REVIEW

AUTONOMIC BALANCE REVISITED: PANIC ANXIETY AND HEART RATE VARIABILITY

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Abstract—The analysis of heart rate variability (HRV) is becoming widely used in clinical research to provide a window into autonomic control of HR. This technique has been valuable in elucidating the autonomic underpinnings of panic disorder (PD), a condition that is marked by reports of heart palpitations. A body of research has emerged that implicates a relative reduction in HRV and cardiac vagal tone in PD, as indicated by various HRV measures. These data are consistent with the cardiac symptoms of panic attacks, as well as with developmental evidence that links high vagal tone with enhanced attention, effective emotion regulation, and organismic responsivity. Implications of these findings for nosology and pathophysiology are discussed. Reports of reduced HRV in PD contrast with portrayals of excess autonomic lability in anxiety. This contradiction is addressed in the context of traditional homeostatic models versus a systems perspective that views physiologic variability as essential to overall stability. © 1998 Elsevier Science Inc.

Keywords: Autonomic nervous system; Heart rate variability; Panic disorder.

INTRODUCTION

The enigma of *panic anxiety*[1] has been the subject of extensive investigation since Da Costa's landmark study of the "irritable heart" in the 1870s [1]. The literatures of medicine, psychiatry, and psychology are rich with reports of this syndrome, which is marked by dramatic, unexpected episodes of intensely disturbing somatic symptoms that are accompanied by feelings of extreme fear. Recurrent incidents of these *panic attacks* are the primary defining feature of panic disorder (PD; see Table 1 for glossary of abbreviated terms) [2]. Numerous labels have been historically used to describe these phenomena such as "nervous heart," "cardiac neurosis," "functional cardiovascular disorder," or its most common variants, "neurocirculatory asthenia" (NCA) and "anxiety neurosis" [3], and it is likely that many cases now designated as PD were subsumed by these diagnoses [4].

The most frequently reported symptoms in panic attacks are palpitations and tachycardia [5]. Other commonly reported features include sweating, shaking, shortness of breath, and chest pains; collectively, these signs suggest autonomic nervous system (ANS) disturbances. As such, investigators have probed the ANS for

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[1] The term "panic anxiety" will be used in this article to collectively refer to PD and syndromes with similar symptomology that were historically designated as "anxiety neurosis," NCA, etc.

aberrations but have yet to uncover a consistent, specific autonomic marker of panic anxiety [6].

An emerging methodology for the study of autonomic activity in psychopathology involves the analysis of HR variability (HRV) [7]. This technique has been very informative with regard to the ANS underpinnings of various clinical disorders, and has also provided insights into the psychophysiology of attention and emotion. HRV indices appear to hold particular promise in the study of ANS activity in panic anxiety. In the present study, research in this area will be reviewed with the aim of advancing an integrative psychosomatic model of panic. A number of relevant themes will be covered, including: (1) previous theories of ANS activity in panic, both specific and general, (2) the relationship of response variability to organismic stability, (3) HRV analysis and its application to PD, (4) HRV and possible developmental antecedents of panic, (5) HRV and the nosology of anxiety, and (6) potential links among panic, HRV, and pathophysiology. In conclusion, a systems-oriented psychophysiological model of panic anxiety will be offered to unite these realms of inquiry.

SYMPATHETIC/ADRENERGIC DYSFUNCTION

The salience of tachycardia in panic attacks has long stimulated a focus on sympathetic nervous system (SNS) disturbances in vulnerability to these episodes. Based on findings of exaggerated responses to epinephrine, early investigators hypothesized an unstable, hypersensitive SNS [8]. Aberrant vagal activity was also considered but discounted when responses to atropine appeared to be normal in NCA patients [9]. However, these conclusions were later dismissed on methodological grounds [10].

