Acute upper airway responses to hypoglossal nerve stimulation during sleep in obstructive sleep apnea

On Line Data Supplement/Methods

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Methods

Patient Population

Thirty patients with moderate to severe obstructive sleep apnea were recruited as part of a multi-center clinical trial and implanted with a novel HGNS system (HGNS® Apnex Medical, Inc.), as previously described [1]. Written informed consent for this study was obtained for the protocol, which was approved by the local institutional review boards. Key eligibility criteria for implantation were (a) an apnea-hypopnea index of greater than 20 episodes per hour (predominantly obstructive hypopneas) (b) and a central apnea index of no greater than 5% on a screening overnight sleep study. Patients with concomitant medical illnesses were also excluded. Of these, 30 patients underwent HGNS titration studies consisting of quantitative measures of airflow over a range of HGNS stimulation intensity during sleep, and provide the patient sample herein.

Experimental Techniques

Baseline Sleep Study: Each patient underwent a baseline overnight sleep study to characterize sleep and breathing patterns. Standard polysomnographic techniques were utilized including surface electroencephalograph (EEG) leads (F3-M2, F4-M1, C3-M2, C4-M1, O1-M2, O2-M1), submental electromyogram (EMG), left and right electrooculograms (L. and R. EOG) to stage sleep. A single modified electrocardiogram (ECG) II Lead placement was employed to monitor cardiac rhythm. Respiratory monitoring included oronasal airflow with nasal pressure cannula and thermistor, oxyhemoglobin saturation (SaO2), and the thoraco-abdominal effort gauges (respiratory impedance monitors). Hypopneas were defined by a >50% in airflow amplitude in the nasal pressure cannula signal during sleep, or a discernable reduction in airflow that was associated with either a $\geq$4% oxyhemoglobin desaturation or an arousal from sleep (a 3s shift in EEG frequency). Apneas were defined by a >90%

reduction in airflow from baseline in both the oronasal thermistor and nasal cannula signal for at least 10 seconds.

HGNS Device and Implantation Procedure: Patients were implanted with a bipolar stimulating lead. A guarded bipolar electrode array was mounted within an insulating cuff. The lead included three electrode contacts placed longitudinally along the nerve body. The polarity of the center electrode was opposite that of two flanking electrodes, and served to focus the stimulation current on the nerve itself with stimulating other nearby muscles or nerves.

The neurostimulator, respiration sensing and stimulation leads were surgically implanted under general anesthesia. Briefly, an incision was made below and parallel to the inferior border of the right mandible. The main right hypoglossal nerve trunk was exposed below the submandibular gland and superior to the digastric tendon, distal to branches innervating the styloglossus and hyoglossus muscles. The cuff of the stimulating lead was placed on the hypoglossal nerve and correct cuff placement was verified intraoperatively with fluoroscopic assessment of pharyngeal opening during brief stimulation. The stimulation lead body was then tunneled below the platysma through the neck to the neurostimulator, which was implanted in the ipsilateral infraclavicular space subcutaneously. Two respiratory impedance sensing leads were tunneled subcutaneously toward the midline and then bilaterally along each costal margin. Following surgery, a healing period of approximately 30 days was allowed without stimulation. Adverse events were related to the implantation procedure and are described in Table E1. Serious events requiring surgical intervention included cuff dislodgement (n=2) and hematoma/infection (n=1). Other adverse events occurred transiently following the implantation procedure.

Awake Titration Study: Approximately one month after HGNS implantation, each patient returned to the clinic for an awake titration study. During the awake titration, stimulation amplitude settings were

increased in a step-wise manner to determine the twitch and tongue movement thresholds at which lingual muscle activation and bulk movement were first observed, respectively.

Titration Sleep Study: Following the awake titration, each patient returned to the laboratory for another overnight sleep study to determine the effect of varying the stimulation intensity (current) on tidal airflow during sleep (see below). Sleep and breathing patterns were monitored as described above. In addition, a mask and pneumotachograph were used to monitor airflow and quantify airflow responses to stimulation (n=26) or nasal cannula in those who did not tolerate the mask and pneumotachograph (n=4). Patients monitored with a nasal cannula did not differ from those with pneumotachograph in age, body mass index or apnea-hypopnea index. A hypnotic was utilized to facilitate sleep monitoring as necessary.

Experimental Protocol

The HGNS stimulation system was designed to track the patient's respiratory pattern and stimulate during the inspiratory phase of each respiratory cycle. In contrast to stimulating each breath during standard therapy, this protocol was performed with a custom stimulation delivery mode which stimulated alternating breaths so that responses in inspiratory airflow could be compared to adjacent unstimulated breaths during sleep. HGNS was applied with increasing current amplitudes from 0 to 4 mA while frequency and pulse width was fixed at 40 Hz and 90 μs (n=26) or at 40 Hz and 60 μs (n=4), respectively. Flow responses in patients stimulated with 40 Hz and 60 μs did not differ from those in patients stimulated with 40 Hz and 90 μs, leading us to combine results from all patients in our analyses.

