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Journal of Sleep Medicine & Disorders

Research Article

Effects of Hypoglossal Nerve Stimulation on Tongue Strength and Endurance: Prospective Study

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Submitted: 26 April 2023

Accepted: 27 June 2023

Published: 27 June 2023

ISSN: 2379-0822

Keywords

- Tongue strength and endurance;
- OSA;
- Iopi;
- Neurostimulation

Abstract

Background: Neuromuscular changes in patients with OSA might occur when treated with the application of unilateral THN.

Objectives: Our aim was to assess whether nightly long-term stimulation of the hypoglossal nerve (N. XII) or CPAP treatment could modify tongue strength and/or endurance and whether there is a difference in tongue strength and/or endurance between OSA patients compared to an age and sex-matched healthy control group.

Materials and methods: We prospectively measured tongue strength and/or endurance by The Iowa Oral Performance Instrument in OSA patients previous to any treatment and after 3 months of neurostimulation. We collected data of 28 male OSA patients (including 9 subjects treated with neurostimulation, and 19 subjects treated with CPAP) and 20 healthy controls. In the CPAP and healthy control groups, patients were divided each time into 2 subgroups according to their BMI.

Results: We did not find any influence of nightly stimulation of the hypoglossal nerve or of CPAP on tongue strength and endurance. We observed no influence of the BMI on tongue strength and endurance; obesity doesn't play a negative role in muscle capacity.

Conclusion: Although it can be theorized that a lack of supportive strength in the pharyngeal musculature is strongly contributive to the pathophysiology of OSAS, these difference could not be measured in awake patients.

INTRODUCTION

Obstructive sleep apnea syndrome (OSAS) is characterized by repetitive episodes of respiratory arrest despite continuous breathing efforts. This condition occurs during sleep and is mainly due to obstruction of the upper respiratory tract with a decrease in oropharyngeal neuromuscular activity in the face of persisting negative inspiratory pressures [1]. Very recently, it was suggested that stimulating the hypoglossal nerve (N.XII) would reshape the tongue enough to enlarge and stiffen the oropharyngeal tract, eventually achieving complete or partial resolution of obstructive sleep apnea (OSA) [2]. The application of unilateral targeted hypoglossal neurostimulation (THN) in patients with untreated severe obstructive sleep apnea for a 12-month period led to clinically and statistically significant improvements in apneas and hypopneas falls in oxygen saturation and sleep fragmentation, i.e. the main pathophysiological events in OSAS. A residual effect after one year of hypoglossal nerve neurostimulation using the THN system was also found: the improvement obtained in the apnea/hypopnea index (AHI), micro-arousal index (MAI) and oxygen desaturation index (ODI) remained unchanged on the first night without stimulation [3-10]. Mechanisms explaining these changes have been proposed, but there are few that have been clearly demonstrated in studies and so far they remain hypothetical and mainly based on our general knowledge of muscle physiology. Stimulation could influence the type of muscle fibers in tongue musculature, resulting in improvement in force or endurance for a given neural output. Another mechanism involved might be that continuous nocturnal stimulation modifies the control of the interaction between agonist and antagonist muscles within the tongue, facilitating the maintenance of a patent pharynx in sleep. This second mechanisms would induced little or no change in tongue strength and endurance.

However, little is known about the effects of chronic stimulation of the hypoglossal nerve (N.XII) on tongue musculature strength and endurance. To assess the extent of neuromuscular changes in patients with OSA treated with the application of unilateral THN, we compared patients with OSA versus healthy control subjects, measuring tongue strength and endurance before and after 3 months of treatment. To take into account the eventual effect on tongue musculature of an improvement in OSA per se, we also studied a group of patients treated with the classical therapy, i.e. continuous positive airway pressure (CPAP). As body weight could increase the volume of the tongue. The eventual influence of body weight was also considered.

