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The strange case of the ear and the heart: the auricular vagus nerve and its influence on cardiac control.

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Abstract

The human ear seems an unlikely candidate for therapies aimed at improving cardiac function, but the ear and the heart share a common connection: the vagus nerve. In recent years there has been increasing interest in the auricular branch of the vagus nerve (ABVN), a unique cutaneous subdivision of the vagus distributed to the external ear. Non-invasive electrical stimulation of this nerve through the skin may offer a simple, cost-effective alternative to the established method of vagus nerve stimulation (VNS), which requires a surgical procedure and has generated mixed results in a number of clinical trials for heart failure. This review discusses the available evidence in support of modulating cardiac activity using this strange auricular nerve.

The ear has been a site of therapeutic interest for millennia, including reports of women in ancient Egypt using a heated needle to cauterise the skin of the ear as a method of contraception (Gori et al., 2007). In ancient Greece, the physician Hippocrates reported that blood-letting from veins on the posterior surface of the ear could be used as a treatment for sexual dysfunction in men (Round et al., 2013). Chinese traditional medicine, first developed over 3000 years ago, has also placed an emphasis on using manual acupuncture of the ear or auricular acupuncture to influence bodily functions through the concept of 'Qi' and meridians – energy pathways associated with an intrinsic 'life force' which are believed to converge at the level of the ear (He et al., 2012).

The ear is the site of a number of unusual reflexes including the pulmonoauricular reflex, described in three tuberculosis patients with referred pain to the ear (Engel, 1979); the auriculogenital reflex in both male and female cats where mechanical or electrical stimulation of the external ear elicited contraction of muscles around the genitalia (Bradford, 1938); and the auriculouterine reflex, reported in a female patient who felt severe pain in her left ear which coincided with menstruation (Engel, 1979). An auriculocardiac reflex has been identified in a patient who experienced bradycardia following stimulation of the posterior wall of the left external acoustic meatus with a cotton-tipped ear probe (Thakar et al., 2008). Referred pain to the ear as a result of angina and myocardial infarction has also been described, highlighting the potential connectivity between the ear and the heart (Amirhaeri et al., 2010; Rothwell, 1993).

The basis of these reflexes may be due to variation in the sensitivity of the auricular branch of the vagus nerve (ABVN), which innervates the skin of parts of the ear and the outer ear canal (external acoustic meatus). This branch of the vagus nerve is

known as Arnold's nerve after the German anatomist Friedrich Arnold (1803-1890), who first observed that irritation of the posterior wall of the external acoustic meatus elicited coughing in a small number of people (Arnold's Reflex). Subsequent studies have shown that such a response occurs in between 1.7%- 4.2% of individuals (Bloustine et al., 1976; Gupta et al., 1986; Tekdemir et al., 1998) and arises due to hypersensitivity of the ABVN (Ryan et al., 2014). This nerve is sometimes known too as the Alderman's nerve, a centuries-old reference to the Aldermen of the City of London and their practice of using rosewater bowls at ceremonial banquets. The banquet attendees were encouraged to place a table napkin moistened with rosewater behind their ears with the belief that this promoted gastric emptying and aided digestion (Treves, 1883).

Anatomy of the Auricular Branch of the Vagus Nerve

The ABVN is a remnant of the embryonic nerve supplying the first branchial arch (Gupta et al., 1986) and is thought to be derived from nerves supplying the lateral line organ in lower vertebrates such as fish, which use these cutaneous nerves to sense vibrations and movement in the surrounding water (Engel, 1979; Hoagland, 1933). In mammals, the ABVN is distributed to the skin of the ear and external acoustic meatus and consists of somatosensory afferent fibres, with their cell bodies located in the jugular ganglion (DuBois et al., 1937). In humans, cadaveric dissection has indicated that the ABVN is the only source of innervation to the cymba concha and further innervates the antihelix, tragus and cavity of the concha (Peuker et al., 2002). However, the skin of the ear receives additional sensory innervation from trigeminal afferents (auriculotemporal nerve) and cervical spinal afferents (great

auricular nerve and lesser occipital nerve; see figure 1), with a variable degree of overlap in the respective dermatomes (Peuker et al., 2002).

How can stimulation of a small nerve in the ear elicit such a wide range of physiological responses? The answer becomes clearer when the vagus nerve is considered in its entirety. Regarded as the main parasympathetic output of the autonomic nervous system, the vagus nerve has an extensive distribution throughout the thorax and abdomen. In its role as the “great wandering protector” of the body, it relays sensory information about the state of the body’s internal organs to the central nervous system via afferent fibres which make up 80% of the nerve (Foley et al., 1937). Upon exiting the cranium via the jugular foramen, the vagus provides innervation to the soft palate, pharynx and muscles of the larynx prior to entering the thorax (Berthoud et al., 2000). At this point, the ‘wandering’ nature of the vagus becomes apparent through its complex distribution to the heart, lungs, liver, adrenal medulla and the gastrointestinal tract up to the splenic flexure of the colon (Clancy et al., 2013). The remaining 20% of vagus nerve fibres are efferent fibres originating from the brainstem which provide parasympathetic control of the viscera and heart (Foley et al., 1937).

The large number of afferent fibres in the vagus has led to it being investigated as a therapeutic pathway for influencing brain activity by means of electrical stimulation. In humans, vagus nerve stimulation (VNS) can be achieved by implanting an electrical stimulator under the skin of the chest which stimulates the cervical vagus nerve via a bipolar lead wrapped around the nerve. VNS was developed in the 1980s in patients with intractable epilepsy, is approved for the treatment of refractory epilepsy and depression and has a well-established safety profile in these patients (Groves et al., 2005; Morris et al., 1999; O'Reardon et al., 2006).

