Heart rate variability - current diagnosis of the cardiac autonomic neuropathy. A review

Rudolf Metelka

Backround. The autonomic nervous system is one of the major homeostatic regulatory systems of the body. Detection of cardiac autonomic neuropathy (CAN), reflected by reduced heart rate variability (HRV), is an independent adverse prognostic factor: sympathovagal balance failure with a sympathetic dominance is the main trigger for lethal arrhythmias and sudden death.
Methods and Results. PubMed database based on original articles from 1983 to 2013 and the author´s clinical experience. This review covers the current status of the methodology and the clinical uses of HRV, especially in the field of internal medicine.
Conclusion. Heart rate variability is making a valuable contribution to the diagnosis of cardiovascular autonomic dysfunction and CAN. It can be assessed from short-term and long-term ECG recordings. It is one of the few methods that allow outpatient CAN diagnosis, monitoring the progress, therapeutic effect and evaluation of patient prognosis. It is used as an independent prognostic factor in combination with other recognized risk factors in risk stratifying after myocardial infarction. It is a unique method of CAN diagnosis particularly in diabetology. Its diagnostic and prognostic potential in other medical fields is being intensively explored.

Key words: heart rate variability, methodology, cardiac autonomic neuropathy

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Department of Internal Medicine III - Nephrology, Rheumatology and Endocrinology, Faculty of Medicine and Dentistry, Palacky University Olomouc, Czech Republic
Corresponding author: Rudolf Metelka, e-mail: rudolf.metelka@fnol.cz

INTRODUCTION

Disorders of autonomic nervous control are part of the development and progression of cardiovascular complications in a variety of diseases. Excessive sympathetic stimulation via the neural and humoral pathway is one of the triggering factors for malignant arrhythmias and sudden death not only in acute coronary syndromes but also in other chronic diseases with cardiac impairment[1]. Detection of cardiovascular autonomic dysfunction, a reflection of which is reduced heart rate variability (HRV), is an independent factor for predicting sudden death from arrhythmic causes.

This review focuses on the current potential of HRV for assessment the the autonomic nervous system (ANS) dysfunction, especially in the area of internal medicine.

NATURE OF HEART RATE VARIABILITY

Heart rate variability reflects the interaction of the two subsystems of the ANS, sympathetic and parasympathetic, which besides affecting other organ systems, also affects the cardiovascular system. As to the cardiac innervation there are on heart rate (HR) cardioacceleratory acting sympathicus (nn. cardiaci) and cardiodecelerator parasympathicus (rr. cardiaci n. vagi). At the level of sympathovagal afferentation there are combined impulses from both vagal mechanoreceptors in the carotid sinus (afferentation by branches of the glossopharyngeal nerve), in the aortic arch, in the pulmonary arteries, subendocardially in the cardiac ventricles and atria (afferent fibers of vagus nerve) and from sympathetic metabo- and mechanoreceptors in skeletal muscles, carotic and subendocardial cardiac chemoreceptors. If present, the fibers mediating pain perception are found in association with sympathetic afferent fibers. The superior ANS control centers are predominantly located in the reticular formation, nuclei of the medulla oblongata and the lower third of the brainstem in a region called the vasomotor center (VMC). The latter is functionally divided into a vagal part with cardioinhibitory function and sympathetic part, functionally divided in the vasoconstrictory and vasodilatory acting areas. VMC activity is under the influence of the cortex, limbic system and hypothalamus. Afferent impulses are processed in the sensory area of the VMC which, in interaction with respiratory center, result in the stimuli leading to efferent innervation vagal and sympathetic area. There are pulse vagal activity with reactivity to stimuli in the order of milliseconds (latency 400 ms) and continuous sympathetic nerve stimuli activity with a latency stimulus-HR change 5 seconds with the maximum effect in 20-30 s (ref.[2]). The central vagal motoneurons have a dominant controlling influence. A typical reflection of the normal sympathovagal regulation is a physiological respiratory arrhythmia with an increase in HR

during inspiration and lowering HR during expiration. In addition to respiratory-dependent variations in HR, there are also non-respiratory HR fluctuations (oscillations of RR interval duration on electrocardiogram - ECG) beat to beat in rhythmic oscillations in particular, vagal activity. This phenomenon, when, in balanced state (supine or standing), the system receptors-VMC-respiratory centre-effectors and value of HR (duration of R-R interval) oscillates synchronously, is known as heart rate variability[2,3].

The ability to respond to stress stimuli is the basis of the ANS examination using HR changes in tests of autonomic cardiovascular function (called Ewing's battery of tests, see below) and later established methods of analysis of heart rate variability (HRV) in short-term ECG recordings (5 min) (ref.[4-6]). Diurnal HR changes (oscillations) are the subject of the investigation of HRV in the long-term records in the classic 24 h Holter ECG.

THE MECHANISM OF AUTONOMIC DYSFUNCTION

In the vast majority autonomic dysfunctions are of secondary multifactorial origin, accompanying a range of diseases with central or peripheral ANS involvement and / or treatment with neurotoxic or cardiotoxic drugs. As a primary disease it can be found in the rare primary autonomic failure[8]. Disruption of autonomic nervous regulation in any reflex chain, i.e. receptor-vasomotor and respiratory centers-effectors, manifests in the corresponding organ system.

Most of our knowledge of the pathogenesis of autonomic dysfunction, including cardiovascular neuropathy, is derived from diabetes mellitus, a disease with high prevalence in the population, with frequent and progressive organ complications resulting from the systemic nature of this metabolically mediated disease with diffuse organ, vascular (macro- and microangiopathy, including vasa nervorum) and nerve fiber involvement. The pathogenesis of autonomic neuropathy in diabetes mellitus is multifactorial[9]. There is involvement of myelinated and unmyelinated nerve fibers with disorders of autonomic innervation in the cardiovascular, gastrointestinal, genitourinary system and skin. In the ANS involvement with cardiovascular manifestations baroreceptors and parasympathetic fibers disabilities precede sympathetic fiber involvement. This can explain a fixed resting tachycardia due to the dominance of the sympathetic effect and impaired parasympathetic HR modulation and baroreflex function. Tachycardia is partially regulated during further progression of cardiac autonomic neuropathy (CAN) with sympathetic denervation, but HR remains higher than in the healthy population. An aspect of advanced cardiovascular autonomic dysfunction with sympathetic impairment is the tendency to orthostatic hypotension[9,10].

