


Heart Rate Variability and Cardiovascular Fitness: What We Know so Far

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Abstract: Fluctuation analysis in intervals between heartbeats provides important indices related to autonomic modulation of heart rate variability (HRV). These indices are considered predictors of morbidity and mortality as they are frequently altered in patients with chronic degenerative diseases, especially in those with cardiovascular and metabolic diseases. Similarly, a reduction in HRV is common with aging. In all cases, cardiovascular fitness is often reduced to below the predicted values. In turn, increases in cardiovascular fitness through regular physical exercise, especially aerobic exercise, represent an important therapeutic tool capable of promoting positive adjustments in cardiac autonomic modulation. These adjustments are characterized by reduced sympathetic modulatory influence and/or increased vagal modulatory influence on the heart, increasing the HRV. Therefore, several methodological tools have been used to assess the degree of impairment of autonomic modulation and the therapeutic effects of physical exercise. In contrast, establishment of strict protocols in experimental design is a main challenge in establishing HRV analysis as a robust parameter for evaluating cardiovascular homeostasis. Thus, this review aimed to contribute to the understanding of autonomic modulation of HRV and its relationship with cardiovascular fitness, highlighting the advances made thus far, the applicability of analysis tools, and the confounding factors observed frequently.

Keywords: heart rate variability, cardiovascular fitness

Introduction

In the last decades, there has been an exponential increase in interest in the investigation of variability in autonomic modulation of cardiovascular parameters, such as heart rate variability (HRV) and blood pressure variability (BPV),¹⁻⁴ as this form of analysis enables noninvasive assessment and evaluation of selective cardiovascular autonomic function. In this case, studies have shown that impairment in cardiac autonomic modulation is directly related to adverse cardiovascular events.⁵⁻⁸

These observations were only possible with the advancement of new computational technologies that allowed the development and creation of easy-to-apply methodological tools. Initial studies were related to the study of HRV modulation, performed using tools based on linear analysis of the time interval oscillations between consecutive heartbeats, providing referential indices of cardiac modulatory parameters attributed to the autonomic nervous system.^{4,6} These autonomic parameters of HRV were initially standardized by the European and American Cardiology Societies and later resulted in the publication of a Task Force (1996), which is still used today as a worldwide reference and basis for the literature on the application and interpretation of tools used.

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From a historical point of view, the first studies that effectively investigated HRV parameters were conducted in the 1960s, when HRV analysis was used to monitor fetal distress.⁹ From the 1970s, new studies correlated HRV parameters with pathophysiological situations, such as the increased risk of mortality, in patients with cardiovascular diseases and/or diabetes associated with autonomic neuropathy.^{10,11} However, the clinical importance of HRV analysis studies has only been consolidated since the 1980s, with the advent of computer techniques associated with the processing of biological signals, when it was shown that reduction in HRV was significantly correlated independently with the prediction of mortality after acute myocardial infarction (AMI).^{12,13} Furthermore, the predictive values of HRV autonomic parameters, when investigated in association with other parameters frequently used in medical practice such as echocardiography and electrocardiography, such as reduced ejection fraction, ventricular ectopic activity, and the presence of late potentials, appear to increase the clinical value of prediction of numerous cardiac pathologies.^{7,8}

Analysis Methodologies

Linear Method

Several linear methods have been developed for the quantification of HRV oscillations. Among them, stand out the analyses in the time and frequency domains. In the time domain, the most common methods used involve statistical and geometric indices, whereas in the frequency domain, the most common method used is spectral analysis. The latter allows the quantification and differentiation of oscillations on the abscissa axis (Hz) according to their frequency of occurrence and assessment of the power of oscillations on the ordinate axis.⁴ In studies investigating long-term heart rate (HR) oscillations (24 h), time domain analysis is generally used. However, in studies investigating short-term HR oscillations (eg, 10 min), frequency domain analysis is preferably used.⁴ Although, new techniques are emerging that address this and enable frequency domain measurement.¹⁴

