Respiratory Physiology & Neurobiology 260 (2019) 53–57

Contents lists available at ScienceDirect

Respiratory Physiology & Neurobiology

journal homepage: www.elsevier.com/locate/resphysiol

Spectral analysis of peri-pharyngeal muscles' EMG in patients with OSA and healthy subjects

Ron Oliven[a], Guy Cohen[b], Mostafa Somri[b,c], Alan R. Schwartz[d], Arie Oliven[a,b,*]

[a] Department of Medicine, Bnai-Zion Medical Centre, Haifa, Israel
[b] Rappaport School of Medicine, Technion Institute of Technology, Haifa, Israel
[c] Department of Anesthesiology, Bnai Zion Medical Center, Haifa, Israel
[d] Sleep Disorders Center, Johns Hopkins School of Medicine, Baltimore, MD, United States

ARTICLE INFO

Keywords:
Obstructive sleep apnea
Upper airway
Genioglossus
Spectral analysis
Centroid frequency

ABSTRACT

Introduction: In addition to dyscoordination of upper airway dilator muscles activity, sleep may also alter the pattern of intra-muscular activation of single motor units (SMUs). Such changes should be identifiable by a state dependent change in EMG power spectrum, i.e., a shift in centroid frequency (fc) during sleep.
Methods: EMGs of the genioglossus and four other peri-pharyngeal muscles were recorded in OSA patients (n = 8), age-matched healthy subjects (n = 7), and 5 young healthy subjects, and fc was calculated for wakefulness and sleep periods.
Results: fc decreased with the onset of sleep and returned to baseline levels after arousal. fc of all muscles decreased similarly and significantly during sleep in the OSA and the age-matched healthy subjects, but not in the young subjects.
Conclusions: The pattern of decrease in fc is compatible with altered synchronization of SMUs during sleep. We speculate that these changes may contribute to the failure of dilator muscles to improve flow limitation during sleep in older subjects.

1. Introduction

The pharyngeal region is a self-supporting collapsible tube whose patency to airflow depends on both anatomic and neuromuscular factors. During wakefulness, a "wakefulness stimulus" (Orem, 1990; Pillar et al., 2001) and reflex activation of upper airway dilator muscles (Malhotra et al., 2000; Doherty et al., 2008) maintain adequate muscle tone and pharyngeal patency. With the onset of sleep, these protective mechanisms are deranged, and dilator muscle activity, as reflected by their EMG activity, declines (Pillar et al., 2001; Malhotra et al., 2000; Doherty et al., 2008; Eckert et al., 2007; Sauerland and Harper, 1976). It has been commonly believed that this sleep-associated decline in dilator muscle activity, primarily that of the genioglossus (GG), the main tongue protrusor, explains the propensity of the pharynx to collapse during sleep (Sauerland and Harper, 1976), leading to partial or complete occlusion in susceptible subjects, i.e., to obstructive sleep apnea (OSA).

However, it is well documented that GG-EMG tends to increase gradually with deepening sleep. Most notable, complete and partial pharyngeal obstruction triggers an increasing drive to the GG, but this enhanced activity only seldom restores pharyngeal patency before arousal (Sauerland and Harper, 1976; Remmers et al., 1978; Berry et al., 1997; Patil et al., 2007; Okabe et al., 1993; Eckert et al., 2013). Several recent studies evaluated the rate of increase in GG-EMG during hypopneas, presenting recordings documenting that substantial increases in GG activity were associated with no or negligible changes in flow (Eckert et al., 2013; Dotan et al., 2013, 2015; Oliven et al., 2018). The cause for this phenomenon is poorly understood. While studying OSA patients under stable mild propofol sedation, we observed that when arousal was prevented, prolonged flow limitation triggered large increases in both tonic and phasic GG activity that exceeded several fold the activity during wakefulness, but did not affect either airflow or the pharyngoscopically observed diameter of the pharynx (Eckert et al., 2013). Although anesthesia differs considerably from normal sleep, the flow-mechanical effect of enhanced GG activity should not be affected by the state of consciousness. The striking increase in GG-EMG activity during partial pharyngeal obstruction, without recognizable effect on the cross-sectional area at the site of pharyngeal (partial) collapse and on flow-mechanics, resembled a form of "electro-mechanical dissociation". In contrast, awakening was associated with the immediate

