CRANIO®
The Journal of Craniomandibular & Sleep Practice

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ycra20

Impact of obstructive sleep apnea on neuromuscular transmission- a descriptive study

Özgür Bilgin Topçuoğlu, Gülgün Çetintaş Afşar, Hande Alibaş & Kayıhan Uluç

To cite this article: Özgür Bilgin Topçuoğlu, Gülgün Çetintaş Afşar, Hande Alibaş & Kayıhan Uluç (06 Jul 2021): Impact of obstructive sleep apnea on neuromuscular transmission- a descriptive study, CRANIO®, DOI: 10.1080/08869634.2021.1952016

To link to this article: https://doi.org/10.1080/08869634.2021.1952016

Published online: 06 Jul 2021.

CRANIO®: THE JOURNAL OF CRANIOMANDIBULAR & SLEEP PRACTICE
https://doi.org/10.1080/08869634.2021.1952016

Taylor & Francis
Taylor & Francis Group

SLEEP

Impact of obstructive sleep apnea on neuromuscular transmission- a descriptive study

Özgür Bilgin Topçuoğlu, MD, MSc[a], Gülgün Çetintaş Afşar, MD[b], Hande Alibaş, MD[c] and Kayıhan Uluç, MD[c]

[a]Department of Electroneurophysiology, Istanbul Kent University, Istanbul, Turkey; [b]Department of Chest Diseases, Sureyyapasa Chest Diseases and Thorax Surgery Training and Research Hospital, Istanbul, Turkey; [c]Department of Neurology, Marmara University, Medical School, Istanbul, Turkey

ABSTRACT

Objective: Obstructive sleep apnea (OSA) is a sleep disorder accompanied by intermittent hypoxia. Neuromuscular transmission (NT) is known to be disturbed under chronic hypoxia. In this descriptive study, it has been aimed to test NT under intermittent hypoxia in OSA.

Methods: Thirty-nine newly diagnosed OSA patients without any comorbidities or conditions that alter NT were included in the study. Jitter analysis was performed using a concentric needle electrode.

Results: The mean jitter value of 39 OSA patients was 25.9 ± 3.7 µs. When compared to the mean reference jitter values, patients in the present study had significantly higher jitter ($p < 0.001$). Seven (17.9%) patients met the electrophysiological criteria for NT failure.

Conclusion: The authors propose that intermittent hypoxia can be the trigger for NT failure in OSA. The interaction between increased oxidative stress and disturbed mitochondrial functions may also contribute.

KEYWORDS

Obstructive sleep apnea; neuromuscular junction; jitter; peripheral nervous system; hypoxia; concentric needle electrode

Introduction

Obstructive sleep apnea (OSA) is a common syndrome that is caused by the collapse of the upper airway during sleep. The intermittent obstruction of the airflow during sleep causes oxygen desaturation and hypercapnia, which contribute to metabolic, cardiovascular, and neurocognitive consequences [1]. Diagnosis of OSA depends on clinical features and increased apnea-hypopnea index (AHI), which is defined as the number of apneas plus hypopneas per hour of sleep, in polysomnography (PSG) [1].

OSA is known to disturb the peripheral nervous system, and OSA patients have increased polyneuropathy (PN) prevalence when compared to the normal population [2–5]. Various contributing factors for PN in OSA, including obesity and other associated metabolic disturbances, may be indicated.

Chronic hypoxia is known to cause polyneuropathy [4–6]. Previously, hypoxia at the tissue level has been shown in OSA patients [5,7,8]. However, unlike chronic obstructive pulmonary disease (COPD), which causes PN via chronic hypoxia, OSA is associated with intermittent hypoxia (IH), and IH has been accepted to be a trigger of oxidative stress in OSA patients [4–6,9].

The neuromuscular junction (NMJ) is a complex synaptic area between a motor nerve terminal and a skeletal muscle fiber. Both pre- and post-synaptic portions of the NMJ are rich in mitochondria, which serve as energy support through oxidative phosphorylation [10,11]. For this reason, the NMJ is highly sensitive to hypoxia [12,13], and neuromuscular transmission has been shown to be delayed in case of hypoxia [14]. The effects of hypoxia on neuromuscular transmission may partially be explained by reduction of active transport of sodium and potassium ions, which result in ineffective depolarization of nerves and muscles [12].