Given the critical role of the vagus nerve in providing parasympathetic innervation to the heart, there has been interest in using VNS to modulate cardiac function. In animals, electrical stimulation of the cervical vagus nerve has been shown to evoke cardiovascular effects, for example by lowering the ventricular fibrillation threshold (Brack et al., 2013). Moreover, VNS is known to reduce incidence of ventricular arrhythmias and mortality during ischemia (Brack et al., 2013) and prevent sudden cardiac death in dogs with myocardial infarction (Vanoli et al., 1991). VNS has also been investigated in animal models of chronic heart failure, a condition characterised by a sustained increase in sympathetic drive and a concurrent withdrawal of parasympathetic activity (Triposkiadis et al., 2009). A sustained improvement in cardiac function and heart failure symptoms has been demonstrated as a result of VNS (Hamann et al., 2013; Kusunose et al., 2014; Li et al., 2004; Sabbah et al., 2011; Zhang et al., 2009).

The results of these animal studies combined with the well-established safety profile of VNS has encouraged investigation into the feasibility and tolerability of VNS in heart failure patients. Preliminary results using VNS showed promise and stimulation of the right cervical vagus nerve with pulses synchronised to the cardiac cycle improved NYHA class, quality of life scores and left ventricular end-systolic volume (Schwartz et al., 2008). Larger studies subsequently showed VNS was associated with a significant improvement in cardiac function, quality of life scores and exercise performance (De Ferrari et al., 2011; Premchand et al., 2014).

However, a recent larger clinical trial concluded that 6 months of VNS failed to have a significant effect on cardiac remodelling and cardiac function in heart failure patients. Nevertheless, the study did show an improvement in quality of life measures and NYHA classification (Zannad et al., 2015). A subsequent international

multi-centre clinical trial using VNS on heart failure patients to assess whether VNS increases the time to first event defined by all-cause mortality or unplanned heart failure hospitalization was discontinued due to a statistical futility in this primary efficacy endpoint (Gold et al., 2016). Although the safety profile of VNS is recognised, the technique requires surgical implantation of the electrodes and a subcutaneous battery pack, with an increased risk of post-operative complications such as infection (Elliott et al., 2011). Other acute side-effects of VNS can include neck pain, coughing, difficulty swallowing and voice alteration alongside nausea and indigestion. In the longer term, hardware failure may necessitate revision surgery, leaving patients at risk of experiencing a relapse in their symptoms until VNS can be restored (Dlouhy et al., 2012). Since the ABVN of the ear can be electrically stimulated through the skin without the need for an expensive surgical procedure, targeting this site may provide an attractive therapeutic alternative with a greater potential for widespread clinical use.

Cardiac effects of tVNS

Non-invasive or transcutaneous vagus nerve stimulation (tVNS) involves the use of either electroacupuncture or specialised contact electrodes to pass a current through the skin, with a high degree of heterogeneity in the literature in terms of stimulus parameters and sites of application on the ear. In recent years the major sites of interest for delivering electrical stimulation to the ABVN have been the inner surface of the tragus (Busch et al., 2013; Clancy et al., 2014; Kraus et al., 2013; Stavrakis et al., 2015; Weise et al., 2015; Zhou et al., 2016), the concha (Ay et al., 2015b; Fang et al., 2015; He et al., 2013b; Liu et al., 2013), and the cymba concha (Frangos et al., 2015; Kreuzer et al., 2014). In parallel with these ear studies, a method said to

allow non-invasive cervical vagus nerve stimulation through the skin of the neck has also been developed and is under investigation in patients with cluster headache (Nesbitt et al., 2015) and migraine (Barbanti et al., 2015). Regardless of the exact nature of the stimulation technique, the majority of the tVNS studies have followed on from invasive VNS in their focus on neurological and psychiatric disorders, but there has been increasing interest in whether or not tVNS could have beneficial cardiac effects.

In anaesthetized dogs, chronic low-level stimulation of the tragus of the right ear reversed atrial remodelling and inhibited the induction of atrial fibrillation elicited by 3 hours of prior rapid atrial pacing (Yu et al., 2013). Subsequent studies stimulating the right or left tragus suppressed atrial fibrillation when performed alongside 9 hours of atrial pacing by preventing the loss of the connexin proteins Cx40 and Cx43 in the atrial tissue (Chen et al., 2015a; Chen et al., 2015b). When the same stimulation protocol was applied to the left and right tragus of conscious dogs with healed myocardial infarction, tVNS was improved cardiac function, alleviated cardiac fibrosis and attenuated left ventricular remodelling (Wang et al., 2014; Wang et al., 2015). This low-level tVNS reduced the plasma concentration of non-specific inflammatory markers such as C-reactive protein and decreased the expression of various factors which regulate cellular remodelling such as transforming growth factor beta 1 and matrix metalloproteinase 9 (Wang et al., 2014; Wang et al., 2015). A decrease in the concentration of plasma noradrenaline was further observed, suggesting that low-level tVNS may decrease sympathetic nerve activity.

