Targeted Hypoglossal Neurostimulation for obstructive sleep apnea. A 1 year pilot Study.*.

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Abstract

CPAP is an effective but cumbersome treatment for obstructive sleep apnea (OSA). Non-compliant patients need alternative therapies.

We studied a tongue neurostimulation approach: Targeted Hypoglossal Neurostimulation (THN) therapy with the aura6000™ System. A multicontact electrode positioned around the main trunk of the XIIth nerve connected to an implanted pulse generator (IPG) stimulates segments of the nerve, activating dilator muscles. The primary objective was to improve the polysomnographically determined apnea-hypopnea index (AHI) at 3 months, and maintain the improvement after 12 months treatment. Thirteen out of 14 operated patients were successfully implanted.

At 12 months the AHI decreased from 45 ± 18 to 21 ± 17, a 53% reduction, p< 0.001. The 4% Oxygen Desaturation Index fell from 29 ± 20 to 15 ± 16 and the Arousal Index from 37 ± 13 to 25 ± 14, both p<0.001. The Epworth Sleepiness Scale decreased from 11 ±7 to 8 ±4, p= 0.09. THN was neither painful nor awakened patients, who all complied with therapy. There were two transient tongue paresis.

The present study represents the longest study of any hypoglossal neurostimulation reported to date. We conclude that THN is safe and effective to treat OSA in patients not compliant with CPAP.

Abstract 200 words
Text 4062 words
Introduction

Obstructive sleep apnea (OSA) is characterized by repetitive episodes of respiratory arrest despite continuing breathing efforts. This condition only occurs during sleep and is due to complete or severe, though incomplete, pharyngeal collapse secondary to the sleep-related decrease in pharyngeal neuromuscular activity (1, 2). Each apnea/hypopnea results in two main consequences: decrease in oxygen saturation, and sleep interruption by short arousals (termed microarousals) allowing the resumption of breathing (3). When these episodes repeat more than 15 or 20 times per hour of sleep, clinical consequences may arise, including fatigue, daytime sleepiness, irritability, cognitive impairment, nocturia and arterial hypertension (4, 5). Beyond 30 apneas/hypopneas per hour of sleep (apnea-hypopnea index, AHI) OSA can lead to myocardial infarctions, cerebrovascular accidents, vehicle crashes and premature deaths (6-11).

Obstructive sleep apnea is readily treated with continuous positive airway pressure (CPAP) applied during sleep, all night and every night, through the nares (12). The positive pressure “pushes” apart the walls of the pharynx, allowing the subject to breathe, hence to sleep (12). Many patients accept this cumbersome treatment and obtain immediate and long lasting relief of their symptoms (13). However, a number of patients are unable to adapt to CPAP and remain untreated (14). Alternative treatments (avoidance of supine decubitus in positional OSA, mandibular advancement devices, surgical modifications of the pharyngeal airway) may be useful in mild OSA, but are of little help in moderate or severe OSA (13). The only proven effective alternative is a tracheostomy, which is seldom considered nowadays. Therefore, the search for new therapeutic options remains necessary.

Electrical stimulation of pharyngeal muscles is a promising alternative to keep the pharyngeal airway open throughout sleep, counteracting the sleep related decrease in muscle tone. The hypothesis that stimulation of the genioglossus could effectively dilate the pharynx, was first tested in the late 1990’s, and more recently in two different industry-sponsored studies (15-18). However, the genioglossus is part of the tongue, a complex structure with intrinsic and extrinsic muscles behaving like a hydrostat (19). The assumption that the genioglossus can be stimulated in isolation, without eliciting co-activation of other extrinsic and intrinsic tongue muscles is probably an oversimplification. Indeed, on the one hand part of genioglossus horizontal segment inserts into the hyoid bone (20), and its activation will therefore modify the force balance that determines the hyoid position with consequent variable reactions from the styloglossus and hyoglossus muscles. On the other hand a change in volume of the tongue due to contraction of the genioglossus will lead to a change in shape depending on the variable activity of the intrinsic tongue muscles, that cannot be predicted from the simple stimulation of the genioglossus alone (21). It is conceivable that stimulating not one but several tongue muscles with a net pharyngeal enlarging effect could achieve resolution of apneas and hypopneas. Since all tongue muscles are innervated by the hypoglossal nerve, it might be possible
to target several muscles with a net favorable effect by selective stimulation in the proximal portion of the hypoglossal nerve, before it branches. This report presents the results of a 12-month safety and efficacy study of this concept.

