CHAPTER 7

Heart Rate Variability: Stress and Psychiatric Conditions

Gary G. Berntson PhD and John T. Cacioppo PhD

Introduction

Psychological states and processes can impact dramatically on dynamic autonomic control of the heart. The literature in this area is far from simple, however, as the effects of stress states and psychiatric conditions on heart rate variability can be diverse. The present chapter will highlight selected aspects of this literature, and consider conceptual approaches that may help organize the diverse findings in this area. Clearly, this is an issue that requires interdisciplinary approaches across multiple levels of analysis, ranging from the psychological to the biological (Cacioppo *et al.* 2000).

Central origins of psychological influences on autonomic function

Brain mechanisms for somatomotor control and coordination have been extensively studied, and the complex, multilevel, hierarchical structure of central somatic motor systems is well recognized. As early as the 19th century, the notable English neurologist, John Hughlings Jackson, emphasized the continuous evolutionary layering and re-representation of motor systems at progressively higher levels of the neuraxis (Jackson 1958). Although spinal and brainstem reflexes organize primitive motor acts and provide important postural support for more complex activities, it is the higher levels in central motor systems that allow for flexibility and adaptability in motor control, and underlie the awesome, graceful movements of an accomplished ballerina.

Historically, research and theory concerning autonomic regulation often focused on the lowest levels of central control. Although Walter Cannon clearly articulated the impact of emotion and other psychological processes on autonomic states (Cannon 1928), he viewed the autonomic nervous system largely as a homeostatic regulatory mechanism (Cannon 1929). Recent research, however, has revealed a re-representation and layering of autonomic functions from the spinal cord to rostral brain networks sufficiently similar reminiscent of those for somatomotor control that they suggest a common evolutionary heritage.

Homeostatic functions of the autonomic nervous system are illustrated by the baroreceptor-heart rate reflex, through which a perturbation in blood pressure triggers a tightly coupled, reciprocal change in the activities of the autonomic branches. Postural hypotension, for example, results in a reflexive decrease in parasympathetic control of the heart, together with a reciprocal withdrawal of sympathetic cardiac control, which synergistically increase heart rate (and contractility). Together with vascular components, these changes serve to compensate for the hypotensive perturbation and normalize blood pressure (e.g. Cacioppo *et al.* 1994). Baroreceptor reflexes are prototypic homeostatic mechanisms, and are organized largely within lower central autonomic substrates at brainstem levels. Through evolutionary development of rostral brain systems, however, these lower autonomic circuits become integrated with higher neural networks (Berntson & Cacioppo 2000).

Limbic and forebrain areas implicated in behavioural processes, including the hypothalamus, amygdala and medial prefrontal cortex, have been shown to issue monosynaptic projections to brainstem reflex networks as well as to autonomic source

E1

nuclei in the brainstem and spinal cord (for review see Berntson & Cacioppo 2000). Through these projections, higher neural processes can modulate or even bypass reflex networks and powerfully alter autonomic outflows. It is now clear that stressors, even as mild as mental arithmetic, can lead to an inhibition and/or a shift in set point of baroreceptor reflexes (Ditto & France 1990; Steptoe & Sawada 1989). Such effects reflect complex modulatory influences of rostral neural systems on lower autonomic substrates, and have necessitated expansion of the simple negative-feedback homeostatic model of autonomic control.

Autonomic space and cardiac chronotropic control

As considered above, brainstem baroreceptor reflexes have highly specific afferent (baroreceptor) inputs, and exert a rather rigid pattern of reciprocal control over the two autonomic branches, such that an increase in activity of one branch is associated with decreased activity in the other. This is apparent in the highly correlated cardiac chronotropic control exerted by the two autonomic branches during orthostatic stress (Berntson *et al.* 1994). Similarly, respiratory sinus arrhythmia is associated with reciprocal changes in the activities of the autonomic branches, which are approximately 180(out of phase. Based on findings such as these, autonomic control has often been considered to lie along a continuum with parasympathetic activation at one end and sympathetic activation at the other (see Fig. 7.1).