A number of human studies have also observed cardiac effects following tVNS. Early pioneering studies in this area were performed on patients with coronary artery disease and angina pectoris who were due to undergo surgery for coronary artery

bypass grafting. Acupuncture needles with electrodes attached were placed into the inferior concha of both ears and electrostimulation was applied for 15 minutes a day for 10 days. This caused a reduction in the incidence of angina pectoris (a reduction which lasted 2-3 weeks), improved the clinical course before and after surgery and decreased the use of vasodilator treatment (Zamotrinsky et al., 1997; Zamotrinsky et al., 2001). During surgery, atrial tissue was removed, and patients who had undergone tVNS were found to have reduced levels of heat shock protein (HSP) 70i and the ATP content of the tissue (Zamotrinsky et al., 1997). Following the surgery, patients who had received tVNS had a significantly reduced incidence of acute heart failure compared to patients who did not receive tVNS (Zamotrinsky et al., 2001). In another study with coronary artery disease patients, Popov et al. (2013) stimulated the auricular branch of the vagus by passing a low frequency electrical current through electrodes on the internal surface of the auricle for 10 days. These stimulation sessions caused nearly two-thirds of patients (62.5%) to report a significant decrease in the intensity of angina attacks with an improvement in general well-being (Popov et al., 2013). When the patient group was considered as a complete cohort, tVNS did not alter any clinical results. However, when patients who responded favourably to tVNS were studied as a separate group, their LF/HF ratio – a non-invasive index of autonomic activity at the sinoatrial node - was significantly lower following tVNS than before treatment, indicating a possible increase in vagus nerve activity to the heart (Popov et al., 2013).

In patients with paroxysmal atrial fibrillation, 1 hour of low level tVNS under general anaesthesia significantly decreased atrial fibrillation duration (induced by burst atrial pacing), significantly increased atrial fibrillation cycle length and significantly decreased systemic levels of the inflammatory factors tumour necrosis factor alpha

(TNF-alpha) and C-reactive protein (Stavrakis et al., 2015). Meanwhile, in patients with chronic heart failure and severe left ventricular dysfunction, a 15 day course of daily tVNS sessions (increasing duration per session, up to 30 minutes) on the internal surface of the auricle significantly increased distance of a 6 minute walk test and improved the clinical condition in the majority of patients. In addition tVNS was shown to have a bradycardiac effect in these patients along with increased levels of heat shock proteins HSP60 and HSP70 in patients who had an initial heart rate of less than 80 bpm. Patients with a heart rate greater than 80 bpm exhibited increased the levels of HSP70 alone (Afanasiev et al., 2016). Cardiovascular disorders therefore appear to be a suitable target for treatment with tVNS (see also supplementary Table 1).

Mechanism of action of tVNS on cardiac function

The central projections of the ABVN have been investigated in the cat and rat. Application of the transganglionic neuronal tracer horseradish peroxidase (HRP) to the central cut end of the ABVN of the cat results in labelled fibres in the principal sensory trigeminal nucleus, spinal trigeminal nucleus, nucleus tractus solitarius and cuneate nucleus in the brainstem (Nomura et al., 1984). In rats, microinjection of cholera toxin subunit B into the junction of the auricular concha and postero-inferior wall of the external acoustic meatus produced labelled fibres in the lateral NTS and the spinal trigeminal nucleus (He et al., 2013a).

In humans, fMRI scans have shown electrical stimulation of the left cymba concha produces significant activation of “classical” central vagal projections including widespread activity in the ipsilateral nucleus of the solitary tract (NTS), bilateral

spinal trigeminal nucleus, dorsal raphe, locus coeruleus, contralateral parabrachial area, amygdala and nucleus accumbens (Frangos et al., 2015). The connections of the ABVN to the NTS may be of particular relevance to the cardiovascular effects observed after tVNS. As mentioned, anatomical tracing studies in the cat (Nomura et al., 1984) and rat (He et al., 2013a) have shown that the ABVN projects to the NTS. Evidence that NTS neurones are activated following ABVN stimulation is derived from studies in which electrical stimulation of the concha in rats with transient focal ischemia elicits *c-fos* staining in the bilateral NTS and locus coeruleus (Ay et al., 2015a).

In rats, a decrease in arterial pressure and heart rate can be elicited through acupuncture-like stimulation of the inferior concha. Increased activity was observed in NTS neurones with discharges synchronised to cardiac rhythm (Gao et al., 2011), suggesting these neurones also received baroreceptor input. Some NTS neurones receiving baroreceptor information are indeed known to project to the dorsal vagal motor nucleus (DVN) and nucleus ambiguus (Deuchars et al., 2000), where cardioinhibitory vagal efferent neurones are located (Izzo et al., 1993). The observation by Yu et al (2013) that cardiovascular effects (reversal of atrial remodelling and inhibition of atrial fibrillation elicited by atrial pacing) following stimulation of the right tragus in anaesthetized dogs are eliminated by transection of both vagus nerves indicates that vagal efferent fibres play a role in such cardiovascular effects (Yu et al., 2013). It is therefore possible to propose that auricular afferents can increase vagal efferent outputs by connections via the NTS (see Figure 2).

In addition to vagal activation, a number of recent studies have shown that auricular stimulation may also influence the activity of the sympathetic nervous system. In

healthy human volunteers with no history of cardiovascular disease, tVNS on the inner and outer surface of the tragus significantly improved heart rate variability (through a shift in cardiac autonomic activity towards relative parasympathetic/vagal dominance) and caused a significant decrease in muscle sympathetic nerve activity as recorded by microneurography (Clancy et al., 2014). Further evidence that electrical stimulation of the ABVN can elicit a decrease in sympathetic activity comes from a study by Wang et al (2014), where a reduction in plasma noradrenaline concentration was observed following bilateral tragus stimulation in conscious dogs with healed myocardial infarction (Wang et al., 2014). Zhou et al (2016) also showed that in anesthetized dogs, 3 hours of right tragus stimulation significantly attenuated the sinus rate acceleration in response to right stellate ganglion stimulation and decreased activity in the right stellate ganglion. In addition, tVNS has been found to decrease expression of c-Fos, nerve growth factor and increase expression of SK2 at both the mRNA and protein level in the right stellate ganglion (Zhou et al., 2016). The circuitry underlying this pathway is unknown, but may be via afferent excitation of NTS neurones that send excitatory inputs to the caudal ventrolateral medulla which in turn sends inhibitory inputs to the rostral ventrolateral medulla, the source of excitatory drive to sympathetic efferents (Guyenet, 2006). Inhibition of the RVLM therefore decreases sympathetic activity (see Figure 2).

tVNS, and not VNS?

