Acute effects of transcutaneous vagus nerve stimulation (tVNS) on tinnitus related mental stress; a case control study.

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ABSTRACT

Objectives Mental stress is associated with imbalance of the autonomous nervous system (ANS) leading to reduced parasympathetic activity. Therefore, treatment of choice for TRMS would be vagus nerve stimulation (VNS). Also, the VNS, when paired with appropriate sound therapy might reduce the tinnitus sensation itself as shown in a rat tinnitus model. Conventional VNS with implanted electrode, however, is an invasive procedure and therefore less suitable for tinnitus treatment. It has been recently shown by functional MRI, MEG and EEG recordings that transcutaneous VNS (tVNS) of the auricular branch of the vagus nerve (ABVN) activates the central vagal pathways in a similar way as implanted VNS. The aim of this study was to investigate acute effects of tVNS on TRMS as measured by heart rate variability (HRV).

Methods The left ABVN of 24 patients with moderate or severe tinnitus and TRMS was stimulated with tVNS continuously for 60 min. HRV parameters were calculated on the basis of the heart beat variability measured with a HRV scanner over a 5 minute period before and immediately after the stimulation. Heart rate also was continuously monitored during the treatment session.

Results As tested by HRV scanning the stress-related HRV-age was higher than the chronological age in 23 out of 24 patients indicating the presence of TRMS. This stress was reduced in 23 out of 24 tinnitus patients with the 60-min tVNS treatment. tVNS seems to have a clearcut beneficial effect on tinnitus-related distress.

Heart rate monitoring during the tVNS treatments showed no cardiac or circulatory effects (e.g. bradycardia) in any of the patients. Conclusion Obviously, the most important strategic goal for succesful tinnitus therapy, is to diminish the TRMS. This study shows, that tVNS seems to reduce the severity of subjective TRMS in tinnitus patients and that this treatment seems to be safe.

BACKGROUND

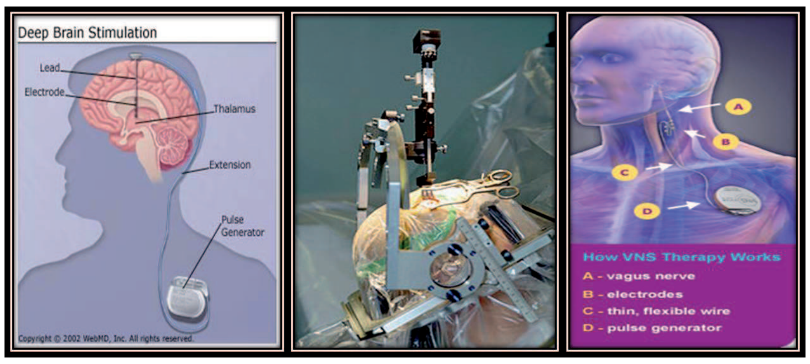
Tinnitus = maladaptive neuronal plasticity in the central auditory pathway (CAP)
Hearing impairment -> weakening of inhibitory networks
-> aberrant neuronal activity in CAP

TINNITUS = CHANGES IN NEURONAL PLASTICITY (1-4,6)
change in therapeutic possibilities: Therapy targets: neurons of CAP (no more cochlear hair cells)
- maldaptive plasticity can be treated (by NEUROMODULATION)

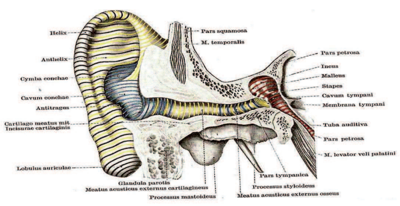
Neuromodulation (electrical brain stimulation)
New "high-tech" treatments for neurologic disorders :
1. deep brain stimulation (DBS) Parkinson's disease, tremor, dystonia
2. VAGAL NERVE STIMULATION (VNS) Used in disorders with maladaptive plasticity : Epilepsy, Depression (over 65000 patients implanted)