In contrast to this linear-continuum model of autonomic control, however, descending influences from higher neural systems are not so constrained. Rather, psychological states and processes associated with rostral neural networks can evoke reciprocal, independent, or even coactive changes in the autonomic branches (Berntson *et al.* 1991, 1993: Koizumi & Kollai 1992). The flexible nature of rostral autonomic control mandates an expansion of the linear model to a bivariate representation of autonomic space, as illustrated in Fig. 7.1.

Even in cases where rostral neural influences foster a generally reciprocal mode of autonomic control, there remain important differences from the pattern of control exerted by baroreceptor reflexes (Fig. 7.2). Selective pharmacological blockades of the autonomic branches revealed that an orthostatic challenge (change from sitting to standing) and standard psychological stressors (mental arithmetic, speech stress and a reaction time task) yield a similar pattern of reciprocal sympathetic activation and vagal withdrawal in human subjects, when considered at the group level (Berntson *et al.* 1994). The response to orthostatic stress displayed minimal individual variation, and the reciprocal changes in the autonomic branches were highly correlated across subjects. In contrast, psychological stressors, typical of those encountered in daily life, yielded wide individual differences in the mode of response, with some subjects con-

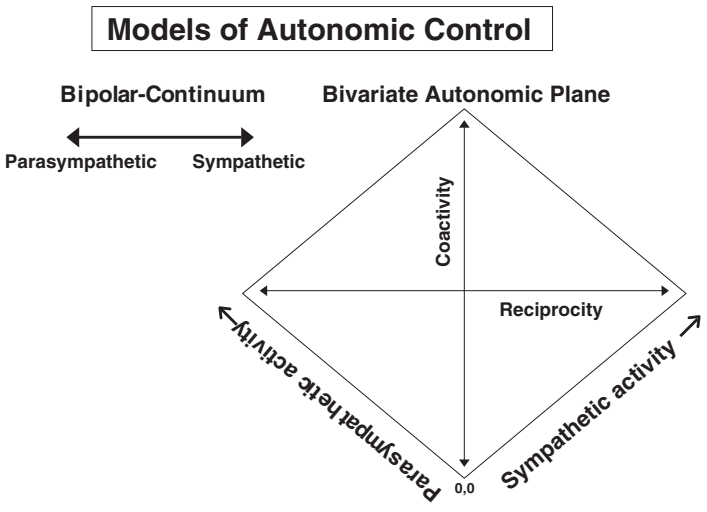

Fig. 7.1 Bivariate model of autonomic space (right), contrasted with the reciprocal bipolar-continuum model of autonomic control (left).

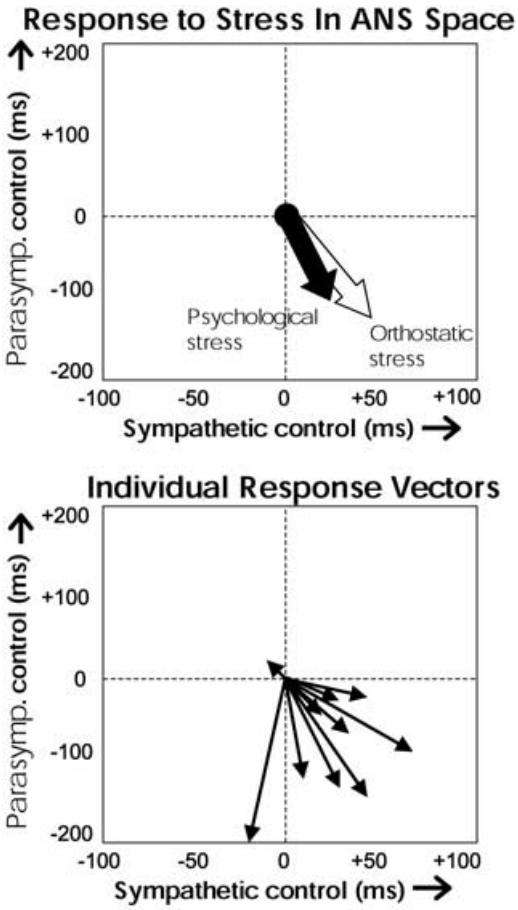

Fig. 7.2 Sympathetically and parasympathetically mediated changes in heart period in response to stress. Top panel: overall group responses to orthostatic and psychological stress. Bottom panel: in contrast to orthostatic stress, there were considerable individual differences in the response to psychological stressors, ranging from largely sympathetic activation to predominantly parasympathetic withdrawal. Arrows represent group (top) and individual (bottom) response vectors from pre-stress baseline, depicted at the intersection of the horizontal and vertical dotted lines. Response vectors were derived from single and dual pharmacological blockades of the autonomic branches (see Berntson *et al.* 1994).