Could the principal advantage of tVNS be its lack of a surgical procedure, or could tVNS provide a more effective therapeutic alternative to VNS? The failure of the VNS trials for the treatment of heart failure could be partly explained by recent observations that the human cervical vagus nerve contains abundant tyrosine

hydroxylase-positive sympathetic nerve fibres distributed throughout the nerve fascicles (Seki et al., 2014; Verlinden et al., 2016). Moreover, Verlinden and colleagues found that the human right cervical vagus contains around twice as many sympathetic fibres as the left cervical vagus (Verlinden et al., 2016). Similar sympathetic structures have previously been observed in the canine cervical vagus nerve, although the fibres were distributed to the periphery of the nerve (Onkka et al., 2013). This apparent evolutionary vestige is in line with other species where sympathetic and vagus fibres may be transmitted to the thorax via a common trunk (Muryobayashi et al., 1968; Onkka et al., 2013). In addition, anatomical studies have documented rich interactions between the right thoracic vagal nerve and the right stellate ganglion at all levels(Ellison et al., 1969; Mizeres, 1955) and the rat superior cervical ganglia have been found to contain bundles of nerve fibres derived from the vagus nerve that are immunoreactive for calcitonin gene-related peptide and substance P (Zaidi et al., 2013). Such anatomical studies suggest that stimulation of the cervical vagus nerve may influence sympathetic activity through these interacting nerve fibres. Indeed, when the cervical vagus was stimulated with intermittent moderate stimulation in dogs, stellate ganglion neuron activity increased (Rhee et al., 2015). This is likely an undesirable effect as enhanced sympathetic nerve activity is associated with cardiovascular disease onset and progression (Triposkiadis et al., 2009).

The question remains why, therefore, could tVNS be effective for treatment of cardiovascular disease? A key consideration is that tVNS increases heart rate variability and, critically, decreases muscle sympathetic nerve activity in healthy humans (Clancy et al., 2014). Further, such cardiovascular diseases are associated with increased inflammation and tVNS reduced plasma levels of non-specific

inflammatory markers in conscious dogs with healed myocardial infarction (Wang et al., 2014; Wang et al., 2015), as well as in patients with paroxysmal atrial fibrillation (Stavrakis et al., 2015). Finally, the pathways through which tVNS functions are not yet known (see Figure 2) – it is conceivable that they provide a more selective route of action than those activated through cervical vagus stimulation. Further investigations into such pathways and the effects of tVNS on the cardiovascular system therefore seem warranted: the strange case of the ear and the heart remains unsolved!

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References

Afanasiev, S.A., Pavliukova, E.N., Kuzmichkina, M.A., Rebrova, T.Y., Anfinogenova, Y., Likhomanov, K.S., Karpov, R.S. 2016. Nonpharmacological Correction of Hypersympatheticotonia in Patients with Chronic Coronary Insufficiency and Severe Left Ventricular Dysfunction. Annals of Noninvasive Electrocardiology.

Amirhaeri, S., Spencer, D. 2010. Myocardial infarction with unusual presentation of otalgia: a case report. International Journal of Emergency Medicine 3, 459-460.

Ay, I., Napadow, V., Ay, H. 2015a. Electrical stimulation of the vagus nerve dermatome in the external ear is protective in rat cerebral ischemia. Brain stimulation 8, 7-12.

Ay, I., Nasser, R., Simon, B., Ay, H. 2015b. Transcutaneous Cervical Vagus Nerve Stimulation Ameliorates Acute Ischemic Injury in Rats. Brain stimulation.

Barbanti, P., Grazzi, L., Egeo, G., Padovan, A.M., Liebler, E., Bussone, G. 2015. Non-invasive vagus nerve stimulation for acute treatment of high-frequency and chronic migraine: an open-label study. Journal of Headache Pain 16, 61.

Berthoud, H.-R., Neuhuber, W.L. 2000. Functional and chemical anatomy of the afferent vagal system. Autonomic Neuroscience 85, 1-17.

Bloustine, S., Langston, L., Miller, T. 1976. Ear-Cough (Arnold's) Reflex. Annals of Otology, Rhinology & Laryngology 85, 406-407.

Brack, K.E., Winter, J., Ng, G.A. 2013. Mechanisms underlying the autonomic modulation of ventricular fibrillation initiation--tentative prophylactic properties of vagus nerve stimulation on malignant arrhythmias in heart failure. Heart failure reviews 18, 389-408.

Bradford, F.K. 1938. THE AURICULO-GENITAL REFLEX IN CATS. Quarterly Journal of Experimental Physiology 27, 271-279.

Busch, V., Zeman, F., Heckel, A., Menne, F., Ellrich, J., Eichhammer, P. 2013. The effect of transcutaneous vagus nerve stimulation on pain perception – An experimental study. Brain stimulation 6, 202-209.

Chen, M., Yu, L., Zhou, X., Liu, Q., Jiang, H., Zhou, S. 2015a. Low-level vagus nerve stimulation: an important therapeutic option for atrial fibrillation treatment via modulating cardiac autonomic tone. International Journal of Cardiology 199, 437-438.

