

# Tongue-muscle Training by Intraoral Electrical Neurostimulation in Patients with Obstructive Sleep Apnea

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**Study objectives:** To investigate the efficacy of tongue-muscle training by electrical neurostimulation of the upper-airway muscles as an alternative therapy option for obstructive sleep apnea syndrome.

**Design:** A randomized, placebo-controlled, double-blind study.

**Setting:** Department of pneumology and sleep laboratory, University of Witten/Herdecke, Germany.

**Patients:** 67 patients with an apnea-hypopnea index of 10 to 40 per hour were randomly assigned to 2 groups: a treatment group of 33 patients (mean age, 50.8 ± 12.1 years; mean body mass index, 29.1 ± 4.4 kg/m<sup>2</sup>) and a placebo group of 34 patients (mean age, 53.3 ± 11.3 years; mean body mass index, 28.9 ± 4.9 kg/m<sup>2</sup>). Fifty-seven patients completed the study.

**Interventions:** Tongue-muscle training during the daytime for 20 minutes twice a day for 8 weeks.

**Measurements and Results:** Treatment efficacy was examined by

polysomnography. Snoring, but not apnea-hypopnea index, improved with stimulation (snoring baseline, 63.9 ± 23.1 epochs per hour; stimulation training, 47.5 ± 31.2; P < .05) but not with placebo training (snoring baseline, 62.4 ± 26.1 epochs per hour; placebo, 62.1 ± 23.8; NS.).

**Conclusions:** Although tongue-muscle training cannot generally be recommended for the treatment of sleep apnea, the method has proven to be effective in the treatment of snoring.

**Key Words:** Sleep apnea, obstructive, CPAP, positive pressure ventilation, laryngeal muscles, electrical stimulation, transcutaneous electrical nerve stimulation.

**Abbreviations:** AHI, Apnea-hypopnea index; OSAS, Obstructive sleep apnea syndrome

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## INTRODUCTION

OBSTRUCTION OF THE UPPER AIRWAY IN SLEEP APNEA SYNDROME (OSAS) IS ASSOCIATED WITH DIMINISHED NEUROMUSCULAR ACTIVITY OF THE DILATING MUSCLES<sup>1</sup> THAT STIFFEN THE PHARYNGEAL AIRWAY DURING INSPIRATION.<sup>2</sup> The ineffective muscle response to hypercapnia, hypoxia, or negative pressure has been proposed as a possible predisposing factor for OSAS.<sup>3</sup> 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.<sup>3</sup> The genioglossus muscle is one of the major pharyngeal dilators that pulls the tongue forward, thereby enlarging the cross-section of the upper airway. Its activity is augmented in patients with OSAS during wakefulness, possibly due to an attempt to compensate for the impairment of upper-airway patency. However, significant decreases in activity have been observed during sleep in patients with OSAS when compared with controls.<sup>4,5</sup> Moreover, in an animal model, Petrof et al<sup>6</sup> found abnormal fiber morphology, inflammatory cell infiltrates, and increased connective tissue in upper-airway dilator muscles. The changes were consistent with muscle injury and were accompanied by changes in the proportions of the muscle fiber types. Series<sup>7</sup> et al described similar increases of the cross-sectional area of muscle fiber and the number of fast-twitch fibers in patients with OSAS.

## Disclosure Statement

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Although continuous positive airway pressure has been proven to be highly effective in the treatment of OSAS,<sup>8</sup> patient compliance is not as good as might be expected.<sup>9</sup> Thus, on the basis of the above-mentioned findings, the question arose whether electrical stimulation of the muscles of the upper airway could be used as an alternative treatment for OSAS. Most studies in this field have investigated the acute effects of neurostimulation of the pharyngeal muscles on upper-airway patency or resistance.<sup>10-16</sup> Experimental surface and intraneural stimulation have been shown to reduce upper-airway resistance in animals, healthy persons, and patients with OSAS.<sup>10-12,14,16-18</sup> In particular, stimulation of the genioglossus muscles resulted in a significant reduction in airway resistance and an increase in the critical collapsing pressure.<sup>10,14,17</sup> With regard to clinical application, results reported to date are contradictory. Schwartz et al found that intraneural stimulation of the hypoglossal nerve significantly improved respiratory disturbances during sleep,<sup>18</sup> while Guillemainault et al, using intraoral or subcutaneous stimulation, failed to achieve effective control of OSAS.<sup>19</sup> Individual investigations involving apnea-triggered nocturnal stimulation reportedly disturbed the patient by arousals that occurred during stimulation.<sup>19</sup>

