Ageing Research Reviews 101 (2024) 102521

Contents lists available at ScienceDirect

Ageing Research Reviews

journal homepage: www.elsevier.com/locate/arr

Heart rate variability and autonomic nervous system imbalance: Potential biomarkers and detectable hallmarks of aging and inflammaging

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ARTICLE INFO

Keywords:
Autonomic nervous system imbalance
Heart rate variability
Inflammaging
Clinical biomarkers
Macrophages

ABSTRACT

The most cutting-edge issue in the research on aging is the quest for biomarkers that transcend molecular and cellular domains to encompass organismal-level implications. We recently hypothesized the role of Autonomic Nervous System (ANS) imbalance in this context. Studies on ANS functions during aging highlighted an imbalance towards heightened sympathetic nervous system (SNS) activity, instigating a proinflammatory milieu, and attenuated parasympathetic nervous system (PNS) function, which exerts anti-inflammatory effects via the cholinergic anti-inflammatory pathway (CAP) and suppression of the hypothalamic-pituitary-adrenal (HPA) axis. This scenario strongly suggests that ANS imbalance can fuel inflammaging, now recognized as one of the most relevant risk factors for age-related disease development. Recent recommendations have increasingly highlighted the need for actionable strategies to improve the quality of life for older adults by identifying biomarkers that can be easily measured, even in asymptomatic individuals. We advocate for considering ANS imbalance as a biomarker of aging and inflammaging. Measures of ANS imbalance, such as heart rate variability (HRV), are relatively affordable, non-invasive, and cost-effective, making this hallmark easily diagnosable. HRV gains renewed significance within the aging research landscape, offering a tangible link between pathophysiological perturbations and age-related health outcomes.

1. Introduction

The notion that aging itself is the predominant risk factor for the development of the most common diseases that reduce the health span, in association with the observation that most of the interventions that extend lifespan in model organisms can delay or prevent many chronic diseases, paved the way for the era of Geroscience (Kennedy et al., 2014). The theory of Geroscience proposes that there are shared underlying causes for all age-related diseases. Therefore, by addressing aging itself rather than solely targeting individual age-related ailments, we can potentially prolong our healthspan (Burch et al., 2014). This hypothesis underscores the critical importance of comprehending how aging enables human disease, so that the geroscience perspective is the translation of the findings in the aging research into useful approaches to improve the health of the older population (Sierra et al., 2021). Efforts to disentangle the complexities of aging have led to the identification of several hallmarks that represent common features of the aging process in different organisms (Lopez-Otin et al., 2013). However, these hallmarks are typically measured through complex molecular analyses. These include assessments of genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient-sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication (Lopez-Otin et al., 2023). Other hallmarks of aging were also proposed, including compromised autophagy, microbiome disturbance, altered mechanical properties, splicing dysregulation, and inflammation (Lopez-Otin et al., 2023; Schmauck-Medina et al., 2022). Some authors proposed to separate the early, molecular origins of changes during aging from cellular and tissue

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https://doi.org/10.1016/j.arr.2024.102521
Received 10 April 2024; Received in revised form 11 September 2024; Accepted 23 September 2024
Available online 27 September 2024

responses and represented the sequential and causative character of changes of the hallmarks of aging (Skowronska-Krawczyk, 2023). Overall, all the identified hallmarks were extensively investigated in the framework of the aging process and of the most common age-related disease development and progression (Tartiere et al., 2024).

In all these models, chronic inflammation was proposed as a hallmark of aging, without any key role in the interindividual variability of the trajectories of healthy or unhealthy aging. However, in 2000, Franceschi et al. published a pioneering paper suggesting a key role for the age-related chronic, low-grade, inflammatory condition, called inflammaging in the trajectory of the aging process (Franceschi et al., 2000). Nowadays, inflammaging is recognized as a relevant risk factor for the development of age-related diseases (Fulop et al., 2018).

Even if the updated list of hallmarks comprehensively captures the key characteristics of the aging phenotype and incorporates pathways that play a crucial role in age-related processes (Lopez-Otin et al., 2023), here we propose to shift the focus from a model that highlights the sequential and causative character of changes in aging to a more systemic characterization of the cause of unhealthy aging, suggesting inflammaging as the central hub which mediates the interactions among of all the identified hallmarks of aging. However, even if this model recapitulates the complex knowledge of the aging process, we cannot ignore that the most cutting-edge issue in the field of the biomarkers of aging is currently the development of therapeutic interventions aimed at achieving healthy longevity. Reaching this goal presupposes the identification of biomarkers that are clinically relevant not only at molecular and cellular but also at the organismal level, emphasizing the synergy between clinical and fundamental studies (Hajj-Boutros et al., 2024). In the quest for clinically measurable biomarkers of aging and inflammaging, we recently hypothesized and proposed a role of Autonomic Nervous System (ANS) imbalance in this framework (Giunta et al., 2024a; Giunta et al., 2024b). Research has shown that the ANS plays a critical role in regulating inflammation through mechanisms like the inflammatory reflex, which was first described by Tracey in 2002 as a complex of efferent signals in the vagus nerve suppressing peripheral cytokine release by macrophages in response to localized and systemic inflammation (Tracey, 2002). The vagus nerve is thus pivotal in controlling the body's inflammatory response. In aging and age-related diseases, a maladaptive imbalance toward an overactive sympathetic nervous system (SNS) tone contributes to a pro-inflammatory state and, ultimately, increased morbidity and mortality (Abboud, 2010). Conversely, there is a diminished parasympathetic nervous system (PNS) activity, which typically exerts anti-inflammatory effects mediated through the activation of the so-called cholinergic anti-inflammatory pathway (CAP) and inhibition of the hypothalamic-pituitary-adrenal (HPA) axis (Giunta et al., 2024b). Therefore, ANS imbalance can fuel systemic inflammation when the neuro-immune-endocrine homeostatic mechanisms between reflex neural circuits and the immune system are compromised (Bellocchi et al., 2022).

Overall, since increasing recommendations emphasized practical applications for enhancing older people's quality of life, shedding light on biomarkers that can be easily measured in asymptomatic older outpatients, we propose to consider ANS imbalance as a biomarker of aging and inflammaging and suggest that some measures of ANS imbalance, including the non-invasive, not-expensive assessment of heart rate variability (HRV).

2. The Autonomic nervous system (ANS) imbalance during aging

ANS imbalance, characterized by sympathetic overdrive and reduced parasympathetic activity, is closely linked to a pro-inflammatory state (Giunta et al., 2024a; Pongratz and Straub, 2014; Tracey, 2007). However, the age-related alterations in SNS and PNS activity do not follow a linear progression, indicating complex interrelationships among various factors (Bruno et al., 2018).

Autonomic dysfunction and dysautonomia are the general terms for disorders that impair ANS functions, describing several disorders, each with varying symptoms ranging from mild to severe (Karemaker, 2017). Dysautonomia, in its various forms, can affect individuals at different life stages. This dysfunction of the autonomic nervous system may emerge with a genetic component during infancy, present as transient episodes in otherwise healthy adolescents, or manifest later in life as neurodegenerative, metabolic, and cardiovascular diseases (CVD). However, increasing evidence suggests that autonomic dysfunction and frailty are two common and complex geriatric syndromes, with a prevalence increasing with age and overlapping unfavorable health outcomes (Debain et al., 2023).

