Respiratory sinus arrhythmia as a non-invasive index of ‘brain-heart’ interaction in stress

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Respiratory sinus arrhythmia (RSA) is accepted as a peripheral marker of cardiac-linked parasympathetic regulation. According to polyvagal theory, the RSA is also considered as the index of emotion regulation. The neurovisceral integration model posits that parasympathetic modulation of the heart marked by RSA is related to complex nervous regulation associated with emotional and cognitive processing. From this perspective, high resting RSA amplitude associated with a greater withdrawal during stressors and subsequent recovery could represent a flexible and adaptive physiological response system to a challenge. Conversely, low resting RSA accompanied by an inadequate reactivity to stress might reflect maladaptive regulatory mechanisms. The RSA reactivity is different with various types of stressors: while the RSA decreases to cognitive tasks indicating a vagal withdrawal, the RSA magnitude increases to emotional challenge indicating an effective cognitive processing of emotional stimuli. The RSA reactivity to stress could have important implications for several mental disorders, e.g. depressive or anxiety disorder. It seems that the study of the RSA, as a non-invasive index of ‘brain-heart’ communication, could provide important information on the pathway linked to mental and physical health.

Key words Cognition - emotion - heart rate variability - respiratory sinus arrhythmia - stress

Introduction

Breathing oscillations influence the firing activity of the sinoatrial node defined as respiratory sinus arrhythmia (RSA). RSA is a consequence of various central as well as peripheral effects from medullary cardiorespiratory centre and reflex responses from pulmonary/cardiovascular receptors resulting in heart rate oscillations in accordance with respiratory cycle. However, RSA is mainly affected by cardiac-linked vagal efferent modulation from the nucleus ambiguus, which is influenced by several central projections (e.g. amygdala, hypothalamus).²Despite the fact that sympathetic activity can contribute to RSA by a specific pattern, it is elevated in the inspiratory period with maximum at the end of inspiration.³ The question that RSA is confined to parasympathetic regulation of the heart has been discussed by many researchers.⁴⁻⁶ Muscarine receptors inhibition by parasympatholytic agent atropine results in diminished RSA magnitude.⁷⁻⁸ However, understanding of RSA is limited by peripheral factors including alterations of muscarinic receptors functioning (e.g. density of distribution, sensitivity).⁹⁻¹⁰
Hence, the peripheral mechanisms involved in cardiac vagal regulation remain unclear\textsuperscript{10}.

RSA as an index of cardiac vagal modulation has been used in the study of emotion and self-regulatory capacity and reactivity\textsuperscript{11,12}. This issue is still discussed in the context of neurophysiological mechanisms influencing RSA, such as breathing, and from the perspective of relation between RSA and stress reactivity, important for the understanding of stress-related disorders\textsuperscript{13,14}. The aim of the present review was to highlight the nature of RSA and discuss implications in psychophysiological research with regard to emotional regulation and stress reactivity.

**Respiratory sinus arrhythmia (RSA) in the context of neurovisceral integration model**

Thayer and Lane\textsuperscript{15,16} reported the significance of cardiac vagal regulation indexed by RSA in the context of neurovisceral integration model. Afferent-efferent vagal central functional consolidation is regulated through the central autonomic network (CAN)\textsuperscript{17}. Morphological central CAN areas include forebrain regions (prefrontal and cingulate cortices; amygdala, hypothalamus), middle and posterior brain regions (nucleus tractus solitarii, nucleus ambiguus). The sympathovagal interaction from the CAN results in multiple instantaneous heart rate variations, i.e. the heart rate variability (HRV)\textsuperscript{15}.

With regard to the heart, the momentary HRV is determined mainly by parasympathetic regulation based on fast metabolism of acetylcholine (sympathetic nerve effect occurs with latency). Thus, the HRV linear analysis provides information about breathing-related effects on the high-frequency band of the HRV (HF-HRV: 0.15-0.4 Hz) while low-frequency band (LF-HRV: 0.04-0.15 Hz) is influenced by contribution of sympathetic modulation mediated by baroreceptor activity. The respiratory-linked HRV indexed by HF-HRV is associated with several central regions such as prefrontal or cingulate cortex\textsuperscript{12,18,19}. Thus, the objective neuroimaging methods underpin the assumption that RSA indexed by the HF-HRV reflects the ‘brain-heart’ bidirectional communication\textsuperscript{6,15}.