* Corresponding author at: Department of Medicine, Bnai-Zion Medical Center, 47 Golomb Str., Haifa 31048, Israel.
E-mail addresses: oliven@technion.ac.il, arie.oliven@b-zion.org.il (A. Oliven).

https://doi.org/10.1016/j.resp.2018.12.002
Received 1 October 2018; Received in revised form 9 November 2018; Accepted 13 December 2018
Available online 13 December 2018

enlargement of the pharynx and restoration of airflow, despite concomitant decreases in GG activity, often with minimal phasic activity. This finding suggested that the central "wakefulness stimulus" involves a muscular activation modality that is not necessarily characterized by increased EMG activity. In later studies, we observed a similar phenomenon during normal sleep, both in OSA patients and healthy subjects: flow limitation could increase GG activity to levels twice as high as those observed in the presence of similar intra-pharyngeal pressures during wakefulness, without improving airflow (Dotan et al., 2015; Oliven et al., 2018). In contrast, the activity of other peri-pharyngeal muscles remained well below their level during wakefulness. We suggested that sleep-induced alteration in co-activation of peri-pharyngeal muscles is likely to play a central role in the failure of neuromuscular mechanisms to maintain pharyngeal patency during sleep in anatomically compromised subjects. Based on these findings, the functional mechanism leading to OSA is not only the delayed and often insufficient increase in the activity of the main tongue protrusor, the GG. Rather, recruitment of the other "accessory" peri-pharyngeal muscles that act in concert with the GG to prevent pharyngeal collapse may be equally important.

In addition to sleep-induced alteration in inter-muscular coordination, sleep-associated changes in the pattern of intra-muscular single motor units (SMUs) recruitment and synchronization could also affect the mechanical efficacy of pharyngeal dilators. It is conceivable that, as in other states of altered consciousness (i.e. stupor, intoxication etc.), central stimulation could provoke high EMG responses during sleep, but ineffectual distribution of SMUs activation could alter the effectiveness of muscle contraction. Several studies reported changes in the pattern of SMUs recruitment during sleep (Bailey et al., 2007; Wilkinson et al., 2008). Changes in SMUs recruitment of a whole muscle or muscle segment can be recognized by analysis of the EMG's power spectrum. Such changes can be quantified by calculating the spectral centroid of the EMG's power spectrum (*fc*). We hypothesized that sleep may induce a change in dilator muscles' EMG power spectrum, a change that may support the possibility that sleep is associated with alteration in the pattern of recruitment of SMUs and, hence, muscle effectiveness. Therefore, we performed power spectral analysis and calculated the *fc* of the GG and four other dilator muscles, in patients with OSA and young and older healthy subjects, during wakefulness and sleep. For this purpose, we used EMGs recorded in our recent study, designed to evaluate responses of dilator muscle (integrated) EMGs to upper airway obstruction (Oliven et al., 2018). The current manuscript presents the results of the power spectral analysis of the EMGs.

2. Methods

The methods, subjects' characteristics and protocol of the study were previously described in detail (Oliven et al., 2018). Briefly, subjects, all males, were 8 patients with OSA and 12 healthy subjects [7 age-matched to the OSA patients and 5 young subjects], all previously diagnosed in a conventional full-night sleep study in the Technion Sleep Laboratory. Anthropometric and sleep data of the study subjects are given in Table 1. All studies were performed in the respiratory research laboratory of Bnai-Zion Medical Centre. The aims and potential risks of the study were explained, and informed consent was obtained from all subjects. The study was approved by the institutional Human Investigations Review Board.

EMGs of upper airway dilator muscles [GG, styloglossus (SG), geniohyoid (GH), sterno-cleido-mastoid (SCM) and sternohyoid (SH)] were recorded via pairs of Teflon coated hook-wire electrodes as previously described (Oliven et al., 2018). The GG and 1–2 additional muscles were studied in each subject. EMG signals were amplified using P122 amplifiers and band-pass filtered at 30–1000 Hz (Grass Technologies, Warwick, RI). C4-A1 and C3-A2 EEG were employed to monitor sleep, and breathing was monitored using a pneumotachometer and intrathoracic pressure (Pes). Analogue-to-digital acquisition of all parameters was performed at 1000 Hz for monitoring and data storage on a digital polygraphic data acquisition system (LabVIEW, National Instruments, Austin TX).

