

Physiological Basis and Clinical Significance of Heart Rate Variability

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KEYWORDS ABSTRACT

Heart rate variability (HRV) serves as a critical non-invasive biomarker of autonomic nervous system (ANS) activity, highlighting the continuous interaction between sympathetic and parasympathetic pathways in modulating cardiovascular activity. This review elucidates the physiological foundations of HRV, including mechanisms such as respiratory sinus arrhythmia, baroreflex oscillations, and thermoregulatory adjustments. Clinically, HRV demonstrates significant utility in predicting cardiovascular risks, diabetic neuropathy progression, psychological stress, and systemic inflammation. Measurement techniques, such as time-domain and frequency-domain analyses, are discussed alongside their methodological challenges, including respiratory artifacts, protocol inconsistencies, and confounding factors like medications. While HRV's prognostic value in conditions like myocardial infarction and heart failure is well-established, debates persist over the interpretation of spectral components, such as the controversial LF/HF ratio. Standardization of protocols and mechanistic clarity are urgently needed to enhance HRV's reliability. By bridging physiological insights with clinical applications, this review underscores HRV's potential as a versatile tool in personalized medicine, while advocating for interdisciplinary research to address existing limitations.

Background

Heart Rate Variability (HRV) refers to the variation in time intervals between consecutive heartbeats. It reflects the dynamic interplay between the sympathetic and parasympathetic divisions of the ANS in regulating cardiac function (1–4). The sympathetic nervous system activates the heart via β -adrenergic receptors during stress or physical demand, increasing the heart rate and cardiac output and resulting in vasodilation. Conversely, the parasympathetic system dominates at rest, slowing the heart rate through muscarinic receptor activation. Although sympathetic activation enhances myocardial oxygen demand via increased heart rate and contractility, this activity results in coronary vasodilation, which is primarily mediated by metabolic byproducts rather than direct neural effects.

HRV arises from three physiological mechanisms:

1. Respiratory sinus arrhythmia (RSA): Cyclic heart rate fluctuations synchronized with breathing, where inspiration transiently inhibits vagal tone, accelerating the heart rate (5,6).
2. Baroreflex oscillations: Blood pressure variability triggers compensatory heart rate adjustments via the baroreceptor pathways (7,8).

3. Thermoregulatory adjustments: Changes in the peripheral vascular resistance to regulate body temperature alter the blood pressure and the heart rate(9,10).

Measurement of HRV

HRV is measured using electrocardiography (ECG) or photoplethysmography (PPG). ECG-derived RR intervals (time between consecutive R-wave peaks) are the gold standard, while PPG uses pulse wave timing from blood volume changes. These intervals, termed NN (normal-to-normal) intervals, form the basis for HRV analysis (1–3). Clinically, HRV serves as a non-invasive biomarker of autonomic balance, with reduced variability indicating ANS dysfunction or heightened cardiovascular risk (3).

Measurement and Interpretation of HRV

HRV is assessed through two primary analytical approaches: time-domain and frequency-domain methods, as standardized by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (2). Time-domain analysis quantifies beat-to-beat variability using statistical measures derived from NN (normal-to-normal) intervals (4). Key parameters include:

- SDNN (standard deviation of NN intervals), which reflects overall HRV and correlates with total autonomic activity.
- RMSSD (root mean square of successive differences): Estimates parasympathetic (vagal) modulation.
- pNNx: (proportion of the number of pairs of successive NNs that differ by more than x ms out of the total number of NNs). NNx is the number of pairs of successive NNs that differ by more than x ms. NNx is used to calculate pNNx using the following formula:

$$pNNx = \frac{NNx}{\text{Total number of NNs}} \times 100$$

The common pNNx used in clinical practice are pNN10, pNN20, pNN30, pNN40, pNN50, pNN60 and pNN70. The unit used to express pNNx is %. The most commonly used pNNx is pNN50 which estimates parasympathetic activity on the heart, same like RMSSD (11).

Frequency-domain analysis decomposes HRV into oscillatory components using spectral techniques like fast Fourier transform (12). This method identifies distinct frequency bands:

- Total power (TP) (0–0.4 Hz), representing global autonomic activity.
- VLF (0.0033–0.04 Hz), linked to thermoregulation and hormonal influences but with debated physiological origins.
- LF (0.04–0.15 Hz), primarily reflecting baroreflex-mediated oscillations rather than direct sympathetic tone.
- HF (0.15–0.4 Hz), corresponding to respiratory sinus arrhythmia and parasympathetic activity.
- LF/HF ratio, often misinterpreted as "sympathovagal balance," remains controversial due to the dual autonomic influences on the LF band.