Cannon's model of unified SNS activation in fear [11] was the cornerstone of many theories concerning somatic disturbances in NCA. These symptoms bear a

Table I.—Glossary of abbreviated terminology

Anxiety-related conditions
  GAD: generalized anxiety disorder
  NCA: neurocirculatory asthenia
  PD: panic disorder

General physiological descriptors
  ANS: autonomic nervous system
  CNS: central nervous system
  SNS: sympathetic nervous system

Cardiovascular terms and indices
  BP: blood pressure
  CV: cardiovascular
  CVD: cardiobascular disease
  ECG: electrocardiogram
  HR: heart rate
  HRV: heart rate variability
  HF: high frequency component of the power spectrum of the ECG (putative vagal index
    that reflects respiratory modulation of HR [~0.25 Hz])
  LF: low frequency component of the power spectrum of the ECG (putative sympathetic
    index that reflects baroreceptor-mediated BP rhythms in HR [~0.10 Hz]
  LF/HF: ratio measure of cardiac autonomic "balance"
  VPC: ventricular premature contraction

striking resemblance to the constellation of reactions that Cannon described as the normal situational response in fear. Thus, it was presumed that recurrent bouts of fear caused periodic discharges of sympathetic activity in the NCA patient who was presumed to be emotionally hypersensitive [10, 12]. In accord with Cannon's model, it was generally held that the locus of dysfunction was in the central (CNS) rather than peripheral nervous system; that is, the hypothalamus was chronically stimulated by fear, which led to frequent provocation of the unified SNS response.

The role of epinephrine in anxiety was considered by Breggin who advanced a theory that integrated central, peripheral, and learned factors [13]. He proposed that the dominant feature of the CNS response in anxiety is stimulation of the release of peripheral epinephrine, which generates the somatic symptoms of panic. These symptoms become associated with anxious feelings and augment the subjective and sympathomimetic aspects of panic, and reinforce future attacks. Furthermore, environmental cues can contribute to an anxious interpretation of the somatic symptoms. Thus, this model synthesized the Cannon, James–Lange [14], and Schachter–Singer [15] views of emotion.

Developments in the study of neurotransmission led to the decline of epinephrine studies and a refocusing on the role of specific adrenergic receptors in panic anxiety. Pitts hypothesized peripheral beta-adrenergic hypersensitivity in panic, based on findings of excess responsivity to beta-agonists [16], and anxiolytic effects of beta-blockers [17]. However, subsequent research has generally shown beta-blockade to be ineffective in panic, and has actually implicated decreased, rather than increased, beta-adrenergic sensitivity [18].

Another strategy has been to explore noradrenergic functioning in the CNS via the use of alpha-2 adrenergic receptor agonists and antagonists [19]. This approach is based on the key role these receptors play in noradrenergic regulation in the locus ceruleus, a critical structure in the neurophysiology of anxiety [20]. Although suggestive evidence of noradrenergic dysfunction in PD has accrued, there are some concerns about the specificity of these inferences. One problem is that noradrenergic regulation in the brain involves the interaction of a variety of receptors in addition to alpha-2, such as alpha-1, beta-adrenergic, cholinergic, dopaminergic, and serotonergic types [18, 19]. Furthermore, the neuroanatomical substrate of anxiety is thought to include a complex of structures that includes the septal area, hippocampus, and raphe nuclei, in addition to the locus ceruleus and hypothalamus [20]. Hence, conclusions regarding discrete receptors or neural structures are potentially misleading.

Pharmacologic manipulation, the most common methodology in this line of research, is beset with confounds. It is difficult to disentangle the influences of the experimental situation and cognitive and conditioned responses to induced peripheral symptoms from direct pharmacologic effects on central anxiety systems [21]. An additional concern is the potential distortion of sympathovagal and alpha–beta-adrenergic interactions in cardiovascular (CV) control by pharmacologic blockade [22, 23].

Broadly speaking, the reductionist practice of equating psychopathology with specific neurotransmitter dysfunctions has significant limitations that have been well articulated in the literature [24–26]. In general, these criticisms are grounded in the notion that clinical disorders emerge from a richly interconnected matrix of biopsychosocial variables. These concerns are particularly germane when considering the

etiology of heterogeneous syndromes such as PD [27, 28]. An alternative tack is to adopt a broad purview of ANS activity. Although this approach has its own problems, it can offer a systems perspective of the autonomic underpinnings of panic anxiety.

GLOBAL AUTONOMIC CHARACTERIZATIONS

The major drawback to global autonomic depictions is that they overlook the complexity of ANS functioning [29, 30]. Thus, phrases such as "autonomic reactivity", which imply mass action, oversimplify and potentially misrepresent ANS activity. Nevertheless, these notions are still frequently found in the literature, probably due to the pervasive influence of models such as Cannon's "fight-or-flight" [11], and generalized activation theory [31].

