Hypoglossal nerve conduction studies in patients with obstructive sleep apnea

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Aim of the work
To identify the correlation between obstructive sleep apnea (OSA) and motor nerve conduction study of hypoglossal nerve in terms of amplitude and terminal latency.
Patients and methods
The present study included 16 adult OSA patients who presented to the Otolaryngology outpatient clinic of the Suez Canal University Hospital. Exclusion criteria included previous significant facial trauma, head or neck cancer, previous surgery (including tonsillectomy or adenoidectomy), previous radiation therapy to head or neck, known diagnosis of peripheral neuropathy, any implanted device (nerve stimulator, implanted pump, pacemaker, and defibrillator), and known pregnancy. All patients were subjected to an assessment protocol that included thorough assessment of history (age, sex, snoring, nasal obstruction, and excessive daytime sleepiness), clinical examinations [BMI, apnea/hypopnea index (AHI), Friedman tongue position (FTP), and Mallampati grading], and electrophysiological studies of hypoglossal nerve.
Results
87.5% of the patients had moderate to severe AHI (15 to >30). The degree of excessive daytime sleepiness was slight in 18.8% of the patients, mild in 50% of the patients, and moderate in 31.3% of the patients. FTP grades ranged from grade II (FTP II) (37.5%) to grade III (FTP III) (62.5%). Mallampati grading of tonsils also ranged from grade 2 (T2) (43.8%) to grade 3 (T3) (56.2%). Seventy-five percent of the patients had delayed distal latency of hypoglossal nerve. The mean distal latency of the patients was 3.24 ± 123 ms, with the range of 2.5–7.7 ms. All the patients had low motor amplitude of the hypoglossal nerve. There were significant positive correlations between excessive daytime sleepiness and BMI, snoring, FTP, Mallampati grading, and decreased hypoglossal nerve distal latency.
Conclusion
Most patients with OSA had significantly impaired hypoglossal nerve conduction in the form of delayed distal latency and low motor amplitude.

Keywords:
amplitude, hypoglossal nerve, latency, nerve conduction study, obstructive sleep apnea

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Introduction

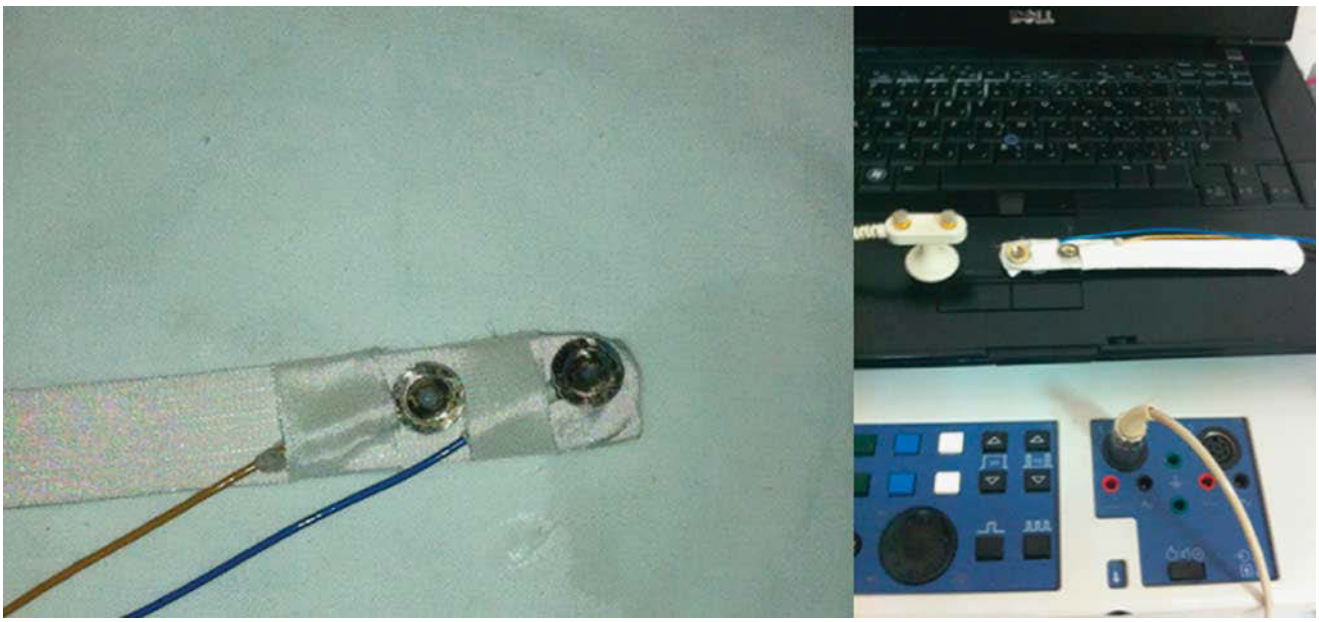
Obstructive sleep apnea (OSA) is a serious condition characterized by repeated apneas of 10 s or longer because of the collapse of soft upper airway structures during sleep. It affects individuals across the life span but is seen more often in midlife and older adults and among those who are obese. Obesity contributes toward OSA by compromising ventilation effort and by encroaching on upper airway structures when fat is distributed in and around the neck, face, and tongue [1].

