



Resting heart rate and heart rate variability in cardiovascular aging: Biomarkers and potential therapeutic targets

Weiguo Zhang*

Las Colinas Institutes, Irving, TX 75039, USA.

*Correspondence to: Weiguo Zhang, Las Colinas Institutes, Irving, TX 75039, USA. E-mail: weiguozha@yahoo.com

Received: March 24, 2026 Accepted: June 29, 2026 Published: June 29, 2026

Cite this article: Zhang W. Resting heart rate and heart rate variability in cardiovascular aging: Biomarkers and potential therapeutic targets. Geromedicine. 2026;2:202617. <https://doi.org/10.70401/Geromedicine.2026.0028>

Abstract

Cardiovascular aging is characterized by progressive loss of regulatory capacity, reduced physiological reserve, and increased vulnerability to stress and disease. Resting heart rate (RHR) and heart rate variability (HRV) provide complementary measures of cardiac automaticity and autonomic regulation, capturing important dimensions of cardiovascular aging. Comparative and epidemiological evidence demonstrates that elevated RHR and reduced HRV predict morbidity and mortality across species and human populations, reflecting cumulative physiological stress and declining regulatory function. Biological pathways associated with these autonomic phenotypes include sympathetic overactivation, parasympathetic withdrawal, neuroendocrine dysregulation, impaired baroreflex function, chronic inflammation, oxidative stress, and mitochondrial dysfunction. Clinical and mechanistic studies indicate that behavioral interventions (e.g., exercise and dietary modulation), pharmacological therapies, and neuromodulatory approaches can favorably influence RHR and HRV, although their causal effects on aging trajectories remain uncertain. Recent advances in wearable technologies and machine-learning-based phenotyping enable continuous assessment of autonomic function in both research and real-world settings. Integrating RHR and HRV into geroscience frameworks may help link autonomic regulation with fundamental aging mechanisms and cardiovascular risk. As accessible, noninvasive measures of physiological resilience and adaptability, RHR and HRV have potential value for advancing precision approaches to healthy cardiovascular aging and longevity.

Keywords: Autonomic nervous system, cardiovascular aging, cardiovascular outcomes, heart rate variability, resting heart rate, risk factors

1. Introduction

Aging is characterized by interconnected cellular and molecular hallmarks^[1], among which the progressive deterioration of intercellular and interorgan communication leads to impaired physiological integration, reduced resilience, and diminished capacity to adapt to stress^[2,3]. Cardiovascular regulation is particularly vulnerable to this process because it depends on precise coordination among intrinsic cardiac automaticity, autonomic neural control, and systemic endocrine and humoral influences.

Cardiac automaticity refers to the heart's intrinsic ability to generate rhythmic electrical impulses, originating primarily in pacemaker cells of the sinoatrial node^[4]. This activity sustains continuous cardiac contraction and relaxation, which drives blood circulation throughout life while remaining dynamically regulated to maintain homeostasis in response to internal and external demands.

The autonomic nervous system (ANS) provides the principal regulatory framework governing cardiac automaticity. By integrating afferent sensory input, central autonomic processing, and efferent sympathetic and parasympathetic outputs, it coordinates heartbeat, blood pressure, respiration, metabolism, and energy balance^[5]. Aging is accompanied by structural and functional alterations throughout this neurocardiac axis^[6], leading to impaired autonomic modulation, reduced physiological reserve, and diminished responsiveness to environmental and metabolic challenges. Consequently, autonomic dysregulation is increasingly recognized as both a hallmark and a potential driver of cardiovascular aging^[2].

Heart rate and rhythm provide accessible, integrative readouts of cardiac automaticity and autonomic regulation. For thousands of years, pulse rate (functionally equivalent to heart rate under normal physiological conditions) has served as a fundamental diagnostic indicator of health status. In modern medicine, resting heart rate (RHR) has emerged as an independent predictor of lifespan,



cardiovascular and all-cause morbidity and mortality across diverse populations^[7,8]. Elevated RHR is consistently associated with increased risk of adverse outcomes in both individuals with established cardiovascular disease (CVD) and those in the general population. This suggests that RHR reflects core aspects of biological aging beyond simply serving as a marker of disease burden.

In addition to cardiac speed, the heart exhibits continuous beat-to-beat variability even under resting conditions. These fluctuations in the intervals between successive cardiac cycles are commonly termed heart rate variability (HRV). HRV reflects the dynamic interplay between sympathetic and parasympathetic influences on the sinoatrial node. Whereas RHR provides a global index of cardiac chronotropy, HRV offers a more sensitive measure of autonomic flexibility, neurocardiac coupling, and adaptive capacity. Accumulating evidence links reduced HRV to aging-related phenotypes, including frailty, impaired stress resilience, metabolic dysfunction, cognitive decline, and increased risk of premature mortality. This positions HRV as a functional marker of biological aging^[2,3].

Given their strong associations with lifespan, functional capacity, and responsiveness to lifestyle and therapeutic interventions, RHR and HRV have attracted increasing attention as both biomarkers and potential intervention targets in cardiovascular aging research.

This review synthesizes evidence from comparative biology, epidemiology, clinical studies, and mechanistic research to examine how RHR and HRV reflect, contribute to, and potentially modulate cardiovascular aging. It also explores their translational value for assessing biological aging and guiding interventions aimed at preserving autonomic function and promoting healthy longevity.

2. RHR and Cardiovascular Aging

2.1 Comparative biology of RHR in homeothermic mammals

Among homeothermic mammals, RHR exhibits an inverse correlation with body size and lifespan, forming one of the most reproducible patterns in comparative biology. Small mammals are characterized by rapid cardiac rhythms and short lifespans, whereas large mammals display slower heart rates and markedly greater longevity^[9]. These relationships broadly follow allometric scaling principles observed in metabolic physiology, in which heart rate scales inversely with body mass (i.e., heart rate $\propto$ body mass^{-1/4})^[7]. This scaling reflects fundamental constraints imposed by metabolic demand, thermoregulation, and cardiovascular design.

The contrast is particularly evident between a shrew and an elephant. A shrew's heart may beat approximately 1,000 times per minute (bpm), whereas an elephant's heart beats at approximately 40 bpm^[10]. Despite their profound biological differences, the total number of heartbeats accumulated over the lifespan of many mammalian species converges on a remarkably similar value of approximately one billion beats^[7,11].

Early conceptual frameworks proposed that organisms possess a finite number of lifetime heartbeats, implying that a faster cardiac rate causally contributes to biological wear. The idea is explained by the fact that pacemaker cells have to undergo continuous cycles of depolarization–repolarization, and cardiomyocytes have to correspondingly undergo contraction–relaxation to sustain systemic perfusion^[12]. Although this “fixed heartbeat” hypothesis may be considered overly simplistic, comparative analyses across mammalian species continue to demonstrate that RHR remains strongly associated with lifespan, even after accounting for body mass and basal metabolic rate^[13]. These findings suggest that RHR signifies deeper principles of physiological organization instead of serving merely as a proxy for body size or energy expenditure.

Deviations from simple allometric scaling provide further insight into the biology of exceptional longevity. Several long-lived mammalian lineages, including primates and certain marine mammals, exhibit lower RHR than predicted by body mass, in parallel with extended lifespan^[14,15]. These few exceptions suggest that longevity is not determined solely by body size or metabolic rate, but also by qualitative differences in cardiovascular organization that remain incompletely understood. Rather than simply exhibiting slower heart rates, long-lived species appear to achieve greater cardiovascular efficiency and stability, potentially through optimized cardiac filling and more refined autonomic regulation. Although direct comparative measurements of autonomic function across species remain limited, these patterns are consistent with the concept that a preserved cardiovascular system and its regulatory capacity, in addition to a reduced cardiac cycle *per se*, contribute to greater longevity.