Nonlinear Method

Nonlinear analyses involving mathematical calculations considering the regulation dynamics of the system in an unpredictable way are also widely studied. Among the nonlinear analyses, Poincare plot analysis, symbolic analysis, entropy, and fractal methods stand out.^{4,15,16}

Heart Rate Variability and Diseases Cardiovascular Diseases

In general, cardiovascular diseases are accompanied by impairments in cardiac autonomic control, characterized by reduced baroreflex sensitivity (BRS), increased sympathetic tone, and/or reduced cardiac parasympathetic (vagal) tone.¹⁷ Most studies have also indicated significant imbalances in the autonomic modulation of HRV. The cause of these imbalances in cardiac autonomic regulation is generally associated, supporting the role of sympathetic nerve activity (SNA) in disease progression.^{18,19} In this case, it is common to observe acute changes in cardiac autonomic control, such as acute myocardial infarction, which is characterized by significantly high sympathetic autonomic drive associated with a reduction in vagal drive, and chronic elevations of the sympathetic drive, as seen in heart failure. This is the final route of most cardiac disease and events, such as myocardial infarction, coronary artery disease, cardiomyopathy, and systemic arterial hypertension. The reason for these adjustments, which can be characterized as adverse because they promote inadequate cardiac adaptations, is based on the pressing need to meet the individual's basal metabolic demand, ie, to maintain a satisfactory cardiac output for all body tissues. However, the chronic character of cardiovascular disease continuously hyperactivates the sympathetic autonomic component, causing long-term impairments.^{20–23} Concomitantly, the literature reveals an increase in stimulation of the renin–angiotensin–aldosterone system, which causes an increase in the concentration angiotensin II and release of reactive oxygen species, favoring oxidative stress and endothelial dysfunction and providing positive feedback on increased SNA.^{19,21,24,25} This reorganization corroborates the global reduction in HRV (Figure 1). In this case, HRV indices are important markers of an increased risk of cardiac events and sudden death in these individuals.^{7,21,26–28}

Metabolic Diseases

In addition to cardiovascular diseases, metabolic diseases such as obesity, metabolic syndrome, and type I and II diabetes mellitus, have similar autonomic characteristics and are associated with a prominent reduction in HRV in addition to impairments in lipid and glucose metabolism, reduction in insulin sensitivity, increased levels of inflammatory markers.^{29–32} The reduction in HRV has been extensively discussed; however, patients with a high

