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RESEARCH ARTICLE

Continuous positive airway pressure in patients with rapid eye movement (REM)-specific obstructive sleep apnea, a retrospective match-controlled chart review [version 1; peer review: 1 approved with reservations]

Rodolfo Soca ¹, Erica Buchner¹, Hrayr Attarian ²¹Sleep Medicine Center, HealthEast Care System, St Paul, MN, 55109, USA²Department of Neurology, Northwestern University, Chicago, IL, 60611, USA

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Abstract

Background: Rapid eye movement (REM) obstructive sleep apnea (OSA) represents 13 to 35% of all OSA cases and is more common in women. Continuous positive airway pressure (CPAP) is the gold standard for treatment of all forms of OSA but we do not know if patients with REM OSA have different pressure requirements than those with non-stage dependent OSA.

Methods: This was a retrospective case control study. We first identified individuals with REM OSA and then tried to identify apnea hypopnea index (AHI), gender, and body mass index (BMI) matching controls that had non-stage specific OSA. Individuals were considered to have REM OSA if the REM AHI was greater than 5 events/hour, and the ratio of REM AHI / non-rapid eye movement (NREM) AHI was greater than 2. Demographic variables and the recommended CPAP pressure were analyzed using paired Student's T-Tests.

Results: Our study included a total of 16 individuals with REM OSA and equal number of AHI, gender, and BMI matching controls. Both groups had similar demographic and polysomnographic characteristics. Individuals with REM OSA required similar CPAP pressures as controls (7.5 cm H₂O vs 7.4 cm H₂O p=0.78).

Conclusion: Individuals with REM require similar CPAP pressures as their AHI, gender, and BMI matching controls.

Keywords

REM OSA, CPAP, obstructive sleep apnea

Open Peer Review

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1

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view

1. Ludovico Messineo , Brigham and Women's Hospital and Harvard Medical School, Boston, USA

Any reports and responses or comments on the article can be found at the end of the article.

Corresponding author: Rodolfo Soca (rodolfosoca@gmail.com)

Author roles: **Soca R:** Conceptualization, Data Curation, Formal Analysis, Investigation, Methodology, Supervision, Validation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Buchner E:** Data Curation, Formal Analysis, Investigation, Methodology, Validation, Writing – Review & Editing; **Attarian H:** Data Curation, Writing – Original Draft Preparation, Writing – Review & Editing

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Introduction

The prevalence of obstructive sleep apnea (OSA) in adults has been estimated to be between 1% to 2% in women and 3% to 4% in men¹. OSA is associated with increased cardiovascular mortality and it is considered an independent risk factor for all cause mortality²⁻⁴. The severity of the disease is usually expressed using the apnea hypopnea index (AHI)⁵.

In a subset of those with OSA, respiratory events happen predominantly or exclusively during rapid eye movement (REM) sleep; this condition is referred to as “REM-related OSA (REM OSA)”. Its prevalence among patients with OSA is 13 to 35% depending on the criteria used to define AHIs⁶⁻⁸. REM OSA has been a topic of debate in the sleep medicine community since we do not know if this form of sleep apnea is part of the spectrum of “general” sleep apnea or a completely different entity with unique risk factors and different treatment needs.

REM OSA does not have a male predilection, in fact it may be even more common in women. Unlike OSA the likelihood of REM OSA decreases with age^{7,8}. REM OSA is not associated with daytime sleepiness or diminished quality of life (QOL)⁹.

It is, however, linked to increased incidence of hypertension¹⁰ and type 2 diabetes¹¹.

CPAP is the gold standard for treatment of both REM and NREM OSA, and both forms of sleep apnea seem to respond in similar ways to CPAP therapy¹². We still don't know if CPAP pressures required to control REM OSA are significantly different than those needed for OSA in general.

We designed this study with the initial hypothesis that individuals with REM OSA would require a lower CPAP pressure than controls. This hypothesis was based on day-to-day observations at our sleep center.

Methods

The Institutional Review Board (IRB) at HealthEast care system approved this study (IRB #HE1511002). The search included all polysomnography (PSG) tests that were completed from January 1st 2014 to December 31st 2014. We searched all patients older than 18 years old who had a baseline evaluation as well as a CPAP titration. REM OSA subjects and controls were required to have NREM and REM sleep during the baseline test and a minimum of 10 minutes of stage REM sleep during the titration.

Identification of individuals and controls

We first identified individuals that met criteria for REM OSA using the sleep center's database. Data was extracted by reviewing the database manually, record by record, and reviewing the polysomnography report; all the variables that were needed for this study were already part of the reports. The dataset that is provided, was used to collect the information on an MS Excel 2013 spreadsheet (Dataset 1¹³). No information regarding CPAP pressure recommendations was accessed during this phase to avoid selection bias. The database was searched a second time in order to identify gender, BMI, and AHI matching controls. Indi-

viduals were considered a matching control if the BMI and the AHI were within 5 kg/m² and 5 events/hour respectively.

