INVITED REVIEW

Transcutaneous Auricular Vagus Nerve Stimulation

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Summary: Invasive vagus nerve stimulation (VNS) is an approved treatment for drug-resistant epilepsy. Besides recognized clinical efficacy in about 60% of patients, there are major drawbacks such as invasiveness and common side effects including hoarseness, sore throat, shortness of breath, and coughing. Invasive VNS applies electrical stimulation to the left cervical branch of the vagus nerve and excites thick-myelinated afferent nerve fibers. Peripheral vagus nerve afferent volley initiates brainstem activity in the nucleus of the solitary tract and provokes typical brainstem and cerebral activation patterns that mediate the anticonvulsive mode of action. Whereas invasive VNS is an established neuromodulatory treatment in drug-resistant epilepsy, transcutaneous VNS (tVNS) of the auricular branch of the vagus nerve is suggested to be an alternative access path to the same neuronal network without invasiveness. Preclinical and clinical studies indicate that especially the cymba conchae of the auricle is selectively supplied by the auricular branch of the vagus nerve. Recent anatomical data demonstrate existence and quantity of thick-myelinated afferent nerve fibers of the left auricular branch of the vagus nerve that carries 21% of thick-myelinated afferent nerve fibers counted in the left thoracic vagus nerve in humans. Projection of auricular branch of the vagus nerve afferents from the auricle to the nucleus of the solitary tract is known from histochemical and electrophysiological experiments in rodents and confirmed in humans by functional imaging. Cerebral activation patterns triggered by invasive and tVNS resemble each other in appearance. Clinical trials in patients address safety and performance of tVNS and provide evidence for application in drug-resistant epilepsy.

Key Words: Brainstem, Concha, Ear, Epilepsy, Neuromodulation, Pain.

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Drug-resistant epilepsy accounts for more than 30% of epileptic patients.[1] Alternative treatment options are resective neurosurgery, deep brain stimulation,[2] and invasive vagus nerve stimulation (VNS).[3] Invasive stimulation of the cervical branch of the vagus nerve has been shown to be effective in clinical trials with a responder rate of approximately 40% to 60%.[3,4] Surgically and technically induced complications include electrode fractures, deep wound infections, transient vocal cord palsy, cardiac arrhythmia under test stimulation, electrode malfunction, and posttraumatic dysfunction of the stimulator.[5] Frequent side effects of chronic, invasive VNS such as hoarseness, cough, dyspnea, and pain are mainly due to bidirectional stimulation of efferent and afferent fibers within the mixed cervical branch of the vagus nerve.

Besides recognized clinical efficacy of invasive VNS, there are major drawbacks such as invasiveness and a great many of side effects because of electrical stimulation of a mixed peripheral nerve. Therefore, there is a medical demand for an alternative medical device that combines selective, noninvasive access to vagus nerve afferents with a low-risk profile.[6]

This review assesses the neuromodulatory technique of transcutaneous VNS (tVNS) on the basis of the following requirements for effective VNS therapy that infers from the concepts of the mechanisms of action:[3,4,7]

1. Vagus nerve supply of the outer ear.
2. Thick-myelinated afferents of the auricular branch of the vagus nerve (ABVN).
3. Access to the nucleus of the solitary tract (NTS) in the brainstem.
4. Elicitation of a typical cerebral activation pattern.

SITE OF tVNS

Transcutaneous vagus nerve stimulation targets the cutaneous receptive field of the ABVN at the outer ear. Several lines of evidence from anatomical and clinical studies reveal topographic anatomy and the functional impact of the ABVN on the autonomic nervous system.