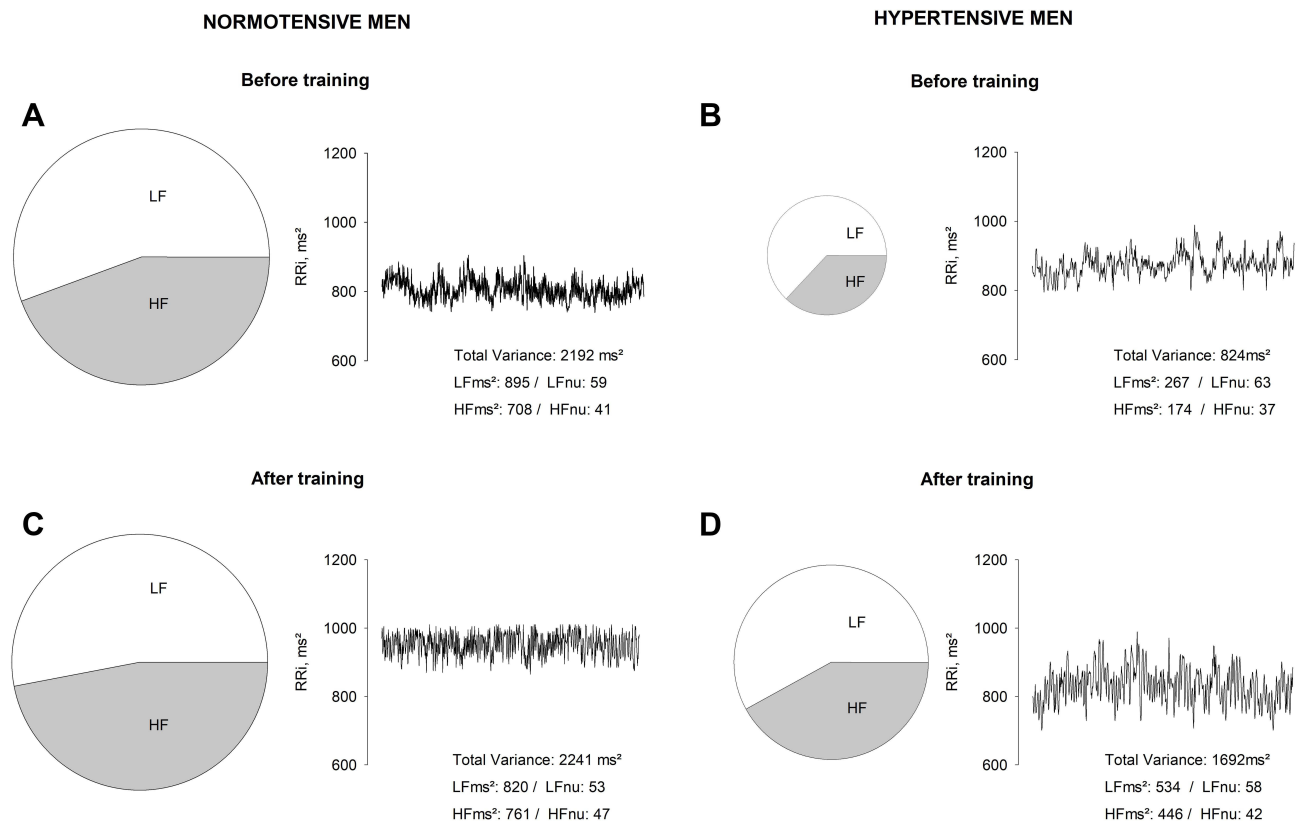


Figure 1 Representative illustration of heart rate variability parameters through spectral analysis in normotensive (**A** and **C**) and hypertensive (**B** and **D**) men obtained in our laboratory, before and after 16 weeks of aerobic physical training. The RR intervals (RRi) in absolute units (ms²) time series are illustrated by the line chart and was used the low-frequency (LF) and high-frequency (HF) bands in normalized units (nu) to indicated the relationship between autonomic modulation balance by the pie chart.

percentage of body fat, increased waist circumference, accumulation of visceral fat, and increased body mass index have decreased vagal modulation and increased sympathetic modulation.^{33,34} Furthermore, changes in glucose and insulin metabolism lead to changes in autonomic control, characterized by increased sympathetic modulation and/or reduced vagal modulation. According to some studies, insulin stimulates the sympathetic autonomic component,³⁵ and increases leptin concentration.^{32,36} In addition, it has been shown that leptin would influence the solitary tract nucleus (NTS) in experimental animals, decreasing the BRS.³⁷ In turn, in metabolic diseases, an increase in pro-inflammatory cytokines, such as interleukin-6 and tumor necrosis factor (TNF)- α , is frequently observed. These cytokines may be responsible, at least in part, for the impairment in endothelial vasodilator function and a reduction in HRV.^{38–40}