For ischemic heart disease it has been found, that myocardial denervation is caused by interruption of neurotransmission in sympathetic fibers accompanying the affected coronary artery. Involved are infarcted, as well as non-infarcted areas distal to the infarct[11]. Sympathetic denervation of the heart muscle also occurs in cardiomyopathy of nonischemic origin - in dilated cardiomyopathy[12], in the advanced stages of autonomic neuropathy in diabetes mellitus[13] and, generally in heart failure[14]. Along with denervation the ongoing chaotic partial sympathetic reinnervation as nearly hyperinervation proceeds from the edge of the affected areas with increased sensitivity to catecholamines. This produces inhomogeneity of action potentials at the border of denervated and reinervating regions, which forms the substrate for lethal arrhythmias and sudden arrhythmic death. In parallel with these processes affecting the sympathetic innervation of the heart, there is a weakened protective function of vagus nerve and properly functioning baroreflex[1,15].

Depending on the degree of sympathovagal control disability as a result of autonomic denervation, the physiological short-term and long-term HR oscillations, respectively HRV and baroreflex function, are reduced. Recent studies point to the primary importance of the baroreflex disability over the sympathetic tone alone, measurable by direct microneurography (MSNA) in peripheral sympathetic nerve fibers (n.peroneus). In this context it is noted that HRV reflects the state of the sympathovagal balance and maintaining baroreflex function reflects the ability of the ANS to respond to stress stimuli[16].

CLINICAL EVIDENCE OF AUTONOMIC DYSFUNCTION

In investigating complex disorders of the ANS in clinical practice there is a clear preference of noninvasive methods. Direct measurement of sympathetic stimuli nerve activities (MSNA) is available only for research purposes. Direct measurement of parasympathetic stimuli nerve activity is not performed. The examinations focus on the search for autonomic dysfunction in cardiovascular, gastrointestinal regions (gastroparesis, intestinal atony or chronic diarrhea without structural correlate), on the search for micturition disorders and sexual dysfunction, for markers of sudomotor, termoregulatory and sensorimotor disorders. Taking the history includes questionnairies on autonomic functions[17]. A history of disorders of peripheral nervous system can be tested using electromyography, quantitative sensory testing (QST) to standardized nociceptive stimuli (termal, mechanical or chemical), sudometry. Visceral nervous disorders can be detected by targeted examinations of the gastrointestinal tract (such as X-ray or scintigraphic examination of gastric emptying and passage through the intestine, esophageal manometry), by urological diagnostic methods targeted at manifestations of neurogenic bladder and sexual dysfunction[18-20].

The identified autonomic or peripheral neuropathy is important for association with organ failure, and it needs to be taken into account in the comprehensive care of the patient but dominantly and significantly associated with the prognosis it is the evidence of cardiac autonomic neuropathy (CAN) (ref.[10,19]).

A clear clinical manifestation of advanced CAN, excluding secondary causes affecting HR and blood pressure (BP) (pain, stress, exertion, dehydration or vice versa hypervolemia, drugs, natural substances as caffeine), is enduring or clearly predominant 24 h sinus tachycardia (HR 90-130/min). There is also included a tendency to hypotension at rest, typically posturally, and intolerance of physical exertion (excluding hypotension in an advanced stage of heart failure, unstable coronary syndromes, significant valvular disease, hypertrophic obstructive cardiomyopathy, etc.). Asymptomatic coronary artery disease (silent ischemia, painless course of acute myocardial infarction) is also one of the manifestations of cardiac denervation within CAN, regularly found in diabetes mellitus[10,19].

Laboratory measurements of markers of increased sympathetic activation, cardiac dysfunction (norepinephrine, renin, angiotensin, aldosterone, adrenomedullin, endothelin-1, NT-proBNP) have prognostic significance, e.g. in heart failure, but they are not useful for clinical CAN diagnosis.

Direct detection of impaired sympathetic innervation (denervation) is possible by scintigraphic examination of adrenergic myocardial innervation using SPECT with MIBG J^{123} (ref.[21]).

Clinical evidence of impaired BP regulation, history of syncope or orthostatic hypotension is available by orthostatic test, head up tilt test (HUTT), determining 24 h BP profile by ambulatory monitoring (ABPM). The most accurate method is the baroreflex assessment in a specialized laboratory[22].

In diabetology there are still used simple tests on autonomic cardiovascular functions (called Ewing's battery of autonomic function tests), from the 1970s, for the diagnosis of cardiovascular autonomic disorders. These are applicable to all diseases with suspected disorder of the ANS (ref.[4]). They are based on an analysis of tachogram (short record of R-R intervals on the electrocardiogram, ECG) at rest and during provocation tests with ANS load. As a result, there is a group of indexes calculated from HR changes (R-R interval) during the tests. Ewing's method of testing for cardiovascular autonomic function is not a diagnostic method for assessing HRV, resp.CAN, but it can represent a patient screening for a more detailed assessment of sympathetic and vagal activity. For this reason, for evidence of CAN, HRV examination is preferable. The usefulness of autonomic functions testing by Ewing in the evaluation of ANS lies in the capture of cardiovascular deregulation[23].

As provoking functional tests of the cardiovascular autonomic function there are currently used:

1. Frequency-controlled breathing (a significant respiratory insufficiency is the only limitation). The basis of the test is controlled deep breathing with a frequency of 6 cycles/min, which enhances the influence of respiration on HR (i.e. HR increase during inspiration (I) and a HR decrease during expiration (E)). For evaluation in Ewing's battery I-E difference and I/E ratio of averaged maximum inspiratory and minimum exspiratory HR values are used. It is also applicable as a standardized autonomic load in short-term recordings of R-R intervals. (Fig. 1).

