

Peer Review

Review of: "The Undervalued Role of 5-Minute HRV in Post-Acute Infection Syndromes: A Commentary"

Paweł Zalewski^{1,2}

1. Department of Exercise Physiology and Functional Anatomy, Collegium Medicum NCU, Nicolaus Copernicus University, Toruń, Poland; 2.

Department of Clinical and Experimental Physiology, Medical University of Warsaw, Warsaw, Poland

Overall, the commentary addresses a highly timely and important issue, namely the diagnosis of post-infectious disorders. Nevertheless, the author is strongly encouraged to reconsider several aspects before the manuscript can be considered for publication.

Although reduced HRV has been observed in patients with Long COVID and ME/CFS, the current evidence base remains limited and characterised by heterogeneity in study designs and findings. Consequently, while HRV shows promise as a biomarker for PAIS, it cannot yet be regarded as validated for routine diagnostic or prognostic use. Demonstrating its clinical utility with confidence will require large-scale, controlled, and longitudinal investigations.

The author states that LF power and the LF/HF ratio are increased as markers of sympathetic activation. However, the interpretation of both LF power and the LF/HF ratio is complex and somewhat controversial. LF power, in particular, does not provide a specific index of sympathetic activity. The author is encouraged to refer to the literature by Bilmann for a more nuanced discussion (<https://pubmed.ncbi.nlm.nih.gov/23431279/>).

HRV-based indices are also altered across a wide range of conditions, including psychiatric disorders. Thus, these indices lack specificity for any single disorder. The commentary should address whether HRV could aid in differentiating CFS from non-specific psychiatric disorders such as major depressive disorder.

The author argues that immune activation impairs the ANS via neuroinflammatory pathways, which is a plausible mechanism; however, mechanistic insights remain speculative. The causal links between T-cell

exhaustion and ANS dysfunction are still under investigation. The commentary should clarify that this is a proposed hypothesis rather than an established fact.

Respiratory rate and depth exert significant influence on HRV. Although confounders are mentioned, the manuscript should place stronger emphasis on the need for respiratory monitoring to enable valid interpretation. Additional questions arise: how should HRV be interpreted in patients with arrhythmias? What about individuals with ME/CFS or Long COVID who also present with long QT syndrome? Furthermore, what steps could be taken towards developing PAIS-specific HRV normative data and harmonised protocols?

To achieve balance, the commentary might briefly acknowledge other autonomic assessment tools (e.g., tilt table testing for orthostatic intolerance, baroreflex sensitivity) that can complement HRV. It is important to recognise that HRV alone has limited interpretability in the broader context of autonomic medicine.

A reference should be provided for Table 1: which studies support the selection of the listed parameters? In addition, why are potentially useful indices such as Heart Rate Asymmetry not included? Are there ready-to-use normative values available for clinical practice? If not, how feasible is their application in daily clinical assessment?

In summary, the commentary highlights an important and timely topic, but revisions are necessary to provide a more balanced, precise, and evidence-based perspective. Clarifying the current limitations of HRV, acknowledging methodological challenges, and situating HRV within a broader spectrum of autonomic assessment would substantially strengthen the manuscript.

Declarations

Potential competing interests: No potential competing interests to declare.