The CAN-mediated HRV is characterized as a non-linear dynamical system with numerous mutual interactions and complexity\textsuperscript{14,15,20}. In contrast, various pathological states are characterized by lower complexity as a non-linear characteristic of heart rate regulation resulting in deficient cardiac responses to many conditions\textsuperscript{21-23}. Thus, the linear HRV analysis does not provide adequate information about complex cardiac dynamics. Therefore, novel non-linear methods assessing the qualitative features [\textit{e.g.} heart rate complexity by symbolic dynamics, heart rate asymmetry (HRA)] have been applied in HRV analysis\textsuperscript{24}.

Specifically, HRA represents the non-linear feature of the heart control associated with breathing cycle characterized by unequal duration of inhalation and exhalation\textsuperscript{25,26}. Karmakar \textit{et al}\textsuperscript{27} concluded that pharmacological parasympatholytic agent atropine or parasympathomimetic scopolamine influences asymmetric patterns, i.e. atropine reduces and scopolamine increases HRA. These studies confirm the link between vagal activity and HRA indices. In addition to breathing, the physiological mechanisms underlying the heart rate accelerations or decelerations can be modulated by other complex factors, such as baroreflex, chemoreflexes, hormones and others\textsuperscript{20}.

The faster HRV oscillations expressing cardiac-linked modulation result in faster variations of consecutive heart beats, i.e. patterns with two similar variations (2LV\%). The symbolic dynamics index 2LV\% indicates the rate of occurrence of these patterns\textsuperscript{28,29}. The 2LV\% declines in response to different stressors (\textit{e.g.} orthostasis or mental tasks); therefore, this index could be predominantly influenced by cardiac vagal regulatory effects\textsuperscript{28,30,31}. Moreover, if these non-linear symbolic dynamics and HRA indices reflect predominantly cardiovagal activity, it should be correlated with the linear index HF-HRV determined by dominant vagal regulatory inputs. Our previous study revealed no significant relations between HF-HRV, 2LV\% and HRA indices\textsuperscript{31}. Therefore, these indices might offer different data about non-linear dynamics in heart rate vagal regulation that is independent on the RSA magnitude quantified by HF-HRV. This assumption, however, should be elucidated by further research.

The effect of breathing pattern: Importantly, the RSA is determined by breathing parameters such as respiratory rate or tidal volume, \textit{i.e.} RSA magnitude is decreased in higher breathing rate and greater with increased tidal volume. Thus, tachypnoea reduces RSA, and bradypnoea with maximal volumes results in pronounced RSA magnitude\textsuperscript{14,32}. The changes in parameters characterizing breathing patterns could influence cardiorespiratory conjunction\textsuperscript{33}. In this context, slow breathing can affect the low-frequency band\textsuperscript{34}. These alterations in breathing pattern...
characterize resting conditions as well as cognitive or emotional activity. Emotional activation was shown to be related to different respiratory activities characterized by augmented tidal volume associated with lower breathing rate resulting in high RSA magnitude, e.g. during meditation. Thus, these psychological states associated with altered breathing pattern might affect RSA size. Denver et al. based on literature review reported that RSA magnitude was not related to breathing parameters. Several studies found no effect of breathing measures on the RSA. Therefore, this field is still a matter of extensive discussion.

Controlled breathing eliminates this controversial aspect; however, this pattern may not represent normal physiological cardiorespiratory interaction. Controlled breathing is associated with voluntary component involving cortical control of respiratory muscle activity accompanied by sympathetic excitation. In cognitive task, the cardiorespiratory coupling may be affected by the motor cortical activation and sympathetic excitation. The effects of voluntary and spontaneous breathing on HRV spectral analysis were reported to be similar in another study.

The RSA variations represent differences in phasic pattern of vagal influences on heart rate. Grossman and Taylor have referred to significant caveats: (i) breathing indices may affect the relation between RSA and parasympathetic heart rate regulation; (ii) RSA recording is influenced by physical activity resulting in individual cardiac-vagal modulation; and (iii) RSA amplitude is influenced by sympathetic modulation. Taken together, these issues should be considered in the correct interpretation of the RSA as a marker of parasympathetic regulation of the heart rate in psychophysiological research.

