Non-invasive vagus nerve stimulation reduces sympathetic preponderance in patients with tinnitus

Ylikoski, Jukka

2017

Ylikoski , J , Lehtimaki , J , Pirvola , U , Makitie , A , Aarnisalo , A , Hyvarinen , P & Ylikoski , M 2017 , ' Non-invasive vagus nerve stimulation reduces sympathetic preponderance in patients with tinnitus ' , Acta Oto-Laryngologica , vol. 137 , no. 4 , pp. 426-431 . https://doi.org/10.1080/00016489.201

http://hdl.handle.net/10138/311765
https://doi.org/10.1080/00016489.2016.1269197

acceptedVersion

Non-invasive vagus nerve stimulation reduces sympathetic preponderance in patients with tinnitus

Ylikoski J[1,2], Lehtimäki J[1,2], Pirvola U[3], Mäkitie A[4], Aarnisalo A[4], Hyvärinen P[4], Ylikoski M[1,2]

[1]Helsinki Ear Institute, Helsinki, Finland,

[2]Vagus Medical Inc., Helsinki, Finland

[3]Department of Biosciences, University of Helsinki, Helsinki, Finland

[4]Department of Otolaryngology-Head & Neck Surgery, University of Helsinki and Helsinki University Hospital

Corresponding author:

Prof. Jukka Ylikoski MD PhD
Helsinki Ear Institute
Halsuantie 1, FI-00420 Helsinki
Finland

E-mail: jukka.ylikoski@fimnet.fi
Website: www.tinnitus.fi

This paper was presented at the Annual Meeting of CORLAS in Bordeaux, France on Aug. 29-31, 2016.

Abstract (word count 200)

Conclusion

Transcutaneous vagal nerve stimulation (tVNS) might offer a targeted, patient-friendly and low-cost therapeutic tool for tinnitus patients with sympathovagal imbalance.

Objectives

Conventionally, VNS has been performed to treat severe epilepsy and depression with an electrode implanted to the cervical trunk of vagus nerve. In this study we investigated the

acute effects of tVNS on autonomic nervous system (ANS) imbalance, which often occurs in patients with tinnitus-triggered stress.

Methods

We retrospectively analysed records of 97 patients who had undergone ANS function testing by heart rate variability (HRV) measurement immediately before and after a 15 to 60 min tVNS stimulation.

Results

The pretreatment HRV recording showed sympathetic preponderance/reduced parasympathetic activity in about three quarters (73%) of patients. Active tVNS significantly increased variability of R-R intervals in 75% of patients and HRV age was decreased in 70% of patients. Either the variability of R-R intervals was increased or the HRV age decreased in 90% of the patients. These results indicate, that tVNS can induce a shift in ANS function from sympathetic preponderance towards parasympathetic predominance. tVNS caused no major morbidity and heart rate monitoring during the tVNS treatment showed no cardiac or circulatory effects (e.g. bradycardia) in any of the patients.

Word count 2634

INTRODUCTION

Patients with severe tinnitus often show associated symptoms, which have features of autonomic dysfunction. These stress-related symptoms are characterized by excessive sympathetic activation and concomitant reduced parasympathetic activation. This type of autonomic imbalance is often manifested as a reduction in heart rate variability (HRV), which can be measured [1].

In general terms, stress is a state of imbalance between what is required and what is possible. As a consequence, autonomic nervous system (ANS) being in charge of the regulation of most of physiological processes, will become overloaded. Therefore, in mental stress, several physiological processes of the body are affected. When a person is exposed to a stressor (like annoying tinnitus), a stress reaction can be triggered [2]. Stress reaction from tinnitus, similarly to that from other stressors, changes the ANS balance: the parasympathetic nervous system is suppressed and the sympathetic nervous system is activated [3,4]. This results in the secretion of the hormones epinephrine and norepinephrine into blood stream, which leads to, for example, vasoconstriction of blood vessels, increased blood pressure, increased muscle tension and an increase in heart rate and decrease in HRV. This process is known as the ‘fight-or-flight’ reaction. When the stressor is no longer present, a negative feedback system stops cortisol production in the body, and a sympathovagal balance is established through homeostasis between the parasympathetic (vagal) and sympathetic system. The two circuits are constantly interacting and this interaction is reflected in HRV. Therefore, HRV provides a measure to express ANS activity, and may consequently provide a measure for stress [1,3]. Furthermore, HRV testing of the affected individual can indirectly be seen as a source of information on the overall severity of the problem that is caused by tinnitus. We also suggest that tinnitus-triggered stress is a valuable model system to investigate mental stress and its treatment.