Table 1
Anthropometric and sleep data of the study subjects. AHI and SO2 data were obtained from conventional sleep studies performed before the current study.

	OSA (n = 8)	healthy	
		older (n = 7)	young (n = 5)
AHI	58.4 ± 9.4	7.6 ± 2.0***	3.8 ± 1.2***
BMI	33.5 ± 4.8	27.2 ± 3.5*	23.6 ± 1.5**
age	53.6 ± 8.7	52.6 ± 10.0	21.2 ± 0.4***
lowest SO2	75.4 ± 8.5	90.4 ± 2.1***	93.8 ± 1.1**
%time SO2 < 90%	18.9 ± 19.1	0.2 ± 0.5**	0*

AHI – apnea/hypopnea index. SO2 – oxygen saturation.
* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$ for comparison with OSA.

The study protocol involved application of variable levels of positive (CPAP) and negative (CNAP) continuous airway pressure to patients with OSA and healthy subjects, respectively, during sleep, to induce prolonged periods of flow limitation. Patients fell asleep on CPAP levels sufficient to prevent flow limitation, and multiple pressure drops (every 3–5 min.) were performed to levels at which flow limitation Pes swings gradually became more negative, associated with high increases in GG activity observed before arousal. Sleep studies were continued for at least 3 h. Breathing was recorded also during wakefulness both before and immediately after sleep (length of recording while awake 55.4 ± 1.8 min.). While awake, the subjects breathed repeatedly for few breaths through variable inspiratory resistances, producing variable levels of negative Pes (-10 to -50 cmH2O). These Pes levels were similar to those observed during obstructed breathing while asleep, and they were associated with increases in peri-pharyngeal muscles' EMG. Multiple maneuvers were performed, with 5–10 cm H_2O pressure differences between maneuvers. Each pressure level was recorded 2–4 times (14).

In addition to the hardware filtering prior to sampling, the recorded EMG signals were processed off-line using MatLab (The MathWorks Inc., USA). Recorded EMG signals were notch filtered at 50 Hz to remove mains noise, and high-pass filtered at 30 Hz to minimize motion artifacts (Schweitzer et al., 1979). In addition, ECG artifacts were removed automatically. Occasionally, when an asynchronous spike in EMG activity was encountered by power spectral analysis, suspected to represent external noise or artefact, the specific frequency content associated with this spike was band-pass filtered and removed from all EMG tracings of the specific muscle of the individual subject. Fast Fourier transform of EMG was used to compute the power spectral density and the power spectra were quantified in terms of the *fc*. Each hour of sleep, as well as the awake periods before and after sleep were analyzed separately for each muscle. The complete period, including tonic and phasic activity, was analyzed *en-bloc*.

All data are presented as mean ± SE. Shapiro-Wilk Normality Test was used to test normal distribution of data. For normally distributed data, paired and unpaired t-tests were used to compare *fc* between sleep and wakefulness and between subject groups and different muscles, respectively. For data not-normally distributed, Wilcoxon signed-rank and Mann-Whitney tests were used for paired and two-sample comparisons, respectively. $P < 0.05$ was considered as statistically significant.

3. Results

The muscles evaluated are given in Table 2. In addition, in 3 subjects (1 OSA and 2 older healthy subjects), GG-EMG was recorded from

Table 2
Peri-pharyngeal muscles evaluated in the OSA and healthy young and older subjects.

healthy		OSA n = 8	
young n = 5	older n = 7		
5	7	8	genioglossus
4	1	2	styloglossus
2	3	4	geniohyoid
–	3	4	sternohyoid
3	2	4	sterno-cleido-mastoid