In this study, the authors aimed to investigate the effect of OSA on neuromuscular transmission by electroneurophysiological assessment. When a motor axon is depolarized, it stimulates all the related muscle fibers more or less, but not exactly at the same time. Even though depolarization occurs in a very short time period, there will still be a variation of time between the firings of the muscle fibers caused by the time deflections of the depolarizations. This variation in the time interval between the firings of neighboring muscle fibers is called "jitter." In other words, jitter reflects the variations in transmission time in the NMJ. Accordingly, increased jitter will indicate a failure in neuromuscular transmission, which may be electroneurophysiologically tested via

CONTACT Özgür Bilgin Topçuoğlu ozgurbilgin1@yahoo.com Istanbul Kent University, Cihangir Mahallesi, Sıraselviler Caddesi, No:71, Beyoğlu, Istanbul 34433, Turkey

jitter analysis [15]. Increased jitter has been shown in chronic hypoxic COPD patients [16]. But to the authors' knowledge, this is the first study to assess neuromuscular transmission in intermittent hypoxic OSA patients.

Materials and methods

Study participants

This prospective study was conducted between January 2015 and January 2017. Patients between the ages of 18 and 70, who were recently diagnosed with OSA in the Sleep Laboratory of Süreyyapasa Chest Diseases and Thorax Surgery Training and Research Hospital, Istanbul were enrolled. OSA was diagnosed based on full-night PSG recordings using the criteria proposed by the American Academy of Sleep Medicine [17]. All patients were questioned for symptoms of peripheral nervous system disorders (i.e., disorders affecting the motor neuron, NMJ, and muscle) and underwent a detailed neurological examination. Patients who had symptoms or signs of a NMJ disorder, who had been previously diagnosed with a NMJ disorder, or who were under any medications that were known to cause NMJ failure, were excluded from the study. Patients with any comorbidities like diabetes mellitus (DM), hypertension, hypothyroidism, or with diseases that cause continuous hypoxia, such as COPD, asthma, interstitial lung diseases etc., and smokers were also excluded. Patients' height and weight were measured. Body mass index (BMI) was calculated by dividing their weight in kilograms by the square of their height in meters. The patients were categorized as normal weight if their BMI was <25 kg/m^2, overweight if their BMI was between 25 kg/m^2 and 29.9 kg/m^2, and obese if their BMI was ≥30 kg/m^2.

This study was designated as a descriptive study without a control group. The patients in the current study were newly diagnosed OSA patients without any comorbidities or any signs or symptoms of a neuromuscular disorder. A control group for such a patient group would consist of age, sex-matched individuals without diagnosis of OSA and without any comorbidities or any signs or symptoms of a neuromuscular disorder, which fulfills the definition of totally healthy individuals. When compared to nerve conduction studies and even regular needle EMG, jitter analysis is a painful and inconvenient procedure that requires concentration, coherence, and participation of the tested individual. Exactly for this reason, in 2016, Stalberg et al. published well-defined reference values of healthy individuals for the most commonly used muscles [18]. The authors preferred to use these meticulously described values for comparison instead of the values of a control group.

Polysomnography procedure

All patients were monitored with nocturnal polysomnography, which was performed with multichannel monitoring that includes neurophysiological electrodes (electroencephalography and electromyography electrodes), chest wall motion, abdominal motion, arterial oxygen saturation, and electrocardiography electrodes (Grass-Telefactor Cephalo, An Astro-med Inc. Product Group, 2005, West Warwick, RI, USA). Oronasal airflow was measured by a thermistor. The oxyhemoglobin saturation was monitored with a finger pulse oximeter with a sampling rate of 1 Hz. The body position was measured by a position sensor attached to the anterior chest wall. Signals recorded in the sleep period were manually analyzed. Apneas were scored when the airflow decreased by at least 90% from baseline for at least 10 s, and hypopneas were scored when airflow decreased by at least 30% for ≥10 s and was associated with a SO2 (oxygen saturation) fall ≥3% [19]. AHI was calculated as the average number of apneas and hypopneas per hour of recording in the sleep period. An AHI ≥5 was used to diagnose the patient with OSA. Patients were classified as having mild OSA when their AHI was between 5 and 14.9, moderate OSA when their AHI was between 15 and 29.9, and severe OSA when their AHI was equal to or greater than 30. SO2 in the sleep period was automatically analyzed, and after manual elimination of possible artifacts, mean SO2 and lowest nocturnal SO2 values were detected.

