HEART RATE VARIABILITY AND ELECTRODERMAL ACTIVITY AS NONINVASIVE INDICES OF SYMPATHOVAGAL BALANCE IN RESPONSE TO STRESS

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A b s t r a c t

The autonomic nervous system (ANS) is a principal regulatory system for maintaining homeostasis, adaptability and physiological flexibility of the organism at rest as well as in response to stress. In the aspect of autonomic regulatory inputs on the cardiovascular system, recent research is focused on the study of exaggerated/diminished cardiovascular reactivity in response to mental stress as a risk factor for health complications, *e.g.* hypertension. Thus, the analysis of biological signals reflecting a physiological shift in sympathovagal balance during stress in the manner of vagal withdrawal associated with sympathetic overactivity is important. The **heart rate variability**, *i.e.* "beat-to-beat" oscillations of heart rate around its mean value, reflects mainly complex neurocardiac parasympathetic control. The **electrodermal activity** could represent "antagonistic" sympathetic activity, the so-called "sympathetic arousal" in response to stress. The detailed study of the physiological parameters under various stressful stimuli and in recovery phase using traditional and novel mathematical analyses could reveal discrete alterations in sympathovagal balance. This article summarizes the importance of heart rate variability and electrodermal activity assessment as the potential noninvasive indices indicating autonomic nervous system activity in response to mental stress.

Key words: cardiovascular system, electrodermal response, heart rate variability, mental load

INTRODUCTION

Autonomic nervous system (ANS) – sympathetic and parasympathetic subsystem - is principal regulatory mechanism for maintaining homeostasis, adaptability and physiological flexibility of the organism. It is well-known that cardiovascular system regulation is extremely sensitive to autonomic regulatory inputs. Psychological stress elicits increased sympathetic activity resulting in changes of cardiovascular system – tachycardia, hypertensive reaction with consequent redistribution of blood flow. This physiological strategy enhanced the probability of survival for mammals faced with a physical threat in nature (1). Proper functioning of the sympathetic-parasympathetic dynamic balance at rest as well as in response to stress enables adaptive response to load – allostasis (2). In contrast, the autonomic imbalance, in which one branch of the autonomic nervous system dominates over the other, is associated with a lack of dynamic flexibility and health. Therefore, the sympathetic overactivity associated with parasympathetic hypoactivation could represent potential pathomechanism leading to increased risk of cardiovascular adverse outcomes and all-cause mortality (3).

However, with recent life-style associated with daily mental load, the impact of psychosocial stress has been a challenge for the cardiovascular system and body homeostasis. Thus, psychological stress is considered as a component of the so-called cardiovascular risk (4). For example, symptoms of elevated sympathetic activity are commonly observed in patients with white coat hypertension – elevated blood pressure as a potential consequence of increased anxiety in a clinical setting (1, 5). From this point of view, the more attention focuses on the evaluation of psychological stress impact on the cardiovascular system. Although numerous studies indicate that exaggerated cardiovascular reactivity to stress is linked with cardiovascular complications (6), recent study referred also to diminished car-

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diovascular reactivity as a risk factor for health complications (7). It seems that further research on this issue is necessary, in particular with regard to the application of noninvasive peripheral markers in the evaluation of the ANS activity. Thus, this work is focused on the potential noninvasive indices of sympathovagal balance assessment – heart rate variability and electrodermal activity - in response to mental stress.

I. Heart rate variability – a potential noninvasive index of complex cardiac parasympathetic control

Principal cardiovascular parameter – heart rate – represents a sensitive marker with rapid adaptation to different stimuli, the mean value of which is determined by intrinsic activity as well as by the parasympathetic and sympathetic neurons terminating at sinoatrial node. Moreover, the heart rate is characterized by continual *"beat-to-beat"* oscillations around its mean value. This physiological phenomenon is called **heart rate variability** (Fig. 1). Heart rate variability (HRV) is a reflection of the sophisticated complex central-peripheral regulatory mechanisms mainly through activity of autonomic nervous system, continual dynamic interaction of excitatory and inhibitory effects as well as the impact of exogenous and endogenous factors – inheritance, sex, age, physical/mental state, and others.

