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Heart Rate Variability in Intensive Care Unit: Clinical Applications and Challenges

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Abstract: *Heart rate variability (HRV), as a non-invasive indicator for assessing autonomic nervous system (ANS) function, has accumulated substantial evidence in prognostic prediction research among critically ill patients. However, its clinical translation has lagged significantly behind, resulting in a pronounced "research-to-practice gap". This review systematically analyzes the specific barriers to HRV monitoring imposed by the intensive care unit setting: (1) intensive therapeutic interventions (sedation and analgesia, vasoactive agents, mechanical ventilation) introduce confounding effects, rendering the HRV signal an amalgam of disease and treatment effects; (2) heterogeneity of extreme pathophysiological states leads to highly individualized variations in ANS response patterns; (3) signal quality impairment caused by high-frequency arrhythmias and electrical interference. In light of these challenges, the conventional HRV analytical paradigm exhibits limitations in the ICU setting, including loss of parameter interpretability, mismatch between static measurements and dynamic clinical conditions, and infeasibility of standardized measurement conditions. This article proposes four strategic approaches: transitioning toward dynamic trend analysis, establishing ICU-specific reporting standards, advancing multimodal data integration, and exploring novel interference-resistant metrics. These strategies aim to provide a roadmap for high-quality research enabling robust clinical application of HRV.*

Keywords: *Heart Rate Variability, Intensive Care Unit, Autonomic Nervous System, Methodological Challenges*

1. Introduction

The autonomic nervous system (ANS) constitutes the principal regulatory framework governing the body's stress response, with its functional integrity demonstrating significant prognostic implications in critically ill patients[1, 2]. Heart rate variability (HRV), defined as the temporal variation in successive beat-to-beat intervals (R-R intervals), serves as a non-invasive marker of ANS modulation of cardiac sinus node function[3]. Accumulating evidence from prospective cohort studies has consistently demonstrated associations between attenuated HRV and adverse clinical outcomes in critical illness. Specifically, reduced HRV has been independently associated with elevated mortality and heightened risk of organ dysfunction in critically illness, including patients with sepsis and traumatic brain injury, and has been integrated into prognostic scoring systems for risk stratification[4-7]. However, despite robust evidence supporting its prognostic utility, HRV monitoring has not been incorporated into standard ICU practice. In contrast, HRV assessment has gained widespread clinical adoption in cardiovascular risk stratification[8] and the evaluation of diabetic autonomic neuropathy[9].

This "research-to-practice gap" suggests that barriers to adoption may not arise from insufficient prognostic value, but rather from fundamental methodological challenges that remain incompletely characterized and inadequately addressed in translating HRV from controlled research environments to the highly complex, dynamic, and artifact-prone ICU setting. Three inherent characteristics of the ICU setting present distinct challenges: (1) direct ANS modulation by therapeutic interventions (including

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sedation and analgesia, vasoactive agents, mechanical ventilation); (2) complex confounding effects of heterogeneous and severe pathophysiological states on HRV signal interpretation; and (3) degraded signal fidelity secondary to frequent cardiac arrhythmias and electrical interference.

This review systematically examines these ICU-specific challenges, critically appraises the applicability and limitations of conventional HRV analysis methodologies in this context, and outlines potential solutions and future research directions for successful clinical implementation of HRV monitoring in ICU.