The prevalence of OSA in the middle-aged population is 4% in men and 2% in women; however, the prevalence increases with age, to an estimated 28–67% for elderly men and 20–54% for elderly women [2].

The etiology of OSA syndrome is attributed to anatomical and functional factors. Anatomical factors include soft tissue and bone abnormalities (such as choanal atresia, micrognathia, mandibular hypoplasia, and other skull base abnormalities). Soft tissue abnormalities include bulky nasal polyp, rhinitis, soft palate redundancy, tonsillar hypertrophy, congenital laryngomalacia, congenital laryngeal web, and adenoid hypertrophy, which are considered the most common anatomic abnormality in children with OSA syndrome [3].

Neuromuscular dysfunction of the oropharynx may be part of the pathophysiology of OSA or it may be a consequence of repeated episodes of hypoxemia or snoring related to OSA. Investigation of the role of

Figure 1



Wooden tongue blade with electrodes fixed in place 2 cm apart.

neuromuscular dysfunction in OSA patients is challenging as needle electromyography (EMG) of the oropharynx is painful and tissue biopsies are invasive [4].

OSA patients have findings of nerve conduction studies (NCSs) suggestive of hypoglossal neuropathy compared with controls, and this difference cannot be attributed to generalized polyneuropathy. If OSA causes hypoglossal neuropathy, the possible etiologies include mechanical forces (vibration from snoring) and hypoxic or ischemic injury [5].

Electrical stimulation of the hypoglossal nerve by an implanted pacemaker can decrease upper airway collapse in OSA patients [6,7].

Selective stimulation of genioglossus muscles with transorally directed hook-wire electrodes improves inspiratory airflow without causing arousal from sleep. It consists of an implantable pulse generator containing a programmable microprocessor, a respiratory pressure sensor, and a tripolar half-cuff peripheral nerve-stimulation electrode [8]. There are two loci of hypoglossal nerve stimulation: the distal branch to the genioglossus muscle and the main nerve trunk. Electrical stimulation of the hypoglossal nerve results in a marked improvement in inspiratory airflow during sleep and reduction of apnea/hypopnea index (AHI) [8].

Patients and methods

This study was carried out as a descriptive cross-sectional study to measure the hypoglossal nerve conduction and to describe the correlation between OSA and motor NCS of hypoglossal nerve in terms of amplitude and terminal latency. It was carried out at Otolaryngology and Rheumatology Departments in the Suez Canal University Hospital.

Patients

Sixteen patients with OSA older than 18 years of age were recruited after obtaining their informed consent. Patients of both sexes between 28 and 57 years of age (42.6 ± 10.5 years) were included. The diagnosis of OSA was made on the basis of assessment of history and clinical examinations.

Patients were excluded if they had a history of previous significant facial trauma, head or neck cancer, previous surgery (including tonsillectomy or adenoidectomy), previous radiation therapy to head or neck, peripheral neuropathy, or any implanted device (nerve stimulator, implanted pump, pacemaker, and defibrillator).

Methods

All patients were subjected to a detailed assessment of medical history with a special focus on a history of snoring, whether it was daily or positional, obstructive episodes including arousals and nocturnal choking, and their number per hour of sleep, excessive daytime sleepiness and determining its degree, whether mild, moderate, or severe, and unilateral or bilateral nasal obstruction.

General examination for all patients included craniofacial morphology, micrognathia, or retrognathia, external head and neck examination for short neck, thyroid swelling, or any signs of hypothyroidism as dry skin, coarse hair and myxedema, and any mandibular or maxillary malformation.

BMI was calculated using the following equation [9]:

$\text{BMI} = \text{weight (kilogram)}/\text{height (meter)}^2$.

Patients were classified as underweight if less than 18.5, within the normal range if 18.5–24.9, overweight if 25.0–29.9, and obese if greater than 30.0.

