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IntechOpen Series
Cardiology and Cardiovascular Medicine,
Volume 14

Heart Rate Variability

Current Practices and Clinical Applications

Edited by Ana Ciobanu



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Published in London, United Kingdom

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<http://dx.doi.org/10.5772/intechopen.1008624>

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First published in London, United Kingdom, 2025 by IntechOpen

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British Library Cataloguing-in-Publication Data

A catalogue record for this book is available from the British Library

Heart Rate Variability – Current Practices and Clinical Applications

Edited by Ana Ciobanu

p. cm.

This title is part of the Cardiology and Cardiovascular Medicine Book Series, Volume 14

Topic: Cardiovascular Electrophysiology

Series Editor: Kaan Kırallı

Topic Editor: Karine Guerrier

Print ISBN 978-1-83634-272-4

Online ISBN 978-1-83634-271-7

eBook (PDF) ISBN 978-1-83634-273-1

ISSN 3033-361X

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IntechOpen Book Series

Cardiology and Cardiovascular Medicine

Volume 14

Aims and Scope of the Series

Today, since molecular science on structural causes of oncological pathologies and their molecular treatments are developing at an unbelievable rate, the primary medical cause of death in the twenty-first century will be cardiovascular disease. Neither pandemics that threaten all humanity nor deterioration in the ecosystem will be able to change this fact. Especially, this century seems poised to witness an incredible struggle against atherosclerotic disease, which develops in the arterial walls and results in narrowing and occlusion of the arterial lumen. In addition to this disease, there has been an increasing prevalence of heart rhythm problems, deterioration of heart valves due to aging, and heart failure. Serious vascular pathologies such as stenosis and occlusion, dissection and rupture, and aneurysmal enlargement are also major concerns. Medical and invasive treatment methods may work to save human lives, but they will never provide a real solution. All kinds of medical, technological, and genetic engineering developments obtained in these processes have not yet been sufficient to alleviate or eliminate cardiovascular disease. This book series, Cardiology and Cardiovascular Medicine, includes three topics. The first, Cardiovascular Diseases and Health, reviews important cardiovascular diseases and the developments in their prognosis. The second topic, Cardiovascular Electrophysiology, illuminates the abnormal functioning of the cardiac conduction system, which is caused by all heart pathologies and negatively affects prognosis. The third topic in this series, Cardiovascular Surgery, details treatment for cardiovascular pathologies and how to regulate normal physiological functions with percutaneous or extracorporeal interventions.

Meet the Series Editor



After completing his studies at the Medicine Faculty of Istanbul University in 1990, Prof. Kaan Kirali fulfilled his mandatory medical service and commenced his residency training at Koşuyolu Heart and Research Hospital in 1992. Following five years of assistant education, he pursued further training in England and the USA in 1998. Specializing in laparoscopic and minimally invasive cardiac surgery, he earned the titles of consultant cardiovascular surgeon in 1998, Assistant Professor in 1999, Associate Professor in 2002, and Chief in 2005 at the same hospital. Prof. Kirali also developed an interest in preventive medicine, obtaining an MSc in Public Health from Istanbul University in 2000. Over the past two decades, he has concentrated his scientific pursuits on cardiovascular repairs requiring specialized experience. With his expertise in coronary artery surgery, minimally invasive cardiac surgery, valve repair, and aortic root surgery, he has established new methods for awake coronary bypass revascularization, a new surgical approach for AVR during first and re-operations, aortic valve-sparing procedure, and radiofrequency ablation. Notably, he pioneered awake complete coronary artery bypass grafting (CABG) with bilateral internal mammary arteries (BIMA) and played a crucial role in advancing aortic root surgery with a new aortotomy incision, simplifying aortic valve interventions. Since the year 2000, Prof. Kirali has expanded his interests to heart transplantation, and in recent years, to left ventricular assist devices. He has served as the head of the transplantation department since 2015 and currently continues his work as the director of Koşuyolu High Specialization Education and Research Hospital in Istanbul, Turkey. In his prolific career, he has authored numerous papers in SCI journals, contributed to various book chapters, and served as an editor and reviewer for multiple academic journals. Additionally, he has edited several international books in the field of cardiovascular medicine.

Meet the Volume Editor



Ana Ciobanu obtained her medical degree in 2009 from the University of Medicine and Pharmacy „Carol Davila”, Bucharest, Romania, and her Ph.D. in 2015. She currently works as a cardiologist in the Cardiology Department at the “Prof. Agrippa Ionescu” Emergency Clinical Hospital. She is a Lecturer at the Faculty of Medicine, University of Medicine and Pharmacy „Carol Davila” in Bucharest, Romania. Her primary research preoccupation is in the non-invasive arrhythmic risk assessment. Her findings demonstrated the usefulness of various electrocardiographic and Holter parameters, including heart rate variability, as markers of arrhythmogenicity across different conditions, and also contributed to a better characterization of the electromechanical physiological correlations. Dr. Ciobanu has actively participated in numerous national and international congresses, presenting her findings through both oral and poster presentations. She has authored more than 40 peer-reviewed publications in cardiology, as well as two books and four book chapters.

Contents

Preface	XIII
Chapter 1 Introductory Chapter: Heart Rate Variability, a Clinical Biomarker with a Broad Range of Applications <i>by Ana Ciobanu</i>	1
Chapter 2 Cardiac Autonomic Regulation: Emerging Biomarkers and Clinical Implications <i>by Rahul Kumar</i>	7
Chapter 3 Heart Rate Variability in Myocardial Infarction: A Marker of Autonomic Dysfunction and Clinical Prognosis <i>by İmran Ceren</i>	25
Chapter 4 Correlations between Heart Rate Variability and Liver and Pancreatic Diseases <i>by Alexandra Mincă, Adina Rusu, Cezarina Lupașcu, Raluca Bursuc, Alina Rîpă, Claudiu Popescu, Amalia Călinoiu and Manuela-Elena Vanghele</i>	39
Chapter 5 Perspective Chapter: Heart Rate Variability in Rheumatic Diseases <i>by Cristina Andreea Vrâncianu, Dragoș Ionuț Mincă, Oana Andreea Popa, Ana Maria Gheorghiu, Luminița Florentina Tomescu and Ana Ciobanu</i>	61

Preface

The assessment of cardiac autonomic activity is known to provide prognostic information in various health conditions and diseases. The analysis of heart rate variability (HRV) has been widely utilized as a non-invasive tool to assess autonomic nervous system function and predict patient outcomes. Traditionally used for arrhythmic risk stratification in cardiology, in heart failure and myocardial infarction, and as a diagnostic marker of diabetic autonomic neuropathy, HRV has significantly expanded its clinical applications in recent years, as research has revealed new insights.

This book provides an overview of the HRV pathophysiological correlates, clinical relevance, and outlines recent advances in this field.

The introductory chapter, “Heart Rate Variability, a Clinical Biomarker with a Broad Range of Applications”, outlines the main applications of HRV in current clinical practice. The second chapter, “Cardiac Autonomic Regulation: Emerging Biomarkers and Clinical Implications”, describes the clinical significance of HRV and the physiological and pathophysiological links between the biomarkers of autonomic activity and the cardiovascular system. The next chapter, “Heart Rate Variability in Myocardial Infarction: A Marker of Autonomic Dysfunction and Clinical Prognosis”, presents a thorough discussion of the pathophysiology of autonomic nervous system dysfunction following myocardial infarction, its relationship with HRV, and the clinical implications of this relationship, emphasizing the prognostic value of HRV in this patient group, as documented in clinical studies. The last two chapters, “Correlations between Heart Rate Variability and Liver and Pancreatic Diseases” and “Perspective Chapter: Heart Rate Variability in Rheumatic Diseases”, address the current evidence regarding the role of HRV assessment in gastroenterological and rheumatic diseases.

Therefore, as outlined in the chapters, HRV has shown its usefulness for monitoring and prognostic assessment across a wide range of diseases in various medical specialties. It also has the potential to become an essential biomarker for personalised medicine. Contemporary wearable devices now facilitate HRV tracking, enabling its real-time assessment in both inpatient and outpatient environments. These technologies enhance patients’ adherence and engagement in monitoring and therapeutic interventions, supporting personalized care.

Despite all the advances in the field, multiple challenges remain. To fully integrate HRV into routine clinical practice, future efforts should focus on developing standardized measurement protocols and conducting prospective clinical trials using the new digital health technologies. HRV is a promising, non-invasive, readily available,

and cost-effective tool, with a growing body of evidence supporting its usefulness for early diagnosis, risk stratification, and therapeutic monitoring across a broad range of medical conditions.

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Introductory Chapter: Heart Rate Variability, a Clinical Biomarker with a Broad Range of Applications

Ana Ciobanu

1. Introduction

The evidence on the link between the sympathetic-parasympathetic imbalance and the risk for arrhythmias, including sudden cardiac death, led to the development of methods for assessing the autonomic nervous system activity [1]. The most widely used of these techniques is heart rate variability (HRV), which offers the advantages of being non-invasive, easy to use, and readily available. HRV measures the variations in the time intervals between successive heartbeats, being a marker of the interactions between the sympathetic and parasympathetic nervous systems. Traditionally used to assess diabetic autonomic neuropathy and to stratify arrhythmic risk after acute myocardial infarction, HRV has broadened its clinical use in recent years.

The most extensively studied clinical applications of HRV are in cardiology, with the strongest clinical evidence for its mortality and arrhythmic risk predictive value in heart failure and myocardial infarction, with lower HRV being associated to worse prognosis, poorer functional classes, and higher hospitalisation rates [1].

The identification of autonomic neuropathy, a complication of diabetes mellitus that is characterised by altered HRV, is another commonly used clinical application. The changes in HRV parameters are associated with a poor prognosis and typically occur before the neuropathy becomes overt clinically [1]. The American Diabetes Association recommends autonomic testing with HRV assessment for all patients with type 2 diabetes at the time of diagnosis and for those with type 1 diabetes 5 years later [2], as a screening strategy for cardiovascular autonomic neuropathy.

In critical care, HRV has shown potential predictive value for hemodynamic changes [3] and the success of weaning from mechanical ventilation in critically ill patients [4].

Due to the direct modulation of HRV by the nervous system, various clinical applications in neurology have also been investigated. For instance, alterations in HRV have been observed in individuals with treatment-resistant epilepsy, particularly around seizures [5]. Additionally, specific changes in HRV parameters have been associated with sudden unexpected death in epilepsy [5, 6]. In stroke patients, it has been demonstrated that changes in HRV parameters correlate with the degree of neurological impairment, recovery potential, complications, and mortality rates [7]. Reduced HRV has also been linked to several neurological conditions, such as multiple sclerosis, myasthenia gravis, Parkinson's disease, and amyotrophic lateral sclerosis, as well as cognitive decline [2].

Recent advancements in the rehabilitation field have led to HRV playing an important role in monitoring and intervention guidance. Individualised exercise prescriptions are made using HRV-guided training for patients undergoing cardiac, pulmonary, and general rehabilitation programmes [8, 9]. Stress reduction, pain management, recovery from stroke, traumatic brain injury, and chronic pain syndromes are all aided by HRV biofeedback, which uses paced breathing to increase vagal tone [10, 11].

HRV has also been used in psychology and psychiatry, where it is being investigated as a biomarker of treatment response, emotional control, and autonomic regulation [12]. Reduced HRV, which reflects impaired vagal tone, is frequently observed in clinical patients with major depressive disorder [12], anxiety disorders [13], and post-traumatic stress disorder [14]. This altered HRV is associated with higher symptom severity, an increased risk of relapse, and poorer responses to therapeutic interventions.

In recent years, numerous HRV applications have emerged in various fields, including rheumatology, gastroenterology, surgery, anesthesiology, paediatrics, haematology, and oncology [2].

Large prospective longitudinal trials on HRV in several clinical specialities are still lacking, despite the fact that commercially available devices provide an accessible option for HRV measurement. Limitations arise primarily from methodological heterogeneity and lack of standardisation, with different HRV parameters analysed and varying recording durations, as well as potential confounding factors, such as concomitant medications altering HRV and comorbid cardiovascular diseases.

2. Conclusions

HRV has evolved from a research tool to a clinical biomarker with a wide range of applications. Its predictive and therapeutic roles are both supported by continuously growing data. Its non-invasiveness and cost-effectiveness make it accessible in both inpatient and outpatient settings. To fully incorporate HRV into clinical practice, standardised measurement protocols, longitudinal research trials, and enhanced integration with digital health technologies are necessary. HRV has the potential to become a helpful biomarker for personalised medicine, supporting risk assessment, targeted therapies, and monitoring for a wide range of illnesses across numerous clinical specialities.

This book aims to provide a comprehensive overview of heart rate variability, describing the measurement methods, its clinical relevance and recent advancements in this dynamic field.

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Cardiac Autonomic Regulation: Emerging Biomarkers and Clinical Implications

Rahul Kumar

Abstract

Cardiovascular homeostasis is maintained through the coordinated activity of the sympathetic and parasympathetic nervous systems of the autonomic nervous system (ANS). The dysregulation of this equilibrium causes the advancement of cardiovascular illnesses (CVDs), including hypertension, heart failure, arrhythmias, and sudden cardiac death. Studies have revealed that newly developed indicators, including baroreflex sensitivity, QT variability index, catecholamine levels, inflammatory cytokines, neuropeptides, and heart rate variability (HRV), continue to be fundamental non-invasive biomarkers for evaluating autonomic function. These biomarkers have demonstrated significant diagnostic and predictive value across a range of clinical disorders, providing valuable insights into the underlying mechanisms of autonomic dysfunction. However, real-time, continuous autonomic function monitoring has become possible with advancements in wearable technology, biosensors, and machine learning. The clinical implications of these biomarkers are examined, with a focus on their utility for risk assessment, early diagnosis, and therapy monitoring. Additionally, the potential of current developments in AI-driven models for autonomic evaluation and machine learning in customized medicine is explored. Additionally included are methodological issues, such as data collection, signal processing, and standardization. Hence, these approaches have the potential to improve patient outcomes. However, challenges such as inter-individual variability, lack of standardized protocols, and limited clinical adoption persist. Therefore, a narrative review was conducted to describe the role of autonomic biomarkers that can be used as accurate and early predictors of cardiovascular disease. HRV has shown promise for some illnesses as a non-invasive, user-friendly, and economical tool for early disease identification, prognosis, mortality prediction, disease monitoring, and biofeedback therapy.

