Neurogenic Changes in the Upper Airway of Patients with Obstructive Sleep Apnea

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Rationale: Controversy persists regarding the presence and importance of hypoglossal nerve dysfunction in obstructive sleep apnea (OSA).

Objectives: We assessed quantitative parameters related to motor unit potential (MUP) morphology derived from electromyographic (EMG) signals in patients with OSA versus control subjects and hypothesized that signs of neurogenic remodeling would be present in the patients with OSA.

Methods: Participants underwent diagnostic sleep studies to obtain apnea-hypopnea indices. Muscle activity was detected with 50-mm concentric needle electrodes. The concentric needle was positioned at more than 10 independent sites per subject, after the local anatomy of the upper airway musculature was examined by ultrasonography. All activity was quantified with subjects awake, during supine eupneic breathing while wearing a nasal mask connected to a pneumotachograph. Genioglossus EMG signals were analyzed offline by automated software (DQEMG), which extracted motor unit potential trains (MUPTs) contributed by individual motor units from the composite EMG signals. Quantitative measurements of MUP templates, including duration, peak-to-peak amplitude, area, area-to-amplitude ratio, and size index, were compared between the untreated patients with OSA and healthy control subjects.

Measurements and Main Results: A total of 1,655 MUPTs from patients with OSA ($n = 17$; AHI, $55 \pm 6/h$) and control subjects ($n = 14$; AHI, $4 \pm 1/h$) were extracted from the genioglossus muscle EMG signals. MUP peak-to-peak amplitudes in the patients with OSA were not different compared with the control subjects (397.5 ± 9.0 vs. $382.5 \pm 10.0 \mu V$). However, the MUPs of the patients with OSA were longer in duration (11.5 ± 0.1 vs. 10.3 ± 0.1 ms; $P < 0.001$) and had a larger size index (4.09 ± 0.02 vs. 3.92 ± 0.02 ; $P < 0.001$) compared with control subjects.

Conclusions: These results confirm and quantify the extent and existence of structural neural remodeling in OSA.

Keywords: motor unit; respiration; tongue; genioglossus; respiratory

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AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Several studies have supported sensory and motor impairments in the upper airway of patients with obstructive sleep apnea. Complex interactions of vibration, inflammation, and hypoxia are reported to contribute. The structure, and innervation, of hypoglossal nerve activity to muscles of the upper airway may affect the neural drive, but is not fully understood.

What This Study Adds to the Field

Structural remodeling of the peripheral branches of the hypoglossal nerve that innervates the largest upper airway dilator muscle (genioglossus) occurs in obstructive sleep apnea. These alterations, collectively referred to as *neurogenic changes*, are likely to arise as a result of denervation, collateral sprouting, and reinnervation.

Controversy remains in the obstructive sleep apnea (OSA) field as to how upper airway neurogenic changes may relate to disease pathogenesis/progression (1, 2). Changes in nerve and muscle function may occur in the pharynx of patients with OSA as a result of the disease (e.g., vibration through snoring [3–5] or hypoxemia [6]), potentially contributing to diminished upper airway muscle function. The muscles of the upper airway including the genioglossus, palatopharyngeus, pharyngeal constrictors, and musculus uvulae in patients with OSA contain a high percentage of type II muscle fibers compared with non-OSA control subjects (7–12), a difference that may represent an adaptive response to mechanical strain and/or neuronal activity. Deeper extrinsic dilator muscles, such as the genioglossus, may also be affected by neurogenic alterations (13), possibly contributing to the observed increase in genioglossus activity (“compensatory neural drive”) in patients with OSA (14).