We have earlier investigated tinnitus-related mental stress (TRMS) clinically using stress questionnaires and with an eMotion HRV scanner in a small series of patients with severe or moderate tinnitus. We found that most of those patients had a significant mental stress

associated with poor HRV [Ylikoski J, personal communication]. It was also shown, that when the patients were treated with transcutaneous vagal nerve stimulation (tVNS) for 45-60 minutes, the HRV was improved in more than 80% of the patients. Thus, tVNS seemed to reduce TRMS.

Vagus nerve stimulation (VNS) has become an established therapy for difficult-to-treat epilepsy during the past 20 years [5]. Vagus nerve provides a unique therapeutical entrance to the brain. Electrical stimulation of this structure in the cervical region – that is the conventional VNS method - allows direct modulative access to subcortical brain areas. The antiepileptic effects of tVNS have been attributed to several processes such as decreased synchrony of synaptic activities in cortical regions, increased synaptic activities in components of the central autonomic system, and decreased synaptic activity in components of the limbic system, such as the amygdala and the hippocampus. And finally, VNS therapy results in intermittently increased release of multiple neuromodulators, including acetylcholine, norepinephrine, serotonin, and brain derived neurotrophic factor [6-7]. All these regions are either innervated directly by the vagus nerve or indirectly through the nucleus of the solitary tract [5].

The methodology of VNS used in epilepsy and depression is an invasive procedure. However, there exists an afferent sensory branch of the vagus nerve, which innervates the outer ear canal and parts of the auricle. This auricular branch of the vagus nerve (ABVN), projects centrally to the nucleus of the solitary tract in the brainstem. It has been demonstrated by fMRI and EEG recordings that tVNS of ABVN activates the central vagal pathways similarly as implanted VNS [8-10]. Therefore, the stimulation of ABVN might be an easy and noninvasive method to be used for patients to obtain the beneficial effects of vagal system activation. The medial part of tragus and concha region has been the target area for tVNS.

Based on our earlier studies and on the recent research we have developed our tinnitus management strategies. The aim has been firstly, to relieve stress reaction of the patient and thus to prevent more serious mood disorders and secondly, to correct failed auditory function of critical neuronal network through induction of activity-dependent neuronal plasticity. Our pilot study shows that this strategy might be beneficial for tinnitus patients [11].

The main cause to analyze and report this retrospective case series is our consistent clinical experience achieved during one year with the use of HRV testing combined with a short-term tVNS in patients with moderate or severe tinnitus-triggered mental stress.

Patients and Methods

This is a retrospective study on a cohort including 97 patients (44 male and 56 female; age range from 18 to 70 years) with acute or exacerbated chronic tinnitus. All patients had been diagnosed with moderate to severe tinnitus defined by a Tinnitus Handicap Inventory Questionnaire (THI) score >32 and mini tinnitus questionnaire (mini-TQ) and were recruited at the Tinnitus Clinic of Helsinki Ear Institute, Helsinki Finland between November 2014 and December 2015. Baseline tinnitus profile values were: THI: 32-100, mean 58, mini-TQ: 10-24, mean 14 (Table 1). Average tinnitus loudness was 62/100 (VAS), annoyance 70/100 (VAS) and awareness 71%.

All patients had been tested with the HRV test after which they underwent a 15-60 minute test trial with tVNS. During this trial the heart rate was monitored and then a new HRV test was performed. As there were no adverse effects, all the tested patients were then instructed to use the tVNS device at home.

