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ORIGINAL CONTRIBUTION

Operative technique of upper airway stimulation: an implantable treatment of obstructive sleep apnea

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Sleep apnea;
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Stimulation therapy

The low success rates for current surgical treatments for obstructive sleep apnea highlight the need for new methods for treating the disorder. This manuscript describes the novel Inspire upper airway stimulation method that through stimulation of the hypoglossal nerve leads to concomitant contraction of the innervated tongue protrusor musculature and increased airway patency. Three components, a stimulating electrode lead, an implantable pulse generator, and a respiration sensing lead, are surgically implanted at 3 separate sites. Detailed descriptions of the surgical method and accompanying illustrations clarify the procedure. Finally, the protocols for activating and titrating the system are detailed. Preliminary clinical investigations on carefully selected patients suggest that the Inspire Upper Airway Stimulation system is an efficacious therapy for treating obstructive sleep apnea.

Obstructive sleep apnea (OSA) is a disorder caused by relaxation of soft tissues in the upper airway during sleep, leading to airway collapse, interrupted breathing, and blood oxygen desaturation. Current OSA treatments include both nonsurgical methods, such as weight loss or continuous positive airway pressure (CPAP),[1] and surgical procedures, such as upper airway soft-tissue[2] and skeletal surgery.

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CPAP is the standard of care for treating moderate-to-severe OSA.[1] However, CPAP can only be effective if used by patients. Several studies demonstrated that less than one-half of patients prescribed CPAP use it regularly. Regular usage was defined as at least 4 hours of use per night on 70% or greater of the days monitored.[3]

Current surgical procedures for OSA have also met with equivocal results. Uvulopalatopharyngoplasty is effective in approximately 50% of OSA patients during long-term follow-up for a period of up to 10 years.[4] For example, the results of invasive surgical treatments for tongue-based obstruction, such as glossectomy, genioglossal advancement,

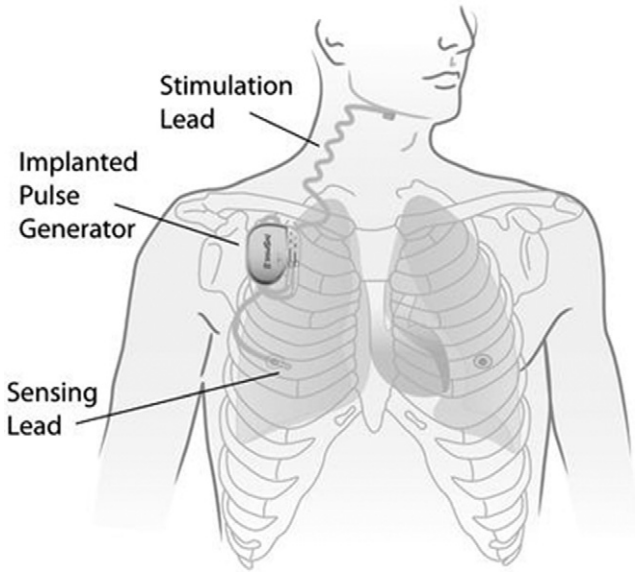

Figure 1 Schematic drawing of the Inspire upper airway stimulation (UAS) system. The implantable pulse generator (IPG) delivers electric pulses through a stimulation lead to the hypoglossal nerve synchronous with respiratory cycles detected by a sensing lead.

hyoid suspension, and radiofrequency treatment, show success rates ranging from 20% to >60% and involve considerable morbidity.[5] Maxillomandibular advancement and tracheostomy are most effective. However, morbidity is high and patient acceptance low.[6] Taken together, patient outcomes with current surgical OSA interventions have been disappointing and suggest that the continuing unmet need requires a treatment paradigm shift.[7]

Here we describe a surgical treatment in OSA patients with pharyngeal obstruction who have failed or cannot tolerate CPAP. The treatment referred to is the upper airway stimulation (UAS) therapy (Inspire Medical Systems, Inc, Maple Grove, MN) and involves functional electrical stimulation of the hypoglossal nerve as a means for increasing the posterior airway space at the level of the oropharynx and the hypopharynx. The goal of this stimulation therapy is to eliminate clinically significant OSA. UAS is currently under investigation in a phase-III Food and Drug Administration trial.

Upper airway stimulation

Unlike current surgical OSA treatments, UAS therapy activates neuromuscular anatomy to increase upper airway caliber without removing or altering soft or skeletal tissue. The Inspire UAS system achieves this by sensing respiration and applying a small stimulus directly to the hypoglossal nerve synchronized to respiration. The stimulation improves airway patency by activating the protrusor muscles of the tongue and thereby mimicking muscle behavior during wakefulness.