2. Postural effects on HR on standing.

a) orthostatic test

Used in Ewing's battery and as a physiologically sufficiently explored autonomic load during spectral analysis of HRV. In condition of normal sympathovagal reactivity during orthostatic test baroreceptor unloading occurs, when changing body position from supine to standing up. (Fig. 2). Due to the predominance and acceleration

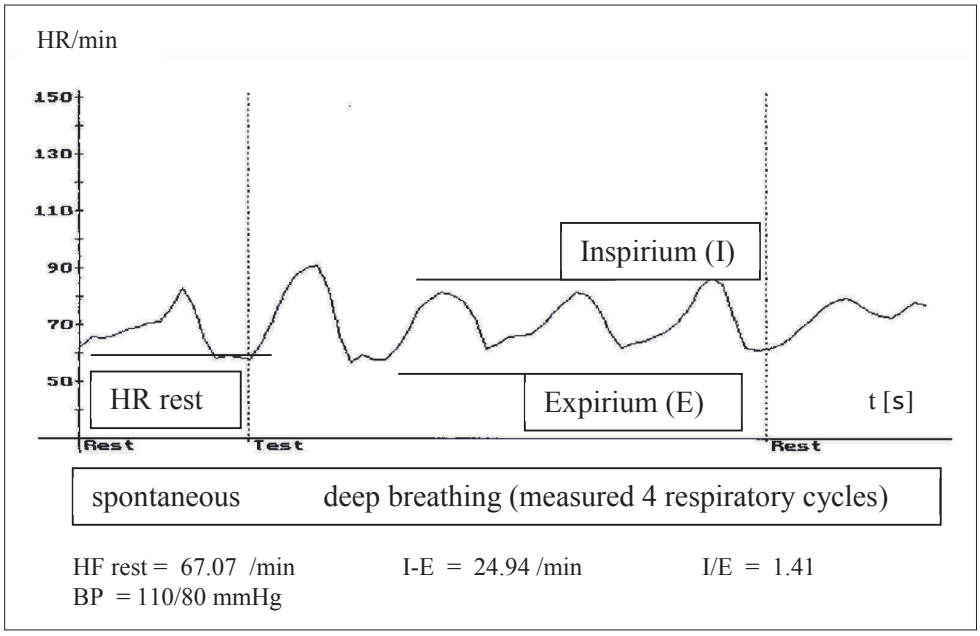

Fig. 1. Deep breathing test protocol. HR rest - HR during spontaneous ventilation before the test; BP- blood pressure; I-E, I/E - difference, resp.the ratio of the averaged maximal inspiratory and minimal expiratory HR values

of the sympathetic activity during 5-10 s HR will slowly increase (HR max, RR min). After that promtly active counter-regulatory vagal activity followes, the reflection of which is the rapid and transient HR decrease (HR min, RR max), untill HR stabilizes at a new value corresponding to a new value in standing position. For testing, RRmax/RRmin ratio (ratio of the longest and shortest R-R interval in a standing position) is a widely used index. This is more suitable for more accurate determination of HR minimum and maximum during the test than by the original Ewing´s index 30:15, defined as the ratio of the duration of the longest R-R interval around 30.beat to the shortest R-R interval around 15.beat after standing up (index 30:15) (ref.[23]). Some authors use the so-called "brake index" BI = (RRmax - RRmin) / RRrest x 100 (the difference between the longest and the shortest R-R interval in relative terms to the base resting R-R interval) (ref.[23,24]). BP measurements before and after the test (in supine and on standing) is used for BP monitoring and detection of hypotension. The critical value is the decrease in systolic BP below 90 mm Hg or more than 20 mmHg and dizziness[25].

b) orthoclinostatic test (supine-standing-supine test) is the modified orthostatic test

This is used for spectral analysis of HRV in short-term recordings. The test performance is the same as in the first two phases of orthostatic test (supine1- standing). Then standing is followed by another supine position (clinostatic phase, marked as supine2).

In the spectral analysis of short-term recordings the HRV indicators are compared for each 5-minute steady state ECG recording. The first supine position (supine1) is an adaptive one, and hence not regularly measured phase. The HRV indicators are measured in the standing position (standing) and repeated supine (supine2). At the same time, BP and respiratory rate are measured[23].

c) head-up tilt test (HUTT, pasive verticalization on a tilting table). This is used in the examination of spectral analysis of HRV in short-term recordings[5].

The original Ewing's battery has included the Valsalva maneuver comprising 15 s lasting forced exspirium against the tube of mercury manometer at the level of 40mmHg. In current clinical practice this is left for difficult standardization (particularly in case of reduced respiratory reserve) and contraindications (advanced diabetic retinopathy or severe hypertension). Other forms of autonomic load there are handgrip, physical load on the ergometer, mental load, cold test, pharmacological tests.

Normal values for indexes of the two most commonly used tests of cardiovascular function by Ewing (i.e. deep breathing test and orthostatic test) are listed in Table 1 (ref.[26,27]).

Table 1. Normal value of indexes in Ewing´s tests battery.

Index	I-E (ref.[26])	I/E (ref.[27])	RR_{max} / RR_{min} (ref.[26])	Ratio 30:15 (ref.[27])
Age 20-29y	20 beat/min	>	>	>
30-39	15 beat/min	>	>	>
40-49	15 beat/min	>	>	>
50-59	12 beat/min	>	>	>