Neurostimulation during sleep induces acute transient improvements in airflow dynamics but can be limited by side effects. Neurostimulation during wakefulness is designed to strengthen the upper-airway muscles and improve their performance during sleep. Muscle training using electrical neurostimulation has been found to effectively strengthen skeletal muscles in pathologic or posttraumatic situations. In healthy muscle, electrical neurostimulation can induce the activity of motor units that are difficult to activate voluntarily.<sup>20</sup> It has been shown that electrical neurostimulation with a frequency of 50 Hz activates both muscle fiber types completely and homogeneously.<sup>21,22</sup> Moreover, in contrast to the structural changes of the upper-airway muscles in the course of OSAS, no inflammatory changes have been observed under electrical stimulation in skeletal muscles.<sup>20</sup> Thus, the question therefore 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.

There have been no controlled studies in large groups comparing neurostimulation of the pharyngeal muscles with either continuous positive airway pressure or placebo. In particular, there have been no investigations on daytime tongue-muscle training. Therefore, we performed a randomized, double-blind, placebo-controlled study to evaluate the efficacy of tongue-muscle training using electrical neurostimulation in patients with mild or moderate OSAS.

## METHODS

### Design

This randomized, placebo-controlled, double-blind clinical study was conducted at a university sleep laboratory. The study was approved by the University of Witten/Herdecke Ethics committee. All patients gave their written informed consent. Patients who met the inclusion and exclusion criteria were randomly assigned to either the treatment or the control group. Examinations were done at baseline as well as after a treatment period of 8 weeks.

### Patients

Patients were enrolled consecutively as they were referred to the sleep laboratory to be examined for hypersomnia. The inclusion criterion was newly diagnosed OSAS (apnea-hypopnea index—the number of apneas plus hypopneas per hour of sleep [AHI]—10 to 40 per hour with clinical symptoms). The exclusion criteria were previous treatment for OSAS, acute heart failure, serious cardiac arrhythmias, other acute diseases necessitating immediate treatment with continuous positive airway pressure, neurologic or psychiatric disorders, pregnancy or lactation, use of drugs acting on the neuromuscular system, wearing of a cardiac pacemaker or cardioverter or defibrillator, insulin-dependent diabetes mellitus, trauma, cutaneous lesions, and prior surgery in the submental region. In the recruitment period of February and March 2002, 67 patients were found to be eligible for participation (Table 1). During the course of the study, 9 patients in the placebo group and 1 patient in the treatment group were lost to follow-up. There was no significant difference between drop-outs and those who completed the protocol in mean age (drop-outs, 57.3 ± 15.3 years; protocol-completed, 51.1 ± 10.8 years), mean body mass index (27.9 ± 5.0 kg/m<sup>2</sup> versus 29.2 ± 4.6 kg/m<sup>2</sup>), neck circumference (40.9 ± 4.7 cm versus 40.9 ± 4.0 cm), or mean baseline AHI (24.7 ± 9.9 versus 26.0 ± 7.7). Four of the 9 drop-outs in the placebo group stopped training because of medical reasons after 0 to 360 minutes (nausea, newly diagnosed psychiatric disease, pacemaker); 1 refused any further treatment of OSAS. Four patients in the placebo group and 1 in the treatment group could not be reevaluated because of professional (n = 3) or personal reasons (n = 2). Although they informed us about their regular training, this information could not be objectively proven and thus these patients were excluded.