Keywords: autonomic nervous system, biomarker, cardiovascular illnesses, heart rate variability, inflammatory markers

1. Introduction

The cardiovascular system is subject to precise reflex control, ensuring a sufficient flow of oxygenated blood to tissues [1]. Cardiac autonomic modulation is the process

by which the sympathetic and parasympathetic branches of the autonomic nervous system (ANS) regulate and synchronize cardiac activities [2]. Moreover, studies suggest that the autonomic nervous system is essential for regulating heart rate, blood pressure, myocardial contractility, and vascular tone, which maintain cardiovascular homeostasis [3]. Previous studies reported that ANS, which regulates the human circulatory system in a complex manner, dynamically balances hemodynamic stability, homeostasis, and sympathetic and parasympathetic activity [4]. Goldberger and co-authors suggested that both internal and external physiological demands and cardiac autonomic control are essential for regulating heart rate, myocardial contractility, and vascular tone [5]. Moreover, the pathophysiology of several CVDs, including hypertension, arrhythmias, sudden cardiac death, and heart failure, is increasingly linked to dysregulation of autonomic tone [6, 7].

Review of the literature suggested that the ANS is a sophisticated neurological network that uses complementary thoracolumbar sympathetic and craniosacral parasympathetic channels to innervate every organ [8]. Further, studies suggested that autonomic outflow to cardiac and vascular targets is reflexively modulated in response to changes in arterial pressure and blood gas levels [9]. In addition, elevated arterial pressure lowers heart rate and sympathetic tone via activating parasympathetic preganglionic neurons in the nucleus ambiguus and dorsal motor nucleus of the vagus [10]. Moreover, the reflex route, such as baroreceptors and carotid chemoreceptors, ensuing changes lessens peripheral vasoconstriction, lowers circulating catecholamine levels from the adrenal medulla, and decreases noradrenergic activation of the sinoatrial node and myocardium [11]. On the other hand, cardiovascular stability is maintained because the increased cholinergic parasympathetic activity simultaneously slows ventricular conduction and reduces sinoatrial node firing [12]. The discovery of new non-invasive and molecular biomarkers that represent cardiac autonomic activity has received a lot of interest in recent years.

Heart rate variability (HRV), which is inversely correlated with cardiovascular morbidity and mortality, has become one of the most reliable markers of autonomic nervous system function among these [13]. Other indicators that have shown promise in identifying early autonomic imbalance and subclinical cardiovascular disease include plasma catecholamines, electrodermal activity, baroreflex sensitivity (BRS), and autonomic-related microRNAs [14–16].

Personalized monitoring and risk stratification are now possible due to the integration of wearable technology, biosensors, and machine-learning-based analytical platforms, which have improved the capacity to collect, analyze, and interpret these biomarkers in real time [17]. Both clinical and community-based health initiatives can benefit from these technologies' scalable solutions. On the other hand, other studies reported that the autonomic dysfunction manifests a variety of clinical symptoms, including sudomotor dysfunction, pupillary abnormalities, gastrointestinal disorders, orthostatic hypotension, and problems with the bladder or sex [18]. Thus, the clinical results can be enhanced using autonomic biomarkers to detect autonomic dysfunction early. Numerous studies have reported that one important biomarker that enables early identification of autonomic imbalance before the emergence of overt clinical symptoms is HRV, a measure of beat-to-beat variability representing sympathetic-parasympathetic balance [19]. Further, HRV helps with risk stratification, diagnosis, differentiation, severity evaluation, therapy monitoring, and the prediction of unfavorable outcomes, including sudden cardiac death [13]. In addition, biomarkers include biochemical indicators that indicate neurohormonal and inflammatory state, pupillary light reflex dynamics, and blood pressure variability [20].

In recent years, autonomic activity assessment has become essential for the emotional, cognitive, and physical neuroscientific fields and should serve as a foundation for therapeutic applications and a theoretical basis for future study [21]. Moreover, despite the ease with which autonomic imbalance may be evaluated, doctors often employ these options sparingly. This also supports a much wider use of HRV as a valid, transdiagnostic, and fully translational dynamic biomarker of stress system sensitivity and vulnerability to stress-related disorders in research and clinical practice [22]. The integration of autonomic indicators into standard clinical practice still faces significant obstacles in spite of these advancements. Authors Billman [23] suggested that inter-individual variability, the absence of standardized evaluation procedures, and a lack of knowledge of the fundamental processes cause autonomic imbalance in illness conditions [23]. Therefore, increasing our knowledge of these indicators and how to incorporate them into clinical frameworks is crucial for enhancing treatment targeting and cardiovascular prognosis.

Therefore, a narrative review of the chapter highlights that autonomic biomarkers, including autonomic-linked baroreflex sensitivity and heart rate variability, can be used as accurate and early predictors of cardiovascular disease. Clinical results for patients with cardiovascular disorders will eventually improve as a result of their integration with wearable technology and machine learning frameworks, which will also improve cardiovascular risk prediction and direct customized treatment plans.

2. Physiology of cardiac autonomic regulation

The complex interplay between the sympathetic and parasympathetic branches of the ANS governs the physiology of cardiac autonomic regulation [24]. Together, these divisions control not only cardiovascular function but also important visceral functions, such as sweating, urination, gastrointestinal motility, arterial pressure, and thermoregulation [25]. The brainstem, autonomic ganglia, or hypothalamus can receive afferent sensory information from visceral organs, which can then modify efferent responses to preserve homeostasis [26]. Before reaching effector tissues, the sympathetic nervous system (SNS) passes via preganglionic fibers that synapse in sympathetic chain ganglia or peripheral ganglia. It begins in the thoracolumbar segments (T1–L2) of the spinal cord [27]. They regulate the physiology of cardiac autonomic control. However, parasympathetic output leaves the body through sacral spinal nerves S2–S4 and cranial nerves III, VII, IX, and particularly X (vagus nerve), affecting the heart, lungs, GI tract, and pancreas, among other thoracic and abdominal viscera [28]. Acetylcholine (ACh) in cholinergic fibers and norepinephrine (NE) in adrenergic fibers are the neurotransmitters used by both divisions; ACh acts on muscarinic and nicotinic receptors, while NE acts via α - and β -adrenergic receptors [29–31]. Depending on the distribution of receptor subtypes in the target organ, these neurotransmitters can cause either excitatory or inhibitory responses [32].

The heart is a prime example of this dual modulation: parasympathetic influence, primarily through vagal efferents to the sinoatrial (SA) and atrioventricular (AV) nodes, slows heart rate and lowers conduction velocity, while sympathetic stimulation, primarily through β 1-adrenergic receptor activation distributed throughout the myocardium, increases heart rate (positive chronotropy) and myocardial contractility (positive inotropy) [33–35]. Additionally, parasympathetic stimulation has little effect on vascular tone, whereas sympathetic stimulation constricts peripheral blood

arteries, particularly in the skin and abdominal viscera [36]. Sympathetic reactions are further amplified by circulating catecholamines, such as NE and epinephrine (EP); NE raises peripheral resistance and arterial pressure, whereas EP primarily enhances cardiac output through β -receptor activation [11].

Studies also reported that the baseline of physiological preparedness is maintained due to the tonic activities, known as sympathetic and parasympathetic tone, which are always partly active [22]. The central autonomic network (CAN) integrates baroreceptor and chemoreceptor inputs to modulate cardiovascular reflexes [37]. A non-invasive biomarker of this autonomic regulation is HRV. The LF/HF ratio is a measure of sympathovagal balance: the high-frequency (HF) components represent vagal tone, and the low-frequency (LF) components represent a combination of sympathetic and parasympathetic influence [13].

The negative cardiovascular outcomes are closely linked to reduced HRV and baroreflex sensitivity (BRS), especially in aging, diabetes, and heart failure populations [14, 38, 39]. Interestingly, the two autonomic divisions frequently display organ-specific dominance even though they can work reciprocally, such as parasympathetic suppression of organs stimulated by sympathetic input [40]. The flexibility of autonomic control is reinforced by lifestyle treatments, such as stress management and physical activity, which enhance parasympathetic tone and HRV [41]. Real-time autonomic function evaluation is now possible, thanks to modern digital health technology and AI-powered monitoring, which has interesting implications in precision medicine for cardiovascular treatment [42]. In general, interpreting pathophysiological situations and enhancing diagnostic and treatment approaches in cardiovascular medicine depend on knowledge of the physiological and neurochemical underpinnings of cardiac autonomic control.

3. The autonomic nervous system and the heart

The cardiovascular system is among the best systems for the functional evaluation of ANS activity because effector tissue responses are quick, accessible, and have a high clinical and prognostic value [14]. However, more than 150 years ago, the French scientist Claude Bernard explained the intimate physiological relationship between the heart and brain [43]. Charles Darwin suggested that the heart and brain were vagally connected in his commentary on his findings, which at the time was astounding [44]. However, normal neurodevelopment and aging are closely linked to the interplay between these two vital organs in the body [19].

Changes in the brain-heart connection brought on by emotional or physical stress may impair normal development, increase susceptibility to stress, and increase the risk of all-cause morbidity and death. The atrial and ventricular myocardium, the atrioventricular (AV) node, and the sinoatrial (SA) node are among the several effector tissues found in the heart [45]. Ion channel modulation affects heart function in three different but related ways: chronotropy, inotropy, and dromotropy. This is especially true of the primary and secondary pacemakers (SA and AV node, respectively). Depending on demand, the ANS primarily affects this modulation through the tonic drives of the sympathetic and parasympathetic cardiac nerves and their asymmetric interactions.

While left-sided sympathetic nervous system (SNS) and parasympathetic nervous system (PNS) fibers innervate the AV node and myocardium, they modulate dromotropic (i.e., influencing the electrical impulse conduction between the SA and

AV nodes (PQ interval of the human ECG)) and inotropic (i.e., influencing force of contraction) activity in a similar way to right-sided SNS and PNS fibers that reach the SA node and influence, particularly, chronotropic activity (i.e., influencing frequency of contraction; SNS: positive chronotropy; PNS: negative chronotropy) [46]. The PNS, which dominates the SNS, continuously regulates resting cardiac activity by tonic inhibition [47].

Furthermore, heart rates (HR) exhibit beat-to-beat variability throughout a broad range, which suggests vagal dominance, since SNS cardiac effect is too gradual and persistent to result in abrupt beat-to-beat alterations (such as respiratory sinus arrhythmia) [48]. Because it enables both longer ventricular filling and greater myocardial contraction, simultaneous PNS and SNS cardiac co-activation results in more efficient cardiac function than SNS activation alone [49]. Autonomic imbalance, on the other hand, results in decreased functional complexity and dynamic flexibility, which in turn increases susceptibility to diseases and compromises heart health. The etiology of cardiovascular illnesses and other comorbidities is largely linked to the PNS because of its tonic inhibitory effect on the heart [50].

4. Pathophysiology of autonomic dysfunction in cardiovascular diseases

The pathophysiology and development of cardiovascular diseases (CVDs) are significantly influenced by autonomic dysfunction, which is defined by an imbalance between the sympathetic and parasympathetic branches of the autonomic nerve system (ANS). By controlling heart rate, myocardial contractility, vascular tone, and blood pressure, the sympathetic nervous system (SNS) and parasympathetic nervous system (PNS) cooperate to preserve cardiovascular homeostasis [32]. Sympathovagal balance is a dynamic equilibrium that regulates cardiovascular responses to stress and preserves stability under physiological settings. However, in pathological situations, this balance is disrupted, favoring vagal withdrawal and sympathetic dominance. This leads to endothelial dysfunction, inflammation, and an increased risk of arrhythmias, as well as structural and electrical remodeling of the heart [14, 51].

The SNS is chronically overactivated in the majority of cardiovascular diseases, especially heart failure, hypertension, and myocardial infarction. The catecholamines norepinephrine and epinephrine, which are released when sympathetic tone rises, initially act as compensatory mechanisms to preserve perfusion but eventually cause negative side effects, such as tachycardia, vasoconstriction, elevated afterload, and myocardial oxygen demand [52]. Prolonged exposure to norepinephrine causes increasing left ventricular dysfunction, unfavorable cardiac remodeling, and down-regulation and desensitization of β -adrenergic receptors. Autonomic imbalance is further exacerbated by sympathetic hyperactivity, which inhibits baroreflex sensitivity (BRS), a vital mechanism for short-term blood pressure regulation [14].

At the same time, parasympathetic withdrawal reduces cardioprotective benefits of vagal tone, such as its capacity to prevent arrhythmias, reduce inflammation, and enhance heart rate variability (HRV). The vagal modulation of sinoatrial node is reflected by the sensitive, non-invasive biomarker HRV. Particularly, after myocardial infarction and in heart failure, lower HRV is highly correlated with higher morbidity and mortality in patients with CVD [6, 13]. Additionally, vagal dysfunction disrupts the endothelium's acetylcholine-mediated nitric oxide release, leading to vascular stiffness and hypertension. This supports sympathetic dominance in a feedback loop [32]. A review of literature suggested that lower HRV is linked to a higher risk

of cardiovascular conditions, such as heart failure, myocardial infarction, and sudden cardiac death [6]. Additionally, HRV is used to track autonomic dysfunction in illnesses, such as diabetes and neurodegenerative disorders, stress, sleep quality, and physical fitness [53]. While HRV interpretation is useful, it must take into consideration a number of confounding variables, including age, medications, posture, and circadian rhythms [4]. However, HRV continues to be an essential tool for comprehending the mechanics of cardiac autonomic regulation and assessing how therapeutic treatments affect autonomic function in both clinical and experimental contexts [13].

Inflammation also connects cardiovascular disease to autonomic dysfunction. Through $\alpha 7$ -nicotinic receptors on immune cells, the vagus nerve-mediated cholinergic anti-inflammatory pathway inhibits the production of pro-inflammatory cytokines [54]. Increased levels of TNF- α , IL-6, and C-reactive protein (CRP), which are linked to atherogenesis, plaque instability, and cardiac fibrosis, result from the blunting of this pathway in autonomic dysfunction [11]. Furthermore, by producing too many reactive oxygen species (ROS), persistent sympathetic overdrive exacerbates oxidative stress, further harming cardiac and vascular tissues and affecting brainstem autonomic regions [55].

In addition to systemic consequences, diabetes and chronic ischemic heart disease are associated with structural alterations in autonomic nerves, known as cardiac autonomic neuropathy. These include decreased neurotransmission, myelinated fiber loss, and vagal efferent degeneration [39]. Such neuropathy weakens the reflex regulation of blood pressure and heart rate by reducing afferent transmission from baroreceptors and chemoreceptors. Furthermore, autonomic dysfunction activates neurohormonal systems, such as the brain natriuretic peptide (BNP) axis and the renin-angiotensin-aldosterone system (RAAS), which lead to fluid overload, vasoconstriction, and salt retention, especially in heart failure [22, 56]. Moreover, these factors—prolonged sympathetic activity, vagal withdrawal, poor reflex control, endothelial damage, inflammation, and neurohormonal dysregulation—make up autonomic dysfunction in CVD. This imbalance promotes disease development and unfavorable consequences in addition to reflecting the severity of the illness. Restoring autonomic balance and improving cardiovascular prognosis are two benefits of therapeutic interventions that target the autonomic nervous system, including β -blockers, vagal nerve stimulation, exercise training, and biofeedback [33, 42].