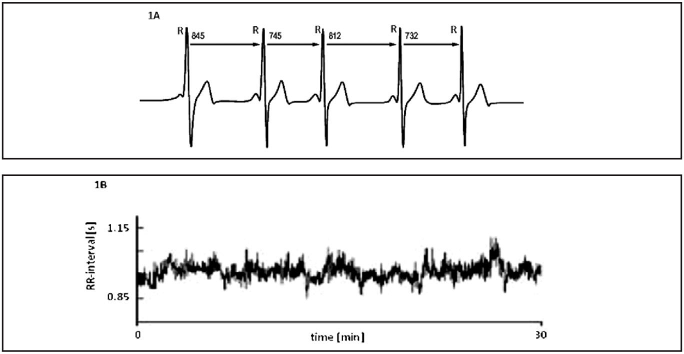

Fig. 1. The example of heart rate beat-to-beat changes - heart rate variability (Fig. 1B) determined by RR intervals from QRS complex (Fig. 1A) (according to Voss et al. (8)).

A critical idea that HRV could reflect central nervous system (CNS) activity was hypothesized in recent studies (9, 10). Benarroch (11) has described the central autonomic network - medial prefrontal cortex, amygdala, hypothalamus, midbrain, nucleus of the solitary tract, nucleus ambiguous, ventrolateral and ventromedial medulla - as an integrated component of an internal regulation system through which the brain controls visceromotor, neuroendocrinne, and behavioural responses that are critical for physiological flexibility and adaptability. Neurovisceral theory discussed that the interplay of sympathetic and vagal outputs of the central autonomic network through sinoatrial node produces the complex beat-to-beat heart rate variability indicating a healthy and adaptive organism (9, 10). Interestingly, integrative theories that link CNS structures to cardiac vagal regulation, such as the polyvagal theory (12), have of late emerged. A central feature of this theory is the existence of separate brainstem centres involved in parasympathetic cardiac control, with distinct evolutionary origins and significance and with divergent influences on cardiac vagal tone related to psychological and behavioral processes (13, 14). Specifically, series of neuroimaging studies have provided evidence that **activity of the prefrontal cortex is associated with cardiac vagal function** evaluated by heart rate variability analysis (15). For example, Ahs et al. (16) concluded that vagal modulation of the heart is associated with activity in striatal as well as medial and lateral prefrontal areas in patients with social phobia. Another study reported the correlations in the superior prefrontal cortex, the dorsolateral prefrontal and parietal cortices activities with parasympathetic-linked cardiac control indexed by the heart rate variability spectral analysis (15). Thus, these objective and sensitive methods confirm the fact that the **heart rate variability** serves **to index central-peripheral autonomic nervous system integration**, and consequently, is a **psychophysiological marker** for adaptive environmental engagement (13, 14), especially as a potential marker of stress (17).

HRV analysis

The RR intervals can be analyzed by traditional - linear methods as well as novel nonlinear methods that describe variability from different aspects. Conventionally used linear methods – time and frequency (spectral) analysis - provide the information about the HRV magnitude, especially the information concerning the **parasympathetic (vagal) neural outflow.** In addition, these methods are best suited and recommended to short-term RR interval recording (5-15 min.) which hold the advantage over long recording: it is more feasible to maintain fixed and strictly standardized conditions necessary for a valid recording (3). In addition, the short-term HRV analysis allows the evaluation of autonomic nervous system activity and the baroreflex-mediated changes in the ANS developing immediately after the onset of physiological stress, *i.e.* vagal withdrawal associated with sympathetic activation. From this point of view, the recent research is focused on other application of new mathematical *nonlinear* approaches for short-term recordings suitable for clinical use.

The *nonlinear methods* of HRV analysis measuring qualitative characteristics of the cardiac time series – *i.e.* complexity, have been shown to be more suitable for a detailed description of heart rate autonomic control system (18, 19). Specially, the **symbolic dynamics** is novel nonlinear analysis designated mainly to short-term recordings and the symbolic dynamics parameter 0V% - parameter which describes the change of heart beat in symbol units, *i.e.* patterns with no variation (all three symbols are equal), may provide the additional information about **sympathetically mediated heart rate fluctuations** (8, 20, 21). It could be very important for study of sympathovagal balance changes in stress. Further research on this issue is needed. Detailed description of different methods of HRV analysis is addressed in Table 1.