Legend: see Fig. 1,2

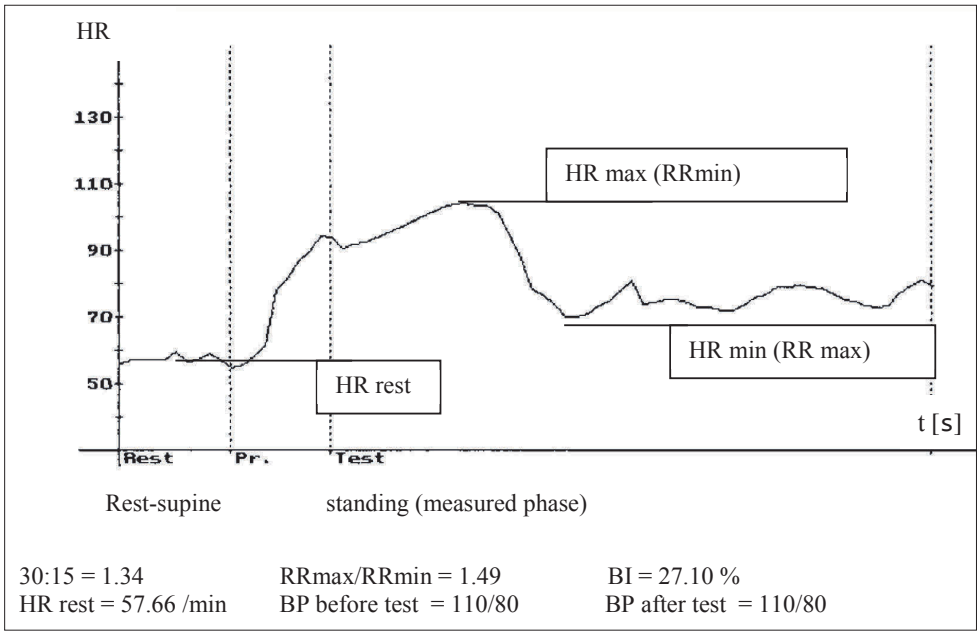

Fig. 2. Orthostatic test protocol. 30:15 ratio between R-R 30. Beat to R-R 15. beat, computed since standing up RRmax/RRmin - ratio of the longest and the shortest R-R standing (measured phase); HR rest - resting HR before test; BI (brake index) - BI=(RRmax – RRmin) / RRrest x 100

The reduction of indexes in Ewing´s battery shows a significantly reduced vagal HR modulation with an indication for a more detailed examination of the sympathovagal balance through the spectral analysis of HRV. Significant reduction of the indicators measured during orthostatic test simultaneously with orthostatic hypotension points to the possibility of severe peripheral autonomic neuropathy with disabilities in the parasympathetic as well as in sympathic system. Orthostatic hypotension also significantly impairs the results of HRV.

METHODOLOGICAL APPROACHES TO THE DETERMINATION OF HEART RATE VARIABILITY

Determination of HRV in a series of so-called NN beats (normal sinus beats,i.e. after eliminating artifacts and premature beats from the unfiltered R-R ECG recordings) in the short-term (5 min) or long-term (18-24 h, preferable 24 h) recordings represents, according to the type of mathematical processing, the HRV analysis in the time domain and / or in the frequency domain (spectral analysis). In summary results HRV is reported as normal or reduced[7].

Assessment of heart rate variability in the time domain

The assessment of HRV in the time domain is the basis for the HRV analysis in long-term (24 h) holter

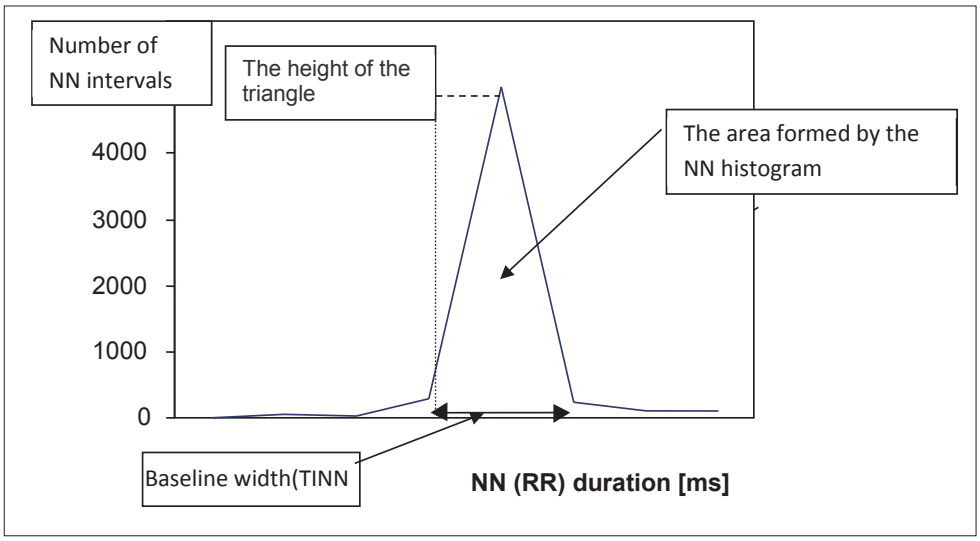

Fig. 3. Geometric methods for HRV measurement. HRV triangular index. NN interval - RR interval of adjacent sinus beats on ECG (RR intervals before and after extrasystoles, artefacts-noise are excluded)

Table 2. Summary of HRV indicators in the time domain (according ref.[7]).

Indicator	Definition
SDNN (nebo SDRR) [ms]	standard deviation of all normal (NN = R-R) intervals during recording (usually 24 h)
SDANN [ms]	standard deviation of the average values of NN intervals calculated from all five-minute segments of the entire recording (24 h)
SDNN index [ms]	mean value of the standard deviations of all NN intervals for all five-minute segments of the entire recording (usually 24 h)
pNN50 [%]	The percentage of adjacent NN intervals differing by more than 50 ms in the recording (usually 24 h)
RMSSD[ms]	the square root of the mean of sum of the squares of differences between adjacent R-R intervals during recording (usually 24 h)
HRV triangular index	the total number of all NN intervals divided by the maximum number of all NN intervals in the distribution histogram (height of the histogram) of all NN intervals
TINN [ms]	Baseline width of the triangular interpolation of the distribution histogram of all NN

ECG recordings. Statistical methods and so-called geometric methods are used. Descriptions and definitions of the indicators used in practice are in Table 2 (ref.[7]). Schematically, the principle of the most widely used geometric methods - HRV triangular index - using interpolation of R-R interval histogram is shown in Fig. 3 (ref.[28]). Other geometric methods are not used in routine clinical practice – e.g. TINN (Fig. 3) (ref.[29]), differential index[30] or scatterplots, determining by the type of points distribution the HRV level (Poincaré or Lorenz plots) (ref.[31]).

