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REVIEW

HEART RATE VARIABILITY AS A METHOD FOR ASSESSMENT OF THE AUTONOMIC NERVOUS SYSTEM AND THE ADAPTATIONS TO DIFFERENT PHYSIOLOGICAL AND PATHOLOGICAL CONDITIONS

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ВАРИАБЕЛЬНОСТЬ СЕРДЕЧНОГО РИТМА В КАЧЕСТВЕ МЕТОДА ОЦЕНКИ СОСТОЯНИЯ ВЕГЕТАТИВНОЙ НЕРВНОЙ СИСТЕМЫ И ЕЁ АДАПТАЦИИ К РАЗЛИЧНЫМ ФИЗИОЛОГИЧЕСКИМ И ПАТОЛОГИЧЕСКИМ СОСТОЯНИЯМ

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ABSTRACT

The autonomic nervous system controls the smooth muscles of the internal organs, the cardiovascular system and the secretory function of the glands and plays a major role in the processes of adaptation. Heart rate variability is a non-invasive and easily applicable method for the assessment of its activity. The following review describes the origin, parameters and characteristics of this method and its potential for evaluation of the changes of the autonomic nervous system activity in different physiological and pathological conditions such as exogenous hypoxia, physical exercise and sleep. The application of heart rate variability in daily clinical practice would be beneficial for the diagnostics, the outcome prognosis and the assessment of the effect of treatment in various diseases.

Key words: *autonomic nervous system, heart rate variability, hypoxia, physical exercise, sleep*

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РЕЗЮМЕ

Вегетативная нервная система контролирует гладкую мускулатуру внутренних органов, сердечно-сосудистой системы и секреторную функцию желез и играет основную роль в процессе адаптации. Вариабельность сердечного ритма является доступным и неинвазивным методом оценки её активности. Настоящий обзор описывает происхождение, параметры и характеристики данного метода и его потенциал для оценки изменений в активности вегетативной нервной системы при таких различных физиологических и патологических состояниях как экзогенная гипоксия, физическая нагрузка и сон. Применение вариабельности сердечного ритма в повседневной клинической практике может повысить качество диагностики, прогноза и оценки эффективности лечения различных заболеваний.

Ключевые слова: *вегетативная нервная система, вариабельность сердечного ритма, гипоксия, физическая нагрузка, сон*

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AUTONOMIC NERVOUS SYSTEM - BASIC CHARACTERISTICS

The autonomic nervous system (ANS) controls the smooth muscles of the internal organs, the cardiovascular system and the secretory function of the glands. It comprises sympathetic (SNS) and parasympathetic (PSNS) branches, which differ in their anatomy and function. Sympathetic effects are diffuse, generalized and fast and serve physiological defense mechanisms in response to extreme stimuli and conditions such as fear, danger, hypoxia, physical exercise, mental stress etc. They comprise tachycardia, hypertension, vasoconstriction, mydriasis, bronchodilation, etc. In contrast, parasympathetic effects are localized and are generally related to the maintainance of restorative and energy-saving

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functions for a longer period of time, e.g. bradycardia, hypotension, myosis, bronchospasm.[1-3] Under stress (physical exercise, hypoxia, etc.) the organism activates the sympathetic nervous system and the hypothalamic-pituitary-adrenal axis, facilitating adaptation. (General Adaptation Syndrome by Hans Selye).[4] However, an extremely strong and long-acting stress can overwhelm the adaptive capacity and result in distress.

Considering the leading role of the ANS in adaptation, the assessment of it and of its branches activity is very important for the characterization of the adaptive processes. Heart rate variability (HRV) is a reliable, informative and applicable in daily practice method for that purpose.

