

Heart Rate Variability (HRV): a mini-review of its basic principles and applications in vascular diseases

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Abstract Heart rate variability (HRV) is a biomarker which is strictly related to the activity of the autonomic nervous system (ANS). It has also been demonstrated that HRV is strictly related to human psycho-physical resilience and, more generally, to human health and aging. The analysis of HRV through different methods, mostly of photoplethysmographic type, is being increasingly employed in several medical disciplines, both as a diagnostic tool and as a prognostic mean to monitor a number of treatments. ANS notoriously influences a wide spectrum of human physiological processes and its unbalance brings several alterations in a number of pathophysiology processes related to cardiovascular diseases and psycho-neuro-biology in general. The HRV analysis technique includes a basal and under "stress" examination, to elicit a series of time-domain and

frequency-domain-based parameters which highlight the orthosympathetic and parasympathetic (vagal) activities. The usage of HRV analysis in vascular diseases may be of interest in a few cases, such as: the diabetic dysautonomia and microangiopathy, the vaso-dystonic acro-syndromes (e.g. Raynaud phenomenon), the autoimmune disease-based "vasculitis" and more generally any vascular ulcer, lymphedema and all types of microangiopathies and cardiovascular diseases. This mini-review describes the basic principles of HRV analysis and its applications in the diagnostic-therapeutic approach to vascular diseases.

Keywords heart rate variability, HRV, autonomic nervous system, microcirculation, aging

Introduction

Heart rate variability (HRV) is strictly related to the activity of the autonomic nervous system (ANS), also named neurovegetative system. It has also been demonstrated that HRV reliably reflects human psycho-physical resilience and, more generally, human health and aging¹⁻⁴. The analysis of HRV by means of several methods, mostly of photoplethysmographic type, is being increasingly employed in a number of medical disciplines, both as a diagnostic tool and as a prognostic mean to monitor several treatments.

The usage of HRV analysis proved of interest also in the management of vascular diseases such as: the diabetic dysautonomia and microangiopathy, the vaso-dystonic acro-syndromes (e.g. Raynaud phenomenon), the autoimmune disease-based "vasculitis", lymphedema

and more in general any vascular ulcer, all types of microangiopathies and cardiovascular diseases.

The ANS is made up of a very fine network of neuronal connections that permeate the entire human organism and that regulate a very wide range of psycho-organic functions independently of the will. The two main branches of the ANS are the orthosympathetic system and the parasympathetic, or vagal, system; the infinite multiplicity of the physiological activities of our mind-body unit derives mainly from the homeodynamics/balance between these two branches.

Overall, it has been clarified that the parasympathetic system is responsible for rest, especially at night, digestion, anabolism in general, and psycho-organic calm. The orthosympathetic system, on the other hand, responds to the

principle of "fight or flight" in the face of stress of any kind, governs especially daytime activities, and therefore has a mainly catabolic activity.

Many scientific studies have shown how the HRV analysis test has proven to be extremely reliable for measuring the state of balance/disequilibrium between these two systems. The functionality of the ANS is in turn related to daily exposure to different types of stressors, which leads to continuous changes in HRV that can be monitored with current devices, thus highlighting the effects of chemical/physical/psychological, internal and/or external, disturbances on the human organism. Furthermore, through HRV analysis it is possible to adequately monitor the effects of any interventions on the nutritional profile and lifestyle aimed at re-establishing a healthy homeodynamics of psycho-organic processes of the subject (e.g. physical activity, breathing, caloric restriction, fasting, specific nutrients, thermal exposure, meditation, etc.).

In recent years, there has been a significant increase in the scientific research utilizing HRV as both an index for clinical trials and as a parameter to evaluate various human activities and psychophysiological interventions that influence the neurovegetative system. In PubMed scientific search engine alone, primarily based on the MEDLINE database, publications containing the term "Heart Rate Variability" rose from 1123 in 1980 to 63226 by the end of January 2025⁵, confirming a growing interest in this biological parameter and in the indices provided by the HRV analysis that reveal the activity of the ANS.

Due to the ascertained and utmost important relationship between mind and body, psychoneurobiology (also known as psychoneuroendocrineimmunology, PNEI) is conquering a growing space and interest in the biomedical research and knowledge. In fact, it has been demonstrated that chronic degenerative diseases (diabetes, obesity, cardio-cerebrovascular diseases, neurodegenerative diseases, autoimmune diseases, cancer, etc.) are strictly related to the psychoneurobiological condition of the individual, hence to the influence of psyche on the cellular pathomechanisms and, more widely, on the inflammatory and aging processes of human being⁶⁻⁸.