2. Physiological Basis and Common Metrics of HRV

2.1. Mechanisms Underlying HRV Generation

HRV emerges from complex, nonlinear interactions among multiple physiological regulatory systems[10], with the brain-heart axis serving as the integrative framework for understanding HRV genesis. Sympathetic and parasympathetic efferent pathways originating from the central nervous system interact with the intrinsic cardiac autonomic nervous system to modulate cardiac chronotropy, thereby maintaining dynamic homeostasis of cardiac rhythm. Parasympathetic influence on sinoatrial (SA) nodal pacemaker cells is mediated through acetylcholine release from vagal terminals, resulting in negative chronotropic effects. Conversely, sympathetic activation accelerates phase 4 diastolic depolarization via norepinephrine and epinephrine release, producing positive chronotropic effects[11]. Direct autonomic control of the SA node is further refined by central and peripheral oscillatory mechanisms. The central autonomic network—comprising functionally integrated brain regions distributed along the neuraxis, including the insular cortex, amygdala, hypothalamus, periaqueductal gray, parabrachial nucleus, nucleus tractus solitarius, and rostral ventrolateral medulla—coordinates descending autonomic outflow[12]. Concurrently, respiratory oscillations, arterial baroreceptor activity, and humoral factors modulate cardiac chronotropy through neural reflex arcs involving peripheral cardiorespiratory centers, including baroreflex and chemoreflex pathways, manifesting electrocardiographically as Mayer waves[13, 14] and respiratory sinus arrhythmia (RSA)[15]. Additionally, the intrinsic cardiac autonomic nervous system, formed through interactions among components of the cardiac pacing and conduction apparatus, constitutes an integral component of this autonomic-electrophysiological network, contributing to phenomena such as intrinsic SA nodal modulation and heart rate fragmentation[16].

2.2. Common Metrics of HRV

HRV analysis methods are primarily categorized into linear and nonlinear approaches. Linear methods, encompassing time-domain and frequency-domain analyses, represent the most widely applied techniques in current clinical practice and research[17-19].

Time-domain analysis quantifies variability characteristics of R-R interval sequences using statistical methods. Principal metrics include: (1) SDNN (standard deviation of NN intervals): reflects the aggregate influence of all periodic variation components on heart rate during the measurement period, with significant dependence on recording duration; (2) RMSSD (root mean square of successive differences): primarily reflects short-term rapid heart rate fluctuations and is closely associated with vagal nerve activity; (3) pNN50 (percentage of successive NN interval differences exceeding 50 ms): similarly reflects high-frequency variations and demonstrates sensitivity to vagal modulation.

Frequency-domain analysis decomposes R-R interval sequences into power spectra of distinct frequency components through Fast Fourier Transform. Major frequency bands include: (1) High frequency (HF, 0.15-0.4 Hz): primarily contributed by RSA mediated by respiratory activity, and is widely employed as an index of parasympathetic nerve activity; (2) Low frequency (LF, 0.04-0.15 Hz): influenced by both sympathetic and parasympathetic nervous systems, predominantly associated with baroreflex regulation; (3) Very low frequency (VLF, 0.003-0.04 Hz): reflects longer-period regulatory processes including thermoregulation and hormonal systems. The LF/HF ratio is commonly used to assess sympathovagal balance.

Nonlinear dynamical methods have been increasingly applied to HRV analysis in recent years, including sample entropy, detrended fluctuation analysis, and heart rate fragmentation. These approaches aim to characterize system complexity, scaling properties, and temporal organization that are not adequately captured by conventional linear analyses[16, 20].

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3. Challenges of HRV Monitoring in the ICU Context

The ICU setting fundamentally differs from the controlled laboratory settings in which HRV measurement standards were established. Internationally recognized guidelines for HRV assessment (e.g., the 1996 Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology[17]) were developed under rigorously controlled conditions: hemodynamically stable subjects in quiet, supine, awake states with spontaneous respiration, recording environments devoid of electromagnetic interference, and exclusion of pharmacological agents with known autonomic effects. In contrast, the ICU represents a markedly suboptimal monitoring environment characterized by critically ill patients with rapidly evolving clinical trajectories, continuous infusion of vasoactive and sedative medications, mechanical cardiorespiratory support, and operation of multiple electronic devices generating electromagnetic interference. These intrinsic characteristics introduce multifaceted, interrelated confounders affecting HRV signal generation, acquisition, and interpretation, thereby limiting direct extrapolation of HRV evidence derived from laboratory settings to ICU bedside monitoring. This section systematically examines these challenges across three hierarchical levels: (1) the therapeutic intervention level—direct autonomic modulation by routine ICU therapies and their confounding effects on HRV signals; (2) the pathophysiological level—interpretive challenges arising from the heterogeneity and temporal dynamics of critical illness states; and (3) the technical implementation level—practical obstacles in signal acquisition and quality assurance.