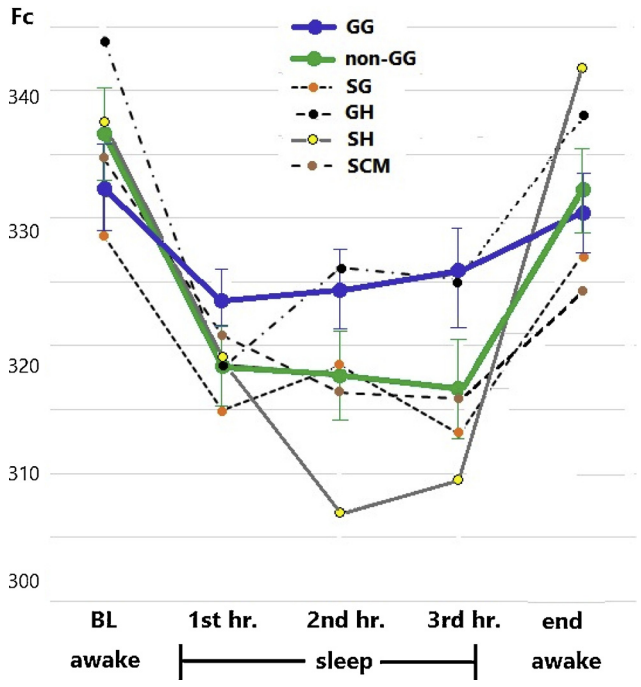

Fig. 1. Mean centroid frequency (Fc) for each one of the single muscles evaluated, as well as the mean values for all non-GG muscles, are presented for the awake periods before and after sleep, and each one of the sleep hours, for all study participants together (OSA patients and healthy subjects).
GG – genioglossus; SG – styloglossus; GH – geniohyoid; SH – sternohyoid; SCM – sterno-cleido-mastoid. SE bars are given for the GG and the non-GG muscle group.

2 sites (near GG insertion into the mandible, as in all subjects, and also from a more posterior site of the GG, for comparison). As no difference in results was observed in these subjects between the two sites of GG-EMG (Oliven et al., 2018), their data were added to the other GG-EMG data, resulting in n = 9 GG-EMG for both the OSA and older healthy subjects. The total number of all other (non-GG) peri-pharyngeal muscles was 14 and 18 for the OSA and healthy subjects, respectively.

Fig. 1 depicts the mean *fc* data of all muscles evaluated. The mean values are presented for the awake stage before sleep, each one of the first 3 h sleep, and the awake stage after final arousal. Sleep was associated with a modest but significant drop in the average *fc* of all muscles. This left-shift of *fc* was more pronounced in the first hour, but there was no significant difference between the first and later sleep hours. Awakening, at the end of the sleep study, was associated with an increase in *fc*, to a level that was not significantly different from that observed before sleep.

The mean *fc* of the 4 non-GG muscles was similar both during wakefulness and during sleep, prompting us to group the non-GG muscles together, as insufficient single muscles were evaluated per each subject-group to enable comparison. Similarly, we grouped together the *fc* of the awake stages before and after sleep, and the 3 sleep hours.

Table 3 compares the *fc* values of the GG and the other 4 muscles (grouped as non-GG), during wakefulness and sleep, in the OSA and all healthy subjects. It can be seen that a modest but statistically significant decrease in Fc was observed for all muscles, except for the GG of healthy subjects, that did not reach significance). However, when analyzing separately the older (age matched to the OSA patients) and the young healthy subjects, we found that changes in *fc* were significant only in the older subjects (Fig. 2). It can be seen that sleep was associated with a significant decrease in *fc* both in GG and non-GG muscles of OSA and age matched subjects, indicating a stage-specific left shift in spectral frequencies independently of the presence of OSA and the muscle evaluated. In contrast, sleep did not affect the *fc* of the GG and other peri-pharyngeal muscles evaluated in the young healthy subjects.

4. Discussion

The main finding of this work is that sleep is associated with a modest but significant decrease in *fc*, i.e. a "left shift" of the power spectrum of the peri-pharyngeal muscles' EMG toward lower frequencies. This shift occurred similarly in OSA patients and age matched healthy subjects, and in all muscles evaluated in this study. In contrast, no significant change in *fc* was observed in the young healthy subjects during sleep. Accordingly, this change in the characteristics of the EMG is likely associated with aging, independent of OSA.

