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Vagus Nerve Stimulation: A Potential Adjunct Therapy for COVID-19

Eric Azabou[1]*, *Guillaume Bao*[1], *Rania Bounab*[2], *Nicholas Heming*[2] and *Djillali Annane*[2]

[1] Clinical Neurophysiology and Neuromodulation Unit, Departments of Physiology and Critical Care Medicine, Raymond Poincaré Hospital, Assistance Publique- Hôpitaux de Paris, Inserm UMR 1173, Infection and Inflammation (2I), University of Versailles Saint-Quentin en Yvelines (UVSQ), Paris-Saclay University, Paris, France, [2] General Intensive Care Unit - Assistance Publique Hôpitaux de Paris, Raymond Poincaré Hospital, Assistance Publique- Hôpitaux de Paris, Inserm UMR 1173, Infection and Inflammation (2I), University of Versailles Saint-Quentin en Yvelines (UVSQ), Paris-Saclay University, Paris, France

The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes coronavirus disease 2019 (COVID-19) through excessive end organ inflammation. Despite improved understanding of the pathophysiology, management, and the great efforts worldwide to produce effective drugs, death rates of COVID-19 patients remain unacceptably high, and effective treatment is unfortunately lacking. Pharmacological strategies aimed at modulating inflammation in COVID-19 are being evaluated worldwide. Several drug therapies targeting this excessive inflammation, such as tocilizumab, an interleukin (IL)-6 inhibitor, corticosteroids, programmed cell death protein (PD)-1/PD-L1 checkpoint inhibition, cytokine-adsorption devices, and intravenous immunoglobulin have been identified as potentially useful and reliable approaches to counteract the cytokine storm. However, little attention is currently paid for non-drug therapeutic strategies targeting inflammatory and immunological processes that may be useful for reducing COVID-19-induced complications and improving patient outcome. Vagus nerve stimulation attenuates inflammation both in experimental models and preliminary data in human. Modulating the activity of cholinergic anti-inflammatory pathways (CAPs) described by the group of KJ Tracey has indeed become an important target of therapeutic research strategies for inflammatory diseases and sepsis. Non-invasive transcutaneous vagal nerve stimulation (t-VNS), as a non-pharmacological adjuvant, may help reduce the burden of COVID-19 and deserve to be investigated. VNS as an adjunct therapy in COVID-19 patients should be investigated in clinical trials. Two clinical trials on this topic are currently underway (NCT04382391 and NCT04368156). The results of these trials will be informative, but additional larger studies are needed.

Keywords: COVID-19, cytokine storm, inflammation, non-drug therapy, vagus nerve stimulation, neuromodulation, outcome

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***Correspondence:**
Eric Azabou
eric.azabou@aphp.fr;
eric.azabou@uvsq.fr

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INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) faced currently worldwide includes in its pathophysiology an excessive inflammatory phase called "cytokine storm" that is closely linked to its high mortality (1, 2). During sepsis, the host response to a pathogen is mediated by the interaction between

pathogen-associated molecular pattern and their receptors located on innate immune cells (3). This interaction leads to activation of the innate immune cell, release of inflammatory cytokines, and recruitment of further cells of the immune system (4). When this immune response is exaggerated, excessive inflammation may lead to end tissue damage. All major organs may be affected during sepsis including altered hypothalamic–pituitary–adrenal and altered cardiovascular responses (5, 6). Disruption of the hypothalamic–pituitary–adrenal axis may translate in patients with sepsis into cardiovascular and organ dysfunction and an increase in the risk of death (5, 6). Impaired heart rate variability and high concentrations of circulating catecholamines and impaired sympathetic modulation are common findings of septic and septic shock patients, reflecting dysfunction of the medullary autonomic centers (7) and suggesting that central autonomic regulatory impairment contributes to circulatory failure (8–10). Clinical patterns concordant with these hypotheses have been documented in COVID-19 patients and support the hypothesis of a potential contribution of a dysfunction in autonomic tone to the cytokine release syndrome and related multiorgan damage in COVID-19 (11–17).

