ACCSCIENCE PUBLISHING

Microbes & Immunity

PERSPECTIVE ARTICLE

Benefit of noninvasive vagus nerve stimulation in vaccine optimization for young children

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Abstract

Whether it is mandatory to vaccinate young children against SARS-CoV-2 and respiratory syncytial virus (RSV) is still an ongoing topic of debate. Indeed, vaccine acceptance for young children is either too low (in the case of COVID-19) or, in some cases, unattainable (with the demand far exceeding the capacity of production in the case of RSV vaccines in some countries). In addition, while vaccines do confer immunity, they can be complicated by inflammatory reactions to the vaccine itself. This inflammatory response is controlled by the nervous system, specifically the vagus nerve. Vagal tone optimization in and of itself confers some level of protection against viral infections such as SARS-CoV-2 or RSV, but the degree of protection has not been adequately evaluated. Even though additional studies are needed to validate a strategy of vagal optimization as an alternative to or co-treatment with vaccines, studies of noninvasive vagus nerve stimulation should be supported by public health agencies as an adjunctive tool providing young children with safe, ready-to-use immunization and protection from vaccine reactions. This recommendation is based on scientific, epidemiological, ethical, and economic considerations.

Keywords: Vagus nerve; Noninvasive stimulation; Vaccine; COVID-19; Bronchiolitis; Children

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Citation: Rangon C, Staats P. Benefit of noninvasive vagus nerve stimulation in vaccine optimization for young children. *Microbes & Immunity.* 2024;1(1):2598. doi: 10.36922/mi.2598

Received: December 31, 2023

Accepted: February 27, 2024

Published Online: March 19, 2024

1. Introduction

The cholinergic anti-inflammatory pathway is a well-known neuro-immunomodulatory pathway, in which acetylcholine (ACh), released by the interaction of vagal nerve with specific nicotinic receptors (α7nAChR), prevents the synthesis and release of pro-inflammatory cytokines.[1] Afferent vagal signals, mediated by pathogen-associated molecular patterns and damage-associated molecular patterns including cytokines, are conveyed to the nucleus tractus solitarius in the brainstem. This, automatically activates efferent motor cholinergic neurons from the dorsal motor nucleus of the vagus (DMV) to prevent hyperinflammation, creating a negative feedback loop.[2] Thus, targeting this cholinergic anti-inflammatory pathway has been well described as a strategy to treat sepsis, as well as a way to mitigate cytokine reactions in disparate diseases, ranging from COVID-19 to rheumatologic diseases.

Electrical stimulation of the vagus nerve has shown efficiency to decrease the inflammatory response in both preclinical studies and clinical trials.[3] Different

modalities of noninvasive stimulation are possible, including transcutaneous (noninvasive) stimulation of the cervical or the auricular vagus nerve, surgical implantation, and natural methods such as Safe and Sound Protocol (SSP).[4,5] Interestingly, transcutaneous noninvasive vagus nerve stimulation (VNS) is well tolerated in infants and has been assessed successfully in different indications, including neonatal opioid withdrawal syndrome[6] and neurorehabilitation.[7,8] Introducing noninvasive VNS in infants and young children as an innovative prophylaxis against both SARS-CoV-2 and respiratory syncytial virus (RSV) responsible for recurrent outbreaks, as well as to inhibit hyperinflammatory reactions that can occur during vaccinations, could potentially mitigate disease severity and inflammatory reactions in this vulnerable population.

2. Heart rate variability (HRV) for predicting survival and identifying vulnerable pediatric populations

HRV, an index of vagus nerve activity, reflects autonomic nervous system (ANS) dynamics.[9] Low HRV is related to enhanced sympathetic and/or attenuated parasympathetic cardiac modulation, notably during stress. Thus, low HRV has been correlated to inflammation (resulting, among others, from the host immune response). A robust inverse relation between the high-frequency power of the HRV (HF-HRV), interleukin-6, C-reactive protein, and fibrinogen, with or without covariate adjustment, was confirmed in a large study involving 836 adults.[10] Low HRV is used to prognosticate disease severity, and an early marker of disease in many populations, including neonates or COVID-19 patients.[11,12]

Moreover, a direct correlation between HF-HRV and vagus neuronal electrical activity has been established in anesthetized rats experiencing an acute baroreflex response.[13] Thus, VNS could potentially modulate HRV. As expected, noninvasive VNS proved to be fully able to increase HRV in healthy volunteers[14-16] as well as in patients.[17-19] Since vagal activity upregulates type I interferon response genes concurrently with downregulation of inflammation in human immune cells,[20] by increasing HRV, noninvasive VNS likely protects against viral infections. Infants and young children under 2 years old are vulnerable against several recurrent pathogens, like the "old" RSV or the more recent SARS-CoV-2 variants.