Nerve Supply of the Outer Ear

The human outer ear is supplied by three sensory nerves, namely the auriculotemporal nerve, the great auricular nerve, and the ABVN (Fig. 1A). On 14 human ears, the complete course of nerve supply was exposed and each branch was defined by identifying its origin.[8] The ABVN and the great auricular nerve were found solely on the antihelix in 73% and 18% of cases, respectively, and 9% showed a double innervation. The ABVN provided ramification for the crura antihelices in 9% of the cases, for the cavity of conchae in 45% of the cases, and for the cymba conchae in 100% of the cases. In 55% of the cases, the ABVN

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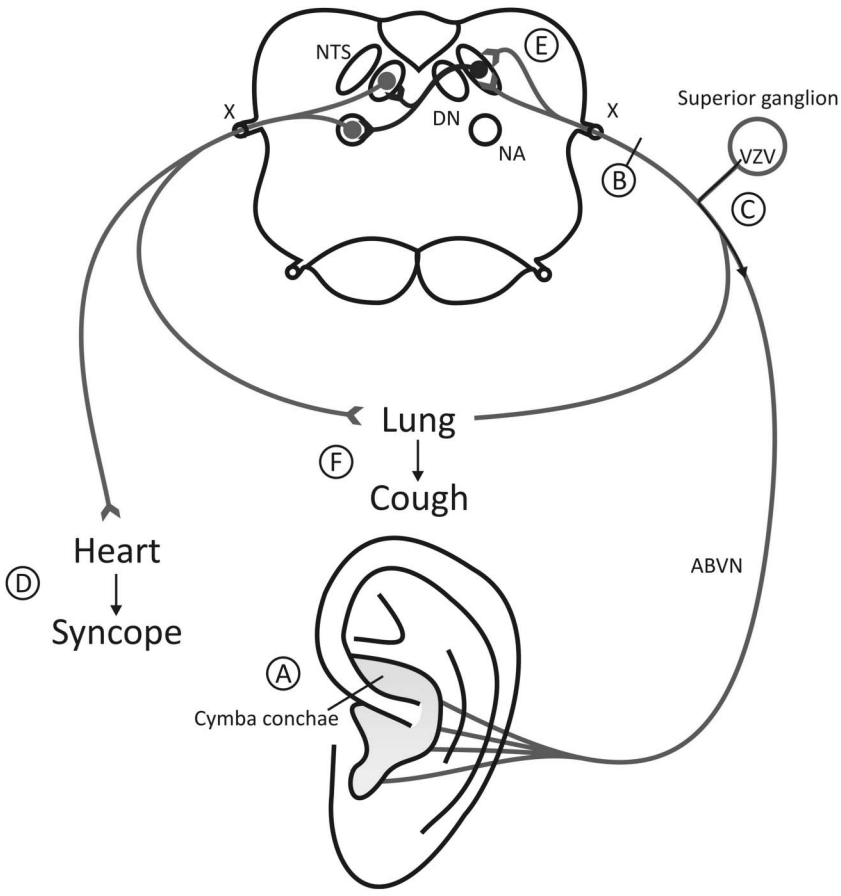

FIG. 1. Brainstem mechanisms of tVNS. Sensory fibers of the auricular branch of the vagus nerve (ABVN) supply the skin of the concha. The cymba conchae is exclusively supplied by the ABVN. Sensory vagus nerve fibers from different organs project via the superior ganglion to the nucleus of the solitary tract (NTS). NTS neurons project to visceral efferent neurons located in the dorsal nucleus of the vagus nerve (DN) and the nucleus ambiguous (NA). Visceral efferent nerve fibers supply, e.g., the heart and the lung. For the sake of clarity, afferent pathways and efferent pathways of the vagus nerve are separately illustrated on the right and the left side of the figure, respectively. A to F refer to the text. X, vagus nerve; VZV, varicella zoster virus causing herpes zoster.

and the great auricular nerve were identified in the cavity of conchae. No region with triple innervation was found. Thus, in all the cases, the ABVN significantly supplied the cavity of concha and exclusively supplied the cymba conchae.