**Table 1**—Anthropometric Data and Baseline Characteristics of the Total Sample.

Parameter	Treatment (n = 33)	Placebo (n = 34)	P value
Age, y	50.8 ± 12.1	53.3 ± 11.3	NS
Body mass index, kg/m <sup>2</sup>	29.1 ± 4.4	28.9 ± 4.9	NS
Neck circumference, cm	40.7 ± 4.2	41.2 ± 4.1	NS
Men, no.	19	25	NS
Apnea-hypopnea index, no./h	24.9 ± 8.5	26.9 ± 7.3	NS
Snoring, epochs/h	64.1 ± 22.8	64.2 ± 24.1	NS
FOSQ, score	88.3 ± 35.3	72.9 ± 42.0	NS
ESS, score	10.2 ± 4.9	10.5 ± 5.1	NS
Attention, %	5.3 ± 5	5.1 ± 5.1	NS

Data are presented as mean ± SD unless otherwise noted.

FOSQ refers to the score of the Functional Outcome of Sleep Questionnaire; ESS, Epworth Sleepiness Scale; Attention, number of missed reactions on the attention test.

## Procedure

After the baseline examination, a technician who was not involved in the examination procedures or in the data evaluation instructed each patient on how the training device was to be used at home. The patients were instructed to use the stimulator for 20 minutes twice a day for 8 weeks and to set the stimulation amplitude at every training session as high as they could tolerate. Patients were asked to enter in a diary the duration of training and the level of stimulation, as well as any side effects. During the home training period, patients could contact 1 of the authors (WR) in the event of any problems. In addition, they were contacted by phone after 1 and 3 weeks by the technician. At the end of the home training period, patients were examined by polysomnography, attention test,<sup>23</sup> Epworth Sleepiness Scale,<sup>24</sup> Functional Outcome of Sleep Questionnaire,<sup>25</sup> serum creatine phosphokinase, and self-assessment questionnaire (side effects). Patient compliance was studied objectively using the built-in time counter and subjectively using a diary.

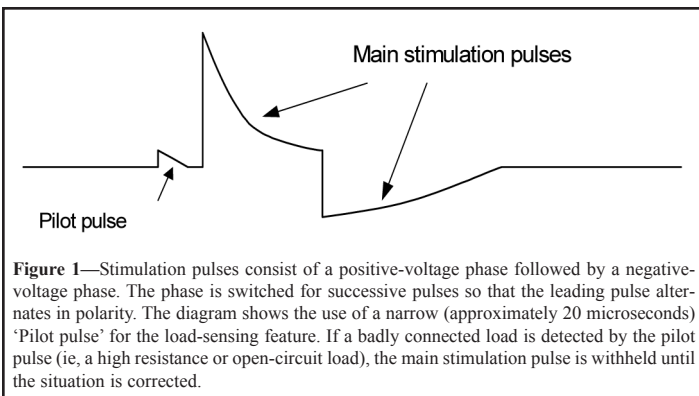
The serial numbers of the devices, together with their assignment to the placebo or stimulation group, were given to the investigating physician in sealed envelopes, which were opened only after completion of the study. Thus, the hospital staff and patients were blinded as to which group the patients had been assigned. The technicians who evaluated the polysomnograms, the performance tests, and the questionnaires were also blinded to the patients' status, and they did not communicate with or instruct the patients.

## Apparatus

The stimulation device (Apone-Stim 400 Muscle Stimulator, BMR Neurotech Ltd., Derrybeg Industrial Estate, Co. Donegal, Ireland) is a single-channel output device that produces a symmetric biphasic output (Figure 1). One electrode is placed in the mouth under the tongue, and the other is placed externally under the chin (Figure 2). The chin electrode is a dual electrode with both a positive and negative lead. The placebo device was identical to the stimulation device but did not deliver an electrical impulse. Under stimulation, but not under placebo, electrical sensations can be felt. The patients were informed that they might, but would not necessarily, experience a sensation of electrical stimulation. They were not informed that there was a difference between stimulation and placebo. Use of the device was recorded by a built-in time counter.