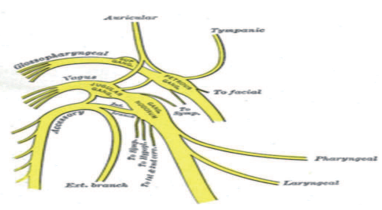
New possibilities TO ALTER or REVERSE MALADAPTIVE NEURONAL PLASTICITY IN TINNITUS:
1. sound therapy (tailor-made music) (Okamoto et al PNAS 2010, Pantev 2012)
2. VNS plus sound therapy (Engineer et al Nature 2011) (6,7)

Drawbacks of (implanted) VNS
- INSERTION OF VNS –ELECTRODE: INVASIVE PROCEDURE
- EXPENSIVE *
*estimated cost for the surgical implantation of VNS: $40,000 to $45.000



Theoretical background
1. There is an auricular branch of the vagus nerve (ABVN, Arnold´s nerve, Alderman´s nerve) which supplies the outer ear and projects centrally to nucleus of the solitary tract (NTS) in the brainstem (8). And
2. Electrical (transcutaneous) stimulation of the Arnold´s nerve stimulates the central parts of the Xth nerve pathway in the same way as by implanted VNS (9-11,14)





QUESTION

1. Does tVNS have therapeutic effect on the tinnitus-induced mental stress in patients and is it safe?

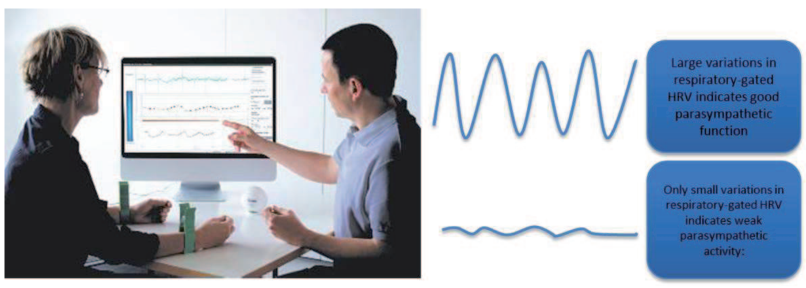
METHODS

Subjects:

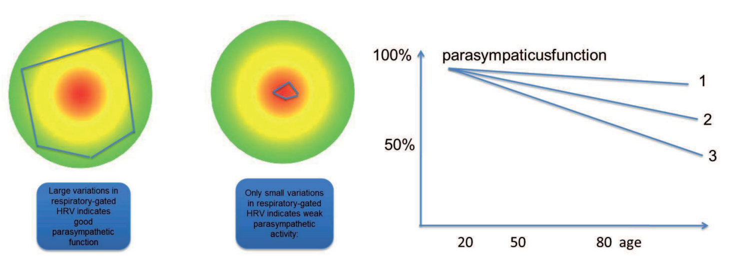
Twenty four patients with acute (duration less than 6 months) moderate or severe tinnitus associated with high level mental stress.
The mean age 29 years (range, 19-71)
Mean tinnitus pitch 6.8 kHz (range, 0.5–12 kHz)
The clinical efficacy and safety was studied by a 60-min tVNS trial using disease specific questionnaires. (12-13)
Baseline values: THI: 42-100, mean 68, mini-TQ: 13-24, mean 19
Tinnitus loudness and annoyance (VAS), minimum 30/100

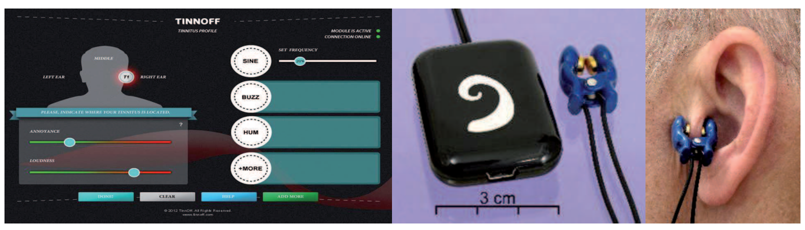
Stress test:

For analyzing dynamics of heart rate variability (HRV) signals (R-R intervals) eMotion HRV measurement system (Mega Electronics Ltd, Kuopio, Finland) was used (15). In the method, HRV signal is first modeled with a time-varying autoregressive model and the model parameters are solved recursively with a Kalman smoother algorithm. Time-varying spectrum estimates are then obtained from the estimated model parameters. The obtained spectrum can 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: 1000 Hz, Accuracy: 1 ms. In eMotion HRV measurement artefacts and interruptions are effectively eliminated with high-end technology and disposable surface electrodes. 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.



