Commentary

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

Willem Gielen[1]

1. North Denmark Regional Hospital, Denmark

Post-Acute Infection Syndromes (PAIS), including ME/CFS and Long COVID, involve immune dysfunction and autonomic nervous system (ANS) imbalance. This commentary emphasizes the value of 5-minute ECG-derived Heart Rate Variability (HRV) as a simple, non-invasive tool to assess ANS dysfunction in PAIS. Reduced HRV reflects parasympathetic withdrawal and sympathetic dominance linked to symptoms and inflammation. Although standardization challenges exist, 5-minute HRV can aid diagnosis, monitoring, and treatment evaluation, offering important insights into PAIS mechanisms and clinical care.

Correspondence: papers@team.qeios.com — Qeios will forward to the authors

Introduction

The COVID-19 pandemic has renewed focus on Post-Acute Infection Syndromes (PAIS), including Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) and Long COVID [1]. These conditions are characterized by persistent symptoms after acute infections. Recent studies have identified T-cell exhaustion and chronic inflammation as key mechanisms underlying PAIS [2][3]. However, the role of autonomic nervous system (ANS) dysfunction, a common clinical feature, remains unclear [4]. This commentary argues that 5-minute ECG-derived Heart Rate Variability (HRV) measurements offer an undervalued tool for assessing ANS dysfunction in PAIS, bridging the gap between immune dysregulation and clinical symptoms.

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The Immune-Autonomic Nexus in PAIS

Patients with PAIS frequently report symptoms indicative of ANS dysfunction, including orthostatic intolerance, post-exertional malaise, and sleep disturbances [1][4]. Chronic immune activation may impair ANS function via neuroinflammatory pathways [5]. T-cell exhaustion, marked by continuous antigen exposure, diminished effector function, and increased expression of inhibitory receptors such as PD-1, CTLA-4, TIM-3, and TIGIT, has emerged as a key factor in the pathogenesis of PAIS [6]. This dysfunctional state, originally described in chronic viral infections and cancer, impairs pathogen clearance and contributes to persistent immune activation and inflammation [7].

The ANS plays a critical role in regulating cardiovascular function and maintaining homeostasis. HRV, a noninvasive marker of ANS activity, provides a window into the dynamic interplay between the sympathetic and parasympathetic branches [8]. By reflecting the balance between these two branches, HRV offers valuable insights into ANS regulation. Reduced HRV has been linked to various conditions, including cardiovascular diseases and autoimmune disorders, making it a potential marker of ANS dysfunction[9].

The Case for 5-Minute HRV

HRV quantifies beat-to-beat heart rate fluctuations regulated by the ANS. Higher HRV indicates a balanced autonomic tone, whereas lower values suggest sympathetic dominance or parasympathetic withdrawal [8]. Although 24-hour HRV monitoring is the gold standard, it is resource-intensive and impractical for routine use. In contrast, 5-minute supine ECG recordings offer a pragmatic alternative. They capture key HRV metrics, such as the Root Mean Square of Successive Differences (RMSSD), which is particularly sensitive to parasympathetic activity [10].

The Task Force of The European Society of Cardiology and The North American Society of Pacing and Electrophysiology provided foundational guidelines for HRV measurement and interpretation. These guidelines emphasize the importance of standardized protocols for ECG acquisition, artifact processing, and HRV analysis, ensuring reliable and reproducible results [11].

Evidence Supporting HRV's Role

Emerging evidence suggests that patients with PAIS exhibit reduced vagal markers (e.g., RMSSD and HF power) and elevated sympathetic markers (e.g., LF/HF ratio). These changes are consistent with the findings of chronic inflammatory states [12]. For instance, studies have found lower VLF power in younger patients with Long COVID and elevated LF/HF ratios in COVID-19 survivors [13]. These results indicate that HRV can effectively reflect the complex interplay between immune dysfunction and ANS regulation in patients with PAIS (Table 1).

HRV Domain	Typical Changes in PAIS	Interpretation
SDNN	Reduced	Overall ANS imbalance
RMSSD	Reduced	Impaired parasympathetic activity
pNN50	Reduced	Diminished vagal influence
HF Power	Reduced	Decreased parasympathetic activity
LF Power	Increased	Heightened sympathetic activity
LF/HF Ratio	Increased	Sympathovagal imbalance

Table 1. HRV Changes in PAIS

HRV in Clinical Diagnostics and Follow-Up

HRV measurements can be integrated with other clinical assessments to enhance the evaluation of patients with PAIS. By combining HRV with blood sample assessments and symptom evaluation, clinicians can gain a more comprehensive understanding of disease mechanisms and patient status. HRV offers a noninvasive and cost-effective method to track autonomic recovery post-intervention, enabling clinicians to monitor disease progression and the effectiveness of therapeutic interventions [10].

Challenges and Considerations

The application of 5-minute HRV measurements in PAIS presents several challenges. Standardized protocols for HRV measurement and analysis are lacking, as are robust normative data stratified by age, sex, and health status of the patients. This limits the comparability and interpretability of HRV findings across studies [14]. Establishing standardized acquisition and analysis methods, along with population-specific normative databases, is crucial for advancing the utility of HRV in PAIS.

Short-term HRV measurements provide snapshots of autonomic function under resting conditions but may not capture the full spectrum of autonomic adaptability or circadian rhythms [15]. Longitudinal studies tracking HRV changes over time, along with immune markers, are needed to clarify the temporal relationship between immune dysfunction and autonomic dysregulation in PAIS.

HRV is influenced by numerous factors, including medication, respiratory patterns, and subtle movements. These confounders must be carefully controlled in both clinical and research settings to ensure the validity of HRV measurements [14].

Conclusion

The 5-minute HRV measurement offers a distinctive perspective on ANS dysfunction in PAIS, serving as a non-invasive and cost-effective approach to correlating immune dysregulation with clinical symptoms. Although challenges in standardization and interpretation remain, the implementation of rigorous methodologies and longitudinal studies could position HRV as a valuable tool in the management of PAIS in the future. Its practical advantages merit increased attention in both research and clinical contexts. While the full potential of HRV in PAIS has yet to be fully realized, its current underappreciation should not hinder its application in clinical practice.

Statements and Declarations

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Potential competing interests

No potential competing interests to declare.

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