Review Article

Auricular vagus nerve neuromodulation: a narrative review of an adjuvant treatment for COVID-19 supported by integrative neurophysiology

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Background and Objective: Neuromodulation is a new area of medicine bringing together therapeutic interventions conferring operational plasticity on neuronal network output. Auricular vagus nerve neuromodulation refers to a group of noninvasive techniques taking advantage of the vagus nerve supply of the ears to provide complementary anti-inflammatory treatments in a wide range of diseases. Recent findings have unraveled the key role of vagus nerve in driving SARS-CoV-2 pathology, questioning a putative role of auricular vagus nerve neuromodulation as an adjuvant treatment in the current pandemic.

Methods: A MEDLINE search of publications in English from January 2000 to February 2022 released 16 articles: 7 reviews, 6 medical hypotheses, 1 case-report and 2 original research articles (1 preclinical study and 1 clinical trial).

Key Content and Findings: Auricular vagus nerve neuromodulation appears as a worth assessing adjuvant treatment to systematically include in future studies since the early stages of SARS-CoV-2 infection. Indeed, aside from being safe, easy and affordable, auricular vagus nerve is thought to lower the host vulnerability, probably through epigenetics modulations. This makes auricular vagus nerve neuromodulation the ideal adjuvant therapeutic tool for pandemics.

Conclusions: While emphasizing the discrepancy between the interest raised by auricular vagus nerve neuromodulation and the lack of completed controlled studies, this narrative review definitely supports further investigation to rigorously validate its preventive use in pandemics, thus hopefully precluding lockdowns.

Keywords: Noninvasive neuromodulation; auricular branch of the vagus nerve (ABVN); coronavirus disease 2019 (COVID-19); preventive treatment

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Introduction

During the last decades, several canonical mechanisms have been challenged in neurology. Firstly, adult neurogenesis has been acknowledged to occur throughout the human brain (1,2). Secondly, the "autonomic" vagus nerve has started to be considered mainly as a key modulator of the microbiota-gut-brain-axis (3,4). At last, peripheral nerves are no longer considered as mere conduits of the central nervous system's command since they actively participate in immunity and inflammation (5). This new way of thinking about neural signaling as outside traditional neurobiology has given rise to the field of nerve-driven diseases, impacting patients worldwide, notably with the current coronavirus disease 2019 (COVID-19) pandemic.

Indeed, the COVID-19 was originally thought to attack almost exclusively the respiratory system leading to severe acute respiratory insufficiency and olfaction disturbances. However, since neurological symptoms tend to occur in patients with serious or critical comorbidities, the neuroinvasive character of SARS-Cov-2 has incidentally drawn attention (6-10). Surprisingly, SARS-CoV-2 is thought to be associated with a broader spectrum of severe and atypical neurological manifestations than prior infections involving β-coronaviruses (namely stroke, intracranial hemorrhage, diffuse encephalopathy, encephalitis, neuromuscular disorders, neurocognitive dysfunction), thus questioning a plausible contribution of the nervous system in the pathogenesis of COVID-19 (11). Recent autopsy-based studies, revealing the presence of SARS-CoV-2 RNA in the cardiovascular and respiratory center of the caudal parts in the brainstem and in the vagus nerve, corroborate the latter hypothesis (12,13). Unexpectedly, a few authors have suggested that therapeutic solutions to COVID-19 pandemic might even come from neuroscience providing a right understanding of the physiopathological mechanism of infection at CNS (14-16).

Therefore, Neuromodulation—which refers to therapeutic interventions conferring operational plasticity on neural network output, through either implantable or non-implantable technologies, could be a promising option for the current pandemic (17). Indeed, neuromodulation has been used so far as an adjuvant treatment for chronic pain as well as psychiatric or neurological disorders (17). Neuromodulation involves mainly electrical stimulation (17) of nervous system structures (central, peripheral, autonomic) or muscles, as well as chemical (epidural or intrathecal drug delivery) (17), magnetic (transcranial magnetic stimulation) (18) and physical (puncture or pressure) (19-21) neuromodulation triggering neuroplasticity.