Jitter analysis using CNE

The authors aimed to measure jitter values to evaluate neuromuscular transmission in OSA patients using disposable concentric needle electrodes (CNE). CNE has almost replaced the traditional single fiber electrode for jitter studies both in daily practice and in research settings. Various studies have demonstrated its usefulness and reliability [15,20,21].

Jitter recordings were performed during voluntary activation of the extensor digitorum communis (EDC) muscle. A disposable CNE (Ambu® Neuroline, Denmark) with a diameter of 0.3 mm and a recording area of 0.02 mm^2 was used.

The Medelec Synergy EMG machine (Viasys Healthcare, Old Woking, UK) with built-in jitter software was used for all jitter recordings and analysis. Low- and high-frequency filters were set to 1 kHz and 10 kHz, respectively. Signals with clear solitary spikes and a fast-rising slope to a well-defined negative peak with a constant shape in consecutive discharges were accepted as apparent single fiber action potentials

(ASFAPs) [22,23]. To avoid having a signal riding another, the time between ASFAP pairs was >150 µs. At least 60–100 consecutive discharges without any notches or shoulders were recorded, and the mean consecutive difference (MCD) was accepted as jitter. In each participant, ≥20 potential pairs with parallel rising phases were recorded from different portions of the muscle, using 3 skin insertions. Universally accepted reference values that were defined earlier for the EDC muscle (mean: 23.4 ± 3 µs, upper limit of mean jitter: 30 µs, upper limit of individual jitter: 43 µs) were used for comparison [18]. Findings were accepted as abnormal if the mean MCD exceeded the upper limit for the EDC muscle or if >10% of individual pairs had jitter value above the upper limit [24].

Statistical analysis

Data were analyzed with SPSS statistical software version 20.0 (Chicago, IL, USA) and MedicReS e-picos calculator (New York, NY USA). Continuous data were expressed as mean ± standard deviation and categorical data using percentiles. The relationship between two continuous variables was tested with Student's *t*-test. The association of three continuous variables was tested with one-way ANOVA. The Tukey table was used for post-hoc analysis. Spearman correlation test was used for correlation analysis. Statistical significance was set at $p < 0.05$.

Ethical approval

All procedures performed in human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by Süreyyapaşa Chest Diseases and Thorax Surgery Training and Research Hospital local ethics committee (Approval no: KAEK-116/ 2014/24/176). Informed consent was obtained from all individual participants included in the study.

Table 1. Demographic and sleep-related features of the patients.

	Mean	SD	Minimum	Maximum
Body mass index (kg/m^2)	32.4	6.1	24.2	52.7
Apnea-hypopnea index (AHI)	37.6	22.0	8.7	110
Mean oxygen saturation (%)	93.9	1.4	91	96
Minimum oxygen saturation (%)	75.7	8.6	52	88

Results

This study included 39 OSA patients (32 males, 7 females) between the ages of 30 and 70 (48.8 ± 10.2) years. Twenty-two (56.4%) of the patients were obese, while 14 (25.6%) patients were overweight. Some demographic and sleep-related features of the patients are depicted in Table 1. Five patients (12.8%) had mild OSA (AHI: 5–15/hour), 11 (28.2%) had moderate (AHI: 15–29.9), and 23 (59%) had severe OSA (AHI ≥ 30).

In total, 781 potential pairs were acquired from 39 patients. Among all recorded potential pairs, 25 (3.2%) had higher jitter values than the individual jitter reference value (43 µs).