The best and longest known trigger for a decrease in *fc* is muscle fatigue, or an effort that cannot be sustained (Cobb and Forbes, 1923; Dimitrova and Dimitrov, 2003). Several researchers examined the possibility that pharyngeal dilator muscles of OSA patients are in the state of chronic fatigue or are prone to fatigue but the studies reported conflicting conclusions (Mortimore et al., 2000; Blumen et al., 2004; Eckert et al., 2011; McSharry et al., 2012). GG fatigue was attributed to increased effort required to maintain pharyngeal patency while awake and/or excessive activation during and following apneas. However, the findings of the present study are not compatible with muscle fatigue: first, the decline in *fc* occurred immediately with the transition from wakefulness to sleep; signs of chronic muscle fatigue should already be present during wakefulness, rather than appearing when muscle activity declines during sleep. Second, a decrease in *fc* was found both in OSA patients and in the healthy age-matched subjects, in whom no dilator muscle fatigue is expected. Accordingly, the shift in power spectrum observed in this study is likely to be a physiological, state dependent phenomenon, suggesting a change in the characteristics of the EMG associated with the transition from wakefulness to sleep.

A large number of studies have evaluated the factors affecting the EMG spectral density under various conditions, including muscle

Table 3
Comparison of *fc* during wakefulness and sleep, in OSA patients and in all healthy subjects, for the EMG of the genioglossus (GG) and the four other (non-GG) muscles. Mean ± SE.

OSA patients				healthy subjects			
muscle	wakefulness	sleep	p	muscle	wakefulness	sleep	p
GG (n = 9)	327.5 ± 2.9	318.1 ± 2.2	< 0.005	GG (n = 14)	334.0 ± 3.5	329.6 ± 2.7	= 0.07
non-GG (n = 14)	337.0 ± 3.1	318.2 ± 3.4	< 0.001	non-GG (n = 20)	330.4 ± 3.0	319.4 ± 3.6	< 0.001

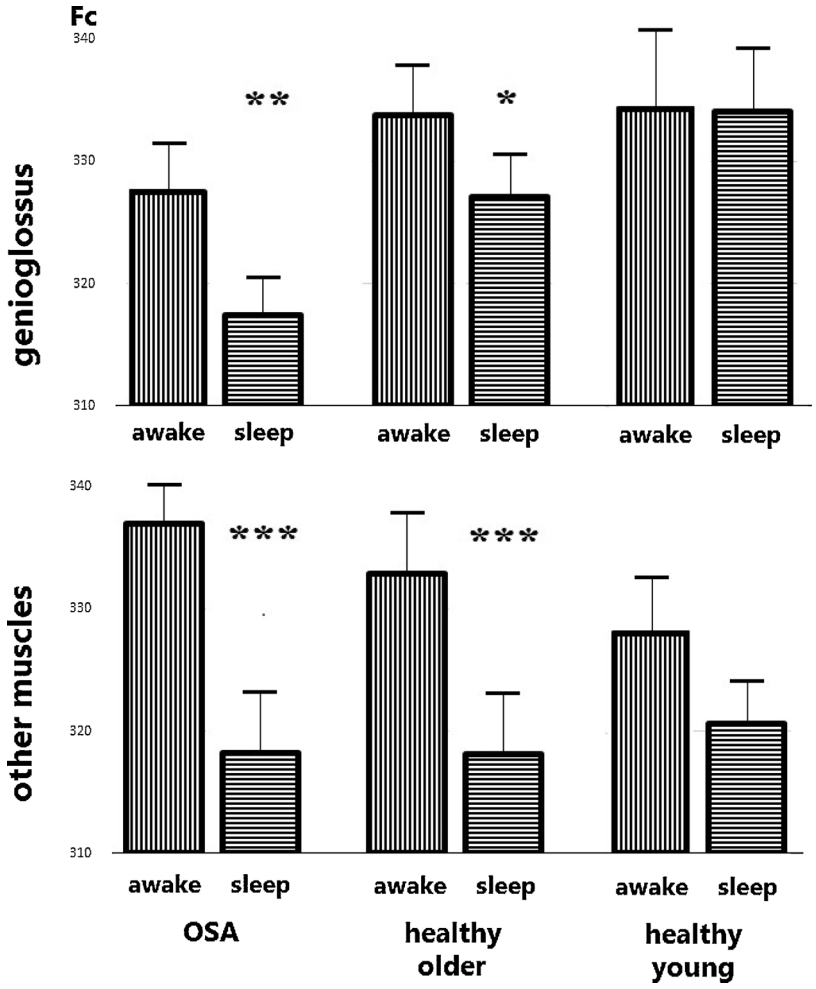

Fig. 2. Genioglossus and other (non-GG) peri-pharyngeal muscles' centroid frequency (Fc) during wakefulness and sleep in the three groups. mean ± SE. * - $p < 0.05$; ** - $p < 0.005$; *** - $p < 0.001$.