Chen, M., Zhou, X., Liu, Q., Sheng, X., Yu, L., Wang, Z., Wang, S., Zhou, S. 2015b. Left-sided Noninvasive Vagus Nerve Stimulation Suppresses Atrial Fibrillation by Upregulating Atrial Gap Junctions in Canines. Journal of cardiovascular pharmacology 66, 593-599.

Clancy, J.A., Deuchars, S.A., Deuchars, J. 2013. The wonders of the Wanderer. Experimental physiology 98, 38-45.

Clancy, J.A., Mary, D.A., Witte, K.K., Greenwood, J.P., Deuchars, S.A., Deuchars, J. 2014. Non-invasive Vagus Nerve Stimulation in Healthy Humans Reduces Sympathetic Nerve Activity. Brain stimulation.

De Ferrari, G.M., Crijns, H.J., Borggrefe, M., Milasinovic, G., Smid, J., Zabel, M., Gavazzi, A., Sanzo, A., Dennert, R., Kuschyk, J., Raspopovic, S., Klein, H.,

Swedberg, K., Schwartz, P.J. 2011. Chronic vagus nerve stimulation: a new and promising therapeutic approach for chronic heart failure. European heart journal 32, 847-855.

Deuchars, J., Li, Y.W., Kasparov, S., Paton, J.F. 2000. Morphological and electrophysiological properties of neurones in the dorsal vagal complex of the rat activated by arterial baroreceptors. Journal of Comparative Neurology 417, 233-249.

Dlouhy, B.J., Viljoen, S.V., Kung, D.K., Vogel, T.W., Granner, M.A., Howard, M.A., 3rd, Kawasaki, H. 2012. Vagus nerve stimulation after lead revision. Neurosurgical focus 32, E11.

DuBois, F.S., Foley, J.O. 1937. Quantitative studies of the vagus nerve in the cat. II. The ratio of jugular to nodose fibers. The Journal of Comparative Neurology 67, 69-87.

Elliott, R.E., Morsi, A., Kalhorn, S.P., Marcus, J., Sellin, J., Kang, M., Silverberg, A., Rivera, E., Geller, E., Carlson, C., Devinsky, O., Doyle, W.K. 2011. Vagus nerve stimulation in 436 consecutive patients with treatment-resistant epilepsy: long-term outcomes and predictors of response. Epilepsy & Behavior 20, 57-63.

Ellison, J.P., Williams, T.H. 1969. Sympathetic nerve pathways to the human heart, and their variations. American Journal of Anatomy 124, 149-162.

Engel, D. 1979. The gastroauricular phenomenon and related vagus reflexes. Archiv fur Psychiatrie und Nervenkrankheiten 227, 271-277.

Fang, J., Rong, P., Hong, Y., Fan, Y., Liu, J., Wang, H., Zhang, G., Chen, X., Shi, S., Wang, L., Liu, R., Hwang, J., Li, Z., Tao, J., Wang, Y., Zhu, B., Kong, J. 2015. Transcutaneous Vagus Nerve Stimulation Modulates Default Mode Network in Major Depressive Disorder. Biological psychiatry.

Foley, J.O., DuBois, F.S. 1937. Quantitative studies of the vagus nerve in the cat. I. The ratio of sensory to motor fibers. The Journal of Comparative Neurology 67, 49-67.

Frangos, E., Ellrich, J., Komisaruk, B.R. 2015. Non-invasive Access to the Vagus Nerve Central Projections via Electrical Stimulation of the External Ear: fMRI Evidence in Humans. Brain stimulation 8, 624-636.

Gao, X.Y., Li, Y.H., Liu, K., Rong, P.J., Ben, H., Li, L., Zhu, B., Zhang, S.P. 2011. Acupuncture-like stimulation at auricular point Heart evokes cardiovascular inhibition via activating the cardiac-related neurons in the nucleus tractus solitarius. Brain Research 1397, 19-27.

Gold, M.R., Van Veldhuisen, D.J., Hauptman, P.J., Borggrefe, M., Kubo, S.H., Lieberman, R.A., Milasinovic, G., Berman, B.J., Djordjevic, S., Neelagaru, S., Schwartz, P.J., Starling, R.C., Mann, D.L. 2016. Vagus Nerve Stimulation for the Treatment of Heart Failure: The INOVATE-HF Trial. Journal of the American College of Cardiology.

Gori, L., Firenzuoli, F. 2007. Ear acupuncture in European traditional medicine. Evidence-Based Complementary and Alternative Medicine 4, 13-16.

Groves, D.A., Brown, V.J. 2005. Vagal nerve stimulation: a review of its applications and potential mechanisms that mediate its clinical effects. Neuroscience & Biobehavioral Reviews 29, 493-500.

Gupta, D., Verma, S., Vishwakarma, S.K. 1986. Anatomic basis of Arnold's ear-cough reflex. Surgical and Radiologic Anatomy 8, 217-220.

Guyenet, P.G. 2006. The sympathetic control of blood pressure. Nature Reviews Neuroscience 7, 335-346.

Hamann, J.J., Ruble, S.B., Stolen, C., Wang, M., Gupta, R.C., Rastogi, S., Sabbah, H.N. 2013. Vagus nerve stimulation improves left ventricular function in a canine model of chronic heart failure. European Journal of Heart Failure 15, 1319-1326.

He, W., Jing, X.-H., Zhu, B., Zhu, X.-L., Li, L., Bai, W.-Z., Ben, H. 2013a. The auriculo-vagal afferent pathway and its role in seizure suppression in rats. BioMed Central Neuroscience 14, 85.

