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Review Article

Childhood Psychopathology and Autonomic Dysregulation: Exploring the Links using Heart Rate Variability

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ABSTRACT

Changes in cardiovascular reactivity have been used as a psychophysiological marker of various emotional states in both children and adults. Recent decades have seen increasing use of heart rate variability as a non-invasive marker of cardiac autonomic function and of central processes involved in autonomic function regulation. Developmental research has linked cardiac vagal tone to an individual's responsivity to environmental challenges and a decrease in vagal component of heart rate variability may reflect deficiencies in emotional regulatory system. Studies with children and adolescents suggest that attenuated cardiac vagal function is seen in various pathophysiological conditions characterised by emotional dysregulation. Thus, alteration in cardiac vagal modulation may be the common mechanism underpinning the association between negative affective states, emotional dysregulation and risk for cardiac disease.

Key Words: Childhood psychopathology; cardiovascular disease; heart rate variability; cardiac vagal tone.

It is being increasingly recognized that childhood emotional disorders are highly prevalent, persistent and are related to the later development of adult onset anxiety and depressive disorders.[1-3] Given the close relationship that exists between childhood emotional disorders and adult psychopathology, there has been suggestion that early intervention during childhood and adolescent years might prevent the later onset of adult psychopathology.[4-6] These findings have spurred considerable interest in understanding the biological underpinning of childhood emotional disorders with particular emphasis on identifying physiological markers of early vulnerability. [7-9] In this regard study of psychophysiological changes that accompany various negative affective states in children has been particularly useful.

Among the various psychophysiological markers, cardiovascular reactivity has attracted considerable attention as it demonstrates a high degree of stability through childhood and adolescence.[10-11] Initial research that studied the association between cardiovascular reactivity and childhood psychopathology noted a consistent association between childhood disruptive behaviour and a lower resting heart rate,[12] as opposed to an elevated resting heart rate in childhood anxiety disorders.[13] These initial observations received further support from the findings that children with high resting heart rate and high anxiety have less disruptive behaviours,[14] and more importantly lower resting heart rate in adolescence was predictive of criminal acts in adulthood.[15] Thus, autonomic under-arousal in children with conduct disorder as manifested by a lower resting heart rate and autonomic hyper-arousal in children with anxiety disorders were hypothesized as possible neurobiological underpinnings of childhood negative affective states.[13] Resting heart rate is

under the dual influence of parasympathetic and sympathetic nervous system and thus, a higher resting heart rate could conceivably be a consequence of either heightened sympathetic modulation to the heart or a withdrawal of cardiac vagal modulation.[16,17] In addition, many emotional states such as anxiety, anger, hostility and response to stressful situations are transitory in nature and involve rapid mobilization of responses to environmental challenges. As affect regulation involves integration of both biological and psychological domain, psychophysiological markers of emotional dysregulation must reflect integration across various domains: affective, cognitive, behavioural, central nervous system and autonomic nervous system.[18] Several psychophysiological measures have been used to index affect regulation. This article will focus on one such psychophysiological measure, heart rate variability and its relationship to negative affective states in childhood and adolescence.

Measures of heart rate variability (HRV)

Neural mechanisms governing cardiovascular system play an important role in maintaining homeostasis by enabling rapid dynamic responses to changing physiologic and environmental challenges. Various physiological manoeuvres have been used to gain a deeper understanding into the functioning of the autonomic nervous system as provocative measures tend to reveal between group differences in cardiovascular autonomic control beyond those seen at rest.[19] Beat-to-beat fluctuations in heart rate and blood pressure are referred to as heart rate variability and blood pressure variability. Many factors like age, level of physical activity, exercise, medications, sleep-wake cycle, respiratory activity, heart rate and posture influence the measurement of HRV.

