10 Heart Rate Variability: A Tool to Explore Autonomic Nervous System Activity in Health and Disease

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Historical Perspective

Within the different rhythmic processes observed in physiology, the heart rate has been one of the first to be studied. The earliest references come from Egyptian papyri (1550 BC), where a dissertation on the heart and the veins in terms of measuring is found, probably with the meaning of "counting" the pulse, recognizing it as related to the heart. The first one who spoke of this calculation was Herophilus of Alexandria (third century BC) who used a clepsydra for this purpose. Subsequently, we find detailed descriptions of the pulse in the treatises of Galen (129–c.199) on the subject. In the Renaissance, Galileo used his pulse to evaluate the oscillations of the pendulum, although it was Santorio (1561–1636) who used the pendulum to measure the frequency and regularity of the pulse. John Floyer (1649–1734) published an essay in 1707 (*The Physician's pulse watch, or an essay to explain the old art of feeling the pulse and to improve it by the help of a pulse watch*), where he described the invention of a portable clock with a second piece that could stop the watch. Thus, he could register pulse and respiration under several conditions. In 1733, Stephen Hales (1677–1761) described for the first time the relationship between the respiratory cycle and heart rate (*Statical Essays, Vol. II Haemastatics*), while in 1847, Carl Ludwig (1816–1895) was the first who documented the respiratory sinus arrhythmia. The recording of the electrical activity of the heart using galvanometers due to Willem Einthoven (1860–1927) in the late nineteenth century and the further development by Jeff Holter (1914–1983) in early 1960s of portable devices capable of recording ambulatory ECG during long periods of time (24 h) allowed further research in the relation of heart rate variations with health and disease [1].

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Sources of HRV

Heart rate is controlled by the periodic depolarization and repolarization of the cardiac pacemaker at the sinoatrial node, located on the posterior wall of the right atrium. Its steady intrinsic frequency range is 100–120 beats per minute. There are several neurohumoral factors that can modify this frequency, determining a lower or higher mean heart rate and beat-to-beat modifications of heartbeat duration. This latter phenomenon is known as "heart rate variability" (HRV) [2]. An intrinsic neural network within the cardiac fat pad provides local control of heart rate. This local network consists of sympathetic and parasympathetic neurons and interneuronal circuits. The spontaneous activity of these neurons even after cardiac denervation suggests an active role in the regulation of heart rate [3].

The origin of respiratory sinus arrhythmia (inspiratory tachycardia and expiratory bradycardia) is found in vagal modulation induced by the respiratory cycle on the heart. This mechanism determines that the duration of the heartbeat is modified following the respiratory rate, with cycles of 2.5–6.5 s in a healthy adult at rest, constituting HRV's high-frequency component (HF, 0.15–0.4 Hz). Two mechanisms could explain this phenomenon. On the one hand, there would be a central coupling of the respiratory oscillator with autonomic centers of the brain stem in the ambiguous nucleus and other related areas. On the other hand, this mechanism would be mediated via a cardiopulmonary reflex. A decrease in intrapleural pressure during inspiration reduces intravascular pressure within the thorax and increases venous return, leading to increased volume in the atrium and right ventricle. Atrial mechanoreceptors would be activated by conducting information through sympathetic and parasympathetic pathways that would result in an increase in heart rate. Only the parasympathetic component of the efferent pathway would be involved because the sympathetic effect on the heart is too slow to follow the respiratory rate. This reflex was first suggested by Francis Bainbridge (1874–1921) in 1915 after observing the increased heart rate in anesthetized dogs during volume infusions in the right atrium [4].

Spontaneous oscillations of blood pressure were first described by Siegmund Mayer (1842–1910) in 1875. The autonomic activity responsible for the genesis of these waves determines that the duration of heartbeats is modified with cycles of 2.5–25 s, constituting HRV low-frequency component (LF, 0.04–0.15 Hz). The main mechanism responsible for these oscillations is the baroreflex. An increase in blood volume distends the baroreceptors of the aortic arch and the carotid sinus, which through the X-pair and the IX-pair, respectively, send information reaching the nucleus of the solitary tract. This stimulates the ambiguous nucleus producing an inhibition of the sympathetic preganglionic chain and stimulation of the dorsal motor nucleus of the vagus. The combined effects result in a decrease in heart rate. In addition, it is believed that there would be a direct central participation by which sympathetic autonomic oscillators would determine hemodynamic oscillations in the absence of peripheral stimuli [5].