ANS imbalance, a condition predisposing to dysautonomia, has been suggested to play a role in the incidence of multiple age-related conditions, including CVD, metabolic and neurodegenerative diseases (Schwarz et al., 2024).

The sympathetic and parasympathetic nervous systems generally have opposing effects on the cardiovascular system (Mancia and Grassi, 2014). Sympathetic activity results in an increase in blood pressure (BP) and heart rate (HR); whereas parasympathetic activity results in a decrease in both parameters. During the early clinical stages of heart failure (HF), an overactive sympathetic nervous system serves a compensatory role, aiming to sustain sufficient cardiac output despite impaired contractility of the myocardium (Gronda et al., 2022). Sympathetic activity determines cardiovascular sympathetic tone which upon persistence, in decades, can lead to a rise in BP and tachycardia, among the most common reasons for medication in adults and older adults (Bolivar, 2013; Fisher et al., 2009). With advancing aging, sympathetic overdrive and reduced baroreflex sensitivity associated with blood pressure increases, with a consequent rising risk of developing cardiovascular complications (Bolivar, 2013; Dauphinot et al., 2013; Fisher et al., 2009). We refer to asymptomatic subjects with 'sympathetic hypertone condition', a status characterized by an increased resting heart rate, highly predictive of the onset of hypertension.

In addition to hypertension, it is increasingly recognized that autonomic dysfunction can manifest as gastrointestinal, urinary, cardiovascular, thermoregulatory, and pupillomotor dysfunction, and can be present in the early stages of neurodegenerative diseases, like Parkinson's disease (PD). Indeed, more than 70 % of early PD patients report having autonomic symptoms, even if typically, at onset these disturbances are mild and rarely severe (Stankovic et al., 2019). Importantly, autonomic dysfunction seems to be a prodromal manifestation of PD, with early autonomic features predicting a faster rate of PD progression (De Pablo-Fernandez et al., 2017). In α-synucleinopathies, the dysfunction of the autonomic nervous system which typically manifests as orthostatic hypotension can lead to severe consequences and pose therapeutic challenges (Lin et al., 2024). Alzheimer's disease (AD) is also commonly accompanied by autonomic dysfunction, so that it was suggested that investigating autonomic dysfunction patterns may aid in making a distinction between different dementia subtypes, as cardiac autonomic dysfunction and AD severity are correlated (Nair et al., 2023). Finally, dysautonomia recently emerged as prevalent also in patients affected by Long-Covid (Giunta et al., 2024a; Marques et al., 2023).

ANS imbalance or mild dysautonomia often progresses to ANS dysfunction and overt dysautonomia. ANS imbalance is one of the most overlooked and misdiagnosed conditions (Novak, 2019). That's probably because the condition can vary widely and take many forms and patients may not appear ill or look sick, yet they have symptoms that make it difficult to work, to be active and, especially for the older subjects, to carry out activities of daily living. Given the rising incidence of autonomic dysfunction with age, it is increasingly regarded as an age-related disorder (Jiang et al., 2022), typically emerging between the ages of 50 and 60, though it can develop at any age (Goldstein et al., 2002). It is estimated that over 70 million people worldwide experience some form of autonomic dysfunction (Goldstein et al., 2002).

Overall, even if the disorders of the autonomic nervous system may affect a large segment of the population, they represent a diagnostic challenge. Autonomic symptom questionnaires are frequently used to assess dysautonomia, but it is unknown whether subjective dysautonomia obtained from autonomic questionnaires correlates with objective dysautonomia measured by quantitative testing. A recent report suggests the lack of correlation between subjective and objective instruments, thus highlighting the limitations of the commonly used questionnaires with some patients overestimating and some underestimating true autonomic deficit (Novak et al., 2024). Therefore, at this time, the use of questionnaires as a replacement for autonomic testing cannot be recommended.

In this framework, efforts should be devoted to identifying feasible and reliable measures of ANS imbalance/mild-dysautonomia, with the aim of tracking the trajectories of aging.

3. Heart rate variability (HRV) in physiology and disease

HRV is a non-invasive method to evaluate the modulation of the ANS on the electrophysiological sinoatrial node. By describing the oscillations between consecutive electrocardiogram R-R intervals, HRV can measure the physiological link between ANS and heart during physiological activities such as exercise, sleep, breathing, eating, and hormonal changes (Forte et al., 2019). Thus, HRV can not only serve as an indicator of cardiac function, but also reflect the central modulation capacity to cope with different types of stressors (Kim et al., 2018; Yperzeele et al., 2015). An increased HRV is correlated with rest, exercise, and good recovery, while a decreased HRV is an effect of stress or illness (Turcu et al., 2023), associated with a pro-inflammatory status (Adam et al., 2023; Cooper et al., 2015). In general, good cardiac autonomic control, which is accompanied by relatively high HRV, is advantageous for both physiological and psychological health. High HRV in populations is related to good health, low stress levels, and low risk of sudden death and it is a useful measure of positive adaptation, performance, and outcomes (Kubota et al., 2017). On the contrary, low HRV is associated with decreased physical fitness, high stress levels, increased risk of cardiovascular and neurodegenerative diseases, and poor adaptations (Souza et al., 2021). Notably, measures of HRV are related to circulating biomarkers of systemic inflammation, such as IL-6, CRP, and fibrinogen (Kop et al., 2010), suggesting an intimate link between inflammation and ANS dysfunction, which may explain the increased risk of mortality and CV events in subjects displaying reduced HRV.

By the early 1970s, several researchers began investigating the relationship between autonomic neural regulation and changes in both arterial pressure waves and heart rate (Hyndman and Gregory, 1975; Katona et al., 1970). For instance, Katona and Jih proposed that periodic changes in heart rate corresponding to respiration could serve as non-invasive markers of cardiac parasympathetic regulation (Katona and Jih, 1975).

This physiological variation of heart rate that occurs with breathing is called respiratory sinus arrhythmia (RSA). It is characterized by an irregular rate where the R-R interval changes by more than 0.12 seconds. This variation happens because intermittent activation of the vagus nerve during respiration causes the heart rate to increase with inhalation and decrease with exhalation (Soos and McComb, 2024). RSA, as detected through ECG, is reduced in older people owing to an age-related decline in ANS function that determines changes in the compliance of arterial walls and diminished vagal responses (Kaushal and Taylor, 2002).

It is important to keep in mind that not only RSA but also, beat-to-beat changes in the heart rate of healthy subjects not synchronized with respiration are vagally mediated (Hirsch and Bishop, 1981). For this reason, the degree of short-term variability of normal-to-normal (NN) sinus beats is used as a dynamical biomarker of cardiac vagal tone modulation (Billman, 2011).

HRV is generally computed based on a full 24-h electrocardiogram (ECG) recording, considered, until now, the gold standard (Shaffer and Ginsberg, 2017). In general, HRV is influenced by several factors and frequently shows very high inter- and intraindividual variability, thus limiting its large use in clinical practice as a diagnostic and or prognostic biomarker. For this reason, many efforts were made by the scientific community to produce an unequivocal definition of HRV. In particular, in 1996 the Task Force of the European Society of Cardiology the North American Society of Pacing Electrophysiology tried to standardize nomenclature and develop definitions of terms, specify standard methods of measurement, define physiological and pathophysiological correlates, and appropriate clinical applications (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). In this guideline, two main methods for HRV analysis were introduced, i.e. linear metrics, including frequency- and time-domain, and non-linear metrics. The most common measures of HRV are reported in Table 1.