Comparative mammalian biology yields two key insights^[9,16,17]: First, RHR represents an integrative physiological phenotype shaped by evolutionary trade-offs among metabolic demand, thermoregulation, and environmental pressures. Second, species with exceptional longevity often deviate from standard metabolic scaling, exhibiting relatively low RHR alongside preserved autonomic flexibility. These features are consistent with enhanced physiological reserve and homeostatic resilience. These characteristics parallel hallmarks of healthy aging in humans, including restrained sympathetic tone, preserved parasympathetic modulation, and improved stress resilience. Unlike fixed interspecies traits such as body size or cardiac structure, RHR in humans can be modulated across the lifespan through behavioral (e.g., exercise and dietary), environmental, and pharmacological interventions. This distinction positions RHR at the intersection of evolutionary constraint and therapeutic opportunity, a concept central to geroscience.

At the same time, comparative frameworks caution against simplistic causal interpretations. Although lower RHR is generally

associated with increased longevity across species, extreme bradycardia or pathological conduction abnormalities is often accompanied by maladaptive processes distinct from healthy aging^[18]. Thus, evidence from mammalian biology supports a model in which optimal ranges of cardiac automaticity, rather than unidirectional reduction, are associated with extended healthspan. Recapitulating, RHR emerges as a conserved, integrative trait linked to lifespan and aging, reflecting systemic regulatory capacity and autonomic balance. While interspecies patterns highlight evolutionary constraints, they also raise a critical question: To what extent do these relationships translate to variability in RHR and aging outcomes within human populations?

2.2 Epidemiological evidence from general population

Epidemiological investigations in human populations provide an opportunity to determine whether the inverse relationships between RHR, longevity, and cardiovascular risk observed across species are also evident within human populations. Over the past several decades, large prospective cohort studies have consistently demonstrated that elevated RHR predicts cardiovascular morbidity and mortality, and all-cause mortality across diverse populations.

Early evidence emerged from long-term, community-based cohorts. Analyses from the Framingham Heart Study (FHS) showed that higher RHR was associated with increased cardiovascular and all-cause mortality over more than three decades of follow-up among 5,209 men and women^[19]. The fact that these associations were observed in individuals free of overt CVD at baseline, suggests that elevated RHR may precede clinically manifest disease. Similar findings were later replicated in the FHS Offspring Cohort^[20].

These observations have been corroborated by several other renowned studies. The Chicago Heart Association Detection Project demonstrated a continuous “dose–response” relationship between RHR and long-term mortality in men^[21]. Likewise, the NHANES Epidemiologic Follow-up Study reported that higher RHR predicted all-cause mortality in both men and women, confirming that this association extends across sexes^[22].

Consistent evidence has also emerged from European populations. In a French cohort of 19,386 individuals, higher RHR independently predicted all-cause, cardiovascular, and coronary heart disease (CHD) mortality in men, with similar trends observed in women^[23]. In another study of 5,713 asymptomatic middle-aged men followed for 23 years, a 15-bpm higher RHR nearly doubled the risk of all-cause mortality and more than tripled the risk of sudden death due to myocardial infarction (MI)^[24]. Comparable findings have been reported in Nordic populations. The FINRISK Study, which included more than 20,000 participants, showed that each 15-bpm increase in RHR was associated with a 24% higher risk of cardiovascular death in men and a 32% higher risk in women, after adjustment for major risk factors^[25]. Similarly, a longitudinal Swedish cohort found that individuals with baseline RHR above 75 bpm had approximately twice the risk of cardiovascular and all-cause mortality compared with those below 55 bpm, and each incremental increase in RHR was associated with a 3% higher risk of all-cause mortality, a 1% higher risk of CVD, and a 2% higher risk of CHD^[26].

Evidence from Asian populations further supports the generalizability of these findings. In a prospective study of 92,562 adults in northern China, individuals in the highest RHR quintile (≥ 81 bpm) had significantly higher risks of MI (hazard ratio: 1.10, 95% CI: 1.01–1.20) and all-cause mortality (hazard ratio: 1.18; 95% CI: 1.13–1.23) compared with those in the lowest quintile (≤ 66 bpm) during a 4-year follow-up^[27]. Similar associations have been reported in Japan and Korea^[28,29].

Particularly noteworthy is the combined analysis of the Taiwan MJ and Norway HUNT cohorts^[30]. Among 692,217 adults followed for 25 years, individuals with RHR between 80 and 99 bpm had substantially reduced life expectancy; at 90–99 bpm, the associated risk was comparable to that of hypertension.

The association between RHR and adverse outcomes extends across the adult lifespan. Cohorts with RHR measured in early adulthood demonstrate that higher RHR predicts cardiovascular disorders and major adverse cardiovascular events decades later, independent of adiposity, smoking, physical activity, and inflammatory status^[29,31–34]. These findings suggest that chronotropic characteristics established early in life may influence long-term cardiovascular aging trajectories^[7]. Most studies measure RHR at only a single time point (specifically, at baseline) to establish correlations; however, the Melbourne Collaborative Cohort Study demonstrated that, during the follow-up of tens of thousands of participants over a decade, a temporal increase in RHR was associated with a greater risk of mortality from CVD and cancer^[35].

Longitudinal analyses incorporating repeated measurements provide additional insight into the dynamic nature of this relationship. Population-based studies show that increases in RHR over time are associated with higher risks of cardiovascular mortality and all-cause death, independent of baseline heart rate and other risk factors^[36]. Individuals with progressively rising RHR trajectories exhibit disproportionately greater mortality risk, suggesting that temporal changes in RHR imply deterioration in autonomic and cardiovascular regulation.

Across diverse geographic regions, large-scale contemporary studies from Europe, North America, and Asia consistently demonstrate that a higher RHR is associated with increased cardiovascular and all-cause mortality, even after adjusting for demographic factors, lifestyle behaviors, and comorbidities^[7,37,38]. [Table 1](#) provides a summary of these landmark findings. Consistent with predictions from comparative biology, this population-based evidence reveals a graded, temporally robust relationship between RHR and

cardiovascular aging, morbidity, and mortality. The strength and reproducibility of these associations across diverse cohorts support the use of RHR as an integrative marker of physiological stress and cardiovascular risk, establishing a strong epidemiological foundation for subsequent clinical and mechanistic investigations.

Table 1. Representative epidemiological studies linking elevated RHR with CV outcomes.

Study/Cohort	Population/Sample Size	Follow-up Duration	Main Outcomes
Framingham Heart Study ^[19]	5,209 men and women of general population	> 30 years	Higher RHR associated with increased CV and all-cause mortality, even in those free of CVD at baseline
Framingham Offspring Cohort ^[34]	Community-based adults	20 years	Elevated RHR in early adulthood predicted long-term CV risk independent of conventional risk factors
Three Chicago Epidemiologic Studies ^[21]	Middle-aged men from general population	1, 15 and 17 years	Higher RHR independently predicted sudden CHD death, and associated with other CVD and non-sudden CHD death
NHANES I Follow-up Study ^[22]	U.S. adult men and women	6-13 years	Elevated pulse/RHR predicted coronary heart disease and mortality across sexes
French IPC Cohort ^[23]	19,386 adults	20 years	Higher RHR independently predicted all-cause, CV, and coronary mortality in men
Paris Prospective Study I ^[24]	5,713 asymptomatic middle-aged men	23 years	A 15-bpm higher RHR nearly doubled all-cause mortality risk and markedly increased sudden death risk
FINRISK Study ^[25]	21,853 participants	6-27 years	Each 15-bpm increase in RHR, the risk of CV death increases by 24% in men and 32% in women
Swedish Population Register Gothenburg ^[26]	Community-based middle-aged men	21 years	RHR > 75 bpm associated with approximately two-fold higher CV and all-cause mortality risk
Kailuan Study ^[27]	92,562 Chinese adults	4 years	Those with highest RHR quintile had significantly greater risks of myocardial infarction and mortality
NIPPONDATA80 study ^[28]	10,546 community dwellers	16.5 years	Higher RHR linked to CVE events, CV and all-cause mortality
KNHANES Cohort ^[29]	31,697 Korean adults	9.2 years	Compared to RHR of 60-69 bpm, the risk of CVD mortality was higher in RHR of < 60 and ≥ 80 bpm
Taiwan MJ + Norway HUNT Cohorts ^[30]	692,217 adults from Asia and Europe	25 years	RHR of 80-99 bpm linked to reduced life expectancy; risks comparable to hypertension at higher RHR levels
Melbourne Collaborative Cohort ^[35]	Tens of thousands of adults	10 years	Temporal increases in RHR over time associated with higher CV and cancer mortality

CV: cardiovascular; CVD: cardiovascular disease; CHD: coronary heart disease; RHR: resting heart rate; CVE: cardiovascular events.