Power spectral analysis of HRV has been used extensively as a non-invasive tool to study the cardiac autonomic nervous system ever since Akselrod and his colleagues characterized the autonomic basis of the observed peaks in the heart rate power spectrum.[20] Power spectral analysis of heart rate variability reveals three spectral components: the very low ($\leq$ 0.04 Hz), low (0.04-0.15 Hz) and high frequency components (0.15-0.4Hz).[21] There is considerable evidence to suggest that the high frequency power is largely a function of parasympathetic influences to the heart. The low frequency power may not solely reflect sympathetic activity but is used, most often normalized for total power, as a representative index of sympathetic influences to the heart.[21,22] The low frequency / high frequency power ratio has been used by several investigators as a marker of sympathovagal balance although the use of this index has been debated in recent years.[23,24]

Brainstem mechanisms in concert with limbic structures such as amygdala are involved in the control of cardiac pacemaker activity.[25] This provides the rationale for the use of HRV as a non-invasive marker of limbic activity. Studies have also shown that HRV is associated with pre-frontal cortex activity,[26] especially the anterior neural circuits that are involved in affective, cognitive and autonomic modulation.[27] Thus, HRV is an index of central and peripheral neural feedback and central nervous system-autonomic nervous system integration and is a useful non-invasive tool to study central processes involved in autonomic regulation thereby emphasizing its relevance in various psychiatric conditions.

HRV and emotional dysregulation in childhood

Emotional regulation and HRV

Porges and his colleagues in a series of studies in infants and children showed that vagal tone as measured by HRV is an index of emotion and attentional regulation.[28] Low vagal tone is associated with poor affect regulation, decreased responsivity to stimuli and

increased vulnerability to stress in infancy and childhood.[29] Infants with difficulties in decreasing vagal tone during a social / attention task at 9 months of age had significantly greater behavioural problems at 3 years of age.[30] Kagan and his colleagues have described the construct of behavioural inhibition, a temperamental attribute in children, which they showed to be related to later development of anxiety disorders.[31,32] Consistent withdrawal when exposed to unfamiliar situations is one of the characteristics of these children. Children who were more likely to show behavioural inhibition to unfamiliar situations had high stable heart rate at both baseline and during cognitive stress compared to children who were not behaviourally inhibited.[33] In addition, there was a greater shift towards low frequency power in HRV under cognitive stress in behaviourally inhibited children. Inhibited and uninhibited children also differed on other physiological indices such as salivary cortisol levels, norepinephrine levels and pupillary size at both baseline and in response to cognitive stress.[31] The authors interpreted these findings as suggestive of heightened sympathetic activity with involvement of neural circuits in the limbic system as the basis for behavioural inhibition.[34] The emphasis on sympathetic arousal in Kagan's hypothesis contrasts with findings from other studies where cholinergic modulation was associated with emotional regulation. These differences are probably related to methodological issues with Kagan and his colleagues using time domain method to analyze HRV as opposed to frequency domain method used by others. Others have noted an excessive vagal reactivity to various environmental challenges among children who are temperamentally shy and angrily reactive.[35,36] In contrast, vagal tone is positively correlated with children's social engagement, with teacher reports of social competence and expression of empathy towards others in distress.[37-39]. Higher vagal tone also appears to protect children who are exposed to marital discord and hostility from developing behavioural problems.[40] Thus, based on these findings Porges has proposed that development of appropriate social behaviour is dependent on the ability to regulate cardiac vagal tone,[30] and cardiac vagal tone mirrors an individual's response and adaptivity to environmental challenges and demands.[41-44]

To summarize, vagally mediated component of HRV reflects adaptivity (mal adaptivity) to environmental challenges and indexes ability (inability) to modulate affect responses. Several structures within the CNS coordinate autonomic, endocrine and behavioural responses to environmental challenges. HRV especially the parasympathetic component indexes this central nervous system-autonomic nervous system integration and consequently is a psychophysiological marker for adaptive emotional regulation[27].

