# HYPOGLOSSAL NERVE CONDUCTION FINDINGS IN OBSTRUCTIVE SLEEP APNEA

SINDHU RAMCHANDREN, MD, MS,[1] KIRSTEN L. GRUIS, MD, MS,[2] RONALD D. CHERVIN, MD, MS,[3] LYNDA D. LISABETH, PhD,[4,5] MARYANN CONCANNON, MSW, RPSGT,[4] JAMES WOLFE, RNCST,[2] JAMES W. ALBERS, MD, PhD,[2] and DEVIN L. BROWN, MD, MS[4]

[1] Department of Neurology, Wayne State University–Detroit Medical Center, Detroit, Michigan, USA
[2] Neuromuscular Program and EMG Laboratory, Department of Neurology, University of Michigan, Ann Arbor, Michigan, USA
[3] Sleep Disorders Center, University of Michigan, Ann Arbor, Michigan, USA
[4] The Cardiovascular Center, Stroke Program, 1500 East Medical Center Drive, SPC 5855, Ann Arbor, Michigan 48109-5855, USA
[5] Department of Epidemiology, School of Public Health, University of Michigan, Ann Arbor, Michigan, USA

*Accepted 2 February 2010*

ABSTRACT: Denervation of oropharyngeal muscles in obstructive sleep apnea (OSA) has been suggested by needle electromyography (EMG) and muscle biopsy, but little is known about oropharyngeal nerve conduction abnormalities in OSA. We sought to compare hypoglossal nerve conduction studies in patients with and without OSA. Unilateral hypoglossal nerve conduction studies were performed on 20 subjects with OSA and 20 age-matched controls using standard techniques. Median age was 48 years in OSA subjects and 47 years in controls. Hypoglossal compound muscle action potential (CMAP) amplitudes were significantly reduced ($P = 0.01$, Wilcoxon signed-rank test), but prolongation of latencies in OSA subjects did not reach significance in comparison to those of controls. Among a subgroup of subjects without polyneuropathy (15 pairs), reduced amplitudes in OSA subjects retained borderline significance ($P = 0.05$). Hypoglossal nerve conduction abnormalities may distinguish patients with OSA from controls. These abnormalities could potentially contribute to, or arise from, OSA.

*Muscle Nerve* **42:** 257–261, 2010

Obstructive sleep apnea (OSA) is a common sleep disorder that affects approximately 2–4% of adults.[1] OSA is a major public health issue because of its association with automobile accidents, decreased quality of life, and cardiac and cerebrovascular events.[2] Although OSA appears to result from intermittent airway occlusion during sleep, the pathophysiology of OSA is not completely understood. The genioglossus, an extrinsic muscle of the tongue innervated by the hypoglossal nerve, is considered one of the most important oropharyngeal dilators to maintain airway patency. Histological changes in the genioglossus of OSA patients suggest neuromuscular impairment of this muscle as a possible consequence or concomitant of OSA.[3]

Needle electromyography (EMG) of oropharyngeal muscles in OSA has demonstrated focal partial denervation,[4] a finding confirmed by microscopic evaluation of palatal tissue.[4,5] However, the significance of oropharyngeal muscle denervation or any type of neuromuscular dysfunction of the oropharynx in OSA is controversial.[6,7] 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. To improve understanding of neuromuscular dysfunction in OSA, we sought to investigate non-invasive nerve conduction studies (NCS) of the oropharynx. Specifically, the purpose of this study was to investigate hypoglossal NCS in patients with OSA and age-matched controls.

## METHODS

**Subjects.** ***OSA Subjects.*** Twenty OSA patients, aged 18–60 years, with an apnea–hypopnea index (AHI) $\geq$20 based on full polysomnography, were identified from the University of Michigan Sleep Laboratory or the outpatient Sleep Disorders Clinic. Exclusion criteria included previous significant facial trauma that caused fracture or facial deformity, head or neck cancer, previous face or neck 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, defibrillator), and known pregnancy.