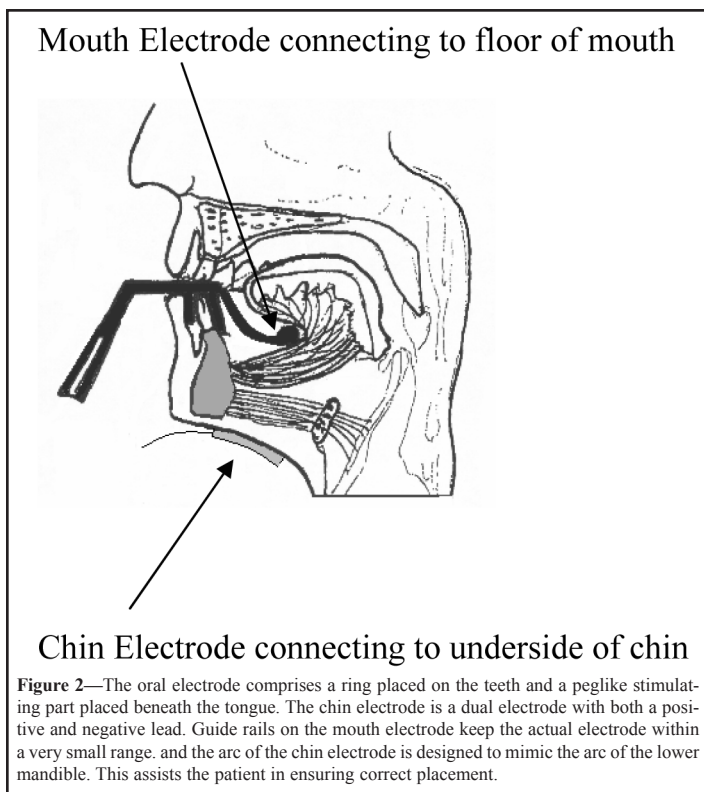
## Stimulation Technique and Safety Aspects

Stimulation pulses consisted of a positive voltage phase followed by a negative voltage phase. The phase was switched for successive pulses so that the leading pulse alternated in polarity. The stimulation parameters were frequency, 50 Hz; pulse width, 200 microseconds; contraction time, 10 seconds; and relaxation time, 20 seconds.<sup>26,27</sup> The net direct current delivered into the load was less than 0.1 mA. Isolation from the user was achieved by means of a transformer. The level of output stimulation current was then fed back to a microcontroller so that the microcontroller could then respond to situations such as a disconnected lead or a poorly



**Figure 1**—Stimulation pulses consist of a positive-voltage phase followed by a negative-voltage phase. The phase is switched for successive pulses so that the leading pulse alternates in polarity. The diagram shows the use of a narrow (approximately 20 microseconds) 'Pilot pulse' for the load-sensing feature. If a badly connected load is detected by the pilot pulse (ie, a high resistance or open-circuit load), the main stimulation pulse is withheld until the situation is corrected.

connected load. The maximum output intensity level was 60% of maximum output level.



