Sleep and Breathing (2021) 25:1875–1884
https://doi.org/10.1007/s11325-021-02300-8

SLEEP BREATHING PHYSIOLOGY AND DISORDERS • ORIGINAL ARTICLE

CPAP treatment in REM-related obstructive sleep apnea: a distinct clinical phenotype of sleep disordered breathing

Xiao Ya Hu [1,2] · Jin-Gun Cho [1,2,3] · Rita Perri [3] · Terence Ting [1] · Khaled Al Oweidat [1] · Stephen Lambert [1] · John Wheatley [1,2,3]

Received: 26 October 2020 / Revised: 3 January 2021 / Accepted: 15 January 2021 / Published online: 23 January 2021

Abstract

Purpose REM-related obstructive sleep apnea (REM-OSA), as defined using revised apnea-hypopnea index (AHI) criteria, might represent a specific OSA phenotype. However, there is a lack of data on outcomes of treatment in this population. This study evaluated the effects of CPAP treatment over 12 months on clinical outcomes for patients with the polysomnography phenotype of REM-OSA.

Methods We conducted a prospective observational study with the following inclusion criteria: subjective sleepiness and diagnostic polysomnography demonstrating $AHI_{REM} \geq 15$ events/h, $AHI_{NREM} < 5$ events/h, and ≥ 30 min of REM sleep. Clinical outcomes assessed included Epworth Sleepiness Scale (ESS), psychomotor vigilanc test reaction time (PVT-RT), and CPAP adherence at baseline, 1, 3, 6, and 12 months; Functional Outcomes of Sleep Questionnaire (FOSQ) and Depression Anxiety Stress Scales (DASS-21) at baseline, 1, 3 and 12 months. The reason is the first 3 outcomes (ESS, PVT, adherence) were assessed at baseline, 1, 3, 6, and 12 months, while the next 2 outcomes (FOSQ, DASS) were assessed at baseline, 1, 3, and 12 months. The edited version is not as clear in separating these outcomes into 2 groups; Functional Outcomes of Sleep Questionnaire (FOSQ); and Depression Anxiety Stress Scales (DASS-21) at baseline, 1, 3, and 12 months. Linear mixed effects models were used to investigate the joint effects of time and average CPAP adherence on our outcomes of interest.

Results Twenty participants completed a minimum of 1 month of CPAP treatment and were included for analysis. During the trial, 8 participants discontinued CPAP (4 before 3 months, 1 before 6 months, 3 before 12 months), and 19 participants completed 12 months of treatment. Baseline ESS was elevated at 12.6 units. Average CPAP usage for all 27 participants over 12 months was 2.9 ± 2.4 h. There was a significant decrease in ESS and increase in FOSQ at all time points, and the decrease in ESS was only seen in the CPAP-adherent subgroup. Decreases in DASS-21 and PVT-RT were not sustained.

Conclusions CPAP treatment in sleepy patients with moderate to severe REM-OSA is associated with reduced sleepiness and improved quality of life.

Trial registration The trial was registered in the Australian New Zealand Clinical Trials Registry: ACTRN12620000576921, 18/05/2020 (retrospectively registered).

Keywords Obstructive sleep apnea · REM sleep · Continuous positive airway pressure · Patient adherence · Sleepiness · Health-related quality of life

✉ John Wheatley
john.wheatley@health.nsw.gov.au

[1] Department of Respiratory and Sleep Medicine, Westmead Hospital, Westmead, NSW, Australia

[2] Westmead Clinical School, Faculty of Medicine and Health, The University of Sydney, Westmead, NSW, Australia

[3] Ludwig Engel Centre for Respiratory Research, Westmead Institute for Medical Research, Westmead, NSW, Australia

Introduction

Obstructive sleep apnea (OSA) syndrome is a common disorder affecting 6–13% of the industrialized world [1, 2], characterized by daytime sleepiness, snoring, and witnessed apneas [3, 4]. Currently, the most effective and widely used treatment for OSA syndrome is continuous positive airway pressure (CPAP) [5].

OSA in which obstructive apneas and hypopneas occur predominantly during rapid-eye movement (REM) sleep is known as REM-OSA and is associated with hypertension, impaired glucose metabolism, and neurocognitive function [6]. REM-OSA prevalence varies between 10 and 36% of patients with OSA, due to differences in study populations and varying REM-OSA definitions [7, 8]. Previous studies also included patients who had a significant degree of non-REM (NREM)-related OSA.

Therefore, a revised polysomnography criteria have been proposed to better define REM-OSA [9]:

1. Apnea-hypopnea index (AHI) during NREM sleep [AHI_{NREM}]<5 events/h
2. AHI during REM sleep [AHI_{REM}]≥5 events/h
3. ≥30 min of REM sleep

This definition provides a more accurate polysomnography-based description of REM-OSA that effectively excludes NREM-OSA and provides clear criteria for diagnosing REM-OSA as a separate clinical OSA phenotype. There are only a few studies that have assessed patient characteristics or response to treatment using this newer REM-OSA criterion [10, 11].

REM-OSA patients are female-predominant, younger, and less obese and have less severe sleep-disordered breathing (SDB) and lower blood pressure, but have similar levels of sleepiness compared with NREM/REM-OSA [12]. It was unclear whether REM-OSA patients formed a specific clinical phenotype of OSA, or if this simply represented an early stage in the development of the more usual clinical OSA syndrome. Despite this uncertainty, careful evaluation of short- and long-term responses to treatment is required to provide evidence of treatment benefit in what would otherwise be regarded as a "milder" form of OSA syndrome.

Therefore, we applied this revised criteria to diagnose patients with moderate-to-severe REM-OSA (i.e. AHI_{REM}≥15 events/h) referred to a tertiary hospital clinical sleep service, and to evaluate their clinical and functional outcomes after a CPAP treatment trial for 12 months.

Methods

Inclusion criteria

We conducted a prospective single-arm, pre-post study using CPAP treatment for 12 months in patients diagnosed with moderate-to-severe REM-OSA at a university teaching hospital (Westmead Hospital, New South Wales, Australia). Participants were initially referred to investigate for SDB between June 2015 and August 2018. They underwent overnight diagnostic laboratory polysomnography (Profusion 4, Compumedics, Abbotsford, Victoria, Australia), and studies were scored using AASM criteria, Version 2.5 (2018).