2.3 Clinical medicine: RHR, morbidity, and mortality in patient populations

Clinical investigations in patient populations provide more direct evidence linking RHR to cardiovascular morbidity and mortality. Across a wide range of cardiovascular disorders, higher RHR consistently predicts adverse outcomes and appears to reflect both disease severity and underlying mechanisms relevant to cardiovascular aging^[39].

Earlier findings came from patients with established CHD. Multiple investigations and subsequent meta-analyses have shown that elevated RHR in patients with stable angina or prior MI is associated with increased risks of developing cardiovascular events and mortality, independent of left ventricular function, ischemic burden, and other prognostic indicators^[40,41].

CHD: Randomized clinical trials targeting heart rate reduction offered evidence of the role of RHR in cardiovascular outcomes. The BEAUTIFUL trial demonstrated that in patients with stable CHD and left ventricular systolic dysfunction, RHR ≥ 70 bpm was associated with increased risks of cardiovascular death and hospitalization for heart failure^[42]. In this study, treatment with ivabradine, a selective inhibitor of the sinoatrial node “funny” current (I_f) that reduces heart rate by slowing pacemaker activity^[43],

reduced the incidence of fatal and non-fatal MI and coronary revascularization among patients with baseline RHR ≥ 70 bpm. These findings suggest that heart rate may serve both as a clinical target and as a modifiable contributor to coronary outcomes.

Beyond CHD, evidence from hypertensive and heart failure populations further supports the prognostic significance of RHR across diverse cardiovascular conditions.

Hypertension: In untreated hypertensive participants enrolled in the Systolic Hypertension in Europe Trial, individuals with RHR exceeding 79 bpm had a nearly 1.9-fold higher risk of all-cause, cardiovascular, and non-cardiovascular mortality compared with those with lower RHR over four years of follow-up^[44]. Similarly, among treated hypertensive patients, on-treatment RHR remained an independent predictor of adverse outcomes^[45]. This highlights the clinical importance of monitoring RHR during antihypertensive therapy and the need to avoid baroreceptor-mediated tachycardia, which can persist in the absence of baroreceptor resetting (as well as excessive treatment-induced bradycardia)^[46,47].

Heart failure: Strong evidence for the prognostic significance of RHR has also emerged from heart failure populations. The Systolic Heart Failure Treatment with the I_r Inhibitor Ivabradine Trial demonstrated that higher RHR strongly predicted adverse clinical outcomes^[48]. In the placebo group, patients with RHR ≥ 87 bpm had more than double the risk of the primary composite endpoint compared with those with lower heart rate. Specifically, the risk increased progressively, by approximately 3% for each 1-bpm increase and by about 16% for every 5-bpm increment in baseline heart rate.

Beyond these conditions, elevated RHR has been associated with adverse outcomes across a range of cardiometabolic disorders, including diabetes mellitus, chronic kidney disease, and acute coronary syndromes^[49-51]. These observations suggest that the prognostic value of RHR extends beyond specific diagnoses and reflects broader pathophysiological processes linking autonomic imbalance, metabolic stress, and vascular dysfunction.

In summary, RHR represents more than a simple marker of disease severity and may actively contribute to morbidity and mortality in clinical populations. The observation that selective heart rate reduction improves outcomes in certain settings, particularly in heart failure and CHD, supports a partially causal relationship between RHR and cardiovascular prognosis. However, the benefits of RHR reduction are not uniform across all clinical conditions. While heart rate-lowering therapies such as β -blockers provide substantial benefits in selected populations, especially patients with heart failure with reduced ejection fraction, the extent to which these benefits are directly attributable to heart rate reduction rather than other pharmacological effects remains uncertain. Furthermore, interventions that lower heart rate have not consistently improved outcomes across all cardiovascular conditions^[52,53]. This variability likely reflects the complex interplay among chronotropic effects, hemodynamic responses, autonomic regulation, and drug-specific pharmacological actions. Moreover, because many heart rate-lowering therapies were not originally developed to selectively target elevated heart rate, it remains difficult to determine the extent to which their clinical benefits are specifically mediated by heart rate reduction itself^[46].

Integrating evidence from comparative biology, population-based cohorts, and clinical studies indicates that elevated RHR is consistently associated with adverse cardiovascular outcomes across species and human populations. Findings from randomized trials further suggest that heart rate may also function as a potentially modifiable determinant of outcomes (Figure 1). These observations raise a fundamental question: Through which mechanisms does heart rate influence cardiovascular health and aging?

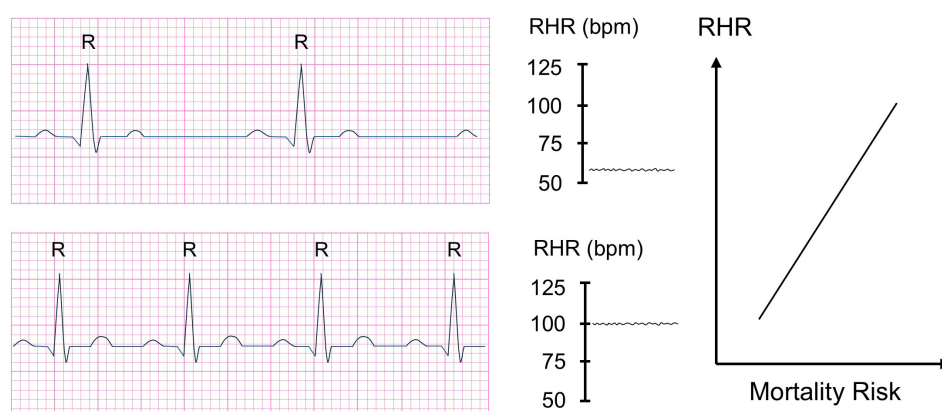


Figure 1. Schematic representation of the relationship between RHR and mortality. Left: ECG tracings illustrating slower and faster heart rate (specifically, differing R-R intervals). Center: The clinical range of a normal resting heart rate (60-100 bpm), identifying typical upper and lower physiological limits. Right: The general relationship between RHR and mortality risk. The conceptual figure represents associations reported in epidemiological and clinical studies and does not imply direct causality. RHR: resting heart rate; ECG: electrocardiogram.

2.4 Mechanisms linking elevated RHR to aging progression and disease development

From a cardiovascular aging perspective, chronically elevated RHR may contribute to a range of adverse processes, including increased myocardial oxygen demand, hemodynamic stress, inflammation, oxidative injury, and pathological remodeling^[54,55]. Evidence from experimental, epidemiological, and clinical studies suggests that elevated RHR is not merely a marker of cardiovascular risk but may actively influence aging-related cardiovascular deterioration through multiple interconnected pathways^[56]. As summarized in Figure 2, these mechanisms converge on autonomic dysregulation, neuroendocrine activation, oxidative stress, inflammation, and structural remodeling, ultimately accelerating cardiovascular decline.