3.1. Confounding Effects of Therapeutic Interventions: Introducing Extraneous Variability into HRV Measurements

Life-sustaining therapies and organ support measures in the ICU invariably become dominant modulators of HRV signals, rendering measured HRV a composite reflection of both disease pathophysiology and therapeutic effects. This therapeutic confounding substantially compromises the utility of HRV as an independent biomarker of disease severity.

3.1.1. Sedative and Analgesic Agents: Pharmacological Modulation of Central ANS Regulation

Sedation and analgesia constitute fundamental components of ICU management; however, virtually all commonly employed agents exert significant effects on HRV. Propofol, the most widely used intravenous sedative, modulates autonomic activity at multiple central levels by potentiating γ-aminobutyric acid (GABA)-mediated inhibitory neurotransmission in cardiac vagal neurons[21]. Post hoc analyses in healthy volunteers and clinical cohorts have demonstrated that propofol infusion induces dose-dependent, reversible reductions in RMSSD and HF power, accompanied by increases in the LF/HF ratio[22].

Benzodiazepines (e.g., midazolam, remimazolam) similarly suppress overall autonomic activity through GABAergic mechanisms[23]. Opioid analgesics (e.g., fentanyl, remifentanil) alter cardiac autonomic regulation by attenuating sympathetic outflow via central opioid receptor activation[24]. These pharmacological effects confound differentiation between disease severity and drug-induced autonomic modulation.

3.1.2. Vasoactive Medications: Potent Exogenous Neurohumoral Interventions

Vasoactive agents are essential for maintaining hemodynamic stability in critically ill patients, with their mechanisms of action conferring profound influences on HRV. Goldberger et al.[25] systematically characterized the complex effects of physiological and pharmacological adrenergic manipulations on HRV: isoproterenol, a β-adrenergic receptor agonist, shifted autonomic balance toward sympathetic predominance, manifesting as increased HF power and decreased LF/HF ratio; propranolol, a β-adrenergic receptor antagonist, induced minimal HRV alterations when administered alone, whereas combined propranolol and atropine administration produced consistent, significant reductions in HRV metrics; epinephrine elevated circulating catecholamine concentrations without inducing substantial HRV changes. A recent comprehensive meta-analysis[26] systematically evaluated the effects of autonomic-modulating medications on HRV parameters. Anticholinergic agents induced significant reductions in time-domain and frequency-domain metrics through parasympathetic blockade, with atropine demonstrating dose-dependent effects—paradoxically, low-dose atropine increased RMSSD and related metrics through central vagal activation mechanisms. Phenylephrine increased HRV through reflex parasympathetic activation, whereas clonidine, an α_2-adrenergic agonist, did not produce significant HRV alterations. These complex pharmacologically induced autonomic responses

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confound accurate assessment of endogenous autonomic reserve through HRV measurements.