Mean jitter value acquired from the EDC muscle of the patients was 25.9 ± 3.7 µs. When compared to the mean reference jitter values of the same muscle published by Stalberg et al. (30 µs), patients in the current study had significantly higher jitter measures, as shown in Figure 1 ($p < 0.001$). Using the reference values from

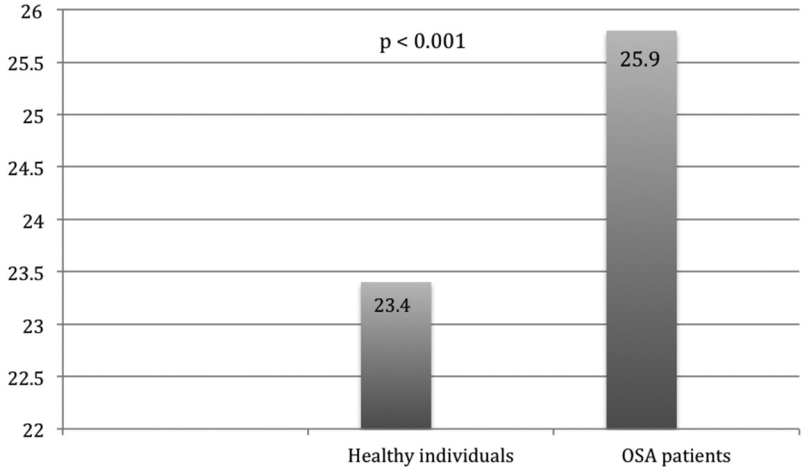

Figure 1. Comparison of mean jitter values between obstructive sleep apnea (OSA) patients and healthy individuals.

the same study, 6 (15.4%) of the patients in the present study had increased mean jitter and 3 (7.8%) had increased individual jitter in >10% of their recorded potential pairs. Impulse blocking was detected in 6 (15.4%) patients; however, none of them had blocking >10% of their recorded potentials. Overall, 7 (17.9%) patients met the electrophysiological criteria for neuromuscular transmission failure.

Mean jitter values of the patients in the current study had no correlation with their AHI, time spent below 90% oxygen saturation, mean or minimum oxygen saturation during sleep ($p > 0.05$ for all parameters). The mean jitter values of mild, moderate, and severe OSA patients were 23.6 ± 2.9 μs, 26.1 ± 4.4 μs, and 26.3 ± 3.5 μs, respectively. The three groups did not show a significant difference in their mean jitter value ($p = 0.342$).

The difference between mean jitter values of obese (26.6 ± 4 μs) and non-obese (24.9 ± 3.2 μs) OSA patients was not significant ($p = 0.162$). Mean jitters of overweight (25.7 ± 2.9 μs) and obese (26.6 ± 4.0 μs) OSA patients were above the normal limits of healthy individuals ($p < 0.001$; Tukey post-hoc analysis showing a significant difference between normal and overweight and normal and obese).

Discussion

This study showed that neuromuscular transmission was disturbed in 17.9% of otherwise healthy OSA patients. In the lack of any other co-morbidities, the authors propose that IH in OSA negatively affects neuromuscular transmission.

Chronic hypoxic situations, such as COPD, are known to be associated both with polyneuropathy and NMJ dysfunction [16,25]. Former studies have shown that the severity of polyneuropathy was correlated with severity of hypoxia in chronic hypoxic conditions [25]. Peripheral nerve dysfunction has also been shown in OSA patients previously, and hypoxia has been the presumed cause [4,5]. This finding led the authors to study the NMJ failure in OSA patients and, similarly, the authors believe that IH during night sleep is the probable cause for NMJ dysfunction in OSA.

Unlike COPD patients whose degree of hypoxia was correlated with the severity of polyneuropathy reported by Pfeiffer et al. [25], in OSA patients in the current study, degree of hypoxia during sleep was not correlated with their mean jitter value. The small sample size may be the reason for inadequate interpretation of such a connection. Additionally, regression analysis and/or correlation analysis would not be suitable for the current sample size. It is clear that hypoxia in OSA is intermittent during sleep, while blood oxygenation is normal during the day. However, since the measures of AHI and oxygen parameters belong to a single night spent in the sleep laboratory, it is not possible to know for certain how long the patients had been experiencing nighttime hypoxia or if the single-night measures are representative of the severity of their hypoxia.