fatigue. Local tissue characteristics, conductance properties, size of the muscle, distance between of recording electrodes and their orientation relative to the muscles' fibers, type of electrodes and the range of frequencies analyzed, all have profound effects on *fc*, resulting in wide differences in *fc* between studies (Dimitrova and Dimitrov, 2003). However, most of these factors are less important when evaluating transient phenomena, like transitions between wakefulness and sleep in the present study. Action potential characteristics (duration, amplitude, shape and negative after-potential) have been shown to alter the power spectrum. The power spectrum depends also on muscle characteristics, like the percentage of slow (type I) and fast (type II) twitch fibers. Theoretically, preferential recruitment of type I or II fibers during sleep could also affect spectral variables. Most relevant for our matter is that recruitment (or de-recruitment) of SMUs, synchronization of SMUs discharge within the muscle, and neural input frequency, all affect the power spectrum. Obviously, any shift in EMG power spectrum can be the result of changes in several of the above parameters, reflecting the net effect of changes in lower and/or higher frequency domains. Therefore, using spectral properties extracted from the EMG for inferring details about the recruitment of SMUs is problematic. Nevertheless, the shift in *fc* observed in the current study points to a state dependent change in one or more of the relevant parameters. Assuming that the transition from wakefulness to sleep is unlikely to cause metabolic changes within the muscle fibers (similar to those occurring, for example, during muscle fatigue), the changes observed may reflect an alteration in the pattern of neural activation of the pharyngeal dilator muscles' SMUs. This possibility is supported by studies that evaluated the pattern of activation of SMUs of the human GG and found significant changes associated with the transition from wakefulness to sleep (Bailey et al., 2007; Wilkinson et al., 2008). Our findings suggest that similar changes occur also in other peri-pharyngeal muscles.

Interestingly, the group of young healthy subjects was the only one that did not exhibit a significant change in *fc* associated with transitions between wakefulness and sleep. It is tempting to speculate that the stability of *fc* indicates that young subjects undergo only minor changes in neural drive to the dilator muscles during sleep, thereby maintaining sufficient muscle efficacy that contributes to the lower prevalence of OSA in young subjects. However, the low number of young healthy subjects in our cohort ($n = 5$) limits the power of this finding, although the total number of peri-pharyngeal muscles evaluated in these subjects ($n = 14$, Table 1) should have been sufficient to recognize a state dependent change in *fc* if present. While differences in muscle tissue composition between young and older subjects could affect *fc*, the similar *fc* in the two groups during wakefulness suggests that the lack of left shift of the EMGs power spectrum in the young subjects during sleep is caused by other mechanisms.

Increased neural drive to the dilator muscles during wakefulness as compared to sleep could have also affected the observed changes in spectral power. However, our study protocol included repetitive introduction of resistive breathing during wakefulness, and induced flow limitation during sleep, both in OSA and in healthy subjects (using continuous negative airway pressure). These manipulations resulted in increasing respiratory efforts associated with increases in GG-EMG during hypopneas comparable to those observed while awake (Oliven

et al., 2018). On the other hand, non-GG muscles, activated during wakefulness similar to the GG (Oliven et al., 2018), were not or negligibly activated by flow limitation during sleep. The similar change in all muscles' *fc* indicates that our findings cannot be explained solely by changes in the intensity of neural drive to the muscles. For technical reasons, our analysis of the EMG power spectrum during sleep included also the short segments of arousal occurring following prolonged flow limitation. However, this technical aspect was similar for all subjects and muscles. It is possible, however, that the decline in *fc* during sleep was actually larger than computed in our study.