Thermoregulation and several hormonal processes are possibly involved in slower variations of heart rate, with cycles of 25 s to 5 min, constituting HRV very low-frequency component (VLF, 0.0033–0.04 Hz). Central processing of the central and peripheral information about temperature is done in the anterior hypothalamus. In this region, neurons whose activity is affected by the thermal stimulation of the preoptic area or the spinal cord have been identified. Thermoregulation exerts an indirect effect on the heart rate through the sympathetic activation triggered by cold. On the other hand, through a direct effect on the sinus node, cooling of the heart produces bradycardia, a mechanism used in cardiac surgery [6]. With regard to hormonal factors, the renin-angiotensin-aldosterone system is thought to influence VLF oscillations. Angiotensin and other factors such as aldosterone would directly or indirectly produce fluctuations in vasomotor tone. These fluctuations in turn would determine, mainly through parasympathetic outflow, fluctuations in the heartbeat [7].

Heart rate also exhibits a circadian rhythm, with ultralow frequency (ULF, <0.0033 Hz) oscillations. This rhythm is partially originated in the basal forebrain and is dependent on the sleep-wake state. This region exerts control of cardiovascular autonomic function through widespread projections to the paralimbic cortex, amygdala, hypothalamus, and brain stem autonomic nuclei [8]. In addition, the suprachiasmatic nuclei of the hypothalamus, considered the central pacemaker for circadian rhythms, regulate physiological functioning with cycles of about 24 h that are adjusted to 24 h mainly by the information of ambient light. These nuclei have projections to the paraventricular hypothalamic nucleus, which in turn modulate ANS activity by sending input to major sites of ANS regulation. HF, LF, VLF, and ULF regions in the power spectra of cardiotachograms (see below) can be described as a "harmonic" (sine wave frequencies) regulation of HRV.

Furthermore, HRV shows also "unharmonic" components within its power spectrum, which indicate a nonlinear dynamic behavior derived from the complex interaction of external influences, internal input, autonomic tone, and central organization. Indeed, nonlinear features are characteristic of complex systems, and the autonomic regulation of the heart can be described as one. As a complex system, it can be characterized by strange attractor's properties, fractal scaling, and the degree of entropy. Heartbeats may be seen as the projection on a line of one trajectory of a dynamical system that will converge to a limited region in space or attractor. Strange attractor's properties include a similar structure at different scales (fractality) and sensitive dependence on initial conditions for the trajectories on them (chaotic behavior). Fractals are geometric objects that have similar structure at different scales. In analogous form, nonlinear processes show a statistically similar dynamic pattern at different scales. In other words, the irregular fluctuations seen at multiple time scales resemble each other, and the pattern of variation across multiple scales of measurement characterizes complex systems. Entropy is a measure of disorder or randomness of a system. Systems tend to evolve from statistically ordered unlikely configurations to statistically disordered more probable configurations [9–12].

Methods for Assessing HRV

The simplest way to assess HRV is provided by the time domain methods (Fig. 10.1). In these methods the intervals between successive normal QRS complexes are measured (RR interval). Among others, simple time domain variables that can be calculated include the mean RR interval (RRM, ms); the standard deviation of all RR intervals (SDNN, ms), which gives a coarse quantification of HRV; and the square root of the mean of the squared differences between adjacent RR intervals (RMSSD, ms), which quantifies high frequency variations of HRV (Table 10.1) [13].