Aging

It is common to observe impairments in cardiovascular autonomic function resulting from the aging process,

especially in women, as aging is marked by ovarian failure, exponentially reducing the production of hormones, especially estrogens, which play a cardiovascular protective role. Clinical and experimental studies have shown that aging is characterized by increases in BPV and reductions in HRV and baroreflex sensitivity.^{41–44} In a previous study, the decrease in low-frequency (LF; 0.04–0.15 Hz) and high-frequency (HF; 0.15–0.5 Hz) oscillations of HRV, when investigated through frequency domain analysis (spectral analysis), indicated reduction in cardiac vagal modulation in elderly individuals.⁴⁵ The vagal autonomic component is responsible for the HF HRV oscillations and also in part for the LF oscillations.^{1,2,4} However, the reduction in HRV LF oscillations also suggests a decrease in cardiac sympathetic modulation,⁴ although studies have shown that aging is associated with increased levels of plasma catecholamines^{46,47} and peripheral sympathetic nervous activity.^{48,49} Thus, a plausible explanation for the alterations in cardiac autonomic modulation is the impairment in baroreflex sensitivity. Studies have shown that HRV LF oscillations are mediated by the sympathetic

autonomic component and depend on the integrity of the baroreflex arc.^{4,50} Further, HRV analysis assesses autonomic modulation of the heart and not cardiac autonomic activity.⁵¹ This is important because while cardiac sympathetic and vagal activity are associated with the autonomic nervous inflow of both components to the heart, resulting in an increase (sympathetic activity) or decrease (vagal activity) in heart rate, sympathetic and vagal autonomic modulation are associated with the instantaneous (phasic) variations in heart rate induced by both, however at different frequencies of occurrence.

Moreover, it is possible that the increase in BPV often found in elderly patients is largely due to the aging process. This statement is based on clinical and experimental studies in elderly patients, which demonstrated that increased BPV in patients with hypertension is associated with greater target organ damage and increased occurrence of cardiovascular events.^{43,52} The cause of the increase in BPV has been widely discussed; however, some studies indicate vascular sympathetic hyperactivity as the genesis of this phenomenon.^{43,53} Other studies have also attributed the reduction in baroreflex sensitivity as a determining cause. It has been postulated that the reduced inhibition of vasomotor centers, resulting from the adaptation of baroreceptors, is responsible for the increase in sympathetic activity and perpetuation of hypertension in some cases.⁵⁴ The other causes involving aging include the evident decrease in compliance and distensibility of the arterial system associated with endothelial involvement.^{55,56} Aging is also a risk factor for the development of chronic degenerative diseases as advancing age promotes structural and functional changes in the heart, vessels, and other organs.^{57,58}

Heart Rate Variability and Cardiovascular Fitness

Current knowledge on cardiovascular disease has triggered a search for ways to improve regulation of cardiac autonomic modulation. Amongst these, the role of regular physical exercise to improve cardiovascular fitness has been increasingly highlighted. It promotes beneficial cardiac autonomic adjustments; moreover, a decreased level of cardiovascular fitness is associated with an increased risk of morbidity and mortality, even in the absence of other risk factors.^{59–62} In this sense, individuals with moderate to high cardiovascular fitness resulting from regular physical exercise, especially aerobic exercise, have a low risk of mortality from chronic degenerative diseases,

especially cardiovascular and metabolic diseases.^{59–64} However, there seems to be no consensus in the literature on the influence of the level of cardiovascular fitness and cardiac autonomic control in healthy individuals. Some studies have found that cardiovascular fitness does not exert any effect on heart rate variability (HRV) in healthy young and middle-aged individuals.^{65–70} These studies hypothesized that autonomic cardiovascular control in healthy individuals operates in an “optimal” condition; thus, physical training would have no additional effect, other than the already known cardiovascular effects, such as reduction in heart rate at rest and faster heart rate recovery.⁷¹ On the other hand, some authors defend the use of HRV analysis to aid in the prognosis of stress and cardiovascular conditioning in athletes, directing the prescription of physical training.^{72–75} The evaluation and monitoring of performance counters during the training cycle may allow individualization of the workload whenever necessary, in order to obtain the highest possible performance of the athlete.^{76,77} At the same time, they can be effective in diagnosing phenomena called overreaching (temporary loss of performance that can be reversed with adequate recovery periods) and overtraining (state of severe and chronic fatigue caused by an imbalance between training, competition, and recovery).⁷⁸ To this end, further studies are required on the effects of cardiovascular fitness on the autonomic modulation of HRV in healthy individuals.