MATERIALS AND METHODS

Study Design

Patients treated with unilateral hypoglossal stimulation participated in an open label, single center, single arm safety and efficacy study in patients with untreated moderate to severe OSA. The Belgian Federal Medicines and Medical Devices Agency (Agence Federale de Medicaments et Produits de Sante) and the Ethics Committee of the Université Catholique de Louvain approved respectively the device and protocol CEHF

2013/039. This study was performed according to "Helsinki's declaration" and to 7th May 2004 Belgian law regarding scientific experimentations on human beings.

Endpoints

The primary endpoints were to assess whether nightly long-term stimulation of the hypoglossal nerve (N. XII) or CPAP treatment could modify tongue strength and/or endurance in OSA patients and whether there is a difference in tongue strength and/or endurance between OSA patients compared to an age and sex-matched healthy control group. The secondary endpoint was to assess, whether BMI influences tongue strength and/or endurance.

Patient Selection

The study includes male individuals between the age of 25 and 70 years old. The use of muscle relaxant drugs was an exclusion criterion for all patients. All subjects gave written consent before the start of the study.

Group I

This cohort included OSA patients treated with the application of unilateral THN (ImThera stimulator) [2]. The patients had either used CPAP at one point in the past and had stopped treatment or refused to use CPAP altogether.

Group II

The second cohort of OSA patients was treated with standard treatment (CPAP). We selected patients suffering from OSAS confirmed by polysomnography, who were eligible for CPAP treatment reimbursement according to the Belgian Social Security rules, which require an apnea-hypopnea index of at least 20 events per hour of sleep. The cohort was divided in two groups according the BMI: above 30 kg/km2 and below 30 kg/m2.

Group III

In this cohort only healthy individual without OSA were included. The cohort was divided in two groups according the BMI: above 30 kg/km2 and below 30 kg/m2.

Polysomnography

Full night polysomnography (PSG) included the recording of three channels of EEG, two EOG, one chin EMG channel and one lead ECG. Snoring was obtained from a microphone glued to the patient's neck. Airflow was assessed with a nasal cannula for nasal flow, and with an oronasal thermocouple for oral flow and as a backup nasal signal. Two inductive uncalibrated elastic bands monitored thoracic and abdominal respiratory movements. Body position was estimated from a sensor placed above the sternum, and oxygen saturation and pulse rate were obtained from a finger sensor of a pulse oximeter. Periodic legs movements were computed from two piezoelectric sensors placed on the right and left ankles (Medatec BrainNet, Brussels, Belgium). The polysomnographies were analyzed by hand according to Rechtschaffen and Kales, with stages 3 and 4 non-REM sleep merged. Micro arousals were scored according to the American Academy of Sleep Medicine, and reported as the number of micro-arousals per hour of sleep or micro arousal index (MAI). Apneas and hypopneas were identified according to the American Academy of Sleep Medicine rules, with hypopneas defined as a >30% decrease in the flow signals lasting at least 10 seconds and inducing a >4% oxygen saturation fall or a micro arousal. The number of apneas and hypopneas per hour of sleep is given as the apnea-hypopnea index. The percentage of apneas and hypopneas in the supine position is also reported. The oxygen desaturation index (ODI) was defined as the number of falls in oxygen saturation >4% per hour of sleep.

Device for measurement of strength and endurance

The Iowa Oral Performance Instrument (IOPI; Model 2.1, IOPI Medical LLC, Carnation, WA) is a portable device that measures the amount of pressure exerted on a small air-filled bulb. Pressures (expressed in kPa) are obtained digitally on a LCD panel on the instrument. A series of LED lights representing percentages in 10% increments of a manually set pressure acts in combination with the build-in timer as a tool for measuring endurance. The IOPI has a high inter- and intra-individual reliability [11-15]. We remark that the instrument doesn't allow assessing one half of the tongue but that it is designed to assess the strength of the tongue as a whole.

Measurement of strength and endurance

Tongue strength was performed 3 times. The highest pressure obtained across the three trials is considered as the participant's Maximal Isometric Pressure (MIP).