HEART RATE VARIABILITY – A HISTORICAL REVIEW

HRV is the variation over time of the period between consecutive heartbeats and it is predominantly dependent on the extrinsic regulation of the heart rate.[5]

Long before the development of the electrocardiograph (ECG) and the modern technologies for HRV registration, physicians realized the potential importance of heart rhythms and their connection with the ANS. The study of these rhythms occupied a leading position in the diagnostics of many diseases in Ancient China. The first documented observation of this phenomenon is attributed to Hales (1733), who monitored the cyclic changes in the blood pressure and the heart rate associated with breathing in horses. By developing the cymograph, Ludwig (1847) managed to record the acceleration of the heart rate during inspiration and its slowing during expiration in dogs, which is probably the first recorded case of respiratory arrhythmia (RA). The subsequent studies of Dondres (1868) focused on the link between breathing, heart rate and the vagus nerve.[6] The invention of the modern electrocardiograph and computerized systems turned the measurement of HRV into an easily applicable method in practice and the „golden standard“ in the noninvasive assessment of the ANS.[5]

HRV ANALYSIS, PARAMETERS AND INTERPRETATION

The detailed HRV analysis includes three main components – time domain, frequency (parametric) domain and non-linear analysis. (Fig. 1)

The time domain analysis provides average values of the variations for different periods of time. The main parameters derived from time domain analysis are SDNN - standard deviation of normal-to-normal inter-beat interval and RMSSD - root mean square of successive RR interval difference. The first parameter is a direct reflection of heart rate variability and presents the overall activity of the ANS, and the second one is associated with the activity of the PSNS.[6-8]

The frequency domain parameters of HRV are calculated by spectral analysis. Based on Fast Fourier Transform or Autoregressive analysis, the variations are divided in frequency bands: HF - high frequency (0.15-0.40 Hz); LF- low frequency (0.04-0.1 Hz); VLF - very low frequency (0.017 – 0.04 Hz) and ULF-ultra low frequency (< 0.017 Hz).

HF reflects the activity of the PSNS while LF is a result of the activity of both the SNS and the PSNS, but since it is the only indicator to assess the activity of the SNS, it is accepted as a parameter describing it. There is still no unanimous opinion on the origins and the interpretation of very- and ultra-low frequencies. It is assumed that VLF is associated with the activity of the renin-angiotensin-aldosterone system, and ULF is dictated by the circadian rhythms but their origin is still unclear and disputable. Total power is a parameter, which corresponds to SDNN. The LF/HF index is thought to reflect the interaction of the two branches of the ANS[5,7] (Table 1).

HRV could also be assessed by non-linear mathematical analysis such as Poincaré plot analysis. It is a geometrical model, presenting each interval as a function of the previous. The three main parameters obtained are: standard deviation one (SD1) - associated with rapid variations between heart beats and standard deviation two (SD2) - responsible for the long-term variations and the relationship between them (SD1 / SD2 index).

Another non-linear parameter is the Sample Entropy (SampEn) – a simple index, reflecting the overall complexity and predictability of the time series of HRV.

Autonomic cardiovascular control is not a simple SNS or PSNS predominance but includes a complex interaction via different circulatory reflexes, such as baro- and chemoreceptor and sympatho-sympathetic reflexes, various molecular and hormonal factors, and central oscillations may also affect the variability and are responsible for the overall complexity of the signal. Under different physiological or pathological conditions any of these mechanisms can become dominant inhibiting some of the others and thereby it may reduce the complexity of the HRV and lead to “simplification”