Multiple studies have demonstrated that a reduction in the tone of the pharyngeal and lingual musculature (hyperrelaxation) is associated with a significant increase in airflow resistance and pharyngeal obstruction. Specifically, the genioglossus muscle as an important tongue protrusor has been identified as the primary dilator of the pharyngeal airway.[8-10] Given that stimulation of the genioglossus muscle increases airway patency and that the hypoglossal nerve (cranial nerve XII) is the principal innervation of this musculature, we reasoned that indirect targeting of the genioglossus muscle through electrical stimulation of the hypoglossal nerve should also increase inspiratory flow. Several clinical investigations of the UAS therapy suggest that it is a valid strategy for reducing OSA. Feasibility studies conducted with the Inspire I stimulation system (Medtronic, Inc, Minneapolis, MN)[11,12] and the Inspire UAS System (Inspire, Inc, Maple Grove, MN)[13] documented the potential of this treatment. The latter is described in this publication.

System components

The Inspire UAS system (Figures 1 and 2) is composed of a stimulation lead, a sensing lead, and an implantable pulse generator (IPG), which together sense respiration patterns and deliver stimulation to the hypoglossal nerve synchronously with inspiration.

Sensing lead

The sensing lead incorporates a differential pressure sensor that detects respiratory cycles by their pressure variations. The pressure waveform is monitored by the IPG, which triggers stimulation therapy synchronously with respiration.

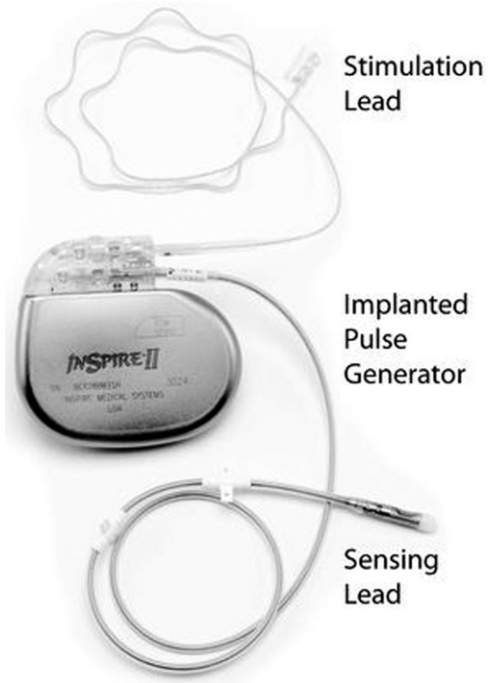

Figure 2 Photos of Inspire UAS system implanted components. The implanted components consist of a stimulation lead, an IPG, and a sensing lead.

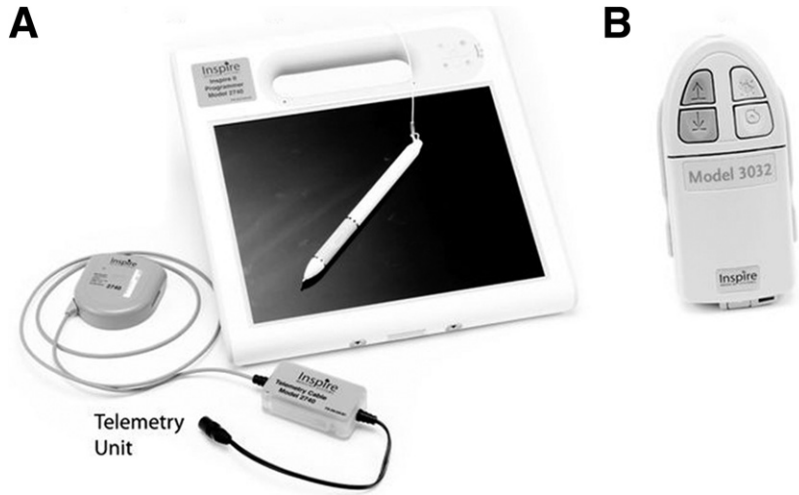

Figure 3 Photos of Inspire UAS system external components. The external components include a physician programmer (A) and a patient programmer (B). The physician programmer communicates with the IPG through telemetry to adjust device settings; the patient programmer turns therapy on or off and adjusts stimulation amplitude in home use.

