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Peer Review

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

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Peer Review Report

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

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General Assessment

This commentary addresses a timely and clinically relevant issue: the potential role of **5-minute, ECG-derived heart-rate variability (HRV)** in Post-Acute Infection Syndromes (PAIS), particularly **ME/CFS** and **Long COVID**. The author highlights that autonomic nervous system (ANS) dysfunction is under-recognized compared with the emphasis on immune dysregulation and proposes 5-min HRV as a simple, non-invasive biomarker. The manuscript is concise and well-structured, but to maximise its impact, it should better integrate existing literature, provide methodological clarity, and offer a balanced discussion of limitations and clinical translation.

Comments

1. Methodological considerations for short-term HRV

Influence of measurement conditions. The commentary should state that 5-minute HRV is strongly affected by **breathing rate, posture, circadian timing, and environmental factors**. Recent reviews note that HRV reliability can be compromised by physiological, lifestyle, environmental, and methodological

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factors, including age, physical activity, drugs, alcohol, time of day, temperature, noise, body position, recording duration, and **respiration**pmc.ncbi.nlm.nih.gov. Breathing is particularly important: respiratory sinus arrhythmia means heart rate increases during inspiration and decreases during expiration; frequency-domain indices (especially HF and LF/HF) are highly sensitive to breathing rate and depthpmc.ncbi.nlm.nih.gov. Controlled breathing is sometimes recommended but can itself alter variability; therefore, researchers should record spontaneous respiration and keep breathing within ~9-24 breaths per minute to ensure HF power reflects parasympathetic activitypmc.ncbi.nlm.nih.gov.

Context of short-term HRV. The commentary notes that 5-min HRV is a pragmatic alternative to 24-h monitoring but does not discuss **ultra-short-term (1–2 min) vs. long-term measures**. Shaffer & Ginsberg (2017) emphasise that normative values depend on recording period and demographic factors and that 24-h HRV and 5-min HRV are not interchangeablepmc.ncbi.nlm.nih.gov. Short-term HRV mainly reflects parasympathetically mediated respiratory sinus arrhythmia and baroreflex activitypmc.ncbi.nlm.nih.gov. A brief comparison would help readers understand the strengths and limitations of the 5-min protocol and reinforce that long-term recordings remain the gold standard.

2. HRV and the neuro-immune interface

Mechanistic link. The commentary argues that HRV bridges immune dysregulation and clinical symptoms but should explicitly mention the **cholinergic anti-inflammatory pathway**. In this reflex, vagal efferent signals release acetylcholine that binds to α7-nicotinic receptors on monocytes/macrophages, inhibiting pro-inflammatory cytokine production; vagal stimulation or α7-agonists reduce cytokine release, whereas vagotomy or α7 gene knockout exaggerates inflammationpmc.ncbi.nlm.nih.gov. High vagally mediated HRV is associated with lower inflammatory marker levelspubmed.ncbi.nlm.nih.gov, supporting HRV as a proxy for neuro-immune communication. In PAIS, chronic immune activation (e.g., T-cell exhaustion) may impair autonomic regulation, while autonomic imbalance can modulate inflammation; linking these concepts would strengthen the commentary.

3. Evidence from Long COVID and ME/CFS studies

Reduced vagal activity. Several studies report that Long COVID patients have lower parasympathetic HRV indices and higher sympathovagal ratios. A systematic review summarising long-term impacts of COVID-19 found lower SDNN and HF power and higher LF/HF ratios in Long COVID patients compared with controlspmc.ncbi.nlm.nih.gov. A BMC Infectious Diseases cross-sectional study using **5-min HRV** reported that individuals under 25 years with Long COVID had significantly lower very-low-frequency (VLF) power and more abnormal autonomic activity; the authors concluded that mild-to-moderate COVID-19 may lead to autonomic dysfunction one month after infectionbmcinfectdis.biomedcentral.com. A Scientific Reports case–control study found that Long COVID participants exhibited reduced mean inter-RR interval, standard deviations and rMSSD during rest and deep breathing, indicating impaired cardiac autonomic controlnature.com. These findings support the author's assertion that 5-min HRV can detect ANS dysfunction in PAIS.