**Table 2**—Polysomnographic and Performance Data.

Parameter	Treatment			Placebo		
	Baseline	Training	Δ	Baseline	Training	Δ
AHI, no.	24.7 ± 8.6	25.3 ± 16.6	0.6 ± 11.8	27.7 ± 6.3	27.9 ± 9.9	0.2 ± 10.1
Snoring, epochs/h	63.9 ± 23.1	47.5 ± 31.2*	-16.9 ± 32.3	62.4 ± 26.1	62.1 ± 23.8†	-0.2 ± 20.5‡
Minimum SaO <sub>2</sub> , %	81.7 ± 6.8	81.4 ± 8.3	-0.3 ± 6.1	82.3 ± 5.8	80.9 ± 5.8	-1.4 ± 5.8
TST, min	316.8 ± 49.2	326.4 ± 44.6	9.6 ± 49.3	329.6 ± 56.3	336.2 ± 41.4	6.6 ± 62.7
Sleep stage, % of TST						
3/4	19.1 ± 13.6	25 ± 35.7	6.8 ± 38.7	23.5 ± 9.8	19.3 ± 11*	-4.2 ± 8.3
REM	11 ± 4.7	12 ± 5	1.1 ± 6.6	12.9 ± 5.2	14.3 ± 4.7	1.4 ± 6.5
WASO, min	39.3 ± 37.5	35.9 ± 45.2	-3.9 ± 30.9	32.1 ± 25.7	28.3 ± 27.4	-3.8 ± 25.9
Arousals, no.	23.7 ± 9.5	23.2 ± 11	-0.7 ± 12.1	23 ± 9.8	24.2 ± 9.6	1.2 ± 9.5
RAI, no.	10 ± 6	11.8 ± 11.8	1.8 ± 11.2	12.5 ± 6.2	12.3 ± 7.2	-0.3 ± 7.6
FOSQ, score	84.8 ± 32.5	102.0 ± 24.4*	4.2 ± 37.7	74.2 ± 36.9	94.8 ± 30.7*	2.6 ± 36.2
ESS, score	10.2 ± 4.9	9 ± 4.3	-1.5 ± 4.1	10.5 ± 5.1	9.4 ± 4.7*	-1.3 ± 3.5
Attention, %	5.3 ± 5	4.7 ± 4.8	-0.2 ± 5.6	5.1 ± 5.1	4.7 ± 4.5	-0.4 ± 3.6

Data are presented as mean ± SD.  
 Δ refers to the change between baseline and training; AHI, apnea-hypopnea index—the number of apneas and hypopneas per hour of total sleep time (TST); Snoring, epochs per hour of TST; REM, rapid eye movement; WASO, wake after sleep onset; RAI, total number of respiratory-related arousals; FOSQ, score on the Functional Outcome of Sleep Questionnaire  
 \**P* < .05—baseline versus training within the treatment or placebo group.  
 †*P* < .05—comparison of placebo group versus treated patients after training.  
 ‡*P* < .05—comparison of the changes (Δ) of treatment versus placebo.

**Table 3**—Compliance

Parameter	Treatment (n = 32)	Placebo (n = 25)
Training time estimated, min	2027 ± 534	2251 ± 587
Training time counted, min	1882 ± 648	1839 ± 800
Intensity minimal	4.9 ± 1.6	8.4 ± 1.8*
Intensity maximal	5 ± 1.6	8.4 ± 1.8*

Data are presented as mean ± SD.  
 \**P* < .001 for treatment versus placebo.  
 Intensity minimal refers to the minimal amplitude of stimulation that the patient set during the study period (Scale, 0-10). Intensity maximal, the maximal amplitude of stimulation that the patient set during the study period (Scale, 0-10).

## Polysomnography

The polysomnograms were performed using the Alice 4 Sleep Diagnostic System (Respironics, Murrysville, Penn, USA). The following parameters were recorded: electroencephalogram C4A1 or C3A2, submental or pretibial electromyogram, electrooculogram, effort (thoracic and abdominal impedance plethysmography), respiratory flow (thermo-elements), snoring signals (laryngeal microphone), oxygen saturation (finger pulse oximetry). The analysis of sleep stages and arousals was carried out in accordance with the guidelines of Rechtschaffen and Kales<sup>28</sup> and the ASDA criteria.<sup>29</sup> An apnea was defined as the cessation of respiratory flow for at least 10 seconds. A hypopnea was defined as a reduction in effort of 50% in comparison with baseline for at least 10 seconds or as any reduction in effort together with an arousal or with a decrease in oxygen saturation of at least 4%. Arousals were defined as respiration induced when they occurred at the earliest with the onset and at the latest within 2 seconds after the end of an apnea or hypopnea. The microphone sensor was an electric condenser microphone (Panasonic WM-62A, Kadoma City, Osaka, Japan). It was coupled to the body surface via an enclosed cavity so that the body surface vibrations were transmitted as hydraulic pressure changes inside the cavity to the microphone's membrane. To quantify snoring, the number of epochs (30 seconds per page) with evidence of microphone signals for at least 2 seconds outside of movement artefacts were counted as described earlier.<sup>30-32</sup>