Table 1. Methods of heart rate variability analysis suitable for short-term recordings (according to Voss et al. (8), Javorka et al. (22)).

Parameters	Number of points	Physiological significance
LINEAR ANALYSIS		
Time analysis		– to inform about the magnitude of HRV
mean HR	300	– mean of heart rate
SDNN	300	– standard deviation of NN intervals - index of total HRV
rMSSD	300	– the square root of the mean squared difference of successive NNs - index of parasympathetic activity
pNN50	300	– the proportion of NN50 divided by total number of NNs – index of parasympathetic activity
spectral analysis		– to inform about individual rhythms amplitude within certain frequencies in HRV – quantitative characteristics of heart rate beat-to-beat changes
HF – HRV	300	– index of parasympathetic activity reflecting respiratory sinus arrhythmia
LF – HRV	300	– baroreceptor activity ?

NONLINEAR ANALYSIS		
Symbolic dynamics		– to evaluate physiological systems from aspect of complexity in cardiac time series – HRV qualitative characteristic
0V%	300	– potential index of sympathetic activity
1V%	300	– ?
2UV%	300	– ?
2LV%	300	– potential index of parasympathetic activity
Time irreversibility		– feature of a nonlinear dynamical system
P%	300	– Porta´s index – to evaluate percentage of negative ΔRR with respect to total number of ΔRR Δ from 0 (23)
G%	300	– Guzik´s index – to evaluate percentage of cumulative square values of positive ΔRR to the cumulative square of all ΔRR (24)
E%	300	– Ehlers´ index – to evaluate of the skewness of distribution of ΔRR (23)

Abbreviations: E% – Ehlers´ index; G% - Guzik´s index; HF-HRV – heart rate variability in high frequency band; HR – heart rate; HRV – heart rate variability; LF-HRV – heart rate variability in low frequency band; NN – normal to normal beats of heart; NN50 - the number of pairs of successive NNs that differ by more than 50 ms; P% - Porta´s index, pNN50 - the proportion of NN50 divided by total number of NNs; rMSSD - the proportion of NN50 divided by total number of NNs; RR - interval between successive Rs; SDNN - standard deviation of NN intervals; 0V – patterns with no variation (all three symbols are equal); 1V – patterns with one variation (two consecutive symbols are equal and the remaining one is different); 2LV – patterns with two like variations (the three symbols form an ascending or descending ramp); 2UV – patterns with two unlike variations (the three symbols form a peak or a valley).

II. Electrodermal activity – a potential noninvasive marker of sympathetic activity

At the beginning of the research concerning the stress, the investigators focused mainly on the sympathetic branch of ANS as one part of complex response to stress, *e.g.* American physiologist Cannon (26) described warning reaction of organism ("fight or flight") in the aspect of sympathoadrenal activation including plasma catecholamine changes. One of potential noninvasive markers reflecting sympathetic activity is **electrodermal activity (EDA)** used in psychophysiological research (7, 10, 27, 28, 29).

Method of EDA measurement is based on content of water and electrolytes in individual parts of organism and on spread of weak electrical current through two electrodes localized on skin surface. It records the voltage changes arising between electrodes. The skin conductance is assessed by Ohm`s law - a reciprocal value of resistance. Value of skin conductance depends on amount of sweat produced by eccrine sweat glands regulating by sympathetic nervous system. When the sweat duct is filled with sweat, more conductive area originates on the nonconductive corneu. Origin of lower resistance is caused by more sweat. The changes of sweat level involved modification of resistance, so we could observe EDA alternations (30).

Moreover, several studies referred to modulation of electrodermal activity by limbic system. This system, together with amygdala activity, influences to changes EDA, which are related with cognitive challenge and autonomic arousal (31). Decline of EDA depends on type and duration of stressor (31).

