Upper Airway Stimulation in Obstructive Sleep Apnea

Best Practices in Evaluation and Surgical Management

Clemens Heiser
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Preface

Obstructive sleep apnea (OSA) is the most prevalent sleep-related breathing disorder. This disease is not only very prevalent, but when not adequately treated, it is also usually progressive and serious. There are many forms of treatment available, both conservative and surgical, varying from continuous positive airway pressure CPAP); oral device therapy; positional therapy in case of positional OSA; and all kind of forms of upper airway surgery by otolaryngologists to maxillofacial surgery by maxillofacial surgeons; weight loss programs, including bariatric surgery, in case of OSA due to morbid obesity; and upper airway stimulation, also known as neuromodulation. There is no doubt that the latter is the most spectacular innovation in decades in the management of moderate to severe OSA in patients with CPAP failure or nonacceptance. Oversimplified: in case the muscles that open the airway during sleep are stimulated, the airway remains patent. The developments in the rapidly expanding field of neuromodulation for OSA in the last decade are nothing less than exciting, spectacular, and impressive.

In this book, we have tried to bring together the latest knowledge and developments of upper airway stimulation, starting with the history of neuromodulation for OSA; the different companies active in this area; diagnostic work-up and patient selection; the different surgical techniques that are out there, including the latest surgical modifications; detailed overviews or short-term and long-term objective and subjective results; complications; trouble shooting; neuromodulation for central sleep apnea; and closed-loop neuromodulation for insomnia. A unique, extensive, and high-quality video library including all different techniques is provided in addition.

We are fully confident that this book will serve as a guide for all doctors who are already active or are starting to work in this new area. It will also be helpful for doctors who provide other treatments of OSA and want to learn more about this new treatment modality.

We are extremely grateful to all our friends in the fascinating world of upper airway stimulation, who were so kind to help us to put this work together. We approached the absolute leaders in this field, and we cannot thank them enough for their efforts. This has made this publication possible. Our deepest gratitude to all key opinion leaders for their help.

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Chapter 1
The Burden of Obstructive Sleep Apnea: A Clarion Call to Act

Song Tar Toh, Adele Chin Wei Ng, and Shaun Ray Han Loh

Contents

Introduction

Obstructive sleep apnea (OSA) is the most common sleep disorder. It is also the most common sleep-related breathing disorder and is associated with multisystem morbidities. Inadequately managed, it leads to increased healthcare utilization with multiple healthcare visits, poor interpersonal relationships, increased absenteeism from work as well as poor workplace efficacy. These translate into huge healthcare and socioeconomic burden.

Over the years since the disease and with its accompanying morbidities were described, there is increasing OSA awareness, diagnostic testing and therapeutic interventions globally. The rate at which OSA was diagnosed increased 12-fold from approximately 108,000 in 1990 to more than 1.3 million in 1998 [1]. In

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subsequent years, the number of patients receiving care for OSA continued to increase, rising from 2.0 million in 2000 to 2.7 million in 2010 [2].

To meet this rising demand, the field of sleep medicine has grown dramatically. The number of accredited sleep physicians and fellowship-trained sleep surgeons have increased globally, so have the number of accredited sleep centres.

It is even more important that with this huge global burden, physicians and surgeons regardless of specialties need to come together to shoulder this burden together.

Global Burden

A recent literature review by Benjafield and colleagues [3] revealed that 936 million adults aged 30–69 years have OSA (apnea-hypopnea index, AHI ≥5 events/h), out of which 425 million (45.4%) have moderate to severe OSA (AHI ≥15 events/h) globally. The number of affected individuals was highest in China, followed by United States, Brazil, and India; other countries in the top ten were Pakistan, Russia, Nigeria, Germany, France and Japan.

The rising global prevalence of OSA may be attributed to the global obesity epidemic, sedentary lifestyles and aging population, as OSA is known to be associated with metabolic syndrome [4], high body mass index (BMI) [5] and increasing age [5]. The higher prevalence in Asian countries such as China may be due to genetic and racial differences in anatomical and skeletal features that increase the likelihood of OSA [6].

In view of the high global burden of OSA, there is a need for healthcare setting appropriate awareness programs, training, diagnostic and management strategies to minimise the negative health and socioeconomic impacts of OSA (Fig. 1.1). It is a

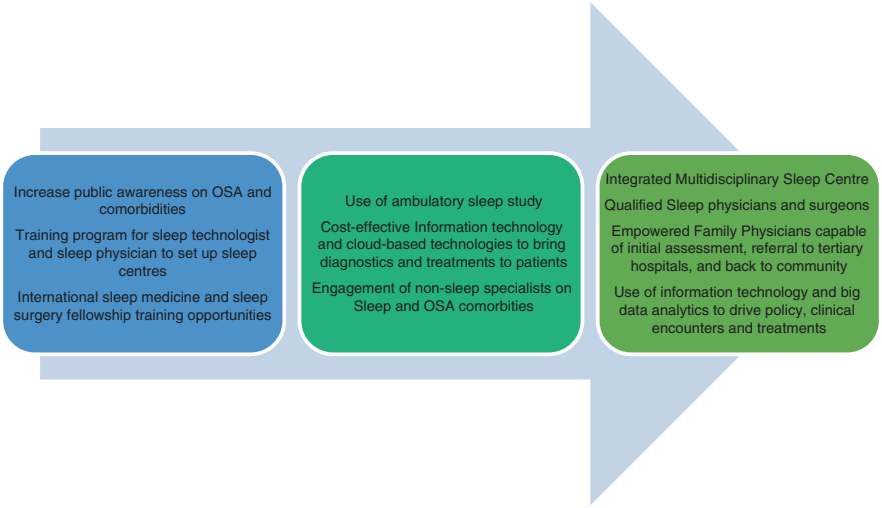

Fig. 1.1 Continuum of strategies to improve awareness and care for OSA

continuum of strategies depending on how advanced the economy and healthcare system is. Within each country and society, this continuum is still applicable as we expect the level of awareness and practice to differ.

In countries where OSA is less recognised, it is important to educate patients and healthcare providers about this condition and its morbidities, concurrent with efforts to avail training opportunities to physicians and surgeons to recognise, diagnose and treat. In countries where technologies or local expertise for diagnosing OSA are not readily available, wearable and cloud-based technologies that allow centralised interpretation of sleep tests can be considered to optimise diagnosis [7, 8]. In countries with a more developed healthcare system, setting up integrated multidisciplinary sleep apnea units starting from family care to tertiary hospital system and back to community will increase the number of patients that will benefit.

Health Implications

The numerous associations and morbidity of OSA include metabolic disturbances, cardiovascular morbidities, neurocognitive deficits, psychosocial consequences, cancer and various other conditions (Table 1.1).

Obesity

Patients with OSA have increased parapharyngeal fat pad volumes [9] and fat deposition in the tongue [10], predisposing them to a narrowed upper airway. The prevalence of OSA in morbid obese patients is as high as 80% [11–13]. Obesity and OSA have a bidirectional causal-effect relationship. Obesity is an established risk factor for OSA [12, 13] yet OSA itself can lead to increased risks of weight gain and obesity. The pathophysiologic relationships between obesity, leptin, lung function, oxygen desaturations, appetite and OSA are well described [14]. Peppard et al. [15] demonstrated that weight reduction of 10% can lead to 26% reduction of AHI; and even greater weight loss of 20% can lead to AHI reduction of 48%. Conversely, a 10% weight gain leads to six times increased odds of developing moderate to severe OSA. However, it has been shown that the effect of BMI on OSA attenuates after age 60 years [11, 13].

Type 2 Diabetes Mellitus

The Sleep Heart Health Study [16] and Sleep AHEAD study [17] demonstrated that the prevalence of OSA in type 2 diabetic patients ranged from 58% to 86% [18]. Patients with moderate to severe OSA are at greater risk of diabetes, with a relative

Table 1.1 Comorbidities associated with OSA

Metabolic
Obesity
Insulin resistance
Type 2 diabetes mellitus
Cardiovascular
Hypertension
Ischaemic heart disease
Arrhythmia
Atherosclerosis
Pulmonary hypertension
Neurological
Stroke
Dementia
Epilepsy
Depression
Poor memory
Impaired vigilance
Ophthalmology
Normal tension glaucoma
Floppy eyelid syndrome
Non-arteritic ischaemic optic neuropathy
Urologic conditions
Enuresis, nocturia
Erectile dysfunction
Malignancy
Increased cancer incidence and mortality
Psychosocial
Road traffic accidents
Healthcare utilization
Absenteeism from work & impaired work productivity

risk of 1.63 compared to patients without OSA [21]. This high prevalence of OSA in diabetic patients has led to the International Diabetes Federation to call for diabetic patients to be screened for OSA and vice versa. Recurrent intermittent hypoxia and sleep fragmentation in OSA cause increased oxidative stress and sympathetic drive, leading to chronic low-grade systemic inflammation resulting in derangement of glucose metabolism, impairment of pancreatic beta cells, adipose tissue function, and glucose homeostasis through impaired insulin sensitivity [19, 20].

Cardiovascular

The Wisconsin Sleep Cohort Study demonstrated that OSA is an independent risk factor of hypertension and patients with moderate OSA were 2.89 times more likely to develop hypertension [22].

The Sleep Heart Health Study showed that patients with OSA have an odds ratio of 2.38 for heart failure, 1.58 for stroke, and 1.27 for coronary heart disease [23]. Study on long-term cardiovascular outcomes also showed higher odds ratio (2.87) of fatal myocardial infarction and stroke in men with untreated OSA [24].

We found that patients with OSA are more likely to have cardiac arrhythmias, especially those who are older and have a higher BMI [25].

Neurologic Disorders

Common neurocognitive disorders experienced by OSA patients include attention deficit, poor vigilance, impaired memory, reduced visuospatial and constructional abilities, as well as poor executive functions (including volition, planning, purposeful actions) [26–28]. Neurologic disorders linked to OSA include stroke, epilepsy, neurodegenerative disease, Alzheimer, Parkinson disease and multisystem atrophy [29].

Ophthalmic Conditions

The most common ophthalmic sequela of OSA is normal tension glaucoma with a prevalence of 3–27% [30]. Patients with OSA have a hazard ratio of 1.88 in developing glaucoma compared with normal controls [31]. Other ophthalmic conditions associated with OSA include floppy eyelid syndrome, non-arteritic anterior optic neuropathy, papilledema, retinal vein occlusion, age-related macular degeneration and central serous retinopathy [32–34]. It is postulated that intermittent hypoxia causes damage to the optic nerve head and retinal ganglion cells, as well as vascular dysregulation leading to poor ocular perfusion and raised intraocular pressure [30].

Implications on Quality of Life

The adverse effects of OSA extend beyond the patient's personal health and has larger social consequences which merit attention.

Patients with OSA often experience poor interpersonal relationships [35] as their excessive daytime sleepiness may manifest as irritability or mood swings [36]. Family and friends may have misconceptions and attribute their behavior to dullness, sluggishness or psychological problems [37]. Coworkers and supervisors may mistakenly view them as being lazy or apathetic [38]. This usually leaves most patients feeling lonely and unsupported [37]. In addition, being sleepy while on duty may lead to occupational accidents and injuries [39].

We found that patients with OSA have a poorer quality of life compared to controls. For every 1% reduction in lowest oxygen saturation measured during polysomnography, there was a decrease in physical function score by 0.59 points and an increase in Epworth Sleepiness Scale by 0.13 points [40].

Additionally, bed partners of OSA patients feel that their sleep quality and quality of life are negatively affected [41–43]. These can be improved after OSA patients receive treatment.

In school-going patients, OSA is associated with poorer academic performance [43–47] due to cognitive deficits such as reductions in attention span, memory, executive function and psychomotor function. These patients also have increased behavioral problems such as somatic complains and aggressive behaviors [48].

Economic Burden

Two recent white papers commissioned by the American Academy of Sleep Medicine conducted an in-depth analysis of the hidden costs of undiagnosed and untreated OSA among American adults [49]. The estimated cost of diagnosing and treating OSA in the United States in 2015 was approximately $12.4 billion. Fifty percent of these costs attributed to continuous positive airway pressure (CPAP) therapy and oral appliance therapy, 43% attributed to surgical treatments, and approximately 7% of these costs attributed to physician office visits and diagnostic testing.

The estimated economic burden of undiagnosed OSA among American adults was $149.6 billion in 2015. With $86.9 billion due to lost productivity and absenteeism; $30 billion due to the increased risk of costly comorbidities such as hypertension, heart disease, diabetes, and depression, and their associated hospital visits; $26.2 billion due to motor vehicle accidents; and $6.5 billion due to workplace accidents [49]. In addition, a meta-analysis conducted by Garbarino and colleagues [51] demonstrated that workplace accidents were almost twice as frequent in OSA patients (odds ratio = 2.18; 95% confidence interval 1.53–3.10) compared to controls, especially those involved in occupational driving.

To diagnose and treat every American adult who has OSA, an additional $49.5 billion is required. However, this expenditure would produce a projected savings of $100.1 billion [49]. This is reflected in a study by Ronald et al [50], whereby physician claims and overnight hospital stays were used twice as frequently by OSA patients in the 10 years preceding their OSA diagnosis.

Clinical Case Series and Cost-Effective Strategies: Diagnosis, Treatment and Reduction in Burden

There are cost-effective strategies to diagnose and treat this disease (Table 1.2).

Table 1.2 Clinical case series and cost-effective strategies in managing OSA [52–60]

Diagnosis	**Outcomes**
Ambulatory studies	Reduction in cost and time to treatment and diagnosis
Treatment	
Lifestyle modifications (e.g., weight loss)	Improved AHI, QOL
Myofunctional therapy	Improved AHI, ESS and QOL
Positional therapy	Improved AHI, ESS and QOL
Oral device (e.g., mandibular advancement device)	Improved AHI, ESS and QOL, better than no treatment, cost-effective
Positive airway pressure & telemedicine	Improved AHI, usage, adherence and compliance, with improved QALY, cost-effective
Upper airway surgery	Improved AHI, snoring, ESS, QOL and QALY, cost-effective
Skeletal surgery	Improved AHI, snoring, ESS, QOL and QALY, cost-effective
Upper airway stimulation	Improved AHI, snoring, ESS, QOL, cost-effective (based on results of STAR trial)

Studies have shown that suitable patients who underwent ambulatory sleep study had a shorter time to diagnosis (21 days versus 79.8 days) and treatment (46.3 days versus 118.4 days) compared to those who underwent in-laboratory polysomnography [52]. Cost-saving of USD$1179.50 per patient was achieved with ambulatory studies in these suitable patients.

In terms of available treatment options, myofunctional therapy is a cost-effective option for patients with mild to moderate OSA [53]. Sadatsafavi and colleagues demonstrated that CPAP is more cost-effective than oral appliances, however, oral appliances is still more cost-effective than no treatment for patients who are unable to tolerate CPAP [54]. For middle-aged men with severe OSA who are intolerant of CPAP, palatopharyngeal reconstructive surgery appears to be cost-effective [55]. Skeletal surgery [56] and hypoglossal nerve stimulation [57] has also been shown in clinical cases series and cost-effective analysis models to be beneficial.

In recent years, there is emerging evidence advocating the use of telemedicine in monitoring CPAP compliance to improve the cost-effectiveness of OSA treatment [58–60]. Information on CPAP compliance, air leaks and residual respiratory events can easily be monitored using cloud-based technologies. There was no difference in CPAP compliance between patients who received teleconsulting and those who opted for in-office consults. However, significant reduction in healthcare cost was reported in the teleconsult group.

Traditional model of care involves referral of a patient with suspected OSA from primary care physician to individual specialists, which often leads to multiple appointments, repetition of evaluations and tests, prolonged wait time to treatment, and lack of coordinated care. This fragmented care is often not cost-effective and unsatisfactory for patient care.

A concerted integrated and holistic approach will help improve outcomes, and this should include: public healthcare policies to increase awareness, screening for "asymptomatic" patients, screening patients with OSA for intervenable subclinical cardiovascular issues, empowering primary physician to diagnose and start

treatment, reducing cost and time to diagnosis and treatment, and constantly innovating and discovering new treatment strategies.

Conclusion

It is evident that OSA is a global health epidemic which may lead to rising healthcare burden and socioeconomic costs if not managed. Holistic management goes beyond multidisciplinary management of this disease. Proactive and holistic approach is pivotal in preventing and treating this disease, containing this growing disease burden that leads to disability and death. Integrated approach using patient-centered care line, screening and prevention of complications, as well as patient education and engagement are essential in ensuring successful intervention and optimized patient outcomes. It is our burden to shoulder.

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Chapter 2
Treatment Options in Sleep Apnea

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Contents

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Background

Obstructive sleep apnea (OSA) is a disorder characterized by repeated episodes of upper airway collapse, leading to nocturnal hypoxemia and associated arousals [1, 2]. The prevalence of moderate to severe sleep apnea, defined as AHI ≥15 and ≥30 respectively, continues to rise in the United States with an estimated 10–17% of men and 3–9% of women having the disorder [3]. This translates to approximately 13 million adults over age 30 in the United States alone [4]. The prevalence of this disorder is significantly higher in certain populations with nearly 50% of the elderly, 55% of those with coronary artery disease, and 37% of those with type I or II diabetes meeting criteria for diagnosis [5–7].

Untreated or under-treated OSA poses a serious public health risk with numerous co-morbidities and health consequences. Most notably, OSA patients are at increased risk for cardiovascular disease and hypertension secondary to chronic nocturnal spikes in heart rate and blood pressure due to arousal and catecholamine release [1]. OSA has also been associated with increased sympathetic burden, metabolic disorders, cerebrovascular disease, insulin resistance, cancer, perioperative complications, and early all-cause mortality [1, 8, 9]. In addition to these, untreated OSA has been associated with reduction of cognition, daytime somnolence, a high prevalence of depression, and increased motor vehicle collision rates [1, 2, 5, 10].

Continuous Positive Airway Pressure (CPAP)

First described in 1981, CPAP continues to be the gold standard for treatment of moderate to severe sleep apnea and is the most efficacious at improving all parameters of sleep apnea severity, including AHI, ODI and O2 nadir, when used as prescribed [11, 12]. Nasal CPAP functions as a pneumatic splint in the upper airway, offsetting the negative pressure created during inspiration and preventing airway collapse [13]. CPAP effectively improves awake performance, quality of life measures, snoring, driving performance, and neurocognitive function [13, 14]. It also reverses many of the health sequelae of OSA by significantly reducing blood pressure, resolving pathological cardiac dysrhythmias, reducing sympathetic activity, improving insulin sensitivity, and improving long-term morbidity and mortality [13].

Despite the proven efficacy of CPAP in treatment of OSA, compliance is remarkably low with up to 50% of patients failing to meet the recommended 4+ hours of usage per night and many not even filling the prescription [15–17]. Few OSA patients wear CPAP for the 6 hours or more a night required to minimize the AHI, therefore CPAP functions to reduce but not eliminate elevated AHI in most users. There are many factors playing a role in patient non-adherence, including

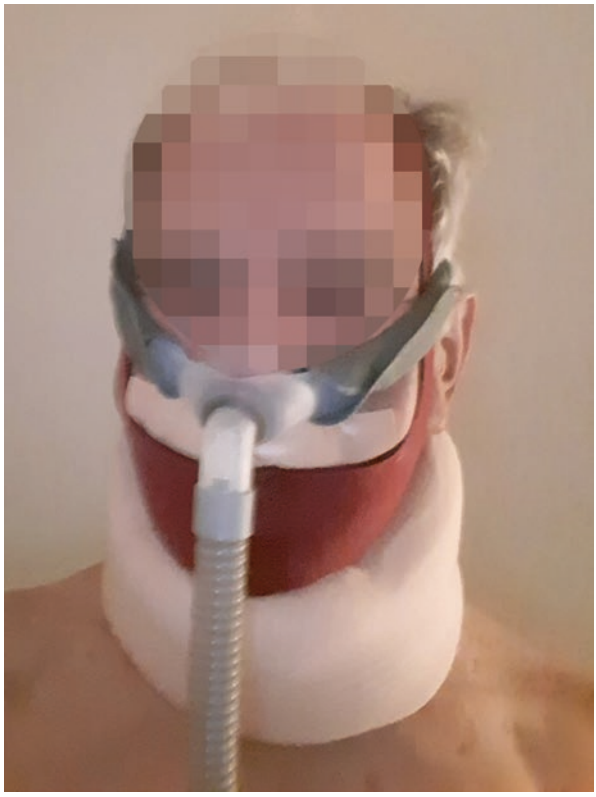

Fig. 2.1 A patient requiring a soft neck collar to prevent jaw opening and leak of CPAP

lack of education, high pressures, nasal obstruction, facial discomfort, social concerns, and claustrophobia [10, 16]. Some patients cannot maintain an effective seal with CPAP without accessory devices (Fig. 2.1). Of those that do comply with CPAP, nearly a third report nasal discomfort and dry mouth [18]. Intolerance for or inadequate therapy with CPAP lead many patients to seek alternative therapies for OSA.

Surgery as Adjunct to CPAP

While CPAP remains gold standard therapy, occasionally the source of noncompliance or intolerance for a patient may be amenable to surgical correction. Often these surgical treatments allow for better airflow, reduce mouth opening, or reduced pressures, improving efficacy and lessening the discomfort of CPAP therapy, and encouraging compliance in previously intolerant patients [19].

Tonsillectomy

In patients with grade III or IV tonsils and low BMI, simple tonsillectomy has strong curative potential [20, 21]. In those who still require CPAP post-operatively, the majority require lower pressures than prescribed pre-operatively [20]. Tonsillar hypertrophy creates preferential mouth breathing during sleep, increasing mouth leak with CPAP, and contributes to CPAP intolerance [20]. Up to half of the patients intolerant of CPAP pre-tonsillectomy are able to utilize the therapy post-operatively, likely secondary to the reduced pressures and removal of an "obstructive feeling" in the pharynx [20]. Due to these findings, primary tonsillectomy is a rational approach to OSA patients with 3 or 4+ tonsils (Fig. 2.2). Repeat home sleep apnea testing can be performed after a period of healing in order to determine if additional PAP therapy is still required. Aside from pain perioperatively, the most common complication associated with tonsillectomy is post-operative bleeding which occurs in approximately 1–2% of cases, however the procedure is generally considered low risk [19, 20].

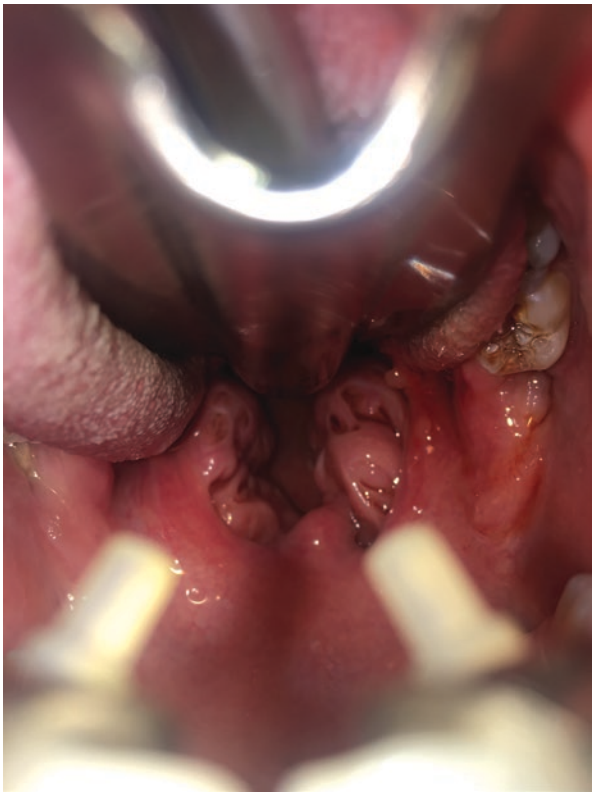

Fig. 2.2 Three-plus tonsillar hypertrophy which can be removed as first-line therapy for OSA

Nasal Surgeries

Obstructive nasal symptoms, secondary to inferior turbinate hypertrophy, internal nasal valve collapse, or deviated septum, are commonly reported by CPAP users and likely contribute to non-compliance [16, 22]. Nasal obstruction worsens during sleep due to supine position, which causes dependent nasal vasocongestion, and is exacerbated by CPAP usage [16, 22]. Nasal surgery is not recommended alone in the treatment of OSA due to insufficient reduction in AHI, but can be used in select patients to improve CPAP adherence by removing nasal obstruction and reducing pressure settings while improving sleep quality, and reducing nocturnal arousals and daytime sleepiness [10, 21, 23]. Even in cases where CPAP is not significantly reduced, the relief of symptoms associated with nasal obstruction is enough to allow patients to use therapy comfortably [10]. A thorough examination of the nasal passages is required for any patient prior to CPAP therapy. If there is a history of nasal congestion, or anatomic evidence of fixed (e.g., deviated septum) or dynamic (e.g., nasal valve collapse; inferior turbinate hypertrophy) blockage, the patient will benefit from application of a nightly nasal steroid spray and/or nasal breathing strips prior to sleep. Dynamic nasal valve collapse due to weakening of the upper lateral cartilages can be an overlooked source of nasal blockage if a modified Cottle

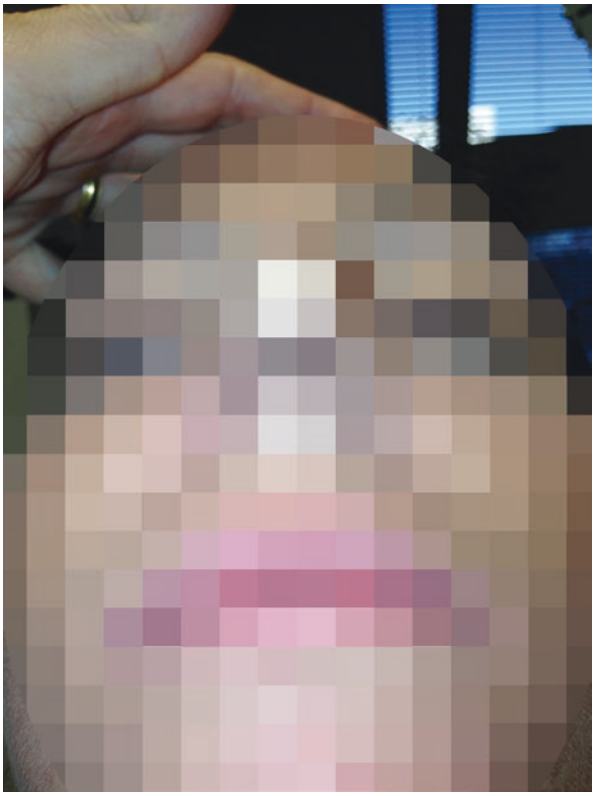

Fig. 2.3 Narrow internal nasal valves that demonstrated collapse on modified Cottle maneuver

maneuver is not performed (Fig. 2.3). If these conservative measures fail to improve nasal breathing, surgical correction prior to CPAP initiation is advised since patients are more likely to be adherent to CPAP therapy long-term if obstacles to CPAP are managed prior to therapy initiation. However, positive outcomes following nasal procedures for patients already using CPAP are highly consistent, and therefore corrective nasal surgery should be offered to any patient with obstructive nasal anatomy who is struggling with CPAP adherence [10].

Mandibular Advancement Devices (MADs)

Mandibular advancement devices (MADs) are an appropriate alternative therapy for select patients unable to tolerate CPAP [16]. They function to reposition the tongue and/or lower jaw, increasing the retroglossal airway space [1]. The ideal candidate for MAD therapy is one with lower BMI and mild to moderate OSA (AHI $\leq$ 30) predominantly associated with supine position [16]. In general, 50% of maximal anterior jaw distraction is needed to manage mild to moderate OSA, whereas 75% of maximal distraction may be required to treat more severe OSA. MADs are not as efficacious at treating OSA as CPAP, but are more comfortable for patients and allow greater adherence to therapy [1, 16]. Greater comfort, adherence, device longevity, and fewer side-effects are present with custom-fitted MADs compared to off-the-shelf boil and bite appliances. Contraindications to MAD therapy include missing teeth, poor dentition, and TMJ dysfunction [16]. The most commonly reported side effects include TMJ discomfort, tooth pain, sialorrhea, or xerostomia [16]. Another important note is that many insurance companies do not cover the cost of MADs and the expense of the device, especially custom-fitted MADS fabricated by a dental sleep specialist, may be prohibitive for some patients [1].

Surgery as Alternative to CPAP

If CPAP or other first-line therapies are intolerable or fail to treat OSA, upper airway surgery can be an option for select candidates. OSA is a disease that can be caused by airway collapse at multiple locations in the upper airway, with a majority of patients having obstructions at more than one level [24]. Surgical treatment can be primary therapy in patients who have severe anatomic obstruction (tonsillar, turbinate, or uvular hypertrophy) that is best corrected surgically [16]. Surgical treatment of airway collapse for OSA is not a "one-size-fits-all" method and thus requires individualized assessment and surgical planning for each patient.

In examining the patient who has failed first-line therapies, it is important to note external anatomy and body habitus that may be effecting collapse in a patient [16]. Parameters such as severity of OSA, BMI, neck size, craniofacial structure, nasal patency, tongue position, palatal anatomy, and tonsil size are important in

determining which surgical options would be most effective for the patient [16, 20, 25]. Polysomnograms are employed in the diagnosis of OSA and in determining the severity of disease pre- and post-operatively [16]. These can be performed in a sleep center or at home.

Next, it is essential to identify the extent of collapse at the different levels of the airway. There is no current gold-standard for determining level of obstruction. The "Nose-VOTE" scoring system is commonly used and identifies collapse or obstruction at the level of the nose, velopharynx, oropharynx, tongue, and epiglottis [26]. This system allows prioritization of specific levels of the airway amenable to surgical correction and can be employed in both awake endoscopy and drug-induced sleep endoscopy (DISE) [25]. Awake endoscopy has historically been the tool utilized to determine levels of airway collapse. In most patients with OSA, the upper airway behaves differently in awake and sleep states [25]. DISE under light propofol sedation provides another layer of information by allowing better visualization of the airway collapse patterns during sleep [16, 25]. DISE provides the sleep surgeon with additional information such as site, severity, and pattern of collapse which can be combined with the findings of sleep apnea testing to formulate a rational treatment strategy. After thorough evaluation of the patient, there are three major categories of airway collapse underlying the disease state: (1) "too little space" or a craniofacial problem, (2) "too much tissue" or a hypertrophy/obesity problem, and (3) "tissue too lax" or increased tissue collapsibility.

"Too Little Space"

Oropharyngeal crowding and collapse can be due to compression of the collapsible soft tissues of the upper airway into a reduced craniofacial or jaw structure. These patients are often younger in age, and non-obese. Physical examination may reveal retrognathia; high-arch maxilla; narrow mandibular arch; open or cross-bite; and Class II or III malocclusion. The tongue may appear to fill the oropharynx (Modified Mallampati III or IV), however the tongue is of normal size within a small jaw structure (relative macroglossia). There are several alternative therapies to CPAP for patients with the above findings.

Maxillo-Mandibular Advancement

Maxillo-mandibular advancement (MMA) is a skeletal surgery designed to enlarge the airway at the velopharynx and oropharynx [27]. MMA functions by advancing the anterior pharyngeal tissues attached to the hyoid, mandible, and maxilla [1]. It is the ideal surgical treatment for patients with significant retrognathia, and/or malocclusion [16]. In these patients, MMA is nearly curative and has been shown to reduce AHI by 87% while improving facial profile and jaw occlusion [16, 27].

Despite its efficacy, MMA is rarely performed due to the length of procedure, the level of technical skill required, and the innate risks of dental malocclusion and nerve injury [16, 27]. The operation requires a substantially longer recovery time than other surgical treatments of OSA, sometimes requires a peri-operative tracheotomy, and is often not well covered by insurance [1, 16].

Maxillary Expansion

Maxillary expansion is utilized to treat patients with OSA and associated transverse maxillary deficiencies. Transverse maxillary deficiencies, secondary to asymmetric development of the mandible and maxilla, manifest as dental malocclusion, narrow and high palatal vault, and elevated nasal floor [28, 29]. These abnormalities increase nasal airflow resistance and are associated with increased risk of nasal obstruction, especially in patients with septal deviation or hypertrophic inferior turbinates [29]. Maxillary expansion alleviates nasal obstruction by increasing the size of the nasal cavity and may reduce pharyngeal obstruction by increasing space in the oral cavity allowing better positioning of the tongue [29]. Recent meta-analysis found that maxillary expansion reduces AHI by more than half and significantly reduces sleepiness [29].

"Too Much Tissue"

A common cause of moderate to severe OSA is too much tissue in the oropharyngeal airway due to adenotonsillar hypertrophy or obesity with increased tongue and pharyngeal fat deposits. In general, these patients have onset of OSA in adolescence and early adulthood which is accompanied by increasing weight gain leading to obesity (BMI $\geq$kg/m^2). On examination, these patients may have hypertrophy of the adenoid, palatine or lingual tonsil, and tongue enlargement (Modified Mallampati III or IV) within a normal jaw structure (acquired macroglossia). Often, impressions of the teeth can be observed scalloping the edges of the enlarged tongue. On DISE, these patients have a base of tongue that fills the oropharyngeal airway with folding of the tongue as evidence by a midline raphe.

Simple Tonsillectomy

Hypertrophic tonsils can play a major role in the development of OSA, as mentioned previously, and simple removal of the tissue can be curative in a select group of patients [20]. Patients with hypertrophic tonsils should be evaluated for collapse at other levels, potentially necessitating multi-level treatment. The ideal candidate

for simple tonsillectomy is one with large, grade III or IV, hypertrophic tonsils and low BMI (<25) [20]. In this patient population, tonsillectomy alone is an effective treatment for OSA and has been shown to significantly improve AHI, nocturnal oxygen saturations, and sleepiness [20].

Lingual Tonsillectomy

The base of tongue is a common location of airway obstruction, seen in up to 70% of patients with OSA [30]. Lingual tonsillar hypertrophy (LTH) is one source of this obstruction and may be easily missed on physical examination unless accompanied by fiberoptic laryngoscopy [31]. In addition to airway obstruction, it can cause dysphagia, otalgia, cough, and globus sensation [31]. Underlying causes of LTH are unknown, but it has been associated with obesity, GERD, smoking, and previous palatine tonsillectomy [32]. There are numerous reported approaches to lingual tonsillectomy such as with diode laser, coblation, microdebridement, harmonic scalpel, and more recently using trans-oral robotic surgery (TORS) [31–33]. Historically this procedure was rarely performed due to difficulties in surgical access, risk of massive intra-operative bleeding, and risk of post-operative airway compromise secondary to laryngeal edema [31, 33]. Surgical approach with TORS allows better visualization of the anatomy and increases the surgeon's ability to move freely, which may allow better control of intra-operative complications and reduce procedure-related morbidity [31, 32]. Regardless of technique used, lingual tonsillectomy can be curative in patients with sole obstruction at this level if the tonsils are entirely removed [31, 33].

Uvulopalatopharyngoplasty (UPPP)

UPPP, first described by Fujita in 1981, is one of the earliest surgical treatments described for OSA [34]. The procedure involves excision of redundant soft tissue at the level of the tonsils, posterior soft palate, and uvula with closure of the tonsillar

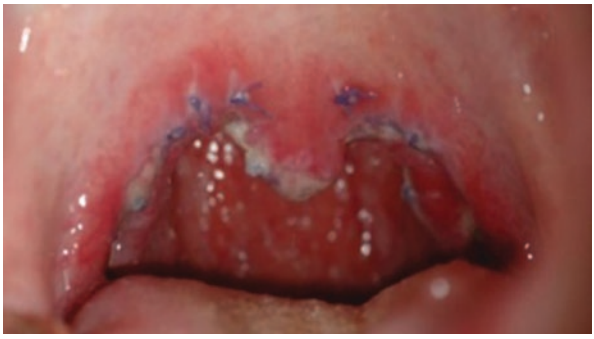

Fig. 2.4 Uvulopalatopharyngoplasty (UPPP) demonstrating currently favored technique of maintaining uvular mass in the midline of the soft palate

pillars to widen the oropharyngeal airway [16, 27] (Fig. 2.4). It is one of the most commonly performed sleep surgeries, alone or combined with a multi-level approach, in the treatment of OSA and has been shown to improve mortality [35]. Post-operative polysomnography results are variable with reported AHI reductions from 33–52% with generally improved success rates when combined in a multi-level approach [16, 21]. Regardless, UPPP has been shown to significantly improve daytime sleepiness, driving performance, depression, sexual function, ventricular function, and serum lipids [5, 36]. There is extensive reporting of temporary and permanent complications associated with UPPP including difficulty swallowing, voice changes, oral pain, taste disturbance, globus sensation, and velopharyngeal insufficiency [34]. The most common complaint is foreign body sensation which may be reduced with newer uvular sparing techniques [34]. Because of these adverse effects, numerous modifications to surgical technique have been made over the years to try to reduce morbidity [16].

Partial Glossectomy

Retroglossal collapse is present in up to 75% of patients with OSA and is most prominent in those with severe disease (AHI >30) and obesity [16, 24]. The physical exam of a patient with macroglossia can show lateral indentations from dentition

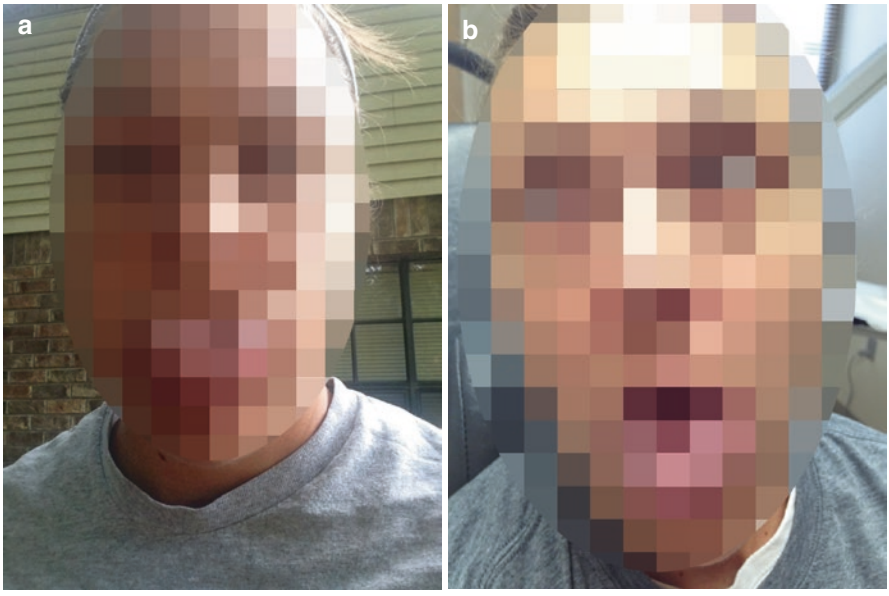

Fig. 2.5 Acquired macroglossia from Beckwith-Wiedemann Syndrome casing OSA before (**a**) and after partial glossectomy (**b**)

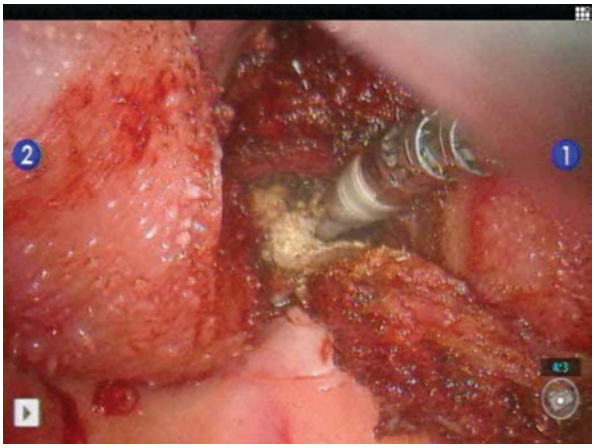

Fig. 2.6 Middle third of base of tongue removed with transoral robotic surgery (TORS)

and often have Friedman tongue position of III or IV [16]. The acquired macroglossia is particularly pronounced in patients with certain metabolic disorders such as Beckwith-Wiedemann syndrome; acromegaly; or amyloidosis (Fig. 2.5). In patients with moderate OSA (AHI 15–30), the SMILE (submucosal minimally-invasive lingual excision) technique can be used. This procedure involves the use of a coblator and is generally less morbid than formal midline glossectomy [16]. In patients with severe OSA (AHI >30), a formal posterior midline glossectomy is more appropriate [16]. This procedure was historically very difficult due to challenges with surgical line-of-sight, but advances in TORS have allowed the tongue base to be much more accessible [16] (Fig. 2.6). Glossectomy, alone or in multi-level approach, is associated with significant improvement in AHI, nocturnal oxygen levels, daytime sleepiness, and snoring [24, 30]. The most common complication reported with glossectomy is loss of or change in taste, which resolves in most patients over several weeks [24].

"Tissue Too Lax"

In certain cases, OSA may result from increased levels of passive airway collapsibility and reduced neuromuscular tone during sleep. In general, OSA of this variety begins in middle-age and after, and is associated with lower BMI and normal tongue size (Modified Mallampati I or II). In these patients, most obstructive events will be recorded during supine sleep or REM sleep due to tongue prolapse into the oropharynx [16]. It is difficult to identify this type of collapse on awake endoscopy due to its dynamic nature, making DISE a much more sensitive diagnostic tool for this group of patients [16].

Tongue Suspension

Functional collapse of the base of tongue during sleep is attributable to reduced neuromuscular tone [16]. Tongue base suture suspension utilizes a suture loop secured to a titanium screw on the lingual aspect of the mandible, effectively advancing the tongue and reducing collapse [16]. This procedure is ideal for non-obese patients without macroglossia and lower levels of OSA (AHI ≤30) and can be an effective adjunct when combined with another procedure such as UPPP [16, 21]. It has been shown to significantly reduce AHI, sleepiness, and snoring and improve nocturnal oxygenation [16, 21, 37]. There is some evidence that this type of procedure does not provide long-term results due to tongue mobility and eventual stretching of the suture material [16, 37].

Hyoid Myotomy and Suspension

Most hypopharyngeal obstructions occur at the base of the tongue, but up to 20% of patients will have significant retro-epiglottic collapse [16]. Hyoid myotomy and suspension effectively advances the supraglottic structures away from the posterior pharyngeal wall, increasing the size of the airway and preventing collapse [16] (Fig. 2.4). Advancement of the hyoid bone in the anterior-superior direction provides tension on the hyoepiglottic ligament in the central hypopharynx and on the stylohoid muscles of the lateral hypopharynx. It is most effective in patients who have significant epiglottic retroflexion on awake or sleep endoscopy [16]. Hyoid suspension is commonly performed with another procedure and significantly improves AHI and success rates compared to the other procedure alone [16, 21, 27]. Even when performed alone, hyoid suspension significantly improves severity of OSA [38]. Complications are very rare, but tend to involve lingual edema or neck seromas [16, 38].

Radiofrequency Ablation (RFA)

RFA is a form of electrical energy that can penetrate deep into tissues with a high level of precision and control [39]. The applied energy causes coagulation necrosis and inflammation in the tissue leading to fibrotic stiffening of the area and tissue reduction [16, 39]. The stiffening effect counteracts the natural collapsibility of the mucosalized, tubular airway. One advantage of RFA is that it can be used at several different levels of the upper airway including the nasal turbinates, soft palate, and base of tongue [39] (Fig. 2.7). Treatment of the palate has a 60% success rate and of

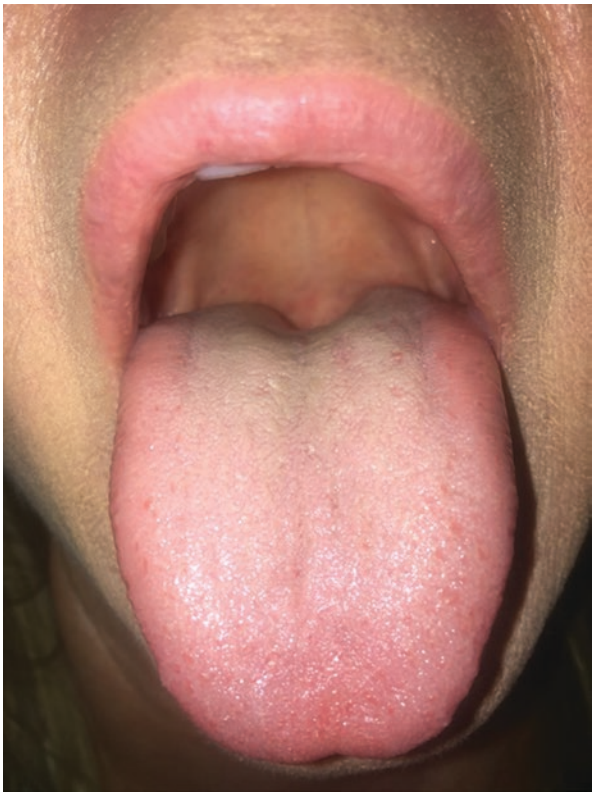

Fig. 2.7 Midline tongue remodeled and stiffened with depression after radiofrequency ablation (RFA)

the tongue with up to 83% success [21]. Patients often require multiple treatments to achieve effective results [39]. RFA can be used alone, but is frequently combined with other procedures for greater effect [16, 21, 39]. RFA is associated with minimal risk and is a low cost option for patients [16]. The effect of the procedure is expected to lessen over time due to tissue remodeling of the scar tissue, however the procedure can be repeated if needed due to its low morbidity and pain.

Hypoglossal Nerve Stimulation

Nerve stimulation therapy involves the implantation of a device that induces protrusion of the genioglossus muscle during sleep in accordance with breathing patterns [1, 21]. In a highly select patient population, the therapy significantly reduces AHI, oxygen desaturation index, and systolic blood pressure [2]. This procedure is discussed in detail elsewhere within this text.

Tracheostomy

Surgical tracheostomy was the earliest treatment of OSA and is highly effective reducing AHI, sleepiness, and mortality [1]. Tracheostomy has high morbidity and is associated with significant changes in lifestyle [21, 40]. Despite its efficacy in treating OSA, due to the significant impact on quality of life, it is reserved as a last line of therapy only for those who have failed all other treatments, have emergent loss of airway, or have severe cardiopulmonary disease such as chronic congestive heart disease [1, 16, 40].

Summary

Obstructive sleep apnea is a multifactorial disorder that requires an individualized treatment plan. CPAP is first line therapy in most cases of moderate-to-severe OSA and currently represents the gold standard of treatment, but is often not tolerated by patients and has a high rate of non-adherence. In these patients, evaluation by a sleep surgeon is an appropriate next step to find effective treatment options as untreated OSA has significant health consequences. Full workup should include history, physical exam, polysomnography, awake endoscopy, and occasionally drug-induced sleep endoscopy (DISE) to effectively identify underlying causes and levels of obstruction or collapse. Therapy should be directed towards the specific levels of obstruction in the patient and may include one or multiple operations.

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Chapter 3
Effect of Hypoglossal Nerve Stimulation on Cardiovascular Outcomes

Everett Seay and Raj Dedhia

Contents

Introduction

The link between obstructive sleep apnea (OSA) and cardiovascular disease has been well-established. Approximately 50% of patients with OSA have hypertension, and an estimated 30% of hypertensive patients also have OSA [1]. Other important clinical outcomes associated with cardiovascular disease include diabetes, stroke, myocardial infarction, heart arrhythmia, and death [2].

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Mechanisms of OSA on Cardiovascular Disease

The mechanism of OSA detriments on the cardiovascular system is driven by oxidative stress caused by repetitive airway obstruction and intermittent hypoxia [1]. Hypoxia and arousals during sleep increase sympathetic activity and decrease parasympathetic activity causing increases in blood pressure and heart rate. Sympathetic hyperactivity promotes inflammatory immune responses and influences the development of resistant hypertension [3, 4]. Patients with OSA have surges in sympathetic activity during sleep and persistent elevated sympathetic tone during wakefulness [5].

Sympathetic activity can be recorded through microneurography (MSNA), an intraneural measurement of nerve activity, usually performed by inserting a fine recording electrode in the peroneal nerve. Wallin et al. first described sympathetic activity through MSNA, measured as bursts per minute, and correlated these measurements with plasma noradrenaline levels [6]. These findings have implications for measuring autonomic activation related to apneic events. In normal subjects, sympathetic nerve activity, blood pressure, and heart rate are lower in deep NREM sleep than while awake [7]. Zoccal et al. demonstrated that hypoxia and hypercapnia increase the sympathetic-respiratory connection, causing abdominal muscle activation and active expiration [8]. During peaks of abdominal activity, bursts in sympathetic activity have been observed [9].

Several biomarkers have been associated with cardiovascular risk in OSA populations. Two widely studied inflammatory markers in OSA are interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-alpha). IL-6 stimulates production of C-reactive protein (CRP) through hypoxic burden and sleep deprivation, which in turn produces cytokines that recruit inflammatory cells [10]. CRP levels are elevated in patients with OSA compared to controls and have been associated with OSA disease severity [11–13]. Treatment of OSA via nasal CPAP reduces CRP levels [14]. Tumor necrosis factor-alpha is a pro-inflammatory cytokine that is responsible for cardiac contractility and sleep regulation [15]. Chronic intermittent hypoxia causes increased cellular and extracellular levels of TNF-alpha. Ciftci et al. observed higher serum TNF-alpha and IL-6 levels in obese patients with OSA after controlling for BMI and age [16]. Vgontzas observed higher TNF-alpha and IL-6 levels in patients with OSA compared to normal controls [17]. While these inflammatory markers provide some degree of cardiovascular risk measurement, their lack of both specificity and mapping to hard clinical outcomes relegates them as suboptimal biomarkers of cardiovascular risk in OSA.

OSA Severity and Cardiovascular Outcomes

Numerous studies have demonstrated the impact of OSA severity on cardiovascular outcomes, with cardiovascular risk following greater OSA severity as measured by the apnea-hypopnea index (AHI) [18–20]. Investigators of the Wisconsin sleep

cohort study found a dose-response association between sleep-disordered breathing (SDB) and hypertension, independent of confounders [18]. Marin et al. studied incident hypertension in patients with OSA, and found increased hazard ratios in patients who were ineligible for CPAP or declined CPAP (1.33 and 1.96 respectively) compared to controls and patients treated with CPAP (1.0 and 0.71 respectively) [19]. In another major epidemiological cohort, Redline et al. found a significant positive association between obstructive AHI and ischemic stroke in men. An adjusted hazard ratio of 1.86 was observed for men with an obstructive AHI between 4 and 19, which increased to 2.86 in men with AHI greater than 19 events/hour. In women, an increased risk was observed at an AHI greater than 25 [20].

OSA is associated with an increased risk of incident heart failure in middle-aged and older men [21]. Gottlieb et al. conducted the Sleep Heart Health Study, a longitudinal study of 4898 patients who were initially free of coronary heart disease over a median 8.7 years. OSA was a significant predictor of incident coronary heart disease in men aged less than or equal to 70 years [adjusted hazard ratio of 1.1 (95% CI 1.0–1.2)]. Men aged 40–70 years with severe OSA were also 68% more likely to develop CHD compared to those without OSA. All men with severe OSA were 58% more likely to develop heart failure than those without OSA. No significant findings were observed in women, although the study was not powered to detect a significant difference among women. One potential limitation noted by the study authors is the healthy-survivor effect: individuals with OSA who are more susceptible to cardiovascular sequelae of OSA are less likely to be alive with good cardiovascular health during study initiation compared to those with OSA who are resistant to its cardiovascular consequences.

Treatment of OSA on Cardiovascular Outcomes

Positive airway pressure (PAP) therapy is the gold standard for treatment of obstructive sleep apnea. CPAP therapy has been associated with acute reductions in sympathetic activity and blood pressure during sleep [5]. Reductions in systolic blood pressure resulting from CPAP use are maintained in the long term by approximately 2.0–2.5 mm Hg [22, 23]. A long term 2–3 mmHg reduction in systolic blood pressure has been associated with a decrease in mortality by 4–8% [24]. Therefore, small reductions in blood pressure resulting from CPAP use likely have clinical significance.

The importance of PAP therapy duration may play an important role in cardiovascular outcomes in patients with OSA. A recent meta-analysis of eight randomized controlled trials (5817 patients) examined the efficacy of CPAP for prevention of major cardiovascular events. There was no evidence for improved outcomes observed in cardiovascular mortality, myocardial infarction, unstable angina, stroke, atrial fibrillation, or heart failure. However, the authors cite variable CPAP adherence as a major limitation among some studies [25]. Similar findings were observed in the SAVE trial; there was no significant difference in outcomes with CPAP compared to usual care in moderate to severe OSA [26]. However, the mean PAP usage was just 3.3 hours per night. Subgroup analysis showed a reduction in stroke risk for

patients using PAP greater than or equal to 4 hours per night. Two randomized controlled trials showed improved cardiovascular outcomes among patients who were adherent to CPAP therapy by the same definition [27, 28]. Since an estimated 46–83% of patients in clinical practice adequately use PAP therapy, the need for PAP alternatives remains clear [29].

Oral appliance therapy (OAT) for treatment of OSA yields similar cardiovascular outcomes in comparison to PAP therapy, despite having a lesser impact on overall AHI reduction. Endothelial function, inflammation, and oxidative stress are reduced by both OAT and CPAP [30–32]. A randomized-controlled trial of OAT showed a 1.8 ± 0.5 mmHg reduction in 24-hour diastolic blood pressure but no significant reduction in systolic blood pressure. Awake blood pressure variables were also reduced in patients using OAT compared to controls [33]. Barnes et al. performed a 3 month crossover trial of 114 patients receiving either CPAP, OAT, or placebo. In patients receiving OAT, investigators found a 2.2 mmHg reduction in nocturnal diastolic blood pressure. OAT therapy also increases heart rate variability during controlled breathing conditions, suggesting an improvements in vagal autonomic activity [34].

Weight loss is an important behavioral modification for treatment of OSA. Although weight loss leads to a reduction in AHI, it rarely cures OSA [35–38]. The importance of weight loss in treatment of OSA may rest in mortality reduction. A meta-analysis of 15 randomized controlled trials suggests a 15% reduction in all-cause mortality resulting from intentional weight loss [39]. Weight loss also treats symptoms commonly seen in the presence of OSA including fatigue, insomnia, and hypersomnolence.

Impact of OSA Surgery on Cardiovascular Outcomes

Surgical therapy for OSA including tracheostomy, skeletal surgery, pharyngeal surgery, and hypoglossal nerve stimulation, is a treatment option for patients unable to tolerate PAP therapy. Halle et al. performed a systematic review of OSA surgery and found tracheostomy is most consistently associated with improvement in cardiovascular outcomes including lower mortality, vascular accidents, and cardiac arrhythmias [40]. Maxillomandibular advancement has been associated with reductions in blood pressure [41–43]. Pharyngeal surgery may have a beneficial effect on mortality but not cardiac arrhythmias, and its effect on blood pressure is unclear [40]. Chen et al. studied 10,339 patients with newly diagnosed OSA, and found those who underwent UPPP had a lower risk of developing cerebrovascular disease (relative risk of 0.45) up to 1 year following surgery compared to those without surgery [44].

Impact of HGNS on Cardiovascular Outcomes

Hypoglossal nerve stimulation was approved in 2014 by the FDA for treatment of patients with moderate to severe OSA who were unable to use PAP therapy. Published 5-year data showed a response rate of 63% in 71 patients undergoing

HGNS, when therapy response was defined as an overall AHI less than 20 events/hour with a 50% reduction in overall AHI. Improvements in sleepiness and quality of life were also noted, indicating long term benefits in some patients [45].

There are few studies investigating the effect of HGNS on cardiovascular outcomes. Woodson et al. studied 46 patients from the Stimulation Treatment for Apnea Reduction (STAR) trial who were randomized to either HGNS therapy maintenance or 1 week of therapy withdrawal [46]. Following 12 months of treatment, therapy maintenance patients had significant improvements in systolic blood pressure (129.1 ± 16.1 mmHg to 122.8 ± 12.6 mmHg; $p < .05$) compared to baseline. However, there was no significant difference in systolic or diastolic blood pressure changes between the therapy maintenance and therapy withdrawal groups. Walia et al. compared clinic-based blood pressure levels between 517 patients initiating PAP therapy with 320 patients from an international registry of HGNS patients [47]. Patients treated with PAP therapy had a greater improvement in diastolic blood pressure and mean arterial pressure compared with HGNS patients. Therapy adherence was 6.2 hours/week greater for HGNS patients. One major limitation of this study was the reliance on the international registry for blood pressure data which is taken from many centers over time.

The effects of HGNS on the autonomic nervous system have not been widely studied. Dedhia et al. analyzed heart rate variability in a subset of 46 HGNS patients from the STAR trial who underwent a 1-week therapy withdrawal following 12 months of HGNS therapy [48]. A spectral analysis of polysomnographic ECG was performed to measure heart rate variability (HRV), specifically the standard deviation of the R-R interval (SDNN), which provides information related to autonomic cardiovascular function during sleep [49]. The SDNN demonstrated significant improvement from baseline to 12-months of HGNS therapy in both light sleep and REM sleep, suggesting improvement in autonomic function during sleep with HGNS. Ikeda et al. analyzed the PAT signal of eight patients before and during HGNS but noted was no significant change in PAT signal before or during stimulation in any patient, suggesting the absence of autonomic system alterations by HGNS [50].

To date, there are no published randomized controlled trials of the effect of HGNS on cardiovascular outcomes. Dedhia et al. are currently conducting a randomized, double-blind, sham-controlled clinical trial examining the effect of HGNS on sympathetic and vascular function [51]. An interim, unpublished analysis of 16 patients undergoing 24-hour ambulatory blood pressure demonstrated no significant difference in systolic pressure for patients during active therapy versus sham therapy, 123.8 mm Hg and 124.0 mm Hg respectively. While these differences were not statistically significant due to lack of power, the observed point estimates were consistent with a potential treatment effect.

Challenges to Future Studies

One challenge investigators face in designing cardiovascular research studies is in blood pressure measurements. Many factors have been shown to influence blood pressure including room temperature, noise, caffeine use, body position, cuff size

and placement [52]. Although in-office blood pressure measurements can be performed under controlled conditions, patients are still subject to the "white coat effect" and the number of readings are limited. To address this, many research studies have opted for 24-hour ambulatory blood pressure monitoring which provide measurements every 30–60 minutes. However, some of the abovementioned factors can still be present in the home environment.

Several unique challenges are specific to randomized controlled trials of hypoglossal nerve stimulation, chiefly sham therapy settings and blinding adequacy. In CARDIOSA-12, an ongoing double-blinded, randomized controlled trial, participants are randomized to either a therapeutic stimulation level or a "sham," subtherapeutic stimulation level [51]. The "sham" level is determined as the minimum stimulation required to either (1) invoke transoral tongue motion or (2) elicit stimulation sensation. One limitation of this sham-controlled approach is an unintended therapeutic effect to "sham" HGNS levels. This unintended response can be assessed by performing a full night efficacy study at the "sham" HGNS level at study initiation. In this way, cardiovascular outcomes can be analyzed while controlling for potential treatment effects in the sham HGNS settings.

Blinding adequacy represents a concern when designing a blinded, sham-controlled HGNS study. In CARDIOSA-12, investigators decided upon a sham-controlled study arm as opposed to complete therapy withdrawal in an attempt to blind participants. Interim analysis of 17 patients revealed suboptimal blinding efficacy with 82% of patients able to correctly determine their therapy assignment. Washout periods between therapy assignments may also necessary to return patients to baseline. However, study length is a major concern as newly treated patients were reluctant to discontinue HGNS therapy for up to 6 weeks to take part in CARDIOSA-12 due to improved symptoms resulting from HGNS.

Data reporting, particularly of treatment AHI, determines HGNS therapy response and may influence interpretation of HGNS on cardiovascular outcomes. A recent analysis of 43 patients by Dedhia and Woodson demonstrated a dramatic difference in treatment AHI depending on whether titration studies or full-night efficacy studies are used [53]. For titration studies, the mean treatment AHI was 7.7 events/hour, compared to 19.2 events/hour from full-night efficacy studies. When defining therapy response by Sher criteria of 50% reduction in AHI and AHI <20 events/hour, HGNS was 91% successful using treatment AHI while 52% successful using full-night efficacy AHI. The observed differences may be attributed due to the selection of therapeutic voltages during periods presence of slow wave sleep and/or the lateral body position, both of which have been associated with decreased AHI [54, 55].

Summary

Obstructive sleep apnea is associated with cardiovascular sequelae including hypertension, diabetes, stroke, myocardial infarction, arrhythmias, and death. The mechanism of these associations is through intermittent hypoxia and arousals

which increase oxidative stress and sympathetic activity. Continuous positive airway pressure is the gold standard for treatment of OSA, yet therapy adherence is an important determinant for reductions in cardiovascular disease risk. There is currently insufficient data to determine the impact of hypoglossal nerve stimulation for treatment of OSA on cardiovascular outcomes. The findings of the ongoing CARDIOSA-12 randomized controlled trial will serve to provide an initial assessment of this topic as HGNS therapy continues to expand its footprint in the treatment of OSA patients.

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Chapter 4
History of Electrical Stimulation in Sleep Apnea

Paul Van de Heyning and Olivier M. Vanderveken

Contents

Electrical Stimulation of the Hypoglossal Nerve for Treatment of Obstructive Sleep Apnea: History, Current State and Future Perspectives

The research and development phases of the fascinating therapy of electrical neurostimulation of the hypoglossal nerve (nervus hypoglossus – twelfth cranial nerve – CN XII) for the treatment of sleep-disordered breathing spans a period of 30–35 years [1–7]. Since then the number of published scientific papers on this topic has steadily increased with a peak in the increase in amount of manuscripts over the last years (Fig. 4.1).

In their key paper, back in 1978, John Remmers et al. described the importance of the genioglossus (GG) muscle in maintaining upper airway patency during sleep in the counter balance with the loss of upper airway muscle tone during sleep [8]. The resulting hypothesis that artificial activation of the GG muscle might be effective in the treatment of obstructive sleep apnea (OSA) was first evaluated by Miki et al. as these authors could demonstrate that upper airway resistance decreased by electrical stimulation of the GG in anesthetized dogs [9]. The first human study was performed by the same research group assessing the efficacy of surface stimulation at the level of the submental region in six OSA patients during sleep [1]. The results

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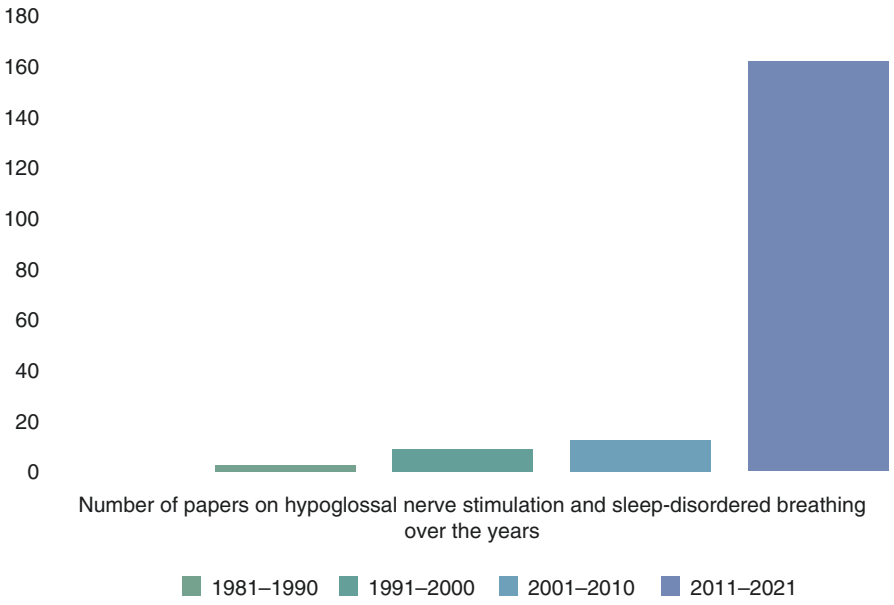

Fig. 4.1 Estimated number of scientific manuscripts published in PubMed about electrical stimulation of the hypoglossal nerve for treatment of sleep-disordered breathing over the years

of this experiment suggested a decrease in the frequency of apneic episodes and longest apnea duration, and an increase in arterial oxygen saturation [1]. The percutaneous electrical stimulation that was employed in this study was not causing arousal neither was it significantly affecting blood pressure or heart rate [10]. The findings suggested that submental electrical stimulation using the technology of apnea demand-type stimulator based on tracheal breath sounds could be a non-invasive and effective treatment for OSA [1, 10]. Subsequently, the observation was made that placement of electrodes for stimulation in the proximal half of the submental region could decrease supraglottic resistance during mouth breathing both in OSA patients and a control group, and that ideally the surface electrodes were 1 cm apart [11]. Apart from the influence of stimulation site, the effectiveness of submental stimulation turned out to be dependent on stimulation intensity with a frequency- and voltage dependency of the effect of stimulation [11]. After these first studies, results of other trials evaluation submental stimulation were published with mixed results [12]. A limited cure rate was reported in an abstract published by Verse et al. [13]: transcutaneous electrical stimulation was reported to reduce the apnea/hypopnea-index (AHI), snoring and daytime sleepiness significantly [13]. Both intraoral and subcutaneous submental stimulation are associated with time-linked arousals [12, 14]. In spite of these discouraging findings a recent flare of clinical trials on these concepts has been noted. After the publication of feasibility studies the protocol of a larger study that evaluates transcutaneous electrical stimulation for OSA was published in 2019 by He et al. [15]. Additionally a notable improvement

in both snoring and mild OSA was reported by Kotecha et al. with a novel intraoral neuromuscular stimulation device using daytime awake neuromuscular electrical stimulation to induce toning of the tongue muscles [7]. This daytime neuromuscular electrical training appears to be well tolerated and effective at reducing snoring while improving sleep quality of both patient and his/her partner [16].

The clinical history of the more invasive direct method of hypoglossal nerve stimulation (HNS) therapy dates back to the four-centre trial evaluating unilateral HNS in eight patients with OSA [2]. This study converges with the first ever surgical procedure for implantable HNS therapy in a human OSA patient at the Antwerp University Hospital in Edegem, Belgium, in June 1996. The hypoglossal nerve stimulation system evaluated in this study (Inspire I stimulating system, Medtronic Inc., Minneapolis, MN, USA; Fig. 4.2) was designed to synchronize the delivery of the CN XII stimulation with the patient's inspiration using an implantable intrathoracic pressure sensor, a programmable pulse-generating system, and a stimulating half-cuff silicone-insulated, guarded, bipolar platinum electrode placed around the main trunk of the nerve at the left side. Using an external programming unit the stimulation parameters and inspiratory sensing algorithms could be adjusted. Impulses were delivered to the hypoglossal nerve via a lead. A self-controlled programming unit was provided for patients to initiate and terminate electrical stimulation. The findings of this particular study could confirm the safety, feasibility and therapeutic potential of implanted HNS with a significant reduction of AHI [2].

The learnings from that early experience in eight OSA patients included that implanted HNS synchronized with ventilatory effort during sleep may indeed provide a potential treatment for OSA and that improvements in OSA were related to CN XII dependent muscle recruitment and not to arousal. During the study, however, there were some technical issues related with stimulation hardware and software [2, 18].

The re-engineered Inspire II system (Inspire Upper Airway Stimulation (UAS) device, Inspire Medical Systems, Inc., Maple Grove, MN, USA; Fig. 4.3) got subsequently launched and evaluated in a clinical multi-centre trial enrolling patients from European and US centres [3]. The second generation implant included improved cuff electrode of the stimulation lead and demonstrated pressure sensing technology. During the surgical implantation the cuff section of the stimulation lead was placed on the medial division of the distal hypoglossal nerve aiming at selective stimulation of the protruding tongue muscles [4, 19].

The findings of the study by Van de Heyning et al. evaluating the Inspire II system have become the evidence base for the current inclusion criteria in routine clinical practice for the application of HNS [3]. After all, the results have clearly demonstrated that this type of HNS therapy is safe and efficacious in selected OSA patients with moderate to severe disease who cannot or will not use CPAP as their primary treatment. In addition, patients turned out more eligible to respond when body mass index (BMI) is not greater than 35 kg/m^2 and when no complete concentric palatal collapse (CCCp) is observed during drug-induced sleep endoscopy (DISE) [20]. The latter being subsequently confirmed in a larger set of OSA patients receiving HNS therapy with the Inspire II device [21].

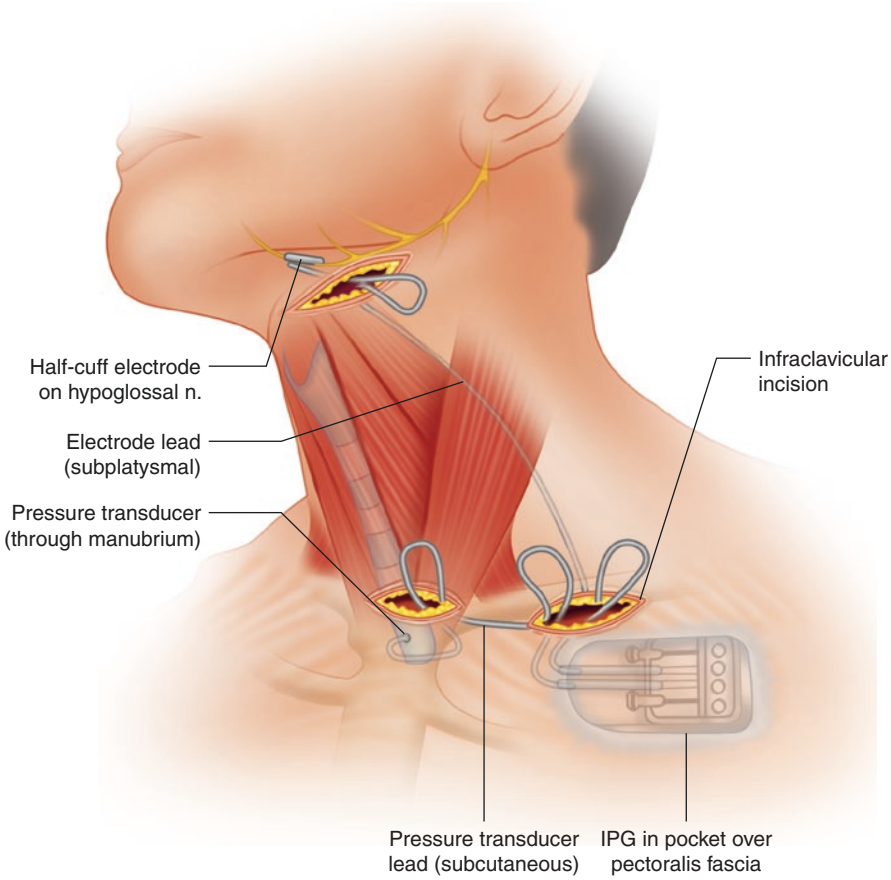

Fig. 4.2 Schematic overview of the different component of the Inspire I stimulating system (Medtronic Inc., Minneapolis, Minn, USA) and surgical access. Implantable pulse generator (IPG) placement in an infraclavicular pocket superficial to the pectoralis major muscle fascia. The nerve-electrode lead and pressure-transducer lead are tunnelled to the IPG pocket and connected to the IPG. (From Eisele [17]; with permission)

A next phase in the clinical evaluation of the second generation Inspire devices for upper airway stimulation therapy using unilateral HNS was the Stimulation Therapy for Apnea Reduction (STAR) Trial. This international multicenter, prospective, single-group trial with participants serving as their own controls evaluated the effectiveness of the therapy in a group of 126 patients with moderate to severe OSA with a history of nonadherence to CPAP. The analysis of the endpoints 12 months after implantation could illustrate that this unilateral stimulation of the hypoglossal nerve, synchronous with ventilation, resulted in significant and clinically relevant reductions in the severity of OSA and self-reported sleepiness, and, meaningful improvements in quality-of-life measures at 1 year [4]. Serious adverse events were uncommon and the side effects were not bothersome to most

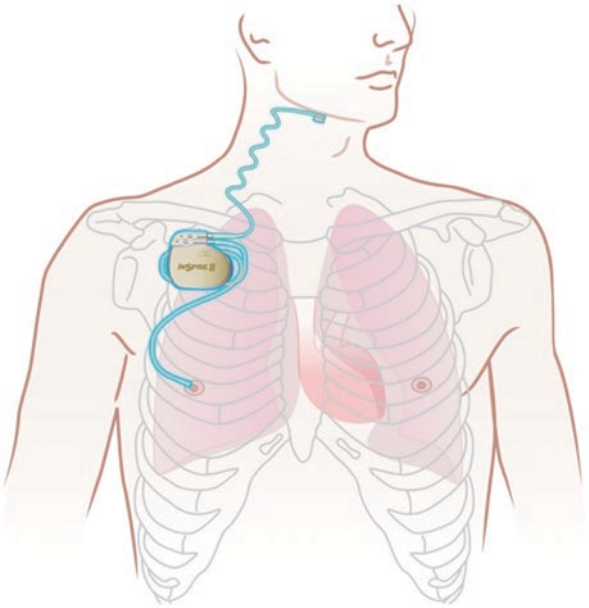

Fig. 4.3 Schematic overview of the different components of the Inspire II-IV therapy concept. The respiration-sensing lead located at the level of the fourth or fifth intercostal space detects in- and expiration of the patient during sleep thereby measuring the respiratory cycle. After conversion of the respiratory signal by the neurostimulator or IPG, placed in an infraclavicular pocket superficial to the pectoralis major muscle fascia at the right site, intermittent stimulating pulses are delivered to the hypoglossal nerve through the stimulation lead onto the cuff electrode around the protruding branches of the hypoglossal nerve. This means that a unilateral respiration-synchronized stimulation of the hypoglossal nerve generates a protrusion of the tongue. (With permission)

patients [4]. In addition, the results of a randomized, therapy-withdrawal part of the trial indicated that the reduction in the severity of OSA was maintained among those who continued the therapy illustrating that the therapy effect is due to stimulation [4].

The one-year follow-up findings of this STAR study published in the *New England Journal of Medicine*, are, up to this date, largely reassuring with regard to the clinical prescription of this innovative and emerging therapy to selected OSA patients.

DISE studies in a subset of patients that were under HNS therapy with the Inspire device, illustrated that HNS responders had larger retropalatal enlargement with electrical neurostimulation of the hypoglossal nerve as compared to non-responders and that the neurostimulation thus was able to increase both the retropalatal and retrolingual areas [22]. This observation of multilevel enlargement induced by upper airway neurostimulation therapy may provide an additional strength to the sustained reductions of OSA severity in selected patients receiving HNS therapy [4, 22].

Subsequently, the results of 5 year follow-up data on STAR trial were published in *Otolaryngology–Head and Neck Surgery* and confirm sustained improvements in sleepiness, quality of life, and respiratory outcomes during 5 years via a unilateral hypoglossal nerve implant in these patients with moderate to severe OSA who have failed nasal CPAP while serious adverse events were uncommon [5]. These results confirmed HNS therapy with the Inspire device as a nonanatomic surgical treatment with long-term benefit for these patients [5].

Meanwhile other systems for HNS therapy were evaluated for the treatment of OSA. Results of most of these trials have been published and confirm the safety and feasibility of implantable systems for HNS therapy for OSA [3, 23–25].

The HGNS system (Apnex Medical, Inc., St. Paul, MN, USA; Fig. 4.4) was evaluated at 12 months following implantation in up to 31 OSA patients [26]. The results revealed a significant decrease in the AHI when applying HGNS together with favorable safety and feasibility of this therapy [26]. The company Apnex Medical ceased operation in 2013.

A next HNS system that has been under investigation is the Aura6000 system (Fig. 4.5) originally developed by ImThera Medical, Inc. (San Diego, CA, USA) and now owned by Liva Nova PLC (London, UK) [19]. The Aura6000 consists of six electrodes within a multi-electrode lead that are placed surgically around the trunk of the hypoglossal nerve [27, 28]. This so-called targeted hypoglossal neurostimulation (THN) uses cyclical neurostimulation to ensure no single nerve fiber is

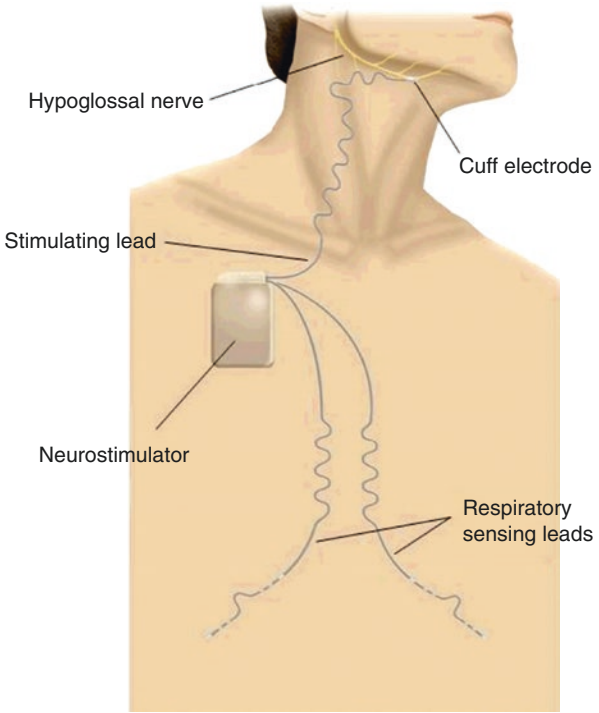

Fig. 4.4 Schematic overview of the implanted components of the HGNS system (Apnex) including a neurostimulator that delivers electrical stimulation to one hypoglossal nerve via a stimulation lead having a distal cuff electrode. Respiration sensing leads detect inspiration using bioimpedance, enabling the system to deliver stimulation synchronous with inspiration. (From Kezirian et al. [26]; with permission)

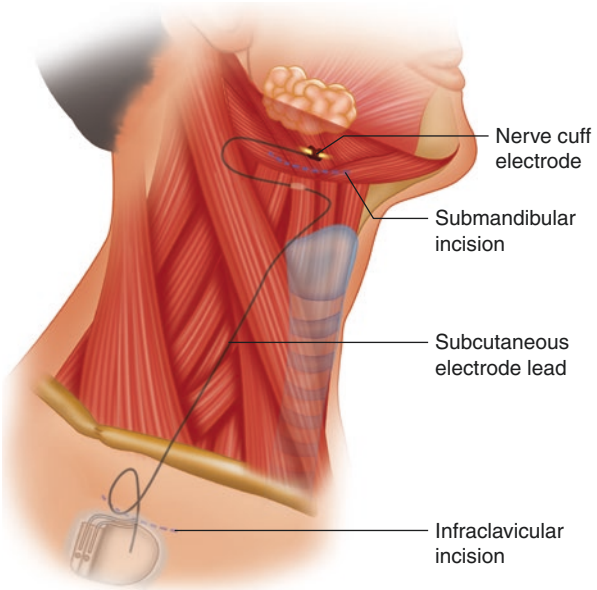

Fig. 4.5 ImThera Aura6000 Medical's targeted hypoglossal neurostimulation system (Liva Nova). A pulse generator is implanted subcutaneously below the clavicle. A submandibular incision is used to expose the hypoglossal nerve trunk, and a lead cuff is placed around the nerve. The wire is passed subcutaneously using a canula and connected to the pulse generator. (From Friedman et al. [27]; with permission)

stimulated continuously to avoid muscle fatigue [19, 23]. The Aura6000 system provides a continuous neurostimulation onto the body of the proximal hypoglossal nerve via the multi-electrode lead, thereby obviating the need for respiration-sensing leads; whereas with the Inspire devices, the hypoglossal nerve stimulation is intermittent and synchronized with the respiration-sensing leads that measure the respiratory cycle. Therefore, this system, in contrast to Inspire and Apnex, does not utilize a sensing lead necessitating only two surgical incisions when implanting the Aura6000 system [27].