The recording protocols used significantly impact the results. Long-term assessments (24-hour ECG) are ideal for time-domain analysis, because they capture circadian variations. Short-term recordings (5-minute stationary ECG) suit frequency-domain methods (2,13). Standardization of posture, environment, and respiratory rate (<9 breaths/minute) is critical to minimize artifacts(14). Although both electrocardiography (ECG) and photoplethysmography (PPG) measure NN intervals, ECG remains the gold standard for accuracy. Clinicians must account for confounding factors like recording duration—SDNN values increase with longer measurements—and avoid comparing studies with mismatched protocols (12,14). Despite its versatility, HRV interpretation requires rigor to address methodological inconsistencies and physiological ambiguities. HRV is

influenced by several factors, such as age, gender, and fitness(2). Higher variability is healthier than lower variability. Athletes typically exhibit higher variability than non-athletes, and young people generally have higher variability than older individuals(15).

Considerations and Controversies

The interpretation and application of HRV are subject to several methodological and physiological controversies.

First: The physiological basis of the low-frequency (LF) band remains debated. While historically linked to sympathetic activity, evidence suggests LF primarily reflects baroreflex-mediated oscillations rather than direct sympathetic outflow, particularly under controlled respiratory conditions (16). This challenges the traditional view of LF/HF ratio as a pure "sympathovagal balance" indicator, complicating its clinical interpretation. Likewise, LF/HF ratio is highly sensitive to environmental and postural changes, limiting their clinical utility in non-standardized settings (17).

Second: The respiratory rate and depth significantly influence spectral analysis. Slow breathing (e.g., <9 breaths/minute) shifts high-frequency (HF) power into the LF range, blurring distinctions between parasympathetic and sympathetic contributions (16). This underscores the need for standardized respiratory protocols during short-term HRV assessments, though such controls are rarely implemented in clinical practice.

Third: Methodological inconsistencies hinder comparability. While 5-minute recordings are recommended for short-term analysis, variations in recording duration, environmental conditions (e.g., physical activity, emotional state), and signal-processing algorithms (e.g., Fourier transform vs. wavelet analysis) can alter results (1–4). For instance, SDNN values increase with longer recordings, complicating cross-study comparisons unless protocols are rigorously unified(18).

Fourth: Confounding factors such as medications (e.g., beta-blockers, antidepressants), comorbidities (e.g., diabetes, anxiety disorders), and even caffeine intake modulate HRV, yet these variables are often inadequately controlled in research and clinical settings (15,19). This limits the reliability of HRV as a standalone diagnostic tool.

Finally: The clinical relevance of certain parameters remains unclear. For example, VLF oscillations are theorized to reflect thermoregulation (17) or renin-angiotensin system activity (20), but their prognostic value is primarily derived from population studies rather than mechanistic insights. Similarly, while reduced HRV predicts adverse outcomes in conditions like heart failure, its utility in guiding individualized therapies is unproven.

These controversies highlight the need for standardized methodologies (17), explicit reporting of confounders, and cautious interpretation of HRV parameters within specific physiological and clinical contexts. Future research should prioritize elucidating the mechanisms behind spectral components and validating HRV's role in personalized medicine.

Uses of HRV in clinical practice and research

HRV has demonstrated significant clinical utility in assessing autonomic function and predicting outcomes across various cardiovascular and systemic conditions. Its applications are supported by extensive research, as outlined below.

HRV in Cardiovascular Diseases

HRV is a well-validated predictor of arrhythmic events and mortality following acute myocardial infarction (AMI)(21). Reduced HRV independently predicts sudden cardiac death and total mortality, even when adjusted for left ventricular ejection fraction (LVEF) or ventricular ectopic activity (22). Time-domain parameters, such as SDNN <50 ms, are practical for risk stratification in clinical settings, while spectral analysis highlights the prognostic significance of VLF components

(13). Another report demonstrated that post-myocardial infarction (MI) patients with type 2 diabetes and SDNN values <70 ms faced a fourfold increase in 3-year mortality risk compared to those with higher SDNN (23). Cardiac Syndrome X (CSX)—characterized by angina with normal coronary arteries—reveals intermediate HRV profiles between healthy individuals and coronary artery disease (CAD) patients. Approximately 60% of CSX patients exhibit autonomic dysregulation, marked by elevated sympathetic activity or suppressed vagal tone, suggesting a transitional pathophysiological state (24,25). Multivariate models combining HRV with LVEF and ventricular ectopy enhance predictive accuracy, particularly for sudden death (21,26). Therapeutic interventions, such as beta-blockers, modestly increase HRV and attenuate the morning surge in sympathetic activity linked to higher mortality (27,28).

In congestive heart failure (CHF), depressed HRV correlates with left ventricular dysfunction, hemodynamic compromise, and New York Heart Association (NYHA) functional class (29–32). Sympathetic activation and vagal withdrawal, driven by neurohormonal dysregulation, contribute to this reduction (29).