## Statistics

Descriptive statistics were computed according to the measurement scale of each variable. Baseline comparisons between treatment and control groups were conducted at a testwise  $\alpha$  level of 5% using  $\chi^2$  tests for nominal measurement-scale variables and, otherwise, Mann-Whitney U tests. Analysis of treatment efficacy was restricted to patients who completed the study according to the protocol (per protocol analysis). Exploratory comparisons between baseline and postintervention examination were done at testwise  $\alpha$  levels of 5% using Wilcoxon matched-pairs test. Concomitant efficacy and tolerability variables were compared between groups in an exploratory way at a testwise  $\alpha$  level of 5% each.<sup>33</sup>

## RESULTS

Thirty-four patients were randomly assigned to the placebo group and 33 were assigned to the treatment group. The anthropometric and baseline characteristics of both groups are summarized in Table 1. According to test-wise comparisons at the 5% level, the groups did not differ significantly in the anthropometric and baseline parameters.

Table 2 contains polysomnography and performance data of the patients who completed the study. The baseline AHI was 27.7 ± 6.3 in the placebo group and 24.7 ± 8.6 in the treatment group (NS). There was no improvement in AHI observed after training in either group.

While the number of snoring epochs remained unchanged in the placebo group (baseline, 62.4 ± 26.1 epochs per hour; placebo, 62.1 ± 23.8; NS) it decreased in the training group (baseline 63.9 ± 23.1 epochs per hour versus 47.5 ± 31.2; *P* < .05). There were no differences in the duration of use of the devices between the treatment and placebo groups. A higher intensity of electrical stimulation was set in the placebo group when compared with the treatment group (maximum intensity: treated patients, 5.0 ± 1.6; placebo, 8.4 ± 1.8; *P* < .001) (Table 3). On a scale of 0 (minimum) to 6 (maximum), treated patients scored the symptoms ery-

thema (treated patients,  $0.4 \pm 0.7$ ; placebo,  $0.2 \pm 1.0$ ;  $P < .05$ ), skin irritation (treated patients,  $0.7 \pm 1.4$ ; placebo,  $0.3 \pm 1.2$ ;  $P < .05$ ), and facial pain (treated patients,  $1.1 \pm 1.8$ ; placebo,  $0.3 \pm 1.0$ ;  $P < .05$ ) higher than did placebo patients. However, the overall level of such symptoms was very low. There were no significant differences in muscle twitches, awakenings during the night, difficulty in falling asleep, headaches in the morning, or dryness of mouth or throat. There was no evidence of retroposition of the tongue from patients' reports and no increase in creatine phosphokinase observed in either group. A similar pretraining to posttraining increase was observed in both groups in the score of the Functional Outcome of Sleep Questionnaire score. There were no differences observed in the Epworth Sleepiness Scale or from the attention test in either group (Table 2).