HRV test and heart rate monitoring

For analyzing dynamics of HRV signals (R-R intervals) the eMotion HRV measurement system (Mega Electronics Ltd, Kuopio, Finland) was used [12]. Stress test with a HRV scan was performed with the patient breathing with a parasympathic stimulating respiratory rate during which the R-R interval variability was registered by wrist electrodes with a one-lead ECG. In eMotion HRV measurement artefacts and interruptions were effectively eliminated with high-end technology (and disposable surface electrodes) [12]. As there is no need for a strap around the chest, eMotion HRV overcomes all common problems and disadvantages associated with chest strap based measurements. During tests and heart-rate monitoring the patients were sitting comfortably in an armchair. Only tests with 100 % measurement quality in the ECG monitoring were used for evaluation. The measurement quality was automatically calculated by the HRV scanner for every test

using the following algorithm: the heart rate curve of every test was subdivided into small segments, which were scanned for implausible changes of the heart rate and missing beats. The percentage of segments without disturbances in relation to the total number of segments yielded the test quality. It ranged from 0 to 100 %. HRV parameters were computed by the HRV scanner for ECG. The R wave was detected by means of an adaptive ECG algorithm using the second derivative of the ECG signal. For the spectral analysis, R-R intervals were linearly interpolated with an interpolation frequency of 5 Hz and subsequently analyzed through a fast Fourier transformation algorithm. The obtained spectrum could be further decomposed into separate components, which is especially advantageous in HRV applications where Low Frequency (LF) and High Frequency (HF) components are generally aimed to be distinguished. Sampling frequency was 1000 Hz, accuracy 1 ms [12,13].

The following HRV parameters were measured during one-minute deep-breathing tests (one-min DBT): mean heart rate (HR), amplitude, and ratio of heart rate oscillation (E-I difference, E/I ratio) (E-I = difference between the highest and the lowest heart rate within a breathing cycle), RMSSD (root means square of successive differences), SDNN (standard deviation of the R-R intervals), and Power LF (LF = low frequency; 0.04–0.15 Hz). One-minute DBT was followed by a five-minute short-term HRV (s-HRV), where the HRV parameters HR, SD1 (= “width” of the Poincare plot, reflecting short term variability), SD2 (“length” of the Poincare plot, reflecting short term variability), SDNN, Stress Index, Power HF (HF = high frequency; 0.15–0.4 Hz), Power LF, Power VLF (very low frequency), and Total Power, were determined as well. Parameters were compared through correlation analysis and agreement analysis by Bland-Altman plots.

The test protocol of s-HRV test was slightly modified during the measurements in this series. Therefore, this report includes s-HRV results only from 28 patients, which were tested with the newest protocol modification.

The results of HRV tests were evaluated on the basis of eMotion tests performed in normal individuals [12,14,15]. The values of s-HRV were expressed as the stress index. HRV was evaluated as good when the stress index was between 60 and 120. The upper limit of normal stress index was 200 and stress index values up to 800-1000 indicate a catastrophically poor parasympathetic function. HRV decreases also naturally with

advancing age [16]. Test results were evaluated and graphically expressed as ”HRV age” based also on test data from normal individuals [12,14,15].

tVNS neurostimulating device

A tVNS instrument consisting of one ear clip electrode connected to a wired neurostimulating device (”SaluSTIM”, Vagus Medical Inc, Helsinki, Finland) was used. The clinical efficacy of tVNS requires activation of thick myelinated afferent fibers of the vagus nerve. The fibers of a sensory peripheral nerve such as the auricular branch of the vagus nerve (ABVN) mediate touch sensation. Consequently, the stimulus intensity of tVNS will be individually adjusted to a level above the individual’s detection threshold and clearly below the individual’s pain threshold. The tVNS device offers a stimulus intensity between 0.1 and 130mA with a stimulation frequency of 25 Hz, and pulse duration of 250 μs. The 15-60 minute test stimulation was performed under medical supervision in the office so that the heart rate was continuously monitored. After the initial 15-60 minute test stimulation, the patients were instructed to use the tVNS device at home for stimulation for 60-90 minutes daily during five days a week.

