Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to Editors

Can neuromodulation support the fight against the COVID19 pandemic? Transcutaneous non-invasive vagal nerve stimulation as a potential targeted treatment of fulminant acute respiratory distress syndrome

ABSTRACT

The COVID-19 pandemic has rapidly spread all over the world and caused a major health care crisis. About 20% of patients develop severe disease and require hospitalisation, which is associated with a high mortality rate of up to 97% in those being ventilated and respiratory failure being the leading cause of death. Despite many therapeutic agents being under current investigation there is yet no panacea available. With increasing rates of infection throughout the world, there is an urgent need for new therapeutic approaches to counteract the infection.

As the nervous system has shown to be a strong modulator of respiratory function and the immune response, we want to highlight pathways involved in regulation of respiratory function, the neuro-immune axis as well as the rationale for a potential targeted treatment of fulminant acute respiratory distress syndrome via transcutaneous non-invasive vagal nerve stimulation in critically-ill COVID-19 patients.

The COVID-19 pandemic has rapidly spread all over the world. As of May 11th there were 4.1 million confirmed cases COVID-19 worldwide and more than 285,000 fatalities with an overall mortality rate of 7% [1]. Whilst 80% of infected people have mild symptoms, about 20% develop severe disease [2]. Patients requiring hospitalization have a fatality rate of 28%, which reaches up to 97% of those being ventilated [3]. Respiratory failure is the leading cause of death (97%) followed by septic shock (84.2%) and myocardial damage (80.5%) [4].

Currently, neither specific therapeutic agents nor vaccines are available for COVID-19. The management of patients mainly focuses on the provision of supportive care, such as oxygenation, intubation and mechanical ventilation [5], followed by supportive treatment of low-dose systematic corticosteroids as well as inhalation of interferon in critical ill COVID-19 patients [6].

Several therapies for COVID-19 are under investigation. Anti-retroviral regimens such as remdesivir and favipiravir have been discussed as a potential therapy [7]. So has the anti-HIV protease inhibitor lopinavir in combination with ritonavir. The anti-malarial agent Chloroquine has shown some effectiveness in inhibiting the exacerbation of COVID-19 associated pneumonia due to its anti-viral and anti-inflammatory activities [8]. However, the specific capacity against corona virus of these agents and their clinical effects are still unknown. Other therapies under investigation are passive immunization via transfusion of convalescent plasma [9].

Accumulating evidence suggests that a subgroup of patients with severe COVID-19 might suffer from a cytokine storm syndrome (CSS). CSS is triggered by viral infection, often under-recognized and often associated with multi-organ failure, in particular, respiratory failure [10]. Predictors of fatality from a retrospective, multi-center study of confirmed COVID-19 patients suggested that mortality might be due to virally driven hyper-inflammation [11]. In this state immunosuppression is likely to be beneficial.

With no panacea available and increasing rates of infection throughout the world, there is an urgent need for new therapeutic approaches.

As the nervous system has shown to be a strong modulator of lung function and the immune response, we want to highlight pathways involved in regulation of respiratory function, the neuro-immune axis as well as the rationale for possible neuromodulatory interventions in critically-ill COVID-19 patients.

Regulation of respiratory function by the autonomous nervous system

The lung is innervated by both the sympathetic and the parasympathetic nervous system, which regulate both contraction and relaxation of airway smooth muscle, providing the dominant control of smooth muscle tone and thus airway caliber, airway glands and microvasculature in the respiratory tract.

Regulation of the neuro-immune axis

Afferent fibers towards the hypothalamus can sense inflammatory processes and activate the cholinergic anti-inflammatory pathway in the presence of inflammation. The neuro-inflammatory pathway with efferent vagus nerve fibers inhibits the release of pro-inflammatory cytokines which reduces inflammation [12]. Nerve endings of the vagus nerve innervate the distal pathways of the lungs and the alveoli [13]. When these nerve endings are disconnected from the targeting pulmonary structure, such as in vagotomy, increase in pro-inflammatory cytokine levels and worsening of lung infection can be observed [14]. Vice versa, vagus nerves stimulation improves pulmonary function [15]. These findings suggest that the neuro-inflammatory reflex may limit the magnitude of lung infections and inflammation.

Of further importance is the cholinergic anti-inflammatory pathway: Vagal nerve fibers innervate the reticuloendothelial system and macrophages within the reticular connective tissue, lymph nodes, spleen and liver [16]. Released acetylcholine deactivates macrophage function and the production of pro-inflammatory cytokines (TNF, IL-1, IL-18) [17]. Interestingly, the release of anti-inflammatory cytokines (such as IL-10) is not inhibited. In models of endotoxemia electrical vagal nerve stimulation has shown to decrease serum concentrations of

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TNF which is thought to reduce the systemic lethal effects of endotoxin with hypotension and cardiovascular shock.

Clinical evidence for vagal nerve stimulation

Various clinical studies have shown the modulation of the immune response with alteration of pro- and anti-inflammatory cytokines following vagal nerve stimulation (VNS) [18]. A study on epilepsy patients who had been implanted with a vagus nerve stimulator and were comorbid for rheumatoid arthritis showed inhibition of TNF-alpha, IL-1beta, IL-6 in peripheral blood samples as well as improvement of clinical rheumatoid arthritis severity [19]. Another study, based on patients who had undergone successful vagal neuromodulation for the treatment of epilepsy and depression showed significantly attenuated histamine-induced increases in peak inspiratory pressure upon electrical stimulation. Additional VNS studies showed improvements in bronchoconstriction and peak inspiratory pressure in patients with exacerbated asthma [20,21].

Rationale for VNS

The nervous system interacts with the immune-system via the neuro-inflammatory pathway as well as the cholinergic anti-inflammatory pathway, and controls respiratory function. Vagal nerve stimulation has shown to modulate these functions.

As COVID-19 leads both to a condition of acute respiratory failure as well as a hyperactive immune-system with the development of a cytokine storm, electrical stimulation of the vagus nerve could be a supporting treatment in the therapy continuum of COVID-19 patients by combined modulation of respiratory function as well as the neuro-immune axis. Given the rapid onset of neuronal modulation, it might counteract the often-described rapid deterioration of patients and stabilize respiratory and immunological function until slow acting medication develop their effect.

Given the transient nature of the disease with a duration of several weeks, we propose the use of non-invasive transcutaneous electrical vagal nerve stimulation over invasive methods such as surgical implantation of cuff electrodes or transcutaneous leads. In upcoming clinical studies, we want to investigate the feasibility and effectiveness of this method in critically-ill patients as well as the potential protective effects on non-intubated patients.

Authors' contributions

Gregor Bara has written the manuscript and developed the rationale. Dirk de Ridder has made critical revisions of the manuscript. Jaroslaw Maciaczyk has made critical revisions of the manuscript and supervision.

Role of funding source

No funding.

Ethics committee approval

As this is a hypothesis no ethics committee approval was required. However, we are preparing an upcoming study to test our hypothesis and obtained ethics committee approval for a further study.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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