From pathophysiological perspective, the attenuated RSA reflecting autonomic dysregulation is considered a risk factor for later cardiovascular adverse outcomes. Samuels referred to the stress aetiology related to cardiovascular diseases suggesting complex interaction between altered cortical/neutral centres regulating cardiac autonomic activity (e.g. frontal lobe, anterior cingulate gyrus, insula, hypothalamus, limbic cortex, mesencephalic reticular formation and others) and peripheral factors (catecholamine toxicity, stress hormones and others) leading to heart injury.

Despite the fact that reduced RSA is a frequent finding in somatic diseases such as obesity or hypertension, the past research was focused on the RSA as a potential psychophysiological marker indicating organism’s flexibility and adaptability with emotions.

**Respiratory sinus arrhythmia (RSA) in the context of emotional regulation**

In the polyvagal theory, the nucleus ambiguus plays an important role in the emotional and social behaviour. Specifically, efferent pathways from the nucleus ambiguus modulate the larynx as an organ important for expression of emotions. In addition, the nucleus ambiguus is connected with cranial nerves involved in the emotional expression and vocalization. Several studies showed the RSA link to affective regulation in people. The RSA could be considered as an index of emotional regulation. However, it is important to note that cognitive control is important for emotions, termed as emotion regulation. According to the neurovisceral theory, Thayer and Lane described the connection between mental and somatic functioning. Higher resting HRV (greater RSA amplitude) represents better cognitive control of emotions necessary for appropriate processing of negative effect. On the contrary, reduced RSA at rest can indicate maladaptive cognitive reflection to emotional conditions. From this context, a prefrontal hypoactivity leading to subcortical excitation can result in the perseverative cognition (e.g. worry, rumination). Therefore, the deficiency in cognitive-emotional circuitry represented by cortical as well as subcortical areas could be connected with several mental disorders.

The vagal reactivity is important, i.e. ‘vagal brake’ is withdrawn in response to a challenge, and parasympathetic inhibition in response to stress could reflect more flexible individual’s adaptability to stress. Taken together, the RSA magnitude (indexed by HF-HRV) at rest and during stress could provide important information related to physiological and behavioural flexibility of the organism including emotional regulation. It is important to note that this assumption is not uniform, particularly in somatic and mental disorders. In somatic diseases, the resting HF-HRV may be substantially influenced by the effect of comorbidities, such as diabetes, hypertension and others. Specifically, lower HF-HRV was found in patients suffering from diabetes compared to non-diabetics, with significant inverse relationship between HF-HRV and fasting insulin and glycaemia. Our previous studies revealed lower HF-HRV in...
development, diabetic, hypertensive and obese patients compared to controls. The lower baseline cardiac vagal control indicates a lower functional reserve autonomic capacity to regulate stress response. Therefore, the significance of resting HF-HRV in the presence of comorbid diseases is questionable.

In mental disorders, the robust vagal withdrawal to stress can be a non-specific index of emotional lability. Our previous study demonstrated a reduced baseline RSA magnitude associated with higher RSA reactivity in the attention deficit hyperactivity disorder (ADHD) group compared to controls. Thus, it remains unclear if these results are associated with the ADHD symptoms or these findings indicate clinically asymptomatic cardiac autonomic dysregulation to posture stress in ADHD patients. The findings concerning the RSA reactivity in response to different stressors are controversial; and this area requires further research.

Developmental aspect: The development of the neural structures involved in the cardiac vagal control is important for social skills, behavioural state, adaptability and flexibility. Vagal myelinization is important for the newborns and the infants prosocial behaviour. Further, the early childhood is a vulnerable age period for the emotion regulation; and the RSA differences may indicate developmental differences. In biopsychosocial developmental model, impulsive children with family and emotional support are socialized through de-escalation of arousal, positive reinforcement, and are protected from delinquency behaviour through appropriate emotional regulation mediated by vagus nerve. In contrast, risk children without family and emotional support are prone to later problems in behavioural and emotional domain due to ineffective vagal regulation of effects. With regard to psychopathology, baseline RSA was similar between ADHD and controls at the age of 4-6 years; however, vagal deficiency was observed in middle childhood and adolescence such as a period characterized by parasympathetic nervous system ‘online’.

The puberty represents a specific period because of central nervous system developmental changes including prefrontal cortex. McAra et al. reported the brain regions of cognitive reappraisal for emotion regulation in various age periods ranged from 10 to 22 years. These authors observed linear age-related increases in the prefrontal cortex activity accompanied by better cognitive functioning important for emotional skills. Further, older adults (55-65 yr) showed diminished prefrontal cortical activation associated with lower cognitive reappraisal of emotions in older adults.