HRV-Scan is performed so that the respiratory rate is adjusted to the level that is known to best stimulate the parasympathetic system





Probe tone frequency was matched to tinnitus pitch individually for each subject with tinnitus profiler (Tinnoff)

The auricular branch of the vagus nerve was stimulated with transcutaneous electric stimulation.

Electric stimulation:

To patients' left tragus At 25 Hz rate Above sensory threshold, at ca. 0.8 mA

RESULTS

Tinnitus related mental stress

As tested by eMotion, the HRV-age was much higher (20-55 years) than the chronological age in 18 patients, somewhat higher (3-17 years) in 5 patients and lower in only one patient (12 years, case 21) (Table).

After the 60-min tVNS the median RR-interval variability was increased (stress diminished) in 19 out of 24 patients, decreased (stress increased) in four and there was no change in one patient. HRV age was decreased in 20 out of 24 patients, there was no change in three patients and one patient (number 10) showed slight increase. In none of the patients was the HRV-age significantly increased after tVNS. There was only one patient (number 11) who showed no improvement (=decreased stress) either by median RR interval variability measurement or by HRV-age count.

Thus, in subjects of this study stress-related HRV-age was higher than the chronological age in 23 out of 24 patients indicating that they had tinnitus related mental stress. This stress was reduced in 23 out of 24 tinnitus patients with the 60-min tVNS treatment.

Adverse effects

Heart ratemonitoring during the 60-min tVNS showed no cardiac or circulatory effects (e.g. bradycardia) in any of the 24 patients.

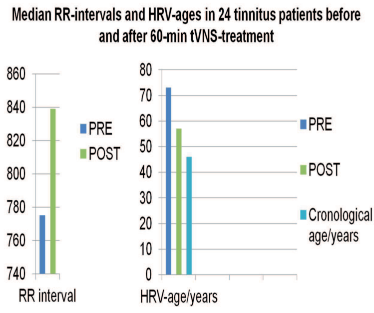
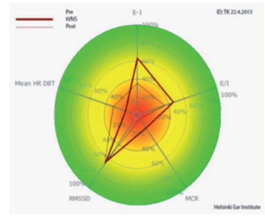
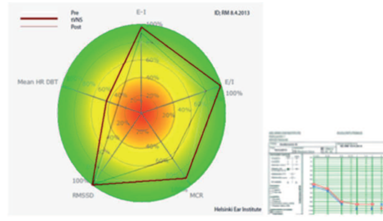


TABLE. Median RR-intervals and HRV-ages in 24 tinnitus patients before and after 60-min tVNS-treatment

Genre	Median RR-Interval	HRV-age/years		Chronological age years	Difference PRE-Chronological age years
F: female; M: male	PRE / POST	PRE	POST		
1. F	689,39 / 773,91	90	74	40	50
2. M	819,69 / 852,86	80	64	42	38
3. F	788,42 / 837,43	71	47	49	22
4. M (no C)	671,49 / 671,73	90	78	37	53
5. M (D)	933,03 / 863,52	57	37	51	6
6. F	554,17 / 601,95	84 (no C)	85	53	31
7. F	834,97 / 839,39	39	34	28	11
8. F	750,81 / 860,34	62 (no C)	63	59	3
9. F	737,64 / 887,26	88	78	63	25
10. M	805,93 / 880,67	79 (i)	85	47	22
11. M (D)	720,80 / 714,46	54 (no C)	54	48	6
12. M (D)	866,84 / 804,85	54	26	37	17
13. M	835,32 / 992,67	58	28	38	20
14. M	834,53 / 908,64	87	77	50	47
15. M	679,43 / 738,81	90	38	35	55
16. M (D)	707,90 / 681,05	90	66	61	29
17. M	654,01 / 769,31	86	81	44	42
18. F	898,89 / 946,93	75	41	42	33
19. M	998,24 / 1198,81	65	65	20	45
20. M	847,44 / 975,67	65	42	37	28
21. F	799,42 / 900,41	34	22	46	-12
22. F	673,81 / 726,09	86	59	60	26
23. M	856,45 / 989,53	90	70	69	21
24. M	644,35 / 724,41	86	58	44	42
Average	775,12 / 839,20	73	57	46	28