Motor unit potential (MUP) durations are increased in neurogenic disorders and, thus, neuromuscular dysfunction can be assessed by MUP analysis (15–17). Increased MUP duration has been attributed to motor unit remodeling as a result of denervation, collateral sprouting, and reinnervation (18–20). Motor units that have reinnervated orphaned fibers will have greater numbers of muscle fibers, and thus typically produce MUPs with an increased area (21). By combining various electrophysiological techniques to study motor units (17, 22), both temporal and spatial resolution can be maximized to explore neuromuscular function in the

TABLE 1. SUBJECT DEMOGRAPHICS FOR STUDY POPULATIONS

Subject Characteristic	Control	OSA
Subjects	14	17
Age, yr	34.4 ± 2.8	42.3 ± 2.4*
Number of units	700	955
Female/male	6/8	2/15
Apnea–hypopnea index, events per hour of sleep	3.7 ± 0.7	54.8 ± 6.1*
Height, cm	169.9 ± 3.2	177.1 ± 2.1
Weight, kg	86.1 ± 7.6	100.7 ± 4.5
Body mass index, kg/m ²	29.4 ± 1.9	32.2 ± 1.4
Neck size, cm	38.4 ± 1.2	42.5 ± 0.7*
Number of units per subject	50.0 ± 4.8	56.2 ± 5.8
Inferior margin of geniohyoid muscle, mm	14.5 ± 1.0	16.1 ± 1.1
Inferior margin of genioglossus muscle, mm	23.8 ± 0.9	26.8 ± 1.0*
Genioglossus width, mm	17.8 ± 0.6	18.2 ± 0.5
Modified Borg Scale score, 0–10	2.6 ± 0.4	2.1 ± 0.2

Definition of abbreviation: OSA = obstructive sleep apnea.

The modified Borg Scale was used to measure the “worst level of pain” experienced by each subject during the recording, with 0 = nothing at all and 10 = maximal.

Values represent means ± SEM, unless otherwise specified.

**P* < 0.05.

upper airway. Whereas selective concentric needle electrodes assess the closest muscle fibers of a motor unit (providing local muscle fiber information [21, 23]), the large detection surface of a concentric needle macro (CNMACRO) electrode provides a more global view of the whole motor unit (24, 25) (see Figure E1 in the online supplement). Thus, in early stages of neuromuscular disorders such as amyotrophic lateral sclerosis and polio, MACRO MUPs typically increase in size, indicating compensatory reinnervation phenomena for the loss of motoneurons (16, 26, 27). Further, the area of the CNMACRO MUP predicts the twitch force generated by the motor unit (28) and, therefore, provides unique insight into the contribution to the muscle force output from a single motor unit. Neuromuscular dysfunction may be important in sleep apnea if such changes contribute to impaired

upper airway motor control, increased pharyngeal collapsibility, and/or muscle fatigue (4, 5, 9, 19, 29–37).

To assess the extent of neuromuscular changes in patients with OSA, we measured the morphology of populations of selective concentric and CNMACRO MUPs. We hypothesized that patients with OSA will have measureable evidence of collateral sprouting, manifested through a larger number of phases and turns yielding more complex potentials, in comparison with control subjects. Such findings could be indicative of reinnervation and potentially important in OSA pathogenesis, helping to define new therapeutic targets for OSA. Preliminary data have been presented as abstracts (38, 39).

METHODS

Further methodological detail is provided in the online supplement. Thirty-three people signed our institutional review board–approved consent form, 2 were excluded for technical reasons, and of the remainder, 17 had OSA and 14 were control subjects (demographics in Table 1). These recordings were all completed at the Brigham and Women’s Hospital in Boston, Massachusetts and all subjects were recruited specifically for this investigation. All subjects were screened to exclude major medical and/or neurological disorders, other than OSA. The local anatomy of the upper airway musculature of each participant was examined by ultrasonography (13, 40) (Table 1).

With the subjects relaxed and lying supine a small reference location was drawn 10 mm posterior to the genial tubercle, and the chin was thoroughly cleaned before the insertion of two concentric needle electrodes into the genioglossus (>25.5 mm). Under topical anesthetic, the first concentric needle was used as a CNMACRO electrode and was positioned approximately 10 mm beyond the genioglossus/geniohyoid aponeurosis, where it remained in position for the entire recording procedure; such that it had a constant recording length. The second selective concentric needle electrode was initially positioned to the same depth and in close proximity (~4 mm) to the CNMACRO electrode, but was manipulated to detect MUPs at independent positions.

