REVIEW ARTICLE

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Auricular vagus nerve stimulation: a new option to treat inflammation in COVID-19?

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INTRODUCTION

COVID-19 is an infectious disease caused by the new coronavirus (SARS-CoV-2), which invades alveolar epithelial cells through angiotensin-2 converting enzyme (ACE2) receptors[1,2]. Infection is triggered by the binding of the spike protein (S) of SARS-CoV-1 or SARS-CoV-2 to ACE2[3] and, through this binding, the virus enters the host cell, where ACE2 is later inactivated. As this enzyme is abundantly found in alveolar epithelial cells and in the myocardium, potentially serious damage can occur in the lungs and heart[2,4].

COVID-19 can cause acute respiratory distress syndrome (ARDS), leading to severe hypoxemia, and is associated with thromboembolic events. In ARDS, small-sized pulmonary blood vessels become more permeable, which leads to fluid leakage into the alveoli, impairing pulmonary gas exchange[5]. ARDS is characterized by generalized inflammation in the lungs, inflammatory cytokine storms, and an imbalance in the sympathetic-parasympathetic activity of the autonomic nervous system (ANS)[6].

Several treatments have been tried for ARDS from COVID-19, based on its pathophysiology using ACE-2 receptors, and some of the most feared complications such as pulmonary thromboembolism. Unfortunately, the results were not promising. The BRACE CORONA trial[7] determined whether discontinuation compared with the continuation of ACE inhibitors (ACEIs) or angiotensin-2 receptor blockers (ARBs) changed the number of days alive and out of the hospital through 30 days in 659 patients hospitalized with mild or moderate COVID-19 who were taking ACEIs or ARBs, and there was no significant difference for those assigned to discontinue vs. continue these medications. The ACTION trial[8] investigated whether patients hospitalized with mild to moderate COVID-19 and elevated D-dimer concentration benefited from therapeutic vs. prophylactic anticoagulation, and results at day 30 have shown that therapeutic anticoagulation did not improve clinical outcomes and increased bleeding compared with prophylactic anticoagulation.

All that said and based on its preclinical effects and some initial clinical studies, auricular vagus nerve stimulation (aVNS) emerges as a promising therapy for the treatment of inflammation in COVID-19, especially its pulmonary manifestations, due to its positive effect on autonomic balance, as discussed in the following sections.

VAGUS NERVE, INFLAMMATORY RESPONSE, AND AUTONOMIC BALANCE

The vagus nerve (10th cranial pair) is the largest and most important nerve in the parasympathetic nervous system and modulates the immune response to inflammatory processes that occur in our body[9,10]. It is composed of sensory (»80%) and motor fibers[11].

Inflammatory mediators released due to any aggression (e.g., pro-inflammatory cytokines) activate vagal afferent fibers that

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convey information to the nucleus of the solitary tract (NST)[9]. Activation of NST neurons originates the anti-inflammatory response in the following two different ways[1]. In the first, known as the hypothalamic-pituitary adrenal axis (HPAA)[12], NST efferents to the paraventricular nucleus of the hypothalamus stimulate the release of corticotropin-releasing hormone (CRH), which stimulates the secretion of adrenocorticotropic hormone (ACTH) from the pituitary gland. ACTH reaches the adrenal gland, stimulating the production of glucocorticoids, which act on the spleen leading to reduction of cytokine release[2]. In the second way, known as "cholinergic anti-inflammatory reflex," NST efferents activate the dorsal motor nucleus of the vagus nerve (DMNV), and its cholinergic motoneurons project to the splenic nerve in the celiac ganglion, releasing acetylcholine (ACh) in the preganglionic terminals and provoking release of norepinephrine (NE) in the spleen, which ultimately inhibits macrophages' cytokines release, decreasing inflammation. Both responses are illustrated in Figures 1 and 2.

A shift in the balance of the ANS toward sympathetic predominance can lead to (chronic) diseases associated with this system[13]. In COVID-19, hyperactivity of the sympathetic nervous system can cause excessive release of plasma epinephrine and norepinephrine, which leads to pulmonary vasoconstriction and increased capillary permeability[14].

At this point, a positive feedback system is created in favor of the sympathetic system that causes an exponential worsening of symptoms. That is, acute lung injury causes an additional imbalance with increased sympathetic tone and significant