Frequency domain methods or spectral analysis convert time domain information into frequency domain information (Fig. 10.2). Usually, the discrete Fourier transform is used for processing the signal, and the squared amplitude calculated for each frequency (the power spectral density) is obtained [13]. By integration within suited frequency limits, the absolute spectral power (ms^2) can be calculated for each band: HF(ms^2, 0.15–0.4 Hz), LF (ms^2, 0.04–0.15 Hz),

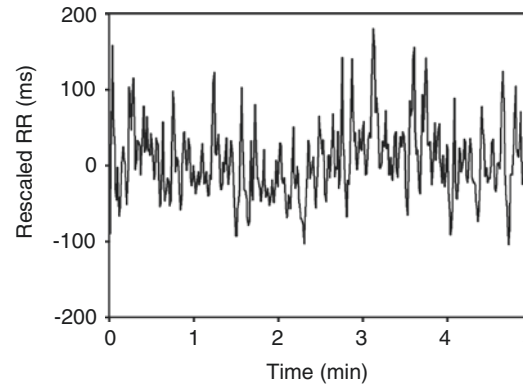

Fig. 10.1 Time domain HRV. Five-minute section of a HRV recording of a young healthy subject. The mean RR interval was subtracted from the original data

Table 10.1 Selected time domain HRV indexes

Index	Definition	Interpretation
RRM (ms)	Mean duration of RR intervals	Reciprocal of mean heart rate
SDNN (ms)	Standard deviation of all RR intervals	Coarse quantification of HRV
RMSSD (ms)	Square root of the mean of the squared differences between adjacent RR intervals	High frequency variations of HRV of parasympathetic origin

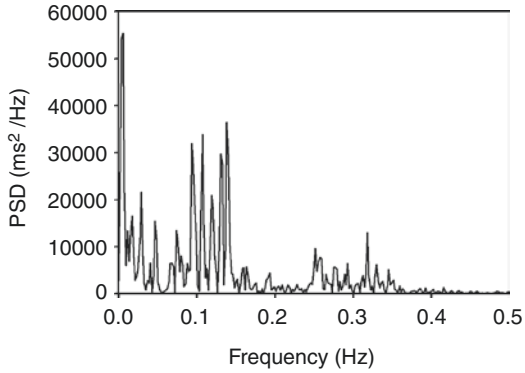

Fig. 10.2 Frequency domain HRV. Spectral density of the same individual of Fig. 10.1 Peaks are observed around 0.3 Hz (high frequency), 0.1 Hz (low frequency), and <0.04 Hz (very low frequency)

VLF (ms^2, <0.04 Hz in short-term recordings or 0.0033–0.04 Hz in long-term recordings), and ULF (ms^2, <0.0033 Hz only in long-term recordings). Total power (ms^2, <0.4 Hz) is an index of overall variability. The LF/HF ratio and other normalized frequency bands indexes are also derived (Table 10.2). By means of the wavelet transform, it is possible to estimate the temporal progress of the frequency spectrum of the signal, providing optimal resolution both in time and frequency domain. Indeed, when time domain information is converted into frequency domain information, time-related information is lost, because Fourier transform provides the accumulated power of a given frequency along a period of time, rather than in a given point in time. Wavelet transform has been introduced to HRV analysis to overcome this problem [14].

The RR time series attractor can be observed by plotting each RR interval against the previous RR interval (Poincaré-plot, Fig. 10.3). An attractor is a unique region in the phase space toward a system which tends to evolve, departing for a large set of initial conditions. Once the attractor is constructed, several numerical methods can be applied to estimate its complexity. SD1 reflects

Table 10.2 Selected frequency domain HRV indexes

Index	Definition	Interpretation
TP (ms^2)	Total power (<0.4 Hz)	Coarse quantification of HRV
ULF (ms^2)	Power in the ultralow-frequency range (<0.0033 Hz). Only in long-term recordings	Circadian HRV variations
VLF (ms^2)	Power in the very low frequency range (<0.04 Hz in short-term recordings or 0.0033–0.04 Hz in long-term recordings)	Possibly originated in hormonal factors and peripheral thermoregulation. Depends mainly on parasympathetic outflow
LF (ms^2)	Power in the low frequency range (0.04–0.15 Hz)	Baroreflex. Depends on sympathetic and parasympathetic outflow
HF (ms^2)	Power in the high frequency range (0.15–0.4 Hz)	Cardiopulmonary reflex. Depends on parasympathetic outflow
ULF (%)	ULF power in percentage units ULF (%) = 100 × ULF/total power. Only in long-term recordings	Relative contribution of ULF HRV
VLF (%)	VLF power in percentage units VLF (%) = 100 × VLF/TP	Relative contribution of VLF HRV
LF (%)	LF power in percentage units LF (%) = 100 × LF/TP	Relative contribution of LF HRV
HF (%)	HF power in percentage units HF (%) = 100 × HF/TP	Relative contribution of HF HRV
LF (n.u.)	LF power in normalized units LF (n.u.) = 100 × LF/(LF + HF)	Relative contribution of LF HRV within LF + HF range
HF (n.u.)	HF power in normalized units HF (n.u.) = 100 × HF/(LF + HF)	Relative contribution of HF HRV within LF + HF range
LF/HF	Low frequency/high frequency ratio	Considered to reflect sympathetic – parasympathetic balance