Childhood psychopathology and HRV

Externalizing disorders of childhood and HRV: Mezzacappa et al in a study of HRV in adolescent males found that antisocial behaviour was associated with deficient modulation of vagally mediated phasic respiratory effects on heart rate.[45] In a related study in male children and adolescents problems with impulse control were associated with decreased vagal component of HRV.[46] In a study of 7-11 years old younger brothers of adjudicated delinquents at risk for delinquency, Pine et al observed that continuous measures of both externalizing and internalizing psychopathology were associated with decrements in vagal components of HRV.[47] These associations were independent of other potential confounders such as age, ethnicity, social class, body size or family history of hypertension. While the study was on high risk subjects, the sample did include children who had obtained high scores on Childhood Behaviour Checklist (CBCL) indicative of significant psychopathology.

Literature suggests that problems with behavioural modulation especially deficits in executive and motivational control appear to be linked to conduct disorder.[48,49] In a study that assessed executive and motivational influences on motor behaviour in 10 year old children,

competence in executive control was associated with greater vagal modulation of HRV.[50] This finding is consistent with earlier observations that antisocial adolescents had deficiencies in both executive control and parasympathetic modulation of HRV.[45] Studies by Porges and colleagues had suggested that vagal modulation of HRV is closely associated with attentional regulation. In clinical samples of children with attention deficit hyperactivity disorder, there was an association of HRV and poor performance on continuous performance tasks.[51] Similar association between reduced HRV especially the vagal component and poorer performance on attentional tasks was observed in 7-12 year old boys exposed in utero to opiates and alcohol.[52] Thus, a variety of behavioural problems and externalizing psychopathology in children and adolescents are associated with deficiencies in vagal component of HRV.

Internalizing disorders of childhood and HRV: While studies of HRV in adult patients with anxiety and depressive disorders have shown decreased cholinergic modulation to the heart,[53,54] studies in childhood emotional disorders and HRV are only beginning to emerge.[55] Mezzacappa et al in a study of 15-year old boys reported that anxiety, based on self-report and ratings obtained from mothers and teachers, was associated with postural induced change in measures of HRV.[43] The authors interpreted their findings as suggestive of heightened sympathetic mediation of HRV in adolescents with anxiety. In contrast, in a study of boys at risk for delinquency, a continuous measure of internalizing psychopathology was associated with decreased HRV mainly in the parasympathetic component.[47] While the aforementioned studies were conducted on non-clinical samples, Monk et al studied 22 children (9-18 years) meeting DSM-IV criteria for various anxiety disorders (separation anxiety disorder, overanxious disorder, panic disorder/ panic attacks, and social phobia) using standardized parent and child interviews and 12 normal children.[56] The investigators used 15 minutes of exposure to 5% CO_2, a stressor known to increase anxiety in patients with anxiety disorders. Anxious children had higher and less fluctuating heart rate at baseline. In addition, children with anxiety disorders showed less change in HRV especially in high frequency power as opposed to healthy controls who exhibited a significant decrease in HRV in the initial phases of CO_2 inhalation. These findings suggest that children with anxiety disorders fail to modulate appropriately the vagal component of HRV when faced with an environmental challenge. This is in agreement with earlier observations that inappropriate vagal modulation in the face of environmental demand is predictive of maladaptive behaviour.[30]

While the aforementioned studies have all used linear measures of HRV, increasingly investigators have begun to employ non-linear measures of HRV in addition to routine linear measures of HRV. In a small study, a significant decrease in a non-linear measure of HRV was observed in children with anxiety disorders (n=7) compared to controls, while linear measures of HRV did not differentiate the groups.[57] The authors interpreted their findings as suggestive of a decrease in vagal function as the Largest Lyapunov Exponent (a non-linear measure used in the study) is diminished by atropine blockade.[58] Similarly, children of parents with panic disorder (who are at an increased risk for developing anxiety syndromes) had significantly lower LLE compared to children of controls.[59] Thus, data from clinically ill population lends support to the earlier findings that vagal modulation of HRV indexes responses to environmental demands and is consistent with clinical observations of maladaptive behavioural patterns seen across diverse situations in children and adolescents with psychopathology[60].