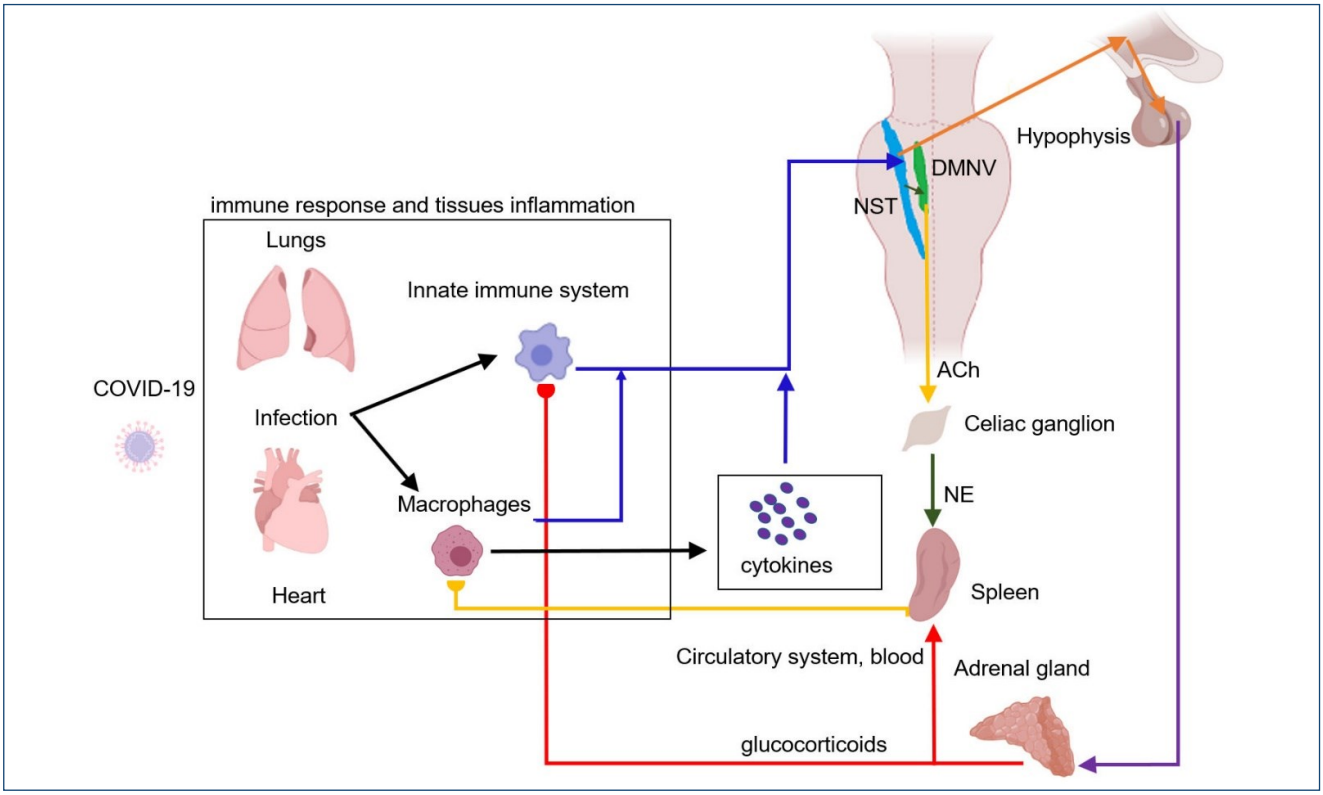

Figure 1. Diagram of the vagus nerve-mediated anti-inflammatory responses. The vagus nerve plays a key role in the neuro-endocrine-immune axis, having a dual anti-inflammatory role through its afferent and efferent fibers. In an infection, such as that caused by COVID-19, a primary immune response leads to the release of pro-inflammatory cytokines, generating an inflammatory process at the site of infection, in this case, the lungs and heart. Released cytokines are recognized by afferent fibers of the vagus nerve (blue arrows; information about inflammation from the lung, heart, and blood) that transmit such information to the nucleus of the solitary tract. The activation of nucleus of the solitary tract neurons is the origin of the anti-inflammatory response, which is generated through two different pathways. The first, known as the "hypothalamic-pituitary-adrenal axis," nucleus of the solitary tract efferents to the hypothalamus (orange arrows) stimulate the release of corticotrophin-releasing hormone, which stimulates the secretion of adrenocorticotropic hormone from the pituitary gland. adrenocorticotropic hormone reaches the adrenal glands (purple arrow), where it stimulates the production of glucocorticoids (cortisol in humans). Glucocorticoids act on the spleen (red arrow), which leads to reduced cytokine release by acting on cells of the immune system. The second, known as the "cholinergic anti-inflammatory reflex", nucleus of the solitary tract efferents to dorsal motor nucleus of the vagus nerve, the dorsal motor nucleus of the vagus nerve (black arrow, green nucleus), and stimulates the cholinergic motoneurons that project to the splenic nerve in the celiac ganglion (yellow arrow). Acetylcholine, released from the preganglionic terminals, excites celiac neurons and provokes the release of norepinephrine in the spleen (NE, green arrow). Then, the splenic response inhibits macrophages' cytokine release, decreasing inflammation. Reprinted with permission from Kaniusas et al.[24].