Statistical analyses

All continuous data were displayed as the mean with the standard deviation and are compared using the paired Student’s t–test or the two sample Student’s t–test when appropriate. In addition the effect sizes for these contrasts are reported to estimate the clinical significance according to Cohen (D 0.2 small, 0.5 medium, 0.8 high). Statistical analyses were done in a two-step-approach for the whole sample. Statistical significance was assumed for a p-value <0.05.

Results

The pretreatment one-minute deep-breathing HRV recording showed lowered resting HRV indicating sympathetic preponderance in 73% of the patients (Table 2). This was characterized by averaged R-R interval variability showing the value of 802 and averaged HRV age (64 years), which was higher than the chronological age (48 years) (Table 2).

Active tVNS significantly increased the averaged variability of R-R intervals and decreased the averaged HRV age as measured by one-min deep-breathing HRV test immediately after the tVNS test stimulation (Figures 1 and 2). tVNS increased HRV as measured by R-R interval variability in 73 (75%) out of the 97 patients (Figure 1). In 20% HRV was decreased and in 5% it remained unchanged. Active tVNS decreased HRV age in 68 (70%) patients, increased it in 16% and HRV age remained unchanged in 14% of the patients (Figure 2). Either the variability of R-R intervals was increased or the HRV age decreased in 87 (90%) of the patients.

The results of s-HRV test in 28 patients showed a pretreatment stress index value of 249 (upper limit of normal is 120) indicating sympathetic preponderance. The tVNS reduced this stress index to a value of 163.

When different parameters of HRV were presented graphically with good parasympathetic function represented by a large triangle and poor parasympathetic function as a very small triangle, the average HRV values of tested patients showed a rather small triangle which was then significantly enlarged after tVNS stimulation (Figure 3).

tVNS caused no major morbidity and heart rate monitoring during the tVNS treatment showed no cardiac or circulatory effects (e.g. bradycardia) in any of the patients.

Discussion

The main problem of patients with disturbing moderate or severe tinnitus is tinnitus-related mental stress (TRMS) [2], which is associated with imbalance of the autonomic nervous system (ANS) with sympathetic preponderance and corresponding reduced parasympathetic activity [3,4]. Therefore, the optimal treatment of TRMS would be by trophotropic (parasympathetic activity enhancing) means. This could be achieved by general relaxation generating methods such as biofeedback, yoga, cognitive behavioral therapy and relaxing music. As vagal nerve is responsible for the parasympathetic function its stimulation might also be a novel possibility to restore the ANS balance. These results indicate that most of the patients with moderate or severe tinnitus show sympatic preponderance and that tVNS may increase the parasympathetic activity and it seems to

reduce TRMS. It is also worth noting that no treatment-related adverse effects were observed in this patient population.

In our earlier study on a series of 24 patients we also analyzed quality of life (QoL) with a questionnaire and found that almost all patients experienced QoL improvement after one week of tVNS therapy [Ylikoski J, personal communication]. In an earlier study we demonstrated by magnetoencephalography (MEG) acute neuromodulative effects of tVNS on evoked auditory cortical responses supporting the idea that tVNS similarly to VNS with implanted electrodes has the potential to enhance neuronal plasticity and, thus, to reverse the maladaptive neuronal plasticity in the auditory cortex [11]. Therapeutic modulation of gamma-band oscillations with vagus nerve stimulation has been recently reported in epileptic patients. tVNS successfully also modulates tinnitus-related beta- and gamma-band activity and thus could have potential as a treatment method for tinnitus [17].

This study did not investigate the therapeutic efficacy of tVNS for tinnitus. However, our preliminary experience from the follow up of patients included in this study indicates that the great majority of patients receiving a combination of tVNS and sound therapy, clearly benefit from that therapy. This would be in accordance with a recent study reporting that VNS paired with tones might be a promising novel treatment for chronic tinnitus [18]. On the other hand, another recent clinical study using tVNS did not report improvement of tinnitus with tVNS alone, although the therapy was found to be safe [19]. We also have now clinical experience on the long-term use of tVNS by a few patients as three of our patients have used tVNS daily for more than three years without any adverse effects. They continue using the device (60-90 minutes per day) because of subjective benefits. Currently, at the same setting where the present study was performed, we offer tVNS treatment for all our patients who show THI scores 50 or over. We regard this as an alternative to a possible need for e.g. tranquilizers.