Endurance measures were performed after the MIP measuring tasks and a resting period of 8 minutes was assured between the two series of measurements.

Anterior and posterior bulb positioning during strength and endurance measures: In this study both anterior and posterior tongue body were assessed.

Swallowing anterior pressure: considering the fact that MIP does not represents a swallowing–related physiological value but rather a maximal effort that is never performed during a regular swallow, anterior tongue pressure was also be recorded while swallowing a coffee spoon of viscosity standardized pudding.

In total 5 measures are taken into consideration: 1) MIP anterior or "MIPant" measured in kPa, 2) MIP posterior or "MIPpost" measured in kPa, 3) Swallowing anterior pressure or "Swalant" measured in kPa, 4) Endurance anterior or "Endant" measured in seconds, 5) Endurance posterior or "Endpost" measured in seconds (Figure 1). These 5 measurements were acquired once for individuals in group III and once before treatment and once after 3 months of treatment for patients in group I and II.

Statistical analysis

Data are presented as mean ± SD. Statistical differences between the baseline and the follow-up visits were assessed using Wilcoxon test. All statistical analyses were performed using SPSS Statistics 23.

RESULTS

Patients

We collected data of 28 male OSA patients (including 9 subjects treated with neurostimulation, and 19 subjects treated with CPAP) and 20 healthy controls. In the CPAP and healthy control groups, patients were divided each time into 2 subgroups according to their BMI. Distribution of age and BMI is shown in [Table 1].

Main outcomes

In comparing OSA patients treated with CPAP or THN and healthy controls at baseline, we could not see any significant differences in tongue strength and endurance. The results are shown in [Table 1]. We observed a tendency towards higher values for tongue strength and endurance in the CPAP group, but this was not statistically significant. The data as presented above were comparable for the healthy controls and OSA patients with a BMI < 30 kg/m2. We observed no influence of the BMI on tongue strength and endurance. The differences between the two BMI groups were not statistically significant.

We did not find any influence of nightly stimulation of the hypoglossal nerve on tongue strength and endurance. The results are shown in [Tables 1,2]. We also could not find any influence of nighty stimulation of the hypoglossal nerve on tongue endurance. A comparison was also performed before and after the therapy and revealed no differences between the groups. The application of CPAP itself did not seem to have an influence on tongue strength and endurance. The results are shown in [Table 1,2].

DISCUSSION

New findings

The main goal of this study was to assess whether nightly stimulation of the hypoglossal nerve (N. XII) could modify tongue strength and/or endurance in OSA patients.

First, we have observed that anterior and posterior tongue strength and endurance between patients suffering from OSAS and an age and sex-matched healthy control group was not different. Although it can be theorized that a lack of supportive strength in the pharyngeal musculature is strongly contributive to the pathophysiology of OSAS, these difference could not be measured in awake patients.

Secondly, our findings seem to show that obesity doesn't play a negative role in muscle capacity, since we have found a comparative strength and endurance despite BMI differences, and therefore the correlation between BMI and OSA is probably due to an increase in tongue volume and narrowing of the pharynx, rather than a weakening of the muscle strength and endurance. To our knowledge, the influence of obesity in tongue strength and endurance has never been described before. Previous studies have shown that there is increased tongue volume and deposition of fat at the base of tongue in patients with OSA compared to controls, implicating that increased tongue fat explains the relationship between obesity and obstructive sleep apnea [16-18].