Regarding the linear metrics, frequency-domain analysis of HRV considers the very-low-frequency (VLF) component, which probably reflects the hormonal changing and thermogenesis, the low-frequency (LF) component (0.04–0.15 Hz), which reflects baroreflex sympathetic control of blood pressure (Eckberg, 1997), and the high-frequency (HF) component (0.15–0.4 Hz), which is assumed to be vagally mediated,

Table 1
Methods of heart rate variability (HRV) measurement.

Method	Components
Linear	
Time-domain	• Standard deviation of all NN intervals (SDNN) • Standard deviation of all RR intervals (SDRR) • Square root of the mean of the sum of the squares of differences between adjacent NN intervals (RMSSD) • Number of pairs of adjacent NN intervals differing by more than 50 ms in the entire recording (NN50 count) • NN50 count divided by the total number of all NN interval (pNN50) • HRV triangular index
Frequency-domain	• Power in ultra-low frequency (≤0.003 Hz) (ULF) • Power in very low frequency (0.0033–0.0400 Hz) (VLF) • Peak/power in low frequency range (0.04–0.15 Hz) (LF) • Peak/power in high frequency range (0.16–0.40 Hz) (HF) • Power in very high frequency (0.50–150 Hz) • LF power in normalized units LF/(Total Power–VLF) × 100 (LF nu) • HF power in normalized units HF/(Total Power–VLF) × 100 (HF nu) • Ratio LF /HF (LF/HF)
Nonlinear	
Poincaré plot	• Area of the ellipse which represents total HRV (S) • Poincaré plot standard deviation perpendicular the line of identity (SD1) • Poincaré plot standard deviation along the line of identity (SD2) • SD1/SD2 % Ratio of SD1-to-SD2
Acceleration/ Deceleration capacity	• Detrended fluctuation analysis, which describes short-term fluctuations (DFA α1) • Detrended fluctuation analysis, which describes long-term fluctuations (DFA α2) • Correlation dimension, which estimates the minimum number of variables required to construct a model of system dynamics (D2)
Other measures related to the autonomic regulation of the heart	
Heart rate fragmentation (HRF)	• Percentage of inflection points (PIP) with a moving window of 1000 NN intervals
Heart rate turbulence (HRT)	• Turbulence onset (TO), as relative change of RR intervals from before to after the ventricular premature complex (VPC) • Turbulence slope (TS), slope of the steepest regression line fitted over the sequences of 5 consecutive sinus rhythm R-R intervals within the 15 R-R intervals after the VPC

driven by respiration, and related to the parasympathetic control of heart rate (Berntson et al., 1993; Laborde et al., 2017). Frequency domain measures are obtained through the spectral analysis of HRV, which is a commonly used method providing a quantitative evaluation of sympathetic and parasympathetic activation of the heartbeat (Akselrod et al., 1981; Miyagi et al., 2022; Shaffer and Ginsberg, 2017).

Regarding the time-domain variables, both the sympathetic and parasympathetic activities influence the standard deviation of normal-to-normal interval (SDNN), which reflects all the cyclic components responsible for HRV (Laborde et al., 2017). This measure, which requires careful editing to exclude "abnormal" beats such as artifacts or ectopic beats (heartbeats originating outside the sinus atrial node), has been associated with cardiovascular risk. Subjects with SDNN values less than 50 ms are classified as unhealthy, while a SDNN >100 ms is considered normal (Kleiger et al., 2005).

Another time-domain measure is the standard deviation of the means of the NN intervals (SDANN), which defines the standard deviation of the average RR intervals for each 5 min-segment of a 24 h ECG recording. Compared to SDNN it minimizes the effects of artifacts, or ectopic beats (Kleiger et al., 2005; Shaffer and Ginsberg, 2017). The root mean square of successive differences (RMSSD) requires a conventional minimum recording of 5 min, even if ultra-short periods of 10 sec, 30 sec and 60 sec have been proposed. It consists of applying the root square of the mean of the sum of the squares of the differences. It is the main measurement in the time domain to estimate vagally mediated changes reflected in HRV. Lower values of RMSSD are to be considered an alarm at the risk of sudden death in epilepsy (Kleiger et al., 2005). The percentage of RR intervals which exceed 50 ms from the previous one (pNN50), and the standard deviation of successive differences (SDSD) are correlated with the HF band, so they describe the vagal activity and could be more feasible than SDNN. RMSSD is normally preferred since it is less influenced by respiration and better correlates with vagal activity (Laborde et al., 2017).

The conventional time and frequency domain HRV measures have been studied as predictors of adverse events in large community-based cohort studies. In a sample of older subjects from the Framingham Study, SDNN, and the power of VLF, LF, and HF components have been associated with all-cause mortality independent of conventional risk factors (Tsuji et al., 1994).

The nonlinear component of HRV evaluates the fluctuations of RR interval time series (Braun et al., 1998). In order to improve the determination of the activity of the ANS, a signal processing technique called Detrended Fluctuation Analysis (DFA), was proposed (Peng et al., 1995; Penzel et al., 2003). DFA extracts the correlations between successive RR intervals on different time scales, both short and long term (Braun et al., 1998). DFAα1 describes the fluctuations short on a scale of 4–11 beats, while DFAα2 represents long-term ones on a scale of 11–20 beats. The first one reflects the mechanism of the baroreceptors, while the second one indicates the efficiency of the regulatory mechanisms that limit the variability of the cardiac cycle. A pattern of completely random RR intervals has a DFα1 value of 0.5, while a totally correlated one, i.e. periodic, has a value of 1.5. Normal values are around 1.05 and deviations from this reference value were associated with physiological aging (Barquero-Perez et al., 2008; Beckers et al., 2006), the clinical course of myocardial infarction (Hsin et al., 2010), sudden cardiac death (Hernesniemi et al., 2024), severity of sleep apnea disorders (Penzel et al., 2003), and congestive heart failure (Barquero-Perez et al., 2008). Notably, a decrease of the DFα1 parameter showed the best accuracy, among other HRV measures, in predicting cardiovascular mortality and sudden cardiac death in a community-based cohort of subjects aged 65 years and older (Makikallio et al., 2001).

The traditional measures of HRV signal, in particular the time domain parameters, have been criticized because they are considered not sufficiently specific to discriminate between vagal and sympathetic effects (1996). These considerations led to the development of a novel approach to the analysis of short-term HRV, termed heart rate fragmentation (HRF). It is derived from measurements of ultra-fast non respiratory HRV patterns. The HRF cadence may provide new dynamical biomarkers to assess the integrity of the neuroautonomic-electrophysiologic network controlling the heartbeat in both healthy and unhealthy subjects (Costa et al., 2017b). HRF increases with advancing aging and in some disease states and may confound the association of conventional HRV metrics such as the percentage of pairs of adjacent normal-to-normal R-R intervals differing by > 50 ms (pNN50), the RMSSD, and HF power with cardiac vagal function and with disease prognosis.

In fact, HRF is considered as a potential cause of lesser prognostic relevance of the HF component than that of other HRV frequency components such as very-low-frequency (0.0033– 0.04 Hz) and LF components (Hayano and Yuda, 2019). Although the exact mechanisms for this phenomenon are unclear, it has been hypothesized that the alternative pacemaker shift within the sinus node caused by sinoatrial degeneration or disorganization may be a potential mechanism. Increased HRF is associated with major cardiac events, atrial fibrillation and cognitive decline (Costa et al., 2017b; Costa et al., 2021a; Costa et al., 2021b). A cohort study on 1011 subjects aged >65 years old without a history of atrial fibrillation (AF) was recently designed to prospectively assess the predictive value of HRV and HRF on cardiovascular events and mortality. A long 17.8-year follow-up was managed. The HRF independently predicts AF occurrence in the general population, and it is able to identify a population at high risk of AF occurrence among the general population (Costa et al., 2021b).