One such portrayal that has been linked with panic anxiety is chronic autonomic hyperarousal, based on findings of elevated tonic HR and skin conductance and diminished response habituation in these variables [32–38]. It has been speculated that a persistent hyperadrenergic state lowers the threshold to ANS symptoms of panic [39]. Lader additionally proposed that high ANS arousal impairs habituation, which leads to a positive feedback loop of further ANS arousal, and that overarousal extends to the somatic and central nervous systems [38]. However, these notions are challenged by reports of no tonic elevations of CV activity in panic [40–44].

Alternatively, autonomic hyperreactivity has been linked with panic susceptibility. In this conceptualization, the ANS is seen as overly responsive to stimuli, rather than having a high tonic level of activity. The hypersensitivity model is buttressed by reports of large ANS responses to anxiogenic stimuli and laboratory challenge tasks in panickers [43–45], as well as dramatic elevations in CV activity that have been observed during panic attacks [39, 46, 47]. Yet, the literature is also replete with reports of normal reactivity levels in panickers and panic episodes [33, 37, 41, 48, 49].

A variety of explanations have been offered for these inconsistencies. As was observed in regard to receptor studies, elevated activity in peripheral ANS measures may be an artifact of the experimental environment [40, 42]. Clinical biases may lead to contradictions between case reports and ambulatory studies [48], and the CV elevations associated with panic may be too transitory to result in elevations in mean levels [50]. Moreover, many theoretical positions downplay the role of actual physiological aberrations and underscore psychological factors such as heightened sensitivity to bodily sensations, catastrophic misinterpretation of these sensations, fear of these sensations, or sensations serving as unconditioned stimuli [51].

The diversity of theories and abundance of conflicting data on ANS activity in panic can be both bewildering and overwhelming. In view of the heterogeneous nature of this syndrome, as well as the phenomenology of symptoms that seem to appear "out of the blue," this dilemma is not surprising. However, a systems model can be valuable by supplying unifying principles toward a broad apprehension of ANS activity in panic anxiety. Systems theory seeks to discover natural laws that are applicable across multiple levels of analysis [52, 53]. This concept is extended in nonlinear dynamical systems, in which parallels in structure and processes over manifold scales are called *fractals* [54]. Striking similarities in functioning at progressively higher degrees of CNS functioning have been noted [55], and clear corre-

spondences are evident at hierarchically increasing levels of complexity in nature, specifically in regard to anxiety [56]. Hence, variability in a single fundamental parameter of a system can potentially yield information about the overall integrity of the system, and HRV changes may specifically signal impairment at multiple levels of the neurocardiac axis [7, 54]. It will be demonstrated here that HRV analysis can be viewed from this framework of "self-similarity" across levels of analysis, and that this approach offers an alternative view of response variability in panic anxiety.

ANXIETY AND EXCESS AUTONOMIC LABILITY

Another popular class of models suggests that anxiety is marked by excess autonomic variability; that is, the ANS is in chronic fluctuation from a steady homeostatic state. In various formulations, this instability is seen as the source of persistent novel stimuli to the CNS, which responds to this input with fear [57], or that frequent somatic oscillations lead to increased perception of bodily sensations, which are then catastrophically misinterpreted [32]. Scattered reports of elevated HRV in panickers support the plausibility of these models [32, 34, 37, 39[2]].

One of the most visible of these representations has been Eysenck's notion of excess autonomic lability in anxiety [58, 59]. In this model, anxiety is viewed as an amalgam of neuroticism and introversion. Neuroticism is characterized by emotional and autonomic lability, both of which are presumably related to an overly responsive limbic system. Connections among the hypothalamus, reticular activating system, and cortex are said to account for a generalized state of overarousal and chronic excess autonomic and affective hyperactivity in "labile" individuals such as anxious neurotics.

Though this model has been undeniably influential and generative, it also has been challenged on a number of bases. Gray's theory posits that anxiety is rooted in the activation of the behavioral avoidance system, which in turn is regulated by the septohippocampal network [20]. His work has challenged both the neuropsychology and dimensional representation of Eysenck's model [60], and the construct of autonomic lability has been further questioned on methodological and empirical grounds [61, 62]. Moreover, the concept of "excess" physiologic lability conflicts with more contemporary views of stability in biological systems as well as a growing body of research on the relationship of HRV to anxiety.