Third, we observed that the application of unilateral targeted hypoglossal neurostimulation (N. XII) (THN) in patients with untreated OSA for a 3-month period did not lead to statistically significant changes in tongue strength and endurance. Neither anterior nor posterior parameters seemed to be influenced by the treatment. The question immediately rises on how this can be explained while previous studies [2], have showed the efficacity of the THN principle in the treatment of OSA. An explication can be found in the complex physiology of the pharyngeal apparatus. The tongue is a hydrostat, like an elephant trump, where the final result of muscle contraction depends on the coordinated action not of one but of all muscles acting together on the hydrostat [6]. The tonic stimulation implicit in the ImThera THN concept, may modify the neural pattern of stimulation of the whole of the tongue muscles, either by modifying the agonist-antagonist balance of forces, or by modifying the motor units that are activated, or even because the cortical areas dealing with tongue representation and activation may have modified their circuitry and functioning. Indeed, hypoglossal nerve dysfunction in obstructive sleep apnea was assessed in patients with OSA versus control subjects by measuring motor unit potential (MUP) on electromyography [4]. It has been observed that the MUPs of the patients with OSAS were longer in duration and had a larger size

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Individual response of patients to THN

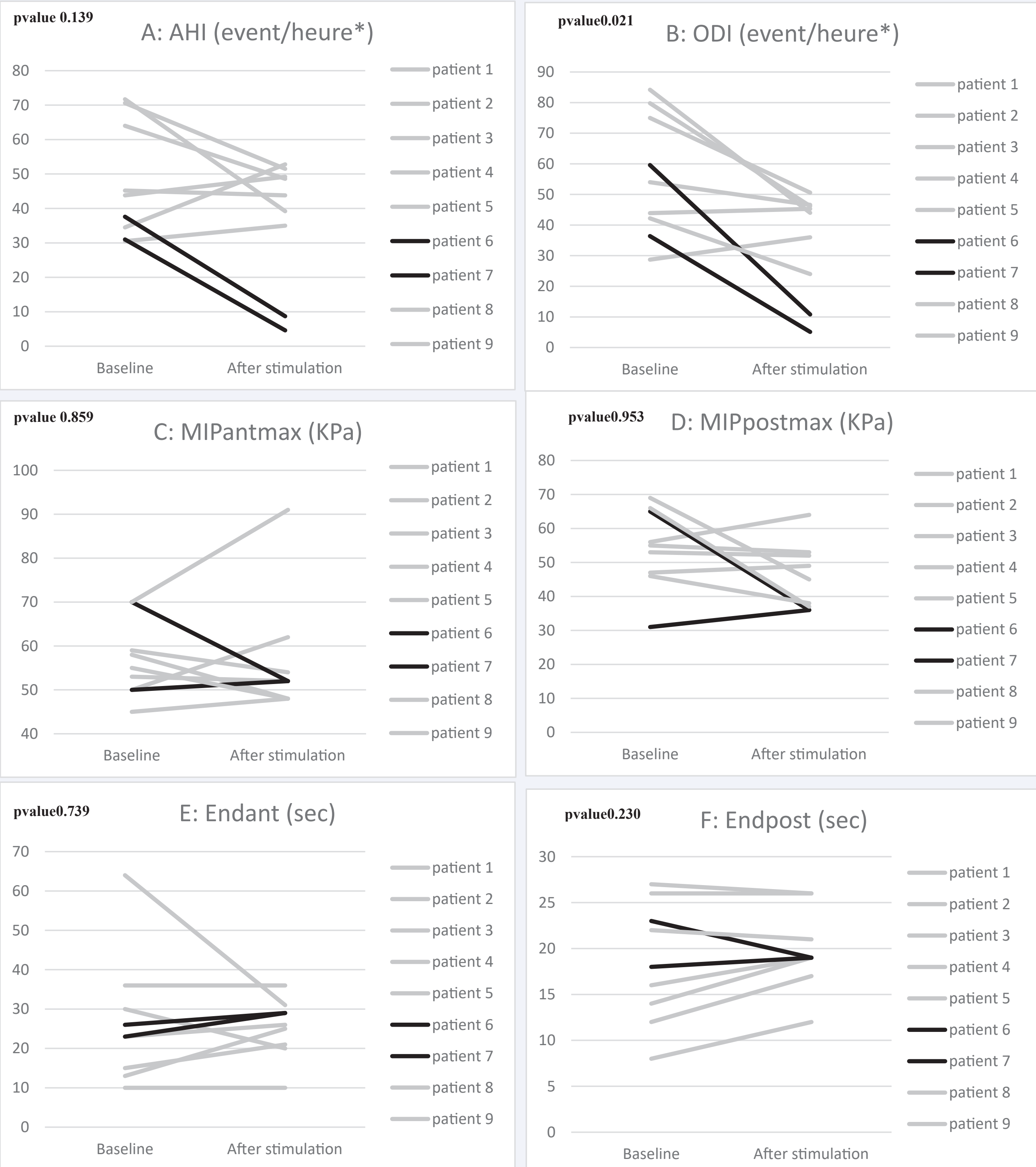

Figure 1 AHI: apnea/hypopnea index; ODI: oxygen desaturation index; MIPant: maximal isometric pressure measured on the anterior part of the tongue;
MIPpost: maximal isometric pressure measured on the posterior part of the tongue;
Endant: endurance measured on the anterior part of the tongue;
Endpost: endurance measured on the posterior part of the tongue.

Table 1: Baseline values for strength and endurance.