5. Emerging biomarkers of cardiac autonomic regulation

5.1 Heart rate variability metrics

The variation in the time intervals between successive heartbeats is known as heart rate variability (HRV), and it is a reliable, non-invasive indicator of autonomic nervous system (ANS) activity [3, 24]. Since the sympathetic and parasympathetic branches of the ANS interact dynamically to produce these beat-to-beat fluctuations, HRV is a crucial tool for evaluating cardiac autonomic control. Because of its predictive potential and simplicity of measurement, HRV has been widely used in digital health technologies, exercise physiology, mental health, and cardiovascular research during the past few decades [13].

A review of the literature suggested that each of the three types of HRV metrics—time-domain, frequency-domain, and nonlinear measures—offers a distinct

perspective on autonomic function. Time-domain measurements examine changes over a certain length of time in the intervals between consecutive normal heartbeats (NN intervals). Typical metrics include root mean square of successive differences (RMSSD), a measure sensitive to short-term, high-frequency fluctuations associated with parasympathetic activity, and standard deviation of NN intervals (SDNN), which represents overall HRV and long-term cyclic components [4]. Another parasympathetic measure that is commonly employed in clinical and research contexts is pNN50, which is the proportion of neighboring NN intervals that deviate by more than 50 ms.

In frequency-domain analysis, the NN interval series is converted into the frequency spectrum, usually with the use of autoregressive models or the Fast Fourier Transform (FFT). These techniques break down HRV into three primary parts: low-frequency (LF) power (0.04–0.15 Hz), which is typically regarded as a sign of both sympathetic and parasympathetic activity; high-frequency (HF) power (0.15–0.40 Hz), which represents parasympathetic (vagal) modulation; and very low-frequency (VLF) power (<0.04 Hz), whose physiological causes are less clear but may include thermoregulation and the renin-angiotensin system [57]. Although the LF/HF ratio is frequently used to evaluate sympathovagal balance, its interpretation is still debatable because autonomic regulation is nonlinear and context-dependent [58].

Additional information on the intricate and fractal structure of cardiovascular control that linear measurements could miss is provided by nonlinear HRV metrics [59]. These include entropy-based metrics, such as Approximate Entropy (ApEn) and Sample Entropy (SampEn), which measure the predictability and regularity of the heart rate time series, and parameters derived from Poincaré plots, such as short-term variability (SD1) and long-term variability (SD2) [3]. While lower numbers suggest less complexity found in pathological situations, including heart failure, diabetes, and depression, higher values often reflect healthy, adaptive autonomic responses [9].

Numerous therapeutic and prognostic applications have found value in HRV measurements. In addition to being linked to poor prognoses in heart failure, diabetic neuropathy, and sudden cardiac death, reduced HRV is a powerful independent predictor of mortality after myocardial infarction [60, 61]. Reduced vagal flexibility is reflected in decreased HRV, which is associated with anxiety, sadness, and poor emotional regulation in psychiatric settings [6]. Additionally, HRV monitoring is being utilized more and more in occupational medicine and sports to evaluate training adaption, stress, tiredness, and recovery.

Continuous HRV monitoring utilizing photoplethysmography (PPG), electrocardiography (ECG), or smartphone-based sensors is now possible because of the advancements in wearable technology. In addition to offering new tools for remote health monitoring and biofeedback therapies, this has made it possible to measure autonomic reactions in real time in ambulatory settings [42]. Confounding variables, including age, circadian cycles, posture, respiratory rate, and medication use, must be taken into account while doing an HRV study. Hence, HRV measures have enormous clinical and technical significance and provide a comprehensive understanding of autonomic function. HRV is positioned to become a key component of predictive and customized medicine in the fields of neurology, behavioral science, and cardiology as its integration with wearable biosensors, artificial intelligence, and mobile health platforms continues to expand.

5.2 Emerging biomarkers of cardiac autonomic regulation

A key component of cardiovascular homeostasis is cardiac autonomic regulation, which is controlled by the dynamic interaction of the sympathetic and parasympathetic nervous systems. Numerous cardiovascular illnesses (CVDs), such as arrhythmias, heart failure, hypertension, and sudden cardiac death, are linked to disruptions in this control [62]. Therefore, finding trustworthy biomarkers that accurately represent the state of autonomic function has emerged as a key research topic for risk assessment, treatment monitoring, and early diagnosis. Heart rate variability (HRV)—a non-invasive measure that measures beat-to-beat changes in heart rate as a proxy for vagal tone and sympathovagal balance—is one of the most well-established biomarkers [3, 24]. Lower HRV is consistently linked to a higher risk of sudden death and cardiovascular mortality, particularly after myocardial infarction [6, 13].

HRV measurements in the time, frequency, and nonlinear domains provide comprehensive information about autonomic modulation and are more often combined with wearable technology for ongoing monitoring. Another physiological indicator that has been proven to be accurate is baroreflex sensitivity (BRS), which shows how autonomic dysfunction impairs the heart's reflexive response to variations in blood pressure [63]. According to La Rovere et al., a low BRS can predict the development of heart failure and arrhythmic death [14]. Ventricular repolarization instability, which is frequently exacerbated under sympathetic dominance, is also measured by the QT variability index (QTVI) [64, 65]. Arrhythmogenic risk is correlated with elevated QTVI, particularly in individuals with long QT syndromes or cardiac failure [66]. Furthermore, although their clinical use is currently restricted, pupillometry and sympathetic skin response (SSR) have been investigated for assessing the sudomotor and ocular autonomic pathways [67].

Catecholamines in the blood, such as norepinephrine and epinephrine, are direct biochemical markers of sympathetic activity. β -adrenergic receptor desensitization and unfavorable cardiac remodeling are linked to chronically increased catecholamines, which are seen in heart failure and hypertension [38]. Alternatively, decreased acetylcholinesterase (AChE) activity may indicate decreased vagal tone and operate as a stand-in for parasympathetic function [68]. Furthermore, it is becoming more well acknowledged that inflammatory biomarkers, including C-reactive protein (CRP), tumor necrosis factor- α (TNF- α), and interleukin-6 (IL-6), are downstream markers of autonomic dysfunction. Atherosclerosis, myocardial fibrosis, and arrhythmias are caused by pro-inflammatory cytokines that are elevated when vagal withdrawal disrupts the cholinergic anti-inflammatory system [50, 54].

The significance of neuropeptides, such as substance P, vasoactive intestinal peptide (VIP), and neuropeptide Y—which regulate autonomic output and aid in cardiovascular remodeling during stress—has also been brought to light by recent developments. Particularly, elevated levels of neuropeptide Y have been connected to the severity of heart failure and are linked to cardiac sympathetic hyperactivity [69]. On the molecular level, genes implicated in cardiac excitability and neurogenic inflammation are targeted by microRNAs (miRNAs), such as miR-133a, miR-1, and miR-21, which have become epigenetic regulators of autonomic remodeling [70]. Furthermore, alterations in autonomic responsiveness and cardiovascular risk profiles are linked to genetic variations in autonomic genes, including nitric oxide synthase 3 (NOS3), cholinergic receptor muscarinic 2 (CHRM2), and β 1-adrenergic receptor (ADRB1) [71–73].

Wearable-derived indicators are becoming more popular in the age of digital medicine. Real-time, continuous evaluation of autonomic function in ambulatory situations is provided via electrodermal activity (EDA), smartwatch-detected arrhythmias, and photoplethysmography (PPG)-based HRV. Preventive measures are made possible by these digital indicators' ability to identify subclinical shifts in autonomic tone prior to the manifestation of clinical symptoms [42]. Moreover, the sensitivity and specificity of autonomic dysfunction identification can be improved using machine learning algorithms to multimodal data, such as skin conductance, respiration, and HRV [74]. Moreover, the field of cardiac autonomic biomarkers is fast growing and now includes digital, molecular, physiological, and biochemical domains. By facilitating early identification, individual risk assessment, and therapy effectiveness monitoring, these new markers have great potential to enhance the clinical management of CVDs. To reach their full translational potential, however, more standardization, validation in sizable populations, and integration into clinical procedures are required.

Therapeutic and Prognostic Applications of Heart Rate Variability (HRV).

A non-invasive biomarker with substantial therapeutic usefulness is heart rate variability (HRV), which measures the variations in heart rate from beat to beat. It has applications in neurology, psychology, immunology, and sports medicine in addition to cardiovascular physiology. The many therapeutic and prognostic uses of HRV are examined in this part, with a focus on how it might be used for illness risk assessment, therapy response tracking, and intervention customization.

6. Prognostic significance of HRV in clinical disorders

6.1 Cardiovascular disease

ANS dysfunction causes the anomalies in HRV parameters, which can be used as a diagnostic tool to evaluate the prognosis of cardiac illnesses [75]. Moreover, the atherosclerosis-driven cardiovascular illnesses and other conditions have also been influenced by heart rate variability (HRV) characteristics [34, 35]. Further, studies reported that time-domain metrics help in the diagnosis of other CVD illnesses, such as CAD, MI, and heart failure [76]. In addition, reduced HRV is associated with a two-fold increased risk of myocardial ischemia in individuals [3]. Further, lower high-frequency (HF) power and low standard deviation of NN intervals (SDNN) are consistently linked to greater death rates after myocardial infarction (MI) [77]. Similarly, reduced HRV is associated with worse left ventricular function and increased sympathetic dominance in congestive heart failure (CHF), which makes it a predictor of sudden cardiac death [4].

A review of the literature has also suggested that a stroke can significantly affect the parts of the brain that control the ANS, especially the brainstem and hypothalamus, when it comes to damage to the central nervous system [78]. Stable HRV depends on the balance between parasympathetic and sympathetic activity, which is maintained in these domains [79]. Hence, autonomic function may be severely disrupted when there is damage to the brainstem, particularly to regions that are essential for cardiovascular control, such as the dorsal motor nucleus of the vagus nerve and the nucleus of the solitary tract. Further, a discernible drop in HRV is frequently the result of an imbalance between the sympathetic and parasympathetic neural systems.

6.2 Diabetes and metabolic syndrome

Diabetes is characterized by increased levels of glucose. The cardiac autonomic neuropathy (CAN) is a major risk factor for cardiovascular damage that can lead to heart attacks, congestive heart failure, and strokes. Studies have also revealed that CAN plays a crucial role in the pathogenesis of progressive vessel atherosclerosis [80]. However, subclinical cardiac dysfunction, interstitial myocardial fibrosis, and metabolic alterations are intimately linked to diabetic autonomic neuropathy [81]. Furthermore, CAN considerably raises the incidence of CVDs and the mortality associated with them [82]. It is unknown whether CAN and the severity of coronary lesions in T2DM patients are independently correlated [83].

6.3 Psychosomatic disorders

A complex interplay of cultural, environmental, and psychological variables contributes to the prevalence of psychosomatic disorders. Gaining knowledge about HRV's function and potential as an indicator of adaptation might help manage and avoid psychosomatic disorders in this heterogeneous group [84]. Healthcare practitioners may evaluate the effects of psychological, environmental, and cultural variables on heart health and create focused treatments to enhance patient outcomes by tracking variations in HRV. HRV is a useful tool for identifying the particular difficulties associated with psychosomatic disorders. Shatri et al. [85] examined the characteristics of patients with psychosomatic diseases at Cipto Mangunkusumo Hospital in Jakarta, Indonesia [85]. However, 80% of patients had functional psychosomatic disorders (FPD) with illnesses such as numerous psychosomatic syndromes, dyspepsia, and functional heart disease, according to a comparison of FPD and structural psychosomatic disorders (SPD) [85]. By contrast, 20% had SPD, primarily resulting from long-term conditions, including diabetes and hypertension. Moreover, anxiety and sadness were the most common psychiatric illnesses, and common psychosocial stresses included issues at work, with family, and with physical ailments. Furthermore, HRV metrics that reveal reduced vagal activity during stress, such as the root mean square of successive differences (RMSSDs) and the proportion of consecutive normal cardiac interbeat intervals longer than 50 ms (pNN50), typically exhibit decreases. Hence, these alterations can act as functional measures of autonomic dysregulation and are consistent with psychological, physical, and environmental stress. Further, they offer important insights into how stress affects both psychological and physiological health [86, 87].

6.4 HRV biofeedback therapy

The progressive return of autonomic balance and improved physiological resilience may be indicated by improvements in HRV measurements, such as elevated high-frequency power or normalized time-domain indices. Studies revealed that patients with enhanced HRV during motor therapy, indicated by physical performance battery and handgrip strength tests, had superior functional results in comparison to those with lower HRV. This implies that HRV might be a responsive parameter linked to treatment effectiveness, in addition to being a passive signal [88]. However, there is mounting evidence that HRV may be used as a feedback mechanism to assess the effectiveness of rehabilitation programs. Studies suggest that, with optimized functional gains and recovery time, physicians can customize rehabilitation programs

through routine HRV measurements [88, 89]. Hence, a patient's HRV stagnating or declining during therapy suggests a sign of inadequate autonomic recovery or over-exertion [90]. Further, clinicians may modify the regimen by adding more cardiovascular conditioning, stress-reduction strategies, or modifying intensity to correspond with physiological capacity.

7. Conclusion and future perspectives

Cardiac autonomic regulation is crucial for maintaining cardiovascular homeostasis by balancing sympathetic and parasympathetic inputs. Dysregulation of this balance contributes to cardiovascular diseases, such as hypertension, heart failure, arrhythmias, and sudden cardiac death. Classical physiological mechanisms and modern non-invasive biomarkers, such as heart rate variability (HRV), are essential for understanding autonomic function. The integration of wearable devices, biosensors, and machine learning platforms offers opportunities for early detection, continuous monitoring, and personalized management of autonomic dysfunction. However, challenges remain, including inter-individual variability, lack of standardization in measurement protocols, and limited clinical adoption of autonomic biomarkers. The present HRV literature is quite heterogeneous, which restricts its clinical practice application. Nevertheless, despite the overcomable research challenges, applications of HRV in critical care and some chronic illnesses show enough evidence to support clinical implementation.

Future research should focus on validating these biomarkers across diverse populations and pathologies, enhancing our understanding of autonomic imbalance, and translating these findings into routine practice. This will lead to better cardiovascular risk prediction, more precise therapeutic targeting, and improved patient outcomes. The convergence of traditional HRV metrics with innovative autonomic biomarkers and digital tools is shaping a more predictive, preventive, and personalized approach to cardiovascular healthcare, promising improved outcomes in patients with cardiovascular and autonomic disorders and setting the stage for next-generation translational research and clinical practice. Moreover, the future of cardiac autonomic regulation research will involve the integration of advanced biosensing technologies, artificial intelligence, and personalized healthcare technologies, which will enable early diagnosis, dynamic risk stratification, and personalized intervention strategies. Therapeutic modulation of autonomic tone through non-invasive techniques and digital therapeutics will lead to targeted therapies. The integration of autonomic biomarkers into public health surveillance and chronic disease management platforms will provide population-level screening and proactive prevention of cardiovascular events.