Complete otorhinolaryngological examination was performed including endoscopic assessment of the nose and nasopharyngeal examination was performed to detect the presence of deviated septum, columellar deformity, nasal valve collapse during inspiration, turbinate hypertrophy, polyps, adenoid hypertrophy, and posterior choanal stenosis or atresia. The uvula was examined for the length and width (widened if >10 mm). Mallampati grading was used for assessment of tonsils, where T0: tonsils were removed, T1: anterior pillar covering the entire tonsil, T2: tonsil lies beyond the anterior pillar, T3: tonsil touches the uvula, and T4: tonsils meet in the midline (kissing tonsils).

Tongue position was graded according to the Friedman tongue position grading scale, where FTP I: if the entire soft palate, uvula, tonsils, and tonsillar pillar are visible, FTP II: only a part of the tonsillar pillars and complete soft palate and uvula were visible, FTP III: only the soft palate was visible, and FTP IV: just the hard palate was visible.

Hypoglossal nerve conduction studies

Dantec Keypoint 4 EMG (Dantec Keypoint, Denmark) was used for hypoglossal NCSs. During the NCSs, patients were in sitting positions. Hypoglossal NCS was performed in all patients using a standard technique (Fig. 1). Two electrodes located and fixed on a tongue blade 2 cm apart were placed on the dorsal surface of the tongue over intrinsic tongue muscles. A ground electrode was placed on the cheek. Bipolar percutaneous stimulation using a 0.02 ms duration and 100 mA electrical stimulus was applied along the base of the mandible, with pressure applied to the stimulator [10].

The duration of the electrical stimulus was increased gradually until a supramaximal compound motor action potential (CMAP) waveform was achieved. Lower limb surface temperatures were maintained above 32°C [10].

The latency and amplitude of the CMAPs were measured from baseline to peak and calculated automatically and the results were interpreted according to Redmond and Di Benedetto [11] (latency, 2.04–2.66 ms, amplitude, 3.45–5.43 mV).

Results

The mean age of the patients was 42.6 ± 10.5 years, with a range of 28–57 years. Half of the patients were younger than 40 years of age. Equal numbers of men and women were included (50% for both sexes), with a ratio of 1 : 1. The mean BMI among the patients studied was 32.8 ± 3.4 kg/m^2, with a range of 24–37 kg/m^2. The majority of the patients studied were obese (n = 13; 81.25%).

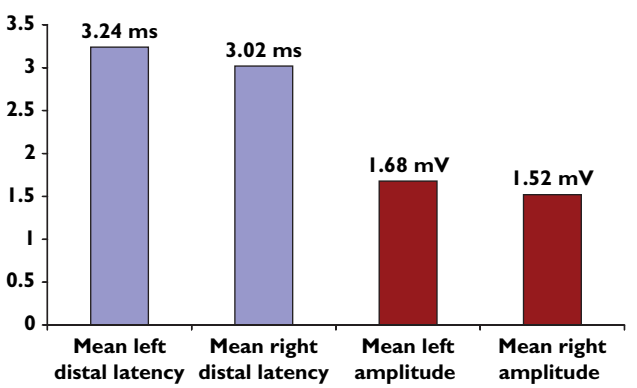
Most of the patients had nasal obstruction (62.5%); 18.8% had unilateral obstruction and 43.7% had bilateral obstruction. Also, the majority of the patients had daily snoring (81.2%), whereas 18.8% of them had positional snoring.

Table 1 shows the outcome measures of OSA of the patients studied. Most of the patients had moderate to severe AHI (15 to >30), with a prevalence of 87.5%. The mean AHI of the patients was 27.1 ± 8.98, with a range of 10–40. The degree of excessive daytime sleepiness was slight in 18.8% of the patients, mild in 50% of the patients, and moderate in 31.3% of the patients. FTP grades ranged from grade II (FTP II) (37.5%) to grade III (FTP III) (62.5%). Mallampati grading of tonsils also ranged from grade 2 (T2) (43.8%) to grade 3 (T3) (56.2%).

Table 1 Outcome measures of obstructive sleep apnea of the patients studied (n=16)

Variables	Total population (n=16) [n (%)]
Apnea/hypopnea index (AHI)	
Mild <15	2 (12.50)
Moderate 15–30	7 (43.75)
Severe >30	7 (43.75)
Mean (SD)	27.1 (8.98)
Excessive daytime sleepiness	
Slight	3 (18.8)
Mild	8 (50.0)
Moderate	5 (31.3)
Friedman tongue position (FTP)	
FTP I	0 (0.0)
FTP II	6 (37.5)
FTP III	10 (62.5)
Mallampati grading of tonsils	
T0	0 (0.0)
T1	0 (0.0)
T2	7 (43.8)
T3	9 (56.2)

Chart 1



The electrophysiological studies of the hypoglossal nerve of the patients studied (n=16).

