Review of: "From Psychostasis to the Discovery of Cardiac Nerves: The Origins of the Modern Cardiac Neuromodulation Concept"

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Potential competing interests: No potential competing interests to declare.

In the present study entitled "*From Psychostasis to the Discovery of Cardiac Nerves: The Origins of the Modern Cardiac Neuromodulation Concept*", the authors suitably provide a deep landscape of neuroanatomical research on cardiac innervation, carefully exploring the novel biomolecular concepts of cardiac neuromodulation. Specifically, they meticulously describe the evolution of anatomical knowledge and physiological concepts of the cardiac autonomic nervous system and the regulation of neuronal responses in heart tissue. Importantly, they try to highlight the significant contribution played by the neuro-cardiac axis in identifying and treating long COVID-19 and long non-COVID-19 acute respiratory infections. Also, the authors suggest that further investigations are needed to dissect and evaluate the involvement of the autonomic nervous system in psychostasis and acute or chronic pulmonary diseases. The text looks fluent and sliding, thus allowing readers to clearly follow the key points of the entire study; however, some revisions regarding the English language in grammar, punctuation, and spelling are needed. Lastly, the present contribution comes with some lacks and pitfalls that need to be addressed before its acceptance.

Readability would be improved by heavy-handed revisions aiming for brevity, clarity, and consistency to better deliver the message. Moreover, besides the historical trajectory of the anatomic-physiological knowledge of the cardiac nervous system as described in the first paragraphs, it would be very interesting to include a paragraph about the regulation of the autonomic nervous system activity through electrical stimulation (such as Vagal Nerve Stimulation, VNS) or denervation of the nerve fibers (such as renal denervation). Also, it would be intriguing to analyze not only the physiological aspect of cardiac innervation but also the potential remodeling and impairment that occurred in the main cardiovascular diseases (CVDs). In this regard, it would be very helpful to add some paragraphs describing the changes in the neuro-cardiac axis pathway assessed in the main CVDs, such as Atrial Fibrillation (AF), Myocardial Infarction (MI), and Heart Failure (HF). Specifically, it would be interesting to describe whether and how cardiac neuromodulation participates in the degenerative remodeling mechanisms that occur in all these CVDs, and how stimulating or inhibiting its activation, heart innervation can positively regulate the cardiac responses, through the main evidence collected by the most recent preclinical and clinical investigations. In this line, it would be interesting to add a scheme that summarizes the different molecular mechanisms that affect heart innervation in the different cardiovascular pathological remodeling phenotypes, like stroke, hypertension, atherosclerosis, AF, MI, and HF, both in experimental and human models. Lastly, to be clearer, the authors should improve the quality of the figures and update the references list, trying to focus on the last, current, and most recent data

and findings of neuro-cardiac axis modulation in both *in vitro* and *in vivo* investigations, and human trials as well, thus improving the rigor of the study and the audience interest in this research area.