Patients with left ventricular hypertrophy (LVH) secondary to hypertension or aortic valve disease exhibit reduced HRV, which inversely correlates with LV mass index (33,34).

Diabetic Neuropathy

The relationship between diabetic neuropathy and HRV has been extensively studied, with consistent evidence highlighting measurable changes in HRV parameters that correlate with disease progression, glycemic control, and clinical outcomes.

Early-stage cardiovascular autonomic neuropathy (CAN) manifests as reduced parasympathetic activity, detectable through HRV analysis before overt clinical symptoms emerge. A study involving 50 children with insulin-dependent diabetes demonstrated that RMSSD and HF power were significantly reduced compared to healthy controls (35). Researchers observed that asymptomatic diabetic patients exhibited marked declines in HRV indices within the first 5–10 years of disease progression, underscoring the insidious onset of autonomic impairment (35). These findings align with reports that identified diminished parasympathetic activity as the earliest indicator of CAN, detectable through short-term HRV recordings even in normoglycemic individuals at risk of developing diabetes (36).

On the other hand, as diabetic neuropathy progresses, sympathetic dominance becomes evident, exacerbating ANS imbalance. Chronic hyperglycemia and oxidative stress drive this shift, reflected in elevated LF power and increased LF/HF ratios, which indicate heightened sympathetic activity (37). According to one report, there is an inverse correlation between TP and HbA1c levels in diabetic patients, which suggests that poor glycemic control leads to increased sympathetic overactivation (60). This phenomenon is further supported by studies linking elevated cortisol levels and inflammatory markers (e.g., tumor necrosis factor- α) to reduced HRV, highlighting the interplay between metabolic dysregulation, neurohormonal stress, and autonomic dysfunction (38,39).

The Atherosclerosis Risk in Communities (ARIC) study, involving 15,800 participants, found that individuals with multiple metabolic disorders (e.g., hypertension, dyslipidemia, diabetes) exhibited significantly lower SDNN values, correlating with heightened cardiovascular risk (40).

Psychological and Mental Health

HRV serves as a critical biomarker in evaluating psychological states, including chronic stress, anxiety, and depression. Reduced HRV, particularly SDNN and HF power, is strongly associated with anxiety disorders and major depressive disorder (MDD) (41). For instance, individuals with untreated MDD exhibit diminished parasympathetic activity, reflected in lower HF power and

elevated LF/HF ratios, indicating sympathetic dominance (42). Chronic psychological stress further exacerbates autonomic imbalance, with studies demonstrating that prolonged stress reduces SDNN and RMSSD, markers of vagal tone(43). These findings underscore HRV's utility in identifying subclinical mental health disturbances and monitoring therapeutic interventions aimed at restoring autonomic equilibrium.

Inflammation and Immunological Monitoring

Research indicates a consistent association between HRV and pro-inflammatory states in both healthy individuals and clinical populations (44,45). Inflammatory conditions correlate with diminished TP, affecting both parasympathetic and non-parasympathetic regulatory indices (44). Patients with nosocomial infections or sepsis exhibit significantly lower HRV compared to controls (45). While HRV's predictive utility for infection risk remains limited, VLF power reduction shows promise as a biomarker in adults across diverse clinical settings (44,45). Alternatively, Chronic inflammatory conditions, such as sepsis or autoimmune disorders, exhibit pronounced HRV suppression, reflecting autonomic-immune crosstalk via the cholinergic anti-inflammatory pathway (46–48). Monitoring HRV in critically ill patients aids in early detection of immunological dysregulation, offering prognostic insights into sepsis outcomes and guiding immunomodulatory therapies (44–49).

Environmental and Lifestyle Modulations

Environmental stressors, such as noise pollution and occupational hazards, significantly alter HRV profiles. Exposure to chronic social stress or high-decibel environments correlates with reduced SDNN and HF power, indicative of sympathetic overactivation (13,43,50). Conversely, lifestyle modifications, including smoking cessation and moderate alcohol consumption, can ameliorate HRV impairment. Heavy smoking diminishes cardiac vagal regulation(51), while moderate alcohol intake transiently enhances HRV metrics in non-dependent users (52). Heavy smokers exhibited increased LF power and LF/HF ratio, along with reduced SDNN, SDANN, RMSSD, and HF power (53). Physical activity also modulates HRV; strenuous exercise initially lowers HRV due to sympathetic surge, whereas regular moderate exercise improves parasympathetic tone (54,55). These insights highlight HRV's role in guiding personalized lifestyle interventions to mitigate autonomic dysfunction.