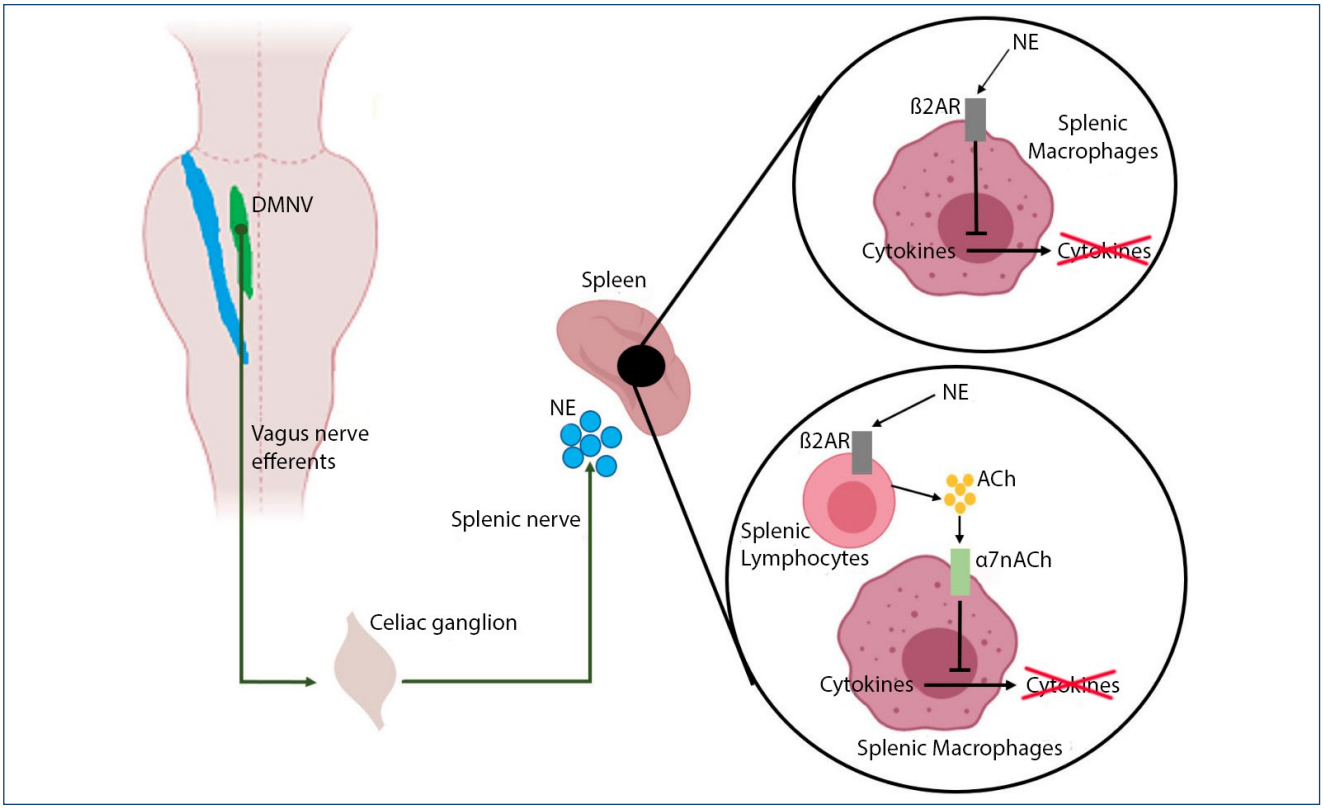

Figure 2. Scheme of the anti-inflammatory activity of the vagal efferents. Vagal efferents arise from the dorsal motor nucleus of the vagus nerve and project to the celiac ganglion, where they synapse with the splenic nerve. dorsal motor nucleus of the vagus nerve efferents activity stimulates the splenic nerve, which releases norepinephrine over the spleen. Norepinephrine binds to β2 adrenergic receptors expressed on splenic macrophages and splenic lymphocytes. Norepinephrine binding on macrophages inhibits the release of pro-inflammatory cytokines by these cells. Norepinephrine binding on lymphocytes provokes the release of acetylcholine, which is recognized by α7-acetylcholine receptors on the membrane of the macrophages. α7-Acetylcholine receptors activation provokes a disruption of the cytokine release pathway. Reprinted with permission from Kaniusas et al.[24].

elevation of plasma interleukins (IL)-6 and 10, accompanied by considerable hemorrhage, edema, consolidation, atelectasis, neutrophil infiltration, alveolar epithelial edema type I, and other deleterious effects[14].

In addition, the loss of autonomic balance worsens the inflammation caused by COVID-19 through the renin-angiotensin-aldosterone system (RAAS), a cascade of vasoactive peptides[15], which has recently been proposed as a mediator of lung injury caused by ARDS[16]. Indeed, activation of the sympathetic nervous system and RAAS seem to be intrinsically and reciprocally linked, at least in the case of patients with hypertension[17].

Finally, there is also a decreased vagal tone in some patients with COVID-19, which implies destabilized sympathetic-vagal balance, favoring the deleterious effects of the disease, as demonstrated in a recent publication[18]. To sum up, the dorsal vagal complex of the brainstem can be a target of SARS-CoV-2 because of its specifically high enrichment in ACE2 and could be reached readily by the virus through two distinct lung-to-brain routes, namely, the vagus nerve and the blood circulation.

INNERVATION OF THE EAR

To understand the effects of auricular vagus nerve stimulation, we need to know the innervation of the ear, which is rich and multiple[19]. The main nerves involved are auriculotemporal nerve (the branch of trigeminal nerve, fifth cranial pair), auricular branch of the vagus nerve (ABVN), and great auricular nerve (GAN), formed by the roots of C1-C2-C3. The ABVN innervates the central region of the auricle: the concha (upper and lower), much of the antihelix, and the internal portion of the tragus (Figure 3).