Eligible participants with REM-OSA were invited to participate in the trial if they were aged ≥18 years, had clinical symptoms of daytime sleepiness, and met the following polysomnography inclusion criteria: AHI_{REM}≥15 events/h, AHI_{NREM}<5 events/h, and at least 30 min of REM sleep on the diagnostic polysomnography. We excluded participants with unstable cardiac or neurologic disease, history of stroke, a previous diagnosis of OSA, refusal to commence or use CPAP therapy, and active psychiatric disorders. Informed consent was obtained prior to study enrolment. The study was approved by the Local Health District Research Ethics Committee (HREC/14/WMEAD/383).

Protocol

Study participants underwent an overnight laboratory-based CPAP titration polysomnography as per laboratory protocol based on Australasian Sleep Association and American Thoracic Society guidelines [13, 14]. An independent qualified sleep physician determined an optimum fixed pressure. Participants were then provided with a CPAP device (S9, ResMed Ltd., Bella Vista NSW, Australia, or Respironics One, Phillips Respironics, Murrysville, PA, USA) at the recommended pressure. We contacted participants via monthly telephone calls to optimize CPAP usage. Participants were followed-up in a review clinic at 1, 3, 6, and 12 months with a clinical examination and review of CPAP adherence using a download of the CPAP device (either ResScan software, version 5.5.0.9285, or EncorePro 2 software, version 2.19.1.0).

Measurements

From our clinical sleep service database, we obtained age, gender, weight, body mass index (BMI), total AHI, REM-AHI, NREM-AHI, blood pressure, and Epworth Sleepiness Scale (ESS) data of all patients who met the polysomnography inclusion criteria during the study recruitment period (Nexus 1.6, Compumedics, Abbotsford, Victoria, Australia).

For study participants who consented for the trial, we also performed baseline functional assessments including Psychomotor Vigilance Test (PVT), Functional Outcomes of Sleep Questionnaire (FOSQ), and Depression Anxiety and Stress Scale-21 items (DASS-21). We obtained follow-up anthropometric, ESS, PVT, and CPAP adherence data at 1-, 3-, 6-, and 12-month visits, and FOSQ and DASS-21 at 1-, 3-, and 12-month visits.

The ESS is an 8-item, self-reported questionnaire that measures the subject's average sleep propensity in daily life [15]. An ESS score > 10 units is consistent with excessive daytime sleepiness. FOSQ is a 30-item, self-reported questionnaire that assesses the impact of disorders of excessive sleepiness on

multiple activities of daily living [16]. Lower scores indicate greater functional impairment. DASS-21 is a set of three self-report scales each containing 7 items designed to measure the emotional states of depression (DASS-21-D), anxiety (DASS-21-A), and stress (DASS-21-S) with higher scores indicating higher levels of negative emotional states [17]. We tested changes in alertness using a computer-based version of the 10-min PVT, which is a sustained visual vigilance/attention reaction time (RT) test [18] and assessed mean reaction time (PVT-RT) as a measure of speed.

CPAP adherence was determined by data downloaded from CPAP devices and measured as the average of total hours used per day over 12 months, including participants who did not complete the study. We defined adherent CPAP use as an average of ≥4 h/night and non-adherent as <4 h/night [19, 20].

Data analysis

Continuous variables were summarized as mean and standard deviation (SD) or median and interquartile range (IQR). Frequencies and percentages (%) were used for categorical variables. We compared baseline variables between groups using the two-sample *t* test or Mann-Whitney test for continuous variables, and Fisher's exact test for categorical variables.

The primary outcome was the within subject change in ESS from baseline across the 12 months from commencement of CPAP therapy. Our secondary outcomes were the within subject changes from baseline in BP, PVT-RT, CPAP adherence, FOSQ, and DASS-21 over the same period. All variables except for FOSQ and DASS-21 were measured at 1, 3, 6, and 12 months. FOSQ and DASS-21 were measured at 1, 3, and 12 months. Our pilot study data estimated that the standard deviation of the within subject change from baseline in ESS at 6 months was 4.5 units. Assuming this standard deviation for within subject change, a sample size of 29 subjects has 80% power to detect a mean change in ESS of 2.3 units at a specific time point, or a change of 3 units at 1, 3, 6, or 12 months with an overall 5% significance level after Bonferroni correction. A sample size of 32 participants was chosen to allow for a dropout rate of up to 10%.

We used linear mixed effects models (LME) to investigate the joint effects of time (considered either a continuous covariate or as a 5-level factor: baseline, 1, 3, 6, and 12 months) and average CPAP adherence (2-level factor: <4 versus ≥4 h/night) on the continuous outcomes of interest (ESS, BP, PVT-RT, FOSQ, and DASS-21). In these models, subject ID was the group identifier, time was fitted as a random effect, and time, adherence, and their interaction were fitted as fixed effects. The interaction term was used to assess whether changes observed in an outcome variable over time depended on adherence status. Diagnostic plots were used to check that the assumptions underlying the LMEs were satisfied. PVT-RT data were log-transformed to stabilize the variance prior to analysis and presented on the natural log-transformed scale.

We performed logistic regression analysis to assess the association between baseline participant characteristics and CPAP adherence. Characteristics with univariable association $p < 0.10$ were included as candidate variables in a multiple logistic regression model. Backward stepwise variable selection was used to find the independent predictors of CPAP adherence. Odds ratios (OR) and their 95% confidence intervals (95% CI) were used to quantify the association. We used IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA), and S-PLUS Version 8.1 (TIBCO Software Inc., Palo Alto, CA, USA) for data analysis using two-tailed tests with a significance level of 5%.

Results

We identified 220 subjects from 2164 referrals who fulfilled polysomnography inclusion criteria for moderate-to-severe REM-OSA, for a prevalence of 10.2% within our sleep service population (Fig. 1). This population was middle-aged (56.0 years), predominantly female (63.6%), obese (BMI 33.5 kg/m^2) but not hypertensive, and without excessive sleepiness (ESS 8.8 units). One hundred eighty-eight of 220 subjects were ineligible for the study or declined participation; therefore, we obtained a convenience sample of 32 participants from this identified population. Three participants dropped out before the 1st month data collection, and two participants did not satisfy inclusion/exclusion criteria on later review. The remaining 27 participants aged 53.2 (12.1) years (mean (SD)) were included for analysis. Subject baseline characteristics are presented in Tables 1 and 2.