Other HRV's Applications

HRV's utility extends beyond the aforementioned contexts, offering insights into diverse systemic disorders. In neuromuscular diseases such as muscular dystrophy, diminished HRV serves as an independent prognostic marker for mortality (56). Similarly, patients with controlled bronchial asthma exhibit higher TP and HF but lower LF and LF/HF ratio compared with uncontrolled asthma patients, indicative of enhanced parasympathetic modulations and higher HRV in the second group (57). Epilepsy research reveals preictal HRV alterations, which precede seizures and may aid in predicting episodic autonomic dysregulation (58,59). Likewise, short-term measurement of RMSSD is a reliable parameter to assess parasympathetically impaired cardiac modulation in Parkinson's patients (60) and multiple sclerosis (61).

Researchers have used HRV as a measure of cardiac autonomic function in individuals with various medical conditions. These include gastrointestinal disorders like peptic ulcer (62), irritable bowel syndrome (63). They also included metabolic and endocrine conditions such as polycystic ovary syndrome (64), thyrotoxicosis (65), Cushing syndrome (66), acromegaly (67), as well as renal and hepatic issues like uremia (68), hemodialysis (69), and hepatic encephalopathy (70). Studies have also explored HRV in pregnancy-related contexts, including preeclampsia (71), during labour (72), alongside urogenital conditions like erectile dysfunction (73), benign prostatic

hyperplasia (74). HRV studies have also explored HRV analysis in diverse conditions, including pharmacological treatments (75,76) and complementary therapeutic approaches (77,78). All this underscores HRV's utility in evaluating ANS changes in various clinical contexts. and emphasizes its adaptability in both clinical and therapeutic settings, spanning disease management, drug interventions, and integrative health strategies.

Limitations

The interpretation and application of HRV face several challenges. A primary issue lies in the debated physiological basis of certain frequency bands, such as the LF component, which has historically been attributed to sympathetic activity but may instead reflect baroreflex-mediated adjustments (16). This ambiguity complicates the clinical translation of metrics like the LF/HF ratio. Additionally, respiratory patterns significantly distort spectral analysis, as uncontrolled breathing rates can blur distinctions between parasympathetic and sympathetic contributions (14). Methodological inconsistencies further hinder progress, including variability in recording durations, environmental conditions, and signal-processing techniques, which limit cross-study comparisons (1–4). External influences, such as medications (e.g., beta-blockers, antidepressants (15,19,27,28), comorbidities (e.g., diabetes, anxiety disorders) (35,40), and lifestyle factors (e.g., caffeine intake) (51–53), also modulate HRV but are rarely accounted for in studies. Lastly, while reduced HRV predicts adverse outcomes in conditions like heart failure (29–32), its mechanistic role in guiding therapies remains unproven, and the clinical relevance of very-low-frequency (VLF) oscillations lacks robust validation (79,80).

Recommendations and Future Directions

To address these challenges, future research should prioritize standardized protocols for HRV measurement, including fixed recording durations, controlled respiratory rates, and consistent postural conditions, to minimize artifacts and enhance reproducibility (14,17). Mechanistic studies are urgently needed to clarify the origins of debated spectral components, such as VLF and LF bands, through controlled experiments and longitudinal designs (79,80). Clinically, exploring HRV's potential in personalized medicine, such as tailoring therapies for heart failure or diabetes, could bridge the gap between risk prediction and actionable interventions. Technological advancements, including validating wearable devices and improving photoplethysmography (PPG) accuracy against gold-standard ECG (1–4), may expand HRV's accessibility without compromising reliability. Integrating artificial intelligence could further refine HRV analysis by accounting for confounders and decoding complex autonomic patterns. Finally, interdisciplinary collaboration is essential to unravel HRV's interactions with neuroendocrine, immune, and metabolic systems, fostering a holistic understanding of autonomic dysregulation across diseases.

Conclusions

HRV provides a unique, non-invasive window into autonomic regulation, offering valuable insights across cardiovascular, metabolic, and psychological disorders. Its physiological basis — rooted in the interplay of respiratory, baroreflex, and thermoregulatory mechanisms— supports its role as a predictor of adverse outcomes in conditions such as heart failure, diabetes, and depression. However, challenges persist, including ambiguities in interpreting frequency-domain metrics (e.g., LF/HF ratio) and methodological inconsistencies in recording protocols. Confounding factors like medications, comorbidities, and environmental stressors further complicate its clinical application. To realize HRV's full potential, future efforts must prioritize standardized measurement guidelines, mechanistic studies to clarify spectral component origins, and integration with emerging technologies like wearable devices and artificial intelligence. By addressing these gaps, HRV can

evolve from a research tool into a cornerstone of clinical practice, enabling tailored interventions and improving patient outcomes in diverse healthcare settings.

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