**Material and Methods**

**Stimulation Device**

The aura6000™ system (ImThera Medical Inc., San Diego, CA) consists of an implantable pulse generator (IPG), a small implant containing the battery and stimulation system (hardware and software), and a multi-electrode lead with a 8 mm soft silicone cuff housing six independent electrodes, connected to the IPG via a subcutaneously tunnelled lead wire. The IPG is implanted in the upper chest, in a subcutaneous pocket, whereas the electrode cuff is furled around the hypoglossal nerve near the middle tendon of the digastric muscle, so that the six stimulating electrodes are radially in contact with the cylindrical body of the proximal hypoglossal nerve.

The IPG battery is rechargeable. Recharging is performed transcutaneously with an external remote control charger (RCC) and charging coil that is placed over the IPG with the help of two magnets. The charging time is about 1 hour. The same RCC is used to start, pause and end each night session of stimulation. The IPG has a log memory to record actual charging and use.

**Implantation surgical procedure**

The surgical procedure was performed under general anaesthesia, and started with the hypoglossal nerve dissection. The cuff electrode was rolled under and around the main trunk of the nerve (see Figure 1) and the electrode was looped and anchored nearby. Thereafter the subcutaneous pectoral pocket was created and the IPG implanted. Using a liposuction cannula a subcutaneous tunnel was created between the two incisions. The lead was passed downwards and connected to the IPG. The electrical integrity was confirmed and the incisions closed. Figure 1 shows a radiological view of the implanted system in one patient.

**Stimulation Protocol**

Initially stimulation was titrated in seated awake patients 3 to 4 weeks after surgery. Each contact was stimulated until the patients felt a painless sensation (sensory threshold). Thereafter each contact was again stimulated until bulk movement was observed via pharyngeal fiberoptic endoscopy (motor threshold). In most patients there was a ventral movement of the base of the tongue pulling with it the epiglottis (see Figure 2 and the video recording in the repository of this paper) and in a minority we saw a stiffening of the hemipharynx with little displacement. The contacts with
greatest effect were selected for stimulation therapy. Patients then underwent the first stimulation polysomnography. Titration was repeated before the final 12 month recordings, this time with patients semirecumbent, and with the use of 2 mg midazolam to facilitate relaxation (and frequently sleep). The tongue bulk movements were assessed at the pharynx through fiberoptic pharyngoscopy and within the mouth by placing the tip of the fiberoptic endoscope at the entrance of the mouth with patients wearing a mouth-piece (see Figure 3).

A detailed description of the device, stimulation technique and surgical procedure are given in Appendix E.

Study Design, Outcomes, Patients and Procedures and Course

Study Design

This was an open label, single site, single arm safety and efficacy study in patients with untreated moderate to severe OSA due to intolerance to CPAP. The device and protocol were approved by the Belgian Federal Medicines and Medical Devices Agency (Agence Fédérale de Médicaments et Produits de Santé), and the Université catholique de Louvain Ethics Committee. The study was registered in ClinicalTrials.gov as “Safety and Efficacy of a Hypoglossal Nerve Implant for the treatment of Obstructive Sleep Apnea (OSA)” NCT01532180.

Outcomes

The primary safety measure was the number and type of adverse events. We recorded adverse events (AE) at each visit, as well as at the time of their occurrence. Patients had full access to the medical and surgical team throughout the study. Adverse Events (AE) were classified as serious (SAE) and simple (sAE) adverse events. We added a category of technical AE, related to the device and affecting patient management but not causing untoward health consequences in themselves.

The primary efficacy measure was the mean change in AHI at polysomnographies performed three and twelve months relative to pre-surgical baseline. Secondary outcomes included mean changes from baseline in the Oxygen Desaturation Index (ODI, see further), Epworth Sleepiness Scale, Fatigue Severity Scale and parameters of sleep quantity and quality.