In a first study published by Mwenge et al. unilateral THN was implanted successfully in 13 out of 14 patients with moderate to severe OSA [23]. The study protocol included follow-up polysomnography 12 months after surgical implantation and a significant reduction in AHI as demonstrated together with improvements in oxygen desaturation index (ODI), arousal index and daytime sleepiness [23]. In a provisional last publication, the authors report the results of an open-label multicentre study suggesting that THN therapy being likely to be safe and effective in selected OSA patients with a baseline AHI lower than 65 per hour sleep and a baseline BMI not higher than 35 kg per square meter [27].

The concept of the Genio™ system for HNS therapy (Fig. 4.6 – Nyxoah SA, Mont-Saint-Guibert, Belgium) is quite different from the three other systems as it provides bilateral stimulation of the nerve and does not consist of an implantable pulse generator or IPG. The Genio™ system is implanted submentally and stimulates the terminal branches of the hypoglossal nerve bilaterally via an implanted neurostimulator that will be activated externally [25]. The external activation is provided by a disposable patch submentally on which the activation chip with its own

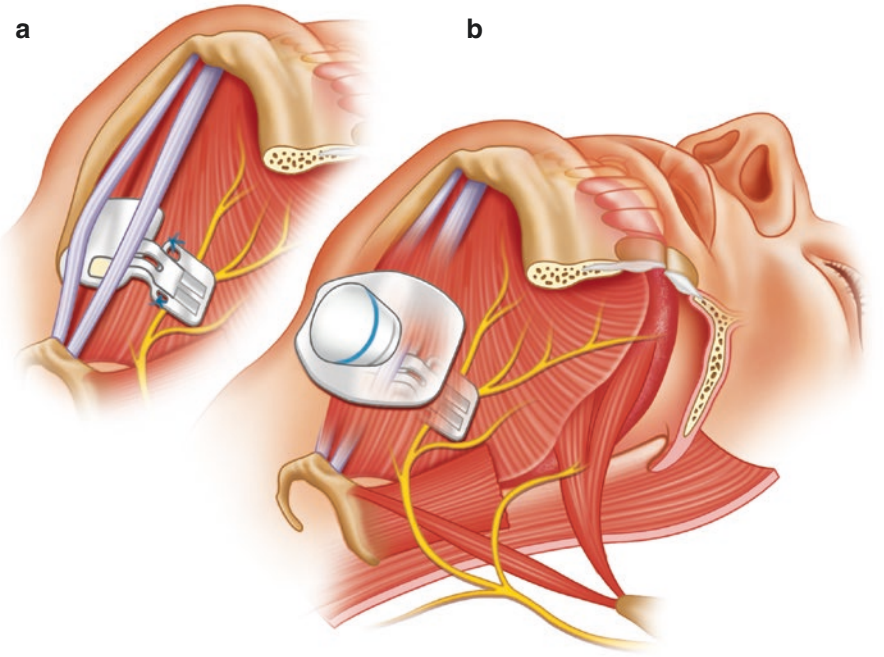

Fig. 4.6 Overview of the components of the Genio™ system for HNS therapy (Nyxoah SA, Mont-Saint-Guibert, Belgium). (**a**) the implanted stimulator straddling the genioglossus muscles and protruding branches of the hypoglossal nerve bilaterally and (**b**) the disposable patch and activation unit. (From Eastwood et al. [25]; with permission)

rechargeable battery will be connected every night. A patented duty cycle algorithm will use the patient's breathing frequency as a reference to make adjustments to the stimulation cycle.

The results published in 2020 by Eastwood et al. report on 27 implanted patients with moderate to severe OSA. The data suggest that the relative non-invasiveness of Genio HNS therapy does not compromise its effectiveness relative to the other methods [25]. During the six-months post-implantation period no serious adverse events occurred and significant improvements in AHI, ODI, quality of life and snoring were noted [25].

Currently, several clinical trials that evaluate Genio therapy are enrolling. The Dual sided hypoglossal neRvE stimulAtion for the treatMent of obstructive sleep apnea (DREAM) study is an international multicentre FDA supervised pivotal trial with the target to implant 134 CPAP intolerant patients with moderate to severe OSA without CCCp on baseline DISE.

At this stage, the data in the literature on the use of Inspire HNS therapy is quite impressive with a proven track record of good adherence to the therapy and evidence on a remarkable clinical efficacy. Up to 30,000 patients did already undergo implantation with Inspire therapy with treatment reimbursement in an increasing amounts of countries worldwide.

The ADHERE Registry is an international multicentre prospective observational cohort study following outcomes of HNS Inspire therapy in patients who have failed CPAP therapy for OSA. The aim of this registry is to assess the outcomes of patients receiving this treatment of OSA in the "real world" setting outside of clinical trials. Up to February 2019 the registry had enrolled more than 1000 patients while an interim analysis on patients that completed their 12-month follow-up demonstrated that also in routine settings the HNS Inspire therapy effect is durable with significant improvements in both subjective and objective OSA outcomes and high adherence to the therapy [29].

Within and outside ADHERE the quest for the additional predictors for more successful HNS therapy is ongoing [29] with further analysis of, among others, the role of cross motor innervation of the hypoglossal nerve and other neuromuscular stimulation aspects of HNS, DISE phenotyping and polysomnographic pathophysiological endotypes [21, 30–32].

Currently, apart from an animal study reporting on electrical stimulation of the superior laryngeal nerve for apnea recovery [33], no evidence on electrical neurostimulation therapy for central sleep apnea can be demonstrated from a review of the existing literature.

In conclusion, many clinical trials and systematic reviews indicate that HNS therapy for selected OSA patients seems to be safe with high rates of compliance and therapy adherence, and, stable outcome results over several years of follow-up [5, 12, 18, 19, 24, 26, 29, 34–37]. A fascinating story of research and development for over 35 years has led to the clinical implementation of this innovative therapy while evaluation and further improvement of HNS therapy for OSA continues.

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Chapter 5
Embryology of the Hypoglossal Nerve

Clemens Heiser and Nico de Vries

Contents

Introduction and Background

The human cranial nerve XII, also known as the hypoglossal nerve (HN or CN-XII henceforth), is both distinct and unique within the mammalian kingdom. The speech faculty and voice apparatus of humans are together also unique within this kingdom. Regardless of which came first, this combination of genotypic and phenotypic uniqueness unarguably sets *Homo sapiens* apart and distinct from all other creatures

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in our ability to willfully articulate speech free of prompting, mimicry and any other manner of techniques utilized in eliciting speech from other animals, be they avian (e.g., parrots), equine (e.g., counting horses) or any other technique of creating something superficially akin to human speech in all its complexity and potency [1]. The price of admission for these apart-and-above faculties is the floating hyoid bone within our long, musical-instrument neck and the propensity for humans to be almost unique in being vulnerable to obstructive sleep apnea (OSA). The only other readily known mammals to incur the burden of OSA are select members of the species *Canis lupus* whose relatively plastic genomes have allowed them to be artificially selected for facial traits mimicking those of their human masters – or perhaps human supplicants. A classic example might be the English bulldog said to be favored by the likes of Sir Winston Churchill. We may not know if the great Churchill suffered from OSA, but one can readily discern the difficulty some dogs have in breathing, even when they are awake and active, simply by listening to their labored breathing while they are awake and alert. Similarly to our dogs with compromised nasopharyngeal patency, it is important to recognize that further downstream toward the passage between our vocal cords lies the vulnerable segment from the soft palate to the epiglottis where the Bernoulli Effect can operate on the Starling Resistor of the relatively soft, compliant retropalatal, oropharyngeal, glossopharyngeal and hypopharyngeal airway segments, giving us OSA.

Human Predisposition to OSA and Hypoglossal Nerve's Unique Role in Treating OSA

The very same CN-XII that gives us speech and predisposes us humans to potentially-debilitating OSA, is precisely the target through which carefully applied neuroelectrotherapeutic energy from an active implantable device system can, in indicated patients who are refractory to Continuous Positive Airway Pressure (aka CPAP), effect meaningful objective and subjective reductions in the burden of OSA for a majority of patients so treated. Given the unique and critical attributes that CN-XII plays in setting humans apart – if not necessarily above and beyond – from all other mammals, one can argue that evolution has tucked it away rather deeply, ensconced away from much, if not all, harm that might befall a human under duress. In fact, violent crimes or traumatic accidents that result in potentially life-threatening harm to the victim are much more likely about exsanguination via jugular veins or carotid arteries, asphyxiation through strangulation which may oftentimes be accompanied by forensic evidence in the form of a severely traumatized hyoid bone; but rarely, if ever, is the person who had a terrible brush with mortality that involved the neck coming away having barely escaped with an intact hypoglossal nerve. Undesirable transection of CN-XII nerve is, in fact, more likely

to occur in a surgical setting whereby the HGN is mistakenly confused for another nearby structure such as salivary duct, sublingual nerve or mylohyoid/anterior belly of digastric muscle nerve. During most head and neck surgery residencies during the modern evidence-based era with extensive anatomic knowledge, especially regarding *no-fly* zones, residents are taught very well that the human hypoglossal nerve is something to recognize, respect and leave alone to the extent possible so that the patient is not inadvertently compromised in any aspect of their speech or swallowing, concomitant to whatever surgical procedure is taking place. Therefore, when upper airway stimulation in general, and selective upper airway stimulation (s-UAS) came into the canon of many leading practitioners of surgeries to lessen the burdens of OSA in CPAP intolerant patients, understandable concerns and misapprehensions surrounding the distal CN-XII came to the fore in relatively short order.

Objectives for Detailed Anatomic Primer on Distal Ramifications of Human Hypoglossal Nerve

The authors of this chapter have had the good fortune to work closely with the distal HN in hundreds of combined implants, and through vicarious teaching, wish to impart relevant, detailed and directive anatomic information about this vital region of the human CN-XII in order to:

- Operate from a factual basis of knowledge about the detailed human HN anatomy as well as all the anatomic structures that either support this nerve complex or can be encountered *en route* to finding one's way to the nerve, preparing it to receive chronic s-UAS and then leaving the premises without unnecessary disruption of the nerve and its supporting structures;
- Enable surgeons new to the surgery to ensure good patient surgical outcomes from the very first implant;
- Prevent the myriad avoidable pitfalls, problems, frustrations and complications that can accompany this unique surgical approach within the larger canon of head and neck surgery;
- Anticipate the likely future that today's techniques, while heavily refined over the preceding 5–10 years' advances, will be further refined and possibly become antiquated as improved technology, information dissemination and therapeutic refinements render quaint that which is currently regarded as on the leading edge;
- Generate a high degree of competence and confidence around this procedure while simultaneously discouraging any cavalier or dismissive approaches along the lines of, "This is just like…so just give me the patients, the equipment and forget about all the pedantry".

Basis for Selective Upper Airway Stimulation

Harking back to evolution's safeguarding of the HN by essentially tucking it away so deep within the neck that it would literally be most quickly accessed by operating from deep-to-superficial, commencing within the oral cavity – an untenable approach due to device-related infection concerns. Instead, the current state of the art is to approach the distal HN in a manner that is most akin to that which may be taken in conducting an excision of the submandibular gland. In fact, the earlier explorations into functional stimulation of the HN for purposes of treating OSA did just that. Eventually, it was established beyond reasonable doubt that the targeted region of the human HN was not that portion typically encountered during a submandibulectomy (postero-inferior), rather it is the most distal aspect of the nerve where it heavily ramifies on the approach to the anterior border of the hyoglossus muscle (anterosuperior) that is directly targeted in s-UAS in order to readily visualize and gently manipulate the many branches of HN's medial, or distal, division towards ensuring that the desirable, helpful branches are both included in the electrical field and the undesirable, hindering branches are excluded from the electrical field. Toward the great benefit of applying this therapy today and advancing it going forward, we must now turn our attention to some esoteric findings regarding human hypoglossal neuromuscular embryology.

Human Hypoglossal Neuromuscular Embryology

During human hypoglossal embryologic development of the hypoglossal nerve and the somites for both its individual branches as well as the somites for the muscles those branches will be innervated, it has been amply demonstrated that the main trunk of the HN will have emerged from the developing brain within roughly 40 days of fertilization, essentially laid in from the brain to the very tip of the future tongue and included within this impressive, early nerve are all the somites, or seeds, for each individual muscle and the somites for the individual nerves that will innervate them. By virtue of this early venturing out of a more-or-less complete HN, a surgical approach that endeavors to treat OSA through application of electrotherapeutic energy to select branches of this nerve complex can operate with a high degree of certainty when it comes to where the anatomic structures should be targeted and what one can find upon arriving at the destination. In summary, the human HN is a highly conserved structure that can be approached in a deterministic fashion. The terminal branches of the human HN and the muscles they innervate are laid out in a fashion, from caudad to cephalad, that stands to reason within the framework of its embryology being highly conserved, and this conservation facilitates an important certainty of the surgical approach.

Muscles Relevant to Upper Airway Stimulation Implant Procedure

For purposes of this specialized chapter, and prior to delineating the surgical objectives vis-à-vis a proscribed approach to dissection and preparation of the HN, one muscle that is reasonably well established as not being innervated by the HN, but plays a role in treating OSA and is typically included for ipsilateral s-UAS, will be swept into the discussion. This muscle is the *Geniohyoid*, which consists of paired, tubular muscle capsules that originate from the genu of the mandible and insert into the body of the hyoid with the contractile action of simultaneously elevating and anteriorly displacing the hyoid. The potency of this so-called *dynamic hyoid suspension* during pulses of s-UAS has been previously described in the literature, including ultrasound demonstration of the phenomenon. The geniohyoid is innervated by a so-called c-1 branch composed of fibers from the first cervical nerve, and travelling alongside the HN until the vicinity of the anterior margin of the hyoglossus muscle at which point separated and arcs inferiorly to its target muscle. The c-1 reliably occupies the inferior-most portion of the branches targeted for s-UAS therapy.

The subset of muscles and accompanying nerves of the human tongue that are unarguably relevant to s-UAS, listed from caudad to cephalad:

- Geniohyoid (c-1)
- Genioglossus-horizontal (GGh)
- Genioglossus-oblique (GGo)
- Transverse/Vertical (T/V)
- Hyoglossus (HG)
- Styloglossus (SG)

Within any given patient, there are definitive, deterministic targets of anatomic identification, recruitment and exclusion for the purposes of achieving tongue motion that will facilitate the patient having the best opportunity to achieve meaningful symptomatic relief from their given OSA.

It is most helpful to categorize these individual muscles by virtue of how they contribute to – or detract from – what has been established as optimal tongue motion. First, and perhaps most obvious, are protrusors, encompassing three extrinsic muscles: Geniohyoid, Genioglossus-horizontal, and Genioglossus-oblique. These three muscles are generally included in the s-UAS stimulation field, excepting that, upon occasion there will be one or more reasons to not include the c-I branch to Geniohyoid. The next group of muscles, for the unique purposes of s-UAS, are labeled and abbreviated in the singular Transverse-Vertical, or T/V and their *en masse* activation serves to stiffen the body and blade of the tongue. T/V are always targeted for inclusion in the s-UAS stimulation field. The third, and final, group of relevant muscles are the extrinsic retractors: Hyoglossus and Styloglossus. Both of these muscles and their innervating branches of HN are always targeted for exclusion, though on occasion small, and typically cryptic, a branch of the

Hyoglossus may inadvertently end up included within the stimulation field, either by being explicitly contained within the cuff or by being so tightly adherent to the nerve that some portion of it can be excited during certain stimulation conditions (e.g., higher device output in a so-called unipolar, or farfield, electrode configuration) that predispose the capture field to essentially reach outside the boundaries of the cuff itself, most notably in the posterosuperior aspect where a final HG branch will be nestled up closely to the cuff boundary.

The Functional Breakpoint

Revisiting the highly conserved general branching pattern of the human HN, the point of separation (i.e., Functional Breakpoint) between branches to include in the s-UAS stimulation field and branches to exclude is identical from patient to patient at a strategic level. This functional breakpoint will always ideally be found and accentuated along the superior aspect of the nerve, between the anterior-most HG branch of which a typical human has three to five discrete HG branches, and the T/V which tends to be monolithic and overtly three-dimensional along the superior, distal HN.

Highly Relevant Anatomic Structures

In accessing the human CN-XII, there is a sequence of discrete anatomical landmarks to identify, interact with, free from one another and – most importantly – be certain to never mistake one for another. Particular structures that can masquerade as another, to the consternation of the operative team and possibly to the detriment of the patient, are:

- Cranial nerve V branches that innervate Mylohyoid Muscle and/or Anterior Belly of the Digastric Muscle, mistaken for HN distal ramifications;
- Ptotic Sublingual (cranial nerve VII) Nerve branch mistaken for HN main trunk;
- Superior border of Anterior Belly of Digastric Muscle mistaken for posterior border of Mylohyoid Muscle.

From late 2011, during the latter implants of the STAR Trial [2], through the present time, meaningful refinements to approaching HN for purposes of s-UAS afford the operative surgical team a definitive approach to reaching the distal HGN regardless of the phenotypic and genotypic heterogeneity thus far encountered, including patient presentations as atypical as Trisomy 21 [3–10], Trisomy 9, Niemann-Pick Syndrome Type C, retro/micrognathia, as well as a wide variety of relevant prior surgeries (e.g., MMA [11, 12], genioglossus advancement, hyoid suspension, etc.). Perhaps the greatest utility of a practical guide to anatomy of the distal HN may come in the form of a navigational recipe that reliably brings the surgeon to the

anatomy in a successful, repeatable manner that starts with the first several implants and continues to be the best method of access regardless of the number of surgical assistants, their relative expertise, familiarity with the s-UAS implant process. Toward that end, hereunder the reader can see such an approach that has met with great success, including minimizing risk and disruption to the HN and its supporting structures as well as to adjacent structures known to be vulnerable to being damaged (e.g., marginal mandibular branch of the cranial nerveVII Facial Nerve).

Vena Comitans of the Hypoglossal Nerve

Given the critical nature of the human HN, particularly to speech and swallowing during times of conscious control and to maintenance of airway patency during times of sleep and unconscious control, there is a substantial metabolic demand and resultant venous return structures, namely in the form of the *vena comitans* of the hypoglossal nerve which is occasionally also referred to as a ranine vein, though the etymology for the word ranine traces to a now-defunct dialect of ancient French and might best be dispensed with in preference to the Latin *vena comitans* so clearly elucidates the role of this anatomic structure. This common vein of the hypoglossal nerve typically forms a singular large vessel that courses coincident with the inferior aspect of the HN main trunk, receiving venules along its length from the various individual nerve branches and many of the myocytes of their innervated muscles. Occasionally there will be a bifurcation, or even trifurcation, of the *vena comitans* with additional, large-caliber veins that may course along the superior aspect of the HN prior to merging with the main, inferior *vena comitans*. While this large vein can be ligated and divided to minimize its ability to obscure the preparation of nerve branches for inclusion within the s-UAS energy field, many practitioners are increasingly preserving the essential structure and integrity of the main *vena comitans* as it can generally be safely separated from the inferior aspect of the HN without insult or injury to either structure, and is oftentimes encircled with a fine caliber vessel loop accompanied with a light clamp to temporarily collapse the vein and displace it inferiorly, being released and re-sanguinated upon placement of the stimulation cuff.

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Chapter 6
Considerations of Facial Skeletal Morphology to Optimize Upper Airway Stimulation

Stanley Yung-Chuan Liu and Mohamed Abdelwahab

Contents

Introduction

The syndrome of obstructive sleep apnea (OSA) is a chronic condition diagnosed by five or more recurrent episodes of partial or complete upper airway collapse resulting in increased passive critical closing pressure of the upper airway (Pcrit) during sleep. Upper airway collapsibility occurs due to the variation in transmural pressure and reduction in the longitudinal tension of the pharyngeal airway. This collapse is a result of either a discrepancy between skeletal size and upper airway muscles with lymphoid tissue, increased laxity of the muscles, or a combination of both [4, 5]. Neuromuscular dysfunction of breathing during sleep plays an important role in the pathophysiology of OSA.

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Diagnosis of OSA mandates an overnight polysomnography. Yet, it does not provide details about the location and pattern of airway collapse [29]. Drug-induced sleep endoscopy (DISE) is a validated tool and may facilitate recommendation of suitable therapy on an individual basis [30]. Additionally, clinical and radiologic analyses provide insight to the anatomical phenotype of OSA patients. For example, increased awareness of skeletal phenotypes such as transverse maxillary deficiency has resulted in introduction of new interventions such as distraction osteogenesis maxillary expansion (DOME) [2, 36, 65].

Advances in surgical management of OSA has also evolved to a patient-centered approach, where upper airway stimulation (UAS) plays a critical role. The therapeutic efficacy of UAS in treating OSA has gained a worldwide interest, especially after publishing the 12 months results of the STAR trial [59], followed by the 5-year outcomes showing consistent results [66]. The updated Stanford Sleep Surgery Protocol has suggested ways to incorporate UAS with classic soft tissue, nasal and skeletal procedures [34, 35, 42, 57]. This update incorporates procedures in a continuum rather than a unidirectional one, as shown in Fig. 6.1. Additionally, the protocol demonstrates the versatility of palatopharyngoplasty in transforming UAS eligibility in the setting of complete concentric collapse [34, 41]. In this chapter, the physiologic synergy between skeletal procedures such as the maxillomandibular advancement (MMA) and UAS will be discussed in detail.

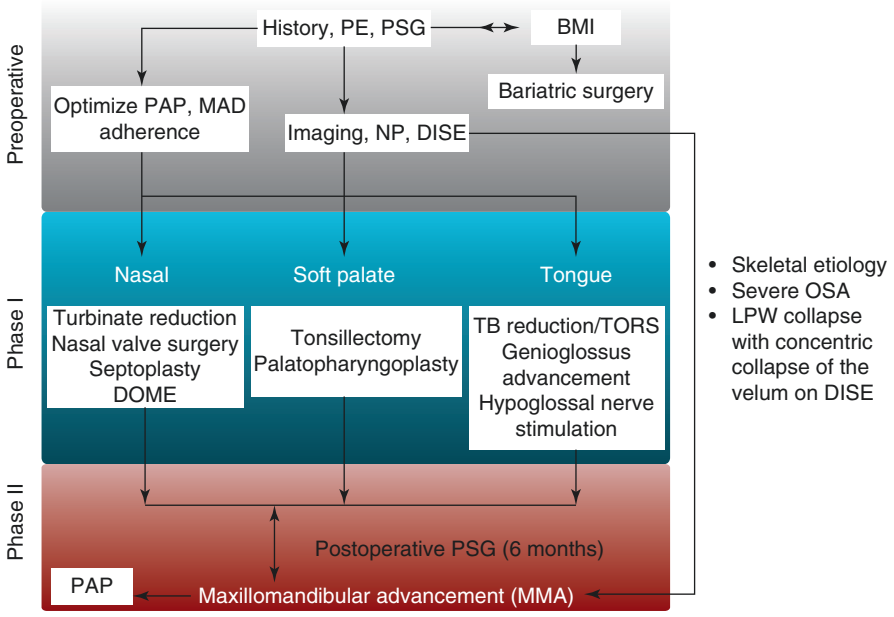

Fig. 6.1 The updated Stanford Sleep Surgery Protocol

Recognizing Soft Tissue and Skeletal Anatomic Risk Factors of OSA

During inspiration in non-OSA subjects, narrowing of the airway is minimal because the dilator muscles activate and counteract negative intraluminal pressure. In OSA subjects, increased dilator muscle collapsibility results in reduction or cessation of airflow [23]. Although it is unclear if airway collapsibility is a sequela or cause of aberrant soft tissue and skeletal characteristics, certain morphologic and physiologic changes are strongly linked to OSA.

OSA is associated with the following soft tissue risk factors:

Soft tissue risk factors	References
Increased upper airway length, soft palatal length and neck circumference.	Shigeta et al. [55]
Decreased distance between the hyoid bone and the posterior pharyngeal wall.	Sforza et al. [54], De Backer [14]
Increased volume of the tongue and lateral pharyngeal walls (MRI).	Schwab et al. [53]
Increased compliance of the soft palate leading to collapse at the velopharyngeal level.	Ciscar et al. [12]
Increased tonic and phasic activation of upper airway dilator muscles, especially the genioglossus muscle, during wakefulness as compared to REM sleep confirmed by electromyography (EMG). On the other hand, their activation is reduced during sleep, consistent with neuromuscular compensation for an anatomically compromised airway.	Mezzanotte et al. [44], Eckert et al. [16]
Decreased response to negative pressure by palatal muscles (particularly levator palatini and palatoglossus).	Mortimore and Douglas [46]
Increased airway mucosal water content consistent with snoring-induced vibratory trauma.	Ryan et al. [51]

OSA is associated with the following skeletal risk factors:

Skeletal risk factors	References
Increased distance between the hyoid bone and posterior nasal spine; and between hyoid bone and mandibular plane.	De Backer [14], Miles et al. [45], Sforza et al. [54], Huon et al. [27], De Backer [14]
Decreased angle and length of the cranial base consistent with anterior-posterior shortening of the cranium, forward position of the cervical spine, and maxillomandibular retrusion.	Steinberg and Fraser [58], Lowe et al. [43]
Decreased SNA and SNB angles suggesting maxillomandibular retrusion.	Cistulli [13]
Increased lower anterior facial height described as the adenoid facies or “long face syndrome”.	Lowe et al. [43], Tangugsorn et al. [60], Tomes [61]
A “clockwise” rotated maxillomandibular complex, with steep occlusal plane.	Lowe et al. [43], Tangugsorn et al. [60], Miles et al. [45]
Decreased maxillary transverse dimension resulting in posterior tongue displacement and increased nasal resistance (Fig. 6.2).	Cistulli [13], Williams et al. [65]

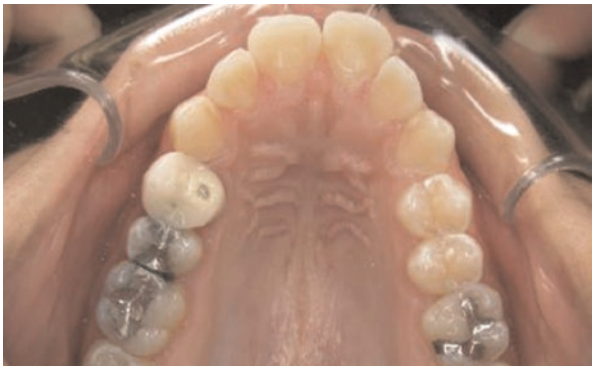

Fig. 6.2 Maxillary transverse deficiency

Anatomical and Physiologic Considerations of the Tongue

The function of the tongue includes swallowing, speech, and respiration; and its dysfunction results in dysphagia, aphasia, and obstructive sleep disorders, respectively [25]. Its anatomy and physiology plays an important role in maintenance of upper airway patency.

The tongue is comprised of muscles oriented in different directions, whose biomechanical properties are similar to a hydraulic system [31]. There are extrinsic and intrinsic muscles. The intrinsic muscles are the superior longitudinal, inferior longitudinal and the transverse and vertical muscles. The superior longitudinal muscle spans the length of the tongue just beneath the mucosa of its dorsal (superior) surface and is the only unpaired muscle of the tongue. The inferior longitudinal muscle spans the length of the tongue just above the mucosa of its inferior (ventral) surface. The transverse (T) muscle connects the medial septum to the lateral aspect of the tongue, and the vertical (V) muscle connects the inferior surface to the superior surface.

The extrinsic group includes the genioglossus, hyoglossus and styloglossus muscles. The genioglossus muscle is a midline muscle that originates from the genial tubercles on the lingual surface of the mandible. It is surrounded by the paramedian septum and is bordered laterally by the inferior longitudinal and hyoglossus muscles. The hyoglossus muscle originates from the hyoid bone and inserts into the inferior-lateral margins of the tongue [52]. The styloglossus originates from the styloid process and inserts along the inferior-lateral margins of the tongue.

Genioglossus Muscle Dysfunction in OSA

A big subset of subjects with OSA generate weak genioglossus activity in response to the negative airway pressure [16]. The genioglossus is the muscle that is the most different between humans and other mammals, where in the latter it's smaller and

limited to the midline [47]. The human genioglossus muscle is larger and can be distinguished by the extrinsic component outside the tongue, and the intrinsic component within the tongue. It is a pair of muscles that originate from the inner midline of the mandible and spreads posteriorly in a 90 degrees arc. All its fascicles enter the intrinsic tongue and terminate in the dorsal tongue, with lateral extensions to the T/V. The lateral fascicles of the oblique genioglossus do not pass directly vertical but course slightly obliquely, and this oblique orientation increases in the tongue base. Anteriorly in the intrinsic component, the muscle is thin, and its fascicles are vertically oriented, with the most anterior fibers forming the frenulum.

The main physiological action of the genioglossus is tongue protrusion, caused by the horizontal compartment and the posterior fascicles of the oblique compartment. Further actions include depression of the tongue dorsum by the more vertically oriented component, antero-flexion and tongue tip retrusion by the most anterior muscle fibers. The midline insertion of the muscle changes the cross-sectional shape of the tongue dorsum contributing to swallowing and speech movements.

Hypoglossal Nerve

The upper airway neuromuscular feedback control loop or reflex has an afferent pathway from the pharyngeal mucosa to the superior laryngeal nerve, and an efferent pathway via the hypoglossal nerve to the genioglossus and other upper airway dilators [15]. The hypoglossal nerve innervates the intrinsic muscles of the tongue as well as the extrinsic tongue muscles: the genioglossus, the styloglossus, and the hyoglossus. Another extrinsic muscle of the tongue, the palatoglossus, interdigitates with the genioglossus, is separately innervated by cranial nerve X [24].

Although the two genioglossus components may appear to be continuous, the components are innervated by different branches of the hypoglossal nerve. The nerve arises from the hypoglossal nucleus in the medulla oblongata and exits the skull through the hypoglossal foramen. It descends into the neck deep between the internal carotid artery and the internal jugular vein, running deep to the posterior belly of the digastric muscle and its tendon. Then it runs deep to the mylohyoid muscle, where it divides into lateral and medial branches. The lateral branches innervate the styloglossus and hyoglossus muscles or exclusion branches, while the medial branch innervates the genioglossus and the intrinsic tongue musculature (transverse and vertical muscles), or else the inclusion branches [28].

Multilevel OSA Surgery

The most vital factor in determining surgical success is precise patient selection [32], and mindful recognition of the anatomical level(s) of obstruction [20]. Riley et al. first outlined the concept of treating multilevel obstruction in OSA [49]. A

high percentage (87–93%) of OSA subjects present with multilevel compared to single-level obstruction [3, 49]. A combination of palate and tongue base collapse was reported to be the most frequently observed collapse pattern, exceeding 25% [64]. Therefore, compared to single level surgery, multilevel surgery generally delivers better outcomes [21]. According to previous systematic reviews, the overall success rates of multilevel surgeries range from 61% to 66% [20, 33], that can be performed either in a single stage or in multiple stages, according to the surgeon's or the patient's preference or as a subsequent procedure in subjects with relapse.

The common approach to multilevel surgery includes palatal surgery e.g., uvulopalatopharyngoplasty (UPPP) or modern palatal reconstructive surgery that addresses the lateral pharyngeal wall as well, (e.g., expansion sphincter pharyngoplasty (ESP), or barbed wire pharyngoplasty (BRP)) with a second procedure for the hypopharyngeal airway. This may be hyoid suspension, genioglossus advancement, radiofrequency volume reduction, or transoral robotic surgery of the tongue base. The success rate in this population is variably reported between 20% and 100% [33]. In select patients, multilevel surgery can be effective with minimally invasive procedures. Such examples include combining radiofrequency reduction of the palate, tonsils, and the base of tongue with or without nasal surgery. Success rates were reported up to 77% [18, 19].

Maxillomandibular advancement (MMA) also exerts multilevel effects on the upper airway [39], with reported surgical success rates around 86% [26]. In the updated Stanford Sleep Surgery Protocol, there are better defined indications of when this can be performed prior to phase one procedures [34, 35, 42, 57].

Maxillomandibular Advancement: Indications and Multilevel Effect

Maxillomandibular advancement (MMA) is a complex upper airway procedure [56], but apart from tracheostomy, it has the highest surgery success and cure rates [67]. The mandible and maxilla are advanced together, maintaining or improving occlusion. Key updates to the contemporary Stanford MMA approaches are highlighted here.

The axis of maxillary counterclockwise rotation is designed to allow for a greater degree of mandibular advancement while optimizing facial esthetics. This is determined at the level of the zygomaticomaxillary buttress, which is quite different than other rotation centers previously described in orthognatic literature (Fig. 6.3). This is not surprising as orthognathic surgery entails making skeletal movements to address skeletal aberrations. MMA has the additional goal of addressing the airway. This is carefully designed during preoperative surgical planning and further optimized intraoperatively.

Piriform contouring after separation of the maxilla during advancement aids in improving functional nasal outcomes. The anterior nasal spine is contoured to avoid undesirable nasal tip projection or over rotation with subsequent adjustment of the

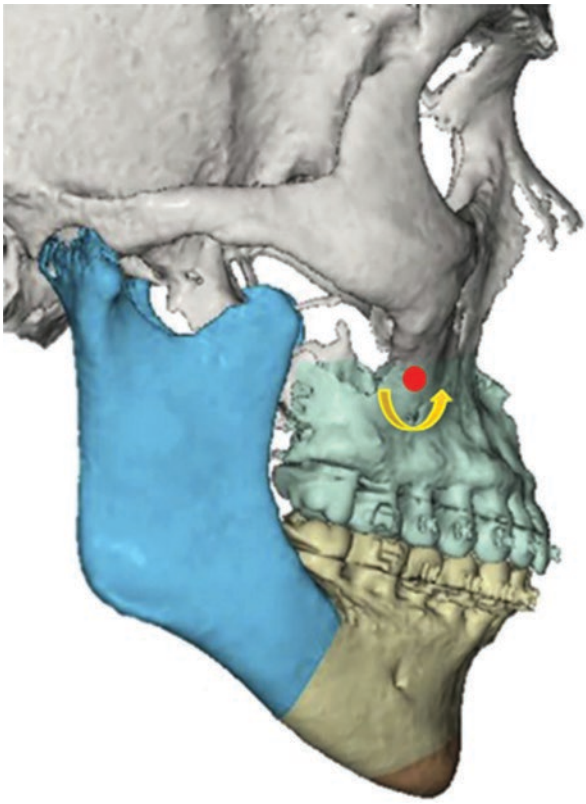

Fig. 6.3 The center of counterclockwise rotation at the level of the maxillary buttress

septal L-strut via an inferior approach (Fig. 6.4). We have elaborated on the various perioperative modifications applied to the nasomaxillary complex starting from case selection and surgical planning to the anesthetic and operative modifications, complete with postoperative nasal care. Corrective nasal surgery rates after MMA have decreased significantly from 18.7% to 6.5% with these implementations [1]. For maxillary stability, we place temporary suspension wires that are bony anchored, in addition to rigid fixation, to provide additional support for the maxilla in its new position (Video 6.1).

For the mandibular sagittal split, the anterior and horizontal osteotomies, shown in Fig. 6.5, have also been refined to optimize bony contact between the split and advanced segments. We found that significantly increased passive bony overlap when the superior horizontal osteotomy is made through the lingula completely (Video 6.2), and the anterior osteotomy just to the midline of the mandible's lower border [10]. Prior to fixation, attention is directed to ensure the proximal (condylar) mandibular segment is rotated with the inferior border now inferior to the distal segment. This effectively lengthens the vertical dimension (Fig. 6.6). This allows a more favorable axis of rotation that places less stress on the temporomandibular joints, despite the large advancement. Genioglossus advancement has been

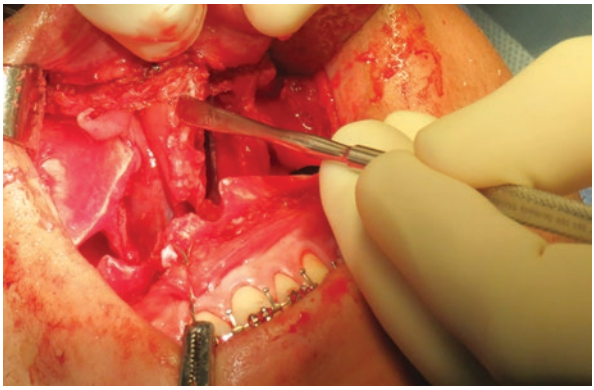

Fig. 6.4 An inferior approach to the septoplasty after the Le Fort 1 osteotomy while the maxilla is retracted inferiorly

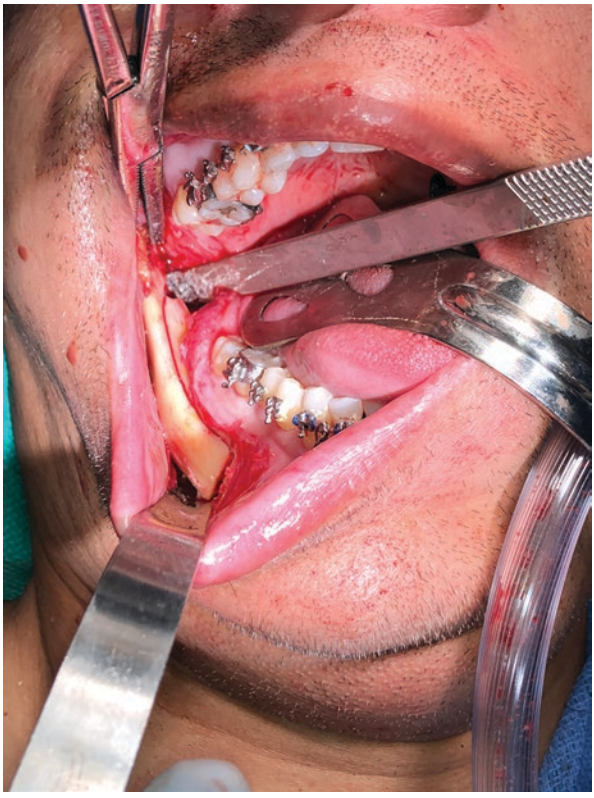

Fig. 6.5 Demonstration of the anterior and sagittal osteotomy after completion before mandibular splitting

streamlined with greater precision by using custom guides and 3D-printed plated to maximize precision and facial balance [37].

MMA expands: (1) the retropalatal portion of the airway by advancing the velum and the attached pharyngeal muscles (particularly the tensor palatini, palatoglossus and palatopharyngeus) [17], and (2) the retroglossal airway by advancing the tongue

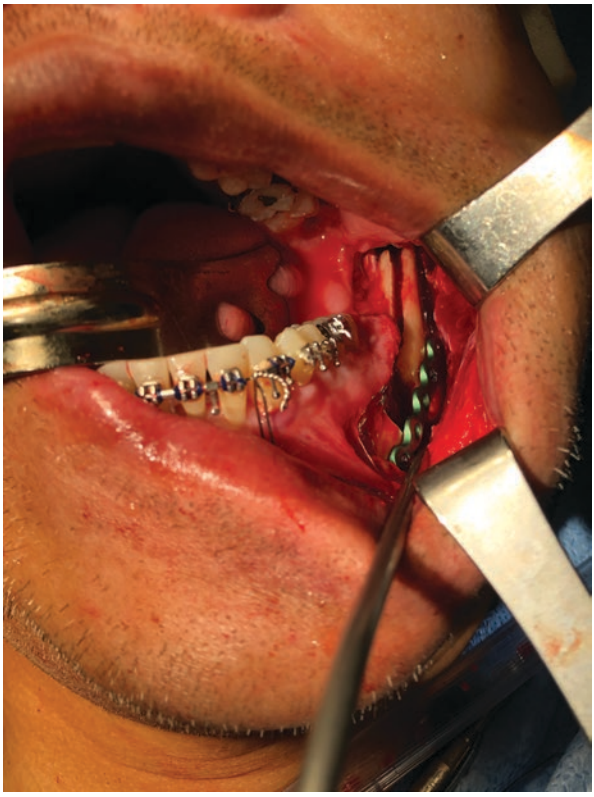

Fig. 6.6 Proper positioning of the proximal segment prior to internal fixation

and the suprahyoid muscles [6]. Via DISE, Liu et al. described the stability of the lateral pharyngeal wall being the most consistent predictor of MMA surgical success [39, 40], correlating with AHI and ODI reduction. When applying computational fluid dynamics (CFD) analysis, the reduction of airflow velocity at the retropalatal airway post-MMA correlated with improved polysomnography results [39]. Maxillary advancement correlates with AHI reduction [26, 67], where an increase of 1 mm corresponds to AHI decrease of 1.34 events per hour. For the mandible, an additional 1 mm advancement correlates with 0.5 mm gain in pharyngeal airway space [22]. For each 1 mm of airway gain, AHI was significantly reduced by 3.58 events per hour. Overall, the mean reduction in a routine MMA is approximately 30.9–50.6 events per hour, based on systematic review [22].

Today, the three primary indications for MMA include: (1) OSA of any severity where patient has concurrent dentofacial deformity, (2) persistent OSA after Phase 1 surgery, and (3) DISE findings of concurrent complete concentric collapse of the velum and lateral pharyngeal wall collapse. There is no upper limit for pre-operative AHI, with the knowledge that patients with very high AHI likely needs interventions after the MMA. With the advent of UAS, its synergistic action with MMA has become a promising therapy for the very severe patient [11, 34].

Upper Airway Stimulation: Indications and Multi-Level Effect

The application of UAS in managing OSA has gained popularity since the Stimulation Therapy for Apnea Reduction (STAR) trial showing 68% reduction in AHI severity. Its indications were outlined after studying responders to this therapy [62]. These include moderate to severe OSA (with AHI from 15 to 65), PAP failure, age more than 22 years, anteroposterior palatal collapse, and BMI less than 32 kg/m^2. Results has shown consistency with 3 and 5 years follow up [66]. Of note, there are certain contraindications; central or mixed apnea greater than 25% of the total AHI, complete concentric palatal collapse on DISE, preexisting anatomic alterations or neurologic disorders, and patients who require MRI on their torso including shoulders. Pediatric use is under clinical trial for patients with Trisomy 21 [8].

The current FDA-approved device used in the US is Inspire®. This device consists of an implantable pulse generator (IPG), stimulation electrode with a cuff placed around the inclusion branches of the hypoglossal nerve and a sensor lead embedded between the internal and external intercostal muscles to detect inspiration. The programmed device stimulates the hypoglossal nerve during timed inspiration to improve airway obstruction in moderate or severe OSA. More recent data from the ADHERE (Adherence and Outcome of Upper Airway Stimulation for OSA International Registry) registry show an overall surgical success rate of 81% [7].

The desired effect of UAS is an unhindered tongue protrusion and stiffening that dilate the pharynx and prevent tongue collapse. Stimulation of the inclusion nerve branches activates the genioglossus, the strongest dilator of the pharynx. Simultaneously, the activated intrinsic tongue muscles stiffen the tongue, preventing posterior pharyngeal collapse [52]. This resolves obstruction at the tongue base and epiglottis. Additionally, there is evidence of "palatoglossal coupling," where the retropalatal region opens with stimulation of the tongue musculature. This is explained by the anatomical interdigitation between the genioglossus and the palatoglossus muscles [24]. The displacement of the tongue mass anteriorly also relieves the pressure on the vulnerable velopharyngeal soft tissue resulting in a multilevel effect on the airway [24].

Combining MMA with UAS as a New Multi-Stage, Multi-Level Treatment Pathway

The utility of UAS has shown to improve sleepiness and quality of life by increasing the anterior-posterior (AP) airway dimension at the retroglossal and retropalatal regions [23]. However, its generalizability is limited by fitting effective selection criteria [63]. Previously, we demonstrated that tissue preserving UPPP consistently converts complete concentric collapse (CCC) of the velum to antero-posterior (AP) collapse, and thus reversing previously ineligible patients due to DISE

findings [41]. Similarly, MMA can convert both CCC and lateral collapse phenotypes reliably [39, 40].

Skeletal surgery for OSA was introduced at Stanford in 1986 as an alternative to tracheostomy [48, 50]. This has provided us with the opportunity to evaluate subjects who had MMA for the longest possible follow-up period. Although MMA has shown long term efficacy in managing OSA [9], the nature of the disease may eventually result in relapse with recurrence of daytime and/or nocturnal symptoms.

Liu et al. has previously reported the first case of a patient who was successfully treated with UAS 15 years after his MMA, when symptoms relapsed. He presented at age 65 with AHI of 21.8 events per hour. He was found to have no collapse of the velum and lateral pharyngeal wall during DISE. Relapse at the tongue level was evident. After UAS, his AHI was 0.7 events per hour on a setting of 1.5 volts. He subsequently reported an Epworth Sleepiness Scale (ESS) of 6 [38].

In recent years, 4 subjects with a mean age of 59.4 ± 9 years with MMA relapse, seen by the lead author, presented with recurrent symptoms and were not CPAP compliant. Their mean AHI prior to MMA was 79.3 events per hour. They would not have been UAS candidates, even if UAS were available at their initial presentation. The mean time to presentation for UAS after MMA in these individuals with relapse of symptoms was 17 years. While the series is limited, all subjects continue to show stability at the velum and lateral pharyngeal wall, but not at the tongue. The mean AHI for the subjects with relapse was 16.5 events an hour. They all achieved surgical cure after UAS.

Building on this experience, we have offered patients who initially present with AHI greater than 65 events an hour, and who also show concentric collapse at the velum and lateral pharyngeal wall collapse, the treatment sequence of MMA followed by UAS (Fig. 6.7). We have six such subjects, and five completed the sequence. The most dramatic example was a 65 year old man presenting with an AHI of 145 events an hour. We performed a modest MMA due to his age, which

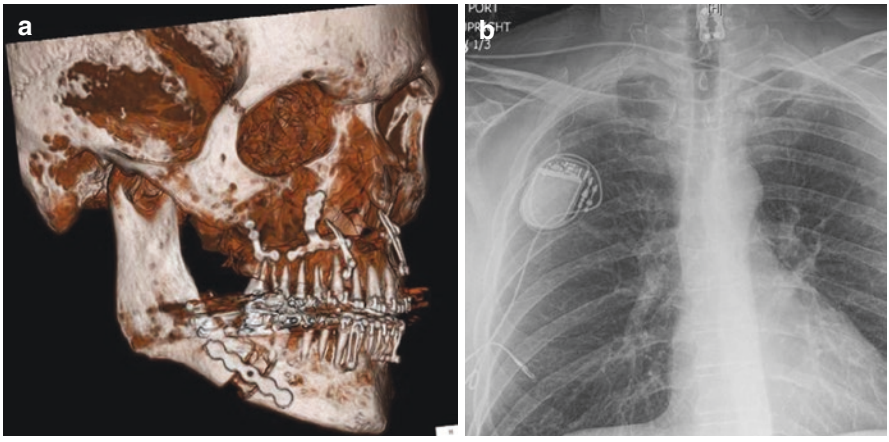

Fig. 6.7 Patient undergoing (**a**) maxillomandibular advancement and (**b**) upper airway stimulation

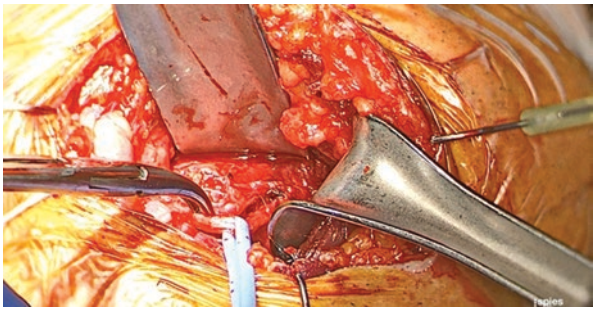

Fig. 6.8 Deep dissection to identify the hypoglossal nerve in a subject previously undergone a maxillomandibular osteotomy. The field shows the deep dissection needed and shows the length required for nerve undermining due to its stretch by the prior mandibular advancement

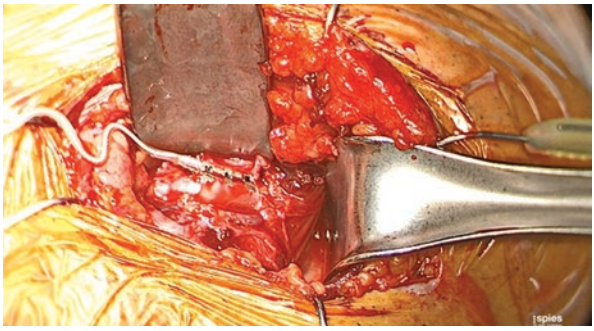

Fig. 6.9 Placement of the cuff around the stretched hypoglossal nerve in a subject who underwent an MMA

reduced his AHI to 28 events an hour. Approximately 11 months later, with UAS following MMA, his AHI is 3.2 events on 2.0 V, an hour with resolution of daytime and sleep-related symptoms.

From a technical perspective, we noted that after MMA, the exposure of the hypoglossal nerve is slightly more challenging. With the anterior and superior movement of the mandible, the hypoglossal nerve trunk for UAS is consistently deeper and requires further dissection (Fig. 6.8). Additionally, there tends to be a need for greater exposure of the medial nerve trunk for room to adequately place of the stimulation cuff (Fig. 6.9).

Conclusion

In summary, airway morphology changes in OSA interferes with upper airway patency and increased collapsibility. There are two main hypotheses for airway collapse: (1) an anatomical hypothesis suggesting an element of skeletal deficiency and/or soft tissue narrowing of the upper airway, and (2) a neuromuscular hypothesis suggesting reduction in dilator muscle activity. The anatomical theory is

supported by the correlation between morphological changes and Pcrit values. On the other hand, the neuromuscular theory is supported by the correlation between pathophysiological EMG values and airway collapse. Managing each requires careful procedural selection. What we can learn from patients with MMA relapse addressed effectively by UAS is the synergistic effect of addressing both structural and neuromuscular etiology of OSA. Management of multi-level obstruction remains fundamental to successful treatment of moderate to severe OSA. The unique and complementary multi-level therapy of MMA and UAS brings a new era to our understanding and ability to care for sleep apnea patients.

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Chapter 7
The Hypoglossal Nerve and Its Anatomical Variability

Clemens Heiser

Contents

Introduction

The anatomy of the hypoglossal nerve (HN) is essential to know, when dealing with upper airway stimulation (UAS). Especially in selective upper airway stimulation (sUAS) the precise cuff placement of the stimulation lead plays a crucial role [1, 2]. Already in earlier pilot studies from 2001, Schwartz et al. could show that unilateral therapeutic electrical stimulation of the HN is feasible and a treatment option for patients with obstructive sleep apnea (OSA) [3]. During these times an upper neck incision was performed, the main trunk of the HN identified by dissection between the submandibular gland and digastric tendon [3] (see Fig. 7.1). This approach to the HN was similar to a submandibulectomy. Not much was known about the high anatomy variability of the nerve and its diversity of the different nerve fibers to the different tongue muscles. It was mainly the work of Mu and Sanders, who published

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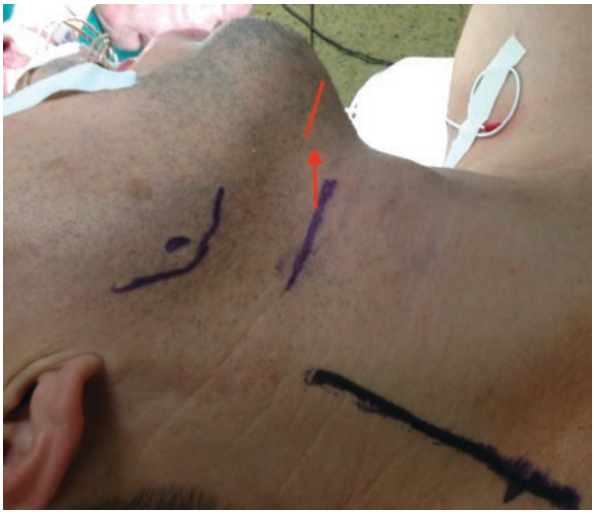

Fig. 7.1 Purple marked the old incision through a submandibular gland resection approach. The red arrow indicates the more anterior approach with a smaller incision [41]

in 2010 the first investigation of the human tongue neuroanatomy [4]. Up to this time the motor control of the human tongue was poorly understood [5]. Fundamental gaps of the terminating branches of the HN within each tongue muscle and the arrangement of motor endplates within each muscle was not examined yet. Mu and Sanders laid the foundation for the neuroanatomy of the tongue, as well as in later researches the complexity of the human tongue muscles and its different movements [6]. First, five adult human tongues were Sihler's stained, which is a whole-mount nerve staining technique and further five human tongues were microdissected into the different muscle groups stained with silver staining and acetylcholinesterase for the motor endplates and banding patterns [4]. With this technique they were able to map out the entire intra-lingual course of the hypoglossal nerve. It revealed that the human tongue innervation is extremely complex and dense. Specially the transverse muscle group has the most complex innervation, which is responsible for compromising the core of the tongue [4, 6]. Three years later both authors developed the first three-dimensional atlas of the human tongue muscles [6]. These graphics are till today the clearest guide to aid clinical or basic science investigators in identifying each tongue muscle in any part of the human tongue [6].

The Anatomic Variability of the Nerve

It is known that the human anatomy and its supplying nerve fibers are very complex [2, 4, 6, 7]. Different extrinsic and intrinsic muscles are innervated by the hypoglossal nerve (Fig. 7.2). These different muscle fibers can from a clinical point of view divided into four main groups (see Table 7.1):

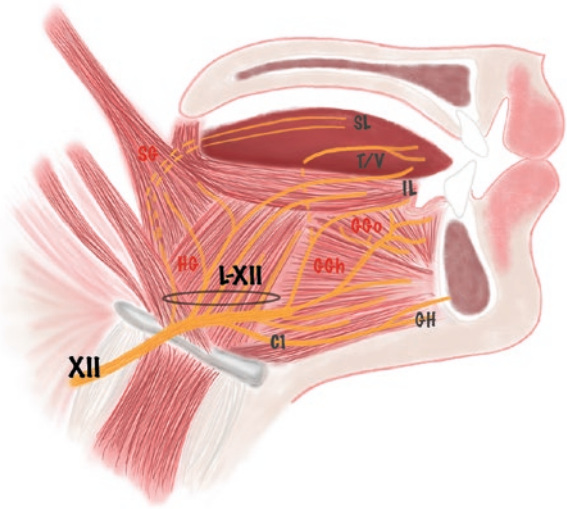

Fig. 7.2 The hypoglossal nerve is devided into a lateral branch (*SG* styloglossus muscle, *HG* hyoglossus muscle) and a medial branch (*GG* genioglossus muscle, *GGo* oblique, *GGh* horizontal, *GH* geniohyoideus muscle, *C1* first cervical nerve). Medial branches are mainly protrusors for the tongue, meanwhile lateral branches are mainly retractors for the tongue. Intrinsic tongue muscles help to stiffen and shaping the tongue (*T/V* transversal & vertical intrinsic muscles, *SL* superior longitudinal muscle, *IL* inferior longitudinal muscle). (The figure has been modified from [12])

Table 7.1 Showing the different muscles with their innervations from the medial or lateral part of the hypoglossal nerve. Furthermore, the attachments are mentioned and the action of the muscles during activation. The effects of the pharyngeal upper airway (opening or stabilizing) is also mentioned, meanwhile it has to be said that it is often unknown for stabilization

Muscle	action	Effect of airway opening	Effect of airway stabilizing	Origin	Insertion	Part of the Hypoglossal nerve
Extrinsic retractors	**Retraction of the tongue**	**Closing**	**Stabilizing in combination with protrusors**	**Bone**	**Tongue body**	**Lateral branches**
M. Styloglossus	Retracting & elevating	Closing	Stabilizing in combination with protrusors	Styloid process	Tongue edge	Lateral branches
M. Hyoglossus	Retracting & depressing	Closing	Stabilizing in combination with protrusors	Hyoid bone	Tongue edge	Lateral branches

(continued)

Table 7.1 (continued)

Muscle	action	Effect of airway opening	Effect of airway stabilizing	Origin	Insertion	Part of the Hypoglossal nerve
Extrinsic protrusors	**Pulling tongue forward & down**	**Opening**	**Stabilizing in combination with retractors**	**Bone**	**Tongue & Bone**	**Medial branches**
M. Genioglossus oblique	Pulling tongue body down	Support opening	Stabilizing in combination with retractors	Mandible	Tongue body	Medial branches
M. Genioglossus horizontal	Protruding Tongue body	Opening	Stabilizing in combination with retractors	Mandible	Tongue base & hyoid bone	Medial branches
Intrinsic stiffeners	**Stiffening tongue**	**Support opening**	**Stabilizing in combination with retractors**	**Tongue body**	**Tongue body**	**Medial branches**
M. transversus linguae	Narrowing	Support opening	Stabilizing in combination with retractors	Median septum	Lateral tongue edge	Medial branches
M. Vertical linguae	Flattening	Support opening	Stabilizing in combination with retractors	Dorsal tongue body mucosa	Ventral tongue body mucosa	Medial branches
Intrinsic shape changers	**Shortening & curling tip**	**Unknown**	**Unknown**	**Tongue body**	**Tongue body**	**Medial & lateral branches**
M. Medial inferior longitudinal linguae	Shortening, curling tip downwards	Unknown	Unknown	Tongue base	Tongue tip (more inferiorly)	Medial branches
M. Medial superior longitudinal linguae	Shortening, curling tip upwards	Unknown	Unknown	Tongue base	Tongue tip (more superiorly)	Lateral branches
M. Lateral inferior longitudinal linguae	Shortening, curling tip downwards	Unknown	Unknown	Tongue base	Tongue tip (more inferiorly)	Lateral branches

Table 7.1 (continued)

Muscle	action	Effect of airway opening	Effect of airway stabilizing	Origin	Insertion	Part of the Hypoglossal nerve
Other important muscles	**Mainly moving hyoid bone**	**Mostly unknown**	**Mostly unknown**	**Bone**	**Hyoid bone**	**C1 or V3**
M. Geniohyoid	Pulls hyoid forward (& mouth opening)	Airway opening	Stabilizing	Mandible	Hyoid bone	C1 (first cervical nerve)
M. Digastric anterior belly	Elevates hyoid bone and depress mandible	Unknown	Unknown	Digastric fossa of the mandible	Hyoid bone via digastric tendon	V3 (mandibular nerve)
M. Mylohoid	Elevates hyoid bone and tongue body	Unknown	Unknown	Length of the mandible	Hyoid bone	V3 (mandibular nerve)

- Extrinsic retractors (styloglossus muscle and hyoglossus muscle);
- Extrinsic protrusors (horizontal and oblique part of the genioglossus muscle);
- Intrinsic stiffeners (transverse and vertical muscles);
- Intrinsic shape changers (superior, medial inferior and lateral inferior longitudinal muscles).

The retractors are mainly responsible for airway occlusion. They are needed during swallowing for the deglutition process to move the tongue body and transport the bolus to the pharynx [8]. These muscle fibers are innervated by the lateral branches of the hypoglossal nerve. The main airway opener muscle is the extrinsic protrudor genioglossus muscle (GG). It is the largest muscle in the tongue and the most important one. The muscle originates from the inner midline of the mandible and fan out in a 90° arc. It can be divided in a horizontal and oblique part, meanwhile for airway opening during selective hypoglossal nerve stimulation the horizontal part is the key target. GG muscle fibers are entering the tongue between the intrinsic stiffeners and shape changers. The GG muscle is innervated by the medial branches of the hypoglossal nerve. The intrinsic tongue muscles are either stiffeners or shape changers of the tongue. They are mainly innervated by the medial or lateral branches of the hypoglossal nerve. Is it important to understand the contribution of the different muscle groups for the tongue movement to stabilize or open the upper airway or even to close it? A high anatomic variability between the different small fibers of the medial and lateral branches of the hypoglossal nerve from a surgical point of view could be detected [2] (see Fig. 7.3).

To open the upper airway a selective stimulation of the correct nerve fibers (mainly the GG muscle) seems to be important. Therefore, it is important to exclude the last / final lateral branch of the hypoglossal nerve and not to mistake these fibers

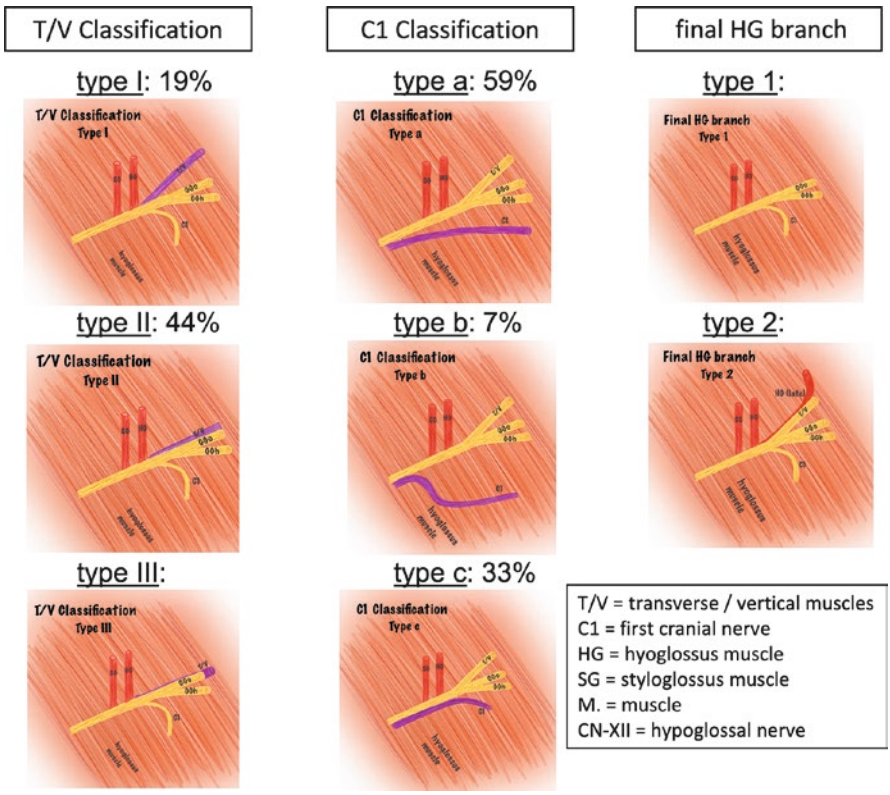

Fig. 7.3 Schematic drawing of the hypoglossal nerve (HN) and its anatomic variability. Three subdivisions were made by Heiser's classification: *T/V* intrinsic transverse and vertical muscles, *C1* first cervical spine nerve, and *HG* final hyoglossus muscle

as the transverse / vertical intrinsic nerve fibers. Furthermore, an active opening of the lower pharyngeal part by moving the hyoid bone actively forward, helps to solve obstructions. That is the reason why the junction of the first cervical nerve (C1) from the main trunk of the hypoglossal nerve needs to be carefully identified. Heiser et al. were the first to describe this anatomical diversity and developed a new surgical classification system [2].

The most important landmark for the nerve during surgery is the hyoglossus muscle. The most peripheral and distal branch of the hypoglossal nerve is running on this muscle (Fig. 7.4). Most of the fibers in the human nerve ramify between the posterior and anterior border of this muscle. All of the branches of this nerve, which need to be selective stimulated during selective hypoglossal nerve stimulation extend beyond the anterior border of this nerve and running immediately superficial to this muscle. One of the important steps during selective stimulation is to identify the final exclusion branch, which will often extend beyond the anterior margin of the hyoglossus muscle before taking off from the main trunk. This late takeoff route in a posterior-superior fashion to innervate the anterior-most hyoglossus muscle

Fig. 7.4 Showing the anatomic landmarks of the muscles. The nerve is not yet dissected and accompanied by a vein

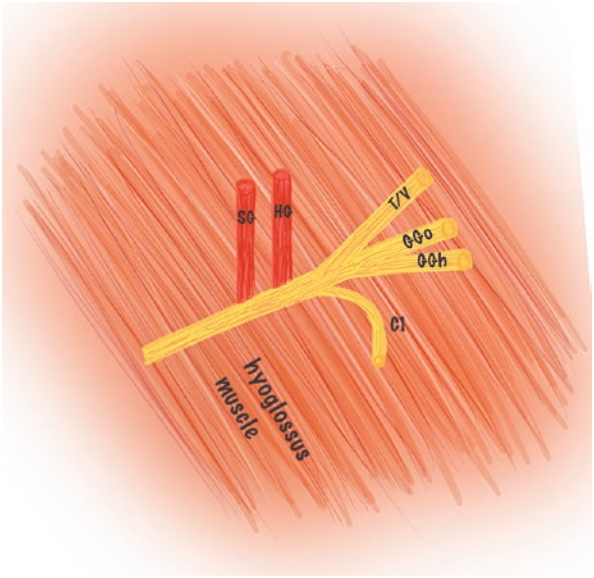

Fig. 7.5 Schematic drawing of the hypoglossal nerve and its end-terminating branches in a usual case. HNS divides into medial branches (m-XII) and lateral branches (l-XII). The lateral fibers are responsible for the styloglossus (SG) and hyoglossus (HG) muscles. The medial fibers are responsible for the transverse and vertical intrinsic muscles (T/V) and the genioglossus muscle (GG) with its horizontal (GGh) and oblique (GGo) compartments. A fine branch of the first cervical spine nerve (C1) runs parallel to the main trunk of HN and then arcs acutely down. All branches run immediately superficial to the hyoglossus muscle until its anterior margin

fibers. The hypoglossal nerve shows a dramatic shift from a mostly monofascicular nerve to one that exhibits manifold branching. The different anatomic variabilities are discussed in the next sections. The general schematic drawing of the nerve is shown in Fig. 7.5.

Latest Hyoglossus Muscle Branch

Two different types of this latest exclusion branch can occur (see Figs. 7.6 and 7.7):

1. Type 1 (Figs. 7.8 and 7.9), which can be found in approximately 33% of the cases, the exclusion fibers for styloglossus and hyoglossus muscle are leaving the main trunk obviously at angles from 60° to 90°. A clearly visible breakpoint between the exclusion (lateral branches of the hypoglossal nerve) and inclusion (medial branches of the hypoglossal nerve) can be identified. Using during surgery an intraoperative neuromonitoring system (see Chap. 9 surgical technique) can be easily validated (see Fig. 7.10 (NIM signal)).
2. But in more than 2/3 of the patients (Type 2) (Figs. 7.11 and 7.12), a late, and sometimes really obscure, final exclusion branch or branches can be detected. These very fine and thin branches, which can be mostly identified by magnification, are predominantly responsible for hyoglossus muscle function. If they are missed for exclusion during cuff placement and mistakenly included a high chance for suboptimal tongue motion ("mixed activation") can occur. It is known that already a single hyoglossus branch can substantially hinder the tongue to move forward [1, 9]. This means that even during intraoperative testing and obviously worse tongue motion a "going back strategy to the stimulation lead" often expose a fine exclusion caliber, which should be then removed from the cuff [10].

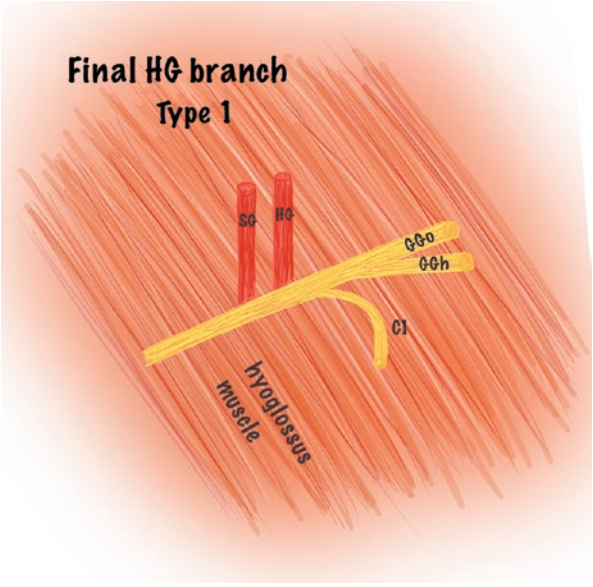

Fig. 7.6 Showing the schematic classification system of terminating end branches of the hypoglossal nerve for the variability of the late hyoglossus branch. Type 1 (33%) = the fibers of hyoglossus muscle are leaving the main trunk at angles from 60° to 90°, with a clearly defined breaking point. *T/V* intrinsic transverse and vertical muscles, *C1* first cervical spine nerve, *HG* final hyoglossus muscle, *GG* genioglossus muscle (*o* oblique, *h* horizontal)

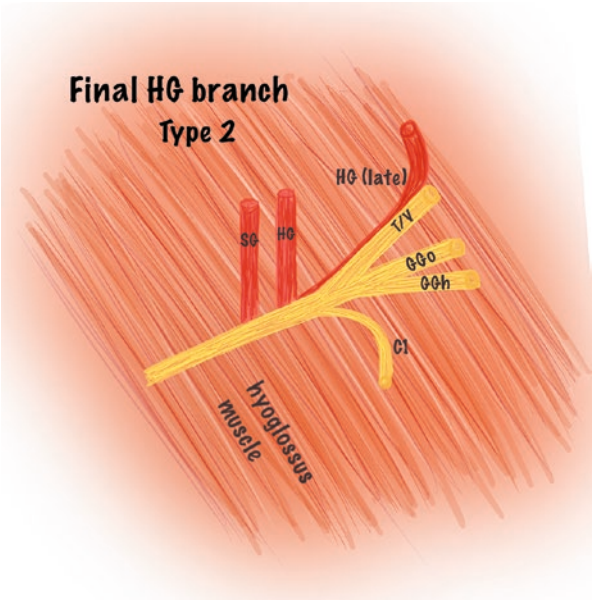

Fig. 7.7 Showing the schematic classification system of terminating end branches of the hypoglossal nerve for the variability of the late hyoglossus branch. Type 2 (67%) = the fibers of hyoglossus muscle are leaving – sometime obscure - late the main trunk. From a surgeon perspective - this can be a challenging case in nerve preparation. *T/V* intrinsic transverse and vertical muscles, *C1* first cervical spine nerve, *HG* final hyoglossus muscle, *GG* genioglossus muscle (*o* oblique, *h* horizontal)

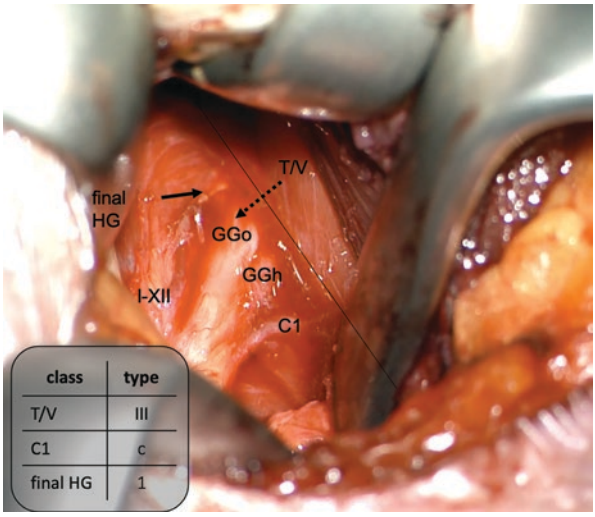

Fig. 7.8 Intraoperative picture of hypoglossus nerve and its high anatomic variability. The black arrow marks the final hyoglossus branch which needs to be excluded. The dotted arrow marks T/V, which runs behind the GGo trunk. The thin black line marks the anterior border of the hyoglossus muscle. (*GG* genioglossus muscle, *GGo* oblique, *GGh* horizontal, *C1* first cervical nerve, *T/V* transversal & vertical intrinsic muscles)

The fascicles from the thin styloglossus muscle and larger hyoglossus muscle are often indistinguishable in the tongue [4]. When using electrical stimulation in one of these small nerve fibers, the delivered energy to the myocytes is believed to excite not only at the terminal motor endplates of the finely innervated portion, but further propagate in a cascading fashion to neighboring myocytes of both hyoglossus and styloglossus muscle. This phenomenon can be found on the nerve integrity monitor

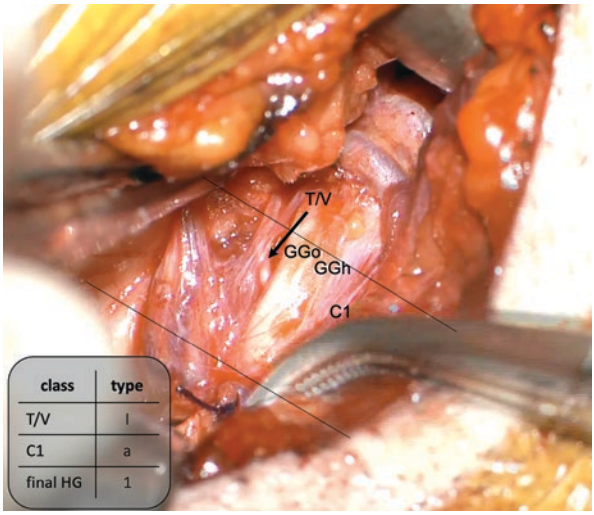

Fig. 7.9 Intraoperative picture of hypoglossus nerve and its high anatomic variability. The black arrow shows T/V. The thin black lines mark the borders of the hyoglossus muscle. (*GG* genioglossus muscle, *GGo* oblique, *GGh* horizontal, *C1* first cervical nerve, *T/V* transversal & vertical intrinsic muscles, *n.a.* not applicable)

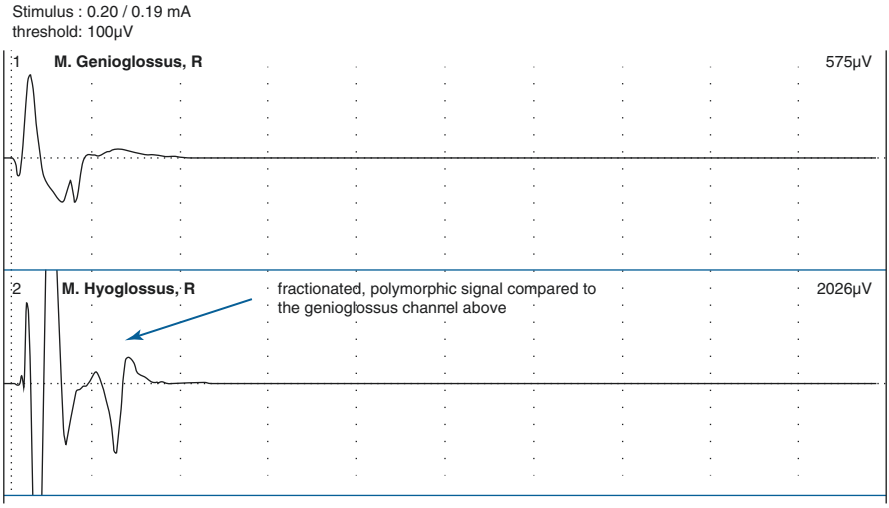

Fig. 7.10 Electromyogram (EMG-) -signals from the intraoperative neuromonitoring with a stimulus of 0.2 mA. The blue arrow shows the fractionated, polymorphic signal in the exclusion channel of the hyoglossus muscle

(NIM) waveforms from stimulation of an individual hyoglossus muscle branch using the bipolar NIM stimulation probe, appearing as a highly fractionated, polymorphic signal instead of a typical compound muscle action potential (CMAP) waveform (Fig. 7.10). This is consistent with a cascading and scattered activation, allowing for prospective exclusion of such a branch. Therefore, the surgical anatomy of the nerve to keep in mind is important knowledge for the implanting surgeon. The combination of anatomic landmarks, nerve anatomy and NIM signal must be applied to identify and carefully exclude such branches.

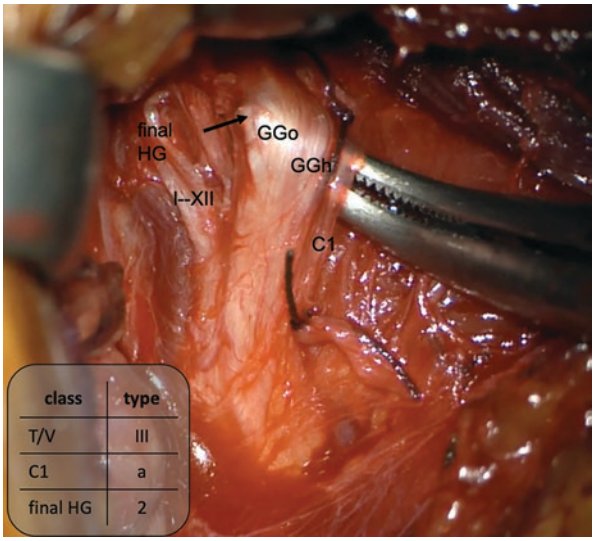

Fig. 7.11 Intraoperative picture of hypoglossus nerve and its high anatomic variability. The black arrow marks the final hyoglossus branch which needs to be excluded. (*GG* genioglossus muscle, *GGo* oblique, *GGh* horizontal, *C1* first cervical nerve, *T/V* transversal & vertical intrinsic muscles)

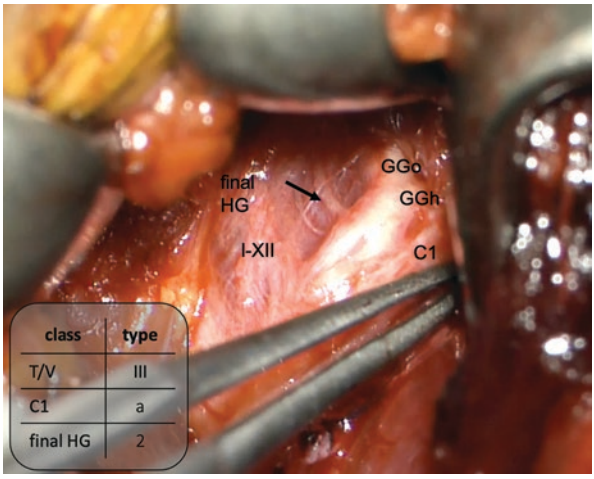

Fig. 7.12 Intraoperative picture of hypoglossus nerve and its high anatomic variability. The black arrow marks the final hyoglossus branch which needs to be excluded. (*GG* genioglossus muscle, *GGo* oblique, *GGh* horizontal, *C1* first cervical nerve, *T/V* transversal & vertical intrinsic muscles)

Transverse and Vertical Intrinsic Lingual Muscles (T/V)

Three different types can be found in the human tongue (See Figs. 7.13, 7.14 and 7.15) [2].