Indeed, RSV is a major cause of bronchiolitis-linked morbidity. Risk factors for RSV encompass younger age, prematurity, co-infection, and comorbidity.[21] Without considering premature infants, RSV is annually responsible for the hospitalization of one in every 56 healthy term-born infants in high-income settings.[22] RSV infection in infants <2 months of age has been associated with profound central autonomic dysfunction with alteration of the entire frequency spectrum of HRV concomitant with apparent life-threatening events and/or prolonged apnea.[23] Moreover, preterm birth by itself confers an even lower vagal tone, possibly contributing to vulnerability in this at-risk population.[24] SARS-CoV-2 has also been shown to cause bronchiolitis requiring hospitalization.[25]

Exposure to multiple viruses, such as SARS-CoV-2 and RSV, would worsen inflammation, lower HRV, and may result in increased morbidity and mortality. Severe COVID-19 illness among children with comorbidities is noted in roughly 30% of cases with underlying conditions such as type 1 diabetes, obesity, cardiac or circulatory congenital abnormalities, and prematurity (for children aged <2 years).[26] All these risk factors are also correlated with a lower vagal tone and HRV.[27-34] It has been hypothesized that the increased morbidity observed in these at-risk populations results from a disruption of the cholinergic anti-inflammatory pathway by SARS-CoV-2, leading to cytokine storm.[2,35-37]

3. A putative "all-in-one" solution against SARS-CoV-2 recurrent infections and/or co-infections

Unlike the RNA vaccines, noninvasive VNS does not target the virus but the host's defense systems,[38] offering a broad protection against reactions to several pathogens. Noninvasive VNS appears particularly relevant not only for virulent new variants,[39] but also in response to waning viral immunity to several common viruses like RSV caused by the lack of exposure due to isolation during the COVID-19 pandemic.[40] Consequently, preventive vagal tone optimization through noninvasive VNS is likely to improve the viral infection outcome in children under 2 years of age.

Interestingly, conventional physical therapy and nasotracheal suction, currently used in acute bronchiolitis for airway clearance, do improve HRV.[41] Thus, it is likely that noninvasive VNS will have a positive preventive effect against severe RSV infection.

Moreover, noninvasive VNS has already been introduced in several clinical trials as an adjunctive therapy to prevent respiratory failure or cytokine storm during the COVID-19 pandemic.[2,42-46] Of note, the results released by the prestigious Harvard Medical School Neuromodulation Center[47] hold significant promise, lending support to incorporating noninvasive VNS for pediatric use.[48] Indeed, a functional interaction between α7nAChR and a region of the SARS-CoV-2 spike protein (S) (using whole-cell

and single-channel recordings) has recently been shown to provide the molecular basis of the involvement of α7nAChRs in COVID-19 pathophysiology.[49] Moreover, *in silico* experiments unveiled the correlation between the strength of SARS-CoV-2 variants binding to α7nAChR and their severity.[50] SARS-CoV-2 binding to α7nAChR is likely to impair the vagus nerve activity[38,51] in addition to macrophage function,[52] ultimately disrupting cholinergic anti-inflammatory pathway,[2] rather than solely competing with Ach.[53] Indeed α7nAChR is expressed in the vagus nerve itself,[54] thereby facilitating SARS-CoV-2 invasion and subsequent detection in the vagus nerve fibers.[55] Therefore, attenuating the SARS-CoV2-mediated dysregulation of the vagus nerve activity, with noninvasive VNS, could lessen the severity of the infection, thereby contributing to sufficient and satisfactory protection against SARS-CoV-2 in young children.