This innervation, particularly the trigeminal areas and the cervical nerves, is often mixed and its limits are variable[20]. One study, which involved dissection of 14 ears from 7 cadavers[19],

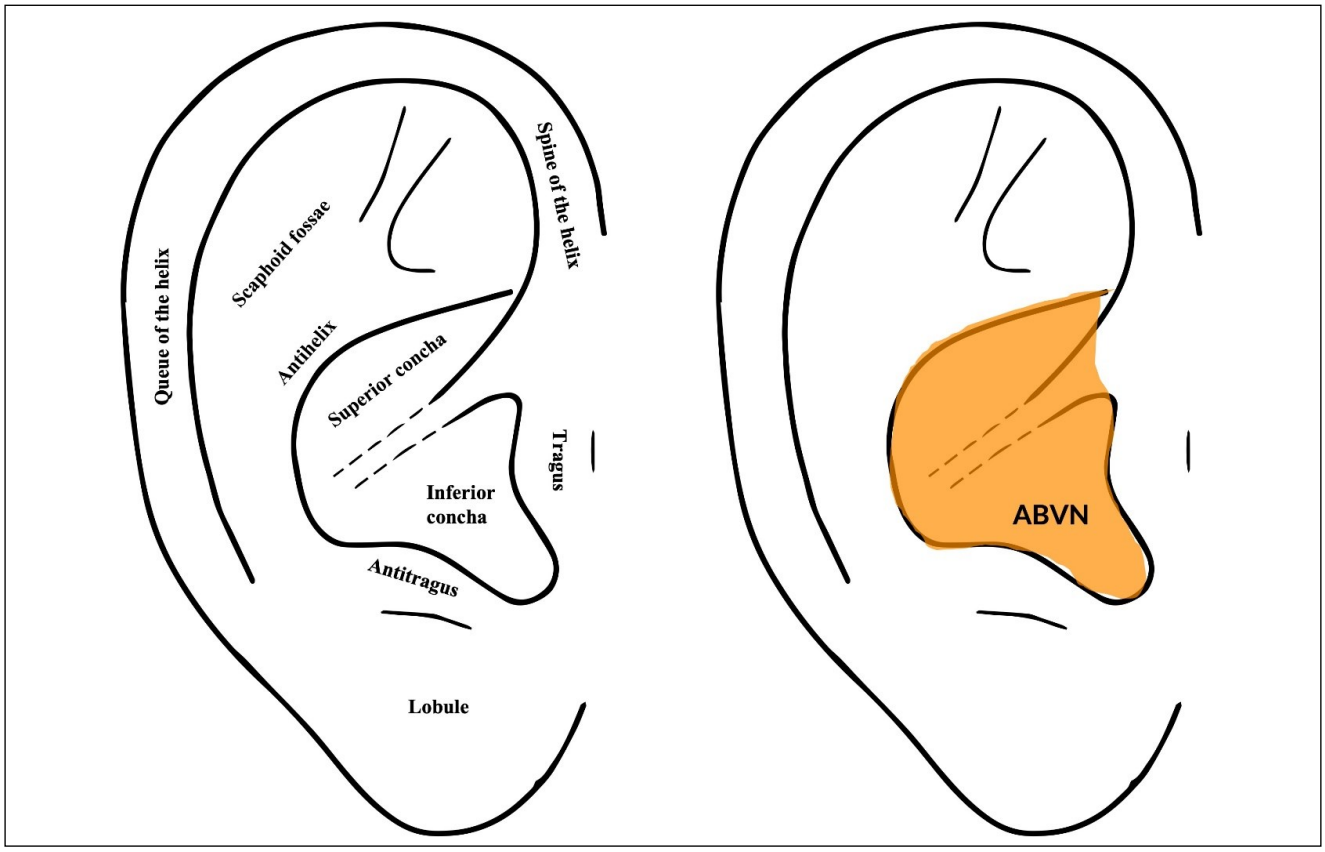

Figure 3. Diagram of the outer ear and area of innervation by the vagus nerve. ABVN: auricular branch of the vagus nerve.

showed the complete course of ear innervation. Its results are displayed in Table 1.

In a recently published review[21], the authors argue that the three main sites in the ear where the vagus nerve can be stimulated are the superior concha, the inferior concha, and the internal wall of the tragus, which covers the external auditory meatus. Evidence supporting the stimulation of these sites comes from both studies with ear dissection in cadavers[19] and functional magnetic resonance imaging (fMRI)[22,23].

It is important to remember that the ear is the only place in the body where the vagus is externalized and can be accessed in a simple and non-invasive way.

Table 1. Innervation pattern of the lateral surface of the ear.