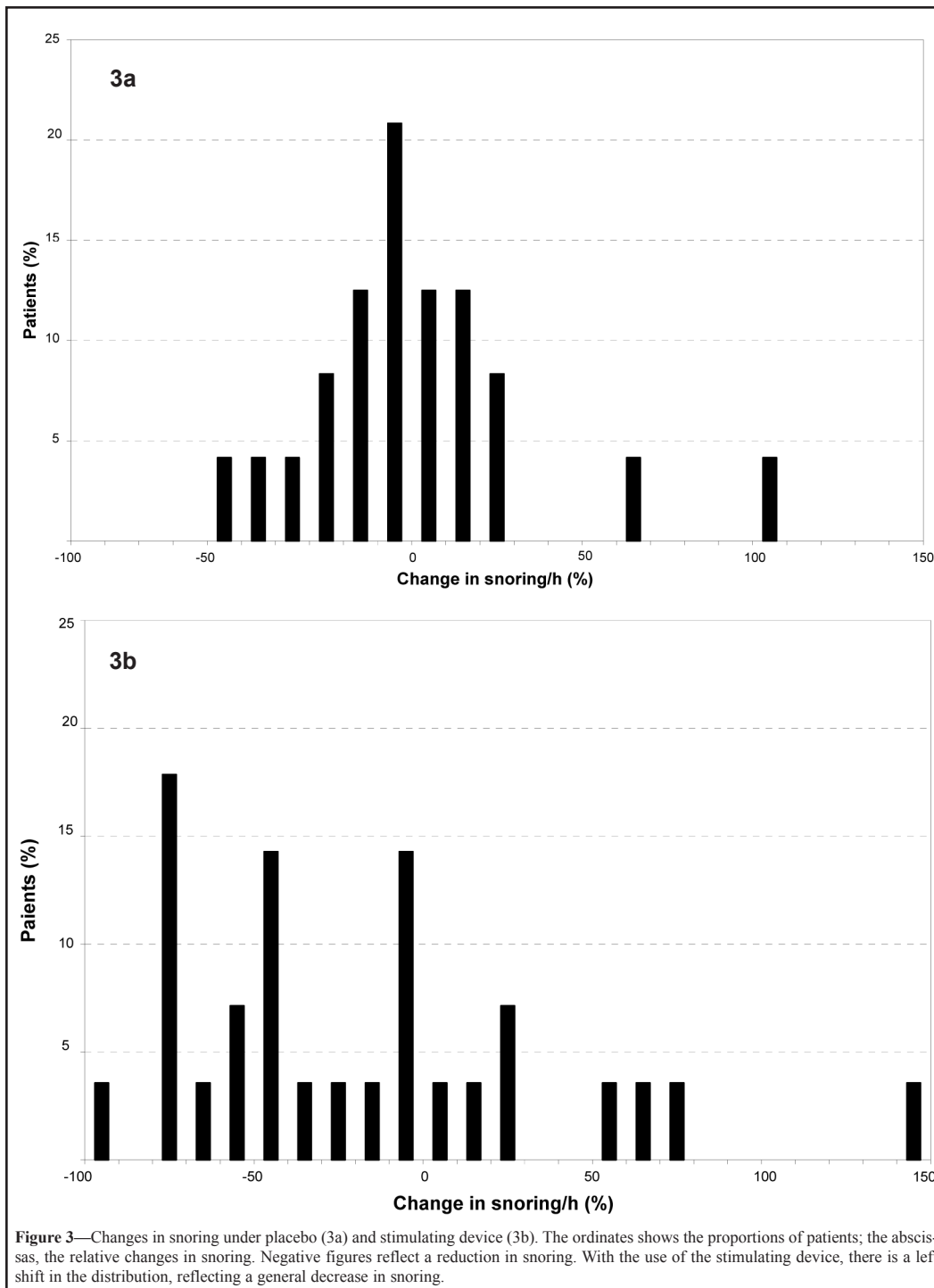
## DISCUSSION

This randomized, placebo-controlled, double-blind study is the first study to investigate training of the tongue muscles by electrostimulation in patients with OSAS. Under stimulation, but not under placebo, patients showed a significant improvement in snoring.

This study describes a new method for which there is no comparable study available to date. With the exception of a single case report, no data have been provided on the use of this method in patients with OSAS.<sup>34</sup>

The activity of the dilator muscles is dependent on the sleep state. With sleep onset, the supraglottic resistance increases in healthy persons. This phenomenon is even more pronounced in snorers and patients with OSAS. It has been described that, when compared with normal cases, patients with OSAS have augmented genioglossus activity during wakefulness.<sup>4</sup> This activity is thought to represent a neuromuscular compensatory mechanism of compromised upper-airway patency.<sup>35</sup> Recent findings indicate that topical receptor mechanisms in the nasopharynx have an important influence on the dilator activity in OSAS.<sup>36</sup> However, at sleep onset, the activity is largely decreased in most patients.<sup>4</sup> Moreover, Carrera et al<sup>37</sup> recently found in vitro that there is a greater genioglossus fatigability in muscles biopsies from patients with OSAS than in genioglossus muscles from control subjects. Furthermore, inflammatory infiltrates, increases of connective tissue indicating muscle injury, and disproportionate increases of 1 muscle-fiber type (IIa) have been demonstrated in the upper-airway dilator muscles.<sup>6,7,37</sup> Therefore, there is no evidence that these morphologic changes in OSAS are beneficial.