4. From biomarker to therapeutic target

HRV biofeedback. The commentary mentions treatment evaluation but could emphasise that HRV is **modifiable**. HRV biofeedback (HRVB) involves paced breathing at an individual's resonant frequency (~4.5–6.5 breaths/min) to maximise respiratory sinus arrhythmia and baroreflex gain. A recent review highlighted that HRVB improves HRV and clinical outcomes in cardiovascular diseases (e.g., increased SDNN and exercise tolerance in coronary artery disease and heart failure)mdpi.com. A pilot study of HRVB for Long COVID (HEARTLOC) showed high compliance and large improvements in symptom scores; RMSSD significantly increased after interventionpmc.ncbi.nlm.nih.gov. Randomised controlled trials in other conditions provide further evidence: a ten-session HRVB programme in prehypertensive adults reduced blood pressure and increased baroreflex sensitivity and HRV indicespubmed.ncbi.nlm.nih.gov; a pilot trial for veterans with PTSD found that HRVB combined with psychotherapy improved depression scores and SDNNpubmed.ncbi.nlm.nih.gov; and a meta-analysis of 14 RCTs concluded that HRVB yields a medium effect size for reducing depressive symptomspubmed.ncbi.nlm.nih.gov. Including these data would broaden the commentary's impact by presenting HRV as both a **diagnostic marker and a modifiable therapeutic target**.

5. Clinical implementation and heterogeneity

Use cases. The author could propose practical applications, such as using 5-min HRV as a **screening tool** for dysautonomia in primary care, as a **monitoring tool** during rehabilitation or pacing interventions, and as part of **digital health platforms** (wearables, apps) for home-based follow-up. Integrating HRV with symptom questionnaires and laboratory markers could provide a comprehensive view of disease progression.

Heterogeneity of PAIS. PAIS comprises a spectrum of syndromes with varying autonomic profiles; some patients show hyperadrenergic states while others exhibit parasympathetic withdrawal. HRV should therefore be interpreted within a **multimodal assessment** that includes tilt-table testing, baroreflex sensitivity, pupillometry, skin conductance, and immunological markers. Highlighting this heterogeneity would caution clinicians against overgeneralisation.

6. Balance and limitations

Nonspecific but sensitive marker. HRV is a sensitive indicator of autonomic activity but is **nonspecific** and affected by numerous factors. Guidelines and checklists recommend controlling for age, gender, physical fitness, health status, body composition, substance use, circadian rhythms, sleep quality, body position, physical activity, stress, noise, temperature, and humiditypmc.ncbi.nlm.nih.gov. They further emphasise that breathing rates below 0.15 Hz (<8 breaths/min) shift respiratory power into the LF band, complicating LF/HF interpretation, and recommend recording the subject's natural breathing ratepmc.ncbi.nlm.nih.gov. These confounders should be acknowledged so that the diagnostic power of HRV is not overstated.

Need for standardisation. The 1996 Task Force of the European Society of Cardiology and North American Society of Pacing and Electrophysiology provided foundational guidance on HRV measurement and underscored the need for standardised methods to avoid incorrect conclusionsescardio.org. Shaffer & Ginsberg (2017) also stress that HRV metrics and norms depend on the recording period and population, cautioning against using general normative values indiscriminatelypmc.ncbi.nlm.nih.gov. The commentary should reference these guidelines to support calls for standardisation of 5-min HRV protocols.

Minor Comments

Literature coverage: Cite recent systematic reviews on HRV in ME/CFS and Long COVID. For example, a 2023 systematic review reported reductions in SDNN, HF power, and increases in LF/HF ratio among Long COVID patientspmc.ncbi.nlm.nih.gov.

Measurement context: Clarify whether the recommendation is for **resting 5-min HRV** or whether task-based protocols (paced breathing, orthostatic challenge) could reveal autonomic dysfunction more sensitively.

Complementary ANS markers: Briefly mention other autonomic measures (baroreflex sensitivity, pupillometry, skin conductance) to situate HRV within a broader autonomic assessment framework.

Strengths

The commentary raises awareness of an **under-recognised physiological pathway**—autonomic dysfunction—in PAIS.

It advocates for a **low-cost, scalable, non-invasive tool** that could be widely deployed in research and clinical settings.

By linking immune dysregulation with ANS imbalance, it encourages **interdisciplinary integration** between immunology and psychophysiology.

Recommendation

This is a relevant and well-argued commentary that should be accepted after **minor revisions**. Revisions should:

Clarify methodological aspects of 5-minute HRV and acknowledge confounding factors.

Explicitly connect HRV to the vagal neuro-immune interface.

Present HRV as both a **marker** and a **modifiable therapeutic target**, citing HRV biofeedback trials.

Include updated references (systematic reviews on Long COVID/ME/CFS and HRVB studies) and reference standardisation guidelines.

With these improvements, the commentary will provide a balanced, mechanistically grounded, and clinically useful perspective on the role of 5-minute HRV in PAIS.

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Declarations

Potential competing interests: No potential competing interests to declare.

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