	ABVN	GAN	ATN
Ascending branch of the helix	20%	–	80%
Knee of the helix	–	9%	91%
Queue of the helix	–	100%	–
Scaphoid fossae	–	100%	–
Anti-helix	73%	9%	18%
Antitragus	–	100%	–
Tragus	45%	46%	9%
Superior concha	100%	–	–
Inferior concha	45%	55%	–
Lobe	–	100%	–

ABVN: auricular branch of the vagus nerve; GAN: great auricular nerve; ATN: auriculotemporal nerve. Adapted from Peuker et al.[19].

AURICULAR VAGUS NERVE STIMULATION

Auricular vagus nerve stimulation (aVNS) is produced by non-invasive auricular electrical stimulation of the vagus nerve[24], through electrodes or miniature needles placed in the concha and/or in the inferior part of the tragus, and both the left and right ear can be used since the afferent information from the vagus merges when reaching the brainstem[25,26].

Invasive (surgically implanted) and non-invasive (transcutaneous or percutaneous) stimulation are the options available to stimulate the vagus nerve. Devices for non-invasive stimulation are based on the existence of a distribution of vagal afferents in the skin region, both in the external ear (the auricular branch

of the vagus nerve) and in the neck (the cervical branch of the vagus nerve). aVNS has been proposed as a new analgesic and anti-inflammatory intervention.

Both cervical vagus nerve stimulation (VNS) and aVNS have comparable physiological effects[25,27]. Brain activity patterns induced by aVNS were similar to patterns induced by cervical VNS[28], with equally favorable therapeutic results.

THERAPEUTIC EFFECTS OF VAGAL STIMULATION

The therapeutic effects of parasympathetic activity induced by aVNS are supported by a wide range of state-of-the-art clinical and experimental data: decrease in pro-inflammatory cytokines (TNF-α, IL-8, IL-1ß, and IL-6), modulation of pulmonary lesions by activating anti-inflammatory pathways, improvement of pulmonary and cardiac functions, adjusting the autonomic imbalance, and so on[14,29,30].

Imbalances in ANS activity have been linked to many clinical disorders, including heart failure[31], inflammatory bowel disease[32], and chronic pain syndromes[33]. In general, reported imbalances involve elevated sympathetic activity associated with a deficit in parasympathetic activity[34].

VNS corrects autonomic imbalance and increases parasympathetic activity[10,24]. A regularization of the autonomic balance will decrease sympathetic activity, which, in turn, will cause vasodilation and, consequently, improve oxygenation. In addition, VNS-mediated nitric oxide release[35], combined with its anti-inflammatory effects, mediates cardiovascular responses, potentially leading to further improvement in tissue oxygenation in terms of a positive feedback system[24,27]. Therefore, it is expected that the respiratory feedback provided by VNS favors the control of pulmonary inflammation.

Next, we will examine some scientific evidence for the use of taVNS.

Pre-clinical evidence

In animal models of inflammation, vagus nerve stimulation results in decreased inflammatory activity and increased anti-inflammatory activity, preventing tissue injury and increasing survival. For example, aVNS reduced the amount of pro-inflammatory cytokines[36] as well as the levels of norepinephrine[28], reinforcing its anti-inflammatory effects and counterbalancing sympathetic hyperactivity. VNS provided favorable effects on rheumatoid arthritis in rats[37], as well as reduced intestinal inflammation induced by surgery and improved intestinal transit[38]. Furthermore, it prevented the development of shock in rats by inhibiting the synthesis of tumor necrosis factor[39] and reduced inflammation in an experimentally induced model of colitis[40]. aVNS demonstrated its efficiency in rats with lethal endotoxemia or polymicrobial infection, reducing the production of tumor necrosis factor through its anti-inflammatory effects[41]. aVNS also suppressed lipopolysaccharide-induced inflammatory responses in toxemic rats by decreasing the levels of pro-inflammatory cytokines, indicating that it modulates immune functions through the cholinergic anti-inflammatory pathway[42].

Laboratory research demonstrates the protective effects of vagal stimulation on the lung[43]. Vagal stimulation protected rats against respiratory distress syndrome induced by *Mesobuthus tamulus* venom, improving respiratory parameters, hypoxemia, pulmonary edema, and histopathological changes, although it did not show the same result in rats with oleic acid-induced ARDS, which seems to indicate different mechanisms of vagal action in these cases[44]. Johnson et al.[45] showed that VNS diminishes the expression of proinflammatory cytokines TNF-α and IL-6 in the respiratory brain nuclei of developing rats, thereby reducing the inflammation caused by lipopolysaccharide instilled in the trachea, and may remain a viable alternative to antibiotics.

Clinical evidence

All the data mentioned below come from observational and interventional studies, small randomized clinical trials, and reviews. Most of the studies mentioned were observational studies, which somewhat limits the level of evidence derived from them.

VNS favorably modulates several cardiovascular parameters, resulting in a reduction in blood pressure[46,47], reduction in arrhythmias[46], and suppression of atrial fibrillation[30], the last one shown by Stavrakis et al. in a small randomized clinical trial. VNS inhibits sympathetic hyperactivity in heart failure[48] and reverses cardiac remodeling after myocardial infarction[49]. Thus, VNS could favorably modulate cardiovascular complications in patients with COVID-19, especially in those with comorbidities, and could reduce the percentage of fatal outcomes[24].