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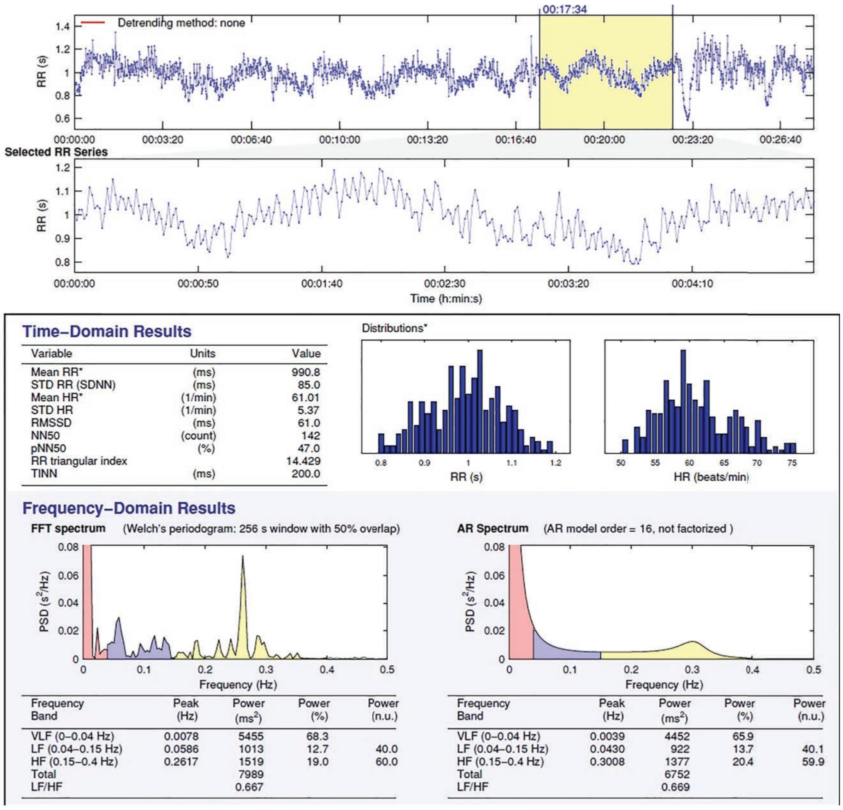

Legend: Time domain parameters: MeanRR (mean beat-to-beat interval), SDNN (standard deviation of normal-to-normal R-R intervals), MeanHR (mean heart rate), STDHR (standard deviation of heart frequency), RMSSD (the square root of the mean squared difference between adjacent N-N intervals), NN50 (number of differences between adjacent RR intervals), pNN50 (percentage of differences between adjacent RR intervals), TINN (triangular interpolation of RR intervals); Frequency domain parameters: VLF (very low frequency), LF (low frequency), HF (high frequency).

Figure 1. A report from HRV analysis with Kubios HRV software.

Table 1. Main parameters from HRV analysis

Parameter	Unit	Interpretation
Time domain		
SDNN	ms	Overall variability
RMSSD	ms	PSNS activity
Frequency domain		
HF	ms^2, nu	PSNS activity
LF	ms^2, nu	SNS and PSNS activity
VLF	ms^2	RAAS, termoregulation, metabolic factor
Total power	ms^2	Overall variability
LF/HF		SNS/PSNS interaction
Non-linear dynamics		
Poincaré plot (SD1)	ms	High frequency fluctuations
Poincaré plot (SD2)	ms	Low-frequency fluctuations
Sample Entropy		Complexity and predictability of the signal

Legend: SDNN (standard deviation of normal to normal R-R intervals), RMSSD (the square root of the mean squared difference between adjacent N-N intervals), HF(high frequency), LF(low frequency), VLF (very low frequency), SD (standard deviation), RAAS (renin-angiotensin-aldosterone system).

of the cardiovascular control.[9]

The advantage of the non-linear analysis is its lesser sensitivity to the length of the heart rate record and the presence of artifacts or short arrhythmias, while the drawback is the lack of consensus on the interpretation and meaning of these parameters.[8,10]

Duration of the record for HRV analysis is very important and is determined by the nature of the research. The frequency domain parameters (HF, LF) are more sensitive to sympathovagal modulation and shorter recording length is preferred (e.g. 5 minutes). Although time-domain parameters can be derived from a short-term investigation, they are more accurately calculated from longer recordings.[7]

ORIGIN OF HRV

The response of the heart to SNS and PSNS signals differs in terms of speed. Its onset is after about 0.5 sec, returning to baseline in approximately 1 sec in vagal stimulation, while sympathetic stimulation exerts its effect more slowly in about 1-2 sec, ebbs off fast in up to 4 sec and returns to baseline after about 20 sec. These values mirror perfectly the frequency domain bands of the HRV – HF and LF.[6]

