 DOI: 10.2478/v10201-011-0011-y

CARDIAC VAGAL CONTROL IN DEPRESSION AND ATTENTION DEFICIT/HYPERACTIVITY DISORDER

Tonhajzerova I.,[1] Ondrejka I. [2], Javorka K. [1], Calkovska A. [1], Javorka M. [1]

[1]Department of Physiology and [2]Clinic of Psychiatry, Jessenius Faculty of Medicine, Comenius University, University Hospital Martin, Martin, Slovak Republic

Abstract

The importance of the vagus nerve in the two way communication between the brain and the heart has been known for over 100 years. Recently, integrative theories that link central nervous system structures to cardiac vagal regulation, such as the polyvagal theory, have of late emerged. Based on the polyvagal theory, the respiratory sinus arrhythmia (as an index of cardiac vagal control) is considered as a psychophysiological marker of many aspects of behavioural functioning and emotion regulation in both children and adults. Although a lack of sensitive heart rate autonomic control likely reflects impaired cardiac nervous system regulation, the sophisticated brain-heart interactions are incompletely understood. Importantly, cardiac vagal dysregulation is associated with the increased risk of cardiovascular morbidity reflecting various pathophysiological states. Thus, we believe that the identifying of cardiac vagal control changes in mental disorders should represent an initial step towards the understanding of a potential pathomechanisms leading to later cardiac adverse outcomes; especially in children and adolescents.

Key words: cardiac vagal regulation, central nervous system, respiratory sinus arrhythmia, heart rate variability, mental disorders

INTRODUCTION

Autonomic nervous system plays a key role in a wide range of somatic and mental disorders. The ANS is generally conceived to have two major branches – the sympathetic system, associated with energy mobilization, and the parasympathetic system, associated with vegetative and restorative functions. The activity of the ANS is in dynamic balance; thus, the autonomic imbalance implying sympathetic overactivity and parasympathetic underactivity is associated with various pathological conditions indicating a lack of dynamic flexibility and health (1).

Psychological states and processes are known to profoundly influence the autonomic nervous control of the cardiovascular system with likely contribution to the increased cardiovascular morbidity in patients with mental disorders (2,3). During this decade the pathomechanisms by which central nervous system (CNS) modulates changes in autonomic nervous system (ANS) in various mental disorders as well the potential links between cognitive/emotional processes and cardiac autonomic regulation have drawn increasing interest (4,5).

1. NEURAL CORRELATES OF THE CARDIAC VAGAL REGULATION

Cardiac function is extremely sensitive to autonomic influences. In healthy systems both branches of the ANS are tonically active with sympathetic activity associated with heart rate acceleration and parasympathetic activity associated with heart rate deceleration (6). The studies concerning the brain-heart connection emphasize the modulation of the cardiac activity by the cortex; thus, an extensive research has been directed at identifying the pathway by which this neurocardiac control is achieved (1, 7). Benarroch (8)

Address for correspondence:
Assoc. Prof. Ingrid Tonhajzerova, MD, PhD, Department of Physiology, Jessenius Faculty of Medicine, Comenius University, Mala Hora 4, 036 01 Martin,Slovak Republic, Phone/fax: +421434131426; e-mail: tonhajzerova@jfmed.uniba.sk

has described the central autonomic network (CAN) as an integrated component of an internal regulation system through which the brain controls visceromotor, neuroendocrinne, and behavioural responses that are critical for goal-directed behaviour and adaptability. Structurally, the CAN includes the anterior cingulate, insular, and ventromedial prefrontal cortices, the central nucleus of the amygdala, the paraventricular and related nuclei of hypothalamus, the periaquaductal gray matter, the parabrachial nucleus, the nucleus of the solitary tract, the nucleus ambiguus, the ventrolateral and ventromedial medulla, and the medullary tegmental field. The primary output of the CAN is mediated through the sympathetic/parasympathetic neurons innervated the heart. Moreover, the interplay of sympathetic and parasympathetic (vagal) outputs of the central autonomic network at the sinoatrial node producing the complex beat-to-beat heart rate variability is characteristic of a healthy and adaptive organism (9). Neurochemically, tonic inhibition of the CAN is achieved by γ-aminobutyric acid (GABA) activity within the nucleus tractus solitarii, and by GABAergic frontal cortex inhibition of subcortical sympatho-excitatory defensive circuits (9, 1). Hence, the importance of the inhibition of cardiac activity by prefrontal cortex is emphasized.

