LETTER TO THE EDITOR

Response to Letter to the Editor Regarding: "The Use of Non-Invasive Vagus Nerve Stimulation to Treat Respiratory Symptoms Associated With COVID-19: A Theoretical Hypothesis and Early Clinical Experience"

To the Editor:

We appreciate the opportunity to comment on the response to our article, "The Use of Non-Invasive Vagus Nerve Stimulation to Treat Respiratory Symptoms Associated with COVID-19: A Theoretical Hypothesis and Early Clinical Experience" by Burger, D'Agostini, and Van Diest (1). We first appreciate the authors' recognition of vagus nerve stimulation (VNS) as an important and evolving field of medicine. They have raised several questions whose answers are important to the advancement of science, conflicts of interest, and how we deal with scientific communication during a pandemic.

First, Burger and coworkers are concerned that our results may not be valid because several of the authors are employees of, or own stock in the company that manufactures the noninvasive VNS device discussed in the paper. We would like to reemphasize that this paper did not report results of a study; the expressed purpose of this paper was to outline a medical hypothesis of how a neuromodulation strategy might help during the evolving pandemic. The fact that some of the authors of this paper have a financial conflict of interest does not detract from the merit of this medical hypothesis. As noted by Burger and coworkers, it is important to disclose potential conflicts of interest, which in this case was done comprehensively and explicitly. The first author was the founder, is a stockholder and continues to work for electroCore on a part time basis.

Burger and coworkers suggest that individuals who own stock in a company should not participate in publishing their scientific theories. Should we not allow other innovators to share their ideas with scientists and the medical community? Should we outright reject scientific papers by the likes of Elon Musk due to his ownership of a company he founded? We think not. Rather, we need to critically evaluate the science, put the work through a critical peer review process and if the work is accepted, provide information to the readers on potential conflicts of interest to allow them to evaluate if any perceived conflicts of interest outweigh the scientific merits of the work. Scientists should get paid for the work that they do, whether it be from an academic institution or private industry. In fact, we oppose the view that is suggested by Burger and coworkers. It is incumbent upon our best scientists, regardless of employment, to submit their work for peer review and publish scientific advances for societal

benefit. The process should involve consideration of the importance of the work, the authors' intellectual honesty, expert scrutiny of the work, and appropriate disclosure of conflicts of interest. These steps were all taken in this case. Full disclosure was made allowing the reader to weigh the risks of potential conflicts with the potential scientific advances presented.

We further agree that transparency is important. In fact, in light of the urgency of the COVID-19 pandemic, many high quality journals began publishing articles prior to peer review. Over 20,000 papers related to the COVID-19 outbreak have been published without peer review on preprint servers such as bioRxiv or MedRxiv (2). Despite this trend, *Neuromodulation* has insisted on following its usual and customary policy including rigorous peer review of all submitted articles. The article was received by its Acting Editor-in-Chief, Dr. Robert Foreman, who assigned three independent reviewers to the manuscript. As an author, Dr. Robert Levy recused himself from any involvement in the review or decision-making process. Of note is that Dr. Peter Staats had been a section editor for *Neuromodulation*; with his employment by electroCore several months earlier, and as required by the journal, he stepped down from this position. Dr. Foreman made the request of the reviewers to address the manuscript with some urgency in light of its critical topic. This request concerning manuscripts dealing with the COVID-19 pandemic has become an industry standard; in a recent report, the median time from receipt to acceptance of peer reviewed COVID-19 journal articles is six days (3). Once unanimous reviews favored publication of the manuscript, Dr. Foreman accepted the manuscript and it was sent for electronic publication. The full conflict of interest policy of the journal is available online (4). Thus, Burger's and coworkers' concerns about transparency and potential conflict of interest were fully considered and addressed as is the case for all such submitted manuscript.

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Conflict of Interest: Peter S. Staats is an employee and was cofounder of electroCore, Inc., and receives stock ownership. Robert Levy has served as a consultant for Abbott, Saluda, Nalu, and Mainstay Medical and has stock options with Nalu and Saluda.

Burger and colleagues seem to believe that publishing early reports like this will lead to an overinterpretation of the findings to the detriment of science. It has certainly been the case that some premature early reports overestimate potential effect; this usually results in correction by the collection of real-world data. This is a concern most notably for early unblinded clinical trials. Our paper, in contrast, concentrated on a medical hypothesis and made no claims about the efficacy of VNS in COVID-19.

Most often, publication of a hypothesis leads to testing of this hypothesis and science advances. Burger and coworkers call for “robust slow science” (1). While no one argues with the benefits of robust science, during a pandemic it cannot and should not be slow. We believe that Burger and coworkers are wrong in this view. The approach of waiting until a large randomized controlled trial is complete to publish a sentinel theory would be irresponsible; early publication of the theory allows other scientists and clinicians to evaluate the ideas and begin their own studies. Burger and colleagues suggest that we “avoid bloating the scientific literature with studies that are uninformative, underpowered, or not preregistered.” We suggest that publication of a new scientific hypothesis is not uninformative and inspires rather than bloats the scientific literature.

We believe scientists need to have robust discussion around novel theories and approaches to disease. In fact, ours was the first report of a neuromodulation therapy for the treatment of COVID-19. Science is more than simply a series of studies; it requires the development of theories, transmitting those theories to other scientists to evaluate and test those theories and having subsequent discussion on future directions for research.

Our paper was titled “The Use of Non-invasive Vagus Nerve Stimulation to Treat Respiratory Symptoms Associated With COVID-19: A Theoretical Hypothesis and Early Clinical Experience.” One cannot draw conclusions on the efficacy of this approach in patients with COVID-19. If Burger and coworkers thought the value of this paper was in its scant clinical observations, they missed the point. The purpose of this paper was to draw attention to a 20-year history of advances in both our understanding of the cholinergic anti-inflammatory pathway and the role of VNS in the modulation of bronchoconstriction, to discuss how coronavirus may be activating the cytokine storm, and to help the readers connect dots that had not previously been recognized or published. We specifically believe it would be irresponsible to not

publish the early work in this field and allow scientists worldwide to evaluate its merit.

This paper took great caution to recognize its limitations and to call for further double blinded randomized controlled trials in assessing VNS in COVID-19. International investigators are currently performing such trials of VNS for respiratory symptoms of COVID-19. These studies can now be found on Clinicaltrials.gov and are actively recruiting patients. In addition, this work, along with tremendous contributions of others, has prompted the initiation of the International Coalition for Study of Neuromodulation in COVID-19. Finally, based in part upon our publication, the United States Food and Drug Administration has issued an Emergency Use Authorization “to treat adult patients with known or suspected COVID-19 who are who are experiencing exacerbation of asthma-related dyspnea and reduced airflow, and for whom approved drug therapies are not tolerated or provide insufficient symptom relief as assessed by their Healthcare Provider, by using non-invasive Vagus Nerve Stimulation (nVNS) on either side of the patient’s neck during the Coronavirus Disease 2019 (COVID-19) pandemic”(5).

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