The HRV indicators analyzed from the long-term (24 h) recordings in the time domain reflect the overall and long-term HRV trends. There are SDANN, SDNN and HRV index and TINN. Among the indicators of short-term trends there are the HRV indicators RMSSD and pNN50 (ref.[7,31]).

Assessment of heart rate variability in the frequency domain. Spectral analysis of heart rate variability

Methods for analyzing cardiotachogram in frequency domain by spectral analysis are divided into nonparametric - fast Fourier transform method (FFT) and parametric – autoregressive method (AR). The results of both methods are well comparable. Spectral analysis can evaluate both short-term and long-term ECG recordings. The advantage of short-term versus long-term records is the ability to standardize testing conditions. Long-term records allow the greater possibility of processing of spectral HRV components reflecting long-term trends.

Detection of CAN by method of spectral analysis of HRV, requires standardized examination conditions excluding interference (physical and mental activity, respiration influences, ECG artefacts). For a more detailed analysis of sympathovagal balance (for objective diagnostics of CAN), short-term ECG recordings are useful. Application the standardized forms of autonomic load (deep breathing, orthoclinostatic or orthostatic test, head-up tilt test) in the examination of HRV spectral analysis in short-term ECG recordings (Fig. 4) is a standardizing and at the same time a stress element for assessing the level and reactivity of both subsystems ANS (sympathetic and vagal, i.e. sympathovagal balance) (ref.[5,7,23]).

Rhythmic HR oscillations (resp.R-R intervals) up to 0.4 Hz are analyzed with this distribution of the basic frequency bands (components) (ref.[7]):

- ultra-low frequency (ULF, the frequency band below 0.003 Hz)
- very-low frequency (VLF, the frequency band in the range 0.003-0.04 Hz)
- low frequency (LF, the frequency band in the range 0.04-0.15 Hz)
- high frequency (HF, the frequency band in the range 0.15-0.4 Hz)

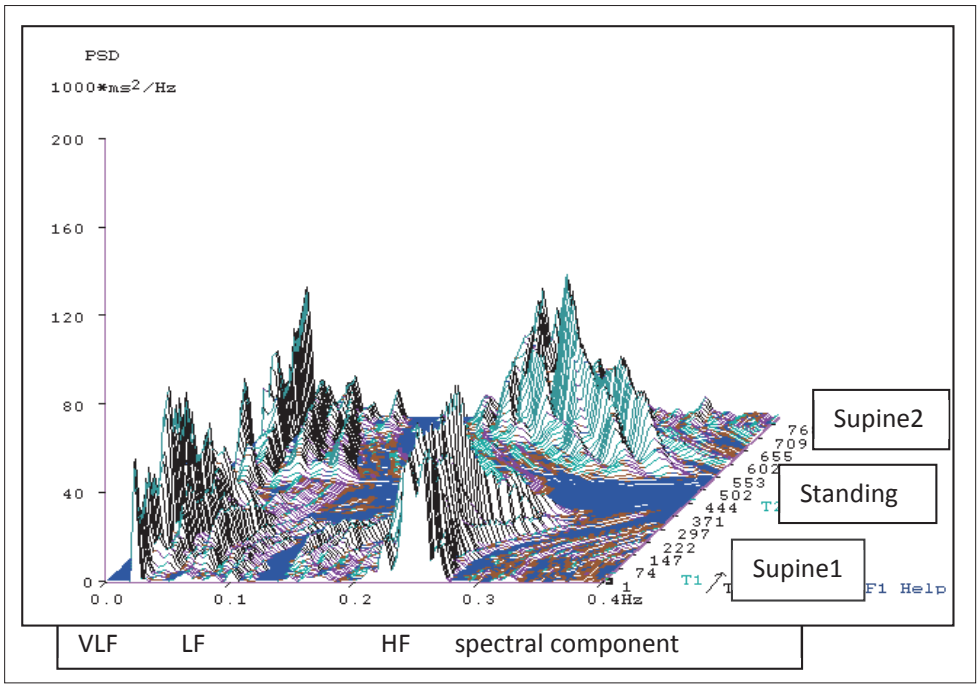

Fig. 4. 3-D image viewing the result of spectral analysis in healthy persons (male, 47 years) during Supine-Standing-Supine test. Short-term recordings (5 min each phase). Own data. Axis X: Analyzed frequency range: 0.02Hz-0.4 Hz. Components: VLF (very low frequency, 0.02-0.04Hz), LF (low frequency, 0.04-0.15Hz), HF (high frequency, from 0.15 to 0.4 Hz) Y-axis: Amplitude (PSD). The spectral power components (Pwr in ms^2 is represented by the integral area. Z-axis: time display (s). The change in spectral power during orthoclinostatic test Supine-Standing-Supine: Supine1 (adaptation phase - not always evaluated) Standing (assessed phase) Supine2 (assessed phase) (according ref.[32]).

Complete range of assessable components (ULF, VLF, LF, HF) can be analyzed only in long-term (24 h) recordings. Short-term recordings (over 5 min) can evaluate LF, HF band and a section of VLF band (0.02-0.04) (ref.[23]). Analysis of VLF can not be carried on records of less than five minutes[7].

In the clinical analysis, it is very useful the visual assessment in the form of 2-D or 3-D view of the graphic layout of spectral components to approximate an idea of the result of analysis on-line (Fig. 4) (ref.32).

Each spectral component is defined by the spectral power in absolute terms (ms^2, TotalPwr, PwrVLF, PwrLF, PwrHF), by the central (modal) frequency (Hz), by the relative value of the total spectral power (LF%, HF%, VLF%) (ref.[32]) or expressed in the normalized units (LF n.u., HF n.u.) from the spectral power not including VLF component. The calculation for LFn.u. = (PwrLF / (Total Pwr - PwrVLF) x100; for HFn.u. = (PwrHF / (Total Pwr - PwrVLF) x100. Relative or normalized values of individual spectral components and ratios of their spectral power (LF/HF, VLF/HF) provide better information about sympathovagal balance changes than absolute values alone, especially in short-term recordings during the stress tests[5-7,33].