With progresses in passive sensing technologies, novel indices have been extracted from 24 h ECG Holter recording, like for instance the Deceleration capacity (DC) of heart rate (Bauer et al., 2006). It carries specific physiological significance as a marker of vagal function on the heart, as it indexes the rate of deceleration of the heart rate in short intervals that are consistent with vagal activity (Pan et al., 2016). This metric, therefore, should allow more direct examination of the relationship of vagal function with health outcomes. Indeed, DC has revealed strong prognostic value in clinical samples with known CVD (Bauer et al., 2006) and diabetes with and without hypertension with a predictive ability often stronger than conventional HRV metrics (Wang et al., 2018). Another measure that has been proposed to capture the proarrhythmic effects induced by alterations of the autonomic nervous system is heart rate turbulence (HRT). First introduced in 1999, HRT describes the short-term changes in heart rate induced by a premature ventricular beat, which consists of a brief heart rate acceleration followed by a gradual heart rate deceleration (Schmidt et al., 1999). Albeit not currently used in clinical practice, multiple evidence showed that HRT exhibits a prognostic value in cardiac death and arrhythmic events in patients with heart failure or prior myocardial infarction (Disertori et al., 2016).

HRV is strongly influenced by the activation and/or inhibition of networks within the central nervous system (CNS), specifically those involving the amygdala, which in turn are determined by several factors, including the emotional status during the involvement in different tasks (Appelhans and Luecken, 2006). In the last years, several studies have investigated the link between brain connectivity as assessed with functional magnetic resonance imaging (fMRI), and HRV. For instance, a study involving 35 male healthy subjects found a set of brain regions including brainstem, thalamus, putamen and dorsolateral prefrontal cortex, that become more strongly coupled with amygdala and dorsal anterior cingulate cortex in relation to increased HRV in resting state conditions (Chang et al., 2013). Another paper reported a strong positive correlation between HRV and amygdala-medial prefrontal cortex (mPFC) connectivity in resting state conditions in both young and older adults (Sakaki et al., 2016).

A more recent investigation found a strong positive correlation between HRV and functional connectivity within cerebral regions involved in the central autonomic network, including the right anterior insula and posterior midcingulate cortex, the right amygdala and thalamus during

slow-wave (i.e. deep) sleep, again supporting the role of CNS in modulating HRV (Kong et al., 2023). Conversely, a study by Tupitsa et al., involving 70 subjects (52 older adults and 18 younger adults) with no history of major neurological disorders, reported a significant global inverse association between HRV and amygdala-medial prefrontal cortex (mPFC) connectivity during the execution of multiple tasks consisting in the regulation of emotional response to visual stimuli (Tupitsa et al., 2023), whereas previous studies had found a positive correlation of these two parameters in resting state conditions (Jennings et al., 2016), thus suggesting an opposite effect of mPFC on HRV in resting state compared to task-based conditions. Interestingly, in the study by Tupitsa and coworkers, older adults showed a slightly positive, albeit non-significant, association, of HRV with mPFC, while in younger adults a significant negative correlation between these two factors was found, thus suggesting a relevant interaction between age and mPFC activity in the context of the execution of a task. However, several limitations of the study, including the unequal representation of younger and older adults in the cohort and the absence of information about some lifestyle conditions potentially influencing HRV like smoking and coffee assumption, induced caution in the interpretation of results, that thus should be verified by future investigations.

The link between brain activity and HRV was also supported by several electroencephalography (EEG) studies, especially during sleep both in physiological and pathological conditions (Chaparro-Vargas et al., 2016; Zhuang et al., 2005).

It is now clear how sleep quality influences HRV. For instance, studies showed that in the context of chronic stress, lower HRV is associated with lower sleep quality and depressive symptoms (da Estrela et al., 2021; Dauphinot et al., 2012). Among factors influencing HRV, a relevant role is played by the transition from waking to sleep, with substantial differences between non-REM and REM sleep (Vanoli et al., 1995). Sympathetic tone drops progressively from wakefulness over sleep stages. In contrast, REM sleep is characterized by increased sympathetic tone (Elsenbruch et al., 1999). Parasympathetic tone increases from wakefulness to non-REM sleep. Periods of wakefulness during sleep were found to have an intermediate position between non-REM and REM (Berlad et al., 1993). These observations support the proposal of integrating HRV assessment using nocturnal ECG into the evaluation of sleep disorders conducted through polysomnography (Penzel et al., 2016). Decreased HRV has been observed also in subjects with obstructive sleep apnea (OSA), the most common sleep-related breathing disorder (Shamsuzzaman et al., 2003). In these patients, diminished vagal tone and higher sympathetic responsiveness result in heightened power of the VLF and LF components, and lower HF modulations (Sequeira et al., 2019). Interestingly, alterations of HRV in patients with OSA are present also during wakefulness and are directly related to the burden of arousal, apnea and hypoxia, leading to the hypothesis the increased cardiovascular mortality in these patients could be mediated, at least in part, by ANS (Qin et al., 2021). Overall, results from studies on subjects with sleep disorders support the notion that HRV changes in response to the dynamic activity of the ANS during different sleep stages could be used as a tool to characterize and estimate the prognostic value of ANS imbalance in sleep disorders (Qin et al., 2022; Roche et al., 2002; Roche et al., 1999). Additionally, HRV could be used to monitor the efficacy of interventions and treatments in reducing the cardiovascular complications associated with sleep-related disorders (Amra et al., 2021).

Altogether, the above-mentioned findings suggest that HRV is regulated by complex CNS networks that probably differ in awareness and in sleep context according to several physiological and pathological factors that still need to be elucidated in depth.

In addition to sleep quality and quantity, the aging process appears to dramatically influence the autonomic nervous system activity. Indeed, heart rate (HR), HRV, and ANS modulation are all profoundly affected by age, even in the absence of disease, consistent with the idea that aging itself is a disease (Lakatta, 2015). In the aging heart, remodeling of the left ventricular wall, partly in response to changes in arterial stiffening, is accompanied by reduced muscarinic receptor density and function (Brodde et al., 1998), which results in an age-related decline of HRV (Antelmi et al., 2004; De Meersman and Stein, 2007; Umetani et al., 1998). Furthermore, with aging there is an attenuation of the responses of both adrenergic and muscarinic receptors to neurotransmitters (Fleg et al., 1985; White and Leenen, 1994). There is evidence for age-related reduced post-synaptic efficiency of beta-adrenergic receptors (Fleg and Strait, 2012). Age-related decline in HRV results in part from reduced efficacy of post-synaptic autonomic receptor responses of sinoatrial node pacemaker cells, but also results from an intrinsic deterioration of sinoatrial pacemaker cells (Liu et al., 2014; Yaniv et al., 2014). This, in part, underlies a reduced sensitivity of the baroreceptors with increasing age.