GROUPS	THN	CPAP (n= 19)		CONTROL (n=20)		P-value
		BMI >30	BMI <30	BMI >30	BMI <30	
Parameters Mean ± SD	N = 9	N = 10	N = 9	N = 10	N = 10	
Age	52 ± 5	55 ± 8	56 ± 11	56 ± 12	48 ± 10	0,402
BMI	30 ± 2	37 ± 5	27 ± 2	32 ± 2	26 ± 2	<0,0001
MIPantmax (kPa)	57 ± 9	64 ± 7	55 ± 18	59 ± 17	56 ± 9	0,645
MIPpostmax (kPa)	54 ± 12	56 ± 10	51 ± 16	49 ± 16	48 ± 15	0,709
Endant (sec)	27 ± 16	26 ± 13	23 ± 14	18 ± 9	19 ± 7	0,433
Endpost (sec)	18 ± 7	14 ± 9	14 ± 11	15 ± 9	18 ± 8	0,65
AHI	48 ± 17	66 ± 28	49 ± 18	6 ± 6	9 ± 15	<0,0001
ODI	56 ± 20	76 ± 37	33 ± 18	2 ± 2	1 ± 1	<0,0001
MA	39 ± 9	52 ± 16	44 ± 14	15 ± 8	14 ± 7	<0,0001
TST	387 ± 71	388 ± 105	358 ± 86	399 ± 59	388 ± 98	0,846

THN: targeted hypoglossal nerve stimulation; **CPAP:** continous positive airway pressure; **BMI:** body mass index; **MIPant:** maximal isometric pressure measured on the anterior part of the tongue; **MIPpost:** maximal isometric pressure measured on the posterior part of the tongue;**. Endant:** endurance measured on the anterior part of the tongue. **Endpost:** endurance measured on the posterior part of the tongue. **AHI:** apnea/hypopnea index; **MAI**: micro-arousal index; **ODI:** oxygen desaturation index. **TST:** total sleep time.

Table 2: Strength and endurance measurements before and after treatment with either CPAP or THN

GROUPS	THN	CPAP	P VALUE
Parameters Mean ± SD	N = 9	N = 9	
Age	52 ± 5	55 ± 9	0,513
AT BASELINE			
BMI	30 ± 2	29 ± 3	0,502
MIPant max (kPa)	57 ± 9	60 ± 17	0,623
MIPpost max kPa)	54 ± 12	54 ± 14	0,942
Endant (sec)	27 ± 16	24 ± 14	0,718
Endpost (sec)	18 ± 7	14 ± 8	0,219
AHI	48 ± 17	53 ± 25	0,611
ODI	56 ± 20	48 +38	0,620
MA	39 ± 9	46 ± 16	0,292
TST (min)	387 ± 71	360 ± 102	0,515
AFTER 3 MONTHS OF TREATMENT			
BMI M3	30 ± 2	29 ± 2	0,352
MIPant max (KPa) M3	56 ± 14	65 ± 15	0,219
MIPpost (KPa) M3	46 ±10	57± 14	0,054 *
Endant (sec) M6	25 ± 8	26,9 ± 14	0,758
Endpost (sec) M3	20 ± 4	14 ± 7	0,082*
AHI M3	37 ± 18	2 ± 2	< 0,01
ODI M3	34 ± 17	1 ± 2	< 0,01
MA M3	26 ± 9	12 ± 6	0,001
TST M3	403 ± 69	382 ± 82	0,564