Cellular senescence basically features mitochondrial degeneration, altered autophagy mechanisms, altered proteasome, free-radical attack to cell components (mitochondrial DNA *in primis*), glycation damages, methylation alteration, nucleic acids degeneration, just to name some of the most relevant biochemical processes. The outcome of these degenerative pathomechanisms is represented by the chronic low grade cellular inflammation, which ultimately brings "inflammaging", a term which defines the root event of human aging^{4,6,8}. The panoply of all these processes is under the influence of the ANS,

hence under the influx of mind-body axis, areas where HRV analysis may play a diagnostic role.

From a psychological standpoint, the loss of HRV variability is a consequence of emotional rigidity, characterized by the tendency to respond to a wide range of situations with a stereotypical reaction, such as sadness, anxiety, distrust, anger, and so on. However, not only is simplicity a hallmark of poor adaptation, but random variations in response to specific stimuli also suggest a lack of modulatory control. Both conditions are unfavorable to healthy aging and indicate a decline in psycho-physical resilience and an increase in systemic vulnerability.

In parallel with the diffusion of HRV analysis in the scientific community, there has been an increase in the production of HRV-based biofeedback devices and in their evolution as biosensors for the general population, offering diagnostic functions and orthodox biofeedback training. Wearable technologies and user-friendly devices now enable the collection of data and information to modulate daily activities and, even more interestingly, to improve lifestyle, nutrition, well-being, and overall health.

Basic principles of HRV

The uniqueness and complexity of the human neurovegetative system have led to an interpretative effort regarding the daily, physiological, and pathological changes in the balance between the sympathetic and parasympathetic system. HRV has proven to be a reliable parameter for assessing overall changes in the ANS in both health and disease, and the analysis of HRV represents a basic tool to integrate PNEI within the current medical approach to chronic degenerative diseases and aging.

HRV is described as the beat-to-beat variation in the temporal intervals between cardiac contractions⁹, namely the distance between systolic phases. HRV consists of changes in the time intervals between consecutive heartbeats, known as inter-beat intervals, which are measured in milliseconds¹⁰. Specific algorithms are used to calculate the intervals between R-R peaks, generating numerical sequences and allowing for the derivation of graphs, indices, and ratios.

Contrary to past assumptions, a healthy heart does not beat like a metronome but rather exhibits complex dynamics, alternating periods of heart rate acceleration, with a decrease in RR intervals, and deceleration, with an increase in RR intervals. Significant variations in these intervals during rest indicate effective vagal activity, reflecting a better capacity to adapt to physical and psychological challenges, which in fact reflects the individual's resilience.

A healthy heart shows high complexity in its oscillations and quickly adapts to sudden physical and

psychological changes through effective cardiac regulation, achieving stability through variation. In contrast, a diseased heart displays regularity and low complexity in its rhythm, responding poorly to abrupt changes due to the deterioration of regulatory mechanisms¹¹. Even more importantly, these fluctuations in heart rhythm closely reflect overall psycho-physical conditions; in fact, a great number of studies have documented that a reduced HRV is a notable risk factor for morbidity and mortality (and for sudden death), associated with vulnerability, physical and psychological stress and diseases¹². The cardiovascular system integrates various control mechanisms, and its oscillatory patterns are unpredictable and chaotic, reflecting the environmental challenges to which individuals must respond. Effective modulation of vagal tone is the main target for maintaining a good dynamic autonomic balance, as the imbalance caused by vagal inhibition is associated with increased morbidity and mortality¹³.

A simplification of HRV dynamics can result from system fatigue due to allostatic overload (the chronic stress excess which overwhelms human coping abilities)¹⁴, or from biological damage to the system's components, as in the case of heart failure that leads to reduced heart rate entropy¹⁵⁻¹⁷.

Psychophysiological systems with poor adaptability become particularly vulnerable to occupational, familial, and social stress, and subsequently to illness. Chronic stress (distress) results in altered patterns of PNEI biochemical mechanisms, with an overall negative impact on health and aging¹⁸. In essence, HRV can reflect the psychological and biological consequences of distress, PNEI dysregulation, and related chronic-degenerative diseases and aging processes: the lower the HRV the worse the general health condition^{19,20}.