Previous studies have applied electrical neurostimulation during sleep with the intention of illustrating acute modifications of airflow dynamics. These investigations provided contradictory results. In 1989, Miki et al<sup>38</sup> carried out a study to investigate the stimulation of the genioglossus muscle in dogs. Under electrical neurostimulation, the resistance of the upper airway was significantly reduced. Based on these results, the same working group<sup>39</sup> 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 seconds in duration. This resulted in a reduction in the apnea index and in the number of oxygen desaturations less than 85%.<sup>38</sup> Guilleminault et al failed to observe an enlargement of the upper airway, under either submental or intraoral stimulation.<sup>19</sup> While Miki et al<sup>34</sup> failed to find any negative effects such as arousals or



**Figure 3**—Changes in snoring under placebo (3a) and stimulating device (3b). The ordinates shows the proportions of patients; the abscissas, the relative changes in snoring. Negative figures reflect a reduction in snoring. With the use of the stimulating device, there is a left shift in the distribution, reflecting a general decrease in snoring.

increased blood pressure or heart rate, Guillemainault et al<sup>19</sup> reported contractions of the platysma, undesired movements of the tongue, and induction of electroencephalographic arousals.

In the light of these reports and prompted by results obtained with peripheral muscle stimulation, the present study did not conduct stimulation during sleep but, instead, focused on training of the tongue muscles during the daytime. Electrical neurostimulation training of skeletal muscle has proven to effectively strengthen not only I muscle fiber type.<sup>21,22</sup> Electrical neurostimulation is not associated with pathologic changes such as inflammation. Thus, 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. The stimulating electrode was placed centrally below the tongue with the aim of achieving stimulation of the genioglossus muscles. This approach is based on studies in animals and awake subjects, in whom a significant reduction in upper-airway resistance was seen only when the genioglossus muscle was stimulated.<sup>17,40-42</sup> In a noncontrolled study on tongue-muscle training, Wiltfang et al<sup>34</sup> found an increase in tongue-muscle power.

Our data do not permit us to conclude that morphologic factors such as anatomic differences in the shape of the upper airway (eg, whether the transverse diameter is longer than the long axis or vice versa) are responsible for the different responses in snoring (Figure 3). Other factors that cannot be excluded are changes in body mass index or body position or variability in the upper-airway function during sleep. Furthermore, it is not yet known how long the therapeutic effect persists and whether prolongation of training beyond 8 weeks, or repetition of training after an interval, might increase the therapeutic effect. There was no significant difference in snoring, as revealed by the self-assessment, between the patient groups after training, which might be due to incomplete answers to the questionnaire.

Whether the study conclusion is hampered by the fact that the placebo subjects experienced no stimulatory sensation might need discussion. We decided to not apply a minimal stimulation, since it is not known whether even weak pulses might have a stimulating effect. Although the absence of sensation during training cannot be excluded as a reason for the larger number of dropouts in the placebo group, counterarguments against this are the individual reasons for dropping out, as described above, and the lack of difference in the use of the device between placebo and treated groups. As expected, the placebo patients selected higher settings of stimulation amplitude. This indicates that the placebo patients used their devices correctly according to the design. However, the use of the devices could not be assessed in the dropouts. Thus adherence with stimulation may be artifactually high in the remaining placebo-treated patients.

## CONCLUSIONS

For patients who snore, electrical neurostimulation treatment for training of the tongue muscles may be considered. Individual responses to treatment should be checked in the sleep laboratory. Furthermore, regular follow-up studies are needed to establish whether secondary treatment failure occurs.

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