Stimulation lead

The stimulation lead incorporates a cuff section that includes 3 electrodes that can be configured in a variety of unipolar or bipolar electrode configurations for stimulation.

Implantable pulse generator

The IPG contains an algorithm that synchronizes hypoglossal nerve stimulation with respiration signals. The algorithm parameters can be adjusted as per the needs of each patient. The IPG's electronics and battery are sealed inside a titanium case. The connector module on top of the IPG attaches to the sensing and stimulation leads.

Physician programmer

The physician programmer consists of a tablet computer and a telemetry unit (Figure 3A). The telemetry unit communicates with the IPG through clothing/skin via short-range radiofrequency telemetry. Telemetry communication allows the physician to noninvasively interrogate IPG status (eg, battery status and UAS system patient usage), adjust stimulation and sensing parameters, monitor respiratory waveforms, and store waveforms and patient programmed settings. The telemetry unit is powered by a wall outlet connection and wirelessly communicates via bluetooth with the physician programmer tablet.

Patient programmer

The patient programmer (Figure 3B) is an external device about the size of a smartphone that is used by the patient to activate nerve stimulation before sleep. The patient places the programmer over his or her body at the implanted IPG site and uses the buttons on the programmer to turn the therapy on or off, temporarily suspend therapy, or make adjustments to the stimulation amplitude (within-physician preselected limits).

Preoperative evaluation

Sleep medicine consult

Inspire UAS therapy is intended for treatment of moderate-to-severe OSA in adults who have failed or do not accept/tolerate CPAP treatment. Preoperative evaluation of patients included a sleep medicine consultation to determine whether a patient is likely to benefit from UAS therapy. Recent investigation included patients who had a body mass index of $\leq$35 and an apnea-hypopnea index of between 15 and 65 events/hour. However, a body mass index of $\leq$32 and an apnea-hypopnea index of $\leq$50 might improve surgical success.[13] Patients with neuromuscular diseases, neurologic deficits, psychiatric disorders, pulmonary diseases, severe cardiac dysfunction, uncontrolled hypertension, or renal dysfunction were excluded from current UAS investigative studies. In addition, investigative studies did not include patients with a history of head and neck cancer or previously treated with invasive pharyngeal or lingual surgery, or radiation therapy.

Surgical consult

Patients were examined while awake with rigid and/or flexible endoscopes for anatomic factors that might predispose them to upper airway obstruction and for functional deficiencies that might impair UAS therapy, such as large obstructing tonsils (size 3 or 4).

In addition to awake evaluation, a drug-induced sleep endoscopy is also performed to assess the patient's site and pattern of obstruction. If using the Velum, Oropharynx, Tongue base, Epiglottis (VOTE) classification of upper airway obstruction (Table 1),[14] the early feasibility study[13] has shown that subjects with complete concentric collapse at the level of the velum were less likely to respond to UAS.

Table 1 Drug-induced sleep endoscopy assessment of upper airway obstruction: the VOTE classification

	Pattern		
Level	A-P	Lateral	Concentric
Velum			
Oropharynx	X		X
Tongue base		X	X
Epiglottis			X

A-P, anteroposterior; X, pattern very rarely visualized.

Operative technique

Conceptually, the procedure may be divided into 9 parts: (1) preparation of incision sites, (2) placement of stimulation lead, (3) verification of tongue response to stimulation, (4) placement of IPG, (5) tunneling of stimulation lead to IPG, (6) placement of sensing lead, (7) tunneling of sensing lead to IPG, (8) verification of sensing, and (9) closure of incisions. Precise order of the major steps can be expected to vary within reason, according to the preferences of the surgeon and the unique conditions of a particular implant procedure.

Operating room preparations

The UAS system is implanted under general anesthesia through 3 surgical incisions in the neck and chest area made on the patient's right side. Choosing the right side improves pressure signals of the sensing lead owing to reduced cardiac pressure oscillations compared with the left side. Appropriate measures (ie, fastidious sterile preparation) should be taken to minimize the risk of device-related infection similar to the surgical procedures for electrically active implanted systems.[15] The neck is gently extended with a shoulder roll, and a positioning cushion is placed under the right half of the chest to better visualize the area where the respiration sensor is to be placed. Prophylactic antibiotics (eg, 2 g cephazoline, or other coverage for skin flora if an allergy to cephalosporins is present) are given intravenously at the onset of anesthesia. Long-acting muscle relaxants must be avoided to accommodate peri- and intraoperative examination of tongue motion in response to electrical stimulation. Transnasal intubation is recommended for the same purpose. Furthermore, a cylindrical gauze packing or a bite block of appropriate thickness is placed between the molar teeth of the left side, to facilitate the inspection of tongue movement during intraoperative assessment of tongue response. The activity of the tongue muscle fibers is monitored using a nerve integrity monitoring system (eg, NIM3.0, Medtronic, Minneapolis, MN). The surgeon should also visually monitor tongue movement through a transparent draping over the patient's mouth. The tongue and the mouth should be disinfected before placing electromyography (EMG) electrodes of the NIM system. The genioglossus muscle is targeted by inserting bipolar EMG electrodes toward the midinferior section of the tongue. The styloglossus muscle may be targeted for definitive exclusion by inserting bipolar EMG electrodes along the ventrolateral surface of the tongue.[15]