Studies reviewed here suggest that alteration in autonomic functions as indexed by HRV is implicated in a variety of psychiatric conditions. This is consistent with the view advanced by Porges and colleagues that HRV especially the vagal component reflect

attentional and emotional regulation, which are implicated in. diverse childhood psychiatric conditions. Findings of reduced HRV and psychopathology across the life span suggest that both may be influenced by similar neurobiological mechanisms such as alterations in limbic system.[33]

Pharmacological treatment in childhood disorders and HRV

Cardiovascular side effects of antidepressant medication including reports of sudden death in children being treated with medication is of great concern.[61,62] Walsh et al noted that desimipramine reduced both low frequency and high frequency components of HRV in subjects younger than 30 years of age.[63] These findings were replicated in another study with tricyclic antidepressant use resulting in a significant decrement in vagal component of HRV.[64] In a more recent study using both linear and non-linear measures of HRV, imipramine even in small doses significantly decreased vagal component of HRV in children who were being treated for enuresis.[65] The effect of medication on measures of HRV in these studies was independent of confounders such as age and psychopathology. As autonomic maturation proceeds at different rates in different children some children may be at greater risk for developing adverse cardiac events on exposure to tricyclic antidepressants.[64] In addition, children with anxiety disorders may be particularly vulnerable to cardiac side effects of tricyclic antidepressants as anxiety is associated with altered cardiac autonomic regulation.[55] These findings assume importance as several studies have suggested an association between decreased HRV and an increased risk for cardiovascular morbidity in adults and children with heart disease.[66-68]

Implications of altered HRV in childhood psychopathology

Studies in adults have implicated various negative affective dispositions such as anger, anxiety, depression and hostility as risk factors for coronary artery disease and cardiac mortality.[69-71] One of the potential mechanisms that link negative affective states and risk for cardiovascular morbidity is altered cardiac autonomic regulation. Considerable evidence exists that decreased HRV especially in the parasympathetic component is associated with an increased risk for cardiovascular morbidity and mortality in adults and children with heart disease[66-68]. Similar associations of decreased HRV in children with emotional and behavioural problems suggest that altered cardiac autonomic regulation during childhood indicates later risk for cardiovascular morbidity. Thus, pathogenesis of coronary artery disease and hypertension may have its origins in childhood.[72,73] A number of studies have shown an association between behavioural profiles in childhood and adolescence and future cardiovascular funtioning[74,75].

The study of autonomic regulation in childhood psychiatric disorders may have important implications for the understanding of etiology and prevention of cardiovascular diseases in adults.[76] Early identification and treatment of negative affective states in childhood may reduce risk for future cardiovascular disease. In a study of middle school students, subjects trained in emotional self-management skills exhibited significantly increased HRV during recovery from stress compared to controls.[77] As decreased vagal function may antedate the onset of several risk factors in relation to cardiovascular illness,[78] enhancing cardiac vagal functioning may positively impact negative affective states,[79,80,81] and confer cardiovascular health benefits.[82,83] More intervention studies targeting children with risky behavioural patterns such as impulsivity, hostility and aggression and those with internalizing pathology are needed to examine the impact on health and behaviour. Future

studies should explore the influence of psychological variables such as attachment status, and parent-child relationship because of their impact on emotional regulation and health.[84,85]