The delay in the excitation of the heart is attributed to the time necessary for the membrane transmission of the impulse. The coupling between the activation of the muscarine receptors and the changes in the membrane ion-channels is accomplished by signal molecules situated close to the cellular membrane and thus the response to parasympathetic activation is fast. In contrast, the adrenergic stimulation requires secondary messenger activation by a cytoplasm proteinkinase delaying the response to sympathetic activation.[6] Respiratory arrhythmia (RA) plays an important role in HF genesis as well. Therefore, HRV parameters are strongly influenced by the rate and depth of breathing, the end-tidal partial pressure of carbon dioxide ($PETCO_2$) and the interplay of inhalation/exhalation in terms of time and dead space.[11-13]

HRV IN DIFFERENT PHYSIOLOGICAL AND PATHOLOGICAL CONDITIONS

Age and gender. In general, women and younger people have higher variability. HRV decreases with age to a similar extent in both males and females. Children not only have higher values in the frequency domain parameters, but also have stronger response to different stressful stimuli.

Fatigue. Immediately after heavy exercise the SNS activity remains high in order to meet the metabolic demands, imposed to the organism, while later (including during sleep after exercise), the PSNS prevails to ensure better recovery.[5,8]

Emotions may change the activity of the ANS in one or the other direction.[14]

Drugs. All drugs, influencing the activity of the ANS, affect the HRV parameters. Therefore, HRV could be used in the assessment of the effectiveness of beta-blockers treatment.

Smoking. Smoking leads to sympathetic predominance and a decrease in the overall variability. Furthermore, smokers react less to maneuvers triggering vagal stimulation (Valsalva). It is believed that exactly these pathophysiological mechanisms are responsible for the detrimental effects of smoking on the heart.

Alcohol. A correlation between the daily alcohol consumption and the vagal activity decrease has been established in people with chronic alcohol abuse.

Myocardial infarction. HRV assessment after myocardial infarction is one of the first and most widely used applications of the method. It could provide important information about sympathetic predominance and impaired vagal control on the heart after myocardial infarction, which are strong predictors of survival and the risk of rhythm and conductive disorders associated with sudden cardiac death.

Arterial hypertension (AH). HRV is strongly decreased in patients with AH-induced left ventricle hypertrophy, which can be explained by the impaired baroreflex sensitivity in this pathological condition.

Nervous system disorders. Various neurological disorders and depression could lead to autonomic dysfunction, which makes HRV an applicable method in neurological and psychiatric practice.

Diabetes leads to autonomic dysfunction and a decrease in the total variability of the heart rate, which is predictive for cardiovascular complications such as sudden cardiac death.

Renal failure. Electrolyte disorders in renal failure are associated with a decrease in all frequency domain HRV parameters. It has been proven that hemodialysis leads to a significant increase in HF in patients with chronic renal failure.[5,8]

HRV DURING EXPOSURE TO EXOGENOUS HYPOXIA AND THE ROLE OF THE ANS IN THE ADAPTATIONS TO HYPOXIA

Prolonged or periodical exposure to exogenous hypoxia leads to a number of adaptations in the systems that intake, transport and utilize oxygen[4,15]. Most of the fast adaptations, such as increase in heart rate, which can be observed immediately after the application of the hypoxic stimulus, are associated with the activity of the ANS.[16,17] A number of studies use HRV to assess the early adaptation to high altitude hypoxic exposure.[18-21] What is more, HRV has been used as a predictor of acute mountain sickness.[22]

Acute exposure to exogenous hypoxia leads to a decrease in the overall variability - Total power and SDNN, as well as LF/HF index increase demonstrating the sympathetic predominance.[23-26] It is caused by the activation of the peripheral chemoreceptors with consequent vasoconstriction and tachycardia, which are better emphasized in higher hypoxic ventilator response (HVR). However, this initial response of the body is partially counteracted by secondary baroreceptor activation caused by the vasoconstriction[27,28]. Thus, the baroreflex stimulation suppresses the SNS activation, caused by acute hypoxia (+). Long-term stay at high altitude and intermittent hypoxic training (IHT) lead to augmented chemoreceptor sensitivity (higher HVR)[30,31]), and a shift from sympathetic to parasympathetic predominance, expressed by increased HRV.[32-34] Thus, many of the adaptations to hypoxia related to the ANS are a result of increased baroreceptor activity, which is supported by the rise in HRV at high altitude sojourn. Our observation of gradually rising parasympathetic activity after a 10-day protocol with one-hour daily normobaric hypoxic exposure supports this statement (Fig. 2).