Placement of stimulation lead and verification of tongue response

The first step of the procedure is the identification of the hypoglossal nerve and placement of the stimulation electrode to confirm a positive tongue response to stimulation. A horizontal upper neck incision approximately 4 to 6 cm long, depending on the neck, is made in a cervical relaxed skin tension line. This is done at least 3 cm inferior to the inferior border of the mandible to avoid injury to the marginal mandibular branch of the facial nerve. The platysma is incised and the inferior border of the submandibular gland is identified and followed down to the intermediate tendon of the digastric muscle, which runs superior to the greater cornu of the hyoid bone. The main trunk of the hypoglossal nerve can be identified deep to the digastric by superiorly retracting the submandibular gland, displacing the tendon inferiorly, and retracting the posterior (free) border of the mylohyoid muscle anteriorly. The ranine vein (vena comitans of the hypoglossal nerve) often runs with the nerve and small branches may cross the nerve. This can be an impediment to the necessary exposure of the nerve. The nerve can be isolated from the vein in most cases, but occasionally, the vein will have to be cauterized or ligated. This must be done delicately to avoid damaging the nerve. For cauterization, bipolar electrical cautery should be used throughout the procedure, with special care near nerve and implanted components.

The main trunk of the hypoglossal nerve can be followed further anteromedially until the surgeon can confirm the branching into lateral (l-XII) and medial (m-XII) divisions.[16] The l-XII branches supply hyoglossus and styloglossus muscles of the tongue, which are both significant retractor muscles. The m-XII branches innervate the intrinsic muscles of the tongue and the genioglossus muscle, which is the principal protrusor of the tongue. From a surgical viewpoint, the m-XII branches run essentially anteriorly in the field, and l-XII branches travel superiorly. Dissection of the nerve anterior to the intermediate tendon of the digastric often leads directly to an exposure that is distal to the fork of the lateral branches. Careful dissection of the nerve can be done to corroborate this. Mono- or bipolar electrical stimulation from the NIM system with a stimulation frequency between 1 and 3 Hz is applied on the main trunk and its branches to assess the tongue movements (retracting or protruding) and register the tongue EMG activity. The targeted segment of the nerve for cuff electrode placement is selected on the m-XII branch by confirming the best observable tongue protrusion with NIM stimulation.

The cuff of the electrode is approximately 1 cm in length and consists of a short inner sleeve and a long outer sleeve. A length of 1 cm of the targeted nerve segment is delicately

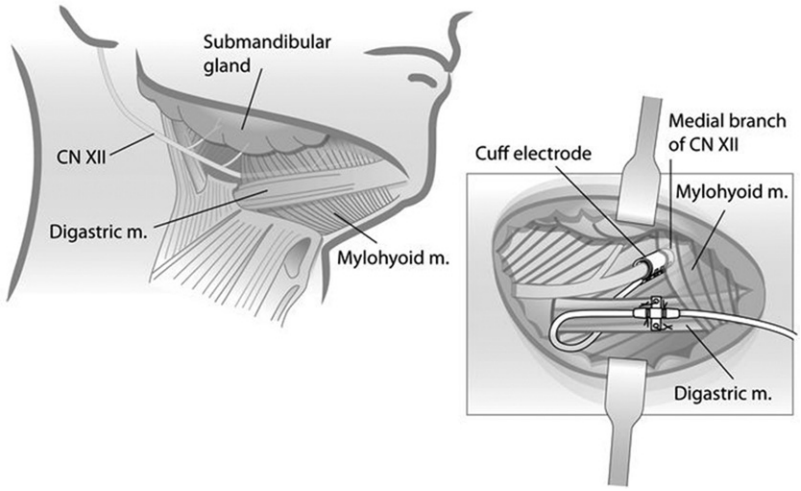

Figure 4 Schematic drawing of stimulation lead placement. The cuff electrode of the stimulation lead is placed on the medial branch of the hypoglossal nerve (CN XII). A strain relief loop is formed between the cuff and a lead anchor that is sutured to the tendon of the digastric muscle.