Total AHI for study participants was mildly elevated at 9.0 (4.1) events/h with an AHI_{REM} of 34.8 (16.5) events/h. They had increased sleepiness with a baseline ESS at 12.6 (5.3) units, and sleep-associated quality of life was reduced (FOSQ 12.5 (3.2) units). DASS-21-D score was moderately elevated at 7 (3–10) units (median (IQR)), DASS-21-A score was moderately elevated at 6 (3.0–9.5) units, and DASS-21-S score was mildly elevated at 8 (5.0–9.5) units. PVT-RT was within normal limits at 414 (327–578) ms. Study participants had significantly higher ESS compared to non-participants ($p = 0.0002$); other baseline characteristics were comparable (Table 1).

During the CPAP trial, 8 participants (30%) stopped using CPAP (4 before 3 months, 1 before 6 months, 3 before 12 months), and 19 participants (70%) completed 12 months of treatment. Mean CPAP usage for all 27 participants over 12 months was 2.9 (2.4) hours. Ten participants (37%) were adherent to CPAP with an average nightly use ≥4 h, and 17 participants (63%) were classified as non-adherent

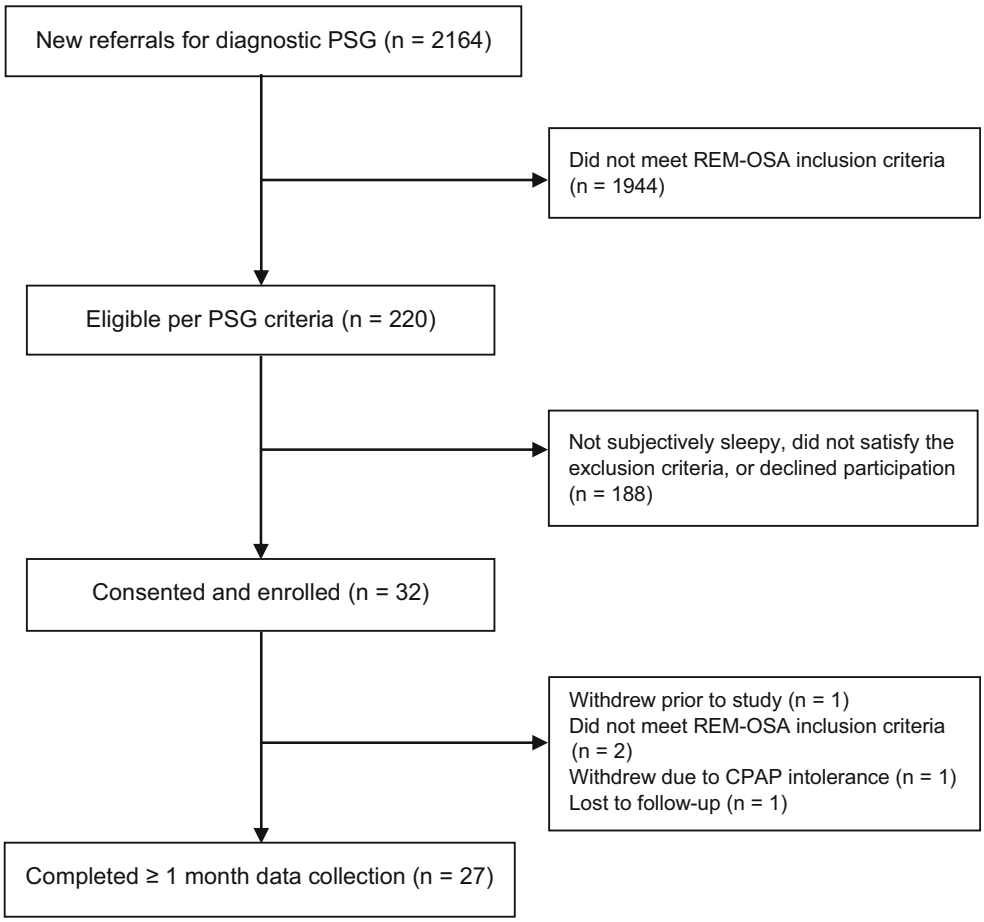

Fig. 1 Subject recruitment flow diagram. The final study sample included 27 participants who completed ≥1 month data collection and were included for analysis

participants (Table 2). Adherent participants were on average 14.5 years (95% CI, 7.5 to 21.4 years) older than non-adherent participants. Logistic regression analysis identified age as the only independent predictor of adherence after adjusting for diastolic BP ($p = 0.052$) and AHI_{REM} ($p = 0.08$). For each year increase in age, the odds of CPAP adherence increased by a factor of 1.25 (95% CI, 1.04 to 1.50; $p = 0.019$).

CPAP treatment resulted in an overall significant decrease in ESS (Fig. 2a, linear trend −0.27 units/month) and increase in FOSQ (linear trend 0.10 units/month) at all measured time

Table 1 Summary statistics for clinical characteristics of patients screened for REM-OSA during study period

	All REM-OSA	Participants	Non-participants	*p*
NumberNumber	220	27	193	0.19
Age (years)	56.0 (14.0)	53.2 (12.1)	56.4 (14.2)	
Female gender (number (%))	140 (63.6%)	19 (70.3%)	121 (62.7%)	0.53
Total AHI (events/h)	8.1 (3.2)	9.0 (4.1)	8.0 (3.0)	0.10
NREM AHI (events/h)	2.4 (1.4)	2.4 (1.4)	2.4 (1.4)	0.96
REM AHI (events/h)	29.4 (11.5)	34.8 (16.5)	28.6 (10.4)	0.06
Weight (kg)	90.2 (25.1)	95.7 (22.6)	89.5 (25.3)	0.10
BMI (kg/m^2)	33.5 (9.0)	35.5 (9.0)	33.2 (9.0)	0.15
Systolic BP (mmHg)	128 (18)	124 (13)	129 (19)	0.28
Diastolic BP (mmHg)	76 (11)	76 (11)	76 (11)	0.96
ESS (units)	8.8 (5.9)	12.6 (5.3)	8.3 (5.8)	0.0002

