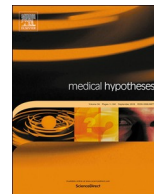




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## Potential of electric stimulation for the management of COVID-19

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### ABSTRACT

The COVID-19 pandemic is the most devastating health emergency that humans have seen over the past century. The war against the disease has been handicapped by unavailability of effective therapeutic options. Till date, there is no clinically approved vaccine or drug for the treatment of COVID-19, and the ongoing search to find a novel therapy is progressing at pandemic pace. Herein, we propose a novel hypothesis based on sound research evidence that electric stimulation can be a potential adjuvant to the currently used symptomatic therapies and antiviral drugs. Based on preclinical evidence, we propose that electric stimulation can improve respiratory functions, inhibit SARS-CoV-2 growth, reduce pain, boost immunity and improve the penetration of antiviral drugs. We envisage that our hypothesis, if used clinically as an adjuvant, may significantly improve the therapeutic outcomes of the current treatment regimen being used around the globe for the management of COVID-19.

### Introduction

The coronavirus disease (COVID-19) is a respiratory infection which has become a devastating global health emergency. It has paralyzed the healthcare system in an unprecedented manner. Respiratory complications are the principal cause of morbidity and mortality in the patients suffering from COVID-19. Currently, there is no effective treatment option available for improving the respiratory condition of patients, except ventilation as breathing support [1]. Electrical stimulation in therapeutic range is reported to be safe for use in or on a part of the body such as ear, anterior neck, legs, eyes, or over areas with injured skin or reduced sensation. Till date, electrical stimulation based treatment has been used for muscle strains, accidental injuries, stroke, respiratory depression, stimulating nerve fibers, for improving localized blood circulation, decreasing edema, restoring motor coordination, for refining cardiac output, improving wound healing process and for sensitizing immune response [2,3]. Electrical stimulation is not a promising therapeutic option for every patient, like as the patients with implanted pacemakers, having deep vein thrombosis, pregnant ladies,

and those with damaged cognition function and others. Most of the times patients undergoing electrical stimulation based therapy feel no pain but in some instance patients have reported needle piercing like sting [4,5].

### Hypothesis

We hypothesize that electric stimulation may be a novel and viable approach to improve therapeutic outcomes in COVID-19 patients. We provide literature evidence that electric stimulation may not only restore the respiratory function but may even boost immunity, reduce pain, delay drug resistance and improve drug penetration.

### Justification of hypothesis

#### Improved respiratory function

Impaired respiratory performance is one of the complications in COVID-19 patients. Spinal cord plays vital and coordinated role in the

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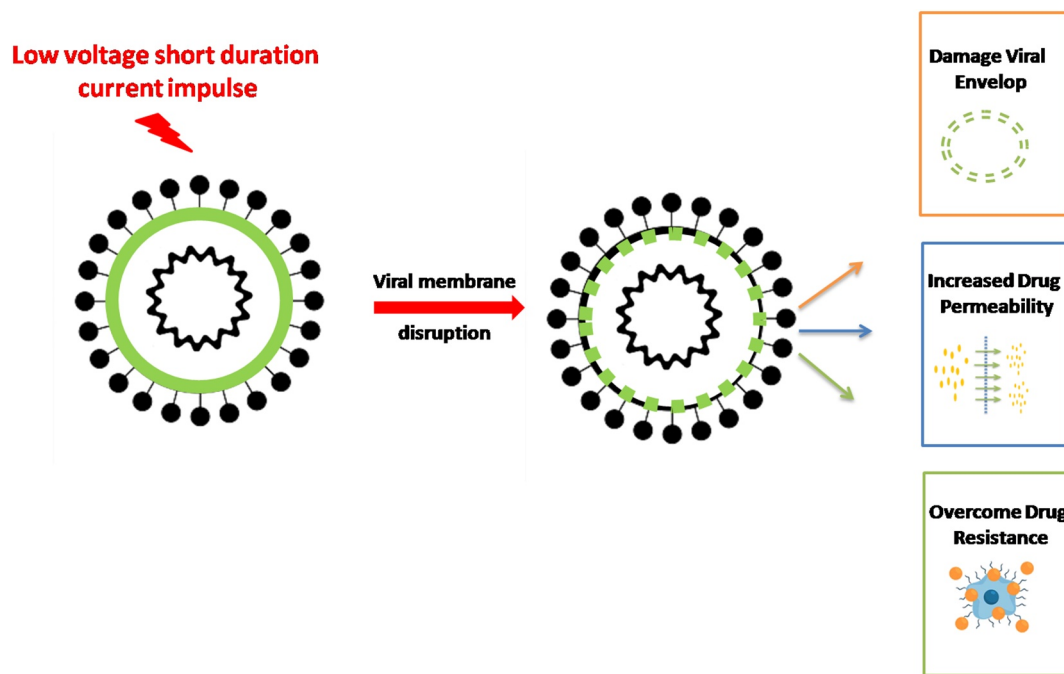
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**Fig. 1.** Effect of electric impulse on coronavirus. Electric impulse may damage the viral envelope by disrupting the membrane. Further, by modulating viral spike protein it may hamper the binding of virus to the host cell receptor. Due to damaged viral envelope there may be increase in drug permeability through damaged/ruptured viral envelop which may enhance drug efficacy. Due to the electric current stimulus, there could be change in the viral membrane protein which may cause resistance to certain drugs. By implementing electric current stimulus in such cases, the probability of drug resistance can be reduced.