Intracranial Section of the Vagus Nerve

A patient with tongue cancer suffered from severe pain in the outer ear (Fig. 1B).[9] This refractory pain was treated by intracranial section of the vagus nerve. During the sectioning of the vagus on the left side, the anesthetist noted that the heart rate dropped to 40. Following section of the vagus root, the cutaneous area of complete anesthesia covered the posterior wall of the external auditory canal, the concha, and, to a slight degree for pain only, the antihelix and antitragus. The authors concluded that there is no doubt that the major supply to the anesthetic area is by means of the vagus nerve.

Isolated Vagus Nerve Palsy With Herpes Zoster

A 31-year-old woman was admitted to hospital because of difficulty of swallowing of fluid, hoarseness, and painful vesicles on the right ear (Fig. 1C).[10] Neurological examination revealed poor elevation of the soft palate on the right side. Herpetic vesicles were present on the right concha and the posterior wall of the external auditory canal. No facial palsy, loss of hearing, or mucosal lesions in the mouth or pharynx were present. The authors diagnosed an isolated vagus nerve palsy because of varicella zoster infection, highlighting the distribution of the cutaneous receptive field of the ABVN.

Auricular Syncope

A 13-year-old girl had been receiving drug treatment for presumed absence epilepsy without any anticonvulsive effect (Fig. 1D).[11] The medical history indicated that recurrent syncopal attacks were precipitated by external auditory canal stimulation. Targeted autonomic function tests confirmed a hyperactive vagal response with bradycardia and lightheadedness provoked by tactile stimulation of the left external auditory canal. Abstinence from ear scratching led to complete alleviation of symptoms without any drug treatment. The authors proposed reflex syncope because of stimulation of the ABVN as the pathophysiological mechanism.

Referred Otalgia

Referred otalgia arises from non-otological, remote diseases and occurs in up to 50% of adult patients who consult a general physician for ear pain (Fig. 1E).[12] Head and neck malignancy is the most important pathology associated with referred otalgia. Twenty-six patients with nonmetastatic lung cancer primarily suffered from auricular pain localized ipsilaterally to the lung mass.[13] Lung masses that abut on or infiltrate visceral vagus

nerve afferents can refer pain to the ear by convergence of visceral fibers from the lung and somatic afferents of ABVN onto common secondary sensory neurons in the nucleus of the solitary tract.

Ear-Cough Reflex

A young boy reported about a chronic dry cough (Fig. 1F).[14] On examination, an accumulation of epidermal cerumen surrounding a skin ulceration in a narrowed external auditory canal was found. Stimulation of the wall of the ear canal with a cotton bud triggered a marked cough reflex. After removal of the accumulated cerumen, the cough disappeared. The ear-cough reflex was elicited in 12 patients.[15] It was bilaterally induced in three patients. Lacrimation was additionally observed in one patient (auriculo-lacrimal reflex). Twenty-one out of 500 patients studied had a clinically positive ear-cough reflex.[16] Gagging and lacrimation were seen in 9 and 10 patients, respectively. While vomiting was present in one case (ear-vomiting reflex), severe cardiac inhibition with syncopal attack was seen in three persons (auriculo-cardiac reflex). Three hundred adults and 100 children with chronic cough, 50 adults with stable pulmonary disease but without chronic cough, as well as 100 adult and 100 pediatric volunteers underwent evaluation consisting of stimulation of the external auditory canal of each ear with a cotton-tipped applicator.[17] Ear-cough reflex was present in 23.3% of adults and 3% of children with chronic cough. The prevalence of the reflex was 2% among healthy adults and children. Because of the greater than 11-fold prevalence of the ear-cough reflex in adults with chronic cough compared with healthy volunteers and adults with respiratory disease but without chronic cough, the authors suggested a concept of cough hypersensitivity syndrome, in which vagal hypersensitivity is proposed to underlie chronic refractory cough. In the absence of auricular symptoms, an otoscope is not usually used in the investigation of patients with chronic cough. Thus, no mechanical stimulation of the outer ear is performed and the ABVN is not stimulated. The diagnostic possibility of chronic cough because of hyperactivity of the ear-cough reflex may therefore be overlooked, resulting in unnecessary examinations of the upper and lower respiratory tracts.[18] Similar reflex phenomena documenting the functional connection between the ABVN and the autonomic nervous system are the gastroauricular phenomenon, the auriculogential reflex, and the auriculouterine reflex.[19]