It is interesting to note that HRV has proven to be the most reliable biomarker for evaluating human resilience^{21,22}, and the quantification of this psycho-biological factor is becoming of paramount importance in medical science, as resilience is likewise considered a key factor in aging²³. In the HRV analysis a number of parameters and graphics are potentially extrapolatable, in order to assess the interaction between the two branches of ANS and their ability to respond to any outer psycho-physical-chemical variation. One of the basic graphical reports, as a starting point in HRV assessment, is represented by the Poincaré plot, which visualizes the relationship between the collected data and the time interval of the examination, providing information about the variability of the heart rate in a determined period of time²⁴.

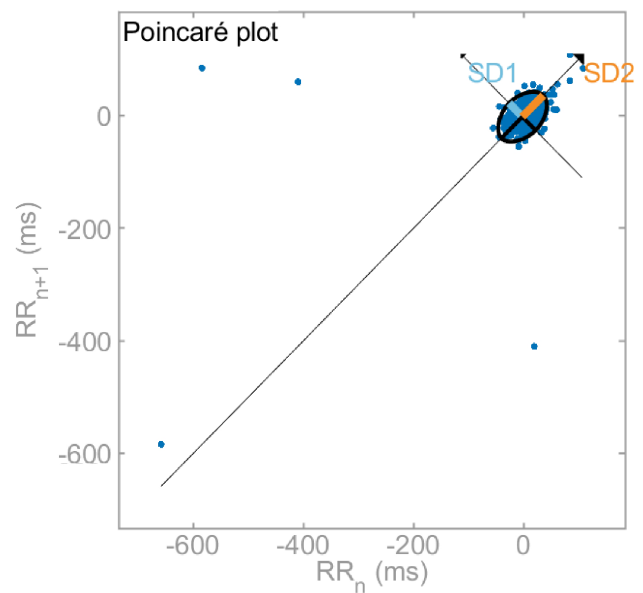


Fig 1A - An example of a HRV Poincaré plot of an old patient affected by a few chronic degenerative diseases

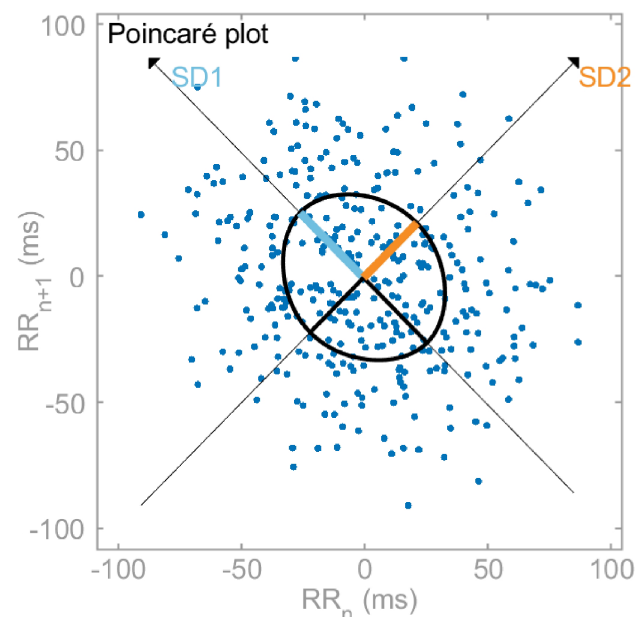


Fig 1B - A graphical representation of the Poincaré plot of a young athlete

In the typical Poincaré plot graphic (see Fig.1A and 1B) the abscissa (horizontal axis, x) is labeled RR_n and represents the current RR interval, which is the time between two consecutive heartbeats measured in milliseconds; the ordinate (vertical axis, y) is labeled RR_{n+1} and represents the RR interval following the previous one, also in milliseconds. In summary, each point represents a pair of consecutive RR intervals: (RR_n, RR_{n+1}) .

This type of plot is used to visualize the dynamics of HRV over time. In the figure 1A and 1B, the two highlighted directions (SD1 and SD2) represent the standard deviations along two main axes.

Basically, SD1 represents the short-term variability of RR intervals and SD2 documents the long-term variability. More in detail, SD1 is perpendicular to the identity line (the diagonal one that goes from the bottom left to the top right).

This parameter (SD1) is mostly associated with parasympathetic activity, especially breathing (so it may properly reflect the classical respiratory sinus arrhythmia). Conversely, SD2 represents is parallel to the identity line and it reflects both sympathetic and parasympathetic components, but more on a longer time scale.

Overall, SD2 cannot be said to equate to the expression of the sympathetic system directly, but an increase in SD2 is objectively associated with sympathetic activity, along with other factors. To have a clearer sympathetic-parasympathetic indication, it is proper to look at the SD1/SD2 index, which can suggest an imbalance of the ANS.

