

# Neurostimulation for Obstructive Sleep Apnea: Investigations

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## Abstract

*Neurostimulation of the upper airway muscles (accessory muscles of respiration) was accomplished in anesthetized dogs and sleeping humans by electrical stimulation of the hypoglossal nerves. Such stimulations relieved partial airway obstructions in dogs. They also aborted (shortened) obstructive sleep apnea events in humans who suffer with obstructive sleep apnea syndrome. In one subject, stimulations delivered in advance of apneic events (by automatic cycling) prevented apneas. Neurostimulation for obstructive sleep apnea may be an important concept for future research and development.*

## Introduction

The causes of obstructive sleep apnea are multifactorial: some are more easily corrected than others. The nasal factor is amenable to surgical or medical treatment; the long soft palate can be surgically shortened; redundant pharyngeal tissues can be excised or tightened; space occupying masses in the airway can be removed; and receding jaws can be advanced. But the unsolved problem is inadequate neuromuscular tone in the tongue and pharyngeal muscles.

Upper airway airflow depends on the balance between two counteracting forces. The diaphragm and chest wall

muscles generate negative intraluminal pressure during inspiration, whereas the upper airway muscles open or stabilize the airway by pulling the tongue and hyoid forward. This occurs during normal inspiration, and it has been measured in the laboratory animal.

For example, in a study in dogs by Miki and others, stimulation of the genioglossus muscle, with needle electrodes in the body of the tongue, produced a significant lowering of upper airway resistance as measured through the transected trachea.<sup>1</sup> It is the hypoglossal nerve that is the motor nerve to the upper airway muscles, the genioglossus probably being most important since it pulls the tongue forward, out of the airway. Other hyoid suspensory muscles are also innervated by the hypoglossal nerve.

It is hypothesized that inadequate tone in upper airway musculature contributes to the airway collapse in obstructive sleep apnea and that such a pathophysiological state could be reversed with electrical stimulation of the hypoglossal nerves.<sup>2-4</sup>

## Animal Studies

A pilot study was performed in mongrel dogs, wherein (under general anesthesia) electrodes were wrapped around the hypoglossal nerves. Electrical stimulations produced visible mass contractions of the tongue, reducing its bulky size. Obstructive breathing was then created with placement of an inflatable balloon into the hypopharynx. It was then inflated until partial airway obstruction--snoring sounds--appeared. When the hypoglossal nerves were stimulated, the airway expanded from tongue contraction, and snoring disappeared.

In the next study, an automatic stimulator was devised, one that was triggered by obstructive breathing events

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(Figure 1). A strain gauge was sutured to the anterior tracheal wall so that it would detect elongation of the trachea (separation of tracheal rings) reflecting intratracheal negative pressure from inspiratory effort.<sup>5</sup> Inspiration against a partially obstructed airway yielded measurable increases in tracheal elongations. The exaggerated negative pressure events, as measured, were processed so that they could activate the hypoglossal nerve stimulators.

Figure 2 illustrates how the armed (activated) electrodes responded to negative pressure and prompted neuromuscular stimulation with relief of airway obstruction (decreased height of respiratory oscillations and disappearance of audible snoring).

In three laboratory animals this design was successfully constructed such that airway obstruction would trigger the hypoglossal nerve stimulator which in turn would relieve the obstruction.<sup>6</sup> These were acute experiments with external apparatuses, however, and no attempt was made to convert this study into chronic experiments.

### Human Studies on Apnea Patients

Next pilot study was done to determine the effects of hypoglossal nerve stimulation during sleep in human subjects with known obstructive sleep apnea. All patients were middle aged and otherwise healthy.

Needle electrodes were inserted percutaneously into what was regarded as close proximity to the hypoglossal nerves. On each side two electrodes were placed, about a centimeter apart. While the patient was still awake, electrical stimulations were delivered, producing visible contractions of the tongue with some degree of protrusion, but mostly reduction in its size or bulk.

Patients were then connected to the polysomnographic recorders, and were allowed to fall asleep. The results from four patients are summarized.

Patient #1 suffers mild obstructive sleep apnea and successfully uses continuous nasal positive air pressure (CPAP) almost every night. Off her machine she averages 20 apneas or hypopneas per hour lasting 20 to 30 seconds each, which usually end in a microarousal.

With stimulation (delivered when an apneic event was observed) we could interrupt or abort the apnea event, shortening its duration. Notable was a consistent interval between the stimulation and the abortion of the apnea. Some stimulations, when delivered late in the apnea events, were associated with microarousals, but when delivered earlier, arousals were absent. This suggested that hypoglossal nerve stimulations produced a local--not a central--effect.

