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Original Article

Altered sleep structure in patients with end-stage renal disease

Rosilene M. Elias [a,b], Christopher T. Chan [a], T. Douglas Bradley [b,c,*]

[a] Division of Nephrology, University Health Network Toronto General Hospital, Toronto, Ontario, Canada
[b] Sleep Research Laboratory, University Health Network Toronto Rehabilitation Institute, Toronto, Ontario, Canada
[c] Division of Respirology, University Health Network Toronto General Hospital, Toronto, Ontario, Canada

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ABSTRACT

Objective: Although symptoms of sleep disturbances are widely recognized in end-stage renal disease (ESRD), the effect of uremia on sleep structure has not been well investigated. We hypothesized that compared to individuals without ESRD, those with ESRD would have altered sleep structure after controlling for the severity of sleep apnea (SA).
Methods: We studied 57 ESRD patients (42 men) and 57 controls (46 men) who had undergone polysomnography. Control subjects were matched to the ESRD patients by age, body mass index (BMI), frequency of periodic leg movements per hour of sleep, and the frequency of apneas and hypopneas per hour of sleep [apnea–hypopnea index (AHI)].
Results: The AHI and the percentage of patients with an AHI ≥15 were similar between ESRD and control groups. However, total ($p = 0.002$), rapid eye movement (REM) ($p = 0.007$), and non-REM ($p = 0.022$) sleep times were lower in ESRD patients than in the control group. In a multivariable analysis adjusted for age, sex, AHI, BMI, arousal index, and diabetes, ESRD remained independently associated with lower REM ($p = 0.021$) and total sleep times ($p = 0.026$).
Conclusion: ESRD is independently associated with reduced total and REM sleep times after controlling for the severity of SA and other variables. Although we could not identify the cause of reduced sleep times, these could be related to uremia or fluid overload or both. Accordingly, our data provide a strong rationale for examining the effects of intensifying dialysis on sleep structure in ESRD patients.

1. Introduction

Although symptoms of sleep disturbances are reported to be common in end-stage renal disease (ESRD), the effect of ESRD on sleep structure has not been well documented. The prevalence of sleep disorders is estimated to be 50%–80% of patients with ESRD. Insomnia, excessive daytime sleepiness [1,2], sleep apnea (SA), periodic leg movements (PLMs), and restless leg syndrome are all common in ESRD patients [3–5]. These data suggest that uremia and/or fluid overload may play a role in the development of some of these sleep disorders.

A few studies have described reduced total sleep time (TST) in ESRD based on objective data from polysomnography [5–7]. However, these studies enrolled patients with SA, which can alter sleep architecture independently of ESRD. Other studies describing reduced sleep time in ESRD have limited reliability because sleep time was evaluated subjectively by questionnaires [8,9]. In addition, even studies of patients with ESRD in which polysomnography was performed did not have a control group with normal renal function matched for age, sex, body mass index (BMI), and severity of SA [5–7]. Because SA is highly prevalent in ESRD patients and contributes to altered sleep structure, it remains unknown whether uremia has an impact on sleep structure independently of the presence of SA.

We have previously demonstrated that patients with other fluid-retaining states including heart failure (HF) [10] and drug-resistant hypertension [11] have reduced sleep time and altered sleep structure compared to subjects without these conditions, independently of SA. On the other hand, we found that sleep time and structure in patients with stroke who were not fluid overloaded did not differ from those without stroke [12]. These observations raise the possibility that chronic diseases associated with fluid retention predispose to alterations in sleep time and structure. We therefore hypothesized that compared to individuals without ESRD, those with ESRD would have reduced total sleep time and altered sleep structure independently of SA severity.

2. Methods

2.1. Study design

We used a cross-sectional study design to compare sleep quantity and structure in patients with ESRD (cases) to subjects without

* Corresponding author. University Health Network Toronto General Hospital, 9N-943, 200 Elizabeth Street, Toronto, ON, Canada M5G 2C4. Tel.: +1 416 340 4719; fax: +1 416 340 4197.
E-mail address: douglas.bradley@utoronto.ca (T.D. Bradley).

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ESRD (controls) matched for age sex, BMI, and presence and severity of sleep apnea (SA).

2.2. Subjects

2.2.1. ESRD patients

Consecutive patients with ESRD referred to our sleep laboratory for polysomnography for investigation of possible SA were included. Inclusion criteria were ESRD on conventional renal replacement therapy (peritoneal dialysis or hemodialysis three times per week) or expected to commence renal replacement therapy within three months of polysomnography. Exclusion criteria were SA on continuous positive airway pressure (CPAP) or other treatment for SA, as well as use of antipsychotic, opioid, sedative, or antidepressant drugs. Demographic characteristics and medical history were recorded. All patients on peritoneal dialysis or hemodialysis were receiving an adequate dose of dialysis (defined as percentage of reduction of urea more than 65%).

2.2.2. Control subjects

Control subjects were subjects without ESRD who were referred for polysomnography because of clinical suspicion of SA. They were matched to the ESRD patients for age, sex, body mass index (BMI), periodic leg movement PLMI, frequency of apneas, and hypopneas per hour of sleep (apnea–hypopnea index [AHI]), and presence of diabetes.