Acknowledgements

The authors thank Usha Martin University, Ranchi, India, for its support. They also thank Dr. Yogender Aggarwal, Assistant Professor, Birla Institute of Technology Mesra, Ranchi, for his valuable suggestions for the improvement of the book chapters.

Funding source

Not any.

Conflict of interest

The authors declare that they have no conflict of interest.

Data availability

Not any.

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Heart Rate Variability in Myocardial Infarction: A Marker of Autonomic Dysfunction and Clinical Prognosis

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Abstract

Myocardial infarction (MI) continues to be a major contributor to global cardiovascular morbidity and mortality, despite advancements in revascularization techniques such as percutaneous coronary intervention (PCI). Recent attention has shifted toward evaluating the autonomic nervous system (ANS) as a key determinant of post-infarction prognosis. Heart rate variability (HRV), a non-invasive marker of autonomic regulation, has emerged as a sensitive tool for assessing cardiac autonomic dysfunction and stratifying cardiovascular risk following MI. Decreased HRV—particularly reductions in time-domain parameters such as standard deviation of normal RR intervals (SDNN) and the root mean square of successive RR interval differences (RMSSD), and altered low-frequency/high-frequency (LF/HF) ratios—has been consistently associated with increased incidence of arrhythmias, major adverse cardiovascular events (MACE), and mortality in both acute and long-term settings. Studies indicate that early reperfusion improves HRV indices, reflecting restored autonomic balance, whereas persistent HRV impairment signals poor prognosis even after successful PCI. Furthermore, advancements in wearable technologies and artificial intelligence have enabled real-time HRV monitoring, expanding its clinical applicability. Incorporating HRV into conventional risk assessment models may enhance the identification of high-risk patients and guide individualized therapeutic strategies. This chapter reviews the physiological underpinnings, measurement methods, clinical relevance, and prognostic value of HRV in the context of MI, with a focus on its potential as an integrative tool in future cardiovascular care.

Keywords: myocardial infarction, heart rate variability, autonomic dysfunction, cardiovascular risk assessment, cardiac functions

1. Introduction

Myocardial infarction (MI) is one of the most critical clinical conditions in modern cardiovascular medicine and continues to be a predominant factor contributing to

both mortality and morbidity worldwide [1, 2]. Recent studies in this field aim not only to focus on structural heart damage but also to gain a more comprehensive understanding of the disease's pathophysiology by considering its effects on the autonomic nervous system (ANS) [3–5].

Acute coronary syndrome (ACS) is a cardiovascular emergency that requires immediate intervention. Its pathophysiology typically involves thrombosis caused by the growth, instability, and rupture or erosion of atherosclerotic plaques [6, 7]. In clinical practice, ACS is categorized into three distinct classifications: ST-elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction (NSTEMI), and unstable angina [8, 9]. Among these, STEMI represents the most severe clinical presentation. Thrombosis following plaque rupture leads to a sudden and significant reduction in myocardial perfusion [1, 3, 7].

Percutaneous coronary intervention (PCI) is presently acknowledged as the benchmark therapeutic approach for STEMI, significantly improving both immediate and prolonged clinical outcomes [6]. However, despite successful PCI, some individuals exhibit a sustained elevated susceptibility to major adverse cardiovascular events (MACE) during the post-discharge period. These events may include angina, recurrent infarction, repeated revascularization, heart failure, and cardiovascular death [10, 11]. Thus, early identification of high-risk patients and the implementation of targeted interventions are critical for improving long-term prognosis.

The heart is continuously influenced by the sympathetic and parasympathetic tone of the ANS, which dynamically regulates heart rate and rhythm. Although ANS imbalance during the acute phase of ACS can be seen as a compensatory mechanism to maintain cardiovascular and systemic homeostasis, its persistence in a disrupted form can lead to severe clinical consequences [12].

At this point, heart rate variability (HRV) emerges as a non-invasive and sensitive parameter that evaluates the balance between sympathetic and parasympathetic tone by analyzing the time intervals between heartbeats [13, 14]. HRV is typically assessed through 24-hour ambulatory electrocardiographic (ECG) monitoring, which continuously records the heart's electrical activity and is highly valuable for diagnosing intermittent arrhythmias and atypical chest pain—conditions that are often difficult to detect using standard ECG [15–17].

Numerous studies have shown that HRV is correlated with mortality risk in cardiovascular diseases [18]. Furthermore, HRV is an important biomarker for assessing the risk of arrhythmias in patients who have experienced MI [19, 20]. In STEMI patients, Holter monitoring is not only essential for arrhythmia surveillance but also plays a key role in long-term risk stratification and optimizing treatment planning [21, 22].

This section will explore in detail the pathophysiology of ANS dysfunction following MI, its interaction with HRV, and the clinical implications of this relationship.

2. Heart rate variability and myocardial infarction

2.1 Physiological basis and measurement methods of HRV

HRV, a marker of ANS function, has long been recognized as a valuable prognostic tool in cardiovascular diseases [4]. HRV can be analyzed using both short-term (typically 5 minutes or shorter) and long-term (usually 24-hour) recordings [23]. Despite the difference in recording duration, reduced HRV is consistently observed in patients with preexisting conditions in both approaches [23].

There are various commercially available devices for measuring HRV. The European Society of Cardiology and the North American Society of Pacing and Electrophysiology developed recommendations through a joint Task Force, which identified multi-lead ECG Holter monitoring as the gold standard for HRV analysis [24]. These systems provide a comprehensive assessment by capturing responses to multiple environmental stimuli. The equipment's intricacy and the strain it places on patients and healthcare professionals are its main drawbacks, though. Alternative methods include blood pressure monitors, pulse oximetry, photoplethysmography, single-lead ECG, and heart sound auscultation. Modern advancements like adhesive single-lead ECG patches and mobile applications with wearable wrist or chest sensors have made HRV monitoring more affordable and accessible, even if auscultation and pulse oximetry are rarely employed for HRV evaluation [25–27].

The clinical use of HRV has been limited by the dependency on 24-hour ECG recordings, which are often impractical for real-time monitoring in acute clinical settings [28]. To overcome this limitation, wearable technologies have been validated and shown to provide accurate HRV measurements, offering a practical alternative to conventional ECG-based systems [28].

Initially used in physiological research to assess autonomic function, HRV is calculated via mathematical formulas using computer-assisted software [23]. HRV measurement techniques are generally categorized into three domains: time-domain, frequency-domain, and nonlinear dynamics [24, 29–31].

Time-domain analyses estimate variations in sinus RR intervals using statistical measures. Common parameters include the standard deviation of normal RR intervals (SDNN), the root mean square of successive RR interval differences (RMSSD), and the proportion of consecutive RR intervals that differ by more than 50 ms (pNN50) [24, 32].

Frequency-domain analysis involves spectral density estimation to assess HRV [24, 33]. This method applies mathematical algorithms to quantify the power of cyclic variations in heart rhythm over time. Frequency bands include high-frequency (HF: 0.15–0.40 Hz), low-frequency (LF: 0.04–0.15 Hz), and very-low-frequency (VLF: 0.003–0.04 Hz) components [24, 32]. Indices such as HF, pNN50, and RMSSD reflect parasympathetic activity, while the LF/HF ratio represents the sympathovagal balance [34]. SDNN is considered a marker of overall autonomic tone [35].

Nonlinear dynamic methods capture complex physiological signal interactions and are based on principles of chaos theory, fractal analysis, and system complexity [36–41]. These approaches provide insights into signal randomness and correlation patterns that go beyond what time- and frequency-domain measures can detect [29, 41]. Thanks to advances in bioengineering, these techniques have become more accessible in recent years.

Overall, HRV indices reflect the dynamic interplay between parasympathetic and sympathetic branches of the ANS, and alterations in this balance are believed to be associated with increased cardiovascular risk [29].

2.2 Autonomic dysfunction and HRV alterations following myocardial infarction

The two main ANS branches, the sympathetic nervous system (SNS) and the parasympathetic nervous system (PNS), cooperate to control the body's hemodynamic reactions [42]. HRV serves as a noninvasive marker of cardiac autonomic modulation [42]. In patients with MI, HRV is diminished due to enhanced sympathetic activity and/or reduced parasympathetic input. This decline in HRV has consistently been linked to an elevated risk of adverse cardiovascular events and increased mortality [43, 44].

The intrinsic activity of the sinoatrial node is influenced by both branches of the ANS—vagal input from the PNS and adrenergic stimulation from the SNS—making the heart rate a reflection of the dynamic balance between these two systems [45]. HRV quantifies the variation in time intervals between successive heartbeats and can be analyzed via time and frequency domain parameters [43, 45]. Time domain indices represent the overall degree of variability, with abnormally low values suggesting autonomic dysfunction. In contrast, higher values may indicate either a healthy autonomic tone or potentially unstable rhythm. Similarly, in frequency domain analysis, reduced values imply impaired autonomic regulation [46, 47].

Numerous studies over recent decades have confirmed that decreased HRV, reflecting cardiac autonomic dysfunction, is strongly linked to a higher incidence of mortality and life-threatening ventricular arrhythmias in patients who have suffered an acute myocardial infarction (AMI). Bonnemeier et al. [48] demonstrated this association in a study of 123 AMI patients who underwent primary PCI. HRV parameters derived from 24-hour two-lead Holter ECG recordings showed significant improvements in both time and frequency domains following early reperfusion, suggesting a restoration of autonomic balance. Notably, HRV values were significantly lower in patients who received late reperfusion therapy. These findings highlight the beneficial role of prompt reperfusion in attenuating cardiac autonomic impairment and improving clinical outcomes in AMI.

Sedziwy et al. [49] further evaluated HRV changes over a 1-year period in 65 patients with or without prior MI, all of whom underwent successful and uncomplicated PCI. Their findings revealed a significant enhancement in time domain HRV parameters during the first 3 months post-PCI, with stability observed through the 6- and 12-month follow-ups. These changes indicated improved autonomic modulation and a shift toward increased parasympathetic influence, detectable as early as 2 weeks post-PCI and sustained for up to a year.

Despite these findings, limited data exist on the progression of HRV in patients who do not undergo primary PCI or thrombolytic therapy, particularly those managed conservatively. Addressing this gap, Bogdan et al. investigated HRV dynamics in patients with acute MI who received conservative management without primary angioplasty or thrombolysis. HRV was evaluated through 24-hour ECG monitoring at baseline, 1 and 6 months after the event, acting as an indirect marker of ANS function. The study demonstrated significant improvements in HRV parameters over time, suggesting partial recovery of autonomic regulation following MI. Increases in SDNN, RMSSD, pNN50, and HF power, coupled with reductions in LF power and LF/HF ratio ($p < 0.001$), pointed to a shift toward enhanced parasympathetic activity. These favorable changes over the 6-month period reflected improved autonomic balance and cardiac recovery. Additionally, the study found a correlation between HRV parameters and left ventricular function. HRV and global longitudinal strain (GLS) were proposed as valuable tools in monitoring post-MI recovery and predicting poor prognosis [50].

2.3 Prognostic value of HRV in MI

Ischemic heart disease remains one of the leading causes of death worldwide, highlighting the importance of accurate risk stratification and early therapeutic interventions in patients experiencing AMI [51]. Since 1996, the prognostic importance of HRV in a number of clinical situations, such as MI, cardiac arrest, congestive heart failure, hypertension, and different arrhythmias, has been acknowledged by guidelines [24].

One of the primary early implementations of HRV in a clinical context was mortality risk stratification following AMI. A study published in 1987, which included AMI patients, showed that those with an SDNN value below 50 ms had a four-fold higher mortality risk over 4 years compared to those with an SDNN >100 ms. This result continued to demonstrate statistical significance after multivariate modeling. HRV has also been associated with clinical/radiological markers encompassing left ventricular systolic function and anomalies in segmental wall kinetics, and pulmonary congestion [52].

While most studies evaluate HRV using 24-hour ECG recordings, shorter recordings also carry prognostic value. In a study including 900 individuals without coronary artery disease (CAD), HRV measured from 2-minute ECG recordings was found to increase the risk of all-cause and cardiovascular mortality in individuals with low SDNN values [53]. Furthermore, low HRV values measured from just 10-second ECG recordings prior to revascularization have been shown to be significantly associated with 2-year mortality [54, 55].

There are other studies that have shown that HRV may be useful in predicting cardiovascular events even in asymptomatic populations. A meta-analysis by Hillebrand et al. demonstrated that low HRV values in individuals without known CAD increased the risk of a first cardiovascular event by 40% [56]. HRV measurements in this analysis were performed over recording periods ranging from 10 seconds to 24 hours. Similarly, Goldenberg et al. reported that reduced HRV is significantly correlated with an elevated risk of MI and adverse cardiovascular outcomes, even among individuals without a prior diagnosis of CAD. Each unit decrease in HRV was associated with a heightened probability of ischemic events, whereas elevated HRV appeared to confer a protective cardiovascular effect [57].

The prognostic value of HRV in terms of all-cause mortality, cardiac mortality and MACE in MI patients has been investigated in many studies. If we look at some of these studies in approximate order of publication; Buccelletti et al. reported that, in patients with SDNN <70 ms after AMI, the risk of mortality was about four times higher. Patients who died showed higher LF and LF/HF ratios, whereas survivors had higher median values for SDNN, RMSSD, PNN50, and HF. This supports the strong association between low HRV and poor prognosis [30]. Similarly, Chattipakorn et al. demonstrated that, in post-MI patients with SDNN <70 ms, cardiovascular mortality significantly increased [58]. The timing of HRV measurement is also crucial; measurements taken during the first 2 weeks to 1 year after infarction have similarly prognostic significance [58–60]. Ablonskyte-Dudoniene et al. reported that low RMSSD in PCI-treated patients increased the 1-year mortality risk by 10 times, while low SDNN increased 5-year mortality by four times. Additionally, low SDNN was significantly associated with the need for revascularization within 5 years [61].

In a meta-analysis evaluating 20 studies by Sen et al. [62], only SDNN, LF/HF ratio, and ultra-low frequency (ULF) were statistically related to mortality in post-MI patients. However, there was significant heterogeneity among the included studies, with follow-up durations ranging from 15 days to 13 years [62].

A recent meta-analysis encompassing 28 cohort studies revealed that, in patients with known CAD, low HRV increased the risk of all-cause mortality and cardiovascular events. This effect persisted in the subgroup analysis of AMI patients [18].