Ear neuromodulation is particularly interesting because it can remotely target the otherwise hardly accessible brain (22-24), allowing non-invasive targeting of the brainstem (23-25). Indeed, the human ear is the only superficial organ, thus easily accessible, supplied by the vagus nerve [auricular branch of the vagus nerve (ABVN)]. Then, the afferent fibers of the ABVN project to the nucleus of the solitary tract (NTS), a critical central node relaying interoceptive feedback from body to the brain (26). Applying the current to the skin of dedicated areas of the ear, and not necessarily directly to the vagus nerve, allows a rapid translation into clinical trials of the preclinical invasive Vagus Nerve Stimulation results. However, the rise of auricular vagus nerve neuromodulation has been slowed down by its lack of standardization.

First, its nomenclature is definitely heterogeneous whatever the nature of the ear stimulation, either electrical or physical. Electrical auricular vagus nerve stimulation (VNS) gathers by itself 10 different terms (27,28). It is designed as auricular VNS (aVNS or AVNS), auricular transcutaneous vagus stimulation (atVNS), low-level tragus nerve stimulation (LL-TNS), low-level tragus electrical stimulation (LLTS), percutaneous auricular VN stimulation (PVNS), respiratory-gated auricular vagal afferent nerve stimulation (RAVANS), Motor Activated Auricular Vagus Nerve Stimulation (MAAVNS), transcutaneous auricular VN stimulation (taVNS or ta-VNS), transcutaneous tragus nerve stimulation (TNS), and transcutaneous VN stimulation (tVNS or TVNS). taVNS and tVNS are the most frequently used terminologies. On the other hand, physical neuromodulation through ears includes at least 6 terms: ear acupressure, auricular acupressure, ear acupuncture, auricular acupuncture, auriculotherapy or auricular neuromodulation. Therefore, we chose the periphrasis "auricular vagus nerve neuromodulation" to represent all the different terminologies cited above.

To further complicate the issue, the stimulation parameters and the target areas of the ear may differ widely among research teams. Many parameters, except current intensity and frequency, vary without standardized pattern. In the field of human neurological trials, frequency is usually set between 20 and 30 Hz and intensity, between perceptual and pain threshold (range, 0.1–10 mA) (29). Fortunately, closed-loop systems (RAVANS, MAAVNS) are about to solve this parametric problem (29).

Table 1 The search strategy summary

Items	Specification
Date of search	February 2022
Databases and other sources searched	Medline
Search terms used	Search terms: vagus nerve and COVID-19 (MeSH) OR vagus nerve and COVID-19 (other terms)
Timeframe	from January 2000 to February 2022
Inclusion and exclusion criteria	Inclusion criteria:
	(I) Articles languages: English
	(II) Article types: all
	(III) Articles only relates to auricular vagus nerve neuromodulation (manual screening of the following words in the abstracts or sometime the whole article : auricular VNS (aVNS or AVNS), auricular transcutaneous vagus stimulation (atVNS), low-level tragus nerve stimulation (LL-TNS), low-level tragus electrical stimulation (LLTS), percutaneous auricular VN stimulation (PVNS), respiratory-gated auricular vagal afferent nerve stimulation (RAVANS), Motor Activated Auricular Vagus Nerve Stimulation (MAAVNS), transcutaneous auricular VN stimulation (taVNS or ta-VNS), transcutaneous tragus nerve stimulation (TNS), and transcutaneous VN stimulation (tVNS or TVNS), ear acupressure, auricular acupressure, ear acupuncture, auricular acupuncture, auriculotherapy or Auricular Neuromodulation)
Selection process	Dr. Rangon conducted independently the selection

Unexpectedly, the emerging consensus arising that COVID-19 outcome depends on neurological issues, may suddenly boost the field of auricular vagus nerve neuromodulation. It is remarkable that Heart Rate Variability (HRV), a non-invasive index of Vagus nerve activity, known for years as a prognosis factor in several non-infectious diseases (30), was recently shown to be also a good prognosis factor in COVID-19 (31-33).