VNS attenuated ventilation-induced lung injury, reducing pro-apoptosis and pro-inflammatory reactions[36,50]. In hemorrhagic shock, vagal stimulation has prevented intestinal barrier failure and lung injury[51], relieving the latter through a decrease in cell permeability[52,53], mainly due to its anti-inflammatory properties.

Huang et al. showed, in a prospective observational trial, that VNS reduces inflammation by restoring balance to the sympathetic-parasympathetic binomial, reducing sympathetic activity, and slowing down the progression of sepsis[54].

In inflammation, respiratory dysfunction, and cardiovascular diseases, aVNS has the effect of reducing the production

of pro-inflammatory cytokines[55,56]; decreasing inflammation in chronic processes such as rheumatoid arthritis, postoperative ileus, and inflammatory bowel disease[12,57]; and systemic inflammation and attenuation of the postoperative acute inflammatory response of pulmonary lobectomy[24,37].

aVNS improves cardiac baroreflex sensitivity[58], increases venocapillary oxygenation in the deep tissues of diabetic patients[24], increases skin temperature in humans with peripheral artery dysfunctions and patients with chronic wounds caused by diabetes[59], and improves symptoms in peripheral obstructive arterial diseases[60]. Systemic effects of aVNS also include improvement of metabolic processes[61,62] (aVNS reduced 2-h glucose tolerance, systolic blood pressure, fasting plasma glucose and glycosylated hemoglobin compared to *sham*), attenuation of neurological disorders[63] (aVNS increased heart rate variability inducing a shift in autonomic nervous system function from sympathetic preponderance to parasympathetic predominance, and can be used to treat tinnitus-triggered stress), improvement of cognitive performance[64] (reducing depressive disorder symptoms without the burden of surgical intervention), and pain relief[27,35] (aVNS significantly improved low back pain, specially neuropathic pain, compared to manual acupuncture in a randomized clinical trial).

Recently, Seitz et al.[65] published a small clinical trial about aVNS and COVID-19 lung inflammation in patients admitted to the intensive care unit (ICU) but not yet ventilated. The study involved 10 patients randomized either to aVNS plus standard of care (SOC) or SOC alone (dexamethasone for at least 10 days and prophylactic anticoagulation therapy). aVNS was performed with the AuriStim device (Multisana, GmbH, Austria), stimulation frequency 1 Hz continuous, 3 h ON/3 h OFF for 24 h, until the patient died or was discharged from the ICU. The results showed decreased pro-inflammatory parameters as follows: a reduction in the C-reactive protein levels by 80%, a reduction in the TNF-α levels by 58.1%, and a reduction in the DDIMER levels by 66%, all after 7 days of treatment. Moreover, there was an increase in anti-inflammatory biomarkers such as IL (interleukin)-10 levels by 66% after 7 days, over the aVNS duration, and without collateral effects.

It seems that both cervical VNS and aVNS are promising options in the treatment of different inflammatory diseases and can help patients with COVID-19[36,66], especially those with significant sympathetic-parasympathetic imbalance. As biophysical principles and results are similar for both forms of vagal electrostimulation, aVNS is promising as it is not invasive. Czura et al.[67] published in 2022 a very complete review of all available neuromodulation strategies to reduce inflammation and improve lung complications in COVID-19 patients.

SIDE EFFECTS AND CONTRAINDICATIONS

aVNS is safe, with minor side effects such as headache, dizziness, skin irritation, or pain[68]. Surface electrodes are used in transcutaneous aVNS (taVNS), making the stimulation not as selective and precise as when using miniature needles, which can contribute to a lower effectiveness of the technique and a higher incidence of side effects. Stimulation is usually done intermittently (around 1 h, 3–4 times a day), with a total duration of stimulation of approximately 3–4 h per day.

On the contrary, percutaneous aVNS (paVNS) employs microelectrodes with needles, which favors a more precise and specific stimulation of nerve endings[25,27]. The skin impedance is much lower, which allows for a more efficient and economical stimulus with minimal side effects such as bleeding (<1%) and skin irritation (<10%)[35,69]. The stimulus is also performed intermittently (3 h ON, 3 h OFF), but remains active day and night, with a much longer stimulation time than in taVNS (12 h vs. 4–5 h), for 2–4 days, offering chronic stimulation for chronic ailments.

Very mild adverse effects of aVNS have been reported[70,71] and observed in a few cases: Arnold's cough reflex, vasovagal reflex, tearing, and bradycardia, all of which are indirect effects of afferent-efferent vagal reflexes. Furthermore, it is known that stimulation of cholinergic nerves can cause bronchial spasm and increase mucus production in the airways[72], which could attenuate the beneficial effects of aVNS in the anti-inflammatory process. Fortunately, these are all very rare side effects, occurring in less than 1% of the patients, and are widely overcome by the potential advantages of aVNS, in view of severity of comorbidities in COVID-19 patients.

aVNS is contraindicated in people with vagal hypersensitivity, hemophilia, *psoriasis vulgaris* at the application site, and patients with active implantable devices, such as pacemakers, because of their possible interference with the pacing device. There are no reports of special adverse events or contraindications for aVNS in viral infections such as COVID-19[24].