A recently published meta-analysis explored studies on patients with CAD and found that HRV parameters are associated with increased risk of all-cause mortality, as well as sudden cardiac death (SCD), non-cardiac death, and non-cardiac mortality ($p < 0.001$). Furthermore, the reduction in SDNN values was associated with other

established risk factors, such as a decrease in LVEF [63]. The significant contribution of this study is its reinforcement and confirmation of the general relationship between ischemic coronary heart disease and HRV. However, it did not include specific findings regarding acute coronary events or STEMI.

In a very recently published study, Rueda-Ochoa and colleagues showed that HRV measurements were associated with both cardiac and total mortality following MI. The main finding of this study was that SDNN is the best index with a statistically significant relationship to cardiac mortality, while the HRV index showed the strongest association with total mortality [5]. In another similar study, Chen and colleagues investigated the relationship between heart rate data obtained through 24-hour Holter monitoring and out-of-hospital MACE in patients who underwent PCI after experiencing STEMI [2]. The findings revealed that reduced HRV (especially SDNN and SDANN indices) and lower deceleration capacity were associated with an increased risk of MACE and cardiac death. Furthermore, frequent premature ventricular contractions (PVC) were also linked to a worse prognosis. SDNN proved to be a strong predictor for both MACE and cardiac death [2].

According to another recent study, patients who survived an AMI and those who died had significantly different SDNN values. Higher SDNN values, a sign of improved autonomic function, were seen in survivors. Higher mortality was linked to low SDNN. Additionally, Increased LF and a higher LF/HF ratio were observed in patients who died, indicating increased sympathetic activity. A trend was observed where as SDNN increased, left ventricular ejection fraction (LVEF) also increased, but this was not statistically significant [50].

The systematic review by Brinza et al. explored the relationship between HRV parameters and mortality as well as major cardiovascular events in patients with STEMI. The results showed that lower time-domain HRV values and higher LF/HF ratios were associated with all-cause mortality. In addition, short and ultra-short-term HRV measurements were found to be associated with similar risks. The review emphasized that HRV could be a strong prognostic marker in STEMI patients [59].

In another recent study, Brinza et al. examined real-time HRV measurements using wearable technology in STEMI patients who underwent primary PCI. Significant decreases were observed in HRV parameters (especially SD2/SD1 ratio and approximate entropy), and these reductions were associated with in-hospital mortality and MACE. Real-time HRV monitoring could be a new tool for clinical risk prediction [4].

If we look at the relationship between HRV and SCD, a review by Huikuri et al. emphasized the role of HRV in predicting SCD and arrhythmic events, suggesting HRV as a non-invasive risk marker [64]. On the other hand, Boskovic et al. reported that in patients who died during 1-year follow-up, post-MI, SDNN was significantly lower. SDNN independently predicted cardiac mortality but did not show a significant relationship with SCD risk [65]. In another study on SCD, Balanescu et al. reported that post-MI patients who experienced SCD had lower RMSSD, SDNN, and HF values, and higher LF and LF/HF ratios. A LF/HF ratio > 2 presented a 98% negative predictive value, but a low positive predictive value (14%). For SDNN <50 ms, the negative predictive value was 97%, though sensitivity and specificity were more limited [66].

HRV has also shown correlation with the Thrombolysis in Myocardial Infarction (TIMI) score; lower SDNN and RR average is associated with higher TIMI scores [67].

Overall, HRV appears to be a useful marker for stratifying the risk of all-cause mortality in STEMI patients. In particular, low SDNN and RMSSD values, along with high LF/HF ratios, have been observed in high-risk patients [54, 55, 61–69].

2.4 Future perspectives

Mortality in patients with STEMI remains high, despite significant reductions following the introduction of PCI and more invasive secondary prevention measures in daily clinical practice. One study observed a 13.7% mortality rate in STEMI patients who underwent primary PCI during a mean follow-up of 3.5 years [70]. This highlights the critical importance of risk stratification for every STEMI patient. However, none of the available risk scores provide perfect predictive power for adverse events [71, 72]. HRV is gaining increasing importance both in research and clinical practice. Including an additional marker such as HRV in traditional risk scores may improve the identification of high-risk patients, ensuring early therapeutic interventions. While HRV has long been recognized as an important biomarker providing insights into ANS functions, its future applications are expected to expand further. Technological advancements and digital health devices may propel the integration of HRV into clinical practice.

Devices such as smartwatches and fitness bands allow for continuous monitoring of HRV, providing individuals the opportunity to track their heart health in real-time. These technologies make HRV a part of daily clinical monitoring.

Additionally, artificial intelligence (AI) is becoming an increasingly important tool in the analysis of medical data. When combined with large datasets, HRV measurements can enable more accurate and personalized health predictions. AI algorithms can analyze HRV parameters to assess patient-specific risks and tailor treatment plans, leading to more precise and efficient healthcare.

The evaluation of HRV was re-emphasized with the advent of advanced technology, which introduced various sensors and wearable devices that allow for straightforward measurement of HRV parameters, even in a contactless manner [73–75].

3. Conclusions

HRV is a non-invasive, easy, and highly useful tool for assessing cardiovascular health and identifying potential risks related to the ANS. Studies have shown that low HRV is strongly associated with MI, SCD, and other cardiovascular diseases. Particularly in STEMI patients, HRV can provide significant prognostic information as it is linked to an increased risk of all-cause mortality, as documented in clinical studies. HRV measurements can be used for early warnings and risk assessments during the treatment process. Therefore, the integration of HRV into clinical practice offers a great opportunity to improve patient management and implement early interventions. In the future, the scope of HRV's applications may further expand. AI and big data analytics will enable more comprehensive analysis of HRV data, contributing to the development of personalized health management and early warning systems.

Conflict of interest

The author declare no conflict of interest.

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Correlations between Heart Rate Variability and Liver and Pancreatic Diseases

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Abstract

Heart rate variability (HRV) is defined as the variation in time intervals between consecutive heartbeats and is utilized as a noninvasive indicator for evaluating autonomic nervous system (ANS) function. Various mechanisms are involved in ANS imbalance and HRV alterations in liver and pancreatic diseases. In chronic liver diseases (CLD), including cirrhosis and its related complications, nonalcoholic fatty liver disease (NAFLD), and hepatic malignancies, reduced HRV indices have been linked to increased disease severity, poor prognosis, and elevated mortality risk. Similarly, in pancreatic disorders such as acute and chronic pancreatitis, pancreatic insufficiency, and pancreatic cancer, alterations in HRV indices have been recognized as possible biomarkers of disease progression and systemic stress response. In CLD patients, elevated levels of pro-inflammatory cytokines, even in the absence of active infection, may indicate a correlation between the often-observed low HRV indices and systemic inflammatory activation. The evaluation of HRV may serve as a valuable and noninvasive tool for assessing ANS function in patients suffering from liver and pancreatic disorders, thereby covering a broad spectrum of pathologies within the gastroenterological sphere.

Keywords: liver diseases, pancreatic diseases, autonomic dysfunction, nonalcoholic fatty liver disease, liver cirrhosis, hepatocellular carcinoma, acute pancreatitis, chronic pancreatitis, pancreatic insufficiency, pancreatic cancer

1. Introduction

Heart rate variability (HRV) is defined as the variation in time intervals between consecutive heartbeats and is utilized as a noninvasive indicator for evaluating autonomic nervous system (ANS) function [1]. HRV reflects the dynamic interaction between the sinoatrial node's pacemaking activity and ANS regulation, serving as an

indicator of the balance between sympathetic nervous system (SNS) and parasympathetic (PNS) influences on cardiac activity [1–3].

The importance of HRV as a prognostic indicator was first demonstrated in the 1994 Framingham cohort study, when it was found that low HRV indices predict a higher risk of all-cause mortality [4]. Recently, HRV has attracted increasing interest as a research area for various medical conditions, including chronic liver diseases (CLD) and pancreatic disorders. Current literature emphasizes the importance of HRV as a valuable tool for prognosis, monitoring, and risk stratification in liver and pancreatic pathology [5, 6]. Briefly, the primary methods of HRV assessment are divided into three categories as follows:

- Time-domain measures: normal-to-normal (N-N) interbeat intervals (mean N-N), standard deviation of N-N intervals (SDNN), standard deviation of the average of N-N intervals for each 5-min period over 24 hours (SDANN), root mean square successive differences (RMSSD), and percentage of adjacent N-N intervals that are >50 msec apart (pNN50);
- Frequency-domain measures: total power (TP), low frequency (LF), high frequency (HF), and LF/HF ratio;
- Nonlinear measures: entropy and fractal scaling provide insight into autonomic complexity [7–9].

Physiologically, the SDNN and SDANN indices represent overall autonomic regulation of cardiac rhythm. In contrast, RMSSD and pNN50 seem to be more associated with parasympathetic (vagal) activity and serve as indicators of respiratory sinus arrhythmia, with RMSSD offering a more accurate assessment than pNN50 [1, 10]. HF components reflect vagal modulation of cardiac function, whereas the LF/HF ratio is commonly interpreted as a marker of sympathetic influence. TP reflects the overall strength of autonomic input to the heart [8].

This chapter aims to synthesize recent research and evidence on HRV across liver and pancreatic diseases, exploring their clinical and pathophysiological relevance.

1.1 Heart rate variability in liver diseases

CLD burden the healthcare system globally, as they are characterized by increased mortality, morbidity, and economic costs [11]. Worldwide, CLD cause over 2 million deaths annually, making up about 4% of global mortality, representing one in every 25 deaths [12]. Complications of cirrhosis cause half of these, the rest being a consequence of viral hepatitis and liver cancer [13].

Considering that both SNS and PNS innervate the liver [14], the relationship between ANS dysfunction and CLD is a topic of current interest, being addressed in several studies [5, 15–19].

Different mechanisms lead to ANS imbalance and HRV changes in liver pathologies. Elevated levels of inflammatory cytokines, especially interleukin-6 (IL-6), may contribute to autonomic neuropathy, resulting in altered cardiac autonomic regulation, impacting HRV, and influencing the development and progression of various diseases [20, 21]. Also, in patients with CLD, the elevated level of pro-inflammatory cytokines, even without active infection, might indicate a correlation between low HRV, often observed, and systemic inflammatory activation [22–24].

1.2 Nonalcoholic fatty liver disease

Nonalcoholic fatty liver disease (NAFLD), a pathology characterized by excessive lipid accumulation in hepatic tissue, affects about 25% of the global adult population and has become the leading cause of CLD worldwide [25]. Evidence has shown a strong association between NAFLD and several comorbidities such as obesity, metabolic syndrome, type 2 diabetes mellitus (T2DM), and cardiovascular disease [25–27].

NAFLD encompasses a broad clinical spectrum, from hepatic steatosis (HS) to more advanced stages such as fibrosis and cirrhosis, and is notably associated with a higher risk of cardiovascular complications [28]. Severe complications, particularly cirrhosis and hepatocellular carcinoma (HCC), are the main factors that contribute to the increased morbidity and mortality linked to the disease [28].

Pathophysiologically, NAFLD represents the consequence of an imbalance in lipogenesis and lipolysis in the liver, fatty tissue, and hepatic inflammation, which influences the severity of the disease [29]. Several studies suggest that increased SNS activity may contribute to both the initiation and progression of NAFLD, thereby raising the risk of disease development. Over the past years, in patients with NAFLD, changes in ANS function and neurotrophic factors have been observed, both of which are essential factors in maintaining physiological homeostasis and regulating liver injury and repair processes [15, 30, 31].

Currently, there are no approved treatments available for NAFLD, as the existing medications mainly focus on addressing inflammation, liver fibrosis, and lipid accumulation [32].

Although the mechanisms underlying the association between HRV and NAFLD are not fully understood, emerging evidence indicates that autonomic imbalance may affect both the risk and progression of NAFLD [5, 15, 33]. Consequently, HRV has attracted increased interest in recent years as a promising noninvasive biomarker for assessing ANS dysfunction in individuals with NAFLD.

A cross-sectional study by Liu et al. [5] demonstrated a significant association between ANS dysfunction—indicated by decreased SDNN and RMSSD—and the prevalence of NAFLD, independently of traditional cardiovascular risk factors [5].

In a small cross-sectional study [6] involving 75 adults (25 individuals with NAFLD without diabetes, 25 with both NAFLD and diabetes, and 25 healthy controls), Kumar et al. concluded that both the severity of NAFLD and the presence of diabetes are associated with impaired cardiovascular autonomic function. The study reported significantly reduced time and frequency-domain parameters—specifically SDNN and TP—in individuals with NAFLD and diabetes compared to healthy controls [6].

The study of a Korean cohort [33] of 154,286 adults with no NAFLD or HS at baseline demonstrated that low HRV (measured by two time-domain: SDNN and RMSSD) assessed by 10-s electrocardiogram (ECG) was correlated with an elevated risk of NAFLD and HS, independently of other risk factors, indicating that ANS imbalance may be an independent factor in disease development and severity [33].

A study conducted between 2011 and 2018 [16] involving 33,899 subjects, initially without NAFLD, demonstrated that 6466 patients (19.1%) developed the disease in an average of 5.7 years. Patients who developed NAFLD had significantly lower values of SDNN, RMSSD, and HF compared to those without, suggesting an increased risk of developing the disease in individuals with consistently increased HR, normalized LF, and LF/HF ratio values. In other words, an overall imbalance in the

ANS—characterized by reduced parasympathetic activity and increased sympathetic activity—may elevate the risk of NAFLD [16].

A pilot, randomized, observational study [34] was conducted in Tyrol, Italy, to investigate the relationship between NAFLD and ANS impairment. The study included a total of 356 patients, categorized by the presence or absence of NAFLD and T2DM. Among these individuals, 32.9% had both NAFLD and T2DM, 19.1% had NAFLD without T2DM, 15.7% had T2DM without NAFLD, and 32.2% had neither condition. All diagnoses were confirmed using imaging techniques (ultrasonography and vibration-controlled transient elastography). A 20-minute resting ECG was conducted to evaluate HRV, focusing on the LF/HF ratio. Findings revealed a high LF/HF ratio, indicating decreased vagal activity. Patients with NAFLD showed cardiac autonomic imbalance, regardless of T2DM and liver stiffness [34].

Since ANS imbalance is a modifiable risk factor, HRV reductions can be detected early, predicting hepatic and cardiovascular outcomes, and serve as both a diagnostic and therapeutic marker target. Incorporating HRV assessment into the routine evaluation of NAFLD patients could improve prognostication and guide interventions [35, 36].

In conclusion, ANS changes, as indicated by HRV, may help identify patients at risk of developing and progressing NAFLD, making it a useful tool in clinical practice.

1.3 Liver cirrhosis

Hepatic cirrhosis is the final stage of CLD, where the normal liver structure is replaced by regenerative nodules, resulting in the loss of its primary functions [37, 38]. Usually, it progresses from asymptomatic, compensated liver cirrhosis to decompensation with multiple complications in several organs, thus leading to liver failure and death [39].

