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Electrical Stimulation of the Upper Airways Muscles

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Abstract

The upper airway muscles are importantly affected in obstructive sleep apnea syndrome (OSAS). The most important dilator, the genioglossus, shows augmented activity during wakefulness which decreases during sleep. Moreover, it shows greater fatigue and structural changes such as abnormal fiber morphology, inflammation and increased connective tissue in OSAS. Because of the crucial role of the muscles in the upper airway patency there is interest if electrical stimulation can improve the efficacy of the muscles and lead to new therapeutic options for OSAS. Indeed, the upper airways resistance can experimentally be reduced in animals, healthy persons and patients with OSAS using surface and intraneural stimulation. To translate these results in clinical application, apnea-triggered stimulation during sleep has been studied. However, although there were some positive effects the results were inconsistent and relevant side effects, such as arousals, were found. Tongue muscle training is the most recent approach to improve the function of the upper airways muscles. However, although snoring significantly improved there was no relevant reduction of respiratory disturbances in general. In conclusion, neurostimulation cannot be recommended for clinical use at this time. However, the available data prove the importance of the muscles in the pathophysiology of OSAS and the partial positive effects in patients encourage to go forward with this approach.

Obstruction of the upper airways in obstructive sleep apnea syndrome (OSAS) is associated with diminished neuromuscular activity of the dilating muscles [1] that stiffen the pharyngeal airway during inspiration [2]. Several factors have been proposed to influence the muscle tone of the upper airways: The ineffective muscle response to hypercapnia, hypoxia or negative pressure may be a possible predisposing factor for OSAS [3]. Moreover, breathing through a narrowed airway generates a greater negative intraluminal pressure, which increases the collapsing force so that pharyngeal muscles must contract more forcefully [3]. The activity of the dilator muscles is dependent on the sleep state. With sleep onset, supraglottic resistance increases in healthy persons. This phenomenon is even more pronounced in snorers and sleep apnea patients. Recent findings indicate that topical receptor mechanisms in the nasopharynx importantly influence the dilator activity in OSAS [4]. However, at sleep onset, the activity decreases largely in most patients [5].

The genioglossus muscle is one of the major pharyngeal dilators which pulls the tongue forward, thereby enlarging the cross-section of the upper airways. It has been described that sleep apnea patients when compared with normal cases have augmented genioglossus activity during wakefulness [5]. This activity is thought to represent a neuromuscular compensatory mechanism of compromised upper airway patency [6]. However, significant decreases in activity are observed during sleep when compared to controls [5, 7]. In an in vitro study, Carrera et al. [8] recently found a greater genioglossus fatigability in OSAS than in control subjects. It has been shown that episodic hypoxia/asphyxia reduces upper airway muscle endurance and selectively impairs pharyngeal dilator responses to physiological stimulation [9]. Moreover, in an animal model Petrof et al. [10] found abnormal fiber morphology, inflammatory cell infiltrates and increased connective tissue in upper airways dilator muscles. The changes were consistent with muscle injury and were accompanied with changes to the proportions of the muscle fiber types. Series et al. [11] described similar increases of the cross-sectional area of muscle fiber and the number of fast-twitch fibers in patients with OSAS. Therefore, there is no evidence that the morphological changes in sleep apnea are beneficial.

In the light of these findings, the question arose if electrical stimulation of the muscles of the upper airways could improve the efficacy of the muscles and could be used as an alternative treatment for OSAS.