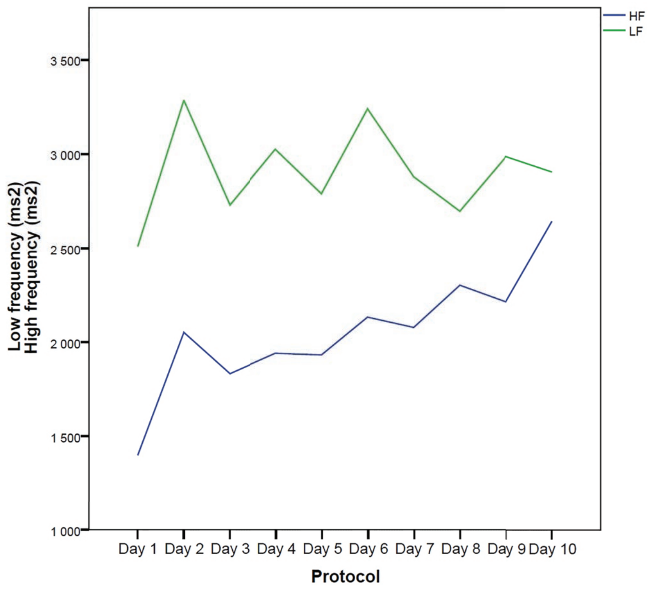

Figure 2. An increase in the PSNS activity (HF), after 10-day protocol with 1-hour intermittent normobaric hypoxic stimulation ($FiO_2 = 12.3 \pm 1.5\%$).

ROLE OF THE ANS DURING AND AFTER PHYSICAL EXERCISE AND APPLICATION OF HRV IN SPORT

ANS plays a key role in the adaptations to physical exercise.[35] It is widely accepted, that elite sportsmen, especially endurance athletes, who face high aerobic demands, have PSNS predominance at rest[36], resulting in bradycardia. Somlev et al. show that HRV parameters (particularly increased SDNN, RMSSD and HF and decreased or unchanged LF and decreased LF/ HF index) correlate with the fitness level in elite athletes.[37,38]

There is no consensus in the literature whether HRV could be used as an indicator of the aerobic capacity of athletes, since it only reflects the dynamics of the ANS, but not the oxygen-utilisation processes in the body. The possible link between maximal oxygen consumption (VO_2max) and HRV is also contradictory.[39-41]

On the other hand fatigue can affect the activity of the ANS. During physical exercise an activation of the SNS and deactivation of the PSNS are observed, while the opposite changes (first, increase in the activity of the PSNS and later sympathetic withdrawal) occur in the recovery period.[42] Measuring the state of PSNS reactivation via HRV may be used in the assessment of the effect of particular physical exercise on the ANS.

Heart rate recovery (HRR) is one of the most frequently used parameters in sport practice for the assessment of the recovery after physical exercise and the presence of fatigue. HRV is a method that could be used for the same purpose[35], since both HRV and HRR are phenomena which are strongly associated with the PSNS reactivation after physical exercise.[43] It has been proven that the intensity of the physical exercise correlates negatively with HRR, as well as with HF and Total power.[44,45] Therefore, HRV analysis could be superior to the widely used simple measurement of the heart rate in the morning regarding the assessment of the recovery during the training process.[46]

HRV DURING NORMAL SLEEP AND IN DIFFERENT SLEEP DISORDERS

Although sleep has been viewed as a static condition of recovery in the past, nowadays, it is known to be a heterogenous state and many biological processes, including cardio-vascular ones, significantly change their activity (both increase and decrease) under the control of the ANS. Therefore, the autonomic regulation in physiological and pathological sleep may be assessed by HRV analysis.[9]