PHYSIOLOGIC VARIABILITY AND ORGANISMIC STABILITY

Cannon's classic homeostatic model depicts a stable internal environment that strives for constancy when faced with external perturbations [63]. This premise is the cornerstone of many biologic models of panic, including those in which ANS activity is held to chronically vacillate from a steady state. The unpredictable recurrence of panic attacks could logically lead to this hypothesis. However, this notion must be reconciled with alternative views of bodily regulation that stress flexible responsivity as the foundation of stability. For example, constancy in body tempera-

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[2] It should be noted that none of these studies used HRV indices capable of distinguishing among ANS sources of variability; details on such measures are supplied in a subsequent section in this article.

ture is enhanced by variability in sweat gland activity; this relationship has been labeled *heterostasis* [64]. There also are instances in which a variable range, rather than a single set point, is maintained, as is often true of body weight. This state of "steady flow" has been termed *homeorhesis* [65].

These examples bespeak a basic principle of the systems view of self-regulation: organismic stability is maintained through variability in the dynamic relationship among system elements [54, 66, 67]. Patterns of organized variability, rather than static levels, are preserved to sustain coherence in the face of constantly changing environments. As such, responsivity is seen as a multiply determined, multidirectional process that is manifested in high levels of variability. These tenets are amplified in the nonlinear dynamics view that order can emerge from apparently random fluctuations in natural processes [68]. This principle can be observed in CNS organization where ostensibly stochastic processes at hierarchically increasing levels of complexity combine to produce coherent patterns of activity [55, 69]. As such, healthy systems are generally *more* labile, and maintain "far-from-equilibrium" dynamics, and conversely, rigid regularity and low temporal complexity characterize disease states [70, 71].

AUTONOMIC REGULATION OF HEART RATE

The analysis of HRV is valuable in demonstrating the implications of complex variability in biological systems. This technique provides a window into the *homeodynamics* of CV functioning—that is, the regulatory processes that maintain CV system stability [72]. HRV data are consistent with the systems view of self-regulation because they indicate that CV health is typically reflected in complex variability rather than strict periodicity [70–78].

HRV is primarily controlled by the continuous interplay of sympathetic and vagal activity [22, 76]. Both time and frequency domain measures have been used to assess HRV, but the latter are increasingly becoming the method of choice among investigators [74, 75, 77, 78]. Specifically, spectral analysis of the electrocardiogram (ECG) is a technique that can distinguish among the intrinsic sources of HRV, as these rhythms occur at different frequencies. These variations allow for the mapping of the ECG power spectra onto indices that reflect autonomic mediation of HR. Short-term intrinsic fluctuations in HR are coupled with internal regulatory mechanisms such as respiration and blood pressure (BP) regulation [74–78]. Typically, a high-frequency (HF) respiratory component ($\sim$0.25 Hz) and a slower, low-frequency (LF) component ($\sim$0.10 Hz) due primarily to baroreceptor-mediated regulation of BP are found in the power spectrum of the ECG. Even slower rhythms (<0.04 Hz), thought to reflect temperature, blood volume, renin-angiotensin regulation, as well as circadian rhythms, are also often present, but the autonomic correlates of these oscillations are uncertain [71, 76–78].

Except at very slow breathing frequencies, the respiratory component is solely mediated by vagal (cholinergic) activity, and consequently, HF spectral power is often used as an index of cardiac vagal tone [74–78]. However, the autonomic underpinnings of the LF component are more controversial. Baroreceptor regulation of BP can be achieved through sympathetic and vagal pathways, so there is a physiologic basis for LF activity to partially reflect sympathetic activity [79, 80]. Still, a number of studies point toward the equivocality of LF power as an index of cardiac

sympathetic influences, and also suggest the presence of vagal activity in this band [81–83]. However, evidence from diverse sources such as autonomic function tests, pharmacologic blockade, psychological stress, direct ANS manipulation, and clinical studies indicates that LF power can be a valid indicator of cardiac sympathetic activity under certain conditions [75, 84–86]. Further research is necessary to clarify the environmental and individual differences factors that affect the degree of sympathetic and vagal regulation that is reflected in LF power.