Specifically, a series of studies using neuroimaging have provided evidence that activity of the prefrontal cortex is associated with vagal function (10, 11). Therefore, it appears that the modulation of cardiac activity by the cortex is vagally mediated. 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 centers 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 (Table 1).

Table 1. Three phylogenetic stages of the neural control of the heart proposed by the polyvagal theory

Phylogenetic stage	Autonomic nervous system component	Behavioural function	Lower motor neurons stage
III	Myelinated vagus	Social communication Self-soothing and calming, inhibit sympathetic-adrenal influences	Nucleus ambiguus
II	Sympathetic-adrenal system	Mobilization (active avoidance)	Spinal cord
I	Unmyelinated vagus	Immobilization (passive avoidance)	Dorsal motor nucleus of the vagus

2. RESPIRATORY SINUS ARRHYTHMIA AS AN INDEX OF CARDIAC VAGAL CONTROL AND EMOTIONAL REGULATION

Respiratory sinus arrhythmia (RSA) refers to rhythmic fluctuation in the heart rate associated with respiration, which results from activity of a branch of vagal fibers from the medullary nucleus ambiguus terminating at the sinoatrial node and it is mediated through physiological mechanisms by which the heart rate increases during inspiration and decreases during expiration (13, 14). As interpreted by Porges in his polyvagal theory (12, 15), the nucleus ambiguus is considered as an origin of the more recently developed „smart“ vagus to facilitate the complex emotion responses/social behaviour. Two sources of structural evidence link RSA to emotion. Efferent fibers from the nucleus ambiguus innervate the larynx, an important structure for communication of emotional state through vocalization (12). Also, afferent fibers of the nucleus ambiguus are believed to terminate in the source nuclei of the facial and trigeminal nerves, which facilitate the emotion behaviours of facial expression and vocalization. Recently, along with structural evidence, empirical studies relating RSA to emotion in humans have accumulated (16, 11). Then, the polyvagal theory posits that the myelinated vagus, originating in the nucleus ambiguus, is a dynamic contributor to the processes of the emotion and social interactions (12, 15). Therefore, the respiratory sinus arrhythmia should be considered as an index of both cardiac vagal and emotional regulation.

One way to index the central control of the heart via the vagus nerve is the use of the short-term **heart rate variability,** *i.e.* the amount of the heart rate fluctuations around the mean heart rate (17). In regard to RSA evaluation, the HRV spectral analysis allows to isolate the faster high frequency (HF) respiratory-coupled influences on the HRV (0.15-0.4 Hz) from slower sources of the HRV reflecting mainly sympathetic and parasympathetic activity via baroreflex. Thus, a spectrally derived index of vagally-mediated heart rate variability (HF-HRV) provides information about the cardiorespiratory oscillations reflecting in the respiratory sinus arrhythmia. Moreover, several studies have documented correlation between HF-HRV and cerebral blood flow in certain cortical (prefrontal, insular cortex) and subcortical regions (10). As such, vagally-mediated HRV serves to index central-autonomic nervous system integration, and consequently, is a psychophysiological marker for adaptive environmental engagement (12).

3. CARDIAC VAGAL CONTROL IN PSYCHIATRIC CONDITIONS

Depression

Generally, impaired cardiac vagal function is likely important contributor to the cardiac adverse outcomes associated with internalizing disorders, *e.g.* major depression (18). Since reduced cardiac vagal modulation is a common finding in adult patients with depression (19), other studies reported unchanged parasympathetic cardiac activity (20). Moreover, depressive disorder is often overlaps with anxiety. Trait anxiety may moderate the relationship between cardiac vagal regulation and depression, with which anxiety is often associated. Low vagal heart rate control was found only in high-anxious subset of a depressed sample (21). In this regard, the reduced vagal modulation of the heart in depression could represent a chronic, consolidated anxiety-related response to everyday hassles and aggravations (22).