THICK-MYELINATED NERVE FIBERS OF THE CERVICAL VAGUS NERVE AND THE ABVN

Clinical efficacy of VNS requires activation of thick-myelinated, afferent fibers of the cervical vagus nerve.[3,7] Preclinical studies demonstrated that selective destruction of C fibers with capsaicin does not affect VNS-induced seizure suppression in rats.[20] These results indicate that myelinated A fibers mediate anticonvulsive effects of VNS. Vagus nerve evoked potentials within 20 ms were prospectively and simultaneously recorded from a surgical wound in the neck and at multiple scalp sites during implantation surgery in 25 patients with drug-resistant epilepsy.[21] Electrical stimulation was delivered using the clinical VNS therapy system. The early component around 3 ms remained unchanged after muscle relaxation while the later peaks disappeared indicating that the early evoked potential originated from afferent nerve activity without any contribution of electromyographic artifacts. Rostral transition of the stimulation resulted in an earlier shift of the early component. The estimated conduction velocity was 27.4 m/s on average. The early component was regarded as directly resulting from ascending neural conduction of myelinated A fibers of the cervical vagus nerve. A preclinical study in rats investigated the effect of various VNS output current intensities on cortical excitability in the motor cortex stimulation model.[22] The hypothesis was that output current intensities in the lower range are sufficient to significantly affect cortical excitability. The study confirmed efficacy of VNS in the motor cortex stimulation rat model and indicated that 0.25 mA is sufficient to decrease cortical excitability and higher output current intensities may not be required.

Existence and quantity of thick-myelinated nerve fibers of the ABVN were addressed in an anatomical study that investigated the amount of such nerve fibers with a diameter of at least 7 μm in 9 left and 9 right auricles of 15 human corpses.[23] Amount of fibers in ABVN were compared to the amount of fibers in the thoracic vagus nerve. A direct comparison of nerve fiber quantities between ABVN and cervical vagus nerves would misleadingly include efferent motor fibers in the same diameter range that exit the cervical vagus nerve and build the recurrent laryngeal nerve. The thoracic vagus nerve does not carry any of these motor fibers and, therefore, qualifies for a direct comparison with fibers of the ABVN. The study of human vagus nerves resulted in average amounts of thick-myelinated fibers of 64 and 78 in left and right ABVN, respectively. Left and right thoracic vagus nerves carried 255 and 466 on average, respectively. Thus, the left ABVN carries approximately 21% of thick-myelinated nerve fibers as compared to the thoracic vagus nerve. These numbers define the maximum amount of thick-myelinated afferent nerve fibers that could potentially by activated by VNS and tVNS, respectively. However, it is unclear to which extent nerve fibers of cervical vagus nerve and ABVN are recruited by neuromodulatory stimulation.

PREFERENTIAL EXCITATION OF THICK-MYELINATED NERVE FIBERS BY tVNS

Thick-myelinated fibers of a sensory peripheral nerve such as the ABVN mediate touch sensation. Consequently, stimulus intensity of electrical tVNS is adjusted to a level above individual detection threshold and clearly below individual pain threshold. The detection threshold is defined as the lowest stimulus intensity that evokes the first perceptible sensation that reliably corresponds to a tingling sensation. The pain threshold is defined as the lowest stimulation intensity that elicits the first pricking or unpleasant sensation. Both psychophysical thresholds are determined by the method of limits with several runs of electrical stimuli applying decreasing and increasing intensity ramps.[24] In 18 healthy volunteers and 36 ears, the electrical detection