Cardiovascular Diseases

However, as noted above, individuals with chronic degenerative diseases often present with impairments in autonomic modulation, resulting in a reduction in HRV. Interestingly, when subjected to a physical training program, mainly aerobic, these same individuals tend to present an increase in HRV (Figure 1), which is often accompanied by a reduction in hemodynamic and metabolic parameters.^{23,79,80} The improvement in HRV due to the increase in cardiovascular fitness may involve multiple factors, such as local and systemic adaptations. Foremost is the obvious adaptation most commonly observed in the morphology and functionality of the heart resulting in a better performance, and consequently, a lesser dependence on the sympathetic autonomic component. This observation is based on experimental and clinical studies that demonstrated a decrease in adverse cardiac remodeling and cardiac fibrosis, in addition to the regulation of β -adrenergic receptor expression, increased cardiac output,

and improved contractility after an aerobic exercise training protocol.^{81–87}

A reduction in circulating blood levels of catecholamines and angiotensin II has also been observed,^{24,25,83,88} in addition to the recovery of endothelial function; increasing bioavailability of nitric oxide (NO); reduction of pro-inflammatory cytokines, such as TNF- α and IL-6; and low oxidative stress.^{79,89–95} Another important effect of physical training seems to involve central neural adaptations; autonomic adjustments also derive from effects on central neural nuclei of cardiovascular control, resulting in increased vagal drive and/or a decrease in sympathetic drive and improvement in baroreflex sensitivity.^{89,96–102} Thus, the sum of local and systemic effects associated with increased cardiovascular fitness results in a more adequate cardiac autonomic modulation, characterized by an increase in HRV.

Metabolic Diseases

Similarly, in individuals with cardiovascular diseases, an increase in cardiovascular fitness through physical exercise is essential for the control and treatment of metabolic diseases. Several studies have indicated a positive relationship between controlled metabolic parameters, cardiovascular fitness, and autonomic modulation of HRV.^{103–106} Among these effects, the improvement in glucose metabolism associated with an increase in insulin sensitivity stands out. Other important effects have also been observed, such as reduction in fat mass, improvement in body composition, and reduction in inflammatory and oxidative stress markers.^{104,105,107–110} Consequently, all these beneficial effects resulting from the increase in cardiovascular fitness can contribute to the improvement on autonomic modulation of HRV. That is, increased cardiovascular fitness results in a better balance of cardiac autonomic modulation, characterized by increased vagal modulation and/or reduced sympathetic modulation,^{106,109,111} which has been observed in patients with major complications and comorbidities due to diabetes.^{112,113} Furthermore, all these benefits of better cardiovascular fitness, in addition to contributing to the regulation of the autonomic modulation of HRV, also contribute to the prevention of cardiovascular diseases and improvement in quality of life in general.

Aging

With advancing age, it is common to observe adjustments in different body systems. Regarding the cardiovascular system, adjustments in autonomic regulation of HRV are

characterized by a prominent reduction. Increased cardiovascular fitness through regular exercise provides important cardiovascular and metabolic benefits to the elderly, such as reduced blood pressure, improved insulin sensitivity, improved endothelial function, and reduced oxidative stress.^{114,115} In addition, physical exercise, especially aerobic exercise, has been shown to be beneficial in increasing HRV in these individuals, mainly by increasing parameters that correspond to the vagal autonomic component.^{116–120} In this regard, studies suggest that increased cardiovascular fitness through regular exercise throughout the life of an individual can mitigate the effects of aging on vagal modulation.^{121–124} However, there is a demand for further investigation, as not all studies report this relationship.^{125–129} Another important effect of greater cardiovascular fitness is its association with the improvement and/or maintenance of cognitive skills.^{130–132} We also highlight the fundamental role of better cardiovascular fitness in the maintenance of health and well-being during aging.