Acute Effects of Neuromuscular Stimulation on the Upper Airways Diameter

Most studies in this field applied electrical neurostimulation during sleep with the intention of illustrating acute modifications of airflow dynamics. These investigations provided contradictory results [12–23]. In 1989, Miki et al. [12] studied the stimulation of the genioglossus muscle in dogs. They found that the resistance of the upper airways increased while the negative tracheal pressure was continuously lowered in the experimental setting. Under electrical neurostimulation, the resistance of the upper airways was significantly reduced. It reached a plateau on a low level with stimulation frequencies of at least 50 Hz. Additionally, Yoo et al. [13] demonstrated in a canine model that nonselective hypoglossus stimulation yielded the greatest improvement in upper airways resistance as compared with that for selective activation of the geniohyoid, genioglossus, and hyoglossus/styloglossus muscles. Odeh et al. [14] performed electrical stimulation of the dilating muscles in dogs and measured flow and pressure profiles of the upper airways. Schnall et al. [15] studied the effects of transmucosal and transcutaneous stimulation in wake healthy persons. In both studies, only stimulation of the genioglossus significantly reduced the upper airways resistance. These results could be confirmed by Bishara et al. [16] who directly stimulated the genioglossus, the geniohyoideus, and the sternohyoideus in dogs. Only the stimulation of the genioglossus muscle was able to reopen a total obstruction.

In conclusion, experimental surface and intraneural stimulation has been shown to reduce upper airways resistance in animals, healthy persons and patients with OSAS. In particular, stimulation of the genioglossus muscles resulted in a significant reduction in airway resistance and an increase in the critical collapsing pressure. Genioglossus stimulation is most important to widen the shape of the upper airways.

Apnea-Induced Neurostimulation: Clinical Application

Investigations on the use of electrical stimulation in patients also provided heterogeneous results. Schwartz et al. [24] found that intraneural stimulation of the hypoglossal nerve significantly improved respiratory disturbances during sleep. Based on their results in dogs, Miki et al. [25] carried out a study on the influence of percutaneous submental electrostimulation of the genioglossus muscles in 6 patients with OSAS. Stimulation was performed during sleep and was triggered by apnea of more than 5 s duration. This resulted in a reduction in the apnea index and in the number of oxygen desaturations to under 85% [25]. Miki et al. [25] did not find any negative effects such as arousals, increased blood pressure or heart rate. In contrast, Guilleminault et al. [26] failed to observe an enlargement of the upper airways either under submental or intraoral stimulation. Moreover, they reported contractions of the platysma, undesired movements of the tongue, and induction of EEG arousals. Oliven et al. [27] studied the effect of stimulation with sublingual surface electrodes and found a reduction of the transpharyngeal resistance and an improvement of the airflow. However, they were not able to reopen obstructive apneas. Moreover, Decker et al. [28] using submental surface electrodes and implanted intraneural electrodes found only an inconsistent termination of the apneas.

Therefore, although neuromuscular stimulation triggered by apneas improves respiratory disturbances during sleep it is – by now – not sufficiently effective to treat the complex sleep apnea syndrome.

Tongue Muscle Training

Muscle training using electrical neurostimulation (ENS) has been found to effectively strengthen skeletal muscles in pathological or posttraumatic situations. In healthy muscles, ENS can induce the activity of motor units which are difficult to activate voluntarily [29]. It has been shown that ENS with a frequency of 50 Hz activates both muscle fiber types completely and homogeneously [30]. Moreover, in contrast to the structural changes of the upper airways muscles in the

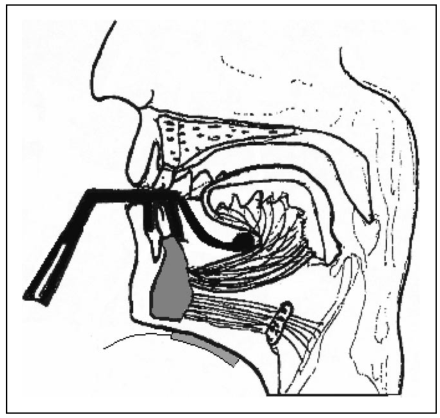

Fig. 1. Stimulation is performed using a chin electrode with both a positive and negative lead and an oral electrode which is placed as a ring on the teeth. The stimulating part of the oral electrode is placed beneath the tongue.