3.1.3. Mechanical Ventilation: Imposed Respiratory Control and Disruption of Respiratory Sinus Arrhythmia

The impact of mechanical ventilation on HRV is particularly profound and mechanistically complex. RSA constitutes the principal contributor to HF components of HRV, with its generation dependent on modulation of vagal efferent activity by spontaneous respiratory oscillations through central respiratory-cardiovascular coupling and peripheral pulmonary stretch reflexes[27]. Mechanical ventilation fundamentally disrupts this physiological process through multiple mechanisms. First, fixed ventilator rates eliminate the inherent variability characteristic of spontaneous breathing patterns; studies have demonstrated RSA attenuation during hyperventilation or respiratory center suppression induced by deep anesthesia[15]. In healthy subjects, controlled rhythmic breathing increased most HRV metrics (excluding LF indices) compared with spontaneous breathing[28]. Second, ventilator parameter adjustments—including respiratory rate, tidal volume, inspiratory depth, and inspiratory-to-expiratory ratio—exert quantifiable effects on RSA magnitude[15, 29-31]. Underlying mechanisms involve the degree of pulmonary stretch receptor activation, intrathoracic pressure fluctuations affecting venous return, and alterations in respiratory-cardiovascular coupling phase relationships. Critically, when these parameters are clinically titrated according to respiratory mechanics and gas exchange requirements, the resultant HRV changes become indistinguishable from pathophysiological alterations attributable to disease progression.

Importantly, these interventions rarely occur in isolation—a typical critically ill patient receives concurrent sedation, vasoactive support, and mechanical ventilation, with the effects of each intervention potentially exhibiting additive or interactive relationships, producing unpredictable aggregate effects on HRV. To date, no studies have systematically evaluated the combined impact of such multifactorial therapeutic regimens on HRV parameters, representing a substantial knowledge gap.

3.2. Pathophysiological Heterogeneity: Intrinsic Disease-Related Signal Complexity

Independent of therapeutic interventions, the inherent pathophysiological characteristics of critical illness pose interpretive challenges for HRV analysis. In contrast to the relatively stable pathological states characteristic of chronic conditions such as cardiovascular disease or diabetes, critical illness encompasses highly dynamic, multi-system dysregulated processes with substantial inter-individual heterogeneity.

3.2.1. Disease-Specific Heterogeneity: Divergent Autonomic Patterns across Different Etiologies

Attenuated HRV represents a common feature across diverse critical illnesses, including sepsis, subarachnoid hemorrhage, traumatic brain injury, cardiogenic shock, and acute heart failure, reflecting the ubiquitous nature of autonomic nervous system dysfunction. However, distinct pathophysiological mechanisms underlie HRV alterations in different disease states.

In sepsis, autonomic dysregulation originates from systemic inflammatory responses. Endotoxins activate innate immune cells via Toll-like receptor-4, with subsequent pro-inflammatory cytokine release (TNF-α, IL-1β, IL-6) triggering excessive hypothalamic-pituitary-adrenal axis activation and catecholamine surge, while vagally mediated cholinergic anti-inflammatory pathway function becomes impaired, resulting in deficient anti-inflammatory regulation[32]. A meta-analysis of 2,283 patients demonstrated significant inverse correlation between SDNN and inflammatory biomarkers[33], with the magnitude of HRV reduction directly reflecting inflammation severity and cholinergic anti-inflammatory pathway dysfunction. This sustained sympathetic hyperactivation contrasts markedly with the paroxysmal patterns observed in other critical illnesses.

Aneurysmal subarachnoid hemorrhage (aSAH) induces acute catecholamine surge secondary to abrupt intracranial hypertension and injury to medullary cardiovascular centers (particularly the nucleus tractus solitarius), conferring risk of acute neurogenic cardiac injury[34]. In a cohort of 326 aSAH patients, those developing neurogenic cardiac injury exhibited elevated LF/HF ratios, with this extreme sympathetic predominance significantly correlating with troponin elevation and electrocardiographic abnormalities, reflecting direct myocardial damage consequent to central nervous system injury[35].

Paroxysmal sympathetic hyperactivity (PSH) following traumatic brain injury exhibits distinctive pathophysiological features. According to the excitation-inhibition ratio (EIR) model proposed by Baguley et al., damage to midbrain-brainstem inhibitory centers disinhibits abnormal allodynic drive

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originating from the spinal dorsal horn, enabling innocuous stimuli (e.g., endotracheal suctioning, patient repositioning) to precipitate sympathetic storms[36, 37]. In HRV analysis, this mechanism manifests as heart rate-HRV uncoupling—markedly elevated heart rate accompanied by paradoxically suppressed HRV parameters, with this dysautonomia persisting for approximately 14 months post-injury[38]. These paroxysmal, stimulus-triggered characteristics differ fundamentally from the sustained pattern in sepsis and the acute-phase burst pattern in SAH[36, 37].