This review studies the proposal of auricular vagus nerve neuromodulation as part of the treatment in SARS-CoV-2 infection. We present the following article in accordance with the Narrative Review reporting checklist (available at https://lcm.amegroups.com/article/view/10.21037/lcm-22-3/rc).

Methods

This narrative literature review consisted of a MEDLINE search of English language publications between January 2000 to February 2022. The keywords used for the search were consecutively: vagus nerve and COVID-19 (MeSH Terms) OR vagus nerve and COVID-19 (other terms). This first step released 44 articles. Then, manual screening of the 16 words cited above referring to auricular vagus nerve neuromodulation was realized for the 44 articles (*Table 1*). Sixteen articles are ultimately selected for analysis (34-49).

Discussion

Our non-exhaustive review (limited to Medline, including only written articles in English and using few keywords) confirms that auricular vagus nerve neuromodulation has been suggested by several scientific teams as a therapeutic solution for the COVID-19 pandemic. In the 16 articles retrieved (34-49), taVNS is the mostly used method [only one article deals with the use of semi-permanent needles (38)] to target respiratory symptoms or mental health.

Our search has retrieved 7 reviews (34,36,37,43,44,46,47), 6 medical hypotheses (35,39,40,41,42,48), 1 case-report on 2 patients (45), and 2 randomized controlled studies [1 preclinical study (49) and only 1 human clinical trial (38)]. This probably reflects the difficulty to launch well-designed clinical trial dealing with non-pharmacological treatments during the pandemic. Indeed, universities and hospital research centers who received major grants for COVID-19 research were mainly interested in pharmacological solutions, traditionally used in the field of immunology and infectious diseases. It is remarkable that the emergency use authorization (EUA) for the treatment of COVID-19 associated dyspnea obtained by the "gammaCore Sapphire™

CV", a cervical VNS (nVNS), another type of noninvasive VNS distinct of auricular VNS, was not supported by a significant result from a randomized controlled clinical trial (http://www.fda.gov/media/139968/download; accessed July 19, 2021). Indeed, the results of the SAVIOR study, launched in 2020 (50) have not been published before April 2022 (51). Noninvasive cervical vagus nerve stimulation could not improve significantly the clinical respiratory outcome of patients hospitalized for COVID-19, although decreasing CRP and procalcitonin levels (51). These results advocate for other clinical trials providing nVNS earlier, ahead of hospitalization.

The reviews and Medical hypothese articles found advocate for auricular vagus nerve neuromodulation therapeutic use during the current pandemic but only cite this option among others, without proving its efficiency. The case-report (45) relates the positive clinical outcome of 2 SARS-CoV-2-infected men (60 and 64 years old respectively) treated by taVNS on both ears (4–5 mA current intensity,133-kHz decrescendo alternating current in bursts of 0.3 ms, 25 Hz, during 60 minutes per day, once in the morning), starting roughly one week after the beginning of the COVID-19 symptoms until recovery (after 8 and 11 days of taVNS treatment respectively), in addition to usual drug treatment (including azithromycin and intravenous injection of methylprednisolone). However, the unmentioned comorbidities of the patients (therefore their prognosis factor), the use of validated efficient drug treatment (injections of methylprednisolone) and the lack of controls cannot allow to distinguish between a spontaneous positive outcome and a potential therapeutic efficiency of taVNS. Nevertheless, this case report proves the feasibility and the good tolerance of taVNS in stage 3 COVID-19 patients.

Moreover, the very recent Korean preclinical randomized controlled study (49), clearly demonstrates the anti-inflammatory effect of taVNS (200 µA, pulse width 200 µs, pulse frequency 15 or 25 Hz, duration of stimulation: 5 or 10 minutes; n=5 to 10 animals) in lipopolysaccharide-treated C57BL/6 mice, via activation of the cholinergic anti-inflammatory pathway (CAP) (5,52). taVNS significantly decreased pro-inflammatory cytokines blood levels as well as CAP-target tissue inflammation (spleen, lung and intestine), depending on the applied frequency (the lower 15 Hz frequency being systematically significantly more efficient). Therefore, electrical auricular vagus nerve neuromodulation was shown to efficiently inhibit an acute systemic and tissue inflammation (but not literally resulting from SARS-CoV-2 infection) through activation of CAP in an animal model, provided the right frequency selection.