However, at a glance, the Poincaré plot graph shows the greater or lesser cardiac variability, as with a lower variability the dots are confined to a small area of the graph (Fig.1A regards a person with various chronic diseases and therefore with a low variability), whereas in the presence of a greater variability there is a dispersion of the dots over a larger area of the graph (Figure 1B is taken from an exam on a young athlete).

Cardiac dynamics data provide both quantitative and qualitative insights into the ANS. In HRV analysis these measurements are elicited using two key methods: time-domain analysis and frequency-domain analysis, each offering distinct and valuable indicators.

Time-domain analysis examines how much variation occurs in the intervals between heartbeats (inter-beat intervals). This variability reflects the dynamic interplay between the sympathetic and parasympathetic branches of the ANS.

Higher variability generally indicates a more adaptable and resilient autonomic response, while lower variability may suggest autonomic dysfunction or distress.

Frequency-domain analysis breaks down HRV into different frequency components, each associated with specific aspects of ANS activity. This method helps quantify the contribution of different autonomic pathways, such as parasympathetic (high-frequency components) and sympathetic (low-frequency components) influences on heart rate regulation.

In summary, time-domain indices describe the overall degree of heart rate variability, reflecting the combined activity of the autonomic branches, while frequency-domain parameters provide a more detailed view of how different components of the ANS contribute to heart rate regulation.

From the biotechnology and practical point of view, through photoplethysmographic sensors it is possible to detect variations in light reflection in the capillaries of the ear (or finger) as influenced by heartbeats.

Real-time HRV processing, both at rest for 5 minutes and during the one minute deep (diaphragmatic) breathing test, relies on hemoglobin's ability to absorb light. The pulsation of blood flow in the capillaries affects the sensor's absorbance due to the resulting variability in hemoglobin content.

It is known that HRV can be studied also capturing the complete electrocardiogram (ECG), instead of the single heart beat detection; furthermore, HRV can be an additional result of ECG Holter examination, analyzing the R-R time intervals of the entire examination procedure (one or two days).

Scientific literature after years of clinical and experimental trials has highlighted a series of scientifically supported and useful indices derived from HRV evaluations; Table 1 describes the main parameters which are investigated in the HRV analysis investigation^{25,26}.

Furthermore, an index between LF and HF has been proposed to assess the sympathovagal balance^{27,28} though this parameter is not fully accepted among specialists of HRV testing²⁹.

Figure 2 shows a typical setting of an HRV examination, with the patient sitting and the computer-based acquisition of data derived from the time/frequency domain-based assessment of the cardiac rhythm through the ear-placed sensor, both in basal condition and during 5 minutes deep (diaphragmatic) respiration.

A number of graphics and numerical analyses may be extrapolated through HRV analysis; figures 3, 4a and 4b describe a type of imaging and of detailed report of the main findings deducible from an HRV test. The validated and gender/age-tailored values for each parameter are usually reported, so to figure out the main pathological outcomes of the examination.

When indicated, the typical investigation method can be accompanied by numerous other types of tests, like tilting test, Valsalva maneuver, etc., sometimes employing other types of body sensors, which examine the variability found in the various parameters of the HRV analysis for a longer period of time (even several days).

Table I - The main parameters derived from HRV analysis

Time-domain parameters	Frequency-domain parameters
Mean Heart Rate (more commonly referred to as heart rate) is defined as the number of heartbeats per minute (BPM - Beats Per Minute). It measures how frequently the heart contracts to pump blood throughout the body	Total Power (TP) It represents the overall energy of the ANS, more specifically of the frequency spectrum of HRV signals, typically measured in milliseconds squared (ms^2). It reflects the autonomic nervous system's activity, encompassing both sympathetic and parasympathetic influences. It is divided into different frequency bands, including Very Low Frequency (VLF), Low Frequency (LF), and High Frequency (HF)
Standard Deviation of Normal-to-Normal Intervals (SDNN) , measured in milliseconds, which numerically expresses the combined action of the sympathetic and parasympathetic branches of the ANS	Very Low Frequency (VLF) band , covering oscillations between 0.0033 and 0.03 Hz, which represents the slowest changes in heart rate and is directly linked to body thermoregulation and the hormonal cycle
Root Mean Square of the Successive Differences (RMSSD) , namely the square root of the mean of the squared differences between adjacent N-N intervals. This is a numerical expression of parasympathetic activity. A low value indicates poor parasympathetic activity due to insufficient recovery or due to high intellectual/emotional stress	Low Frequency (LF) band , encompassing oscillations between 0.03 and 0.15 Hz, represents slower changes in heart rate. It is an indicator of sympathetic activity and reflects the effectiveness of the baroreceptor reflex in the interaction between the cardiovascular and respiratory systems
Mean Heart Rate Range (MHRR) it indicates the difference between the maximum and minimum heart rates during each respiratory cycle. MHRR is expressed in beats per minute, as the average of these differences for each measured cycle	High Frequency (HF) band , encompassing oscillations between 0.15 and 0.40 Hz, represents the fastest changes due to parasympathetic activity