threshold with single pulse stimulation (200 μs duration) averages out at 0.8 ± 0.3 mA in the cymba conchae.[25] This intensity conforms to published thresholds as measured in the face or the forearm.[26–28] Touch sensation is clinically assessed by the mechanical detection threshold via application of von Frey filaments.[27] The mechanical detection threshold in the area of the cymba conchae in 14 ears corresponds to 0.5 ± 0.7 mN, which is very similar to thresholds in the face and the forearm.[27,29] Electrical and mechanical detection thresholds and evoked tingling sensation in patients and volunteers indicate preferential activation of thick-myelinated Aβ fibers of the ABVN by tVNS.

PROJECTION OF ABVN FIBERS TO THE NTS

The NTS is the main target of VNS. Central projections of the ABVN of cats were examined by transganglionic horseradish peroxidase transport. After topical application of horseradish peroxidase to the central cut end of the ABVN, neurons in the superior ganglion of the vagus nerve were labeled. Main terminal labeling was seen ipsilaterally in the NTS. Within NTS, labeled terminals were detected in the interstitial, dorsal, dorsolateral, and commissural subnuclei.[30] Similar labeling of NTS was reported in dogs.[31] Animals were randomized to active tVNS or sham and c-Fos immunohistochemistry was performed to identify the brain regions activated by tVNS.[32] Stimulation of the left cavum concha resulted in bilateral c-Fos staining in the nuclei tractus solitarii and the loci coerulei in all animals. There was no c-Fos staining in any part of the brainstem in sham control animals.

Under anesthesia, the tracer cholera toxin subunit B was subcutaneously applied into the junction of cavity of the auricular concha and posteroinferior wall of the external acoustic canal in rats.[33] Transganglionically labeled fibers terminated on the caudal part of lateral NTS. Nucleus of the solitary tract neurons with afferent input from the auricle was identified by extracellular discharge signals recorded by glass microelectrodes under tVNS. Extracellular single-unit recordings were carried out in NTS of rats during electroacupuncture stimulation at auricular concha.[34] Electroacupuncture excited 49.3% (34/69) of total neurons recorded in NTS and inhibited 4.3% (3/69).

CEREBRAL ACTIVATION PATTERN UNDER VNS

Vagus nerve stimulation has been shown to activate a central nervous system network involving NTS, locus coeruleus, parabrachial nucleus, hippocampus, and other areas of the brain.[4,35,36]

An functional MRI study in healthy volunteers addressed the brainstem and cerebral activation pattern under tVNS.[37] Twelve healthy adults underwent two functional MRI scans in the same session. Electrical stimulation was applied to the earlobe (control) and left cymba conchae. Cymba conchae stimulation, compared with earlobe (control) stimulation, produced significant activation of the classical central vagal projections such as widespread activity in the ipsilateral NTS, bilateral spinal trigeminal nucleus, dorsal raphe, locus coeruleus, and contralateral parabrachial area, amygdala, and nucleus accumbens. Deactivations were observed bilaterally in the hippocampus and hypothalamus. These findings provide evidence in humans that the central projections of the ABVN are consistent with the classical central vagal projections and can be accessed noninvasively via tVNS of the external ear. These results were confirmed by a recent functional MRI study that additionally applied electrical stimulation to the inner tragus and the inferoposterior wall of the ear canal.[38] Stimulation at the ear canal resulted in the weakest activation of the NTS, the recipient of most afferent vagal projections, and of the locus coeruleus, a brainstem nucleus that receives direct input from the NTS. Stimulation of the inner tragus and cymba conchae activated these two nuclei as compared to sham. However, statistical analysis showed that only stimulation of the cymba conchae produced a significantly stronger activation in both the NTS and the locus coeruleus than did the sham stimulation. The authors concluded that tVNS at the cymba conchae properly activates the vagal pathway and results in its strongest activation and thus may be the optimal location for tVNS therapies applied to the auricle.