He, W., Jing, X., Wang, X., Rong, P., Li, L., Shi, H., Shang, H., Wang, Y., Zhang, J., Zhu, B. 2013b. Transcutaneous auricular vagus nerve stimulation as a complementary therapy for pediatric epilepsy: A pilot trial. Epilepsy & Behavior 28, 343-346.

He, W., Wang, X., Shi, H., Shang, H., Li, L., Jing, X., Zhu, B. 2012. Auricular acupuncture and vagal regulation. Evidence-Based Complementary and Alternative Medicine 2012, 786839.

Hoagland, H. 1933. ELECTRICAL RESPONSES FROM THE LATERAL-LINE NERVES OF CATFISH. I. Journal of General Physiology 16, 695-714.

Izzo, P.N., Deuchars, J., Spyer, K.M. 1993. Localization of cardiac vagal preganglionic motoneurones in the rat: immunocytochemical evidence of synaptic inputs containing 5-hydroxytryptamine. Journal of Comparative Neurology 327, 572-583.

Kraus, T., Kiess, O., Hosl, K., Terekhin, P., Kornhuber, J., Forster, C. 2013. CNS BOLD fMRI effects of sham-controlled transcutaneous electrical nerve stimulation in the left outer auditory canal - a pilot study. Brain stimulation 6, 798-804.

Kreuzer, P.M., Landgrebe, M., Resch, M., Husser, O., Schecklmann, M., Geisreiter, F., Poeppl, T.B., Prasser, S.J., Hajak, G., Rupprecht, R., Langguth, B. 2014. Feasibility, Safety and Efficacy of Transcutaneous Vagus Nerve Stimulation in Chronic Tinnitus: An Open Pilot Study. Brain stimulation 7, 740-747.

Kusunose, K., Zhang, Y., Mazgalev, T.N., Van Wagoner, D.R., Thomas, J.D., Popovic, Z.B. 2014. Impact of vagal nerve stimulation on left atrial structure and function in a canine high-rate pacing model. Circulation, Heart Failure 7, 320-326.

Li, M., Zheng, C., Sato, T., Kawada, T., Sugimachi, M., Sunagawa, K. 2004. Vagal nerve stimulation markedly improves long-term survival after chronic heart failure in rats. Circulation 109, 120-124.

Liu, R.P., Fang, J.L., Rong, P.J., Zhao, Y., Meng, H., Ben, H., Li, L., Huang, Z.X., Li, X., Ma, Y.G., Zhu, B. 2013. Effects of electroacupuncture at auricular concha region on the depressive status of unpredictable chronic mild stress rat models. Evidence-Based Complementary and Alternative Medicine 2013, 789674.

Mizeres, N.J. 1955. Isolation of the cardioinhibitory branches of the right vagus nerve in the dog. The Anatomical Record 123, 437-445.

Morris, G.L., 3rd, Mueller, W.M. 1999. Long-term treatment with vagus nerve stimulation in patients with refractory epilepsy. The Vagus Nerve Stimulation Study Group E01-E05. Neurology 53, 1731-1735.

Muryobayashi, T., Mori, J., Fujiwara, M., Shimamoto, K. 1968. Fluorescence histochemical demonstration of adrenergic nerve fibers in the vagus nerve of cats and dogs. Japanese journal of pharmacology 18, 285-293.

Nesbitt, A.D., Marin, J.C., Tompkins, E., Ruttledge, M.H., Goadsby, P.J. 2015. Initial use of a novel noninvasive vagus nerve stimulator for cluster headache treatment. Neurology 84, 1249-1253.

Nomura, S., Mizuno, N. 1984. Central distribution of primary afferent fibers in the Arnold's nerve (the auricular branch of the vagus nerve): A transganglionic HRP study in the cat. Brain Research 292, 199-205.

O'Reardon, J.P., Cristancho, P., Peshek, A.D. 2006. Vagus Nerve Stimulation (VNS) and Treatment of Depression: To the Brainstem and Beyond. Psychiatry (Edgmont (Pa. : Township)) 3, 54-63.

Onkka, P., Maskoun, W., Rhee, K.-S., Hellyer, J., Patel, J., Tan, J., Chen, L.S., Vinters, H.V., Fishbein, M.C., Chen, P.-S. 2013. Sympathetic nerve fibers and ganglia in canine cervical vagus nerves: Localization and quantitation. Heart Rhythm 10, 585-591.

Peuker, E.T., Filler, T.J. 2002. The nerve supply of the human auricle. Clinical Anatomy 15, 35-37.

Popov, S., Afanasiev, S., Kurlov, I., Pisklova, A. 2013. Drug-Free Correction of the Tone of the Autonomic Nervous System in the Management of Cardiac Arrhythmia in Coronary Artery Disease. International Journal of Biomedicine 3, 74-77.

Premchand, R.K., Sharma, K., Mittal, S., Monteiro, R., Dixit, S., Libbus, I., DiCarlo, L.A., Ardell, J.L., Rector, T.S., Amurthur, B., KenKnight, B.H., Anand, I.S. 2014. Autonomic regulation therapy via left or right cervical vagus nerve stimulation in patients with chronic heart failure: results of the ANTHEM-HF trial. Journal of cardiac failure 20, 808-816.

Rhee, K.S., Hsueh, C.H., Hellyer, J.A., Park, H.W., Lee, Y.S., Garlie, J., Onkka, P., Doytchinova, A.T., Garner, J.B., Patel, J., Chen, L.S., Fishbein, M.C., Everett, T.t., Lin, S.F., Chen, P.S. 2015. Cervical vagal nerve stimulation activates the stellate ganglion in ambulatory dogs. Korean circulation journal 45, 149-157.

Rothwell, P.M. 1993. Angina and myocardial infarction presenting with pain confined to the ear. Postgraduate Medical Journal 69, 300-301.