In the place of absolute values (in ms^2) of spectral power components VLF, LF and HF logarithmic values can be used. This reduces the distortion caused by high variance of absolute values usually found even in good representative patient samples.

For comparison of several measurements, where the average HR differs significantly (stress tests, 24 h recordings), the coefficients of variation of individual spectral components (CCV VLF, LF CCV, CCV HF) can be used, but they are not preferred[32,34].

For practical purposes another more robust method has been introduced for assessing HRV by spectral analysis of HRV during ortoclinostatic load (performed in supine-standing-supine test) with the summed spectral power in the LF and HF bands measured during all three phases of the test. Results are given in logarithmic values. By means of this method HRV can be assessed using a few associated indicators, representing both basic level of sympathovagal balance, as well as the range of sympathovagal reactivity under the orthostatic load[35].

Physiological interpretation of spectral analysis of HRV parameters

Spectral analysis in contrast to the analysis in the time domain analysis allows evaluation of the ANS subsystems. Total heart rate variability is represented by the total spectral power (TotalPwr, expressed in ms^2) in the range from 0.003 to 0.4 Hz (Fig. 4) (ref.[3,7]).

Spectral area ranged from 0.15 to 0.4 Hz, high frequency (HF), is considered an area of vagal influence. HF component is also called the respiratory component for compliance of its central frequency with the respiratory frequency, which is under vagal influence. The value of HF spectral power changes according to the respiratory activity. It is directly dependent on the tidal volume, inversely dependent on the respiration rate and enhances during regular ventilation[2,5,36-38]. Vagal activation by means of deep controlled breathing at frequency f = 0.2 Hz, i.e. 12 breath/min, can be helpfull to distinguish the respiratory-dependent HF component from LF component in HRV assessment during short-term recordings in patients with decreased spontaneous respiration frequency near 6 c/min, when the HF central frequency shifts towards the LF area to the value near 0.1 Hz. Using breathing frequency controlled at 12 c/min HF central frequency shifts to the right to 0.2 Hz (ref.[36,39]).

Opinions on the origin of low-frequency component (LF, range 0.04-0.15 Hz) in the HRV are not uniform. LF component is under the sympathetic and vagal influence[5-7]. It reflects sympathetic modulation effects on vasomotor tone and fine baroreflex regulation[16,40]. Its section component around 0.1 Hz, called the Mayer wave, is also consistently found in spectral analysis of systolic BP (ref.[5,6,41]). Without a properly functioning baroreflex even at high sympathetic neural activity (for example measured by MSNA or cardiac norepinephrine spillover) the LF spectral component of HRV may not be present at all[42,43]. This is one of the reasons why some authors dispute the direct contribution of sympathetic activity to LF components of the HRV and attribute it to the modulating baroreflex activity[16,43,44].

In the ortoclinostatic test (supine-standing-supine) and in head up tilt test the behavior of components LF and HF is markedly different depending on the body position. Standing produces augmentation of LF and reduction of HF in absolute and relative power (due to baroreceptor unloading and hence reduced vagal activity). HF unlike LF is again augmented in the repeated supine position (Supine2) (ref.[5,6,23]).

The physiological nature of very low frequency (VLF, very low frequency, 0.02-0.05 Hz) and ultra-low frequency (ULF ultra low frequency, below 0.003 Hz) components is not clear. VLF is usually related to the thermoregulatory sympathetic vascular activity and to oscillations in the renin-angiotensin system[37,45]. This indirect relationship of VLF to the sympathetic activity (its relative proportion of the total spectral power, VLF%) is supported by finding of VLF% increase in direct proportion to the intensity of physical load[46] and particularly strong correlation VLF and ULF powers with lethal arrhythmias and sudden arrhythmic death[47]. There is an opinion that VLF also reflects the influence of parasympathetic activity[45]. The most likely is the multifactorial origin of VLF as physiological oscillations and pathological maladaptation of homeostatic regulatory systems run interdependently at both neural (ANS) and the hormonal and metabolic level[48]. Inconsistencies of opinion on the origin of VLF led to the recommendation to exclude VLF from the analysis and the use LF and HF components in the form of normalized units (n.u.) in relative terms to the difference "TotalPwr - PwrVLF" (ref.[5,6]).

In summary of the current view, the vagal and sympathetic subsystems cannot be evaluated separately and independently of each other, but only in interaction. LF and HF components spectral power values and LF-to-HF ratio (representing the index sympathovagal interac-

tion) in short-term spectral analysis of HRV can describe only the level of sympathovagal balance and the gain of baroreflex mechanisms under the given conditions[40]. It is unacceptable to simplify the interpretation of LF components to a direct measure of sympathetic or HF only to parasympathetic tone. Good short-term ECG recording (2-15 min according to analytical methods, usually 5 min) under standardized conditions is an essential condition for a valid ANS regulation assessment using HRV. The basis of assessment takes into account the absolute values of total spectral power, LF and HF component values and LF-to-HF ratio compared with the age appropriate healthy population. LF and HF in absolute values are only for approximative assessment. Normalized units of LF and HF components (LFn.u., HFn.u.) are preferred before their relative values (LF%, HF%). Assessment of changes in power spectral components LF and HF during tests with autonomic load provides a valuable information about sympathovagal reactivity. The optimal approach to obtain complete information about autonomic nervous regulation is the simultaneous assessment of HRV and systolic BP variability with the calculation of baroreflex sensitivity[40,49].