The study participants were compared with non-participants and were significantly sleepier ($p = 0.0002$). Data expressed as mean (standard deviation) apart from gender. *AHI* apnea-hypopnea index, *NREM* non-rapid eye movement, *REM* rapid eye movement, *BMI* body mass index, *BP* blood pressure, *ESS* Epworth Sleepiness Scale

Table 2 Summary statistics of baseline demographics and clinical characteristics for participants by CPAP adherence

Baseline characteristics	Adherent (n = 10)	Non-adherent (n = 17)	p
Age (years)	62.3 (5.7)	47.8 (11.7)	<0.001
Female, n (%)	8 (80.0%)	11 (64.7%)	0.67
BMI (kg/m^2)	35.6 (8.6)	35.4 (9.5)	0.97
Systolic BP (mmHg)	122.1 (13.3)	124.5 (13.4)	0.66
Diastolic BP (mmHg)	71.1 (10.4)	79.6 (10.0)	0.05
REM AHI (events/h)	42.3 (15.8)	30.4 (15.8)	0.08
NREM AHI (events/h)	2.8 (1.4)	2.2 (1.4)	0.27
Total AHI (events/h)	9.7 (2.8)	8.7 (4.7)	0.65
ESS (units)	14.1 (5.3)	11.7 (5.2)	0.26
FOSQ (units)	12.6 (3.8)	12.5 (2.9)	0.91
DASS-21-D (units)	5.5 (1.3–9.8)	7 (4–10)	0.37
DASS-21-A (units)	4.5 (1.3–8)	6 (4–10)	0.16
DASS-21-S (units)	6.5 (5–9)	8 (6–10)	0.28
PVT-RT (ms)	430 (340–598)	370 (323–559)	0.54
CPAP average use per day over 12 months (h)	5.7 (1.1)	2.1 (1.3)	

Adherent participants defined as average CPAP usage ≥4 h/night; non-adherent participants <4 h/night. Data are presented as mean (standard deviation) or median (interquartile range). Gender expressed as a percentage. *ESS* Epworth Sleepiness Scale, *FOSQ* Functional Outcomes of Sleep Questionnaire, *DASS-21-D* Depression Anxiety Stress Scale-21-Depression, *DASS-21-A* Depression Anxiety Stress Scale-21-Anxiety, *DASS-21-S* Depression Anxiety Stress Scale-21-Stress, *PVT-RT* Psychomotor Vigilance Test reaction time

points compared with baseline values (Tables 3 and 4). Decreases in PVT-RT and DASS-21 were not sustained over 12 months. There was no significant change in BP at any time point.

There was no statistically significant interaction between the effect of time on ESS treated as a 5-level factor and adherence status on ESS ($p = 0.27$). When time was treated as a continuous covariate, there was borderline evidence (interaction $p = 0.068$) of a difference between the estimated 0.45 units/month ($p = 0.003$) within subject ESS decline in the adherent subgroup compared to the 0.13 units/month ($p = 0.245$) decline in non-adherent subjects. ESS was comparable between the two groups at baseline ($p = 0.19$). However, the adherent group had a significant decrease in ESS at each time point which was not present in the non-adherent group (Fig. 2b). There were no significant differences between adherent and non-adherent groups for FOSQ, PVT-RT, and DASS-21 at any time point.

Discussion

To our knowledge, we present the largest study reporting clinical outcomes for CPAP treatment in sleepy patients with a strictly defined moderate-to-severe REM-OSA phenotype (i.e. REM_{AHI}≥15 events/h). In this group of clinically sleepy REM-OSA patients, treatment with CPAP for up to 1 year was associated with a significant decrease in sleepiness and improvement in sleep-related quality of life. However, no sustained improvements in negative emotional states or alertness were observed. Overall group CPAP adherence was poor, but greater adherence was associated with increasing age and with a decrease in sleepiness.

Definitions of REM-OSA

Our prevalence of moderate-to-severe REM-OSA was 10.2% of all patients referred to our sleep service during the study period. Previously described REM-OSA prevalence using older criteria was 14–36% of OSA patients [7, 8], and this variability is likely due to the varying definitions for REM-OSA within different populations. One historical definition utilized an overall AHI≥5 events/h, with AHI_{REM}/AHI_{NREM} ratio ≥2 (definition #1) [7], but this generalized definition of REM-OSA did not effectively exclude patients with significant coexisting NREM-OSA, potentially resulting in a heterogeneous patient population [9]. Additional qualifying criteria in other studies included various degrees of adjustment for AHI_{NREM}, including AHI_{NREM}≤15 events/h (definition #2, currently most widely used in the literature) [8] or AHI_{NREM}<10 events/h [2].

One study evaluated the effect of various definitions of REM-OSA on prevalence, #1, #2, and a "strict" definition with AHI_{NREM}<8 and > 10.5 min of REM sleep duration, and found that the prevalence was 36.7%, 24.4%, and 13.5%, respectively [21] which demonstrates that REM-

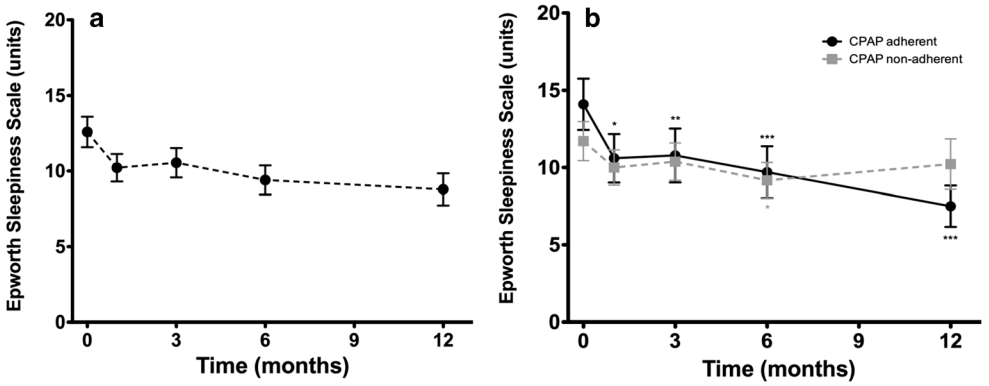

Fig. 2 **a** Change in ESS as whole group compared with baseline (all time points $p < 0.01$). Data expressed as mean with error bars representing SEM. **b** Change in ESS from baseline (0 months) between CPAP-adherent and non-adherent groups over 1, 3, 6, and 12 months. There was a consistent reduction in ESS at all time points for the CPAP-adherent group which was not present in the non-adherent group (linear mixed effects). Data expressed as mean with error bars representing SEM. $*p < 0.05$, $**p < 0.01$, $***p < 0.001$ (all relative to 0 months)