The physiological maturation of neurocardiac regulatory mechanisms should also be considered. For example, the maximal increase of cardiac vagal activity indexed by HF-HRV was found between 9 and 14 yr in the group of 5400 children. Another study found HRV increase during the first decade reflecting a gradual development of the parasympathetic nervous system. Our study revealed increase in RSA magnitude (indexed by HF-HRV and deep breathing test) indicating augmentation of cardiovagal activity in the group of 206 boys and girls aged 15-19 years. A systematic review summarized that HRV values are typically higher in younger adult participants with emphasis on the necessity of HRV standard values for individual age periods. Processes responsible for age-related influences could involve maturation of central brain regions, changes in neurotransmitters, growth of the heart, receptor’s level (sensitivity and density) and other unknown mechanisms. It seems that the developmental process is important for RSA understanding in the emotional and cognitive regulation at the different age periods.

**Respiratory sinus arrhythmia (RSA) in response to the acute cognitive/emotional stress**

Porges suggested that stress could be specified by abnormal autonomic functioning characterized by decreased vagal modulation; thus, the RSA quantification might be used for assessment of stress response. RSA responses to different stressful stimuli showed large variability. Previous studies confirmed a parasympathetic decrease marked by RSA to cognitive stress. However, other authors concluded that the two cognitive tasks had dissimilar effects on RSA reactivity. While the continuous working memory task requiring high cognitive control had a substantial inhibitory effect on the parameters characterizing RSA, the perceptual attention task involving low cognitive control had a limited inhibitory effect on the RSA measures. The intensity of cognitive control thus seems to be an important determinant of differential effects of cognitive tasks on RSA. The literature shows large inconsistencies in the RSA responses to emotional tasks. In certain studies, specific emotional states produced an increase in RSA relative to a resting baseline, while others found RSA reduction or no
RSA alterations in response to similar states\(^{47,79}\). For clinical implications, the RSA reactivity to stress could have important implications for specific conditions associated with affective regulation\(^{12}\).

Therefore, we aimed to show that RSA response could be different from cognitive and emotional stress. Ten healthy non-obese cases between 22 and 23 yr were examined in the special psychophysiological laboratory. The electrocardiography signal was recorded during the protocol: rest – mental arithmetic test (cognitive test) – rest – negative emotional stress (video clip with dental intervention) – rest (recovery phase). The duration of each period was six minutes suitable for short-term HRV analysis\(^{80}\). However, the participants were not instructed about the precise order of individual stressors to minimize a potential impact of cognitive processing before the examination. The results displayed a distinct response pattern of the RSA indexed by HRV time parameter [root mean squared successive difference of RR intervals (rMSSD)] to different stressors: decreased vagal activity (significantly lower rMSSD) in response to cognitive test (arithmetic test), and increased RSA magnitude (significantly higher rMSSD) to negative emotional task. In addition, the HRV parameter returned to baseline values after the stress was over (unpublished results, Table). These results were in accordance with the studies which found a cardiac-linked parasympathetic decrease indexed by reduced RSA magnitude to cognitive stress indicating physiological adaptive response system\(^{31,57,81,82}\). It seems that these findings can contribute to the understanding of RSA reactivity in emotional stress.

The stress reactivity is also influenced by age. Kudielka et al\(^ {85}\) found reduced heart rate reactions in older people (60-76 yr) compared to younger adults (19-32 yr) and children (9-15 yr). Despite the fact that resting RSA could show two-year stability, the RSA reactivity is characterized by steady responses only in adult people\(^ {86}\). In addition, while active cognitive stressors are accompanied by sympathetic control of the heart rate associated with a vagal withdrawal, the passive emotional stress is associated with increases in parasympathetic system due to potential immobilization effect\(^6\). The evaluation of such effects requires further systematic investigation.

**Conclusion**

Cardiac vagal function indexed by RSA may reflect activity of complex neural system responsible for adequate cognitive-affective regulation. High resting RSA amplitude associated with a greater withdrawal during stressors and subsequent recovery could represent a flexible physiological response system. It seems that RSA stress-linked reactivity depends on the type of stressors: while the RSA decreases to cognitive tasks indicating a vagal withdrawal, the RSA magnitude increases to emotional stimulus indicating a proper cortical-subcortical functioning, i.e. effective cognitive processing of emotional stimuli.

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