sistently showing largely sympathetic activation, others primarily vagal withdrawal, and still others a reciprocal pattern of autonomic response (see Fig. 7.2). Hence, there was no significant correlation between the responses of the autonomic branches to psychological stress. This difference was not attributable to greater error variance in the response to psychological stress, as individual the response patterns were highly stable across tasks. Rather, these findings reveal that people differ in how they respond to psychological stressors (individual response uniqueness) and that these differences are relatively stable across time (individual response consistency). In contrast, these individual differences are not apparent when the stressor engages predominantly brainstem systems (e.g. orthostatic stress). This is also documented by the finding that hostility is highly correlated with the autonomic response to cognitive stressors, but not the autonomic responses to tilt (Sloan *et al.* 2001).

The complexities of rostral influences on autonomic control probably underlie the disparate literature on autonomic function in stress, anxiety, and psychiatric conditions. This should not be surprising, as behavioural manifestations also vary widely across these conditions, and indeed, even among subjects within a given condition. Consequently, it may be unrealistic to expect a simple pattern of altered autonomic control in various psychological and psychiatric states. Indeed, in addition to the individual differences outlined above, there are also differences in how people respond to distinct psychological tasks (stimulus response specificity). The tasks discussed above involve active cognitive processing and response (e.g. mental arithmetic, reaction time), and are generally associated with varied degrees of parasympathetic withdrawal and sympathetic activation. In contrast, more passive cognitive tasks, such as perceptual illusions, focused attention, or response inhibition may be accompanied by parasympathetic activation or coactivation of both the parasympathetic and sympathetic branches (Somsen *et al.* 1991; Berntson *et al.* 1996; Campbell *et al.* 1997; Jennings & Van der Molen 2002)

A meaningful understanding of the relationships between autonomic functions and cognitive processes, stress, and psychiatric conditions will depend on a greater appreciation of the role and complexity of rostral neurobehavioural systems. It is the complexity of rostral influences on autonomic control that likely contributes to the diversity in autonomic functions in stress, anxiety, and psychiatric conditions. The task confronting investigators is to identify the moderator variables underlying this diversity, and to understand their interactions and functional implications. Such moderator vari-

E1

ables can derive from three general sources: (1) contextual variables (types of tasks and their context, related to stimulus response specificity); (2) appraisal variables (how individuals appraise or interpret the condition, associated with individual response uniqueness); (3) individual differences in neural, neurochemical, and physiological variables associated with autonomic control (also related to individual response uniqueness).

Effects of stress on heart rate variability

Stressors are often associated with an increase in sympathetic cardiac control, a decrease in parasympathetic control, or both. Associated with these reactions is a frequently reported increase in low frequency (LF, centred around 0.1 Hz) heart rate variability, a decrease in high frequency (HF, 0.12 or 0.15–0.4 Hz) power, and/or an increase in the LF/HF ratio. Aspects of this general response pattern have been reported for: (a) acute laboratory psychological/cognitive stressors such as mental arithmetic, reaction time tasks, Stroop interference task, or speech stress (Berntson *et al.* 1994; Friedman *et al.* 1996; Delaney & Brodie, 2000; Hughes & Stoney 2000; Jain *et al.* 2001); (b) real-life acute stressors such as college examinations (Lucini *et al.* 2002), earthquakes (Lin *et al.* 2001), as well as typical day-to-day hassles (Sloan *et al.* 1994); and even (c) the level of chronic perceived stress associated with trait anxiety (Dishman *et al.* 2000). The Berntson *et al.* (1994) study on the autonomic effects of acute laboratory stressors, for example, reported a stress-related decrease in HF heart rate variability (LF was not quantified), associated with a significant reduction in parasympathetic cardiac control and an in sympathetic control, as revealed by selective pharmacological blockades of the autonomic branches.