Patient Selection

We selected patients suffering from full polysomnography confirmed OSA who were eligible for CPAP treatment reimbursement according to the Belgian Social Security rules, which require an apnea-hypopnea index of at
least 20 events per hour of sleep. Patients had used CPAP in the past and had stopped treatment or refused to use CPAP altogether. Some patients had already failed various surgical treatments (see Table 1). All patients gave written consent before the start of the study.

Inclusion criteria consisted of baseline AHI ≥20, refusal of CPAP treatment, BMI 25 - 40 kg/m², age 25 - 70 years, modified Mallampati score from I to III and palatine tonsils assessed as grade 0, 1, or 2 (18). There was no preferential selection of subjects for apnea or hypopnea indices. Exclusion criteria included pregnancy, central sleep apnea (CSA), diagnosis of restless leg syndrome or insomnia, presence of a syndromic craniofacial abnormality, clinically enlarged tonsils (grade 3 or 4), modified Mallampati score of IV, presence of obstructive nasal polyps, current alcohol or drug abuse, psychiatric disorders, and subjects unable to give a valid informed consent or to comply with follow-up requirements.

Procedures

Polysomnography

Full night polysomnography (PSG) included the recording of three channels of EEG, two EOG, one chin EMG channel and one lead ECG. Snoring was obtained from a microphone glued to the patient’s neck. Airflow was assessed with a nasal cannula for nasal flow, and with an oronasal thermocouple for oral flow and as a backup nasal signal. Two inductive uncalibrated elastic bands monitored thoracic and abdominal respiratory movements. Body position was estimated from a sensor placed above the sternum, and oxygen saturation and pulse rate were obtained from a finger sensor of a pulse oximeter. Periodic legs movements were computed from two piezoelectric sensors placed on the right and left ankles (Medatec BrainNet, Brussels, Belgium). The polysomnographies were analyzed by hand according to Rechtschaffen and Kales, with stages 3 and 4 non-REM sleep merged. Microarousals were scored according to the American Academy of Sleep Medicine, and reported as the number of microarousals per hour of sleep or microarousal index (MAI). Apneas and hypopneas were identified according to the American Academy of Sleep Medicine rules, with hypopneas defined as a ≥30% decrease in the flow signals lasting at least 10 seconds and inducing a ≥4% oxygen saturation fall or a microarousal. The number of apneas and hypopneas per hour of sleep is given as the apnea-hypopnea index. The percentage of apneas and hypopneas in the supine position is also reported. The oxygen desaturation index (ODI) was defined as the number of falls in oxygen saturation ≥4% per hour of sleep.

Study Course

Patients were seen one week after surgery for evaluation of the surgical sites and recording of AEs. The first titration procedure was performed approximately one month after surgery, followed by a first PSG with stimulation parameter adjustments. During the night, stimulation
parameters were further adjusted aiming to decrease residual apneas and hypopneas. This involved changing the stimulation current, the contact stimulation time, the stimulation frequency or the cathodic phase duration on the previously selected contacts. Changes sometimes succeeded in improving the situation. Other times the changes induced arousal with painful sensations. Patients were discharged home with this first set of parameters and instructed to start daily treatment. Patients used the dedicated RCC to initiate a sleep session, followed by a 45 minutes delay before stimulation started for predetermined 7 hour duration. They were then seen at regular visits until the third month, where a new PSG was performed. Again, stimulation parameters were adjusted during sleep to improve residual events, and patients left the following morning with the new settings. Again, patients were seen at regular intervals and whenever they needed between scheduled visits. Adverse events were always sought and recorded, and when time permitted the compliance log was downloaded. Final data were recorded at twelve months, after a new titration, during a final PSG.

Statistical analysis

Data are presented as mean ± SD. Statistical differences between Baseline and both follow-up visits were assessed using a linear, repeated measures regression model. To accommodate model assumptions, a logarithmic transformation was necessary for apnea-hypopnea index (AHI), arousal index, oxygen desaturation index (ODI) and sleep latency. A compound symmetric covariance matrix was adequate to model the inter-subject variability for all endpoints. To determine if a significant number of patients responded to treatment at both 3 months and 12 months, χ² tests for equal binomial proportions were performed; p values < 0.05 were considered to be of statistical significance. All statistical analyses were conducted in SAS Version 9.2 (SAS Institute, Cary, NC), and were performed by an independent consultant (INTEGRA Group, Brooklyn Park, MN).