OSA prevalence is highly and proportionately dependent of the quantity of NREM-OSA permitted by the definition. In order to separate the NREM component and ensure that there is adequate REM sleep time to accurately estimate the severity of REM-OSA, Mokhlesi et al. [9] proposed the definition using $AHI_{NREM} \leq 5$ events/h and ≥ 30 min of REM sleep. When this definition was applied to a population of patients referred to a sleep laboratory in Jordan for evaluation of OSA, the prevalence of REM-OSA fell from 18% using definition #1 to 2.7% [11].

Table 3 Summary statistics for clinical variables by months on study ($n = 27$) together with p value for test of linear time trend within participants from LME model

Clinical variable	Baseline	1 month	3 months	6 months	12 months	Linear trend p value
All participants						
Systolic BP (mmHg)	123.6 (13.2)	127.9 (17.4)	121.2 (15.0)	122.9 (17.7)	126.4 (17.0)	0.929
Diastolic BP (mmHg)	76.2 (10.8)	77.6 (8.8)	75.9 (10.2)	77.8 (13.7)	79.5 (12.6)	0.489
ESS (units)	12.6 (5.3)	10.2 (4.7)	10.5 (4.6)	9.4 (4.5)	8.8 (4.6)	*0.003*
FOSQ (units)	12.5 (3.2)	13.6 (3.1)	13.3 (3.9)	N/A	14.4 (3.8)	*0.005*
DASS-21-D (units)	7 (3–10)	4 (2–7)	2 (1–9.3)	N/A	5 (2–7)	0.284
DASS-21-A (units)	6 (3–9.5)	4 (2–7)	4 (2–6.8)	N/A	4 (1–8)	0.944
DASS-21-S (units)	8 (5–9.5)	6 (3.5–10.5)	5 (2.3–12.5)	N/A	6 (2.5–8)	0.056
PVT-RT (ms)	414 (327–578)	348 (303–422)	373 (303–475)	321 (294–424)	318 (307–386)	0.229#
CPAP use per day (hrs)	N/A	3.4 (2.3)	3.6 (2.2)	3.4 (2.0)	2.9 (2.4)	0.308
Non-adherent participants						
Systolic BP (mmHg)	124.5 (13.4)	127.9 (19.4)	119.2 (13.2)	121.1 (22.7)	126.8 (18.7)	0.670
Diastolic BP (mmHg)	79.6 (10.0)	77.9 (10.3)	76.4 (11.9)	77.5 (17.7)	83.6 (14.5)	0.825
ESS (units)	11.7 (5.2)	10.0 (4.7)	10.4 (4.4)	9.2 (4.0)	9.9 (4.7)	0.245
FOSQ (units)	12.5 (2.9)	13.6 (3.3)	13.1 (3.8)	N/A	14.8 (4.0)	0.065
DASS-21-D (units)	7 (4–10)	4 (2–7)	2 (0–10)	N/A	6 (3–7)	0.852
DASS-21-A (units)	6 (4–10)	5 (3–8)	4 (2–7)	N/A	5 (1–8)	0.513
DASS-21-S (units)	8 (6–10)	9 (4–11)	7 (4–14)	N/A	7 (4–9)	0.095
PVT-RT (ms)	370 (323–559)	340 (300–418)	356 (254–415)	300 (272–639)	328 (309–412)	0.477#
CPAP use per day (hrs)	N/A	2.1 (1.6)	2.2 (1.4)	2.3 (1.2)	2.3 (1.3)	0.922
Adherent participants						
Systolic BP (mmHg)	122.1 (13.3)	127.8 (14.3)	124.0 (17.6)	125.0 (9.6)	125.9 (16.2)	0.780
Diastolic BP (mmHg)	71.1 (10.4)	77.2 (6.3)	75.1 (7.8)	78.1 (7.2)	75.0 (8.7)	0.320
ESS (units)	14.1 (5.3)	10.6 (5.0)	10.8 (5.2)	9.7 (5.3)	7.6 (4.5)	*<0.001*
FOSQ (units)	12.6 (3.8)	13.7 (3.1)	13.6 (4.3)	N/A	13.9 (3.6)	*0.043*
DASS-21-D (units)	6 (1–10)	5 (2–7)	3 (1–4)	N/A	4 (1–6)	0.172
DASS-21-A (units)	5 (1–9)	2 (1–6)	2 (1–5)	N/A	3 (1–8)	0.478
DASS-21-S (units)	7 (5–9)	5 (1–6)	3 (2–5)	N/A	3 (2–8)	0.357
PVT-RT (ms)	430 (340–598)	356 (306–426)	416 (343–482)	364 (314–424)	318 (306–361)	0.273#
CPAP use per day (hrs)	N/A	5.5 (1.8)	5.3 (1.7)	4.7 (2.0)	4.8 (1.2)	0.730

#p value for linear trend of log transformed PVT-RT

Data presented as mean (SD) or median (IQR)

Table 4 Mean within patient change in ESS, FOSQ, log(PVT-RT), and DASS subscales over 12 months for all participants (n = 27) and for adherent and non-adherent subgroups