Contrasts in the frequency response characteristics of adrenergic and cholinergic neurotransmission result in differential sympathetic and vagal effects on HR control [76]. Adrenergic stimulation is narrowband (it has negligible impact above 0.10 Hz) and has delay between release and target organ effect. As a consequence, this activity (which is reflected in the LF but not HF band) has limited control over beat-to-beat HRV. Furthermore, these characteristics apply to adrenergic stimulation that stems either directly from cardiac sympathetic innervation or from circulating adrenal catecholamines; both effect a "coarse," rather than "fine" tuned regulation of HR. In contrast, cholinergic activity is broad band and rapidly effective. Thus: (1) vagal influences (as reflected in HF power) dominate beat-to-beat adjustment of HR; (2) high vagal tone enhances the sensitivity of HR control; and (3) high vagal tone is generally associated with increased HRV [74–78].

The ratio of LF to HF power has been recommended by Malliani and associates to index relative levels of sympathetic and vagal activity, as opposed to using the absolute levels of either [75]. Use of this metric is supported by studies in which higher ratios (greater relative sympathetic control) have been found in states that are associated with increased sympathetic and decreased vagal activity [84, 85, 88–91]. However, the LF/HF ratio is better interpreted in conjunction with the LF and HF referents from which it is derived [91]. Finally, it should also be noted that there are limitations to the application of the classical fast Fourier transform method of spectral analysis to HRV, and the alternative autoregressive approach has been recommended as more robust to artifact and nonperiodicities in the data [74, 75, 84].

The dynamic relationship among spectral components can also be estimated by quantification of the "spectral reserve" of the CV system. A broad power spectrum with a 1/f-like frequency distribution is characteristic of a healthy HR time series [54]. Spectral reserve can be gauged by plotting the ECG spectra on double-log axes of power and frequency, and by calculating the slope of the regression line fitted to these points [73]. Flat slopes are associated with high levels of complex HR variability, and steep slopes reflect narrowband spectra, diminished HF power, and less spectral reserve. These latter attributes are the hallmarks of a rigid, unadaptable system, and steeper slopes have been associated with pathophysiology, aging, and conditions of increased sympathetic and decreased vagal activation [54, 70, 73, 85]. Alternatively, greater spectral reserve suggests a loosely coupled dynamic structure that allows for flexible responsivity.

PANIC ANXIETY AND HRV

The HRV literature discloses two distinct flaws in prevailing approaches to the examination of ANS activity in panic anxiety. First, the widespread emphasis on SNS aberrations may be misplaced in view of the import of vagal activity in HR modula-

tion. Second, the presumption of excess physiologic lability in anxiety generally conflicts with a systems perspective of variability in biological systems, and specifically with HRV research. Collectively, these points beget a prediction of low vagal tone and *reduced*, rather than elevated HRV in panic anxiety.

One aspect of this hypothesis pertains to the relationship between HRV and tachycardia. A consequence of increased sympathetic activity and decreased vagal tone is poor control of HR, which can engender a vulnerability to tachycardia [30]. Imprecision in autonomic CV control has been posited as the chief defect in syndromes such as NCA and anxiety neurosis [92]. This imbalance could be expressed as decreased HRV, diminished HF power and spectral reserve, and an increased LF/HF ratio.

In fact, a groundswell of research has emerged that has reported low HRV, decreased cardiac vagal tone, and elevated sympathetic HR control in panic anxiety. A consistent association has been found between panic and diminished HRV, reduced HF power, increased LF power, elevated LF/HF ratio, and decreased spectral reserve [93–107]. These findings have emerged from independent laboratories across a wide range of conditions that are commonly employed in studies of both panic and ANS function. Furthermore, impaired HRV has been found in both tonic (in panickers under nonpanic conditions) and phasic (during panicogenic manipulations such as hyperventilation and infusions of isoproterenol, lactate, and yohimbine) manifestations of panic. This point is significant in view of the importance of detecting physiological markers of clinical anxiety in nonepisodic states [108].

One research group has reported anomalous findings of no unusual HRV or diminished vagal tone in PD [6, 109]. Although the meaning of these discrepant findings is not entirely clear, the investigators speculate that factors such as age, fitness, and illness severity may account for inconsistencies in the literature. Such variables certainly should be taken into consideration when conducting HRV research. However, it should also be noted that spectral analysis was not conducted in these studies; rather, only the respiratory component of HRV was assessed via other techniques. Hence, there was no use of indices that reflect various aspects of the HR power spectra that have been so valuable in other studies of panic, and are used widely in the mainstream of HRV research. As such, the singularity of these negative findings must be considered against the consensus of aberrant HRV in PD that has accrued across diverse investigations and methodologies.