Results

Patients

Fourteen patients (one female) took part in the study. Their main anthropometric characteristics, co-morbidities and history related to OSA are described in Table 1. Thirteen patients had moderate to severe obstructive sleep apnea and one patient with previously diagnosed severe obstructive sleep apnea presented with both obstructive and central apneas (he had been implanted with a morphine pump for chronic back pain and was consuming hypnotics at the time of the study).

Acute Surgical Results
Thirteen subjects were successfully implanted. One subject could not be included in the study because of a defective IPG connector discovered during surgery. All materials were then explanted, and the subject recovered without harm but did not participate further in the study. The IPG was implanted on the right side in all but one subject. This subject had a right-side Port-a-Cath®. Ten subjects were discharged the day after surgery, whereas three subjects in whom wound drainage persisted were kept in hospital an extra day. Pain was well controlled with simple pain medicines. All subjects could drink and eat during the evening after surgery. All subjects could speak and had control of tongue movements on arrival to the ward. Mean surgical time was 110 minutes (range, 85 - 145 minutes).

Main Outcomes

Figures 2 and 3 show the type of motion we observed during titration, with enlargement of the pharyngeal airway and flattening of the oral hemitongue. Motion of both tongue base and oral tongue should facilitate nasal and oral breathing. Video images and voice sound changes induced by stimulation can be obtained from the Journal Repository. Figure 3 shows that different contacts can stimulate different nerve fibers and lead to different motions of the tongue, some enlarging the pharynx and palate-lingual space, others having no beneficial effect. Table 2 shows the main outcome data. In all thirteen subjects AHI decreased significantly at 12 months from 45.2 ± 17.8 (baseline) to 21.0 ± 16.5 (Table 1 and Figure 4) the Oxygen Desaturation Index decreased from 29.2 ± 19.6 to 15.3 ± 16.2 and the Arousal Index from 36.8 ± 12.5 to 24.9 ± 13.7. Whereas at baseline only 35 ± 28% of apneas and hypopneas were observed in the dorsal decubitus, the percentage increased at 3 (47 ± 35) and 12 (56 ± 27) months, a significant difference (p<0.03). Total Sleep Time did not change throughout the study, mean values exceeding 400 minutes (Table 2). The BMI did not change throughout the study (initial and final BMI 31 ± 3 kg/m²).

We failed to obtain satisfactory clinical results in three subjects. One subject had an unusually large and long uvula (see Figure 2, C and D), one subject had predominant CSA and in the last subject (the most severe and obese subject, baseline AHI 80, BMI 39), no particular cause was found. A subset analysis was completed excluding these subjects: the mean AHI for the remaining 10 subjects (responders) decreased from 41.5 ± 13.1 to 14.3 ± 8.8 at 3 months and 13.2 ± 5.5 at 12 months, ODI decreased from 23.1 ± 10.2 to 7.6 ± 4.1 at 3 months and 7.8 ± 5.3 at 12 months, and micro-arousals decreased from 34.8 ± 6.7 to 21.0 ± 9.0 at 3 months and to 20.4 ± 8.1 at 12 months. Although the differences between baseline and 3 and 12 months data are greater, there is no change in the general trend of the results.

Daytime sleepiness decreased significantly at 3 months and showed a tendency to decrease at 12 months whereas subjective fatigue as measured by the Fatigue Severity Scale (FSS) tended to decrease at both 3 and 12 months (see Table 3). FSS scores for responders decreased from 4.5 ± 1.3 to 3.8 ± 2.0 at 3 months and to 3.3 ± 1.5 at 12 months. ESS scores for
responders decreased from 9.4 ± 4.4 to 5.6 ± 5.4 at 3 months and 7.0 ± 4.3 at 12 months.