Patient #2 underwent a uvulopalatopharyngoplasty (UPPP) about a year earlier, which had converted him from a severe sleep apnea sufferer into a mild one, with apneas

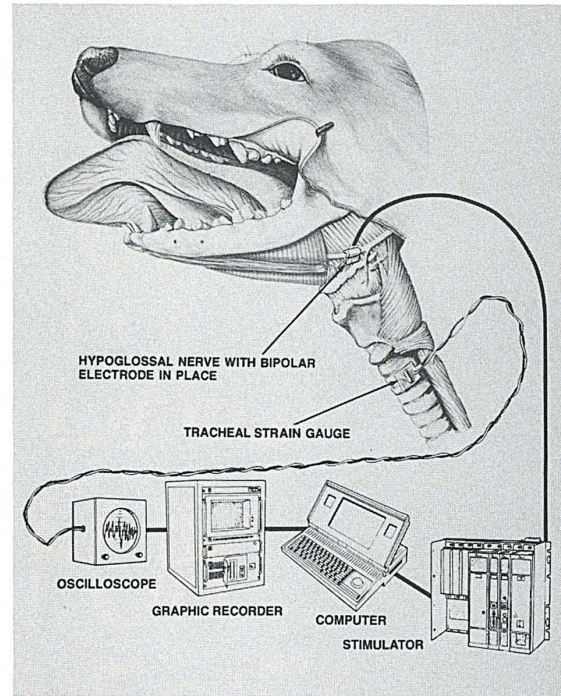


**FIGURE 1.** Apnea-activated tongue stimulator: Schematic of device to detect negative inspiratory airway pressure (from tracheal elongation) which triggered hypoglossal nerve stimulation to relieve airway obstruction by tongue contraction.

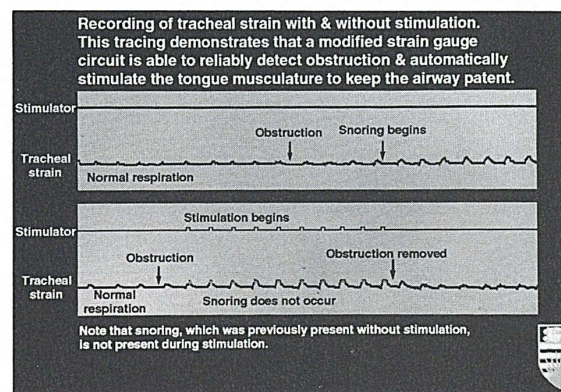


**FIGURE 2.** Tracheal inter-ring distance during inspiration and expiration represent oscillations of intra-tracheal airway pressure. Partial airway obstruction exaggerated the oscillations and produced snoring. Hypoglossal nerve stimulation triggered by exaggerated negative pressure relieved that pressure and the snoring sounds.

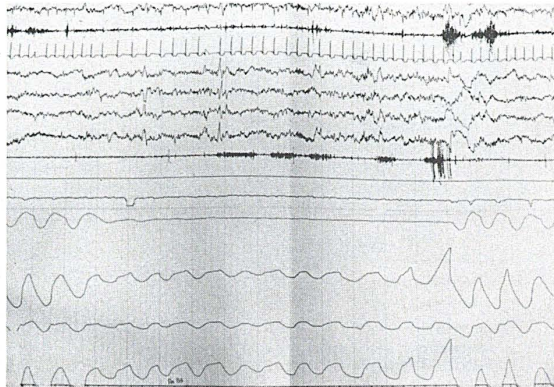


**FIGURE 3.** Polysomnographic recording from obstructive sleep apnea patient #4. Patient's typical obstructive sleep apnea episodic pattern.

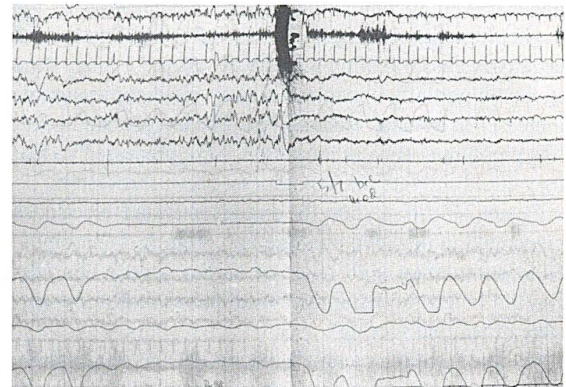


**FIGURE 4.** Polysomnographic recording from obstructive sleep apnea patient #4. Aborted (shortened) apneic episode from late stimulation of the hypoglossal nerves.

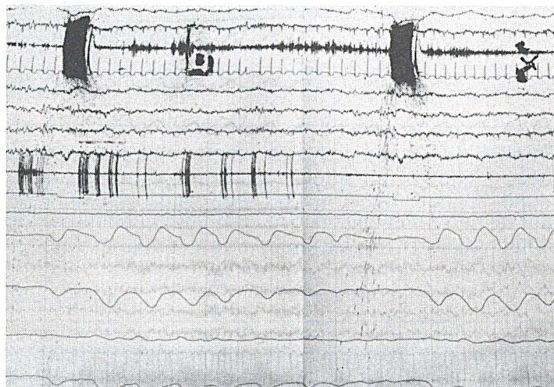


**FIGURE 5.** Polysomnographic recording from obstructive sleep apnea patient #4. Aborted (shortened) apneic episode from early stimulation. Note absence of arousal.