Clinical variable	1 month	3 months	6 months	12 months
All participants				
ESS (units)	−2.37 (0.80)**	−2.33 (0.87)**	−3.38 (0.91)***	−3.97 (1.13)***
FOSQ (units)	1.06 (0.27)***	1.01 (0.44)*	N/A	1.59 (0.45)***
Log(PVT-RT)	−0.17 (0.05)**	−0.10 (0.05)	−0.10 (0.05)*	−0.12 (0.05)*
DASS-21-D (units)	−1.93 (0.57)**	−2.31 (0.99)*	N/A	−1.60 (0.88)
DASS-21-A (units)	−1.67 (0.51)**	−1.87 (0.79)*	N/A	−0.24 (1.01)
DASS-21-S (units)	−0.96 (0.72)	−1.28 (0.78)	N/A	−1.93 (0.95)*
Non-adherent participants				
ESS (units)	−1.71 (1.02)	−1.72 (1.13)	−2.80 (1.20)*	−1.81 (1.44)
FOSQ (units)	1.10 (0.34)**	0.83 (0.56)	N/A	1.49 (0.60)*
Log(PVT-RT)	−0.18 (0.06)**	−0.14 (0.07)*	−0.12 (0.07)	0.12 (0.08)
DASS-21-D (units)	−2.32 (0.73)**	−2.37 (1.32)	N/A	−0.81 (1.17)
DASS-21-A (units)	−1.69 (0.66)*	−2.44 (1.01)*	N/A	−1.11 (1.33)
DASS-21-S (units)	−0.45 (0.90)	−0.75 (0.99)	N/A	−2.12 (1.32)
Adherent participants				
ESS (units)	−3.50 (1.33)*	−3.30 (1.39)*	−4.39 (1.39)**	−6.70 (1.62)***
FOSQ (units)	0.99 (0.45)*	1.24 (0.69)	N/A	1.63 (0.68)*
Log(PVT-RT)	−0.10 (0.08)	−0.03 (0.08)	−0.08 (0.08)	0.12 (0.08)
DASS-21-D (units)	−1.25 (0.95)	−1.97 (1.64)	N/A	−2.11 (1.40)
DASS-21-A (units)	−1.63 (0.86)	−1.19 (1.21)	N/A	0.63 (1.57)
DASS-21-S (units)	−1.83 (1.18)	−2.15 (1.23)	N/A	−2.04 (1.49)

Mean change analysed using linear mixed effect models. Data presented as mean change (standard error). *p < 0.05, **p < 0.01, ***p < 0.001 (relative to 0 months)

Overall, our data have demonstrated that applying the new criteria resulted in a relatively high prevalence of moderate-to-severe REM-OSA. Hence, REM-OSA likely remains a prevalent OSA phenotype in a sleep clinic referred population, though its prevalence may vary dependent upon ethnic background and source of referrals.

Clinical phenotype of REM-OSA

A caveat with attempting to characterize the clinical phenotype of REM-OSA in past studies is the variable definitions of REM-OSA, and that the instruments used may not have been sensitive enough to assess the relevant phenotype characteristics.

The moderate-to-severe REM-OSA population characteristics defined using the revised diagnostic criteria from our database were in broad agreement with previous studies which have shown that REM-OSA patients are female-predominant and have less severe overall OSA [2, 7, 12], except one study that showed an association with hypertension [10]. Previous studies have also found similar levels of sleepiness in REM-OSA compared with NREM/REM-OSA patients, and no significant difference in BMI [11, 21].

Our enrolled participants had characteristics which were representative of our moderate-to-severe REM-OSA population, apart from hypersomnolence (mean ESS score 12.6 vs 8.3 units) as our study required subjective sleepiness as an inclusion criterion. At baseline, our sleepy REM-OSA participants had reduced sleep-related quality of life (FOSQ) and negative emotional states with elevated DASS-21 scores. Previous studies demonstrated increased anxiety and depression in REM-OSA patients compared to NREM/REM-OSA patients despite no difference in ESS scores [21, 22], although others have not found an independent association between REM-OSA and impaired health-related quality of life [23, 24]. We cannot exclude that the hypersomnolence contributed to the presence of negative emotional states and impaired quality of life in our participants. Despite increased sleepiness, there was no impairment in attention as shown by the normal Psychomotor Vigilance Test results which likely reflects the association of impaired performance with loss of sleep itself, rather than disruption to a particular sleep stage or change in sleep quality [25].

Clinical outcomes of CPAP treatment for REM-OSA

Most studies examining REM-OSA were limited to demographic and clinical characteristics of the patients [7, 8, 11, 12, 21]. The only study examining the effect of treatment was a retrospective observational study using the previous REM-

OSA definition (i.e. AHI_{REM}/AHI_{NREM} ratio of ≥2 and AHI_{NREM}≤15 events/h), demonstrating an improvement in functional outcomes with CPAP treatment, including ESS, depression symptoms, fatigue, and FOSQ [26].

Our main finding was that CPAP treatment reduced the ESS score in our participants with moderate-to-severe REM-OSA by 3.5 units over 12 months (ESS minimum important difference (MID) in OSA = 2 units) [27], despite the overall mild severity of OSA in the group (average AHI 8.1 events/h). There were reductions in ESS in the CPAP-adherent subgroup at all measured time points, while ESS reduction did not reach significance for the non-adherent subgroup. This is in keeping with previous literature, which showed that reduction in ESS was apparent with CPAP usage of more than 4 h [20], with a linear dose-response relationship between increased usage and achieving normal levels for subjective sleepiness in NREM/REM-OSA. Clearly, CPAP adherence is an important factor for improvement in excessive sleepiness in both REM and NREM/REM-OSA.

There was also a statistically and clinically significant improvement in functional outcomes of sleep as measured by a decrease in FOSQ of 1.6 units (MID = 1 unit) [28]. This was achieved despite the low average CPAP use of 2.9 h/night, which was surprising as it has previously been shown that improvement in FOSQ was achieved at a high CPAP usage of >7 h/night for NREM/REM-OSA [20]. There was no significant difference in FOSQ improvement between adherent and non-adherent groups.

The impact of CPAP on other measured secondary end points demonstrated only borderline significant changes that were highly influenced by subject dropouts and large variability in measurements over time points.

CPAP use in REM-OSA

The average usage of CPAP in this study is lower (2.9 h/night) compared to other CPAP studies, based on a meta-analysis over 20 years which demonstrated an average of 4.6 h/night [29]. We also had a high drop-out rate with only 19 of 27 participants completing 12 months of treatment. Major reasons for study discontinuation included poor CPAP tolerance due to nasal congestion, dryness, and mask discomfort. The non-adherent subgroup had higher levels of depression, anxiety, and stress than the adherent subgroup, but this did not reach statistical significance. The only independent variable positively associated with improved CPAP adherence was increasing age, which has previously been demonstrated for NREM/REM-OSA patients [30]. Nevertheless, approximately 30% of the enrolled participants completed 1 year of treatment with satisfactory compliance, demonstrating that CPAP treatment is feasible and worthwhile in selected sleepy moderate-to-severe REM-OSA patients with only mild OSA severity overall, with older patients likely to do better.