2.3. Polysomnography

Overnight polysomnography was performed using standard techniques and criteria for scoring sleep stages and arousals from sleep [13,14], to determine objectively the onset, duration, and distribution of sleep stages. Sleep efficiency (SE) was calculated as total sleep time expressed as a percentage of the time spent in bed after lights out. Both REM sleep and all stages of non-REM sleep were quantified as time in minutes during the night. All subjects slept on a single pillow with the bed flat. Since our laboratory allows free wake-up time in the morning, total sleep time was not truncated by early wake-up times at the ending of the night technologists' shifts. Arousals from non-REM sleep were defined as an abrupt shift of electroencephalographic frequency, including α, θ, and/or frequencies >16 Hz (but not spindles) that lasted ≥3 seconds, with ≥10 seconds of stable sleep preceding the change. Scoring of arousals during REM sleep required, in addition, a corresponding increase in submental electromyographic activity lasting ≥1 second. The arousal index (ArI) was quantified as the frequency of arousals per hour of sleep. Electromyographic recordings of leg movements were made from the anterior tibialis muscles using standard surface electrodes. PLMs were defined, using standard criteria from the American Sleep Disorders Association [15] and the second edition of the International Classification of Sleep Disorders coding manual [16], as a series of at least four consecutive leg movements lasting 0.5–5 seconds, with an amplitude of ≥1/4 of that due to dorsiflexion of the toe during calibration and separated by intervals of 5–90 seconds. To avoid overscoring of PLMs that might have occurred secondary to arousals, leg movements that occurred after the onset of an arousal were not scored as PLMs. Similarly, to avoid overscoring of PLMs that might have occurred secondary to the termination of respiratory events, only leg movements that occurred during regular breathing or began and ended ≥0.5 second before resolution of an apnea or hypopnea were classified as PLMs [17]. The PLM index was quantified as the frequency of PLMs per hour of sleep.

Thoracoabdominal motion was monitored by respiratory inductance plethysmography and nasal airflow by nasal pressure cannulas (Binaps model 5500, Salter Labs, Arvin, CA, USA). Arterial oxyhemoglobin saturation (SaO_2) was monitored by pulse oximetry. Apnea was defined as a >90% reduction of the respiratory inductance plethysmography sum channel for ≥10 seconds, and hypopnea was defined as a ≥30% reduction in the respiratory inductance plethysmography sum channel lasting ≥10 seconds, associated with a ≥3% desaturation or an arousal from sleep [18]. Apneas were classified as obstructive if there was thoracoabdominal motion and as central if there was no thoracoabdominal motion. Hypopneas were classified as obstructive in the presence of out-of-phase thoracoabdominal motion or airflow limitation on the nasal pressure channel. Hypopneas were classified as central in the presence of in-phase thoracoabdominal motion and without airflow limitation on nasal pressure. The AHI was calculated. Signals were recorded on a computerized sleep recording system (Sandman, Nellcor Puritan Bennett Ltd, Ottawa, ON, Canada). A sleep apnea disorder was defined as an AHI ≥15. Sleep apnea was defined as obstructive if ≥50% of apneas and hypopneas were obstructive and as central if >50% of apneas and hypopneas were central.

The protocol was approved by the Research Ethics Boards of the University Health Network Toronto Rehabilitation Institute.

2.4. Statistical analysis

ESRD patients were compared with the non-ESRD control subjects to assess differences in total sleep time and indices of sleep structure. A Student *t*-test was used for normally distributed continuous variables and a Mann–Whitney *U* test for non-normally distributed variables, according to the Kolmogorov–Smirnov test. The χ^2 or Fisher exact test was used to compare nominal variables as appropriate. Analysis of covariance was used to determine whether differences in sleep variables were independent of potential confounding factors including age, sex, BMI, AHI, and diabetes. A multivariable logistic analysis was also performed with TST categorized as ≤5 hours, or >5 hours as the dependent variable and with age, sex, diabetes, BMI, and AHI as the independent variables, using multiple forward stepwise likelihood ratio method. Data are presented as mean ± standard deviation (SD). A p value of ≤0.05 was considered significant. Analyses were performed using SPSS 20 (SPSS Inc, Chicago, IL, USA) and Prism 6 (GraphPad Software, Inc) statistical software packages.

3. Results

3.1. Subject characteristics

We studied 57 ESRD patients (42 men and 15 women) and 57 control subjects (46 men and 11 women) whose characteristics are shown in Table 1. Among patients with ESRD, seven were on peritoneal dialysis, 43 were on hemodialysis, and seven started dialysis within three months after polysomnography. Because of the heterogeneous subsets of patients within the ESRD group, we further tested differences among patients on peritoneal dialysis, on hemodialysis, and not yet on dialysis to avoid residual confounding. There was no difference among these groups in the percentage of diabetes, obesity (defined as a BMI >30 kg/m^2), and age ≥60 years (all

Table 1
Patient characteristics of the patients.

Characteristic	Control n = 57	ESRD n = 57	*p*
Age, y	52.9 ± 13.2	51.7 ± 16.5	0.670
Male sex, n (%)	46 (80.7)	42 (73.7)	0.504
BMI, kg/m^2	31.3 ± 6.4	29.4 ± 8.6	0.182
Diabetes, n (%)	15 (26.3)	8 (14.0)	0.160

Abbreviations: ESRD, end-stage renal disease; BMI, body mass index.
Values are expressed as mean ± SD or n (%).