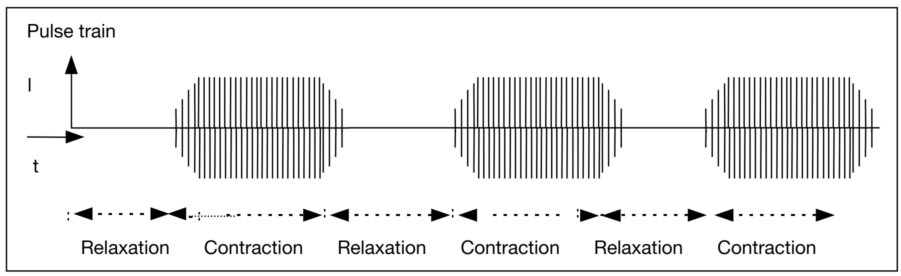

Fig. 2. Stimulation consists of a relaxation cycle and a contraction cycle. The contraction cycle consists of two parts, a ramp-up phase (1.5 s) and contraction phase. The relaxation cycle consists of a ramp down phase (1.0 s) followed by a phase of no stimulation. Only during the contraction cycle and ramp down phase are stimulation pulses transmitted in a pulse train between the electrodes.

course of sleep apnea, no inflammatory changes have been observed under electrical stimulation in skeletal muscles [31]. Neurostimulation of the upper airways muscles during sleep induces acute transient improvements in airflow dynamics but can be limited by side effects. Taking together the findings on the training of skeletal muscles and the effects of neurostimulation on the upper airways, the question arose whether training of the tongue muscles during the daytime might improve the strength of the dilator muscles and, therefore, reduce nocturnal respiratory disturbances without impairing sleep quality. The rationale of the tongue muscle training was to improve the maximum muscle activity by stimulating both the fast- and the slow-twitch fibers more homogeneously and to maintain a sufficient activity level in spite of the fall during sleep.

Only few data on the tongue muscle training from clinical trials are available. In a noncontrolled study, Wiltfang et al. [32] found an increase in tongue muscle power and reported sufficient training effects in a single case. However, controlled studies in large groups on daytime tongue muscle training comparing with either CPAP or placebo were needed. Therefore, a randomized, double-blind, placebo-controlled study to evaluate the efficacy and compliance of a tongue muscle training by electrical neurostimulation in patients was recently published [33]. The stimulating electrode was placed centrally below the tongue with the aim of achieving stimulation of the genioglossus muscles (fig. 1). The stimulation device produced a symmetric biphasic output. The net direct current delivered into the load was <0.1 mA (fig. 2). 57 patients with mild or moderate OSAS (apnea/hypopnea index (AHI) 10–40/h) practiced tongue muscle training for 20 min twice a day during the daytime for 8 weeks.

There was no significant change in the AHI or the sleep profile either under placebo or stimulation. However, snoring improved significantly under stimulation (baseline 63.6 ± 23.1 epochs/h, stimulation 47.5 ± 31.2, $p < 0.05$) but not under placebo. There was a small subgroup of patients with a baseline AHI <25/h whose AHI decreased significantly. The reduction of snoring was even more pronounced in this group of responders. In contrast, under placebo no responders were to be found. The conclusions of the study are limited by several aspects. It was not possible to take morphological factors such as anatomical differences in the shape of the upper airways, BMI, body position or variability in the upper airway function during sleep into account. As it is not known whether even weak pulses might have a stimulating effect, even applying minimal stimulation in the placebo group was avoided. However, the absence of sensation during training cannot be excluded as a reason for the larger number of drop-outs in the placebo group [33].

It is not clear how long the therapeutic effect in the responders persists and whether a longer duration of training beyond 8 weeks, or repetition of training after an interval, might be beneficial. However, at this time the results do not permit recommending tongue muscle training as an alternative treatment in patients with OSAS. Nevertheless, the partially positive results encourage further studies on methods which aim at influencing the muscle function [33].

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