HRV and chronic degenerative diseases/aging

Health was defined as "the ability to adapt" in a Lancet editorial published a few years ago³⁰, underscoring the importance of coping, resilience, and adaptation for healthy aging. Likewise, aging leads human beings to undergo a continuous, dynamic process of responding to internal and external challenges by drawing on psycho-physical resources. The greater these resources, the higher the likelihood of living and aging in good health, since greater resilience (and thus higher HRV) indicates a more

effective response to life's challenges and a faster return to equilibrium.

Psychoneurobiology science has clearly highlighted the close (both positive and negative) relationship between mind and body, as well as the key role of the stress axis in the onset and progression of chronic-degenerative diseases at all levels^{31,32}. Engaging in daily activities and facing stress involves mobilizing especially the sympathetic system's resources. Once a goal is reached, these resources recede to allow room for parasympathetic system activity.

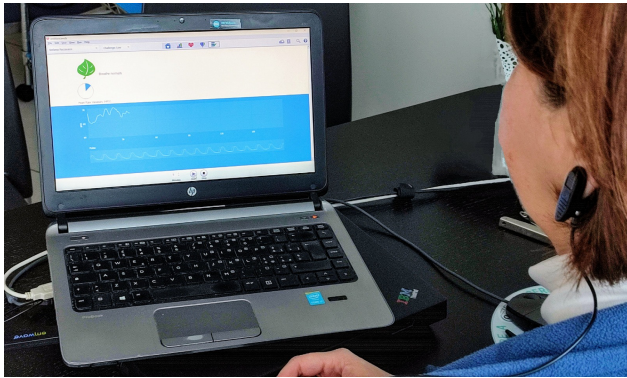


Fig 2 - An example of HRV investigation setting, using emWave Pro Plus (R) device

If there is insufficient tone in either system or if one system dominates, completing tasks and managing stress may become ineffective and inadequate for maintaining health and well-being.

Relatively to HRV examination, numerous publications have proved how periods of chronic stress lead to a decrease of HRV, together with an increase in LF band frequencies and a reduction in HF band activity and of RMSSD, with an overall loss of energy (i.e. total power) and balance between the two branches, thus reflecting the natural rise in sympathetic system activity at the expense of the parasympathetic system³³.

Excessive sympathetic activity, primarily due to an unhealthy, stressful lifestyle adopted by large segments of the population in highly urbanized areas, is one of the causes of many disorders stemming from a lack of balanced parasympathetic action (e.g., sleep dysregulation, altered chronic stress management), or from resource depletion (nutrient deficiencies).

The HRV investigation may be performed in different ways, but it anyway involves the deep/diaphragmatic guided test; this specific modality permits to assess the variability of the ANS under a peculiar "stress" condition. In fact, beyond the well-known modulation of the heart rate exerted by respiration, it was shown that breathing has a significant impact on the ANS (particularly on the vagus nerve); specifically, just one minute of deep/slow breathing has been found to produce a highly significant physiological increase in SDNN and RMSSD values, shifting them from the lower end of the normal range toward medium or higher levels of sympathetic and parasympathetic tone.

In agreement with the most reliable literature data, the most adequate indications to HRV examination have been summarized in table 2 below, whereas adjunctive indications more specifically pertinent to vascular medicine, will be detailed in the following section.