***Control Subjects.*** Twenty patients without a generalized neuromuscular (neuropathy, myopathy, or neuromuscular junction) disorder were identified from the University of Michigan EMG laboratory after performing an EMG study for clinical purposes. The aforementioned exclusion criteria for OSA subjects were also applied for controls. The Berlin questionnaire was used to exclude those with a high risk of sleep apnea.[8] Control subjects were initially individually matched on age $\pm$5 years; this was later expanded to $\pm$7 years.

**Abbreviations:** AHI, apnea–hypopnea index; BMI, body mass index; CMAP, compound muscle action potential; CPAP, continuous positive airway pressure; EMG, needle electromyography IQR, interquartile range; NCS, nerve conduction studies; OSA, obstructive sleep apnea

**Key words:** clinical neurophysiology, EMG, hypoglossal nerve, nerve conduction studies, sleep apnea

**Correspondence to:** D.L. Brown; e-mail: devinb@umich.edu



Published online 7 May 2010 in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/mus.21690

**Study Procedures.** Reports of diagnostic polysomnograms performed in a sleep laboratory accredited by the American Academy of Sleep Medicine were used to determine initial sleep apnea severity for each OSA subject. Studies had been recorded following standard techniques, and they were scored by technologists using previously described quality-control methods and published scoring criteria,[9] similar to those recommended for clinical research and clinical studies.[10,11] Obstructive sleep apnea for this study was defined by an AHI $\geq$20 with obstructive apneas plus hypopneas exceeding the number of central apneas. This non-standard AHI threshold was selected to maximize the chances of finding a difference between OSA and control subjects by eliminating those with less severe disease. Medical records were reviewed, and a history of diabetes was abstracted, supplemented by patient report. Height and weight were self-reported. The speech of each subject was assessed during the encounter by an EMG technologist, and presence of dysarthria was noted. The electrophysiological studies were performed by a registered EMG technologist or a board-certified neurologist with fellowship training in EMG.

***Cranial Nerve Testing.*** A right hypoglossal (cranial nerve 12) NCS was performed on all subjects using a standard published technique (Fig. 1).[12] Both a recording and a reference electrode, positioned 2 cm apart on a tongue blade, were placed on the dorsal surface of the hemi-tongue, over intrinsic tongue muscles. A ground electrode was placed on the cheek. Bipolar percutaneous stimulation using a 0.02-ms duration, 100-mA electrical stimulus was applied along the base of the mandible, with pressure applied to the stimulator.[12,13] The duration of the electrical stimulus was gradually increased until a supramaximal compound muscle action potential (CMAP) waveform was achieved.

***Limb Testing.*** Control subjects were recruited from patients who had nerve conduction studies performed as clinically indicated for mononeuropathies ($n = 8$); unilateral upper extremity numbness, pain, or weakness ($n = 5$); unilateral lower extremity numbness, pain, or weakness ($n = 1$); bilateral upper extremity symptoms ($n = 1$); bilateral lower extremity symptoms ($n = 4$); or four extremity distal numbness or burning ($n = 1$). Twelve control subjects had only upper extremity NCS, but no symptoms or examination findings to suggest lower extremity abnormalities. Seven of the controls had abnormal EMGs, including unilateral median neuropathy at the wrist ($n = 3$), ulnar neuropathy at the elbow ($n = 2$), lateral antebrachial cutaneous mononeuropathy ($n = 1$), and tibial neuropathy ($n = 1$). The OSA subjects had limb NCS performed in accordance with the following protocol: sural sensory and peroneal motor NCS were performed in the right leg. If both studies were normal, no further NCS were performed. Otherwise, additional NCS were performed in accordance with established research NCS standards.[14] Lower limb surface temperatures were maintained above 32°C. Polyneuropathy was defined as electrodiagnostic evidence of an abnormal amplitude or latency of the sural sensory NCS and one other separate nerve.[14]