REFERENCES

1. Manssis K. Childhood anxiety disorders: lessons learnt from the literature. Can J Psychiatry 2000; 45:724-730.
2. Keller MB, Lavori PW, Wunder J, Beardslee WR, Scwartz CE, Roth J. Chronic course of anxiety disorders in children and adolescents. J Am Acad Child Adolesc Psychiatry. 1992; 31:595-599.
3. Battaglia M, Bertella S, Politi E, Bernardeschi L, Perna G, Gabriele A, et al. Age at onset of panic disorder: influence of familial liability to the disease and of childhood anxiety disorder. Am J Psychiatry 1995; 152: 1362-1364.
4. Biederman J, Faraone SV, Hirshfeld-Becker DR, Friedman D, Robin JA, Rosenbaum JF. Patterns of psychopathology and dysfunction in high risk children of parents with panic disorder and major depression. Am J Psychiatry 2001; 158:49-57.
5. Bhat A, Srinivasan K. Psychopathology in adolescent offspring of parents with depression and panic disorder. J Indian Assoc Child Adolesc Mental Health 2006; 2:100-107.
6. Aronen ET, Kurkela SA. Long-term effects of an early home-based intervention. J Am Acad Child Adolesc Psychiatry 1996; 35:1665-1672.
7. Pine DS, Coplan JD, Papp LA, Klein RG, Martinez JM, Kovalenko P, et al. Ventilatory physiology of children and adolescents with anxiety disorders. Arch Gen Psychiatry 1998; 55:123-129.
8. Granger DA, Serbin LA, Scwarzman AE, Lehoux P, Cooperman J, Ikeda S. Children's salivary cortisol, internalizing behaviour problems, and family environment: results from the Concordia Longitudinal Risk Project. Int J Behav Dev 1998; 22:707-728.
9. Rowe DC, Stever C, Gard JM, Cleveland HH, Sanders ML. The relation of the dopamine transporter gene (DAT 1) to symptoms of internalizing disorders in children. Behav Genetics 1998; 28:215-225.
10. Mathews KA, Woodall KL, Stoney CM. Changes in and stability of cardiovascular responses to behavioural stress: results from a four-year longitudinal study of children. Child Dev 1990; 61:1134-1144.
11. Murphy JK, Alpert BS, Walker SS, Wiley ES. Children's cardiovascular reactivity: stability of racial differences and relation to subsequent blood pressure over a one-year period. Psychophysiology 1991; 28:447-457.
12. Kindlon DJ, Tremblay RE, Mezzacappa E, Earls F, Laurent D. Longitudinal patterns of heart rate and fighting behaviour in 9-12 year old boys. J Am Acad Child Adolesc Psychiatry 1995; 34:371-377.
13. Rogeness GA, Cepeda C, Macedo CA, Fischer C, Harris WR. Differences in heart rate and blood pressure in children with conduct disorder, major depression, and separation anxiety. Psychiatr Res 1990; 33:199-206.
14. Tremblay RE, Pihl RO, Vitaro F, Dobkin PL. Predicting early onset of male antisocial behaviour from preschool behaviour. Arch Gen Psychaitry 1994; 51:732-739.
15. Raine A, Venables PH, Williams M. Autonomic orienting responses in 15-year old male subjects and criminal behaviour at age 24 years. Arch Gen Psychaitry 1990; 47:1003-1007.
16. Bernston GG, Cacioppo JT, Quigley KS, Fabro VT. Autonomic space and psychophysiologic response. Psychophysiology 1994; 31:44-61.
17. Mezzacappa E, Kindlon D, Earls F, Saul JP. The utility of spectral analytic techniques in the study of the autonomic regulation of beat-to-beat heart rate variability. Int J Methods Psychiatr Res 1994; 4:29-44.
18. Schore AN: Attachment and the regulation of the right brain. Attachment Hum Dev 2000; 2:23-47.
19. Srinivasan K, Sucharita S, Vaz M. Effect of standing on short-term heart rate variability across age. Clinical Physiol Functional Imaging 2002; 22:404-408.
20. Akselrod S, Gordon D, Ubel FA, Shannon DC, Barger AC, Cohen RJ. Power spectrum analysis of heart rate fluctuation: a quantitative probe of beat-to-beat cardiovascular control. Sci 1981; 213:220-222.
21. 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: 1043-1065.
22. Kingwell BA, Thompson JM, Kaye DM, McPherson GA, Jennings GL, Esler MD. Heart rate spectral analysis, cardiac norepinephrine spillover, and muscle sympathetic nerve activity during human sympathetic nervous activation and failure. Circulation 1994; 90:234-240.