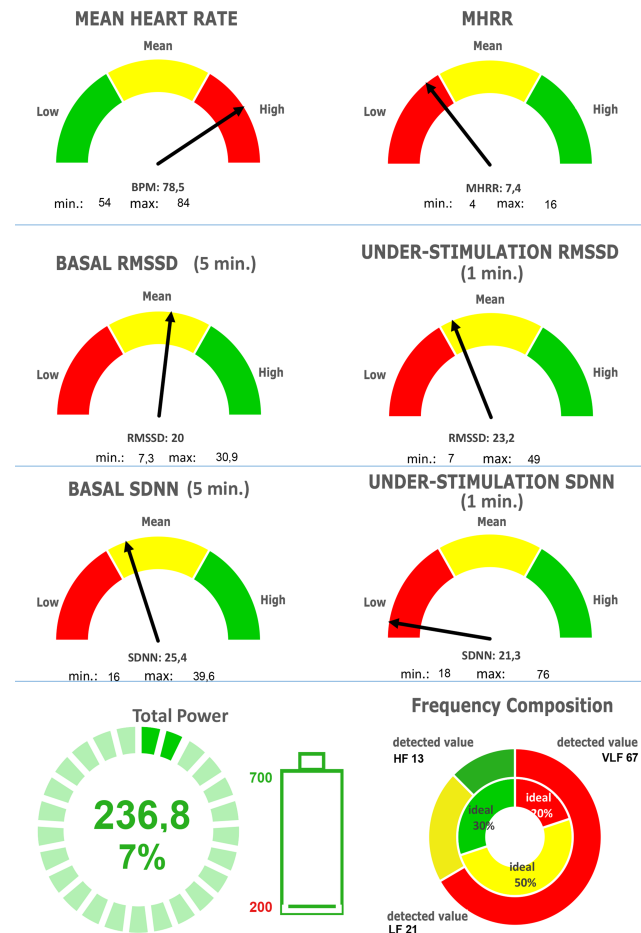


Fig 3 - Graphical imaging of the main parameters of the HRV analysis

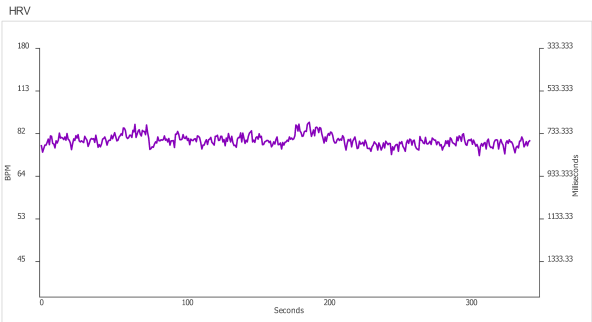
Application of HRV Analysis in Vascular, Autoimmune, and Diabetic Diseases

Numerous publications have highlighted the relevancy of HRV as a biomarker in vascular, autoimmune, and diabetic conditions, suggesting that ANS alterations may contribute to the onset and progression of these diseases.

In particular, Raynaud's phenomenon and diabetes mellitus with ulcerative complications exhibit distinct patterns of autonomic dysfunction, characterized by reduced HRV and of both sympathetic and parasympathetic activity; thus, HRV analysis has been regarded as an important tool for the monitoring and management of these vasculopathic patients.

HRV Assessment

Name
Gender Female
Age 84
Date lunedì 30 dicembre 2024 09:15:16
Duration 5:37 Minutes

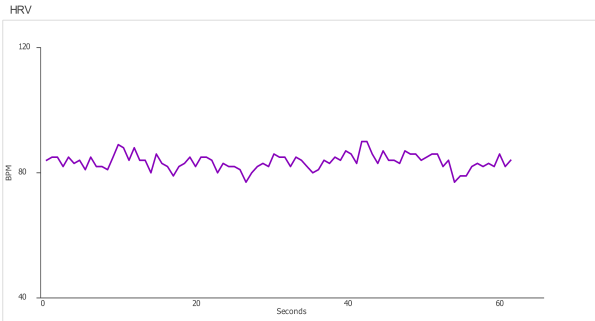


MEASURE	YOUR VALUE	LOG	UNITS
Duration	05:37 (5.6)		Mn:Sec (minutes)
Number of RR Intervals	440		
Mean Heart Rate	78.5		Beats Per Minute (BPM)
Mean Inter Beat Interval	765.0		Milliseconds (ms)
SDNN	25.4		Milliseconds (ms)
RMSD	20.0	3.0	Milliseconds (ms)
Total Power	236.8	5.5	milliseconds-squared/Hz
Very Low Frequency	152.6	5.0	milliseconds-squared/Hz
Low Frequency	47.3	3.9	milliseconds-squared/Hz
High Frequency	28.9	3.4	milliseconds-squared/Hz
Low Frequency/High Frequency ratio	1.6	0.5	milliseconds-squared/Hz
Normalized Coherence	35.6		Percent

Fig 4A - A detailed report of the main findings of the HRV test. A graphical report of basal 5 minutes investigation.