In this context, the analysis of HRV can be used as a form of clinical assessment of cardiovascular homeostasis, which is a predictor of cardiovascular mortality, and in the prescription of physical training, since this approach provides information on the integrity of the autonomic function and possible disorders of the autonomic modulation of the heart due to health conditions, advancing age, and level of cardiovascular fitness.^{4,8,133–136}

Cautions with Using HRV Analysis

There is no doubt about the importance of analyzing the variability of intervals between heartbeats as an assessment that allows the identification of the physiological mechanisms that guide the regulation of heart rate, such as sympathetic and vagal autonomic components. However, standardization of methodologies that permit reproducibility between evaluators/researchers is essential, especially when it comes to a widely disseminated tool in the scientific community and in clinical practice. In this case, the experimental design is perhaps more important than the tool used in the evaluation. In our literature review, we found widespread use of HRV analysis but lack of details about the methodology employed. Below, we discuss the two main factors: sex and age.

For many years, men and women were included in the same study group for HRV analysis. Now, we know that this can introduce an important bias in the results.^{127,137} More recent studies have shown that women before menopause have lower oscillations of the sympathetic autonomic

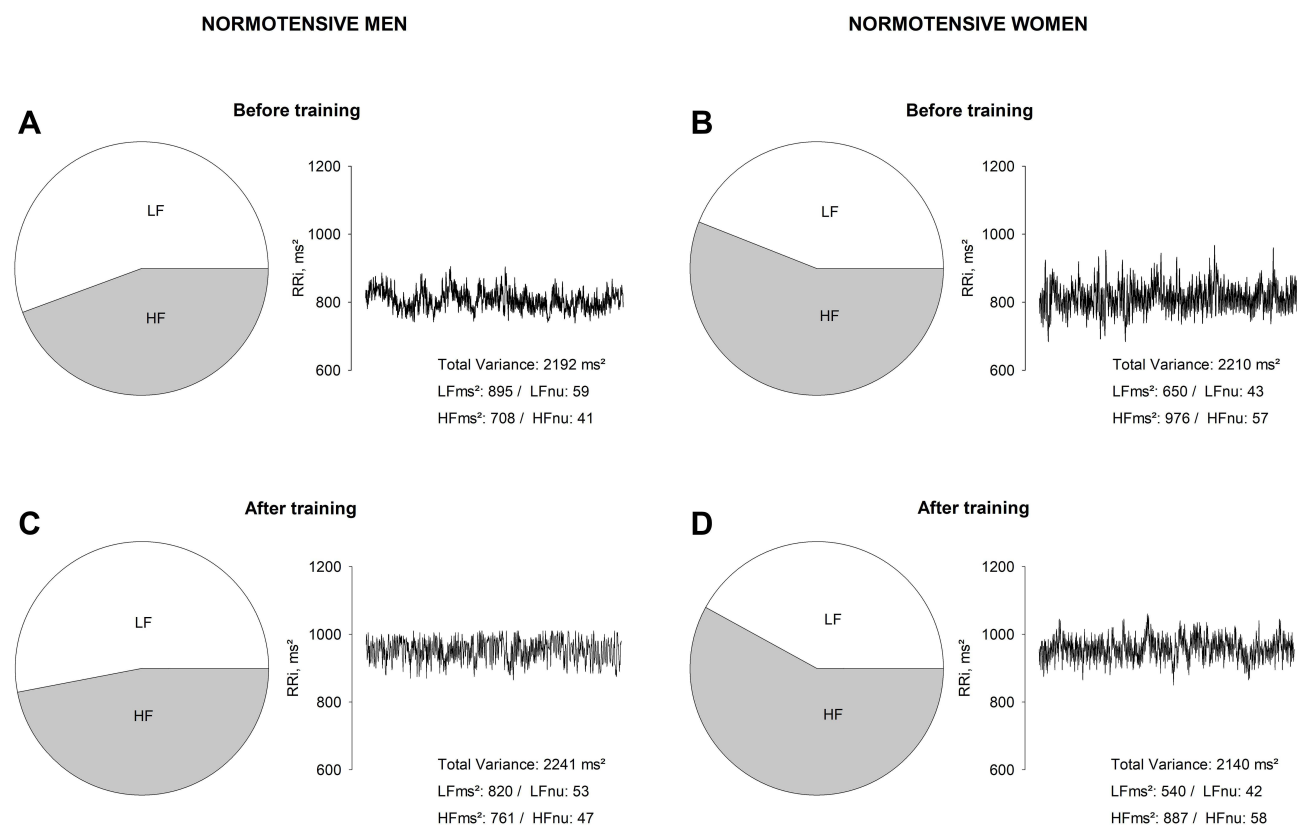


Figure 2 Representative illustration of heart rate variability parameters through spectral analysis in normotensive men (**A** and **C**) and women (**B** and **D**) obtained in our laboratory, before and after 16 weeks of aerobic physical training. The RR intervals (RRi) in absolute units (ms²) time series are illustrated by the line chart and was used the low-frequency (LF) and high-frequency (HF) bands in normalized units (nu) to indicated the relationship between autonomic modulation balance by the pie chart.

component and greater oscillations of the cardiac vagal autonomic component when compared to age-matched men (Figure 2),^{69,70,138,139} including individuals with a history of systemic arterial hypertension.²⁶