Autonomic dysregulation in cardiovascular critical illness primarily stems from baroreceptor dysfunction. In cardiogenic shock, precipitous decline in cardiac output results in arterial baroreceptor unloading with compensatory sympathetic activation; however, sustained catecholamine exposure induces β-adrenergic receptor downregulation and desensitization, culminating in "catecholamine resistance"[39].

3.2.2. Disease Trajectory Dynamics: Evolution from Compensatory to Decompensatory States

Animal studies in murine hemorrhagic shock models demonstrate that HRV components exhibit stage-dependent alterations across different severities of hemorrhagic shock[40]: HRV displays augmented LF and RSA power during the hypotensive phase, with variable degrees of recovery following volume resuscitation. From a pathophysiological perspective, septic shock patients may exhibit hyperdynamic states with sympathetic predominance during early phases, whereas end-stage cardiogenic shock or severe brain injury may manifest relative parasympathetic predominance or global autonomic failure.

3.2.3. Multiple Organ Dysfunction: Collapse of Physiological Complexity

The progression of multiple organ dysfunction syndrome (MODS) further complicates HRV interpretation. From a systems biology framework, healthy organisms are characterized by complex, orchestrated interactions among organ systems, manifesting as dynamic coupling of multiple physiological oscillators (cardiac rhythm, respiration, blood pressure, thermoregulation)[41]. HRV theoretically reflects the degree of coupling among these multi-organ oscillatory networks, whereas MODS is characterized precisely by disruption of this inter-organ coordinated communication. Consequently, HRV attenuation may simultaneously reflect both impaired autonomic innervation of the heart and loss of systemic physiological complexity[42, 43].

As a window into autonomic function, the clinical utility of HRV extends beyond merely identifying dysfunction; more importantly, it lies in elucidating disease-specific pathological mechanisms through integrated analysis of variability patterns, temporal evolution trajectories, and correlated biomarkers, thereby informing precision therapeutic strategies.

3.3. Technical Challenges in Signal Acquisition and Quality Assurance

Although critically ill patients routinely undergo continuous electrocardiographic monitoring, acquisition of high-fidelity ECG signals in the ICU environment remains challenging. Beyond common artifacts including motion artifacts and myoelectric interference, critically ill patients experience additional confounding factors: ectopic rhythms and arrhythmias arising from severe metabolic derangements, electromagnetic interference from multiple medical devices, and electrode displacement or inadequate skin contact resulting from frequent procedures and patient repositioning, all of which compromise data reliability and temporal continuity[44].

3.4. Synergistic Challenge Interactions: The Systemic Nature of the Problem

Critically, the three challenge categories delineated above do not exist in isolation but are intricately interconnected and mutually amplifying. For example, deep sedation (therapeutic intervention) reduces both baseline HRV magnitude and signal amplitude, thereby decreasing the signal-to-noise ratio and rendering previously tolerable electromagnetic interference (technical challenge) clinically unacceptable. Similarly, hemodynamic instability in MODS patients (pathophysiological state) necessitates frequent vasoactive medication titration (therapeutic intervention), with each adjustment introducing novel autonomic perturbations while concurrent blood pressure fluctuations activate baroreceptor reflexes, altering frequency-domain HRV components and rendering differentiation between "disease progression" and "therapeutic adjustment" nearly impossible.

This systemic complexity indicates that simple transplantation of laboratory-derived HRV analytical methods to the ICU is fundamentally untenable. Rather, a paradigmatic shift is required: from pursuing

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idealized "pure physiological signals" toward extracting robust, clinically interpretable information within complex environments; from static, single-timepoint measurements toward identification of dynamic temporal trends; from isolated HRV metrics toward integrated, multimodal data interpretation frameworks.

