claassen, 2012; Poryazova et al., 2015).

The impact of the treatment of newly diagnosed OSA on sleep architecture as assessed by spectral EEG analysis in patients with subacute stroke is unknown. Our hypothesis was that there would be a greater reduction in delta and alpha oscillations in stroke subjects with OSA, treated for one month with CPAP therapy, compared to those not treated, as a result of reduced nocturnal awakenings and arousals and reduced perturbations in cerebral blood flow, promoting greater neurological recovery. Therefore, the objectives of our study were to evaluate spectral EEG analysis during sleep in those stroke patients with OSA both treated with and without CPAP therapy and to determine if there was a correlation between spectral EEG analysis changes and neurocognitive or functional outcomes. We analysed prospective data from a randomized controlled trial evaluating the neurocognitive and functional outcome of CPAP therapy in subjects with OSA and stroke.

2. Methods

2.1. Study design and subjects

Data collected from a previous randomized controlled trial in patients with subacute stroke and newly diagnosed OSA, were included for analysis (Ryan et al., 2011). In brief, this study randomized stroke patients with OSA to a control group, which received standard stroke occupational and physiotherapy for the duration of the trial or a treatment group that in addition, received CPAP for their OSA. Subjects had baseline and one month assessments including motor, neurocognitive testing, subjective assessment of sleepiness with the Epworth sleepiness scale (ESS) score and polysomnography performed. For the purpose of this study, only subjects with available baseline and one month follow-up polysomnography and those who were adherent to CPAP (median use $\geq$4 h/night for 70% of the time) were included for analysis. Patients with an apnea-hypopnea index (AHI) of $\geq$ 15 were classified as having sleep apnea.

2.1.1. Subjects

Eligible patients were those adult patients admitted from acute care facilities to the stroke rehabilitation unit within 3 weeks of stroke onset with the following inclusion criteria: 1) completed ischemic or hemorrhagic stroke confirmed by a neurologist based on: a) history of sudden onset of a neurological deficit lasting more than 24 h, b) neurological deficit on physical examination, and c) brain lesion compatible with the neurological deficit on computerized tomography or magnetic resonance imaging of the brain; and 2) OSA on an overnight attended PSG as described below. Exclusion criteria were: 1) brainstem strokes that could increase aspiration risk while on CPAP, 2) patients with previously diagnosed OSA on therapy, 3) concomitant central nervous system diseases such as dementia, Parkinson's disease, multiple sclerosis or Huntington's disease, 4) history of psychosis, 5) traumatic brain injury; and 6) anosagnosia, global aphasia or Wernicke's aphasia, and for this study 7) benzodiazepine medications.

The study was approved by the Research Ethics Board of the Toronto Rehabilitation Institute and all subjects provided written consent prior to participation (registered at clinicaltrials.gov. NCT00221065).

2.2. Polysomnography (PSG)

Eligible patients underwent a clinical assessment followed by an overnight PSG in the Toronto Rehabilitation Institute Sleep Research Laboratory. Routine PSGs were performed using standard techniques and scoring criteria for sleep stages and arousals from sleep (Iber C, 2007; Rechtschaffen A, 1968). Thoracoabdominal movements and their electronic sum were monitored by respiratory inductance plethysmograph (RIP) (Respitrace; Ambulatory Monitoring Inc., White Plains, NY) (Chadha et al., 1982) Arterial oxygen saturation (SaO_2) was continuously monitored by a pulse oximeter (Nellcor, Puritan Bennett, LLC). All data were recorded on a computerized sleep scoring system (Sandman, Nellcor Puritan Bennett Ltd., Ottawa, ON). Sleepiness was assessed subjectively by the (ESS).

2.3. Power spectral analysis of the EEG

Raw EEG signals were recorded with band-pass filters spanning 0.3 Hz to 35 Hz and sampled at a minimum of 128 Hz. Standard power spectral density (PSD) analysis of raw EEG signals was performed based on fast Fourier transformation (FFT). For each subject, the C3-A2 EEG channels were exported as raw data for the entire sleep period during both REM and NREM sleep. PSD was calculated using the standard Welch method, in which each 30 s EEG epoch is partitioned into 5 s segments with 50% overlap between successive segments. Therefore, 12 segments are derived from each epoch. Each segment is then windowed using the Hamming window and FFT is calculated and squared to obtain the PSD (Jenni and Carskadon, 2004). PSD arrays of all segments in each epoch were then averaged to obtain a single PSD representative of the whole epoch. The Welch method is more robust to noise because averaging the PSD spectra cancels away transient noise and retains consistent data. All epochs containing saturated values due to patient wakefulness and external interference were removed. Bad channels were rejected. The resulting spectral distribution was split into the following frequency bands: delta (0.8–4.0 Hz); theta (4.1–8.0 Hz); alpha (8.1–13 Hz); and beta (13.1–20 Hz) (Zhang et al., 2008). The average 5 s power spectra for the sleep period time, in addition to the average for the first 50% (T1) and the latter 50% (T2) sleep period of the night for each frequency band was determined.

2.4. Statistical analyses

Descriptive data are reported as mean $\pm$ SD or percentages, unless otherwise indicated. For continuous descriptive variables, the independent samples *t*-test was used, while the Fisher exact/chi-squared test was used for categorical variables. Within group differences between wave frequencies from baseline to follow-up were analyzed by the paired *t*-test, while between group differences were analyzed using repeated measures ANOVA analysis. To justify repeated measures analysis, the Kolmogorov-Smirnov test was used to check for normality and non-parametric behaviour. Associations were assessed by Pearsons correlation or Spearmans tests depending on normality. All statistical analyses were performed using the IBM SPSS Statistics 21 package. Statistical inferences were based on 2-tailed tests and used a $P < 0.05$ threshold for statistical significance (2).

3. Results

3.1. Characteristics of the subjects

Twenty-three of the 44 subjects enrolled in the original study were included for analysis. This includes 9 and 14 subjects from the control and CPAP groups, respectively. Five subjects were excluded due to benzodiazepine use, 2 subjects due to CPAP adherence < 4 h per night, 7 due to inadequate quality data on one of the PSGs and 7 due to absence of a follow-up PSG at one month. There were no significant differences between groups for all baseline characteristics (Table 1). Within the control group there were no significant improvements in ESS, or any of the sleep variables during the trial (Table 2). However, within the CPAP–treated group, there were significant reductions in the ESS and AHI, as well as an increase in minimum sleep pulse oxygen saturation that were also greater than in the control group. Mean pulse oxygen saturation also improved within the CPAP group. There were no significant differences in sleep architecture within and between the control and CPAP-treated groups. Mean ($\pm$ SEM) CPAP adherence