Collectively, the evidence for attenuated vagal tone and augmented sympathetic HR control in panic, as revealed through HRV analysis, appears to be strong. This cardiac regulatory mode impairs flexible responsivity in HR and thereby increases the risk of tachycardia, which fits well the symptomology of panic. Furthermore, this pattern has been linked with cognitive and affective functioning in developmental studies that further reinforce its connection with panic, as will be outlined in what follows.

HRV AND COGNITIVE–AFFECTIVE DEVELOPMENT

A stream of HRV research with broad implications for cognitive and affective regulation may hold particular significance for panic anxiety. Developmental evidence has shown that high levels of HRV and cardiac vagal tone are associated with

adaptive responsivity to the external environment. For example, the ability to sustain attention and avoid distraction is positively correlated with vagal tone in infants and children [110, 111]. Infants with low HRV also display impoverished stimulus responsivity and poor emotional control [112, 113]. Thus, HRV indices seem capable of assessing vital developmental aspects of self-regulatory behavior due to the capacity of HRV to reflect neural feedback mechanisms of CNS–ANS integration. A network of CNS structures serve as the foundation of these processes that organize response variability and modulate psychophysiological resources in attention and emotion [110–113].

A developmental link between low HRV and risk for adult anxiety disorders has been specifically proposed. Longitudinal studies by Kagan and colleagues have revealed a consistent pattern of high and stable HRs in behaviorally inhibited infants and children [114, 115]. These shy children are disturbed by novelty and avoid exploration of the environment. This depiction is consistent with developmental research that links low HRV with unresponsivity, distractibility, and emotional dysregulation. Furthermore, the psychophysiological concomitants of behavioral inhibition in children bear a remarkable similarity to those that have been found in adult PD. Finally, children of adults with PD are more likely to be behaviorally inhibited, and are also more prone to the development of a late-childhood anxiety disorder [114]. As such, the developmental evidence provides theoretical and empirical ties to the HRV findings in panic anxiety.

These findings also fit the considerable support for a genetic component in panic [4, 116]. It is notable that HRV differences that predict outcomes in a number of domains of functioning are found prenatally and in preterm infants [78]. Adrenergic–cholinergic balance in the CNS can affect perceptual–cognitive abilities that are molded during critical prenatal periods [117, 118]. In the overall context of the developmental research, these findings suggest that: (1) individual differences in central and peripheral autonomic balance emerge early in development; (2) these differences are reflected in HRV measures as well as in affective and cognitive domains; (3) low HRV and diminished vagal tone mark a developmental risk for adult panic anxiety *vis-à-vis* deficiencies in these abilities; and (4) these variables potentially appear to be influenced by genetic, intrauterine, or early environmental factors.

Low HRV and reduced vagal tone in infants and children are best viewed from a vulnerability–stress model of psychopathology [119]. From this perspective, psychopathology is seen as the outcome of complex interactions of genetic, physiologic, and environmental factors. Hence, low vagal tone is viewed as a biologic trait that is a predisposing risk for, but not necessarily unique to, PD. This position is in accord with recommendations that the quest for genetic markers of anxiety should be focused on broad temperamental traits such as behavioral inhibition rather than on specific anxiety disorders [120].

PANIC, NOSOLOGY AND HRV

Nosologic controversies have long been at the forefront of the anxiety literature. The importance of these issues was recognized by Freud, who coined the term *angstneurose* (anxiety neurosis) in arguing for a syndrome distinguished from NCA by its sexual etiology and symptomology [121]. This distinction provoked criticism,

and Freud's prescience was apparent in his response, which acknowledged that various combinations of hereditary, physiologic, and acquired factors could eventuate in anxiety neurosis, and that the boundaries between these factors are often blurred [122].

