Editorial

Vagal Tone is the Key Factor in COVID-19 Recovery

G. K. Pal

COVID-19 is a major healthcare problem worldwide. Unfortunately, specific treatment for COVID-19, which is an acute-infective inflammatory-immunological condition, is still lacking. Vagal nerve stimulation (VNS) has been reported to attenuate inflammation both in experimental models and in human beings. The development non-invasive VNS, a non-pharmacological adjuvant therapy, has recently been tried to reduce the burden of COVID-19 and the disease severity. VNS has been suggested as an adjuvant treatment for the management of COVID-19.

The vagus nerve plays an important role in maintaining cardiovascular homeostasis and in modulating inflammation. The vagus nerve has mostly viscero-sensory afferents and parasympathetic efferents, to- and from discrete brainstem nuclei. The vagal viscero-sensory afferents arise in all viscera as free and ramified nerve terminals belonging to glutamatergic neurons, the cell bodies of which are located in the nodose ganglion (close to the spinal cord in the neck) and project to the nucleus tractus solitarius in the brainstem.[1] The vagal efferents consist essentially in the axons of the large cholinergic neurons stacked in the dorsal motor nucleus of the vagus, that project to all viscera and trigger their actions via cholinergic, local neurons located in intra-visceral ganglia. The synaptically interconnected afferents and efferents of the vagus nerve within the dorsal vagal complex of the brainstem yield reflex circuits that provide the anatomical substratum of the vital homeostatic regulations. These connections are currently being reconsidered with brain imaging approaches, both in human subjects and in animal models. 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.[1] Inflammatory reflex signaling, which is enhanced by electrically stimulating the vagus nerve, significantly reduces cytokine production and attenuates disease severity.

Transcutaneous VNS of auricular branch of the vagus nerve that has exclusively afferent fibers, targets only the afferent arm of the vagus nerve. Auricular VNS is mostly used in pharmaco-resistant epilepsy, depression, hypertension, and other diseases.[2] A recent report on the use of auricular VNS to inhibit both peripheral and central inflammation has suggested a link between auricular VNS suppression of inflammation and effectiveness in reducing depression severity.[3] Similar to COVID-19 symptoms, a randomized trial on 100 respiratory distressed patients showed that auricular VNS significantly decreases IL-6 and IL-10 levels, reduce the incidence of postoperative pneumonia and shorten duration of hospitalization time.[4] Therefore, auricular VNS suppression of neuroinflammation and depression may turn out to be a neuroprotective in the context of COVID-19. Clinical respiratory benefits in two ambulatory COVID-19 patients using VNS have been reported,[5] and there are many ongoing prospective randomized controlled study on VNS in patients with moderate to severe COVID-19 respiratory symptoms. VNS attenuates inflammation and non-invasive transcutaneous vagal nerve stimulation as a non-pharmacological adjuvant help reduce the disease burden of COVID-19.[6]

Vagus nerve is the key integrator of anti-inflammatory reflex.[7] Understanding the components of vagal anti-inflammatory reflex pathways has therapeutic implications, since they could be targeted in various means to stimulate anti-inflammatory regulation in TNFα-related diseases such as inflammatory bowel disease and rheumatoid arthritis. The vagal nerve stimulation, either as an invasive or non-invasive procedure, is becoming increasingly the objective of many researches to evaluate the potential effectiveness of vagus nerve stimulation (VNS) to alleviate chronic inflammation. Role of vagus nerve as the key integrator of anti-inflammatory reflex and the efficacy of VNS as a therapeutic tool will be the target of many future clinical researches in finding-out a promising solution to the management of immuno-inflammatory diseases such as COVID. Till date, many of these studies do not explain the detailed mechanisms of the therapeutic benefits of VNS. Hence, future studies should focus on the mechanisms by which VNS alters autonomic tone and that will be the key to the further our understanding of VNS modification in health and disease. It is known that the VNS interacts with the body's immune system to modify inflammatory tone by inhibiting the release of proinflammatory

G. K. Pal
Editor-in-Chief, IJCEP, Senior Professor of Physiology, JIPMER, Puducherry - 605006, INDIA.

***Correspondence**

Dr. G. K. Pal
Editor-in-Chief, IJCEP, Senior Professor of Physiology, JIPMER, Puducherry - 605006, INDIA.

Email: drgkpal@gmail.com

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cytokines and facilitating the activity of antiinflammatory cytokines.[6] There are overwhelming data to suggest that vagal nerve is an important component of the immune response, and manipulating vagal tone is a way to improve the immune system. Using VNS to manipulate vagal tone provides an exciting new opportunity for minimally invasive therapeutic intervention.

In slow types of yogic breathings (pranayamas) such as anulom-vilom (alternate nostril breathing), chandranadi (left nostril breathing), sitkari and sheetali (cooling breaths), and bhramari (breathing with vibrations through ear like a humming bee), respirations are slower, deeper, and more prolonged with greater duration of expiration. By reducing inspiration and lengthening expiration, the vagal nerve traffic is more strengthened. This improves vagal discharge and increases vagal tone. Thus, the heart rate is reduced, and the heart rate variability (HRV) is improved. It has also been explained that in slow pranayamas, gradual and graded increase in lung volume and rib cage increases nerve traffic from thoracic cage proprioceptors that strengthen vagal tone through the central limbic-hypothalamic influence of the sensory projections to thalamus and cortex. Furthermore, it has been observed that slow pranayamas augment cerebral blood flow and oxygenation that improves neuronal activities of the brain centers including those present in the limbic areas, hypothalamus, and medulla, the centers of autonomic discharge. This improves sympathovagal outflow by facilitating vagal discharge. Thus, slow pranayamic breathings are very effective in increasing vagal tone and decreasing sympathetic tone. Practice of slow pranayamic breathing has been reported to reduce the burden of COVID-19 and facilitate the recovery from the disease.[8]

As the practice of slow pranayama such as chandranadi type activates vagal drive, it will be of great scientific interest to explore that pranayama could be the best nonpharmacological and nonsurgical method of vagal nerve stimulation.[9] Works are ongoing to explore the possibility of doing VNS through such controlled breathing exercise. It will be a great scientific discovery to perform VNS of different grades through practice of different degrees (intensities and duration) of slow pranayama, which will be the natural way of achieving vagal stimulation without having risks and perils of surgical and pharmacological interventions. It has been suggested that pranayamas as part of the yogic practices can yield the effects of VNS. It has been reported that practice of slow pranayama facilitates the recovery from COVID-19.[10] It appears that vagal tone of the individual is the key to the recovery from COVID-19. Yoga and physical exercises are known to facilitate vagal tone.

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