1-Minute HRV Deep Breathing Assessment

Name
Gender Female
Age 84
Date lunedì 30 dicembre 2024 09:28:02
Duration 1:00 Minute



MEASURE	YOUR VALUE	REFERENCE RANGE†
Mean Heart Rate (BPM), bpm	84.1	54.9 - 92.2
Mean Inter-beat Interval (IBI), msec.	713.9	650.5 - 1092.5
Mean Heart Rate Range (MHRR), bpm	7.4	3.8 - 16.4
SDNN, msec.	21.3	18.3 - 76.3
RMSD, msec.	23.2	7.4 - 49.4
Normalized Coherence, %	* 34.9	50.0 - 100.0

Fig 4B - A graphical report of one minute investigation (under diaphragmatic breathing stressor)

Table II Indications to HRV Analysis
Diagnostics of the autonomic nervous system (ANS)
Chronic degenerative diseases: diabetes, obesity, autoimmune diseases, cardiovascular and neurodegenerative diseases, neoplasms, mood disorders
Diagnostics of psycho-biological resilience and monitoring of targeted interventions to improve resilience and the PNEI system
Unhealthy aging
Monitoring of competitive/amateur physical activity

Overall, altered ANS and HRV have been associated with an increased cardiovascular risk and with the progression of several vascular, autoimmune, and diabetic pathologies^{34,35}.

Being ANS deregulation co-responsible for whichever alteration in the microcirculation/tissue unit, in terms of diagnostics, HRV analysis may be properly included among the most useful investigations (together with capillaroscopy, laser-Doppler flowmetry for example) in these cases, together with the classical colour-duplex ultrasound and blood testing examinations.

Diabetes mellitus is known to damage neurons, involving also the ones of the ANS, which causes initially the parasympathetic and later the sympathetic system deterioration.

In fact, hyperglycemia and hyperinsulinemia link to an increase of free radicals and of advanced glycation ending products which typically injury peripheral nerves, especially small fibers³⁶.

Progressively, the sympathetic hypertonicity of diabetic patients affects cardiovascular functions and induces vasospasm at microcirculation level, testifying a denervation of the sympathetic vasomotor component³⁷. Similarly, a decreased baroreflex sensitivity takes place and the altered sympathetic neural system induces an increased release of myocardial catecholamines, with adrenergic response, exacerbating the vicious cycle at central and peripheral level.

Literature data suggest that a diminished parasympathetic autonomic tone is detected first in the early cardiac autonomic diabetic neuropathy. As a result, there is a sympathetic predominance, which may result in a higher resting heart rate and in a number of alterations of several parameters (such HF, LF and their ratio) at the HRV analysis³⁸. During the course of type 2 diabetes mellitus, a progressive increase of the sympathetic predominance (vagal withdrawal) has been demonstrated as well³⁹.

Concerning primary Raynaud's phenomenon, several authors^{40,41} found a series of statistically significant changes in the frequency-domain HRV parameters, mostly indicating a hypertonic sympathetic system with LF predominance, lower HRV and a vagal activity reduction. These findings may explain the decrease of the venulo-arteriolar reflex and the typical hyper-constriction followed by an altered vasodilation of the smallest capillaries, when these patients are exposed to certain triggering factors, such as cold, stress, drugs, coffee etc.

In secondary Raynaud's phenomenon (as in autoimmune diseases) HRV derangements may be more pronounced, with a greater sympathetic output and a significantly decreased HRV⁴²⁻⁴⁴.

In most studies HRV analysis proved significantly sensitive to detect early the ANS changes related to the acrosyndrome and/or to the originating autoimmune disease.

Conversely, Lindberg et al.³⁴ examined patients with Raynaud's phenomenon and ANS activity by means of HRV analysis, plasma catecholamine levels, and cardiac scintigraphy. They found an attenuated plasma norepinephrine response after tilt test, a decreased cardiac sympathetic activity through cardiac scintigraphy, but no statistically significant difference in HRV parameters between patients and controls.

More comprehensively, a systematic review and metanalysis⁴⁵ documented that type 2 diabetes patients, compared to healthy controls, have a series of clear HRV derangements, as follows: lower R-R intervals, lower SDNN and especially lower RMSSD, lower total power (expression of a decreased energy of the ANS), as well lower LF and HF. Interestingly, the majority of these alterations quantitatively correlated with the level of glycated hemoglobin. Overall, this literature review provided evidence about the usefulness and the remarkable diagnostic/prognostic value of the HRV analysis in diabetic disease and about the sympathetic/parasympathetic decreased activity, which leads to cardiac autonomic neuropathy.