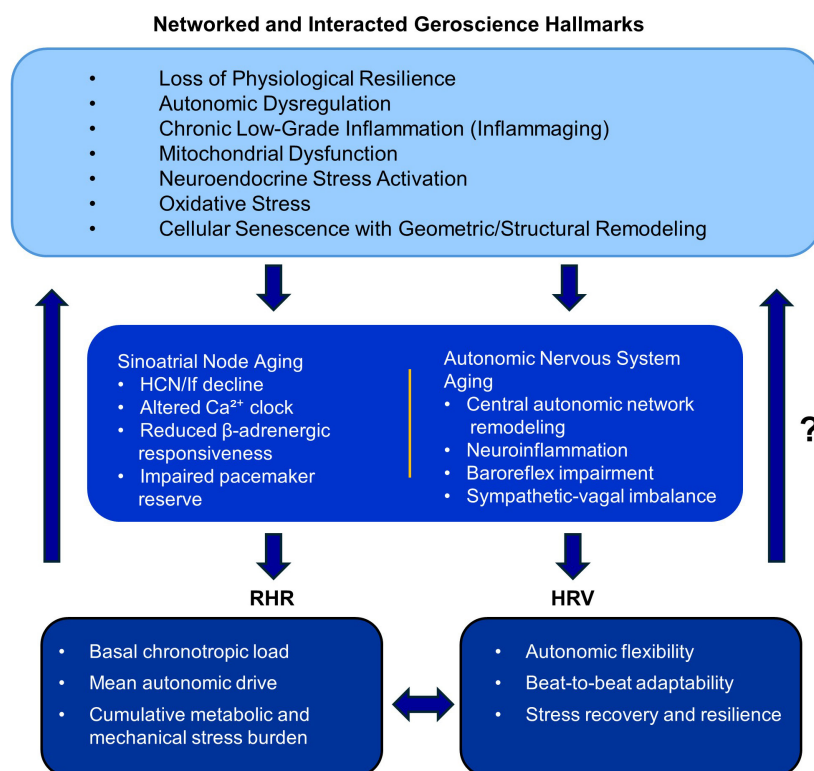


Figure 2. RHR and HRV as integrative phenotypes of cardiovascular aging. Cardiovascular aging is driven by interconnected hallmarks of cardiac aging, including mitochondrial dysfunction, dysregulated neurohormonal signaling, inflammation, impaired proteostasis and macroautophagy, genomic instability, epigenetic alterations, and cellular senescence^[149]. These processes converge on autonomic regulation and cardiac automaticity through central-peripheral neurocardiac pathways. The baroreflex, a key short-term regulatory mechanism linking arterial pressure to cardiac vagal control, is depicted as a functional component of this integrated system and contributes to the regulation of both RHR and HRV. RHR reflects the level of autonomic drive and the basal chronotropic demand imposed on the heart, integrating cumulative sympathetic activity, metabolic influences, and stress exposure. In contrast, HRV reflects the flexibility and regulatory capacity of autonomic control, capturing the dynamic ability to adapt to physiological perturbations. Although mechanistically intertwined and shaped by shared biological substrates, RHR and HRV provide distinct and complementary information. Their joint assessment offers a multidimensional functional readout of cardiovascular aging, linking molecular aging processes to systems-level regulation and clinical risk. RHR: resting heart rate; HRV: heart rate variability.

Autonomic Imbalance and Sympathetic Overactivation: A central mechanism linking elevated RHR to cardiovascular aging is persistent autonomic imbalance characterized by increased sympathetic activity and reduced parasympathetic (vagal) modulation^[57,58]. Aging is accompanied by a progressive shift toward sympathetic dominance, reflected by altered heart rate regulation at rest, during exercise, and throughout recovery, as well as reduced HRV (see Section 3)^[59,60].

Chronic sympathetic activation increases myocardial oxygen demand, shortens diastolic filling time, and impairs coronary perfusion, thereby promoting ischemia, metabolic inefficiency, and cardiomyocyte stress. It also stimulates adrenergic vasoconstriction, activates the renin-angiotensin system, impairs endothelial function, and reduces baroreflex sensitivity^[61,62]. Over time, these alterations contribute to arterial stiffening, vascular dysfunction, myocardial fibrosis, and diminished physiological resilience, hallmarks of cardiovascular aging^[63]. Thus, elevated RHR reflects aging-related autonomic dysregulation and declining cardiovascular adaptability.

Psychological Stress and Neuroendocrine Activation: Psychological and psychosocial stress are important modulators of heart rate and autonomic tone. Activation of central autonomic networks and the hypothalamic-pituitary-adrenal (HPA) axis increases circulating catecholamines and glucocorticoids, promoting persistent tachycardia, hypertension, and metabolic dysregulation^[64].

Repeated or chronic stress exposure contributes to “allostatic load”, representing the cumulative physiological burden imposed by prolonged neuroendocrine activation^[65]. Elevated RHR may therefore reflect persistent neurocardiac activation and impaired recovery from stress, providing a physiological link between psychosocial stressors and accelerated biological aging. Stress-related increases in heart rate are frequently accompanied by reduced HRV, further indicating diminished autonomic flexibility and adaptive capacity.

Oxidative Stress, Inflammation, and Cellular Injury: Elevated RHR increases metabolic demand in cardiomyocytes and vascular cells, leading to enhanced mitochondrial respiration and greater production of reactive oxygen species (ROS). Sustained tachycardia may therefore amplify oxidative stress, overwhelm antioxidant defenses, and promote molecular damage to lipids, proteins, and DNA^[66].

Oxidative stress is a major driver of cardiovascular aging and contributes to mitochondrial dysfunction, impaired calcium handling, cellular senescence, and chronic low-grade inflammation^[67]. In parallel, sympathoexcitation and reduced parasympathetic activity promote a pro-inflammatory milieu through activation of adrenergic and renin-angiotensin signaling pathways and attenuation of the cholinergic anti-inflammatory reflex^[68-70].

Together, oxidative stress and inflammation contribute to endothelial dysfunction, atherosclerosis, myocardial fibrosis, and arterial stiffening, creating a self-reinforcing cycle that progressively amplifies cardiovascular injury. Experimental studies further suggest that heart rate reduction attenuates oxidative stress and preserves mitochondrial function, supporting a mechanistic link between chronotropic load and molecular aging pathways^[71].

Hemodynamic Stress and Structural Remodeling: Beyond its neurobiological and molecular effects, chronically elevated RHR imposes cumulative mechanical stress on the myocardium and vasculature. Higher RHR shortens diastole, reduces coronary perfusion time, and increases pulsatile load^[72]. These effects over time promote left ventricular hypertrophy, myocardial fibrosis, arterial stiffening, and adverse vascular remodeling, all of which impair cardiovascular efficiency and reserve.

The concept of chronotropic load integrates RHR over time, emphasizing that sustained elevations (even within clinically normal ranges) may contribute to cumulative cardiovascular wear across the lifespan. This is supported by evidence from comparative biology and epidemiology linking RHR trajectories to aging and survival.

Integration with Biological Aging: Elevated RHR represents more than a simple biomarker of cardiovascular risk. It reflects the cumulative effects of autonomic dysregulation, neuroendocrine stress, oxidative injury, inflammation, and chronic hemodynamic strain. These interconnected processes progressively erode cardiovascular resilience and accelerate functional decline, placing elevated RHR within the broader biological framework of cardiovascular aging (Figure 2).

An important nuance is that age-related changes in heart rate are not uniform across the lifespan^[73]. While elevated RHR is consistently associated with increased cardiovascular risk and adverse aging-related outcomes in epidemiological studies, some human and experimental studies have reported reductions in intrinsic heart rate with advancing age, likely reflecting age-associated remodeling of the sinoatrial node, degeneration of the cardiac conduction system, reduced β -adrenergic responsiveness, and alterations in autonomic regulation^[74,75]. At the cellular level, aging is accompanied by changes in key pacemaker mechanisms, including reduced activity of hyperpolarization-activated cyclic nucleotide-gated channels responsible for the funny current (I_f), impaired intracellular calcium cycling, and disruption of the coupled-clock system that coordinates membrane ion channel activity with sarcoplasmic reticulum calcium release^[76]. These observations do not necessarily contradict the prognostic significance of elevated RHR. Rather, they highlight the distinction between age-related physiological changes in cardiac pacemaking and the relative risk associated with RHR within a given age group. Thus, among individuals of similar age, a higher RHR generally remains associated with greater cardiovascular risk, whereas age-related reductions in intrinsic heart rate may reflect underlying biological changes of the aging myocardium.