EDA analysis

Methods of evaluation of EDA can be divided into two main groups: exosomatic and endosomatic – invasive manner of EDA recording (32, 33, 34). The exosomatic measurement is based on the recording of tonic and phase level (30). Measurement in **tonic level** represents skin conductance level providing the information of baseline sympathetic activity without stimulus for environment. The recording in **phase level** reflects changes of discrete stimulus (*e.g.* ocular, auditory, olfactory perception) providing the information about sympathetic arousal (32, 36). The EDA evaluated parameters are following: amplitude of skin conductance response (SCR), latency, rise time, half recovery time of SCR (Fig. 2) (30, 36). EDA, as an index of sympathetic activity, increases during the cognitive and emotional stressors. Consequently, the sympathetic activity decreases during recovery phase, so the EDA activity reduced too (Fig. 3). The EDA can be evaluated by nonlinear analysis as a recurrence quantification analysis, which it evaluates changes in function of ANS.

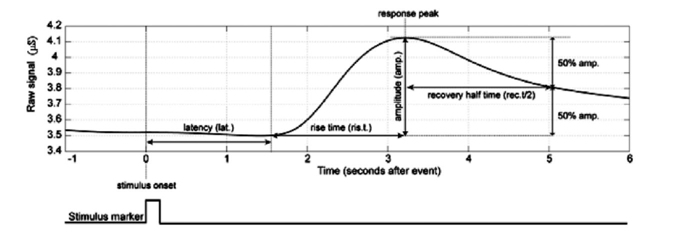

Fig.2. Evaluated parameters of electrodermal activity (EDA) in phase level. Detailed explanation of the parameters is discussed in the text (according to Dawson et al. (30), Murphy (34), Sokolov (35), Boucsein (37)).

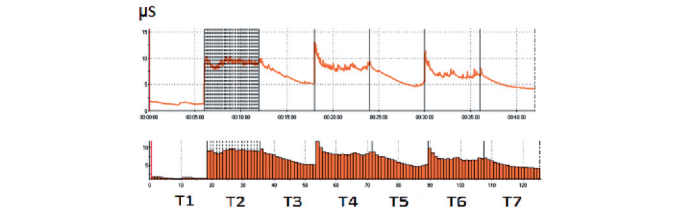

Fig. 3. Continual recording of electrodermal activity before, during and after mental load in young healthy man. T1, T3, T5, T7 – rest phase; T2, T4, T6 – mental load (Department of Physiology, JFM CU)

III. Stress - impact on the sympathovagal balance indexed by HRV and EDA

Autonomic nervous system dynamic balance in response to acute stress is changed in the manner of sympathetic excitation (arousal) associated with reciprocal decrease of the parasympathetic activity (vagal withdrawal) (38, 39). Interestingly, simple mean value of heart rate could provide important information concerning the ANS activity during stress (Fig. 4). For example, Oldehinkel et al. (40) referred to low mean heart rate as a marker of stress resilience. Our study (41) revealed tachycardic reaction and decrease of parasympathetic activity indexed by HRV high-frequency band indicating vagal withdrawal in response to arithmetic test (Fig. 5). These results were in agreement with other studies (42). Moreover, several authors found out altered heart rate variability complexity evaluated by nonlinear analysis (43). It seems that novel nonlinear approach for HRV analysis could represent sensitive method for neurocardiac regulation/dysregulation providing important information concerning qualitative characteristics of cardiac time series - nonpredictability (44), irregularity (45, 46) or asymmetry (25, 47) in response to stress.

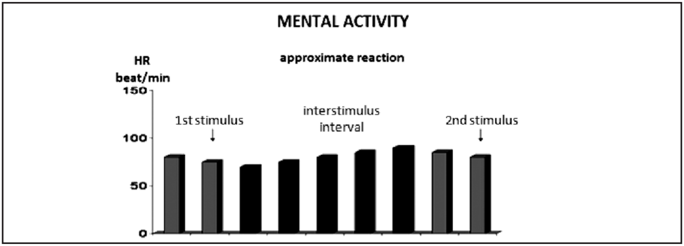

Fig. 4. The changes of mean heart rate (HR) in response to stress stimulus characterized by HR deceleration before stress stimulus (anticipatory response), the HR acceleration in response to stress and consequent HR deceleration to another stimulus (according to Tonhajzerova et al. (41)).