Safety Data

Adverse events and serious adverse events

One patient underwent surgery but could not be implanted due to a defective IPG connector. Two patients experienced transient ipsilateral hemitongue paresis, lasting two and three months respectively with full recovery thereafter. In one patient this was asymptomatic whereas the other one could not whistle during this time. No other subjective complain was recorded due to hemitongue paresis. Postoperative swelling lasted for two weeks in one patient. Three leads broke in two patients, one early in the study and two at the end of the study. One patient was re-operated and re-implanted, but his replaced lead broke at the end of the study. One IPG failed by the middle of the study and was replaced, and the patient completed the study. One patient had a Twiddler's phenomenon. The IPG was manually repositioned, and the stimulation continued without further trouble. There were no deaths in the study. No patient asked to exit the study or have the system explanted. All patients, including the non-responders continue to use the system. There were no infectious or haemorrhagic complications.

Technical adverse events

All patients experienced one or more technical AEs. The most frequent was transient therapy interruptions due to malfunctions of the external devices used in this study (RCC and charging coil) that needed repair or replacement. All patients could continue into the study after these malfunction events were taken care of. Several patients reported uncomfortable stimulation at some point during the study (resolved by reducing the stimulation settings), whereas two patients requested upward adjustments because the stimulation was less well perceived. In three patients a sleep session started during daytime with an unexpected surprising but painless effect. Table E-1 summarizes all adverse events.

Discussion

The application of unilateral Targeted Hypoglossal Neurostimulation in patients with untreated severe obstructive sleep apnea for a 12 month period led to clinically and statistically significant improvements in apneas and hypopneas, falls in oxygen saturation and sleep fragmentation, i.e. the main physiopathological events in Obstructive Sleep Apnea Syndrome. Subjective symptoms of daytime sleepiness and fatigue tended to improve, although they were not abnormal at baseline.
We studied patients with mostly severe OSA. Only two of them had AHI < 30 (25 and 26 respectively), all others had AHI between 31 and 80 per hour. Patients were not particularly healthy, having many co-morbidities commonly seen in OSA (see Table 1). Yet, most patients showed large improvements, with final AHI and ODI results below what can be considered as a serious health risk. The surgical literature on OSA usually classifies patients as responders or non-responders based on a 50% decrease in AHI and/or >20 events per hour (17). This is not at all evidence based. The figure of 30 AHI may be more relevant, with several long-term mortality studies pointing to it as the frontier between surviving and dying in patients with OSA (6, 10, 11, 20), and constituting the frontier between moderate and severe OSA (22). If we consider the former classification, 9 out of 13 patients (69%) were responders. If we consider the 30 AHI figure, 77% of the patients were responders.

Pilot feasibility studies are generally less restrictive in their exclusion criteria than later studies. Indeed, they enable the identification of patients less likely to respond to a treatment. The two previous pilot industry-sponsored studies conducted to date have reported a lower response rate than the present study. For instance, the seminal paper by Eastwood et al. selected patients with predominant hypopneas but less than 20% apneas. The mean apnea index in those subjects was 4.8 at baseline whereas in the present subjects the figure was 13.4, suggesting that airway obstruction was less severe in their group (17). Similarly, in the pilot study sponsored by Inspire Medical Systems, only 6 out of 20 patients (30%) were responders during the first phase of the study, with responders having a baseline AHI below 30 (23). Our subjects showed a higher rate of response. We believe this may be due to a different mechanism of action. Our hypothesis is that the two prior studies sought to stimulate a single protrusor muscle, which could result in antagonistic activation of other tongue muscles with a final net obstructing effect, whereas in the present study we sought to stimulate an undetermined number of tongue muscles, eventually both protractor and retractor ones, seeking a final net favorable movement both in the pharynx and mouth, a concept consistent with the hydrostat model of the tongue (19). Of course, this remains speculative at this time and should be further investigated in future studies. As in the other studies, not all of our subjects responded as expected. Particular characteristics may have affected therapy performance and should be avoided through stricter inclusion criteria in future studies. For instance, Patient 5 had the highest BMI (39 kg/m²). One may wonder whether morbid obese patients might require bilateral rather than unilateral stimulation. Patient 8, initially with pure obstructive sleep apnea, had needed the implantation of a morphine pump and was included into the study with both obstructive and central apneas. This is certainly not an indication for THN. Patient 10 had an unusually long and thick uvula, that perhaps should have been resected before the study.