Exceptions to this pattern include the forehead cold pressor manipulation (Hughes & Stoney 2000), water immersion and diving (Schipke & Pelzer 2001), and some attentional paradigms (e.g. Berntson *et al.* 1996), during which HF power may increase in both absolute and relative units. The increase in HF power in the cold pressor and immersion conditions may reflect a concurrent evocation of the dive reflex (see Gooden 1994), superimposed on a mild stress response (Friedman *et al.* 1996). In others cases, including attentional tasks, autonomic coactivation may represent an integrated response to specific cognitive reactions such as the orienting response (Quigley & Berntson 1990).

The relation of specific behavioural and psychological states to distinct patterns of autonomic control is an especially important issue for further investigation, from both the clinical and neuroscientific perspective. The construct of stress, however, is exceedingly broad and poorly defined. It is clear that no single pattern of autonomic adjustments, and associated changes in heart rate variability, will apply universally across distinct stressors. Of particular importance in future research will be a refinement in our conceptualization of stress, as well as the cognitive and behavioural responses individuals display to those stressors.

Heart rate variability in psychiatric conditions

Because psychiatric conditions derive from or impact on psychological processes, many of the issues and caveats raised above apply also to these conditions. The involvement of higher cerebral systems in psychopathological states predicts a considerable degree of complexity in the pattern of autonomic control. Space precludes a thorough consideration of autonomic function across the wide array of psychiatric states, so we limit our focus on anxiety disorders and depression, as illustrative of the impact of psychiatric states on autonomic control.

Anxiety

There is now an extensive literature on anxiety and autonomic control that documents complex links between behavioural and cardiovascular systems. Although some anxiety disorders, such as panic disorders and specific phobias, may be associated with enhanced autonomic activity or reactivity to threat-related cues, anxiety states such as generalized anxiety disorder may also be characterized by an overall diminished autonomic lability for non-threat cues (for review see Berntson *et al.* 1998). A similar diminished lability has been reported even for trauma-related material in post-traumatic stress disorder (Cohen *et al.* 2000).

A rather common finding in the literature on anxiety and autonomic control is diminished heart rate variability in anxiety disorders, especially in the

HF band (Thayer *et al.* 1996; Friedman & Thayer 1998; Cohen *et al.* 2000), which is associated with vagal control (ESC/NASPE Task Force 1996; Berntson *et al.* 1997). This has been considered to reflect a reduction in vagal control and an associated loss of autonomic 'flexibility' (Friedman & Thayer 1998; Monk *et al.* 2001). The reduction in HF variability may be reflected in diminished total heart rate variability, despite a potential selective increase in LF variability (Yeragani *et al.* 1998).

The specific origins of anxiety-related effects on autonomic function remain to be clarified, but likely relate to alterations in higher neurobehavioural systems (Hugdahl 1996; Berntson *et al.* 1998). Although simple conditioned fears can be established and maintained largely by subcortical structures (including the amygdala; LeDoux 2000), more generalized anxiety states entail an attentional focus on threat-related cues together with a response bias that likely depend on higher-level cortical/cognitive processes (for review see Berntson *et al.* 1998). In this regard, cortical regions, such as the medial prefrontal cortex, that have been implicated in anxiety are the very areas that have been shown to have direct monosynaptic projections to brainstem autonomic centres and source nuclei (see Berntson *et al.* 1998).

The specific psychological origins of the autonomic features of anxiety states remain unclear. There is considerable overlap between autonomic characteristics of anxiety and those associated with stress, which raises the possibility that some of the autonomic accompaniments of anxiety may represent features of a stress response. A salient aspect of anxiety is the attentional focus on threat-related cues, which might be expected to trigger a stress reaction. In this regard, part of the complexity in the literature may be attributable to individual differences in stress reactions as discussed above (individual response uniqueness), as well as the existence of distinct categories of anxiety disorders that may be associated with different patterns of autonomic function (stimulus response specificity). We will consider below some general research strategies for addressing these issues.