The latest decade has led to an accelerated development of technology for determining HRV, using numerous devices that were created specifically for the pre-hospital self-monitoring of health status. These devices are cardiac implantable electronic devices (i.e., pacemakers, implantable defibrillator or cardiac resynchronization therapy) with their intrinsic algorithm for detecting HRV. Other devices are short- and long-term ECG Holter monitoring (even more than 48 h), smartphone and smartwatches (Theurl et al., 2023). In contrast to long-term HRV analysis, short-term investigations (i.e. <30 min ECGs, *e.g.* 5-min ECGs), provide a test result almost immediately, thus being suitable for ambulatory care, patient monitoring and all those applications where the result is urgently needed (Bodapati et al., 2017; Pinna et al., 2007; Voss et al., 2015). Recently it was demonstrated that ultra-short HRV (usHRV), assessed with $\leq$ 15-s ECGs, can be measured using standard and wearable ECGs; it was correlated with standard short-term HRV and predicted increased risk of cardiovascular events in a large population (Orini et al., 2023).

The broad diffusion of HRV into the clinical practice is hindered by the absence of standardized cutoff values for HRV measures. Establishing clinical decision limits requires a thorough understanding of the biological variability of HRV, which is notably high due to a wide number of physiological, such as food intake, exercise, body position (supine or standing), and time of the day (Hayano et al., 2001; Hayano et al., 1990), and pathological conditions, even at subclinical stages. It is plausible that, in the future, the use of machine learning techniques and large datasets will help define clear HRV thresholds. This will enable the identification of high-risk individuals and the differentiation between healthy and unhealthy aging.

4. Focus on hearth rate variability (HRV) to measure ANS imbalance in aging/inflammaging

Even if the molecular and cellular mechanisms that fuel inflammaging were extensively investigated, the most relevant challenge is now how to measure the levels of the proinflammatory status called inflammaging in asymptomatic subjects that are at risk of derailing through an unhealthy aging trajectory. The hypothesis that inflammaging affects healthy aging promoting age-related disease development, multimorbidity, and frailty by interfering with homeostatic signaling, which we recapitulated in Fig. 1, is supported by mechanistic studies on cellular and animal models (Ferrucci and Fabbri, 2018; Furman et al., 2019). Here, we postulate for the first time ANS imbalance may be considered as a reliable hallmark of aging and inflammaging (Fig. 1). Now, the main challenge is how to measure ANS imbalance and translate this metric to inflammaging estimation. Given the complexity of the autonomic system, there is no single test that precisely reflects the function of a specific branch of this system. Therefore, it is not uncommon to order numerous tests based on diverse reflexes (Thomas et al., 2019).

Several studies demonstrated age- and gender-related variations in long-term HRV, assessed by means of a 24-hour ECG, reporting that autonomic activities diminish with age in both genders and that gender-

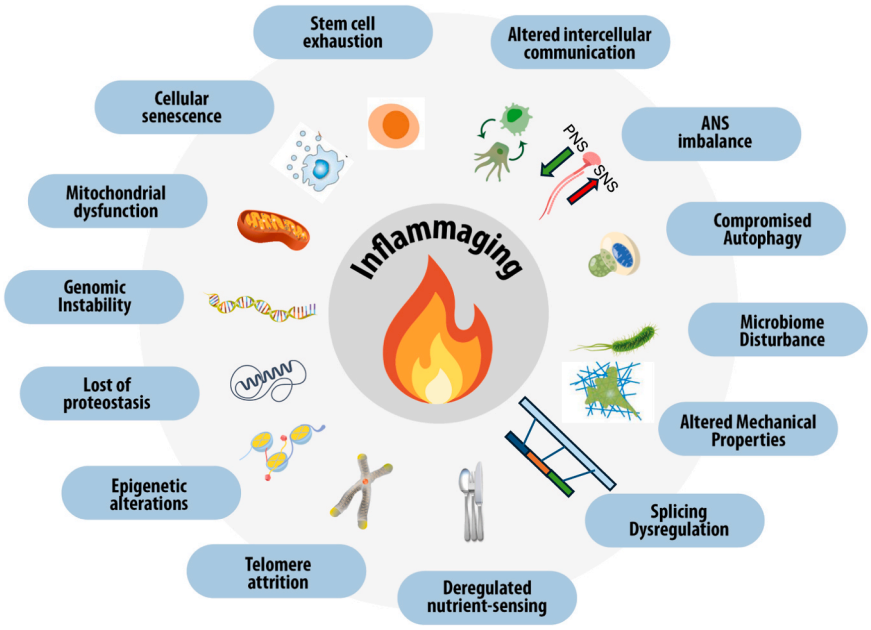

Fig. 1. The hallmarks of inflammaging. A systematic representation of the hallmarks of aging, depicting inflammaging as the central hub which mediates the interaction among all the other identified hallmarks of aging. Autonomic nervous system (ANS) imbalance is included as a new hallmark.

related variation in parasympathetic regulation decreases during aging (Porta et al., 2001; Voss et al., 2015). In a study on a sample of healthy subjects ranging from 10 to 99 years old, all HRV measures decreased rapidly from the second to fifth decades (Zulfiqar et al., 2010). However, if the HRV-sympathetic function continues to decrease throughout life, the decrease in HRV-parasympathetic function, evaluated as RMSSD, has been reported to reach its nadir in the eighth decade, followed by a reversal and a progressive increase to higher levels, more characteristic of a younger population, thus depicting a U-shaped age-related trend (Geovanini et al., 2020; Zulfiqar et al., 2010). These results were confirmed in a large registry-based study aimed at investigating time-domain 24-h HRV parameters in functionally active individuals over 40 years of age and with satisfactory cognitive function defined as the self-capacity to interact with an interviewer (Almeida-Santos et al., 2016). The parasympathetic outflow component of HRV presented a U-shaped pattern with its nadir around the 7th decade of life, for both genders, and it was comparatively lower in men and patients with diabetes (Almeida-Santos et al., 2016). Importantly, HRV trajectories are not explained by increased prevalence of cardiometabolic problems, such as hypertension and dyslipidemia, and/or medication use (Almeida-Santos et al., 2016; Jandackova et al., 2016).

When HRV measurements were performed in a rural population, the U-shaped age-related trend previously reported for HRV parasympathetic function, evaluated as RMSSD, was confirmed, (Geovanini et al., 2020). Notably, these findings were confirmed in another study assessing HRV among young adults, octogenarians, and centenarians, which revealed a similar U-shaped trajectory for HRV indices reflecting parasympathetic outflow (RMSSD and pNN50), suggesting that an increase in HRV parasympathetic variables in old subjects may reflect heightened chances of longevity. On the contrary, the global autonomic index SDNN presented an age-related reduction, which did not ameliorate in centenarians and low SDNN values (<19 ms) were associated with early mortality also in centenarians (Hernandez-Vicente et al., 2020).