1. Type I (20% of the cases) (Figs. 7.9 and 7.13) can be easily identified as the uppermost portion of the distal hypoglossal nerve. The breakpoint between protrusors and retractors is readily identified for cuff placement.
2. Type 2 (44% of the cases) (Fig. 7.14) are very close to the main trunk of the medial hypoglossal branch. All superior branches are insinuated within a mono-

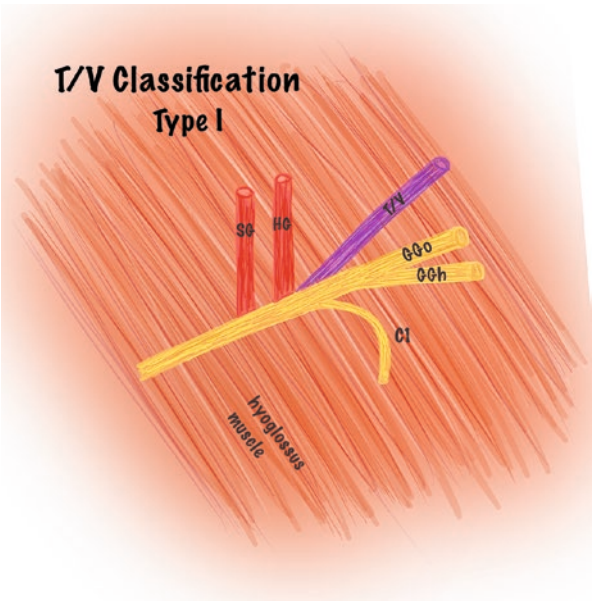

Fig. 7.13 Showing the schematic classification system of terminating end branches of the hypoglossal nerve for the variability of T/V. In type I (20%) T/V is the uppermost portion of the distal hypoglossus nerve. *T/V* intrinsic transverse and vertical muscles, *C1* first cervical spine nerve, *HG* final hyoglossus muscle, *GG* genioglossus muscle (*o* oblique, *h* horizontal)

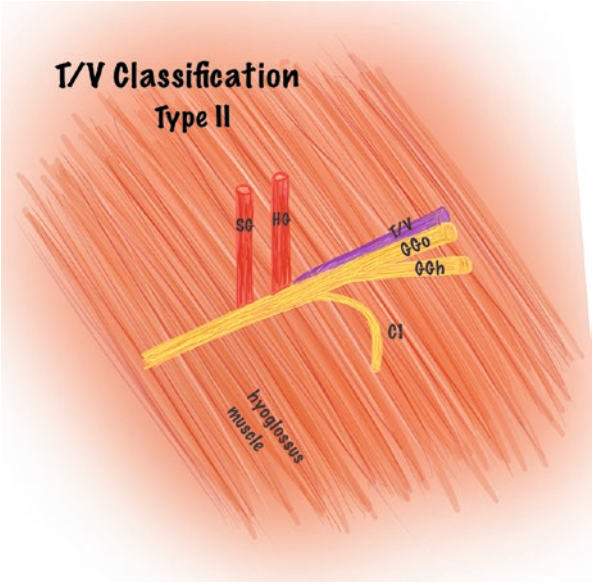

Fig. 7.14 Showing the schematic classification system of terminating end branches of the hypoglossal nerve for the variability of T/V. In type II (44%) T/V is very close to the genioglossus fibers. *T/V* intrinsic transverse and vertical muscles, *C1* first cervical spine nerve, *HG* final hyoglossus muscle, *GG* genioglossus muscle (*o* oblique, *h* horizontal)

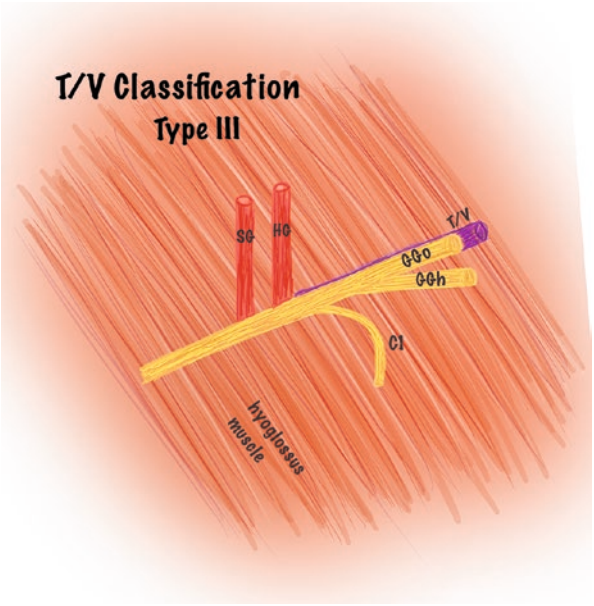

Fig. 7.15 Showing the schematic classification system of terminating end branches of the hypoglossal nerve for the variability of T/V. In type III (37%) T/V is hidden by the genioglossus fibers. Advanced techniques in surgical training are needed to discern the breaking point. *T/V* intrinsic transverse and vertical muscles, *C1* first cervical spine nerve, *HG* final hyoglossus muscle, *GG* genioglossus muscle (*o* oblique, *h* horizontal)

lithic branch to the oblique and horizontal genioglossus fibers. Advanced NIM techniques are needed to identify the functional breakpoint between the lateral (exclusion) and medial (inclusion) branches.

3. Type 3 (37% of the cases) (Figs. 7.8, 7.11, 7.12, and 7.15) the fibers are hidden by the main medial branch of the hypoglossal nerve and are lying deeper. A "role over" maneuver of the nerve during surgery by using a small swap can help in identifying these fibers in combination with advanced NIM techniques.

First Cervical Nerve (C1)

For the first cervical nerve (C1) three different types are known, depending on the point of where C1 leaves the main trunk. Schematic drawings can be found in Figs. 7.16, 7.17 and 7.18.

1. Type a (60% of the cases) (Figs. 7.9, 7.11, 7.12, 7.16, and 7.19) shows a C1, which runs parallel to the hypoglossal nerve and leaving the main trunk in a shallow/oblique angle. This C1 type is easily to include into the stimulation lead.
2. Type b (10% of the cases) (Figs. 7.17 and 7.20) shows a C1 which leaves the main trunk very proximal and early in a deep angle. In this type C1 can be hard to find and needs to be mobilized to include in the stimulation lead. In some cases, an extensive mobilization is needed to release the final hyoglossus branch earlier so the stimulation lead can shift posteriorly to accommodate C1 without tension on the cuff margin.

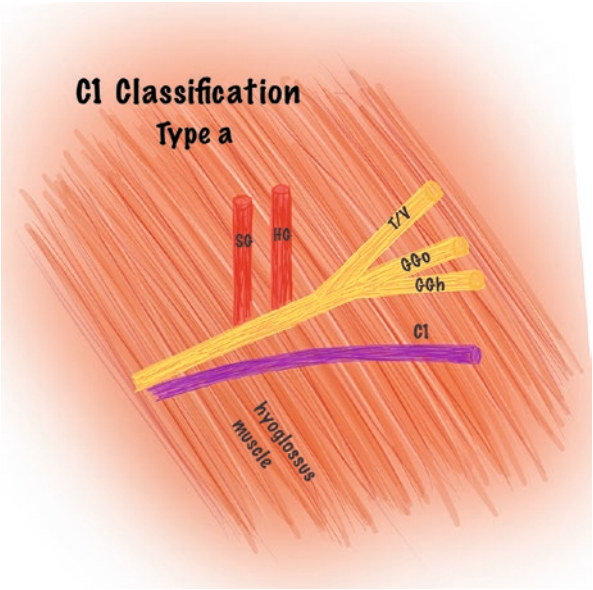

Fig. 7.16 Showing the schematic classification system of terminating end branches of the hypoglossal nerve for the variability of C1. In type a (59%) C1 takes of the main trunk at a shallow/oblique angle. *T/V* intrinsic transverse and vertical muscles, *C1* first cervical spine nerve, *HG* final hyoglossus muscle, *GG* genioglossus muscle (*o* oblique, *h* horizontal)

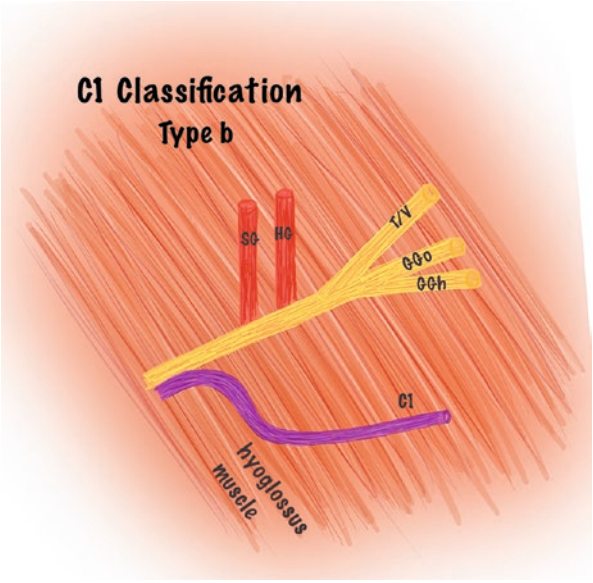

Fig. 7.17 Showing the schematic classification system of terminating end branches of the hypoglossal nerve for the variability of C1. In type b (7%) C1 takes of the main trunk very early in a deep angle. *T/V* intrinsic transverse and vertical muscles, *C1* first cervical spine nerve, *HG* final hyoglossus muscle, *GG* genioglossus muscle (*o* oblique, *h* horizontal)

3. Type c (30% of the cases) (Figs. 7.8 and 7.18) shows a C1 which runs parallel to the hypoglossal nerve (as in type a) but leaves the main trunk very distally and late in a deep and acute angle. In some cases, a careful mobilization during surgery similar to type b, but definitely less extensive helps to include C1 in the stimulation lead.

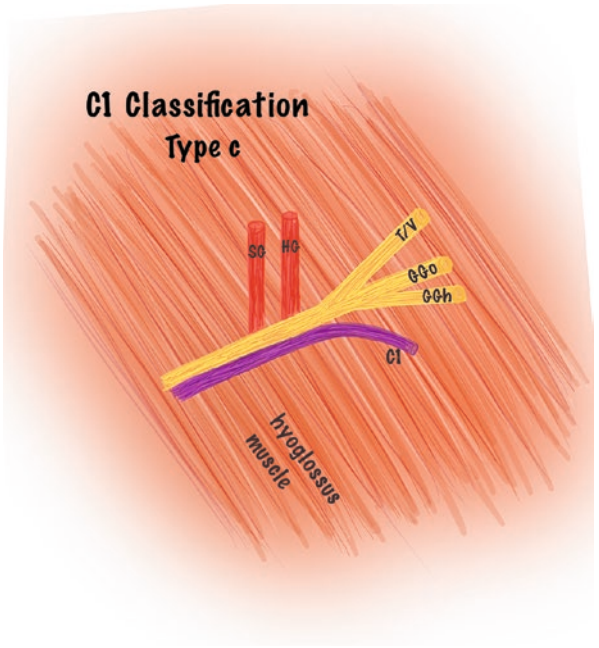

Fig. 7.18 Showing the schematic classification system of terminating end branches of the hypoglossal nerve for the variability of C1. In type c (33%) C1 runs parallel to the main trunk and takes off late. *T/V* intrinsic transverse and vertical muscles, *C1* first cervical spine nerve, *HG* final hyoglossus muscle, *GG* genioglossus muscle (*o* oblique, *h* horizontal)

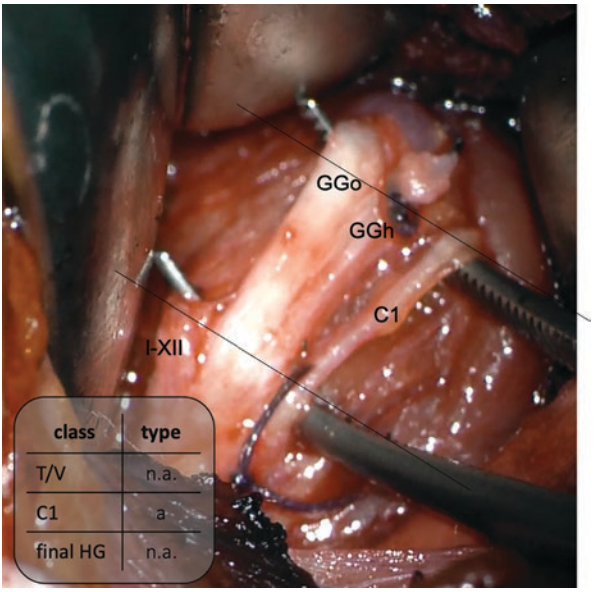

Fig. 7.19 Intraoperative picture of hypoglossus nerve and its high anatomic variability. The thin black lines mark the borders of the hyoglossus muscle. (*GG* genioglossus muscle, *GGo* oblique, *GGh* horizontal, *C1* first cervical nerve, *T/V* transversal & vertical intrinsic muscles, *n.a.* not applicable)

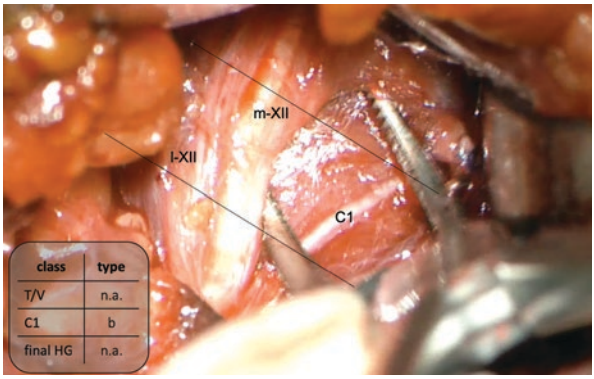

Fig. 7.20 Intraoperative picture of hypoglossus nerve and its high anatomic variability. The thin black lines mark the borders of the hyoglossus muscle. (*GG* genioglossus muscle, *GGo* oblique, *GGh* horizontal, *C1* first cervical nerve, *T/V* transversal & vertical intrinsic muscles, *n.a.* not applicable)

Summary

In selective hypoglossal nerve stimulation, the postoperative tongue motions are associated with therapy outcome and success [1, 9]. It is important and one key success factor for the implanting surgeon to develop a full command of distal human hypoglossal neuroanatomy to obtain a successful correct placement of the stimulation lead. Therefore, the knowledge of the variety of branching patterns is essential and one will undoubtedly encounter. When a more challenging pattern is encountered, combined application of advanced anatomic discernment techniques (anatomic knowledge, advanced NIM techniques, direct observations of muscle activations when stimulating individual branches, etc.) should be used for the end attainment of optimal tongue motions.

Pathophysiology & Mechanisms of Stimulation

With selective hypoglossal nerve stimulation, it is possible to stimulate the main airway opener "*the genioglossus muscle*". Adding the intrinsic muscles of the tongue to the stimulation as the transverse/vertical stiffeners, an unhindered stiffened protrusion of the tongue leads to open the whole upper airway of the pharynx [11]. It seems to be relevant that the effect of stimulation on anterior-posterior and lateral dimensions of the airway is relevant, particularly regarding the role of airway shape for OSA therapies. [11] Safiruddin et al. showed that the effect of stimulation was higher in its enlargement if the stimulation amplitude was increased [11].

Velum

It is known since 2015 that during selective hypoglossal nerve stimulation an opening or a stimulation effect on the soft palate (velum) can be seen. [11–13] It seems to be one key factor of clinical success if patients are responding to therapy or not,

if the soft palate is opening during stimulation [11]. Furthermore, a linkage between the retropalatal and retrolingual region exists in patients who are responding to therapy. However, these linkages are not being fully understood, and thus unable to be utilized in proactive identification of patients likely to exhibit them [13]. One reason for this effect on the soft palate could be the displacing the majority of tongue mass anteriorly, thereby relieving pressure on the vulnerable soft tissues of the velum. So, the soft palate gets the chance to maintain patency during respiration, which is its innate ability, instead being impinged upon the tongue resting against it. Therefore, an unhindered protrusion of the tongue is needed, which can be achieved by also stimulating the intrinsic muscles. [11] Another and probably major effect for enlargement of the soft palate is the "*palatoglossus coupling*" [13]. It can be also a contribution or addition to the displacing effect of the tongue mass. The palatoglossus muscle is a thin muscle running in the anterior pillar of the soft palate, which is the link of the velum to the tongue base [14, 15] (See Fig. 7.21). Already in the late 1990s Ferguson et al. could demonstrate that oral appliances by moving the mandible passively forward enlarge the retropalatal region. [16] During

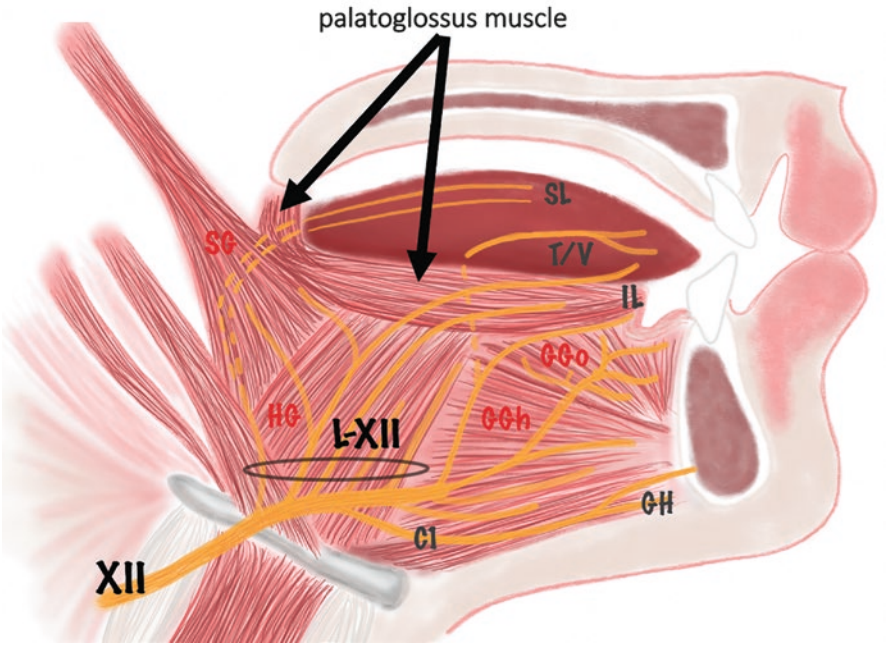

Fig. 7.21 Showing the palatoglossus coupling [13], which is a thin muscle running in the anterior pillar of the soft palate [14, 15]. By activating the tongue protrusion the palatoglossus muscle acts like an anchor and pushes the soft palate forward to open the velopharyngeal airway. *SG* styloglossus muscle, *HG* hyoglossus muscle, *GG* genioglossus muscle, *GGo* oblique, *GGh* horizontal, *GH* geniohyoideus muscle, *C1* first cervical nerve, *T/V* transversal and vertical intrinsic muscles, *SL* superior longitudinal muscle, *IL* inferior longitudinal muscle). (The figure has been modified from [12])

these time Ferguson and colleagues concluded that the mandible needs to be maximal protruded to obtain a therapeutic effect. Regarding stimulation therapy of the hypoglossal nerve the palatoglossal muscle is like an anchor of the soft palate. The unhindered stiffened and elongated protrusion of the tongue helps pulls on the soft palate through the palatoglossus muscle to enlarge and open the retropalatal region. [13]

ElShebiny et al. published a study in 2017, in which they concluded that the hyoid arch is responsible for the soft palate effect. [17] From physiology studies in dogs it is known that a linkage is existing by pulling the hyoid bone and its attachments forward to open not only the tongue base but also the velum. [15] What is the hyoid arch? It consists of bones, muscles and ligaments in the pharynx. The hyoid arch forms the anterior pharyngeal wall, which is known for speech and swallowing. Is it known that moving the hyoid arch forward can occur with glossopharyngeal breathing. [18, 19] During selective hypoglossal nerve stimulation the hyoid with its arch is moved forward, if C1 is included in the stimulation cuff. [20, 21] ElShebiny et al. concluded that moving the hyoid arch changes airway volume by negative or positive airway pressure [17]. It is not the airway size that changes the hyoid position or tongue length. [17]

In summary, it can be concluded that it is not exactly clear or known how the effects on the velum can be explained. Probably it is a combination of all above-described hypothesis, which can lead to the retropalatal enlargements: "*tongue mass forward*", "*palatoglossal coupling*" and "*hyoid arch*". It can also depend on individual phenotypes what the mechanism describes this effect in detail. Recently published data from Kent et al. considers even a different mechanism, which will be described in Chap. 21 oropharyngeal wall.

Oropharyngeal Wall

The pharynx is a mobile structure, which is attached to the mandible and hyoid bone ventrally and to the thyroid cartilage caudally. These few anchorages give the pharynx the dynamic of multiple modifications of its shape and tension in all directions. It is known in multiple studies that the caudal traction of the trachea increases airflow and diameter of the upper pharyngeal airway [22–29], ,Kent et al. could show in their clinical trial, that patients with a lateral pharyngeal wall collapse, that is generally undesirable for hypoglossal nerve stimulation therapy [30, 31], can benefit from stimulating of the ansa cervicalis, which is responsible to activate the sternothyroid muscle to perform a caudal traction on the pharyngeal patency (see also Chap. 9).

Tongue Base

The selective stimulation of the medial branches of the HN is mainly responsible for the opening of the tongue base. [14] The genioglossus (GG) muscle is activated, which is a fan-shaped extrinsic tongue muscle. [4] The muscle is mainly responsible for the majority of the tongue body and arises from the mental spine of the mandible to the bottom of the tongue. Furthermore, there are also some insertions at the hyoid bone. The muscle can be divided into an oblique and horizontal part, what was first found out in the canine. [4, 32] The horizontal part of the GG pulls the tongue base more forward and the oblique fibers depress the tongue back. [4, 6] Some authors argue that major effects can be seen, when both sides (left and right GG) are acting together. [33] This hypothesis is particularly interesting because 50% of human beings have a cross motor innervation of the hypoglossal nerve. [34, 35] This means, that the right hypoglossal nerve is also supporting with its nerve fibers the contralateral side of the tongue and vice versa. In former studies Heiser et al. could show that this bilateral innervation seems to have a more positive outcome on the velum during stimulation and seems to be associated with a better impact on the clinical outcome. [35] So, bilateral stimulation of the hypoglossal nerve could be a solution for non-responders or patients who are having a non-sufficient airway opening.

The main upper airway dilatator GG muscle is important for maintaining pharyngeal patency. [36] It seems to be that the reduction of the GG muscle activity is an important contributor mediating rapid eye movement (REM)-related sleep apnea. [37] The EMG of the GG muscle differs from sleep stage to sleep stage. It decreases to a similar extent from wakefulness to stable NREM to tonic REM to phasic REM sleep in healthy men and women and also OSA patients. [37–39] So it is also known that reduced EMG activity of the GG muscle during REM sleep is an important factor for OSA. [37]

Summarizing these results implies that the stimulating of the GG muscle is the key factor for opening the upper pharyngeal airway.

Epiglottis

The forward protrusion of the stiffened tongue during stimulation needs to be achieved for a good clinical outcome. [1, 9, 40] In favor exclusion of selected lateral (l-XII) branches of extrinsic retractor muscles (i.e., styloglossus and hyoglossus) are important. [6] Furthermore to explicit tongue muscles, the geniohyoid (GH) muscle is supplied by nerve fibers from the first cervical nerve (C1). It carries predominantly motor fibers, but also a small meningeal branch, which is responsible for the dura around the foramen magnum [33]. C1 runs in most of the cases parallel to the hypoglossal nerve, with phenotypic variability evident from person to person.

[2] Inclusion of these small fibers, when practical, helps to move the hyoid bone anteriorly. This motion during stimulation, can be viewed as dynamic hyoid suspension. Due to its high variability, it is sometimes difficult to visualize and include the C1. [2, 20] Pulling the hyoid bone forward via the stimulation of C1 during selective hypoglossal nerve stimulation helps to open the tongue base on one hand and on the other hand to straighten up the epiglottis in an anterior-posterior dimension. [20] This technique prevents the epiglottis of touching the back of the pharyngeal wall.

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Chapter 8
Patient Selection, Including Drug Induced Sleep Endoscopy

Pien F. N. Bosschieter and Nico de Vries

Contents

Introduction

As in all surgery, – this holds true for general surgery and upper airway surgery for OSA - patient selection is crucial. This is not different in upper airway stimulation (UAS) but in addition to regular preoperative considerations, there are some which hold true exclusively for UAS.

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In addition, UAS is the new kid on the block, and patient inclusion criteria for UAS differ per country. National and international guidelines and reimbursement policies differ accordingly and are in fact still shifting. But not only local differences in inclusion criteria are of importance, other aspects need to be taken into account as well. Such aspects regarding patient selection of UAS include the presence and development of complex sleep disturbances, positional OSA, high BMI, central and mixed apnea, ethical considerations and drug induced sleep endoscopy (DISE) findings. In this chapter these patient selection factors will be discussed in detail, and how they are shifting, with special emphasis on DISE.

Inclusion Criteria Then and Now

In the original STAR (Stimulation Therapy for Apnea Reduction) inspire upper airway stimulation clinical trial, the criteria for AHI were 20–50, with a BMI <32 [1]. Patients would have to have less than 25% of mixed and central events, and patients should have no positional OSA (POSA), defined as at least twice as much events in supine sleeping position as compared to other sleeping positions, and have CPAP failure [2–5].

UAS is presently widely available in the USA, Germany and the Netherlands. In the USA, FDA approval was subsequently obtained for AHI 15–65, and BMI <32. In Germany, these criteria presently are AHI 20–50 and BMI <35. In the Netherlands, in the period 2017–2020 AHI 30–50 and BMI <32 was agreed upon, but approval for a broader inclusion to the original AHI 20–50 was obtained in 2021 [6] (Table 8.1).

Mixed Sleep Disturbances

Patients with complex sleep disturbances such as both OSA and insomnia can be poor candidates for UAS. Such patients might react well to UAS itself, but for these individuals it might be difficult or even impossible to fall asleep with the UAS system ON. Or when they wake up in the course of the night, they may have great difficulty to fall asleep again with the UAS system ON. In some unlucky patients such situations have been so difficult to manage that complete well working systems were removed on request of a disappointed patient.

Table 8.1 Differences in inclusion criteria for different countries

AHI	BMI	Country
20–50	<32	STAR-trial
15–65	<32	USA
20–50	<32	Netherlands
15–65	<35	Germany

For the sleep surgeon, it might be difficult to distinguish between poor sleep and awakening due to OSA only, or due to a combination of OSA and another sleep disturbance. It is strongly advised to not only look at an AHI but discuss the sleep study in detail with an experienced somnologist in order to avoid any disappointing outcomes.

Patients with a high arousal/awakening index, – patients who wake up easily already in case of mild stimulation -, might be difficult to treat with UAS as well.

Other patients who do not have other sleep disturbances before UAS might develop mixed and central apnea after implantation, as happens in normal upper airway surgery for OSA as well. This phenomenon is called *treatment emerging apnea* [7]. The phenomenon is somewhat difficult to understand from a pathophysiological perspective, but the easy way is that apparently the breathing center has become used to certain nocturnal O2 and CO2 levels and has a tendency to keep these levels stable after getting rid of the obstructive component. Why some people will develop treatment emerging apnea while most patients do not, is totally unclear. Fortunately, treatment emerging apnea might disappear in the course of time in case the obstructive component has been resolved. It is however impossible to predict who will develop treatment emerging apnea, and when (after how long) and if treatment emerging events will disappear.

POSA

Positional OSA (POSA) is defined as having at least twice as much events in the supine sleeping position as compared to the other sleeping positions.

There are various modifications in the definition of POSA; while Cartwright looked at the Apnea Index (AI) [8], present systems use the apnea hypopnea index (AHI); some exclude less than 10% supine position more than 90% of supine position [9, 10].

Old school positional therapy (PT) were variations on the tennis ball technique, the application of tennis balls, squash balls or the like sutured into the backside of the pyama or T-shirt. All these devices have in common that they are uncomfortable, the long term compliance is very low and “old school positional therapy” should not longer be advised. New generation smart devices include a strap attached on the trunk in which a small light weight flat device records the sleeping position, which gives a subtle vibrating stimulation in case patients turn to their back during sleep. The aim is that the soft stimulation will lead to an arousal, but not an awaking. Studies have shown that new generation PT works in positional OSA, and PT is actually already reimbursed in the Netherlands since 2017 [11–13]. In other European countries reimbursement might be expected in the near future. The first USA study, the POSAtive study, showed PT to be non inferior to CPAP in moderately severe POSA patients [14]. Finally it has to be realized that POSA is particular common in early stage disease. More than 56% of mild OSA patients are positional, while at the other side of the spectrum, the great majority of severe OSA patients are

non positional [2]. So the majority of the UAS candidates (severe OSA patients) are non positional.

But these rare patients with severe OSA who are very positional, with a difference of at least twice as much events in supine position as compared to lateral sleeping position would intuitively pose challenges in UAS. The stimulation level that is needed to overcome events in supine position might be too high for events in lateral position. The basic question is if UAS is first line treatment in positional patients anyhow: the presently available new smart devices for PT should be considered first. But PT does not work always and in all patients, while there may be contraindications for PT as well, such as back and shoulder ailments. In such cases UAS might be still considered as second line treatment with the caveat that different power settings might be needed in different sleeping positions. This might pose a titration challenge. Recently this question was answered in a study by Steffen et al. [3] which showed that results of UAS in positional patients are equal to non positional patients.

Sometimes, the effect of UAS is more pronounced in lateral position than in supine sleeping position. Patients have become positional during UAS. In such case additive PT after partial effective UAS is useful, as can also happen in upper airway surgery, oral device treatment of after weight loss in bariatric surgery [15–19].

BMI

Patients with a BMI above 32 were in the beginning regarded as not good candidates for UAS. Recent insights are that the BMI itself may be less important as along as the DISE findings are favorable (no complete concentric collapse on soft palate level). Some patients might have a normal neck circumference, with relatively much abdominal fat. This has not yet been incorporated in guidelines and reimbursement, but might be a consideration in commercial patients. The fact that in the German post market study [20] the results were as good in patients with a BMI 32–35 underlines this idea. In addition, recent data from the ADHERE study show that the success rate in patients with a BMI <32 are around 80%, vs 65% in patients with a BMI >35.

Central and Mixed Apnea

Presence of more than 25% of central and mixed events is an exclusion criterion for UAS as well. However, it is a clinical reality in upper airway surgery that after elimination of the obstructive component, mixed and central events may decrease or disappear in the long term. This might be the case in UAS as well, but so far experience with this is lacking [21].

Ethical Considerations

Sometimes the surgeon is faced with an ethical dilemma: in case one selects only the very best patients for UAS, results might be expected to be very good as well.

Other patients might be not ideal, – e.g., a patient might have a mixed sleeping problem, or a considerable positional component, relatively high BMI, high central and mixed component and total obstruction during DISE at all levels. Still, clinically relevant improvement might be achievable. In some situations when all other options have failed, one might opt to embark on UAS in not ideal patients and accept that the results might be not as good as in the more suitable candidates. For researchers who want to report the best results possible, such patients are perhaps less attractive, but from a patient perspective such a policy is very defensible and commendable.

DISE

Drug-induced sleep endoscopy (DISE) is a dynamic three-dimensional upper airway evaluation technique. Fiberoptic transnasal examination is performed under unconscious sedation. Unique information about the collapsible segment of the upper airway provides insights in addition to other evaluation methods to guide treatment selection. This three dimensional dynamic assessment is a valuable addition to standard two dimensional imaging procedures that provide only two-dimensional assessments during wakefulness in upright position. While DISE is not a perfect reflection of the collapse patterns of the upper airway during a whole night of sleep, in different sleep stages and different sleeping positions, presently there is no other procedure that record upper airway collapse patterns better.

Historically, fiberoptic evaluation of the upper airway under sedation was developed in a number of centers in Europe (notably England, the Netherlands, Germany, Belgium, Italy) in the late 1980s. Many fancy names were given to the procedure and suggested in the course of time (e.g., sleep endoscopy, sedated endoscopy, dormoscopy, somnoscopy, etc) but in the long run the procedure was coined “drug-induced sleep endoscopy”.

DISE is not indicated in all patients with OSA. In general, DISE is mostly performed in case upper airway surgery is considered. More controversially, DISE can also be performed in case other CPAP alternative treatment modalities such as oral device therapy, positional therapy in positional OSA, or combined treatment is considered. For this chapter, it is important to realize that DISE is essential and pivotal in case UAS is considered.

The original STAR (Stimulation Therapy for Apnea Reduction) clinical trial involving 126 OSA patients across the United States and Europe began in 2010 to evaluate the safety and efficacy of Inspire therapy. One-year STAR Trial results were published in the New England Journal of Medicine [1], in January 2014.

Inspire therapy received approval by the United States Food and Drug Administration (FDA) in April of that year.

The STAR trial was also the first trial in which the FDA approved of DISE as selection tool for patient inclusion [22]. As such, the STAR trial has been pivotal for acceptance and popularization of DISE, in particular in the USA. It is very simple; in case DISE is not performed, UAS is not permitted.

Various DISE classification systems around the world have been proposed. There are at least seven systems reported in the literature, varying from too comprehensive to as simple as possible. The use of the VOTE (**V**elum, **O**ropharynx, **T**ongue base, **E**piglottis) classification system is recommended [23, 24]. VOTE is by far the most used DISE classification system. In the "European Position Paper on drug induced sleep endoscopy" [25, 26] the DISE procedure is described in detail.

In the VOTE classification the four different levels of the collapsible segment of the upper airway are assessed during DISE and score as: 0: no obstruction, 1: partial obstruction and 2: total obstruction, while X means not visible. In addition to scoring severity, the direction or configuration is scored as well: obstruction is either anteroposterior (AP), lateral, or concentric.

Velum Velum is soft palate and uvula, and lateral pharyngeal wall at this level. Velum obstruction is related to the palate and occurs due to the soft palate, uvula, or lateral pharyngeal wall tissue at the level of the velopharynx. Airway closure related to the velum can occur with collapse in an anteroposterior, concentric, or, less commonly, lateral configuration. Because it is not always possible to distinguish between the soft palate, uvula, and lateral pharyngeal walls at the level of the velopharynx on DISE, VOTE groups them under the umbrella of the Velum. The lateral pharyngeal walls at this level of the velopharynx can interact with the remainder of the lateral wall tissues, and the VOTE Classification aims to describe these separately.

Oropharyngeal Lateral Walls, Including Tonsils The oropharyngeal lateral walls include the palatine tonsils and the lateral pharyngeal wall tissues that include muscles and parapharyngeal fat pads. Oropharyngeal lateral walls collapse only in a lateral configuration. In the presence of lateral wall collapse, it might be difficult to determine whether the tonsils are the sole source of airway obstruction or whether the other lateral pharyngeal tissues also contribute. This distinction can have important implications for treatment selection and outcomes.

Tongue Base of tongue obstruction is a common DISE finding. It only occurs in anteroposterior collapse.

Epiglottis Epiglottic collapse may occur in an anteroposterior (so called "floppy epiglottis") or lateral configuration. Distinction should be made between primary epiglottis collapse (collapse of the epiglottis exclusively), or secondary collapse (the base of tongue pushes the epiglottis backwards). The epiglottis has long been under recognized as a factor in patients with sleep disordered breathing. Up to 24% of patients with OSA demonstrate partial or complete epiglottic obstruction during DISE. The identification of epiglottic collapse is unique to DISE, as it cannot not be

demonstrated by means of standard evaluation techniques, such as awake laryngoscopy with or without Müller's maneuver.

Very recently it was found through DISE that epiglottis collapse occurs almost exclusively in supine position. Turning of the head and trunk to lateral position, or rotation of the head only during DISE, almost always resolves epiglottis collapse [27].

In sum, not all forms of obstruction are possible at all levels: at palate level AP, lateral and concentric are all possible; at oropharyngeal level lateral obstruction only; base of tongue is exclusively AP, while epiglottis may be both AP as lateral. At all levels, both partial and complete collapse occurs, and obstruction can be unilevel or multilevel. In more severe OSA, more often multilevel (vs unilevel), complete (vs partial or no obstruction) and complete concentric collapse at palatal level (CCCp, vs AP) will be found as compared to mild or moderate OSA.

For UAS, the only exclusion criterion is CCCp. CCCp is "bad news" for upper airway surgery as well as for MRA treatment [22, 28]. Originally the idea was that in UAS all other forms of obstruction were allowed, but intuitively, it made the most sense to focus at exclusive base of tongue collapse. Patients with exclusive palatal obstruction, without base of tongue collapse, while strictly speaking eligible, were regarded far less good candidates. Experiences with upper airway surgery had shown that in general, unilevel obstruction is more favorable than multilevel, partial collapse is better than complete collapse and anteroposterior better than concentric [29]. One would expect that this would hold true for UAS as well.

So in the VOTE terms; the collapse pattern of patient A at the table below would be expected to have the best outcome; the collapse patterns of patient C the worst, with the one of patient B somewhere in the middle. Recent studies however have shown that the results in isolated palatal collapse are in fact as good as in isolated base of tongue collapse. In particular, it were Mahmoud and Thaler who recently reported a success rate of UAS in isolated palatal collapse of 88% [30] (Table 8.2).

This leads to a paradigm shift. Currently, in most sleep surgery centers, patients with an isolated palatal collapse seeking help for their OSA through upper airway surgery, would be offered one of the modern forms of palatal surgery, such as expansion sphincter pharyngoplasty, or barbed reposition pharyngoplasty [31, 32]. And while results of such reconstructive techniques may still be reasonable in case of mild to moderate OSA, a success rate of 88% is by far not achieved in severe OSA by any form of palatal surgery [33, 34]. So the question arises; should one still try

Table 8.2 Three collapse patterns: A, B and C according to VOTE

Patient	A	B	C
V	0	1	2
O	0	1	2
T	2	1	0
E	2	1	0

(relatiively cheap) palatal surgery first, and accept a success rate of far less than that the 88% one achieves with UAS, and keep UAS in reserve, or should we skip palatal surgery altogether and embark on UAS directly?

It has also become clear that CCCp occurs more often in patients with a high BMI. This is however a reversible phenomenon. In overweight patients with CCCp, the collapse pattern can reverse to more favorable A-P collapse, making patients eligible for UAS.

Finally, early work by Safiruddin et al. [35] has shown that UAS opens the upper airway in a dose dependent manner: the higher the power setting, the more opening of both retrolingual as well as retropalatal airway.

In unexplained UAS failures, or partial responses post UAS, repeated DISE might be considered with UAS ON an OFF and in different unipolar and bipolar power settings. In some UAS failures the base of tongue collapse is taken care of, but the palatal collapse responds less well. In such cases additional palatal surgical reconstruction techniques can be considered as salvage surgery.

Commercial Implantation

Occasionally, well-to-patients who do not fulfill the criteria may opt for paying for the procedure themselves. Patients who do fulfill the criteria, but who live in countries where UAS is not yet available, might do the same. In particular CPAP compliant patients who fulfill all other criteria well, but want to get rid of their CPAP raise this question frequently. Other patients may fall out of the criteria only marginally, but seem good candidates otherwise. Experience in such individual patients has given important insight in selection criteria. Patients with a high BMI, but during DISE no complete concentric collapse at palatal level, may do well with UAS. The conclusion is that for patient selection, DISE is far more important than BMI.

In patients with a high central and mixed component, UAS may lead to clinically relevant improvement of both obstructive, mixed and central components [21].

It has to be realized that these findings are in individual patients and such promising results need to be confirmed in larger series.

Conclusion

UAS inclusion criteria are shifting and patient selection is also gradually on the move. 10 years of experience in more than 30,000 patients (as per June 2022) has provided important insights on who and who not to operate. Still, and in retrospect easy to say, mistakes in inclusion might occur (in general, do not implant in insomniacs!).

While the original inclusion criteria were deliberately chosen to obtain the highest change of success, this does not mean that UAS in all other patients would fail.

From a patient perspective it might still be commendable to carefully consider UAS in not totally ideal candidates as well, in whom clinical relevant improvement can be achieved.

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Chapter 9
Overview of Different HN-Stimulation Systems: Inspire

Clemens Heiser and Joachim Maurer

Contents

Inspire

Introduction

During the 1980ies several studies have been performed to test electrical stimulation of the genioglossus muscle to improve pharyngeal patency in obstructive sleep apnea (OSA) patients [1–5]. The results back then were not yet promising and initially abandoned. The main electrically stimulation technique was followed by direct muscle stimulation [1]. Patients were often aroused by stimulation and improvement in pharyngeal patency could have been related to pharyngeal musculature activation during arousal [3–5].

Since the mid-late 1990ies hypoglossal nerve stimulation has been performed in a first-in human trial [6]. During these times Eisele et al. published a trial in 15

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patients undergoing a surgical procedure that was exposing the hypoglossal nerve and applying an electrical stimulation as well [7]. The main trunk of the hypoglossal nerve was exposed for this procedure without separation of the different nerve fibers or even a highly selective stimulation. The authors were able to show that direct stimulation of the nerve can improve airflow in patients with OSA [7]. Even back then the authors concluded that mainly the medial branches of the hypoglossal nerve need to be stimulated and lateral fibers for the tongue retrusor muscles need to be excluded. Another important topic during this feasibility study was that one patient showed bradycardia intraoperatively. The authors concluded that this event was related to vagal nerve stimulation. As final conclusion a more distal placement of the electrode may avoid unwanted vagal nerve reflex effects and muscle activation [7].

Paul van de Heyning, former head of the ENT Department at University of Antwerp, Belgium implanted in 1996 the first patient worldwide with the Inspire I stimulation system (Medtronic Inc., Minneapolis, Minnesota, USA). A clinical trial followed with eight patients, where five out of eight patients had to be explanted [6]. But in summary, as proof of concept, this study showed that hypoglossal nerve stimulation (HNS) can be an effective therapy for OSA patients. Consecutively, Inspire Medical Systems was founded in 2007 out of Medtronic to develop a second generation HNS-system, which addressed design deficits of the previously used Inspire I device. Further clinical trials followed, which are described in the chapter clinical evidence.

Components of the System

The Inspire System (Inspire II/IV System, Golden Valley, MN, USA) consist of three components:

- stimulation lead;
- implantable pulse generator (IPG);
- sensing lead

The stimulation lead is placed around the medial hypoglossal nerve fibers, which are selectively chosen during surgery (see chapter implant techniques) [8]. The IPG is placed pre-pectoral and connected through a neck tunneling to the stimulation lead. The sensing lead is placed underneath the IPG in the second intercostal space and connected to the IPG. The IPG contains of the battery, which does not require charging and a processing unit to detect respiratory efforts, using signals obtains from the sensing lead and deliver stimulation in a timely manner. The sensing lead has a pressure- sensitive membrane that converts the mechanical energy of respiration into an electrical signal. The stimulation lead delivers stimulation to the hypoglossal nerve via three electrodes inside a flexible, passively fixated stimulation cuff [8].

Further details on the implant technique are discussed in Chap. 13 (Table 9.1).

Table 9.1 Showing the different muscles with their innervations from the medial or lateral part of the hypoglossal nerve

Muscle	Action	Effect of airway opening	Effect of airway stabilizing	Origin	Insertion	Part of the hypoglossal nerve
Extrinsic retractors	**Retraction of the tongue**	**Closing**	**Stabilizing in combination with protrusors**	**Bone**	**Tongue body**	**Lateral branches**
M. styloglossus	Retracting & elevating	Closing	Stabilizing in combination with protrusors	Styloid process	Tongue edge	Lateral branches
M. hyoglossus	Retracting & depressing	Closing	Stabilizing in combination with protrusors	Hyoid bone	Tongue edge	Lateral branches
Extrinsic protrusors	**Pulling tongue forward & down**	**Opening**	Stabilizing in combination with retractors	**Bone**	**Tongue & bone**	**Medial branches**
M. genioglossus oblique	Pulling tongue body down	Support opening	Stabilizing in combination with retractors	Mandible	Tongue body	Medial branches
M. genioglossus horizontal	Protruding Tongue body	Opening	Stabilizing in combination with retractors	Mandible	Tongue base & hyoid bone	Medial branches
Intrinsic stiffeners	**Stiffening tongue**	**Support opening**	Stabilizing in combination with retractors	**Tongue body**	**Tongue body**	**Medial branches**
M. transversus linguae	Narrowing	Support opening	Stabilizing in combination with retractors	Median septum	Lateral tongue edge	Medial branches
M. vertical linguae	Flattening	Support opening	Stabilizing in combination with retractors	Dorsal tongue body muscoa	Ventral tongue body mucosa	Medial branches
Intrinsic shape changers	**Shortening & curling tip**	**Unknown**	**Unknown**	**Tongue body**	**Tongue body**	**Medial & lateral branches**
M. Medial inferior longitudinal linguae	Shortening, curling tip downwards	Unknown	Unknown	Tongue base	Tongue tip (more inferiorly)	Medial branches
M. Medial superior longitudinal linguae	Shortening, curling tip upwards	Unknown	Unknown	Tongue base	Tongue tip (more superiorly)	Lateral branches

(continued)

Table 9.1 (continued)

Muscle	Action	Effect of airway opening	Effect of airway stabilizing	Origin	Insertion	Part of the hypoglossal nerve
M. lateral inferior longitudinal linguae	Shortening, curling tip downwards	Unknown	Unknown	Tongue base	Tongue tip (more inferiorly)	Lateral branches
Other important muscles	**Mainly moving hyoid bone**	**Mostly unknown**	**Mostly unknown**	**Bone**	**Hyoid bone**	**C1 or V3**
M. geniohyoid	Pulls hyoid forward (& mouth opening)	Airway opening	Stabilizing	Mandible	Hyoid bone	C1 (first cervical nerve)
M. digastric anterior belly	Elevates hyoid bone and depress mandible	Unknown	Unknown	Digastric fossa of the mandible	Hyoid bone via digastric tendon	V3 (mandibular nerve)
M. mylohyoid	Elevates hyoid bone and tongue body	Unknown	Unknown	Length of the mandible	Hyoid bone	V3 (mandibular nerve)

Furthermore, the attachments are mentioned and the action of the muscles during activation. The effects of the pharyngeal upper airway (opening or stabilizing) is also mentioned meanwhile it has to be said that it is often unknown for stabilization

Clinical Outcomes of Inspire System

Respiratory Parameters

The first clinical results of selective hypoglossal nerve stimulation have been published in 201**2** with 22 patients [9]. Van de Heyning et al. showed that in t**his** patient cohort with a Body Mass Index (BMI) less than 32 kg/m^2 and apnea-hypopnea index (AHI) less than 50 events/hour and **absence of** a **soft palate** complete concentric collapse during drug-induced sleep endoscopy**,** a significant AHI reduction of 74% **was achieved** (AHI 38.9 ± 9.8 events/hour to 10.0 ± 11.0 events/hour) [9]. Various other clinical studies followed in the following years. Table 9.2 gives an overview of the most important clinical studies. Thereby, three are of particular clinical importance:

- STAR Trial, which led to FDA approval [10–12]
- German Post-Market Study and [13–15]
- the international ADHERE register [16–18]

The STAR trial included 126 patients, which were followed for a period of 5 years. Woodson and co-authors could show that the AHI reduction in this patient cohort remained constant over this time period [12]. The STAR trial was also the

Table 9.2 Summary of Inspire research articles investigating different topics

1. Effects on severity of OSA

						AHI (in events per hour)		ODI (in events per hour)	
Year	Authors	Title	Design	Follow-up	N	Pre	Post	Pre	Post
2014	*Strollo PJ* et al.	Upper Airway Stimulation for Obstructive Sleep Apnea	Prospective	12 months	126	32.0 ± 11.8	15.3 ± 16.1	28.9 ± 12.0	13.9 ± 15.7
2016	*Heiser C* et al.	Selective upper airway stimulation for obstructive sleep apnea: a single center clinical experience	Prospective	12 months	31	32.9 ± 11.2	7.1 ± 5.9	30.7 ± 14.0	9.9 ± 8.0
2017	*Steffen A* et al.	Outcome After One Year of Upper Airway Stimulation for Obstructive Sleep Apnea in a Multicenter German Post-Market Study	Prospective	12 months	60	31.2 ± 13.2	13.8 ± 14.8	28.5 ± 16.6	13.7 ± 14.9
2018	*Woodson BT* et al.	Upper Airway Stimulation for Obstructive Sleep Apnea: 5-Year Outcomes	Prospective	60 months	97	32.0 ± 11.8	12.4 ± 16.3	28.9 ± 12.0	9.9 ± 14.5
2018	*Heiser C* et al.	Post-Approval Upper Airway Stimulation Predictors of Treatment Efficacy in the Adhere Registry	Prospective	12 months	508	36.3 ± 15.7	10.3 ± 11.5	n.a.	n.a.
2019	*Thaler E* et al.	Results of the ADHERE Upper Airway Stimulation Registry and Predictors of Therapy Efficacy	Prospective	12 months	1.017	35.8 ± 15.4	14.2 ± 15.0	n.a.	n.a.

2. Effects on severity of life quality

						ESS (in points)		
Year	Authors	Title	Design	Follow-up	N	Pre	Post	Further endpoints
2014	Strollo PJ et al.	Upper Airway Stimulation for Obstructive Sleep Apnea	Prospective	12 months	126	11.6 ± 5.0	7.0 ± 4.2	Adherence to therapy: 86% usage every night
2016	Heiser C et al.	Selective upper airway stimulation for obstructive sleep apnea: a single center clinical experience	Prospective	12 months	31	12.6 ± 5.6	5.9 ± 5.2	Adherence to therapy: 39.1 ± 14.9 h/week

(continued)

Table 9.2 (continued)

2. Effects on severity of life quality								
						ESS (in points)		
Year	Authors	Title	Design	Follow-up	N	Pre	Post	Further endpoints
2017	Steffen A et al.	Outcome After One Year of Upper Airway Stimulation for Obstructive Sleep Apnea in a Multicenter German Post-Market Study	Prospective	12 months	60	12.4 ± 5.7	6.5 ± 4.5	Adherence to therapy: 39.1 ± 14.9 h/week
2018	Woodson BT et al.	Upper Airway Stimulation for Obstructive Sleep Apnea: 5-Year Outcomes	Prospective	60 months	97	11.6 ± 5.0	12.4 ± 16.3	
2018	Heiser C et al.	Post-Approval Upper Airway Stimulation Predictors of Treatment Efficacy in the Adhere Registry	Prospective	12 months	508	11.8 ± 5.5	6.7 ± 4.7	Adherence to therapy: 5.7 ± 2.2 h/night Surgical adverse events: 2% Patient satisfaction: 94%
2019	*Thaler E* et al.	Results of the ADHERE Upper Airway Stimulation Registry and Predictors of Therapy Efficacy	Prospective	12 months	1.017	12.4 ± 5.7	6.5 ± 4.5	Adherence to therapy: 5.6 ± 2.1 h/night Surgical adverse events: 2% Patient satisfaction: 93%

3. Effects on sleep parameters and vigilance								
						Arousal-Index (events / hour)		
Years	Authors	Title	Design	Follow-up	N	Pre	Post	Further endpoints
2017	Hofauer B et al.	Effects of upper-airway stimulation on sleep architecture in patients with obstructive sleep apnea	Prospective	3 months	26	24.3 ± 15.1	15.0 ± 7.5	Reduction %N1-sleep 31% (23.2 ± 14.2 to 16.0 ± 13.0) Increase %REM-sleep 42% (9.5 ± 5.0 to 13.5 ± 10.3) Reduction respiratory arousals 85% (9.3 ± 7.1 to 1.4 ± 1.7)

2018	Philip P et al.	Hypoglossal nerve stimulation on sleep and level of alertness in OSA	Prospective	6 months	10	n.a.	n.a.	Reduction %N1-sleep 64.4% (11.8 ± 10.6 to 4.2 ± 1.9) Improvement in vigilance measured with MWT 47.2% (25.0 ± 12.8 to 36.8 ± 7.0)
2019	Bohorquez D et al.	Upper Airway Stimulation Therapy and Sleep Architecture in Patients With Obstructive Sleep Apnea	Retrospective	Retrospective	35	38.8 ± 4.0	30.3 ± 4.0	Reduction %N1-sleep (16.7 ± 2.1 to 10.1 ± 1.6) Increase %N3-sleep 62.8% (10.5 ± 2.2 → 17.1 ± 3.0)

4. Patient satisfaction

						Change in life quality (measured with ESS, FOSQ in points)		
Years	Authors	Title	Design	Follow-up	N	Pre	Post	Further endpoints
2018	Hofauer B et al.	Patient experience with upper airway stimulation in the treatment of obstructive sleep apnea	Prospective	2 months	102	12.9 ± 4.6	7.0 ± 4.6	Adherence to therapy (hours/week): 40.0 ± 14.2 Attitude towards UAS therapy in 5 dimensions (1 = positive attitude; 5 = negative attitude): 1.422 ± 0.085
2018	Hasselbacher K et al.	Patient-reported outcome: results of the multicenter German postmarket study	Prospective	12 months	60	12.4 ± 5.7 (ESS) 13.2 ± 3.6 (FOSQ)	6.5 ± 4.5 (ESS) 17.5 ± 3.0 (FOSQ)	Improvement in snoring: 70% report no or only slight snoring Patient satisfaction: 77% “UAS therapy better than CPAP”; 82% “would choose UAS therapy again”; 96% “would recommend UAS therapy to family / friends”; 96% “satisfied or very satisfied with UAS therapy”

(continued)

Table 9.2 (continued)

5. Comparative trials										
							Therapy group		Control group	
Years	Authors	Title	Design	Follow-up	N (therapy / control)	Comparator	Pre	Post	Pre	Post
2014	Woodson BT et al.	Randomized Controlled Withdrawal Study of Upper Airway Stimulation On OSA: Short- and Long-term Effect	Randomized controlled withdrawal study	6 months	46 (23/23)	Non-treatment	AHI: 31.2 ± 12.3	AHI: 8.9 ± 9.1 (71.5%)	AHI 30.1 ± 11.4	25.8 ± 16.2 (14.1%)
							ESS: 11.2 ± 5.3	ESS: 5.6 ± 3.9 (100%)	ESS: 11.3 ± 5.0	ESS: 10.0 ± 6.0 (100%)
2018	Shah J et al.	Uvulopalato-pharyngoplasty vs CN XII stimulation for treatment of obstructive sleep apnea: A single institution experience	Comparative cohort study	Retrospektiv	40 (20/20)	Soft palate surgery (UPPP)	AHI: 38.9 ± 12.5	AHI 4.5 ± 4.8 (88.4%)	AHI: 40.3 ± 12.4	AHI: 28.8 ± 25.4 (28.5%)
							ESS: 11.0 ± 4.9	7.0 ± 3.4 (31%)	ESS: 13.0 ± 4.7	ESS: 8.0 ± 5.0
2018	Huntley C et al.	Comparing Upper Airway Stimulation to Expansion Sphincter Pharyngoplasty: A Single University Experience	Comparative cohort study	Retrospektiv	108 (75/33)	Soft palate surgery (ESP)	AHI: 36.7 ± 20.7	AHI: 7.2 ± 11.1 (88.4%)	AHI: 26.6 ± 20.3	13.4 ± 19.0 (28.5%)
							ESS: 11.1 ± 4.1	ESS: 5.3 ± 3.3	ESS 10.6 ± 4.5	ESS: 7.0 ± 5.9
2018	Yu JL et al.	Transoral Robotic Surgery Versus Upper Airway Stimulation in Select Obstructive Sleep Apnea Patients	Comparative cohort study	Retrospektiv	115 (62/53)	Transoral tongue base reduction (TORS)	AHI: 40.5	AHI: 7.2 (88.4%) Therapy response (AHI < 5): 70.3%	AHI: 39.2	AHI: 26.5 (28.5%) Therapy response (AHI < 5): 10.0%

2018	Huntley C et al.	Comparing Upper Airway Stimulation to Transoral Robotic Base of Tongue Resection for Treatment of Obstructive Sleep Apnea	Comparative cohort study	Retrospektiv	100 (76/24)	Transoral tongue base reduction (TORS)	AHI: 36.6 ± 20.6	AHI: 7.2 ± 11.1 Therapy response (Sher-criteria): 86.6%	AHI: 35.7 ± 25.7	AHI: 20.5 ± 19.9 Therapy response (Sher-criteria): 54.1%
2020	Huntley C et al.	Comparison of Traditional Upper Airway Surgery and Upper Airway Stimulation for Obstructive Sleep Apnea	Comparative cohort study	Retrospektiv	698 (465/233)	Soft palate surgery (UPPP, ESP) tongue base reduction	AHI: 35.5 ± 15.0	AHI: 14.1 ± 14.4 (60.2%) Therapy response (Sher-criteria): 70%	AHI: 35.0 ± 13.1	AHI: 19.3 ± 16.3 (44.8%) Therapy response (Sher-criteria): 48%
							ESS: 11.9 ± 5.5	ESS: 7.3 ± 4.7	ESS: 11.3 ± 5.1	ESS: 5.9 ± 4.0
2020	Mehra R et al.	Upper Airway Stimulation versus Untreated Comparators in Positive Airway Pressure Treatment Refractory Obstructive Sleep Apnea	Comparative cohort study	12 Mo.	330 (230/100)	Non-treatment	AHI: 33.7 ± 13.4	AHI: 14.7 ± 13.8	AHI: 34.9 ± 16.4	AHI: 26.8 ± 17.6
							ESS: 12.3 ± 5.5	ESS: 7.2 ± 4.8	ESS: 10.9 ± 5.4	ESS: 12.8 ± 5.2

AHI and ODI are presented in events per hour. *ODI* oxygen desaturation index, *AHI* apnea hypopnea index, *N* numbers, *ESS* Epworth-Sleepiness Scale, *FOSQ* functional of sleep questionnaire, *CPAP* continuous positive airway pressure

first trial with a therapy withdrawal arm. Forty-six participants were randomized to a therapy maintenance ("ON") group or therapy withdrawal ("OFF") group for a minimum of 1 week. Short-term withdrawal effect as well as durability at 18 months of primary (AHI and Oxygen Desaturation Index) and secondary outcomes (arousal index, oxygen desaturation metrics, Epworth Sleepiness Scale, Functional Outcomes of Sleep Questionnaire, snoring, and blood pressure) were assessed [19]. Withdrawal of therapeutic upper airway stimulation resulted in worsening of both objective and subjective measures of sleep and breathing, which were resumed after therapy was reestablished and resulted in sustained effect at 18 months follow-up. Reduction of obstructive sleep apnea severity and improvement of quality of life were attributed directly to the effects of the electrical stimulation of the hypoglossal nerve [19]. This study was the next milestone for the success of selective hypoglossal nerve stimulation and lead to approval by the United States Food and Drug Administration (FDA) in 2014.

Afterwards in 2014 the German Post-Market study was initiated to evaluate safety and efficacy in a real world clinical setting. Three centers in Germany (Luebeck, Mannheim, Munich) included 60 patients in this trial. Data from 3 years follow-up are available and show that the adherence measured with the usage time remains stable at approximately 45 hours per week at 2 and 3 years [13–15]. Steffen et al. showed that the adherence measured with the usage time was stable at approximately 45 hours per week at 2 and 3 years. The median AHI was reduced from 28.6/h (baseline) to 9.0/h (2 years) and 10.0/h (3 years), as also the median oxygen desturation index (ODI) decreased from 27.0 to 6.3/h (2 years), and 8.3/h (3 years), which can be interpreted as normalization of daytime sleepiness. Furthermore, the median Epworth Sleepiness Scale (ESS) improved from baseline 13 points to 4 (2 years) and 6 (3 years).

Serious device-related adverse events were rare, with two-device explantation between 12 and 36 months postoperatively.

Sleep Parameters

Despite HNS has shown great effects on respiratory parameters, sleep parameters should not be affected by stimulation during night because of stimulation induced arousals. So far three clinical trials with focusing on this topics have been previously published [20–22] (see Table 9.2).All of them showed a significant percentage reduction in N1-sleep and increase in N3-sleep. Furthermore Hofauer et al. showed an increase in REM-sleep [20]. Across all three studies respiratory arousals were reduced, and no increase in stimulation arousals could be detected. Significant improvement across several sleep architecture parameters have been seen, but for sure further studies are needed to understand also longitudinal effects of this procedure on sleep [22].

Comparative Clinical Trials of Inspire System with Anatomy-Altering Surgery

Different trials have compared the novel technique of hypoglossal nerve stimulation to traditional multilevel OSA surgery (see Table 9.2). Traditional upper airway surgery is still the most common surgical procedure for treating OSA with surgery. Identification of the obstruction levels and subsequently addressing it to remove redundant tissue and combine this with reconstruction of palate and/or pharynx is the idea behind most procedures. The most common performed procedure is tonsillectomy with uvulopalatopharyngoplasty (UPPP) addressing the palate and oropharynx [23]. Huntley et al. compared HNS with UPPP in 2018 and 2020 showing that HNS is superior to traditional surgery [24, 25]. Also, a comparison between HNS and "doing nothing" – "being untreated" shows a clear superiority [26]. A more detail overview of the different trials is shown in Table 9.2.

Patients' Experience with the Inspire System

Adherence to therapy in OSA – especially in the long term – is discussed to be one of the key factors for reducing cardiovascular morbidity and mortality in patients [27, 28]. The adherence in selective hypoglossal nerve stimulation was investigated in several trials [14, 29, 30]. One of the key factors for therapy adherence is the fact that patients need to activate the stimulation with a remote control every time before usage [31]. This differs from the classical surgical treatment options of OSA, which did not require further compliance because the anatomic changes are permanent. Hofauer et al. investigated 102 patients, who received a unilateral respiration-synchronized stimulation system (Inspire, Golden Valley, USA). The aim of this analysis was to investigate the adherence of patients with this system. A usage time of 5.7 hours per night was described. 74.5% of the patients used the therapy more than 4 hours per night and 50% of the patients used the therapy even more than 6 hours per night [29]. The authors also evaluated the patient's opinion about the stimulation therapy. Most of the patients strongly agreed to the statement that "upper airway stimulation reduces the problems caused by my sleep apnea", which demonstrates the adoption of this treatment method by patients.

In another trial, which was set up by the same group, Hofauer et al. investigated patients who were implanted with the same stimulation system to answer a questionnaire on their subjective sensation of the stimulation, the use of different functions, side effects and an inventory for the description of the attitude towards upper airway stimulation [32]. Again, an objective therapy usage of 5.7 hours per night could be detected, meanwhile the subjective reports of the patient usage time revealed 6.8 hours per night. This discrepancy between subjective and objective

measurement, known as recall bias, is common in patient-reported outcomes, and occurs also i.e. when measuring sleeping time [33]. This phenomenon was also detected here. Furthermore a strong correlation between the postoperative AHI and the personal satisfaction after implantation was found [32]. A higher usage time could be detected in patients, who experienced greater subjective benefits from hypoglossal nerve stimulation according to their self-reported questionnaire outcomes [30]. Different other clinical trials where the focus was not on adherence revealed the same results. In 2014 Kezirian et al. published 12-months data from 31 patients, which received an Apnex HGNS® system, with an average usage time 5.4 hours per night [34]. In 2016 Kent et al. even showed in 20 patients a mean usage of 7.0 hours per night [35]. Larger trials as the German Post Market Study with 60 patients had an average usage time of 5.6 hours per night at 12 months after implantation [14]. Comparing the high adherence with HNS therapy to other treatment options as the standard treatment continuous positive airway pressure (CPAP), raises a few questions, why there is a relevant difference in utilization. In example, in the SAVE study, the adherence with CPAP was just 4.4 hours per night [36].

A possible reason for the superior adherence to upper airway stimulation is the intensive support and coaching which patients receive. Several in- and outpatient visits to the center are necessary before the treatment is fully activated on therapeutic levels. Patients treated today are highly motivated to get and to use therapy since they failed the standard therapy and actively decided for HNS. All of these interventions are also known to promote adherence to CPAP therapy [37]. Furthermore, hypoglossal nerve stimulation was only accessible for a long time to a few hospitals, which were certified to perform this surgery and received a reimbursement.

Another factor that could contribute to a higher adherence is the easier application of the therapy, which requires only to press the activation button on the remote control. Finally, initial data show little impairments of sleep with stimulation therapy, which can also drive therapy adherence [20].

In addition, patients who apply for an implantation of a HNS device are better educated about their disease and the associated risks of OSA—characteristics which also differentiate the adherent from the non-adherent CPAP user [15]. At our both centers, patients have a close connection to responsible surgeons and sleep technologists, which helps to identify usage problems at an early stage or technical problems and increases chances to overcome misunderstandings. This finding is nonetheless of further interest by virtue of non- compliance with CPAP being a necessary precursor to indication for this therapy, thereby skewing the population with a *de facto* failure bias.

Procedures

The surgical procedure and clinical pathway are described in the Chaps. 13 and 14.

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Chapter 10
Overview of Different HN-Stimulation Systems: Livanova

Ofer Jacobowitz

Contents

Introduction

Implantable hypoglossal neurostimulation (HGNS) is the first therapy that directly targets the loss of muscle tone during sleep in patients with obstructive sleep apnea (OSA). It is a timely new addition to the list of OSA treatments as various modalities are not always accepted or are not sufficiently effective. Personalization of OSA treatment is thus needed and certain patients will favor an implanted device that activates with a push of a button rather than wearing a device externally or intraorally. HGNS seems to fit well into the current digital age where so many have become virtually inseparable from their electronic devices.

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Targeted Hypoglossal Neurostimulation (THN) Concept and Design

Targeted hypoglossal neurostimulation was predicated on the lingual hydrostat model and the unique microanatomy of the human hypoglossal nerve [1]. The tongue may be considered a muscular hydrostat, like an elephant's trunk or a chameleon's tongue. It is a relatively incompressible complex of muscles that are interdigitated at various angles and can form a wide array of shapes and activities [2, 3]. To generate a physiological function, there is complex activation of different tongue muscles that simultaneously may mechanically recruit other attached tongue muscles for the final effect. For the upper airway, this was demonstrated experimentally, where stimulation of the hypoglossal nerve (HGN) trunk or concurrent surface stimulation of protrusors and retrusors improved airflow better or similarly as just stimulating the genioglossus muscle [4, 5]. Likewise, in a rat model, HGN trunk stimulation resulted in upper airway patency but denervation of the intrinsic muscles via nerve branch transection resulted in a diminished response [6]. Thus, for the THN approach, it was decided to devise an implantable pulse generator (IPG) and stimulation lead, capable of a wide array of stimulation patterns in order to select favorable groups of muscle activation for upper airway patency.

The human HGN was discovered to have a unique microanatomical structure, suitable for THN [1]. In the proximal, submandibular segment of the HGN, the nerve is *not fasciculated* (Fig. 10.1), but likely has a specific organization of fibers.

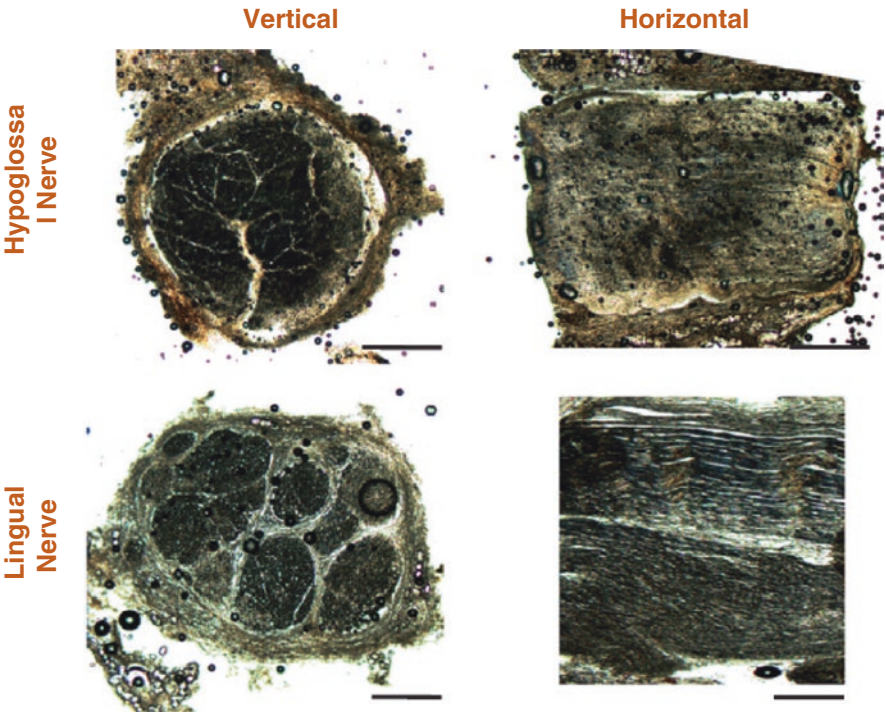

Fig. 10.1 Microanatomy of the Human Hypoglossal Nerve [1]

The implication of the absence of fascicles covered by perineurium is that surface stimulation of the HGN at the submandibular segment using an electrode can result in current spread within the HGN with activation of multiple muscles. The discovery of this unique microanatomy of the HGN by researchers at ImThera Medical [1] was incorporated into the design of the implantable Aura6000 system for THN.

The Aura6000 system is designed for complex activation of the HGN and is capable of a very large array of stimulation patterns. The IPG supplies constant current via six independent channels that correspond to six contacts on the stimulation lead cuff. The cuff design allows for stimulation of different points along the circumference of the HGN, thus allowing for selection of regions within the nerve trunk favorable for airway patency. Furthermore, the system allows for simultaneous activation of multiple contacts, thus greatly increasing the permutations for selective activation. Use of a multi-contact electrode can thus be used for current steering topographically within the HGN as shown in an experimental model [7]. The system uses a rechargeable battery that is charged a few times a week by the patient using a remote controller and charge amplifier (Fig. 10.2).

Unlike other HGN stimulation systems, the Aura6000 does not incorporate a sensing lead for respiratory cycle detection. By cycling stimulation between several contacts, the duty cycle can be reduced to 50%, 33% or lower, depending on how many contacts are used in a typical activation cycle (Fig. 10.3). This allows for almost continuous stimulation of the HGN with little risk of fatigue. Indeed, to date, no patients experienced HGN fatigue from stimulation. The typical effect of contact activation is stiffening and re-shaping of the tongue, with only a small amount of protrusion, thus tongue abrasions are only a rare risk. More importantly, activation results in pharyngeal wall stiffening, which is likely responsible for effectiveness of the therapy. The tongue-pharynx coupling mechanism is not well understood, and palatoglossus coupling has been proposed as a mechanism. The author proposes

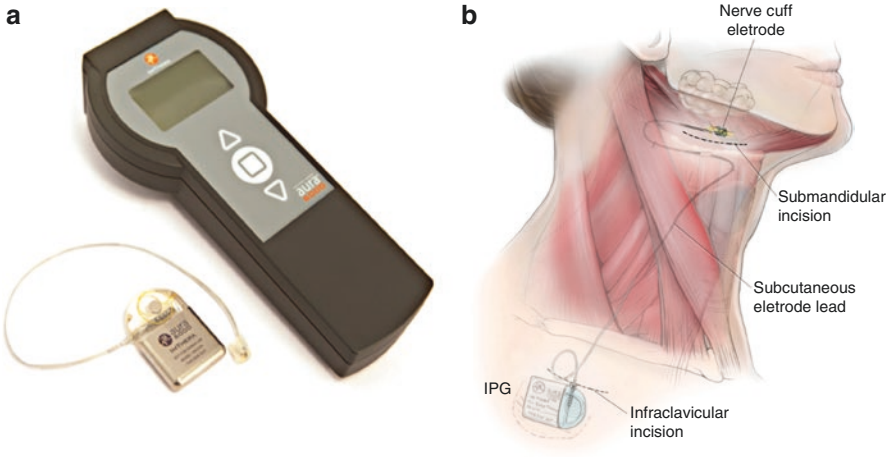

Fig. 10.2 Aura600 System. (**a**) Implantable pulse generator (IPG) and Remote Controller-Charger (RCC). (**b**) Scheme of implanted components [11]

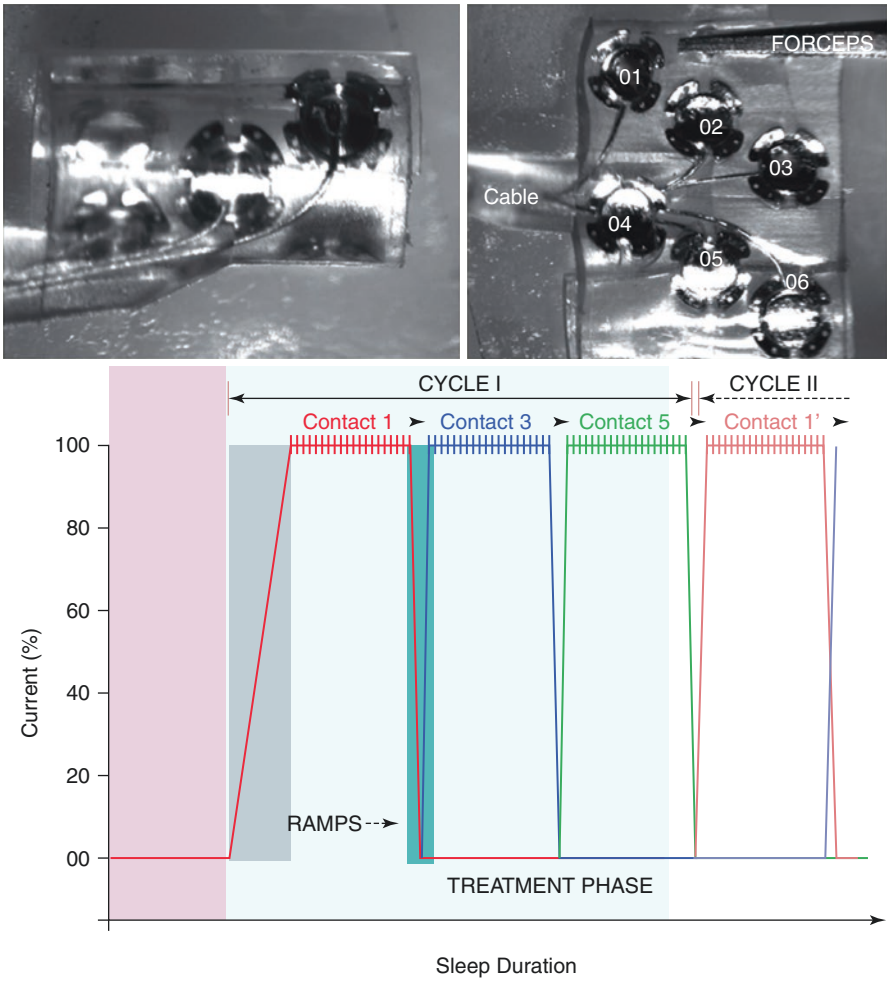

Fig. 10.3 Sample Stimulation Scheme [1]

that a more attractive explanation is that the transversalis muscle is anatomically connected with the superior pharyngeal constrictor at the tongue base [8].

Patient Selection

Selecting appropriate candidates for a particular OSA therapy is important for non-CPAP modalities, as each has its unique mechanism of action that applies to specific patient endotypes. Current selection criteria for the Aura6000 device include features from anthropomorphic and polysomnographic analysis.

Anatomically, the BMI upper limit is 35 kg/m^2, and exclusions include those with major craniofacial anomalies, tonsillar hypertrophy, or marked macroglossia.

The goal is to exclude those whose soft tissue or skeletal may be too unfavorable for HGN to overcome. Polysomnographic criteria include Apnea Hypopnea Index (AHI) of 20–65, apnea index ≤30, and less than 25% mixed or central apneas as a proportion of the overall AHI. Here, markedly severe OSA is restricted. In addition, those with mixed/central OSA that likely have high loop gain endotype (controller instability) for respiration are not deemed to be good candidates. Drug-induced sleep endoscopy is not used for patient selection. These criteria will undergo further refinement with greater clinical experience and additional diagnostic features will likely be identified.

Surgical Technique

The Aura6000 system is simple to implant as it does not require a sensing lead or hypoglossal branch testing and dissection. The location of cuff placement is on the HGN trunk. Antibiotics may be given, per surgeon's preference.

1. A standard curvilinear 5 cm incision is marked in the submandibular region, about 3–4 cm below the level of the mandible, approximating the location of the intermediate tendon of the digastric muscle (Fig. 10.4).

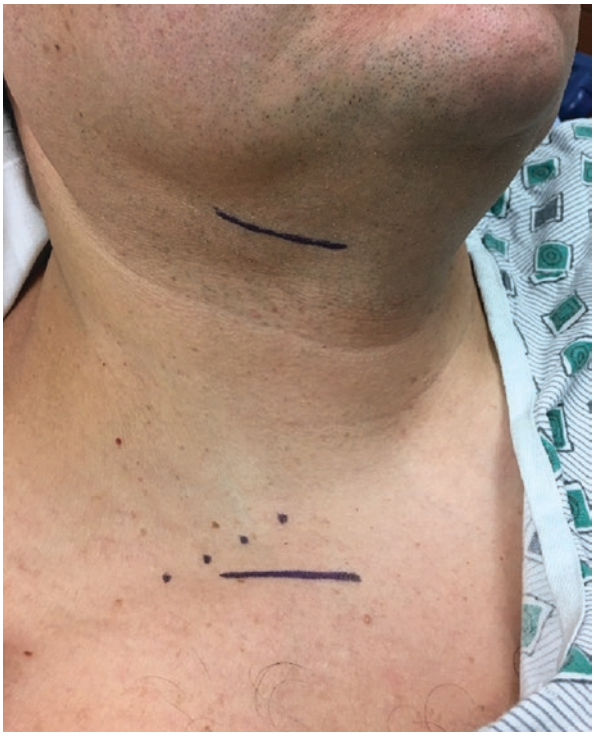

Fig. 10.4 Surgical marking for implantation. (Dotted line marks clavicle. Solid lines are for incisions)

2. While the patient is sitting, a chest incision is marked about 5 cm in length, >4 cm from the midline. Initially a horizontal incision was recommended, about 4–5 cm inferior to the clavicle, but in authors opinion, an oblique incision is preferable for cosmesis. The author's preference is to mark the outline of the IPG on the skin (Fig. 10.4).
3. The neck incision is performed to the subplatysmal plane. Dissection is performed to localize the lower border of the submandibular gland, and the hyoid bone is palpated. The digastric anterior and posterior portion are identified.
4. The intermediate digastric tendon is retracted with a vessel loop and the HGN is then identified via blunt dissection within the triangle bounded by the submandibular gland and the digastric bellies.
5. The HGN is dissected circumferentially a distance of 2 cm or greater, at a location proximal to its lateral branching, preserving perineurium and also the *venae commitante* whenever possible (Fig. 10.5).
6. The cuff is unfurled using traction on the two attached polypropylene loops (Fig. 10.6). An assistant is of benefit during this portion of the procedure. The silicone portion of the cuff is grasped with a curved forceps to insert the sleeve edge under the HGN. Once the cuff is in position, traction is released and the cuff self-closes. The lead wire is oriented posteriorly. The polypropylene loops are then removed (Fig. 10.7).
7. The chest incision is made through the skin and a pocket is dissected to <1 cm depth. Limited dissection is advised to avoid making a pocket larger than the IPG. The IPG is inserted for sizing, logo facing up, and is then removed.

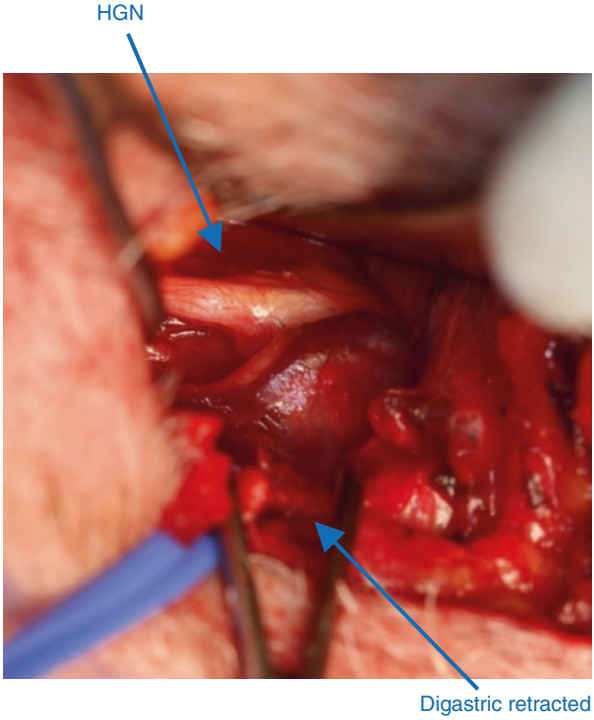

Fig. 10.5 Exposure of the HGN trunk

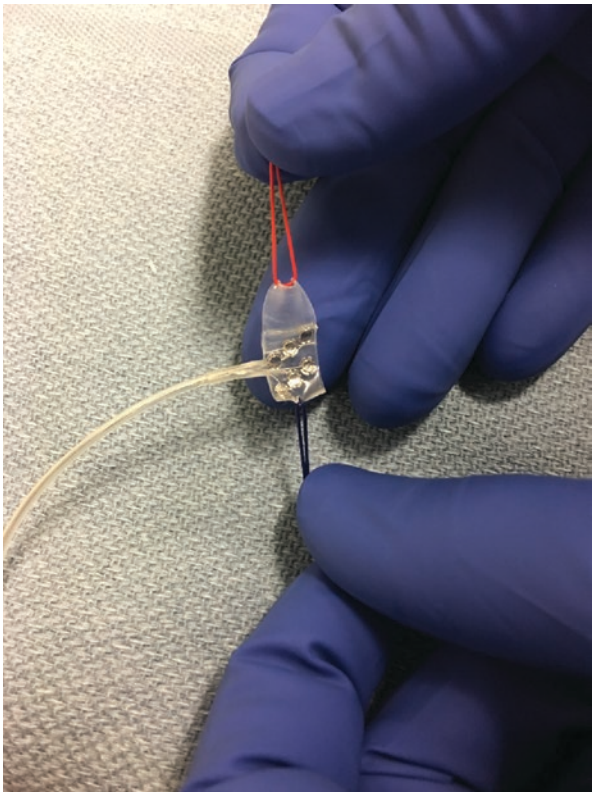

Fig. 10.6 Contact cuff

8. Tunneling using a Codman passer tool is performed subcutaneously to connect the incisions. The tool is bent 15° prior to insertion. The obturator is removed and the lead wire is carefully inserted into the lumen of the passer and is retrieved in the chest wound.
9. The lead wire tip is rinsed, inserted into the IPG slot, and the IPG is placed in the chest pocket for testing. Impedance testing and activation/interrogation is performed, ensuring contraction of the tongue muscles for each contact. A torque wrench is used to secure the wire tip within the IPG.
10. The lead wire in the neck is made to form an S-loop and is secured using a non-absorbable sutures applied over a silicone cuff superficially. The IPG is secured via non-absorbable sutures passed through the appropriate holes in the IPG and the muscle fascia to prevent flipping of the IPG (Twiddler's syndrome). An occlusive dressing is placed.
11. The wounds are rinsed with copious amounts of saline and closed in layers using meticulous technique for cosmetically acceptable scar (Fig. 10.8).
12. The patient may be discharged home the same day, as clinically appropriate. Vigorous activity is avoided for a period of 3–4 weeks after surgery.