23. Furlan R, Guzzetti S, Crivellaro W, Dassi S, Tinelli M, Baelli G, et al. Continuous 24-hour assessment of the neural regulation of systemic arterial pressure and RR variabilities in ambulant subjects. Circulation 1990; 81:537-547.
24. Eckberg DL. Sympathovagal balance: a critical appraisal. Circulation 1997; 96:3224-3232.
25. LeDoux JE. Emotion: clues from the brain. Annual Rev Psychol 1995; 46:209-235.
26. Lane RD, Reiman EM, Ahern GL, Thayer JF. Activity in medial frontal cortex correlates with vagal component of heart rate variability during emotion. Brain Cog 2001; 47:97-100.
27. Thayer JF, Lane RD. A model of neurovisceral integration in emotion regulation and dysregulation. J Affect Disord 2000; 61:201-216.
28. Porges SW: Orienting in a defensive world: mammalian modifications of our evolutionary heritage. A polyvagal theory. Psychophysiol 1995; 32:301-318.
29. Porges SW: Vagal tone: A physiologic marker of stress vulnerability. Pediatrics 1992; 90:498-504.
30. Porges SW, Doussard-Roosevelt JA, Portales AL, Greenspan SI. Infant regulation of the vagal "brake" predicts child behavior problems: A psychobiological model of social behavior. Dev Psychobiol 1996; 29:697-712.
31. Kagan J, Reznick S, Snidman N. The physiology and psychology of behavioural inhibition in children. Child Dev 1987; 58:1459-1473.
32. Reznick JS, Kagan J, Snidman N, Gersten M, Baak K, Rosenberg A. Inhibited and uninhibited behaviour: a follow-up study. Child Dev 1986; 57:660-680.
33. Kagan J, Reznick JS, Snidman N. Biological bases of childhood shyness. Sci 1988; 240:161-171.
34. Kagan J, Snidman N. Temperamental factors in human development. Am Psychologist 1991; 46:856-862.
35. Donzella B, Gunnar MR, Krueger WK, Alwin J. Cortisol and vagal tone responses to competitive challenge in preschoolers: associations with temperament. Dev Psychobiol 2000; 37:209-220.
36. Schmidt LA, Fox NA, Schulkin J, Gold PW. Behavioral and psychophysiological correlates of self-presentation in temperamentally shy children. Dev Psychobiology 1999; 35:119-135.
37. Fox NA, Field TM. Young children's responses to entry into preschool: psychophysiological and behavioural findings. J Appl Dev Psych 1989; 10: 527-540.
38. Eisenberg N, Fabes RA, Murphy B, Maszk P, Smith M, Karborn M. The role of emotionality and regulation in children's social functioning: A longitudinal study. Child Dev 1995; 66:1360-1384.
39. Fabes RA, Eisenberg N, Eisenbud L. Behavioral and physiological correlates of children's reactions to others in distress. Dev Psychol 1993; 29:655-663.
40. El-Sheikh M, Harger J, Whitson SM. Exposure to interparental conflict and children's adjustment and physical health: the moderating role of vagal tone. Child Dev 2001; 72:1617-1636.
41. DiPietro JA, Porges SW. Vagal responsiveness to gavage feeding as an index of preterm status. Pediatric Res 1991; 29:231-236.
42. Hofheimer JA, Wood BR, Porges SW, Pearson E, Lawson EE. Respiratory sinus arrhythmia and social interaction patterns in preterm newborns. Infant Behav Dev 1995; 18:233-245.
43. Porges SW, Lipsitt L. Neonatal responsivity to gustatory stimulation: The gustatory-vagal hypothesis. Infant Behav Dev 1993; 16:487-494.
44. Porter FL, Porges SW, Marshall RE. Newborn pain cries and vagal tone: parallel changes in response to circumcision. Child Dev 1988; 59:495-505.
45. Mezzacappa E, Tremblay RE, Kindlon D, Saul JP, Arseneault L, Segun J, et al. Anxiety, antisocial behaviour and heart rate regulation in adolescent males. J Child Psychol Psychiatry 1997; 38:457-469.
46. Allen MT, Matthews KA, Kenyon KL. The relationship of resting baroreflex sensitivity, heart rate variability and measures of impulse control in children and adolescents. Int J Psychophysiology 2000; 37:185-194.
47. Pine DS, Wasserman GA, Miller L, Coplan JD, Bagiella E, Kovelenku P, et al. Heart period variability and psychopathology in urban boys at risk for delinquency. Psychophysiology 1998; 35:521-529.
48. Moffitt T. The neuropsychology of conduct disorder. Dev Psychopathology 1993; 5:135-152.
49. Seguin JR, Pihl RO, Harden PW, Tremblay RE, Boulerice B. Cognitive and neuropsychological characteristics of physically aggressive boys. J Abnorm Psychol 1995; 104:614-624.