Depression

Depression has been often, but not universally, been reported to be associated with an overall reduction in total heart rate variability (Krittayaphong *et al.* 1997; Gorman & Sloan 2000; Carney *et al.* 2001; Agelink *et al.* 2002; Yeragani *et al.* 2002). This has generally been characterized by reduced HF variability, as well as other measures of vagal control of the heart (Watkins *et al.* 1999; Agelink *et al.* 2002; Yeragani *et al.* 2002), but these results also have not always been uniform (Carney *et al.* 2001).

Relations between depression and autonomic function are potentially important clinically, because depression is an independent risk factor for cardiovascular disease and for cardiac morbidity and mortality after myocardial infarction (for reviews see Gorman & Sloan 2000; Sheps & Sheffield 2001; Rugulies 2002). Moreover, decreased heart rate variability and vagal control of the heart are negative predictors of outcome after myocardial infarction (ESC/NASPE Task Force 1996; Malik 1998; La Rovere *et al.* 2001), which raises the possibility that the autonomic correlates of depression (decreased vagal and increased sympathetic control) may mediate in part the relation between depression and cardiovascular disease. Although the current picture is somewhat more complex than this, heart rate variability remains a important predictor of cardiac risk (Lombardi 2002). Conversely, HF heart rate variability is a predictor of outcome in major depressive disorders (Rottenberg *et al.* 2002).

In addition to the physiological mechanisms that underlie the relation between depression and cardiac function, which are addressed elsewhere in this volume, an important question arises as to the origin of the link between depression and heart rate variability. Depression is not a monolithic psychological state, and the relevant psychological dimensions that impact the pattern of heart rate variability have not been clearly established. A depressed mood, in and of itself, may not be the critical determinant, as depressed mood (indexed by the Beck Depression Inventory) is not necessarily accompanied by a significant decrease in basal HF heart rate variability, although it has been reported to be associated with an enhanced HF reduction to stress (Hughes & Stoney, 2000). In this regard, a reccent meta-analysis revealed that clinical depression is a stronger predictor of coronary heart disease than is merely a depressed mood (Rugulies 2002). Although the distinction between clinical depression and depressed mood may be one of magnitude or degree, they may also reflect other associ-

ated behavioural factors, such as diet, sleep patterns, or activity levels.

Alternatively, the relations between depression and heart rate variability may be mediated by other psychological factors. Anxiety, for example is a common accompaniment of depression, and Watkins *et al.* (1999) report that the level of anxiety in a depressive sample correlated with reduced vagal regulation of the heart as indexed by baroreflex cardiac control, whereas the level of depression was not predictive of either baroreflex control or HF variability. Moreover, anxiety itself is a predictor of coronary heart disease (Kubzansky *et al.* 1998), and may contribute to the relation between depression and health. In this regard, the reduced heart rate variability in depression may represent a chronic, consolidated anxiety-related response to everyday hassles and aggravations. This could have substantial health implications, to the extent to which such a response fosters a suboptimal pattern of cardiac control. There are a number of alternative routes by which psychological or behavioural factors can impact health status (e.g. see Cacioppo *et al.* 2002), and this is an exceedingly important issue for further interdisciplinary research.

Directions for further research

The relations between behavioural/psychological processes and autonomic control are intricate and complex, as the neurobehavioural systems that give rise to these relationships represent some of the most sophisticated processing systems of the brain. Psychophysiology has advanced considerably over the decades, from a relatively limited focus on peripheral end organ responses (heart rate, skin conductance, etc.) to its current appreciation of the interactions between central systems and peripheral organs, and the impact of cognitive and emotional process on these interactions.

Further progress in this area will benefit from increased interdisciplinary research, which entails an integration of multiple levels of analysis ranging from the psychological to the organ system to the cellular. One impediment to such research is what has been referred to as the category error, or the lack of one-to-one mapping between the terms, constructs and theories of the distinct levels of analysis. This is likely a contributor to the lack of isomorphism between constructs such as anxiety and depression on the one hand, and physiological functions on the other. Important in future efforts will be a refinement in the constructs at each level of analysis, as they are informed by information derived from alternative levels of analysis. This will provide for a progressive reduction of category errors, and allow for an alignment or calibration of information across levels of analysis. Of particular importance in these studies will be the elucidation of the physiological and cellular mechanisms underlying psychophysiological relations.