NMJ function is highly dependent on mitochondria serving in energy support, regulation of calcium, synaptic transmission, etc. [10]. IH and ischemia-reperfusion injury in OSA have been shown to cause mitochondrial damage and alteration of mitochondrial DNA by means of oxidative damage [9]. OSA is also known to cause an escalation in oxidative stress, and reactive oxygen metabolites have been found to be increased in OSA patients [26,27]. Oxidative stress certainly plays a crucial role in NMJ degeneration [10]. The authors believe that, at the cellular level, the interplay between increased oxidative stress and disturbed mitochondrial function may contribute to NMJ transmission failure in OSA patients.

One of the major risk factors for OSA is obesity [1]. Obesity alone or together with DM is a well-known cause of polyneuropathy [28,29]. Likewise, NMJ dysfunction in OSA patients might have been caused by obesity or its consequences. The present study population included no diabetic patients but only 3 normal-weighted OSA patients. For this reason, it was not possible to make a comparison between normal, overweight, and obese patients. When the authors compared the overweight and obese patients with the reference values defined by Stalberg et al. [18], it was noted that the jitter of the patients in the present study was increased relative to the reference values. But, since BMIs of the patients in the mentioned reference study are not available, it would not be fair to oppose or support the additional effect of obesity on the NMJ failure of the OSA patients.

While the effects of chronic hypoxia on the neuromuscular junction are known and noticed, the consequences of intermittent hypoxia are widely underestimated. Despite some limitations, the current study is a step forward in determining the effects of intermittent hypoxia during sleep on the NMJ.

Limitations

One limitation of the present study is that it was based on data from a single center. In addition, the present descriptive study had a relatively small number of participants and no control group. The results of the study should be replicated with a larger study population. The authors used disposable CNE, which has a broader recording area than the original single fiber electrode for jitter analysis. Although the authors used

appropriate settings described for jitter analysis with CNE and strict inclusion criteria to avoid potential pitfalls, more sensitive measurements like single fiber EMG should be used to support the present findings.

Conclusion

Neuromuscular transmission is disturbed in OSA patients, as shown by jitter analysis with CNE. The IH during sleep is the proposed cause of the NMJ dysfunction in OSA.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