Round, R., Litscher, G., Bahr, F. 2013. Auricular Acupuncture with Laser. Evidence-Based Complementary and Alternative Medicine 2013, 984763.

Ryan, N.M., Gibson, P.G., Birring, S.S. 2014. Arnold's nerve cough reflex: evidence for chronic cough as a sensory vagal neuropathy. Journal of thoracic disease 6, S748-752.

Sabbah, H.N., Ilsar, I., Zaretsky, A., Rastogi, S., Wang, M., Gupta, R.C. 2011. Vagus nerve stimulation in experimental heart failure. Heart failure reviews 16, 171-178.

Schwartz, P.J., De Ferrari, G.M., Sanzo, A., Landolina, M., Rordorf, R., Raineri, C., Campana, C., Revera, M., Ajmone-Marsan, N., Tavazzi, L., Odero, A. 2008. Long

term vagal stimulation in patients with advanced heart failure First experience in man. European Journal of Heart Failure 10, 884-891.

Seki, A., Green, H.R., Lee, T.D., Hong, L., Tan, J., Vinters, H.V., Chen, P.-S., Fishbein, M.C. 2014. Sympathetic nerve fibers in human cervical and thoracic vagus nerves. Heart Rhythm 11, 1411-1417.

Stavrakis, S., Humphrey, M.B., Scherlag, B.J., Hu, Y., Jackman, W.M., Nakagawa, H., Lockwood, D., Lazzara, R., Po, S.S. 2015. Low-level transcutaneous electrical vagus nerve stimulation suppresses atrial fibrillation. Journal of American College of Cardiology 65, 867-875.

Tekdemir, I., Aslan, A., Elhan, A. 1998. A clinico-anatomic study of the auricular branch of the vagus nerve and Arnold's ear-cough reflex. Surgical and Radiologic Anatomy 20, 253-257.

Thakar, A., Deepak, K.K., Shyamkumar, S. 2008. Auricular syncope. Journal of Laryngology and Otology 122, 1115-1117.

Treves, F. 1883. Surgical applied anatomy Cassell, London.

Triposkiadis, F., Karayannis, G., Giamouzis, G., Skoularigis, J., Louridas, G., Butler, J. 2009. The Sympathetic Nervous System in Heart Failure: Physiology, Pathophysiology, and Clinical Implications. Journal of the American College of Cardiology 54, 1747-1762.

Vanoli, E., De Ferrari, G.M., Stramba-Badiale, M., Hull, S.S., Jr., Foreman, R.D., Schwartz, P.J. 1991. Vagal stimulation and prevention of sudden death in conscious dogs with a healed myocardial infarction. Circulation Research 68, 1471-1481.

Verlinden, T.J., Rijkers, K., Hoogland, G., Herrler, A. 2016. Morphology of the human cervical vagus nerve: implications for vagus nerve stimulation treatment. Acta neurologica Scandinavica 133, 173-182.

Wang, Z., Yu, L., Wang, S., Huang, B., Liao, K., Saren, G., Tan, T., Jiang, H. 2014. Chronic Intermittent Low-Level Transcutaneous Electrical Stimulation of Auricular Branch of Vagus Nerve Improves Left Ventricular Remodeling in Conscious Dogs With Healed Myocardial Infarction. Circulation: Heart Failure 7, 1014-1021.

Wang, Z., Zhou, X., Sheng, X., Yu, L., Jiang, H. 2015. Unilateral low-level transcutaneous electrical vagus nerve stimulation: A novel noninvasive treatment for myocardial infarction. International Journal of Cardiology 190, 9-10.

Weise, D., Adamidis, M., Pizzolato, F., Rumpf, J.J., Fricke, C., Classen, J. 2015. Assessment of Brainstem Function with Auricular Branch of Vagus Nerve Stimulation in Parkinson's Disease. PloS one 10.

Yu, L., Scherlag, B.J., Li, S., Fan, Y., Dyer, J., Male, S., Varma, V., Sha, Y., Stavrakis, S., Po, S.S. 2013. Low-level transcutaneous electrical stimulation of the auricular branch of the vagus nerve: A noninvasive approach to treat the initial phase of atrial fibrillation. Heart Rhythm 10, 428-435.

Zaidi, Z.F., Matthews, M.R. 2013. Source and origin of nerve fibres immunoreactive for substance P and calcitonin gene-related peptide in the normal and chronically denervated superior cervical sympathetic ganglion of the rat. Autonomic Neuroscience 173, 28-38.

Zamotrinsky, A., Afanasiev, S., Karpov, R.S., Cherniavsky, A. 1997. Effects of electrostimulation of the vagus afferent endings in patients with coronary artery disease. Coronary artery disease 8, 551-557.

Zamotrinsky, A.V., Kondratiev, B., de Jong, J.W. 2001. Vagal neurostimulation in patients with coronary artery disease. Autonomic Neuroscience 88, 109-116.

Zannad, F., De Ferrari, G.M., Tuinenburg, A.E., Wright, D., Brugada, J., Butter, C., Klein, H., Stolen, C., Meyer, S., Stein, K.M., Ramuzat, A., Schubert, B., Daum, D., Neuzil, P., Botman, C., Castel, M.A., Onofrio, A., Solomon, S.D., Wold, N., Ruble, S.B. 2015. Chronic vagal stimulation for the treatment of low ejection fraction heart failure: results of the NEural Cardiac TherApy foR Heart Failure (NECTAR-HF) randomized controlled trial. European heart journal 36, 425-433.