Table 2 Correlations between excessive daytime sleepiness and the significant variables studied

Variables	Pearson's correlation coefficient	P-value
BMI	0.5	0.049*
Snoring	0.546	0.029*
Friedman tongue position (FTP)	0.51	0.044*
Mallampati grading	0.52	0.039*
Right distal latency	0.437	0.05*
Left distal latency	0.327	0.217

*Significant at $P \leq 0.05$.

Table 3 Correlations between apnea/hypopnea index and the significant variables studied

Variables	Pearson's correlation coefficient	*P*-value
Age	0.612	0.012*
BMI	0.716	0.002**

*Significant at $P \leq 0.05$.
**Highly significant at $P \leq 0.01$.

Chart 1 shows the electrophysiological studies of the hypoglossal nerve of the patients studied. Most of the patients had delayed distal latency of the hypoglossal nerve (75% of the patients in the right and left hypoglossal nerves). The mean left distal latency of the patients was 3.24 ± 1.23 ms, with a range of 2.5–7.7 ms, whereas the mean right distal latency of the patients was 3.02 ± 0.61 ms, with a range of 2.4–4.6 ms.

All the patients had low motor amplitude of the hypoglossal nerve (100% of the patients in the right and left hypoglossal nerves). The mean left motor amplitude of the patients was 1.68 ± 0.61 mV, with a range of 0.6–2.5 mV, whereas the mean right motor amplitude of the patients was 1.52 ± 0.79 mV, with a range of 0.6–3.2 mV

Table 2 shows the correlations between excessive daytime sleepiness and significant studied variables. The Pearson correlation coefficient test was used for correlation. Excessive daytime sleepiness was considered as the dependent variable, whereas the other variables were considered as the independent variables. There were significant positive correlations between excessive daytime sleepiness and BMI, snoring, FTP, Mallampati grading, and right distal latency. This means that the patients with higher BMI, snoring, FTP, Mallampati grading, and right distal latency had more severe daytime sleepiness ($P \leq 0.05$).

Table 3 shows the correlations between AHI and the significant variables studied. The Pearson correlation coefficient test was used for correlation. AHI was considered as the dependent variable, whereas the other variables were considered as the independent variables. There were significant positive correlations between AHI and age and BMI. This means that the patients with higher age and BMI had higher AHI ($P \leq 0.05$).

Table 4 shows the correlations between FTP and the significant variables studied. The Pearson correlation coefficient test was used for correlation. FTP was considered as the dependent variable, whereas the other variables were considered as the independent variables. There were significant positive correlations between FTP and age, BMI, snoring, excessive daytime sleepiness, and Mallampati grading. This means that the patients with higher age, BMI, snoring, excessive daytime sleepiness, and Mallampati grading had higher FTP ($P \leq 0.05$).

Table 5 shows the correlations between Mallampati grading and the significant variables studied. The Pearson correlation coefficient test was used for correlation. Mallampati grading was considered as the dependent variable, whereas the other variables were considered as the independent variables. There were significant positive correlations between Mallampati grading and age, BMI, snoring, AHI, excessive daytime sleepiness, FTP, right distal latency, and right amplitude. This means that the patients with higher age, BMI, snoring, AHI, excessive daytime sleepiness, FTP, right distal latency, and right amplitude had higher Mallampati grading ($P \leq 0.05$).

Table 4 Correlations between Friedman tongue position and the significant variables studied

Variables	Pearson's correlation coefficient	*P*-value
Age	0.493	0.05*
BMI	0.621	0.01*
Snoring	−0.62	0.01*
Excessive daytime sleepiness	0.51	0.044*
Mallampati grading	0.878	<0.0001**

*Significant at $P \leq 0.05$.
**Highly significant at $P \leq 0.01$.

Table 5 Correlations between Mallampati grading and the other variables studied

Variables	Pearson's correlation coefficient	*P*-value
Age	0.663	0.005**
BMI	0.751	0.001**
Snoring	0.545	0.03*
Apnea/hypopnea index (AHI)	0.542	0.03*
Excessive daytime sleepiness	0.52	0.039*
Friedman tongue position (FTP)	0.878	<0.0001**
Right distal latency	0.478	0.05*
Left distal latency	0.377	0.150
Right amplitude	0.436	0.05*
Left amplitude	0.102	0.708

*Significant at $P \leq 0.05$.
**Highly significant at $P \leq 0.01$.

There were significant positive correlations between BMI and age, snoring, AHI, excessive daytime sleepiness, FTP, and Mallampati grading. This means that patients with higher age, snoring, AHI, excessive daytime sleepiness, FTP, and Mallampati grading had higher BMI ($P \leq 0.05$).