Strengths and limitations

There are some limitations to our study. Firstly, as our study was observational in design without a control arm or randomization, it is not possible to prove that CPAP intervention over 12 months was the sole reason for improvement in sleepiness and quality of life. However, the consistent reduction in ESS at all measured time points in the CPAP-adherent group compared with the non-adherent group supports the benefit of CPAP in this population. Secondly, our participants consisted of patients who presented to a sleep centre with subjective daytime sleepiness, and therefore, the outcomes for our participants may not be representative of all people fulfilling the revised diagnostic criteria for moderate-to-severe REM-OSA. Thirdly, we acknowledge that the final sample sizes of recruited participants ($n = 27$) and associated subgroups (non-adherent, $n = 17$; and adherent, $n = 10$) were small and likely limited our ability to detect significant differences. Although we did not demonstrate consistent improvements in PVT or DASS-21, we cannot exclude the possibility of a type II error leading to this outcome, and the study is likely inadequately powered to draw conclusions for some of the secondary outcomes. Finally, the duration of CPAP use by participants was highly variable (from 1 month to more than 1 year), further limiting our ability to detect significant changes in our clinical outcomes for the group.

However, there were several strengths of our study. We measured CPAP adherence objectively from CPAP downloads which eliminated recall bias. We also used standardized outcomes to assess responses to treatment, and measurements such as ESS and FOSQ have been validated for OSA. We also used novel definition criteria specific for REM-OSA in order to address the clinical outcomes in this homogenous group of patients without any significant NREM-OSA, which is distinct from the previous definitions.

Conclusion

To date, this is the first study examining the effect of CPAP in sleepy patients with moderate-to-severe REM-OSA defined by the revised diagnostic criteria [9]. At baseline, our REM-OSA participants had overall mild OSA but with symptoms of increased sleepiness, reduced quality of life, and negative emotional states. There was a significant and sustained improvement in subjective sleepiness and sleep-related quality of life during 12 months of CPAP treatment despite suboptimal CPAP adherence overall. REM-OSA likely represents a clinically relevant OSA phenotype, where patients with relatively mild OSA overall may demonstrate excessive

sleepiness and reduced quality of life, which may be improved by CPAP therapy. Further studies with a larger patient group would be necessary to demonstrate if there are also clinically significant improvements in emotional states and relevant cardiovascular outcomes.

Acknowledgements We thank Dr. Karen Byth, biostatistician, University of Sydney and Westmead Hospital, for statistical analyses and advice. We also thank Westmead Hospital Sleep Laboratory, Westmead, NSW, Australia, for their support.

Authors' contributions Xiao Ya Hu designed data collection tools, monitored data collection, cleaned and analysed the data, and drafted and revised the paper. Jin-Gun Cho wrote the statistical analysis plan, analysed the data, and revised the draft paper. Rita Perri implemented the trial and collected the data. Terrence Ting and Khaled Al Oweidat contributed to initial project planning and preliminary data analysis. Stephen Lambert contributed to initial project planning and collected and analysed data. John Wheatley initiated the project, designed data collection tools, implemented the trial, monitored data collection, analysed the data, and revised the draft paper. He is the guarantor.

Data availability The data that support the findings of this study are available from the corresponding author, JW, upon reasonable request.

Compliance with ethical standards

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

Ethics approval The study was approved by the Human Research Ethics Committee of the Western Sydney Local Health District [HREC/14/WMEAD/383].

Consent to participate Informed consent was obtained from all individual participants included in the study.

Consent for publication Participants gave consent for their data to be published in a journal.