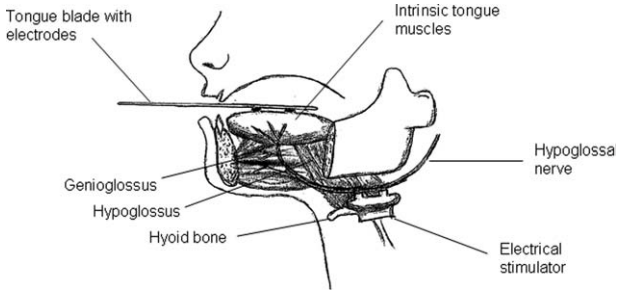


**FIGURE 1.** Hypoglossal nerve conduction testing.

**Statistical Methods.** Baseline characteristics were calculated using frequencies and percents, or medians and interquartile ranges (IQRs), and were compared between OSA subjects and controls using the Wilcoxon rank-sum tests or Fisher's exact tests. The percentage of abnormal hypoglossal NCS values was calculated based on published normal values. Values were designated as abnormal if they were not within this 95% confidence interval (CI).[13] The Wilcoxon signed-rank test was used to compare hypoglossal nerve amplitudes and latencies between OSA and control subjects. These analyses were repeated to exclude pairs where the OSA subject had NCS results consistent with polyneuropathy. To test the discriminatory ability of the hypoglossal amplitude value in separating OSA from control subjects, we calculated the c-statistic. Statistical analyses were performed using S-Plus (version 7.0) for Windows and SAS (version 9.1) for Windows. The project was approved by the institutional review board of the University of Michigan. Written informed consent was obtained from each subject.

## RESULTS

Baseline characteristics of the 20 OSA subjects and 20 age-matched controls are reported in Table 1. The median AHI on diagnostic polysomnograms for patients with OSA was 47 (range 28–68); the median minimum oxygen saturation was 88% (85–90). Only 3 (15%) OSA subjects were not using positive airway pressure therapy. Five (25%) of the OSA subjects were found to have polyneuropathy using NCS criteria. None of the controls had

**Table 1.** Baseline characteristics, expressed as median (interquartile range) or number (%).

| | OSA ($n = 20$) | Control ($n = 20$) | *P*-value |
|---|---|---|---|
| Age | 48 (39–52) | 47 (42–52) | 0.85 |
| Male | 15 (75%) | 11 (55%) | 0.32 |
| Height (inches) | 70 (66–72) | 68 (65–71) | 0.49 |
| Weight (pounds) | 233 (209–276) | 187 (170–215) | 0.0027 |
| Body mass index | 32 (30–41) | 28 (26–30) | 0.0019 |
| Diabetes | 4 (20%) | 0 (0%) | 0.11 |
| Hypertension | 10 (50%) | 6 (30%) | 0.14 |
| Ischemic stroke | 1 (5%) | 1 (5%) | 1.00 |

*OSA, obstructive sleep apnea.*

evidence of polyneuropathy, as dictated by the exclusion criteria. Of the 9 control subjects who had sural NCS performed, none had an abnormal latency or amplitude. Sural nerve testing, in both the entire group and the 15 pairs without polyneuropathy, showed conflicting results: the amplitudes were lower in the OSA group and the latencies were longer in the control group (Tables 2 and 3). No subject had dysarthria.

Compared with published normal values, 13 (65%) of the OSA subjects had an abnormal hypoglossal CMAP amplitude, and 10 (50%) had an abnormal latency. In contrast, 3 (15%) of the control subjects had an abnormal hypoglossal amplitude, and 4 (20%) had an abnormal latency. Amplitudes were significantly reduced, but prolongation of latencies did not show significant differences between OSA subjects and controls (Table 2). The c-statistic for hypoglossal amplitude was 0.81. This suggests good discrimination between OSA and control subjects. Among the 15 pairs of subjects without polyneuropathy, the reduced amplitudes in OSA subjects were borderline significant (Table 3).

## DISCUSSION

This prospective study of 20 OSA patients and 20 individually age-matched control subjects shows that OSA patients have NCS findings suggestive of a hypoglossal mononeuropathy compared with controls, and that this difference cannot be attributed to a generalized polyneuropathy. If OSA causes hypoglossal mononeuropathy, the possible etiologies include 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.[15] However, it remains unclear whether vibration during snoring is sufficient to produce hypoglossal nerve injury. Nerve ischemia generally affects large myelinated axons, which reduces CMAP amplitude and slows distal nerve conduction. However, we cannot explain how ischemia might affect the hypoglossal nerve and not peripheral nerves more generally. To our knowledge, relative ischemic thresholds of hypoglossal nerves, as compared with other nerves, have not been studied.