In contrast to adults, the studies relating the cardiac vagal control and adolescent major depression are rare. The adolescence could be a critical and vulnerable age-period to a potential depression-induced cardiac autonomic dysregulation due to developmental and brain maturational changes (23). In our studies, the HRV linear (spectral) and nonlinear (symbolic dynamics) analysis revealed reduced cardiac vagal control in adolescent girls with major depression prior to pharmacological treatment (Fig. 1, 2). These results were in agreement with other studies related to adult depression and extend them into the adolescent age. Since cardiac vagal dysregulation is associated with increased risk of cardiovascular morbidity, this finding underscores the importance of impaired cardiac vagal control in adolescent major depression (24, 25).

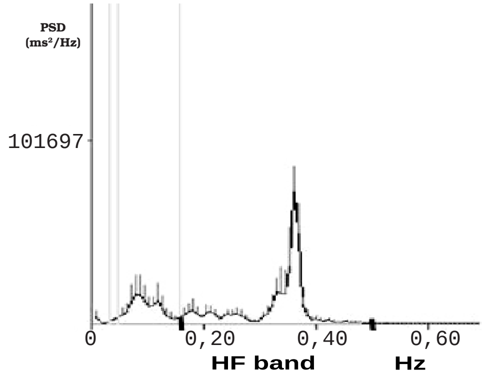

Fig. 1 Graphic protocol of the heart rate variability spectral analysis in 17-year-old healthy subject. HF band reflects predominantly the respiratory sinus arrhythmia as an index of cardiac vagal control. HF – high frequency.

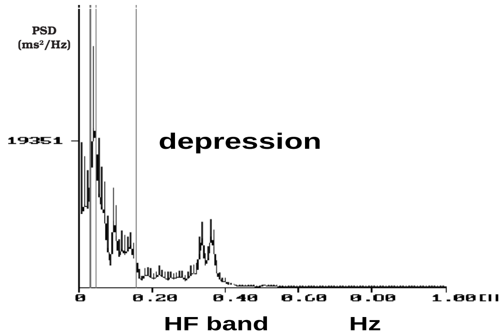

Fig. 2 Graphic protocol of the heart rate variability spectral analysis in 17-year-old patient with major depression. Reduced HF band refers lower respiratory sinus arrhythmia indicating impaired cardiac vagal control in adolescent patient with major depression. HF – high frequency.

Attention deficit/hyperactivity disorder (ADHD)

ADHD as one of the most commonly diagnosed externalizing mental disorders among children characterized by distractibility, hyperactivity, impulsive behaviours and the inability to remain focused on tasks or activities. Some studies found deficient respiratory sinus arrhythmia in children with ADHD. For example, Crowell et al. (26) compared autonomic profiles of preschool children (aged from 4 to 6 yrs) with ADHD and oppositional defiant disorder (ODD) with controls. Children with ADHD and ODD were not significantly different in baseline RSA, but authors referred to a potential impaired cardiac vagal regulation in later age-period related to emotion dysregulation and lability.

We studied the cardiac vagal control using the HRV spectral analysis under rest and physiological stress stimulus (orthostasis) in children with ADHD. Our results indicated decreased cardiac vagal modulation in a supine position and in response to standing (27). Beauchaine (4) referred to reduced respiratory sinus arrhythmia, indicating altered cardiac vagal control, as a potential marker of the dysregulated emotional states. Additionally, the excessive vagal reactivity could characterize emotional lability. In our study, the vagal reactivity during orthostasis was significantly higher in ADHD group compared to controls (-36% vs. -23%). Thus, it is questionable whether our findings of lower cardiac vagal control combined with higher vagal reactivity are related to the feature of the ADHD (i.e. emotional lability due to emotional immaturity) or it is reflection of subclinical abnormal dynamic activation of the ANS in response to posture change in children with ADHD (27). Moreover, it seems that emotional maturation should represent an important factor connected to parasympathetic-linked cardiac activity.