THN: targeted hypoglossal nerve stimulation; **CPAP:** continous positive airway pressure; **BMI:** body mass index; **MIPant:** maximal isometric pressure measured on the anterior part of the tongue; **MIPpost:** maximal isometric pressure measured on the posterior part of the tongue; **Swalant:** swallowing anterior pressure**. Endant:** endurance measured on the anterior part of the tongue. **Endpost:** endurance measured on the posterior part of the tongue. **AHI:** apnea/hypopnea index; **MAI**: micro-arousal index; **ODI:** oxygen desaturation index. **TST:** total sleep time. M3: after 3 months

index compared with control subjects and thus support previous data [18-21], and the hypothesis that indicate that neurogenic changes occur in patients with OSA. This said, they seem not to affect, in any way, the whole organ strength or endurance. The final result is that the tongue activation can now result in effective pharyngeal lumen re-opening, whereas this was not the case before stimulation. Improvement in AHI, MAI and ODI found after long-term stimulation might therefore be the result of all these contributing factors without increasing or decreasing tongue strength and endurance. The hypotheses presented above are speculative at this point, but have been shown to exist in animals or humans and underline that OSA has both an anatomic and neural component in its pathogenesis and that neural stimulation cannot only result in muscle hypertrophy, but can perhaps induce changes in muscular activation [7]. Although we did not find clear changes in the variables in patients treated with CPAP or chronical stimulation of the hypoglossal nerve, this does not mean that tongue strength and endurance can't play an important role in the pathophysiology of OSAS. Because the dilator muscles of the upper airway play a critical role in maintaining an open airway during sleep, pharyngeal muscle training has been advocated by many researchers with exercises such as singing, didgeridoo and instrument playing and has been explored to treat OSA [8, 9].

Strengths of the study: A particular strength of this study is that it includes a comparison between a treatment that stimulates tongue musculature (i.e. THN), and another one that results in a decrease in tongue muscle's tone (i.e. CPAP). This should have brought to light any difference in muscle consequences, had one existed. This study emphasizes the coexistence of multiple mechanisms existing in the pathogenesis of obstructive sleep apnea syndrome.

This study has several limitations. The study group is small and could explain why, for some endpoints, if a tendency was observed; it could not be statistically confirmed. We underline the need of performing these measurements in a large sized population to confirm our findings. The lack of female subjects poses a problem in extrapolating our findings to the general population. Finally, the decrease in the AHI and ODI was mild in the neurostimulated patients (although highly significant statistically, contrary to the tongue muscle parameters), which may in part explain the weakness of the change in the strength and endurance measures.

Clinical applicability of the study: IoPi enables simple and quick measurement of the tongue strength and endurance in patients with sleep apnea syndrome but is not applicable in neurostimulation treatment. This tool should be measured in oropharyngeal exercises where the whole tongue muscles are involved.

In conclusion, in this small study we could not find any influence of nightly stimulation of the hypoglossal nerve on tongue strength or endurance in awake patients. The long-term use of CPAP did not seem to modify these parameters either. In comparing OSA patients treated with CPAP and healthy controls, we could not find any significant differences at baseline in tongue strength and endurance. Finally, BMI seems to have no influence on tongue strength and endurance.

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