Not surprisingly, U-shaped trajectories like those reported for HRV were observed for the most relevant biomarkers of inflammaging, such as circulating cytokines and microRNAs (Mensà et al., 2019; Mensà et al., 2020; Spazzafumo et al., 2013). For many chronic diseases the incidence rates do not increase monotonically with age: instead, they first increase, reach their maximum values, and then decline, possibly with different trajectories according to the disease considered and some people with exceptional longevity never develop major chronic conditions (Akushevich et al., 2013). To explain the observed mortality trend in humans it was hypothesized that a human population is a mixture of two sub cohorts of individuals, the labile and the stable. The mortality rate in the population of labile individuals is initially higher, but its rate of increase during aging is slower than that of stable individuals (Yashin et al., 2001). These different trends of mortality rate in the same population can explain the U-shaped trajectories observed for some biomarkers of aging/inflammaging (Olivieri et al., 2023). Initially, the biomarker levels may decline with age but then increase among those who have successfully reached very old ages, such as centenarians. This unique pattern, which applies also to time domain measures of HRV **(**Fig. 2**A)**, indicates that the biomarkers are not merely reflecting chronological age but are instead associated with biological processes that are relevant to aging and longevity. Notably, also the frequency domain and non-linear measures of HRV may track trajectories of unhealthy aging. Indeed, while modest variations of metrics such as the power spectral density **(**Fig. 2**B)** and the detrended fluctuation analysis components **(**Fig. 2**C)** are observed in healthy aging, these differences become particularly evident in subjects suffering from CVD, and were associated with increased all-cause and cardiovascular mortality (Barquero-Perez et al., 2008; Bigger et al., 1995; Huikuri et al., 1998; Stein et al., 2009). Therefore, we suggest that HRV may be used as a predictor of unsuccessful aging and disease development.

As previously mentioned, HRV may be overestimated by the presence of erratic sinus rhythms, which may limit the prognostic role of traditional time and frequency HRV analysis (Nicolini et al., 2012; Stein et al., 2002). The HRF analysis introduced by Costa allows to differentiate between the erratic rhythm and autonomic regulation (Costa et al., 2017a; Costa et al., 2018). HRF increases with aging and provides additive value to classical HRV changes in cardiovascular conditions, such as coronary artery disease or adverse cardiovascular events (Costa et al., 2018; Hayano et al., 2020; Lensen et al., 2020). The increased HRV observed in older subjects could reflect the increased burden of erratic sinus rhythm rather than an increased chance of reaching a healthy longevity. Therefore, we suggest that HRV might be used as a predictor of disease development, even if HRV changes observed during aging

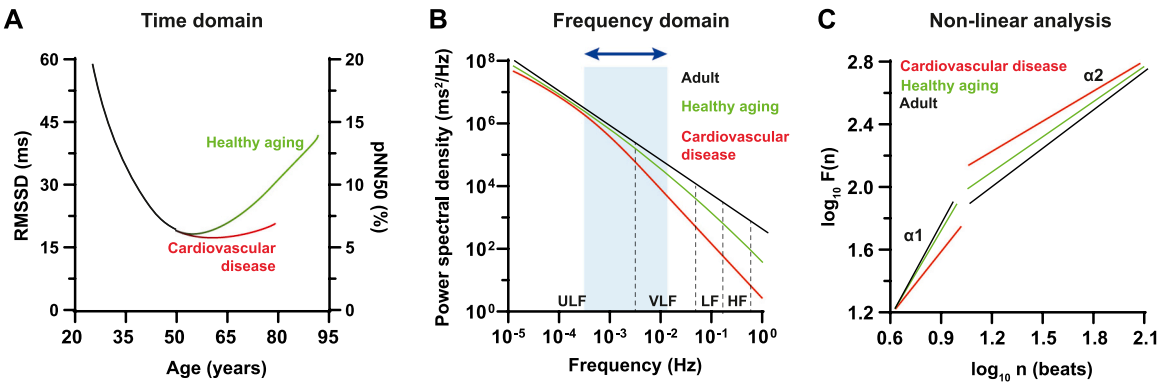

Fig. 2. Age-related trajectories of heart rate variability (HRV) measurements. Summary of the changes in representative (A) time domain (RMSSD and pNN50), (B) frequency domain (power spectral density of ultra-low, very low, low, and high-frequency components), and (C) non-linear measures (detrended fluctuation analysis alfa1 and alfa2) in healthy aging (green lines) and in subjects with cardiovascular disease (red lines). The area highlighted in blue indicates the spectrum of frequency in which the maximal differences in PSD slope are observed. See the text for details on the specific measures.

need to be interpreted with caution and contextualized within comorbidities with a proven autonomic dysfunction component.

In a recent work analyzing data from a total of 700 healthy subjects, HRV followed a scaling relationship with age with an abrupt change at the age of 12 years (Garavaglia et al., 2021). Below the age of 12, the results were gender-independent, while above that age, there was a slight dependence on gender (Garavaglia et al., 2021). In a recent report, a set of sympathetic and parasympathetic tests, including a six-lead ECG and a respiratory belt were proposed to a small healthy cohort between the ages of 18 and 45 years and body mass index (BMI) <30 (Debnath et al., 2021). The sympathetic and parasympathetic parameters determined in this study seemed to be valuable diagnostic tools for autonomic function and underlying disorders (Debnath et al., 2021).

The presence of nonlinear information in human HRV, was in deep investigated during aging in female and male subjects, as well as the effect of BMI. It was observed that larger BMI and HR were associated with the presence of more linear variations in HRV, while the female sex was associated with the manifestation of nonlinear patterns (Calderon-Juarez et al., 2023). Gender differences in HRV were associated with hormonal influence on autonomic activity, but no conclusive results were reported (Bai et al., 2009; von Holzen et al., 2016). Further, in women, cardiometabolic problems were associated with a faster decline in the standard deviation of all intervals between R waves (Jandackova et al., 2016).

Overall, these results suggested that i) a healthy longevity depends on preservation of autonomic function, in particular HRV parasympathetic function, despite the early age-related decrease, and that ii) persistently high HRV in older subjects represents a marker predictive of longevity.

Differences in HRV according to the healthy lifestyle score were also reported, suggesting that maintaining healthy lifestyles is positively associated with vagal functioning, and these beneficial adaptations may be lost if not sustained (Jandackova et al., 2019).

One of the best characterized treatments to increase parasympathetic activity and decrease the sympathetic/parasympathetic ratio that increases with age, is physical exercise (Raffin et al., 2019). In healthy older people, intensive endurance training could enhance parasympathetic parameters of HRV through daytime and nighttime 24 -hour ECG Holter recording (Pichot et al., 2005). Recent results suggest that different exercise interventions induced an enhancement of HRV in sedentary middle-aged adults, supporting the notion that exercise-related changes in HRV are associated with changes in body composition and cardiometabolic risk after the intervention program (Navarro-Lomas et al., 2022). When the effects of endurance, resistance, coordinative, and multimodal exercise interventions on resting HRV and secondary health factors were analysed in healthy older adults aged 60 years in average and over, beneficial effects were observed on cardiac autonomic control (Bahameish and Stockman, 2024; Grassler et al., 2021). Also delayed HR and blood pressure recovery after exercise test are known as reliable indices of autonomic dysfunction. Recent observations revealed a significant association between autonomic dysfunction and increased pulse pressure in normotensive middle-aged healthy subjects, suggesting a possible role for this variable as a useful marker of autonomic dysfunction (Lee et al., 2023). Overall, these results suggest that HRV may track the effects of anti-aging approaches.

Reduced HRV was observed in asymptomatic patients with type 1 diabetes mellitus (T1DM) compared with healthy subjects (Hajdu et al., 2023). The assessment of the association between the longitudinal evolution of HR and different HRV metrics with incident type 2 diabetes mellitus (T2DM), suggested that autonomic dysfunction precedes the development of T2DM, especially among younger individuals (Wang et al., 2023). Heart rate variability assessment of neonates of pregestational diabetic mothers has shown alterations in the ANS (Mercado et al., 2023).