References

[1] Jordan AS, McSharry DG, Malhotra A. Adult obstructive sleep apnoea. Lancet. 2014;383(9918):736–747.
[2] Bilgin Topcuoglu O, Oruc O, Afsar GC, et al. Ulnar nerve entrapment at elbow in obstructive sleep apnea patients: a randomized controlled trial. Sleep Breath. 2017a;21(1):45–51.
[3] Bilgin Topcuoglu O, Oruc O, Sarac S, et al. Carpal tunnel syndrome in obstructive sleep apnea patients. Noro Psikiyatr Ars. 2017b;54(4):307–311.
[4] Ludemann P, Dziewas R, Soros P, et al. Axonal polyneuropathy in obstructive sleep apnoea. J Neurol Neurosurg Psychiatry. 2001;70(5):685–687.
[5] Mayer P, Dematteis M, Pepin JL, et al. Peripheral neuropathy in sleep apnea. A tissue marker of the severity of nocturnal desaturation. Am J Respir Crit Care Med. 1999;159(1):213–219.
[6] Appenzeller O, Parks RD, MacGee J. Peripheral neuropathy in chronic disease of the respiratory tract. Am J Med. 1968;44(6):873–880.
[7] Hasday JD, Grum CM. Nocturnal increase of urinary uric acid: creatinine ratio. A biochemical correlate of sleep-associated hypoxemia. Am Rev Respir Dis. 1987;135(3):534–538.
[8] Maillard D, Fleury B, Housset B, et al. Decreased oxyhemoglobin affinity in patients with sleep apnea syndrome. Am Rev Respir Dis. 1991;143(3):486–489.
[9] Lacedonia D, Carpagnano GE, Crisetti E, et al. Mitochondrial DNA alteration in obstructive sleep apnea. Respir Res. 2015;16(1):47.
[10] Jang YC, Van Remmen H. Age-associated alterations of the neuromuscular junction. Exp Gerontol. 2011;46(2–3):193–198.
[11] Lee CW, Peng HB. The function of mitochondria in presynaptic development at the neuromuscular junction. Mol Biol Cell. 2008;19(1):150–158.
[12] Hubbard JI, Loyning Y. The effects of hypoxia on neuromuscular transmission in a mammalian preparation. J Physiol. 1966;185(1):205–223.
[13] Kass LJ, Bazzy AR. Chronic hypoxia modulates diaphragm function in the developing rat. J Appl Physiol (1985). 2001;90(6):2325–2329.
[14] Millis RM, Stephens TA, Harris G, et al. Relationship between intracellular oxygenation and neuromuscular conduction during hypoxic hypoxia. Life Sci. 1984;35(24):2443–2451.
[15] Kouyoumdjian JA, Stalberg EV. Concentric needle single fiber electromyography: comparative jitter on voluntary-activated and stimulated Extensor Digitorum Communis. Clin Neurophysiol. 2008;119(7):1614–1618.
[16] Gulbas G, Kaplan Y, Kamisli O, et al. Neuromuscular transmission in hypoxemic patients with chronic obstructive pulmonary disease. Respir Physiol Neurobiol. 2013;189(1):112–116.
[17] Berry RB, Budhiraja R, Gottlieb DJ, et al. Rules for scoring respiratory events in sleep: update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events. Deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine. J Clin Sleep Med. 2012;8(5):597–619.
[18] Stalberg E, Sanders DB, Ali S, et al. Reference values for jitter recorded by concentric needle electrodes in healthy controls: a multicenter study. Muscle Nerve. 2016;53(3):351–362.
[19] Silber MH, Ancoli-Israel S, et al. The visual scoring of sleep in adults. J Clin Sleep Med. 2007 Mar 15;3(2):121–31. Erratum in: J Clin Sleep Med. 2007 Aug 15;3(5): table of contents. PMID: 17557422
[20] Ertas M, Baslo MB, Yildiz N, et al. Concentric needle electrode for neuromuscular jitter analysis. Muscle Nerve. 2000;23(5):715–719.
[21] Farrugia ME, Weir AI, Cleary M, et al. Concentric and single fiber needle electrodes yield comparable jitter results in myasthenia gravis. Muscle Nerve. 2009;39(5):579–585.
[22] Sanders DB, Arimura K, Cui L, et al. Guidelines for single fiber EMG. Clin Neurophysiol. 2019;130(8):1417–1439.
[23] Stalberg E, Sanders DB, Kouyoumdjian JA. Pitfalls and errors in measuring jitter. Clin Neurophysiol. 2017 Nov;128(11):2233–2241.
[24] Sanders DB, Stalberg EV. AAEM minimonograph #25: single-fiber electromyography. Muscle Nerve. 1996;19(9):1069–1083.
[25] Pfeiffer G, Kunze K, Bruch M, et al. Polyneuropathy associated with chronic hypoxaemia: prevalence in patients with chronic obstructive pulmonary disease. J Neurol. 1990;237(4):230–233.
[26] Christou K, Markoulis N, Moulas AN, et al. Reactive oxygen metabolites (ROMs) as an index of oxidative stress in obstructive sleep apnea patients. Sleep Breath. 2003;7(3):105–110.

[27] Lavie L. Obstructive sleep apnoea syndrome--an oxidative stress disorder. Sleep Med Rev. 2003;7(1):35–51.
[28] O'Brien PD, Hinder LM, Callaghan BC, et al. Neurological consequences of obesity. Lancet Neurol. 2017;16(6):465–477.
[29] Tesfaye S, Chaturvedi N, Eaton SE, et al. Vascular risk factors and diabetic neuropathy. N Engl J Med. 2005;352(4):341–350.