Currently, the global burden of the disease is high, causing over 1 million deaths annually and significant deterioration of quality of life. While the cases of cirrhosis caused by B or C viruses are decreasing, those caused by NAFLD or alcohol consumption are increasing [12].

This pathology is linked to a wide range of extrahepatic manifestations, including cardiac involvement. It is well-known that cirrhotic patients often present a hyperdynamic circulatory state, characterized by increased blood volume and cardiac output, decreased peripheral vascular resistance, and notable autonomic imbalance. Vagal impairment—recognized as an independent predictor of mortality in cirrhotic individuals—may contribute to the development of hepatic encephalopathy through various mechanisms, including delayed gastrointestinal transit, small intestinal bacterial overgrowth, bacterial translocation, and systemic endotoxemia [40, 41]. Patients with ANS impairment and hepatic cirrhosis might be more predisposed to develop liver encephalopathy [42].

Studies demonstrated that systemic inflammation and neuropsychiatric impairment are important prognostic factors in cirrhosis, being correlated with HRV reduction and increased cytokine levels [43–45].

Various scoring tools are used in everyday clinical practice to predict prognosis and liver transplant indication (MELD - Model for End-Stage Liver Disease; UKELD or Child-Pugh), but the ANS impairment found in cirrhosis is not taken into account in any of them, even if the relationship between autonomic imbalance and cirrhotic cardiomyopathy is a well-known and studied complication regarding this pathology [46, 47]. HRV in liver cirrhosis (LC) is an increasingly researched topic in recent years [17, 48].

In 2023, Miceli et al. conducted a cross-sectional, observational cohort study [17] on 157 patients with cirrhosis and portal hypertension, without a history of alcohol abuse. For HRV assessment, each patient was monitored by a 24-hour Holter ECG, and time-domain indices were analyzed (SDNN, SDANN, and RMSSD). It was observed that Child-Pugh class and MELD score were directly correlated with RMSSD and inversely correlated with SDANN. Also, the consequences of portal hypertension (the presence of ascites and the size of the esophagogastric varices) were inversely associated with SDANN and SDNN. Thus, they confirmed the correlations between the time-domain index (SDANN), Child-Pugh class, and the size of varices and ascites, validating the ANS's role in cirrhotic decompensation [17].

Another recent study [49] on 150 patients suffering from liver cirrhosis and 110 healthy controls demonstrated that SDNN, pNN50%, HF, LF, and HF/LF were significantly lower in the cirrhosis group. Also, the Child-Pugh Score was inversely correlated with SDNN ($r = -0.5429$, $p < 0.001$), RMSSD ($r = -0.375$, $p < 0.001$), pNN50% ($r = -0.6037$, $p < 0.001$), HF ($r = -0.2033$, $p = 0.0125$), and LF ($r = -0.3674$, $p < 0.001$) [49].

As mentioned before, remarkably, several studies have demonstrated the correlation between decreased HRV and poor prognosis in liver cirrhosis, separately from the MELD or Child-Pugh scores, the latter being the most commonly used tool in current practice to assess the severity of liver disease in patients waiting for liver transplants [44]. Thus, in conjunction with other severity scores of CLD, HRV can contribute to the accuracy of prognosis for these patients and the decision for transplantation.

1.4 Hepatic cancer

HCC, the most common primary liver cancer and often a complication in CLD patients, is the leading cause of death among patients with liver cirrhosis [48, 50]. Worldwide, HCC is the sixth most frequently diagnosed cancer and the third leading cause of cancer deaths [51]. Thus, significant advances have been made in its prevention, diagnosis, and treatment [52, 53].

Given that many cancer patients have symptoms that could suggest ANS imbalance (fatigue, gastroparesis, constipation, postural low blood pressure), its role in oncological pathologies has emerged as a novel area of study, with HRV serving as a quantitative marker of autonomic dysfunction [18]. ANS is an essential factor in modulating inflammation and immune responses. Thus, HRV may be a valuable tool in offering insights into cancer progression. Studies have shown that decreased HRV is associated with poorer outcomes in different neoplasms, including liver cancer. Also, low HRV in patients with neoplasms seems to correlate with the decrease in quality of life and shorter survival [54]. A systematic review [54] including 19 studies found that higher HRV was associated with improved survival rate across different cancers, such as breast, prostate, and lung cancer, demonstrating that increasing HRV indices appears to be a favorable prognostic factor for increased survival rate [54].

Autonomic imbalance is often present in patients with HCC, potentially driven by tumor burden, systemic inflammation, and underlying liver cirrhosis [55]. Recent studies demonstrate that low HRV in HCC is associated with advanced tumor stage, poor performance status, and poor vital prognosis [19, 56].

The pathophysiological mechanisms underlying reduced HRV in HCC are not fully elucidated but seem to include systemic inflammation, increased sympathetic activity, and cytokine dysregulation. These changes may influence tumor growth,

metastasis, and treatment resistance. Clinically, HRV can serve as a noninvasive tool for patient monitoring and risk stratification, complementing existing personalized management approaches.

Ciurea et al. investigated [56] the prognostic value of HRV in newly diagnosed HCC subjects. Analyzing data from 2014 to 2018 on 231 patients monitored by a 24-hour Holter ECG before any specific therapy, it was found that an SDNN below 110 ms was independently associated with reduced overall survival. Specifically, patients with lower HRV had a hazard ratio of 3.646 for death, indicating a significantly higher risk of death compared to those with higher HRV. This could suggest that HRV can serve as a noninvasive biomarker to identify HCC patients at elevated risk, potentially guiding early therapeutic interventions [56].

A Taiwanese study [19], which was conducted between 2006 and 2007 on 33 adult subjects with terminal HCC without a history of smoking, alcohol, or drug use, evaluated the association between the cardiovascular autonomic system and time to death in patients with final-stage HCC. HRV was recorded by 5-minute ECGs, and frequency-domain indices (TP, LF, HF, and LF/HF ratio) were analyzed. All the subjects died in the 3-month follow-up time, with a median of 11 days. A significant association was found between TP and HF and time to death. Thus, it was demonstrated that increased HRV frequency-domain indices correlate with longer time to death in terminal HCC patients, highlighting an essential prognostic factor in this category. Proper prognosis of the expectation of life in end-stage oncological pathology is an important factor for patients, their caregivers, and physicians in palliative care planning [19].

Therefore, HRV emerges as a valuable, relatively simple, effective, and promising biomarker in the progression and prognosis of HCC.

1.5 Heart rate variability in pancreatic diseases

Pancreatic disorders, including acute and chronic pancreatitis, pancreatic cancer, and pancreatic exocrine insufficiency (PEI), currently represent a group of conditions with significant morbidity and mortality [57]. Acute pancreatitis (AP) represents one of the most common gastrointestinal causes of hospitalization worldwide [58]. Pancreatic cancer remains one of the deadliest malignancies due to its late presentation and aggressive progression [59]. Disruption of ANS regulation has been increasingly implicated in the pathophysiology and progression of pancreatic diseases. Pain, inflammation, metabolic dysregulation, and neuroimmune interactions in pancreatic disorders may all influence autonomic output. Autonomic imbalance, particularly a shift toward sympathetic dominance and reduced vagal activity, can exacerbate systemic inflammation and metabolic instability. HRV, as a surrogate for autonomic tone, thus offers a promising avenue for monitoring these changes.

1.5.1 Acute pancreatitis

AP, a frequent gastroenterological emergency, is an inflammatory disorder of the pancreas that presents with varying degrees of severity [60]. It often presents with epigastric tenderness upon palpation, upper abdominal pain radiating to the back, and fever [61].

AP progresses from one of several pathophysiological disturbances: acinar cell injury in the pancreatic tissue, faulty intracellular enzyme transport, or duct obstruction [62]. These disturbances can result from causes such as alcohol consumption, gallstones,

post-endoscopic procedures, trauma, hypertriglyceridemia, hypercalcemia, viruses, parasites, or medications. The activation of pancreatic enzymes, like trypsin, within the pancreas leads to increased proteolytic and lipolytic activity [60]. When combined with duct blockages from gallstones, these activated enzymes become trapped in the pancreas, causing damage to pancreatic cells [63]. This damage then triggers the release of inflammatory mediators, such as IL-6, interleukin 8 (IL-8), and tumor necrosis factor- α , which attract neutrophils and macrophages to the inflamed area [64].

The activation of neutrophils and macrophages triggers the release of inflammatory cytokines, leading to vascular injury, vasodilation, and increased vascular permeability. Fluid accumulation within the pancreatic tissue causes compartment syndrome, which sustains an inflammatory cascade by disrupting microcirculation in the parenchyma. Additionally, the ongoing disease process results in decreased blood volume and pressure, resulting in diminished perfusion to various organs, especially the gut and kidneys. This cascade causes intestinal barrier failure, renal dysfunction, and ultimately, multiple organ failure.

The compromised gut barrier facilitates bacterial translocation, which is the primary reason for the shift from a sterile state to an infectious disease. The release of inflammatory cytokines, including IL-6, IL-8, and TNF- α , into the bloodstream during AP progression leads to disruptions in autonomic function. All these pathophysiological changes can be monitored by evaluating HRV parameters, which have also been associated with predicting morbidity and mortality.

AP is classified by its severity, primarily using the 2012 modified Atlanta classification, which divides AP into three categories: mild, moderately severe, and severe. Various scoring systems are utilized to assess high-risk patient groups for developing severe AP. These systems include the Acute Physiology and Chronic Health Evaluation II (APACHE II) score, the Bedside Index of Severity of Acute Pancreatitis (BISAP), and the Sequential Organ Failure Assessment (SOFA). Each of these systems uses clinical and physiological factors to predict risk.

Even though HRV was first used in clinics for the evaluation of fetal hypoxia [65], its application has expanded to other medical fields, such as anticipating mortality risk in critically ill patients in intensive care units [66] and the progression of cardiovascular and neurological conditions, such as atrial fibrillation, myocardial infarction, heart failure, and Parkinson's disease, among others [66]. AP is also known to affect the modulation of the ANS in the heart, making it highly likely that HRV will be included as a risk stratification tool for AP. HRV assesses the variations in heart rate, but numerous factors influence HRV in the progression of acute AP, including pain, anxiety, drug effects, hypoxia, and physiological regulations that increase cardiac function, as well as overstimulation of the SNS and PNS manifestations of the ANS [67].

Zhang et al. showed in their research [68] that normalized high frequency and LF/HF can prognosticate infected pancreatic necrosis better than the APACHE II and that LF/HF prognosticates MODS better than APACHE II [68].

Viswanathan et al. [69] identified heart rate measured *via* ECG as a significant predictor of severe AP, establishing a threshold of 90 beats per minute, which demonstrated a sensitivity of 71.5% and a specificity of 74.5%. In addition, Shan et al. demonstrated a fine correlation between a 12-hour episode of elevated heart rate over 100 beats per minute and mortality less than 90 days in AP patients in the intensive care units [70].

The application of HRV monitoring has drawbacks. A patient's age is a significant factor in HRV, as a physiological decline in HRV is expected in this group of patients [71, 72]. Furthermore, cardiac dysrhythmias such as atrial fibrillation, heart blocks, or ectopic beats impact HRV monitoring. They may lead to an underestimation of

these patients, who are naturally more vulnerable to mortality due to AP. Given the straightforward nature of HRV monitoring, examining its use as a possible diagnostic tool for AP is a worthwhile pursuit. Therefore, further research is needed to confirm this association between HRV measurements and the evolution of AP, as well as to assess its efficacy in predicting severity in the future.

1.5.2 Chronic pancreatitis

Chronic pancreatitis is a progressive fibroinflammatory condition marked by permanent structural damage to the pancreatic tissue, ultimately resulting in impaired exocrine and endocrine function. Risk factors include alcohol and tobacco use, genetic polymorphisms, and recurrent episodes of AP [73].

HRV is an indicator of variations in the ANS and may represent an early sign of many diseases. In gastroenterological practice, the use of HRV analysis has a broader application, given the interaction of compartments of the vegetative nervous system in various gastroenterological pathologies, such as gastroesophageal reflux disease, peptic ulcer, AP, chronic pancreatitis, and pancreatic cancer [74].

In patients with chronic pancreatitis, ANS has shown potential as an effective method for pain management [75]. Usual pain perception represents a complex process involving a balance between the SNS (pro-nociceptive) and the PNS (anti-nociceptive). The dysregulation of the nervous system can lead to chronic pain [76]; thus, the increase in the parasympathetic tone may lead to visceral pain hypersensitivity [75].

For assessing the relationship between ANS imbalance, pancreatic exocrine function, and chronic pancreatitis, Sabat et al. [77] evaluated the autonomic function using HRV indices along with the Spielberger-Khanin anxiety questionnaire. The primary objective was to examine how variations in HRV are correlated with PEI, as evaluated through patient-reported measures of outcomes. The results suggested a statistically significant correlation between the amplitude of the mode and the stress index, as well as the duration of chronic pancreatitis. The study indicates compensatory activation of the sympathetic division of the ANS with the worsening of exocrine insufficiency, as indicated by the fecal α -elastase content, and an increase in sympathicotonia, as measured by the stress index. Also, a decrease in the functional reserve of patients with chronic pancreatitis was revealed. A factor that increases exocrine pancreatic deterioration is a decline in the psycho-emotional state due to a decrease in adaptive potential. The reported data may serve as proof of concept for the inclusion of agents to stabilize the ANS [77].

1.5.3 Pancreatic insufficiency

Pancreatic exocrine insufficiency (PEI) is a disorder marked by inadequate secretion or delivery of digestive enzymes (lipase, amylase, and proteases), leading to maldigestion, malabsorption, and progressive nutritional decline [78]. Traditionally considered a gastrointestinal condition, pancreatic insufficiency is increasingly recognized for its systemic implications, particularly on cardiovascular and autonomic function. Recent literature has highlighted a link between pancreatic insufficiency and altered HRV, a noninvasive marker of ANS activity.

The pathophysiology of PEI involves a disruption in the pancreatic secretory response, which may stem from chronic pancreatitis, cystic fibrosis, pancreatic surgery, or neoplasms [79]. Reduced enzyme output correlates closely with steatorrhea,

nutrient loss, and malnutrition [80], all of which have downstream effects on electrolyte balance and cardiac function [81].

Electrolyte disturbances are common due to malabsorption and chronic diarrhea. Deficiencies in potassium, magnesium, and calcium can compromise myocardial conduction and autonomic regulation [81]. Hypokalemia increases the risk of arrhythmias, hypomagnesemia can prolong QT intervals, and hypocalcemia impairs myocardial contractility, all of which influence HRV and cardiovascular stability [81]. Furthermore, chronic dehydration from steatorrhea and osmotic diarrhea contributes to orthostatic hypotension and compensatory sinus tachycardia [82]. These compensatory mechanisms, while adaptive in the short term, reflect a shift in autonomic tone that may be detrimental over time.