The increasing interest in ANS imbalance measurements is related to the possibility to identify variation in asymptomatic patients, and thus to apply these tests as screening tests in apparently healthy subjects. Overall, HRV decreases with age, suggesting that it can be considered a hallmark of aging, but at the same time, an accelerated HRV reduction can be observed in prodromal phases of several age-related diseases, suggesting that HRV may be considered also as a hallmark of inflammaging.

5. ANS imbalance, HRV, and inflammaging

Evidence from numerous animal models shows that vagal activity regulates inflammatory responses by decreasing cytokine release. HRV is a reliable index of vagal regulation and should be inversely related to levels of inflammatory markers. When the relationship between systemic inflammation and both high (HF-HRV) and low frequency (LF-HRV) HRV was assessed, after controlling for sympathetic effects measured by urinary norepinephrine and other confounders, LF-HRV was found to be inversely associated with fibrinogen, C-reactive protein (CRP) and interleukin 6 (IL-6), while HF-HRV was inversely associated with fibrinogen and CRP (Cooper et al., 2015). These results support the existence of the vagal anti-inflammatory pathway, which acts independently of sympathetic activity and gender.

A recent systematic review including 159 studies showed that the standard deviation of R-R intervals (SDNN) and power in HF-HRV had the strongest associations with inflammatory markers compared to other time- and frequency-domain measures of HRV (Williams et al., 2019). Overall, the authors proposed that indices of HRV can be used to index

the activity of the neurophysiological pathway responsible for adaptively regulating inflammatory processes in humans. A recent study on cardiovascular diseases (CVD) underscores the association between elevated CRP and IL-6 and lower HRV in CVD patients affected by depressive conditions (Li et al., 2024). Other observations confirmed that the measurement of resting HRV and CRP may be helpful in detecting CV disease in depressed patients so that low HRV and elevated serum CRP might induce physicians to prompt management of CV risk factors (Singh et al., 2024).

Interestingly, environmental factors like air pollution and elevated temperatures significantly disrupt vagal tone in older adults, worsening inflammation and affecting heart rate variability (HRV) (Rajagopalan et al., 2018). Specifically, both low- and high-frequency power, along with SDNN (standard deviation of NN intervals), have been linked to short-term changes in ambient temperature during warmer seasons, with ambient ozone further influencing this relationship (Ren et al., 2011). Additionally, exposure to particulate matter (PM10 and smaller) has been shown to reduce HRV in the elderly (Chang et al., 2007; Huang et al., 2021; Park et al., 2008), as these particles can settle in the lower respiratory tract, triggering local inflammation and oxidative stress (Breitner et al., 2019). Environmental and social factors can lead to epigenetic modifications, such as changes in chromatin structure and microRNA expression, which may influence heart rate variability (HRV) and autonomic function from early life and persist into old age (Aghagoli et al., 2019; Jovanovic et al., 2017; Liu et al., 2021).

At the molecular and cellular level, a significant but not yet extensively investigated link between inflammaging and ANS imbalance is the modulation of macrophage functions and phenotypes that affect both conditions. HRV and leukocytes are associated in the context of healthy aging. In a large cohort of young and healthy adults, inflammatory parameters were strongly associated with increased HR and decreased HRV, suggesting an important interaction between inflammatory pathways and ANS imbalance (Aeschbacher et al., 2017). High-sensitivity CRP (hs-CRP) and leukocyte count with its subtypes were inversely associated with HRV and positively associated with HR (Aeschbacher et al., 2017). HRV and leukocytes appeared to be associated also in the context of metabolic diseases (Albarado-Ibanez et al., 2019; Papaioannou et al., 2013).

In obese individuals, resting heart rate (RHR) correlated positively with proinflammatory M1 monocytes, activated CD8+ T lymphocytes, and peripheral levels of important inflammatory mediators (Al-Rashed et al., 2021). These results suggested that RHR monitoring could be used as a non-invasive clinical indicator to identify individuals with obesity at an increased risk of developing macrophage-related inflammation.

Monocyte-derived macrophages are increasingly appreciated to have distinct responsiveness when exposed to inflammatory stimuli (Viola and Boeckxstaens, 2021). CAP has been identified in the spleen whereby noradrenaline released by splenic nerves binds to ß2-adrenergic receptors (β2-AR) on CD4+ T cells which, in turn, release acetylcholine (ACh), that binds to α7 acetylcholine receptors (α7-AChR) expressed by splenic macrophages, thus inhibiting the production of inflammatory cytokines, including tumor necrosis factor (TNF) (Bellinger and Lorton, 2018). However, the role of ACh-secreting CD4+ T-cells in the CAP is still controversial and largely based on the absence of this anti-inflammatory pathway in mice lacking T-cells (Huston et al., 2006). Using four non-lymphopenic transgenic mouse models, it was recently found that, besides acting on CD4+ T-cells, noradrenaline released by splenic nerve terminals acts directly onto β2-AR on splenic myeloid cells to exert an anti-inflammatory effect (Simon et al., 2023).

In vitro studies revealed that stimulation with CAP agonists suppressed M1 and promoted M2 macrophage polarization and inhibited the formation of macrophage foam cells by regulating genes related to cholesterol metabolism (Qian et al., 2021). M1 and M2 macrophages are two extremely polarized forms of mononuclear phagocyte *in vitro* differentiated with distinct phenotypic patterns and functional properties (Murray et al., 2014). The M1 macrophages, which are stimulated by Toll-like receptor ligands play host defense function and produce proinflammatory cytokines and chemokines such as TNF-α, IL-1β, and IL-6, whereas the anti-inflammatory M2 macrophages are associated with tissue repair, wound healing, and endocytic clearance by secreting reparative cytokines and enzymes, including IL-10, arginase 1 (Arg1), transforming growth factor (TGF)β and also IL-6 (Yunna et al., 2020). Even if the original concept of M1 and M2 macrophages was linked to an already well-accepted Th1/Th2 paradigm, *in vivo* it can be expected a wide range of different intermediate macrophage phenotypes, depending on the microenvironment and natural signals they receive. However, the simplification of M1/M2 macrophages became widely used not only in experimental models but also in clinical settings. The understanding that efferent vagus nerve can release ACh to activate the α7-nAChR implies that the net effect of α7-nAChR activation is to mitigate excessive cytokine production by macrophages, thereby restraining inflammation (Roa-Vidal et al., 2023; Wang et al., 2003). Importantly, bacterial and viral infections have the potential to disrupt this delicate innate balance (Delgado-Velez et al., 2015).

In this view, ANS imbalance and inflammaging could be intimately linked to the chronic persistence of M1 macrophages, and impaired M2 functions during time, which fuel systemic inflammation and accelerate endothelial dysfunction. This vicious circle starting from M1 persistence associated with significantly increased proinflammatory systemic mediators (IL1, TNF-alpha and IL-6), and concluding with endothelial dysfunction and endothelial cell death, is present in all the most common age-related diseases, and it was extensively discussed in the framework of inflammaging (Giuliani et al., 2023; Tudorache et al., 2022), but not in the view of ANS imbalance. M1/M2 imbalance, characterized by increased persistence of M1 phenotype releasing proinflammatory mediators, and HRV reduction appear as two features of ANS imbalance that can be easily measurable.