In contrast to CPAP or to pharmacologic therapies, THN requires a surgical approach. This implies by necessity that surgery should have a very low rate of surgical complications, since it is a necessary step but does not in itself
constitute the treatment of OSA. We saw no serious surgery-related adverse event, and surgical pain was modest and fast subsiding. Of the two more serious adverse events, hemitongue paresis, one was asymptomatic (patient’s tongue tip deviated slightly to the left when protruding the tongue). The other patient sole symptom as long as the paresis continued was the inability to whistle. Both patients recovered without sequellae. The surgical procedure was rather simple, with the hypoglossal nerve being readily accessible below the digastric muscle. Mean surgery time was less than two hours despite time devoted to photography and video recordings which would not occur in clinical practice. Implantation of the IPG at the thoracic site was simple, facilitated by the small size of the implant. It is our impression that surgeons well trained in ENT or maxillofacial surgery should be able to readily perform surgical implantations.

The THN method of hypoglossal nerve stimulation, uses cyclical stimulation to insure that no single nerve fiber is continuously stimulated. This should minimise the risk of nerve or muscle fatigue, of which we did not observe any clinical manifestation in this long-term study. Other “closed-loop” systems stimulate during inspiration, requiring extra leads to follow and identify inspiratory time (17). The THN method appears in this regard as simpler, in that it obviates the need for sensors and extra hardware, decreasing the surgical procedure time and associated risks. Titration was performed first in awake patients. Whereas this seemed to suffice for the initial procedure, Midazolam was used later to allow a longer and more detailed view of the changes in tongue position during stimulation. However, we obtained no further improvement in the results after the last titration.

Patients found the treatment comfortable, and the need to charge the IPG for one hour daily did not seem to represent an obstacle to compliance. Charging time and frequency should decrease as new and better batteries become available.

This study had limitations. The study group is small, and thus results could be biased by outliers. This does not seem to be the case when one examines the individual data, shown in Figure 4. The prototype devices needed repairs and changes, but once these were performed all patients could continue into the study, and none of these technical adverse events (except the two last electrode breaks) resulted in study interruptions. This needs of course to be solved before large scale studies are undertaken.

The subjective results might seem less impressive than the objective data. However, the subjective results were not abnormal at baseline (a frequent finding in sleep apnea studies). Therefore, there was less room for improvement. By contrast, one of the strengths of the study is its very long-term duration, the longest study of hypoglossal neurostimulation reported to date.

In conclusion, we have found THN to be safe and effective in improving patients with untreated severe obstructive sleep apnea, intolerant to CPAP,
allowing most patients to move from a severe to a mild form of the disease. Therapeutic improvement was obtained at 3 months post-implant and maintained at 12 months without signs of adverse effects.
References


9. Rodenstein D. Sleep apnea: traffic and occupational accidents; individual risks, socioeconomic and legal implications. Respiration 2009; 78: 241-248


Table 1. Patients anthropometric data, medical and sleep history.

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*Patient 1 had his electrode lead broken early into the trial, was re-operated later on and was recorded as Patient 9. M: Male; F: Female; S= smoker; AHT: arterial hypertension; D: diabetes; d: depressive symptoms; BC: breast cancer; CEA: congenital esophageal atresia (corrected); GERD: gastro-esophageal reflux, HT: hypothyroidism; G: gout; CP: chronic pain; O: osteoporosis; HC: hypercholesterolemia; UL: urinary lithiasis. CBP: chronic back pain; PLM: periodic legs movements; CABG: coronary artery bypass surgery.
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<td>36.8 ± 12.5</td>
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<td>69.8 ± 11.4</td>
<td>77.2 ± 14.6</td>
<td>0.037</td>
<td>72.4 ± 9.9</td>
<td>0.446</td>
</tr>
<tr>
<td>Stage 1 NREM sleep (%TST)</td>
<td>10.6 ± 6.1</td>
<td>8.4 ± 4.5</td>
<td>0.190</td>
<td>8.7 ± 7.1</td>
<td>0.467</td>
</tr>
<tr>
<td>Stage 2 NREM sleep (%TST)</td>
<td>67.2 ± 7</td>
<td>67.8 ± 8.1</td>
<td>0.766</td>
<td>64.5 ± 12</td>
<td>0.478</td>
</tr>
<tr>
<td>Stages 3-4 NREM sleep (%TST)</td>
<td>5.2 ± 5.6</td>
<td>7.2 ± 5.3</td>
<td>0.243</td>
<td>9.2 ± 9.1</td>
<td>0.188</td>
</tr>
<tr>
<td>Stage REM (%TST)</td>
<td>17.2 ± 5.6</td>
<td>16.7 ± 6.2</td>
<td>0.804</td>
<td>17.9 ± 5.6</td>
<td>0.731</td>
</tr>
</tbody>
</table>