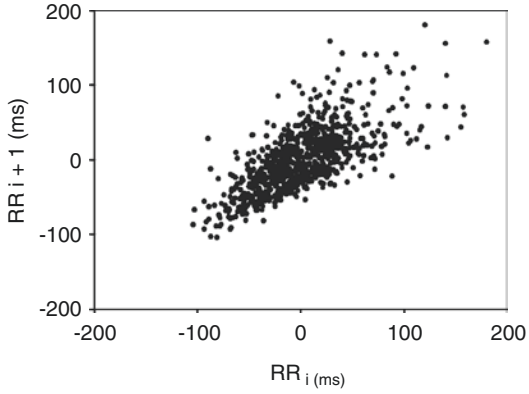

Fig. 10.3 Poincaré Plot of the same individual of Fig. 10.1. RR intervals are depicted as a function of the previous RR intervals, composing the heart rate attractor

short-term HRV while SD2 reflects long-term HRV. Both indexes include linear and nonlinear HRV features [12]. The quantification of the statistical entropy features of the system can be performed by measures such as "ApEn" or "SampEn." Basically, they quantify the order of the RR interval time series by taking the logarithm of the probability that patterns being close to each other at the beginning will remain closer in subsequent observations. Regular sequences will result in lower ApEn values, whereas random behavior is associated with larger ApEn values. An increase of entropy values usually reflects parasympathetic predominance situations [12]. The detrended fluctuation analysis is a technique that characterizes the pattern of beat-to-beat variation across multiple scales of measurement, through the short- (α1) and long-term (α2) fractal correlation scaling exponent alpha. α1 correlates inversely with short-term HRV measurements, while α2 correlates inversely with long-term HRV measurements. Values of α close to 0.5 are associated with white noise (no correlation between values), whereas values close to 1.5 are associated with Brownian noise (strong correlation between values). Values near 1 are characteristic of fractal-like processes, associated with the dynamic behavior of time series generated by complex systems, such as the autonomic regulation of the sinus rhythm of a healthy subject (Table 10.3) [12].

Table 10.3 Selected nonlinear HRV indexes

Index	Definition	Interpretation
SD1, SD2	Dispersion of the points around the minor (SD1) and major (SD2) axis of an ellipse fitted to the attractor	Set of numerical values toward which a system tends to evolve. SD1 reflects short-term HRV, while SD2 reflects long-term HRV. Both indexes include linear and nonlinear HRV features
ApEn, SampEn	Entropy measurement of heartbeat time series	Random behavior is associated with larger ApEn values. Usually reflects parasympathetic predominance
Short- (α1) and long-term (α2) scaling exponent alpha	Fractal correlation properties of heartbeat time series as calculated by detrended fluctuation analysis	Highly correlated heartbeat time series will result in higher scaling exponent alpha. α1 correlates inversely with short-term HRV measurements, while α2 correlates inversely with long-term HRV measurements. Values of α close to 0.5 are associated with white noise, whereas values close to 1.5 are associated with Brownian noise. Values near 1 are characteristic of the dynamic behavior of complex systems

HRV indexes are correlated between them. An increase in heart rate is associated with a reduction in SDNN, RMSSD, HRV power at all frequency bands, entropy values, and attractor dimension and with an increase in scaling exponent α. However, these relations are not linear. The mathematical functions that describe them are different when considering sleep or waking states, which possibly reflect different configurations of ANS functioning [15]. In addition, it has been proposed that nonlinear HRV is a characteristic of the phase transition-like dynamics that a healthy human heart rate exhibits between the different behavioral states of the sleep-wake cycle [16, 17].