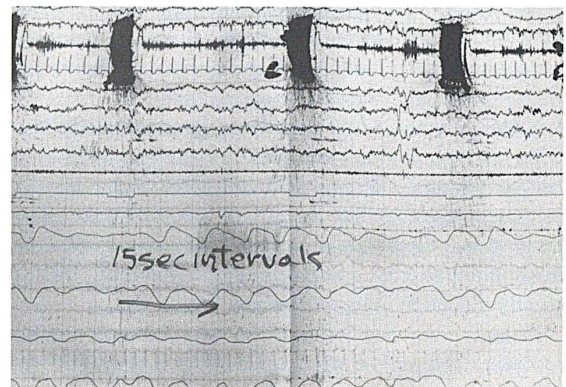


**FIGURE 6.** Polysomnographic recording from obstructive sleep apnea patient #4. Absence of apneic episodes when stimulation is delivered every 15 seconds.

of about 18 to 21 seconds duration. Early stimulation could reproducibly abort and shorten the apneic periods, with no arousal effect.

Patient #3 underwent a UPPP several years earlier which brought some improvement, but he persists with obstructive sleep apnea, measuring 15 to 33 seconds. Stimulation aborted apnea events so that their duration could be shortened to any duration that we chose. Hypopneic events were similarly aborted by stimulation. Late stimulations were associated with microarousals; others were not.

Patient #4 also had a UPPP but it made little difference in his severe obstructive sleep apnea. He uses CPAP, but

begrudgingly. He suffers repetitively with long apneas followed by arousals and five breaths or so; then he relapses into his apneas.

With stimulation we could abort his apnea at almost any time during the event and microarousals were not associated, whether in early stimulation or later (Figures 3-5).

Most interesting of all, we then tried apnea prophylaxis, by delivering stimulations regularly at 15 second intervals during a stage of his sleep when he was otherwise obstructing after every fifth breath. As long as the automatic (every 15 second) stimulations were being delivered, apneas were prevented altogether (Figure 6). Then if stimulations

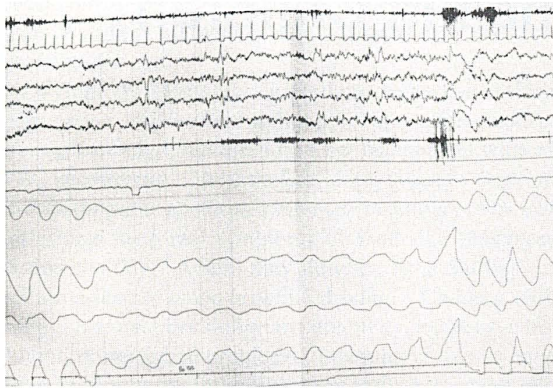


**FIGURE 7.** Polysomnographic recording from obstructive sleep apnea patient #4. Reappearance of patient's typical apnea patterns when stimuli are stopped.

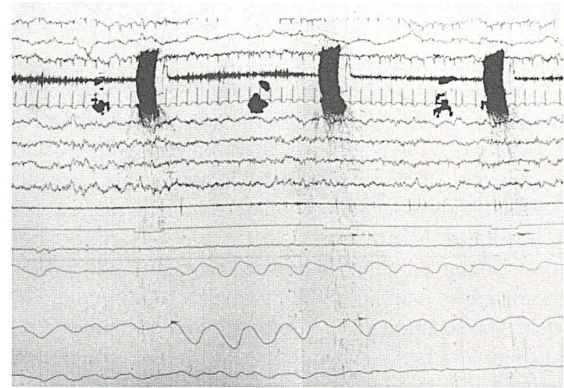


**FIGURE 8.** Polysomnographic recording from obstructive sleep apnea patient #4. Absence of apneic episodes when cyclical stimulation is reinstated. Note presence of deep stage sleep.

stopped, he relapsed into long apneas (Figure 7); but when stimulations were reinstated, apneas were again prevented completely (Figure 8). Furthermore, as evident in the recordings, he maintained deep stage sleep without arousals.

In general, there were no ill effects of the procedures. None of the patients found the stimulations to be particularly painful. If we delivered them when the patients were awake, they did say that it was annoying, since they could feel the tongue contractions as well as contraction under the chin (myelohoid). Only on one patient did we perform "control" stimulations: electrodes were placed in the back of the neck and in one of the toes. The neck control produced no effects whatsoever. The toe control triggered leg motion and arousal.

### Conclusions and Commentary

Electrical stimulation of the accessory muscles of respiration in the upper airway via the hypoglossal nerve was shown to relieve partial airway obstruction in anesthetized dogs and to interrupt obstructive sleep apneic events in humans.

This raises the possibility that a device could be constructed to deliver such stimulations, either on-demand or on-automatic-cycle, to produce a more physiologic reversal of the disease process than does any of the currently available treatments for obstructive sleep apnea. However, clinical application of the concept will require investigations into the long-term effects of nerve stimulations, and into the optimal timing of nerve stimulations.<sup>7</sup> Miniaturization and implantation of the devices might also be required.

The diaphragmatic pacemaker might serve as the technological prototype for future investigations. The authors

encourage other investigators to consider neurostimulation as a potentially important new frontier in management of this distressing disorder of obstructive sleep apnea.

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