Fat-soluble vitamin malabsorption (A, D, E, K) and water-soluble deficiencies, particularly vitamin B12 and thiamine, are common in pancreatic insufficiency. Vitamin B12 deficiency leads to neuropathy and anemia, which can impair autonomic balance and result in compensatory tachycardia [83]. Thiamine deficiency, although often associated with alcoholism, may also emerge in PEI due to chronic nutrient loss and, in severe cases, causes beriberi disease, a condition with overt cardiovascular effects [84].

Inflammation plays a central role in both the etiology and cardiovascular consequences of pancreatic insufficiency. Inflammatory cytokines activate sympathetic outflow and suppress parasympathetic tone, reducing HRV and heightening cardiovascular risk [85]. This inflammatory-autonomic interface is especially relevant in conditions such as chronic pancreatitis, diabetes, and opioid-related gastrointestinal dysmotility [86].

Sangnes et al. provided direct evidence that PEI in diabetes is associated with low HRV indices (RMSSD and HF). This suggests that ANS impairment may contribute to PEI and diabetes [87].

Furthermore, studies such as Luo et al. have shown that interventions such as gastric electrical stimulation can improve pancreatic output and possibly autonomic tone. HRV improvements post-organ transplantation have also been linked to enhanced metabolic and cardiovascular health [88].

While PEI does not directly alter heart rhythm, its consequences (electrolyte imbalance, nutrient deficiency, dehydration, inflammation) converge to impair autonomic flexibility and reduce HRV. As HRV serves as a prognostic marker for cardiovascular risk, its assessment could prove valuable in patients with PEI, particularly those with comorbid diabetes or malnutrition.

Clinicians should routinely monitor electrolyte levels, nutritional status, and autonomic signs in PEI patients. Tools such as ECG, serum panels, and HRV analysis can detect early disturbances and guide timely intervention.

PEI is a multisystem condition with implications that extend well beyond the gastrointestinal tract. Reduced HRV in these patients reflects an underlying autonomic imbalance driven by nutritional, metabolic, and inflammatory disruptions. Recognizing and addressing these systemic effects is critical. HRV, as a dynamic and sensitive biomarker, offers a promising tool for early diagnosis, risk stratification, and therapeutic monitoring in individuals affected by PEI.

1.5.4 Pancreatic cancer

The SNS plays a central role in the body's stress response, often called the "fight-or-flight" reaction, and also in controlling cardiovascular functions, glucose metabolism, and pro-inflammatory processes. Studies suggest that the SNS can significantly impact neoplasm progression and treatment results, particularly in advanced-stage

(stage IV) cases [89]. Its neurotransmitters have been shown to potentially promote cancer cell proliferation by influencing cell-cycle dynamics and stimulating the release of growth factors [89].

In particular, the pancreas is extensively innervated by sympathetic neuronal fibers. It is hypothesized that stimulation of these fibers may worsen disease progression by fostering a microenvironment that promotes tumor growth [90].

Pancreatic cancer ranks among the most aggressive and deadly forms of malignancy, with a notably poor prognosis and a five-year survival rate ranging from only 15–25%, despite advancements in cancer therapies [91–93]. This highlights the need for novel biomarkers that can support early detection, hinder disease progression, and help in predicting treatment outcomes.

The goal is to find a marker that is easy to use, inexpensive, and accessible to everyone. HRV can serve as one of these markers—it is measured and already utilized in trials. It is known that a relationship exists between cancer prognosis and the autonomic regulation of the cardiovascular system [94].

Some studies show that low HRV may be involved in cancer development and progression: it is associated with metabolic syndrome, inflammation, and higher stress levels, changes seen in impaired ANS in oncological patients [95]. Clinically manifested by fatigue, sleep changes, and distress, these are symptoms of autonomic dysfunction, which can decrease HRV [94].

The vagus nerve, a major component of the PNS, plays an essential role in regulating HRV [1]. Several studies have investigated the association between vagal activity and neoplasms, suggesting that vagal nerve stimulation may slow cancer progression by mitigating inflammation, oxidative stress, and excessive sympathetic activation [96]. In the study conducted by Couck et al. [96], vagal nerve activity was examined to explore its association with HRV and survival outcomes in patients with advanced pancreatic cancer. Their findings revealed that higher HRV, as recorded using ECG, was positively associated with vagal activity and correlated with improved overall survival in these patients [96]. In 2016, Anker et al. [97] evaluated resting heart rate in 145 individuals with pancreatic, colorectal, and non-small cell lung cancers, comparing the results to those of healthy controls. They observed that cancer patients exhibited an RHR exceeding 75 beats per minute, significantly higher than that of the control group, and associated with a poorer prognosis [97]. Further research by Anker et al. in 2020 found that patients with pancreatic, lung, and colon cancers showed reduced HRV, frequent episodes of non-sustained ventricular tachycardia, and elevated baseline heart rates relative to healthy participants [98].

These studies demonstrate an indirect correlation between cardiac electrical activity and the development of malignancies. It has been hypothesized that HRV may serve as a prognostic indicator for various cancers, including pancreatic cancer [54]. However, for the moment, the direct cause-and-effect between HRV and pancreatic cancer could not be demonstrated [98].

Kloter et al. [54] conducted a comprehensive review of 19 clinical studies involving cancer patients across a wide range of diagnoses. The reviewed studies included 332 patients with pancreatic cancer, 208 with colorectal cancer, 133 with non-small cell lung cancer, 127 with head and neck cancers, 125 with gynecologic malignancies (including uterine, cervical, and ovarian cancers), 113 with prostate cancer, 91 with gastrointestinal cancers, 51 with lung cancer, 43 with HCC and hepatobiliary cancers, 40 with brain metastases, 36 with liver cancer, 35 with metastatic carcinoid tumors, 33 with primary brain tumors, 28 with stomach and esophageal cancers, 22 each with genitourinary cancer and acute leukemia, 13 with non-acute leukemia, 19 with breast

cancer, four with sarcoma, and three with bladder cancer. In an additional 704 cases, the cancer type was not specified. The findings revealed a consistent association between cancer progression and reduced HRV, indicating ANS dysfunction, particularly diminished parasympathetic activity. Moreover, higher HRV was positively correlated with improved survival outcomes in cancer patients [54].

However, HRV is highly sensitive in stressful situations and can change rapidly, so the design of Kloter et al.'s retrospective studies cannot be reproduced, and the results are limited. That was relevant because HRV measurement (short-term ECGs of seconds to minutes) may have been influenced by stressful situations (like medical consultations where the patient discussed the diagnosis or progression of the disease or adverse reactions to the treatment). As a result, the authors noted that such tools may not accurately reflect the patient's overall HRV patterns. Consequently, they recommended the use of 24-hour Holter ECG monitoring for more reliable assessment of HRV in oncological patients [54].

In a retrospective study conducted by Petrescu et al. [94] between October 2017 and June 2020, a total of 53 patients with newly diagnosed pancreatic cancer were evaluated. Of these, 14 patients survived beyond 24 months following diagnosis, while 27 patients passed away within that same period. Before receiving any form of treatment, all participants underwent 24-hour Holter ECG monitoring to assess HRV. The study found that lower HRV indices were significantly associated with decreased survival rates, suggesting that reduced HRV may serve as a negative prognostic marker in individuals newly diagnosed with pancreatic cancer [94].

Given the ANS's key function in regulating numerous physiological processes, including tumor growth, invasion, and metastasis, attention has focused on the potential of HRV to predict survival among oncological patients. Consequently, multiple studies have explored the relationship between HRV indices and survival rates in individuals with pancreatic cancer. These studies employed various HRV analysis methods, including time-domain, frequency-domain, and nonlinear techniques, to assess changes in HRV [56, 95, 99].

Gams et al. [100] studied the effects of cancer on cardiac function, analyzing differences based on sex using transgenic mouse models of pancreatic and liver cancer. They found that female cancer mice exhibited a lower median HR and higher HRV compared to their male counterparts. These results suggest that sex should be recognized as a significant factor when employing HRV as a cancer biomarker [100].

In conclusion, HRV might serve as a valuable biomarker in assessing cancer progression [54]. Understanding the changes in ANS function could help specialists with early detection, diagnosis, and sex-specific predictions of survival in pancreatic cancer [99, 101]. However, this field is still in its early research stage, and further studies are needed to fully understand the subtle interconnections of the human body.

2. Conclusion

Regarding the above evidence, the assessment of HRV might be a valuable, noninvasive tool for evaluating ANS function in patients with liver and pancreatic diseases, thus encompassing a wide range of pathologies in the gastroenterological sphere. In CLD, such as cirrhosis and its complications, NAFLD, and hepatic cancer, decreased HRV indices have been associated with disease severity, poor prognosis, and increased mortality risk. Also, in pancreatic pathology, including acute and chronic pancreatitis, pancreatic insufficiency, and cancer, HRV alterations have

emerged as potential biomarkers of disease progression and systemic stress response. The integration of HRV analysis into routine clinical practice may provide early signs of ANS dysfunction, guide risk stratification, and offer prognostic data. In conclusion, HRV represents a promising factor in the personalized management of liver and pancreatic diseases.

Conflict of interest

The authors declare no conflict of interest.

Acronyms and abbreviations

ANS	autonomic nervous system
AP	acute pancreatitis
CLD	chronic liver diseases
HCC	hepatocellular carcinoma
HF	high frequency
HR	heart rate
HRV	heart rate variability
HS	hepatic steatosis
IL-6	interleukin 6
IL-8	interleukin 8
LF	low frequency
NAFLD	nonalcoholic liver disease
PEI	pancreatic exocrine insufficiency
PNN50	percentage of adjacent N-N intervals that are >50 msec apart
PNS	parasympathetic nervous system
RMSSD	root mean square successive differences
SDNN	standard deviation of N-N intervals
SDANN	standard deviation of the average of N-N intervals for each 5-min period over 24 hours
SNS	sympathetic nervous system
TP	total power

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Perspective Chapter: Heart Rate Variability in Rheumatic Diseases

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Abstract

Heart rate variability is a valuable non-invasive marker of autonomic nervous system function, reflecting the balance between the sympathetic and parasympathetic systems. Rheumatic diseases are characterised by systemic inflammation, autoimmune activity, and sometimes direct involvement of the cardiovascular system. These factors can influence autonomic nervous system function, thereby affecting heart rate variability. There is a growing acknowledgement of reduced Heart rate variability (HRV) in rheumatic diseases, which is associated with systemic inflammation, autonomic dysfunction, and an increased cardiovascular risk. Despite its clinical relevance, autonomic dysfunction remains under-recognised in rheumatology. This chapter reviews the current evidence regarding HRV alterations in rheumatic diseases and highlights its utility in disease monitoring, risk assessment, and potential therapeutic modulation.

Keywords: heart rate variability, systemic sclerosis, systemic lupus erythematosus, rheumatoid arthritis, ankylosing spondylitis

1. Introduction

Heart rate variability (HRV) is a well-known non-invasive tool that provides insights into the complex interplay between the sympathetic and parasympathetic nervous systems that regulate the cardiac rhythm. As a dynamic marker of autonomic function, HRV has demonstrated its usefulness in risk stratification and prognosis assessment across various clinical conditions that alter the sympathetic and parasympathetic balance, including rheumatic diseases. Autonomic dysfunction is often overlooked in rheumatology, despite its significant contribution to the overall disease burden. Over the past decade, many studies have linked reduced HRV to systemic inflammation, cardiovascular complications, and overall worse outcomes in patients with rheumatic diseases.

HRV is defined as the temporal variability between consecutive heartbeats. High HRV indicates a healthy, adaptable cardiovascular system with balanced autonomic regulation, while low HRV reflects sympathetic dominance, abnormal vagal modulation, and reduced physiological resilience.

Time-domain parameters, such as the standard deviation of all NN intervals (SDNN) and the root mean square of successive differences (RMSSD), along with frequency-domain parameters, including low-frequency (LF) and high-frequency (HF) components, reflect sympathetic and parasympathetic modulation [1]. LF is often associated with both sympathetic and baroreflex activity, while HF is predominantly affected by the vagal tone [1], and the LF/HF ratio reflects the sympathovagal balance [2]. Together, these indices provide a comprehensive and non-invasive assessment of autonomic nervous system function and its dynamic influence on cardiovascular physiology.

Many studies have linked rheumatic diseases to dysfunction of the autonomic nervous system, characterised by poor vagal function and sympathetic dominance. This association is believed to arise from dysfunction of the cholinergic anti-inflammatory pathway mediated by the vagus nerve [3].

This chapter aims to synthesise the current understanding of HRV changes across major rheumatic diseases and to provide practical insights for clinicians regarding its relevance to disease monitoring, cardiovascular risk stratification, and potential therapeutic targets.

2. Systemic sclerosis

Systemic sclerosis (SSc) is a connective tissue disease characterised by immune-mediated fibrosis and vasculopathy affecting multiple organs, including the heart. Cardiac involvement, often subclinical in early stages, may remain undetected for years, contributing silently to progressive myocardial dysfunction, significant morbidity, and mortality. Early detection is crucial for improving patient outcomes.

The pathogenesis of SSc involves a genetically predisposed individual exposed to environmental triggers, resulting in a persistent, self-perpetuating process marked by early vascular injury, immune activation, and, ultimately, fibrotic tissue remodeling [4, 5]. Myocardial fibrosis and microvascular damage can lead to arrhythmias, ventricular dysfunction, and heart failure.

In a study by Ferri et al. [6], resting electrocardiograms showed abnormalities in 42% of SSc patients, while 30% had rhythm disturbances. More sensitive 24-hour Holter monitoring revealed a higher burden of arrhythmias, including supraventricular arrhythmias in 66% of patients and ventricular arrhythmias in 90%. These included multiform premature ventricular contractions in 40%, brief runs of ventricular tachycardia in 28%, and sustained episodes in 13% [6].

During 24-hour Holter recordings, autonomic parameters such as heart rate variability and heart rate turbulence (HRT) can be evaluated. HRT, which measures sinus rhythm fluctuations following premature ventricular beats, has emerged as an independent marker for predicting malignant arrhythmias and sudden cardiac death, although its broader clinical use still requires validation [7, 8]. Multiple studies have documented impairments in both HRV and HRT in patients with SSc, demonstrating underlying cardiac autonomic dysfunction. This dysfunction, characterised by increased sympathetic dominance and reduced vagal tone, is present in both limited (lcSSc) and diffuse (dcSSc) forms of the disease, with a more pronounced progression observed in dcSSc over time [9–13].