The studies outlined above highlight the need for a more comprehensive and realistic framework for models of central autonomic control. Especially important will be the elucidation of the interactions between these central autonomic substrates and neurobehavioural, neuroendocrine, and immune systems. Of additional importance will be a recognition of the multiple, interacting levels of functional representation in central substrates that may underlie distinct aspects of psychophysiological relations. The benefit of such interdisciplinary, multilevel analyses will be a more comprehensive understanding of the relations between the mind and body, their health significance, and means of intervention.

References

Agelink, M.W., Boz, C., Ullrich, H. & Andrich, J. (2002) Relationship between major depression and heart rate variability. Clinical consequences and implications for antidepressive treatment. *Psychiatry Research*, **113**, 139–149.

Berntson, G.G., Bigger, J.T., Eckberg, D.L. *et al.* (1997) Heart rate variability: origins, methods, and interpretive caveats. *Psychophysiology*, **34**, 623–648.

Berntson, G.G. & Cacioppo, J.T. (2000) From homeostasis to allodynamic regulation. In: *Handbook of Psychophysiology* (eds J. T. Cacioppo, L. G. Tassinary & G. G. Berntson), pp. 459–481. Cambridge University Press, Cambridge.

Berntson, G.G., Cacioppo, J T., Binkley, P.F., Uchino, B.N., Quigley, K.S. & Fieldstone, A. (1994). Autonomic cardiac control: III. Psychological stress and cardiac response in autonomic space as revealed by pharmacological blockades. *Psychophysiology*, **31**, 599–608.

Berntson, G.G., Cacioppo, J.T. & Fieldstone, A. (1996) Illusions, arithmetic, and the bidirectional modulation of vagal control of the heart. *Biological Psychology*, **44**, 1–17.

Berntson, G.G., Cacioppo, J.T. & Quigley, K.S. (1991) Autonomic determinism: the modes of autonomic control, the doctrine of autonomic space, and the laws of autonomic constraint. *Psychological Reviews*, **98**, 459–487.

Berntson, G.G., Cacioppo, J.T. & Quigley, K.S. (1993) Cardiac psychophysiology and autonomic space in humans: empirical perspectives and conceptual implications. *Psychological Bulletin*, **114**, 296–322.

Berntson, G.G., Sarter, M. & Cacioppo, J.T. (1998) Anxiety and cardiovascular reactivity: the basal forebrain cholinergic link. *Behavioural Brain Research*, **94**, 225–248.

Cacioppo, J.T., Berntson, G.G., Binkley, P.F., Quigley, K.S., Uchino, B.N. & Fieldstone, A. (1994) Autonomic cardiac control. II. Basal response, noninvasive indices, and autonomic space as revealed by autonomic blockades. *Psychophysiology*, **31**, 586–598.

Cacioppo, J.T., Berntson, G.G., Sheridan, J.F. & McClintock, M.K. (2000) Multi-level integrative analyses of human behaviour: the complementing nature of social and biological approaches. *Psychological Bulletin*, **126**, 829–843.

Cacioppo, J.T., Hawkley, L.C., Crawford, L.E. *et al.* (2002) Loneliness and health: potential mechanisms. *Psychosomatic Medicine*, **64**, 407–417.

Campbell, B.A., Wood, G. & McBride, T. (1997) Origins of orienting and defensive responses: an evolutionary perspective. In: *Attention and orienting: Sensory and Motivational Processes* (eds P. J. Lang, R. F. Simons & M. T. Balaban), pp. 41–68. Erlbaum, Hillsdale, NJ

Cannon, W.B. (1928) The mechanism of emotional disturbance of bodily functions. *New England Journal of Medicine*, **198**, 877–884.

Cannon, W.B. (1929) Organization for physiological homeostasis. *Physiological Reviews*, **9**, 399–431.