Heart Rate Variability in Selected Physiological Situations

Gender Related Changes of HRV

HRV measures change during the regular menstrual cycle. SampEn and HF HRV components decrease from the follicular phase to the luteal phase, whereas normalized LF components and LF/HF as well as resting heart rate increase. SampEn shows significant correlations with spectral indexes, free T4 concentrations, and the ratio of estradiol to progesterone concentrations. Thus, the hormonal fluctuations that occur during the luteal phase of the cycle are associated with a shift toward sympathetic prevalence [18]. During pregnancy, changes in HRV indexes are observed within the first 6 weeks after conception, showing a decrease in almost all HRV indexes. It was also found that VLF, LF, HF, and normalized HF were significantly decreased, and LF/HF significantly increased in pregnant subjects in the third trimester as compared to the first trimester. The results indicate that during gestation, sympathovagal balance shifts progressively from a higher vagal modulation toward a higher sympathetic modulation [19–21]. Finally, although HRV is not associated with vasomotor symptom frequency or intensity in perimenopausal and postmenopausal women, an increase in VLF component is described associated to hot flash periods, which may be involved in the regulatory mechanisms of hot flashes [22, 23].

Aging

Aging is associated with alterations in the neural and endocrine mechanisms that regulate heart rate. Parasympathetic and sympathetic regulations become attenuated, renin and angiotensin levels are reduced, and circadian hormonal and temperature rhythms lose amplitude. Consequently, heart rate oscillations show decreased amplitude at all frequency levels with an overall reduction in HRV. Moreover, increasing age is related to alterations in fractal organization of heartbeat dynamics as well as to a loss of complex variability. These changes might lead to an impaired ability for stress adaptation and seem to be a common feature with many diseases [24–27].

Cognitive Function

Several studies show that resting autonomic patterns can influence cognitive performance. Possibly, some amount of sympathetic activation reflected by intermediate HRV values would be necessary for optimal cognitive performance. In this regard, it was reported that subjects with higher HF (higher parasympathetic activity) perform better at executive function tasks, probably by concomitant lower anxiety [28]. On the other hand, lower resting baroreflex sensitivity, usually associated with a reciprocal reduction of parasympathetic activity and an increase of sympathetic activity, predicted higher values in all parameters of attentional capacity [29]. In addition, better performance in a decision-making task was associated with increased LF. The sympathetic prevalence may be necessary to adjust cardiovascular function to cope with increased mental demand [30]. Autonomic changes during meditation techniques deserve a separate comment. A prominent peak in absolute LF, not attributed to an increase in sympathetic activity, is usually found in meditation techniques derived from different traditions. Breathing patterns achieved during meditation are associated with a synchronization of respiratory and heart rate variations (i.e., cardiorespiratory coupling), which is reflected in this characteristic increase in the LF power [31–33].

Physical Activity

During exercise, the resulting tachycardia is accompanied by a reduction of total HRV power. Thus, although LF absolute values seem unchanged, normalized LF and LF/HR ratio increases, reflecting the typical sympathetic activation associated with physical activity [13]. This pattern may vary within different subjects,

and a decrease in nonlinear indexes as SampEn may be robust for identifying brief physical activity episodes. On the other hand, long-term HRV indexes are relatively stable at various activity levels [34]. Of interest, extreme activation of the sympathetic nervous system underlying vigorous exercise leads to a marked reduction in global HRV power and increased nonlinear indexes as SampEn, a pattern also similar to situations with increased propensity to ventricular fibrillation [35]. Physical training is associated with higher HRV indexes reflecting vagal predominance which is considered a possible mechanism by which physical activity reduces coronary heart disease risk [36].

Postprandial Changes of Heart Rate Variability

The regional distribution of ANS within the body makes plausible that the same stimulus triggers different responses in different physiological systems and specifically in cardiac and gastrointestinal activity. In this regard, typical postprandial parasympathetic prevalence within abdominal compartment was associated with a decrease of HF and LF around 30–60 min after a meal, with a concomitant increase in the LF/HF ratio, characteristic of sympathetic predominance [37]. The different autonomic configurations of body compartments make in turn plausible the hypothesis that the disruption of the sleep-wake cycle and other circadian rhythms leads to changes in the balance of the autonomic activity of the thoracic and muscular compartment (toward a predominance of the sympathetic branch) and the intra-abdominal compartment (toward a predominance of the parasympathetic branch) [38].

