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Peer Review

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

Fiorenzo Moscatelli[1]

1. Pegaso University, Naples, Italy

I have carefully read your commentary, “The Undervalued Role of 5-Minute HRV in Post-Acute Infection Syndromes,” and commend you for spotlighting a pragmatic, clinically approachable tool—short-term ECG-derived HRV—in a field where objective, scalable markers of autonomic dysfunction remain scarce. The manuscript is timely, clearly motivated by the clinical heterogeneity of PAIS/ME-CFS/Long COVID, and organized in a way that clinicians can follow: from an overview of the immune–autonomic nexus, to the rationale for five-minute recordings, the current evidence, clinical integration, challenges, and a concise conclusion. The choice to anchor the discussion in established standards (Task Force; Shaffer & Ginsberg) is appropriate, and the clinical framing—diagnosis, monitoring, and treatment evaluation—is appealing to readers in general medicine and rehabilitation. That said, several areas require substantive revision to strengthen scientific precision, temper over-interpretation, and improve presentation and referencing.

The introduction would benefit from a clearer through-line that connects immune perturbations to measurable autonomic signals via specific mechanisms, ideally the inflammatory reflex/vagal anti-inflammatory pathway, before moving to the practicality of five-minute HRV. At present, the immunology segment (T-cell exhaustion markers such as PD-1, CTLA-4, TIM-3, TIGIT) is informative but somewhat disconnected from the HRV argument; consider tightening this section and explicitly mapping how persistent antigen exposure and cytokine signaling plausibly depress vagal indices (e.g., RMSSD/HF) in PAIS. To broaden the clinical relevance and to pre-empt confounding, I strongly recommend incorporating two studies that show how body composition and nutritional status modulate HRV in otherwise healthy women: Triggiani et al., Clin Physiol Funct Imaging (2017) and Triggiani et al., PLoS One (2019). These papers will allow you to acknowledge that reduced HRV in PAIS may be amplified—or

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mimicked—by adiposity patterns and weight extremes, thereby motivating more rigorous covariate handling in both research and clinical interpretation.

Your central claim—that five-minute supine ECG recordings can serve as a practical window into autonomic imbalance in PAIS—is reasonable. However, two interpretive cautions are essential. First, the manuscript currently presents LF power as a sympathetic marker and the LF/HF ratio as a "sympathovagal balance" index. This view is contested and, without caveat, risks overstating physiological specificity. Respiratory rate, baroreflex function, and methodological choices (e.g., windowing, detrending) influence LF/HF substantially; readers would benefit from explicit language that LF and LF/HF are context-dependent and not direct measures of sympathetic tone. Second, you reference VLF changes in Long COVID; please note that VLF is not reliably estimated in five-minute segments and is generally discouraged for short-term spectral interpretation. Here, the text should make clear that any discussion of VLF pertains to longer recordings, or else be removed/qualified to avoid methodological inconsistency. These clarifications will materially improve scientific rigor without undermining your core message.

The "Case for 5-Minute HRV" section makes a persuasive practicality argument but should be expanded to state, as concrete, reproducible guidance, the minimum acquisition and processing requirements that underpin valid short-term HRV. Specify posture (supine), pre-recording rest duration, time of day, caffeine/nicotine/exercise abstention windows, breathing conditions, and ambient conditions (temperature, noise). Critically, ask authors to log or measure respiratory rate during the recording; HF interpretation hinges on this, and paced breathing—if used—should be reported with frequency. On processing, define artifact thresholds, ectopic beat detection/correction rules, acceptable maximum interpolation percentage, and the exact algorithms for time- and frequency-domain metrics. Naming the frequency-domain method (e.g., Welch's periodogram with window length and overlap) and the frequency bands used will prevent ambiguity and aid reproducibility in clinical and research settings. These elements can be summarized in a brief paragraph or an appendix and will substantially raise the practical value of the piece.

In "Evidence Supporting HRV's Role," the narrative usefully bridges PAIS symptomatology and HRV patterns, and Table 1 is a helpful orienting device. Yet, in its current form, the table reads as a deterministic mapping from metric to mechanism. Consider softening the language ("commonly reduced," "often increased," "consistent with") and adding citations directly in the caption or footnotes for each row to avoid the impression of overgeneralization. Where possible, include indicative magnitude

ranges (for example, order-of-magnitude differences or standardized mean differences from key studies) rather than directionality alone; even approximate effect sizes, with cautionary language, help clinicians judge signal-to-noise. If you choose to keep the LF/HF and LF rows, add a one-sentence footnote acknowledging ongoing debate and respiratory confounding to prevent misapplication in clinical triage. Finally, if VLF remains mentioned, clearly delimit that VLF should not be interpreted from five-minute data.