50. Mezzacappa E, Kindlon D, Saul JP, Earls F. Executive and motivational control of performance task behaviour, and autonomic heart rate regulation in children: physiologic validation of two-factor solution inhibitory control. J Child Psychol Psychiat 1998; 39:525-531.
51. Borger N, van der Meere J, Ronner A, Alberts E, Geuze R, Bogte H. Heart rate variability and sustained attention in ADHD children. J Abnorm Child Psychol 1999; 27:25-33.
52. Suess PE, Newlin DB, Porges SW. Motivation, sustained attention, and autonomic regulation in school-age boys exposed in utero to opiates and alcohol. Exp Clin Psychopaharmacol 1997; 5:375-387.
53. Yeragani VK, Srinivasan K, Balon R, Ramesh C, Berchou R. Lactate sensitivity and cardiac cholinergic function in panic disorder. Am J Psychiatry 1994; 151:1226-1228.
54. Carney RM, Saunders RD, Freedland KE, Stein P, Rich MW, Jaffe AS. Association of depression with reduced heart rate variability in coronary artery disease. Am J Cardiol 1995; 76:562-564.
55. Srinivasan K. Childhood anxiety disorder and heart rate variability. In Sanfelippo, AJ (Ed.). Panic disorder: New Research. New York: Nova Science Publishers 2005, pp 65-81.
56. Monk C, Kovelenko P, Ellman LM, Sloan RP, Bagiella E, Gorman JM, et al. Enhanced stress reactivity in paedriatic anxiety disorders: implications for future cardiovascular health. Int J Neuropsychopharmacology 2001; 4:199-206.
57. Yeragani VK, Rao KAR, Pohl R, Jampala VC, Balon R. Heart rate and QT variability in children with anxiety disorders. Depression Anxiety 2001; 13:71-77.
58. Hagerman I, Berglund M, Lorin M, Nowak J, Sylven C. Chaos deterministic regulation of heart rate variability in time and frequency domains: effects of autonomic blockade and exercise. Cardiovascular Res 1996; 31:410-418.
59. Srinivasan K, Ashok MV, Vaz M, Yeragani VK. Decreased chaos of heart rate time series in children of parents with panic disorder. Depression Anxiety 2002; 15:159-167.
60. Chorpita BF, Barlow DH. The development of anxiety: the role of control in the early environment. Psychol Bull 1998; 124:3-21.
61. Riddle M, Gellern B, Ryan N. Another sudden death in a child treated with desimipramine. J Am Acad Child AdolescPsychiatry 1993; 32:792-797.
62. Riddle MA, Nelson JC, Kleinman CS, Rasmusson A, Leckman JF, King RA, et al. Sudden death in children receiving Norpramin: a review of three reported cases and commentary. J Am Acad Child Adolesc Psychiatry 1991; 30:104-108.
63. Walsh BT, Giardina EGV, Sloan RP, Greenhill L, Goldfein J. Effects of desimipramine on autonomic control of the heart. J Am Acad Child Adolesc Psychiatry 1994; 33:191-197.
64. Mezzacappa E, Steingard R, Kindlon D, Saul P, Earls F. Tricyclic antidepressants and cardiac autonomic control in children and adolescents. J Am Acad Child Adolesc Psychiatry 1998; 37:52-59.
65. Srinivasan K, Ashok MV, Vaz M, Yeragani VK. Effect of imipramine on linear and nonlinear measures of heart rate variability in children. Pediatric Cardiol 2004; 25:20-25.
66. Bigger JT, Kleiger RE, Fleiss JL, Rolnitzky LM, Steinman RC, Miller JP. Components of HR variability measured during healing of acute myocardial infarction. Am J Cardiol 1988; 61:208-215.
67. Kleiger RE, Miller JP, Bigger JT, Moss AJ. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. Am J Cardiol 1987; 59:256-262.
68. Gordon D, Herrera VL, McAlpine L. Heart rate spectral analysis: a non-invasive probe of cardiovascular regulation in critically ill children with heart disease. Pediatr Cardiol 1988; 9:69-77.
69. Kawachi I, Sparrow D, Vokonas PS, Weiss ST. Symptoms of anxiety and risk of coronary artery disease. Circulation 1994; 90:2225-2229.
70. Musselman DL, Evans DL, Nemeroff CB. The relationship of depression to cardiovascular disease. Arch Gen Psychiatry 1998; 55:580-592.
71. Miller TQ, Smith TW, Turner CW, Guijarro ML, Hallet AJ. A meta analytic review of research on hostility and physical health. Psychol Bull 1996; 119:322-348.
72. Williams CL, Hayman LL, Daniels SR, Robinson TN, Steinberger J, Paridon S, et al. Cardiovascular health in childhood: a statement for health professionals from the committee on atherosclerosis, hypertension, and obesity in the young (AHOY) of the council on cardiovascular disease in the young. Am Heart Assoc Circulation 2002; 106:143-160.
73. McGill HC Jr, McMahan CA, Zieske AW, Sloop GD, Walcott JV, Troxclair DA, et al. Associations of coronary heart disease risk factors with the intermediate lesion of atherosclerosis in youth. The pathobiological determinants of atherosclerosis in youth (PDAY) research group. Arteriosclerosis Thrombosis Vascular Biol 2000; 20:1998-2004.