A number of publications reported a spectrum of coherent outcomes regarding the HRV reduction and alterations in diabetic foot and diabetic neuropathy^{35,36}, diabetes type 1 and endothelial dysfunction⁴⁶. Tuttolomondo et al. specifically found that patients with diabetic foot, in comparison to diabetics without ulcers, had a lower LF/HF ratio, greater parasympathetic activation (HF% = 21.23 vs. 11.10; $p = 0.002$) and a negative correlation between HRV and the reactive hyperemia index, suggesting a link between endothelial dysfunction and altered autonomic regulation. Interestingly, HF higher values in ulcerated patients compared to the non-ulcerated diabetics indicated a progressive increase of the parasympathetic action in later phases of the disease, so to compensate the deranged ANS balance.

Chhotaray et al.⁴⁷ underscored the predictive role of HRV analysis in patients with diabetes and autoimmune disease, providing a clear link among inflammation, HRV, and vascular dysfunction. In fact, chronic inflammatory conditions, such as autoimmune diseases and diabetes, but also atherosclerosis and neurodegenerative diseases and others, are accompanied with ANS deterioration, hence with HRV reduction.

Overall, integrating HRV analysis into diabetes management could therefore offer significant advantages in patient risk stratification, facilitating the early detection

of the initial stages of autonomic neuropathy, thus allowing for more timely interventions through lifestyle modifications, psychoneurobiology-targeting measures, optimized nutrition, and specific treatments aimed at preserving the integrity of the ANS.

Autoimmune diseases were also called vasculitis in the past nomenclature, just because of their relevant involvement of the vascular system, especially at microcirculation level.

Beyond the complexity of the pathophysiology mechanisms of autoimmune diseases, a large number of publications have however highlighted the strict correlation between autoimmune diseases and ANS/HRV degeneration⁴⁸⁻⁵³; by virtue of this link between PNEI and autoimmune diseases a more holistic diagnostic/therapeutic has been advocated in these patients, including also HRV analysis, so to detect the deregulated stress-axis impact on the immune system.

A recent eminent editorial⁵⁴ put HRV analysis at the center of any diagnostic/prognostic pathway of

rheumatologic/autoimmune disease, suggesting a series of possible implementations of the applications of HRV assessment in this field of mostly incurable chronic degenerative diseases, which basically depend upon an altered PNEI system of the subject.

In recent years HRV analysis has been proposed and applied also in lymphedema management⁵⁵⁻⁵⁸, and a few studies have highlighted both the presence of a reduced HRV (vagal component primarily) in these specific patients and significant improvements of a few parameters (e.g. reduction of LF/HF) after manual lymphatic drainage and/or after a cycle of complex decongestive treatment.

Lastly, we had occasion to demonstrate a series of evident changes in HRV parameters (e.g. RMSSD increase), in patients undergoing compression garments for veno-lymphatic diseases, which attests to an effect of lower limb compression therapy on the ANS of the subjects, mostly explainable through a reduction of the activity of the ortosympathetic system (as vagal fibers are absent in the lower limbs)⁵⁹.

Conclusion

Notwithstanding a few possible issues regarding the reliability of the (mainly short-term) HRV measures related to a few factors (such as sleep, coffee, drugs, timing, etc.) which may influence the outcomes of the exam^{60,61}, literature data and our personal experience confirm that integration of HRV analysis into clinical practice could provide new diagnostic and therapy-monitoring opportunities for the management of aging processes, of chronic degenerative diseases in general and, more specifically, of a few vascular diseases. In fact, Raynaud's phenomenon, the vascular diseases related to autoimmune diseases, diabetic micro-macro-angiopathy and neuropathy and, lastly, lymphedema are all ailments which are somehow linked to ANS degeneration and HRV may be useful to qualify and quantify this derangement.

This and other considerations have brought to employ more extensively HRV analysis in biomedical science, as a tool for: a) early screening for autonomic dysfunction and psychoneurobiology imbalance, allowing timely interventions to reduce degenerative evolution and the risk of severe complications, b) personalized therapeutic strategies (e.g., beta-blockers, sympathomimetic drugs, vagal stimulation techniques, c) to tailor anti-inflammatory therapies and autonomic modulation strategies.

Ultimately, by integrating HRV into clinical practice for these diseases, healthcare providers could enhance early diagnosis, improve risk stratification, and personalize treatment strategies, thereby supporting a more proactive and targeted approach within a more integrated and holistic medicine.

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