Concentric needle signals were filtered (10 Hz to 10 kHz) and amplified (×200 μV) (Sapphire 2; TECA, Pleasantville, NY). The CNMACRO signals were detected with the cannula of the CNMACRO referenced to a remote surface electrode (24). The CNMACRO signals were filtered (10 Hz to 6 kHz) and amplified (×10k). A ground was

Figure 1. Typical example of genioglossus data with four motor units concurrently active during quiet breathing. Shown is a typical example of data extracted from a recording from a single subject. From bottom to top: respiratory airflow, selective concentric needle electromyography (EMG), concentric needle macro (CNMACRO) EMG (recorded from the cannula of the concentric needle), tidal volume, and the instantaneous discharge frequency of four single motor units extracted after the decomposition of the raw composite concentric needle EMG signal. Inset: The averaged selective concentric needle motor unit potential (MUP) templates and the ensemble averaged CNMACRO MUPs. Calibrations of the selective concentric needle MUPs and CNMACRO MUPs, 100 μV and 2 milliseconds.

Figure 2. Neurophysiological features measured from the selective concentric needle motor unit potential templates. Selective concentric needle motor unit potential (MUP) analysis provides quantitative insight into the physiology of the motor unit. As such, it is possible to differentiate the normal muscle from neurogenic injury by MUP analysis. Global features included in the analysis were the duration of the motor unit potential as measured between the onset of the first and the offset of the last peak of the MUP (22). Duration is related to the number of muscle fibers contributing to the motor unit. Peak-to-peak amplitude is calculated as the voltage difference of the MUP and is determined by the diameter and number of muscle fibers closest to the electrode. Area is calculated by measuring the rectified MUP (over the duration). Area is less sensitive to measurement error than amplitude and is able to characterize atypical potentials. The number of phases (indicated by the black numbered circles) of the MUP are defined as the number of baseline crossings. The number of turns are defined as a change in the direction of the MUP waveform with a magnitude of at least 25 μ V. To quantify further MUP complexity, a number of indices were used, including the following: area/phase ratio, which is better able to distinguish myopathic MUPs from normal MUPs than area alone. The area/amplitude ratio (63) and size index are parameters that assist in discriminating between neurogenic and normal MUPs and control for the influence of needle position (43). The relative irregularity coefficient (45) captures the complexity of the MUP by quantifying detailed features of the MUP and is calculated as follows: $RIR = [(S - 2A)/2A] \times 100$ (where A is the amplitude, and S is calculated as the sum of the absolute values of the intersample changes seen in the MUP waveform template, i.e., the irregularity in the MUP template). Thus, with partial denervation there is structural remodeling with surviving axons projecting small branches ("collateral sprouting") to reinnervate muscle fibers denervated by the loss of axons. These new branches conduct impulses with a lower velocity over longer distances, reflected as more complex MUP waveforms. All parameter values were manually inspected by a single investigator using DQEMG and who was blinded to subject status. The structures of the concentric needle macro (CNMACRO) MUPs were also measured, using these reference points.

placed over the right clavicle. All electromyographic (EMG) signals were sampled at 25 kHz (Spike2; CED, Cambridge, UK), and stored for offline analysis. During the procedure the subjects had documented

TABLE 2. MATCHED SUBJECT DEMOGRAPHICS: SUBANALYSIS FOR AGE- AND BODY MASS INDEX-MATCHED INDIVIDUALS

Subject Characteristic	Control	OSA
No. of subjects	9	9
Age, yr	37.4 $\pm$ 3.4	37.7 $\pm$ 3.8
Number of units	475	420
Female/male	1/8	1/8
Apnea-hypopnea index, events per hour of sleep	4.2 $\pm$ 1.0	45.9 $\pm$ 8.3*
Height, cm	175.8 $\pm$ 3.3	177.5 $\pm$ 2.7
Weight, kg	97.3 $\pm$ 9.7	95.0 $\pm$ 3.4
Body mass index, kg/m ²	31.2 $\pm$ 2.5	30.3 $\pm$ 1.4
Neck size, cm	41.1 $\pm$ 0.9	41.4 $\pm$ 1.0
Number of units per subject	52.8 $\pm$ 6.7	46.7 $\pm$ 6.7
Inferior margin of geniohyoid muscle, mm	14.1 $\pm$ 1.2	15.7 $\pm$ 1.4
Inferior margin of genioglossus muscle, mm	23.9 $\pm$ 1.2	26.5 $\pm$ 1.2
Genioglossus width, mm	18.3 $\pm$ 0.5	17.7 $\pm$ 0.8

Definition of abbreviation: OSA = obstructive sleep apnea.