(no C) = no change (D) = decrease (i) = increase





Case reports: tVNS for 60 min, HRV scanning before and after stimulation

Patient 1, excellent benefit
36-y man with acute acoustic trauma (AT) from explosion of pressure cooker. 6 kHz tinnitus (loudness 9/10 VAS, annoyance 8/10 VAS) was associated with severe distress: THI 90/100, Mini-TQ: 24/32. Mild (20dB) AT-related hearing impairment (dip) at 4.0 kHz, left ear

Patient 2, no benefit
55-y old man with congenital SNHL, now profound and has problems communicating even with highly effective hearing aids (in cochlear implantation consideration).
AG: at 0.125, 0.250 and 0.5 kHz thresholds (50-90dB) and 100dB at 1.0 kHz in right ear. Tinnitus loudness and annoyance 10/10 (VAS). THI 82/100,
Mini-TQ 20/32

DISCUSSION

The linkage between chronic tinnitus and stress is commonly accepted. It is well known, that the major problem of a tinnitus patient is not the sensation of tinnitus itself, but the stress reaction triggered by tinnitus. For instance, we have recently found, that patients with acute noise-induced tinnitus can experience a significant stress reaction. This stress reaction can develop within one week to a catastrophic level often leading to sleep disturbances which further worsens the vicious circle by increasing tinnitus annoyance (16).

Based on the current study, most of the patients with acute tinnitus of at least moderate severity and THI scores higher than 30 have a significant mental stress when tested by eMotion HRV scanner: 23 out of 24 subjects showed higher HRV-age than chronological age, this difference being very large in most cases (in 18 of 23). When the patients were stimulated with a 60-min tVNS the HRV-age was reduced in 20 of 24 and the median RR-interval variability was increased in 19 of 24 patients. Thus, tVNS seems to reduce the tinnitus-associated mental stress, which is often the major problem in tinnitus patients.

In general terms, stress is a state of imbalance between what is required and what is possible. As a consequence, our autonomous nervous system (ANS) that is in charge of the regulation of most of our physiological processes, becomes overloaded. Therefore, in mental stress, several physiological processes of the body are affected. When a person is exposed to a stressor, (like annoying tinnitus), his ANS balance is changed: the parasympathetic nervous system is suppressed and the sympathetic nervous system is activated (17). This results in the secretion of the hormones epinephrine and norepinephrine into the blood stream which leads to, for example, vasoconstriction of blood vessels, increased blood pressure, increased muscle tension and a change in heart rate and heart rate variability. 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. HRV, therefore, provides a measure to express the activity of the ANS, and may consequently provide a measure for stress. Furthermore, HRV test can indirectly be seen to give information about the overall severity of the problem that is caused by tinnitus to the affected individual. We also suggest that tinnitus-triggered stress is a valuable model system to investigate mental stress and its treatment.

Basing on our earlier studies and on the recent research regarding new stress/mood disorder we have developed tinnitus management strategies aiming 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 (18).

Vagus nerve stimulation is an attractive field in medicine, because high vagal activity has been considered to indicate good health and high level of well being. As our study suggests, tVNS might offer a new, targeted therapeutic tool for one clinical entity in which sympatho-vagal-imbalance is involved. Further, if appropriately performed efficacy studies also demonstrate that our tVNS-treatment strategy is effective in tinnitus related mental stress, this could be a starting point for the use of therapeutic tVNS in a wider spectrum of illnesses.

CONCLUSIONS

transcutaneous vagus nerve stimulation (tVNS) seems to reduce the severity of tinnitus-related mental stress and , therefore, probably also the tinnitus-associated distress in most patients no adverse effects were observed during the tVNS performed in the current study.

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Conflict of Interest: Jarmo Lehtimäki, Matti Ylikoski and Jukka Ylikoski are board members Oy Tinnoff Inc.

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