During sleep, stimulus current was titrated from the twitch threshold (n=25) or from bulk tongue movement (n=5) determined during awake titration to maximally tolerated levels (i.e., until patients could no longer reinitiate sleep). Stimulation current was incremented in approximately 0.1 to 0.3 mA

steps until the airflow response to stimulation plateaued or the patient aroused from sleep (see below). Inspirations were stimulated repeatedly at each current level on alternating breaths whereas the standard therapy mode is to stimulate on every breath. Arousals were considered to have occurred if stimulation was accompanied by any shift in EEG rhythm [2] either during or immediately after the stimulation burst, an increase in heart rate , or if maximal inspiratory airflow did not return to baseline levels at the offset of stimulation, as previously described [3].

Data Analysis

Airflow responses to HGNS were characterized during stable periods of NREM sleep as follows. Maximal inspiratory airflow ($V_I$max) was measured during stimulated breaths and adjacent unstimulated breaths during stable NREM sleep, as previously described [3]. At low levels of stimulation, airflow during stimulated breaths was insufficient to stabilize the breathing pattern and breaths were measured during obstructive apneas and hypopneas when stimulated breaths were bracketed by unstimulated breaths of similar $V_I$max amplitude. Breaths were also assessed for the presence or absence of inspiratory flow limitation (IFL or non-IFL) at each stimulation level. In patients studied with nasal cannula (n=4) rather than pneumotachograph (n=26), flow was approximated by taking the root mean square transform of the nasal cannula signal [4]. Flow signals from patients studied with nasal cannula (n=4) and uncalibrated pneumotachograph (n=5) were then scaled to the mean level of stable non-flow limited airflow in same sex patients studied with a calibrated pneumotachograph (n=21). Sensitivity analyses demonstrated no differences in baseline characteristics (demographic, anthropometric, sleep apnea severity indices) and current thresholds at capture and peak flow response thresholds (see below), leading us to combine data from uncalibrated and calibrated groups.

Airflow responses to increasing current were characterized as follows. The *flow capture threshold* was defined by the current level at which airflow increased during stimulation compared to adjacent

unstimulated breaths. The *peak flow threshold* was defined by the minimal current level associated with (a) the elimination of IFL (n=17), or when IFL persisted, (b) a peak in airflow (n=3) or a plateauing of $V_I$max with increasing current (n=10). Airflow at the peak flow threshold was taken to be the *peak flow* obtained during NREM sleep in response to stimulation. It is worth noting that marked decreases in airflow were observed in one patient at high stimulation amplitudes well above the peak flow threshold. Current levels at the flow capture and peak flow thresholds were used to define the *stimulus response slope*, which was taken to be a measure of the sensitivity of the response to stimulation. In addition, *unstimulated baseline levels of airflow* were measured to assess for stability in the state of pharyngeal patency during sleep over the range of current applied.

Statistical Analysis

Paired t-tests were used to compare airflow on and off stimulation (peak vs. baseline) and two-sample t-tests were used to compared demographic, anthropometric and flow response parameters between IFL and non-IFL subgroups. Least squares linear regression was utilized to characterize airflow responses to graded levels of stimulation and the drift in unstimulated levels of airflow across stimulation levels. The Pearson product moment correlation coefficient was calculated to examine the association between baseline and peak flow across the entire group. Least squares linear regression was also used to assess for drift in unstimulated baseline levels of airflow across current levels. The sensitivity of flow response to stimulation current was examined in 25 patients in whom stimulation was applied at sufficiently low amplitude to define the flow capture threshold. Groups were stratified by the presence or absence of IFL at the peak flow threshold. Demographic, anthropometric and flow response parameters were compared between subgroups with two sample student t-tests. Results were expressed at means $\pm$ SEM, except in Table 1 where values are represented as mean $\pm$ SD. Statistical significance was inferred at a $p<0.05$ level.

Table E1: Procedure-Related Adverse Events

Adverse Event	% of all participants (n/N)
Edema (swelling) of tissues or nerves	6.7% (2 / 30)
Lip Weakness	6.7% (2 / 30)
Abnormal scarring (keloid or hypertrophic)	3.3% (1 / 30)
Change in salivary flow	3.3% (1 / 30)
Transient hypoglossal nerve paresis	3.3% (1 / 30)
Transient spinal accessory nerve paresis	3.3% (1 / 30)
Tongue muscle fatigue, weakness or soreness	3.3% (1 / 30)
Cuff dislodgement	6.7% (2 / 30)
Hematoma /Infection (Explant required)	3.3% (1 / 30)

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