The “Clinical Diagnostics and Follow-Up” section would be stronger if it shifted from general assertions to a light-touch, stepwise proposal for integration. For example, advise clinicians to use five-minute, supine HRV at baseline alongside symptom inventories (orthostatic intolerance scales, PEM questionnaires) and a small core set of laboratory markers of inflammation and autonomic-adjacent physiology (e.g., CRP, IL-6, morning cortisol), then repeat HRV at defined intervals during rehabilitation or pharmacologic trials. Suggest presenting an illustrative clinical vignette (even hypothetical) to show how RMSSD and HF trends can corroborate symptom changes while cautioning that HRV is supportive, not diagnostic. At a minimum, temper phrases that could be read as endorsing HRV for diagnosis; emphasize instead its role as an adjunct for monitoring and hypothesis generation in complex, multisystem conditions.

With respect to statistical analysis, this is a commentary without new data, so there is no inferential analysis to audit. Nevertheless, where you summarize external studies, the argument would benefit from a more quantitative backbone. When citing exemplar findings (e.g., reductions in RMSSD/HF or elevations in LF/HF in PAIS), provide the study design, sample size, effect direction and approximate magnitude, and whether results persisted after adjustment for age, sex, BMI, and medication. If space permits, a small, narrative “mini-synthesis” contrasting cross-sectional vs. longitudinal evidence would sharpen the take-home message and set realistic expectations about sensitivity to change.

The “Challenges and Considerations” section correctly foregrounds the lack of standardization and normative data as major obstacles. To make this section maximally useful, specify what “good enough” looks like today. For example, suggest that clinics beginning to adopt HRV report z-scores or percentiles against at least age- and sex-stratified norms (even if imperfect), always record respiratory rate, document medications affecting autonomic tone (beta-blockers, anticholinergics, SNRIs), and repeat measures at the same time of day. You may also wish to include a short note on device class: explicitly state that the commentary focuses on ECG-derived HRV and that PPG-derived short-term HRV from

wearables can be informative but carries additional artifacts and proprietary processing considerations. This will pre-empt misinterpretation by readers who work primarily with consumer devices.

The conclusion is clear and appropriately concise. I would recommend softening any phrasing that could be construed as implying immediate diagnostic utility. An optimal close would reinforce HRV as a low-burden, complementary signal that, when standardized and interpreted in context, can support clinical reasoning and longitudinal care—but is not a standalone diagnostic test for PAIS.

Presentation and language require attention before indexing. The PDF contains numerous broken ligatures and encoding artifacts (“re�ects,” “in�ammation,” etc.), distracting hyphenations, and duplicated footer elements that interrupt reading flow. A careful copy-edit should restore proper characters, standardize capitalization (e.g., “autonomic nervous system” vs. “ANS”), and enforce consistent tense and person throughout. Table 1 would benefit from explicit definitions (e.g., RMSSD as ms; SDNN as ms; HF/LF in absolute or normalized units with band limits) and a note on whether values refer to time- or frequency-domain metrics from five-minute recordings. Consider adding a brief glossary box for non-specialist clinicians.

The reference list needs thorough standardization. There are inconsistent formats, repeated links/DOIs, and occasional duplication (e.g., the same DOI line appearing twice). Several entries lack page ranges, issue numbers, or have mismatched year/DOI metadata. Please adopt a single style (e.g., Vancouver or journal-specific), verify each citation’s bibliographic fields, and remove redundant Qeios or PubMed lines. Ensure that web links are stable and, where possible, prefer the canonical DOI over multiple URLs. It would also help to balance foundational older sources (Task Force 1996; Sztajzel 2004) with recent methodology pieces and to explicitly cite papers that problematize simplistic LF/HF interpretations to signal balance. Finally, add the two Triggiani studies recommended above to the introduction; they directly support your call for controlling adiposity and weight-related confounding when interpreting HRV in PAIS populations.

In sum, this commentary addresses an important and under-utilized tool and is close to being a practical signpost for clinicians. The key revisions are conceptual nuance around LF/LF-HF and VLF in five-minute data, explicit and reproducible measurement/processing guidance, a slightly more quantitative synthesis of the evidence base, a careful tempering of diagnostic claims, and a full copy-edit and reference overhaul. With these changes, the manuscript will offer a more robust, clinically actionable, and methodologically careful case for five-minute HRV in PAIS. My recommendation is accept pending major revisions.

Declarations

Potential competing interests: No potential competing interests to declare.