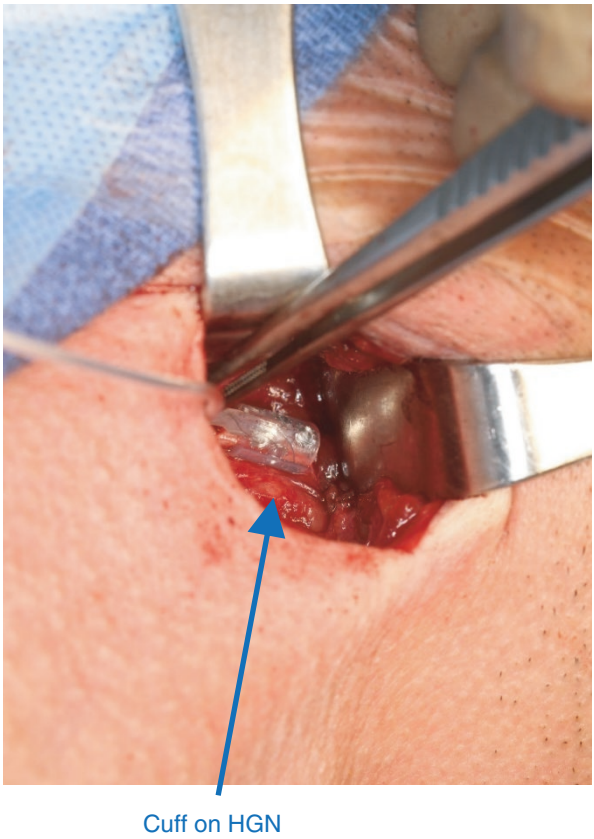

Fig. 10.7 Contact cuff placement

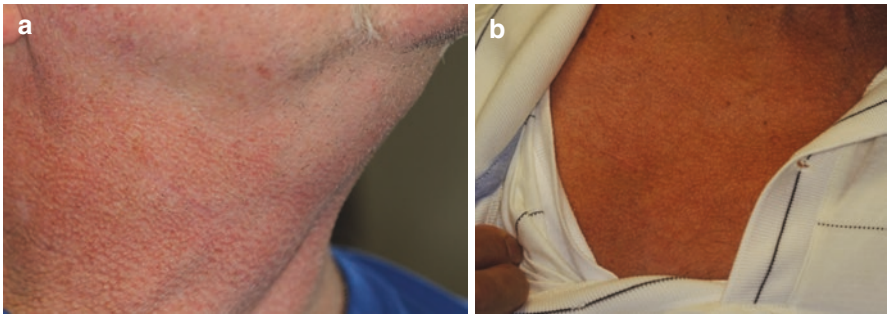

Fig. 10.8 Cosmesis of incisions for implantations after one year. (**a**) neck. (**b**) chest

Postoperative Management

Patients may return to work within a few days and pain is typically mild, treated with acetaminophen. Radiographs are not performed post operatively. At about one-month post-operatively, the patient is seen in clinic for determination of sensory and

motor thresholds and upper limits. IPG stimulation settings are adjusted by wireless connection using the patient's RCC (remote control and charger) that communicates with the IPG and a software interface used by the physician. Subsequently, a titration polysomnogram is performed to select contacts that result in airway patency when activated. Typically, 2–3 contacts are activated to reduce the duty cycle and avoid the risk of fatigue. Subsequent titrations in the sleep lab may be performed to improve efficacy and to reassess response, as some patients may improve over time. Adherence data is downloaded during follow up visits.

Complications

As expected for an implantable system, the procedure-related complications include hematoma, infection, and localized pain. There have been some cases of transient, mild tongue paresis. Device-related complications included malfunction causing pain, device failure, and lead revisions, requiring explantation and/or replacement. IPG replacements can be performed under local anesthesia. Lead revision was performed in 2 cases. Patients did not sustain tongue abrasions from activation. Treatment-related discomfort was treated by adjustment of stimulation parameters.

Clinical Trials

The Aura6000 system has been CE-marked since 2012 and is presently investigational in the U.S.A., with the pivotal confirmatory OSPREY (Treating Obstructive Sleep Apnea using Targeted Hypoglossal Neurostimulation) FDA trial having begun in late 2021. The Aura6000 system was developed by ImThera Medical (San Diego) who was recently acquired by Livanova PLC (London, UK).

The initial THN trial (THN1) included 13 CPAP-intolerant adult patients with BMI <40, and AHI ≥20 [9]. There were 13 patients with at baseline a mean BMI of 30.8 ± 3.4 and mean age of 50.0 ± 10.2. The baseline AHI was 45.2 ± 17.8 and ODI (Oxygen Desaturation Index) was 29.2 ± 19.6. After 1 year, the mean AHI declined to 21.0 ± 16.5 ($p < .001$) and the ODI from 29.2 ± 19.6 to 15.3 ± 16.2 ($p < .001$). One patient developed central sleep apnea after morphine pump implantation for unrelated reasons. There were 10/13 responders, with AHI decrease of 50% or greater. At one 1-year followup, for the responders, the mean AHI declined from 41.3 ± 13.1 to 13.2 ± 5.6 and the ODI declined from 23.1 ± 10.2 to 7.8 ± 5.3 ($p < .001$ for both). The micro-arousal rate also declined, from 36.8 ± 12.5 to 24.9 ± 13.7 ($p < .001$) for the entire group and from 34.8 ± 6.7 to 20.3 ± 8.1 ($p < .001$) for the responders. The only serious events were related to lead breakage, and one defective lead connector and IPG.

Seven of the 10 responders underwent polysomnographic testing for two nights after one year of stimulation, where in a randomized fashion, stimulation was active

one night and not used on the other night [10]. The mean baseline AHI was 43 ± 14, and ODI was 23 ± 12 and with simulation declined to 15 ± 5 and ODI 9 ± 3, respectively. During the testing night *without stimulation*, the AHI and ODI were 14 ± 8 and 8 ± 5, respectively, thus not significantly different from the values obtained with stimulation on. This persistent airway patency effect with short term withdrawal was uniquely reported for this system but needs to be confirmed.

The pilot study was followed by an extended safety and feasibility study (THN2) of 43 patients in US and European centers [11]. The upper BMI limit was 37 kg/m^2, the central sleep apnea percentage was limited to 10% and positional sleep apnea was excluded. Patients were assessed for safety and effectiveness outcomes at 6 months. The AHI was 35 ± 23, and ODI was 32 ± 22 at baseline, and at 6 months were 25 ± 23, and 24 ± 22, respectively (both with $p < 0.01$). The Epworth Sleepiness Scale (ESS) score was 12 ± 5 at baseline and 8 ± 4 at 6 months ($p < 0.001$). The response rate with 50% AHI decrease was 35%. For responders, the AHI declined from 36 ± 19 to 9 ± 6 and the ODI from 33 ± 19 to 8 ± 6 (both $p < 0.0001$). There were three serious adverse events, being a hematoma, device malfunction needing replacement, and surgery to reposition one device. Analysis of the results from this trial and comparison of responders to non-responders lead to refinement of exclusion criteria to include BMI ≤ 35, AHI ≤ 65, Apnea index ≤30 and those with of ≥15/hour Oxygen Desaturations of ≥10%. Presumably, this would lead to excluding those with very severe upper airway collapsibility or possibly pre-existing neuromuscular dysfunction from chronic intermittent hypoxia.

On this basis, the THN3 parallel, two-armed, randomized controlled trial of 138 patients was performed, beginning in 2015. It is the only true randomized clinical trial for effectiveness of HGNS. Inspire Medical's STAR trial only randomized *responders t*o therapy off, and did not randomize all treated patients [12]. All enrolled patients in THN3 underwent 2 screening polysomnogram studies for enrollment. After surgical implantation patients were 2:1 randomized to stimulation start at 1 month or at 4 months post-operatively (control group). Safety was assessed as well as effectiveness for AHI, ODI and quality of life at 12 or 15 months from implantation. AHI response was defined as ≥50% reduction and ODI response as ≥25% reduction. In addition, ESS, FOSQ and EQ-5D quality of life tools were assessed at the end points. Patient were followed for 5 years for safety assessment. The results of the THN3 trial will be forthcoming shortly in 2022.

The confirmatory OSPREY FDA IDE trial (ClinicalTrials.gov identifier NCT04950894) began in late 2021. It is an open-label, prospective, cross-over randomized trial of up to 150 CPAP-intolerant patients with moderate or severe OSA. Device enhancements were performed by Livanova, PLC, for this confirmatory trial. Enrolled patients will be implanted and then randomized 2:1 to start stimulation at month 1 post-implantation (active group) or at month 7 post-implantation (control group). Safety and efficacy will be determined for both groups at month 7, and then at month 13. Primary outcome endpoints are the AHI responder rate of the active group versus the control group at month 7, and the incidence of serious adverse events. Investigators and outcome assessors will be blinded to

polysomnographic outcomes. Secondary outcomes are comparison of the month 7 decrease in ODI, and quality of life surveys including the ESS, FOSQ and EQ-5D.

Future Perspectives

As with all non-CPAP treatments for OSA, improving identification of patients who would benefit from treatment and excluding those who will not important. As such, certain patient endotypes may be more suitable for HGNS. In a recent study of HGNS, those with higher arousal threshold and lower loop gain were more likely to succeed [13]. Thus, selecting for those with lower arousal index and no significant levels of central sleep apnea in screening polysomnography may be considered.

Simple testing of the integrity of the neuromuscular hypoglossal system or tongue-pharynx coupling to assess candidacy in the clinic is very much desired.

MRI compatibility is a desirable feature, as the Aura6000 is not approved to be used with MRI and the Inspire System is only conditionally approved for MRI (non-torso).

Titration of the Aura6000 system is complex given the many permutations of stimulation arrays and versatility of the device. Future automatic titration protocols are desirable to simplify the process.

Improvement in effectiveness is always a future goal. Given the safety of treatment, bilateral hypoglossal stimulation may be considered.

Summary

The Aura6000 is a HGNS system capable of complex patterns of activation of the HGN and achieving airway patency in sleep. It is simple and safe to implant on the hypoglossal nerve trunk. Stimulation utilizes six contacts to stimulate different zones within the HGN. Clinically meaningful improvements in the AHI, ODI and quality of life have been demonstrated in clinical trials for a subset of patients. The system is approved for use outside the USA under CE-mark and is undergoing confirmatory IDE testing in the USA.

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Chapter 11
Overview of Different HN-Stimulation Systems: Nyxoah

Richard Lewis

Contents

Introduction

The Genio System™ by Nyxoah is the first bilateral HN stimulator to undergo clinical trials in humans. Compared to the other available HNS devices currently available, it has several unique features: (1) it stimulates both hypoglossal nerves simultaneously (2) it is passive (contains no battery) (3) energy is delivered to the device transcutaneously, and (4) it is not timed to respiration, but stimulates in a programmable duty cycle. The Genio System™ is indicated in patients with moderate to severe OSA, who have failed or refused device use, have grade 0–2 tonsils, and a BMI <32. Six weeks after the implant, the patient starts using the device on a low setting. Two weeks later, they undergo awake and asleep titration (DISE) plus an overnight sleep study with titration. This is repeated at 3, 4 and 6 months post-surgery.

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The Device

The implantable stimulator (IS) consists of two bipolar electrodes connected to a receiver and circuit board, encased in a silicon envelope. The bipolar electrodes are housed in flexible legs which allow for movement of the genioglossus muscles (GG), and for variations in neuroanatomy (see Fig. 11.1a). The IS is a passive implant, containing no battery. Power is delivered via an adhesive patch placed on the skin below the chin. Attached to this is an activation chip (AC) and battery (see Fig. 11.1b). Each morning, the patient removes the patch, takes the AC off the patch and places it in a recharger. The patch is discarded. The patient specific stimulation parameters are stored within the AC, and are set by the sleep lab staff and treating physician during the titration studies. The patient also has the ability to increase and decrease the intensity of the stimulation by a remote control.

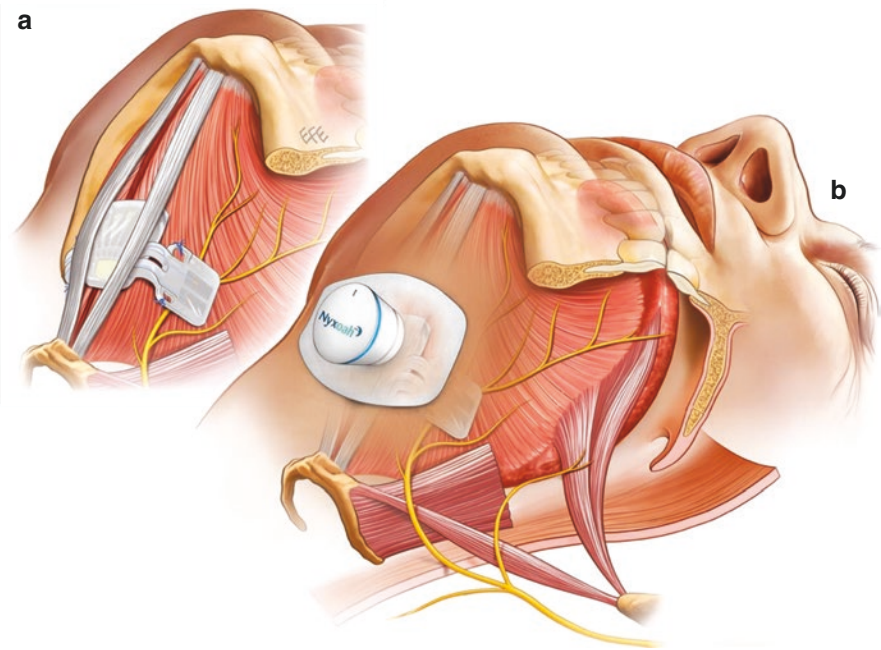

Fig. 11.1 Submental musculature showing (**a**) the implanted stimulator straddling the genioglossus muscles and hypoglossal nerve branches bilaterally and (**b**) the disposable patch and activation unit

Implantation Technique

The IS is implanted under general anaesthesia via a 6 cm submental incision. The mylohyoid is split vertically in the midline, and the geniohyoid (GH) muscles are separated and retracted laterally. The hypoglossal nerve (HN) is then identified bilaterally, lateral to the genioglossus (GG) muscles. A pocket is created on the superior aspect of the HN to insert the electrodes. Intraoperative nerve monitoring is used to exclude the most distal tongue retrusor branch of the HN, which is the branch to hyoglossus. Most commonly this is seen leaving the distal HN near the anterior border of hyoglossus muscle (HG) and passing superiorly on the surface of the muscle [1, 2]. Bipolar electrodes connected to the NIM monitor (Medtronic, USA) are inserted into the GG in the floor of the mouth prior to draping the patient. A further electrode is inserted into the HG muscle during the surgery to determine if the HG is being stimulated, and to ensure that the implant electrodes are placed distal to the last branch to HG. The position of the IS is checked intraoperatively by the use of an external stimulator whilst observing the NIM responses (high in the GG, low or absent in the HG), as well as tongue protrusion and endoscopic confirmation of anterior movement of the tongue base and epiglottis [3]. The position of the electrodes is adjusted as needed. Two sutures are placed in each electrode to fix them to the underlying muscle. The GH and mylohyoid muscles are then sutured back together, and the wound closed in layers. The patient is discharged home the same day or on the first postoperative day.

Titration

The parameters which can be modified are the stimulus train length, the stimulus amplitude, and the pulse width and frequency (Fig. 11.2).

The device is activated at 6 weeks post-implantation, and a low power setting is used initially to enable the patient to get used to the device. Two weeks later, an overnight sleep study is performed with various different settings trialled to reduce the severity of OSA. During the sleep study, a device is attached to the activation chip (AC) which communicates by Bluetooth to a computer running a program to change the settings in the AC. The stimulation settings can therefore be altered remotely without disturbing the patient during sleep. This process is repeated at 4 and 6 months. Typically, there is gradual habituation to the device which enables increased intensity of stimulation and better control of OSA. A stimulus "ramp-up' is programmed into the AC. When the patient turns the device on at night, the stimulus starts at a very low level, and gradually ramps up over 30 min until it reaches the predetermined stimulus settings. This improves patient comfort during the transition to sleep.

Results

The first clinical trial was completed in 2018 [4]. This was a prospective, single arm treatment study. A total of 27 patients were implanted, with 22 completing the protocol. The sleep studies were reported by an independent sleep physician

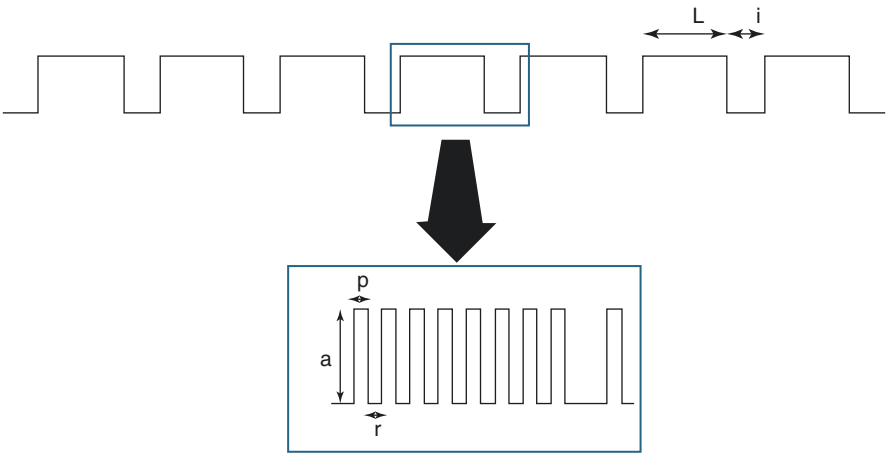

Fig. 11.2 Stimulation parameters included stimulation ON time (train length, L); stimulation OFF time (train interval, i); stimulation amplitude (a), pulse duration (r) and the pulse frequency. (From Eastwood et al. [4])

using AASM 2014 criteria. All PSG results are whole-night data rather than the best titration results from only part of the night as is often reported [5]. On a per protocol basis, the mean AHI reduced from 22.2 ± 12.0 to 11.0 ± 9.5 events per hour (Fig. 11.3). The ODI4% reduced from 18.2 to 8.0 events per hour (Fig. 11.4). The two quality of life instruments used were the Epworth Sleepiness Score and the FOSQ. These improved from 10.8 to 7.4, and 15.2 to 17.7 respectively (Fig. 11.5).

The data on clinical efficacy of the Genio™ system is limited at present, however it does suggest clinical efficacy equivalent to other forms of hypoglossal nerve stimulation [6, 7] A new study is currently underway comparing outcomes in patients with and without complete concentric collapse of the retropalatal airway on DISE (BETTER Sleep Study). Whether or not bilateral HN stimulation is superior to unlateral stimulation remains to be seen. It is apparent from the Inspire literature that a proportion of patients undergoing unilateral stimulation exhibit symmetrical tongue protrusion suggesting propagation of the stimulus to both hypoglossal nerves. Furthermore, patients with Inspire implants who demonstrate symmetrical tongue protrusion tend to have superior outcomes to those with asymmetrical or mixed tongue protrusion, suggesting that bilateral stimulation may be more effective than unilateral stimulation [8, 9].

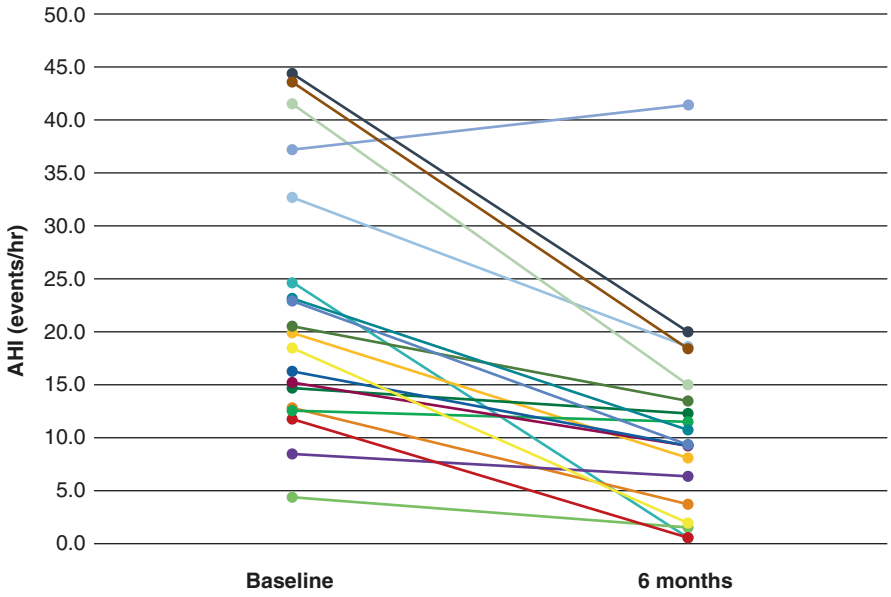

Fig. 11.3 Change in Apnea Hypopnea Index (AHI) for each participant from baseline to 6 months post-implantation. Each coloured line represents an individual participant using per protocol analyses (n = 19). (From Eastwood et al. [4])

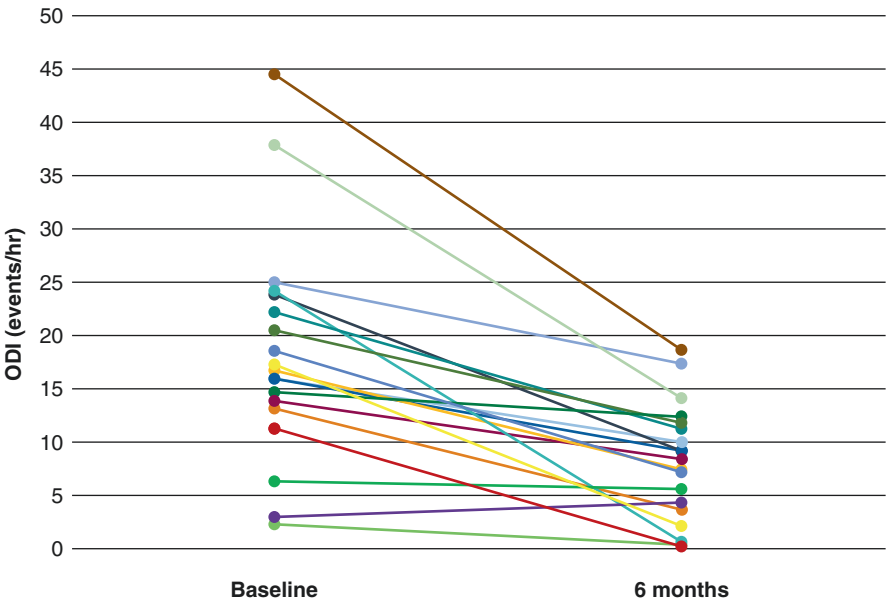

Fig. 11.4 Change in 4% Oxygen Desaturation Index (ODI) for each participant from baseline to 6 months post-implantation. Each coloured line represents an individual participant using per protocol analyses (n = 19). (From Eastwood et al. [4])

Outcome	Baseline (N=19)	6 months (N=19)	Mean Difference (95% CI)	P-value
Sleep Disordered Breathing				
AHI, events/hr	22.2 (12.0)	11.0 (9.5)	11.2 (15.5 to 6.9)	<0.0001
ODI, events/hr	18.2 (10.4)	8.0 (5.4)	10.2 (13.9 to 6.4)	<0.0001
SaO_2<90%, % time	5.5 (6.3)	2.2 (3.2)	3.3 (5.2 to 1.4)	0.0016
AI, events/hr	9.6 (10.6)	5.0 (9.0)	4.5 (9.4 to -0.4)	0.0673
HI, events/hr	11.3 (6.4)	5.9 (4.7)	5.4 (7.8 to 3.0)	0.0002
Symptoms				
ESS	10.8 (5.3)*	7.4 (5.4)	3.7 (6.6 to 0.9)	0.0129
FOSQ-10	15.2 (3.4)	17.7 (2.4)	2.4 (0.9 to 4.0)	0.0038
Sleep Architecture				
Sleep Efficiency, %	83.7 (11.6)	87.0 (9.4)	3.3 (–0.4 to 7.1)	0.0785
NREM Stage 1, %	13.5 (8.2)	8.6 (4.1)	4.9 (8.8 to 1.1)	0.0149
NREM Stage 2, %	60.1 (9.0)	66.7 (10.0)	6.8 (1.5 to 12.1)	0.0148
NREM Stage 3, %	8.2 (7.3)	3.3 (4.6)	4.9 (7.2 to 2.6)	0.0002
REM, %	18.2 (6.7)	21.2 (7.7)	3.0 (–0.7 to 6.8)	0.1078
Arl, events/hr	25.5 (8.5)	13.9 (6.0)	11.7 (15.9 to 7.5)	<0.0001

AHI=apnea hypopnea index unless otherwise specified. AHI=apnea hypopnea index; ODI=4% oxygen desaturation index; SaO_2<90%=proportion of the night spent at an oxygen saturation below 90%; AI-apnea index; HI=hypopnea index; ESS=Epworth sleepiness Scale; FOSQ10=the 10-item Functional Outcomes of Sleep Questionnaire; NREM sleep=non rapid eye movement; REM sleep=rapid eye movement; Arl=arousal index. *N=18.

Fig. 11.5 Outcome measures for per protocol analyses. (From Eastwood et al. [4])

Conclusion

Bilateral HN stimulation with the Genio™ system by Nyxoah is a novel, minimally invasive way to deliver stimulation to both HN's. Early results indicate clinical efficacy comparable to other HN stimulation systems, with no significant adverse events. Further knowledge is being gained in the next clinical trials of the device, including improvements in titration protocols and patient selection.

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Chapter 12
Upper Airway Stimulation Therapy; an Evaluation of Outcomes

Colin Huntley and Maurits Boon

Contents

Introduction

Obstructive sleep apnea (OSA) is a disease characterized by recurrent episodes of upper airway obstruction during sleep resulting in ventilatory and thus sleep disturbance. The anatomic locations contributing to the obstructive episodes include the palate, oropharyngeal walls, base of tongue, and larynx. Obstruction can occur at an isolated level or a combination of locations. Each obstructive event leads to ventilatory disruption, resulting in alterations in the oxygen and carbon dioxide levels in the blood. There is also a catecholamine surge secondary to sympathetic nervous system stimulation resulting in alterations in heart rate and blood pressure [1]. Additionally, the obstructive events can lead to sleep disruption contributing to poor sleep quality.

OSA has significant impact on sleep quality and quality of life. It has also been shown to be associated with a number of medical comorbidities. Patients carrying a diagnosis of OSA have shown increased rates of fatigue and sleepiness. The Epworth Sleepiness Score (ESS) and Functional Outcomes of Sleep Questionnaire (FOSQ)

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are two validated measures of daytime sleepiness and fatigue both of which are abnormal in the OSA population compared to normal controls. In addition to quality of life measures, a comorbid diagnosis of OSA is associated with multiple medical comorbidities including depression, anxiety, hypertension, cardiac arrhythmia, coronary artery disease, stroke, among others. These disease states are more common in the OSA patient and can be more difficult to treat with uncontrolled sleep apnea [2–5].

The primary treatment modality employed for the management of obstructive sleep apnea is positive airway pressure though either continuous or bilevel devices. The air pressure provides a pneumatic split, maintaining patency of anatomic locations prone to collapse and contributing to obstruction. Positive pressure allows for good control of apnea levels and improvement in daytime fatigue, blood pressure, cardiac arrhythmia, among other cardiovascular risks associated with OSA. However, positive pressure therapy can be difficult to tolerate for many patients [6].

There are a number of alternative options available when treating patients with OSA who have been unable to adapt to positive airway pressure therapy. Weight loss and positional therapy can be effective in select patients. Oral appliance therapy, allowing for mandibular advancement has shown effectiveness in controlling the apnea hypopnea index (AHI) burden and limiting comorbidities. Multiple surgical options exist to address the pharyngeal airway, the tongue base, and epiglottis. These remain a mainstay of treatment despite varying success. Discussion of all of these options is beyond the scope of this chapter.

Upper airway stimulation therapy (UAS) has emerged as an additional treatment option, recently gaining FDA approval in 2014 (Inspire Medical Systems Minneapolis, MN) after initial feasibility trials and a subsequent human trial describing significant treatment success [7]. The idea of stimulating the tongue musculature to treat OSA dates back to the 1980–1990s. A number of approaches were utilized including electrical stimulation of the palate and tongue via the submental and sublingual routes [8–11]. When the hypoglossal nerve was directly stimulated, specifically the branches innervating the genioglossus muscle, the primary protrusor of the tongue, a significant improvement in the apnea hypopnea index (AHI) and O_2 nadir were seen [12, 13].

Since the initial inquiries into utilizing neuromodulation to manage OSA, the technology has developed significantly. Currently there are three devices that exist which act to stimulate the hypoglossal nerve to improve upper airway obstruction in OSA. Two of these devices are still undergoing investigation and will be discussed elsewhere in this book. One device is FDA approved (Inspire Medical Systems Minneapolis, MN) and currently in clinical use. The rest of the chapter will reference the Inspire® device as the vast majority of the published data evaluates its effectiveness.

Outcomes

There have been multiple peer reviewed publications assessing outcomes of UAS therapy to date. These studies represent a mixture of industry sponsored multi-institutional studies and single institution experiences. Through some of these

studies, efforts have been made to construct predictive models to identify ideal patient characteristics for this technology. Comparisons to more traditional sleep surgery to assess UAS outcomes have also been performed.

The initial outcome study, the Stimulation Therapy for Apnea Reduction (STAR) trial, was published in the New England Journal of Medicine in 2014. This evaluated 126 patients undergoing UAS implantation and assessed subjective quality of life and objective polysomnographic variables at 2, 6, and 12 months. At the 12 month visit, the full night AHI, assessed through polysomnogram (PSG), decreased from a median baseline of 29.3 to 9 events per hour. The functional outcomes of sleep questionnaire (FOSQ) score increased from a mean of 14.3 to 17.3. The Epworth sleepiness score (ESS) decreased from 11.6 to 7. This study provided preliminary data showing the impact UAS can have on disease and symptom severity in select patients [7]. This cohort of patients was subsequently followed, assessing QoL indices and PSG outcomes at 18, 24, 36, 48, and 60 months. The data showed maintenance of AHI control and symptoms with continued use and with low complication rates [14–18]. The STAR trial served as an initial evaluation of a cohort of patients showing significant decline in AHI and symptom relief.

Clemens Heiser, MD and his group evaluated 60 patients undergoing UAS implantation at multiple German centers in their post-market study. Two night home sleep studies were performed at baseline and again at 6 months after implantation. They found a median decline in AHI from 28.6 at baseline to 8.3 at 6 months postoperatively. They also found normalization of the ESS from a mean of 12.8 at baseline to 7 at 6 months. The mean usage of the device at the 6 month follow-up was 42.9 h per week [19]. This same group published a follow-up study where an additional home sleep study was performed at 12 months. Again, they showed significant improvement in the AHI with a median value of 9.5 at 12 months. 73% of the cohort met the Sher criteria of surgical success (AHI <20 and at least 50% reduction). In addition, the adverse event rate was very low in this study cohort [20].

In addition to the STAR and German post-market data, there have been numerous publications on outcomes evaluating single and multi-institutional experiences. Kent et al. published their experience with 21 patients undergoing UAS implantation. They found a decline in AHI from 33.3 preoperatively to 4.3 at the postoperative titration PSG. This entire cohort had failed or been intolerant to positive pressure therapy. 55% had also attempted oral appliance therapy and had ineffective control of disease or intolerance to therapy. 50% had undergone prior upper airway surgery for OSA management with incomplete resolution of disease [21]. Huntley et al. published a series of 97 patients undergoing UAS implantation at 2 high volume clinical centers. They found no difference in the preoperative demographic data or disease severity between the two institutions. Postoperative outcomes also showed no difference in treatment AHI or ESS values. This data suggests that the results of UAS therapy in appropriately selected patients is reproducible at high volume centers [22]. In addition, Vonk et al. performed a retrospective cohort study including 44 patients undergoing UAS implantation [23] The primary aim was to evaluate respiratory outcomes, surgical success, and adverse events after short term follow-up. The total median AHI and ODI significantly decreased from 37.6 to 8.3 events per hour ($p < 0.001$) and from 37.1 to 15.9 events per hour ($p < 0.001$), respectively. The surgical success rate was 88.6 per

cent. The most common therapy-related adverse event reported was (temporary) stimulation-related discomfort.

The one caveat to these early studies is the polysomnographic outcome data was captured during a titration PSG, similar to a CPAP or bilevel titration study. This type of study provides a limited assessment of disease control at a particular stimulation level. Not a full night assessment.

The ADHERE registry is an ongoing multinational multicenter registry of patients who are undergoing OSA management with UAS. To date, there have been three published outcome studies intended to assess apnea control in a large patient cohort and establish predictors for treatment response. The first study was published in 2018. This included 301 patients across 10 multinational centers enrolled in the registry. This cohort consisted largely of male (82%), Caucasian (97%), overweight (mean BMI 29.2) patients. The mean AHI decreased from a baseline of 35.6 to 10.2 postoperatively. The postoperative assessment was through a mix of titration PSG and full night type 3 PSG. There was a low rate of surgical or device related adverse events with no postoperative infections reported [24]. The second study of the ADHERE registry, published by Heiser et al. in 2019, included 508 patients from 14 multinational centers. The authors again showed good AHI control with 81% of patients reaching success as defined by Sher (AHI <20 and at least 50% reduction). The cohort was analyzed in univariate and multivariable models to assess predictors of success. In the univariate model, each year of increase in age was associated with a 4% increased odds of treatment success. Also, for each 1 unit increase in BMI a 9% a decreased odd of success was found. In the multivariable model, only increasing age persisted as a predictor of success [25]. The third derivation of the ADHERE data was published by Thaler et al. in 2019. This study included 1017 participants. Of this cohort, 69% of patients met Sher success criteria at 12 months postoperatively. The ESS was well controlled with a decline from a baseline of 11.4 to 7.2 at the 12 month postoperative visit. Utilizing univariate regression models to identify predictors of success, female sex was identified as a predictor of improved outcomes. Lower BMI was also found to improve outcomes with an 8.5% increased odds of better outcome with each unit decrease in BMI. The adverse events reported in this study were minimal. The mean usage of therapy was 5.6 h per night at 12 months after implantation [26]. This is a significant finding since all patients undergoing this treatment modality were not able to tolerate positive pressure therapy.

Adherence to Therapy

Upper airway stimulation, like CPAP, requires the patient to activate the device nightly. Thus, the therapy is reliant on patient adherence for efficacy. With the current hypoglossal nerve stimulation technology, compliance can be objectively measured by use of the patient programmer or, alternatively, by interrogating the remote. There have been several studies documenting patient usage. In the initial paper from

the ADHERE registry, Boon et al. published an objectively measured compliance with a median device usage of 6.5 h per night [27]. This could be attributed to high satisfaction with the therapy as documented in this study. Subsequently, this population has been followed and represents the largest cohort studied to date with upper airway stimulation. In the most recent publication analyzing this population, Thaler et al. demonstrated continued high compliance with a median device usage of 5.7 h per night [26].

Predictors of Success

The ADHERE registry provided outcome data on a large cohort of patients undergoing UAS therapy and showed it to be a safe procedure. It also provided some potential predictors of treatment success. Separate publications have also assessed the impact of demographic variables on treatment success. Increasing BMI has long been associated with increased OSA severity and diminished surgical outcomes. Currently, one of the indications for UAS therapy in the United States is a BMI less than 35. In Germany, the upper limit is a BMI of 35. Huntley et al. evaluated a BMI of 32 as a cutoff in a cohort of American and German patients at two centers. This cohort included 113 patients with a BMI less than 32 and 40 patients with a BMI greater than 32. Other than BMI, there was no difference in demographic, preoperative PSG, or quality of life variables. Postoperatively, no significant differences were seen in titration AHI, O_2 Nadir, ESS or success rate between the two groups. This study suggests that body morphology, not overall BMI value, may play more of a predictive role in surgical outcomes [28].

Other research has assessed the role prior surgery has had on UAS outcomes. Traditional surgical intervention for OSA involves ablation of redundant tissue or reconstruction of the upper airway soft tissues. Since UAS takes advantage of the normal neuromuscular physiology of tongue protrusion to relieve upper airway obstruction, prior manipulation of upper airway anatomy or scar formation could, in theory, impact outcomes. The publication by Kent et al. showed good disease control with 50% of the study cohort undergoing prior upper airway surgery [21]. Kezirian et al. evaluated the ADHERE cohort of patients to assess the impact of prior surgery on UAS outcomes. They found no change in response to UAS therapy in all comers undergoing prior upper airway surgery. Subgroup analysis evaluating those undergoing prior palate, prior hypopharyngeal, and prior palate and hypopharyngeal surgery also did not reveal diminished response to UAS therapy [29]. Huntley et al. assessed 164 patients undergoing UAS at two institutions. They compared the outcomes of those undergoing prior palate surgery for OSA to those who had not and found no difference in postoperative AHI, ESS, or rate or surgical success between the two groups [30].

In summary, in appropriately selected patients, UAS can offer good control of OSA symptoms and disease severity. Female gender, age, and BMI may have an impact on outcomes, but more data is needed to create definitive models.

Patients undergoing prior surgery for OSA are not precluded from benefitting from this intervention.

UAS Vs Traditional Sleep Surgery

As discussed earlier in this chapter, there are a number of surgical options for management of OSA. Tracheotomy allows for bypass of the upper airway obstruction and, in theory, elimination of the disease. UPPP was introduced in the 1980's by Fujita. Caples et al. performed a meta-analysis reviewing outcomes of surgical interventions for OSA. They assessed 15 studies and found an overall 33% decline in the AHI with the use of UPPP [31]. Since that time, other procedures have been developed to alleviate obstruction at the level of the palate, oropharynx, and hypopharynx. The majority of the outcome studies assessing the various surgical interventions for management of OSA use polysomnographic variables as the primary outcome measures. Recently, data has started to emerge evaluating the impact of sleep surgery on physiologic outcomes. To date, the majority of this data surrounds UPPP and shows positive impact on cardiovascular disease, cerebrovascular disease, pulmonary hypertension, atherosclerosis, and depression [32–36].

Recently, data has emerged comparing UAS outcomes to more traditional surgical interventions for OSA. Shah et al. compared patients undergoing an uvulopalatal flap or expansion sphincter pharyngoplasty to UAS. The palate surgery cohort was selected to meet the same inclusion criteria as UAS (BMI <32 and AHI 20–65). They found significantly better control of AHI with UAS therapy [37]. Huntley et al. compared 33 patients undergoing expansion sphincter pharyngoplasty to 75 undergoing UAS. They found a significantly lower postoperative AHI in the UAS group (7.25 vs 13.47 events/hour) despite a significantly higher preoperative value (36.76 vs 26.60) [38].

Two studies have compared UAS outcomes to transoral robotic base of tongue reduction. Yu et al. compared 20 patients undergoing lingual tonsillectomy utilizing TORS who met criteria for UAS to 27 UAS patients. They found significantly improved AHI reduction (33.3 vs 12.7 events/hour) in the UAS group compared to the TORS cohort ([39]). Huntley et al. compared 24 patients undergoing TORS lingual tonsillectomy, midline glossectomy, and epiglottoplasty to 76 undergoing UAS. 2/3 of the TORS cohort underwent additional palate surgery for management of their OSA providing a multilevel intervention. The authors found a significantly lower postoperative AHI in the UAS group. They also found a significantly lower hospital length of stay and readmission rate in the UAS group [40].

In appropriately selected patients, UAS may offer superior outcomes to more traditional interventions. However, these traditional interventions are still very appropriate for management of OSA in many patients and UAS is only suitable for select candidates. With correct patient phenotyping, we can select the appropriate surgical approach to alleviate disease burden.

Physiologic Outcomes

It is well established that a history of OSA increases the risk of a number of comorbid cardiovascular diseases. OSA has been linked to an increased risk of hypertension, cardiac arrhythmia; specifically atrial fibrillation, cerebrovascular disease, among others. We also know OSA has an impact on quality of life such as daytime fatigue and excessive sleepiness [2–5].

Some literature has shown that management with positive pressure therapy can offer improvement in a number of these variables. Improvements in hypertension and the risk of recurrent atrial fibrillation after ablation have been shown with the use of CPAP [41, 42]. There is suggestion that there is a dose dependent response with more improvement in cardiovascular comorbidity with increased use of positive pressure therapy [43, 44].

As stated earlier in this chapter, data has started to emerge evaluating the impact of more traditional sleep surgery, specifically UPPP, on physiologic comorbidities attributed to OSA. With regard to UAS there has been some introductory data into its role in controlling comorbidities. Steffen et al. assessed glucose metabolism and hedonic drive for food at baseline and 12 months after UAS therapy. Their initial evaluation found improvements in measures of insulin resistance and hedonic food drive with UAS therapy [45]. Walia et al. compared a group of patients treated with CPAP to UAS using blood pressure measures as an end point. They found the PAP group to have greater improvements in the diastolic blood pressure and mean arterial pressure compared to the UAS group. However, UAS showed improved ESS and better usage than the PAP group [46].

This preliminary data shows that UAS is well tolerated and offers improved quality of life. UAS is also likely to offer improvements in associated comorbidities, but more data is needed to definitively confirm this statement.

Complications

The safety of UAS has been evaluated through a number of studies. The evaluation of safety parameters has included both complications related to surgical implantation of the device and complications related to device activation and nerve stimulation. In the study published by Kent et al. Two seromas were noted and one patient had prolonged incisional discomfort. There were no instances of infection or paresis of the hypoglossal or marginal mandibular nerves. After activation of the device, 3 patients had complaints of dry mouth and one with a mild tongue abrasion, all of which spontaneously resolved [21].

In the latest publication from the ADHERE database, an excellent safety profile was found. At the time of the final visit, approximately 12 months after implantation, there were no instances of tongue weakness or infection. One patient had swallowing or speech related complaints and 8 had complaints of incisional discomfort.

After activation, 8% had complaints of stimulation-related discomfort and 4% noted an abrasion of the tongue. 2 total patients required surgical revision [26].

Thus far, one study has prospectively evaluated swallowing function with UAS therapy. In theory, repetitive stimulation of the tongue may result in oral or oropharyngeal phase dysphagia. Huntley et al. utilized the EAT10 eating assessment tool questionnaire in 27 patients to assess the impact of UAS therapy on postoperative swallowing function. The EAT10 tool was administered preoperatively and at least 3 months after device activation. There was no difference in the findings suggesting no detrimental impact of UAS on swallowing function [47].

UAS therapy has been shown through a number of publications to be a safe procedure and a very well tolerated therapy for management of OSA.

Summary

UAS therapy is a novel therapy utilizing innate neurophysiological activity of the tongue to alleviate upper airway obstruction leading to OSA. It is an appropriate intervention to offer to select patients with moderate-severe OSA who have been unable to tolerate positive pressure therapy. It has been shown to be well tolerated by patients and offer good control of OSA disease severity measured through polysomnographic variables and quality of life measures. UAS therapy has demonstrated a good safety profile with low surgical and device related complications rates. With adequate control of OSA disease burden, UAS may offer benefit to associated comorbidities, but more data is needed to definitively confirm this statement.

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Chapter 13
Surgical Techniques in Upper Airway Stimulation

Clemens Heiser, J. Ulrich Sommer, and Nico de Vries

Contents

Surgical Techniques

Introduction

During the 1980's first approaches for electrical stimulation of the pharyngeal airway had been investigated [1, 2]. The thought was to increase genioglossus muscle neuromuscular activity. Already during these times Eisele et al. hypothesized that pharyngeal occlusion during sleep in patients with obstructive sleep apnea (OSA) is

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caused by decreased activity in the genioglossus muscle. Electrical stimulation of the muscle could result in an improvement tone of the muscle and restore pharyngeal patency during sleep [3]. It is mainly the pioneering work by the group of Schwarz, Eisele and Smith, who figured out that hypoglossal nerve stimulation directly instead of genioglossus muscle stimulation could be superior. Several different investigators have explored different electrical approaches to stimulation the pharynx. Surface electrodes have been placed on the upper neck skin in an attempt to move the tongue forward [4, 5]. Another group placed surface transoral electrodes into the region of the hypoglossal nerve [6]. Also percutaneous electrodes placed into the region of the hypoglossal nerve have been tried [7, 8]. Major drawbacks of these studies were that it was not clear if the genioglossus muscle was selectively stimulated with the electrodes. Consequently, many patients woke up from arousals during sleep, which occurred with these stimulation techniques. The authors concluded that the pharyngeal patency improvement was caused because of the arousals during stimulation. So, it was clear, that a direct stimulation of the hypoglossal nerve is needed to activate the main airway opener – the genioglossus muscle.

The first surgical approach was described by Eisele et al. in 2000 [3]. Already during these times, the stimulation electrode was placed in two locations of the nerve. One location was in contact with the distal branch of the hypoglossal nerve to the genioglossus muscle, the other location was at the main trunk of the nerve distal to the ansa hypoglossi branch. Eisele et al. figured out that the motor response to stimulation of the hypoglossal nerve is site-specific. The distal location revealed a tongue protrusion and contralateral deviation, while the proximal location showed a tongue retrusion and ipsilateral deviation. Today, depending on the different stimulation systems and techniques different surgical approaches and techniques are needed, which will be discussed in this chapter as related to the system.

Implant Technique

Breath-Synchronized Stimulation System

Inspire 1 System

The first generation was developed by Medtronic during the 90's [3]. General anesthesia with avoidance of long-acting muscle relaxants is needed to perform an implantation of the Inspire system. Perioperative antibiotics were given to the patient every 6 h for 24 h intravenously. A nasotracheal intubation was performed to visualize tongue movements intraoperatively very easy. The neck was placed in extension, and upper chest prepped and draped sterile. Three incisions as today were needed. The main difference to the system as used today was the breathing sensor, which was during these times a pressure transducer through the manubrium sterni. These techniques are not used today anymore, which is the reason why it is not described in detail here. For further information we refer to the original publication [3].

Inspire 2 and 4 Systems

Operative Technique [3]
The steps involved in implantation of the Inspire upper airway stimulation (UAS) System are discussed below. The most important aspects of successful implantation are strict sterile technique, careful attention to neuro-monitoring feedback, meticulous dissection and identification of the CN XII branches, and accurate placement of the sensing lead (see Fig. 13.1).

Induction and Body Positioning
The patient is induced under general anesthesia. If it is possible nasal intubation is preferred in order to visualize tongue movement *durante operationem* without hindrance of a trans oral intubation tube. The patient's neck is extended with a shoulder roll and slightly turned to the left. An additional roll or positioning pillow is placed under the patient's right chest, to facilitate exposure of the lateral chest wall.

Placement of Neuro-Monitoring Electrodes, Prep and Draping
The intra-oral neuro-monitoring electrodes are placed. Two Prass paired electrodes (18 mm in length) are used (see Video 13.1). The first is placed along the ventrolateral aspect of the right tongue directed posteriorly, just underneath the mucosa (see Fig. 13.2, red electrode). This allows monitoring of the styloglossus and hyoglossus muscles for consideration of branches of the nerve to be excluded. The second is placed

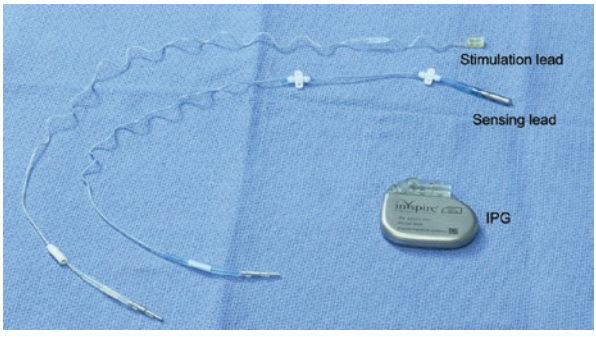

Fig. 13.1 The system consists of three components: simulation lead, sensing lead and implantable pulse generator (including battery and a chip for stimulation)

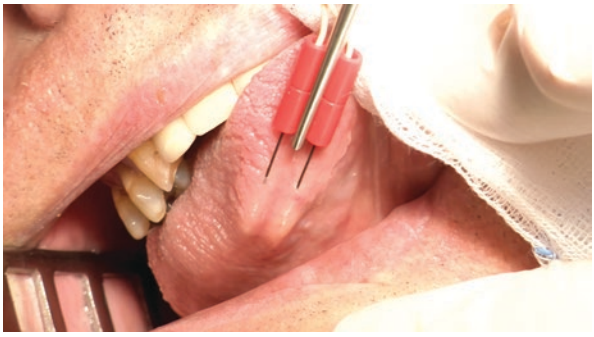

Fig. 13.2 Placing the (red) electrode for exclusion channel

in the right anterior floor of mouth a few millimeters aside of the midline, directed in a vertical direction just posterior to the mandible. This allows monitoring of the genioglossus muscle for purposes of branches to be included in the stimulation cuff (see Fig. 13.3, blue electrode). Furthermore, an earth electrode is placed next to the surgical field, for example in the left shoulder region. All electrodes should be fixed and secured with tape, creating a loop with enough slack for the cables to move freely with the tongue while stimulating (see Video 13.1). A sterile prep is then performed, encompassing all incisions in a single operative field. The field is covered with an Ioban™ drape. The mouth is covered with a transparent drape (such as a 1010™ drape) to allow for visualization of the tongue and its movement during the procedure (Table 13.1).

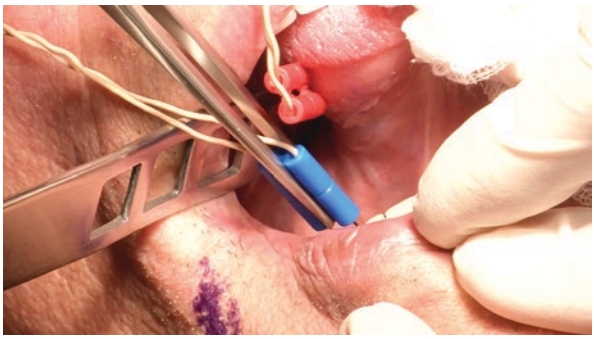

Fig. 13.3 Placing the blue electrode for inclusion channel

Table 13.1 Showing the different muscles with their innervations from the medial or lateral part of the hypoglossal nerve

Muscle	action	Effect of airway opening	Effect of airway stabilizing	Origin	insertion	Part of the Hypoglossal nerve
Extrinsic retractors	**Retraction of the tongue**	**Closing**	**Stabilizing in combination with protrusors**	**Bone**	**Tongue body**	**Lateral branches**
M. Styloglossus	Retracting & elevating	Closing	Stabilizing in combination with protrusors	Styloid process	Tongue edge	Lateral branches
M. Hyoglossus	Retracting & depressing	Closing	Stabilizing in combination with protrusors	Hyoid bone	Tongue edge	Lateral branches
Extrinsic protrusors	**Pulling tongue forward & down**	**Opening**	**Stabilizing in combination with retractors**	**Bone**	**Tongue & Bone**	**Medial branches**
M. Genioglossus oblique	Pulling tongue body down	Support opening	Stabilizing in combination with retractors	Mandible	Tongue body	Medial branches

Table 13.1 (continued)

Muscle	action	Effect of airway opening	Effect of airway stabilizing	Origin	insertion	Part of the Hypoglossal nerve
M. Genioglossus horizontal	Protruding Tongue body	Opening	Stabilizing in combination with retractors	Mandible	Tongue base & hyoid bone	Medial branches
Intrinsic stiffeners	**Stiffening tongue**	**Support opening**	**Stabilizing in combination with retractors**	**Tongue body**	**Tongue body**	**Medial branches**
M. transversus linguae	Narrowing	Support opening	Stabilizing in combination with retractors	Median septum	Lateral tongue edge	Medial branches
M. Vertical linguae	Flattening	Support opening	Stabilizing in combination with retractors	Dorsal tongue body muscoa	Ventral tongue body mucosa	Medial branches
Intrinsic shape changers	**Shortening & curling tip**	**Unknown**	**Unknown**	**Tongue body**	**Tongue body**	**Medial & lateral branches**
M. Medial inferior longitudinal linguae	Shortening, curling tip downwards	Unknown	Unknown	Tongue base	Tongue tip (more inferiorly)	Medial branches
M. Medial superior longitudinal linguae	Shortening, curling tip upwards	Unknown	Unknown	Tongue base	Tongue tip (more superiorly)	Lateral branches
M. Lateral inferior longitudinal linguae	Shortening, curling tip downwards	Unknown	Unknown	Tongue base	Tongue tip (more inferiorly)	Lateral branches
Other important muscles	**Mainly moving hyoid bone**	**Mostly unkown**	**Mostly unkown**	**Bone**	**Hyoid bone**	**C1 or V3**
M. Geniohyoid	Pulls hyoid forward (& mouth opening)	Airway opening	Stabilizing	Mandible	Hyoid bone	C1 (first cervical nerve)
M. Digastric anterior belly	Elevates hyoid bone and depress mandible	Unknown	Unknown	Digastric fossa of the mandible	Hyoid bone via digastric tendon	V3 (mandibular nerve)
M. Mylohoid	Elevates hyoid bone and tongue body	Unknown	Unknown	Length of the mandible	Hyoid bone	V3 (mandibular nerve)

Furthermore, the attachments are mentioned and the action of the muscles during activation. The effects of the pharyngeal upper airway (opening or stabilizing) is also mentioned meanwhile it has to be said that it is often unknown for stabilization

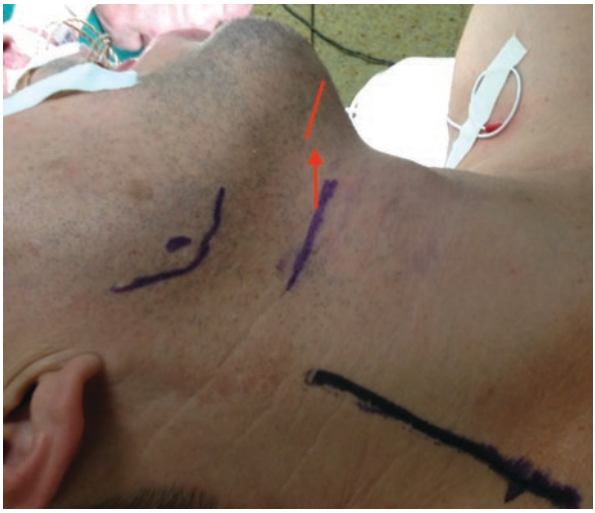

Fig. 13.4 Neck incision for selective unilateral hypoglossal nerve stimulation: purple marked the old incision through a submandibular glad resection approach. The red arrow indicates the more anterior approach with a smaller incision

Incision Placement

Three incisions are necessary (see Video 13.2). The first, for the stimulator lead placement, is in the right submental neck, starting about a centimeter to the right of midline, and extending back about 3–5 cm, to the anterior edge of the submandibular gland, about one finger's breadth below the mandible (see Fig. 13.4). The resulting incision line is approximately midway between the hyoid bone and inferior border of the mandible. The second, for the IPG placement, is at the right anterior chest wall, midway along the clavicle, and about 3–4 cm inferior to it, and 5 cm in length. The third, for the sensor lead placement, is positioned horizontally along the lateral chest, at about the fifth or sixth rib (see Video 13.3). The lateral extent of this incision is the middle of the axilla and the medial extent is the inferolateral border of the pectoralis major. It is also about 5 cm in length.

Placement of the Stimulator Lead

The placement of the stimulator lead is the most important and technically demanding part of the procedure. The incision is carried through the platysma muscle, whereupon the anterior belly of the digastric muscle is found, fanning out and overlying the mylohyoid. Once the digastric muscle and tendon have been identified, the anterior edge of the submandibular gland is found, as is the posterior edge of the mylohyoid muscle (see Fig. 13.5, see Video 13.4).

In some cases, the submandibular gland overlays the digastric tendon, which then needs to be retracted superoposteriorly before revealing the tendon and mylohyoid. The latter is retracted anteriorly to expose the hyoglossus muscle. The hypoglossal nerve main trunk can be identified in this location, at the anterior edge of the submandibular gland. Open with a retractor the mylohyoid muscle like the curtain in the theater (see Figs. 13.6 and 13.7, see Video 13.5).

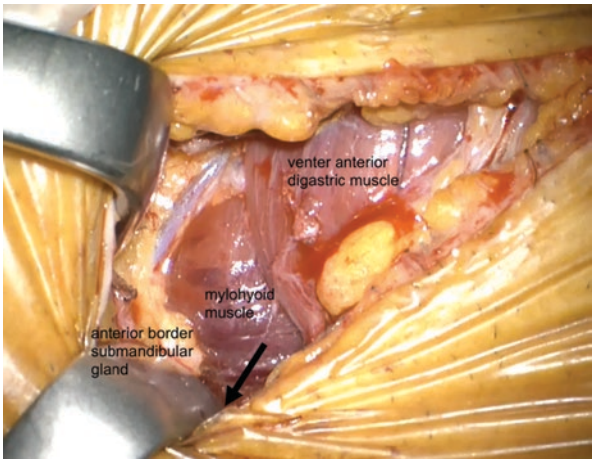

Fig. 13.5 Important landmarks to find the main trunk of the hypoglossal nerve. The black arrow marks the region where deeper preparation is needed [9]

Fig. 13.6 Showing the anatomic landmarks of the muscles. The nerve is not yet dissected and accompanied by a vein

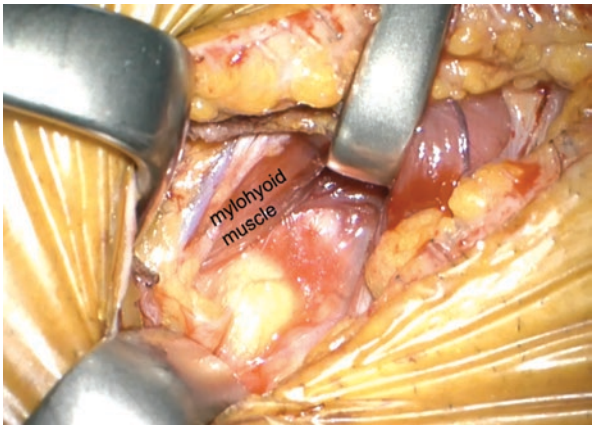

Fig. 13.7 The retractor for the mylohyoid muscle opens the view on the main trunk of the hypoglossal nerve such as a curtain of a theater

Fig. 13.8 The ranine vein is separated from the main trunk of the hypoglossal nerve to get optimal visibility of the nerve. # marks the main trunk of the hypoglossal nerve; * marks the first cervical spinal nerve (C1).

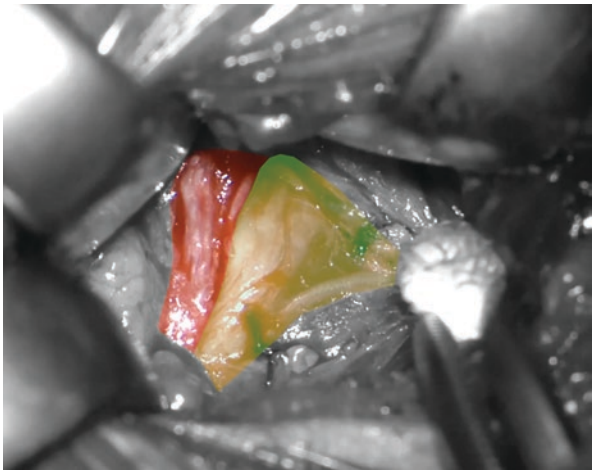

Fig. 13.9 The red area marks the region, which fibers (lateral XII) need to be excluded and green are the region, which fibers need to be included (medial XII) in the stimulation lead

The large ranine vein (vena comitans of hypoglossal nerve) most often overlies the anterior branching of the hypoglossal nerve and needs in some cases to be suture ligated and divided to properly dissect out the relevant branches (see Fig. 13.8). The authors started to protect the vein and dispensed with ligation.

Once this has been accomplished, the anterior branching is investigated, isolating the retraction branches to be excluded (hyoglossus and styloglossus) and the protrusion branches to be included (genioglossus) (see Fig. 13.9). The neuro-monitor is crucial to this identification [14]. A bipolar probe for the neuro-monitoring is recommended, providing a narrower field of stimulation for selectivity between

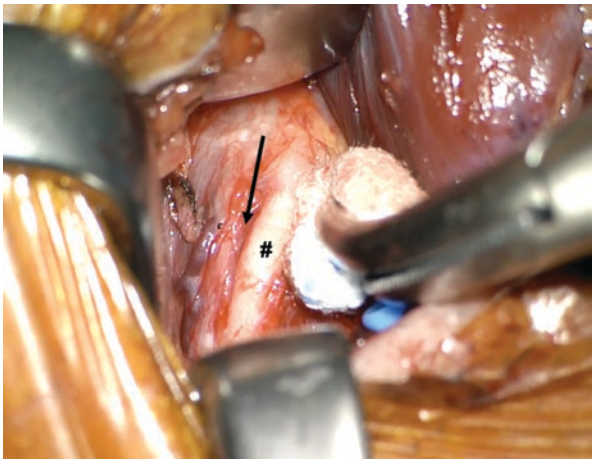

Fig. 13.10 The black arrow marks the accompanying vasa nervorum, which are marking the border between lateral and medial branches of the hypoglossal nerve (#)

closely coupled branches. In most of the cases accompanying vasa nervorum are running along the surrounding soft tissue of the nerve, marking the border between lateral and medial branches of the hypoglossal nerve (see Fig. 13.10, see Video 13.10).

If the separation of the main fibers can be clearly identified, the next step would be examining with NIM to verify and confirm that all exclusion and inclusion fibers have been prepared for cuff placement (Fig. 13.11). A complete mapping of the hypoglossal nerve can be found in Video 13.11.

In some cases, NIM might not provide a clear determination for excluding the lateral branches. In such a situation, the stimulation and resulting contralateral or bilateral tongue protrusion helps to confirm the targeted fibers are included for the cuff placement (see Videos 13.9 and 13.11).

Once isolated, the cuff of the stimulator electrode is placed around the nerve. A small overholt is used to undermine the nerve and make a "hole" for the stimulation lead (see Fig. 13.12).

This is accomplished by passing the long outer sleeve of the cuff under a 1 cm long segment of the nerve and positioning the inner sleeve of the cuff over the nerve branches to be included (see Figs. 13.13 and 13.14).

The lead is then passed under the digastric tendon in a gentle loop and anchored on its lateral aspect with two permanent sutures. Bacitracin infused saline should be irrigated around and into the cuff to help evacuate any air retained in the cuff. This surgical site is then packed off with gauze soaked in a bacitracin-saline mixture.

IPG Placement

The IPG pocket is subsequently developed (see Video 13.6). The pocket should be placed as medial as possible as it is allowed from an aesthetics viewpoint. The anterior chest wall incision is made, and dissection is carried down to the fascia

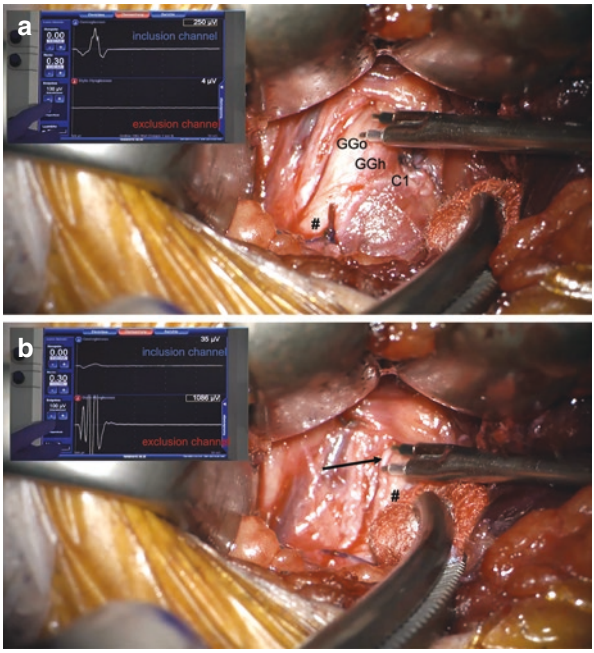

Fig. 13.11 Figure 8 (**a** + **b**): (**a**) Stimulating the GGo fibers shows a clear EMG response in the inclusion channel of the NIM. (**b**) The black arrow marks the last fiber of the hypoglossal nerve which needs to be excluded. EMG signal is presented in the exclusion channel. *GGh* = horizontal genioglossus muscle; *GGo* = oblique genioglossus muscle; *C1* = first cervical nerve; # = main trunk hypoglossal nerve

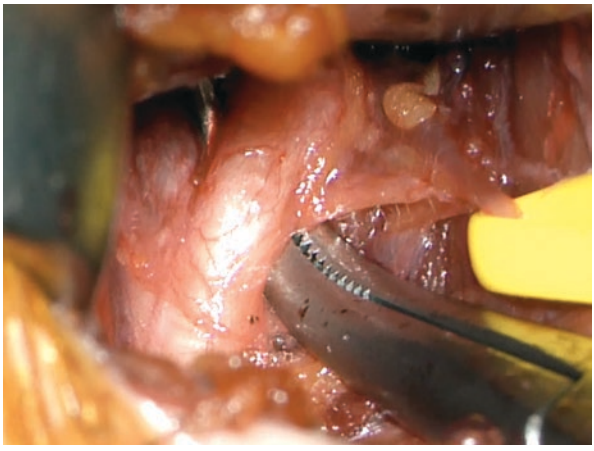

Fig. 13.12 An overholt is used to undermine the nerve to prepare placing the stimulation lead

overlying the pectoralis major muscle. Special care should be taken to avoid disrupting the fascia as intact fascia will serve as the anchor for the IPG. A pocket is made in this location, approximately 5 by 6 cm in dimension, which will be sufficient to house the IPG. This pocket may be readily created with blunt dissection, by the fingers, once one has entered the right tissue plane. It is also packed off with gauze soaked in a bacitracin-saline mixture.

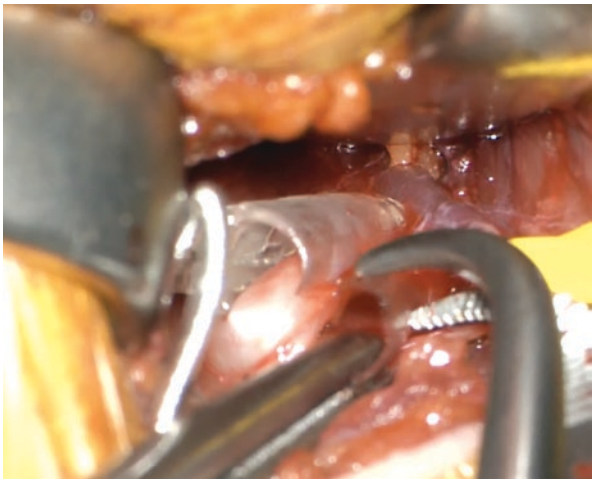

Fig. 13.13 Positioning of the stimulation lead, which has a long outer sleeve and smaller inner sleeve

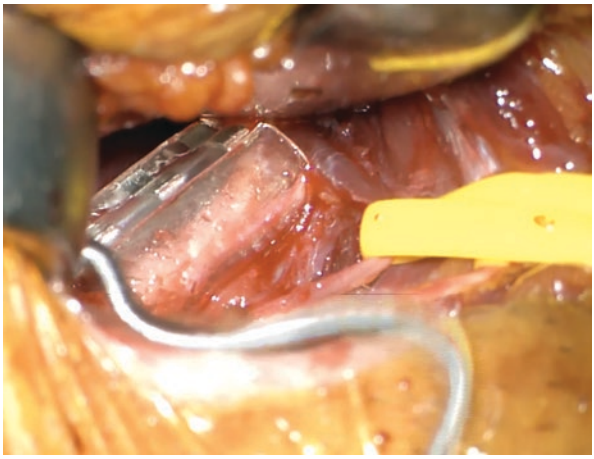

Fig. 13.14 Stimulation lead placed around the hypoglossal nerve. A vessel loop (yellow) keeps the vein out of the operating room, which was not ligated, but separated instead from the nerve

Placement of the Sensor Lead

The incision for the sensor lead is made next and carried down through fat to the serratus anterior muscles (see Figs. 13.15 and 13.16, see Video 13.7).

This is retracted superiorly, and the fifth and sixth ribs are identified. Blunt dissection is performed through the external intercostal muscle to identify the internal intercostal muscle (see Fig. 13.17). A tunnel is made in between the external and internal intercostal muscles, approximately 6 cm in length taking care to avoid the neurovascular bundle on the inferior aspect of the rib. The sensor lead is then passed into this pocket. This should be facilitated by placement of a ¼ inch (0.6 cm) malleable retractor into the tunnel, with the lead being passed underneath it. Alternatively, it may be placed with a long clamp (see Figs. 13.18 and 13.19).

It is critical to make sure that the sensing portion of the lead is facing toward the pleura. The lead is then anchored at two separate sites. The fixed anchor which lies

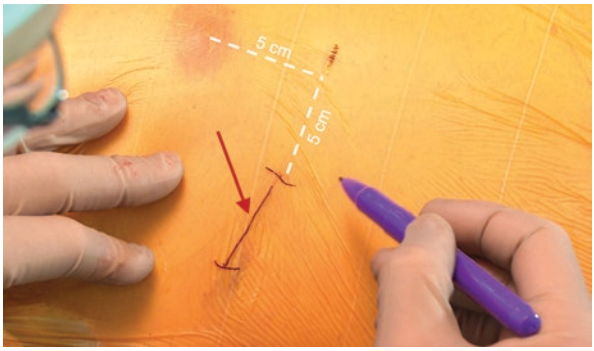

Fig. 13.15 Planning the incision for the sensing lead. A 4 to 5 cm skin incision is performed 5 cm down below the nipple (mamilla) and 5 cm lateral to it. The red arrow marks the incision line

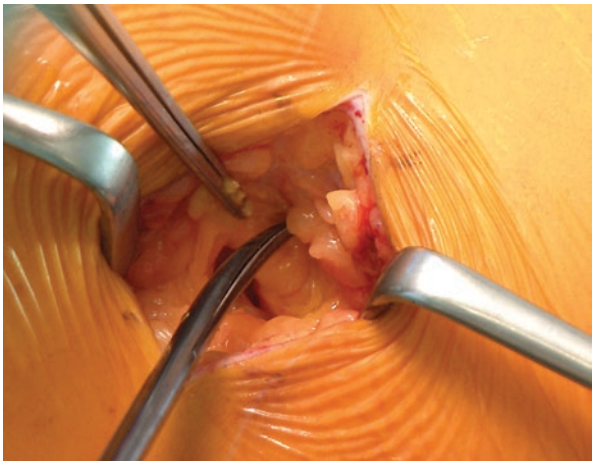

Fig. 13.16 Dissection through the soft tissue to the muscle layers

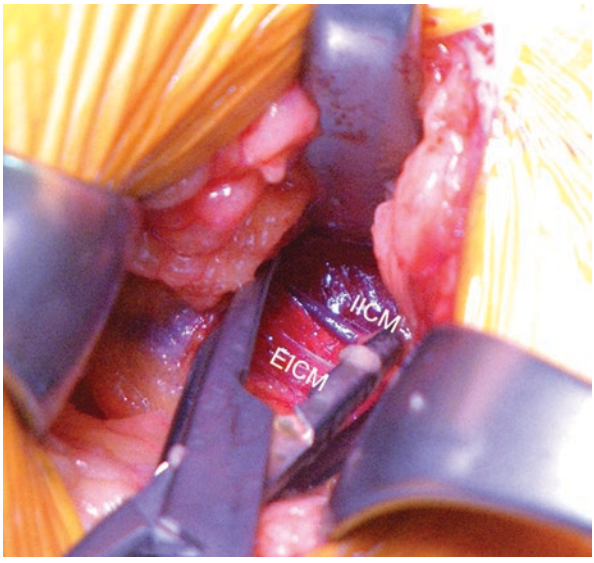

Fig. 13.17 Blunt dissection to the external and internal intercostal muscles. EICM = external intercostal muscle; IICM = internal intercostal muscle

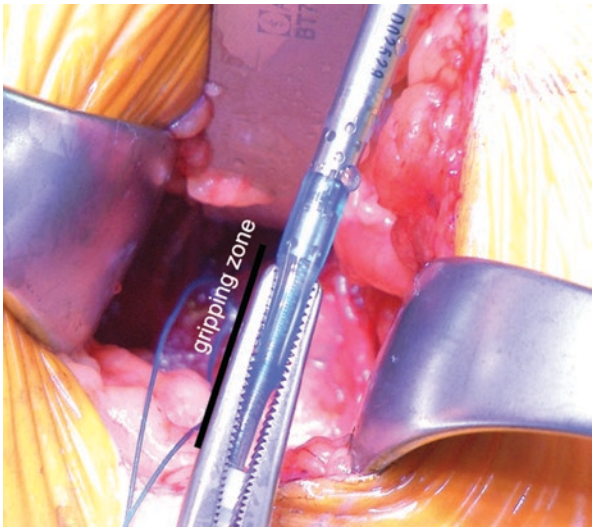

Fig. 13.18 The sensing lead can be hold with a clamp at the gripping zone, which is marked with a black bar

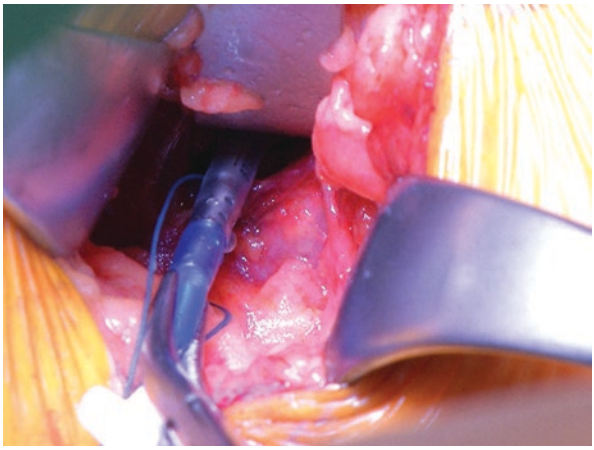

Fig. 13.19 Placing the sensing lead facing to the pleura

most proximal to the sensor is addressed first. It is anchored to the fascia just outside the pocket making sure to keep the ridges which run parallel to the anchor facing away from the chest wall. The second anchor is fixed, after a gentle loop is created, and should be positioned lateral and superior to the first. This site is then packed off with gauze soaked in a bacitracin-saline mixture. It is important not to use any sharp instruments to grasp the sense lead during the placement.

Tunneling the Leads

The leads for the sensor lead and stimulation lead are next tunneled with the provided disposable tunneling device. Some initial dissection with a Kelly clamp or the like is useful to shorten the distance that must be blindly tunneled. The sensor lead is tunneled first. This is done from the medial-superior aspect of the lateral chest wall incision and carried up to the inferior aspect of the anterior chest wall site. The stimulator lead is tunneled second. The device is bent to match the curve of the neck

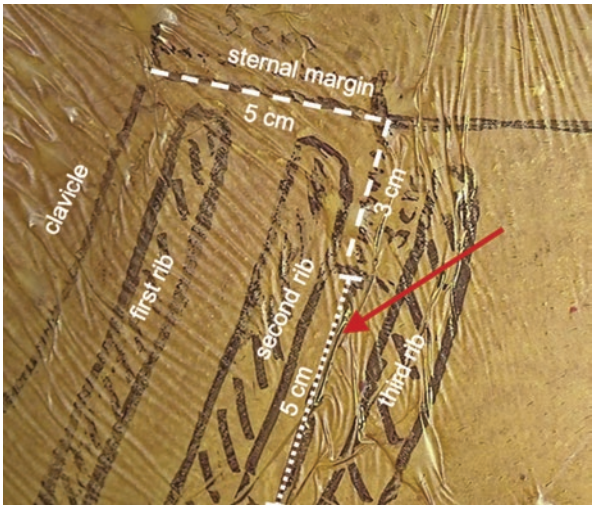

Fig. 13.20 Planning one incision to place the IPG and sensing lead. The red arrow marks the incision line of 5 cm

so that the lead will pass over the clavicle. Care must be taken to avoid the external jugular vein, having identified it beforehand where possible. The lead is brought out at the superior-medial aspect of the anterior chest wall site. The leads are then attached to the IPG in the prescribed manner.

Two Incision Technique [10]
A new technique of placing the sensor, is to place it in the second intercostal space between the second and third rib using the IPG pocket. The third incision is in this approach not needed anymore, and the IPG and respiratory sensing lead placement takes place though a single chest incision (see Fig. 13.20). To protect the medial pectoral nerve, it is recommended to place the 5 cm IPG incision no more than 9 cm from the sternal margin directly over the second intercostal space between the second and third ribs. The medial edge of the incision (5 cm long) should be at least 2–3 cm from the sternal margin and approximately 5 cm below the clavicle over the second intercostal space (see Fig. 13.20).

Keep in mind that the sternocostal head of the pectoralis major muscle tends to be thinner here compared to the 3-incision technique (see Fig. 13.21). It is important not to use the midclavicular line for incision planning because between medical professionals a high variance exists. As already mentioned, the lateral and medial pectoral nerve need to be preserved during this procedure. Further explanations can be found in the original publication from David T. Kent et al. [10]

After preparing the 5 × 5 cm IPG pocket on the pectoralis major fascia, which is incised, cold and blunt dissection to the second intercostal space is used (see Fig. 13.21).

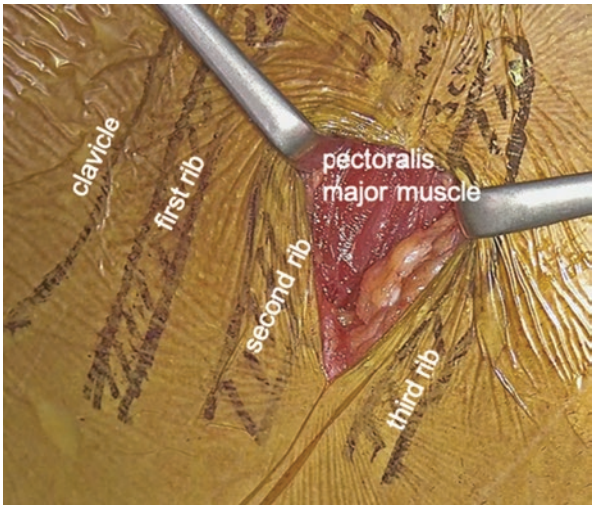

Fig. 13.21 After the 5 cm incision exploring the pectoralis major muscle

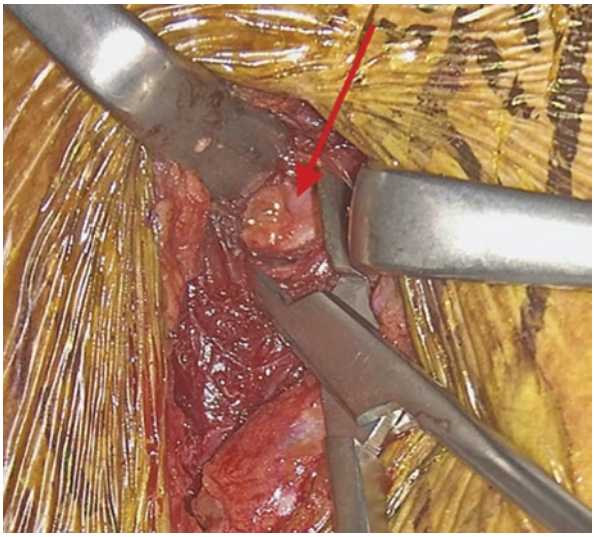

Fig. 13.22 Showing the pleura if preparation is too deep. Avoid any manipulation here in order to prevent a pneumothorax

A thin layer of fatty tissue appears over the second intercostal space (see Fig. 13.22). The change of internal intercostal muscle fiber direction is sometimes less obvious than more laterally in the chest wall where the fiber angle change is closer to 90° (see Fig. 13.23).