Subanalysis included subjects who were matched for age, sex, and body mass index.

Values represent means $\pm$ SEM, unless otherwise specified.

* $P < 0.05$.

wakefulness as they breathed through a nasal mask attached to a pneumotachograph. All the recordings (Figure 1) were obtained without the subject's experiencing pain as measured on the basis of a 0- to 10-point Borg Scale (13).

Extraction of Single Motor Unit Activity

Customized software (Spike2 scripts) converted the EMG signals into DQEMG format. Motor unit potential trains (MUPTs) were extracted from both the concentric needle EMG signals offline, using the DQEMG analysis system (version 3.4, revision 166) (41, 42). MUPs from EMG signals were decomposed on the basis of absolute threshold detection criteria (slope threshold, 0.3 V/s; amplitude threshold, 50 μ V; time interval, 0.2 ms). MUPs were averaged for each MUPT from both the selective concentric needle and CNMACRO signals. Measured MUP template features included the following: duration, amplitude, area, number of phases, and number of turns (see Figure 2). Calculations of area-to-amplitude ratio; size index (43), calculated as $2 \times \log_{10}[\text{amplitude (mV)}] + [\text{area/amplitude (ms)}]$; and relative irregularity coefficient (44, 45), calculated as $RIR = [(S - (2 \times \text{amplitude})) / (2 \times \text{amplitude})] \times 100$ (S is calculated as the absolute value of the intersample changes seen in the MUP template) were made. All MUP

TABLE 3. KEY RESULTS FROM 31 SUBJECTS

Subject Characteristic	Control	OSA
Number of units	700	955
Duration, ms	10.3 $\pm$ 0.1	11.5 $\pm$ 0.1*
Amplitude, μ V	382.5 $\pm$ 10.0	397.5 $\pm$ 9.0
Area, μ V $\cdot$ ms	514.6 $\pm$ 13.3	589.7 $\pm$ 12.2*
Phases	2.8 $\pm$ 0.03	3.0 $\pm$ 0.03*
Turns	3.6 $\pm$ 0.06	3.8 $\pm$ 0.05*
Area-to-amplitude ratio	1.4 $\pm$ 0.02	1.6 $\pm$ 0.02*
Size index	3.9 $\pm$ 0.02	4.1 $\pm$ 0.02*
Relative irregularity coefficient	19.4 $\pm$ 0.7	25.9 $\pm$ 0.7*
Area/phase, μ V $\cdot$ ms	182.9 $\pm$ 4.6	203.1 $\pm$ 4.3*
MUPTs/contraction	3.1 $\pm$ 0.1	3.5 $\pm$ 0.1*
Mean firing rate, Hz	17.0 $\pm$ 0.2	17.7 $\pm$ 0.2
Number of CNMACRO units	446	668
CNMACRO duration, ms	13.0 $\pm$ 0.3	14.9 $\pm$ 0.3*
CNMACRO amplitude, μ V	42.9 $\pm$ 2.0	57.6 $\pm$ 2.1*
CNMACRO area, μ V $\cdot$ ms	106.2 $\pm$ 4.4	143.6 $\pm$ 5.2*
CNMACRO size index	4.3 $\pm$ 0.1	4.3 $\pm$ 0.1

Definition of abbreviations: CNMACRO = concentric needle macro; MUPTs = motor unit potential trains; OSA = obstructive sleep apnea.

Values represent means $\pm$ SEM, unless otherwise specified.

* $P < 0.05$.