The activity of the SNS and the PSNS shows circadian and ultradian variations between the states of wakefulness, NREM (Non rapid eyes movement) and REM (Rapid eyes movement) sleep. While N1 to N3 sleep stages (NREM) are those of increasing synchronization with a decrease in heart rate and blood pressure (gradually increasing PSNS activity), the activation of the cardiovascular system during REM sleep may be even higher than during wakefulness (SNS predominance, mainly due to PSNS withdrawal). Thus, falling asleep is associated with an increase in the overall variability and HF and a decrease in LF and the transition to REM is related to a decrease in HRV, increase in LF and LF/HF and a parasympathetic withdrawal with decreased HF. These fluctuations in the activity of the ANS may explain the higher rate of cardio-vascular incidence in the early morning hours, when REM sleep is mostly concentrated (+).

Different sleep disorders are associated with a different model of HRV changes. Obstructive sleep apnea (OSA) is a pathological condition, characterized by repeated apneas and/or hypopneas during sleep with preserved or increasing breathing effort due to a total or partial closure of the upper airways during inspiration. This leads to impairment of the chemo- and baroreflex regulation with a consequent SNS hyperactivation and PSNS withdrawal, which is additionally increased by arousals.[49] SNS activation in OSA patients is present during the day as well, which is associated with higher cardiovascular risk.[50] Patients with OSA have decreased HRV and HF and increased LF and LF/HF.[9] What is more, the severity of OSA strongly correlates with the LF/HF increase, which makes this index very suitable for monitoring of OSA patients.[51]

The opposite changes have been described with CPAP (Continuous positive airway pressure) treatment - a significant increase in the overall variability, a decrease in the sympathetic hyperactivity and an improvement in the baroreflex control (HF rise and LF/HF fall). These changes in the activity of the ANS and the HRV parameters are observed even after a single session of CPAP treatment.[52,53]

Cheyne-Stokes periodic breathing during sleep is a phenomenon, which is often observed in patients with chronic heart failure (CHF).[54] Szollosi et al found that it generates a very low frequency band (VLF) fluctuations in the HRV in a 10-minute recording that includes apnea periods. Therefore, HRV is capable of differentiating patients with OSA from patients with central sleep apnea (CSA), since each of these sleep disorders leads to a different model of VLF changes lower in OSA and higher in CSA[55]) (Fig. 3).

Since HRV is strongly dependent on respiration, the analysis of the results according to the ANS activity should be made with caution in patients with sleep breathing disorders to avoid misinterpretation.

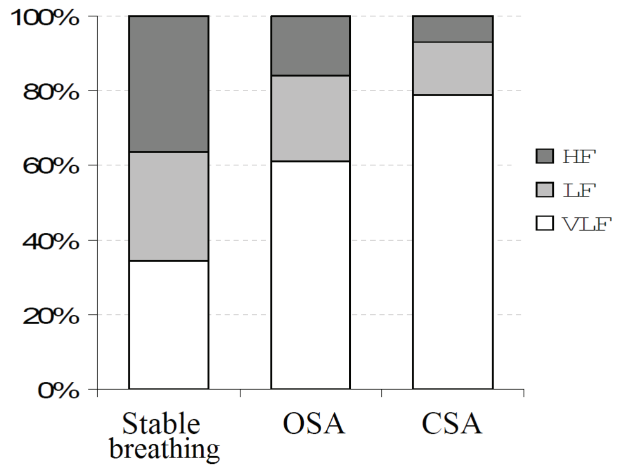

Figure 3. Difference in frequency distribution of HRV analysis in normal sleep, obstructive sleep apnea (OSA) and central sleep apnea (CSA). *Adapted to Szollosi I.*[53]

CONCLUSIONS

HRV is a highly sensitive and informative method for the assessment of different physiological and pathological conditions, related to changes in the activity of the ANS. Its application in the daily clinical practice would be beneficial for the diagnostics, the outcome prognosis and the assessment of the effect of treatment in various diseases. It could also be applied in the sports and alpine practice to improve the individual performance of the athletes.

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