Discussion

OSA is a common sleep disorder that affects ~2–4% of adults (women and men); OSA is a major public health issue because of its association with automobile accidents, decreased quality of life, and cardiac and cerebrovascular events [12].

Neuromuscular dysfunction of the oropharynx may be part of the pathophysiology of OSA or it may be a consequence of repeated episodes of hypoxemia or snoring related to OSA. Investigation of the role of neuromuscular dysfunction in OSA patients is challenging as needle EMG of the oropharynx is painful and tissue biopsies are invasive [10].

As peripheral nerve denervation and reinnervation can result in loss of muscle tone, loss of hypoglossal axons to tongue muscles could increase susceptibility to airway narrowing. This suggests that hypoglossal nerve dysfunc-

tion may promote OSA. The genioglossus is an important pharyngeal dilator, and decreases in genioglossus activity during sleep are greater in OSA patients than controls [13].

Furthermore, stimulation of the hypoglossal nerve may relieve upper airway obstruction in OSA. These observations combine to support the hypothesis that chronic hypoglossal nerve dysfunction could increase susceptibility to airway collapse during sleep. Thus, a bidirectional relationship may exist, where OSA may result in hypoglossal dysfunction, which in turn may worsen OSA [13].

Although OSA appears to result from intermittent airway occlusion during sleep, the pathophysiology of OSA is not completely understood. Histological changes in the genioglossus of OSA patients suggest neuromuscular impairment of this muscle as a possible consequence or concomitant with OSA [14,15].

Some theories suggest that hypoglossal mononeuropathy is caused in OSA by mechanical forces (vibration from snoring) and hypoxic or ischemic injury. Clinical and animal studies have shown that vibration has the capacity to cause snoring-induced focal demyelination more than axonal injury. However, whether vibration during snoring is sufficient to produce hypoglossal nerve injury remains unclear. Nerve ischemia generally affects large myelinated axons, which reduces the CMAP amplitude and slows distal nerve conduction [4].

To improve understanding of neuromuscular dysfunction in OSA, we tested noninvasive NCS of the tongue. Specifically, the purpose of this study was to investigate hypoglossal NCS in patients with OSA. The main objective was to identify the correlation between OSA and motor NCS of the hypoglossal nerve in terms of amplitude and terminal latency.

We found that most of the patients (75%) had delayed distal latency and all the patients (100%) had low motor amplitude of the hypoglossal nerve.

Our results showed that there were significant positive correlations between excessive daytime sleepiness and BMI, snoring, FTP, Mallampati grading, and right distal latency of the hypoglossal nerve. There were also significant positive correlations between AHI and age and BMI.

Ramchandren *et al.* [10] also reported that there was a significant correlation between the OSA and BMI.

Also, BMI has been shown to be associated with reductions in amplitude and slightly faster velocities in sensory and mixed nerves; a consistent relationship between BMI and motor amplitudes or latencies has been identified [16].

Although we did not directly assess for primary muscle pathology, our findings are consistent with a hypoglossal neuropathy, which could explain some of the pathological muscle findings others have identified in OSA [10,17].

Our findings are supported by a recent needle EMG study carried out by Saboisky *et al.* [16]. They found increased duration and area of genioglossus motor unit action potential in OSA patients. This finding is consistent with previous denervation and subsequent reinnervation because of axonal loss. The electrodiagnostic evidence of neurogenic findings in two separate muscles innervated by the hypoglossal nerve, the genioglossus and intrinsic tongue muscles, suggests localization of dysfunction to the nerve rather than muscle tissue.

Tongue muscle histopathology in OSA patients has been attributed to a myopathy postulated to result from 'activity-induced injury' [16].

The results of Ramchandren *et al.* [10] showed that OSA patients have NCS findings suggestive of a hypoglossal mononeuropathy and these findings cannot be attributed to a generalized polyneuropathy.

Genioglossus biopsies have showed increased type II muscle fibers in OSA patients compared with controls [18], another finding consistent with motor nerve partial denervation that is notably absent in OSA patients treated with chronic continuous positive airway pressure [19].

This study provides new evidence of hypoglossal nerve dysfunction in OSA using a noninvasive technique.

However, our data cannot definitively determine whether hypoglossal nerve dysfunction is caused by OSA and/or is in part responsible for OSA, or whether it is an epiphenomenon.

Conclusion

This study provides new evidence of hypoglossal nerve dysfunction in OSA using a noninvasive technique.

However, our data cannot definitively determine whether hypoglossal nerve dysfunction is caused by OSA and/or is in part responsible for OSA, or whether it is an epiphenomenon.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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