HRV, proven effective in identifying autonomic imbalance, is a non-invasive analysis that correlates with myocardial injury, arrhythmias [10, 14], reduced sleep, and quality of life [12]. While some investigations found no significant differences

between SSc subtypes [15], others reported decreased overall HRV power in dcSSc, suggesting a more generalised autonomic disruption [11, 16]. Chronic inflammation and fibrotic changes are believed to drive these autonomic alterations [13, 17–19]. Additionally, decreased baroreflex sensitivity has been noted as a contributing factor to HRV abnormalities in these patients [20]. Longitudinal studies show that while HRV metrics remain stable in healthy individuals, they decline in dcSSc patients, indicating that disease progression, not ageing, is the primary cause of autonomic deterioration [13]. A study by Zlatanovic et al. [16] showed a significant impairment of both autonomic function and cardiac mechanics, even without overt cardiac symptoms. The alteration of HRV correlated independently with both left and right ventricular diastolic dysfunction and longitudinal strain, supporting a tight pathophysiological link between autonomic imbalance and myocardial remodelling [16]. Modified Rodnan skin score (mRSS) was significantly correlated with HRV indices and biventricular structural and mechanical parameters, suggesting that skin involvement may serve as a surrogate marker for underlying cardiac changes [16]. These associations were consistent regardless of traditional risk factors, highlighting the relevance of autonomic assessment in the routine evaluation of SSc patients [16]. This establishes HRV as a valuable tool for early detection and monitoring, with potential implications for therapeutic targeting [16, 21, 22].

Heart rate turbulence (HRT) has gained attention as a strong, independent prognostic marker for mortality in cardiovascular disease, including SSc [23, 24]. Abnormal HRT values, particularly reduced turbulence onset (TO) and turbulence slope (TS), reflect impaired baroreflex function and advanced autonomic impairment [25]. The worsening of HRT parameters has been correlated with longer disease duration in SSc, especially in those with the diffuse subtype [26]. A significant limitation of HRT is that its measurement requires the presence of ventricular premature beats (VPBs), which are not observed in all patients [23]. However, when VPBs are present, HRT provides a stronger prediction of mortality than HRV alone [23, 24].

Combined assessment using HRV and HRT offers a broader and more precise understanding of cardiac autonomic regulation in SSc. HRV provides insight into both parasympathetic and sympathetic activity and is especially valuable when VPBs are absent [23], while HRT adds specific prognostic information when VPBs are detected [24]. Lower HRV parameters, such as low-frequency (LF) and high-frequency (HF) power, have been linked to increased mortality, supporting the presence of autonomic dysfunction even in early disease stages [15, 26, 27]. The presence of this dysfunction may precede overt cardiac involvement. Although sudden cardiac death is not frequent in SSc, case reports suggest it may occur more often than previously recognised, particularly in patients with significant autonomic imbalance [21, 22]. Incorporating both HRV and HRT into routine assessment protocols may improve early identification of high-risk patients and contribute to more personalised management strategies.

Thus, HRV emerges as a highly informative and non-invasive marker for evaluating cardiac autonomic dysfunction in systemic sclerosis, particularly in those with the diffuse cutaneous subtype. HRV reflects both parasympathetic withdrawal and sympathetic overactivity—alterations that correlate closely with subclinical myocardial dysfunction, ventricular strain abnormalities, and markers of disease severity such as the Rodnan skin score. These associations, observed even in asymptomatic patients, highlight the importance of incorporating HRV analysis into routine screening and longitudinal follow-up. While heart rate turbulence (HRT) may provide additional prognostic insights in specific contexts, HRV remains the more broadly applicable tool for early detection, risk assessment, and guiding individualised clinical care in SSc.

3. Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterised by the production of autoantibodies that target nuclear and cytoplasmic antigens [28]. It predominantly affects women of reproductive age, and its heterogeneity in clinical presentation is well-known [28]. Globally, the incidence rate varies between 1.4 and 49.0 per person-years [29–31], with prevalence ranging from 13 to 7.713.5/100.000 [32, 33]. It involves multiple systems with various clinical manifestations, including renal, dermatological, neuropsychiatric, and cardiovascular symptoms [28, 34]. Along with infections, neoplasia, and renal failure, cardiovascular impairment is a leading cause of morbidity and mortality in SLE patients [35]. Being a significant social and public health burden, SLE requires a multidisciplinary approach, as current therapy does not completely cure the disease but instead slows its progression and prevents complications [34].

The centrepiece of SLE pathogenesis involves acute and chronic inflammation, immune dysregulation, and the production of autoantibodies, leading to tissue damage and disruption across multiple systems [36]. The inflammation affects autonomic function, acting on the central nervous system and modulating the peripheral inflammatory responses.

Autonomic imbalance, defined as increased sympathetic nervous system (SNS) and decreased parasympathetic nervous system (PNS) activity, was reported in SLE. SNS, PNS, and their neurotransmitters are both involved in acute and chronic inflammation. During the acute inflammation process, the SNS activity increases, and the hypothalamic-pituitary-adrenal axis is activated, with sympathetic neurotransmitters acting on immune cells and developing anti-inflammatory mechanisms at the tissue level [37]. Also, growing evidence reveals that autonomic nervous system dysfunction may correlate with SLE disease activity, the presence of autoantibodies, and neuropsychiatric manifestations [38–40].

In 2016, Thanou et al. [38] studied 53 SLE patients, predominantly women, with a median age of 46 years at baseline. The clinical assessment comprised the following indices: Systemic Lupus Erythematosus Disease Activity (SLEDAI), British Isles Lupus Assessment Group (BILAG), the physician global assessment (PGA), and the safety of oestrogens in Lupus Erythematosus National Assessment-SLEDAI Flare. Additionally, a 5-minute electrocardiogram was conducted for each patient to assess heart rate variability (HRV). It was demonstrated that both frequency-domain (HF power, LF/HF ratio) and time-domain indices (pNN50) were inversely correlated with disease activity (BILAG and PGA), plasma soluble tumour necrosis factor receptor II (sTNFR_{II}), monokine induced by interferon gamma (MIG), plasma stem cell factor (SCF), interleukin (IL)-1 receptor antagonist (IL-1RA), and IL-15. Furthermore, the variability of RMSSD was inversely related to SLEDAI variability. No correlation between HRV and the presence of serological markers (anti-dsDNA antibodies and reduced complement levels) was observed. Thus, a potential interdependence between the autonomic nervous system, SLE disease activity, and a possible usefulness of vagal modulation as adjunctive therapy in SLE was suggested [38].

Another prospective cross-sectional study [41] involving 111 SLE patients and 100 healthy controls aimed to investigate the association between autonomic nervous system dysfunction, cardiovascular impairment, SLE disease activity, and health-related quality of life. The clinical evaluation used SLEDAI and the Systemic Lupus Erythematosus International Collaborating Clinics Group damage index. Health-related quality of life was assessed through the self-administered 12-item Short Form

(SF-12) questionnaire, from which physical and mental domains could be calculated. Low values of SDNN, TP, RMSSD, and HF power, and a high LF/HF ratio were found in the SLE group compared to controls. In terms of HRQoL, low HRV indices (RMSSD, HF power, TP, and RS ratio) were correlated with lower SF-12 physical scores, but no change in mental scores was observed, suggesting that autonomic nervous system imbalance may contribute to low physical health-related quality of life in SLE patients [41].

In a study by Poliwczak et al. [42] on 26 SLE women and 30 healthy controls, HRV indices were calculated using 24-hour ambulatory monitoring ECG. A significant association was found between low HRV indices (SDANN, RMSSD, p50NN) and the SLE group. Additionally, while HRV time-domain indices (SDNN and SDANN) were positive and significantly correlated with SLE duration, RMSSD, HF, and LF/HF ratio were inversely correlated with disease duration. The autonomic nervous system imbalance in SLE was thus demonstrated [42].

In conclusion, patients suffering from SLE experience cardiac autonomic imbalance, which leads to reduced HRV indices. These changes may be related to inflammatory cytokines and disease activity, thereby increasing the risk of arrhythmias and emphasising the importance of therapeutic strategies focused on mitigating these autonomic alterations [43, 44]. Incorporating HRV into the management of SLE patients may improve their outcomes. This can be approached through pharmacological or electrical treatments or cognitive behavioural therapy. Therapies are rapidly entering clinical research programmes and may apply to SLE and other clinical inflammatory disorders [45].

Despite these promising insights, several limitations persist concerning clinical trials involving SLE patients. Variability in HRV measurement protocols, small sample sizes, and heterogeneity in disease symptomatology, clinical presentation, and treatment strategies hinder data interpretation.

4. Rheumatoid arthritis

Rheumatoid arthritis (RA) is an autoimmune disease characterised by persistent systemic inflammation and joint destruction, associated with increased cardiovascular risk [46]. Autonomic nervous system dysfunction is prevalent in almost 60% of RA patients [47]. Impaired cardiovascular reflexes and altered HRV represent the main pattern, indicative of reduced cardiac parasympathetic activity and elevated cardiac sympathetic activity. HRV parameters are negatively correlated with the levels of inflammatory cytokines (interleukin-6 and rMSSD, LF power; interleukin-10 and LF/HF ratio; trend for tumour necrosis factor- α and LF power) and patient-reported pain [48]. Reduced HRV is also associated with higher disease activity and functional disability assessed using EuroQol-5D, Health Assessment Questionnaire (HAQ), and Disease Activity Score-28 (DAS-28) [49].

Studies consistently show that RA patients present significantly reduced HRV in comparison to healthy controls, independent of traditional cardiovascular risk factors [50]. Autonomic nervous system dysfunction is present at an early stage of the disease, with persistence after 5 years, despite antirheumatic therapy [50]. A decrease in HRV could represent an early sign of developing hypertension in RA patients [50].

In a prospective cohort study, Koopman et al. [51] found that autonomic nervous system dysfunction is similar in individuals at risk of developing RA and in patients with established RA, being significantly higher than in healthy subjects. Additionally,

it plays a role as a predictor for the development of arthritis. Resting heart rate was significantly higher at baseline in individuals who subsequently developed RA [51].

Research on HRV changes during the treatment of RA is scarce. Holman et al. conducted an exploratory, double-blind study over 52 weeks, involving 33 patients (25 with RA and 8 with psoriatic arthritis), assessing parasympathetic, sympathetic, total power, and tension index measurements at the start of anti-tumour necrosis factor (TNF) therapy with etanercept or adalimumab. They concluded that anti-inflammatory therapies, particularly tumour necrosis factor (TNF) inhibitors, appear to partially restore HRV, underscoring the dynamic relationship between inflammation control and autonomic function [52]. Poor anti-TNF response or non-response was associated with low parasympathetic activity, low total power, and high sympathetic activity [52].

In 2019, Marsal et al. [53] enrolled 30 subjects who had a poor response to conventional synthetic disease-modifying antirheumatic drugs (DMARDs) and up to one biological DMARD. They were assigned to a non-invasive, wearable vagus nerve stimulation device for up to 30 minutes per day, which delivered pulses of 20 kHz. The study was prospective, multicentre, and open-label and resulted in a clinically meaningful reduction of disease activity as assessed by DAS-28 [53].

In conclusion, HRV monitoring in RA patients could provide important insights into disease severity, stress response, and the efficacy of therapeutic interventions. As research progresses, integrating HRV measurement into the management of RA may offer a more comprehensive approach to patient care, facilitating better outcomes through personalised treatment strategies.

5. Ankylosing spondylitis

Ankylosing spondylitis (AS) is a chronic autoimmune disease that primarily affects the axial skeleton, particularly the spinal joints, sacroiliac joints, and surrounding tendons and ligaments. The presence of chronic inflammation is associated with increased cardiovascular risk in this population [54].

Data on HRV changes in ankylosing spondylitis patients is limited. A meta-analysis published in 2024 [54] found significantly reduced HRV parameters compared to healthy controls, with an increased LF/HF ratio. Additionally, the reduced HRV correlated with disease activity indices, such as the Bath ankylosing spondylitis disease activity (BASDAI) score, and with C-reactive protein levels, indicating an association of parasympathetic dysfunction with the severity and active course of the disease [54, 55].

Thus, the available evidence suggests that ankylosing spondylitis is associated with autonomic dysfunction, as indicated by reduced HRV and an elevated LF/HF ratio. These changes not only mirror disease activity and systemic inflammation but may also contribute to the increased cardiovascular risk observed in this patient population.

6. Conclusions

The clinical utility of HRV monitoring in rheumatology is manifold. HRV provides a non-invasive, easy-to-repeat measure of autonomic and cardiovascular health, offering insights into systemic inflammation, subclinical cardiovascular involvement, and disease activity. Future research must aim to establish standardised

HRV measurement protocols, validate clinically meaningful cutoffs, and explore interventions such as autonomic modulation therapies to improve patient outcomes in rheumatic diseases.

Wearable technologies now facilitate longitudinal HRV tracking outside clinical settings, potentially revolutionising patient monitoring.

Recognising and addressing HRV alterations could transform the care of patients with rheumatic diseases, shifting focus towards more precise management strategies that integrate autonomic and cardiovascular health.

Acronyms and abbreviations

ANS	autonomic nervous system
AS	Ankylosing spondylitis
BASDAI	Bath ankylosing spondylitis disease activity
BILAG	British Isles Lupus Assessment Group
DAS-28	Disease Activity Score-28
dcSSc	diffuse cutaneous systemic sclerosis
DMARDs	synthetic disease-modifying antirheumatic drugs
HAQ	Health Assessment Questionnaire
HF	high-frequency
HRT	heart rate turbulence
HRV	heart rate variability
lcSSc	limited cutaneous systemic sclerosis
LF	low-frequency
PNN50	percentage of adjacent N-N intervals that are >50 msec apart
PNS	parasympathetic nervous system
RA	rheumatoid arthritis
RMSSD	root mean square successive differences
SDNN	standard deviation of N-N intervals
SDANN	standard deviation of the average of N-N intervals for each 5-min period over 24 hours
SLE	systemic lupus erythematosus
SLEDAI	Systemic Lupus Erythematosus Disease Activity Index
SNS	sympathetic nervous system
SSc	systemic sclerosis
TP	total power
TNF	tumour necrosis factor
VPBs	ventricular premature beats

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Edited by Ana Ciobanu

The link between the sympathetic-parasympathetic imbalance and the risk for arrhythmias led to the development of methods for assessing the autonomic nervous system activity. Currently, the most widely used method is heart rate variability, a readily available non-invasive tool. Heart rate variability measures the variations in time intervals between consecutive heartbeats, indicating the interaction between the sympathetic and parasympathetic nervous systems. In addition to its established roles in cardiology and diabetes, its clinical applications have expanded in recent years to encompass various health conditions and diseases. This book offers a comprehensive overview of heart rate variability, detailing its clinical relevance and recent advances in this rapidly evolving field.

Kaan Kırallı,
Cardiology and Cardiovascular Medicine Series Editor

Published in London, UK

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ISSN 3033-361X

ISBN 978-1-83634-272-4