4. Discussion

4.1. Epidemiological and scientific issues

Neither previous SARS-CoV-2 infections nor serial vaccinations, including a bivalent vaccine, seem to be able to "markedly" protect against the Omicron subvariants.[39] Moreover, monoclonal antibodies capable of neutralizing the original Omicron variant are largely inactive against the new emerging subvariants. In addition, vaccine responsiveness in minors being afflicted with childhood diseases could be affected by their innate and adaptive immunity.[56,57] On the contrary, noninvasive VNS presents a marked efficiency in mitigating the inflammatory response triggered by several recurrent pathogens and is thought to be safe, even for newborns,[8] but has not been established as a preventive treatment for COVID-19 or other viral infections yet.

It may be time to consider noninvasive VNS as a new paradigm in managing infectious diseases, to optimize reciprocally innate and adaptative immunity without enhancing autoimmunity. Indeed, for centuries, the molecular mechanisms by which hematopoietic cells initiate and maintain host immunity are given much emphasis in the realm of immunology, which are classically divided into innate (rapid but unspecific immunity) and adaptive immunity (slower but specific defenses).[58] Nevertheless, in the last two decades, this compartmentalized concept of immunity has been challenged by the discovery of an innate immune memory named "trained immunity," as innate immunity also turned out to be modulated by previous encounters with pathogens.[59] Simultaneously, Kevin Tracey and his team found that vagus nerve and cholinergic signaling play a pivotal role in neural regulation of immunity.[1,60] Interestingly, activation of α7nAChR nicotinic receptor, essential in the cholinergic anti-inflammatory pathway and innate immunity, has also been shown, to be important for the regulation of adaptive immune responses at a later stage.[61,62]

Actually, vagus nerve, a pivotal component of the microbiota-gut-brain axis, optimizes immune regulation by influencing circadian clocks,[63] the latter emerging as the master regulators of immunity[64,65] and health.[66] Indeed, the ANS has been shown to coordinate circadian functions of hematopoietic stem cells,[67] notably through a dual cholinergic signaling.[68] VNS is known to modulate intrinsic biological rhythms in epileptic patients, as one of the complications reported in trials was induced sleep abnormalities.[69] Moreover, research has revealed that noninvasive auricular VNS exhibited time-varying efficiency, with circadian rhythms.[70] This is not surprising since the dorsal vagal complex itself houses a local network of autonomous circadian oscillators.[71,72] Thus, cholinergic modulation of the immune system via vagus nerve stimulation could help complement the properties of innate and adaptive immune memory, providing a fast, broad-spectrum, specific, long-term, and self-harmless host defense (Figure 1).

4.2. Ethical issues

COVID-19 vaccines do not either completely prevent vaccines from SARS-CoV-2 infection or obstruct human-to-human transmission, with the degree of protection they might have against long COVID-19 symptoms remaining controversial.[73] Besides, because of molecular mimicry existing between SARS-CoV-2 and human components,

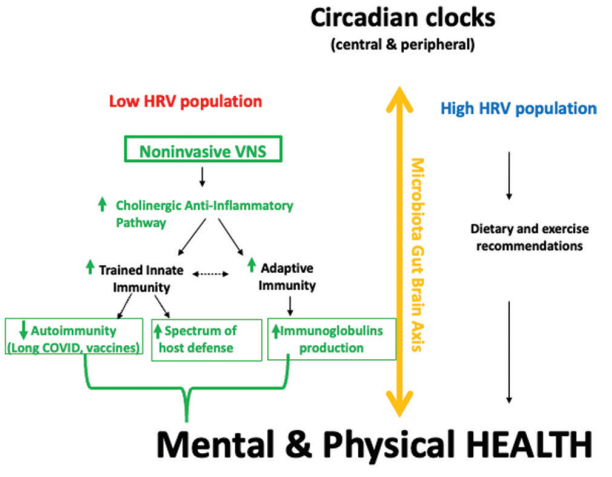

Figure 1. Noninvasive vagus nerve stimulation (VNS) reciprocally enhances trained immune and adaptive immunity. Noninvasive VNS could help prevent severe infections, without augmenting autoimmunity, in populations with low high rate variability, by modulating the microbiota-gut-brain axis.