control of respiratory system. Over the past years, stimulation of spinal cord has emerged as a promising strategy for augmenting respiratory function. Further, it may aid in recovery of neurological functions including cough, breathing and motor control. Diaphragm supplies the key driving force for inspiration, amounting for approximately 65% of the total vital capacity in healthy population. Each hemidiaphragm is innervated with its ipsilateral phrenic nerve, which is primarily derived from C3 to C5 lower motor neurons. Stimulating this region with low voltage electrical current has been reported to improve respiratory output and overall respiratory function [5,6]. Homes and co-workers in the middle of 20<sup>th</sup> century designed an electrical apparatus which stimulates the muscles which surround the respiratory system. This technique was successfully used in patients suffering with emphysema, asthma, silicosis and bronchitis [7]. Linder *et al.*, demonstrated the benefits of functional electrical stimulation (FES) to muscle which was partially or totally paralyzed due to a lesion in upper motor neuron. Mechanistically, when FES is given to abdominal muscles it causes contraction which in turn may compress the air in the lungs, sufficient to produce cough [5]. Same technique can be employed in COVID-19 patients which has the potential to stimulate respiratory system. Furthermore, a smooth muscle tissue irradiating device was found to dilate the respiratory airway leading to improved gaseous exchange and reduced mucus secretion in the lungs [8]. Collectively, by adapting electrical stimulus based approach against COVID-19 pandemic, it may potentially improve the lung and respiratory muscle functions which may allow better therapeutic outcomes in patients.

#### Anti-viral effect

Treating the coronavirus by an electric stimulus may sound absurd, however literature provides interesting findings and indicates that electric stimulation may be an effective approach to reduce viral burden in COVID-19 patients. Furthermore, the application of electric current is known to improve drug penetration [9]. A short impulse of low voltage current can irreversibly damage the viral membrane. Low voltage current causes alteration in membrane permeability which results in

disruption of viral membrane and spike protein that can hamper viral activity. Electric stimulation may result in improved drug permeability through damaged viral membrane and provide enhanced drug penetration. Our hypothesis may contribute to a better perception of the effects by giving low voltage current to COVID-19 patients with potential to improve therapeutic benefits if used along with clinically used treatment regimen (Fig. 1).