From a clinical perspective, it may be useful to consider intermediate RHR risk states such as “high-normal” RHR (e.g., 85-100 bpm) or “pre-tachycardia”^[4,77,78], analogous to the concepts of prehypertension and prediabetes. Such stratification helps facilitate earlier identification of individuals at increased risk for cardiovascular dysfunction and aging-related decline.

The framework of RHR also provides a conceptual bridge to HRV. Whereas RHR reflects baseline physiological load and generalized autonomic tone, HRV captures the dynamic adaptability of autonomic regulation. Reduced HRV indicates impaired flexibility and diminished capacity to respond to physiological challenges (see Section 3). Together, elevated RHR and reduced HRV provide complementary perspectives on autonomic dysfunction in cardiovascular aging.

3. HRV and Cardiovascular Aging

HRV refers to beat-to-beat variation in cardiac cycle length and is quantified from the time intervals between adjacent normal heartbeats (normal-to-normal intervals)^[79]. Commonly used HRV indices across time-domain, frequency-domain, and non-linear analyses are summarized in Table 2.

Table 2. Common HRV indices, their measurement domains, definitions, and physiological significance.

HRV Index	Type	Definition	Physiological Significance
SDRR	Time-domain	Standard deviation of all RR intervals, including abnormal/ectopic beats	Reflects total RR variability, non-autonomic factor can inflate values
SDNN	Time-domain	SD of NN intervals	Reflects overall HRV and long-term autonomic regulation
RMSSD	Time-domain	Root mean square of successive differences between adjacent NN intervals	Reflects short-term parasympathetic (vagal) activity
pNN50	Time-domain	Percentage of NN intervals differing by > 50 ms	Indicates parasympathetic modulation
HF	Frequency-domain	High-frequency power (0.15-0.40 Hz)	Reflects parasympathetic (vagal) activity, particularly respiratory-related variability
LF	Frequency-domain	Low-frequency power (0.04-0.15 Hz)	Reflects a mix of sympathetic and vagal influences; interpretation as a pure sympathetic marker is contested
VLF	Frequency-domain	Very low-frequency power (0.003-0.04 Hz)	Associated with thermoregulation and long-term regulatory processes
ULF	Frequency-domain	Ultra-low-frequency power (≤ 0.003)	Reflects circadian rhythms, metabolism, and the renin-angiotensin system; requires 24-hour recordings
LF/HF Ratio	Frequency-domain	Ratio of LF to HF power	Proposed index of sympathovagal balance; interpretation is debated due to the dual-input nature of the LF component
TP	Frequency-domain	Total variance in HRV signal, including VLF, LF, and HF components	Reflects overall autonomic nervous system activity

HRV: heart rate variability; NN: normal-to-normal; TP: total power.

Although mathematically related to heart rate, HRV provides distinct physiological information regarding ANS regulation. Early clinical observations demonstrated that fetal distress is preceded by alterations in beat-to-beat intervals before changes in average heart rate occur^[2,80]. Experimental studies further support this difference: In heart rate-controlled conditions, HRV indices vary significantly even when mean heart rate is held constant, indicating that HRV is not a simple mathematical derivative of heart rate, but a reflection of underlying autonomic modulation^[81]. Similarly, metabolic interventions such as glucose and fructose supplementation can reduce HRV without altering mean heart rate^[82]. These observations indicate that HRV captures physiological information complementary to, and not fully reflected by, RHR.

3.1 Epidemiological evidence linking HRV to cardiovascular aging

Epidemiological studies over the past several decades have examined the relationships among HRV, aging, and cardiovascular outcomes across diverse populations. Early studies documented a pronounced age-related decline in HRV^[83]. Cross-sectional and longitudinal analyses showed progressive reductions in time- and frequency-domain measures, persisting even in healthy populations without overt CVD^[84,85]. These observations indicate that reductions in HRV accompany aging and may reflect alterations in autonomic regulation beyond clinically manifest disease.

Prospective evidence linking HRV to cardiovascular outcomes emerged from the FHS. In 2,501 participants with a mean age of 53 years and 3.5 years of follow-up, reduced HRV predicted incident cardiovascular events, including angina pectoris, MI, coronary death, and congestive heart failure^[86]. Specifically, with the exception of the low-frequency (LF) to high-frequency (HF) power ratio, reduced HRV indices remained significantly associated with increased risk of adverse outcomes after adjustment for conventional risk factors. A one-standard deviation decrease in log-transformed standard deviation of normal-to-normal intervals (SDNN) was associated with a hazard ratio of 1.47 (95% CI: 1.16–1.86) for incident cardiac events after multivariable adjustment. Earlier analyses from the same cohort also showed that reduced HRV predicted all-cause mortality. Among elderly participants, each one-standard deviation decrease in SDNN was associated with a 1.38-fold increase in mortality risk (95% CI: 1.13–1.70), while the same decrease in LF power corresponded to a 70% higher risk of death after adjustment for demographic and clinical factors^[87].

Other population-based studies confirm these observations. For instance, European cohort analyses, including the Zutphen Study, demonstrate that reduced HRV predicts both fatal and non-fatal coronary events, supporting its generalizability as an epidemiological marker of cardiovascular risk^[88].

The prognostic significance of HRV is further reinforced by findings from the Atherosclerosis Risk in Communities Study, in which reduced HRV predicted CHD events and all-cause mortality over a 4-year follow-up^[89]. The results of the latest cardiovascular disease, living and ageing in Halle study were in line with the previous findings^[90]. Importantly, this relationship is graded and continuous, with progressively lower HRV associated with higher risk, indicating that HRV functions as a quantitative marker of cardiovascular vulnerability rather than a dichotomous abnormality. Of particular note are the results of the Rotterdam Study^[91], which revealed a U-shaped relationship between SDNN and cardiac mortality during a 4-year follow-up; however, this finding was likely influenced by underlying cardiovascular pathologies within the elderly population, as well as by the use of short-duration electrocardiogram recordings lasting only 10 seconds. [Table 3](#) provides epidemiologic representative studies linking reduced HRV with cardiovascular outcomes.

Table 3. Representative epidemiological studies linking reduced HRV with CV outcomes.

Study	Population	Follow-up Time	Main Findings
Framingham Heart Study ^[86]	2,501 adults (mean age 53 years)	3.5 years	Reduced HRV predicted incident CV events, each SD decrease in SDNN associated with 1.47 times greater hazard for new cardiac events
Framingham Heart Study ^[87]	736 adults (mean age 72 years)	4 years	Lower LF independently predicted all-cause mortality; each SD decrease in LF associated with 1.70 times greater hazard for all-cause mortality
Zutphen Study ^[88]	878 adults (40-60 years), and 885 adults (65-85 years)	15 years, and 5 years	Lower HRV predicted mortality from all causes
Rotterdam Study ^[91]	5,272 adults (≥ 55 years)	4 years	Both lower and higher Heart HRV predict cardiac mortality
ARIC Study ^[89]	Middle-aged adults of general population	4 years	Lower HRV predicted CHD events and mortality; association was graded and continuous
CARLA Study ^[90]	1,779 adults (45-83 years)	4-8 years	Lower HRV associated with CV risk factors and mortality

HRV: heart rate variability; CV: cardiovascular; SDNN: standard deviation of normal-to-normal intervals; LF: low-frequency; SD: standard deviation; ARIC: atherosclerosis risk in communities; CHD: coronary heart disease; CARLA: cardiovascular disease, living and ageing in Halle.