Brain activation pattern under tVNS clearly shares features with changes in brain activity observed during invasive VNS.[35]

ANTICONVULSIVE EFFECTS OF tVNS IN DRUG-RESISTANT EPILEPSY

Transcutaneous vagus nerve stimulation was applied to seven patients with drug-resistant epilepsies for a period of nine months.[39] Patients applied tVNS three times per day for a time period of 1 hour each. The primary outcome of the study based on the number of seizures as documented by the patient's seizure diary. After nine months, an overall reduction of seizure frequency was observed in five out of seven patients. A randomized, double-blinded controlled trial assessed efficacy and safety of tVNS versus control stimulation in patients with drug-resistant epilepsy.[40] Primary objective was to demonstrate superiority of add-on therapy with tVNS (stimulation frequency 25 Hz, n = 39) versus active control (1 Hz, n = 37) in reducing seizure frequency over 20 weeks. Secondary objectives comprised reduction in seizure frequency from baseline to end of treatment, subgroup analyses, and safety evaluation. Treatment adherence was 84% in the 1 Hz group and 88% in the 25 Hz group, respectively. Mean seizure reduction per 28 days at end of treatment was −2.9% in the 1 Hz group and 23.4% in the 25 Hz group ($P > 0.05$). In contrast to controls, a significant reduction was found in seizure frequency in patients of the 25 Hz group who completed the full treatment period (20 weeks; n = 26, 34.2%, $P < 0.05$). Adverse events were usually mild or moderate and comprised headache, ear pain, application site erythema, vertigo, fatigue, and nausea. Four serious adverse events were reported including one sudden unexplained death in epilepsy patients in the 1 Hz group, which was assessed as not treatment-related. tVNS had a high-treatment adherence and was well tolerated. Superiority of 25 Hz tVNS over 1 Hz tVNS could not be proven in this study. Fourteen pediatric patients with intractable epilepsy were treated by tVNS of the bilateral auricular concha using an ear vagus nerve stimulator.[41] The baseline seizure frequency was compared with that after 8 weeks,

from week 9 to 16 and from week 17 to the end of week 24, according to the seizure diaries of the patients. One patient dropped out after 8 weeks of treatment because of lack of efficacy, while the remaining 13 patients completed the 24-week study without any change in medication regimen. The mean reduction in seizure frequency relative to baseline was 31.8% after week 8, 54.1% from week 9 to 16 and 54.2% from week 17 to the end of week 24. No severe adverse events were reported during treatment. The authors concluded that tVNS may be a complementary treatment option for reducing seizure frequency in pediatric patients with intractable epilepsy.

SUMMARY AND CONCLUSION

Invasive VNS is applied to the cervical branch of the vagus nerve and requires neurosurgical intervention. Main intended use of invasive VNS is the treatment of drug-resistant epilepsies with clinically relevant anticonvulsive effects in about 60% of patients. Common side effects are hoarseness, sore throat, shortness of breath, and coughing. Invasive VNS excites thick-myelinated nerve fibers. Propagating action potentials of the cervical vagus nerve access the main target NTS initiating a typical cerebral activation pattern.

Transcutaneous vagus nerve stimulation is a transcutaneous and noninvasive method of electrical stimulation of the auricular branch of the vagus nerve that primarily supplies concha and antihelix of the auricle. tVNS excites thick-myelinated nerve fibers of the ABVN that access the NTS via the auriculo-vagal afferent pathway. tVNS provokes a typical cerebral activation pattern similar to cervical VNS. Recently, two randomized controlled trials and two pilot trials with patients suffering from drug-resistant epilepsies addressed safety and clinical performance of tVNS. Besides application of tVNS as treatment option in drug-resistant epilepsy, the neuromodulatory technique may be appropriate to identify potential responder to invasive VNS.

Besides the approved intended use for drug-resistant epilepsy and depression, recent clinical trials addressed efficacy of tVNS in chronic pain as well.[42–46]

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