The sensing lead is placed between the external and internal intercostal muscles (see Fig. 13.24).

Then the two anchors are fixed superficial to the pectoralis major muscle.

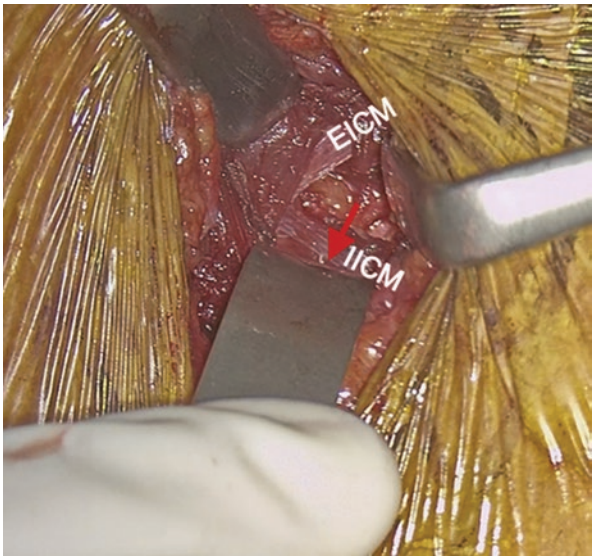

Fig. 13.23 Keep in mind the fiber directions of the thin intercostal muscles. *EICM* = external intercostal muscle; *IICM* = internal intercostal muscle

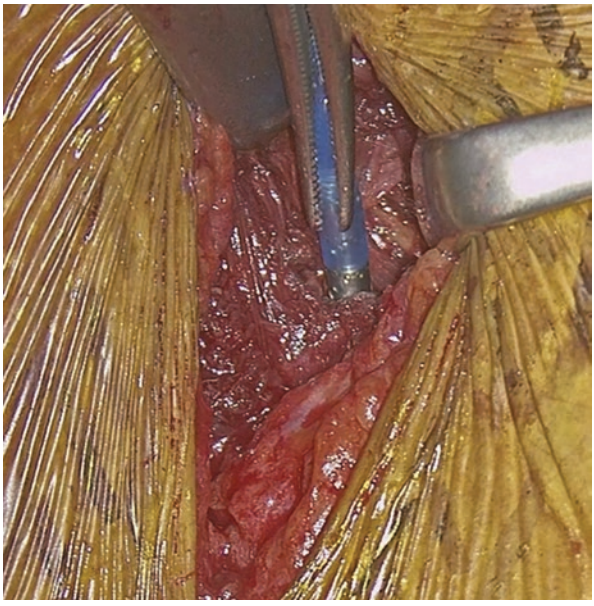

Fig. 13.24 Placing the sensing lead in the 2nd intercostal space between the internal and external intercostal muscles. The tip of the lead should point away from the sternum

Device Interrogation/Verification

The IPG is placed in the right chest pocket after connecting the stimulation and sensing lead to the IPG (see Fig. 13.25). Therefore, the manufacturer etching should face out with leads attached, into the anterior chest wall pocket (see Fig. 13.26).

The next is to control the function of the system. After interrogation, the validation of the sensor waveform is performed by running stimulation from 1.0 V down

to 0.5 V and below, as appropriate (see Video 13.8). If a sufficient tongue motion can be detected, or sometimes where necessary, palpated, the IPG is anchored with two sutures in place - ideally to the pectoralis fascia. The existing holes with two permanent sutures are in the left upper corner of the IPG (see Fig. 13.25). The sutures should be placed with a loose sling to avoid excess tension on the chest wall. This could create a discomfort feeling for the patient when moving.

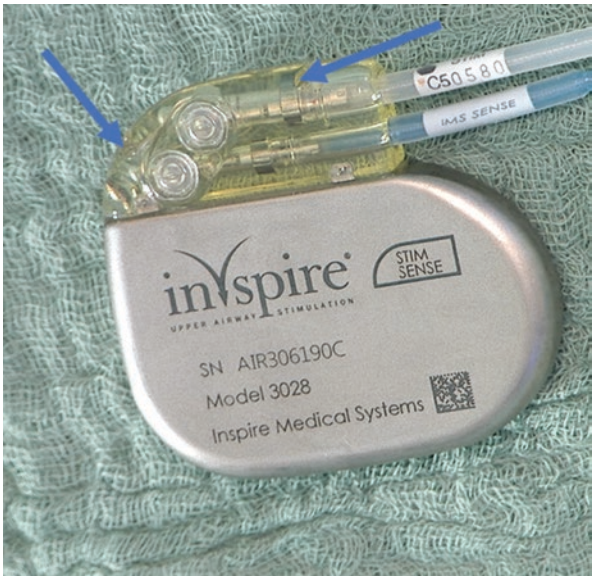

Fig. 13.25 Implantable Pulse Generator (IPG). The blue arrows indicate the suture holes to place the IPG on the fascia of the pectoralis major muscle

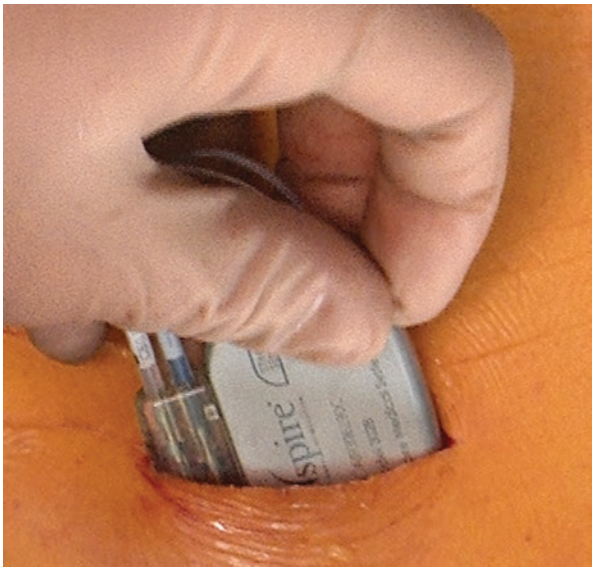

Fig. 13.26 Placing the IPG in the right chest wall pocket

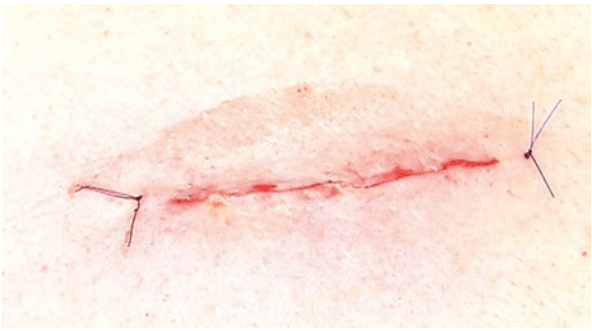

Fig. 13.27 Closing suture using intracutaneous suture

Closure/Dressings

The three incisions should be closed in multiple layers (see Fig. 13.27). Finally, steri-strips are applied with pressure dressings. Wound drainage should not be done to risk of infection. Pressure dressings can be done with elastic tape overlain (e.g., Medipore™ or Hypafix™). After 48 h the wound dressing can be removed.

Postoperative Care

On the same day or one day after an antero-posterior chest x-ray and lateral neck x-ray are obtained (see Figs. 13.28 and 13.29). This is needed to document the position of the IPG and its leads and to rule out a pneumothorax. It is desirable if the chest x-ray incorporates the upper neck as well as the lung fields to allow visualization of the entire implant.

Patients are discharged to home depending on the customs of the country (day care, or 1–3 days after surgery). Patients are advised to limit right arm movement and heavy lifting for 2–3 weeks. One week after surgery evaluation of the wounds takes place and usually sutures are removed 7 to 10 days after implantation. Patients need to be informed that the device remains inactive for at least 4 weeks until the stimulation is turned on in an ambulatory setting. Patients should not expect to feel any stimulation. Nevertheless, there will be some patients who report they already feel significantly better after the operation, which is due to a placebo effect.

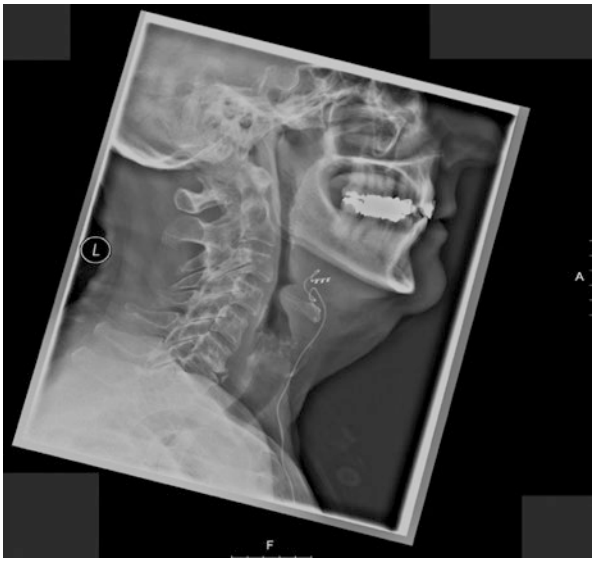

Fig. 13.28 X-ray (lateral neck) of an implanted selective hypoglossal nerve stimulation system (Inspire II, Inspire Medical Systems, Golden Valley, USA)

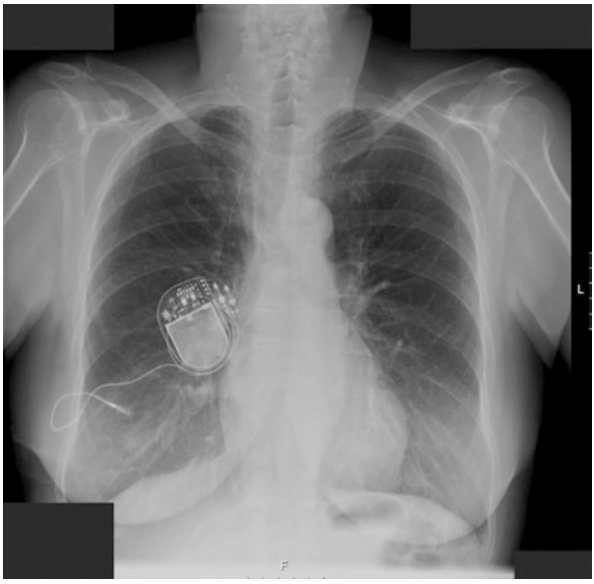

Fig. 13.29 X-ray (anterior posterior chest) of an implanted selective hypoglossal nerve stimulation system (Inspire II, Inspire Medical Systems, Golden Valley, USA). The implantable pulse generator is presented in the right chest wall as well as the sensing lead in the intercostal space

Tonic Stimulation System

LivaNova, former: ImThera Aura 6000 System

Therapy Description
The aura6000 system (LivaNova PLC, London, United Kingdom) consists of two implanted components: an implanted pulse generator (IPG) and a stimulation lead. This IPG has a rechargeable battery and electronics system for the stimulation integrated. This electronic system consists of hardware and software.

A cable runs from the IPG to a multi-electrode lead with an 8 mm soft silicone cuff housing. This electrode lead consists of six independent electrodes that are each connected to an independent current source, providing a wealth of access points to the nerve. The contacts are distributed evenly between 2 flaps and at the extremity of each flap is present a red or a blue thread. These threads are surgical guides to assist in the placement of the cuff around the nerve and should be removed prior to closing the incisions (Fig. 13.30).

No sensing lead is required as the stimulation paradigm is independent of the breathing cycle and aims at generally restoring the tongue tone. This is achieved by targeting the different muscles of the tongue, retrusors as well as protrusors, as allowed by the proximal placement of the electrode. The simplicity of the design translates for the patient into reduced risk (reduced infection probability and elimination of conditions such as pneumothorax). For surgeons, this simplicity translates into a shorter procedure time, surgeries often requiring less than an hour to complete. In addition, the unique stimulation paradigm significantly reduces the exposure to tongue abrasion as is frequently observed in protrusion-based therapies.

Patient Setup
The surgical procedure is performed under general anesthesia via transnasal or oral intubation. Of course, nasal intubation is always preferable to have an easier access to visualize the tongue motions although this is not required for this therapy. The patient's neck should be extended. In some cases, a shoulder roll can be used, and the head is slightly turned to the left.

Fig. 13.30 Multielectrode lead with red and blue threads

Surgical Procedure

The whole procedure can be watched in Video 13.12. For this surgical procedure intraoperative neuromonitoring (NIM) is not needed, however nerve confirmation with a disposable nerve locator is recommended. The first step of the surgical procedure is the hypoglossal nerve dissection. A horizontal 3 to 4 cm incision is performed two fingers below the mandible as surgeons are used to it during submandibulectomy (Fig. 13.31).

Subcutaneous preparation with cutting through the platysma leads in the next preparation step to the submandibular gland (see Figs. 13.32 and 13.33).

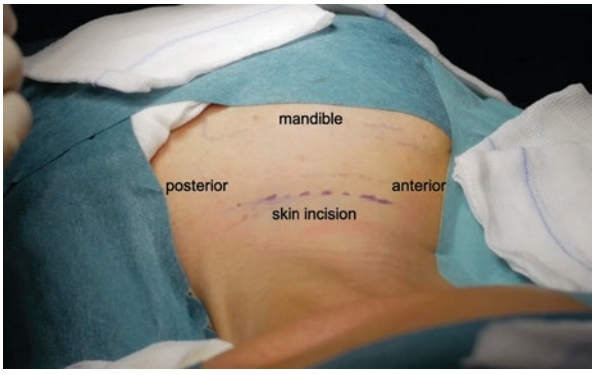

Fig. 13.31 Skin incision is performed two fingers below the submandibular gland as familiar with submandibular gland resection

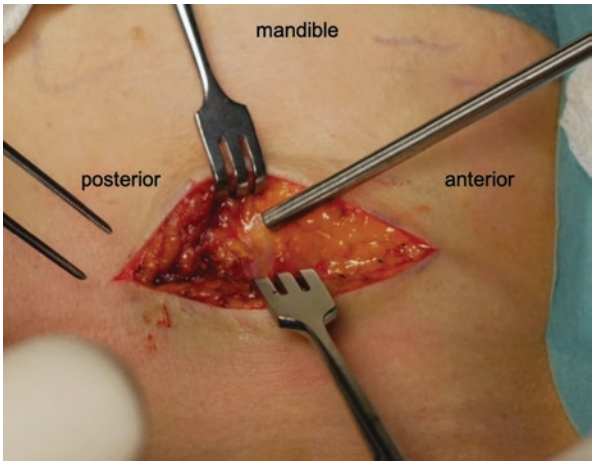

Fig. 13.32 Subcutaneous preparation

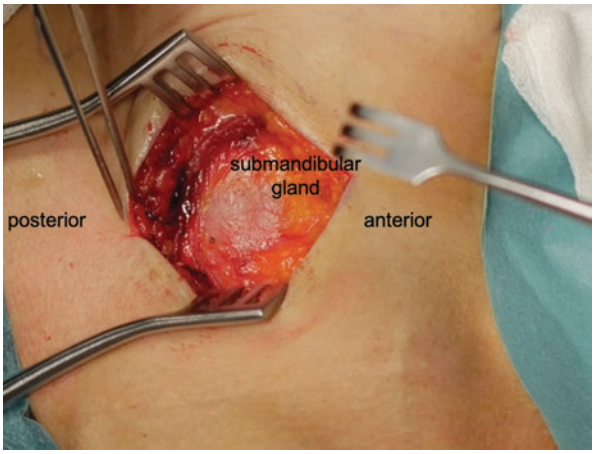

Fig. 13.33 Preparation of the submandibular gland. Stay inferiorly to avoid injury of the mandibular nerve

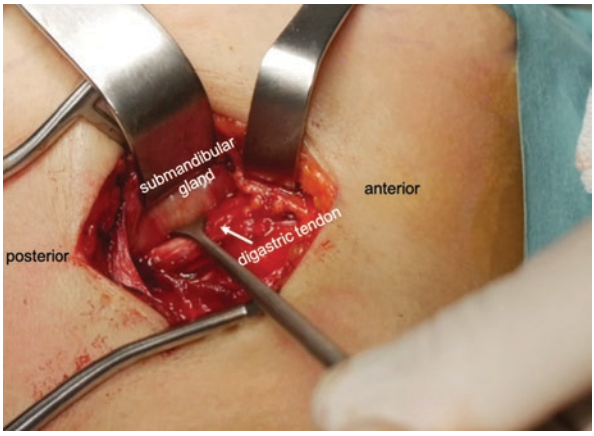

Fig. 13.34 Submandibular gland is lifted up and the digastric tendon is prepared

Lifting the gland in mandible direction helps to visualize the digastric tendon at the hyoid bone and to find the main trunk of the hypoglossal nerve (see Figs. 13.34, 13.35 and 13.36). Eventual satellite veins running along the nerve should be separated from the nerve and addressed according to surgeon preference. A section of around 1.5–2 cm of nerve should be dissected and exposed to allow for the electrode cuff to furl around the nerve. In contrast to the other surgical procedures of hypoglossal nerve stimulation (Inspire, Nyxoah) the stimulation cuff is placed around the main trunk of the hypoglossal nerve (see Fig. 13.36). After electrode placement, the self-wrapping electrode requires no further anchoring on the nerve but needs to be rotated counterclockwise so that the lead exits superiorly from the cuff (see Fig. 13.37). After this rotation, the electrode is looped and anchored on the tendon of the digastric muscle thanks to a suture sleeve that clips on the electrode cable, 5

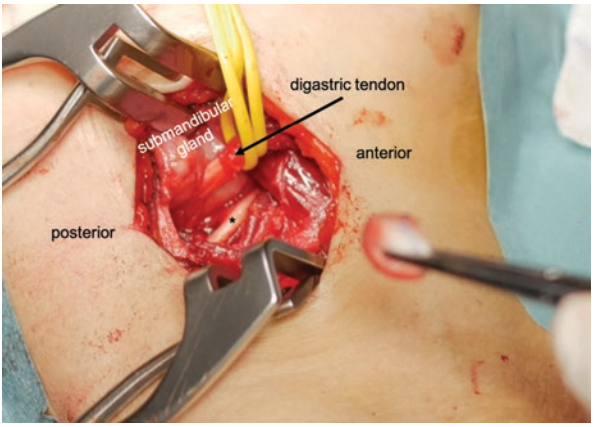

Fig. 13.35 Submandibular gland is lifted, and the digastric tendon also lifted up by a vessel loop. The star marks the main trunk of the hypoglossal nerve

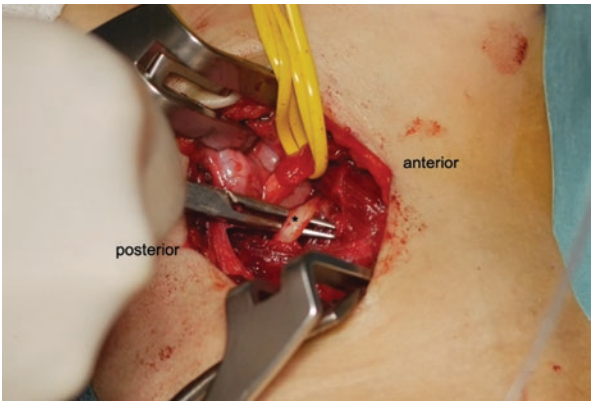

Fig. 13.36 Submandibular gland is lifted, and the digastric tendon also lifted up by a vessel loop. An overhold is used to undermine the main trunk of the nerve. The star marks the main trunk of the hypoglossal nerve

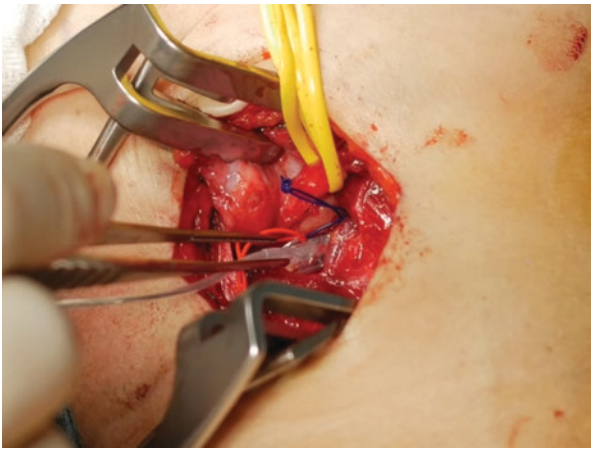

Fig. 13.37 The stimulation cuff is placed around the main trunk of the hypoglossal nerve

to 6 cm away from the cuff and 1 to 2 cm below the cuff. The six stimulating electrodes are in radial contact with the cylindrical body of the proximal hypoglossal nerve (Fig. 13.38).

Then the IPG is implanted in the upper right chest – a subcutaneous pocket. Two fingers below the clavicula, a parasternal horizontal 4 cm incision is performed. The pocket depth needs to be between 5 and 7 mm (maximum of 10 mm) and extra fat tissue may have to be removed to ensure proper depth. A skin flap gauge like the Med-El Skin Flap Gauge 6, P/N #03543 can be used to ensure correct depth and planarity of the pocket surface. The stimulation lead is connected to the IPG via a subcutaneously tunneled lead wire as also already described in the previous chapter. Staying medial in the neck tunneling helps to avoid damaging the external jugular vein (see Fig. 13.39). The tunneling device is not part of the provided kit. While a variety of options are available to perform this step, the use of a Codman Shunt Passer, product # 82–1515 has been successfully used for this purpose.

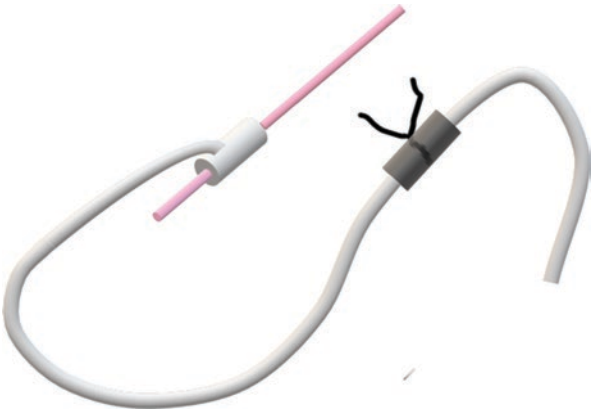

Fig. 13.38 The electrode is looped and anchored to the tendon of the digastric muscle

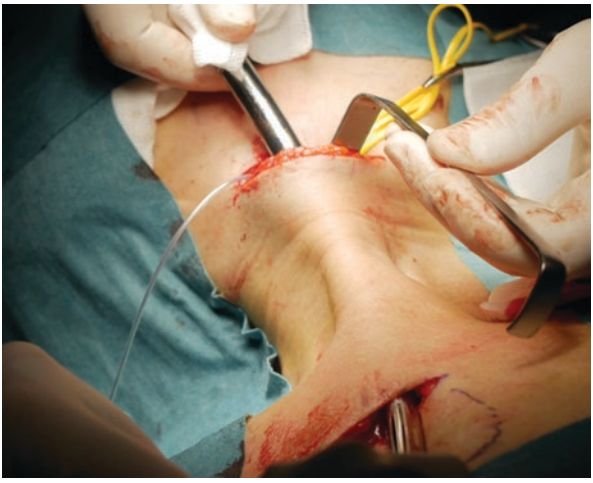

Fig. 13.39 Tunneling the electrode from the hypoglossal nerve to the right chest

In some patients with thick necks, it can make sense to perform an ultrasound in advance and highlighting the vein with a surgical marker in advance.

After performing the above steps, the final checkup is performed by confirming the electrical integrity through impedance measurement and motor thresholds determination. The IPG is then secured in the pocket with 2 permanent sutures inserted in the suture holes, and all incisions are then closed by a double layer of subcutaneous and skin sutures.

The overall procedure is performed in 40–80 min, depending on surgeon's experience and particular patient anatomy, the presence of satellite veins around the main trunk of the nerve being the most common source of variation in surgery time.

Patient Selection

Patient selection follows a set of traditional approaches as well as some unique perspectives. In particular, DISE to eliminate Complete Concentric Collapse in the oropharyngeal area is not deemed predicting the outcome of the therapy. While there is agreement on the fact that patients exhibiting such characteristic present maximum flaccidity of the tissues in this area, other selection mechanisms that are less invasive than DISE can be used. See the below table for the main characteristics of proper patient selection:

Showing the inclusion criteria for target hypoglossal nerve stimulation: BMI = Body Mass Index; AHI = apnea hypopnea-index, FTP = Freiedman tongue position, LTH = lingual tonsils hypertrophy

Criteria	Acceptable range
BMI	< 35 kg/m2
AHI	Within 15–65 range
AI (Apnea index)	< 30 events/h of sleep
Lingual tonsils hypertrophy	LTH 0, LTH 1, LTH 2
Tonsils	0, 1, 2
Friedman tongue position	FTP I, IIa, IIb, III

Influence of positionality & sleep stages: For patients presenting an exceptionally high supine AHI (in comparison with the non-supine one) or an exceptionally high REM AHI (in comparison with the NREM one), some caution should be observed to properly evaluate the risk/benefit ratio for the subject.

Presence of central or mixed apneas: care should be taken to ensure that the subject is not affected by Central Sleep Apnea or Cheyne-Stoke breathing as these conditions originate from central origin and cannot be corrected through the stimulation of the hypoglossal nerve. Presence of central events consecutive to wake to sleep transitions are physiologic in nature and will find their resolution with that of the obstructive events that eventually lead to these transitions.

Post-Operative Management

The procedure can be performed in an outpatient setting, and based on the surgeon's opinion, patients can be released the same day without having to extend their

hospital stay overnight. Upon release from the hospital, patients need to avoid lifting heavy objects or performing sharp neck movements for a duration of 4 weeks. This will ensure proper development of fibrotic tissue around the cuff electrode, ultimately ensuring its proper securing.

In terms of safety, the Aura6000 Therapy presents a favorable profile: THN2 study (Targeted Hypoglossal Nerve Stimulation for the Treatment of Obstructive Sleep Apnea: Six-Month Results, Friedman et al., DOI: 10.1002/lary.25909) reported a total of 66 adverse events for an implanted population of 46 patients. Short term non serious adverse events (pain, paresis, paresthesia for most of them) all were transient and resolved with minimal or no intervention. Eight of the 12 serious adverse events were related to the device or the procedure, with three of them requiring a revision or a device replacement.

Therapy Initiation & Titration
After 4 weeks, the subject should return to the sleep lab for therapy initiation and receive individualized settings that will be determined during a polysomnography examination. During this night, the therapy will be evaluated and adapted to the patient's needs to provide an improved and restorative sleep.

Bilateral Hypoglossal Nerve Stimulation System

Nyxoah

General Patient Setup
The surgical implantation is performed in supine position with a preferred nasotracheal intubation of the patient (see Fig. 13.40). The whole surgical procedure can be watched in Video 13.13.

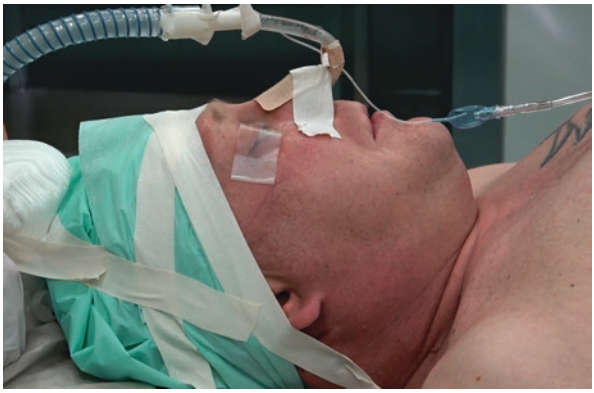

Fig. 13.40 Specific patient set up with supine position and nasal intubation

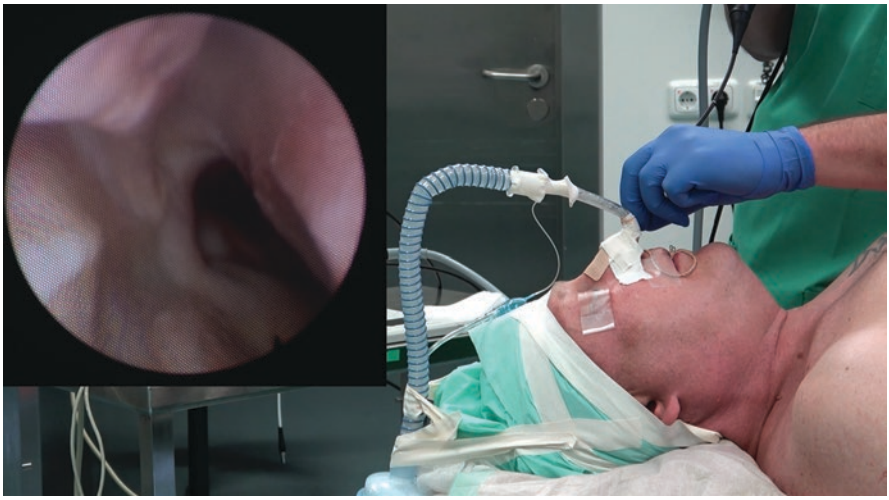

Fig. 13.41 Placing a transnasal endoscope to visualize the upper airway during stimulation tests

When judging the tongue movement during stimulation a nasotracheal intubation is the airway management method of choice. It can help for a better overview and additional clearance. Furthermore, the first dose of antibiotics should be administered at this stage.

The next step is placing a flexible endoscope transnasally to visualize the epiglottis and tongue base to assess airway opening during stimulation tests conducted (see Fig. 13.41).

The next step includes the setup of the Nerve-Integrity-Monitoring (NIM) System (see Fig. 13.42). The system should be set up to 4 channels and bipolar use. NIM will help to facilitate identification of the hypoglossal nerve branches and specifically the arborization of the nerve to exactly locate the perfect spot for the paddle electrodes of the implant. As already discussed in chapter 4c the identification of the different nerve fibers is essential for selective hypoglossal nerve stimulation. This is accomplished by excluding the retractor fibers (exclusion channels, Styloglossus/Hyoglossus) and including the protrusors-fibers (inclusion channels, Genioglossus). Two electrodes are placed in the floor of mouth to detect EMG signals from the genioglossus muscles on each side (blue and red electrode in Fig. 13.42). These EMG signals are in the inclusion channels. The electrodes should be placed on the side of the midline, avoiding the frenulum and Whartin's duct [11]. The next two electrodes are responsible for the exclusion channel labeled "Stylo-, Hyoglossus". The electrodes are placed in the lateral portion of the tongue at a very shallow angle on both sides of the tongue (red electrode for the right side in Fig. 13.42). It is important that the electrode stays just below the mucosa, 5 cm from

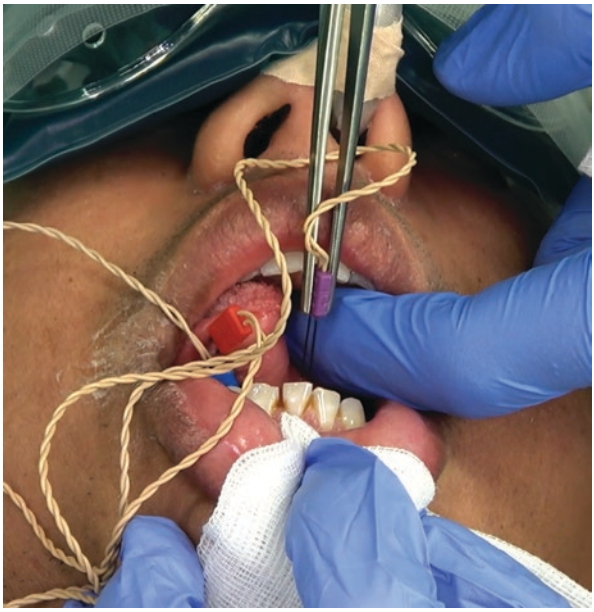

Fig. 13.42 Set up for the intraoperative neuromonitoring system

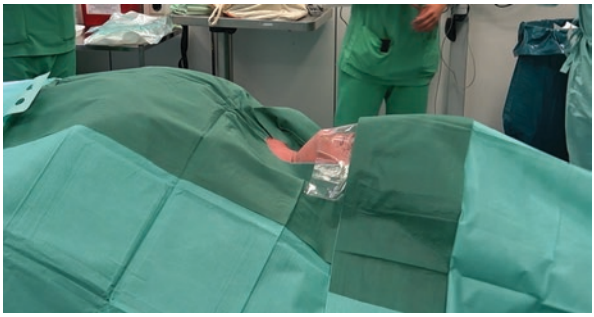

Fig. 13.43 Patient set up with scrubbing and draping

the tip of the tongue. Placing these two electrodes on both sides helps to identify the main retractors (exclusion) during the surgical implant. Furthermore, an earth electrode is placed next to the surgical field, for example in the shoulder region. All electrodes should be fixed and secured with tape, creating a loop with enough slack for the cables to move freely with the tongue while stimulating. Then the impedance is checked with the NIM system to confirm proper electrode resistances before continuing with the surgery.

To avoid bleeding during implantation it is recommended to inject local anesthetic in a 2% combination with epinephrine. Try to target the designated incision site and spread out the injection at an area of about 6 by 3 cm.

For scrubbing and draping the mouth and nose portion are left uncovered. The transparent draping is placed upwards from the chin in a way that the foil loosely covers the mouth (Fig. 13.43). Ensure that tongue movement can be observed during stimulation. Afterwards a final drape is put over the bag, leaving a clear view of the mouth.

Implantation Technique

The Genio system consists of two parts, an internal part, the implantable stimulator, and an external part, the activation chip (Figs. 13.44 and 13.45).

The surgery starts with marking the incision side before starting with the surgery (see Figs. 13.46 and 13.47).

First the mandible bone is marked as cranial structure. Then a midline is drawn from mentum to the thyroid notch. This is the most important landmark, which is needed to reference frequently for re-orientation during surgery. The thyroid notch and hyoid bone are marked. Finally, the actual incision line is drawn, which is centered about 1 cm cranial of the hyoid bone and 6 cm in length (see Figs. 13.46 and 13.47). After deepening the incision through the platysma, keep on following this line and raise a subplatysmal flaps to the mentum and down to hyoid bone (see Figs. 13.48 and 13.49).

This will help to receive a better visibility of the surgical area. The next step is to identify the two anterior digastric muscles. After exposing these muscles and when these are huge, a lateral mobilization can help (see Fig. 13.50).

Then a vertical dissection in the midline through the fat tissue is performed to fully expose the mylohyoid muscle (see Fig. 13.50).

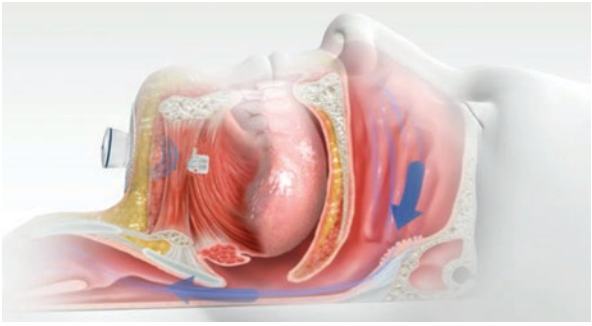

Fig. 13.44 Showing a schematic overview of the technology of the Genio system (Nyxoah, Belgium). It consists of two components: an external activation chip, and an implantable stimulator

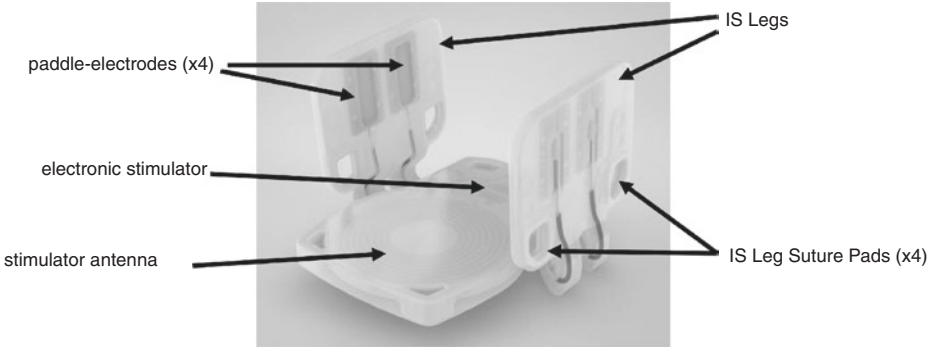

Fig. 13.45 The implantable stimulator for bilateral hypoglossal nerve stimulation in more detail. In each leg two paddle electrodes are existing to stimulate the nerve fibers. IS = internal stimulator

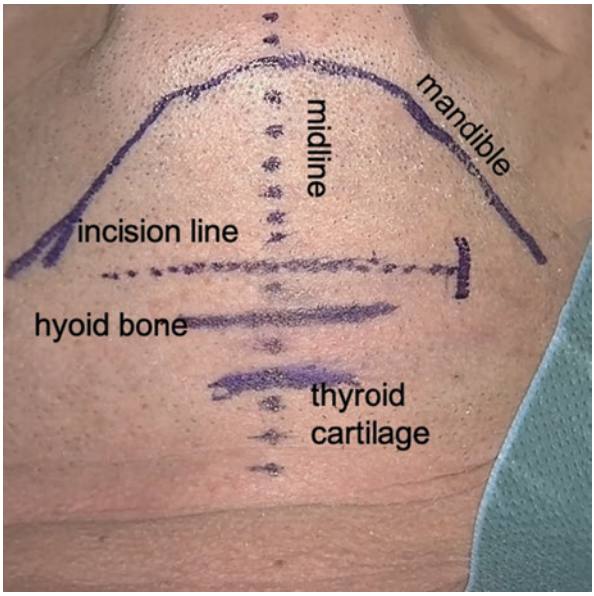

Fig. 13.46 The important landmarks for the correct incision are: the mandible bone, the thyroid notch and the hyoid bone. The midline from mentum to the thyroid notch for orientation during surgery (dotted vertical line). The incision line is about 6 cm

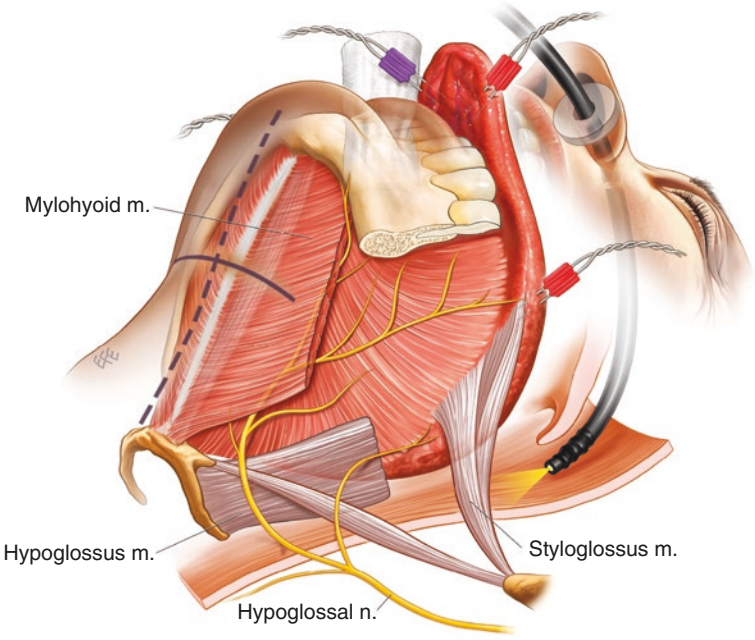

Fig. 13.47 Showing a schematic drawing of the anatomic landmarks and placement of intraoperative neuromonitoring during bilateral hypoglossal nerve stimulation

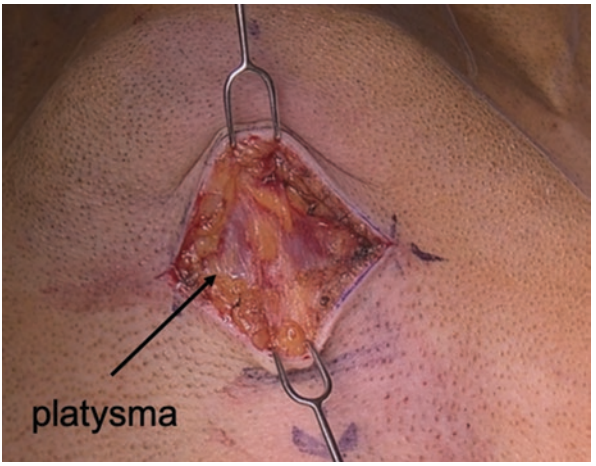

Fig. 13.48 Incision line. Platysma is marked by the black arrow

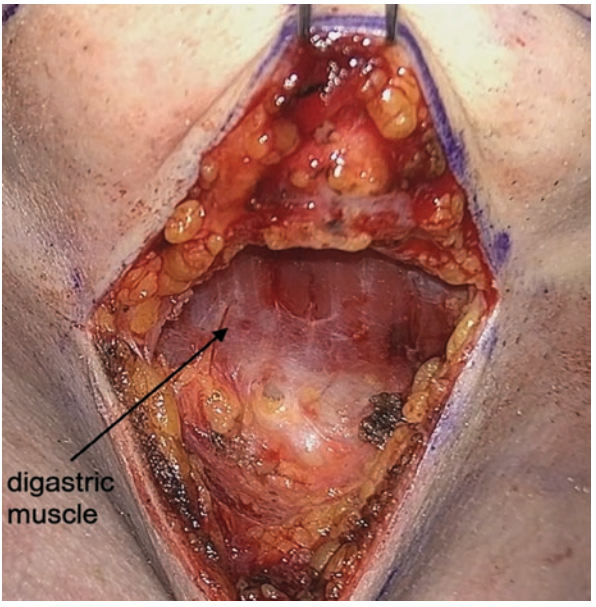

Fig. 13.49 After incision through the platysma the two anterior bellies of the digastric muscles are exposed (black arrow)

After the horizontal fibers of the mylohyoid muscle are identified, divide the muscle fibers vertically. It is important to strictly keep in the midline from hyoid to mentum. After finishing the dissection of the mylohyoid muscle, the vertical fibers of the geniohyoid muscles become apparent (see Figs. 13.51 and 13.52).

To get an approximate idea of the anatomical situation and especially the midline, dissect to both sides laterally of the geniohyoid muscle and the hypoglossal nerve may be identified for the first time in the fat tissue. In most of the cases veins are running next to the nerve fibers (see Fig. 13.53).

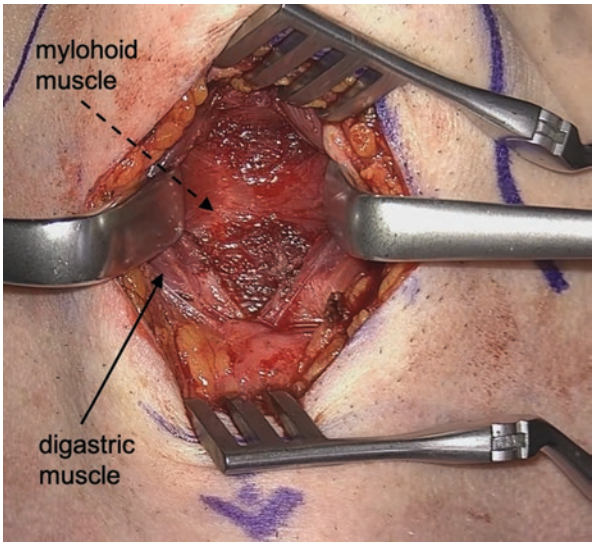

Fig. 13.50 The retractors are holding the digastric muscle, meanwhile the horizontal fibers of the mylohyoid muscle appear

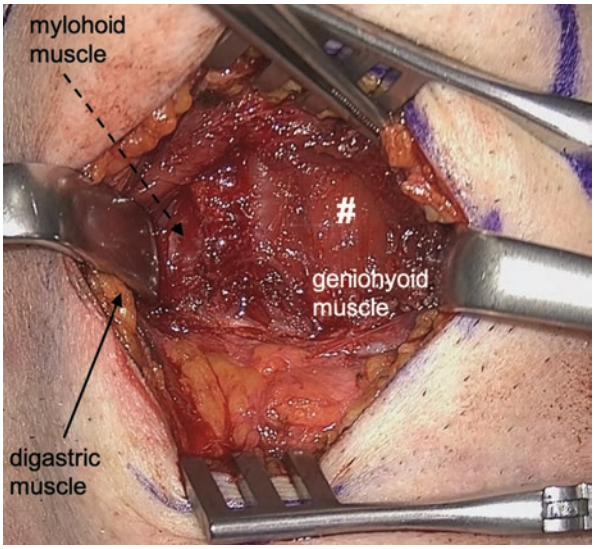

Fig. 13.51 The retractors are holding the digastric muscle, meanwhile the horizontal fibers of the mylohyoid muscle are severed. The vertical fibers of the geniohyoid muscle (marked with a white rhombus) are identified

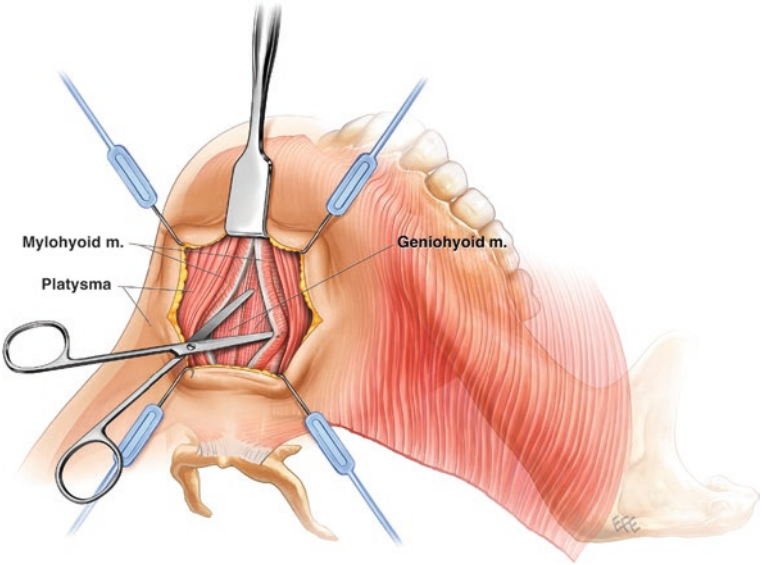

Fig. 13.52 Schematic drawing of the dissection of the mylohyoid muscle to the geniohyoid muscle

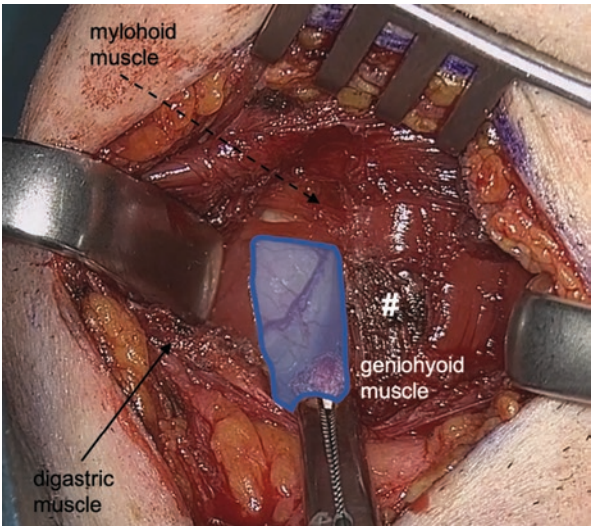

Fig. 13.53 The blue area marks the fatty tissue, where the hypoglossal nerve can be expected (right side of the patient)

Once the geniohyoid has been exposed, the well-defined midline of the geniohyoid - which is also called "*fatty raphe*" - must be identified (see Figs. 13.54 and 13.55). Sometimes this can be challenging. It is crucial to be gentle during dissection to avoid excessive bleeding. Elevating the mylohyoid from the geniohyoid muscles might help to identify the plane and determining the midline between the two muscle bellies left and right (Fig. 13.55).

Expose the genioglossus muscle underneath the geniohyoid muscle and dissect both bellies from each other. Keep in mind that the geniohyoid muscle-fibers enter the hyoid bone helps during this step. The last step of the muscle preparation is to identify the lateral borders of the genioglossus muscle. By exploring the fat tissue lateral to the genioglossus muscle, it is now easy to locate the hypoglossal nerve. It can be very helpful to confirm the suspected structure to be the hypoglossal nerve by using the NIM. Use blunt dissection (for example by using a peanut) and/or small gauze swabs to passively expand the area and to create more space for the legs of the implantable stimulator (see Figs. 13.56 and 13.57).

The paddle electrodes will slide into this space afterwards. If it is necessary, ligate the small veins running with the hypoglossal nerve, but in case bipolar electrocauterization is used, care should be taken not to damage the small fibers of the hypoglossal nerve (see Figs. 13.58 and 13.59).

In some cases, it can be helpful to turn down the NIMs amperage to approximately 0.3 mA (or even 0.1 mA) to allow further differentiation of the different nerve branches. It is essential to locate the protruding fibers of the hypoglossal

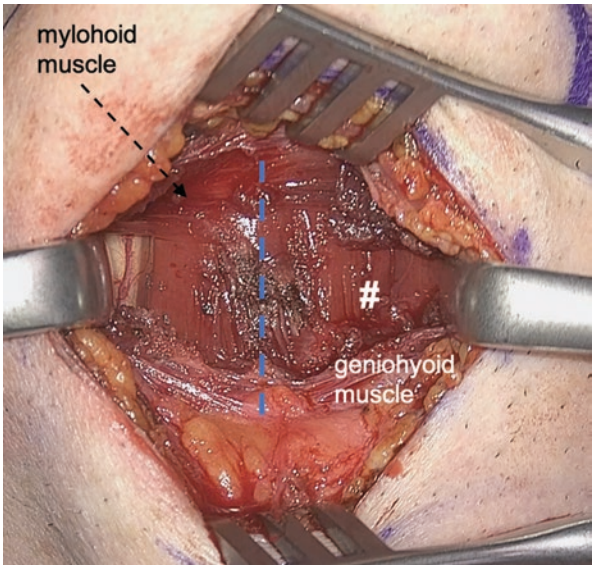

Fig. 13.54 The blue line marks the "*fatty raphe*" where the dissection is followed to go between the geniohyoid and genioglossus muscle

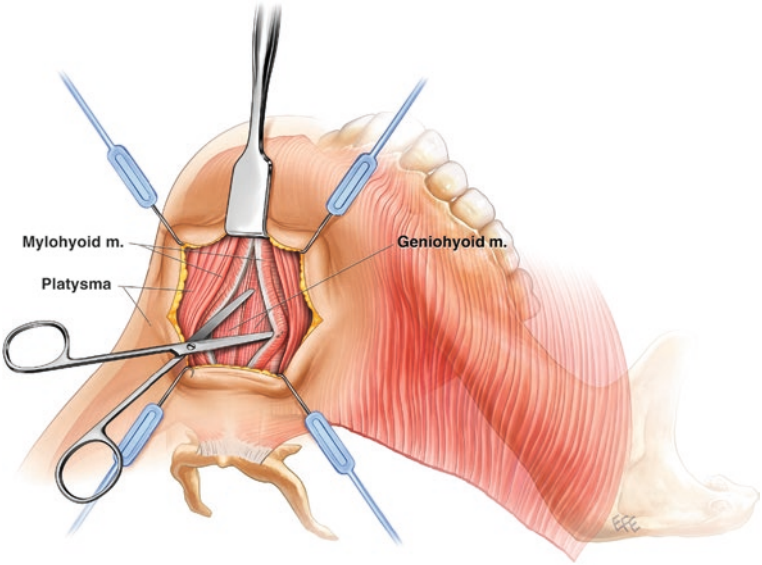

Fig. 13.55 Schematic drawing of the surgical separation of the different muscle layers to get access to the hypoglossal nerve

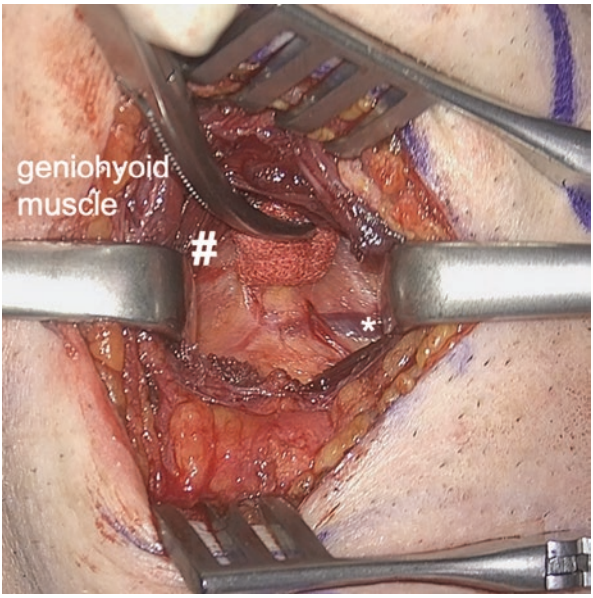

Fig. 13.56 The white rhombus marks the geniohyoid muscle which is hold by the retractor medially. The white star marks the ranine vein where the distal hypoglossal nerve fibers can be identified (left side of the patient)

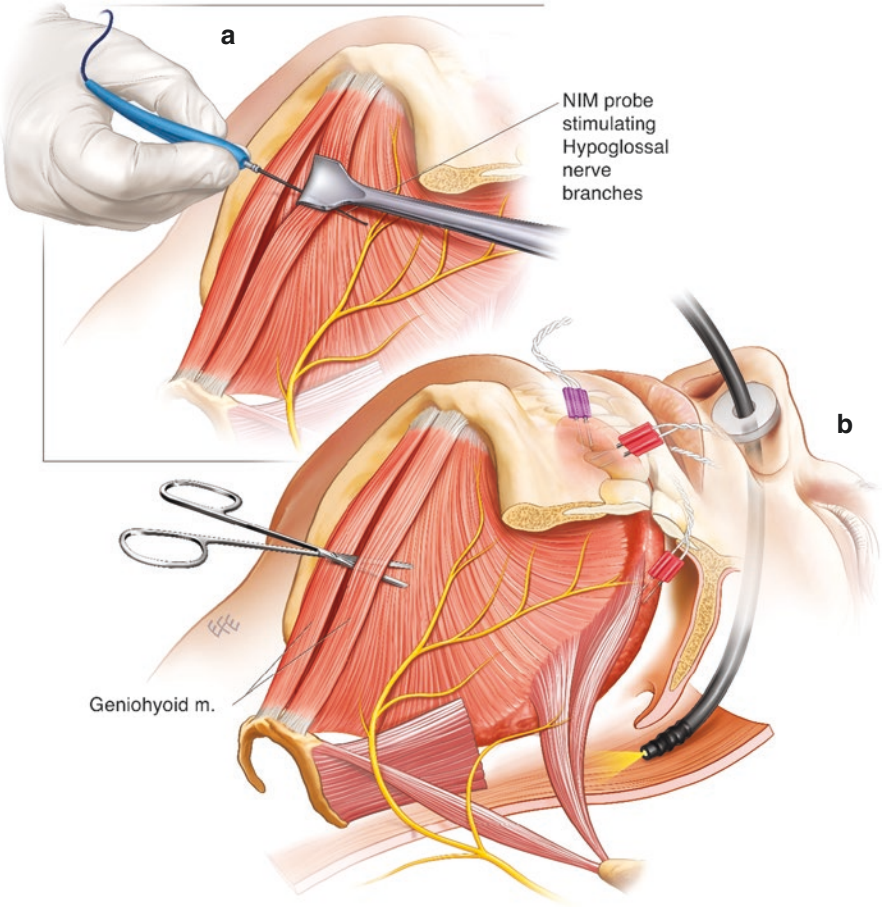

Fig. 13.57 Schematic drawing of the separation between the geniohyoid and genioglossus muscle to exposure the branches of the hypoglossal nerve and testing with intraoperative neuromonitoring

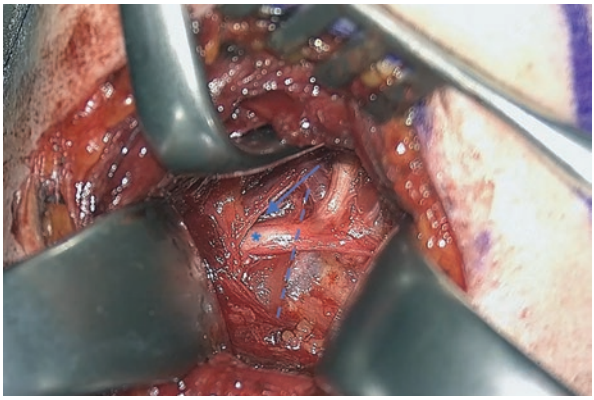

Fig. 13.58 (right side of the patient) The hypoglossal nerve (blue star) and its terminating distal fibers. The blue dotted line is the anterior border of the hyoglossus muscle. The blue arrow marks the area, where the pocket between the medial and lateral fibers of the hypoglossal nerve is formed

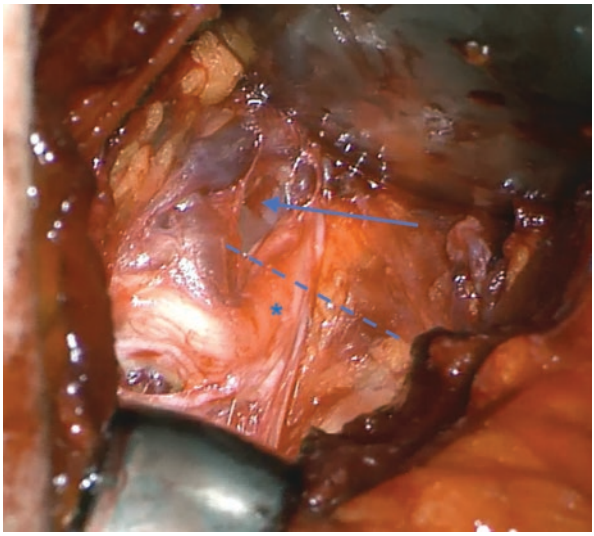

Fig. 13.59 (left side of the patient) The hypoglossal nerve (blue star) and its terminating distal fibers. The blue dotted line is the anterior border of the hyoglossus muscle. The blue arrow marks the area, where the pocket between the medial and lateral fibers of the hypoglossal nerve is formed

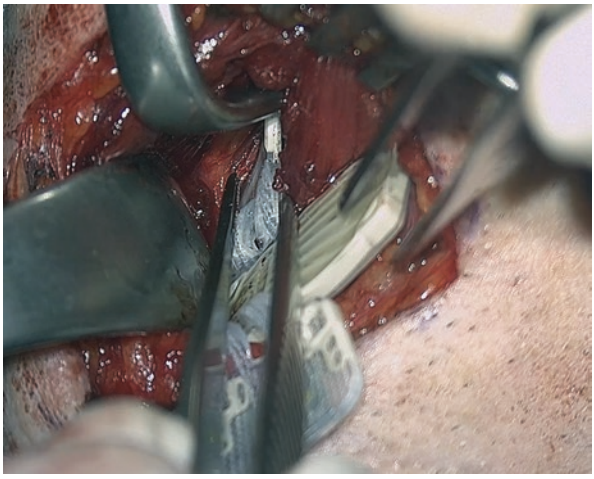

Fig. 13.60 Placing the paddle electrodes into place

nerve with C1 and, if present, also the retracting ones, by using NIM. The nerve on both sides needs to be exposed. Once the pockets are formed to fit the legs of the implant and genioglossus motor points are identified, the implantable stimulator's paddle electrodes are slid into place (see Figs. 13.60 and 13.61).

Avoid using sharp instruments when manipulating and do not grab the implantable stimulator at the electrodes. The Implantable Stimulator should sit on the genioglossus muscle "*like a saddle on a horseback*" (see Figs. 13.62 and 13.63).

Ensure correct orientation, the antenna portion of the implant is facing towards the anterior part of the chin and is in a rather flat position on the genioglossus muscle. The implantable stimulator should not touch the mandible nor slide under the hyoid bone.

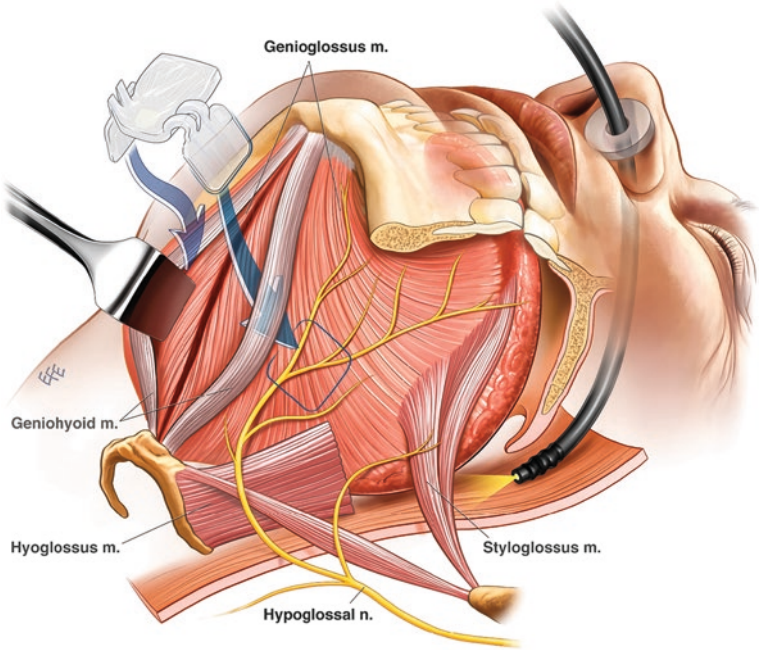

Fig. 13.61 Schematic drawing of the placement of the implantable stimulator for bilateral hypoglossal nerve stimulation

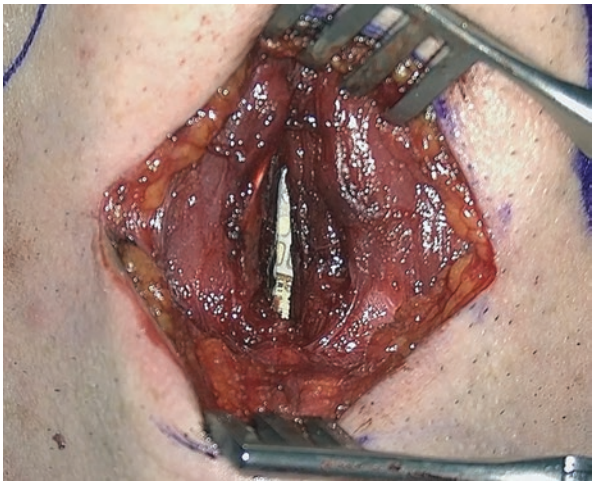

Fig. 13.62 The implantable stimulator is placed in the mouth floor on the genioglossus muscle with its paddle electrodes on the distal medial fibers of the hypoglossal nerve

External Stimulator for Device Testing

To ensure proper function of the implant and optimal device placement, an external stimulator is used repeatedly (see Fig.13.64). This ensures the implant to have excellent contact with the nerve on both sides, with the aim of providing the most

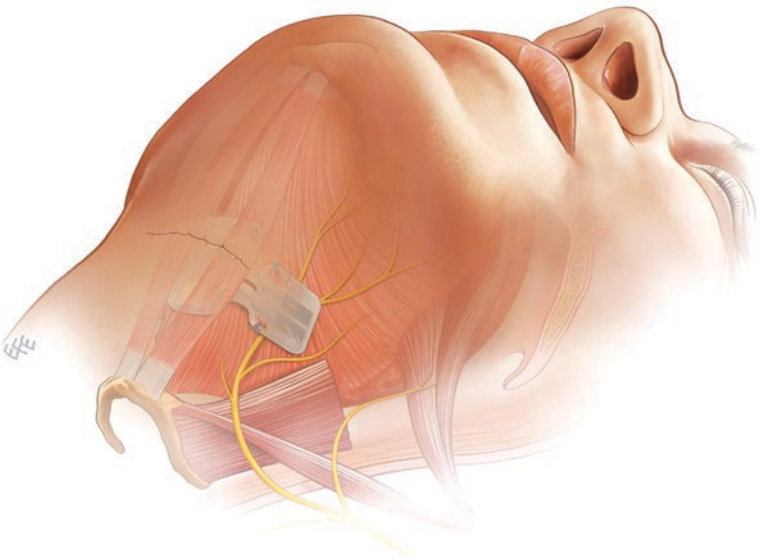

Fig. 13.63 The Implantable Stimulator sits on the genioglossus muscle "like a saddle on a horseback"

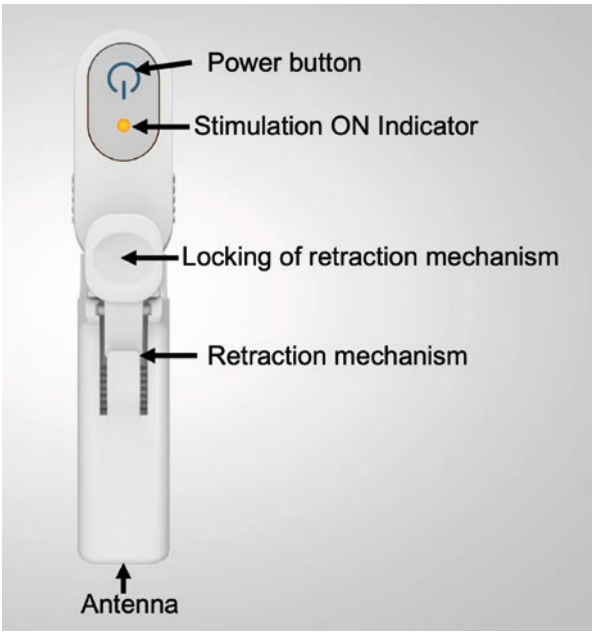

Fig. 13.64 The external stimulator for bilateral hypoglossal nerve stimulation in more detail, which is needed for intraoperative testing during surgery

efficient stimulation. During testing with the external stimulator make sure to receive a straight strong tongue protrusion. If any curling or even a retracting of the tongue motions occurs, it is most likely to have retracting branches of the hypoglossal nerve included (styloglossus and/or hyoglossus muscle) under the paddle electrodes. Adjustment of placement of the implantable stimulator is needed to ensure symmetric forward tongue movement (see Figs. 13.65, 13.66 and 13.67).

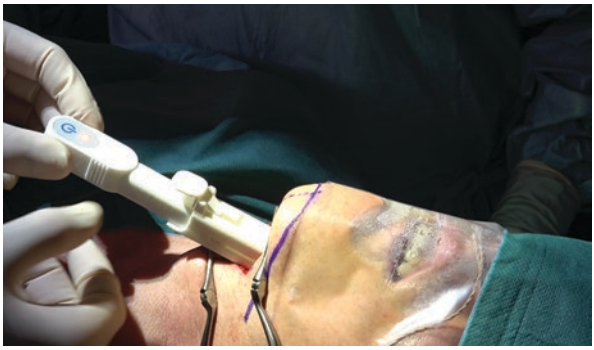

Fig. 13.65 External stimulator for device testing

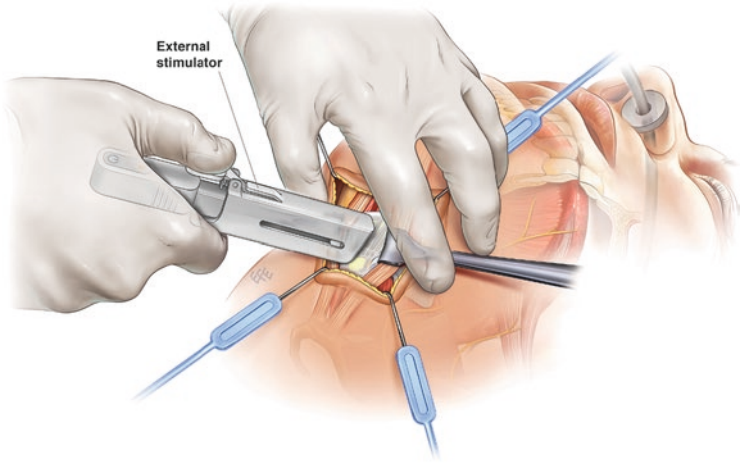

Fig. 13.66 Schematic drawing of the use of the external stimulator for intraoperative testing

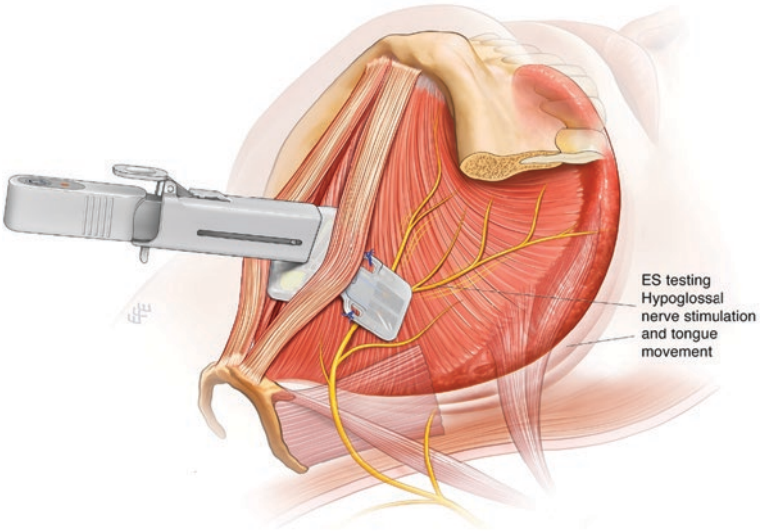

Fig. 13.67 Schematic drawing of the use of the external stimulator for intraoperative testing

Fixation of the Implantable Stimulator "Parachute Technique"
After satisfying tongue motion have been accomplished, four ligating clips are placed next to each dedicated suturing hole. Then the depth of the genioglossus/implantable stimulator to the skin surface is measured. It must be within a range of up to 3.5 cm to the skin surface where the disposable patch will be placed. If the distance is larger, a lipectomy should be performed to minimize the distance. The next step is to carefully remove the implant from the implantation site. Then sutures through the genioglossus muscle fibers and a light but not loose knot on the muscle is placed. Keep the sutures apart from each other and suture through the designated sutures holes of the implant legs (see Fig. 13.68). Extreme caution should be exercised in order not to puncture the implant with the needle as a puncture likely leads to implant failures due to liquid integrating over time. When all 4 sutures are attached to the implant, the implant is slided back into the created pockets. Ensure the paddle electrodes are facing towards the identified spots of the nerve branches and gently tie up the sutures. This technique is called "parachute technique after Lewis" (see Fig. 13.69).

Testing with Activation Chip
After the fixation of the implantable stimulator, remove the self-retaining retractor and temporary close the wound. If needed, a single suture may be used, therefore. Connect the activation chip to the Bluetooth snap device and a disposable patch and place everything into a sterile pouch. Then put the activation chip in place and confirm airway opening with the endoscope and observe the tongue motion visually to judge proper and balanced tongue motions. The stimulation may be inadequate when the tongue is not protruding nicely at a 30% amplitude level, 35 Hertz, 120 microseconds pulse length. In such a situation, consider repositioning the device. If

Fig. 13.68 The black arrows mark the suture holes in the implantable stimulator

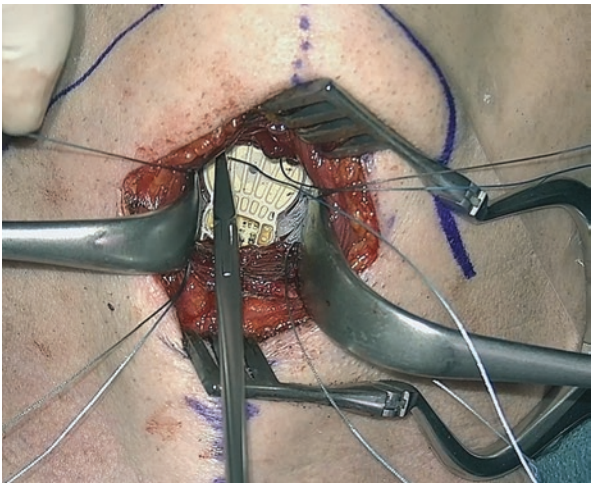

Fig. 13.69 Parachute technique to perform the fixation of the implantable stimulator

the tongue clearly moves to one side while stimulating, leave the leg of the implant sutured on the better protruding side and only reposition the paddle electrode at the less optimal side. Only when stimulation outcome is positive and the stimulation is resulting in a good tongue motion with good airway opening, close the different muscle layers and proceed suturing the skin. Never be satisfied with an average or doubtful result. After skin closure, a wound dressing should be applied. Again, a final testing can be performed to ensure that the implant positioning has not changed during the closure of the surgical area. The results during this test should be comparable to the interim test. If there are any doubts regarding the tongue motion at this stage, the surgical area should be opened again, and the implant should be repositioned. Better be safe now as sorry at first activation of the implant. This is an important note, which you should consider for every implant: **"Never be satisfied with doubtful results"**.

Advanced NIM Techniques

Especially in selective hypoglossal nerve stimulation the placement of the stimulation electrode (Inspire) or the stimulation patch (Nyxoah) is essential. Therefore, the exact identification of the individual nerve fibers with the associated muscle groups is crucial. After the two anatomists MU & Sanders created the basic structure in 2010 and 2013, the interpretation of the NIM signal is particularly important when identifying the medial and lateral end branches. For this it is necessary to find the so-called "functional breakpoint" (see chapter HN and its anatomical variability). Because of this, it should first be reminded that the tongue is a muscle, made up of different muscle groups. So, there is always the risk that during intraoperative neuromonitoring EMG signals are diverted from other muscle groups, which can then be incorrectly assigned to the derived muscle as EMG signals.

Since Heiser et al. has described the anatomy of the hypoglossus nerve in detail, it is helpful not only to make a quantitative, but also a qualitative interpretation of the NIM signal. Figures 13.70 and 13.71 show a schematic drawing of a NIM signal.

Normally, the classic signal shows an upward curve starting from a baseline activity, which then deflects downwards compared to the baseline (see Fig. 13.71). Different visual interpretation of this signals needs to be considered:

- Signal morphology:
  - Baseline-to-peak amplitude
  - Peak-t-peak amplitude
  - Duration (signal width)
  - latency
- frequency
- Artefacts in other channels (crosstalk/far-field)
- Signal amplitude compared to other channels

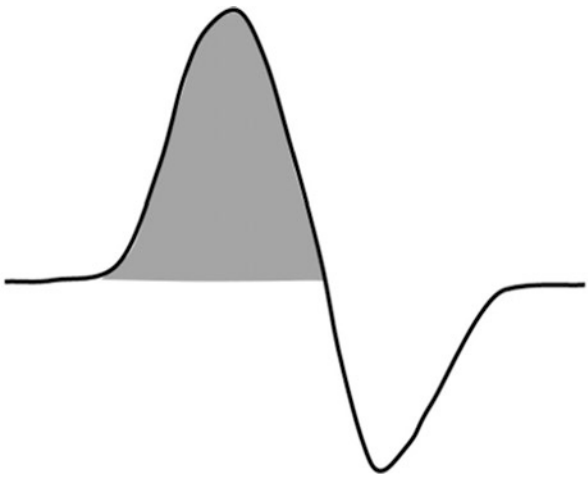

Fig. 13.70 Schematic drawing of NIM signal. NIM = intraoperative nerve monitoring

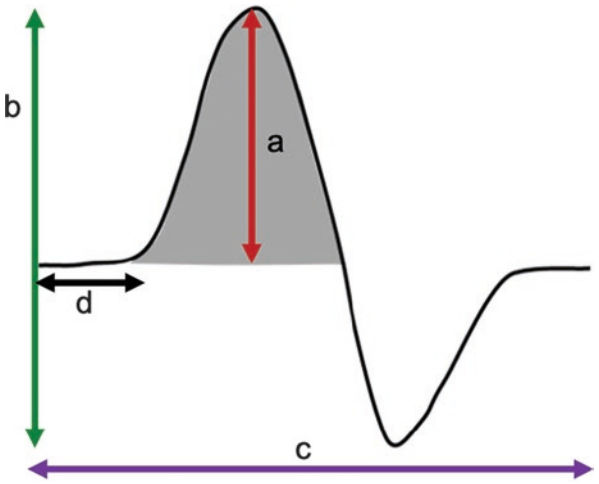

Fig. 13.71 Schematic drawing of NIM signal: signal morphology: red line (**a**) = baseline-to-peak amplitude; green line (**b**) = peak-to-peak amplitude; purple line (**c**) = signal duration or signal width, black line (**d**) = signal latency

So, signal morphology is the first part, which should be investigated (see Fig. 13.71). The Baseline- or Peak-to peak amplitude helps to judge on the strength of the signal. For distinguishing the signal later between last inclusion or exclusion branch signal width is important.

If the nerve with its accompanying vein is searched for and an intraoperative irritation occurs for the first time, which is more of an accidental origin (due to dissection, for example), then you often get a signal that is high-frequency, low-amplitude and long latency in both channels, as well as a long signal duration (see Fig. 13.72).

If the main trunk of the hypoglossal nerve is explored, carefully stimulation and NIM interpretation should be considered with a decreased stimulation amplitude of 0.3 mA. This helps to make sure to have the correct nerve identified. In rare cases a lower lingual nerve can be mistaken to be the hypoglossal nerve. Furthermore, higher amplitudes of stimulation are need due to a lot for soft tissue around the nerve. Increase the stimulation amplitude step by step till 1.0 mA, if needed. The typical NIM signal of the main trunk is shown in Fig. 13.73. It is characterized with a high amplitude, short latency, and long signal duration at least in one of the two channels (Fig. 13.73).