Beyond clinical endpoints, reduced HRV is also associated with subclinical markers of cardiovascular aging. Lower HRV correlates with arterial stiffness, endothelial dysfunction, systemic inflammation, and adverse metabolic profiles in individuals without overt CVD^[70,92], suggesting that autonomic dysregulation is closely linked to early aging-related pathophysiology.

These findings collectively support HRV as a marker of cardiovascular aging and an independent predictor of morbidity and mortality. The consistency of these associations across diverse populations underscores the importance of autonomic regulation in cardiovascular health and aging.

3.2 Clinical evidence: HRV, cardiovascular morbidity, and mortality

Clinical investigations have examined the relationship between HRV and cardiovascular outcomes in patients with established disease. In contrast to epidemiological studies in general populations, these studies are typically conducted in high-risk settings, such as post-MI, heart failure, diabetes, and chronic kidney disease, where autonomic dysfunction is prevalent and cardiovascular aging is often accelerated. Across these conditions, reduced HRV has been consistently associated with increased morbidity and mortality.

Post-MI and Ischemic Heart Disease: Early studies in post-MI patients provided some of the first clinical evidence linking autonomic dysfunction to adverse outcomes. In a landmark study of 820 patients recovering from acute MI, 24-hour Holter recordings obtained shortly after the event were used to assess HRV, and patients were followed for 31 months. Mortality risk was 5.3-fold higher among those with SDNN < 50 milliseconds (ms) compared with those with SDNN > 100 ms^[93].

Subsequent investigations extended these findings using frequency-domain analyses. In 715 patients studied two weeks after MI, reductions in LF and HF power were modestly associated with mortality, whereas reductions in total power, ultra-low-frequency, and very-low-frequency (VLF) power showed stronger associations after multivariable adjustment during four years of follow-up. Reduced VLF power was particularly linked to arrhythmic death^[94]. The prognostic value of impaired autonomic regulation after MI

was subsequently confirmed and expanded by the ATRAMI study^[95].

Despite the strength of these associations, most studies are observational. Reduced HRV may represent irreversible myocardial damage, impaired baroreflex sensitivity, or broader systemic aging processes as opposed to acting as a direct causal driver of mortality.

Heart Failure: Chronic heart failure is characterized by parasympathetic withdrawal and sustained sympathetic activation, resulting in a persistent hyperadrenergic state^[61,96]. Reduced HRV in this setting reflects marked sympathovagal imbalance and impaired autonomic regulation^[97].

In the prospective UK-Heart Study, 433 patients with heart failure were followed longitudinally. Each 41.2-ms reduction in SDNN was associated with a higher risk of all-cause mortality (risk ratio 1.62; 95% CI, 1.16–2.44). Mortality increased progressively across SDNN categories: 5.5% for SDNN > 100 ms, 12.7% for 50–100 ms, and 51.4% for < 50 ms^[98]. Reduced HRV predicted mortality independently of New York Heart Association class and left ventricular function, reinforcing its value as a marker of autonomic dysfunction and disease severity.

Whether reduced HRV actively contributes to disease progression or primarily reflects advanced pathophysiology remains unresolved.

Diabetes and Metabolic Disease: Autonomic dysfunction is a well-recognized complication of diabetes and is frequently manifested by reduced HRV. A meta-analysis of 25 case-control studies (2,932 participants) demonstrated significantly lower HRV across multiple indices in patients with type 2 diabetes mellitus, including SDNN, root mean square of successive differences, pNN50, total power, LF power, and HF power^[99].

Cardiac autonomic neuropathy (CAN), also referred to as diabetic autonomic neuropathy, is a major complication characterized by progressive autonomic impairment and marked reductions in HRV^[100]. A meta-analysis of 26 studies involving 14,597 participants confirmed that CAN, identified by reduced HRV, is a strong predictor of cardiovascular events and mortality, conferring approximately a three-fold higher risk (risk ratios 3.16 and 3.17, respectively) compared with individuals without CAN^[101]. Risk appears graded, with “definite” CAN carrying greater prognostic significance than “possible” CAN, and with stronger effects observed in type 1 compared with type 2 diabetes.

As HRV impairment often precedes overt CVD, autonomic dysregulation may represent an early manifestation of accelerated cardiovascular aging. However, coexisting metabolic, inflammatory, and vascular abnormalities can complicate causal interpretation.

Other Clinical Populations: Reduced HRV has also been associated with adverse outcomes in chronic kidney disease, hypertension, stroke, and atrial fibrillation^[102–105]. Across these conditions, lower HRV consistently correlates with increased cardiovascular and all-cause mortality, underscoring its broad prognostic relevance.

Interpretation, Strong Associations but Limited Causal Evidence: While strong and consistent associations between reduced HRV and adverse outcomes have been demonstrated, direct evidence establishing a causal relationship remains limited. Most studies are observational, and HRV is closely confounded by disease severity, structural cardiac and neural abnormalities, inflammation, and neurohumoral activation.

Interventions targeting autonomic modulation, such as β -adrenergic blockade, exercise training, dietary interventions (e.g., caloric restriction), and vagal nerve stimulation, often improve HRV alongside clinical outcomes^[2,106–111]. However, these interventions typically have pleiotropic effects, and heterogeneity in study design and patient populations complicates interpretation of their impact on clinical endpoints^[112]. It therefore remains unclear whether improvements in HRV directly mediate risk reduction or instead reflect broader improvements in cardiovascular and autonomic function^[113].

The clinical investigations demonstrate that reduced HRV is consistently associated with increased morbidity and mortality across diverse high-risk patient populations. The relationships are robust, graded, and largely independent of conventional risk factors, supporting HRV as an integrative marker of autonomic dysfunction and disease severity^[114]. The relationship between HRV and mortality is schematically illustrated in [Figure 3](#).

3.3 HRV as an integrative marker of cardiovascular aging

Many of the biological pathways linking reduced HRV to cardiovascular aging overlap with those discussed for elevated RHR ([Section 2.4](#)) and include autonomic imbalance, neuroendocrine activation, inflammation, oxidative stress, and impaired baroreflex regulation ([Figure 2](#)).

Autonomic Imbalance and Loss of Vagal Modulation: A central feature of cardiovascular aging is progressive remodeling of autonomic regulation, characterized by sympathetic predominance and withdrawal of parasympathetic (vagal) control^[58,70,97]. On this point, HRV provides a functional index of autonomic balance, with reduced variability reflecting diminished vagal modulation and impaired regulatory flexibility.

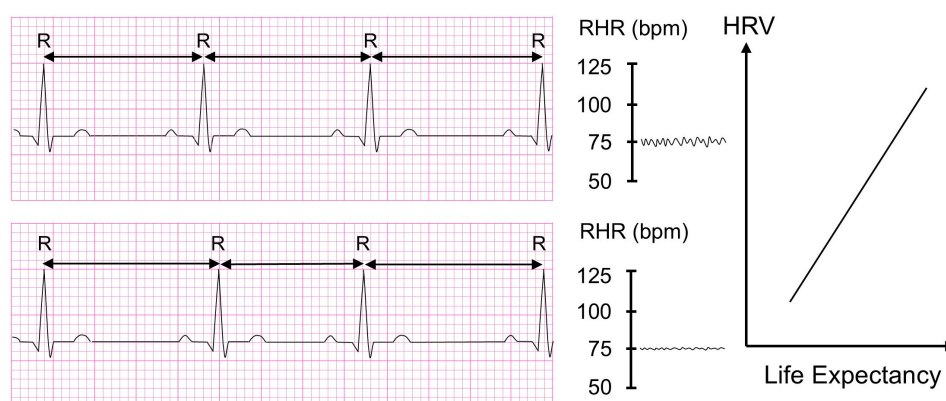


Figure 3. Schematic representation of the relationship between HRV and longevity. Left: A depiction of consecutive beat-to-beat intervals on an ECG. R-R intervals in the upper panel are with relatively less fluctuations, whereas in the lower panel with greater fluctuations. Center: Comparative scenarios demonstrating that identical average heart rates can emerge from apparently different degrees of HRV. Right: Conceptual illustration of the relationship between HRV and life expectancy. This proposed association is derived primarily from observational epidemiological and clinical studies and should not be interpreted as evidence of a direct causal relationship. The association may also be non-linear and is simplified here for illustrative purposes. HRV: heart rate variability; ECG: electrocardiogram; RHR: resting heart rate.