4. THE POTENTIAL PATHOMECHANISMS LEADING TO CARDIAC VAGAL DYSREGULATION IN MENTAL DISORDERS

Their understanding is complicated by the large number of cortical, subcortical and brainstem structures coordinating cardiac vagal control (28). Firstly, some authors emphasize the neural correlates of vagal function and the role of brain, particularly the inhibitory role of the prefrontal cortex. Thus, the prefrontal cortex and its abnormalities (e.g. prefrontal hypoactivity) could play a critical role in cardiac autonomic dysregulation associated with depression because of the failure of the prefrontal cortex to inhibit amygdala as a region that mediates cardiovascular and autonomic responses (7). Similarly, in ADHD children, the deficit in frontal functioning connected to limbic system and consequent alteration of baroreflex function as well as the modifications in a network of brain region are supposed (29). Secondly, behavioural/lifestyle factors should be associated with impaired cardiac vagal function in mental disorders. Rottenberg (30) revealed that the diagnosis of depression exerts a small-to-medium effect on cardiac vagal control and referred to other factors influencing cardiac function (e.g. lack of physical activity). Thus, it seems that the question related to predominant role of the neurobiological basis, including neurotransmitter's changes/ hypothalamo-hypophysis-adrenal axis dysfunction, or behavioural/psychological effects on the vagally mediated heart rate control, remains unclear.

5. CONCLUSION

The deficiency of the cardiac vagal control indicating impaired autonomic neurocardiac integrity in mental disorders is associated with increased risk of cardiovascular morbidity. We suggest that an interdisciplinary approach, including the integration of basic physiological research and pedopsychiatry, may contribute to the elucidation of the pathomechanisms and to the early diagnosis of the heart rate dysregulation in young people with mental disorders.

REFERENCES

1. Friedman BH. An autonomic flexibility-neurovisceral integration model of anxiety and cardiac vagal tone. Biol Psychol 2007; 74: 185-99.
2. Kim CK, McGorray SP, Bartholomew BA, Marsh M, Dicken T, Wassertheil-Smoller S. Depressive symptoms and heart rate variability in postmenopausal women. Arch Inter Med 2005; 165: 1239-44.
3. Yeragani VK. Heart rate and blood pressure variability: implications for psychiatric research. Neuropsychobiology 1995; 32: 182-91.
4. Beauchaine T. Vagal tone, development, and Gray´s motivational theory: Toward an integrated model of autonomic nervous system functioning in psychopathology. Dev Psychopathol 2001; 13: 183-214.
5. Thayer JF, Brosschot JF. Psychosomatics and psychopathology: looking up and down from the brain. Psychoneuroendocrinology 2005; 30: 1050-58.
6. Levy MN. Autonomic interactions in cardiac control. Annal NY Acad Sci 1990; 601: 209-21.
7. Thayer JF, Lane RD. Claude Bernard and the heart-brain connection: Further elaboration of a model of neurovisceral integration. Neurosci Biobehav Rev 2009; 33: 81-8.
8. Benarroch EE. The central autonomic network: functional organization, dysfunction, and perspective. Mayo Clin Proc 1993; 68: 988-1001.
9. Thayer JF, Lane RD. A model of neurovisceral integration in emotion regulation and dysregulation. J Affect Disord 2000; 61: 201-16.

