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Review

Origins of and implementation concepts for upper airway stimulation therapy for obstructive sleep apnea

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ABSTRACT

Upper airway stimulation, specifically hypoglossal (CN XII) nerve stimulation, is a new, alternative therapy for patients with obstructive sleep apnea hypopnea syndrome who cannot tolerate positive airway pressure, the first-line therapy for symptomatic patients. Stimulation therapy addresses the cause of inadequate upper airway muscle activation for nasopharyngeal and oropharyngeal airway collapse during sleep. The purpose of this report is to outline the development of this first-in-class therapy and its clinical implementation. Another practical theme is assessment of the features for considering a surgically implanted device and the insight as to how both clinical and endoscopic criteria increase the likelihood of safe and durable outcomes for an implant and how to more generally plan for management of CPAP-intolerant patients. A third theme is the team building required among sleep medicine and surgical specialties in the provision of individualized neurostimulation therapy.

Contents

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1. Introduction

Obstructive sleep apnea (OSA) is a prevalent (9–17% in the United States) adult human sleep disorder caused by episodes of complete or partial collapse (obstruction) of the upper airway during sleep [1,2]. Repetitive apneas and hypopneas produce sleep hypoxemia and sleep fragmentation, which if left untreated, leads to a number of cognitive, behavioral, and cardiovascular morbidities [1].

The properties of the oropharynx and/or velopharynx are under dynamic neuromuscular control. Sleep is essential for the well-being, and OSA occurs because failure of functional patency [3]. Patency is compromised by a diminished drive to the upper airway muscles, combined with a collapsible airway [1]. Sleep-related loss of upper airway muscle tone is partly responsible [4,5]. This general reduction not only affects the genioglossus muscle but other upper airway muscles, such as the ala nasi, which affects the patency of the anterior nares [6,7]. Reductions in drive in the absence of a collapsible airway will result in non-obstructive apnea, referred to as central apnea and/or central hypopnea. Thus, it is the anatomy that determines whether obstruction or near-obstruction (hypopnea) occurs when airway tone and activation falls below a threshold that can maintain patency [8]. Meanwhile, it is upper airway activation that reopens the closed airway, with or without arousal from sleep [9]. Then, once the airway reopens, a period of recovery occurs, determined by activation. In 80% of the time, an arousal from sleep occurs, with maintenance of sufficient drive in the upper airway muscles for unobstructed ventilation, before neuromuscular drive falls again as gas exchange recovers and the patient falls back to sleep. If the drive is insufficient for the anatomy, another obstructive event will ensue. Cycle extremes are determined by the gain of the control and controlled system of the ventilatory system, a property called "loop gain" [8,10]. These recurrent apneas are clinically important and lead to the development of OSA syndrome.

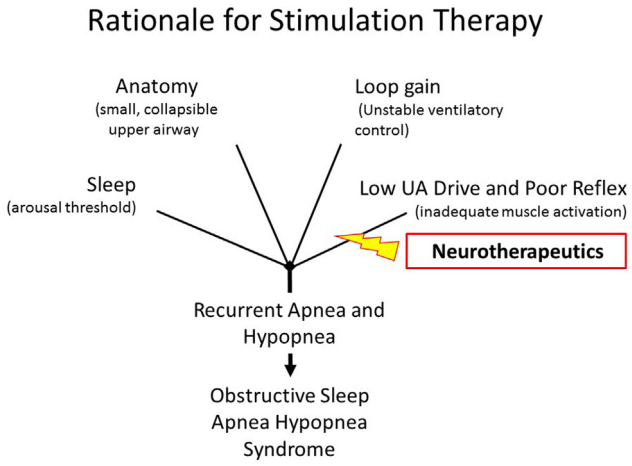

Fig. 1 – The four pathogenic pathways that in combination lead to recurrent OSA and to the development of the syndrome. If inadequate muscle activation could be reversed, even by itself, recurrent sleep apnea could be reversed at least in a subset of patients. Upper airway muscle and nerve stimulations are collectively called neurotherapeutics.

To summarize, 4 pathways, acting in combination, contribute to the pathophysiological mechanism and underlie the clinical treatment of OSA (Fig. 1). These are anatomy (small airway size and high pharyngeal compliance), low activation levels and reflex responses of muscles that keep the airway open (inadequate upper airway muscle drive), loop gain (controls on overshoot and undershoot of ventilatory responses), and sleep itself (specifically the arousal threshold) [11,12]. These pathways can be measured in human subjects [13] and estimated from elements in the polysomnogram [14–16], and will be used to individualize therapy in the future.

The first and most common treatments are focused on the pathway of an inadequately stiff and large upper airway, that is, the anatomy. Continuous positive airway pressure (CPAP) takes advantage of the ability of positive pressure to inflate the collapsible site of upper airway obstruction, keeping the channel open, thus preventing OSA and its associated sleep disruption [17,18]. CPAP secondarily reduces upper airway muscle activity [6] and, by lung inflation, loop gain [1], and permits uninterrupted sleep. Despite efficacy in the polysomnography laboratory, chronic use is limited by patient tolerance and adherence, rather than by direct side effects of the mask and tubing [19]. When adherence is defined as greater than 4 hours of nightly use, about a third of patients with moderate to severe OSA have been reported to be non-compliant to treatment [19,20].

Oral appliance therapy is an alternative approach designed to fit over the teeth and hold or advance the mandible and tongue forward, thereby creating greater or stiffer pharyngeal airway space. Clinical effectiveness is similar to that of CPAP and, like CPAP, reports of use are better initially but decline over time [21]. However, therapy is less consistently effective in patients with more severe OSA, and therapy can result in pain in the temporomandibular joint and teeth movement in approximately 20% of patients [22]. Critical closing pressure (anatomy) is improved with oral appliance therapy [22], but whether or not it is also accompanied by muscle activation is not known. Effects on sleep are reported for those that improve, but whether oral appliance therapy results in changes in the arousal threshold is not known.

Site-selective surgery on soft tissues or bony structures when effective improves OSA and critical closing pressure [23]. While no data exists for how it might affect other pathways, it could improve sleep stability and respiratory