Sample Size and controls

Based on preliminary sample-size calculations, we aimed to identify 50 individuals with REM OSA and 50 controls in order to detect a pressure difference of 1 cwp with a significance level of 0.05 Power 0.8. This was based on a separate estimate of the mean CPAP pressure recommended at the lab (9 cwp; SD=2.45; D=0.41). We only found 16 matching controls.

Polysomnography (PSG) values and definitions

PSG tests were scored by a certified PSG technologist the night of the test using the American Academy of Sleep Medicine Scoring Manual v 2.0⁵.

REM OSA definition

Individuals were considered to have REM OSA if the REM AHI was greater than 5 events/hour, and the ratio of REM AHI / non-rapid eye movement (NREM) AHI was greater than 2. REM sleep duration had to be greater than 15 minutes.

OSA definition for controls

Individuals were considered appropriate controls if they had an AHI greater than 5 events/hour and within 5 events/hour of the REM OSA match. The NREM AHI had to be greater than 5 events/hour and the ratio of REM AHI to NREM AHI had to be 1 or less. REM sleep duration had to be greater than 15 minutes.

CPAP pressure

The recommended CPAP pressure was the lowest pressure that eliminated respiratory events during the test, including supine REM sleep.

Other variables

We collected demographic, clinical, and polysomnographical variables such as age, gender, Body mass index (BMI), presence of diabetes, presence of hypertension, recording time, total sleep time, Epworth score (to assess daytime sleepiness), STOP BANG Score (to assess risk for OSA), and percentage of each sleep stage.

Statistical analysis

Descriptive characteristics for demographic information were summarized as mean with standard deviation for continuous variables and as frequency for categorical variables.

Continuous and categorical variables were compared using paired Student's T-Tests and Chi-square tests, respectively. All hypothesis tests were 2-sided, with a significance level of 0.05. All analyses were performed using R® for Mac OS X GUI version 1.67.

Results

We were able to identify a total of 16 individuals with REM OSA who had gender, AHI, and BMI matching controls for a total of 32 subjects in the study. Table 1 summarizes the demographic and clinical characteristics of individuals with REM OSA and controls.

Table 1. Demographic and polysomnography (PSG) characteristics.

	REM- OSA ^d	Controls	p-value
Age, years (SD)	51 (11)	59 (13.44)	0.50
% Female	63%	63%	1
BMI, Kg/M ² (SD)	36.35 (7.49)	33.25 (9.64)	0.73
ESS ^a (SD)	8.5 (5.67)	10.0 (5.01)	0.27
STOP BANG (SD)	3.5 (1.41)	4.0 (0.79)	0.03
Hypertension	44%	38%	0.72
Type 2 Diabetes	6%	13%	0.54
PSG Parameters			
% split night tests	63%	63%	1
Recording time, minutes (SD)	235.25 (131.34)	260.50 (131.72)	0.90
Sleep Time	203.50 (112.25)	191.00 (110.91)	0.97
Sleep Efficiency (SD)	84% (11.10)	81.80% (11.59)	0.73
Stage REM duration, minutes (SD)	36.50 (41)	40.75 (23.18)	0.87
% Stage N1 (SD)	9.35 (5.15)	11.65 (5.79)	0.13
% Stage N2(SD)	48.40 (6.83)	52.85 (12.33)	0.46
% Stage N3 (SD)	23.10 (11.28)	17.50 (11.41)	0.06
% Stage REM (SD)	16.55 (8.27)	18.10 (6.30)	0.65
OSA Severity			
Total AHI ^f (SD)	14.50 (6.85)	14.85 (7.20)	0.75
REM AHI (SD)	58.70 (20.49)	7.65 (10.55)	<0.0001
NREM ^e AHI (SD)	6.60 (6.79)	14.75 (8.35)	0.006
Apnea Index (SD)	3.30 (3.32)	2.95 (4.25)	0.57
Hypopnea Index (SD)	10.05 (6.47)	9.60 (7.13)	0.73
CAI ^c (SD)	0.00 (0.50)	0.00 (0.53)	0.51
Supine AHI (SD)	18.90 (26.86)	26.86(18.96)	0.23
ODI ^g 4%	10.30 (7.12)	11.70 (7.84)	0.80

a- ESS= Epworth Sleepiness Scale Score

b- HI= Hypopnea Index

c- CAI= Central Apnea Index

d- REM OSA = Rapid eye movement related obstructive sleep apnea

e- NREM = Non rapid eye movement

f- AHI = Apnea hypopnea index

g- ODI = Oxygen desaturation index

Both groups were very similar in terms of age, daytime sleepiness, diabetes, hypertension, and sleep architecture parameters. Subjects with REM-OSA had a slightly lower score in the STOP-BANG questionnaire (3.5 vs. 4.0 p= 0.03).

Figure 1 shows the recommended CPAP pressure for the REM OSA group and controls. There was no significant difference between the groups.

Dataset 1. Rapid eye movement related obstructive sleep apnea (REM OSA) dataset

<https://dx.doi.org/10.5256/f1000research.16688.d226331>

Discussion

To our knowledge our study is the first comparing nPAP treatment requirements for individuals with REM OSA. We found that

Figure 1. Recommended Continuous positive airway pressure (CPAP).

individuals with REM OSA required similar nCPAP pressures as gender, AHI, and BMI matched controls.