Kumagai *et al.*, proved that electric stimulus elicited anti-viral effects against HIV-1. For assessing the sensitivities of low electrical potential against human immunodeficiency virus type 1 (HIV-1) and its target cells, HIV-1 and MAGIC-5 cells were stimulated with a constant direct current having a potential of 1.0 V (vs. Ag/AgCl). HIV-1 was kept under incubation for 3 h at 37 °C on an electrode made up of poly-L-lysine-coated indium-tin oxide, and then stimulated by a constant electrical potential. HIV-1 was observed to be damaged up to a significant extent by electrical stimulation. In particular, after applying a 1.0 V potential for 3 min, HIV-1<sub>LAI</sub> and HIV-1<sub>KMT</sub> infection were found to be inhibited by about 90%. HIV-1 was found to be damaged to a greater extent by electrical stimulation than the MAGIC-5 cells which indicates the safety profile of electric stimulus to normal cells and at the same time lethal effect against HIV [10,11]. This interesting study revealed the anti-HIV effect of low voltage electric stimulus. Likewise, electric current based strategies are reported to treat herpes simplex virus, herpes zoster virus and other viral diseases as well [12]. These promising findings clearly provide preclinical proof for the probable antiviral effects of electric stimulation. Furthermore, one of the complications of COVID-19 is the emergence of opportunistic infections. Electric stimulation owing to its antimicrobial effects, can suppress such infections as well [13].

#### Pain management

Electroanalgesia which is an electric stimulus based treatment and is used to relieve pain. There are well established studies that claim the efficacy of this approach in pain management. In fact, electrical stimulation is not a latest treatment for pain, for the first time it was used