Sleep-Wake Cycle

During wakefulness, reflex loops (respiratory sinus arrhythmia, baroreflex, and chemoreflexes) and central autonomic network areas (mid-cingulate cortex, insula, and amygdale) contribute to an increased heart rate, increased sympathetic activity (SNS), and decreased parasympathetic activity [39]. In addition, changes in HRV within wake states are associated or predict the operational levels of higher cortical functions, including alertness [40] and decision-making [30], suggesting a role of autonomic function in these processes.

Parasympathetic predominance during NREM sleep is characterized by slow EEG rhythms associated with decreased brain activity compared to wakefulness in subcortical (brain stem, thalamus, basal ganglia, basal forebrain) and cortical (prefrontal cortex, anterior cingulate cortex, precuneus) areas, suggesting a lower central command in cardiac autonomic control [39]. In this regard, it has been demonstrated that the degree of network connectivity and the strength of physiological interactions between different central and peripheral systems are minimal during slow sleep [41]. HRV studies during this sleep stage have revealed that there is a decrease in the LF component and an increase in the HF component relative to wakefulness [42–44]. The HF component is strongly associated with changes in the delta EEG band, preceding them in about 12 min [45]. As for the nonlinear components of HRV, slow-wave sleep is characterized as a stage with a higher degree of nonlinear variability in relation to wakefulness, manifested by a lower fractal correlation and a higher degree of entropy [16]. These findings are consistent with the parasympathetic prevalence characteristic of this stage and can be interpreted as associated with a decrease in non-reflex central influences [43].

During REM sleep, autonomic cardiac regulation is shared between central control in relation to amygdala activity and homeostatic control of the cardiovascular system by reflex arcs, leading to an increase in heart rate, with sympathetic predominance and decreased parasympathetic activity [39]. Consistently, the degree of network connectivity and the strength of physiological interactions between different central and peripheral systems are intermediate between NREM sleep and wakefulness [41]. This possibility is supported by the observation that the response of

peripheral centers to changes in blood pressure is modified and by the fact that the thermal or electrical stimulation of diencephalon structures is not accompanied by concomitant changes in certain autonomic functions [46]. During this stage, a pattern of increase in linear HRV is observed. Studies differ in their reported values for REM sleep, with maxima for the LF component and nulls for the HF component [42–44, 47, 48]. In comparison with wakefulness, no significant changes have been reported in the nonlinear dynamics of autonomic cardiac regulation [16, 49]. Variations in heart rate are particularly marked during the phasic stage of REM sleep and tend to coincide with ocular movements and with theta activity bursts of this stage [50]. Taken together, these findings would reflect a partial release of central modulation on peripheral autonomic activity.

Apart from variations in cardiac autonomic activity associated to sleep stages, an endogenous circadian rhythm has been demonstrated in heart rate and HRV, in the absence of sleep masking effects, general activity, postural changes, and light. The results suggest that circadian control of heart rate is not entirely mediated by the sleep-wake cycle and that autonomic modulations are influenced by the circadian regulation. Peak values of this rhythm are seen during late wakefulness for heart rate and during the latter part of the sleep period for HRV measurements. In addition, the administration of melatonin is capable of advancing the endogenous circadian rhythm phase of heart rate and SDNN, RMSSD, and HF [51].

Heart Rate Variability in Selected Clinical Conditions

Type 2 Diabetes Mellitus

The relationship between the presence of diabetes and alterations in cardiac autonomic regulation is well known. This extends to subjects with insulin resistance and to the offspring of type II diabetics patients with no history of diabetes or hypertension where the mean values of HRV are decreased. Low HRV in healthy people is associated with an increase of developing this disorder. In addition, low HRV in patients with diabetes increases the risk of complications and mortality compared with those with normal HRV values. Among other parameters, SampEn and HF HRV are better discriminants to detect autonomic dysfunction. From a circadian point of view, the amplitude of day-night variations in HRV is decreased in subjects with diabetes. These findings support the use of HRV as a risk indicator in type II diabetics [52–54].