From a biological perspective, aging is accompanied by progressive remodeling of autonomic regulatory networks at both central and peripheral levels. Emerging evidence indicates that age-related changes within the central autonomic network, together with neuroinflammation, impaired baroreflex signaling, and dysregulated neurohormonal control, contribute to altered sympathetic-parasympathetic interactions and reduced autonomic adaptability. These changes may be further amplified by age-associated vascular stiffening and impaired afferent signaling from cardiovascular mechanoreceptors, resulting in diminished reflex control of heart rate and blood pressure^[115-117]. Consequently, reductions in HRV observed with aging likely reflect not only altered cardiac autonomic output but also a broader age-related deterioration in neural and cardiovascular homeostatic regulation^[118].

Experimental and clinical studies demonstrate that vagal activity stabilizes cardiac electrophysiology, modulates heart rate responses, and preserves baroreflex sensitivity. Reduced vagal tone, implied particularly by the diminished HF component of HRV and related time-domain indices, is associated with arrhythmogenesis, endothelial dysfunction, and impaired blood pressure regulation. HRV therefore captures the progressive deterioration of central-peripheral autonomic circuits with aging and chronic disease.

Chronic Stress and Allostatic Load: Low HRV is consistently observed in individuals with chronic stress, depression, and anxiety^[119], conditions that independently predict adverse cardiovascular outcomes^[120,121]. Sustained activation of the HPA axis and the sympathetic nervous system contributes to prolonged neurocardiac activation and impaired recovery following stress exposure^[122].

The neuroendocrine burden in turn contributes to allostatic load over time, representing cumulative physiological wear that accelerates cardiovascular aging^[123]. Reduced HRV therefore serves as a marker of accumulated stress exposure and impaired adaptive capacity, linking psychosocial influences to biological aging processes^[124].

Inflammation, Oxidative Stress, and Cellular Dysfunction: Reduced HRV has been consistently associated with systemic inflammation and oxidative stress, two closely interconnected hallmarks of cardiovascular aging^[125-127]. The vagus nerve plays a central role in the cholinergic anti-inflammatory pathway, whereby efferent vagal signaling suppresses pro-inflammatory cytokine production^[128,129]. Consequently, reduced vagal activity is associated with increased circulating inflammatory markers, including C-reactive protein, interleukin-6, and tumor necrosis factor- α ^[130].

A meta-analysis of 51 human studies identified SDNN and HF as the HRV indices most strongly associated with inflammatory biomarkers^[131]. Concurrently, autonomic imbalance may contribute to oxidative stress through enhanced sympathetic activation, excessive ROS production, impaired nitric oxide bioavailability (particularly neuronally derived and subject to its endogenous inhibition), and mitochondrial dysfunction^[132-135]. Thus, reduced HRV may reflect a physiological state characterized by impaired anti-inflammatory regulation, increased oxidative injury, and diminished cellular repair functionality.

Baroreflex Dysfunction and Loss of Regulatory Reserve: Baroreflex sensitivity declines with aging and CVD^[61,136] and is closely linked to HRV^[2]. Because the baroreflex serves as a key regulator of cardiovascular homeostasis, impairment of this system limits the ability to buffer fluctuations in blood pressure and heart rate.

Reduced HRV in this regard reflects compromised regulatory reserve and reduced adaptability to physiological challenges. As such, HRV provides a useful functional measure of the integrated capacity of cardiovascular control systems.

Marker Versus Mediator of Cardiovascular Aging: A central question is whether reduced HRV actively contributes to cardiovascular aging or primarily reflects underlying pathophysiology. Current evidence supports a hybrid model in which HRV functions predominantly as an integrative marker of autonomic and systemic dysregulation, while also participating in modifiable regulatory pathways.

Interventions such as exercise training^[137,138], nutrition^[2,139,140], neural modulation^[58,111], as well as pharmaceutical therapies^[141,142] often improve HRV alongside cardiovascular health. However, these interventions have pleiotropic effects, and it remains unclear whether improvements in HRV directly mediate clinical benefit or reflect broader physiological improvements.

Interpretation of HRV also requires caution. Just as a very low RHR (bradycardia) is not invariably advantageous, higher HRV is not universally beneficial, and HRV does not mean the same thing for everyone^[125,143]. Elevated HRV may occur in pathological conditions such as cardiac conduction abnormalities or atrial fibrillation, so exceptionally high HRV, particularly in older adults, can be a byproduct of pathological conditions rather than vibrant health, and is not necessarily indicative of enhanced autonomic flexibility^[144]. Individuals exhibiting extreme HRV values, either at baseline or following interventions, should therefore be interpreted within the appropriate clinical context.

Another limitation is the absence of universally accepted normative ranges across HRV metrics, compounded by substantial inter-individual variability related to age, sex, physical fitness, and measurement conditions. HRV declines progressively with advancing age, largely reflecting reductions in parasympathetic activity and autonomic flexibility^[83]. Furthermore, not all HRV metrics demonstrate uniform or linear age-related declines, particularly in older populations^[145,146]. Consequently, HRV is often most informative when assessed longitudinally within individuals rather than interpreted as a single absolute value. These considerations underscore the need for metric-specific interpretation and caution when applying HRV in both clinical practice and aging research.

In summary, reduced HRV reflects the integrated effects of autonomic dysregulation, chronic stress, inflammation, oxidative injury, and impaired baroreflex function. Its ability to capture physiological adaptability and regulatory capacity makes HRV a valuable biomarker of cardiovascular health and aging trajectories.

4. Integrating RHR and HRV as Biomarkers of Cardiovascular Aging

RHR and HRV represent complementary yet mechanistically interconnected dimensions of cardiac automaticity and autonomic regulation. Elevated RHR reflects sustained chronotropic load associated with sympathetic predominance, reduced vagal restraint, and cumulative exposure to stress-related biological processes, whereas HRV captures the dynamic adaptability of autonomic control. Together, these measures provide complementary perspectives on cardiovascular aging.

Another related manifestation of cardiovascular aging is “chronotropic competence”, defined as the ability to appropriately increase heart rate in response to physical activity or metabolic demand. Age-related impairment of this response, termed chronotropic incompetence, is associated with reduced exercise capacity, diminished physiological reserve, and increased cardiovascular risk, and may partly reflect the age-related alterations in cardiac pacemaking and autonomic regulation discussed in [Section 2](#). Chronotropic incompetence has emerged as an independent predictor of adverse cardiovascular outcomes and mortality^[147,148].

Although HRV and chronotropic competence assess distinct physiological domains, both reflect the adaptive capacity of the cardiovascular system. HRV primarily reflects autonomic flexibility and beat-to-beat regulation under resting conditions, whereas chronotropic competence reflects the ability to mount an appropriate cardiovascular response during exercise or physiological stress. Thus, reduced HRV and chronotropic incompetence may be viewed as complementary indicators of impaired cardiovascular adaptability and resilience during aging.

Some shared mechanisms, including autonomic imbalance, neuroendocrine activation, inflammation, oxidative stress, and baroreflex dysfunction, underlie both increased RHR and decreased HRV. Within this framework, **RHR reflects the level of autonomic drive, whereas HRV reflects its flexibility and regulatory capacity**. Rather than being viewed in isolation, these measures may be used together to define a multidimensional phenotype of cardiovascular aging and physiological reserve ([Figure 2](#)).