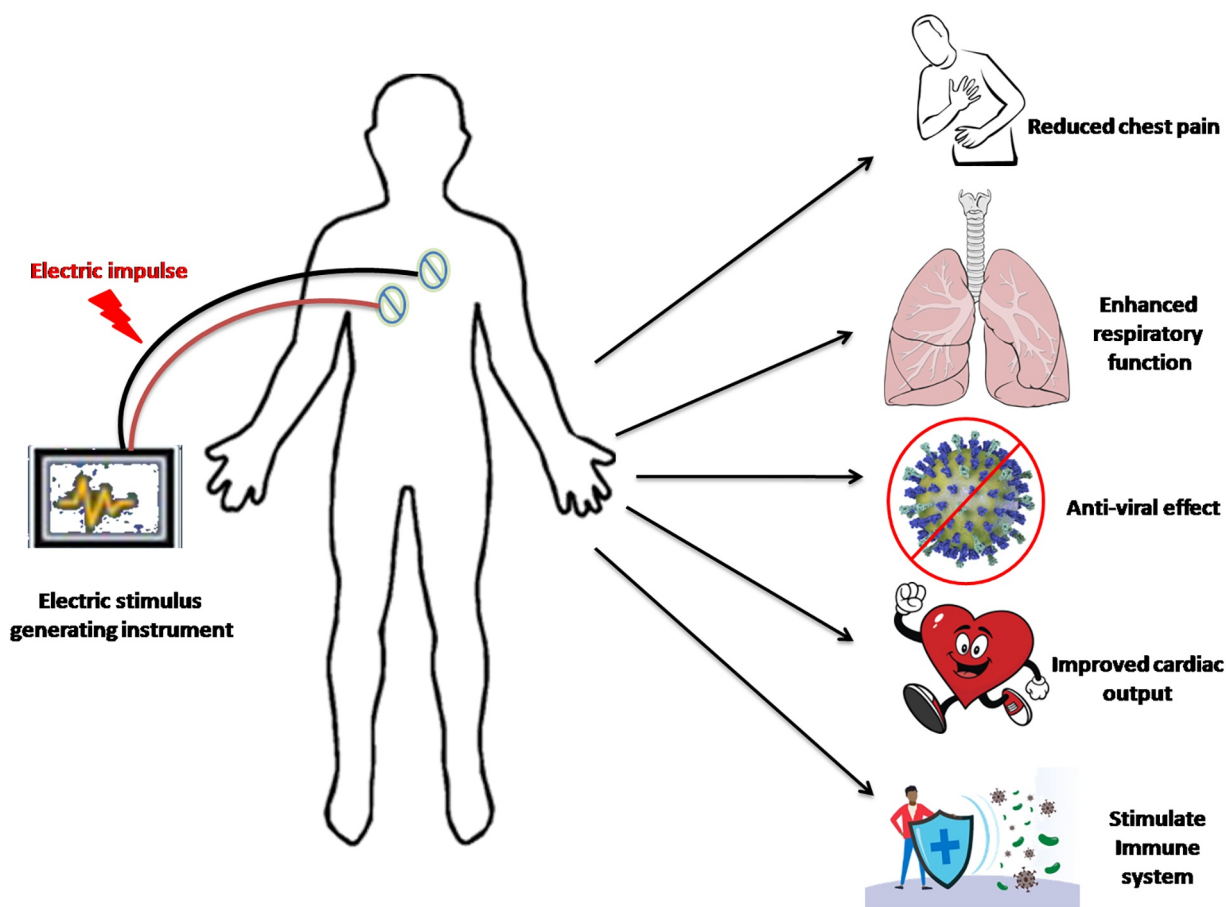


Fig. 2. Therapeutic benefits of electric stimulation on COVID-19 patients. After giving low voltage current, which may directly sensitize and damage the coronavirus envelope and may provide anti-viral effect. The applied current may stimulate the chest muscle resulting in reduced chest pain and improved breathing efficiency by instigating the collapsed alveolar tissues to regain normalcy. Moreover, electric impulse can potentially improve cardiac output by stimulating cardiac muscles and can boost immunity by activating the T & B cells resulting in increased immunity.

in 1<sup>st</sup> century where the electric torpedo fish, which generates electric shock, was applied at the head of patients who were suffering with chronic headaches [14]. The COVID-19 patients experience chest pain. Electroanalgesia works by dual mechanism, first by reducing the pain gradually or and secondly by increasing the ability of the patient to bear pain. Evidence suggest neurophysiological and neurochemical gains upon clinical use of electrical stimulation [15]. Transcutaneous electrical neural stimulation (TENS) is used to curb pain in patients, which is carried out by the placing electrodes over the area of pain like chest or over the peripheral nerve which supply stimulus to the affected area [12]. The deep body implants and superficial applications of electric stimulus based devices not only relieve pain but may also improve impaired functions of brain and other organs as well [16].

*Stimulation of immune system*

Electric stimulus has been reported to boost the immune cells by a variety of mechanisms. Electrical or pharmacological stimulation of efferent vagal neurons in rodents is claimed to inhibit the systemic rise in the levels of pro-inflammatory cytokines and avert the progression of septic shock after administrating lipopolysaccharide. This resulted in anti-inflammatory effects as well by modulation of cholinergic anti-inflammatory pathway [17]. Pares et al., showed that electric stimulus regulates the expression of immune cells as based on findings in *Xenopus laevis* embryos. These findings suggest bioelectricity as a new mechanism through which innate immune responses may be regulated [18]. In a similar study, it was claimed that nanosecond pulsed electric fields (nsPEF) induces the immune response. The neutrophil-

differentiated HL-60 cells were exposed to nsPEFs which led to release of the extracellular chromosomal DNA, and this released DNA appears to be equivalent to neutrophil extracellular traps (NETs) that serves as a host defense mechanism against dreadful pathogens [19]. Altogether, these findings suggest that applying this electrical stimulus based idea to the COVID-19 cases may come as a novel adjuvant therapy that may reduce the rate of mortality and could reduce patient’s sufferings.

**Therapeutic implications of the hypothesis**

Our literature driven hypothesis provides preliminary evidence to invoke interest in the probable therapeutic benefits of electric stimulation against the global pandemic of COVID-19. We provide the scientific rationale which strongly indicates electric stimulation may inhibit the growth of SARS-CoV-2, improve respiratory and cardiac function, reduce pain, boost immunity and improve drug penetration. Electric stimulation may significantly improve the therapeutic outcomes during the ongoing war against COVID-19 pandemic. Further, it may be used as a preventive measure by boosting immunity or as a treatment strategy in combination with other drugs. We envisage that this hypothesis will bring attention of the clinical and medical fraternity to electric stimulation and may serve as a potential “point-of-start” for further clinical research in this hitherto unexplored direction for treatment of COVID-19. Fig. 2 shows the overall proposed therapeutic benefits of electric stimulation against COVID-19.

### Author contributions

Prince Allawadhi, Amit Khurana, Sachin Allwadhi, Uma Shanker Navik, Kamaldeep Joshi, Anil Kumar Banothu conceptualized and wrote the manuscript. Kala Kumar Bharani wrote the manuscript and approved the final version.

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None.

### 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.

### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.mehy.2020.110259>.

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