CARDIOVASCULAR FUNCTIONAL DIAGNOSTICS METHODS

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ABSTRACT

Effective functional diagnostics is a priority of EU strategy on prevention of health status. Effective non-invasive functional diagnostics cardiovascular methods are methods for examination of Central Nervous System (CNS) and Autonomous Nervous System (ANS) functions through analyses of Heart Rate Variability (HRV), Blood Pressure Variability (BPV), and baroreflex sensitivity. Cardiovascular functional diagnostics methods might enhance our understanding of physiological and pathophysiological mechanisms of mental work load and stress, ethiopathogenesis of cardiovascular diseases.
Key Words: functional diagnostics; Heart Rate Variability; Blood Pressure Variability; Baroreflex sensitivity; Cardiovascular Diseases.

РЕЗЮМЕ

Приоритет на европейската стратегия за превенция на здравния статус е ефективната функционална диагностика. Ефективни сърдечно-съдови неинвазивни функционално диагностични методи са методите за изследване на ЦНС и ВНС, посредством анализ на вариативността на сърдечния ритъм и артериалното налягане, и барорефлексната сензитивност. Сърдечно-съдовите функционално диагностични методи допринасят за изучаване на физиологичните и патофизиологични механизми на умственото работно натоварване и стреса, етиопатогенезиса на сърдечно-съдовите заболявания.
Ключови думи: функционална диагностика; вариативност на сърдечния ритъм; вариативност на артериалното налягане; барорефлексна сензитивност; сърдечно-съдови заболявания.

World Health Organization (WHO) indicates that one of the most important health topics is an early diagnosis and prevention of morbidity and mortality of Cardiovascular diseases (CVD). Effective functional diagnostics is a priority of EU strategy on prevention of health status. Populations of low- and middle-income countries of the EU are exposed to a greater extent to morbidity and mortality of CVD, and have less access to an effective functional diagnostics (1). Until 2030 the mortality from CVD will reach 23.6 millions. In low- and middle-income countries of EU individuals are exposed to a greater extent to the influence of cardiovascular risk factors inducing, and have a low access to CVD prevention (2). Next trend of EU public health policy is on health prevention through research studies. The accent is on transformation of research studies into clinical programs, elaboration of new intervention programs and therapies, effective functional diagnostics methods, stimulation of preventive strategies, medical technologies, and effective health systems.

Effective non-invasive functional diagnostics cardiovascular methods are methods for examination of Central Nervous System (CNS) and Autonomous Nervous System (ANS) functions through analyses of Heart Rate Variability (HRV), Blood Pressure Variability (BPV), and baroreflex sensitivity.

Cumulative influence and effect of stressogenic social, economic, professional, aging, and environmental factors affect neural-regulated cardiovascular function. The influence of these stressors changes the functional state and activity of CNS, and ANS. HRV, BPV and baroreflex sensitivity are functional non-invasive methods for investigation of ANS and CNS regulated cardiovascular function (3-12). Cardiovascular function might be studied through beat-to-beat analysis of heart rate and blood pressure monitoring.

Since the time of the earliest measurements of heart rate and arterial blood pressure it was observed that signals of cardiovascular origin though almost periodical were characterized by slight cycle-by-cycle variations in both amplitude and time domain. Discrete series describing these oscillations (either as a function of cardiac cycles or equivalently as time fluctuations obtained from these variables by means of interpolation techniques) are generally referred to as variability signals. Technological progress in the field of data collection and analysis of heart rate and arterial blood pressure variability has led to more sophisticated approaches to rhythmic circulatory phenomena and to their more frequent investigation by power spectral analysis.

Power spectral analysis of cardiovascular parameters is a promising non-invasive method for assessment of the ANS and CNS regulated cardiovascular function. Determination of neural control is of particular clinical interest since diagnosis, therapy and prognosis of CVD might rely on the balance between sympathetic and parasympathetic activity. Based on experimental and clinical studies the general concept is that very low-, low-, and mid-frequency oscillations (0.00 – 0.15 Hz) reflect sympathetic and parasympathetic activities whereas respiration-related high-frequency oscillations (0.2 - 0.4 Hz) reflect the parasympathetic tone (9). Power spectrum reflects the amplitude of heart rate and blood pressure fluctuations present at different oscillation frequencies. Spectral variability measures are defined as the total spectral energy in a considered frequency band, i.e. the integral of the spectral density function in the relative frequency area.