These mechanisms align with established hallmarks of aging^[149], particularly mitochondrial dysfunction, dysregulated neurohormonal signaling, and chronic inflammation. In addition, age-related alterations in proteostasis, macroautophagy, genomic stability, epigenetic regulation, and cellular senescence may indirectly contribute to autonomic dysfunction and cardiovascular decline. Collectively, these observations support the view that RHR and HRV reflect systemic aging processes that contribute to cardiovascular decline.

5. Wearable Technologies and Continuous, Personalized Assessment

An important recent development in cardiovascular aging research is the rapid expansion of wearable technologies capable of continuously monitoring physiological signals related to autonomic regulation. Historically, assessment of RHR and especially HRV was largely confined to clinical settings, research laboratories, or specialized autonomic testing facilities. Advances in wearable

sensors, mobile health platforms, and consumer electronics have expanded the ability to measure cardiovascular function repeatedly under real-world conditions^[137,138].

This transition has particular relevance for the study of cardiovascular aging. Traditional clinical measurements provide only a brief snapshot of physiological status, whereas wearable devices enable longitudinal assessment of RHR and HRV across various behavioral and environmental contexts. Such monitoring may provide a more comprehensive view of physiological recovery, stress adaptation, and functional reserve, features increasingly recognized as important components of healthy aging^[2,7].

Wearable-derived data may facilitate earlier identification of individuals experiencing accelerated cardiovascular aging. Deviations from an individual’s usual RHR or HRV trajectory may precede overt CVD development and provide insights into evolving autonomic dysfunction, cumulative stress exposure, and reduced physiological reserve. This longitudinal approach is particularly valuable given the substantial inter-individual variability observed in both RHR and HRV.

The growing accessibility of wearable technologies has expanded autonomic monitoring beyond specialized clinical settings to the general population. Continuous data collection may help characterize individual response patterns, identify variability in treatment responses, and support more individualized approaches to cardiovascular risk assessment and management. Advances in artificial intelligence and machine learning may further enhance the utility of wearable-derived RHR and HRV data by integrating longitudinal autonomic measurements with behavioral, clinical, and other physiological information to identify patterns associated with cardiovascular aging and disease risk^[150]. Although challenges related to device accuracy, standardization, data interpretation, and clinical validation remain, wearable technologies provide a practical means of incorporating RHR and HRV measurements into longitudinal studies and preventive cardiovascular care^[114,137,138]. Rather than relying solely on population-based reference values, longitudinal wearable data allow assessment of deviations from an individual’s own physiological baseline, potentially providing a more sensitive approach to detecting early changes in cardiovascular function.

6. Conclusive and Perspective Remarks

Cardiovascular aging is characterized by a progressive loss of regulatory capacity, altered intersystem signaling, reduced physiological reserve, and increased vulnerability to stress^[2,3,7,56]. Within this framework, RHR and HRV emerge as complementary indicators of cardiac automaticity and autonomic regulation, capturing core dimensions of the aging process. Across epidemiological and clinical settings, both metrics consistently track cardiovascular morbidity and mortality, underscoring their value as indicators of cardiovascular aging.

RHR reflects the basal chronotropic state of the heart, shaped by autonomic tone, metabolic state, and cumulative stress, whereas HRV indexes the dynamic adaptability of autonomic regulation and the capacity of neurocardiac systems to respond to internal and external perturbations^[7,97]. Elevated RHR and reduced HRV share overlapping biological substrates including autonomic imbalance, neuroendocrine activation, inflammation, oxidative stress, and impaired baroreflex function, and should be viewed as convergent manifestations of a common decline in physiological regulation. As such, both may serve as early indicators of premature cardiovascular aging, identifying individuals in whom aging-related processes are accelerated relative to chronological age.

These autonomic phenotypes are closely linked to fundamental mechanisms of aging, including inflammaging, mitochondrial dysfunction, oxidative stress, and cardiovascular remodeling^[151]. Reduced HRV and elevated RHR reflect diminished physiological resilience and impaired adaptive capacity, and should be viewed as manifestations of underlying aging biology rather than merely downstream markers of disease. Table 4 summarizes the complementary physiological and clinical information provided by these two metrics.

Table 4. The roles of RHR and HRV in cardiovascular aging.

Feature	RHR	HRV
Scientific Status	Emerging Risk Factor for accelerated biological aging and allostatic load.	Important Marker of systemic physiological resilience and autonomic flexibility.
Core Representation	Basal Chronotropic Demand: The heart’s “idling speed” under neuroendocrine pressure.	Dynamic Adaptability: The capacity for neurocardiac systems to respond to perturbations.
Biological Substrate	Cumulative sympathetic demand, metabolic rate, and chronotropic state.	Vagal anti-inflammatory control and integrity of neuroimmune signaling.
Aging Hallmark Link	Primarily associated with cellular senescence and structural cardiovascular remodeling.	Closely linked to “inflammaging”, the loss of homeostatic regulatory capacity and the altered communication.

Clinical Significance	Predicts long-term morbidity by tracking the “wear and tear” of sustained demand.	Reflects immediate and longitudinal capacity for stress recovery and adaptation.
Technological Synergy	Standardized via traditional clinical vitals and spot-check monitoring.	Optimized through wearable AI-phenotyping and real-world longitudinal data.
Interventional Goal	Aimed at reducing unnecessary chronotropic strain and metabolic burden.	Aimed at restoring autonomic “plasticity” and enhancing vagal tone.

RHR: resting heart rate; HRV: heart rate variability.

Important limitations should also be recognized. Although elevated RHR and reduced HRV are consistently associated with adverse cardiovascular outcomes, these associations do not necessarily imply causality. Evidence supporting a direct causal role, particularly for HRV, remains incomplete. Moreover, whether interventions aimed specifically at modifying RHR or HRV can alter cardiovascular aging trajectories or extend healthspan has yet to be conclusively demonstrated. In some contexts, RHR and HRV may function both as markers and partial mediators of disease processes.

Future research should focus on incorporating RHR and HRV into broader frameworks of biological aging alongside traditional cardiovascular risk factors. While chronological age is non-modifiable^[152], it inadequately captures inter-individual variability in aging trajectories^[153]. In this regard, RHR and HRV may serve as accessible biomarkers that bridge conventional cardiovascular risk assessment with geroscience, facilitating earlier identification of at-risk individuals and informing interventions that target underlying aging mechanisms.

The growing availability of longitudinal autonomic data through wearable technologies provides an important foundation for these efforts. Advances in artificial intelligence and computational phenotyping may further enhance the utility of RHR and HRV by integrating autonomic biomarkers with behavioral, clinical, and other physiological data. Such approaches may improve detection of cardiovascular aging patterns and help evaluate responses to preventive or geroprotective interventions.

Future interventional studies should also determine whether sustained modulation of autonomic function can meaningfully alter cardiovascular aging trajectories and improve clinically relevant outcomes in geromedicine^[154], not only focusing solely on short-term physiological changes. Establishing such causal relationships will be essential for determining whether RHR and HRV function solely as biomarkers of cardiovascular aging or also represent actionable therapeutic targets.

In conclusion, RHR and HRV should be regarded not merely as clinical vital signs, but as biomarkers closely linked to the biology of aging. From the perspective of autonomic regulation, cardiovascular aging can be conceptualized as a system-level decline in physiological adaptability. The joint consideration of RHR and HRV provides a multidimensional framework linking autonomic control, the hallmarks of aging, and cardiovascular risk, with important implications for risk stratification, targeted interventions, and the promotion of healthy longevity.

Declarations

Acknowledgements

ChatGPT (OpenAI) was utilized to improve the readability and grammatical accuracy of the text. No AI tools were used to generate data, perform analysis, or formulate the core scientific arguments. The author takes full responsibility for the integrity, originality, and accuracy of the work.

Authors contribution

The author contributed solely to the article.

Conflicts of interest

The author declares no conflicts of interest.

Ethical approval

Not applicable.

Consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Funding

None.

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