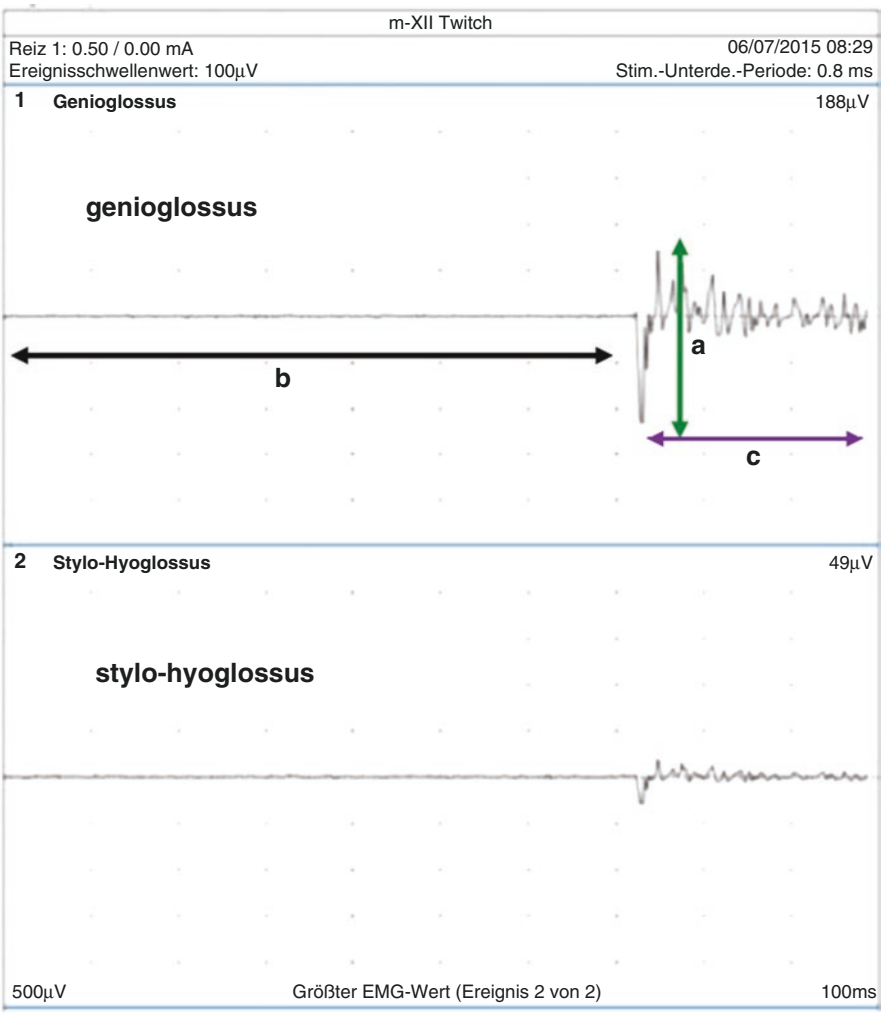

Fig. 13.72 Two-channel NIM recording: artefacts during dissection at the hypoglossal nerve. It is a high frequency, low-amplitude (green line (**a**)), long latency (black line (**b**)) and long signal duration (purple line (**c**))

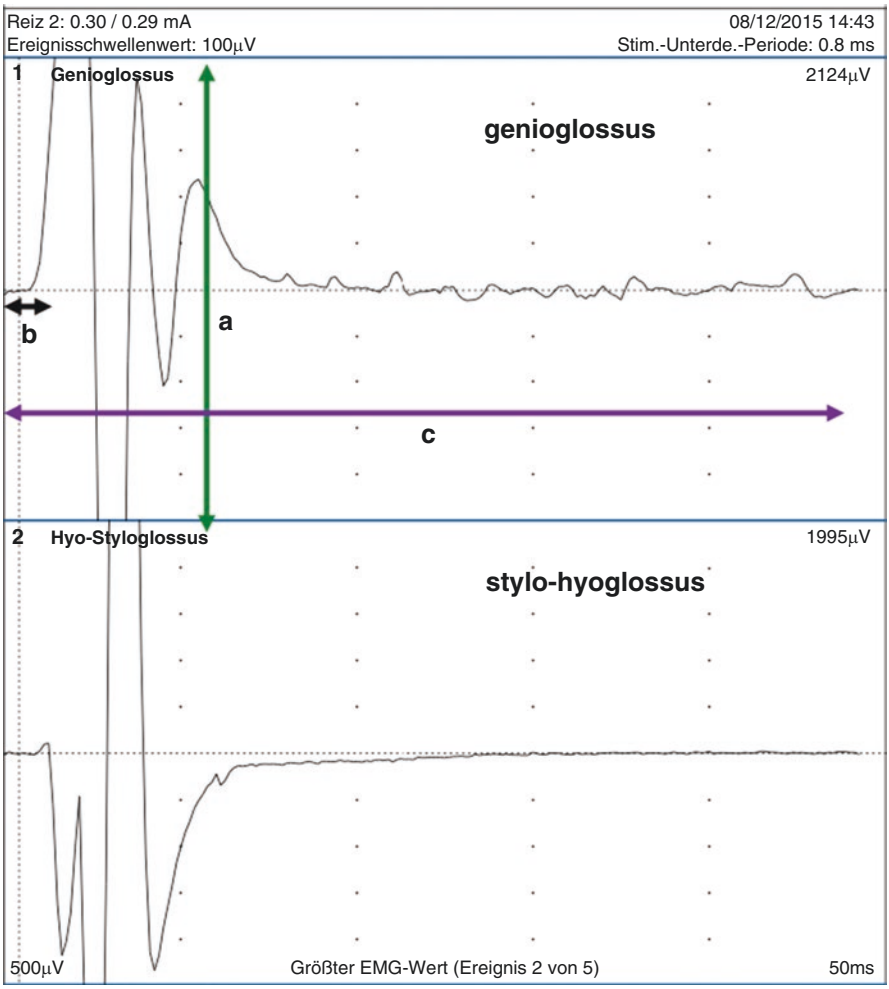

Fig. 13.73 Two-channel NIM recording: 0.3 mA stimulation at the main trunk of the hypoglossal nerve and its NIM signals: high-amplitude (green line (**a**)), short latency (black line (**b**)) and long signal duration (purple line (**c**))

Further dissections and stimulations with the NIM system occur more different types of NIM signals. A typical stylo-hyoglossus signal is shown in Fig. 13.74. It is characterized through a polymorphic, low amplitude, fractioned, high frequent EMG signal. At the end, the signal is slowly tapering off (Fig. 13.75).

If genioglossus muscle is activated in combination with the intrinsic vertical and transverse muscle fibers a typical EMG signal in both channels can be detected

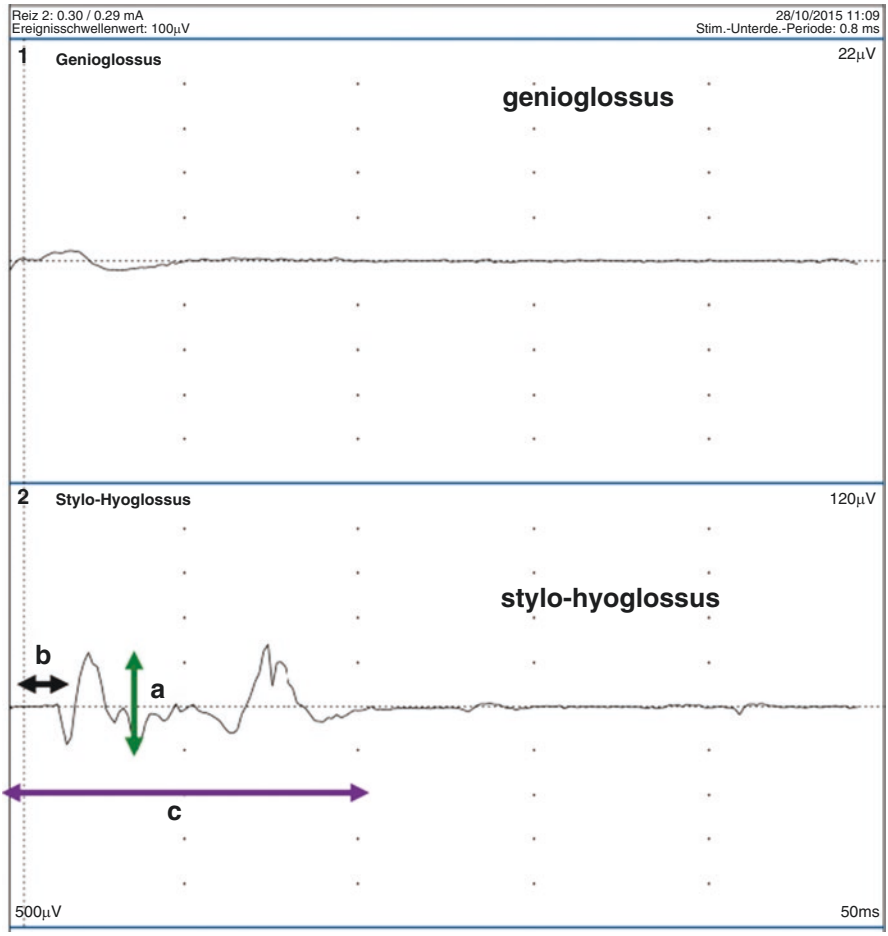

Fig. 13.74 Two-channel NIM recording: 0.3 mA stimulation lateral branches of the hypoglossal nerve (fibers for exclusion of the hyoglossus muscle) and its NIM signals: low-amplitude (green line (**a**)), short latency (black line (**b**)) and long signal duration (purple line (**c**)) with a polymorphic, fractioned and high frequency. At the end the signal is slowly tapering off

(see Fig. 13.76). A clear high amplitude EMG activity in the inclusion channel with a shorter signal duration occurs together with a mirrored far-field EMG signal due to intrinsic vertical and transverse muscles fibers in the exclusion channel. The blue vertical bars indicate the start and end of the EMG signal. It should be exposed that the signal in the exclusion channel (stylo-hyoglossus) ends when the EMG signal also ends in the genioglossus channel.

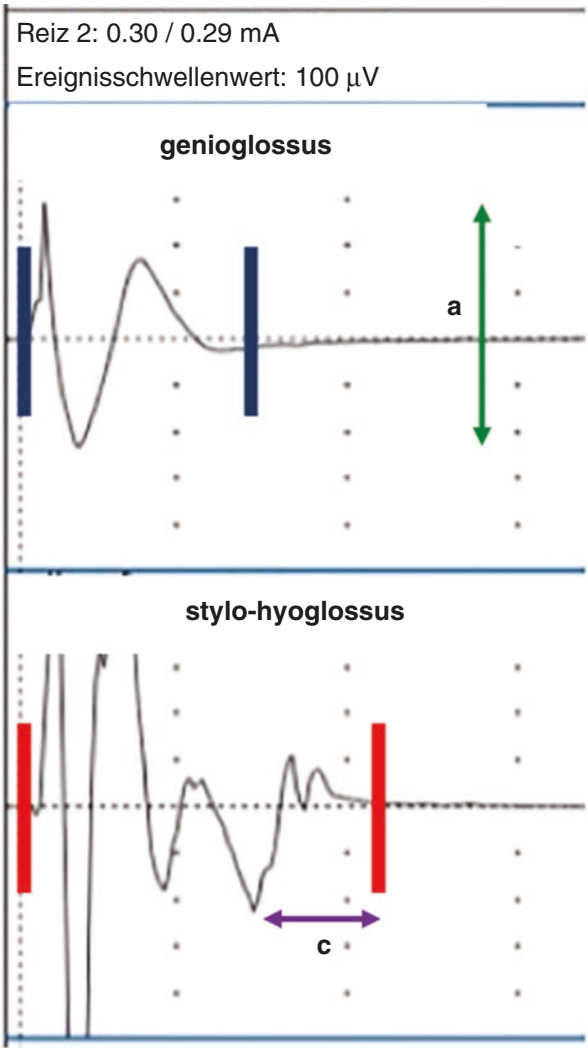

Fig. 13.75 Two-channel NIM recording: 0.3 mA stimulation medial branches of the hypoglossal nerve, which are still including a retractor branch (genioglossus muscle, intrinsic vertical and transverse muscles and hypoglossus muscle fibers) and its NIM signals: lower-amplitude in the inclusion channel (green line (**a**)). Longer signal duration (purple line (**c**)) in the hyoglossus channel. Inconsistent siognal patterns between the genioglossus and stylo-hyoglossus channel. The blue and red vertical bars mark the start and end of the EMG signals. Notice the longer EMG signal in stylo-hyoglossus channel

A mixed activation, where the medial branches of the hypoglossus nerve are still including a retractor branch for the hyoglossus muscle an EMG signal as in Fig. 13.75 occurs. It is characterized through an inconsistent signal pattern inclusion vs. exclusion. Often a lower amplitude in the inclusion channel can be found. And a longer EMG signal, when already the EMG pattern in the inclusion channel has stopped, can be detected in the exclusion channel. It is a fractioned, choppy signal due to a prolonged muscle activation.

Figure 13.77 shows different EMG signals for different stimulation settings.

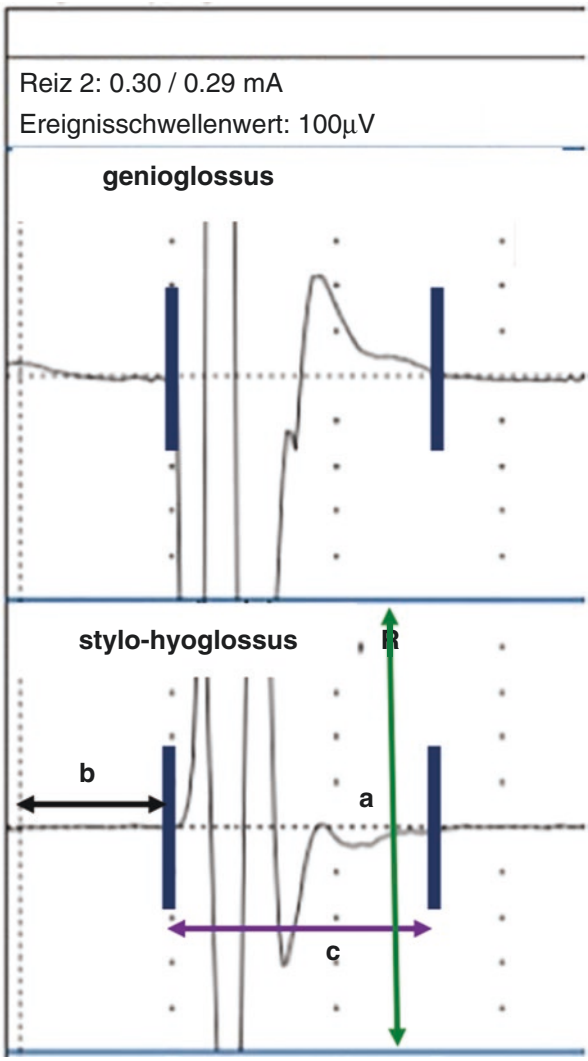

Fig. 13.76 Two-channel NIM recording: 0.3 mA stimulation medial branches of the hypoglossal nerve (genioglossus muscle, intrinsic vertical and transverse muscles) and its NIM signals: high-amplitude (green line (**a**)), short latency (black line (**b**)) and shorter signal duration (purple line (**c**)). It is a monomorphic clear EMG signal. In the exclusion channel a mirrored far-field signal can be recognized

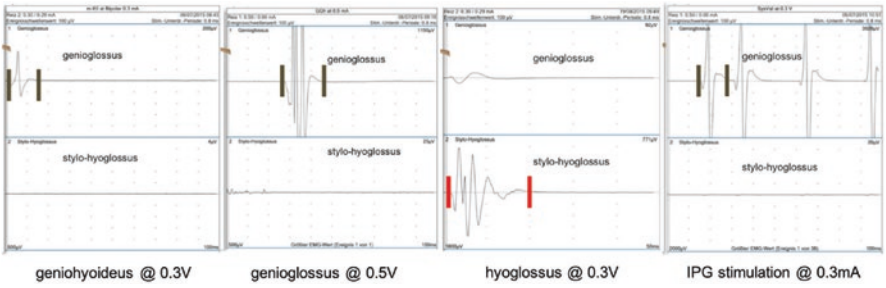

Fig. 13.77 Two-channel NIM recording with different stimulation settings – described at the bottom and added stimulation amplitude. The vertical bars always mark the start and ending of the EMG signals

Summary

All different implant techniques are aiming to place a stimulation lead/cuff/plate around fibers of the hypoglossal nerve. Two available systems (Inspire and Genio) are placing their leads selectively for an active opening of the upper airway around the hypoglossal nerve, while the Aura6000 system is targeting the main trunk of the hypoglossal nerve, which makes the surgical access easier. The longest surgical time is needed for the Inspire system due to three incisions or probably in the future the two-incision technique. All surgical techniques have been used in clinical routine since many years. It depends on the surgeon and patient selection and preference and local availability, which system is the most favorable at the implantation site.

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Chapter 14
Treatment Pathway

Ryan J. Soose and Maria V. Suurna

Contents

Overview: HNS Clinical Care Pathway

HNS therapy represents a unique medical-surgical hybrid treatment for obstructive sleep apnea (OSA) – consisting of both a surgical procedure and an adjustable medical device. As such, the HNS clinical care pathway differs substantially from the traditional sleep apnea surgery model. Unlike traditional anatomy-altering reconstructive surgery where the results are often assessed at one time point after the healing phase is complete, HNS therapy can be titrated in the clinical or sleep laboratory setting to optimize outcomes across a longitudinal care model. Successful application of HNS therapy requires (1) proper preoperative patient selection and

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Fig. 14.1 Clinical care pathway overview before and after HNS system implantation. After clinical, polysomnographic, and anatomic screening, qualified candidates undergo device implantation, most commonly as an outpatient. At 1 month postop, the device is activated, and patient starts using the therapy. After another month of therapy accommodation and self-titration at home, patients undergo postoperative sleep testing first to assess objective outcome measures and second to further titrate therapy and optimize settings for transition to long-term management

anatomical phenotyping, (2) proper surgical implant execution, and (3) proper therapy programming and long-term management.

The current clinical care pathway consists of a multidisciplinary preoperative evaluation that includes sleep and general medical screening, diagnostic sleep apnea testing, and anatomy phenotyping with physical examination and sedated endoscopy (Fig. 14.1) After completion of the informed consent process, appropriate candidates undergo outpatient surgical implantation of the system as described in Chap. 13. The device is activated in the office setting 4 weeks after implantation. Patients then begin nightly therapy use during an initial accommodation period that includes gradual self-titration through a preset range of parameters to optimize comfort as well as symptom improvement. As with any OSA medical device therapy, close clinical follow-up is recommended in order to assess therapy adherence and patient-reported outcome measures including an objective adherence report downloaded from the device.

Implanted patients then complete postoperative sleep testing with in-lab polysomnography and/or home sleep testing to further titrate therapy and to assess objective outcome measures. Once adequate adherence and results have been achieved, successfully managed patients are transitioned to a long-term management plan for the duration of the expected battery life of the device of about 10+ years. For patients struggling with either inadequate therapy adherence, persistent symptoms or elevated AHI, device data download, clinical reassessment, and targeted therapy modifications are performed to optimize outcomes. Furthermore, as with any OSA treatment plan, multimodality therapy should be considered which may include weight loss, positional therapy, additional surgical modifications of the airway, oral appliance therapy, or other adjunctive treatments to further augment the effectiveness of HNS.

Preoperative Evaluation

Patient Selection/Indications/Screening

A comprehensive sleep history, full medical history, and physical examination with anatomic phenotyping remains the cornerstone for the initial evaluation of all patients considering HNS therapy. Based on the available literature and FDA

labeling, HNS therapy is considered second-line therapy for select group of adult patients age 18 and older with moderate-to-severe OSA apnea-hypopnea index (AHI) between 15 and 65 events per hour, who have failed or cannot tolerate positive airway pressure (PAP) treatment. Additional preoperative guidelines include central and mixed apnea events comprising <25% of the total AHI and absence of a complete concentric palatal collapse on drug-induced sedated endoscopy (DISE).

DISE is currently recommended to evaluate the anatomical location and pattern of pharyngeal collapse prior to proceeding with HNS therapy. Particular attention is paid to the pattern of palatal collapse and the degree of multilevel coupling between the tongue protrusion and enlargement of the retropalatal space. Early feasibility studies demonstrated that patients with absence of complete concentric collapse at the palatal level were more likely to achieve HNS therapy success [1, 2]. Significant obesity is a relative contraindication, depending on clinician judgment and the remainder of the patient's anatomic and physiologic phenotype. Current recommendations and evidence support therapy success in patients with body mass index (BMI) ≤35 kg/m^2 [3, 4]. Please see Chap. 7 for more detailed description of the patient selection and preoperative screening process, including the DISE procedure.

It is important to recognize, that although screening guidelines exist, patient selection must be determined on an individual basis within the broader clinical context taking into consideration the patient's age, occupation, skeletal structure, pharyngeal anatomy, nasal airway, obesity and fat distribution, comorbid sleep disorders, medical and psychiatric comorbidities, OSA pathophysiology, and suitability for general anesthesia and surgical intervention. Patients with hypoventilation syndromes, central sleep apnea, or other complex sleep-related breathing disorders due to chronic medical conditions may not be suitable candidates. Similarly, significant comorbid sleep disorders (e.g., severe insomnia), cognitive impairment, physical limitations (e.g. head and neck cancer, breast cancer reconstruction, or chest wall deformity), or specific imaging requirements (e.g., anticipated magnetic resonance imaging of the chest or abdomen) may be relative contraindications to implantation. Individual patient's decision to undergo device implant surgery should take into account realistic treatment expectation based on their personal, medical and surgical history.

The number of patients using HNS therapy is growing rapidly and it is already in the thousands. It is critical to understand predictors of therapy response and long-term success to help guide patient selection. Using treatment success criteria defined by AHI reduction of at least 50% from baseline and an AHI <20 events/hour, large studies suggest increasing age, decreasing body mass index, and female gender are associated with greater likelihood of HNS therapy success [5, 6]. Despite the published inverse correlation between outcomes and BMI, a multicenter retrospective review found no difference in postoperative AHI, oxygen desaturation nadir, subjective daytime sleepiness, or success rates in patients with BMI greater than 32 kg/m^2 when compared to those with BMI below 32 kg/m^2, suggesting that select patients with an elevated BMI can still be successfully treated with HNS therapy [4]. Advances in anatomic and physiologic endotyping based on clinical, radiographic, endoscopic, and/or polysomnographic markers have the potential to strengthen patient selection criteria and bolster outcomes.

Perioperative Care

Implant Procedure

For the current FDA-approved HNS device manufactured by Inspire Medical, implantation involves an approximately 2-hour outpatient surgery under general anesthesia. After induction of standard general endotracheal anesthesia, needle electrodes are placed in the genioglossus muscle and the hyoglossus/styloglossus muscles for intraoperative nerve integrity monitoring. HNS implant is preferably placed on the right side. Presence of other implanted devices on the right side, anatomic limitations due to prior surgeries or trauma, and occupational needs may require HNS system implantation on the left. Following standard sterile prep and drape, a small incision is made in the upper neck parallel to a natural skin crease and carried down to the floor of the submandibular triangle where the hypoglossal nerve is identified. Nerve monitoring is used to selectively capture the distal tongue protrusor branches supplying the genioglossus muscle and to exclude branches innervating the tongue retractor muscles. The stimulation cuff electrode is placed around the distal protrusor branches and secured to the digastric tendon [7, 8].

A second incision is made on the ipsilateral upper chest and a subcutaneous pocket overlying the pectoralis fascia is developed for placement of the implantable pulse generator (IPG). The respiratory sensor is inserted through the same incision between the external and internal intercostal muscles in approximately the second or third intercostal space, with the sensor facing the pleura, and secured to the chest wall. The sensing lead is tunneled into the upper chest pocket and both leads are connected to the IPG, which is secured to the pectoralis fascia [7, 8].

The sterile telemetry unit is then brought into the field and connected to the IPG. Intraoperative nerve stimulation to confirm presence of characteristic electromyographic (EMG) activity and direct visualization of functional tongue movement helps to properly identify correct placement of the stimulation cuff. In cases with ipsilateral tongue retraction during intraoperative device testing, the cuff electrode position should be re-assessed for proper placement and ensure that lateral branches to the hyoglossus/styloglossus muscles are excluded from the cuff. Respiratory sensor lead placement and function are assessed by visualizing characteristic respiration wave pattern after tuning on the device. After confirmation of a good sensing waveform and confirmation of unrestricted, forward tongue protrusion, the wounds are irrigated, closed, and dressed [9].

Postoperative Course

All patients undergoing UAS implantation should be appropriately counseled on the risks of surgery, recovery process and post-surgical expectations. In contrast to anatomy-altering pharyngeal and skeletal sleep surgery procedures, most patients can be safely discharged home the same day since most of them are not obese, there

is no surgical manipulation of the airway, and need for opioid medication use for pain control is minimal. In situations when travel distance is a consideration or monitoring of certain medical conditions and postoperative anesthesia-related issues is required, patients can be monitored overnight.

Although serious adverse events were rare in the Stimulation Therapy for Apnea Reduction (STAR) trial [10], potential procedure-related adverse events include bleeding, infection (including the need for device explantation), hematoma/seroma, injury or weakness of the hypoglossal or marginal mandibular nerves, and pneumothorax. Other potential complications include persistent long-term pain, IPG migration, device lead damage, lead visibility and device exposure (Table. 14.1). Knowledge of the anatomy, adherence to proper procedure steps and careful dissection are essential to avoiding these complications.

Management of perioperative anticoagulation is done in collaboration with the patient's surgeon, primary care physician, cardiologist, and/or anesthesiologist. In most cases, surgery can proceed without discontinuation of aspirin. If a patient is on warfarin, the medication should be stopped 5 days prior to surgery with low-molecular weight heparin or enoxaparin bridging. New oral anticoagulants such as

Table 14.1 STAR Trial summary of adverse events. *Other unrelated serious adverse events included cardiac conditions: coronary artery disease, arrhythmias, and chest pain (n = 8), accidents or injuries (n = 11), and other surgeries (n = 12). **Skin cellulitis. ¥One death from a cardiac event thought to be unrelated to the device and one death related to a homicide. (Reproduced with permission from Strollo et al. [10])

Adverse events	No. of events	Number of participants with event (%)
Serious adverse event	35	27 (21%)
Device-revision	2	2 (2%)
Death, unrelated‡	2	2 (2%)
Other unrelated‡	31	23 (18%)
Procedure-related non-serious adverse event	169	72 (57%)
Post-op discomfort related to incisions	46	33 (26%)
Post-op discomfort not-related to incision	39	31 (25%)
Temporary tongue weakness	35	23 (18%)
Intubation effects	18	15 (12%)
Headache	8	8 (6%)
Other post-op symptoms	22	14 (11%)
Mild infection	1	1 (1%)
Device-related non-serious adverse event	190	85 (67%)
Discomfort due to electrical stimulation	80	50 (40%)
Tongue abrasion	33	26 (21%)
Dry mouth	13	13 (10%)
Mechanical pain associated with device presence	8	8 (6%)
Temporary internal device functionality compliant	14	12 (10%)
Temporary external device usability or functionality complaint	8	7 (6%)
Other acute symptoms	25	19 (15%)
Mild or moderate infection**	1	1 (1%)

Apixaban, Dabigatran and Rivaroxaban should be discontinued approximately 48 hours prior to surgery. Perioperative anticoagulation is associated with an increased hematoma and bleeding risk, however, in most cases anticoagulation can be restarted 24 hours postoperatively.

After surgery and prior to discharge all patients obtain an upright chest and neck radiographs in the post-anesthesia care unit to document baseline device position, to assure proper electrode placement and rule out pneumothorax. One of the potential symptoms after surgery include lower lip weakness or asymmetric smile due to an incision of the ipsilateral platysma, or rarely secondary to neurapraxia of the marginal mandibular nerve. Temporary weakness of the tongue on protrusion in the postoperative period can be observed – likely associated with neurapraxia from hypoglossal nerve dissection and reported in less than 1% of cases [11] and most patients can be managed successfully with observation. Patients should be informed about swelling and bruising around the incisions and tunneled lead sites following the procedure which are expected to resolve over time. Over-the-counter acetaminophen and/or non-steroidal anti-inflammatory medication are commonly used for incision-related discomfort.

Unlike after traditional OSA surgery, there are no dietary restrictions postoperatively and patients may advance their diet as tolerated. The symptoms of dysphagia, voice changes or globus sensation reported immediately after surgery are most likely related to intubation and muscle dissection, and usually resolve within several days. Studies looking at the long-term voice and swallowing problems after HNS implantation showed no changes in voice handicap and swallowing function [12, 13].

Patients are instructed to avoid strenuous or repetitive activity of the ipsilateral arm for the first 2-3 weeks. An arm immobilizer such as an arm sling can be used to limit lifting and arm motion. Tension or tethering of the tunneled neck stimulation lead is a rare side effect and can be avoided with precise subplatysmal lead placement. Neck stretching and massage in the first month can help prevent tension/tethering of the tunneled stimulation lead in the neck often visible with neck extension.

Post-Implant Therapy Management

Device Activation

The STAR trial established the foundation for the current therapy initiation and device programming protocol. Device activation is usually performed 4–6 weeks after implant placement. When acute neurapraxia and poor tongue mobility are noted, it is recommended to wait for resolution prior to HNS therapy activation. Device activation is initiated with standard default stimulation settings – bipolar electrode configuration [+-+], pulse width = 90 μs, rate = 33 Hz. Proper system function is confirmed, and functional threshold defined as the lowest amplitude at

which tongue protrusion passes the mandibular incisors is established. Initial amplitude is set at or just below the functional threshold. The device is then programed to with patient-control range of ten 0.1 V increments. For example, for established functional threshold of 1.0 V the stimulation intensity range can be set as 0.8–1.7 V. This allows self-titration by patients to optimize their comfort and symptom control. If patient has suboptimal tongue motion at the default bipolar settings, response to HNS with unipolar settings [-o-; o-o; ---] should be explored. The therapy start time and pause time are set based on patient's preferences and sleep habits, typically 30 minutes therapy start delay and 15 minutes therapy pause. Once the initial therapy settings are determined, the patient is instructed on use of the remote control and self-titration by gradually increasing the stimulation level every 2–4 nights with the goals of achieving control of OSA symptoms while keeping comfortable stimulation intensity.

Therapy Titration

After a one-month or more period of accommodation to the therapy and self-titration to establish the balance between stimulation comfort and symptomatic relief, follow-up sleep testing is arranged to assess the objective effectiveness of the therapy. Sleep testing may be used to further titrate and fine-tune the stimulation parameters for optimal outcomes. In the STAR trial, in-lab titration studies at 2-months and 6-months were used to adjust treatment parameters. Using wireless telemetry, electrical parameters can be adjusted in real-time during polysomnography, similar to a PAP titration. Similar protocol has been utilized in the post clinical trial setting. Patients would undergo a polysomnography study with overnight therapy optimization. The optimal therapy setting is described as the voltage required to eliminate obstructive events while patient is asleep. During sleep study the technician increases the therapy voltage every 10 minutes in increments of 0.1 V until oxygen desaturation and airway obstruction is eliminated. Ideally optimal settings can be established in supine position during REM stage of sleep. However, it is not always feasible during one-night study. After the sleep study the therapy stimulation therapy range is adjusted based on the overnight observations. The patients are instructed to use the therapy every night for the entire duration of sleep. The patient returns for follow up in 6–12 months for device check and adjustment. At that time, it is recommended that HST is performed to assess therapy efficacy.

It should be noted that the titrated AHI from an in-lab therapeutic study data may not be representative of long-term outcomes and emphasizes the need for full-night assessment. Full-night efficacy studies, in the form of multi-night home portable monitoring, are most commonly recommended at 6–12 months postoperatively and are included in the global clinical registry methodology. Thereafter, patients may be transitioned to long-term follow-up with the sleep medicine physician to monitor adherence, side effects, and ongoing clinical response, similar to longitudinal management of CPAP.

In the past few years, to improve efficiency and patient compliance with follow up, several HNS implant centers have modified their approach to therapy optimization. After initial device activation in a 4–6-week postoperative period patients are instructed on self-titration of the therapy. A follow up to assess subjective outcomes of the therapy is performed after 1–2 months of the therapy use. If patient reports no concerns with the therapy and favorable symptomatic improvement, a follow-up HST is arranged to assess full-night treatment efficacy. If the treatment HST confirms adequate disease control, the patient is instructed to continue the therapy use at the current stimulation settings and transitioned to a long-term care model. In cases with inadequate objective outcomes and/or inadequate subjective response, office-based therapy adjustments and/or in-lab PSG titration may be performed.

Therapy Adherence

As with any medical device for OSA, HNS outcomes are directly tied to the therapy use – also referred to as therapy *compliance* or *adherence*. Furthermore, poor therapy adherence is often directly associated with therapy side effects, which include various device-related, stimulation-related, and/or psychosocial-related complications. Long-term adherence to OSA medical device therapies remains one of the biggest challenges in OSA treatment. The STAR trial reported 86% of participants using the therapy nightly at the 12-month mark [10]; however, this adherence data represented self-report rather than objective analysis. Subsequent case series from individual institutions representing real-world clinical practice (outside of the multicenter STAR trial) reported objective adherence data. Current technology allows for download of objective therapy use data from the pulse generator using the telemetry unit and clinician programmer, as well as from the most recent model of the remote.

Early published objective adherence data was limited to total hours of therapy usage since the last device interrogation, which was then reported as mean nightly or weekly use. At a mean 7.8 months follow-up, *Kent* et al. reported mean objective adherence of 7.0 ± 2.2 hours/night [14]. *Heiser* et al. reported similar high adherence rates at 12 months follow up with a mean of 6.6 ± 2.7 hours/night according to the data downloaded from the device [15]. Comparing HNS outcomes of 97 consecutive patients at two centers, *Huntley* et al. also reported favorable adherence in the first year with 63.4% and 78.8% of the participants at the respective centers using the therapy over 40 hours/week [16].

More recently, *Heiser* et al. reported on 508 HNS patients from the multicenter Adherence and Outcome of Upper Airway Stimulation for the OSA International Registry (ADHERE) with a mean objective nightly use of 6.4 ± 2.0 hours/night at the first post-titration time point (n = 344 patients) and 5.7 ± 2.2 hours/night at the final visit of the study (n = 229 patients). Furthermore, using a logistic regression model they showed increasing therapy adherence was associated with increasing

age, lower BMI, and increasing AHI [17]. Thaler et al. published the results of 1017 patients implanted with the HNS who were enrolled in the ADHERE registry. At the 12-months post implant, mean objective therapy use was 5.6 ± 2.1 hours/night [11]. Suurna et al. reviewed the ADHERE registry data and found that therapy related discomfort negatively affected therapy adherence and outcomes [18].

Therapy-Related Side Effects

Potential therapy-related side effects should be discussed with patients pre-operatively including possible tongue abrasion or ulceration, sleep disturbance or insomnia resulting from stimulation, and inadequate therapy response. There is no evidence that therapy use adversely affects swallowing. Tongue abrasion and stimulation-related discomfort are the most common therapy-related non-serious side effects, reported in 21% and 40% respectively in the first 12-months of the STAR Trial [10] (Table 14.1). The multicenter international ADHERE registry data showed that 23% of patients reported treatment-related adverse events during the post-titration and final visits, which most commonly consisted of stimulation-related discomfort, tongue abrasion, or insomnia/arousal [17].

Further studies are needed to examine association of specific side effects and patient factors with therapy adherence and outcomes. Akin to the CPAP literature, future investigations of HNS therapy should focus on patient education, patient selection, and post-implant troubleshooting algorithms to further optimize therapy comfort and adherence. Additionally, technology advances could provide clinicians with more detailed and granular, and even remotely accessed, nightly adherence data for better longitudinal management.

Long-Term Follow-Up

MRI Restrictions and Battery Life

While strict MRI incompatibility was a concern with the first generation of the approved HNS device, the current model of the implantable system allows conditional MRI use for head and extremity imaging. Current IPG battery life is estimated at 10–12 years. The patients will need to undergo IPG replacement surgery or consider alternative treatments when the battery expires. Efforts of research and development of HNS technology are focused to produce a smaller MRI-compatible IPG, reduce operative time, improve battery life, incorporate the respiratory sensor into the IPG, optimize comfort features, and develop more sophisticated and comprehensive data monitoring software.

Therapy Optimization

Post-implant therapy management will play an increasingly important role in the successful longitudinal care of HNS patients, particularly as this treatment modality becomes more accepted and widespread globally (Fig. 14.2). Although many HNS patients have straightforward therapy response, there is a substantial subset of the implanted population with suboptimal outcomes, similar to that reported with CPAP and other medical device treatments. Some patients achieve adequate AHI reduction and symptomatic response, but struggle to maintain nightly adherence due to discomfort with the therapy. Other patients demonstrate excellent therapy adherence, however, they fail to achieve adequate disease control with elevated AHI and/or persistent OSA-related symptoms.

Advanced electrical programming can be performed in the office when device settings (e.g. amplitude, pulse width, rate, electrode configuration) can be systematically analyzed and modified with or without concurrent upper airway endoscopy to improve long-term outcomes. As clinically indicated, the addition of positional therapy, weight management, lowering of nasal resistance, mandibular repositioning, upper airway surgery, chin strap and other adjunctive measures can be considered to further improved efficacy and outcomes of HNS.

In summary, for patients with partial or suboptimal response to HNS, development of standardized best-practice approaches to therapy troubleshooting and modifications are underway. As with other OSA treatment devices, optimization of the long-term outcomes of HNS can be achieved with implementation of close clinical follow up, device data download, patient education and targeted advanced device programming. Although industry-sponsored recommendations for sleep laboratory titration protocols, as well as office-based therapy troubleshooting and advanced

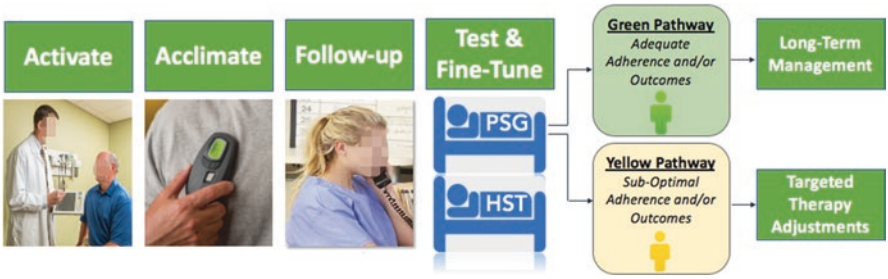

Fig. 14.2 A standardized post-implant patient care pathway. The post-implant care pathway includes device activation 4-weeks after implant followed by a 6–12 weeks period of therapy adaptation and accommodation as well as close clinical monitoring with patient education and support. A brief check-in within 1 month after the initial activation visit, either by phone call or face-to-face visit, is critical to ensure the best possible outcomes. The accommodation period is followed by sleep testing to assess objective outcome measures and follow-up office visit to assess both therapy adherence and patient-reported outcome measures. Successfully managed patients may be transitioned to a longitudinal care program, whereas patients with inadequate adherence and/or effectiveness may be further assessed with a standardized troubleshooting program in which targeted therapy adjustments and other interventions can improve outcomes

titration are available, peer-reviewed evidence based practice guidelines are still evolving. For complicated or refractory cases, there may be a role for drug-induced sleep endoscopy for further therapy optimization. Additional research is needed to determine whether such therapy titration protocols change outcomes and which interventions have the most meaningful effect.

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Chapter 15
Trouble Shooting

Armin Steffen and Benedikt Hofauer

Contents

Both the implantation of a system to stimulate the upper airway as well as the postoperative follow-up and titration are well standardized processes [1, 2]. The aim of the following chapter is to illustrate potential unexpected situations during these phases and to describe solutions.

Trouble Shooting During Implantation

Advanced Candidates for Surgery

To prevent potential troubles during the implantation special considerations should already be paid during the selection process to identify candidates, who require special consideration in the planning of the surgical procedure [3].

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Gender-Specific Peculiarities

Although the implantation does not differ between women and men, peculiarities must be observed in women. In preoperative evaluation in women particular attention to previous surgical interventions in the chest area should be paid. In the case of breast augmentation, the position of the implants should be determined with the help of surgical reports, as this is relevant for tunneling. A position of the implant above or below the pectoralis muscle is conceivable here. In any position there is a risk that the implant will be injured during tunneling. It is therefore particularly important to pay attention to a controlled preparation on the muscle fascia. In women with a history of breast cancer, this can affect the preparation (scar tissue and post-radiogenic changes), so that it may be necessary to switch to a left-sided implantation. Staging may be compromised in women at increased risk of breast cancer because MRI of the chest can no longer be performed after implantation. There are no contraindications to mammography after implantation, but the assessment on the pacemaker side may be affected by the foreign material or make the placement of the breast difficult in parallel plate compression [4].

The positioning of the IPG, the cut for the pacemaker pocket and the breathing sensor must be discussed with the patient for cosmetic reasons and to avoid pressure from the bra. This may require a deeper cut to prepare the pacemaker pocket and insertion of the respiratory sensing lead in the submammarian fold [4].

Left-Sided Implantation

The standardized implantation is typically performed on the patient's right side. In some situations, however, an implantation on the opposite side, i.e. the left side, may be indicated. Possible reasons for this include the presence of another pacemaker on the right-hand side or certain professional or private obstacles (e.g., hobbies such as hunting). In these cases, the implantation can also be carried out on the left side, but some special features should be taken into account.

The anatomical landmarks are identical on both sides, but the stimulation cuff is specially designed for insertion on the right side. If the cuff is now to be implanted on the left side, the positioning of the inner and outer flaps must be attached to the nerve in exactly the opposite direction. However, there are no reports that this adversely affects effectiveness.

The main reason why the implantation is performed on the right side is that the breath sensor on the left side may be disturbed by detecting the heartbeat instead of the breath excursion and the smaller lung volume. It is therefore important for left-sided implantation that the breathing sensor is positioned more laterally in order to increase the distance to the heart [4, 5].

Other Implantable Medical Devices

A variety of different implantable devices are conceivable and currently no contraindications for stimulation therapy of the upper respiratory tract have been described. However, if there are other implants or pacemakers, pay attention to special features and check whether a left-sided implantation is required.

In the case of active implants, such as other pacemakers or ICDs, it is necessary to clarify whether these have an adverse effect on one another. Consultation with the medical colleague who is familiar with the other implant can be helpful and necessary here (see section "Activation").

There are two main concerns, especially with implantable defibrillators (ICD): Can the upper airway stimulation (UAS) adversely affect the ICD (triggering defibrillation) or the ICD the UAS (damage to the implanted material due to defibrillation)? If one of these two implants is applied when the other is already in place, it is currently recommended here that both implants are tested intraoperatively (including different electrode configurations and stimulation intensities) and that interactions are excluded. The UAS electrode configuration should be set to bipolar to minimize the resulting electrical field. If an implantable defibrillator triggers in a patient who also has a hypoglossal nerve stimulation system, then the function of the UAS system should be checked [4, 6].

Intraoperative Situations

The implantation process can be divided in the following parts:

- Implantation and placement of the stimulation cuff
- Tunneling of the leads (neck and chest)
- Implantation and placement of the IPG
- Implantation and placement of the sensing lead
- Technical checks

During all of these parts specific intraoperative difficulties are possible.

Implantation and Placement of the Stimulation Cuff

The preparation of the hypoglossal nerve and the correct placement of the stimulation cuff represent a certain challenge. There can be various difficulties, which should be avoided if possible. Correct placement of the skin incision is important in order to avoid damage to the marginal mandibular nerve and to avoid having to start the preparation at an unfavorable location. Therefore, the marking of anatomical and surgical landmarks is recommended. Furthermore, the preparation of the

individual layers should be carried out thoroughly, especially the posterior border of the mylohyoid muscle must be shown exactly so that the preparation of the individual fibers can always be started at the same point on the hypoglossal nerve. Different courses of relevant nerve branches were described and classified using a classification system [7, 8]. This knowledge of possible variations should make the preparation easier for the surgeon. Different parameters can be helpful when deciding where exactly the cuff should be inserted. (1) The anatomical relationships (usually the lateral branch from the medial bundle is divided at the level of the front edge of the hyoglossal muscle), (2) the direct visualization of muscle contraction and (3) the neuromonitoring should be taken into account. In the unlikely event of intraoperative damage to the hypoglossal nerve, preparation and implantation on the contralateral nerve can be considered (after consultation with the patient). After the placement of the stimulation cuff when testing the effect of the stimulation a missing or abnormal tongue movement represents another trouble at this stage. If no tongue movement can be generated at all, first thing is to check if air is inside the stimulation cuff, which hinders the stimulation leads to have contact to the nerve. In this case, the cuff should be flushed with saline solution. Additionally, the correct assembly of the leads and IPG should be checked. If still no movement can be generated at stimulation intensity, but the surgeon is convinced to have the cuff placed at the correct position, the implant should be left in place and the nerve should get time to regenerate and after an interval of 1 month the stimulation should be checked again. In the case of an unfavorable tongue movement (left sided protrusion, mixed activation), the cuff should be removed and the nerve fibers should be checked [9]. The most common explanation is an exclusion (retraction) fiber, usually hiding on the back side of the medial branches. Finally, if the absence of abnormality of the tongue motion cannot be explained by one of the above mentioned reasons, technical explanations should be evaluated [5].

Special care is necessary for patients who had already undergone neurosurgical approaches for cervical spine surgery, submandibulectomies, pervious sleepsugry such as hyoidthyroidpexia or even neck dissections including the submental level with adjuvant radiotherapy. In these cases, the anatomical landmarks are more difficult to be identified and the hypoglossal nerve branches might be turned, so retractor branches appear more lateral and are higher likely to be falsely included [5, 10].

Tunneling of the Leads

The tunneling of the electrode cables, especially in the neck area, is a part of the procedure that cannot be fully controlled. Bleeding may occur especially in patients with previous neck surgery or prominent external jugular vein. To avoid this, the neck should be inspected before the preparation begins and abnormal vascular courses should be marked. The preparation can either be superficial to the platysma (advantage: fewer vessels, disadvantage: more superficial position of the electrode) or directly below the platysma (advantage: electrode better covered and less visible, disadvantage: higher risk of vascular injuries). In order to minimize the risk of vascular injuries, the tunnel should be prepared from cranial and caudal with surgical

clamps. This should be done with care especially in patients with anticoagulation medication such as heparin or aspirin. It should always be ensured, that the tunnel runs directly below the platysma and one does not penetrate into the depth of the soft tissues of the neck. If bleeding occurs in the course of the tunnel despite this precaution, then it is usually venous bleeding that can be stopped by applying pressure from the outside. If this is not sufficient or arterial bleeding is the reason, an additional incision on the neck to identify and treat the source of the bleeding is required. The patient should be informed about this eventuality in advance. The tunneling of the sensing lead on the lateral chest into the IPG pocket is unproblematic while specific patient characteristics (such as prior chest surgery) should be considered [5].

Implantation and Placement of the IPG

The preparation of the IPG pocket as well as the placement of the IPG in the pocket is comparatively unproblematic, as long as the IPG is fixated properly within the pocket to avoid willfully (manipulation of the patient) or involuntarily displacement of the IPG. A too large preparation of the pocket increases the risk for the newer IPG with smaller diameters (Inspire IV) to flip within the pocket with more extensive shoulder movement [5].

Implantation and Placement of the Sensing Lead

There are two main difficulties in placing the breathing sensor, one of which is realistic and one of which is theoretical. When checking the breath curve after inserting the breathing sensor, it is often not possible to derive a satisfactory breath curve. If this is the case, mechanical ventilation during anesthesia should first be switched to manual ventilation by the anesthetist and the anesthetist should be asked to ventilate the patient with slow and deep breaths. At the same time, neither the operator nor the assistant should be supported on the patient and thus impair the breathing excursion. If this does not solve the problem, the position of the sensor should be evaluated. The most common cause is a too superficial position of the sensor, i.e. not between the external and internal intercostal muscle, but superficially from it. Another explanation can be a blockage of the sensing electrode due to excessive contact with the rib above or below the prepared intercostal space. In addition, the selected intercostal space may be too deep for a good breathing signal (the fifth or sixth intercostal space is recommended). In all cases, the sensing electrode should be repositioned. The correct insertion of the electrode should also be checked as well, since the notch at the tip of the electrode should always point towards the lungs. If this is not the case, the electrode must be rotated. Special care must be paid to insert the sensing lead without contacting the outer tip as this may cause damages to the lead isolation [5].

Pneumothorax caused by the preparation or insertion of the respiratory sensor is only of theoretical risk. So far there are no published cases [11, 12]. If the pleura

should be injured intraoperatively, the sensing electrode should not be inserted in this space and the structures should be closed superficially to the pleura. X-ray control of the thorax should be carried out immediately postoperatively and adequate therapy of the pneumothorax should be carried out (drainage, follow-up checks).

Telemetric Checks

At the end of the surgical procedure the entire system is checked telemetrically. In addition to the impedances, the correct functioning of the stimulation cuff and the breathing sensor are checked. Test stimulation of the hypoglossal nerve is performed, paying attention to tongue movement. A bilateral protrusion or a right-sided protrusion should appear here, all other movements have been described as unfavorable for the effect of the stimulation therapy [13]. If there is an unfavorable movement, repositioning the stimulation cuff should be considered. If no movement can be stimulated, one should first check whether there is still air inside the stimulation cuff that prevents the electrodes from coming into contact with the nerve. If this is the case, then the cuff should be rinsed with saline. If this is not the case, the intactness of the stimulation electrode or the pacemaker should be checked and nerve damage should be considered if necessary. The derivation of the breathing movement is also checked. It is important to ensure that inhalation and exhalation movements are clearly recognized. It has to be noted that the respiratory movement of the awake patient as well as of the anesthetized patient differs significantly from the sleep breathing. If a meaningful breathing curve cannot be derived under mechanical ventilation, then the anesthetist should give the patient ventilation with slow and deep breaths (as already described).

Early Postoperative Complications

Postoperative Bleeding and Hematoma

In the postoperative course, especially in multimorbid patients with anticoagulation, subsequent bleeding or hematoma in the operating area can occur. In both cases, timely hemostasis or hematoma removal is recommended with the aim of avoiding critical blood loss and preventing postoperative infections. The risk of postoperative bleeding appears to be slightly increased by not using wound drainage, which would represent a potential source of infection.

Wound Infection

Postoperative wound infections pose a general surgical risk and should be avoided if possible, especially when implanting foreign material. Measures such as the perioperative administration of antibiotics and the use of incision drapes are intended to

minimize this risk. In a current publication, only two infections were reported in a cohort of 1017 patients (<1%) [12]. According to a current review on the diagnosis and therapy of infections in cardiological electrical implants, implant-associated infections occur in 1.7–9.5% of cases [14]. In the event of a postoperative implant infection, the appropriate antibiotic treatment, ideally after microbiological testing, as well as the explantation of the entire inserted system is recommended. In the infection-free interval, an implantation on the opposite side can be considered after critical evaluation of the indication.

Dislocation of Components of the Stimulation System

On the first postoperative day, the course of treatment involves checking the position of the implanted components of the stimulation system by means of X-rays of the lateral neck and thorax (Fig. 15.1) [15]. If a dislocation of one of the implanted components is noticeable (usually the stimulation cuff or respiratory sensor is used), early revision and replacement is recommended, since wound healing and scar formation progress with increasing duration after implantation and so does the preparation in the respective areas can significantly complicate.

Paralysis of the Hypoglossal Nerve

The motion of the hypoglossal nerve is evaluated directly postoperatively and again during the further postoperative course. In case of repeated cuff position changes intraoperatively, enormous stretching during preparation, or very often nerve testing with increased voltage, tongue motion imbalance could occur. If the nerve was cut through, nerve reconstruction techniques comparable in facial nerve repair in salivary gland surgery must be applied. Administration of steroids in order to facilitate the restitution of the hypoglossal nerve can be considered. If the weakness of the

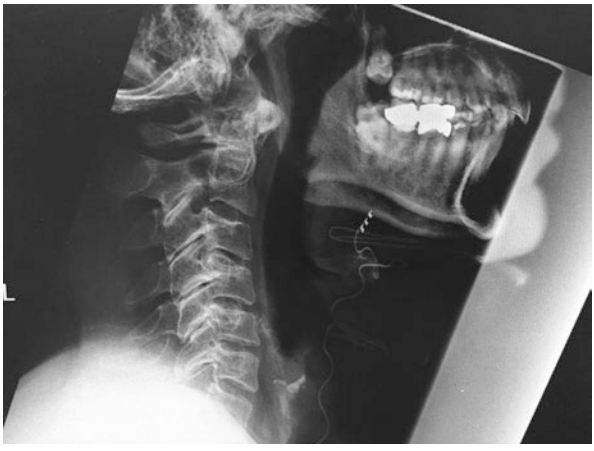

Fig. 15.1 A dislocation of the stimulation cuff is seen in this patient on the x-ray of the lateral neck. This can be seen from the atypical position not in line with the direction of the hypoglossal nerve

hypoglossal nerve is not completely reversible at the time point of the first activation of the system, than the system should not be activated at this stage but postponed until the nerve's recovery.

Trouble Shooting Situations in the Postoperative Pathway

Activation

During the structured process of activation (*see* Chap. 14), at several steps caveats may occur and the list of the following observed situations are incomplete.

No or Only Instable Connection to the Implant Can Be Established Via Telemetry

If the telemetry header is placed appropriately over the implant, thick subcutaneous fat/tissue and/or thick clothing with metal bearing garment can disturb the connection. For the later, the header should be placed directly to the skin. For the first, instable connection is annoying but rarely impossible. The surgeon should be contacted to thin out the tissue next time. Sometimes, video monitors or other electronic items may interfere the connection, so the room should be changed.

If the telemetry contact alone already provokes a tongue protrusion or sensation, this indicates a technical issue, especially with the sensing lead. The activation process should be completed and other possible observations need further contact to the manufacturer.

Abnormal or Homonymous Impedances Occur

In single or several electrode configurations, the impedances are higher than 7.000 Ω. Here, more than the usual 1.5 and 2.0 V should be tested whether this changes. Higher voltages correlate with higher threshold in function thresholds [16]. If a proper tongue protrusion is provoked, this should be registered but needs no specific intervention.

If abnormal low impedances below 200 Ω occur, this might be a hint for a technical failure in that specific electrode, e.g., in off minus off for the center electrode (here, the same for bipolar +-+!). Normally, no tongue motion or even sensing can be provoked even at highest voltages. All five electrode configuration should be tested including those which are clinically rarely used: bipolar - + - and unipolar - off - [9]. If the center electrode is affected, the thresholds are similar in - off - and - - -. The protocolled impedances during implantation should be compared and it is recommended to contact the implanting surgeon and the manufacturer for further

technical follow-up. If proper OSA reduction could be established with alternative electrode configuration, the patient is followed the usual pathway.

If homonymous impedances occur and change higher and lower at increasing voltages, respiratory sensing needs attention. In some patients, during later follow-up highly variable thresholds and abnormal sensing pattern occur which may indicate broken sensing lead isolation or other implant damage. The implanting surgeon and the manufacturer should be contacted.

No Tongue Motion at Several Electrode Configurations Despite Highest Voltage and Normal Impedances

If no tongue motion results in all electrode configuration even at highest voltage and despite normal impedances, the surgeon should be contacted whether tongue motion was normal during implantation. Awake tongue motion should be checked to rule out nerve paralysis in highly mobilized branches. A repeated X-ray is conducted to check for changed cuff position. Rare but real is a dislocation of the cuff, so an early revision surgery should be discussed.

No Tongue Motion at Specific Electrode Configurations Despite Highest Voltage and Abnormal Impedances

See above section "Abnormal or Homonymous Impedances Occur"

Abnormal High Voltages for Thresholds

Every patient gets the voltage necessary for tongue motion. There are patients with clear tongue protrusion already with 0.3 V at bipolar configuration, other might need 3.0 for sensation level [17]. No specific action is needed.

Only Submental Activation Without Tongue Protrusion

Here, several aspects could cause this phenomenon. In case of highly mobilized hypoglossal nerve during implantation or coagulation of the concomitant vein, some branches show minor signs of neuropraxia. Interestingly, in a broader electric field using unipolar electrode configuration such as - - -, quite often a tongue motion results. Therefore, patient's activation should be delayed for several weeks or started with unipolar configuration but a repeated follow-up check should be scheduled. Another explanation might be the partially dislocation or the superselective stimulation of the C1 branch without proper inclusion of the protrusor branches [8, 18]. Both situations could only be differentiated over time. In case of improper cuff placement *and* insufficient OSA control, a reposition of the cuff should be discussed.

Low Amplitudes in Respiratory Sensing

In several cases, the patient is nervous during the activation and the breathing pattern is different from normal sleep. Activation protocol is conducted as normal but patient's follow-up should be more cautious [19]. During the polysomnographic titration, attention should be paid to proper sensing. In regular cases, no specific action is needed. In suboptimal OSA control, an advanced titration focussing on improving the sensing signal is recommended. Instead of regular PSG titration at month two since implantation, a home sleep test based control is discussed [17]. Patients with improper sensing signals are no ideal candidates for this alternative therapy adjustment pathway.

Irregular Pattern in Respiratory Sensing

In case of sharp spikes or abstruse amplitudes in respiratory sensing, a broken isolation could cause this. Other hints are tongue motions already at the telemetry test activation and/or homonymous impedances. The surgeon and the manufacturer must be contacted and the patient's pathway needs close follow-up as a revision surgery for the sensing lead might be needed.

Synchronic Existence with Cardiac Implantable Electronic Devices

In such cases, a potential conflict because of electric interference should have been tested already during implantation [20]. Nonetheless, in borderline situations or more sensitive cardiac defibrillation system settings, an activation of the hypoglossal nerve implant should be done at the cardiac pacemaker unit to check for potential cross-talk in several electrode configuration at highest tolerable voltages. For other electric neurostimulation appliances such as deep brain stimulation, vagal stimulation in epilepsy, or chronic back pain modulators, the specific specialty should be contacted, ideally before implantation.

Early Therapy Adaption Phase

Problems with Handling the Remote

It is strongly recommended to agree a scheduled follow-up call with the patient about 10–14 days after the activation (see *Chap. "Activation"*). This allows the proper handling of the remote to be enhanced and first experiences on sleep behavior to be checked. There is often uncertainty over the pause function, making the patients unsure whether they have paused or stopped the therapy and some suspect technical issues. A repeat of the training focusing on the therapy status light ring

will help in most cases. Inviting the bedpartner or a family member to join the activation minimizes handling problems.

Subjectively Low or No Stimulation in the Morning

Particularly within the first nights of usage, a very large number of patients contact the sleep center. They report a powerful tongue protrusion at the beginning of the night but experience no or only a little stimulation in the morning. The patient should be informed about the somatosensory neural adaptation. Several patients have already had awkward experiences that they could not feel the stimulation in the morning, only to be disturbed by tongue protrusions while brushing their teeth or drinking. Another explanation is if the therapy duration setting is too short, especially in longer sleep periods such as at the weekend. In these cases the settings should be adjusted next time. And lastly, the situation can be used to increase voltage and – in case of strong impulses at the beginning – the start should be raised up. Doubtful patients can be convinced that the presumed diminishing stimulation is not occurring through the results of the polysomnography.

Impulses That Are Too Weak or Too Strong Despite Unchanged Voltage Settings Within the First Weeks

In cases of a stimulation that is too strong or too weak, at the most outer voltage level after several weeks, it is strongly recommended to schedule the patient for assessment. The same technical check-ups should be done as during the initial activation (see Chap. 14). The threshold settings at several electrode configurations and the impedances at the minimum of two voltages can be compared with the previous values.

When the stimulation at the highest installed voltage is too weak, one can observe increased thresholds and impedances. If the voltage range is adapted to the actual thresholds and the tongue protrusion is the same as the functional threshold at activation, the problem is solved. The reason for these threshold changes in such a short time span is unclear. Changes in the cuff position, which lead to a greater distance between nerve branches and electrodes, are thought to be one possibility.

If the changes are made shortly before the scheduled polysomnographic titration, sometimes it is advisable to postpone the sleep lab night and to give the patient more time to get accustomed to the new voltages.

More Snoring Than Before

Some bedpartners of patients complain of more snoring during the adaption phase. This can be observed more often in patients with higher portions of apnea index instead of hypopnea index within the apnea hypopnea index. Without stimulation, a

complete breathing stop results in no snoring. Now, with the stimulated airway opening, some narrowing still exists and provokes snoring. If tolerated by the patient, the voltage should be increased. Most bedpartners are able to sleep better with soft snoring patients rather than being worried about breathing stops.

Coexisting Insomnia

Especially when patients have problematic usage of the first line-therapy PAP, then often other sleep disorders such as insomnia or psychiatric diseases such as depression exist. If the sleep debt - arising from the time with untreated OSA - is diminishing, other negative factors become more evident. These patients experience typical monosymptomatic sleep disturbances from depression or insomnia and have problems to fall asleep or, to sleep through the night. As they haven't encountered this before activated upper airway stimulation, it is not unusual that they blame the stimulation for this. In several cases, it helps to inform the patient to be more cautious with voltage increase when awakenings occur and to instruct him to use the pause function or re-start the stimulation. If the patient needs more time to fall asleep, the start delay should be increased. In more severe cases, the specific medication and/or the behavioral treatment options should be adapted or applied together with the general physician or psychiatrist.

Unwanted Results

There are several cofactors with negative impact of therapy response [21]. Some of them are more accepted such as being overweight [11]. Whereas for others including previous sleep surgery there are split opinions [22–24]. It is advised that the potential effects of overweightness *and* the status post sleep surgery should be weighted on patient selection via DISE. Both contribute to the exclusion obstruction pattern "complete concentric collapse at velum level" [25]. Beside these negative co-factors, which are obvious before implantation, there are others that manifest later. Examples are tongue motion patterns [9, 26], insufficient sensing signalling [19], or postoperative X ray analysis [15].

There are several options to optimize insufficient OSA reduction with usual therapy adjustment techniques (see Chap. 5h). These should be applied based on the suspected individual cause, the risks of the adjustment option, the centre's experience and resources, waiting list duration and others (Table 15.1). It is crucial to maintain close communication with all participants experiencing unsatisfactory results and to respect patient's wishes.

Table 15.1 Examples of techniques to optimize unwanted results and their indications

Techniques to optimize unsatisfactory results
The re-evaluation of comorbidities
Especially insomnia, alcohol abuse and depression
Changes of impulse configuration [16]
More intense impulse allows a reduction of voltage and maybe higher tolerance
Patient comfort settings such as start delay
Higher voltages might be tolerated when longer asleep
Advanced polysomnographic titration
Focusses more on proper respiratory sensing [19] and effects of different electrode configurations [9] which may have other patency effects on the airway
Change of electrode configuration and HST control [17]
Especially for patients who feel very uncomfortable in sleep labs
Weight reduction programs including bariatric surgery
= Reduced neck fat masses may have less frequent negative collapse patterns [27] and allows to reduce voltage to more tolerable levels
Wake endoscopy [28]
Allows easy accessible visualisation of stim effects of different electrode configurations and residual obstruction sites.
Drug-induced sleep endoscopy [29, 30]
Allows visualisation of stimulation effects of different electrode configurations and residual obstruction sites in a closer to sleep situation rather than wake endoscopy
Additional soft palate surgery [22]
In residual soft palate obstruction requiring intolerable high voltages

Other Technical Observations

Most technical observations rely on respiratory sensing but there are cases in which one or more electrodes have lost proper function. Here, no threshold can be documented despite the highest voltage installed at that electrode configuration. For example, if the outer electrode is damaged, bipolar +-+ and - o - is affected but unipolar - - - an o - o show normal function (but often, similar thresholds). It is very important to differentiate between technical observations from improper remote handling at the beginning and strong external electric field interference or mechanical forces. Besides MRI and monopolar cautery in medical areas, there are more possibilities of interference today. Every center will have stories of patients with awkward tongue sensations when close to a military radar unit or walking through old theft protection in shopping centers. If insufficient handling or external electric or mechanical interference are excluded, patients should be scheduled for a telemetric check-up including impedances, respiratory sensing, and thresholds at several electric impedances. As some abnormal observations occur without any effect for

Table 15.2 Red flags during the telemetry assessment in suspected abnormal technical function

Red flags during the telemetry assessment in suspected abnormal technical function
Awkward respiratory sensing with permanent spikes in the respiratory curve and/or flattening of the curve in cases with initially proper sensing
Abnormal or homonymous impedances in several volts (1.5 V, 2.0 V, and more)
Non-congruent increase and decrease in impedances despite an increase of volts
Abnormal shifting of thresholds
Sensitive threshold is reached during telemetry testing

the patient, it is strongly recommended to have the data from implantation, activation, and follow-ups for comparison. There are important signs that indicate abnormal technical function (Table 15.2). If in doubt, it is always advisable to contact the manufacturer.

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Chapter 16
Hypoglossal Nerve Stimulator in Pediatric Down Syndrome Patients

Matthew P. Partain and Christopher J. Hartnick

Contents

Introduction

Down Syndrome (DS) is one of the most common genetic disorders in the United States, with a prevalence estimated at 8.27 people per 10,000 in 2008 [1]. Individuals with DS are exceptionally vulnerable to obstructive sleep apnea (OSA) secondary to alterations in craniofacial and oral musculature development, smaller tracheal caliber, lingual tonsillar hypertrophy, relative macroglossia, as well as low muscle tone. OSA occurs when the upper airway becomes intermittently obstructed during sleep. This results in incomplete ventilation leading to blood-gas irregularities and sleep fragmentation. The prevalence of OSA is about 55–80% in the pediatric population with DS compared to 1–5% of the general pediatric population. OSA is best diagnosed with polysomnography (PSG), and is determined by an apnea-hypopnea index (AHI) score. In children, mild OSA is an AHI of 1–5 events/h., moderate OSA is between 5 and 10 events/h., and severe OSA is >10 events/h. [2–4]

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Adenotonsillectomy is the primary treatment for the management of OSA in children, including those with DS, and it is often successful in the general pediatric population relieving sleep disturbance symptoms. In contrast, children with DS have resolution of the OSA (AH < 1 event/h) in only 16–33% of those undergoing tonsillectomy [5, 6]. The Center for Disease Control estimates 6000 babies are born with DS every year [7]. Multiplied by 18, that is 108,000 under 18 years of age. If we use the low prevalence estimate of OSA in this population at 55%, then 60,000 have OSA to varying extents. With tonsillectomy at best improving AHI < 1 in 33% of these patients, that leaves us with a pediatric DS population of around 40,000 in total who have persistent OSA that are potential hypoglossal nerve stimulator implant candidates.

Untreated OSA is associated with learning and behavioral problems, long term morbidities affecting growth, the central nervous system, as well as cardiovascular and metabolic systems. Additional adverse sequalae include significant decrease in quality of life and association with lower mean verbal IQ scores and lower cognitive flexibility than in children with DS who do not have OSA [3, 4, 8].

In the case of OSA refractory to adenotonsillectomy, it behooves the pediatric otolaryngologist to pursue evaluation of the patient for other sites of upper airway obstruction. These sites include the base of tongue, pharyngeal side wall collapse, crowding associated with obesity, and lingual tonsil hypertrophy. Anatomical considerations such as midface hypoplasia and glossoptosis may also play a significant role. Evaluating these children with recalcitrant OSA in a combined multidisciplinary approach including Pediatric ENTs, Oral Maxillofacial surgeons, and Sleep Medicine practitioners provides the best route to optimize care.

When faced with these patients a series of questions must be asked and answered by the providers:

1. What severity of OSA is “severe enough” to warrant further treatment and why?
2. What is the anatomic cause of the obstructive sleep apnea?
3. Can the child comply with nighttime positive pressure ventilation?
4. What other surgeries are available if needed for these patients?

Breslin et al. studied a community cohort of school-age children with DS to examine the relationship between OSA and cognition. [8] Their results raised concerns regarding the comorbidity of OSA and DS. They found that verbal IQ was 9 points lower in children with OSA (AHI > 1.5 events/h) and DS compared to those DS patients without OSA. These children also showed deficits in executive function. In the study, children were matched for age, BMI, and background health status. While it is clear that we should be treating patients with AHI greater than 10, it remains controversial what the “end goal” of treatment should be. Is it an AHI < 5 or a significant decrease in positive pressure threshold that allows for tolerance of therapy? Is it the lack of need for positive pressure or an AHI < 1.5 as suggested by Breslin et al.? More work needs to be done to ask and answer these important questions.

Continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP), is an appropriate option for children with moderate or severe OSA. It is also reasonable to consider for children with recalcitrant OSA despite adenotonsillectomy, those with craniofacial abnormalities, or families that wish to pursue a non-surgical approach to their child's OSA [9]. CPAP and BiPAP can be an excellent solution for a patient's OSA, but compliance and long-term uses with the treatment is essential for improvement in the child's OSA. Many providers will perform mask fitting and trials of pressure introduction in the office setting to assess the child's tolerance to CPAP therapy. Lack of adherence to CPAP therapy in children is a common problem. Other problems with therapy include poor mask fitting, irritation of skin and eyes, nasal congestion, high arched palates, inability to tolerate high peak pressures, and anxiety with wearing a mask on the face or nose. This is especially prevalent in those with DS. Effective CPAP adherence depends on the persistent coaching by the child's parents and the family must have tools and support for troubleshooting problems [10, 11].

In a multicenter series of 94 children (<19 years old) with OSA, CPAP therapy was administered at a median pressure level of 8cmH2O was effective in 86% of children, meaning it was well tolerated throughout the night, resolved hypoxia during sleep for the patient, or had marked improvement in other polysomnographic abnormalities [12, 13]. Effectiveness was defined in this study as resolution of clinical symptoms, normal oxyhemoglobin saturation during sleep and improvement of PSG abnormalities. Of the children whom did not have an effective result on CPAP, only one adhered to the therapy, which suggests that poor adherence was the primary reason most children failed therapy. Adherence to CPAP therapy has long been the most difficult aspect of CPAP therapy in DS patients with OSA.

With regards to the anatomical cause of the patient's recalcitrant OSA after adenotonsillectomy, this requires further investigation by the pediatric otolaryngologist. Upper airway structural causes for OSA include a deviated nasal septum, lingual tonsil hypertrophy, soft tissue crowding of the tongue, soft palate and parapharyngeal fat pads, as well as midfacial and mandibular hypoplasia. Other contributing factors include relative macroglossia and glossoptosis, with resulting pharyngeal collapse during inspiration, especially during REM sleep [14]. A major goal in the treatment of persistent OSA is determining the pattern of airway obstruction in the patient during sleep. Drug-induced sleep endoscopy (DISE) consists of flexible fiberoptic assessment of the airway from the nares up to the vocal cords under pharmacologic sedation designed to simulate natural sleep. Upper airway collapse is a highly dynamic state, and real-time endoscopic assessment can provide valuable information beyond the PSG and clinical exam into where the upper airway obstruction is taking place. This allows for effective diagnosis of site of obstruction and for surgical planning in children. Several classifications exist to attempt to standardize the DISE procedure as a major limitation of the technique is variance in how it is performed and interpreted by providers [15, 16].

VOTE classification for adults was first described by Kezirian et al. in 2011 as a method for characterizing DISE findings that focused on the specific structures of the upper airway that contribute to obstruction: the velum, oropharyngeal lateral walls, tongue base, and epiglottis. These anatomical sites of the upper airway were then classified as to the degree of obstruction (none, partial, complete) and the configuration of the obstruction (anterior/posterior, lateral, concentric). Limitations to this classification include its oversimplification that overlooks interactions between the different subsites of the upper aerodigestive tract as well as its design for adults and not specifically children.

Chan et al. in 2014 developed a scoring system for DISE findings that also took into account pediatric specific areas of obstruction, namely the choanae and the arytenoids. It also took into account adjunct airway adjustments needed for airway support such as jaw thrust or an oral airway. Validation of any scoring system for DISE is difficult due to the lack of a true "gold standard" for assessing degree and site of airway obstruction in OSA.

Further surgical options based on anatomic level of obstruction in recalcitrant OSA include, septoplasty, sphincter pharyngoplasty, tongue base and midline glossectomy surgery, oro-maxillary facial surgery, orthodontics, mandibular distraction, and tracheostomy. These surgical options can lead to postoperative complications such as bleeding, prolonged hospitalizations, and significant caregiver burden [17–19].

Hypoglossal nerve Stimulation (HGNS) (Inspire® Upper Airway Stimulation System) is an established surgical treatment for refractory moderate-to-severe OSA in adults that is attributable to isolated anterior/posterior tongue base collapse that proved unable to tolerate CPAP therapy. The Food and Drug Administration (FDA)-approved STAR trial in the early 2010s showed long term clinical effectiveness of HGNS in improving primary metrics (AHI and oxygen desaturation index) as well as improved secondary outcomes such as subjective sleepiness and sleep-related quality of life via the Epworth Sleepiness Scale [20, 21].

In 2015 the FDA approved a multi-center, prospective, single-arm pilot study to evaluate HGNS in adolescents with DS and OSA [22, 23]. Patients were identified through a multidisciplinary clinic for patients with DS at the participating sites. Inclusion and exclusion criteria can be found in (Table 16.1). Patients that met inclusion criteria underwent an in-lab PSG, and a DISE to confirm anterior/posterior tongue base collapse was present and the major contributing factor to the patient's upper airway obstruction. VOTE classification was used to remain in step with the STAR study in adults. Preoperative quality of life evaluations were done with the OSA-18 Survey [24]. Subjects then underwent surgical placement of a HGNS. The Stimulator was activated 1 month after surgery and subjects then underwent repeat sleep study evaluation and device titration and 1, 2, 6 and 12 months after implantation. Although the operative steps of HGNS are well described in adults, there are surgical modifications necessary to conduct and optimize this procedure in the pediatric population.

Table 16.1 The inclusion and exclusion criteria

Inclusion Criteria
Only children and young adults with Down Syndrome age 10–21 years with prior adenotonsillectomy will be considered for the study.
Subjects must have BMI <95th percentile for age
All subjects must have moderate to severe OSA (AHI >10, AHI <50, no more than 25% AHI attributable to central events) based on prior in-lab polysomnography performed after adenotonsillectomy.
Subjects must have either tracheotomy or be ineffectively treated with CPAP due to noncompliance, discomfort, un-desirable side effects, persistent symptoms despite compliance use, or refusal to use the device.
Children and their parents must be willing to have stimulation hardware permanently implanted, and be willing to participate in follow-up visits, postoperative polysomnography, and questionnaire completion.
Children's parents must complete a questionnaire confirming that their child is capable of communicating feelings of pain or discomfort. They must also confirm they are able to assess their child for adverse effects related to device implantation.
Children and their parents must be proficient in English for this pilot study in order to ensure full disclosure during the consent process, as well as have the ability to communicate with all staff, at all times, regarding any questions about participation or concerns about this device.
In order to participate, subjects will require written consent from both parents. All study subjects must provide written assent as well.
Exclusion Criteria
Subjects will be excluded if they meet the following criteria: BMI >95th percentile for age, apnea hypopnea index (AHI) <10 or >50 on in-lab polysomnography (PSG), central or mixed apneas accounting for >25% of the total AHI, any anatomic finding on physical exam or drug induced sleep endoscopy (DISE) that would compromise the performance of stimulation (e.g. concentric soft palate collapse), other medical conditions resulting in medical instability (e.g. congestive heart failure, recent open heart surgery, immunosuppression, or chronic lung disease or aspiration), presence of another medical condition requiring future magnetic resonance imaging (MRI), history of cholesteatoma, or patients with another implantable device which could interact unintentionally with the Inspire system.
Subjects in whom general anesthesia for a surgical procedure is contraindicated due to other medical illnesses or conditions will be excluded.
Subjects with a life expectancy < 12 months will be excluded.
Subjects who are unable to communicate pain or discomfort to their caretaker/parent, based on parental or investigator assessment, will be excluded.
Subjects with a history of bleeding or clotting disorders and those on blood thinning or NSAID medications will be excluded from participation.
Subjects taking muscle relaxant medication will be excluded from participation.
Female subjects who are pregnant or plan to become pregnant during the study period will be excluded. All female subjects will undergo urine beta-HCG testing on the day of procedures requiring general anesthesia (DISE, implantation, and any other unanticipated surgical procedures related to implantation). Subjects who are positive will not undergo surgical implantation or procedures under general anesthesia.
Subjects deemed unfit for participation by investigators or any other reason will be excluded.

Surgical Technique and Pediatric Modifications to Hypoglossal Nerve Stimulation for Obstructive Sleep Apnea

Preparation and EMG Placement

Patients are intubated with an age-appropriate nasotracheal tube through the left naris. Electromyography (EMG) leads are placed in the genioglossus and hyostyloglossus muscles using Prass-paired 18 mm electrodes (Medtronic, Dublin, Ireland). During sterile preparation, it is important to use a translucent sterile drape (3 M, St. Paul, MN)(10-10/Ioban) to allow for visualization of the tongue and electrodes during device interrogation (Figs. 16.1 and 16.2).

Incision Modification for Pediatric Patient

A 4 cm transverse submental incision is made approximately 0.5 cm from the midline and 1 finger breadth below the mandible. A 5 cm incision should be made over the fourth to sixth rib for both the pleural sensing lead as well as insertion of the implantable pulse generator (IPG). This is different than the adult implantation, for which three separate incisions are made (Fig. 16.3).

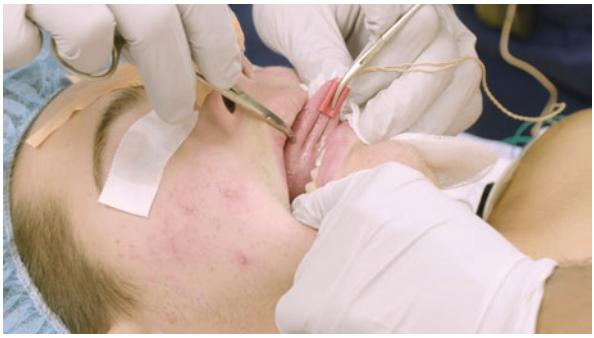


Fig. 16.1 The red lead is placed along the tongue in the styloglossus

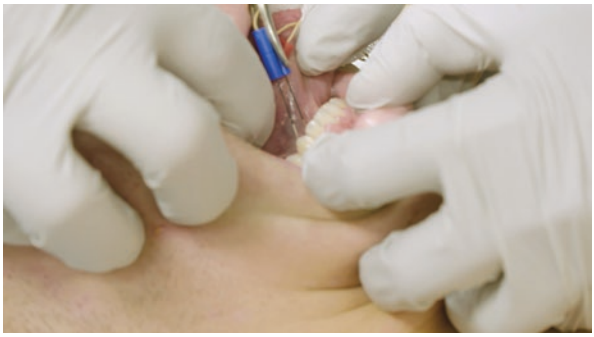


Fig. 16.2 The blue lead is placed in the floor of mouth in the region of the genioglossus taking care to be just lateral and anterior to Wharton's Duct

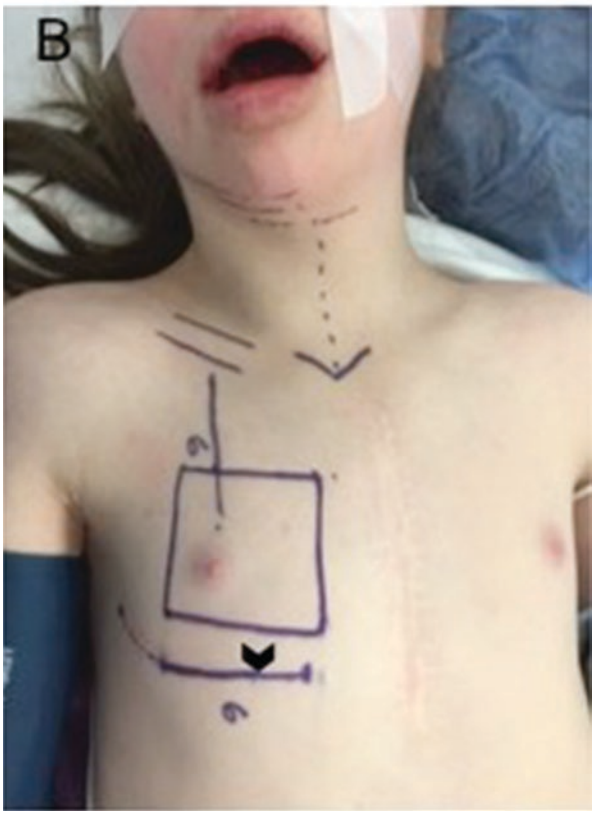


Fig. 16.3 Preoperative markings showing both the submandibular incision and chest incisions. The pocket for the implant is situated superiorly to the chest incision. A point 4 cm lateral to the incision along the superior edge of the rib is marked out as the ideal position for the sensor lead to be tunneled

IPG Pocket Modification

Prior to the insertion of any leads, the pocket for the IPG placement is dissected. The incision is made in the chest site (not a third incision, as described in the adult literature) to identify the pectoralis fascia. In children, the third infraclavicular incision for IPG placement is not necessary and therefore is spared. A plane is created superficial to the pectoralis fascia and extended superiorly to about 2–3 cm below the clavicle. This technique is best completed with a lighted breast retractor and extended Colorado needle tip cautery. This is a relatively bloodless plane. No drains should be needed at the end of the case. Because there is no infraclavicular incision to secure the device in a traditional way, two 2–0 silk stitches are placed at the top of the pocket through the pectoralis fascia. These are used to secure the implant at the top of the pocket at the end of the case, once the implant has been interrogated (Figs. 16.4, 16.5 and 16.6).