Specific treatment for COVID-19 is unfortunately lacking (18, 19). However, given the high mortality rate and economic damage to date, great efforts are being made worldwide to produce successful drugs (20). Particularly, pharmacological strategies that restore inflammatory control or inhibit cytokine release are being evaluated (21–23). Several drug therapies targeting this excessive inflammation, such as tocilizumab, an interleukin (IL)-6 inhibitor, corticosteroids, programmed cell death protein (PD)-1/PD-L1 checkpoint inhibition, cytokine-adsorption devices, and intravenous immunoglobulin have been identified as potentially useful and reliable approaches to counteract cytokine storm in COVID-19 patients (1, 2, 18, 24–32). Little attention is currently paid for non-drug therapeutic strategies targeting inflammatory and immunological processes that may be useful for reducing COVID-19-induced complications and improving patient outcome (33–35).

VAGUS NERVE STIMULATION A POTENTIAL ADJUNCT THERAPY IN COVID-19

Modulating the activity of cholinergic anti-inflammatory pathways (CAPs) described by the group of KJ Tracey (36–44) has indeed become an important target of therapeutic research strategies for inflammatory diseases and sepsis (37, 38, 45–47). In fact, the CAP pathways innervate the spleen through the efferent vagus nerve and the splenic nerve relay and act on macrophages by transforming adrenergic stimulation into a cholinergic signal by the T cells of the spleen, which plays an anti-inflammatory effect (48).

About 80% of the vagus nerve is composed of afferent sensory fibers carrying information from the periphery to the brain (49). Within the central nervous system, the vagus primarily projects to the nucleus of the solitary tract (NTS), releasing excitatory neurotransmitters (glutamate and aspartate), inhibitory neurotransmitter (gamma-aminobutyric acid), acetylcholine, norepinephrine, and neuropeptides implicated in signal transduction (49). In turn, the NTS has widespread efferent pathways to the parabrachial nucleus, reticular formation, basal forebrain, amygdala, hippocampus, hypothalamus, dorsal raphe, cerebellum, and spinal cord (50). NTS projections to brainstem nuclei (locus coeruleus and dorsal raphe magnus) modulate serotonin and norepinephrine release to the entire brain (51). Through efferent and afferent fibers, the vagus nerve plays a role in maintaining cardiovascular homeostasis and in modulating inflammation (52). The autonomic nervous system regulates the production of cytokines, through interactions with the hypothalamic–pituitary–adrenal axis, leading to the release of anti-inflammatory glucocorticoid hormones. Vagal efferent fibers also release acetylcholine (Ach), which, by interacting with α7-subunit-containing nicotinic receptors found in tissue macrophages, and dendritic cells, inhibit the release of proinflammatory cytokines such as tumor necrosis factor alpha (TNFα), IL-1β, IL-6, and IL-18 (36, 53). Inflammatory reflex signaling, which is enhanced by electrically stimulating the vagus nerve, significantly reduces cytokine production and attenuates disease severity in animal models of inflammatory diseases and in experimental models of sepsis (36, 54–57). Electrical stimulation of the vagus nerve attenuates inflammation in a variety of pathological conditions with little side effects (36, 58, 59). Recently, Meneses and colleagues demonstrated that vagus nerve stimulation attenuates the inflammatory response in the central nervous system induced by peripheral lipopolysaccharide challenge in rats (60). Kohoutova and colleagues recently demonstrated that vagus nerve stimulation attenuates multiple organ dysfunction in a porcine model of sepsis (61). These findings suggest that VNS could be a promising adjunctive therapy targeting inflammatory pathways in COVID-19 patients. VNS might attenuate sepsis-related inflammatory processes leading to endothelial activation, impaired microcirculation, multiorgan failure, and death. VNS may also exhibit favorable cardiovascular effects during sepsis, including antiarythmogen, decreased myocardial oxygen consumption, and improved diastole (62). Vagus nerve stimulation has a favorable safety track record. Implanted VNS devices have been used for decades to treat refractory partial-onset seizures and severe recurrent refractory depression with confirmed safety and only mild to moderate side effects that are predictable improve over time (63–65). More recently, non-invasive transcutaneous vagus nerve stimulation devices (t-VNS) have been developed and commercialized (66). Evidence from preclinical models (61, 67) as well as from several clinical reports (47, 68) is accumulating (68–72). Boezaart and Botha reported a drastic reduction of two COVID-19 patients treated with t-VNS (69). Non-invasive VNS as adjunct therapy in COVID-19 patients might alleviate organ dysfunction and improve patients' outcome. Randomized controlled studies assessing the effectiveness of non-invasive vagus nerve stimulation as adjunct therapy to current best medical practice for COVID-19 are needed (72). Two studies