Reproducibility of HRV measurements

From clinical trials it is known that all HRV indicators are age and sex dependent (negative correlation) (ref.[50-53]). It is also necessary take into account that, particularly for short-term spectral analysis within a clearly defined group (by age, gender, race), there are high not negligible inter- and intraindividual variations of the absolute and relative values of all HRV indicators[53]. For these reasons, it is therefore not well defined range of normal values of the spectral indicators of HRV (ref.[33]) and determining the level of HRV using spectral analysis consists in comparison with the values found by various authors with age-appropriate healthy population[33,50,54]. On the other hand, it is also shown, that the short-term HRV analysis in both the time domain and spectral analysis characterizes the unique sympathovagal regulation of person examined[55]. Further, the results of HRV analysis in the time and frequency domain in short-term and long-term recordings are steady and reproducible for at least 3-4 months for individuals without substantial change in health state and hence allow long-term monitoring[47,55-57].

Limitations of the method include disorders of sinus rhythm, multiple premature beats and implanted pacemaker. Factors fundamentally affecting the HR and BP and, in general, autonomic function should be taken into account in HRV assessment and, where possible, they should be eliminated at least 24 h before the examination. These include strenuous physical and mental activity, smoking, consumption of caffeine, alcohol, drugs and other substances affecting the ANS. The examination should ideally be performed in a quiet room with comfortable temperature, after a light meal[34,58]. Discontinuation of drugs influencing BP and HR is often practically imposible and depends on aims of the test. In case of HR near 100 beats/min, it is recommended for improving the examination representativeness to repeat the recording.

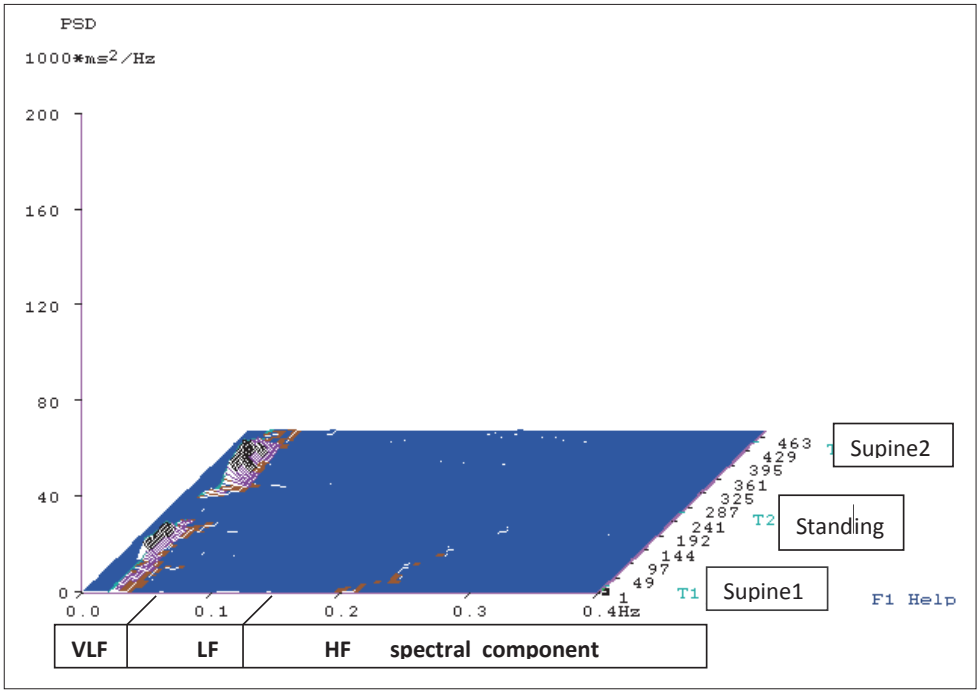

Fig. 5. 3-D preview of the result of spectral analysis in 33-year-old diabetic man (type I), with severe cardiac autonomic neuropathy during supine-standing-supine test. The dominant manifestation of CAN is reduction in overall spectral power with the absence of HF and LF components. (Own data). Legend: see Fig.4.