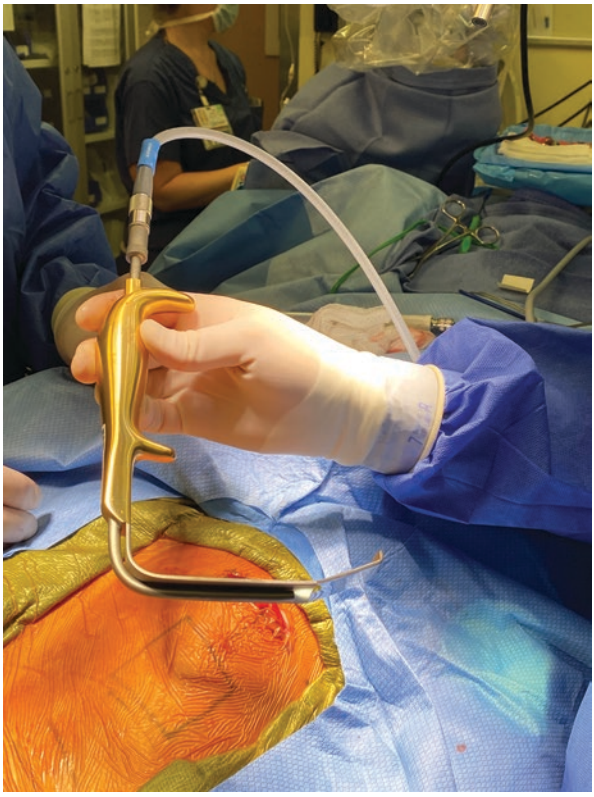
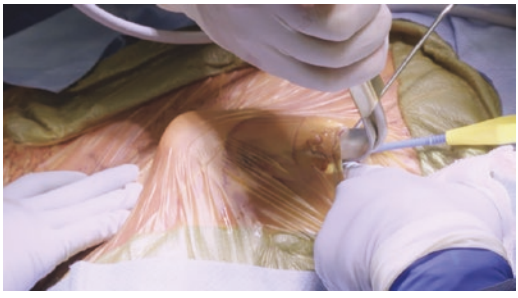
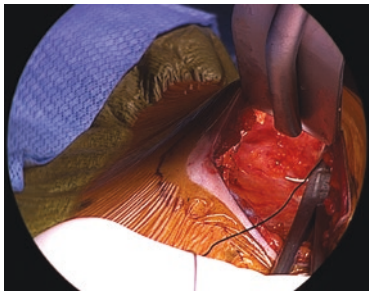


Fig. 16.4 This is the lighted breast retractor used at our institution

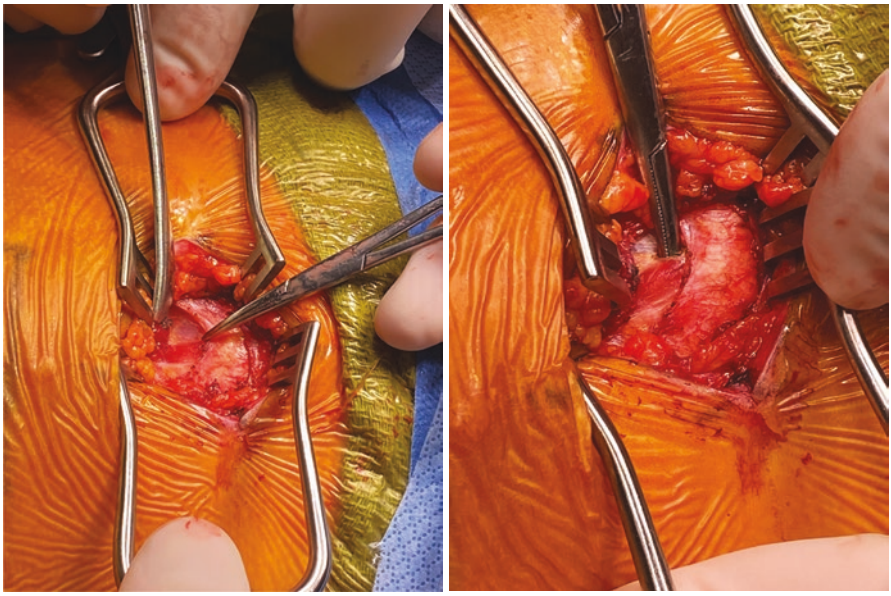




Figs. 16.5 and 16.6 Creation of the chest pocket and placement of a stitch at the top of the pocket

Sensor Lead Insertion Modifications

Through the previously dissected chest incision, taking care to stay just superior to the rib to avoid the neurovascular bundle, a plane is dissected between the internal and external intercostal muscles with the help of a small malleable retractor. The sensor lead is placed into this site, advancing laterally into the intercostal tunnel.



Figs. 16.7 and 16.8 Identification of the external intercostal muscle and the plane between the internal and external intercostals denoted by the hemostat

This is not advanced medially, as described in the adult literature, because the sensor may pick up artifact secondary to cardiac motion. The sensor lead is then anchored down in the typical fashion (Figs. 16.7 and 16.8).

Stimulation Lead Insertion Technique

The Hypoglossal nerve is identified through the creation of a triangle in the 1b neck. The submandibular gland is isolated and retracted superior-laterally. The mylohyoid is retracted anteriorly. The Digastric tendon is isolated and vein loops can be used to retract it inferiorly (Fig. 16.9).

The nerve can then be encountered in a broad field and the surrounding Renin veins can be ligated. As the dissection along the nerve is mobilized anteriorly, the medial branches to the genioglossus and geniohyoid should be identified for inclusion (Fig. 16.10).

The main branch point at which lateral and medial branches occur should be noted, and EMG monitoring should be used to assess for any exclusion nerve fibers with a late branch point. Once late branches have been excluded, a right-angle, dissection can be used to dissect circumferentially around the nerve to create a tunnel underneath the nerve through which an additional vessel loop can be used to facilitate identification of inclusion branches and provide gentle retraction. Angled

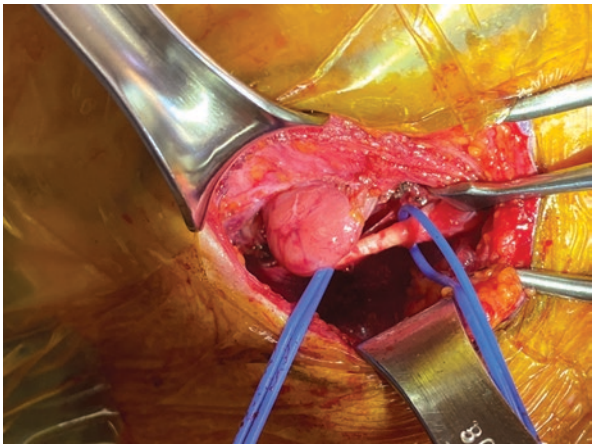


Fig. 16.9 The superficial 1b triangle. The digastric tendon has vein loops, the mylohyoid is retracted anteriorly. The submandibular gland's inferior and medial fascia has been dissected and the gland is mobilized

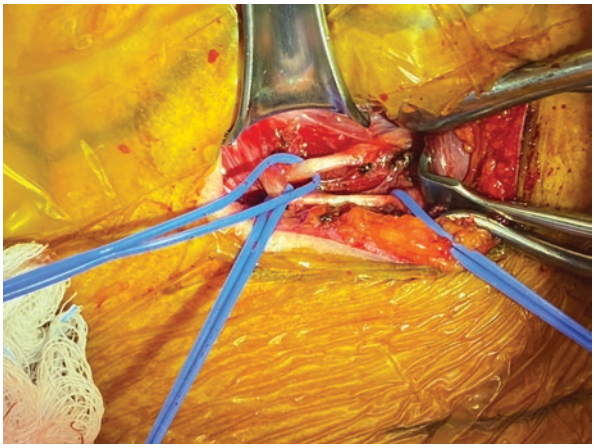


Fig. 16.10 Posterior mobilization of the hypoglossal nerve allows for placement of a vein loop

forceps and a right-angle dissector are used to pass the stimulation lead cuff circumferentially around the exposed nerve. The electrode is then anchored to the digastric tendon in standard fashion (Figs. 16.11 and 16.12).

Lead Tunneling, IPG Insertion, and Closure

First, a trocar is inserted from the chest incision and tunneled up to the neck incision. Because there is no infraclavicular incision, or halfway point, it is important to maintain constant palpation of the clavicle as a landmark to ensure appropriate tunneling of the trocar superficial to the clavicle and into the neck incision itself. Once the distal tip of the trocar is in the neck incision, the stimulation lead is then attached to the trocar and tunneled inferiorly down to the chest incision, and then

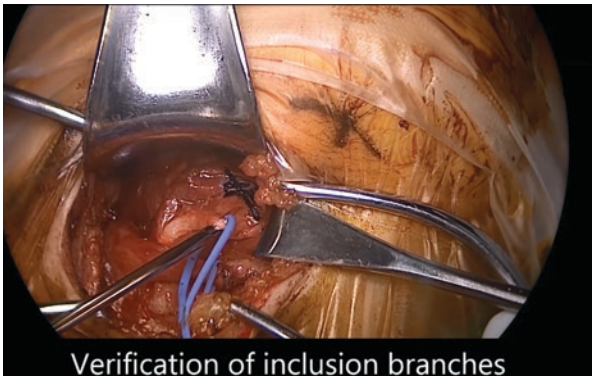


Fig. 16.11 Verification of the inclusion nerves using the Prass nerve stimulator

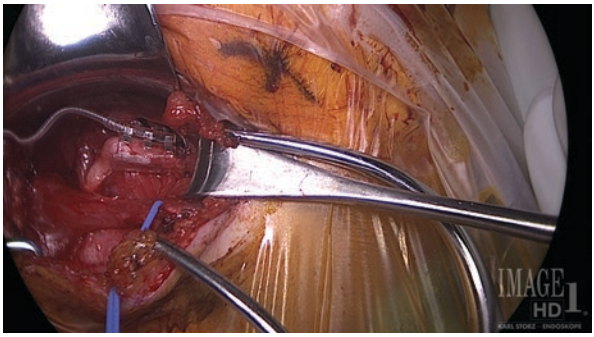


Fig. 16.12 Placement of stimulator cuff around the inclusion branches of the hypoglossal nerve

both the stimulation and sensor lead are inserted into the IPG similar to the adult technique. The device is interrogated to ensure the tongue protrudes in an acceptable manner. The previously placed 2-0 silk stitches are then passed through the IPG. The IPG is placed into the chest incision and the silk stitches are tied down allowing the IPG to sit snugly at the top of the pocket. If the sutures are secured at the superior extent of the raised flap, they should pull the IPG superiorly as they are tied down (Fig. 16.13).

The incisions are then closed in a multilayered fashion. A Tegaderm (3 M, St. Paul, MN) and non-occlusive gauze over the submental incision is left in place for 7 days. A postoperative chest film is completed to rule out pneumothorax.

The results of the first 20 adolescents with DS to undergo HGNS within the FDA study was reported in 2019. Data showed HGNS was effective in acutely reducing AHI. There was improvement in OSA-18 scores that reflected good patient tolerance of the device as well as caregiver satisfaction with the therapy. The median percent reduction in AHI compared to pre-operative AHI was 85%, and 70% of patients were corrected to mild OSA [25].

There were two notable events requiring revision surgery. In the first case, there was extrusion of the stimulating lead wires through the submental incision. This occurred approximately 3 months after surgery and the patient had been frequently picking at his incision site. Since then, the surgical dressings over the multilayer

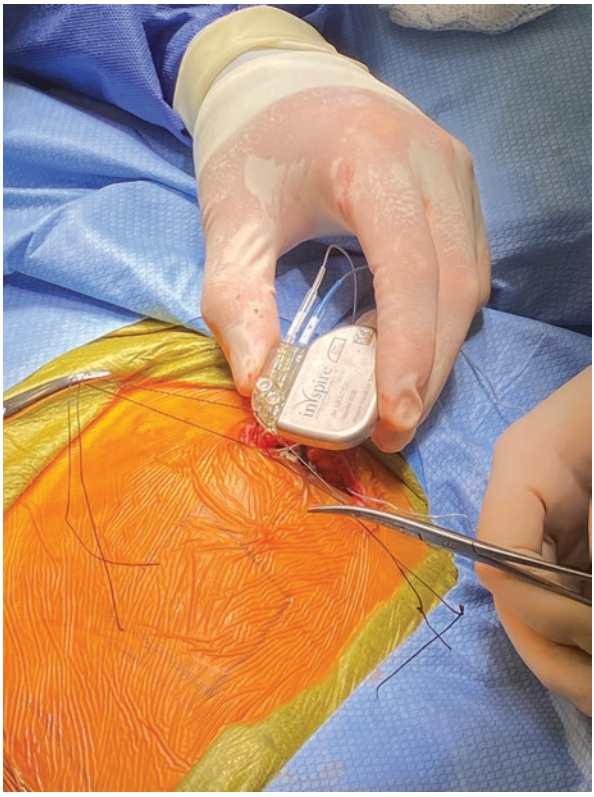


Fig. 16.13 The silk stitches are passed through the IPG lead and once the lead is placed into the chest pocket, the silk stitches are tied down

closures stay on for additional week post op. We have found temporarily covering the wound with a non-adherent dressing and adhesive bandage to be adequate to break the disruptive habit of picking.

The second adverse event was experienced following the implantation of a new, MRI-conditional version of the Inspire device. The sensor lead was not fully inserted into the implantable pulse generator (IPG) processor at the time of surgery despite apparent full insertion and good signal on interrogation of the device. We hypothesize that a small air bubble at the insertion site prevented full insertion. Since that time, holding pressure on the electrode to prevent any slippage while it is screwed in place helps to minimize this complication.

The frequent PSGs and follow ups in the post-operative period proved helpful in allowing us to intervene on patients whose electrode placement required revised configuration of the device around the hypoglossal nerve branches to optimize therapy. Higher voltages during their 2-month PSG titration were not achieving optimal results, therefore further interrogation of device settings was pursued. This led to reconfiguring of the device via widening the pulse width and rate of pulsation. This permitted a lower voltage to achieve better tongue protrusion and improvement of excursion of the tongue on DISE.

There are questions that still remain with regards to OSA in the pediatric DS population. With regards to the HGNS, the final results of the FDA study are pending. We wonder how stable this implant is over time as patients continue to grow and develop. We also wonder if there are other pediatric populations that this surgery is indicated for. Breslin et al's study showed an AHI >1.5 had neurocognitive deficits in the DS population compared to those without, but is that achievable for all patients? Will multimodality treatments both surgical and medical be required to optimize a patient with severe OSA? Future studies will need to evaluate what is a "successful" AHI reduction for patients with OSA and DS with regards to neurocognitive function.

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Chapter 17
Daytime Polysomnography in Upper Airway Stimulation

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Contents

Introduction

In patients with obstructive sleep apnea (OSA) treated with upper airway stimulation (UAS), the device is activated with standard settings approximately 4–6 weeks after implantation. The device will be slowly up-titrated at home until patient's symptoms such as decreased sleep quality, daytime sleepiness and snoring have

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improved. An in-lab overnight titration polysomnography (PSG) is subsequently performed once patients are accustomed to the stimulation and subjective symptoms have improved. The main purpose of the titration is to establish a comfortable but effective device setting to maintain upper-airway patency during sleep. This titration is manually performed by a trained sleep technician. During this titration the UAS device settings are optimized and titrated until respiratory events are normalized. Electrode configuration, stimulation amplitude and stimulation pulse width and rate can be adjusted. The final settings should minimize the occurrence of obstructive events and should not cause arousals [1].

Traditionally titrations are performed in-lab and overnight which is logistically challenging and expensive. The regular shift from working during the day to working through the night time has serious negative effects on the somnologist's chronobiology and biorhythm. The technologist who performs the titrations is the day after the titration not available for a day time shift, while many technologists for a variety of reasons are not available for night titrations anyhow.

Another havoc presented itself during the COVID-19 pandemic. Sleep laboratories were often imposed to resign overnight hospital beds due to shortages. As a result overnight sleep studies were often postponed resulting in long waiting lists. Also the growing amount of patients with UAS device asks for a more accessible way to perform titrations.

An alternative for an overnight titration is a daytime titration. Several studies have investigated the role of a daytime PSG in diagnosing OSA, concluding that a daytime PSG is a viable and effective alternative [2–4]. Other studies have investigated the role of a daytime PSG in CPAP titrations, concluding that a daytime PSG is a useful tool for CPAP titration [5–8].

A daytime PSG is a valuable alternative for an overnight PSG to perform titration in the context of UAS optimization. The benefit of a daytime PSG for titration is that sleep technicians do not have to work during the night and sleep studies will not have to be postponed due to bed and staff shortage.

Methods

For the titration, patients are admitted the night prior to their daytime titration PSG and instructed not to sleep and not to consume caffeine, nicotine or alcohol during the night. The next morning the UAS device system is checked and subsequently all components are applied to perform the PSG. At 08:00 a.m. patients are asked to go to sleep. Patients sleep in a soundproof room with no daylight. The PSG is observed by a sleep technician, who at the same time performs the titration. The sleep technician checks if all sleep stages are reached while the optimization process takes place.

Polysomnography

A standard polysomnography (SomnoscreenTM, SOMNOmedics GmbH, Randersacker, Germany) was performed in all patients. To determine the stages of sleep, an electroencephalogram (F3, F4, C3, C4, M1, M2, O1, O2), electro-oculogram and electromyogram of the submental muscle were obtained. Nasal airflow was measured by a nasal cannula/ pressure transducer inserted in the opening of the nostrils. An oronasal thermal flow sensor was used to determine the difference between the temperature of exhaled and ambient air to estimate airflow and detect mouth breathing. Arterial blood oxyhemoglobin was recorded with the use of a finger pulse oximeter. Thoracoabdominal excursions were measured qualitatively by respiratory effort belts placed over the rib cage and abdomen. Body position was determined by a position sensor, which differentiates between the upright, left side, right side, prone and supine position. Limb movements were detected with an anterior tibial electromyogram with surface electrodes. Electrocardiography was performed to score cardiac events and snore sensor was applied for occurrence of snoring.

Scoring

The sleep stages are scored manually by an experienced sleep investigator in 30-s epochs according to the American Academy of Sleep Medicine (AASM) scoring manual, with N3 representing slow wave sleep. Both daytime PSG and follow-up PSG were scored by the same sleep technician and neurosomnologist.

Titration

The main purpose of titration is to optimize the UAS device settings until respiratory events are eliminated or reduced to a clinically satisfactory level. The sleep technician pays attention to several titration parameters such as amplitude, polarity and stimulation duration. The sleep technician starts the UAS therapy once the patient is in consolidated sleep and the individual start delay of the UAS device has expired. The stimulation level starts with 0.2 V amplitude below the functional threshold and is therefore unlikely to provoke an arousal. The stimulation setting is increased with 0.1 V or 0.2 V amplitude when four or more serial obstructive events or loud ambiguous snoring occur. The patient is observed in all non-rapid eye movement (NREM) sleep stages and REM sleep, preferably containing REM sleep in supine position, for optimal titration settings. The titration is finished when the patient slept for 30 minutes straight with the final settings, ideally with an AHI <5.

Preferably these 30 minutes contain rapid eye movement (REM) sleep and sleep in supine position. When this is not achieved, the sleep technician ends the titration when the patient has slept through at least two full sleep cycles.

Discussion

This is the first prospective study which demonstrates that a daytime PSG to perform titration is a feasible alternative for a conventional overnight titration for OSA patients with UAS therapy. Patients slept significantly shorter during the daytime PSG, nevertheless this was enough time to complete the titration successfully with 30 minutes sleep in final therapeutic settings in 84.2% of the patients. Furthermore, 94.1% of the patients had a positive experience with the daytime titration and did not experience any discomfort. Respiratory OSA outcomes were significantly reduced during titration and were maintained at the 12-months follow-up.

To the best of our knowledge, no other study has investigated the role of daytime PSG for titration of UAS. A few studies have already proven that daytime PSG is an appropriate procedure for titration of CPAP [2, 5, 6, 8, 9]. The American Academy of Sleep Medicine (AASM) clinical practice guideline states that a CPAP titration should be carried out for at least 3 hours during NREM and REM sleep in supine position [10]. This is comparable to our study where patients on average slept 3.4 ± 1.0 hours while all sleep stages were observed including REM in supine position in final settings in 31.6% of the patients.

To ensure patients were able to sleep during the daytime PSG, they were asked to stay awake the night before the titration. A concern might be that overnight sleep deprivation in OSA patients alters sleep architecture and AHI results. For example, Persson and Svanborg observed an increase of AHI in OSA patients after sleep deprivation, suggesting that daytime studies are not suitable to determine the severity of OSA [11]. In our study however, the daytime PSG was used to titrate the UAS therapy. Our results show that there are no significant differences between the AHI at the 12-months follow-up: 12.0 [6.7; 24.9] and the titration AHI 9.0 [3.3; 17.0] ($p = 0.158$). This means that the optimal settings found during titration were effective even with a possible altered AHI at the time of titration. On the other hand, a significantly shorter period of REM sleep was found during the daytime PSG 12.9 ± 8.1 compared to 24.7 ± 7.7 overnight PSG (% of TST) ($p = 0.007$). Since it is known that during REM sleep oxygen desaturation is more severe than during NREM sleep in patients with OSA, this could have underestimated the OSA severity during titration [12]. Again our results at 12-months follow-up showed no significant difference and therefore this argument had no influence on our titration. Also the supine body position often increases the severity of apneas during therapy. Our study did not correct for the effect of body position during the daytime PSG. However, no significant differences were found for % TST in supine position between baseline, titration and follow-up PSG.

Our experience with activation and titration has developed over the past few years. We know now it pays off to be flexible and to take more time to adjust and

find a therapeutic but comfortable setting for patients. Whenever patients report subjective improvements during the first few months, this implies good therapy response. The titration could then be postponed or in the future even be replaced by a PSG at home to confirm therapy response. In this study device settings changed based on titration outcomes in 47.4% of the patients, suggesting that in all other cases the optimal settings were already found previously. Potentially this would obviate the need for titration in certain patients. A recent study by Steffen et al. assessed the use of home sleep tests for the treatment-adjustment phase of UAS. They concluded that home sleep tests had clinical advantages and were useful as a second-line titration control method under several conditions [13]. In addition, in a recently published case study, Huyett and Stagnone described the use of pulse oximetry as an addition to home titration for UAS therapy optimization before actual in-lab titration. They also concluded that certain patients could possibly directly proceed to a home sleep test instead of in-lab PSG titration [14].

When comparing sleep architecture, sleep efficiency was similar for the daytime PSG compared to the overnight follow-up PSG ($p = 0.177$). These results are comparable with Miyata et al. who also found no significant difference for sleep efficiency when comparing a daytime PSG with an overnight PSG for diagnosing OSA [10]. Sleep latency was significantly shorter during the daytime PSG, with 3.0 [1.1; 10.0] minutes compared to 7.6 [5.8; 17.0] minutes overnight. The overnight sleep latency is comparable with a normal sleep latency for healthy people between 50 and 64 years [15]. Sleep deprivation the night before titration might explain the shorter sleep latency during the daytime PSG [16]. No significant difference was found for N2 and N3 sleep during the daytime PSG compared to the follow-up overnight PSG. The amount of N2 and N3 sleep found in this study is similar to the study of Boulos et al. who investigated sleep architecture in healthy people between 50 and 64 years. The independent effect of OSA on sleep architecture remains unclear. Shahveisi et al. found that OSA independently has the tendency to increase N1 sleep [17]. This perhaps could explain the significant difference we found in the amount of N1 sleep during the daytime PSG 7.8 [6.1; 13.2] % of TST compared to the overnight PSG 4.5 [2.2; 5.0] % of TST ($p = 0.003$). Titration was performed during the daytime PSG meaning that therapy was not consistent resulting in occasional OSA compared to the follow-up overnight PSG where therapy was used the entire night.

We found similar results regarding respiratory outcomes with UAS therapy during titration and 12-months follow-up compared to similar larger studies. First, the results of the recently published ADHERE study show a median AHI reduction from 32.8 [23.6; 45.0] events per hour at baseline to 9.5 [4.0; 18.5] events per hour after 12 months [18]. These are similar to our results; a reduction in AHI from 40.4 [34.6; 46.9] events per hour at baseline to 12.2 [6.7; 24.9] events per hour after 12 months. In the original STAR trial, the AHI decreased from 28.2 events per hour at baseline to 8.7 events per hour at 12 months [19]. Furthermore, device usage in our study (48 [42; 54] hours per week) was comparable to a similar study (47.0 [38.5; 52.0] hours per week after 6 months) [13].

The growing amount of patients using UAS therapy asks for a more accessible way to perform titrations. Performing these titrations during the night makes it very

labor-intensive and expensive. The technician is subsequently not available for the day shift and many sleep technicians dislike and/ or are not available for night shifts because of understandable personal circumstances. The benefit of a daytime PSG is that more titrations can be performed and sleep technicians do not have to work during the night. The implications of performing daytime PSG for titration include being able to perform more titrations with shorter waiting time and less labor-intensive work for sleep technicians. Patients positively experienced our daytime study and were willing to repeat it in the future if necessary.

Daytime titrations are a valuable and viable alternative for conventional overnight titrations. Our findings have led to the implementation of daytime titrations as standard of care in our hospital. This contributes to easier logistics and better work circumstances for sleep technicians without jeopardizing titration quality.

Appendix

Appendix 1 Excluded Patients for Analysis (n = 4)

Record number	Reason exclusion
110001	Technical interruptions, not able to register 30 minutes of continuous sleep.
110002	Technical interruptions, software failure (update and flatline signals). No setting found for functional therapy.
110007	Connection problems IPG, therefore continual repositioning and no entire sleep cycle registered.
110021	Connection problems IPG, therefore frequent awakenings and no NREM 3 and REM sleep.

IPG Implantable pulse generator, *REM* rapid eye movement, *NREM* non rapid eye movement

Appendix 2 UAS Device Polarity Setting and Amplitude Outcome

Patient (n = 19)	Setting pre-titration Amplitude in V	Setting after titration Amplitude in V	Amplitude changed? (yes/no)
1	2.3 Unipolar (0 - 0)	2.3 Unipolar (0 - 0)	No
2	2.1 Bipolar (+ - +)	1.6 Unipolar (0 - 0)	Yes[a]
3	1.3 Bipolar (+ - +)	1.1 Bipolar (+ - +)	Yes
4	2.3 Bipolar (+ - +)	2.5 Bipolar (+ - +)	Yes

Patient (n = 19)	Setting pre-titration Amplitude in V	Setting after titration Amplitude in V	Amplitude changed? (yes/no)
5	0.8 Bipolar (+ - +)	1.3 Bipolar (+ - +)	Yes
6	1.2 Unipolar (0 - 0)	2.6 Bipolar (+ - +)	Yes[a]
7	1.1 Unipolar (0 - 0)	1.8 Bipolar (+ - +)	Yes[a]
8	2.1 Bipolar (+ - +)	2.1 Bipolar (+ - +)	No
9	2.3 Bipolar (+ - +)	2.3 Bipolar (+ - +)	No
10	0.9 Bipolar (+ - +)	0.9 Bipolar (+ - +)	No
11	1.7 Bipolar (+ - +)	1.7 Bipolar (+ - +)	No
12	1.7 Bipolar (+ - +)	0.9 Unipolar (0 - 0)	Yes[a]
13	2.1 Unipolar (- 0 -)	4.4 Bipolar (+ - +)	Yes[a]
14	2.6 Bipolar (+ - +)	2.6 Bipolar (+ - +)	No
15	3.9 Bipolar (+ - +)	3.9 Bipolar (+ - +)	No
16	3.1 Bipolar (+ - +)	3.1 Bipolar (+ - +)	No
17	1.0 Bipolar (+ - +)	1.0 Bipolar (+ - +)	No
18	1.2 Bipolar (+ - +)	0.7 Unipolar (0 - 0)	Yes[a]
19	2.4 Bipolar (+ - +)	2.4 Bipolar (+ - +)	No

[a]Polarity setting also changed

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Chapter 18
Phrenic Nerve Stimulation in Central Apnea

Henrik Fox

Contents

Background of Phrenic Nerve Stimulation

Documented first ideas on extrinsic diaphragm movement initiation through phrenic nerve stimulation date back into 1783 and were first postulated by the German physician Christoph Wilhelm Hufeland. Hufeland recommended this approach in use for asphyxia therapy initially. In 1855 French neurologist Duchenne de Boulogne had a similar idea, but none of the two pioneer proposals were ever tried in a clinical setting. Nonetheless, one-year later Hugo Wilhelm von Ziemssen first performed diaphragm pacing as asphyxia treatment in a 27-year-old patient with charcoal fumes that rhythmically faradized her phrenic nerves and through this approach he

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saved her life. In 1872 Duchenne then declared that phrenic nerve stimulation would be the “best means of imitating natural respiration”.

This development process was interrupted because of advances in mechanical ventilation, why in physician’s opinion mechanical ventilation was considered more effective than phrenic nerve stimulation. Nevertheless, in 1948 phrenic nerve stimulation was revived by Sarnoff et al. at Harvard University in Boston, Massachusetts, who performed their research on dogs. This group also conducted experiments on a five-year-old patient with phrenic nerve stimulation that suffered from complete respiratory paralysis after cerebral aneurysm rupture. They called their process electrophrenic respiration and Sarnoff and his group guided external, artificial respiration stimulation on the patient for a total of 52 hours.

The next step of phrenic nerve stimulation happened in 1968, when physicians John P. Judson and William W. L. Glenn researched on radiofrequency transmission to “adjust the amplitude of stimulation, and to control the rate of stimulation externally”. In cooperation they developed a commercially available device in the early 1970s and this Breathing Pacemaker received FDA pre-market approval in 1987 for “chronic ventilatory support because of upper motor neuron respiratory muscle paralysis”. In the 1980s a “sequential multipole stimulation” device was developed in Tampere, Finland and this phrenic nerve stimulation technology was commercialized in Europe in 1990.

Evaluations and research on phrenic nerve stimulation in the 1990s explored long-term phrenic nerve stimulation and the researchers stated that phrenic nerve pacing is a valid option “for the properly screened patient but that expense, failure rate, morbidity and mortality remain excessive and that alternative methods of ventilatory support should be explored”.

Up todate, the United States Medicare system declares indication of phrenic nerve stimulation for “selected patients with partial or complete respiratory insufficiency” and phrenic nerve stimulation “can be effective only if the patient has an intact phrenic nerve and diaphragm”.

With this understanding, diagnoses for phrenic nerve stimulation indication are in patients with spinal cord injury, central sleep apnea, congenital central hypoventilation syndrome (i.e., Ondine’s curse), as well as diaphragm paralysis. These devices are surgically implanted, and the electrode is surgically placed around the phrenic nerve, which can either be performed in the neck area, i.e., cervically, or in the chest, i.e., thoracically, as preferably executed in modern procedures. Notably, these implantation practices require invasiveness and surgical tissue preparation that are accompanied by unavoidable risks such as bleeding, infection, nerve and vessel injury, scar tissue formation and wound healing disorders potentially. Approaches like minimal-invasive methodologies through the use of a thoracoscope have been designed to reduce the risks and invasiveness for phrenic nerve electrode and device stimulation implantation.

Canada based company Lungpacer Medical developed their transvenous device on the premises that traditional mechanical ventilation, although lifesaving, can be harmful, because traditional mechanical ventilation requires sedation and misuses

the diaphragm muscle which leads to atrophy. Moreover, positive-pressure ventilation can damage the lungs in the sense of ventilator induced lung injury and traditional mechanical ventilation bears the risk to cause ventilator associated pneumonia. In addition to that traditional mechanical ventilation through endotracheal tubes is usable for a limited time only and further steps of long-term traditional mechanical ventilation require tracheostomy that comes with a high risk of acquiring nosocomial bacterial and fungal infections [1]. They promise through their intravenously inserted catheter and through rhythmical stimulation of the phrenic nerve to help patients that have failed or that would typically fail to be weaned of mechanical ventilation or are prone to become ventilator dependent. The company promises that their phrenic nerve stimulation would prevent or even reverse diaphragm muscle atrophy and increase weaning success from mechanical ventilation more often. Phrenic nerve stimulation uses the background of physiologic negative pressure ventilation which should avoid volume or pressure trauma to the lungs and is believed to come with a more physiological lung-protective respiration pattern. Lungpacer promises that their therapy through transvenous phrenic nerve stimulation is lung protective, patients have a chance to faster recovery, have a shorter stay on intensive care units, and they promise improved health outcomes and lower healthcare costs. With their technique, in May 2020, Canada based company Lungpacer Medical, gained FDA approval for phrenic nerve stimulation with emergency use for their device.

Founded in the year 2006 the company Respicardia Incorporation, based in Minnetonka, Minnesota, USA developed a fully transvenously implantable device for phrenic nerve stimulation. Their focus is in particular on treatment of predominant central sleep-disordered breathing. The fully transvenously implantable remedē® device is still undergoing clinical testing in various trials and treatment of predominant central sleep-disordered breathing is delivered through nocturnal unilateral phrenic nerve stimulation. The system includes a stimulation lead that is placed in the so called epicardiophrenic vein that accompanies the phrenic nerve along the left side of the heart.

Phrenic Nerve Stimulator Device Implantation

Device implantation can be performed in local anesthesia only [2]. Device pocket formation is made very similar to traditional pacemaker implantation in the infraclavicular area, but in contrast to traditional pacemaker implantation where most devices are placed into the left pectoral area, remedē® device implantations are preferably done into the right pectoral area [2]. This allows a second device implanted (pacemaker, ICD, CRT) on the left side additionally [2].

As first described by Augostini [2], the remedē® system consists of a stimulation lead, a sensing lead and the impulse generator device itself [2]. Guide wires are inserted after subclavian vein puncture and a guiding catheter follows the wire into the left brachiocephalic vein under fluoroscopy surveillance. Anatomy is portrayed

through contrast dye application to identify the bifurcation into the epicardiophrenic vein. Through introduction of the wire into the epicardiophrenic vein, which closely accompanies the phrenic nerve, the stimulation lead is advanced in a position along the heart using a typical "over-the-wire" technique. Because of the close neighborhood with the nerve, phrenic nerve stimulation becomes feasible with this transvenously implanted stimulation lead.

Alternatively, or if positioning of a stimulation lead in individual cases is not possible, likewise for anatomical reasons for instance, a spiral stimulation lead can also be placed into the right brachiocephalic vein. This right-sided position allows phrenic nerve stimulation too, but usually requires more power output and the right sided position may imply a less fixed positioning. The right-sided stimulation lead is helically modeled, and after venography it is implanted into the superior vena cava using a stylet to modify its curve during the implantation procedure.

Moreover, an optional sensing electrode can be placed into the azygos vein to monitor respiration and to adjust the stimulation therapy. In general, a sensing lead is optional to implant, and available studies show no difference in therapy effectiveness or safety outcomes in patients with or without a sensing lead of that setting [3], but a proposed benefit commending a sensing lead implantation is that remedē® system software diagnostic tools may display information of higher respiratory signal quality, which may reduce the number of patient visits required for therapy titration [3]. Placement of the sensing electrode is also handled transvenously through placing a wire and guiding catheter into the azygos vein, as close to the diaphragm as possible. Positioning is surveyed through multi-plain fluoroscopy also [3].

Finally, all electrodes are plugged into the remedē® device following device and electrodes are suture fixated in the pectoral pocket. Before closing and completion of the procedure, the device and its stimulation functions are tested through sensing touch-feeling of actual diaphragm movement on the patient. Typically, a 20 Hz, 150-μs pulse width of 4 mA of current cause perceptible diaphragmatic contraction [4]. Importantly, a system check is essential to identify undesired feeling sensations remote from the diaphragm area that require adjustment of stimulation or even stimulation lead repositioning in scarce cases. These ambiences are called remote extra respiratory sensations (ERS), that are defined as twitching, tingling, or verbose discomfort in the ipsilateral shoulder or neck during diaphragmatic contraction [4].

If everything is set up to the patient's satisfaction the procedure is closed following skin suture closure and wound dressing. Further device interrogations are conducted through an external programmer with placement of an interface on the skin were the remedē® device is situated.

In an early study of 2011 implanted heart failure patients that had been followed for 4 years, the authors not only studied device implantation procedure at their high-volume center, but also analyzed battery longevity and replace procedures of this novel technology of phrenic nerve stimulation [5].

Therapy Application

Programming of the remedē® device allows not only definition of stimulation hours during the night, which usually are programmed along with the usual sleep hours the patient is used to. Moreover, programming allows individual modulation of simulation intensity in all possible sleeping positions. Different phrenic nerve stimulation intensities can be programmed for supine, prone, right- or left sided position and the stimulation therapy interruption is assessed when the patients rise into a sitting position. In addition to that the external programmer involves readouts of diagnostic parameters that reflect therapy efficacy, including the preferred sleeping positions and stimulation effectiveness in the individually preferred sleeping position. With the external programmer electrode configuration (cathode– anode electrode pair) is regulated to achieve optimal therapy delivery and diaphragm movement but avoiding undesired remote sensations [4]. Moreover, diagnostics provide an activity monitor that illustrates the patient's movement quantity over a complete day which is meant to show improvements of daily physical activity through nocturnal phrenic nerve stimulation.

Phrenic nerve stimulation tolerance is individually variable in patients and patients may learn to engage with therapy application, beginning with low stimulation intensity in the early phase. As soon as patients synchronize breathing with the programmed stimulation breathing rate and depth, therapy tolerance is usually good, but this process of learning to accept stimulation therapy is individually different. For this reason, the device comes with a nightly titration to begin with a lower stimulation intensity during dozing off into sleep and stimulation intensity would than increase based on individual programming during the night to deliver most effective stimulation to overcome breathing cessations and apneas of central sleep apnea.

Central Sleep Apnea and Phrenic Nerve Stimulation

Prevalence of Central Sleep Apnea

The prevalence of central sleep apnea significantly varies with the population that is examined. In the general population central sleep apnea is a rare phenomenon, but in patients with neurological or renal disorders and in particular those with cardiovascular disease and heart failure, central sleep apnea prevalence rises up to 30–50% [6, 7]. Also, opioid users develop central sleep apnea and there is also an uncommon idiopathic form of central sleep apnea.

Diagnostic of Central Sleep Apnea

Central sleep apnea is diagnosed and determined by overnight, multichannel cardiorespiratory polysomnography recording [8]. Herein, thoracic and abdominal movements are recorded and interpreted by a trained health care professional or sleep physician to ascertain the diagnosis of central sleep apnea. Central sleep apnea is defined as an apnea with open airways or hypopnea with no airway obstruction, why centrals arise from the absence of central breathing control according to definitions of the American Academy of Sleep Medicine [8]. The number of respiratory events is summarized in an index including the total of apneas and hypopneas per hour, the apnea-hypopnea-index [8].

Mechanisms and Clinical Impact of Central Sleep Apnea

Central sleep apnea derives from a temporary interrupted central (brainstem) derived respiratory initiative that leads to breathing cessation and the absence of respiratory muscle activity as well as airflow [9]. Central sleep apnea is characterized by the absence or a decrease in inspiratory effort and a lack of typical obstructive features, such as flattening, paradoxical thoracoabdominal movements or snoring [9]. In patients with heart failure central sleep apnea often appears in a periodic breathing pattern named after the two physicians to first describe this respiratory pattern, John Cheyne [10] and William Stokes [11]. To be absolutely precise, very first description dates back into 1781 of James Hunter [12] which makes the historically correct naming of this breathing pattern: Hunter-Cheyne-Stokes respiration [10–12].

Hunter-Cheyne-Stokes respiration [10–12] appears as repeated, periodic breathing cycles of deep and rapid crescendo-decrescendo ventilation with phases of hyperventilation that are followed by an apnea and cross over from hypopnea. It is characterized by temporary cessation of central respiratory drive, resulting in cessation of respiratory muscle activity and airflow.

Central sleep apnea on the whole is associated with a wide spread of neurohumoral and hemodynamic consequences that are believed to be unfavorable to the failing heart [13, 14]. Although insufficiently studied so far, underlying pathophysiology of central sleep apnea and its effect on heart failure is unsatisfactorily understood yet [15]. It is known that central sleep apnea is associated with impaired quality of life as well as deterioration in clinical outcomes [7, 15, 16].

Studies have identified predictors that promote central sleep apnea development in heart failure patients, such as male sex, greater New York Heart Association functional class, lower left ventricular ejection fraction, hypocapnia awake ($PaCO2 < 38$ mm Hg), atrial fibrillation, greater N-terminal prohormone of brain natriuretic peptide (NT-proBNP) level, and cardiac dysrhythmia, including ventricular arrhythmia. Importantly, there is no questionnaire that would allow a reliable screen to detect central sleep apnea in heart failure [17].

Central sleep apnea connotes of insomnia, fatigue, daytime sleepiness, nightly awakenings, poor sleep quality, shortness of breath, paroxysmal nocturnal dyspnea, nocturia, hypoxemia, difficulties to concentrate [6] and reduced functional physical performance capacity [18]. Often the spouse or the partner discovers breathing cessations of the person concerned during the night and while sleeping without the patient self-noticing. Central sleep apnea favors cardiac dysrhythmia occurrence [16, 19, 20]. The complexity in this context is that heart failure itself, but also central sleep apnea, share these identical symptoms, why often patients and physicians attribute heart failure to be responsible for the symptoms, why central sleep apnea is frequently overseen. Moreover, prognosis is even worse in heart failure when patients have the comorbidity of central sleep apnea additionally [21].

Central sleep apnea has additional adverse impact, in particular in heart failure patients, because central sleep apnea attributes to hypoxia which triggers oxidative stress, systemic inflammation and endothelial dysfunction, which then further contributes to heart failure progression [22]. Also, hypertension and in particular pulmonary hypertension upgrowth has been linked to central sleep apnea [23]. In addition, during the alternating central sleep apnea phases of hyperventilation sympathetic nerve activation is the consequence, which account for arousals and impaired sleep quality in patients and increased sympathetic tone promotes cardiac arrhythmia [22]. Adding to this, central sleep apnea in heart failure patients comes with impaired functional physical performance capacity [24]. All these effects of central sleep apnea contribute to worse prognosis for the combination of central sleep apnea and heart failure and hypoxemic burden has been shown to be the most robust predictor of mortality in this context [25, 26]. However, only few data is available about the potential of the new emerging treatment of phrenic nerve stimulation to challenge these surrogate endpoints and mortality so far.

Clinical Trials and Outcome Parameters on Phrenic Nerve Stimulation with the Remedē® Device

Around the hour of birth of the remedē® device a first multicenter clinical trial of 57 patients of whom 31 patients had heart failure reported statistically significant reduction of central respiratory events after activation of the remedē® device compared to the control night before phrenic nerve stimulation [27]. Initial apnea-hypopnea-index was 50 ± 15/hour and mean central apnea index was 28 ± 14/hour. After initiation of phrenic nerve stimulation with the remedē® device polysomnography reevaluations at 3 and 6 months documented a more than 50% apnea-hypopnea-index reduction with an apnea-hypopnea-index of 22 ± 14/hour ($p < 0.01$) and a central apnea index down to 5 ± 9/hour ($p < 0.01$). Moreover, this study also found statistically significant improvements in quality of life for patients under phrenic nerve stimulation, measured through the Minnesota Living with Heart Failure questionnaire ($p < 0.01$). Furthermore, New York Heart Association functional class improved ($p < 0.01$).

The remedē® system pivotal trial led to remedē® FDA approval in 2017 [28]. This prospective, randomized clinical trial tested the endpoints of primary effectiveness in an intention to treat at 6 months through comparison of the proportion of subjects with a ≥ 50% reduction of the apnea-hypopnea-index between treatment and control group. In addition to that it tested primary safety as an endpoint, defined as freedom from serious adverse events associated with remedē® system implant in an intention to treat analysis at 12 months and secondary endpoints were analyzed such as central-apnea-index, apnea-hypopnea-index, arousal index, percentage of rapid eye movement sleep, patient global assessment, oxygen desaturation index and the sleep questionnaire Epworth Sleepiness Scale. The trial randomized 151 patients, 73 into treatment group and 78 into control group. Control group had the remedē® system implant, but not activated for 6 months, while phrenic nerve stimulation was activated in the treatment group 1 month after device implantation. Mean age was 65 ± 12 years, 86% male, body mass index 31 ± 5 kg/m^2. 42% had a concomitant cardiac device implanted.

In the intention to treat at 6 months endpoint analysis for primary effectiveness of comparison of the proportion of subjects with a ≥50% reduction of the apnea-hypopnea-index, the treatment group had a 51% lower apnea-hypopnea-index, while the apnea-hypopnea-index was lower in the control group by 11% ($p < 0.01$). Regarding safety the study reports a 97% implant success rate, with a 3.4% lead revision rate. The average duration of an implantation procedure was 2.7 ± 0.8 hours. No deaths related to the implantation procedure, the system or therapy delivery is reported.

Moreover, all secondary endpoints analyzed are reported to have met statistical significance with a p value <0.01 for central-apnea-index, apnea-hypopnea-index, arousal index, patient global assessment, oxygen desaturation index and the Epworth Sleepiness Scale in comparison of treatment and control group, only percentage rapid eye movement sleep was improved by 2.4 ± 7.9% through remedē® therapy with a p value of 0.02.

In a subgroup analysis of heart failure patients, the proportion of subjects with a ≥ 50% reduction of apnea-hypopnea-index was 58% in the treatment group versus a 4% reduction for the control group ($p < 0.01$). With these findings the authors emphasize that remedē® therapy is not only effective and safe, but therapy delivery is provided throughout the night, independently from the patients' adherence, because patients' adherence is a known major issue in particular in mask-based positive airway pressure therapies.

These results have been shown to be sustained throughout 12 months with persisting effectiveness and safety in a long-term follow up of the initial pivotal trial study population [29]. This investigation reported even a further ≥50% reduction of the apnea-hypopnea-index after 12 months of therapy of 67% (95% confidence interval 53–78%) while the former control group after 6 months of therapy reached 55% to reduce the initial apnea-hypopnea-index by ≥50% (95% confidence interval 43–67%). In this investigation patient global assessment was found to be improved in 60% of the treatment group patients after 6 months of phrenic nerve stimulation

therapy and this study reports these improvements to persist throughout 12 months. The authors report reproducibility of treatment efficacy through assessment in the former control group that had the implanted remedē® device activated sixth month later than treatment group.

Serious adverse events within the 12 months of follow-up occurred in 13 patients in the treatment group and 12 patients in the control group. The study's clinical events committee reviewed all events which occurred as vascular disease, atrial fibrillation, atrial flutter, chest pain, complication of heart failure therapy, coronary artery disease, heart failure, myocardial infarction, pericardial effusion, sick sinus syndrome, sudden death or sustained ventricular tachyarrhythmia and no direct relationship in context with delivered phrenic nerve stimulation as determined by the committee.

This analysis was then extended for a 36-month long-term follow up to investigate whether remedē® phrenic nerve stimulation would preserve over a long-run therapy benefit and safety too [3]. Although this investigation followed the primary pivotal trial study population with an outpatient polygraphy examination at 36 months instead of an inpatient polysomnography, the investigators have been able to show sustainability of phrenic nerve stimulation even throughout 36 months of therapy application [3]. This study found then the proportion of treatment group patients achieving a $\geq$ 50% reduction of apnea-hypopnea-index with 60% at 6 months, 67% at 12 months, 64% at 18 months and 60% at 24 months. While this proportion seems to sustain at a level around two thirds of patients, more importantly after 24 months of phrenic nerve stimulation the percentage of rapid eye movement sleep further increased through ongoing therapy application from only 10% at baseline, through 14% at 6 months up to 19% at the 24 months follow up. In addition to that, the most robust predictor of mortality in heart failure patients with sleep apnea, hypoxemic burden is sustainably improved through phrenic nerve stimulation therapy application from initially 33 minutes of nocturnal oxygen saturation below 90% down to 15 minutes at 24 months [3].

There is little evidence, with indication that treatment of central sleep apnea may also improve left ventricular ejection fraction [30] and interestingly, this has been shown in this 36 months follow up trial too [3]. The investigators can show small but statistically significant improvements on left ventricular ejection fraction in the phrenic nerve stimulation treatment group throughout follow-up in the subset of heart failure patients [3]. They demonstrate the baseline left ventricular ejection fraction of 27% to improve in paired changes from baseline to 12 months by 4%, 18 months by 8% and by 6% at 24 months after therapy activation [3].

Implant procedure-, device- or therapy-delivery related serious adverse events through 24 months of follow-up have been assessed in this evaluation with a rate of 10% of patients affected with events like concomitant device interaction, lead component failure, lead dislodgment, lead displacement, implant site hematoma, implant site infection, impending pocket erosion, inadequate lead position, feeling sensation in an area remote from the diaphragm, noncardiac chest pain or elevated transaminases [3].

Phrenic Nerve Stimulation and Nocturnal Hypoxia

Trials have identified nocturnal hypoxemic burden to be the most robust predictor of mortality in heart failure patients with sleep apnea [25], why phrenic nerve stimulation therapy was tested for this benchmark also [26]. The remedē® phrenic nerve stimulator 36 months follow-up investigation has shown to drop nocturnal hypoxemic burden through phrenic nerve stimulation, measured as nocturnal oxygen saturation below 90%, from 33 minutes at baseline of down to 15 minutes at 24 months [3]. It is important to know that the threshold impacting mortality is a time limit of 22 minutes spend nightly with an oxygen saturation below 90%, as recently reported [25]. Through phrenic nerve stimulation it has been demonstrated that 50% of the treatment group patients who had a burden of more than 22 minutes of an oxygen saturation below 90% improved to a total of less than 22 minutes at 6 months follow up through phrenic nerve stimulation compared to 32% in the control group without phrenic nerve stimulation [26]. Hereby, the median nocturnal oxygen saturation came from below 90% at baseline to stay below 22 minutes at 6 months when phrenic nerve stimulation therapy was delivered in the full per protocol and heart failure populations analysis [26]. Another study of 24 heart failure patients that were enrolled outside the pivotal trial population also tested nocturnal hypoxemic burden and the impact of nightly phrenic nerve stimulation to address this mortality-relevant aspect in patients with heart failure and sleep apnea [18]. In that study hypoxemic burden, determined as time of oxygen saturation <90%, significantly improved from 81 ± 55.8 minutes at baseline up to 27.9 ± 42.8 minutes after 6 months of phrenic nerve stimulation therapy delivery ($p < 0.01$) [18].

Nevertheless, the actual impact on mortality in this population has to be tested in a large prospective mortality trial in the future for application of phrenic nerve stimulation.

Phrenic Nerve Stimulation and Physical Capacity

With these promising, but to date incompletely studied, clinical endpoints, more deeply looking towards survival and morbidity, even less is known whether phrenic nerve stimulation influences physical capacity in heart failure patients with central sleep apnea. For this background a prospective trial of 24 heart failure patients with typical physical capacity restrictions has been designed and conducted, investigating a typical cohort with a mean age of 67.1 ± 11.2 years and 88% male patients [18]. The study tested standardized 6-minute walk distance in this patient cohort at baseline and after 6 months follow-up using phrenic nerve stimulation. The study cohort started at an initial 369.5 ± 163.5 m 6-minute walk distance which after 6 months of phrenic nerve stimulation therapy statistically and clinically significantly improved up to 410 ± 169.7 meter; ($p = 0.035$). The clinical significance in this context derives from a large meta-analysis that illustrates that each 1-m increase

of 6-minute walk distance was associated with a 1% decrease for the risk of all-cause mortality but also cardiovascular events. This large study of more than 10.000 patients translates 6-minute walk distance to be significantly associated with mortality, making this endpoint markedly meaningful [31].

Device Specific Aspects

Battery Longevity and Exchange Procedure

In the very first study to investigate battery longevity and remedē® device phrenic nerve stimulator exchange procedure, the mean battery life duration was 4.2 ± 0.2 years until replacement became necessary, but this early data consisted of three patients only [5]. Nevertheless, this is the first independent description of device replacement procedures and in that study mean procedure time was 25 ± 5.1 minutes, and no radiation or contrast dye application was necessary with no major complications occurring in those first patients studied [5]. The total hospital stay for the replacement procedure was 2 days in total for all patients [5].

Challenges in Implantation Procedure

Although implantation success rates of 97% at first attempt for remedē® device phrenic nerve stimulator have been reported [28], phrenic nerve therapy implantation, in particular for the leads, can be challenging in individual cases [32]. In a single-center, high-volume center study of 27 heart failure patients with particular contraindications for masked-based therapies, indication for remedē® device phrenic nerve stimulator has been made [32]. This study investigated challenging cases and in seven of these provocative procedures lead implantation attempts (24%) required additional intravascular interventional facilities to achieve effective phrenic nerve implantation [32]. To gain full functionality of effective phrenic nerve stimulation in these special cases, additional techniques such as balloon angioplasty became inevitable [32].

Procedural venography revealed a large variety of vein anatomy and patients can have other vessels crossing or tributaring into the targeted epicardiophrenic vein. Vessel tortuosity and venous valves may complicate an implantation procedure, or the procedure can become unsuccessful, if no additional helping tools are available in addition to a common implantation approach. In particular, visualization of the targeted epicardiophrenic vein can be challenging in some cases making a guidewire placement impossible if contrast dye-based imaging cannot depict a path into the targeted epicardiophrenic vein. In this study, in 2 patients introduction of a guidewire was not possible because the ostium of the targeted epicardiophrenic vein

could not be identified [32]. The study reports of a rate of 25% to use angioplasty maneuvers for anatomical obstacles in these patients that had hampered a stimulation lead placement into the targeted epicardiophrenic vein [32]. Not only angioplasty techniques can be helpful to increase phrenic nerve stimulation lead implantation success, but also utilization of bare metal stents, originally designed for coronary interventions, can be helpful too. In this study bare metal stents were placed into the vein in one patient and only with this approach lead placement became possible [32].

In addition to that, implantation procedures, vein access and catheter placement can be hampered because of pre-existing leads of pacemakers, implantable cardioverter-defibrillators, cardiac resynchronization therapy or other transvenously implanted devices. Moreover, the prepositioned leads can also lead to adhesions within the brachiocephalic vein, making advancement of additional leads challenging. In this situation also conventional angioplasty balloons can be helpful, as used in this study and through their inflation passage past the prepositioned cardiac device leads became possible through implantation of intravascular interventional techniques to improve phrenic nerve stimulation lead placement in selected challenging patients [32]. In this study 23 leads (7 bipolar and 16 quadripolar) have only been placeable through additional use of intravascular interventional techniques, expanding implantation success of phrenic nerve stimulation lead placement [32]. Allover in this study no relevant complications occurred from application of interventional techniques to achieve a 93% phrenic nerve stimulation lead implantation success rate [32].

Conclusion and Outlook

In particular in cardiovascular patients the prevalence of central sleep apnea is high, adding up to about 50% of patients to have moderate to severe central sleep apnea. These are especially found in the cohort of patients with heart failure, and central sleep apnea shares typical symptoms with heart failure like fatigue, sleepiness, adynamia and distraction, making a diagnosis through anamnesis impossible. For this background, polygraphy screening is recommended.

Treatment of central sleep apnea can improve symptoms and is currently widely under scientific investigation. Phrenic nerve stimulation is a novel therapy option to treat predominant central sleep apnea, like the fully transvenously implantable remedē® device phrenic nerve stimulator, that has been shown to be safe and effective for predominant central sleep apnea treatment in long-term treatment, with recent follow-up data showing endured, secure and reliable therapy effects from 36 months to 5 years recently. The system is designed to deliver individualized, consistent, overnight therapy for predominant central sleep apnea through generation of a physiologic negative intrathoracic pressure, in contrast to established masked-based therapies that are based on positive airway pressure application.

Nevertheless, rationale of treatment of central sleep apnea and Hunter-Cheyne-Stokes-respiration is questioned, but presently it is part of current vital scientific discussion, because since the results of the "Treatment of Sleep-Disordered Breathing with Predominant Central Sleep Apnea by Adaptive Servo Ventilation in Patients with Heart Failure" (SERVE-HF) trial, with adverse events and increased mortality in the treatment group, some believe central sleep apnea is a compensatory mechanism to counter heart failure, why treatment is accused harmful. Whether the new principle of induction of physiologic intrathoracic negative pressures makes a difference, until today, no final answer is available in this debate.

However, cyclical episodes of apneas and arousals are associated with hypoxia and norepinephrine release, which are shown to contribute to myocardial ischemia and fibrosis, as well as progression in worsening of cardiac function and increased risk for atrial and ventricular arrhythmia occurrence. Presence of sleep apnea also induces a proinflammatory milieu and the presence of sleep apnea has been associated with an increased risk to develop dementia and worse diabetes control. Until now, it is not receivable where phrenic nerve stimulation will rank in and what its value in central sleep apnea treatment will position, in particular in its competition with established and less costly masked-based therapies. Moreover, traditional masked-based therapies come with an unbeatable advantage so far, that they bring the ability to not only resolve central respiratory events, but also obstructive respiratory events, while obstructive respiratory remain untreated when phrenic nerve stimulation is implanted.

Phrenic nerve stimulation has been proven to enhance quality of life and sleepiness is alleviated in patients treated in trials available, appraised through Epworth Sleepiness Scale, although questionnaires are known to have extensive limitations in detection of sleepiness in cardiovascular patients. Remarkably, the Minnesota Living With Heart Failure questionnaire shows impressive improvements in heart failure patients treated with fully implantable phrenic nerve stimulation and in polysomnography recordings, also REM sleep increases in available trials.

First trials are available on functional physical performance capacity under phrenic nerve stimulation suggesting beneficial impact.

Implantation of phrenic nerve stimulation device can be challenging and requires practice. Serious adverse events reported are comparable to other cardiac device implantation procedures. In individual cases implantation of phrenic nerve may be challenging, but procedures may be overcome through implementation of interventional techniques known from regular catheterization laboratories routine.

Replacement procedures are reported to be feasible, and performance appears comparable to other cardiac device replacements. Concomitant devices, that are present in about 50% of patients, seem to have no relevant interaction, appearing safe, but it may require individual adjustment of programming in either device in single cases.

Hypoxemic burden is documented to be the most robust predictor of mortality in heart failure patients with sleep apnea. Phrenic nerve stimulation has been shown to significantly reduce hypoxemia. Therapy acceptance of stimulation by patients

appears to be good and reports of patient requests to discontinue phrenic nerve stimulation are scarcely reported in available trials, although patient tolerance of phrenic nerve stimulation may require a specific patient learning process and patients often initially have to engage into stimulation.

First trials of phrenic nerve stimulation are promising, resulting in CE mark for the European Union, as well as FDA approval in 2017. Transvenous, unilateral phrenic nerve stimulation appears to be a safe and effective therapy to treat predominant central sleep apnea through direct stimulation of the phrenic nerve. This approach is believed to restore a more natural respiration pattern, leading to improved symptoms, sympathetic surges, and clinical outcomes. Nevertheless, more data is needed on the therapy and interactions with heart failure and comorbidities. In addition to that, battery longevity should be improved in further device generations and more investigations are required regarding exchange procedures, device handling in specific cases like potential dislocations or infections. Also, more data is needed on long-term effects and functional physical performance capacity and beyond all questions a mortality trial is warranted to test the impact of phrenic nerve stimulation on mortality.

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Chapter 19
Stabilizing Sleep Through Closed-Loop Acoustic Stimulation; Implications for Obstructive Sleep Apnea Treatment

Lucia M. Talamini

Contents

Sleep apnea and insomnia, both disorders with high prevalence in the general population, frequently co-occur. Indeed, 39–58% of sleep apnea patients report symptoms indicative of comorbid insomnia [1], while 43% of insomnia patients have co-morbid obstructive sleep apnea (OSA; as defined by an AHI of at least five) [2]. Furthermore, the prevalence of co-morbid insomnia among individuals with OSA, and the rate of OSA among those with insomnia are increased compared to general population estimates [3].

The mechanisms underlying the comorbid relationship between sleep apnea and insomnia are poorly understood, but may involve the following factors: for one, physical, medical or practical circumstances that hamper sleep for a prolonged period of time can, through a range of mechanisms, lead to maladaptive behaviors and notions with regard to sleep that, in turn, lead to self-maintained insomnia. This insomnia may persist even when the original cause of the sleep problems is gone. Thus, a 'somatic' disorder like sleep apnea can facilitate the development of insomnia. In addition, several forms of sleep apnea treatment involve features that can negatively influence sleep and, through similar mechanisms as just described, contribute to the development or maintenance of insomnia. Finally, it has been proposed that successful sleep apnea treatment might uncover latent insomnia, although this mechanism is not supported by evidence (see [4–6] for discussions).

Patients with comorbid insomnia and sleep apnea (COMISA) present with many diagnostic and treatment challenges. In view of the overlap in complaints of the two disorders (e.g., difficulty maintaining sleep, daytime fatigue, etc.) diagnosing

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comorbid insomnia in the context of sleep apnea can be challenging. It is still more difficult, even for well-trained clinicians, to attribute insomnia complaints to factors that are independent of the sleep apnea, secondary to the somatic sleep disturbance, secondary to the treatment thereof, or to some mix of those factors [7]. This complicates treatment choices, for instance regarding the order in which the two disorders should be addressed. The shared symptomatology also complicates the measurement of treatment responses in COMISA patients, as it is not always clear to which disorder these should be attributed [8].

Regardless of the underlying causes, treatment of co-occurring insomnia in sleep apnea patients is important for therapeutic outcome. Indeed, a significant proportion of patients still sleep poorly, in spite of successful continuous positive airway pressure (CPAP) or other sleep apnea treatment, due to insomnia symptoms [9]. Furthermore, the presence of insomnia can have a negative impact on the process and outcomes of sleep apnea treatment. Indeed, insomnia symptoms prior to sleep apnea treatment are a strong predictor of poor therapy adherence for several forms of treatment, including mandibular advancement devices, positive airway pressure (PAP) and CPAP [10–13]. Thus, treatments that stabilize sleep could in principle address insomnia symptoms that are independent of the OSA and also favor tolerance for and adherence to sleep apnea treatment.

Having said this, current treatment options for insomnia are limited. Cognitive behavioral therapy for insomnia (CBTi), the first-choice treatment, is moderately effective, with approximately 60% of patients showing a therapeutic response and about 40% achieving clinical remission at the end of (~6 session) treatment; rates that drop considerably at later follow up [14, 15]. Moreover, CBTi is resource and cost intensive and not readily available to the bulk of patients. Pharmacological treatments do not restore normal sleep physiology, have no demonstrated long-term efficacy and have side effects, including REM sleep suppression, negative discontinuation effects on sleep, risk of addiction, as well as drowsiness and negative cognitive effects during waking. Therefore, these are only recommended for short-term interventions in very specific cases.

Given these limited options, dealing with insomnia in the context of sleep apnea may be challenging. First of all, there is little empirical evidence on the effectiveness of CBTi in COMISA patients. This effectiveness may depend strongly on the extent to which the insomnia is independent of, or rather secondary to the sleep apnea, which, as indicated previously, can be difficult to judge. In case of independent insomnia CBTi might work. However, patients that suffer from secondary insomnia may find CBTi frustrating and cumbersome, causing them to disengage from the treatment process. Also, it can be envisaged that some aspects of CBTi might be unsuitable for COMISA patients. For instance, bedtime restriction therapy (an effective behavioral component of CBTi; [16]) may pose additional risks for COMISA patients, who complain of elevated daytime sleepiness prior to treatment [17]. Finally, CBTi takes several weeks to produce therapeutic results, which in the context of another protracted therapeutic trajectory aimed at the sleep apnea is less than ideal.

Fast acting sleep enhancing therapies might be preferable in COMISA patients. Hypnotics, which fit this criterion, are however contraindicated, as most of them

(e.g., benzodiazepines) have muscle relaxant properties that can exacerbate OSA [17, 18]. The newer nonbenzodiazepine agents, such as zolpidem and eszopiclone, seem to have less effect on airway patency [19, 20]. Still, the use of hypnotic or sedating pharmaceuticals in subjects with OSA remains questionable, especially since longer-term use is often required.

Co-occurring insomnia can form a particularly poignant problem in the case of invasive treatment options for sleep apnea, such as hypoglossal nerve stimulation (HNS). A proportion of patients treated through this approach, experiences disturbances during sleep caused by HNS, leading to arousals and awakenings. Patients with insomnia often cannot fall asleep with the upper airway stimulation system on. This is a very disappointing and frustrating outcome in patients who previously had failed many others OSA treatments, and regarded HNS as their *ultimum refugium.* In addition, HNS is very expensive, while in those patients who experience HNS failure and demand removal of the whole implanted system the risk of hypoglossal nerve damage during explantation exists.

In this context, alterative, fast-acting methods to stabilize sleep against either endogenous or external disturbing influences are of considerable interest. A few approaches are currently under investigation, including vestibular stimulation through gentle rocking [21], transcranial electrical stimulation or transcranial magnetic stimulation [22] and closed-loop acoustic stimulation of sleep slow oscillations (SO) [23–25]. The latter approach seems the most promising, given its non-invasiveness, suitability for miniaturization and ease of use, all of which facilitate clinical and at-home applications [26].

The term closed-loop neurostimulation (CLNS) refers to automatized methods to guide stimulations by neural activity. Such procedures have gained popularity in the context of sleep research, where empirical approaches to investigate the functional dynamics of brain activity are complicated by the absence of behavioral output. CLNS allows researchers to perform precise manipulations of neural activity patterns to assess their functional relevance (e.g., through behavioral assessment following sleep) [27].

CLNS procedures were first developed in the context of animal studies [28, 29]. For example, in one study hippocampal sharp-wave ripples were automatically detected and interrupted with an electrical pulse, to assess their role in memory consolidation [28]. In humans, CLNS procedures have been used to temporally align stimulus presentations to features of the (intracranial) EEG, such as to spindles [30], SOs [23, 25] and theta activity [31]. The most sophisticated of these procedures, developed in our lab, are based on flexible, near real-time modeling of the EEG signal's oscillatory dynamics (Fig. 19.1a) [25, 33, 34]. This allows prediction of upcoming brain activity, and precise targeting of manipulations to features of interest in the predicted activity, for instance oscillatory phase (Fig. 19.1b).

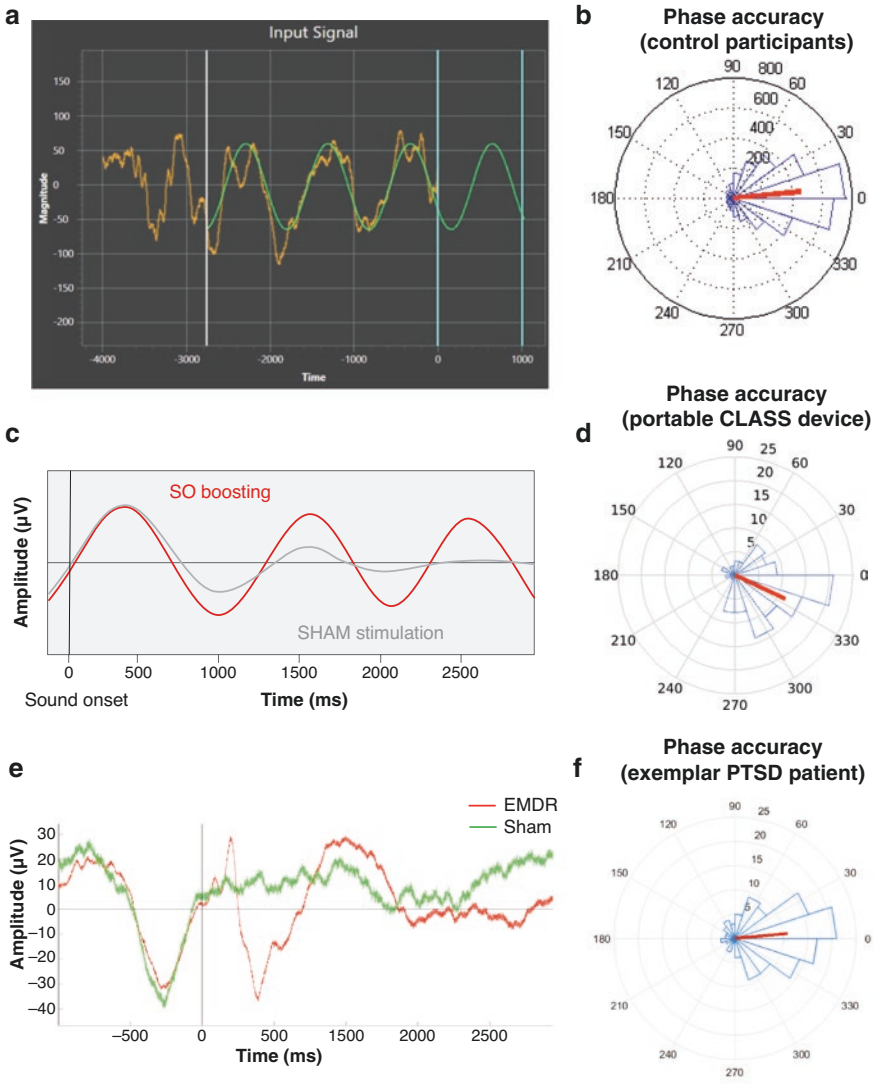
Using this technology, we have recently tested the hypothesis that memory reactivation and consolidation during sleep are specifically linked to SO positive halfwaves (hereafter called SO up-waves). These EEG deflections are evoked by synchronized, neuronal depolarizations in underlying corticothalamic networks,

Fig. 19.1 Details of the closed-loop neurostimulation method used in our lab. (**a**) The EEG signal (Fz-M1; in orange) is modeled in real-time, through a sine fitting procedure (in green). Model extrapolation is used to predict upcoming oscillatory dynamics and estimate the temporal occurrence of a slow oscillation (SO) target phase in a short future time window (between the two blue lines). (**b**) SO phase targeting accuracy (target phase 0°) in young healthy subjects, for a total of 4281 predictions. Mean phase error was 5.71° ± 50.74° (SD). (**c**) Schematic showing the typical evoked response potential (ERP) to auditory stimuli targeted at 0°. These stimuli tend to evoke long SO trains (in red), relatively to no stimulation (in grey). (**d**) Phase targeting accuracy (target phase 0°) using a prototype portable CLASS device, based on a commercially available EEG headband (ZMax by Hypnodyne) ported to a tablet running software developed in-house (collaboration with Okazolab Ltd, Delft, The Netherlands). The analysis regards 97 stimulations in a representative healthy subject. Mean phase error was −19.4° ± 53.4° (SD) (the offset from target phase may reflect an artifact in the beta-software). (**e**) ERP (Fz-M1) to CLASS stimuli (target phase = 0°) in a representative PTSD patient participating in an ongoing study in our lab [32]. In this study auditory cueing during sleep is done using EMDR clicks (red trace; n = 100) to reactivate and enhance positive memories of the treatment and, therewith, treatment efficacy. The ERP to EMDR clicks is contrasted to a sham stimulation condition (i.e. silence; green trace, n = 36). The ERPs are phase-locked to stimulus onset (0 on x-axis). Presenting EMDR clicks elicited a boosting of slow oscillations, as compared to the sham condition. (**f**) Accuracy of SO phase targeting in the same PTSD patient, combined across EMDR and sham cues (136 stimulations). Mean phase error was 5.23° ± 56.0° (SD), suggesting that similar phase targeting accuracy and SO boosting performance can be reached in a population with disturbed sleep as in young healthy subjects. (Panels (**e**) and (**f**) are courtesy of van der Heijden and van Marle [32])

and are associated with enhanced plasticity and connectivity [35, 36]. Conversely, the negative SO half-waves reflect periods of neuronal hyperpolarisation. Our results confirmed the hypothesis, showing that subtle auditory memory cues, targeted to the start of SO up-waves enhance memory for the associated information. On the other hand, cues targeted to the negative half-wave promote forgetting [34].

Interestingly, precise up-wave cueing also boosts the SO dynamic, inducing long SO trains (Fig. 19.1c) that effectively increase the duration and percentage of deep sleep across the night [34]. We have recently observed that such sleep deepening can also be achieved independently of memory manipulation, using simple sound pulses (e.g., white noise) to boost SOs (paper in preparation). Of note, global deepening of sleep was not reported in previous studies in which SO phase targeting was less precise [23, 25] or involved rhythmic stimulation [23, 24, 37]. It can be envisaged that such rhythmic stimulations, which do not take into account the momentary oscillatory dynamic of brain activity, may in fact disturb slow wave activity. Thus, precise SO phase-locking and the use of single acoustic stimuli appear to be essential facilitating parameters in closed-loop acoustic sleep stimulation (CLASS) procedures.

These and other studies using closed-loop approaches have generated strong evidence on sleep-dependent memory consolidation and its underlying neural mechanisms. On a more practical level, the observation that sleep can be deepened and memories can be manipulated has invited exciting ideas for application, for instance in the treatment of sleep, memory and affective disorders [26]. Current research on such applications suggests that CLASS is well tolerated in subjects with disturbed sleep, and that accurate SO phase targeting and SO boosting can also be achieved in



these conditions (Fig. 19.1e, f). Of particular interest is the possibility to apply CLASS to insomnia treatment through devices for home-use. Given the state of maturity of portable EEG technology and advanced microelectronics the development of such devices appears feasible (Fig. 19.1d). This type of application could offer major health care benefits, providing a low cost, broadly applicable treatment option for a highly prevalent and currently undertreated disorder.

While findings thus far are promising, many open questions need to be addressed on the way toward putative treatments. One of these regards the extent to which induced deep sleep is equivalent to spontaneous deep sleep and conveys similar

benefits. For instance, spontaneous sleep deepening is associated to the progressive inhibition of sensory input to thalamocortical circuits and, therewith, enhanced sleep stability against sensory disturbances. It is not yet known whether this is also the case for sleep enhanced through CLASS. However, a study that induced sleep deepening by gentle rocking stimulation showed that this reduced spontaneous arousals, suggesting, indeed, an increased arousal threshold [21]. Also, recent findings from our lab suggest CLASS can stabilize sleep against disruption by environmental noise [38].

Spontaneous deep sleep is also associated with a shift towards autonomic and endocrine parameters that favor molecular biosynthesis and other basic processes, which, in turn, support host defense responses [39, 40], glucose metabolism and other cell metabolic functions [41, 42]. Such processes are crucial for growth, recovery and general health. A few recent studies suggest that rhythmic acoustic stimulation targeted to SOs intensifies some of these characteristics, including parasympathetic activity, reduced cortisol levels, increased aldosterone levels and reduced T and B cell counts, but not others, such as growth hormone levels, and several indices of metabolic control [43–45]. It should here be noted that the stimulation procedures used in these studies, while inducing immediate K-complex-like responses to sounds, did not evoke global sleep deepening. As such, better outcomes might be expected with procedures, such as our own, that do deepen sleep.

Another open question is how sleep physiology will respond to closed-loop SO boosting over multiple nights. As a final, critical step, controlled clinical trials in subjects with insomnia and in other patient populations will be needed to assess the methods therapeutic potential. Of note, studies in this direction will be greatly facilitated by the development of a CLASS device for ambulant studies in clinical and home settings, which was recently achieved in our lab.

In conclusion, advances in neurotechnology and the neurobiology of sleep have brought forth possibilities to influence sleep physiology, including the deepening of sleep through acoustic enhancement of slow oscillation dynamics. These findings hold promise for the treatment of comorbid insomnia in sleep apnea and in other disorders, such as PTSD, which are currently difficult to treat. Moreover, the prospect of a low-cost CLASS device for treatment in the home environment could potentially offer a solution for insomnia treatment in general. At present, the high prevalence of insomnia in modern societies and the highly resource intensive first-choice CBTi treatment (in terms of cost and specialized health care providers) result in only a minority of patients receiving appropriate care. CLASS-based sleep enhancement therefore warrants further investigation, to assess the potential of such procedures to bring solutions to the aforementioned problems.

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Chapter 20
Special Cases in Hypoglosal Nerve Implantation

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Contents

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Abbreviations

CIED	Cardiac implantable electronic device
CSA	Central sleep apnea
CVD	Cardiovascular disorders
DISE	Drug-induced sleep endoscopy
HNS	Hypoglossal nerve stimulation implant
IPG	Implanted pulse generator
MS	Multiple sclerosis
OSA	Obstructive sleep apnea
PD	Parkinson disease
PSG	Polysomnography
PTSD	Posttraumatic sleep disorder
RLS	Restless legs syndrome
SBD	Sleep-related breathing disorders
UAS	Upper airway stimulation

Introduction

The placement of a Hypoglossal Nerve Stimulation Implant (HNSI) is a surgical technique, which requires specialized training by the surgeon in accordance with best practices deemed by the product manager, Inspire Medical Systems, Inc. (Golden Valley, MN). These are a set of guidelines for patient selection that have been suggested by the company, for every center implanting to have the same results and guarantee the best outcome. Beyond these requirements, in medicine all treatments must be individualized, taking into account particular feature(s) of the patient that might effect a change in the result of the proposed treatment.

Treatment and care of every patient with OSA should be carried out in an interdisciplinary and an integral way, knowing that this is a complex disease that not only affects the diverse organs of the body but also mood and their quality of life.

The objective of this chapter is to discuss special situations that may be encountered when choosing the right candidate for surgery, diverse conditions that may need to be changed during surgery, and follow-up that may need to be individualized to obtain the best benefits.

Table 20.1 Selection criteria

Clinical evaluation	Polysomnography (PSG)	Drug-induced sleep endoscopy (DISE)
Complete ENT and head and neck exam	<65 obstructive events/h	Antero-posterior tongue base and palate collapse
Body mass index ≤35	<25% mixed and central events/h	Avoid concentric collapse at the palate

Selection of Adequate Candidates for a Hypoglossal Nerve Stimulator Implant

Established patient selection criteria includes selection criteria are summarized in Table 20.1.

Beyond these criteria, the indications for treatment must be individualized to each patient. For this reason, a survey was prepared and sent to those surgeons who regularly perform hypoglossal nerve stimulation implant surgery, to collect information about the most difficult challenges they have found in patient selection, while performing the surgery and during post-operative management. According to their responses, patient selection seems to be the major challenge, as therapy can be difficult to manage if response is inadequate despite meeting manufacturer-set basic criteria.

As we consider patient selection, a complete physical exam is considered paramount (head and neck and DISE), but there is also a need to review the psychological condition of patients to be implanted. It is of the utmost importance to correctly set patients' expectations regarding the ability of the device to "solve" their sleep disturbance.

HNS and Sleep Disorders Related with OSA

It is common for a patient to have besides OSA additional other sleep disorders, psychiatric or cardiological disorders at the same time. This is important to take into account when establishing a treatment for OSA, as the beneficial results of the Hypoglossal Nerve Stimulator Implant may be conditioned by the presence of these other disorders possibly influencing the outcome of the surgical procedure. Besides, the duration and amount of sleep needed in an individual varies according to genetic, psychological, social, cultural, and environmental and sleep habits factors [1]. The following pages discuss the significance of the above-mentioned comorbidities for HNS.

Sleep Disorders

Insomnia

Sleep-related disorders are highly prevalent and with considerable repercussions on the morbidity and mortality of the population [2], with OSA being the most frequent, followed by insomnia. In many instances, the symptoms of these two disorders overlap, accompanied by low arousal thresholds, which complicate diagnosis and treatment. Sweetman et al. wrote a review of the prevalence, characteristics, and theoretical pathophysiology relationships between co-occurring insomnia and OSA [3]. Luyster reports that 39–58% of OSA patients suffer from co-morbid insomnia and sleep apnea (COMISA) [4]. An increase in its prevalence has been demonstrated in certain groups of patients, such as sexual assault victims or US military personnel. Patients suffering from COMISA report greater sleep disturbance, as well as greater daytime symptoms than patients with either disorder alone [3]. Such patients have greater difficulty in establishing definitive and adequate treatment for their OSA. It is well established that insomnia treatment leads to an increased acceptance and use of CPAP therapy with a great benefit over the long term [5–7]. However, treatments used for insomnia may produce a decreased muscle tone of the upper airway, exacerbating the symptoms of OSA [8–10].