The power spectrum consists of frequency bands ranging from 0 to 0.5 Hz, and can be classified into four bands: the ultra low frequency band (ULF), the very low frequency band (VLF), the low frequency band (LF), and the high frequency band (HF) (10, 12, 13).

Variable	**Units**	**Description**	**Frequency range**
Total power	ms2	variance of all NN intervals	<0.4 Hz
ULF	ms2	ultra low frequency	<0.003 Hz
VLF	ms2	very low frequency	<0.003-0.04 Hz
LF	ms2	low frequency power	0.04-0.15 Hz
HF	ms2	high frequency power	0.15-0.4 Hz
LF/HF	ratio	ratio of low-high frequency power	

Short-term spectral recordings (5 to 10 minutes) are characterized by the VLF, HF and LF components, while long-term recordings include a ULF component in addition to the three others. The table above shows the most used frequency domain parameters. The spectral components are evaluated in terms of frequency (Hertz) and amplitude which is assessed by the area (or power spectral density) of each component. Thus, squared units are used for the absolute values expressed in ms squared (ms^2). The total power of cardiointervals (RR interval) variability is the total variance and corresponds to the sum of the four spectral bands, LF, HF, ULF and VLF.

The HF component is generally defined as a marker of vagal modulation. This component is respiration-mediated and thus determined by the frequency of breathing.

The LF component is modulated by both the sympathetic and parasympathetic nervous systems. In this sense, its interpretation is more controversial. Some scientists consider LF power, particularly when expressed in normalised units, as a measure of sympathetic modulations; others interpret it as a combination of sympathetic and parasympathetic activity. The consensus is that it reflects a mixture of both autonomic inputs. In practical terms, an increase of the LF component (tilt, mental and/or physical stress, sympathomimetic pharmacologic agents) has been generally considered to be a consequence of sympathetic activity. Conversely, β-adrenergic blockade resulted in reduction of the LF power. However, in some conditions associated with sympathetic overexcitation, for example in patients with advanced CHF, the LF component was found to be drastically diminished, reflecting thereby the decreased responsiveness of the sinus node to neural inputs.

The LF/HF ratio reflects the global sympatho-vagal balance and can be used as a measure of this balance. With an average normal adult in resting conditions, the ratio is generally between 1 and 2.

ULF and VLF are spectral components with very low oscillations. The ULF component might reflect circadian and neuroendocrine rhythms and the VLF component long period rhythms. The VLF component has been found to be a major determinant of physical activity and was proposed as a marker of sympathetic activity .

Research teams evaluating the effect of mental work load on ANS activity and clinical utility of HRV consider following spectral measures of HRV: spectral powers of RR intervals in the low-frequency, mid-frequency and high-frequency bands (9, 14).

Low-frequency band is limited between 0.02 and 0.06 Hz. Peripheral vascular resistance exhibits intrinsic oscillations with a low-frequency. These oscillations might be influenced by thermal skin stimulation and are thought to arise from thermoregulatory peripheral blood flow adjustments. The fluctuations in peripheral vascular resistance are associated with fluctuations with the same frequency in blood pressure and heart rate and are mediated by sympathetic nervous system (15);

Mid-frequency band is the band between 0.07 – 0.14 Hz. The 10-second rhythm in heart rate originates from self-oscillation in the vasomotor part of the baroreflex loop. These intrinsic oscillations result from the negative feedback in the baroreflex and are accompanied by synchronous fluctuations in blood pressure (Mayer waves) (16). The frequency of the oscillations is determined by the time delay of the system. They are augmented when sympathetic tone is increased and they decrease with sympathetic or parasympathetic blockade.

High frequency band is the area between 0.15 – 0.4 Hz. The inspiratory inhibition of the vagal tone causes heart rate fluctuations with a frequency equal to respiratory rate. The inspiratory inhibition is evoked primarily by control irradiation of impulses from the medullary respiratory to the cardiovascular center. Variations in HF band can mainly be attributed to respiratory sinus arrhythmia (RSA). RSA can be abolished by atropine or vagotomy and is parasympathetically mediated.