Figure 3. Measured and calculated variables from the selective concentric needle and concentric needle macro (CNMACRO) motor unit potentials (MUPs). Histogram display with the patients with obstructive sleep apnea (OSA) depicted in *black* and control subjects in *white*. Gray opacity depicts where there is overlap in the distribution of results for patients with OSA and control subjects. Medians are indicated by arrows in each panel, and in each circumstance the value for control subjects is at *left* and the distribution for patients with OSA is shifted to the *right*. (A–G) The measured variables from selective concentric needle MUPs, including the following: (A) duration, (B) peak-to-peak amplitude, and (C) area. (D–G) The calculated variables from the concentric needle MUPs, including the following: size index calculated as $2 \times \log_{10}(\text{amplitude (mV)}) + (\text{area/amplitude (ms)})$ (D), area to amplitude ratio (E), area/phase ratio (F), and relative irregularity coefficient (G). (H–J) The measured variables from CNMACRO MUPs, including the following: (H) duration, (I) amplitude, and (J) area. Significance is given where appropriate in the respective panels.

feature values of all the subjects were evaluated by a single investigator in accordance with standardized criteria (22).

A subanalysis was performed on nine patients with OSA and nine control subjects (Table 2) matched for age, sex, and body mass index (BMI). Statistical differences were assessed by one-way analysis of variance (ANOVA) and, when data were not normally distributed, then Kruskal-Wallis ANOVA on rank was performed with Dunn's method post-hoc analysis. Statistical significance was set at $P < 0.05$. Values are given as means $\pm$ SEM unless otherwise specified.

RESULTS

Total Analysis

Data were extracted from 31 subjects, yielding a total of 503 successful unitary recordings from the genioglossus muscle with concentric needle and CNMACRO electrodes (Table 1). From these detected signals a total of 1,655 valid MUPTs were

extracted from the selective concentric needle (OSA, 955; control subjects, 700), and 1,114 CNMACRO MUPs were identified with the aid of DQEMG (OSA, 668; control subjects, 446). On average, the number of MUPTs extracted per recording was higher for the patients with OSA compared with the control subjects (3.4 ± 0.1 vs. 3.1 ± 0.1 ; $P < 0.05$, Dunn's method).

Motor Unit Potentials

All MUPTs extracted from selective concentric needle EMG signals were detected during normal eupneic breathing. An example of a typical recording is shown in Figure 1. Selective concentric needle MUPs detected in the patients with OSA had longer durations, greater area, and larger size index, area-to-amplitude ratio, and relative irregularity ratio, but not greater amplitude, than control subjects (*see* Table 3, Figures 3, 4A–F, and 5; and Supplementary Table E1 for one value/

Figure 4. Mean measured and calculated variables from the concentric needle motor unit potentials. Each panel represents key averaged variables measured and calculated from all the individual concentric needle motor unit potentials (MUPs). The solid columns depict patient with obstructive sleep apnea (OSA) data and the shaded columns represent control subject data. Significance is given where appropriate in the respective panels.

subject). Although the initial aims of the study did not include age as a factor, age was retrospectively studied. We did not observe an interaction between age and groups (Figure E1). The more complex MUPs, measured on the basis of the relative irregularity, were detected in the patients with OSA and an association was found with minimal oxygen saturation detected from the overnight polysomnography examination ($r = -0.639$, $P = 0.0002$; Figure 6).

CNMACRO Motor Unit Potentials

The CNMACRO MUPs are more sensitive than selective concentric MUPs to changes in the total number of muscle fibers than to local reorganization of muscle fibers within a motor unit (46). Therefore, they can be used to measure reinnervation in terms of the number of active muscle fibers in a motor unit. CNMACRO potentials resemble a small surface-detected motor response. An example of a typical recording is shown in Figure 1. All CNMACRO MUPTs were estimated by trigger-averaging the cannula (CNMACRO needle electrode was

maintained at a constant depth of approximately 10 mm, based on ultrasound measures)-detected EMG signals at the times of individual motor unit discharges during normal eupneic breathing. Not all sites that detected an MUP had an adequately measureable CNMACRO MUP. CNMACRO MUPs detected in the patients with OSA had longer durations, larger amplitudes, and greater areas than those detected in control subjects (Figure 3G–I and Figure 5).