Even with the use CPAP, which is considered the gold standard treatment in patients diagnosed with OSA, this problem can be seen. Philip et al. showed in their study that insomnia symptoms and its severity are related to CPAP treatment compliance, adversely effects efficacy of treatment of OSA [11]. For this reason, it is always advisable to objectively assess the degree of insomnia and to treat this comorbidity with cognitive and behavioral therapy to increase long-term therapy adherence [12]. As with the use of CPAP, insomnia is a factor that makes therapy adherence difficult in patients implanted with HNS because the patient may stay awake and the electrical stimulus on the tongue may be felt, creating a sense of despair and more difficulty falling asleep. The Adhere Registry study detected insomnia due to HNS in 5% of patients post-operatively [13]. Our survey showed that most implant-centers consider OSA combined with insomnia is a frequent comorbidity which can affect outcome and therefore needs to be addressed preoperatively especially in patients with excessive daytime sleepiness as their major complaint.

Central Sleep Apnea (CSA)

A high percentage of CSA events (above 25%) is an important parameter that has been indicated to be avoided for implantation. CSA may occur when CPAP therapy is first used and tends to improve with time. As Eckert et al. have found, correcting an anatomically narrow upper airway with continuous positive airway pressure (CPAP) in a patient with primarily OSA can also lead to apparent

treatment-emergent central apnea [14]. There have been anecdotal descriptions on the development of CSA immediately after HNS surgery. Most surgeons conclude that this may happen the same way as with CPAP but it tends to improve with time with the continuous use of HNS. In our survey, one surgeon commented that they had seen a patient within the limit amount of CSA, before surgery that dramatically worsened with Cheyne Stokes breathing. No explanation was given about treatment for this effect. In other cases, CSA improved with HNS. For example, Rajagopal et al. report a patient with predominantly CSA who responded well to HNS [15].

Hypersomnolence

Excessive daytime sleepiness (EDS) is another important factor that may be seen in OSA but could also be related to other sleep disorders such as narcolepsy type 1, narcolepsy type 2, idiopathic hypersomnia and recurrent hypersomnia or lack of sleep (Berkowski et al.) [16]. Ferini-Strambi et al. and Garbarino establish a relationship between daytime sleepiness and OSA, considering a fundamental point in the diagnosis, a complete clinical history that includes lifestyle habits (excessive caffeine, substance abuse, poor sleep hygiene), medication that could have side effects such as fatigue or sedation, and some other medical or psychological problems [17, 18]. Therefore, idiopathic hypersomnia may co-exist with OSA and can determine unsatisfactory results while treating the disorder [16]. These diseases should be screened ahead of time to avoid false expectations in patients that could be implanted with HNS, but they should not be considered a contraindication for its implementation.

Circadian Rhythm Disorders

Sleep-wake disturbance in shift workers and delayed sleep-wake disorder is also believed to be related to insomnia and likewise can adversely affect results in the treatment of OSA. However, to our knowledge, there is no information about its effects on the outcome of HNS placement surgery.

Bruxism, Periodic Limb Movements (PLM) and Restless Legs Syndrome (RLS)

Implantation of patients with Bruxism, Periodic limb movements (PLM) and Restless legs syndrome (RLS) seem frequent according to answers given within the survey, and major difficulties in treating these patients were not observed. The concomitant use of medication for RLS may relieve the symptoms in conjunction with HNS.

Recently, investigators have demonstrated the benefit of HNS treatment in patients with RLS, obtaining results that highlight the importance of treating OSA in patients with difficult to control RLS: over 70% of the patients reported improvement in RLS symptoms following initiation of therapy [19, 20].

Regarding bruxism, this entity is a sleep disorder that occurs in 8% of the general population. Hamdan et al. report a case of severe OSA complicated by bruxism, demonstrating HNS implantation to be effective, suggesting that this disorder is not a contraindication for this kind of therapy [21].

Parasomnias

To our knowledge at this moment, there have been no descriptions of the implantation of HNS in patients with parasomnias.

Psychiatric Disorders

Patients with OSA may also suffer from psychiatric disorders. Depression and anxiety are very commonly seen and are also associated with comorbid insomnia. These patients need preoperative counseling because many of them are under the impression that their anxiety and insomnia will resolve with OSA therapy. Escobar-Córdoba et al. carried out a study of psychiatric implications of OSA where they showed that the disorder most frequently found in patients with sleep apnea is depression, and is thought to be due to sleep fragmentation, which alters the production of neurotransmitters at the level of the brain. It was followed by anxiety, probably related to the release of catecholamines at night [22].

Patients who suffer from a post-traumatic sleep disorder (PTSD), common in war veterans, pose a challenge for the surgeon as well, as they may require more intensive follow-up and changes in the device settings after HNS implantation. According to the survey, they have difficulty reaching comfort level, and can suffer from depression that plays a role in their lack of use or abandonment of therapy and therefore follow-up. Wallace et al. showed that veterans with insomnia appeared to be less adherent to HNS than those without it, although these results varied after titration [23].

There clearly is a need for a combined treatment of psychiatric and sleep-related disorders. Treatment of OSA (with the placement of an HNS) may improve OSA symptoms, sleep fragmentation, attention, concentration, memory, changes in mood, mobility and enthusiasm with a reduction of irritability. However, there may well be a need for a combination of psychoactive drugs and psychoeducation. In

some cases, the symptom control in OSA can achieve a reduction in the dose of psychoactive, and even allow a complete withdrawal of the medication [22, 24, 25] Psychoeducation allows the sufferer to learn about their disease [26] and may improve outcomes.

There are no articles that include the relationship between patients with chronic pain and opioid dependence and treatment with HNS since in most cases, patients with these problems have been excluded from studies as possible confounders to surgical efficacy.

Neurologic Disorders

Cognitive Impairment

Over the last decades, various studies have been carried out trying to relate neurological disorders with OSA. Aloia et al. studied the cognitive impairment of patients with OSA, concluding that sleep fragmentation and hypoxemia are the two most commonly implicated etiological mechanisms [27]. Following the same line of work, Lim et al. demonstrated that although therapy for sleep apnea markedly improves daytime symptoms, cognitive changes such as impairment in attention, verbal fluency, memory, complex reasoning may persist, particularly in those patients with severe OSA and significant oxyhemoglobin desaturations. Many of these neurologic changes appear persistent despite CPAP therapy. This could be related to the fact that the neurons that are more metabolically active and the hippocampus, are more vulnerable to injury than other structures [28, 29]. Nevertheless, Zimmerman et al. studied the benefits provided by CPAP in patients with OSA, concluding that impaired verbal memory performance may be reversible with optimal levels of CPAP treatment [30].

Migraine

It is well known that some of the triggers of migraine episodes are stress or emotional disturbances, factors that can also be altered by sleep disorders [31]. However, there seems to be no clear relationship between migraine and OSA in the general population [32]. Russell asserts that OSA increases the risk of sleep apnea headache, but there are some other conditions, such as increased intracranial pressure, that can also cause morning headache. Nevertheless, it is always recommended to treat OSA in those kinds of patients. The use of CPAP has demonstrated to improve sleep apnea headache [33].

Parkinson's Disease

The brain areas that are responsible for psychomotor functions are preferentially affected and may be particularly susceptible to the repeated, intermittent hypoxemia seen in OSA. Moreover, fluctuations in oxygen availability, rather than fragmented sleep, are more likely to be associated with tissue damage [27, 34]. This fact could explain that certain neurological diseases, such as Parkinson's disease (PD) or essential tremor have been seen related to OSA.

Therzaghi et al. studied the relationship between PD and treatment with CPAP in patients with OSA, given the high prevalence of this disease in patients with PD. Patients with adequate CPAP tolerance improved their daytime sleepiness [35].

There are no studies showing a benefit of the use of HNS with regard to neurologic disorders, although in our survey some surgeons mentioned they had implanted patients with both Parkinson's disease (PD) and with migraine without any special implications for the treatment.

Cardiovascular Disorders

OSA has been increasingly identified as an important risk factor for cardiovascular disorders (CVD). Tietjens et al. published a detailed review of the literature relating OSA to patients with CVD, describing a practical clinical approach to the evaluation and management of known or suspected OSA in patients with CVD [36].

As CVD is so frequent, many such patients have been implanted with HNS. These patients are usually taking anticoagulation or antiplatelet aggregation medication that may make the risk of bleeding or hematoma during and in the immediate postoperative period more frequent. Therefore, surgeons should perform adequate and detailed hemostasis of the operated areas. There have been descriptions of hematoma formation in some cases, and conservative management avoiding external drainage or needle aspiration is recommended. If there is no airway compromise it is not necessary to evacuate the hematoma, it will resolve over time and there is only a small possibility of infection with expectant management.

Special Considerations

Other Implantable Devices

A recent feasibility study showed that the simultaneous use of HNS with transvenous Cardiac Implantable Electronic Devices (CIED) is safe, effective and without any device-device interactions as described by Parikh et al. [37]. They studied retrospectively 14 ad hoc patients with CPAP-intolerant, moderate-to-severe OSA and pre-existing CIEDs undergoing HNS implantation (Inspire II) that were followed up

for 12 months. All the HNS devices were implanted on the opposite side of the CIED. All CIEDs were programmed bipolar. HNS were programmed either unipolar or bipolar. A significant reduction in median AHI at the end of a 1-year follow-up after the implantation of the HNSI was obtained in their analysis [37].

Based on our survey, HGS has also been performed in a patient with an occipital nerve stimulation. The surgeon should be aware that the occipital nerve stimulation causes artifacts which interfere with the intraoperative neuromonitoring. Therefore, care should be taken to turn off the occipital nerve stimulation before the procedure.

Placement in Children with Down Syndrome

HNS implantation as a treatment for OSA is usually carried out in adults, but implantation in children with Down Syndrome (DS) is currently being conducted through an investigative protocol sponsored by Inspire Medical Systems. (See also Chap. 5). In the majority of children, adenotonsillar enlargement produces OSA, and surgical intervention tends to partially or completely correct sleep disturbance. It is known that the prevalence of OSA in children with Down syndrome is higher than in the rest of the pediatric population, reaching estimated rates between 30–60% [38]. In these children, symptoms persist after adenotonsillectomy in up to 50% of cases [39]. Bowe et al. and Diercks et al. presented two cases in which the placement of this device was carried out in the pediatric age [39, 40]. In the first case, although the biggest challenge seemed to be the small size of the patient's chest, this did not pose any difficulty for placement. It was carried out by placing the IPG in a more medial area, which allowed better access to the rib surface, as well as greater ease for the creation of the IPG pocket, with direct access to the pectoralis major muscle. In the second case, a 14-year-old patient presented a long-standing tracheotomy due to severe OSA. The patient was decannulated approximately 4 months after activation and successful titration of the implanted HNS.

Recently, Caloway et al. performed an update on HNS in children with DS and OSA. This study analyzes the results of a total of 20 adolescents with DS who underwent hypoglossal nerve stimulation surgery because of refractory OSA and conclude that the placement of an HNS provides important benefits in this group of patients, reaching significant average reduction of AHI and improvement in OSA related QOL. They also found an improvement in functioning capacity and behavior, according to family members. Further studies are needed in order to assess the neurocognitive benefits that HNS can offer to this group of patients [41].

Surgical Technique

The placement of the generator and the sensor lead should be carefully checked for female patients. The surgeon should discuss and check where the incisions will be performed, asking and seeing where the patient's bra strap and underwire fall,

performing the incision above or below this level, to avoid surgical scar irritation, discomfort or tenderness. The IPG pocket and incision this should be placed a bit lower than in men to allow the IPG to be buried in the upper portions of breast tissue. This may better mask the bulge that can be associated with the IPG [42], and prevent untoward movement of the IPG up toward the clavicle when the patient is supine. Mammography is not contraindicated post-implantation and patients can continue to receive routine mammography, as per current guidelines.

There have been also descriptions of difficulty encountered in female patients that have had previous breast surgery. Prior mastectomy, breast reconstruction or breast augmentation all can be challenging when tunneling the subcutaneous plane for connection between the leads with the IPG. The authors consider this circumstance to be similar to patients with CIEDs. Tabatabai et al. published a case in which there was a spontaneous migration of the implanted device within 4 months after implantation. These authors established a possible relationship between obesity, abundant breast tissue and this surgical complication, considering them as potential risk factors for device migration. They also concluded that the risk of this complication can be assessed before implantation and avoided with preimplantation position planning. Anchoring the device in two locations should ameliorate this potential risk. “Twiddler’s syndrome” is a known complication of CIED. This syndrome is caused by the migration of the CIED due to the manipulation of the device by the patient itself [43]. This risk may also be mitigated by anchoring with two separate locations.

Placement of the IPG may be challenging in patients who habitually shoot with rifles as professionals or recreational hunters. IPG placement should be considered on the left side in this situation especially in right-handed persons.

Post-Operative Care

It also has been recommended made for patients to avoid brisk movements and exercise for 4 weeks postoperatively, while the implanted device integrates into the body.

Tabatabai et al. also reported a submandibular exposure of the stimulating cable [43]. This same type of complication has been seen but not reported in one of our patients, occurring 3 years after implantation, and resulting in the patient cutting the lead as he confused it with a residual suture extrusion. Exchange of the stimulation lead was performed without any difficulty and the cuff was easily placed thanks to a fibrotic channel that had been formed around the nerve, making the replacement easy and safe. This complication might be related, to having placed the cable very superficial at the incision site at the submandibular area. It is recommended to place the cable deep below the platysma muscle to avoid this complication.

Jonas et al. presented a case of a female patient suffering from CPAP intolerance due to claustrophobia and anxiety, with silicone prostheses for breast augmentation, who underwent HNS surgery. Given the lack of experience in the placement of an

implant associated with breast prostheses, the surgical procedure was performed under ultrasound guidance when tunneling the cables, ensuring not only the correct placement of the device but also the integrity of the silicone breast implant after the procedure. Conversely, a case of a female patient has been reported that suffered an incidental rupture of her saline breast implant, using a blind technique while tunneling [44].

Deep et al. describe a new successful way of implantation of the IPG below the pectoralis muscle, in a patient that presented with skin necrosis and infection, in the setting of having suffered, 6 years before, breast cancer that required bilateral mastectomy and postoperative chemoradiation. Twenty-nine days after the HNS placement, the skin of the area around the IPG began to necrotize, with subsequent IPG exposure and purulent secretions. Despite surgical debridement and intensive antibiotic treatment, persistent infection was observed that required extraction of the IPG with the replacement of new the device. The IPG was placed under the pectoralis major muscle, on the contralateral side [45].

HNS and Head and Neck Cancer

Payne et al. showed that there is a higher prevalence of OSA in patients with head and neck cancer after any treatment modality [46]. Some articles show that the identification and treatment of OSA can influence tumor behavior and affect the patient's clinical course. The clinical suspicion of OSA may be greater in patients with active disease or in those who have received radiotherapy. Thus, for these patients, primary treatment with CPAP would be recommended. However, persistent hypoxia is sometimes found, despite adequate CPAP therapy [47]. In these cases, HNS placement may be considered.

Post-op swallowing and speech difficulties after HNS surgery may occur in patients that have undergone radiotherapy treatment, especially because of disruption of microvascular circulation, leading to tissue fibrosis. Zheng et al. reported a case of an HNS implantation after radiation therapy for tonsillar carcinoma. They established the importance of assessing the possible poor condition of the tissues before implantation, as well as carefully considering the location and dose of radiation and prior neck dissections. They also considered that the titration process might be more challenging and require more periodic surveillance, although in this case, the results were satisfactory [48].

Other Surgical Considerations

Precise knowledge of submental anatomy combined with intraoperative neuromonitoring and neurostimulation techniques can guide implantation and improve surgical results [49].

Inclusion of C1 nerve with the protruder fibers during placement in the stimulation cuff has been suggested for opening the airway at the level of the hyoid as it innervates the geniohyoid muscle [50]. Recently Kumar et al. have published that this step is not necessary as it doesn't improve outcomes [51].

Other Special Problems

According to answers given within the survey, there have been patients that have presented intolerance to the device that began 1–2 years post implantation, requiring a new titration to readjust the initial configuration of the device. Similarly, some surgeons describe cases of patients having difficulty sleeping with HNS, as they mention "hearing the device", not noticing any effect, not tolerating the device. These situations must be analyzed individually, paying special attention to the subsequent titration. A strict follow-up should be carried out, trying to correct the cause to achieve satisfactory results both in the objective and subjective areas, assessed by the patient.

Positional Sleep Apnea and HNS

Positional OSA is a type of phenotype that is observed in some patients. Several studies show that the frequency and duration of apnea is, in approximately 56–75% of patients, influenced by body position [52]. Oksenberg et al. showed that patients with Positional OSA enjoy a more restful sleep and are more alert during daytime hours, if they follow an adequate treatment [53]. The placement of an HNS should be equally assessed in this type of patients, although they could be difficult to titrate because of the possible need of different amplitude in supine/non-supine position. Chow et al. performed an analysis on the effect of sleeping position on the efficacy of HNS and demonstrated that HNS may be less effective in the supine position, supporting the importance of evaluating sleeping position preference during patient selection [54]. Strohl et al. reflect on the importance of assessing the positional effects on AHI after placement of a HNS [55]. In some cases, a combination of HGS and positional treatment avoiding supine position may be necessary in order to achieve satisfactory results.

Titration

Advanced titration of HNS therapy involves changes of the electrode configurations to optimize muscle recruitment, which can, in some instances, convert an initial non-responder into a responder [56, 57]. Different types of electrode configurations

may result in different tongue motion and variable palate movement, with different therapy outcomes. It is essential to understand the mechanism of tongue muscle activation resulting from hypoglossal nerve stimulation under various electrode configurations.

During HNS device programming, in addition to voltage adjustment, an electric field setting can be changed as necessary to optimize the therapy response. The system offers five electrode configurations that create different electric fields and effects on branches of the hypoglossal nerve. Various possible mechanisms explain changes in tongue motion with different stimulation voltages and different electrode configurations. Tongue movement patterns are likely affected by the type of nerve branches included in the cuff, electric field, voltage, and cuff rotation.

It may be necessary to perform titration at least yearly after the first titration depending on how the patient feels, previous sleep study and also previously reached parameters. In some cases, there may be a need to change the voltage, or electrode configuration, especially between activation-first titration and at 12 months. The changes seen may be related to a recovery of nerve fibers after implantation [58].

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Chapter 21
Ansa Cervicalis Stimulation for Obstructive Sleep Apnea

David T. Kent

Contents

Introduction

Uvulopalatopharyngoplasty (UP3) was first described for snoring in 1955, but tracheostomy was considered the only surgical therapy for the treatment of obstructive sleep apnea (OSA) prior to Fujita's popularization of the procedure in 1981, designed to "bring the palatal arch forward." [1–3] Forty years later, all upper airway surgeries for OSA, including hypoglossal nerve stimulation, are designed to stabilize the pharynx by either removing or radially dilating the soft tissue structures of the upper airway to displace them anteriorly. Nevertheless, the pharynx is also distensible along its entire length, and physiologic studies have demonstrated that caudal traction from the trachea decreases upper airway collapsibility substantially. Ansa cervicalis stimulation (ACS) has recently been proposed as a mechanism for

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replicating the effects of tracheal traction on the upper airway. The evidence behind caudal traction and the available data for ACS are discussed.

Radial Dilation of the Upper Airway

Fujita's initial description of UP3 stated it was designed to "bring the palatal arch forward, resulting in a significant increase in the anteroposterior dimension of the oropharyngeal space" based on observations that the velopharynx was the most collapsible site of the pharynx during sleep, with many patients having a "shallow" oropharynx [2]. Further research has demonstrated that UP3 reduces the length of the soft palate and radially dilates the velopharynx. Other upper airway procedures, such as maxillomandibular advancement, also modify the upper airway primarily by statically dilating it at one or more levels radially, increasing its caliber [4, 5].

Hypoglossal nerve stimulation (HNS) is a novel approach to surgical OSA therapy that dynamically dilates the pharynx by protruding the tongue [6], as opposed to the static, permanent anatomic changes induced by other surgeries. Substantial effort has been put into quantifying the effects of HNS on the pharyngeal anatomy of sleeping patients. Goding et al. documented transient forward movement of the tongue base and hyoid bone on fluoroscopy, with patient outcomes dependent on the degree of anterior displacement observed [7]. Saffirudin et al. determined that HNS dilated the retropalatal space, likely through anterior mechanical traction effects of the tongue on the soft palate translated through the palatoglossus muscle [8]. HNS non-responders had less retropalatal dilation than responders, presumably due to increased compliance of the lateral pharyngeal wall with a decreased effect of mechanical tongue protrusion [8, 9]. Further investigations with pharyngeal manometry and endoscopy have demonstrated that HNS radially dilates multiple levels of the pharynx, reducing collapsibility by increasing cross-sectional area, which permits more negative intralumenal pressures to build before airway collapse begins [10]. Nevertheless, HNS does not substantially alter intrinsic pharyngeal wall compliance, and mapping the change in cross-sectional area per unit change in pressure revealed that the slope of the pressure-area curve did not change with HNS. Instead, the larger caliber airway resisted collapse until a more negative inspiratory pressure gradient was established, but then collapsed at the same rate as the unstimulated airway with further changes in pressure.

Biomechanical Factors Affecting Airway Collapse

The pressure at which the airway occludes (the critical closing pressure [P_{CRIT}]) is governed by a tube law summing the transmural pressures across the airway wall as determined by pharyngeal cross-sectional area and the net dilating or compressive

forces of surrounding tissues (P_{EX}) determined by summing external peripharyngeal tissue pressure, pharyngeal dilator muscle forces, and the intraluminal pressure generated by respiratory activity. The shape of the pressure-area (or tube law) curve, is controlled in part by the intrinsic compliance of the pharyngeal wall (C_{PH}) [11, 12]. C_{PH} is, in turn, controlled by forces that determine compliance of the pharyngeal wall including wall stiffness, governed by active pharyngeal constrictor muscle tone; passive mechanical wall stress applied by dynamic external forces that tense the airway anteriorly or caudally; and the shape of the pharyngeal wall [11, 13, 14].

Level-dependent pharyngeal collapse can be modeled by quantifying the underlying biomechanical determinants of P_{EX}, maximal cross-sectional area (as determined by static structures, such as lymphoid tissue or the relative size of the maxillomandibular enclosure), and local pharyngeal wall compliance, or C_{PH} [10]. These factors may vary between airway levels and altering one or more of them will affect collapsibility. Prior work has demonstrated that HNS and mandibular advancement primarily reduce P_{EX}, shifting the pressure-area curve of the pharynx such that it resists collapse until more negative intralumenal pressures create the same transmural pressure gradient: the slope of the pressure-area curve is not altered [10]. Tracheal traction is hypothesized to exert its effects primarily by increasing C_{PH} through mechanical stretching of pharyngeal tissues.

Caudal Tracheal Traction in Animals

Descent of the trachea and other thoracic contents was recognized as an intrinsic component of inspiration in the early twentieth century [15], but it was many years before investigators recognized its association with upper airway patency. Animal experiments evaluating pharyngeal dilator muscles in the 1980s initially observed phasic respiratory activity in the infrahyoid strap muscles associated with increases in upper airway patency, but these muscles were also observed to have little activity during quiet respiration [16, 17]. It was the discrepancy between infrahyoid muscle activity and caudal traction effects that led Van de Graaf to document the effect of tracheal traction on upper airway patency in 1988. He demonstrated in six tracheotomized dogs that upper airway resistance decreased by 51 ± 11% with maximal phrenic nerve stimulation, leading him to hypothesize that caudal tracheal traction had several effects on the upper airway including pharyngeal unfolding, reduced wall compliance, decompression of peripharyngeal tissue pressure, and generation of a net outward force vector on the mobile hyoid bone when combined with suprahyoid muscle activity (Fig. 21.1) [16]. Several experiments have documented a decrease in overall pharyngeal collapsibility in various animal and physical models with caudal tracheal traction [11, 18–21], and investigations of the underlying mechanisms have supported aspects of Van de Graaf's hypotheses.

Collapsible biological conduits require wall folding to reduce the cross-sectional area of the lumen [13]. Folds are contours that deviate from the baseline wall architecture as cross-sectional area reduces and have been investigated using elastic shell

theory [12, 13]. Elastic shell theory predicts that the pressure required to induce wall folding can be described by the equation: $P = n^2–1$, where P is the transmural pressure and n is the number of formed wall folds [13]. Perhaps unintuitively, resistance to collapse therefore increases with the number of wall folds. Investigators have used a thin-walled latex collapsible tube model to investigate the effects of longitudinal strain (i.e. caudal traction) on P_{CRIT} and wall folding conformation [14]. With longitudinal strain less than 25%, the tube folded into a bifold pattern at external pressures (*i.e.* P_{EX}) of 4–6 cmH_2O. Longitudinal strain of 25% resulted in a transition to a more stable trifold pattern with a marked resistance to flow limitation up through external pressures of 20 cmH_2O (Fig. 21.2), followed by a decrease in

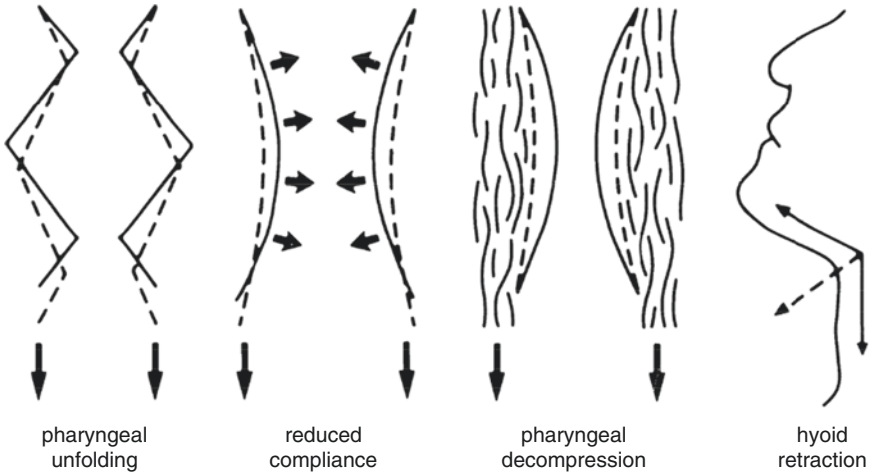


Fig. 21.1 Caudal tracheal traction has been hypothesized to reduce upper airway collapsibility through multiple mechanisms including pharyngeal unfolding, reduced wall compliance, decompression of peripharyngeal tissue pressure, and generation of a net outward force vector on the hyoid bone [19]

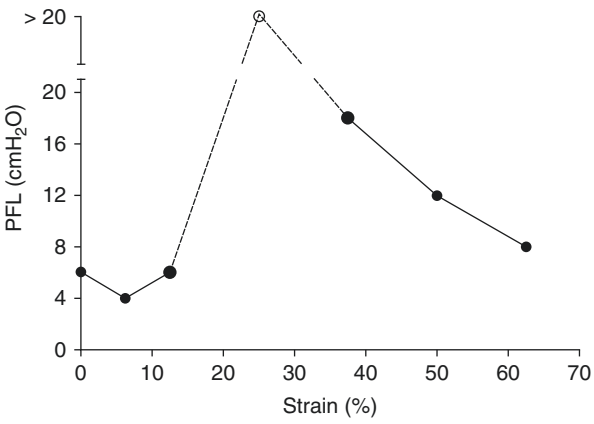


Fig. 21.2 Mechanical longitudinal strain and airflow limitation in a collapsible latex tube model. Resistance to airflow limitation was greatest at a 25% strain. P_{FL} = external pressure at which flow limitation first developed [14]

flow limitation resistance at strains of 37.5% and greater, suggesting that the optimal degree of strain for a collapsible tube may be less than the maximum possible.

Others have investigated the effect of caudal traction on peripharyngeal tissue pressure and hyoid bone movement in animal models. Kairaitis et al. investigated changes in P_{EX} associated with tracheal traction in a tracheotomized rabbit model by placing pressure transducer catheters surgically into the submucosal tissues [22]. Tracheal traction decreased transmural pressure more than the observed decrease in P_{EX}, suggesting additional mechanisms, such as wall fold patterns and mechanical strain, were responsible for airway stabilization with caudal traction. Amatoury et al. conducted a similar rabbit experiment with additional sensors in the peripharyngeal tissues and also used computed tomography imaging to assess changes in upper airway length, hyoid bone displacement, and cross-sectional area [23]. Caudal traction was observed to decrease P_{EX} to the greatest degree rostral to the hyoid bone, whereas the greatest effects on pharyngeal cross-sectional area were at the level of the hyoid bone.

Changes in hyoid bone position with genioglossus, supra-, and infrahyoid strap muscle activity have been investigated by several groups. The human hyoid bone is freely mobile without rigid connections to the osseocartilaginous framework of the upper airway, allowing it to perform a critical function as a fulcrum, transferring applied loads from one direction to another [24]. Tongue protrusion and mandibular advancement have been observed to displace the hyoid bone and other airway soft tissue structures anteriorly, radially dilating the pharyngeal airway [11, 18, 25, 26]. Tracheal and infrahyoid muscle pull have been observed to generate different effects on airway structures by depressing the hyoid position caudally, decreasing peripharyngeal tissue pressure and inducing mechanical strain in the pharyngeal walls [11, 18, 21–23]. Importantly, animal models have demonstrated an interactive effect of combined anterior and caudal displacement of airway soft tissues on airflow and collapsibility. Rowley et al. demonstrated in a cat model that the effect of tongue displacement on pharyngeal maximal inspiratory airflow and collapsibility was increased when combined with tracheal displacement [11]. A validated computational finite element model for rabbits developed by Amatoury et al. demonstrated that anterior and caudal displacement of airway structures had different and interacting effects on the upper airway, with anterior displacement stretching and stiffening the soft palate whereas caudal displacement increased pharyngeal wall stiffness throughout the constrictor muscles and soft palate. The authors hypothesized that the hyoid bone played a critical role in this interaction, acting as a pivot for load transfer between different regions of the airway. Holding the hyoid bone in a fixed position in the model eliminated the translation of anterior displacement effects to infrahyoid regions and likewise prevented the translation of caudal traction to suprahyoid airway structures, including the tongue.

Caudal Tracheal Traction in Humans: The Role of End-Expiratory Lung Volume

Human beings have a uniquely mobile hyoid bone, whereas cats and many other mammals have a shorter pharynx and bony connections from the hyoid to the skull base, restricting its vertical movement [27]. Because tracheal cannulation experiments are highly invasive, after establishing the importance of caudal tracheal traction on airway patency in animals, investigators have focused human caudal traction physiology experiments on the manipulation of thoracic volume instead of direct tracheal instrumentation.

During normal inspiration, diaphragmatic contraction generates a negative intrathoracic pressure resulting in expansion and descent of the lungs within the thorax. The downward pull of the lungs is translated to the bronchial tree and large airways, pulling caudally on the laryngeal and pharyngeal structures [15, 28]. Several changes in respiration and caudal traction occur at sleep onset in humans. Transitioning from an upright to horizontal position (whether supine or non-supine) reduces gravitational pull on abdominal contents, allowing abdominal viscera to shift rostrally against the diaphragm, reducing thoracic volume with a concomitant decrease in lung volume and caudal tracheal traction [29–35]. Diaphragmatic effort simultaneously declines with the transition into sleep, with a greater contribution of intercostal muscles towards inspiratory activity [29, 30, 36]. The decline in diaphragm activity is similarly associated with a decrease in thoracic and lung volume at sleep onset [29]. Men may be more predisposed to changes in end-expiratory lung volume (EELV) with sleep onset as they have more pyramidally shaped thoraces than women (Fig. 21.3), with a greater proportion of volume at the base of the lungs and a greater dependence on diaphragmatic activity for maintenance of EELV [37–41].

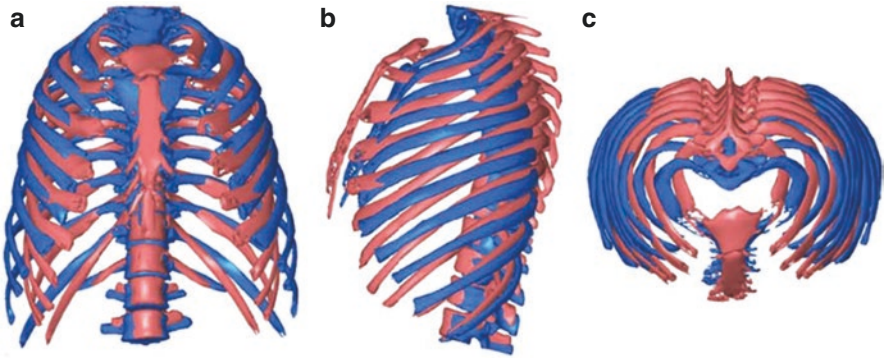


Fig. 21.3 Sexual dimorphism in the human skeletal thorax. Men (blue model) have more pyramidally shaped thoraces than women (red model), with a greater proportion of volume at the base of the lungs creating greater dependence on the diaphragm for volume changes [41]. (**a**) Anterior-posterior view; (**b**) Sagittal view; (**c**) Axial view

Initial investigations into caudal movements of the airway were concerned with the physiology of respiration, as investigators had not yet associated caudal traction with airway patency. In 1925, Macklin observed the carina to descend 21 mm during maximal inspiration in a subject [15]. Mitchenson and Yoffey investigated the hyolaryngeal structures in awake, upright subjects and observed hyolaryngeal descent of 6.4 mm during inspiration in five subjects whereas there was no descent in 14 others [42]. They postulated that activity of the suprahyoid musculature may have restricted caudal movement during wakefulness as they observed 9.5 mm anterior displacement of the tongue and hyoid bone in 78% of subjects, hypothesizing that co-activation of opposing muscle forces contributed to airway patency.

Just as in animals, research has shown that changes in lung volume alter pharyngeal collapsibility in humans. In 1990, Sériès and colleagues placed nine patients in a sealed extrathoracic shell (*i.e.* iron lung) to document the effect of passive changes in lung volume on upper airway collapsibility [43]. They observed that decreasing extrathoracic pressure by 10 cmH_2O increased thoracic volume and decreased pharyngeal resistance by 73.4 ± 7.4%. Several groups have further investigated the effect of changes in EELV on upper airway collapsibility, when the airway is most hypotonic and lung volume is at its nadir. Stadler et al. monitored physiologic changes in EELV at sleep onset in healthy controls and obese OSA patients and found that OSA patients experienced an overall greater decline in EELV at sleep onset, with the greatest declines occurring at the onset of obstructive apneas (89.6 ± 14.2 mL; $p < 0.001$) [29]. They also determined that acute abdominal compression during sleep in 15 obese males with OSA decreased EELV by 0.53 ± 0.24 L ($P = 0.045$) and increased P_{CRIT} (1.4 ± 0.8 versus 0.9 ± 0.9 cmH_2O; $P = 0.039$) [34]. Stanchina et al. manipulated lung volume in 19 healthy controls sleeping in an iron lung and reported that reducing lung volume by 1 L increased P_{CRIT} (4.3 ± 0.5 cmH_2O vs 5.4 ± 0.6 cmH_2O, $p = 0.04$) [35]. Another group studied 17 patients with OSA in an iron lung and found that an increase of 421 ± 36 mL in lung volume permitted therapeutic CPAP pressures to be decreased from 11.9 ± 0.7 to 4.8 ± 0.7 cmH_2O ($p < 0.001$). Conversely, when lung volume was reduced by 567 ± 78 mL in 8 subjects the CPAP level had to be increased from 11.9 ± 0.7 to 17.1 ± 1.0 cmH_2O ($p < 0.001$) to prevent flow limitation, suggesting that a substantial component of the therapeutic effect from CPAP derives from its increase of EELV [44]. To investigate this, the same team used an iron lung to maintain thoracic volume after therapeutically titrating CPAP to abolish flow limitation in another 12 OSA patients during NREM sleep [45]. By maintaining increased thoracic volume, mean AHI decreased from 62.3 ± 10.2 to 37.2 ± 5.0 events/hour ($p = 0.009$) despite the absence of positive airway pressure [45]. Other researchers recognized that manipulation of CPAP to measure P_{CRIT} caused changes in EELV, and therefore used an iron lung to apply an equivalent extrathoracic pressure before decreasing CPAP to assess P_{CRIT} at high, low, and baseline EELVs [28]. In doing so, they determined that $\Delta P_{CRIT}/\Delta EELV$ was −2.0 ± 0.2 cmH_2O/L ($p < 0.001$) and did

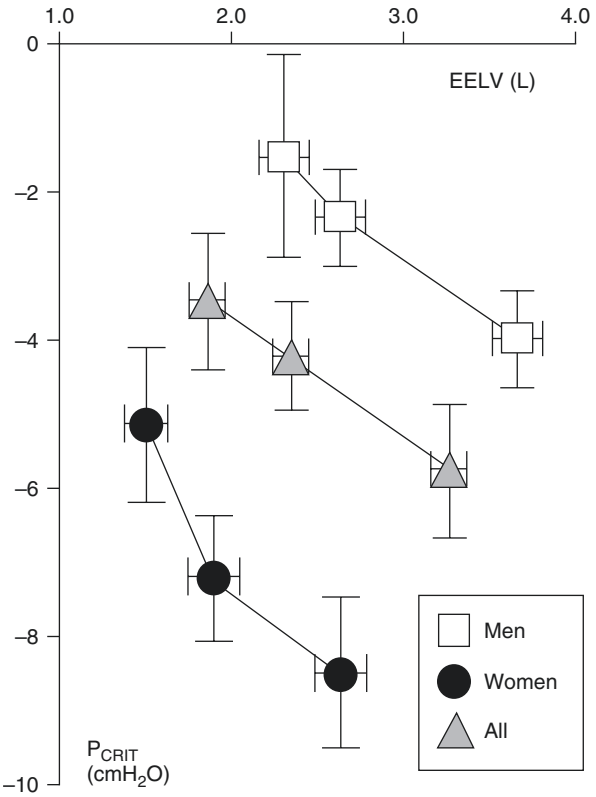


Fig. 21.4 Isovolume relationships between upper airway collapsibility (P_{CRIT}) and end-expiratory lung volume (EELV) are represented for men, women, and the entire group at reduced, baseline, and elevated lung volumes. The change in P_{CRIT} per change in EELV was not different between men and women (P = 0.16) [28]

not differ between men and women (P = 0.16; Fig. 21.4). Taken together, these findings suggest that relatively small changes in thoracic volume have substantial effects on upper airway collapsibility in humans. Hillman et al. sought to determine whether it was thoracic or lung expansion that was responsible for the change in upper airway collapsibility by measuring maximum inspiratory flow while applying bilateral transcutaneous cervical phrenic nerve stimulation at high and low intensities to generate diaphragmatic contraction [46]. Lung volume increased by 761 ± 556 mL during high stimulation with a maximum inspiratory flow increase of 137 ± 108 mL/s. The increase in lung volume correlated with the airflow increase ($r = 0.65$, $P < 0.01$) and, importantly, outward displacement of the abdominal wall from diaphragmatic contraction produced no change in airflow unless accompanied by lung volume change. Phrenic nerve stimulation and resultant diaphragmatic contraction are intrinsically coupled with generation of negative (collapsing) intralumenal pressures. In a state of upper airway collapse and airflow limitation, diaphragm contraction did not independently improve airway patency; it was only after sufficient lung expansion that airway collapsibility improved.

A decline in lung volume during sleep appears to play a central role in increasing upper airway collapsibility. Even in awake subjects, changes in lung volume account

for 61% of the change in pharyngeal resistance when continuous negative pressure is applied to the airway [47]. Changes in airway mechanics with horizontal positioning and sleep onset help explain this phenomenon. Early experiments observed that functional residual capacity (*i.e.* EELV) decreased as much as 0.9 L with a change in position from upright to horizontal, closely associated with an elevation in resting diaphragmatic position and a decline in diaphragmatic excursion that were themselves associated, meaning that as the diaphragm displaced higher into the thorax it also moved relatively less through respiration. The authors attributed changes in lung volume to shifts in abdominal viscera position and the relative pressures between the abdominal and thoracic compartments when changing position [31, 48]. Obesity appears to exacerbate this effect, as obese individuals have been observed to have a lower total lung capacity and EELV than control subjects [32]. Somewhat surprisingly, the relative decline in lung volumes with postural changes appears to be much lower in obese subjects than in controls, perhaps because potential thoracic volume has already been compromised by increased extrapulmonary loading even when upright. Patterns in respiratory muscle effort also change at sleep onset, affecting lung volumes. Investigations of sleeping subjects in 1981 characterized a shift from primarily diaphragmatic respiratory effort during wakefulness to primarily intercostal muscle driven respiration while falling asleep supine [30].

EELV has clear impacts on pharyngeal collapsibility through caudal traction on the hyolaryngeal structures, but direct manipulation of EELV via diaphragmatic contraction with stimulation of the phrenic nerve generates a negative pressure in the airway that can cause collapse and inspiratory flow limitation if not carefully controlled [46, 49, 50]. Nevertheless, another mechanism exists for applying caudal traction to the pharynx: infrahyoid muscle contraction pulls the hyoid bone and thyroid cartilage caudally, along with their pharyngeal attachments.

Infrahyoid Muscle Contraction in Animals

The infrahyoid muscles have respiratory, speech, and swallowing functions [16, 17, 51–58]. Andrew documented inspiratory activity in the sternothyroid (ST) muscle of the rat in the 1950s [58]. Subsequent animal studies in the rabbit, dog, and cat confirmed inspiratory activity in other infrahyoid muscles [16, 51, 55, 59, 60]. Efforts then began to quantify the effects on infrahyoid muscle-induced caudal traction on upper airway patency. Roberts et al. investigated the infrahyoid muscles in rabbits [16]. They found that increased tension of the sternohyoid (SH) or ST muscles dilated the pharynx circumferentially, primary in the oro- and nasopharynx. Nasal occlusion caused marked increases in strap muscle activity. Electrical stimulation of the bilateral SH and ST muscles significantly reduced P_{CRIT} ($p < 0.01$) by

2.5 ± 1.7 cmH_2O and 4.3 ± 3.8 cmH_2O, respectively. The investigators also applied standardized degrees of tension to mimic bilateral SH and ST muscle tension effects on airway collapsibility and found a distinct mechanical advantage to the ST over the SH ($p < 0.01$; Fig. 21.5). Strohl et al. stimulated upper airway dilator muscles in dogs, finding that stimulation of any infrahyoid muscle dilated the pharynx and reduced upper airway collapsibility, most notably in the velopharynx [61]. In 1995,

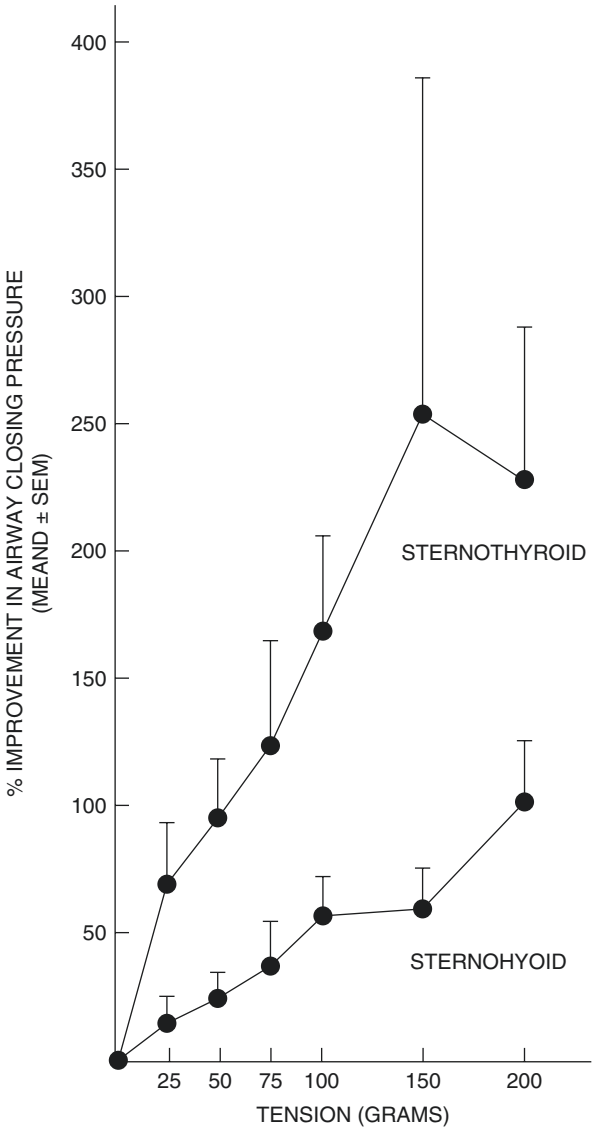


Fig. 21.5 Effects of sternohyoid and sternohyoid mechanical traction on upper airway collapsibility. The sternothyroid muscle had a distinct mechanical advantage over the sternohyoid muscle ($p < 0.01$) [17]

Eisele et al. directly stimulated the hypoglossal nerve and ansa cervicalis in five anesthetized cats, reporting that stimulation of the medial branch of the hypoglossal nerve and the infrahyoid muscles decreased P_{CRIT} by 10.1 ± 2.9 and 6.3 ± 2.8 cmH_2O, respectively [62]. Combining supra- and infrahyoid muscle stimulation decreased P_{CRIT} by 9.7 ± 3.4 cmH_2O. There was no significant difference in maximum inspiratory airflow measurements between hypoglossal nerve and combined supra- and infrahyoid muscle stimulation via the ansa cervicalis. Notably, the authors did not test combined stimulation of the hypoglossal nerve and ansa cervicalis to generate anterior and caudal traction forces simultaneously.

Rowley et al. did test combined tracheal and tongue displacement in a cat model, although traction forces were generated mechanically in both vectors instead of by neurostimulation [11]. Isolated upper airways were prepared in six anesthetized cats by sectioning the trachea below the second or third ring. No independent effect of tongue displacement was observed on P_{CRIT}, nasal resistance, or maximum inspiratory airflow until the tongue was distracted greater than 2.5 cm (maximum obtainable was 3.5 cm), but an independent effect of tracheal traction was observed on all three ($p < 0.001$). Perhaps most importantly, there was an interactive effect observed between tongue and tracheal displacement on maximum inspiratory airflow. As tracheal displacement increased, the effect of tongue displacement on decreasing P_{CRIT} and increasing maximum inspiratory airflow became increasingly robust. The authors hypothesized the interactive effect was due to differences in the mechanisms underlying their influences on upper airway collapsibility: while tongue displacement generated radial dilation forces, tracheal displacement generated changes in stiffness of the airway wall through longitudinal strain (Fig. 21.6). Their results suggest that combining HNS with ACS may have a greater effect on airway collapsibility than either stimulation modality in isolation.

Human Infrahyoid Muscles and the Ansa Cervicalis: Relevant Anatomy

In humans the infrahyoid muscles, or strap muscles, consist of four paired muscles that link the hyoid bone and thyroid cartilage to the sternum and scapula: the thyrohyoid, omohyoid, SH, and ST muscles (Fig. 21.7). The thyrohyoid muscle approximates the hyoid bone and thyroid cartilage, although in practice these structures can only separate a few millimeters due to the broad, fibrous, ligamentous and membranous attachments between the two. The ST muscle pulls the thyroid cartilage caudally and is partially overlaid by the more superficial SH muscle, which pulls the hyoid bone caudally. The omohyoid muscle consists of two muscle bellies separated by an intermediate tendon, connecting the hyoid bone to the scapula.

The infrahyoid muscles are variably innervated by one or more branches of the ansa cervicalis, an anatomically variable plexus of nerve fibers formed by a combination of cervical nerves 1 through 4 (C1-C4) with the exception of the thyrohyoid

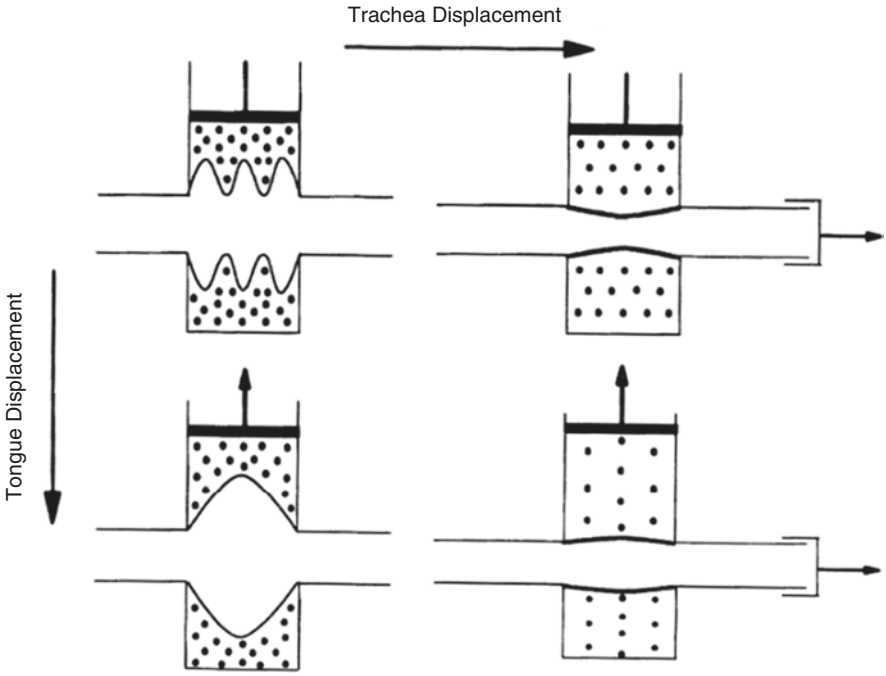


Fig. 21.6 Interacting forces of tongue and tracheal displacement on upper airway collapsibility in a cat model. It was hypothesized that interactivity was due to differences in the mechanisms underlying their influences on upper airway collapsibility: while tongue displacement generated radial dilation forces, tracheal displacement generated changes in stiffness of the airway wall through longitudinal strain [11]. Trachea and tongue displacement have interactive effects on airway collapsibility. Increasing tracheal traction increases longitudinal tension in the pharyngeal wall, represented by increasing thickness of the wall line in the diagram. Tongue displacement decreases external tissue pressure, represented by a decrease in the concentration of dots in the surrounding tissue

muscle, which receives a dedicated cervical spine nerve innervation from a branch that leaves the hypoglossal nerve separately from the ansa cervicalis [63, 64].The mean diameter of the ansa cervicalis ranges from 0.79 to 1.3 mm depending on where it is measured along its course [63]. The superior root originates from a confluence of C1 and C2 that anastomoses briefly with the extracranial portion of the hypoglossal nerve before branching inferiorly as it loops underneath the occipital artery [65]. The inferior root is more variable, being composed of fibers from some or all of C2–C4. These contributions combine in various patterns, passing deep or superficial to the internal jugular vein to join with the superior root individually or jointly, ultimately forming the loop of the ansa cervicalis (Fig. 21.8). The position of the loop summit is also quite variable and can range in height from immediately inferior to the occipital artery to 4 cm superior to the sternum. Nevertheless, it is most frequently found deep to the omohyoid tendon as it crosses the great vessels

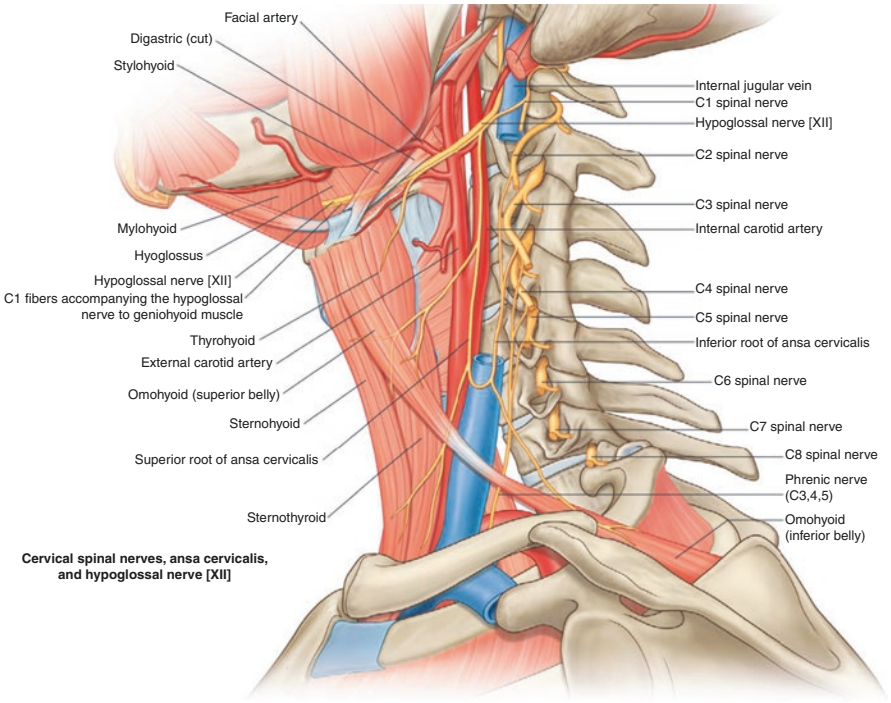


Fig. 21.7 The infrahyoid musculature and ansa cervicalis. Four paired muscles link the hyoid bone and thyroid cartilage to the sternum and scapula: the thyrohyoid, omohyoid, sternohyoid, and sternothyroid muscles. The omohyoid muscle consists of two muscle bellies separated by an intermediate tendon, connecting the hyoid bone to the scapula. The infrahyoid muscles are innervated by the ansa cervicalis, an anatomically variable plexus of nerve fibers formed by any combination of cervical nerves 1 through 4 (C1-C4). (Gray's anatomy, 2nd ed)

[63]. On gross examination, the superior root appears to carry C1-C2 fibers anterograde from the hypoglossal nerve branch point to distal muscle targets, but the majority of superior root fibers are actually efferent motor fibers originating from the inferior root that join the hypoglossal nerve to innervate distal suprahyoid targets [64]. The superior root is, therefore, composed mostly of retrograde, ascending cervical spine nerve fibers.

The omohyoid and SH muscles almost always receive a dual innervation from the ansa cervicalis [65]. The superior belly of the omohyoid muscle is innervated by a branch from the superior root in 85% of cases, and receives a dedicated branch from the hypoglossal nerve in another 10%. The nerve branch to the superior belly of the omohyoid muscle also supplies the superior part of the SH muscle in 93.1% of cases, which otherwise has its own dedicated branch from the ansa cervicalis. Innervation of the inferior belly of the omohyoid muscle is highly variable, originating from various aspects of the ansa cervicalis. The inferior belly of the SH and the totality of the ST muscle have a more constant and reliable innervation. In almost

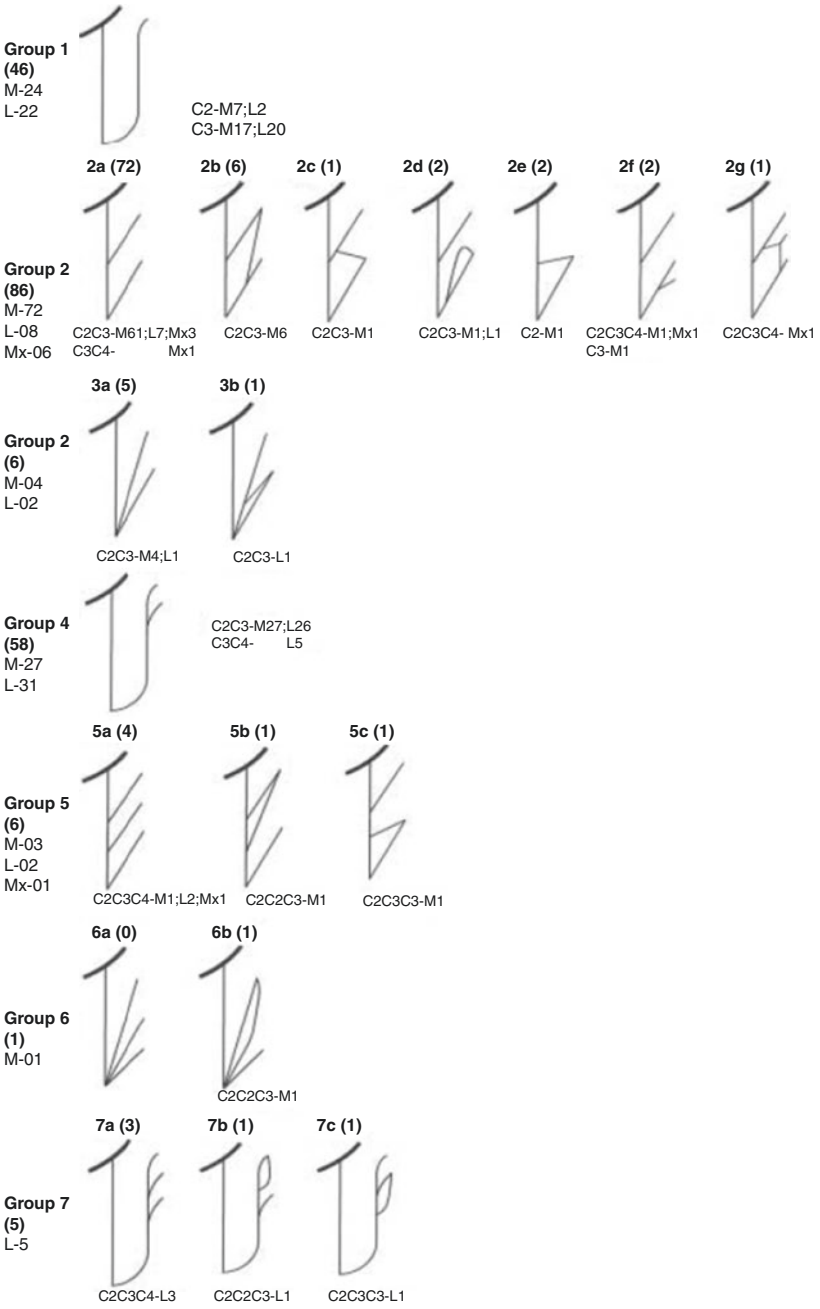


Fig. 21.8 Branching patterns of the ansa cervicalis nerve plexus. The superior root originates from a confluence of C1 and C2 that anastomoses briefly with the extracranial portion of the hypoglossal nerve before branching inferiorly as it loops underneath the occipital artery. The inferior root is more variable, being composed of fibers from some or all of C2-C4 that combine in various patterns before forming the loop of the ansa cervicalis [65]

all cases, a common trunk (average width: 0.9 mm) arises from the loop of the ansa cervicalis to supply both muscles, entering the lateral aspect of the muscles approximately 2 cm above the clavicle [63, 65]. Rarely, the two muscles receive dedicated nerve supplies from the ansa cervicalis loop that may enter their target muscles slightly higher up on the lateral border [65].

Ansa Cervicalis Stimulation for Obstructive Sleep Apnea

The human hyolaryngeal complex is quite mobile compared to animals and has been observed to shift vertically over 2 cm with strap muscle contraction during voluntary pitch change maneuvers [52]. Nevertheless, there are comparatively few data evaluating infrahyoid strap muscle function and effect on human upper airway collapsibility. Oliven et al. monitored SH and other accessory dilator muscle activity in 20 sleeping patients and found that all were substantially reduced despite increases in genioglossus muscle tone over that of wakefulness [66–68]. The authors hypothesized that muscle activity is not the only important factor in maintenance of upper airway patency: efficient coordination of single motor units within and between various airway dilator muscles working in concert may also be important.

Despite a series of animal studies demonstrating infrahyoid strap muscle effects on airway patency in animals, such studies have only been recently attempted in humans. Kent et al. hypothesized that supraphysiologic contraction of the infrahyoid musculature via ACS would reduce upper airway collapsibility, especially when combined with HNS [69]. To avoid the morbidity of open surgical dissection, the investigators developed techniques for ultrasound localization and percutaneous neurostimulation of the hypoglossal nerve and branch of the ansa cervicalis to the ST (Fig. 21.9) [70]. The ST muscle was targeted for stimulation as it has previously shown a mechanical advantage for stabilizing airway patency in rabbits and because its single site of innervation is anatomically constant, as opposed to the more variable and dually innervated SH muscle (Fig. 21.10) [17, 63, 65]. They studied eight patients with OSA during drug-induced sleep endoscopy with a mean AHI of 43.2 ± 8.9 events/hr and mean body-mass index of 32.1 ± 2.5 kg/m^2, measuring changes in maximum inspiratory airflow as a marker for upper airway collapsibility. Isolated, intermittent HNS increased maximum inspiratory airflow from baseline by 285%, or 260 mL/s (95% CI, 216–303). Isolated, intermittent ACS demonstrated a 298% improvement in maximum inspiratory airflow to 473 mL/s (95% CI: 407–539; $p < 0.001$). While the change in airflow between the two independent stimulation modalities was not significantly different, adding intermittent ACS to flow-limited inspiration during HNS increased maximum inspiratory airflow by 151%, or 205 mL/s (95% CI: 174–236; $p < 0.001$, Fig. 21.11). In an additional case report, the same team described adding continuous ACS to flow-limited inspiration during

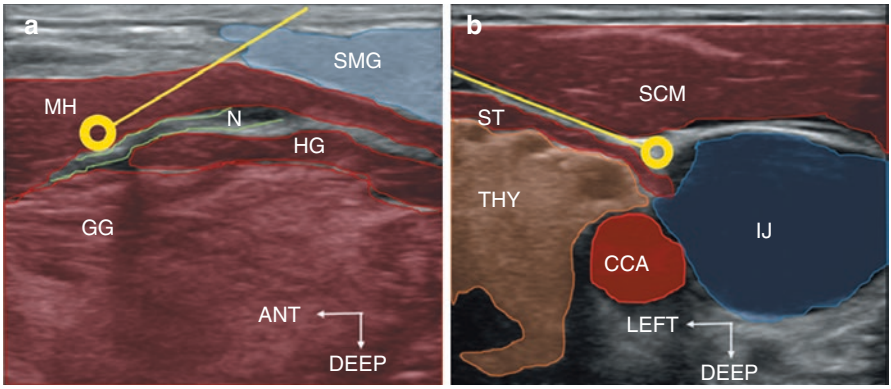
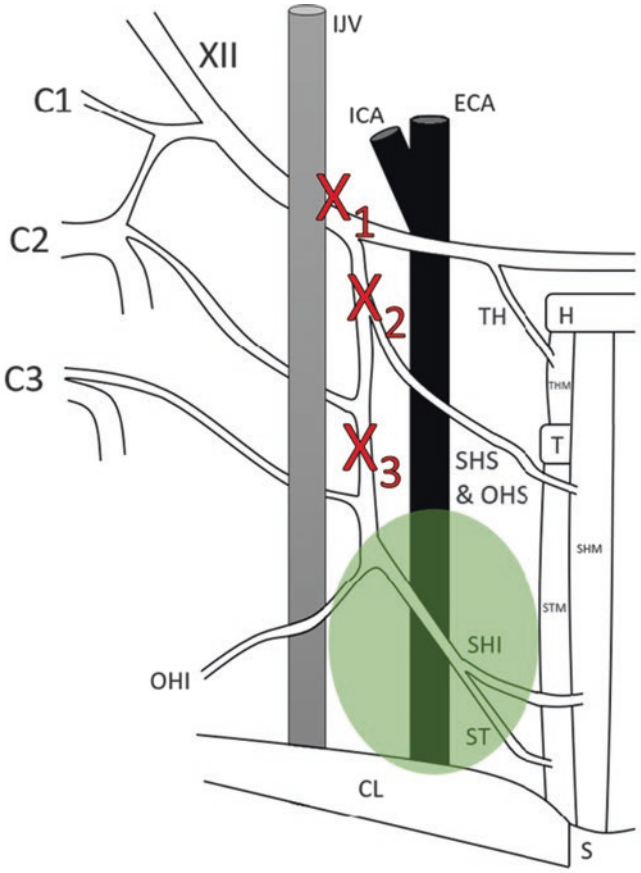


Fig. 21.9 Ultrasound localization and percutaneous neurostimulation of (**a**). The hypoglossal nerve and (**b**) The branch of the ansa cervicalis to the sternothyroid muscle [70]. (**a**) Ultrasound image of right hypoglossal nerve in a parasagittal plane traversing between mylohyoid and hyoglossus muscles to distal insertion. EMG needle course in yellow. SMG submandibular gland, MH mylohyoid, HG hyoglossus, GG genioglossus, N hypoglossal nerve, ANT anterior. (**b**) Ultrasound localization of right sternothyroid muscle innervation by ansa cervicalis in the axial plane. Nerve is triangulated, not visualized. EMG needle in yellow. SCM sternocleidomastoid muscle, ST sternothyroid muscle, IJ internal jugular vein, CCA common carotid artery, THY thyroid gland

HNS in a single patient (BMI: 31.0 kg/m^2) with severe OSA (AHI: 41.8 events/hr) [71]. They reported that ACS increased maximum inspiratory airflow by 405 ± 64 mL/s (mean ± SEM) from a baseline of 178 ± 94 mL/s, and that continuous, simultaneous ACS and HNS increased maximum inspiratory airflow by 1200 ± 208 mL/s from a baseline of 363 ± 173 mL/s. Cross-sectional area at the velopharynx was also assessed with flexible nasopharyngoscopy. Isolated ACS, HNS, and combined stimulation increased cross-sectional area by 1.2-, 2.5-, and 4.3-fold, respectively. Kent and colleagues hypothesized that ACS causes longitudinal tension in the pharyngeal walls via mechanical strain and tensioning of the soft palate caudally, similar to its effects in animals. Further research is required to determine the mechanism of effect for ACS in humans as well as patient characteristics that predict response.



	X_1	X_2	X_3	ST Trunk
Independent ansa control	X	✓	✓	✓
All anterograde fibers	✓	X	X	✓
Predictable anatomy	✓	✓	X	✓
Complete sternothyroid innervation	X	X	X	✓

Fig. 21.10 Potential ansa cervicalis neurostimulation sites. Only the common trunk of the ansa cervicalis to the sternothyroid (ST) muscle and inferior belly of the sternohyoid muscle offers independent control of the infrahyoid strap muscles from the hypoglossal nerve, all anterograde nerve fibers, predicable anatomy, and complete capture of the nerve supply to an infrahyoid muscle (the sternothyroid). (Adapted from Banneheka [65])

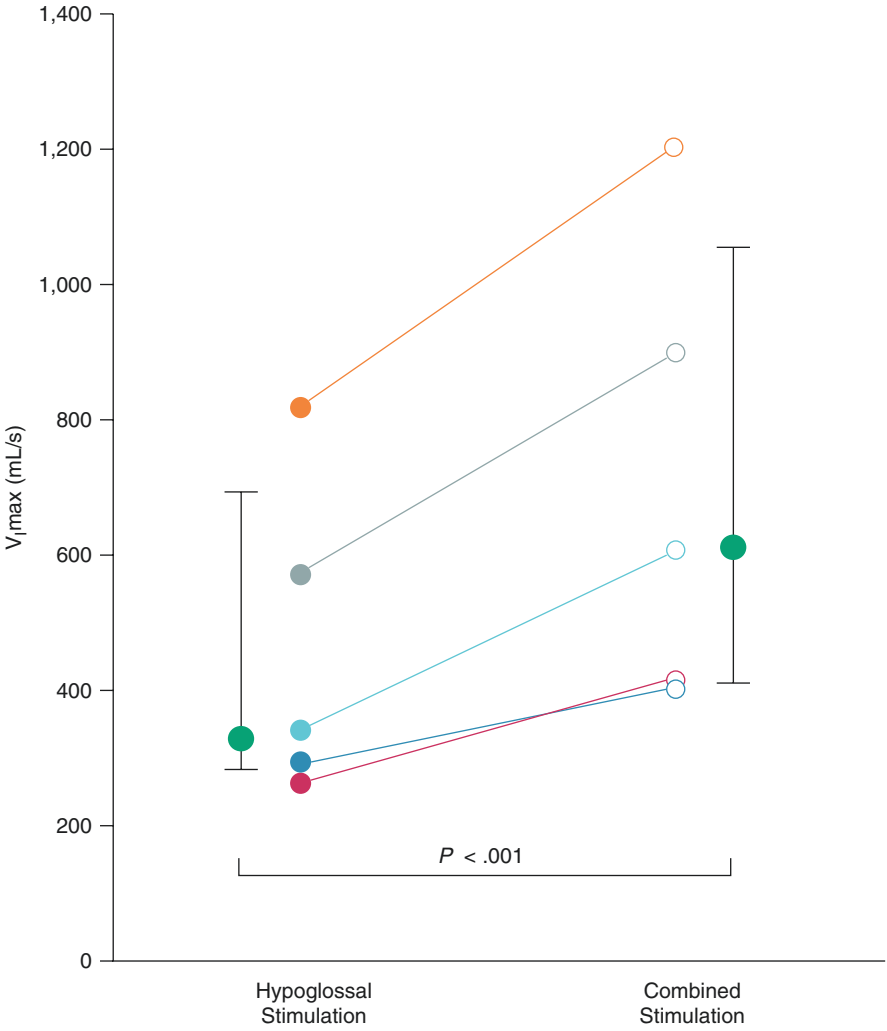


Fig. 21.11 Isolated continuous hypoglossal nerve stimulation (HNS), and HNS combined with ansa cervicalis stimulation (ACS). Adding intermittent ACS to flow-limited inspiration during HNS increased maximum inspiratory airflow ($V_I$max) by 151%, or 205 mL/s (95% CI: 174–236; $p < 0.001$) [69]

Conclusions

HNS is an effective therapy for OSA for a portion of the population intolerant to PAP, but it does not substantially alter pharyngeal wall compliance and, in isolation, is not a viable treatment option for most patients with OSA. Evidence for caudal tracheal traction in animals suggests that it modifies pharyngeal wall compliance and peripharyngeal tissue pressure. In humans, EELV and its associated changes in

caudal traction are substantively associated with upper airway collapsibility. ACS in humans may generate similar effects. Initial pilot experiments during sedated endoscopy demonstrated airflow changes comparable to those observed with isolated HNS, and combined ACS and HNS yielded greater improvements in airflow than either modality in isolation, suggesting an interactive effect that may lead to improved respiratory neurostimulation (RNS) strategies for patients with OSA. Further research is required to determine how ACS and its interactions with HNS may best benefit patients. Acute neurostimulation studies will need to move from sedated examinations to naturally sleeping humans in order to demonstrate whether meaningful changes in acute physiologic measures persist. Ultimately, implantable devices will be required to determine whether ACS with or without HNS represents a new RNS strategy yielding meaningful changes in polysomnographic and patient-centered outcomes.

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Chapter 22
Future Perspective of Electrical Stimulation in Sleep Apnea

Nico de Vries and Clemens Heiser

Contents

In *Homo Deus* Yuval Noah Harari writes:

"Cyborg engineers will go a step further, merging the organic body with non-organic devices such as bionic hands, artificial eyes, or millions of nanorobots that will navigate our bloodstream, diagnose problems and repair damages". The third kind of engineering will dispense with organic parts altogether. "Neural networks will be replaced by intelligent software, which could surf both virtual and non-virtual worlds, free from the limitations of organic chemistry." Once the human mind has been separated from its biological base, "human history will come to an end and a completely new process will begin". Harari further envisions: In the future we'll gradually merge with machines thanks to biometric sensors and brain-computer interfaces. This may sound like science fiction, but it's already a reality."

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And elsewhere in the book: “Humans will merge with computers and machines to form cyborgs — part-organic, part-bionic life forms” . Harari continues. “You could surf the Internet with your mind; you could use bionic arms, legs, and eyes; you will augment your organic immune system with a bionic immune system, and you will delegate more and more decisions to algorithms that know you better than you know yourself.”

Harari is a true visionary and we have not reached this stage yet. But we certainly have entered the era of neuromodulation and it is here to stay. Common implants are cardiac pacemakers, cochlear implant, lens replacement for cataract, hip and knee replacement, among others. There is even a journal solely devoted to neuromodulation, named, nor surprisingly, Neuromodulation. In this journal the application in a great variety of disorders is discussed such as movement disorders, cancer pain, chronic critical limb ischemia, complex regional pain syndromes, failed back surgery syndrome, fecal incontinence, gastric disorders, medical refractory angina, medical refractory epilepsy, migraine, medical refractory headache, neuropathy, neuropathic pain, painful peripheral neuropathy, Parkinsons’ disease, pelvic floor disorders, peripheral vascular disease, spasticity and urologic disorders.

If we go back to our topic, what is the future of neuromodulation in sleep apnea? OSA is a highly prevalent disease with serious health implications. It is accompanied with significant morbidity, the mortality rate is increased, while is it associated with increased risk to be involved in traffic and occupational accidents. There is no doubt adequate treatment is indicated.

Colin Sullivan introduced CPAP in 1981, a simple yet genius invention which has saved numerous of lives in the last 40 years. CPAP has become a multi billion business. We are of opinion that Dr Sullivan deserves the Nobel Prize for it. However, in spite of all R&B that has been put into it by the CPAP industry in the last four decades, CPAP still has issues that are difficult to overcome.

Roughly one of four patients has problems with using it, for a variety of reasons. These problems involve not being able to fall asleep with it, involuntarily taking if off during sleep, skin irritation because of the mask, mask leakages, blocked nose and claustrophobia, to mention some of them. Many patients do use their CPAP but not all hours of sleep, seven nights per week. Good compliance is of the essence; even the best devices only work when they are used. Widely used compliance definitions includes use of 4 hours/ 5 nights, or 4 hours/ seven nights per week, which is strange when one realizes, in particular in the 4hs/5nights compliance definition, that the patient receives treatment approximately 40% of the total sleeping time, while the other 60% he/she is not.

Forty years since the introduction of CPAP have passed and times have gradually changed. While nobody argues that CPAP, – when always used, and when the patient has no problem with using it for the rest of his/her live, – is still good treatment. In the meantime, a large variety of CPAP alternatives have seen the light. We now know that treatment of mild, early stage OSA, moderate OSA and severe OSA might differ. Is the patient perhaps suffering from positional OSA? Then positional therapy with new generation positional devices might be first treatment.

Oral devices are in mild to moderate OSA almost as effective as CPAP but often with higher compliance. Oral devices are not always possible because of poor dental status and other oral contraindications. They can have side effects such as stiff and painful jaws in the morning, dry mouth or increases saliva production, and in the long run changes in position of the lower front teeth. Still the compliance is often higher that that of CPAP, which actually tells us a lot about how unpleasant CPAP use might be. The higher compliance of oral devices brings us on the topic of "mean disease alleviation": the real life effect of any treatment is the product of effectiveness and compliance.

Sleep surgery, on good indication has also gained momentum, but still might be accompanied with severe postoperative pain, serious complications, side effects, not seldom irreversible, and with sometimes mediocre results. Still, in particular younger patients often tend to take their chances with upper airway surgery because they find the prospect of being dependent on a CPAP device or oral device not very attractive, or even unacceptable. Bariatric surgery, in morbid obese patients with OSA, who are unable to lose weight themselves, can also be a highly effective intervention.

What is possible regarding the various treatment options differs considerably per country. In many places in the world, CPAP is still sadly the only reimbursed therapy. "One size fits all". Other countries reimburse oral device treatment as well, but other treatments might not payed for.

On the other side of the spectrum, in the Netherlands, not less than seven forms of OSA treatment are reimbursed on good grounds. CPAP, oral device therapy, positional therapy (PT) with new generation positional devices in case of positional OSA, upper airway sleep surgery, maxillofacial surgery, bariatric surgery, weight loss programs and upper airway stimulation are all reimbursed on the good indication. (Upfront combination therapy, e.g., sleep surgery with PT, sleep surgery with PT, PT with oral device therapy, remains somewhat of an issue, but this is beyond the scope of this text).

Treatment diversification is the key word. We have entered the era of patient centered individualized medicine. In the ideal situation, after a thorough work up with a comprehensive sleep study, – and DISE in case indicated, – the patient and doctor discuss all available options with their respective ups and downsides. After this process of shared decision making, the preferred treatment emerges. UAS might be one of the options.

As discussed in this book, UAS is highly effective, safe, patient friendly, has little risk, is accompanied by a low complication rate, and has a high compliance. There are well defined indications and it is not indicated as first treatment line in all patients, in early stage disease or in positional OSA. We believe the indication for UAS will be come less restricted in the future. Indications may become wider for patients:

- with higher and lower AHI than the current cut-off points;
- with higher BMIs than 32;
- with more than 25% mixed and central sleep apnea;
- UAS combined with other treatment need to be further explored as well.

To make this possible, trials to prove the effectiveness and safety in these particular patient groups are mandatory.

Other indications are being explored as reported in this book, as discussed in the chapters on Phrenic nerve stimulation in central sleep apnea, Down's syndrome and closed loop neuromodulation in insomnia.

At present UAS is available only in a limited number of countries. The current neuromodulation industries have wisely and justly decided to roll out UAS in a very careful and controlled manner. To start a program in new countries, there should be a realistic expectation that insurance companies will cover it. In new centers the right infrastructure should be present, for preoperative work-up (full polysomnographies, sufficient experience with DISE), well trained surgeons, and access to postoperative polysomnography, including titration. Trained industry staff should be readily available to be present during implants and titration nights, and for trouble shooting in case needed. As discussed in this book, overnight polysomnographic titration may be replaced in total or partially, by day time titration.

Will UAS Become Cheaper?

An often raised question is if it can be expected that the costs of the whole UAS package, including pre-, peri- and postoperative care will go down. We believe there might be some room for lower price but perhaps not too much. In the first place pacemakers are expensive. While implantation of expensive pacemakers in cardiology is totally acceptable and regarded completely normal, apparently we need to get used to the idea that this expensive treatment can also be necessary in well selected cases with sleep apnea. Sleep apnea is not necessarily a condition in which only cheap therapy should be provided.

Some price reduction might be gained by not admitting patients routinely to IC units, to perform surgery in daycare instead of during an 1–2 day hospital admittance, by performing polysomnography with titration in daytime, by reducing the number of sleep studies, perhaps by deleting DISE in the preoperative work-up if other ways of assessment of the upper airway might emerge, and by using cheaper forms of sleep studies than full polysomnography.

The problem is that we should not compromise on crucial parts of the whole process and can not jeopardize the excellent results that are obtained at present, by giving up essential steps that are being performed for very good reasons.

Different Companies

As soon as a medical device company is successful, it is to be expected that other companies will try to step in as well. If entering the market is possible, is to a large extend related to existing patents. A new company that produces a device that is not

essentially different from the already existing device will have difficulty to get a new patent approved. In case of a brilliant idea for a significantly and essentially different system one might be able to get a patent approved. Less elaborative simpler systems can be envisioned with comparable results. There is always room for innovation. Existing leading companies do no sit still as well.

Combination Therapy

UAS is mostly positioned as monotherapy. Results on the good indications are usually so good that no other adjunctive treatment is needed. But some times additional treatment is indicated. One can think of adding palate surgery in case of good effect of UAS on base of tongue level but less on palate level, better effect in lateral sleeping position than in supine position, in which situation is it logical to add positional therapy with new generation positional devices, adding sleep medication in case of other sleep disturbances, weight reduction programs might work better when the patient feels better after UAS, combined UAS with oral devices and the like. In case of extreme OSA, even combined bimaxillary osteotomies and UAS, in two tempi might be an option. Closed loop neuromodulation in case of coexisting insomnia is discussed in this volume.

In conditions such as hypertension and AIDS, combined treatment is normal with far superior outcome than that of monotherapy. Insurance companies need to get used to the idea that combined treatment in sleep apnea can lead to even better results. Combined therapy will also help to wider indications. The possibilities are numerous. We only have to prove that it makes sense.

Conclusion

In sum, UAS is by far the most exciting innovation in the treatment of sleep apnea since the introduction of CPAP 40 years ago. Colin Sullivan with his CPAP has built a cathedral and we have no intention to destroy it. But we have entered the era of individualized medicine and treatment diversification. One size fits all no longer applies. UAS is a spectacular and very valuable addition to the treatment armentarium that is to our disposal. With increasing experience and knowledge, we can expect wider application and even better outcomes for our patients.

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C. Heiser, N. de Vries (eds.), *Upper Airway Stimulation in Obstructive Sleep Apnea*, https://doi.org/10.1007/978-3-030-89504-4