Carney, R.M., Blumenthal, J.A., Stein, P.K. *et al.* (2001) Depression, heart rate variability, and acute myocardial infarction. *Circulation*, **104**, 2024–2028.

Cohen, H., Benjamin, J., Geva, A.B., Matar, M.A., Kaplan, Z. & Kotler, M (2000) Autonomic dysregulation in panic disorder and in post-traumatic stress disorder: application of power spectrum analysis of heart rate variability at rest and in response to recollection of trauma or panic attacks. *Psychiatry Research*, **96**, 1–13.

Delaney, J.P. & Brodie, D.A. (2000) Effects of short-term psychological stress on the time and frequency domains of heart-rate variability. *Perceptual and Motor Skills*, **91**, 515–524.

Dishman, R.K., Nakamura, Y., Garcia, M.E., Thompson, R.W., Dunn, A.L. & Blair, S.N. (2000) Heart rate variability, trait anxiety, and perceived stress among physically fit men and women. *International Journal of Psychophysiology*, **37**, 121–133.

Ditto, B. & France, C. (1990) Carotid baroreflex sensitivity at rest and during psychological stress in offspring of hypertensives and non-twin sibling pairs. *Psychosomatic Medicine*, **52**, 610–620.

ESC/NASPE (European Society of Cardiology/North American Society of Pacing and Electrophysiology) Task Force (1996) Heart rate variability: standards of measurements, physiological interpretation, and clinical use. *Circulation*, **93**, 1043–1065.

Friedman, B.H. & Thayer, J.F. (1998) Anxiety and autonomic flexibility: a cardiovascular approach. *Biological Psychology*, **47**, 243–263.

Friedman, B.H., Thayer, J.F. & Tyrrell, R.A. (1996) Spectral characteristics of heart period variability during cold face stress and shock avoidance in normal subjects. *Clinical Autonomic Research*, **6**, 147–152.

Gooden, B.A. (1994) Mechanism of the human diving response. *Integrative Physiological and Behavioural Science*, **29**, 6–16.

Gorman, J.M. & Sloan, R.P. (2000) Heart rate variability in depressive and anxiety disorders. *American Heart Journal*, **140**, 77–83.

Hugdahl, K. (1996) Cognitive influences on human autonomic nervous system function. *Current Opinion in Neurobiology*, **6**, 252–258.

Hughes, J.W. & Stoney, C.M. (2000) Depressed mood is related to high-frequency heart rate variability during stressors. *Psychosomatic Medicine*, **62**, 796–803.

Jackson, J.H. (1958) Evolution and dissolution of the nervous system (Croonian Lectures). In: *Selected writings of John Hughlings Jackson*, Vol. 2 (ed. J. Taylor), pp. 45–63. Basic Books, New York [original work published in 1884].

Jain, D., Joska, T., Lee, F.A., Burg, M., Lampert, R. & Zaret, B.L. (2001) Day-to-day-reproducibility of mental stress-induced abnormal left ventricular function response in patients with coronary artery disease. *Journal of Nuclear Cardiology*, **8**, 347–355.

Jennings, J.R. & Van der Molen, M.W. (2002) Cardiac timing and the central regulation of action. *Psychological Research*, **66**, 337–349.

Koizumi, K. & Kollai, M. (1992) Multiple modes of operation of cardiac autonomic control: development of the ideas from Cannon and Brooks to the present. *Journal of the Autonomic Nervous System*, **41**,19–28.

Krittayaphong, R., Cascio, W.E., Light, K.C. *et al.* (1997) Heart rate variability in patients with coronary artery disease: differences in patients with higher and lower depression scores. *Psychosomatic Medicine*, **59**, 231–235.

Kubzansky, L.D., Kawachi, I., Weiss, S.T. & Sparrow, D. (1998) Anxiety and coronary heart disease: a synthesis of epidemiological, psychological, and experimental evidence. *Annals of Behavioural Medicine*, **20**, 47–58.

La Rovere, M.T., Pinna, G.D., Hohnloser, S.H. *et al.* (2001) Baroreflex sensitivity and heart rate variability in the identification of patients at risk for life-threatening arrhythmias: implications for clinical trials. *Circulation*, **103**, 2072–2077.