Our findings are complemented by a recent needle EMG study[16] that found increased duration and area of genioglossus motor unit action potentials in OSA patients. This finding is consistent with prior denervation and subsequent reinnervation due to 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. Although we did not directly assess for primary muscle pathology, our findings are

**Table 2.** Comparison of nerve conduction results between OSA ($n = 20$) and control ($n = 20$) subjects.

| | OSA median (IQR) | Control median (IQR) | *P*-value |
|---|---|---|---|
| Hypoglossal nerve amplitude (mV) | 2.35 (1.60–3.38) | 4.45 (3.45–5.43) | 0.01 |
| Hypoglossal nerve distal latency (ms) | 2.75 (2.20–2.93) | 2.38 (2.04–2.66) | 0.10 |
| Sural peak latency* | 3.3 (3.1–3.6) | 3.7 (3.7–3.9)† | 0.01 |
| Sural amplitude* | 8.6 (6.3–14.3) | 20.6 (14.8–24.2)† | 0.002 |
| Sural NCV* | 47.5 (41.0–53.8) | 48.3 (43.8–48.3)† | 0.9 |
| Peroneal distal latency* | 4.7 (4.2–5.2) | 4.3 (4.0–4.9)† | 0.4 |
| Peroneal amplitude* | 4.9 (2.8–7.6) | 5.2 (4.0–9.4)† | 0.3 |
| Peroneal NCV* | 43.5 (40.0–46.3) | 47.0 (45.9–49.3)† | 0.03 |

**When the nerve conduction was not recordable, a score of zero was assumed.*
*†Measurements from controls were done on a limited sample: sural ($n = 9$) or peroneal ($n = 8$).*

**Table 3.** Comparison of nerve conduction results between OSA patients without polyneuropathy ($n = 15$) and their age-matched control subjects ($n = 15$).

| | OSA median (IQR) | Control median (IQR) | *P*-value |
|---|---|---|---|
| Hypoglossal nerve amplitude (mV) | 2.40 (1.95–3.15) | 4.10 (3.45–5.25) | 0.05 |
| Hypoglossal nerve distal latency (ms) | 2.60 (2.20–2.90) | 2.15 (2.00–2.58) | 0.15 |
| Sural peak latency* | 3.30 (3.25–3.60) | 3.75 (3.63–3.88)† | 0.03 |
| Sural amplitude* | 13.50 (8.10–15.00) | 21.30 (12.65–28.83)† | 0.05 |
| Sural NCV* | 50.00 (46.70–53.80) | 47.50 (44.52–48.30)† | 0.29 |
| Peroneal distal latency* | 4.50 (4.15–5.05) | 4.10 (4.00–4.80)† | 0.33 |
| Peroneal amplitude* | 7.00 (3.10–7.70) | 4.25 (3.85–8.10)† | 0.97 |
| Peroneal NCV* | 44.00 (41.55–47.75) | 46.75 (45.82–51.05)† | 0.20 |

*When the nerve conduction was not recordable, a score of zero was assumed.
†Measurements from controls were done on a limited sample ($n = 6$).

consistent with a hypoglossal neuropathy, which could explain some of the pathological muscle findings others have identified in OSA.[17]