Mechanically, the tongue functions as a muscular hydrostat, requiring high level of internal synchronization to perform its many tasks (Kier and Smith, 1985). Similarly, peri-pharyngeal muscles need to act in concert to maintain pharyngeal patency to airflow (Van Lunteren and Strohl, 1986). Functional-MRI studies have documented that human sleep is an active state during which brain activity is temporally organized in a regionally specific manner (Drummond et al., 2004). Widespread sleep-associated changes in brain activity are coordinated across multiple cortical and subcortical regions (Picchioni et al., 2013). These sleep-induced changes in organization and coordination may also affect the activation and coordination of the upper airway dilator muscles. It is possible that as in states of stupor (e.g. encephalopathy, intoxication etc.), when large muscle force but no coordinated tasks can be performed, sleep may be associated with both intra- and inter-muscular dyscoordination, that impedes mechanical efficacy of the upper airway dilator muscles. These alterations in muscle coordination may constitute a vital part of the "wakefulness stimulus" (Orem, 1990; Pillar et al., 2001), explaining why high levels of GG-EMG activity during sleep fail to alleviate pharyngeal obstruction during sleep and sedation, while much lower activity is sufficient to maintain adequate upper airway patency while awake.

In conclusion, comparing the effect of transitions from wakefulness and sleep in OSA and healthy subjects on the EMG power spectrum, we found a decrease in *fc* during sleep in all older subjects and all peripharyngeal muscles evaluated. As muscle fatigue is an improbable explanation for the shift in power spectrum toward lower frequencies observed in this study, we speculate that our findings may be explained by a sleep-associated change in the central activation of SMUs. Whether and how such changes in the pattern of activation of SMUs affect dilator muscle contraction remains to be elucidated. However, if these changes lessen the mechanical efficiency of the dilator muscles, they could explain why intense activation of the GG, the main tongue protrusor, fails to ameliorate pharyngeal patency during normal and drug-induced sleep. If validated, this hypothesis implies that new treatment modalities should be directed to improve SMUs coordination during sleep, in addition to augmenting drive to the pharyngeal dilator muscles.

Funding

This work was supported by United States-Israel Binational Science Foundation grant 2011491.