4. Toward Novel HRV Analysis Approaches for ICU Application: Challenge-Driven Response Strategies

To address the aforementioned challenges, future research and clinical practice must undergo the following paradigmatic transformations:

4.1. From Static Measurements to Dynamic Trajectories—Prioritizing Temporal Trend Analysis

Research emphasis should transition from quantifying absolute HRV values toward characterizing temporal evolution patterns. This includes evaluating rates of change in HRV parameters over time and identifying distinctive trajectory phenotypes. Extended monitoring periods (e.g., 24-hour continuous recording) offer unique advantages in capturing circadian rhythm disruption and overall physiological instability. Advanced statistical methodologies, including group-based trajectory modeling (GBTM) and mixed-effects models, can identify subgroups within heterogeneous populations sharing common temporal patterns with prognostic significance[45].

4.2. Establishing ICU-Specific HRV Reporting Standards

Enhancing between-study comparability and interpretability necessitates mandatory reporting of core confounding variables. Future high-quality ICU-HRV investigations should minimally report[46]: (1) sedative, analgesic, and vasoactive medication profiles (agent, dose, infusion rate); (2) sedation depth assessments at measurement timepoints (e.g., Richmond Agitation-Sedation Scale [RASS], Sedation-Agitation Scale [SAS]); (3) mechanical ventilation parameters (mode, set respiratory rate, tidal volume); (4) arrhythmia burden during analysis windows; and (5) concurrent physiological variables (mean heart rate, body temperature, arterial blood pressure). Such standardization will facilitate robust meta-analyses and development of externally valid clinical prediction models.

4.3. From Isolated Metrics to Multimodal Integration—Contextualizing HRV Within Physiological Networks

HRV should not be interpreted in isolation. Integration with continuous arterial pressure monitoring enables calculation of baroreflex sensitivity, providing comprehensive cardiovascular autonomic assessment. Temporal correlation analysis with inflammatory biomarkers (e.g., interleukin-6, C-reactive protein) can elucidate neuro-immune crosstalk in critical illness pathogenesis. Fusion with neurophysiological monitoring (e.g., bispectral index, intracranial pressure) facilitates investigation of brain-heart axis significance in neurocritical care. Multimodal data integration represents a critical approach to resolving HRV signal ambiguity.

4.4. Exploring Novel Metrics Demonstrating Enhanced Robustness to Confounding

Traditional linear time- and frequency-domain metrics exhibit vulnerability to certain confounders. Investigation of nonlinear dynamical indices (e.g., entropy measures, detrended fluctuation analysis) and heart rate fragmentation metrics may provide complementary information for characterizing physiological complexity and identifying specific pathological states, while demonstrating relative resistance to certain confounders[47-49]. However, the clinical utility and performance characteristics of these metrics in ICU populations require large-scale prospective validation.

5. Conclusions and Future Perspective

The translational value of HRV in critical care medicine extends beyond merely accumulating associations with adverse outcomes; rather, it depends on developing robust measurement, analytical, and interpretive frameworks that comprehensively address the complexity inherent to the ICU environment. Future research must embrace paradigmatic shifts: from cross-sectional observational designs toward longitudinal dynamic monitoring approaches; from simple reporting of HRV values

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toward rigorous standardized reporting incorporating therapeutic confounders; from pursuing isolated prognostic biomarkers toward exploring HRV as both a risk stratification tool and mechanistic probe, interpreted within multimodal physiological contexts. Only through such challenge-driven, problem-oriented investigation can HRV transition from a research variable with unrealized potential into a practical clinical tool capable of reliably reflecting intrinsic physiological reserve and risk trajectory in critically ill patients in real-time, ultimately advancing the paradigm of precision critical care medicine.

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