Oropharyngeal muscle histopathology in OSA patients has been attributed at times to a myopathy[6,7,18,19] postulated to result from "activity-induced injury."[19] Other investigators, however, have interpreted the pathological changes to be of unclear etiology, or ascribed them to both neurogenic and myopathic causes.[20,21] Some recent histopathological investigations of uvulopalatopharyngoplasty samples clearly demonstrated muscle fiber type grouping, grouped atrophy, and angulated atrophic fibers consistent with denervation and reinnervation from axonal loss without histopathological evidence of a primary myopathy.[22] Genioglossus biopsies have demonstrated increased type II muscle fibers in OSA patients compared with controls,[17] another finding consistent with motor nerve partial denervation that is notably absent in OSA patients treated with chronic continuous positive airway pressure (CPAP).[3] As peripheral nerve denervation and reinnervation can result in loss of muscle force and power,[23] loss of hypoglossal axons to oropharyngeal muscles could increase susceptibility to airway collapse. This suggests that hypoglossal nerve dysfunction may promote OSA. The genioglossus is an important pharyngeal dilator, and decreases in genioglossal activity during sleep are greater in OSA patients than controls.[24] Furthermore, stimulation of the hypoglossal nerve may relieve upper airway obstruction in OSA.[25,26] 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 may in turn worsen OSA.

Peripheral neuropathy, and more specifically an axonal pattern of sensory nerve dysfunction, has been identified in OSA.[27–29] Treatment with CPAP may improve this peripheral neuropathy,[29] which suggests that OSA may be causally related to a sensory peripheral neuropathy. However, when we excluded subjects with electrodiagnostic evidence of a generalized peripheral neuropathy, hypoglossal nerve dysfunction was still apparent in those with OSA. Therefore, the hypoglossal nerve abnormalities that we identified in OSA subjects seem unlikely to result from a widespread large-fiber neuropathic process. The limb NCS results interestingly showed lower sural amplitudes in the OSA subjects and longer latencies in the controls, which is difficult to reconcile. However, these differences are not likely to be clinically significant given that the interquartile ranges did not cross the normal value threshold.[30] We therefore postulate that the differences resulted from chance.

Among the limitations of our study, sleep apnea in the control subjects was excluded based on a validated questionnaire rather than the "gold standard" of polysomnography. However, inadvertent inclusion of some subjects with OSA in the control group would have decreased our ability to identify a difference in hypoglossal NCS. Furthermore, it is possible that the abnormal hypoglossal NCS seen in some controls were due to undiagnosed sleep apnea. Similarly, if CPAP use eventually improves hypoglossal nerve dysfunction, the use of CPAP in most of our OSA subjects would also have reduced rather than enhanced differences between groups. The presence of diabetes was recorded based on known history; patients were not screened for diabetes or pre-diabetes. Because no brain imaging was performed, we do not have information on white-matter hyperintensities or lacunar disease, which may be associated with diabetes, hypertension, and OSA. We also do not have information on possible brainstem abnormalities. However, as all subjects had at least screening NCS, subclinical large-fiber diabetic neuropathy should have been identified.[14] Control subjects who did not have lower extremity NCS could have had mild subclinical polyneuropathy; however, this

could only have decreased the differences between groups.

There was a small but significant difference in body mass index (BMI) between the OSA and control groups. Although BMI has been shown to be associated with small reductions in amplitude and slightly faster velocities in sensory and mixed nerves, a consistent relationship between BMI and motor amplitudes or latencies has not been identified.[31,32] Even the microvolt differences in sensory and mixed nerve amplitudes related to BMI[31] are not taken into account in clinical EMG interpretation. Furthermore, although fat in the tongue increases with increasing BMI in the posterior tongue, BMI is not known to correlate with fat in the intrinsic tongue muscles, the region of the tongue with the lowest fat content.[33] Taken together, this information argues against BMI as a confounder in the current study.

This study has provided new evidence of oropharyngeal nerve dysfunction in OSA by means of a non-invasive technique. However, our data cannot definitively determine whether hypoglossal nerve dysfunction is caused by OSA and/or is in part responsible for OSA, or is an epiphenomenon. Further research is necessary to understand the relationship between hypoglossal nerve function and upper airway collapse. Future studies could include hypoglossal NCS in OSA patients who do not snore as well as longitudinal assessment of newly diagnosed OSA patients with and without treatment with CPAP.

This study was supported by Career Development Awards (K23 NS055200 to K.L.G., K23 NS050161 to L.D.L., and K23 NS051202 to D.L.B.) from the National Institute of Neurological Disorders and Stroke (NINDS). The investigators were supported by these grants, not the project per se.

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