LeDoux, J.E. (2000) Emotion circuits in the brain. *Annual Review of Neuroscience*, **23**,155–184.

Lin, L-Y., Wu, C-C., Liu, Y-B., Ho, Y-L., Liau, C-S. & Lee, Y-T. (2001) Derangement of heart rate variability during a catastrophic earthquake: a possible mechanism for increased heart attacks. *Journal of Pacing and Clinical Electrophysiology*, **24**, 1596–1601.

Lombardi, F. (2002) Clinical implications of present physiological understanding of HRV components. *Cardiac Electrophysiology Review*, **6**, 245–249.

Lucini, D., Norbiato, G., Clerici, M. & Pagani, M. (2002) Hemodynamic and autonomic adjustments to real life stress conditions in humans. *Hypertension*, **39**, 184–188.

Malik, M. (1998) Heart rate variability. *Current Opinion in Cardiology*, **13**, 36–44.

Monk, C., Kovelenko, P., Ellman, L.M., Sloan, R.P., Bagiella, E., Gorman, J.M. & Pine, D.S. (2001) Enhanced stress reactivity in paediatric anxiety disorders: implications for future cardiovascular health. *International Journal of Neuropsychopharmacology*, **4**, 199–206.

Quigley, K.S. & Berntson, G.G. (1990) Autonomic origins of cardiac responses to non-signal stimuli in the rat. *Behavioural Neuroscience*, **104**, 751–762.

Rottenberg, J., Wilhelm, F. H., Gross, J.J. & Gotlib, I.H. (2002) Respiratory sinus arrhythmia as a predictor of outcome in major depressive disorder. *Journal of Affective Disorders*, **71**, 265–272.

Rugulies, R. (2002) Depression as a predictor for coronary heart disease. A review and meta-analysis. *American Journal of Preventive Medicine*, **23**, 51–61.

Schipke, J.D. & Pelzer, M. (2001) Effect of immersion, submersion, and scuba diving on heart rate variability. *British Journal of Sports Medicine*, **35**, 174–180.

Sheps, D.S. & Sheffield, D. (2001) Depression, anxiety, and the cardiovascular system: the cardiologist's perspective. *Journal of Clinical Psychiatry*, **62** (Suppl. 8), 12–16.

Sloan, R.P., Bagiella, E., Shapiro, P.A. *et al.* (2001) Hostility, gender, and cardiac autonomic control. *Psychosomatic Medicine*, **63**, 434–440.

Sloan, R.P., Shapiro, P.A., Bagiella, E. *et al.* (1994) Effect of mental stress throughout the day on cardiac autonomic control. *Biological Psychology*, **37**, 89–99.

Somsen, R.J., Molenaar, P.C., Van der Molen, M.W. & Jennings, J.R. (1991) Behavioural modulation patterns fit an animal model of vagus–cardiac pacemaker interactions. *Psychophysiology*, **28**, 383–399

Steptoe, A. & Sawada, Y. (1989) Assessment of baroreceptor reflex function during mental stress and relaxation. *Psychophysiology*, **26**,140–147.

Thayer, J.F., Friedman, B.H. & Borkovec, T.D. (1996) Autonomic characteristics of generalized anxiety disorder and worry. *Biological Psychiatry*, **39**, 255–266.

Watkins, L.L., Grossman, P., Krishnan, R. & Blumenthal, J.A. (1999) Anxiety reduces baroreflex cardiac control in older adults with major depression. *Psychosomatic Medicine*, **61**, 334–340.

Yeragani, V.K., Roose, S., Mallavarapu, M., Radhakrishna, R.K. & Pesce, V. (2002) Major depression with ischaemic heart disease: effects of paroxetine and nortriptyline on measures of nonlinearity and chaos of heart rate. *Neuropsychobiology*, **46**, 125–135.

Yeragani, V.K., Sobolewski, E., Igel, G. *et al.* (1998) Decreased heart-period variability in patients with panic disorder: a study of Holter ECG records. *Psychiatry Research*, **78**, 89–99.