The results of the present study should be interpreted with great caution because they only represent a retrospective case series. However, the consistent improvement of HRV - a seemingly useful marker of mental stress – in 90% of our patients suggests that tVNS might be a useful therapeutic means in severe tinnitus. This study encourages further controlled clinical studies on the usefulness of tVNS in tinnitus. More importantly, this study offers additional support to the idea, that tVNS might offer a new, targeted

therapeutic tool for patients in whom sympathovagal imbalance is involved. Further, tVNS would be patient-friendly and of low-cost. Also a more general effect of tVNS on sympathetic activity was recently demonstrated in healthy subjects. In a sham-controlled study, active tVNS increased HRV already during one 15-minute treatment session, while sham treatment did not result in any kind of change in HRV [20]. Vagus nerve stimulation is an attractive method in the field bioelectric medicine, because high vagal activity has been considered to indicate good health and high level of well-being [3-5]. Our study suggests, that tVNS might offer a novel therapy for tinnitus related mental stress but it may have therapeutic potential also in a wider spectrum of illnesses.

Litterature

[1] Akselrod S, Gordon D, Ubel FA, Shannon DC, Berger AC, Cohen RJ. Power spectrum analysis of heart rate fluctuation: A quantitative probe of beat-to-beat cardiovascular control. Science. 1981;213:220–2.

[2] Andersson G, Lyttkens L, Larsen HC. Distinguishing levels of tinnitus distress. Clin Otolaryngol Allied Sci. 1999;24:404-10.

[3] Thayer JF, Ahs F, Fredrikson M, Sollers III JJ, Wager TD. A meta-analysis of heart rate variability and neuroimaging studies: Implications for heart rate variability as a marker of stress and health. Neurosci Biobehav Rev. 2012;36:747–56.

[4] Chalmers JA, Quintana DS, Abbott MJ-A, Kemp AH. Anxiety disorders are associated with reduced heart rate variability: A meta-analysis. Front Psychiatry. 2014;5(80):1–11.

[5] Yuan H, Silberstein SD. Vagus Nerve and Vagus Nerve Stimulation, a Comprehensive Review: Part III. Headache. 2016;56(2):259-66.

[6] Hassert DL, Miyashita T, Williams CL. The Effects of Peripheral Vagal Nerve Stimulation at a Memory-Modulating Intensity on Norepinephrine Output in the Basolateral

Amygdala. Behav Neurosci. 2004;118:79.

[7] Dorr AE, Debonnel G. Effect of vagus nerve stimulation on serotonergic and noradrenergic transmission. J Pharmacol Exp Ther. 2006;318:890.

[8] Kraus T, Hösl K, Kiess O, Schanze A, Kornhuber J, Forster C. BOLD fMRI deactivation of limbic and temporal brain structures and mood enhancing effect by transcutaneous vagus nerve stimulation. J Neural Transm. 2007;114:1485-93.

[9] Polak T, Markulin F, Ehlis AC, Langer JB, Ringel TM, Fallgatter AJ. Far field potentials from brain stem after transcutaneous vagus nerve stimulation: optimization of stimulation and recording parameters J Neural Transm. 2009;116:1237-42.

[10] Dietrich S, Smith J, Scherzinger C et al. A novel transcutaneous vagus nerve stimulation leads to brainstem and cerebral activations measured by functional MRI. Biomed Tech. 2008;53:104-11.

[11] Lehtimäki J, Hyvärinen P, Ylikoski M, Bergholm M, Mäkelä JP, Aarnisalo A, Pirvola U, Mäkitie A, Ylikoski J. Transcutaneous vagus nerve stimulation in tinnitus: a pilot study. Acta Otolaryngol. 2013;133:378-82.

[12] Tarvainen MP, Georgiadis S, Lipponen JA, Hakkarainen M, Karjalainen PA. Time-varying spectrum estimation of heart rate variability signals with Kalman smoother algorithm. Conf Proc IEEE Eng Med Biol Soc. 2009:1-4.