This was a very simple and limited study that was designed to test our hypothesis that individuals with REM OSA required lower CPAP pressures than controls. There has been debate about whether REM OSA constitutes a different phenomenon or is just very similar to any other form of OSA. Our results suggest that, REM OSA is not different than NREM OSA.

Age, gender, and AHI have been identified as predictors of CPAP pressure needs but none of those studies have looked at the stage in which the respiratory events happen.^{14,15} Since REM OSA has a different gender and BMI association than the general OSA population, we were able to isolate the effect of the REM component by looking at gender, AHI, and BMI matched controls^{16,17}.

Our study had the limitation of a small sample size because it was difficult to identify an adequate number of matching controls. With our small sample size, the study was underpowered to detect smaller differences in CPAP pressure needs. We still think that publishing our results could be important because there are no other studies, regardless of sample size, that have looked into this topic.

Data availability

F1000Research: Dataset 1. Rapid eye movement related obstructive sleep apnea (REM OSA) dataset, <https://doi.org/10.5256/f1000research.16688.d226331>¹³

Grant information

The author(s) declared that no grants were involved in supporting this work.

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Open Peer Review

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Version 1

Reviewer Report 03 July 2019

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Ludovico Messineo

Division of Sleep and Circadian Disorders, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA

In this simple study, Roca and colleagues compare CPAP requirements in patients with obstructive sleep apnea (OSA) and rapid eye movement (REM) related OSA. Their conclusion is that both groups require similar therapeutic CPAP levels.

Although the authors acknowledge that their study is underpowered and thus potentially unable to detect any statistical difference between the two groups (also considering the retrospective design), the main message of the manuscript results are too strong given such preliminary results. Therefore, I would suggest some adjusting in wording to put less emphasis on the clinical outcome of this work (i.e. in the abstract: "Individuals with REM **might** require similar CPAP pressures"; in the discussion: "Our results suggest that, REM OSA **could be** not different than NREM OSA **for what concern CPAP needs**").

Furthermore, I have a number of other concerns:

- Su and colleagues found lower CPAP requirements following titration in a bigger, non-AHI matched population of REM-OSA vs OSA,¹ which would deserve a comment in the discussion.
- The very high REM AHI in the REM OSA group (was this high number driven by people with the shortest amount of REM?) could lead to an out-of-proportion increase of CPAP at the titration (especially if this was done automatically, see also next point) and consequently to higher average CPAP requirements for the whole group. Consider discuss this further as a potential bias for the results.
- How were the recommended CPAP levels obtained? After titration (and, if so, automatic CPAP or manual titration) or after follow-up?
- For OSA prevalence, much more recent estimates exist.
- A quote is missing at the end of the second paragraph.
- Define acronyms before using them (i.e. cwp).

References

1. Su CS, Liu KT, Panjapornpon K, Andrews N, et al.: Functional outcomes in patients with REM-related obstructive sleep apnea treated with positive airway pressure therapy. *J Clin Sleep Med*. 2012; 8 (3): 243-7 [PubMed Abstract](#) | [Publisher Full Text](#)

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Obstructive sleep apnea

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 07 Dec 2019

rodolfo soca

We thank Dr. Ludovico Messineo for taking the time to review our article and providing valuable feedback about our paper.

We have rewritten our manuscript to incorporate the main points from Dr. Messineo's review as explained below:

- The main suggestion from Dr. Messineo relates to the strong message that was conveyed despite the fact that our study had a small sample size. We agree with the suggestion completely. We changed the wording in the abstract to convey the fact that our study "suggests" that CPAP pressure needs could be similar between REM and NREM OSA. We also changed the wording of our discussion section to convey the same message.

- We agree with the suggestion about including more information about the lower CPAP pressure needs that were identified by Su et al. We added some wording to the introduction and to the discussion to mention their results and our explanation as to why we think that we obtained different results: their study had a high proportion of women in the REM OSA group.
- Regarding the relationship between REM duration, REM AHI, and recommended CPAP pressures, we agree with the reviewer that the topic is interesting but we decided to address it in these comments rather than adding more text to our results.
- While we found a negative correlation between REM sleep duration and REM AHI for the REM OSA group (Pearson's coefficient $r = -0.56$), we did not find a relationship between the final CPAP pressure and the duration of REM sleep (Pearson's coefficient $r = -0.04$).
- We thank the reviewer for noting our limited explanation regarding the recommended CPAP pressure. We added wording to the methods section to explain that the recommended CPAP pressure was obtained manually during the CPAP titration study.
- We added some wording to highlight the fact that our prevalence data comes from the Wisconsin Sleep Cohort study.
- We thank the reviewer for noting that a quote was missing at the end of our second paragraph, this was certainly a very relevant reference for us. Reference added.
- We apologize for the use of an acronym that was not defined. We updated our manuscript and changed "cwp" with the appropriate and more standard unit "cm H₂O"

Once again, we thank the reviewer for this insightful review and welcome any comments about this newer version of the manuscript.

Very respectfully,

The Authors.

Competing Interests: The authors do not have any competing interests to disclose.

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