Overall, the balance between sympathetic and parasympathetic outflow modulates a complex set of conditions converging on inflammaging. Altering vagal tone and/or manipulating acetylcholine signaling, resulting in interactions between the immune and autonomic systems could contribute to modulating inflammaging levels (Wells and Tonkin, 2016). Vagus nerve stimulation (VNS) has been identified as an innovative immunosuppressive treatment strategy in animal models. To estimate its clinical potential a recent meta-analysis was conducted, with the aim of assessing whether VNS can reduce inflammatory proteins and/or immune cells in humans (Schiweck et al., 2024). The subgroup analysis of 4 long-term studies with acute inflammation showed significant results confirming that VNS decreased CRP significantly more than sham stimulation. Additional subgroup analyses including stimulation duration, stimulation method (invasive/non-invasive), immune stimulation, and study quality did not affect the results. However, heterogeneity was high, so that, given the low number of studies for each disease, a disease-specific analysis was not possible (Schiweck et al., 2024). In conclusion, while numeric effects were reported in individual studies, the current evidence does not substantiate the claim that VNS impacts inflammatory cytokines in humans, even if it may be beneficial during acute inflammatory events. Other authors responded to these observations that one aspect that was not discussed is the seemingly commonly held belief that VNS can be equated to activation of the CAP (Reardon, 2024). The stimulation of afferent vagal fibers has been demonstrated to drive non-CAP pathways to regulate systemic inflammation (Komegae et al., 2018; Murray et al., 2019). As a consequence, while VNS could represent a shorthand for CAP activation, other non-CAP pathways that are exploited by VNS could be more effective in the treatment of certain conditions. Differential activation of these complex pathways could presumably result in differential effects on clinical inflammation.

In addition to the putative application in the framework of chronic inflammatory disorders, VNS has already a well-established efficacy in controlling refractory epilepsy, episodic cluster headache, migraine, obesity and severe depression (Garamendi-Ruiz and Gomez-Esteban,

2019); it has also gained increasing attention in the context of stroke rehabilitation, even if in this regard the body of evidence is not still universally considered solid enough (Malakouti et al., 2024). Specifically, some meta-analyses have documented that VNS is able to reduce the frequency of both generalized and focal seizures and it is well tolerated by patients (Mao et al., 2022; Panebianco et al., 2022). Interestingly, recent investigations suggest also the potential efficacy against epilepsy of transcutaneous auricular vagus nerve stimulation as an alternative approach instead of the classical invasive VNS, but until now the quality of studies is not so high to support the routine use of this strategy in clinical practice (Lampros et al., 2021).

Of note, a meta-analysis of 12 studies showed only a modest effect on both LF HRV and HF HRV by VNS in patients who underwent surgery to treat drug-resistant epilepsy, thus suggesting a low likelihood that VNS would cause a significant cardiovascular autonomic dysfunction (Wu et al., 2021). However, it is important to underline that VNS reduces the frequency of seizures by 50–55 % on average and rarely represents a definite solution for drug-resistant epilepsy (Duncan, 2020). On the other hand, it could represent a valid approach to reduce the antiseizure drug burden and, consequently, the drug-related side effects (Duncan, 2020).

In summary, VNS is a well-tolerated and quite efficacious strategy to contrast some different disturbances. Interestingly, as mentioned above, many papers suggest that a possible common basis of the positive effects of VNS in diverse disease contexts is its putative anti-inflammatory action (Bazoukis et al., 2023; Wang et al., 2021), which is probably exerted by modulating different molecular pathways, including those involved in inflammasome activation (Tang et al., 2020). Furthermore, VNS could ameliorate systemic inflammation by reducing intestinal permeability and modulating the gut-brain axis (Langness et al., 2015). Notably, VNS can modulate the inflammatory response through the brain-gut axis, providing a non-pharmacological treatment option that could complement existing therapies for inflammatory bowel diseases (Bonaz et al., 2017). Considering that in many chronic diseases, including autism spectrum disorders and age-related diseases like for instance Alzheimer's and Parkinson's disease, inflammation, both at systemic and brain levels, is increasingly recognized as a probable key factor, VNS is being tested for these conditions in ongoing clinical trials (NCT06259201; NCT05575271; NCT06476912).

6. Conclusions and perspective

All the biomarkers identified in aging research converge on inflammaging, which is recognized as one of the most important causes of common age-related diseases. ANS imbalance, also defined as autonomic dysfunction, can be highlighted as an additional hallmark of inflammaging, with several available tests to measure heart rate variability (HRV), making it a valuable proxy measure for ANS imbalance. It is important to recognize autonomic dysfunction as a predictor of morbidity at its onset. Therefore, after anamnestic and objective examinations by trained specialists, selected asymptomatic older individuals should be screened for autonomic imbalance by HRV investigation, an established source of accurate, cheap, and non-invasive insight into autonomic outflow and the relationships between HRV and health state, providing an understanding of how HRV measurements can be interpreted and used. A high HRV might be associated with a healthy status, while a low HRV might be considered a predictor of disease and a risk factor for adverse outcomes.

Overall, the main advantage of assessing health status/inflammaging using HRV is that it is a non-invasive test, does not need sophisticated biochemical analysis, and is not associated with pain, discomfort, or related fear or trepidation. Therefore, the measurement of HRV is acceptable for all populations, including the oldest. While HRV testing using portable devices or wearables has been explored, clinically relevant HRV assessments should be conducted by trained cardiologists under controlled conditions. Moreover, interpreting HRV measurements requires an accurate understanding of factors such as comorbidities and cardiac rhythm disturbances, which may increase biological variability and affect the measurements, especially in older subjects.

Overall, HRV tests can help track the effects of interventions like exercise or dietary changes aimed at delaying aging. The purpose of this brief report is to stimulate further interest and to raise awareness in relation to the usefulness of assessing autonomic balance using HRV. HRV is emerging as a translationally relevant biomarker of inflammaging, and its measure in association with the systemic levels of several proinflammatory molecules, such as IL-6, CRP and TNF-alpha, could contribute to estimating the risk of developing age-related diseases and conditions. These conceptual frameworks are essential for distinguishing biomarkers that are relevant from a mechanistic perspective from those with clinical applicability and feasibility.

Further exploration of HRV in clinical contexts is imperative. This review advocates for longitudinal investigations to ascertain HRV reliability in prognosticating mortality, frailty, and age-related diseases. Particularly, investigations should expand into the genetic and epigenetic regulation of HRV, since also small-magnitude epigenetic modifications during infancy may greatly influence autonomic function and aging (Breton et al., 2017). Moreover, environmental influences, such as air pollution exposure, deserve focused research, especially in the elderly, as they may exacerbate ANS imbalance by inducing short- and long-term changes in HRV. Establishing robust evaluation criteria, diagnostic thresholds, and effective treatments for improving HRV will be crucial for integrating it into routine clinical practice as a biomarker for both aging and inflammaging. Finally, we anticipate that the insights presented herein will stimulate research aimed at improving HRV and, by extension, enhancing life expectancy and quality of life in older populations.

Author contributions

FO and SG conceived the idea. All authors contributed to the writing, reviewing, and editing of the original manuscript. All authors read and approved the final manuscript.

Funding

This work was supported by Next Generation EU, in the context of the National Recovery and Resilience Plan, Investment PE8 – Project Age-It: "Ageing Well in an Ageing Society". The views and opinions expressed are only those of the authors and do not necessarily reflect those of the European Union or the European Commission. Neither the European Union nor the European Commission can be held responsible for them. Open access funding was provided by Università Politecnica delle Marche within the CRUI- CARE Agreement.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We thank Dr. Marzio Marcellini (IRCCS INRCA) for drawing Figs. 1 and 2.

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