COVID-19 vaccines or SARS-CoV-2 infection *per se* can even trigger the development of autoimmune diseases in predisposed patients,[74,75] further favoring the emergence of long COVID-19.[76] The autoimmune vaccine-related adverse effects are common in vulnerable patients (interestingly, those with lower vagal tone) for whom, as it happens, vaccination is currently recommended. One apparent solution to this would be the removal of mRNA sequences coding for peptides homologous to humans' from the SARS-CoV-2 vaccines.[77]

There is a growing line of evidence that microbiome diversity may protect from pathogens,[59] including SARS-CoV-2, and from SARS-CoV-2-induced autoimmunity alike.[60,78,79] As proven, notably, by vagotomy experiments,[80] the vagus nerve naturally links microbiota to the immune and the central nervous systems. Interestingly, VNS itself has been associated with changes in the gut microbiome.[81] Mere auricular acupressure, known to increase HRV,[70] demonstrated a significant reduction of early adverse events following COVID-19 immunization.[82] Moreover, remarkably, a recent study suggested that 4 weeks of at-home self-administered transcutaneous auricular VNS may have a mild to moderate effect on reducing long COVID-19 mental fatigue,[83] supporting the central role of autonomic impairment in COVID-19 pathophysiology.[84-87] Children affected by long COVID-19 are likely to benefit from noninvasive VNS.

More research and randomized controlled trials are definitely needed to assess transcutaneous VNS on vaccinated patients to determine if it can block the long-term sequelae of COVID-19 and/or enhance vaccine efficacy. In the same way, trials of transcutaneous VNS in non-vaccinated individuals are mandatory to determine the efficacy of vagal stimulation, by itself, in the prevention of severe viral illnesses. Vulnerable patients should be stratified according to their HRV as already suggested[23] and followed up for a longer term in upcoming larger clinical trials to generate more reliable data to inform recommendations. A more thorough evaluation is definitely a worthwhile endeavor despite the substantial financial support required to achieve this goal.

4.3. Economic issues

Noninvasive VNS provides an avenue to decrease the severity of illnesses (induced by RSV and/or future variants) and, thus, the number of hospitalizations, potentially alleviating the financial burden inflicted on the existing healthcare systems. Moreover, long COVID-19 presents an enormous economic burden likely due to its prolonged nature for years as more than half of the infected patients claimed that post-COVID-19 clinic failed to improve their long COVID-19 severity 1.5 years after infection regardless of variants of SARS-CoV-2.[88] Therefore, it is of great clinical importance to immediately consider the adoption of an inexpensive preventive tool to halt the development of long-term sequelae. As questioned and commented on by the late Hal E. Broxmeyer, the father of cord blood transplantation, "Will linking the brain with that of hematopoiesis and vice versa be a next frontier to investigate for potential health benefits?. Regardless, work in this direction, no matter how preliminary or simplistic at the beginning, is well-worth the effort. The longer we wait to start, the longer it will be before we get answers".[89] His remark has shrewdly attested to an old saying that "time is money," aptly defining the struggle we are confronting now.

Meanwhile, research assessing nVNS coupled to vaccination is aimed to optimize vaccination regimes and cut down the number of injections necessary to confer a broad and long-term immune memory, by making the most of the circadian rhythms.[64]

5. Conclusion

Neuromodulation therapies have become a mainstay in healthcare delivery, in areas as diverse as pacemakers for bradycardia, and sacral implants for urinary incontinence. Noninvasive VNS has been granted approval by U.S. Food and Drug Administration (FDA) for primary headaches since 2017, and even received an emergency use authorization for difficulty breathing during the recent COVID-19 pandemic. The vagus nerve is known to control many of the physiologic functions of the body and there is sound physiologic rationale for studying VNS as an adjunctive therapy facilitating immunization in young children. Additional studies are needed to validate this hypothesis, but with the growing body of relevant evidence, international and research organizations (WHO, UNICEF, NIH) should pay more attention to the data on noninvasive neuromodulation and support further research in this growing field. Indeed, a new paradigm, including noninvasive neuromodulation as an adjunct to care in the treatment of disease is likely to be both effective and cost-effective in some of humankind's greatest health-care problems.

Acknowledgments

None.

Funding

None.

Conflict of interest

Claire-Marie Rangon declares she has no competing interests. Peter Staats owns patents on vagus nerve

stimulation in viral infections such as COVID-19 and is the founder of the ElectroCore company.

Author contributions

Conceptualization: All authors
Writing – original draft: Claire-Marie Rangon
Writing – review & editing: Peter Staats

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

Not applicable.

Further disclosure

Peter Staats is a Former Director in the Division of Pain Medicine at Johns Hopkins University.

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