TYPES OF NERVOUS FIBERS AND STIMULATION PARAMETERS

Nerve fibers can be classified into three groups based on their diameter: groups A (Aα, Aβ, Aγ, and Aδ), B, and C. Different types of nerve fibers have different diameters and thicknesses of the myelin sheath (Table 2), which correspond to different conduction speeds, with thicker myelinated fibers typically linked to faster conduction speeds[73].

Table 2. Classification of the nerve fibers.

Type of nerve fiber	Diameter (μm)	Conduction velocity (m/s)	Afferent/Efferent	Type
Aα	13–20	80–120	Both	Sensory and motor
Aβ	6–12	33–75	Both	Sensory and motor
Aγ	5–8	4–24	Efferent	Motor
Aδ	1–5	3–30	Afferent	Sensory
B	<3	3–14	Afferent	Autonomic
C	0.2–1.5	0.5–2	Afferent	Sensory and motor

Adapted from Yap et al.[73].

At the cervical level, the vagus nerve consists mainly of small-diameter unmyelinated C fibers (65–80%), a smaller portion of intermediate-diameter myelinated B fibers, and large-diameter myelinated A fibers[74]. Kraus et al.[75] showed that, in the treatment of epilepsy, the destruction of peripheral C fibers did not influence the VNS-suppression of induced seizures, and the therapeutic effects of VNS were attributed to the maximum recruitment of thickened A and B afferent nerve fibers[76]. Other authors[77] have shown that aVNS does not cause painful sensations in participants, which suggests that afferent C axons and thin myelinated Aδ axons are not activated.

As with the stimulation of the cervical branches of the vagus nerve with low-intensity electrical currents, the ideal would be that ABVN stimulation activates only thick myelinated fibers, without activating the reduced diameter unmyelinated C fibers with their higher stimulation thresholds. ABVN is a general sensory fiber and is one of the few branches of the vagus that does not contain motor fibers. As such, the myelinated fibers found in ABVN would be expected to be sensory axons from group A rather than autonomic fibers from group B. Only one study determined the number of myelinated axons that are present in ABVN[78]. According to this study, about 50% of the measured myelinated axons had a diameter between 2.5 and 4.4 μm, suggesting that they belong to the Aδ group. Almost 20% of the axons showed a diameter >7 μm, suggesting that these fibers belong to the Aβ class. However, ABVN contains almost six times less class Aβ nerve fibers than those found in the cervical branch of the vagus nerve. This number also varied widely between individuals, which may explain why some individuals do not experience therapeutic effects after treatment with aVNS, as well as explain the anatomical basis behind the mechanism and efficacy of aVNS[21].

A tingling sensation should be targeted, as pointed out by some studies[79,80]. This is because the non-painful stimulus of ABVN would recruit more of the myelinated Aβ fibers in the ear, responsible for mechanoreception and touch sensation, and not the Aδ fibers, responsible for the sensation of pain and temperature. As already mentioned, thicker Aβ fibers are more easily recruitable than smaller Aδ fibers[25]. For this effect to be obtained, the stimulus must be performed with lower current intensities, always below the painful threshold.

Another important parameter to optimize the recruitment of Aβ fibers is the stimulation frequency[81]. Slightly higher frequencies, between 20 and 25 Hz, are better for peripheral electrical stimulation of the parasympathetic nervous system, while lower frequencies (between 0.5 and 10 Hz) are better for the sympathetic nervous system. This is because higher frequencies show a shorter duration of the depolarization period and, therefore, are only able to recruit larger and more easily excitable nerve fibers[27], such as Aβ fibers, which can indirectly modulate the parasympathetic nervous system. On the contrary, more recent studies[82,83] have shown good results in inflammatory diseases with the use of low frequencies as well, and therefore the ideal frequency has not been established yet.

Many studies have shown that stimulus efficiency has been increased by burst stimulation for 3–4 h a day[25,84]. A burst can be defined as the discharge of impulses for a short time, followed by an off interval. One or more nerve impulses triggered by vagal sensory afferences in response to single electrical stimuli are less likely to influence systemic regulation or brain activity (e.g., sympathetic-vagal balance) than a rhythmic sequence of these impulses[25,85].

Therefore, from a practical point of view, based on studies published in recent years, there is a potential role for aVNS to treat inflammation, as in COVID-19 and other conditions. However, there is still no convincing evidence from properly designed studies to endorse a formal recommendation. All we can say is that it is a very attractive experimental therapy that deserves further investigation.