HRV and BPV are increasingly used to examine disease-related changes in the autonomic tone or the effects of therapeutic interventions (17, 18). Hypertension remains one of the most significant cardiovascular risk factors – in 70% the cause for the excess of mortality in hypertensive individuals is mild hypertension. Significant topic in diagnosis and therapy of essential arterial hypertension is determination of autonomic cardiovascular control through the study of HRV and BPV. Short-term heart rate and blood pressure variability recordings registered in laboratory supine rest conditions show that essential hypertension is characterized by a greater low-frequency power and a smaller high-frequency power of RR intervals (19). Similar results were reported in the studies of Julius and Johnson, 1985 (20) and Folkow, 1982 (21). These studies reveal that in essential hypertension cardiac sympathetic tone is increased and cardiac vagal tone and modulation are decreased. HRV and BPV can be used to assess the effects of antihypertensive drugs on cardiac autonomic tone. Antihypertensive drugs have significant effect on autonomic tone. Effect direction and magnitude might be estimated by frequency-domain measures of HRV and BPV. The link between the sympathetic nervous system activity assessed by HRV, BPV and baroreflex sensitivity and the hypertensive state might be supported by the clinical evidence showing the efficacy of drugs therapy interfering with sympathetic control.

Baroreflex sensitivity is determined by computing the modulus (gain) of the transfer function between changes in systolic blood pressure (input) and heart rate interval (output).
Baroreflex sensitivity might compute by the gain (mmHg/ms) in baroreflex using trigonometric regressive spectral analysis (TRSA) (22). TRSA is a method for mapping of beat-to-beat recorded autonomic cardiovascular measures: HRV, and systolic and diastolic BPV. TRSA examines baroreflex sensitivity by computation of cross correlations $R>0.7$ between corresponding pairs of frequencies ($fr_{HR} \approx fr_{BP}$) in very-low-, low- and high-frequency bands of variances of HRV and BPV (23).

Research interest in baroreflex sensitivity (BRS) as an indicator of cardiac autonomic control has grown in recent years (24). Available studies in cardiovascular psychophysiology elucidate decreasing of BRS in different cardiovascular diseases, including arterial hypertension, coronary artery disease, and congestive heart failure (25). Low BRS was associated with increased blood pressure levels in arterial hypertension (26). Reduced arterial compliance and increased sympathetic activity have also been suggested to be responsible for the decreased BRS in hypertension (27, 28). There is also evidence that impaired baroreflex regulation is not only a consequence of hypertension but also may contribute to the development of hypertension (29, 30). Baroreflex impairment is considered a major causal mechanism because of the important role of the baroreflex in reducing blood pressure and enhancing heart rate oscillations (31).

The involvement of baroreceptor reflex control in regulating cardiovascular reactions to mental stress tests has also been explored. The simultaneous increase in systolic blood pressure and heart rate typically observed in response to mental stress test implies the disruption or overriding of short-term baroreflex regulation. Cardiac baroreflex sensitivity is suppressed during mental stress tests (32). Time-domain and frequency-domain analyses for computer evaluation of the arterial baroreflex have showh that the sensitivity of the baroreceptor-heart rate reflex is much lower in essential hypertensive than in normotensive subjects for each hour of the 24 hours thereby confirming previous conclusions obtained by studying the baroreflex with laboratory techniques (33).

In summary it can be stated that the main function of baroreceptor reflexes (baroreflexes) is to buffer acute changes of blood pressure. Impairment of the baroreflexes (e.g. by denervation of the sino-aortic afferents) results in a hyperreactivity to external stimuli. Human studies show that the sensitivity of the baroreflex is diminished during reactivity tasks such as dynamic and isometric exercise, and during mental arithmetic tasks. Individuals with decreased baroreflex sensitivity reveal increased blood pressure lability. Baroreflex sensitivity is inversely related to overall blood pressure variability (which depends primarily on the lowest-frequency powers) and directly related to overall heart rate variability. This change implies that baroreflex influences are not limited to fast parasympathetically mediated blood pressure and heart rate fluctuations but extend to the low and very low frequency fluctuations, considered sympathetically and parasympathetically mediated. Baroreflex sensitivity is influenced by both divisions of the Autonomic Nervous System: sympathetic and parasympathetic activity. During mental stress blood pressure and heart rate elevations are associated with suppression of cardiac baroreflex sensitivity.

HRV, BPV and baroreflex sensitivity are cardiovascular functional diagnostics methods which have considerable potential to assess the function of the ANS and CNS in healthy individuals to assess the effect of mental work load on functional state, and to study the ethiopathogenesis of diseases in patients with cardiovascular and non-cardiovascular disorders. Functional diagnostics methods might enhance our understanding of physiological and pathophysiological mechanisms of mental work load and stress, ethiopathogenesis of cardiovascular diseases, and the mechanism of action of medications. Identification of individuals at risk for subsequent morbidity and non-risk groups necessitate future prospective studies to determine the sensitivity, specificity and predictive values of HRV, BPV and baroreflex sensitivity.

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