Subanalysis of Matched Groups

To control for the variation in age between the patients with OSA and control subjects, a subanalysis was performed on nine age-, sex-, and BMI-matched subjects (see Table 2 for demographic properties). This analysis included 420 MUPs from patients with OSA and 475 from control subjects (for results see Table 4; and Table E2 for one value/subject). In this analysis selective concentric needle MUPs of the patients with OSA had a longer duration, greater area, larger amplitude ratio, larger size index, and greater area-to-amplitude ratio, but not greater

Figure 5. Mean measured variables from the concentric needle macro (CNMACRO) motor unit potentials (MUPs). Each panel represents key averaged variables measured and calculated from all the individual CNMACRO MUPs. The *solid columns* depict patient with obstructive sleep apnea (OSA) data and the *shaded columns* represent the control subject data. Significance is given where appropriate in the respective panels.

amplitude compared with the control subjects. The average number of MUPTs per recording was not larger in the patients with OSA compared with the matched control subjects. Consistent with the larger group comparison, CNMACRO MUPs detected in the matched patients with OSA resemble neurogenic MUPs with larger amplitudes (47) and greater indices than those detected in control subjects (Table 4).

DISCUSSION

Our study supports the hypothesis that patients with OSA have neurogenic changes in the genioglossus. We found MUP waveforms with increased durations, areas, and complexities, suggesting the peripheral axons have sprouted to adjust to changes in physiological requirements. These findings are similar to those seen in neuropathies, for example, vibration-induced injuries (48, 49). These data strongly indicate the presence of “neurogenic” changes in OSA (6, 10, 11, 13, 19, 30–32, 36, 50–52).

Established EMG techniques are available to study subtle changes in motor units (17, 22). We combined two techniques: (1) selective concentric needle electrodes to detect primarily from the closest muscle fibers of a motor unit, together with (2) the nonselective recordings of concentric needle macro (CNMACRO) electrodes, to assess the density and distribution of the whole cross-section of a motor unit (21, 23). For diagnosing neuromuscular disorders (15), MUP measurements are reliable indicators that have been well validated by histology (53). Our selective concentric needle data show evidence for

Figure 6. Mean relative irregularity coefficient versus minimal oxygen saturation. More complex motor unit potentials (MUPs), as calculated with the relative irregularity, are associated with minimal oxygen saturation detected from the overnight polysomnography examination. The Pearson correlation coefficient was calculated from the mean value of 29 subjects ($r = -0.639$; $P = 0.000188$). The *open circles* depict the healthy control subjects while *solid circles* depict the untreated patients with obstructive sleep apnea. The two *open squares* on the x axis represent two control subjects from whom minimal oxygen data were not obtained (not included in the correlation).

a 14% increase in MUP duration, a finding consistent with reinnervation due to an increased number of fibers innervated by a single axon (18–20, 54). This finding is supported by Boyd and colleagues (30), who elegantly demonstrated an overexpression of neural cell adhesion molecule protein in palatal muscles of patients with OSA, a finding that implies active collateral sprouting. Furthermore, we found that the complexity of the MUP waveforms (as assessed by the relative irregularity coefficient [44, 45], i.e., normalized length of MUP) to be increased by 33% in patients with OSA and to correlate with minimal oxygen desaturations (see Figure 6). The OSA compensatory neural drive hypothesis is supported by evidence that the amplitude of the multiunit EMG is increased in patients with OSA (14). As the multiunit electromyogram is dependent on the number and complexity of MUPs it is often used as an estimate of the neural drive to the muscle. Genioglossus multiunit EMG amplitude corresponds to the sum of MUPs. Thus, changes in the global features of MUPs (see Figure 2) can influence motor unit potential summation and modulate EMG amplitude independent of the output from the hypoglossal nerve (e.g., Reference 53). Direct associations connecting MACRO MUP size and muscle force have been previously established (25, 27, 28, 55). Thus, the increased CNMACRO potentials (see Figure 5) may indicate that the genioglossus motor units in patients with OSA have increased force generation per activation. The observed increase in MUPs is also consistent with previous investigations that have shown histological differences in muscle fiber types in snorers and patients with OSA (7–9, 11, 12, 56). Thus, genioglossus muscle fibers in patients with OSA may have the ability to produce higher twitch forces, although possibly at the expense of longer recovery times, that is, fatigability (9, 57, 58).