Obesity

Regarding the presence of obesity, a reduction of SDNN, RMSSD, and absolute and relative HF HRV is observed, pointing to a relative prevalence of sympathetic activity [55]. Circadian alterations of HRV are also described. The LF/HF ratio increases at certain points in the afternoon in association with high plasma insulin concentrations [56]. Interestingly, increases and decreases in the LF/HF ratio were respectively detected in response to gain and weight reduction achieved through an experimental design [57].

Dyslipidemia

It has been reported an inverse association between short-term HRV and triglycerides in elderly people and between short-term HRV and the LDL/HDL ratio in elderly men but not women [58]. A further study demonstrated an inverse relationship between 24 h HRV indicators reflecting parasympathetic activity (RMSSD) and total cholesterol, LDL, and LDL/HDL, adjusted for various demographic and clinical factors including levels of noradrenaline [59].

Hypertension

ANS disorder, clinically manifested as a hyperkinetic circulation characterized by elevations in heart rate, blood pressure, cardiac output, and plasma norepinephrine levels, has been systematically

demonstrated in hypertension. Increased sympathetic activity has been reported using spectral analysis of HRV [60]. Specifically, compared to control ones, subjects with primary hypertension have decreases in LF and HF components of HRV both during the day as well as the night. The day-night differences in HRV increase after 1 year of treatment with angiotensin-converting enzyme inhibitors [61]. In subjects with hypertension and left ventricular hypertrophy (but without coronary pathology), there is a decrease or absence of sleep-wake differences in heart rate, RMSSD, LF, and HF, thus evidencing alterations in the circadian rhythm of cardiac autonomic control [62]. In addition, flattening of the circadian rhythm of heart rate is independently associated with an increased risk of all-cause mortality [63].

Ischemic Heart Disease

As described above, existing evidence support the notion that cardiovascular risk factors are associated with altered HRV patterns. Also, autonomic imbalance may provide a unifying framework within which to investigate the impact of those factors and other psychosocial determinants on cardiovascular disease [64]. When considering established cardiovascular disease, impaired HF oscillations of heart rate are the most prominent feature in patients with uncomplicated coronary artery disease. On the other hand, patients with prior myocardial infarction and impaired left ventricular function have a reduced overall heart rate variability and a specific spectral pattern with a reduced LF spectral component. In addition, patients with prior myocardial infarction have higher ApEn values and lower scaling exponent values, indicating that heart rate dynamics are more random. These measures have revealed to be strong predictors of fatal arrhythmias [65].

Stroke

Autonomic imbalance has been identified prior to atrial fibrillation [66]. Global HRV, quantified by SDNN indicator, is a strong predictor for ischemic stroke development in apparently healthy subjects. The mechanism is unclear, but it is probably due to a decrease in parasympathetic activity that increases the risk of arrhythmias [67]. HF HRV is significantly reduced in patients with acute cerebral infarction [68], while elderly survivors of ischemic or hemorrhagic stroke show lower total HRV and LF HRV long after the event [69]. In the presence of a hemispheric or trunk stroke, changes similar to those described for coronary disease are observed, where all HRV components are similar during the day and at night, indicating the abolition of circadian rhythmicity of cardiac autonomic regulation [70]. HRV differences between hemorrhagic and ischemic stroke are not well established [71].

Mild Cognitive Impairment/ Alzheimer's Disease

Several works have shown that central components of the ANS, mainly insular cortex and brain stem, are affected in early stages of Alzheimer's disease, manifesting itself as a parasympathetic dysfunction that contributes to the progression of the disease [72]. This pattern is maintained in later stages of the disease, where RMSSD and spectral components are lower in patients than in controls. In addition, HRV was found to be significantly correlated with the degree of cognitive impairment [73].