Zhang, Y., Popovic, Z.B., Bibevski, S., Fakhry, I., Sica, D.A., Van Wagoner, D.R., Mazgalev, T.N. 2009. Chronic vagus nerve stimulation improves autonomic control and attenuates systemic inflammation and heart failure progression in a canine high-rate pacing model. Circulation, Heart Failure 2, 692-699.

Zhou, X., Zhou, L., Wang, S., Yu, L., Wang, Z., Huang, B., Chen, M., Wan, J., Jiang, H. 2016. The Use of Noninvasive Vagal Nerve Stimulation to Inhibit Sympathetically Induced Sinus Node Acceleration: A Potential Therapeutic Approach for Inappropriate Sinus Tachycardia. Journal of cardiovascular electrophysiology 27, 217-223.

Figures

Figure 1: Anatomical landmarks and cutaneous innervation of the external ear. Three nerves contribute to the cutaneous innervation of the lateral aspect of the ear: the auricular branch of the vagus nerve (ABVN), the auriculotemporal nerve (ATN) and the great auricular nerve (GAN). There is a variable degree of overlap in the distribution of these cutaneous nerves.

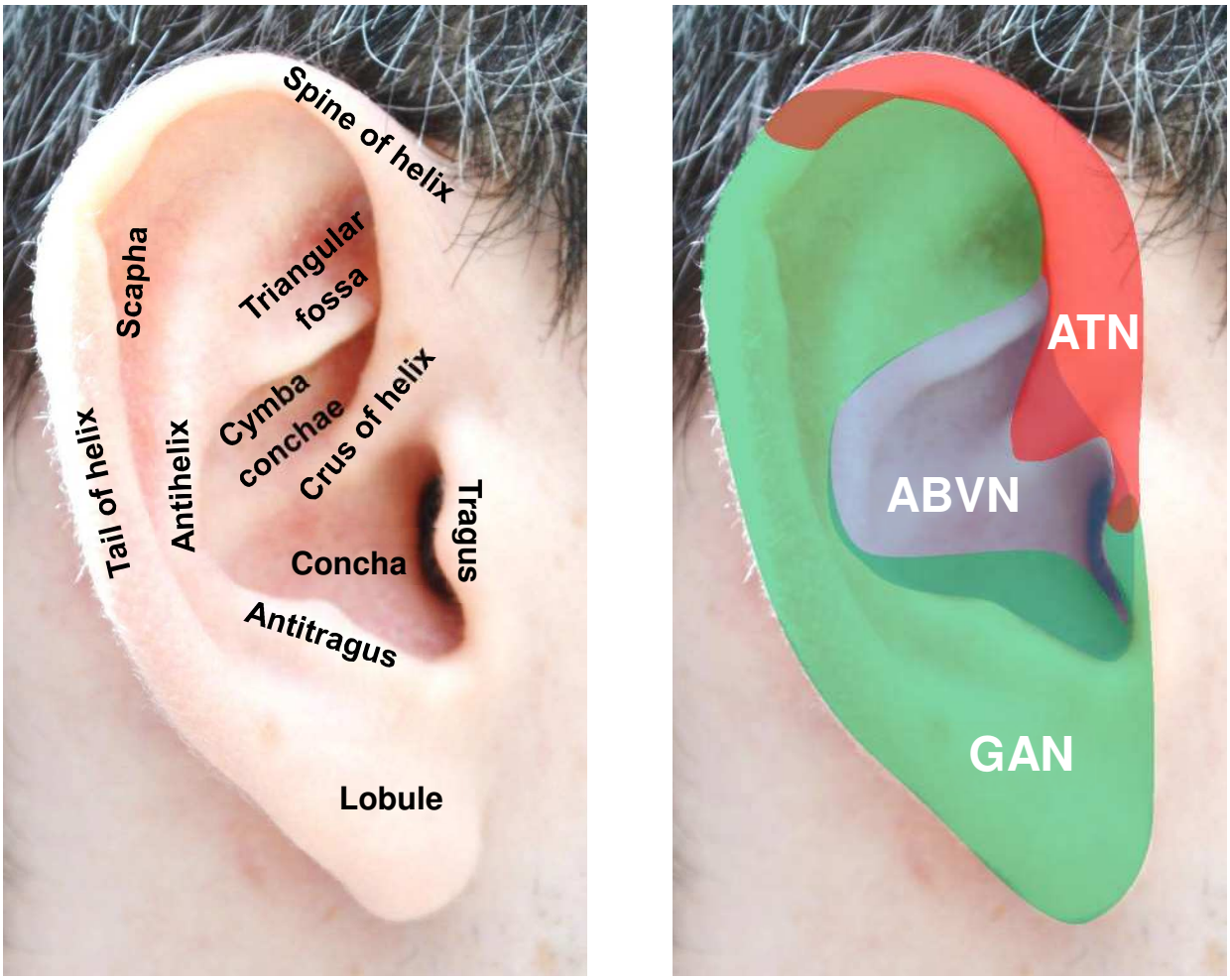

Figure 2: Schematic of potential pathways though which stimulation of the auricular branch of the vagus nerve (ABVN) could influence the heart. Stimulation of the ABVN increases input to the nucleus of the solitary tract (NTS) in the medulla and influences the activity of NTS neurones projecting to the cardioinhibitory vagal efferent neurones of the DVN and NA. These vagal efferent neurones propagate the vagal tone to the sinoatrial node (SA). Stimulation of the ABVN may also excite NTS neurones sending excitatory projections to the caudal ventrolateral medulla (CVLM). The CVLM inhibits the rostroventrolateral medulla (RVLM) which is the primary source of excitatory drive to sympathetic preganglionic neurones in the intermediolateral cell column (IML) of the spinal cord. This inhibition would decrease sympathetic activity