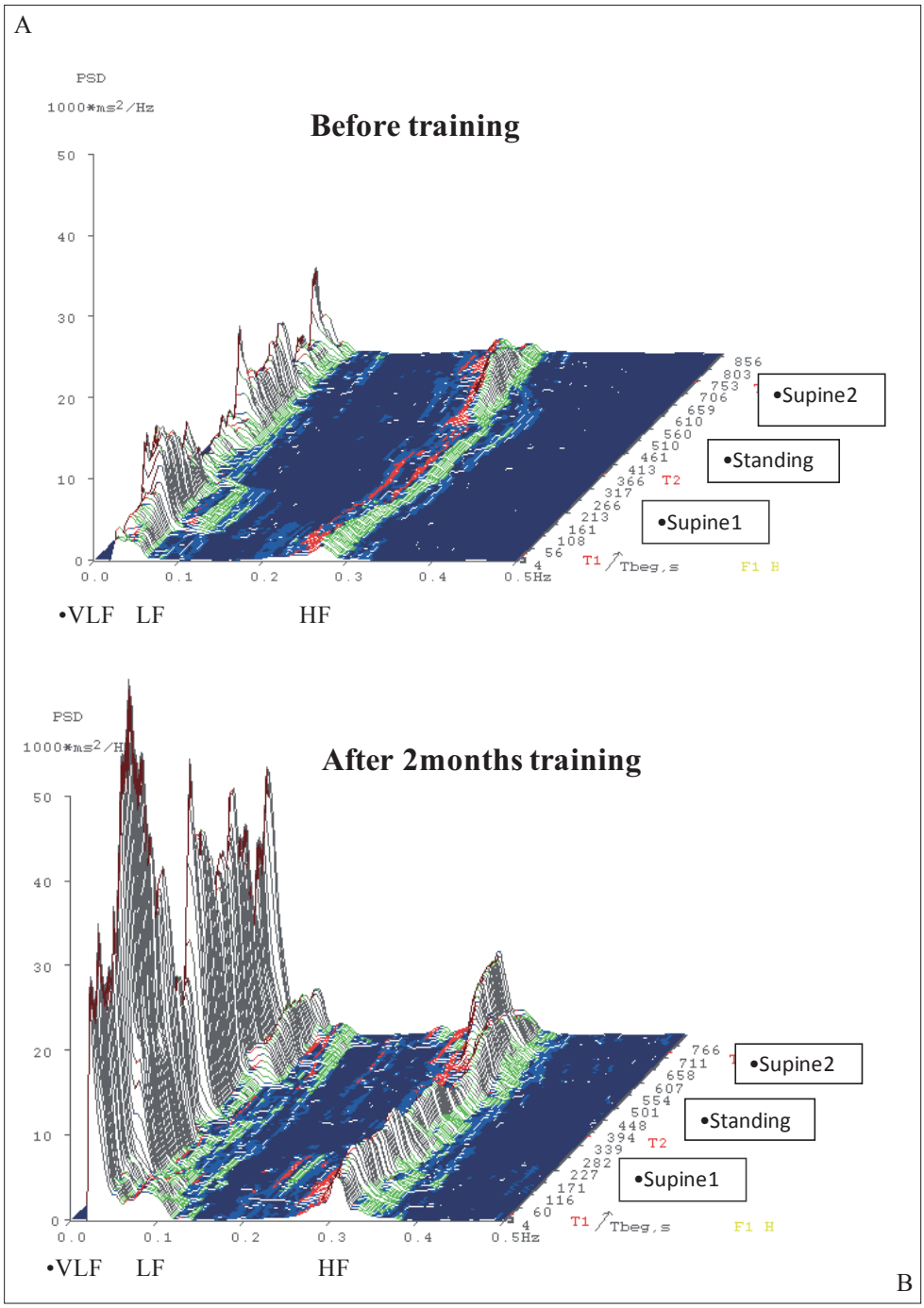

Fig. 6 A,B. The influence of physical rehabilitation following myocardial infarction on the results of spectral analysis of heart rate variability[62]. Own data.

Heart rate variability as part of the diagnostic algorithm and monitoring of the autonomic dysfunction in clinical practice

CAN evidence for diseases with neuropathy has two meanings. The first as a diagnostic proof of the cardiac autonomic dysfunction in relation to treatment currently used and possible use in monitoring the progression of autonomic dysfunction and treatment effect. The second aspect is the dominant role of CAN in the prognostic evaluation among autonomic neuropathies proven in multiple systems.

In this sense, the determination of cardiovascular autonomic function disorders is actively used from the diagnostic and prognostic point of view in diabetology since the 1970s (Fig. 5) (ref.[19]). Since 1996 it has been recommended as the risk stratification method in patients after myocardial infarction[7]. Application of HRV assessment is intensively investigated in many other diseases affecting the ANS with cardiovascular manifestations. It refers to Parkinson's disease, Alzheimer's dementia[59,60], haematological malignancies (amyloidosis) (ref.[61]), patients in chronic hemodialysis[62], systemic inflammatory diseases[63]. As a diagnostic auxiliary tool HRV can be used in testing

the patients with syncope[64], sleep apnea[65], in psychiatry in diagnosis and during treatment of depression[66]. It is a recognized method for monitoring critical conditions in neonatology[67]. It is applicable for monitoring of the training within the controlled rehabilitation after myocardial infarction and in heart failure (Fig. 6A,B) (ref.[68-70]). It is used in sports for training load rating[71].

Heart rate variability as a prognostic indicator

Prognostic value of HRV is established and included in the "recommendations" for risk stratification after myocardial infarction, namely for the development of malignant arrhythmias and sudden arrhythmic death[7]. HRV as independent risk factor also has the potential for prognostic applications in myocardial involvement of non-ischemic origin.

For prognostic purposes at coronary heart disease (CHD) the basic HRV analysis of long-term ECG recording (24 h) in the time domain by statistical or geometric method is considered to be sufficient (Table 2). The most frequently used prognostic indicators there are the standard deviation of all normal RR intervals (SDNN) and the triangular index (HRV triangular index). The values SDNN < 50 ms and HRV index <15 (24 h recording), representing a total HRV, are considered to be significantly reduced, the value SDNN <100 ms and HRV index < 20 for slightly reduced. Parallel HRV analysis in time and frequency (spectral) domain is not required[7]. In case of 24 h spectral analysis the reduced values of ULF (cutpoint spectral power PwrULF < 1600 ms^2) and VLF components (cutpoint spectral power PwrVLF <180 ms^2) are the strongest predictors for prediction of sudden cardiac death and arrhythmic death (evidenced for the next 2.5 year period). As the cutpoint for LF component there is given PwrLF < 35 ms^2, for HF component PwrHF < 20 ms^2 and for the ratio LF/HF value < 0.95. For initial screening there can be used HRV spectral analysis of short-term ECG recordings. Correlation between spectral analysis of 24 h and short-term recordings is good (for most indicators there are given coefficients $r > 0.75$) (ref.[72]).

To increase its predictive ability HRV is used in combination with other recognized risk factors (NYHA functional classification, rales present during the acute phase of myocardial infarction, reduced left ventricular ejection fraction, positive late potentials, repetitive ventricular arrhythmias) (ref.[72-74]). The sensitivity of combination HRV with other risk factors is in the range of 29-58%, specificity up to 99% (ref.[73]). Positive prediction value for malignant arrhythmias and sudden death, for death from all causes ranges within 22-58% (ref.[72,73]). Normal values for indicators HRV also have a high prognostic value. In most studies HRV alone or associated with the absence of other significant risk factors has negative predictive value for the occurrence of sudden death or malignant ventricular arrhythmia greater than 90% (77-97%) (ref.[73,74]).

CONCLUSION

Heart rate variability is making a valuable contribution to the diagnosis of cardiovascular autonomic dysfunction and CAN. It can be assessed from short-term and long-term ECG recordings. It is one of the few methods that allow outpatient CAN diagnosis, monitoring the progress, therapeutic effect and evaluation of patient prognosis. It is used as an independent prognostic factor in combination with other recognized risk factors in risk stratifying after myocardial infarction. It is a unique method of CAN diagnosis particularly in diabetology. Its diagnostic and prognostic potential in other medical fields is being intensively explored.

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