Values are Mean ± SD, number of patients are given between brackets
TST: Total Sleep Time; NREM: non REM sleep; REM: Rapid Eye Movements.
**Table 3. Change in Symptoms**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>3 Months</th>
<th>p-value</th>
<th>12 Months</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESS</td>
<td>10.8 ± 6.2</td>
<td>6.7 ± 5.4</td>
<td>0.023</td>
<td>7.9 ± 4.2</td>
<td>0.094</td>
</tr>
<tr>
<td>FSS</td>
<td>4.5 ± 1.6</td>
<td>3.6 ± 1.8</td>
<td>0.071</td>
<td>3.6 ± 1.5</td>
<td>0.085</td>
</tr>
</tbody>
</table>

ESS: Epworth Sleepiness Scale; FSS: Fatigue Severity Scale; data are Mean ± SD.
Legend for figures

Figure 1
A: Surgical detail showing the hypoglossal nerve with the electrode cuff furled around its main trunk. The white band at the bottom of the figure is lowering the middle tendon of the digastric muscle.

B: Thoracic X-ray showing the implantable pulse generator, connector and electrode cuffed with 6 contacts furled around the hypoglossal nerve.

Figure 2: Endoscopic view of the pharynx in two patients, seen from the oropharynx downwards. A and B: Patient implanted on the left side. Posterior pharyngeal wall is on top, base of the tongue (thick black arrow) with apposed uvula (thin black arrow) on bottom. The epiglottis is seen in between (white arrow). A: during natural breathing without stimulation. B: during stimulation the left hemitongue projects anteriorly, pulling with it the epiglottis. The change in voice of this patient during stimulation while she repeats “un deux trois quatre” (one two three four) can be heard in the repository of the Journal where a video of the pharynx during stimulation can also be seen.

C and D: Patient implanted on the right side. Posterior pharyngeal wall (P) is on top, base of the tongue (B) on bottom. The uvula (U) was particularly thick and long. C: without stimulation. D: during stimulation the right hemitongue projects forward pulling the epiglottis with it and enlarging the pharynx.

Figure 3: Example of different motions of the oral tongue according to stimulation through different contacts. A: Oral tongue at rest. The upper white arrow signals the hard palate, the star signals the soft palate, the thin white arrow shows the lingual medial sulcus. The double white arrow shows the oral tongue. B: Useful Stimulation: Right hemitongue stimulation results in flattening and forward motion, enlarging the tongue-soft palate space (this should facilitate nasal and oral breathing); C: Useless Stimulation: Right hemitongue stimulation in the same patient with a different contact. This results this time in deepening of the medial sulcus without forward movement, and without any improvement in pharyngeal space.

*Figure 4:* Apnea Hypopnea Index scores at baseline, 3 months and 12 months post implantation periods for all patients. (A) Boxplots of entire (open boxes) and responder (solid boxes) groups showing the 75th and 25th percentiles by the upper and lower margins, the mean values by an open circle and the median values by the horizontal line at the baseline, 3 months and 12 months time points. Whiskers represent the maximum value (top) and the minimum value (bottom) of the dataset. (B) Line graphs showing individual data of all 13 patients. Closed circles are for responder patients and the open squares are for non-responder patients. Different shades represent the distribution of AHI in normal, mild, moderate and severe OSA.
Figure 1

A

B
Figure 2
Figure 3

A

B

C
Figure 4