Code availability N/A

References

1. Bixler EO, Vgontzas AN, Ten Have T, Tyson K, Kales A (1998) Effects of age on sleep apnea in men: I. Prevalence and severity. Am J Respir Crit Care Med 157(1):144–148. https://doi.org/10.1164/ajrccm.157.1.9706079
2. Resta O, Carpanano GE, Lacedonia D, Di Gioia G, Giliberti T, Stefano A, Bonfitto P (2005) Gender difference in sleep profile of severely obese patients with obstructive sleep apnea (OSA). Respir Med 99(1):91–96. https://doi.org/10.1016/j.rmed.2004.05.014
3. Partinen M, Telakivi T (1992) Epidemiology of obstructive sleep apnea syndrome. Sleep 15(6 Suppl):S1–S4. https://doi.org/10.1093/sleep/15.suppl_6.s1
4. Ward Flemons W, McNicholas WT (1997) Clinical prediction of the sleep apnea syndrome. Sleep Med Rev 1(1):19–32. https://doi.org/10.1016/s1087-0792(97)90003-4
5. McDaid C, Duree KH, Griffin SC, Weatherly HL, Stradling JR, Davies RJ, Sculpher MJ, Westwood ME (2009) A systematic review of continuous positive airway pressure for obstructive sleep apnoea-hypopnoea syndrome. Sleep Med Rev 13(6):427–436. https://doi.org/10.1016/j.smrv.2009.02.004
6. Alzoubaidi M, Mokhlesi B (2016) Obstructive sleep apnea during rapid eye movement sleep: clinical relevance and therapeutic implications. Curr Opin Pulm Med 22(6):545–554. https://doi.org/10.1097/MCP.0000000000000319
7. Haba-Rubio J, Janssens JP, Rochat T, Sforza E (2005) Rapid eye movement-related disordered breathing: clinical and polysomnographic features. Chest 128(5):3350–3357. https://doi.org/10.1378/chest.128.5.3350
8. Koo BB, Patel SR, Strohl K, Hoffstein V (2008) Rapid eye movement-related sleep-disordered breathing: influence of age and gender. Chest 134(6):1156–1161. https://doi.org/10.1378/chest.08-1311
9. Mokhlesi B (2012) REM-related obstructive sleep apnea: to treat or not to treat? J Clin Sleep Med 8(3):249–250. https://doi.org/10.5664/jcsm.1904
10. Mokhlesi B, Finn LA, Hagen EW, Young T, Hla KM, Van Cauter E, Peppard PE (2014) Obstructive sleep apnea during REM sleep and hypertension. Results of the Wisconsin sleep cohort. Am J Respir Crit Care Med 190(10):1158–1167. https://doi.org/10.1164/rccm.201406-1136OC
11. Al Oweidat K, AlRyalat SA, Al-Essa M, Obeidat N (2018) Comparing REM- and NREM-related obstructive sleep apnea in Jordan: a cross-sectional study. Can Respir J 2018:9270329–9270326. https://doi.org/10.1155/2018/9270329
12. Visvalingam V, Lambert S, Perri R, Cho J, Mai S, Wheatley J (2011) Characteristics of patients diagnosed with REM related obstructive sleep apnoea (OSA) using revised diagnostic criteria. Sleep and Biological Rhythms 10 (A 092):33
13. Douglas JA, Chai-Coetzer CL, McEvoy D, Naughton MT, Neill AM, Rochford P, Wheatley J, Worsnop C (2017) Guidelines for sleep studies in adults - a position statement of the Australasian Sleep Association. Sleep Med 36(Suppl 1):S2–S22. https://doi.org/10.1016/j.sleep.2017.03.019
14. Schwab RJ, Badr SM, Epstein LJ, Gay PC, Gozal D, Kohler M, Levy P, Malhotra A, Phillips BA, Rosen IM, Strohl KP, Strollo PJ, Weaver EM, Weaver TE, Systems ATSSoCAT (2013) An official American Thoracic Society statement: continuous positive airway pressure adherence tracking systems. The optimal monitoring strategies and outcome measures in adults. Am J Respir Crit Care Med 188 (5):613–620. https://doi.org/10.1164/rccm.201307-1282ST
15. Johns MW (1991) A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 14(6):540–545. https://doi.org/10.1093/sleep/14.6.540
16. Weaver TE, Laizner AM, Evans LK, Maislin G, Chugh DK, Lyon K, Smith PL, Schwartz AR, Redline S, Pack AI, Dinges DF (1997) An instrument to measure functional status outcomes for disorders of excessive sleepiness. Sleep 20(10):835–843
17. Lovibond PF, Lovibond SH (1995) The structure of negative emotional states: comparison of the depression anxiety stress scales (DASS) with the Beck depression and anxiety inventories. Behav Res Ther 33(3):335–343. https://doi.org/10.1016/0005-7967(94)00075-u
18. Basner M, Dinges DF (2011) Maximizing sensitivity of the psychomotor vigilance test (PVT) to sleep loss. Sleep 34(5):581–591. https://doi.org/10.1093/sleep/34.5.581
19. Weaver TE, Grunstein RR (2008) Adherence to continuous positive airway pressure therapy: the challenge to effective treatment. Proc Am Thorac Soc 5(2):173–178. https://doi.org/10.1513/pats.200708-119MG
20. Weaver TE, Maislin G, Dinges DF, Bloxham T, George CF, Greenberg H, Kader G, Mahowald M, Younger J, Pack AI (2007) Relationship between hours of CPAP use and achieving normal

levels of sleepiness and daily functioning. Sleep 30(6):711–719. https://doi.org/10.1093/sleep/30.6.711
21. Conwell W, Patel B, Doeing D, Pamidi S, Knutson KL, Ghods F, Mokhlesi B (2012) Prevalence, clinical features, and CPAP adherence in REM-related sleep-disordered breathing: a cross-sectional analysis of a large clinical population. Sleep Breath 16(2):519–526. https://doi.org/10.1007/s11325-011-0537-6
22. Geckil AA, Ermis H (2019) The relationship between anxiety, depression, daytime sleepiness in the REM-related mild OSAS and the NREM-related mild OSAS. Sleep Breath 24:71–75. https://doi.org/10.1007/s11325-019-01838-y
23. Chami HA, Baldwin CM, Silverman A, Zhang Y, Rapoport D, Punjabi NM, Gottlieb DJ (2010) Sleepiness, quality of life, and sleep maintenance in REM versus non-REM sleep-disordered breathing. Am J Respir Crit Care Med 181(9):997–1002. https://doi.org/10.1164/rccm.200908-1304OC
24. Khan A, Harrison SL, Kezirian EJ, Ancoli-Israel S, O'Hearn D, Orwoll E, Redline S, Ensrud K, Stone KL, Osteoporotic Fractures in Men Study Research G (2013) Obstructive sleep apnea during rapid eye movement sleep, daytime sleepiness, and quality of life in older men in osteoporotic fractures in men (MrOS) sleep study. J Clin Sleep Med 9(3):191–198. https://doi.org/10.5664/jcsm.2474
25. Tilley AJ, Wilkinson RT (1984) The effects of a restricted sleep regime on the composition of sleep and on performance. Psychophysiology 21(4):406–412. https://doi.org/10.1111/j.1469-8986.1984.tb00217.x
26. Su CS, Liu KT, Panjapornpon K, Andrews N, Foldvary-Schaefer N (2012) Functional outcomes in patients with REM-related obstructive sleep apnea treated with positive airway pressure therapy. J Clin Sleep Med 8(3):243–247. https://doi.org/10.5664/jcsm.1902
27. Crook S, Sievi NA, Bloch KE, Stradling JR, Frei A, Puhan MA, Kohler M (2019) Minimum important difference of the Epworth sleepiness scale in obstructive sleep apnoea: estimation from three randomised controlled trials. Thorax 74(4):390–396
28. Billings ME, Rosen CL, Auckley D, Benca R, Foldvary-Schaefer N, Iber C, Zee PC, Redline S, Kapur VK (2014) Psychometric performance and responsiveness of the functional outcomes of sleep questionnaire and sleep apnea quality of life instrument in a randomized trial: the HomePAP study. Sleep 37(12):2017–2024. https://doi.org/10.5665/sleep.4262
29. Rotenberg BW, Murariu D, Pang KP (2016) Trends in CPAP adherence over twenty years of data collection: a flattened curve. J Otolaryngol Head Neck Surg 45(1):43. https://doi.org/10.1186/s40463-016-0156-0
30. May AM, Gharibeh T, Wang L, Hurley A, Walia H, Strohl KP, Mehra R (2018) CPAP adherence predictors in a randomized trial of moderate-to-severe OSA enriched with women and minorities. Chest 154(3):567–578. https://doi.org/10.1016/j.chest.2018.04.010