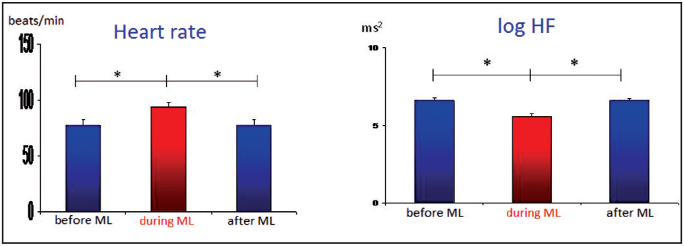

Fig. 5. Mean values of heart rate and logarithmic values of spectral activity in high-frequency band (logHF) of heart rate variability before, during and after mental load (ML) in healthy young people. $^*p<0.05$ (according to Tonhajzerova et al. (41)).

However, the sympathetic activity evaluation using HRV spectral analysis is questionable: although several studies referred that low-frequency band reflects mainly sympathetic activity (48), other recent studies emphasized vagal impact on the low frequency band. Sloan et al. (49) determined the changes in low-frequency band of HRV spectral analysis (LF-HRV) and plasma concentration of catecholamines as a gold index of sympathetic activity. This study revealed decreased LF-HRV in spite of the increased concentration of plasma catecholamines in response to mental stress. Similarly, our results pointed out the reduced LF-HRV during the arithmetic test (41). We assume that a change of the ANS dynamic balance could depend on the baroreceptor's activity. If the parasympathetic activity decreases and sympathetic activity rises in response to stress, the resulting low-frequency band activity will depend on proportional change in these subsystems (50, 51).

On the other hand, the electrodermal activity could provide clear information about sympathetic excitation in response to stress. Our pilot results showed the increased EDA indicating sympathetic arousal in response to cognitive stressor (arithmetic test, Stroop test) in young medical students. Surprisingly, these EDA values did not return to baseline level during the time period of 5 minutes after stress. It seems that sympathetic hyperactivity remains prolonged in recovery phase; however, these findings need further elucidation (52).

The mechanisms of sympathovagal balance modification in response to stress are still unclear. Their understanding is complicated by the large number of cortical, subcortical and brainstem structures regulating autonomic activity (53). Lovallo (7) referred to neurophysiological model individual structure consists of central and peripheral nervous system, connected to stress reactivity (psychological stressor) at three basic levels: 1. limbic system and its interaction with prefrontal cortex; 2. hypothalamus and brainstem; 3. peripheral organs (*e.g.,* heart). Thus, level I interactions between the prefrontal cortex and the limbic system also establish the outflow to Level II, which includes the hypothalamus and brainstem. Consequently, the hypothalamus and brainstem forms the final common pathways for outputs to the body. They can be influence reactivity because of variations in homeostatic set points and output gain factors. Finally, at Level III are the peripheral tissues that can determine response magnitudes. Individual differences in response may reflect distinction in autonomic outputs or intrinsic differences in tissue structure (7). The recent studies refer to function dorsomedial hypothalamus and other central pathways involved in the cardiovascular response to emotional stress (1).

The second pathway participating in individual response to stress could involve behavioural and psychological factors. For example, the change of individual subsystems autonomic nervous system is similar to orthostatic test as a physical stimulus. In contrast, the response to psychological stressors (*e.g.* mental arithmetic test) is associated with higher interindividual reactivity depending on individual personal characteristics (e.g. type A/B/X behaviour, low or high responders, emotion, habituation, adaptation, *etc.*) (27, 54). Thus, interpretation of these results is complicated. We suggest that autonomic nervous system activity in response to stress might reflect a combination of the biological/nonbiological mechanisms mentioned above or other unknown factors modulating final response to stress.

CONCLUSIONS

Dynamic balance of autonomic nervous system is changed in response to stress in the manner of parasympathetic activity decline (vagal withdrawal) with reciprocal increased of sympathetic activity (arousal). Importantly, the altered autonomic reactivity during stress is associated with higher risk of health complications including cardiovascular system. Therefore, the detailed study of physiological reactivity using cardiovascular parameters (*e.g.* heart rate variability as an index of parasympathetic activity) analysis by novel mathematical approach as well as other variables characterized autonomic nervous system activity (*e.g.* electrodermal activity as an index of sympathetic activity) under various stressful stimuli and recovery phase could provide important information of a “stress” issue.

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