Below, we propose three different types of aVNS for the treatment of COVID-19 and its inflammatory manifestations,

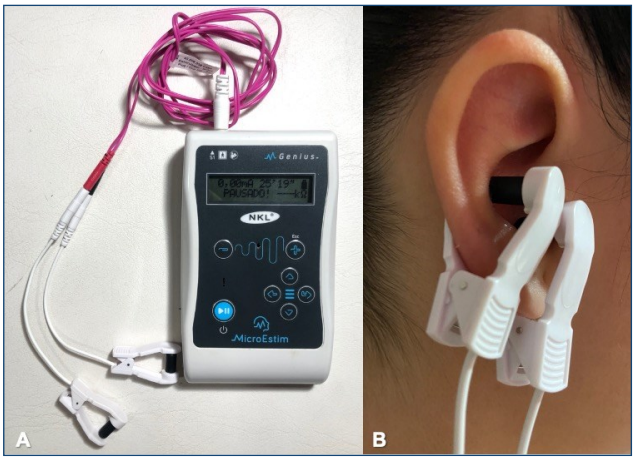

Figure 4. MicroEstim device and electrodes positioned on the ear (upper and lower concha) for stimulation. (A) MicroEstim (NKL Produtos Eletrônicos, Brusque, SC) with ear electrodes. (B) Electrodes positioned on the ear, on the upper and lower concha.

which can be implemented using a cutaneous electrical stimulation device:

1. Burst stimuli at frequency of 20–25 Hz, pulse width of 500 μs, intensity below pain threshold, 30 s ON/30 s OFF; this option is mostly used in taVNS;
2. Continuous stimuli at a frequency of 1 Hz, pulse width of 500 μs to 1 ms, intensity below pain threshold (generally <1.5 mA);
3. In this third option, we propose a new concept of vagal stimulation based on very recent studies[85,86]. Stimulus frequency of 1 Hz, pulse width of 1 ms, maximum intensity of 1.5–2 mA (only required to feel a tingling sensation), train of 100 biphasic pulses every 200 ms (0.2 s), remaining without any stimulus for 0.8 s, and repeating the stimulus again in the same way in the subsequent seconds. This is a new concept of burst, in which a very fast pulse sequence is sent within a 1 Hz period, which proved to be more effective in tested *in-silico* models and pre-clinical settings to excite Aβ fibers and produce vagal neuromodulation[85,87].

Electrodes or needles should be placed on the superior concha, or on both the superior and inferior concha, and connected to the equipment (Figures 4 and 5). In paVNS, the microelectrodes with needles are connected *via* wires to a stimulation device fixed in the neck (Figure 5), and the points should be selected by transillumination[85] of the outer ear (to visualize auricular vascularization) or by electrical point detection[35,69].

The stimulus must be performed every day for as long as the patient remains hospitalized, with intervals of at least 3 h between sessions.

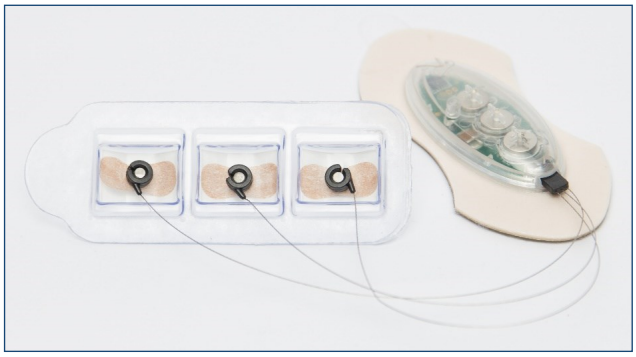

Figure 5. AuriStim for percutaneous auricular vagus nerve stimulation.

CONCLUSIONS

Vagus nerve stimulation modulates parasympathetic anti-inflammatory pathways and reestablishes sympathetic-vagal balance, which may help in the treatment of respiratory and cardiac diseases. As it is a simple and safe clinical procedure, it may have a promising role as a co-adjuvant treatment for inflammatory manifestations caused by COVID-19 and similar viruses, requiring larger clinical studies before a more solid recommendation can be made about its use.

One of the simplest ways to stimulate the vagus nerve and restore autonomic balance is through stimulation of its auricular branch (aVNS), which, in addition to producing effects like those achieved by cervical vagal stimulation, has the advantage of being non-invasive.

aVNS is a procedure with few side effects and contraindications, occurring in less than 1% of cases. Furthermore, different devices are available on the market with European CE certificates and American FDA approval for various pathologies.

There is still a vast field of research for this therapeutic method, involving different populations at risk (such as the elderly), other potentially serious inflammatory diseases, and different stimulation parameters.

AUTHORS' CONTRIBUTIONS

FMS: Conceptualization, Formal Analysis, Methodology, Project administration, Supervision, Visualization, Writing – original draft, Writing – review and editing. **LBS:** Conceptualization, Data curation, Formal Analysis, Validation, Visualization. **RCLR:** Conceptualization, Formal Analysis, Methodology, Writing – original draft. **MBS:** Data curation, Project administration, Validation. **RBSP:** Data curation, Project administration. **EK:** Methodology, Supervision, Writing – review and editing. **SLMC**: Supervision, Validation. **LWC:** Visualization, Writing – review and editing. **JCS:** Writing – review and editing.

Acquired knowledge:

In this review article, we discuss the mechanisms of action of transcutaneous atrial vagal stimulation (taVNS) and its therapeutic effects, providing experimental and clinical evidence that supports its use in inflammation, sympathetic-vagal balance, and respiratory and cardiovascular dysfunctions in COVID-19. Finally, we propose stimulation parameters based on recent studies for the treatment of the latter.

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