Conflicts of interest

None

References

Bailey, E.F., Fridel, K.W., Rice, A.D., 2007. Sleep/wake firing patterns of human genioglossus motor units. J. Neurophysiol. 98, 3284–3291.
Berry, R.B., McNellis, M.I., Kouchi, K., Light, R.W., 1997. Upper airway anesthesia reduces phasic genioglossus activity during sleep apnea. Am. J. Respir. Crit. Care Med. 156, 127–132.
Blumen, M.B., Perez de La Sota, A., Quera-Salva, M.A., Fracher, B., Chabolle, F., Lofaso, F., 2004. Tongue mechanical characteristics and genioglossus muscle EMG in obstructive sleep apnoea patients. Respir. Biol. Neurobiol. 140, 155–164.
Cobb, S., Forbes, A., 1923. Electromyographic studies of muscle fatigue in man. Am. J. Physiol. 65, 234–251.
Dimitrova, N.A., Dimitrov, G.V., 2003. Interpretation of EMG changes with fatigue: facts, pitfalls and fallacies. J. Electromyo Kinesiol 13, 13–36.
Doherty, L.S., Cullen, J.P., Nolan, P., McNicholas, W.T., 2008. The human genioglossus response to negative airway pressure: stimulus timing and route of delivery. Exp. Physiol. 93, 288–295.
Dotan, Y., Pillar, G., Tov, N., Oliven, R., Steinfeld, U., Gaitini, L., Odeh, M., Schwartz, A.R., Oliven, A., 2013. Dissociation of EMG and mechanical response in sleep apnoea during propofol anaesthesia. Eur. Respir. J. 41, 74–84.
Dotan, Y., Pillar, G., Schwartz, A.R., Oliven, A., 2015. Asynchrony of lingual muscle recruitment during sleep in obstructive sleep apnea. J. Appl. Physiol. 118, 1516–1524.
Drummond, S.P., Smith, M.T., Orff, H.J., Chengazi, V., Perlis, M.L., 2004. Functional imaging of the sleeping brain: review of findings and implications for the study of insomnia. Sleep Med. Rev. 8, 227–242.
Eckert, D.J., McEvoy, R.D., George, K.E., Thomson, K.J., Catcheside, P.G., 2007. Genioglossus reflex inhibition to upper-airway negative-pressure stimuli during wakefulness and sleep in healthy males. J. Physiol. 581 (Pt 3), 1193–1205.
Eckert, D.J., Lo, Y.L., Saboisky, J.P., Jordan, A.S., White, D.P., Malhotra, A., 2011. Sensory-motor function of the upper airway muscles and respiratory sensory processing in untreated obstructive sleep apnea. J. Appl. Physiol. 111, 1644–1653.
Eckert, D.J., White, D.P., Jordan, A.S., Malhotra, A., Wellman, A., 2013. Defining phenotypic causes of obstructive sleep apnea. Am. J. Respir. Crit. Care Med. 188, 996–1004.
Kier, W.M., Smith, K.K., 1985. Tongues, tentacles and trunks: the biomechanics and movement of muscular hydrostats. Zool. J. Linn. Soc. 83, 207–324.
Malhotra, A., Fogel, R.B., Edwards, J.K., Shea, S.A., White, D.P., 2000. Local mechanisms drive genioglossus activation in obstructive sleep apnea. Am. J. Respir. Crit. Care Med. 161, 1746–1749.
McSharry, D., O'Connor, C., McNicholas, T., Langran, S., O'Sullivan, M., Lowery, M., McNicholas, W.T., 2012. Genioglossus fatigue in obstructive sleep apnea. Respir. Physiol. Neurobiol. 183, 59–66.
Mortimore, I.L., Bennett, S.P., Douglas, N.J., 2000. Tongue protrusion strength and fatiguability: relationship to apnoea/hypopnoea index and age. J. Sleep Res. 9, 389–393.
Okabe, S., Chonan, T., Hida, W., Satoh, M., Kikuchi, Y., Takishima, T., 1993. Role of chemical drive in recruiting upper airway and inspiratory intercostal muscles in patients with obstructive sleep apnea. Am. Rev. Respir. Dis. 147, 190–195.
Oliven, R., Cohen, G., Dotan, Y., Somri, M., Schwartz, A.R., Oliven, A., 2018. Alteration in upper airway dilator muscle co-activation during sleep: comparison of patients with OSA and healthy subjects. J. Appl. Physiol. 124, 421–429.
Orem, J., 1990. The nature of the wakefulness stimulus for breathing. Prog. Clin. Biol. Res. 345, 23–30.
Patil, S.P., Schneider, H., Marx, J.J., Gladmon, E., Schwartz, A.R., Smith, P.L., 2007. Neuromechanical control of upper airway patency during sleep. J. Appl. Physiol. 102, 547–556.
Picchioni, D., Duyn, J.H., Horovitz, S.G., 2013. Sleep and the functional connectome. Neuroimage 80, 387–396.
Pillar, G., Fogel, R.B., Malhotra, A., Beauregard, J., Edwards, J.K., Shea, S.A., White, D.P., 2001. Genioglossal inspiratory activation: central respiratory vs mechanoreceptive influences. Respir. Physiol. 127, 23–38.
Remmers, J.E., deGroot, W.J., Sauerland, E.K., Anch, A.M., 1978. Pathogenesis of upper airway occlusion during sleep. J. Appl. Physiol. 44, 931–938.
Sauerland, E.K., Harper, R.M., 1976. The human tongue during sleep. Electromyographic activity of the genioglossus muscle. Exp. Neurol. 51, 160–170.
Schweitzer, T.W., Fitzgerald, J.W., Bowden, J.A., Lynne-Davies, P., 1979. Spectral analysis of human inspiratory diaphragm electromyogram. J. Appl. Physiol. 46, 152–165.
Van Lunteren, E., Strohl, K.P., 1986. The muscles of the upper airways. Clin. Chest Med. 7, 171–188.
Wilkinson, V., Malhotra, A., Nicholas, C.L., Worsnop, C., Jordan, A.S., Butler, J.E., Saboisky, J.P., Gandevia, S.C., White, D.P., Trinder, J., 2008. Discharge patterns of human genioglossus motor units during sleep onset. Sleep 31, 525–533.