freed circumferentially from the underlying tissues, with care to avoid bleeding or harm to the nerve by coagulation or vigorous traction (which can cause neurapraxia). A curved dissector (eg, mixter or right angle clamp) is passed underneath the nerve, and one of the corners of the outer sleeve is presented with a fine forceps (eg, Gerald forceps). The outer sleeve is grasped with the mixter/clamp and then gently pulled underneath the nerve. The short sleeve is then unfurled with the forceps and wrapped around the hypoglossal nerve, bringing the electrodes in direct contact with the nerve. The long sleeve is finally released and placed around the inner flap.

The functional tongue protrusion response to stimulation is verified by using the physician programmer. The stimulation lead is then brought either over or under the digastric. To secure the stimulation lead in place, a strain relief loop is created, and the lead is fixed to the digastric tendon with 2 permanent (ie, nonabsorbable) braided sutures (size 4-0). The sutures are secured to the lead in specially designed grooves. Placement of the strain relief loops is intended to avoid tension on the cuff electrode during patient head movement. The lead should be guided either under or over the digastric muscle, depending on where the most relaxed position of the cuff electrode is. In this way, the lead will best accommodate neck motion without placing stress on the cuff-to-nerve interface (Figure 4).

Placement of IPG and tunneling of stimulation lead

The IPG is typically implanted in a subcutaneous pocket in the right midinfraclavicular region through an anterior axillary incision common in cardiac pacemaker implantation. Alternatively, an axillary incision in the delto-pectoral groove can be used for improved cosmetic outcome. An infraclavicular pocket is created superficial to the pectoralis major muscle fascia to accommodate the IPG. The stimulation lead is subcutaneously tunneled into the pocket space with a tunneling device. The lead should not be tunneled in a subplatysmal plane to avoid injury to the external jugular venous system.

Placement and tunneling of sensing lead

A third incision approximately 5 cm long is made horizontally at the fourth to sixth right intercostal space, with the lateral edge anterior to the midaxillary line. The dissection is carried down to the posterior border of the pectoralis major muscle for access to intercostal muscles. A pocket is bluntly dissected at the superior border of the underlying rib. A tunnel of 3 to 5 cm is created using a blunt curved clamp between the external and internal intercostal muscle (Figure 5). The end of this tunnel is situated between the anterior axillary line and the midclavicular line. The blunt dissection may be facilitated by palpating the tip of the

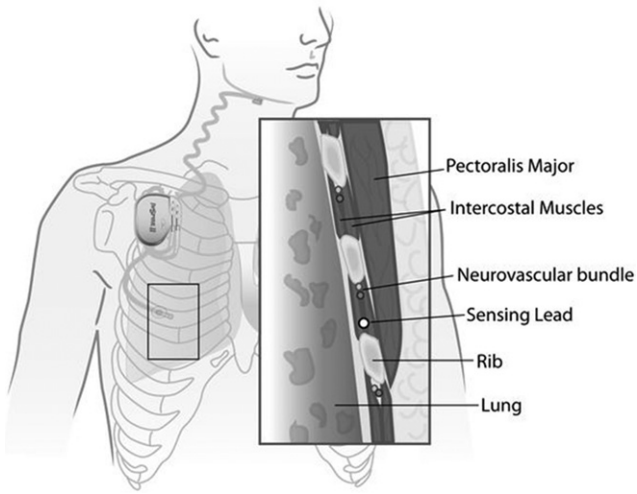

Figure 5 Schematic drawing of sensing lead placement. The sense lead is placed between the internal and external intercostal muscles at the superior border of the fourth to sixth rib.