evaluating the efficacy of non-invasive VNS in COVID-19 patients are now on going using the gammaCore® non-invasive vagal nerve stimulation device. The gammaCore® (electroCore, Inc., Basking Ridge, NJ) is handheld and requires no surgery or implants. The device is applied by healthcare providers or patients to the skin at the neck over the vagus nerve to deliver periodic doses of VNS non-invasively. Tariq Cheema and colleagues are conducting a prospective, randomized, controlled investigation designed to assess the reduction in respiratory distress in a COVID-19 population: the SAVIORII study NCT04382391. The primary objective is to reduce initiation of mechanical ventilation in patients with COVID-19 compared to the control group. Secondary objectives are to evaluate cytokine trends/prevent cytokine storms, evaluate supplemental oxygen requirements, decrease mortality of COVID-19 patients, and delay the onset of mechanical ventilation. The second ongoing clinical trial using the same device is conducted by Carlos Tornero and colleagues NCT04368156: the SAVIOR study. The SAVIOR study is a prospective, randomized, controlled study assessing vagus nerve stimulation in COVID-19 respiratory symptoms (72). The primary outcome measures were incidence of changes in specific clinical events such as the proportion of subjects requiring mechanical ventilation, days to onset of mechanical ventilation, oxygen support requirements, O_2 saturation, pain levels, PaO_2/FiO_2, coagulation, laboratory measurements related to circulating cytokines and inflammation, live discharge from the hospital, patient length of stay, mortality, need for intensive care, shortness of breath, device-related serious adverse events, and adverse events. The results of these trials will be informative, but additional, larger, studies are needed.

DISCUSSION

COVID-19 remains a major healthcare issue worldwide. Excessive inflammation and its end organ consequences are key elements in the pathogenesis of COVID-19-induced multiple organ dysfunction (19, 26, 32). Specific treatment for COVID-19 is unfortunately lacking. Several promising pharmacological strategies aimed at modulating inflammation in COVID-19 are being evaluated worldwide. However, little attention is currently paid for non-drug therapeutic strategies targeting inflammatory and immunological processes, which may be useful for reducing COVID-19-induced complications and improving patient outcome (33–35). Vagal neurostimulation has a wide field of therapeutic benefit for patients and should be combined with the best current medical strategies (15, 17, 69, 70). Vagus nerve stimulation attenuates inflammation both in experimental models and preliminary data in man. The development non-invasive vagal nerve stimulation (t-VNS), a non-pharmacological adjuvant, may help reduce the burden of COVID-19 and deserve to be investigated. The aim of this paper is to promote the emergence of original studies assessing non-invasive VNS as an adjuvant treatment for the management of COVID-19.

AUTHOR CONTRIBUTIONS

EA and DA conceived the manuscript. EA, NH, GB, RB, and DA were involved in early discussions and mapping the concepts that led to this paper and wrote the first draft of the manuscript. All authors read and critically reviewed drafts of the manuscript.

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