10. Lane RD, Reiman EM, Ahernm GL, Thayer JF. Activity in medial prefrontal cortex correlates with vagal component of heart rate variability during emotion. Brain Cogn 2001; 47: 97-100.
11. Lane RD, McRae K, Reiman EM, Chen K, Ahern GL, Thayer JF. Neural correlates of heart rate variability during emotion. Neuroimage 2009; 44: 213-22.
12. Porges SW. Orienting in a defensive world: Mammalian modification of our evolutionary heritage. A polyvagal theory. Psychophysiology 1995; 32: 301-18.
13. Berntson GG, Bigger JT, Eckberg DL, Grossman P, Kaufmann PG, Malik M, Nagaraja HN, Porges SW, Saul JP, Stone PH, van der Molen MW. Heart rate variability: Origins, methods, and interpretive caveats. Psychophysiology 1997; 34: 623-48.
14. Javorka K. Heart rate variability. Mechanisms, evaluation, clinical implications. Martin: Osveta; 2008; 204p. (in Slovak).
15. Porges, SW. The polyvagal theory: new insights into adaptive reactions of the autonomic nervous system. Cleve Clin J Med 2009; 76 (Suppl. 2): 86-90.
16. Frazier TW, Strauss ME, Steinhauer SR. Respiratory sinus arrhythmia as an index of emotional response in young adults. Psychophysiology 2004; 41: 75-83.
17. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Circulation 1996; 93: 1043-65.
18. Carney RM, Freedland KE. Depression and heart rate variability in patients with coronary heart disease. Cleve Clin J Med 2009; 76: S13-17.
19. Kikuchi M, Hanaoka A, Kidani T, Remijn GB, Minabe Y, Munesue T. Heart rate variability in drug-naive patients with panic disorder and major depressive disorder. Prog Neuropsychopharmacol Biol Psychiatry 2009; 33: 1474-78.
20. Bär KJ, Greiner W, Jochum T, Friedrich M, Wagner G, Sauer H. The influence of major depression and its treatment on heart rate variability and pupillary light reflex parameters. J Affect Disord 2004; 82: 245-52.
21. Watkins II, Grossman P, Krishnan R, Blumenthal JA. Anxiety reduces baroreflex cardiac control in older adults with major depression. Psychosom Med 1999; 61: 334-40.
22. Berntson GG, Cacioppo JT. Heart rate variability: Stress and psychiatric conditions. In: Camm AJ, Malik M, editors. Dynamic electrocardiography. New York Futura; 2004. p.56-63.
23. Thayer JF, Sollers III JJ, Labiner DM, Weinand M, Herring AM, Lane RD. Age-related differences in prefrontal control of heart rate in humans: A pharmacological blockade study. Int. J Psychophysiol 2009; 72: 81-8.
24. Tonhajzerova I, Ondrejka I, Javorka M, Adamik P, Turianikova Z, Kerna V, Javorka K, Calkovska A. Respiratory sinus arrhythmia is reduced in adolescent major depressive disorder. Eur J Med Res 2009; 14 (Suppl.4): 280-83.
25. Tonhajzerova I, Ondrejka I, Javorka K, Turianikova Z, Farsky I, Javorka M. Cardiac autonomic regulation is impaired in girls with major depression. Prog Neuropsychopharmacol Biol. Psychiatry 2010; 34: 613-18.
26. Crowell SE, Beauchaine TP, Gatzke-Kopp L, Sylvers P, Mead H, Chipman-Chacon J. Autonomic correlates of attention-deficit/hyperactivity disorder and oppositional defiant disorder in preschool children. J Abnorm Psychol 2006; 115: 174-78.
27. Tonhajzerova I, Ondrejka I, Adamik P, Hruby R, Javorka M, Trunkvalterova Z, Mokra D, Javorka K.. Changes in the cardiac autonomic regulation in children with attention deficit hyperactivity disorder (ADHD). Ind J Med Res 2009; 130: 44-50.
28. Henry BL, Minassian A, Paulus MP, Geyer MA, Perry W. Heart rate variability in bipolar mania and schizophrenia. J Psychiatr Res 2010; 44: 168-76.
29. Börger N, van der Meere J, Ronner A, Alberts E, Geuze R, Bogte H. Heart rate variability and sustained attention in ADHD children – attention deficit-hyperactivity disorder. J Abnorm Child Psychol 1999; 27: 25-33.
30. Rottenberg J. Cardiac vagal control in depression: A critical analysis. Biol Psychol 2007; 74: 200-11.

Acknowledgement:
This work was supported by European Center of Excellence for Perinatologic Research No. 26220120016, co-financed from EU sources.

Received: December 20, 2010
Accepted: February, 1, 2011