74. Trieber F, Turner J, Davis H, Thompson W, Levy M, Strong W. Young children's cardiovascular stress responses predict resting cardiovascular functioning 2 ½ years later. J Cardiovascular Risk 1996; 3:95-100.
75. Ewart C, Kolodner K. Negative affect, gender, and expressive style predict elevated ambulatory blood pressure in adolescents. J Pers Soc Psychol 1994; 66:596-605.
76. Jemerin J, Boyce W. Psychobiological differences in childhood stress response. II cardiovascular markers of vulnerability. J Dev Behav Pediatrics 1990; 11:140-150.
77. McCraty R, Atkinson M, Tomasino D, Goelitz J, Mayrovitz HN. The impact of an emotional self-management skills course on psychosocial functioning and autonomic recovery to stress in middle school children. Integrative Physiol Behav Sci 1999; 34:246-268.
78. Thayer JF, Lane RD. The role of vagal function in the risk for cardiovascular disease and mortality. Biol Psychol 2007; 74:224-242.
79. Sartory G, Olajide D. Vagal innervation techniques in the treatment of panic disorder. Behav Res Ther 1988: 26:431-434.
80. Murata T, Takahashi T, Hamada T, Omori M, Kosaka H, Yoshida H, et al. Individual trait anxiety levels characterizing the properties of Zen meditation. Neuropsychobiology 2004; 50:189-194.
81. Nolan RP, Kamath MV, Floras JS, Stanley J, Pang C, Picton P, et al. Heart rate variability biofeedback as a behavioral neurocardiac intervention to enhance vagal heart rate control. Am Heart J 2005; 149:1137.
82. Cohen H, Matar MA, Kaplan Z, Kotler M. Power spectral analysis of heart rate variability in psychiatry. Psychother Psychosom 1999; 68:59-66.
83. Sullivan GM, Kent JM, Kleber M, Martinez JM, Yeragani VK, Gorman JM. Effects of hyperventilation on heart rate and QT variability in panic disorder pre- and post-treatment. Psych Res 2004; 125:29-39.
84. Stevenson-Hinde J, Marshall PJ. Behavioural inhibition, heart period, and respiratory sinus arrhythmia: An attachment perspective. Child Dev 1999; 70:805-816.
85. Sceeringa MS, Zeanah CH, Myers L, Putnam F. Heart period and variability findings in preschool children with posttraumatic stress symptoms. Biol Psychiatry 2004; 55:685-691.

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