The cross-sectional design of this study means that it is not possible to identify the causative nature of this remodeling. Although it is likely that neurogenic changes are due to the mechanical strain induced by tissue vibration (48), negative pharyngeal pressure swings may also result in eccentric muscle contractions causing

TABLE 4. KEY RESULTS FROM SUBANALYSIS OF NINE MATCHED SUBJECTS

Subject Characteristic	Control	OSA
Number of units	475	420
Duration, ms	10.18 ± 0.16	11.62 ± 0.17*
Amplitude, μ V	390.33 ± 12.40	377.67 ± 12.56
Area, μ V·ms	525.77 ± 16.01	595.76 ± 18.23*
Phases	2.87 ± 0.03	2.99 ± 0.04
Turns	3.61 ± 0.07	3.71 ± 0.07
Area-to-amplitude ratio	1.44 ± 0.02	1.64 ± 0.03*
Size index	3.94 ± 0.03	4.14 ± 0.03*
Relative irregularity coefficient	20.43 ± 0.87	25.38 ± 0.92*
Area/phase	186.20 ± 5.60	204.84 ± 6.45*
MUPTs/contraction	3.4 ± 0.19	3.5 ± 0.18
Mean firing rate, Hz	18.0 ± 0.26	16.8 ± 0.28*
Number of CNMACRO units	288	322
CNMACRO duration, ms	12.69 ± 0.38	13.30 ± 0.54
CNMACRO amplitude, μ V	42.60 ± 2.39	47.96 ± 2.56*
CNMACRO area, μ V·ms	107.58 ± 5.37	112.05 ± 7.34
CNMACRO size index	4.5 ± 0.13	3.9 ± 0.10*

Definition of abbreviations: CNMACRO = concentric needle macro; MUPTs = motor unit potential trains; OSA = obstructive sleep apnea.

Values represent means ± SEM, unless otherwise specified.

* $P < 0.05$.

peripheral nerve damage. We speculate that this damage is likely to occur in the presence of hypoxemia, as has been demonstrated in nerve conduction studies (6). Investigation into the role of neuromuscular dysfunction in patients with OSA remains challenging, as needle biopsies are invasive and the upper airway dilator muscles are difficult to isolate.

Our study has strengths including the use of ultrasound guidance to ensure genioglossus placement of electrodes, in contrast to prior studies (59, 60). In addition, we argue that studying the muscle during eupneic breathing is of the utmost importance in terms of relevance to OSA, in contrast to recording ballistic voluntary tasks as is conventional in diagnostic EMG (59, 60). Last, we assessed a large unbiased sample of motor units in a large number of patients and thus believe we have performed the most thorough electrophysiological evaluation of the upper airway in humans to date.

Despite these strengths, we acknowledge a number of weaknesses. First, our groups were incompletely matched for age, sex, and BMI, although our findings were similar when using an age-, sex-, and weight-matched subset. Thus, we do not expect these factors to confound the results significantly. Third, we were unable to obtain measurements before and after therapy in our patients, which may yield valuable insight into the potential reversibility of the changes observed in future studies. However, we regard the electrophysiological methods used to be robust and well validated (42, 43, 61, 62) and less susceptible to sampling bias than biopsy in humans. Despite these acknowledged limitations, we believe our findings provide an important advance in the literature.

In summary, the results of this study indicate that neurogenic changes occur in patients with OSA. It is likely that no single mechanism can explain all the data concerning the alterations in motor unit potentials observed; rather, it is likely that our findings reflect factors predisposing to OSA combined with effects of snoring-induced vibration injury plus hypoxemia (6, 48, 49). Clearly, structural neurogenic changes are present in patients with OSA. Further work is required to establish how these observed changes affect upper airway muscle function during sleep.

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