Cancer

Autonomic activity may be an important marker in cancer due to its role in modulating inflammation and oxidative stress. HRV indexes have been used in several studies to assess autonomic profiles within this disease. Decreased heart rate variability (mainly reduced SDNN) is associated with shorter survival times in patients with several types of cancer, pointing out that higher vagal nerve activity might play a protective role in cancer [74]. Specifically, breast cancer survivors exhibit a decrease in overall variability (SDNN) and parasympathetic activity (RMSSD, HF HRV)

when compared to women without the disease [75]. Higher SDNN and RMSSD predict lower levels of carcinoembryonic antigen in colorectal cancer patients, supporting the hypothesized role of vagal activity in tumor modulation [76]. In prostate cancer patients, SDNN and RMSSD inversely predict PSA levels at 6 and 24 months, being particularly significant in metastatic prostate cancer, indicating stage moderation [77]. A study reported that SDNN univariately predicted poor survival in non-small cell lung cancer [78], while another one found that SDNN and RMSSD predict survival time independently of confounders but only in patients under 65 years old [77].

Anxiety

Stressors, anxiety, and anxious personality traits are associated with increased cardiac frequency and lower values of parasympathetic HRV indexes during wakefulness, with the effects of stressors and concerns extending to the subsequent nighttime sleep period. These results are independent of other behavioral variables including sleep quality and may mediate the increased cardiovascular risk associated with stress due to the observed reduction in parasympathetic activity [79].

Depression

Depression has been often reported to be associated with an overall reduction in total HRV, generally characterized by reduced HF HRV and reduced complexity. These are similar findings to those of aging. A reduced HRV characterizes decreased psychological flexibility, emotional dysregulation, and defective social engagement, which in turn are linked to hypoactivity of the prefrontal cortex [80]. Depression is also recognized as an independent adverse prognostic factor in patients recovering from an acute coronary episode [81, 82]. Subjects with major depressive disorder have a reduction in HRV in all frequency components both during the day and during the night. In addition, during the night they present a reduction in nonlinear HRV. Taken together, these findings point out a greater sympathetic activation throughout the whole day. It was observed that HRV indicators correlate with sleep quality, but not with depression scores, which shows that sleep disorders typical of depression play an important role in the alteration of autonomic regulation [83].

Schizophrenia

Schizophrenia is characterized by abnormalities of cortical structures concerned with autonomic control, including prefrontal, cingulated, temporal areas and the hippocampus. Symptom development theories in schizophrenia have long incorporated the notion of autonomic dysfunction, including pupillary, vasomotor, sweating, heart rate, salivation, and temperature changes, most of them suggesting increased sympathetic prevalence as an important feature in the expression of psychosis. HRV pattern in acute schizophrenia is consistent with this notion, since RMSSD index is diminished [84]. In stable schizophrenia, subjects exhibit normal autonomic activity at rest and in response to mental stress, but they maintain HRV stress-related changes further than stimulus cessation, in the form of larger relative LF HRV component [85, 86].

Social Determinants of Health

Extensive research has shown that adverse environmental and working conditions, such as shift work and excessive workload, are related to disease. Psychosocial workload and working time have been associated with low HF HRV [87]. In night shift work, typical patterns of autonomic predominance are inverted, with increased sympathetic activity during the night (wake period) and increased parasympathetic activity during the day (sleep period), making evident the strong dependence of the autonomic regulation on the sleep-wake cycle [88]. When these conditions are maintained for extended periods, sympathetic activity (LF HRV and LF/HF ratio) during sleep

in these professionals is greater than that of their colleagues in the morning shift [89]. Finally, the lack of exposure to natural light may result in the loss of the circadian rhythm of cardiac autonomic activity, as it was shown in prolonged confinement experiments [90, 91].

Conclusion

The analysis of the autonomic modulation of heart rate provides information about the state of the ANS in several physiological and clinical situations. It is now widely accepted that the interaction of several biological (genetic, biochemical, biophysical), psychological (personality, mood, behavior), social (family, work, society), and ecological (living environment) factors plays an important role in the preservation of quality of life and health. The ANS is structural and rhythmically interfaced between the forebrain and internal and external environments, to regulate energy, matter, and information exchanges. Its overall function is to maintain the body homeostasis and to react predictively or adaptatively to changes in the internal and external environment. All body systems are dependent and affected by the action of others and by external factors in a multilevel and dynamic organization. Thus, the biopsychosocial nature of the individual is expressed by the function of the ANS, which can be explored by the analysis of the variability of heart rate. In turn, autonomic imbalance, as evidenced by alterations in HRV, may configure a final common pathway to increased morbidity and mortality from a host of conditions and diseases [92–94].

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