The causes of these differences have not been fully elucidated; however, the beneficial effect of ovarian hormones on cardiovascular autonomic control is a very important variable, since estrogens seem to be able to increase the vagal influence on the heart, in addition to reducing the sympathetic influence on the heart and vascular beds.^{140–142} These effects are consistent with other studies that observed autonomic impairments resulting from ovarian failure, such as a reduction in HRV and baroreflex sensitivity.^{143–146} These studies also discuss the mechanisms involved in this process, mainly the influence of estrogen on the different sites involved in cardiac autonomic regulation, including central neural sites, in addition to interfering with the expression and/or responsiveness of β -adrenergic receptors that affect the cardiac contractile response.^{81,147–150}

Similar to the female sex hormones, androgens also appear to influence cardiac autonomic control, and some

studies have shown a close relationship between these hormones and the autonomic nervous system.^{151–153} Thus, testosterone levels in men, as well as estrogen levels in women, are important factors that might determine the differences in cardiovascular autonomic control of the sexes.

Furthermore, it is very common to find studies that present a wide age range in experimental protocols. This is a mistake because with aging, there is a tendency for reduction in HRV. In this case, the inclusion of younger age groups may overestimate the values of older age groups, and vice versa. Another important point is that the responses observed to a particular procedure or physical training in a younger group may not be reproduced in an older group.

Conclusions

In summary, there is a close relationship between cardiovascular fitness and HRV. This relationship was more evident in patients with cardiovascular and metabolic diseases and in aging, especially in those whose

cardiovascular fitness and HRV were below the predicted values for age and sex. The challenge is to develop techniques and interpretation of increasingly accurate data, as well as standardizing the application of these techniques.

Highlights

1. Autonomic modulation parameters of heart rate variability are considered predictors of morbidity and mortality;
2. Heart rate variability is often impaired in patients with cardiovascular and metabolic diseases;
3. Aging reduces heart rate variability preponderantly;
4. Aerobic exercise is essential to attenuate autonomic impairments;
5. There is no consensus that aerobic exercise training potentiates cardiovascular autonomic modulation in healthy individuals;
6. Women in reproductive age and age-matched men show distinct regulations in cardiac autonomic modulation;
7. Heart rate or pulse intervals records requires strict criteria.

Disclosure

The authors report no conflicts of interest in this work.

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