Unfortunately, the only clinical trials on auricular vagus nerve neuromodulation and COVID-19 (38), although randomized, controlled and double-blind, was not able to show any significant effect of auricular vagus nerve. This is probably due to the small size of the population samples in each arm (14 in the auricular neuromodulation group and 15 in the sham group). Indeed, the study was stopped prematurely after a mid-term evaluation requested by the Ethical committee. Inclusions had not been pondered according to prognosis factors. Thus, by that time, the two arms of the study were not comparable (the auricular neuromodulation group having a median age ten years older and more masculine (80% of men versus <50% in the sham group). Therefore, the absence of significance reported by this unique clinical trial does not conclude that auricular vagus nerve neuromodulation is ineffective.

Likewise, other clinical observations, published poorly understood so far, strongly support the idea that VNS is able to improve the outcome of COVID-19 patients. For instance, knowing that the spleen is the CAP main target organ, it is noteworthy that splenectomized patients have a higher risk of hospitalization or death during SARS-CoV-2 infection (RR 1.44) (53). Moreover, recent vagotomy experiments have proven that vagus nerve is essential to hypothalamic pituitary axis (HPA) (54), probably via the secretion of prolactin releasing peptide from NTS neurons to hypothalamic neurons (26). As a result, the reactive physiological activation of vagus nerve during viral infections, including SARS-CoV-2 infection, could be responsible for the observed hyperprolactinemia (55). Conversely, this could explain why HIV patients with hypoprolactinemia had higher risk of death from opportunistic infections (56). Last but not least, the paradoxical "happy hypoxemia" also argues for a crucial central role of vagus nerve during SARS-CoV-2 infection. Indeed, as mentioned earlier (26), NTS neurons are involved in interoceptive signals transmission from the body to the brain. SARS-CoV-2 invasion of NTS after a retrograde trafficking from the lung, via the vagus nerve, might be responsible for turning "happy hypoxemia" on.

Auricular vagus nerve neuromodulation does not seem to be able to prevent SARS-CoV-2 infection (53,57) but is more likely to lower the host vulnerability to the virus, probably through epigenetics modulations. Epigenetic mechanisms modify chromatin structure and gene expression without changing the DNA sequence thanks

to transcriptional and post-transcriptional regulations of genes (58). Indeed, a recent study showed that invasive vagus nerve stimulation was able to activate specific histone modifications and DNA methylation changes, revealing important epigenetic alterations associated with cognitive improvements (59). The severity of SARS-CoV-2 infection seems to be correlated to a specific plasma *ACE2* profile, dependent on age, gender and ethnic groups (60-62). Therefore, auricular vagus nerve neuromodulation would be indicated, as a priority, to the elderly men with co-morbidities (overweight, diabetes, hypertension…). The latter target population happens to be the one with the lowest measure of HRV (63), and as auricular vagus nerve neuromodulation has been shown to increase HRV (64), this rationale fits perfectly.

In addition to be safe and suitable for the vulnerable target population, auricular vagus nerve neuromodulation is easy to learn by non-medical staff (65) and can be affordable worldwide, depending on the type of stimulation (the treatment with semipermanent needles described in reference 38 costs less than 3 euros). At last, boosting the host's defenses against pathogens, whatever their identity (notably the emerging virulent SARS CoV-2 variants), makes auricular vagus nerve neuromodulation the ideal adjuvant therapeutic tool for pandemics, for both curative and preventive purposes.

Conclusions

Although no validated recommendations for clinicians could be drawn from this narrative review, the converging arguments conveyed advocate auricular vagus nerve neuromodulation as an adjuvant therapeutic option to fully consider in pandemics. Larger studies are definitely needed to optimize the stimulation parameters, requiring a stronger support from governments and public research concern.

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Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://lcm.amegroups.com/article/view/10.21037/lcm-22-3/rc

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Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://lcm.amegroups.com/article/view/10.21037/lcm-22-3/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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