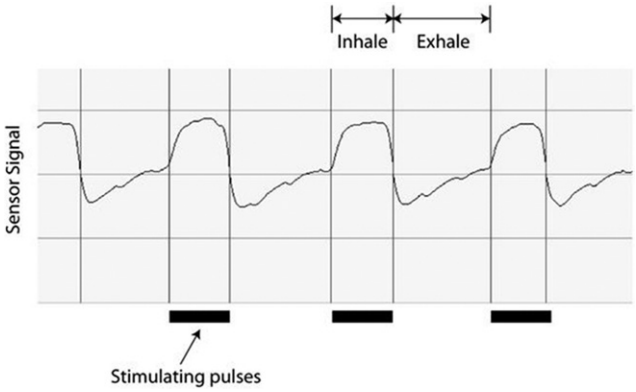

Figure 6 Inspire UAS stimulation timing. Stimulation pulses start when the patient begins to inhale and stop when the patient begins to exhale. The timing of the synchronization can be adjusted by sensing parameters.

curved clamp while advancing it along the superior border of the underlying rib. The respiration sensor is placed in this tunnel, with the sensing side facing the lung. The tunnel should be narrow enough to firmly accommodate the sensing lead and not allow the pressure sensor to slide over the underlying rib and blunting the pressure input to the sensor. Care is taken to avoid dissecting infracostally, as the intercostal neurovascular bundle is located at the inferior border of the rib. The lead is fixed by suturing the first anchor to the underlying fascia and the second anchor to the subcutaneous tissue pointing toward the IPG pocket. The sensing lead is then tunneled subcutaneously into the IPG pocket space using the tunneling device and then connected to the IPG.

Verification of sensing and closure of incisions

The physician programmer module is used to verify and store respiration signals. The function of the entire system (respiration sensor, IPG, and stimulation lead) at this point could be verified, if deemed appropriate, by the surgical team.

The size of the IPG pocket is matched as closely as possible to the IPG dimensions so the IPG and extra length of stimulation and sensing leads wrapped under the IPG fit snugly with minimal movement but without being so tight as to place undue tension on the suture line. The IPG is sutured in a hanging position to the underlying fascia, with the IPG's laser-inscribed surface facing out. Doing this will ensure a good signal transmission between internal (IPG) and external (physician as well as patient programmer) telemetry units. The IPG is sutured with a secure but loosely applied (small air knots) nonabsorbable braided suture (2-0) using the suture hole at the left upper corner of the IPG. This loose suture loop avoids tissue necrosis and dislocation of the IPG over time. At the same time, minimal movements of the IPG owing to shoulder and chest movements remain possible. Meticulous hemostasis is achieved, and all wounds are copiously irrigated. Antibiotic or antiseptic may be added to the irrigant. All wounds are closed in multiple layers, with fastidious attention to proper coverage of all internal prosthetics. In general, drainage is not recommended to reduce the potential for infectious contamination of the implanted components. Pressure dressings should be applied, although they are not necessary in all cases.

Postoperative care and complications

Although an overnight hospital stay best accommodates postoperative monitoring, other patient-specific variables, such as insurance coverage, may necessitate the procedure being done on an outpatient basis. Notably, a number of operations during the investigative studies were performed on an outpatient basis without complications. Common pain killers (eg, paracetamol) are sufficient in most cases and may be used during postoperative days 2 to 5. Patients should avoid vigorous movement of the right arm and shoulder for the first 2 weeks. The pressure dressings (if applied) are removed on day 7; sutures on day 10.

Morbidity and complications

As the procedure does not open a major body cavity or viscera, morbidity is low. Pain is mostly related to the incisions and until now has not lasted more than a few days. Hematoma and seroma can occur, eventually requiring antibiotic or surgical treatment. If any component becomes contaminated and causes repetitive or chronic infection that is resistant to common therapy, the system should be explanted. Temporary tongue weakness may occur during the first 2 to 3 weeks after the implant. Hypoglossal palsy has not occurred in any of the trials.

System activation and titration

The UAS system is activated 1 month after the procedure, and stimulation amplitude thresholds for nerve capture, functional tongue response, and subdiscomfort level are obtained during wakefulness. Based on the voltage at the functional tongue response level, the UAS therapy will be titrated the following night. Special consideration is given to both the amplitude voltage administered and the quality of synchronization between respiration and stimulation (Figure 6). If the patient requires some time to get acquainted to the stimulation signal, the titration night may be postponed for a few days or weeks. The patient is sent home with a patient programmer. The patient may adjust the stimulation voltage within a certain range predefined by the physician according to therapy titration during sleep. Follow-up visits are necessary during the first year to adjust the settings of the patient programmer as the patient grows more accustomed during the first months of treatment.

Conclusions

UAS therapy offers an alternative to CPAP in patients with moderate-to-severe OSA. With this UAS method, there is

no permanent alteration of the upper airway anatomy. Furthermore, no unanticipated safety concerns have been observed from early feasibility studies.[13] Large-scale clinical investigations are currently underway to provide confirmation of therapy efficacy.

Acknowledgment

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