[13] Task force heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Circulation. 1996;93(5):1043–65.

[14] Löllgen D1, Müeck-Weymann M, Beise RD. The deep breathing test: median-based expiration-inspiration difference is the measure of choice. Muscle Nerve. 2009;39(4):536-44.

[15] Weinschenk SW, Beise RD, Lorenz J. Heart rate variability (HRV) in deep breathing tests and 5-min short-term recordings: agreement of ear photoplethysmography with ECG measurements, in 343 subjects. Eur J Appl Physiol. 2016;116(8):1527-35.

[16] De Meersman RE, Stein PK. Vagal modulation and aging. Biol Psychol. 2007;74:165–73.

[17] Hyvärinen P, Yrttiaho S, Lehtimäki J, Ilmoniemi RJ, Mäkitie A, Ylikoski J, Mäkelä JP, Aarnisalo AA Transcutaneous vagus nerve stimulation modulates tinnitus-related beta- and gamma-band activity. Ear Hear. 2015;36:76-85.

[18] De Ridder D1, Kilgard M, Engineer N, Vanneste S. Placebo-controlled vagus nerve stimulation paired with tones in a patient with refractory tinnitus: a case report. Otol Neurotol. 2015;36(4):575-80.

[19] Kreuzer PM, Landgrebe M, Resch M, Husser O, Schecklmann M, Geisreiter F, Poeppl TB, Prasser SJ, Hajak G, Rupprecht R, Langguth B. Feasibility, safety and efficacy of transcutaneous vagus nerve stimulation in chronic tinnitus: an open pilot study. Brain Stimul. 2014;7(5):740-7.

[20] Clancy JA, Mary DA, Witte KK, Greenwood JP, Deuchars SA, Deuchars J. Non-invasive vagus nerve stimulation in healthy humans reduces sympathetic nerve activity. Brain Stimul. 2014;7:871-7.

Corresponding author:

Prof. Jukka Ylikoski MD PhD
Helsinki Ear Institute
Halsuantie 1, FI-00420 Helsinki
Finland

E-mail: jukka.ylikoski@fimnet.fi

Website: www.tinnitus.fi

Conflict of Interest: Lehtimäki J, Ylikoski J, Ylikoski M and are board members Vagal Medical Inc.

Legends for the Tables and Figures:

Table 1. Baseline tinnitus profile data in 97 patients with moderate or severe tinnitus.

Table 2. One-minute deep breathing test (1-min DBT) HRV data of 97 patients with moderate or severe tinnitus before (PRE) and after (tVNS) the test tVNS-stimulation. The 1-min DBT parameters reported here are: HRV age; Flexibility = E-I, difference between the highest and the lowest heart rate within a breathing cycle; Dynamics = RMSSD, root of the mean square of successive differences; Tone = mean HR in DBT.

Figure 1. A. The pretreatment HRV recording showed sympathetic preponderance indicated by low values in variability of R-R intervals. Active tVNS significantly increased the averaged variability of R-R intervals. B. tVNS increased HRV as measured by R-R interval variability in 73 (75%) out of the 97 patients. In 20% HRV was decreased and in 5% it remained unchanged.

Figure 2. A. The averaged HRV age (64 years) was higher than the chronological age (48 years) as measured by variability of R-R intervals. Active tVNS significantly decreased the averaged HRV age (from 64 to 56 years). B. After the test tVNS stimulation HRV age was decreased in 70% of the patients.

Figure 3. Various parameters of HRV (Dynamics, Flexibility, Tone) can be graphically presented as shown here: A. A large triangle indicates a good HRV with high vagal activity = parasympathetic preponderance and a very small triangle indicates poor parasympathetic function. B. Averaged results of HRV measurements in 97 patients showed a rather small triangle (red), indicating poor parasympathetic function. With a short term (15 min) tVNS treatment this triangle was enlarged (blue), indicating improved parasympathetic function.

Dynamics = RMSSD, root of the mean square of successive differences; Flexibility = E-I, difference between the highest and the lowest heart rate within a breathing cycle; Tone = Mean HR in DBT (deep-breathing test)