In the century that has passed since this debate, the mixed etiology of panic syndromes has persistently stymied researchers. Freud's label of "anxiety neurosis" was widely adopted to encompass conditions marked by diffuse anticipatory anxiety as well as acute anxiety attacks. However, this term was dropped in DSM-III in favor of two distinct entities: PD and generalized anxiety disorder (GAD) [123]. This differentiation was stimulated by Klein's "pharmacologic dissection" of symptoms in anxiety neurosis by tricyclic antidepressants [27]. PD refers to cases marked by recurrent unexpected panic attacks, and GAD describes individuals whose primary symptom is apprehensive expectation. Though Klein's initial finding has received mixed support [124, 125], the distinction between PD and GAD was retained in subsequent editions of the DSM. Yet, problematic issues remain such as the frequent comorbidity of PD with other anxiety disorders and depression [2, 5].

Do HRV indices reinforce the nosologic categories of the anxiety disorders? This issue has been addressed in several investigations from our research group. One series of studies was driven by the striking contrast between the CV symptoms of PD and blood phobia. Panic attacks are associated with increases in HR and BP, sympathetic activation and vagal withdrawal, and a general state of agitation. Alternatively, the phobic response to blood stimuli often ends in pronounced deactivation—vasovagal syncope (fainting). This reaction is diphasic; a momentary increase in HR and BP is followed by bradycardia and hypotension, which results in a loss of consciousness [108]. This response is thought to reflect sympathetic activation followed by inhibition and concomitant vagal rebound [126]. Interestingly, blood phobia has the strongest familial history of the anxiety disorders [116].

Based on these differences, we predicted that blood phobics would display greater HRV and relative cardiac vagal dominance in comparison to panickers. This hypothesis was supported in several studies of HRV under conditions of rest and various laboratory tasks, none of which elicited panic or syncope [93, 94, 100]. Panickers generally displayed reduced HRV and low vagal tone over these conditions, and spectral indices were particularly useful in distinguishing these anxiety disorders on the basis of their underlying ANS characteristics. Moreover, nonanxious controls exhibited more HRV and vagal tone than either anxiety group [93].

The thorny comparison of GAD and PD is less clear. The literature on ANS activity is less extensive in GAD than in PD, and is mostly based on traditional measures of peripheral sympathetic activity [127]. Hoehn-Saric and colleagues have not found evidence of either elevated CV or ANS activity in GAD with such measures [128–130]. However, GAD was found to be associated with a restricted range in HR and skin conductance responses, which was characterized as reduced ANS "flexibility" [127, 129]. These researchers have also reported diminished electrodermal (EDA) variability in PD [131].

There are indications that GAD and PD have comparable HRV qualities. Stressful cognitive processes and worry have been found to suppress HRV and vagal tone [83, 85, 132, 133], and worry is the hallmark of GAD [2]. We have found elevated

HR, reduced vagal tone, and decreased complex HRV in GAD subjects in comparison to nonanxious controls [99, 133]. Persistent concern about panic attacks is a defining feature of PD; this activity may have the same effect on attenuating vagal tone as worry. Thus, it is consistent that low HRV is found in both PD and GAD. Studies that directly compare these disorders on HRV measures are necessary to clarify this issue. Furthermore, such research must speak to the literature on HRV and development, as well as the relationship between vagal tone and information processing, to address questions of differential etiology and symptomology of PD and GAD.

HRV analysis has also been advanced as a means to study ANS activity in the affective disorders [7]. This approach is potentially informative in view of the frequent comorbidity of PD and depression, but the findings to date have been mixed. Decreased vagal activity in major depression (melancholic type) has been inferred from HRV indices in several studies [98, 134, 135], but was not evident in brief reactive depression [98]. Yeragani and associates found no significant HRV differences between depressed and control samples, but reported less cardiac sympathetic activation and more HRV in depression than in PD [101, 105]. "Anxious depressives" have been shown to have higher resting HRs than those with either depression or PD alone [136], although HRV was reported to be lower in melancholic depression than in "neurotic" depression (dysthymia) [135]. Delineation of subgroups appears to be important in studies of depression and HRV. Because tricyclic antidepressants can suppress HRV [134, 135], and are used to treat PD and depression, this research has both nosologic and therapeutic implications.

The study of HRV in clinical disorders seems better suited to a functional, rather than nosological, approach to psychopathology. The latter view treats each mental disorder as a discrete diagnostic entity. In contrast, the functional perspective employs a dimensional strategy that regards psychopathology as an aggregate of fundamental dysfunctions such as disturbances of affect, perception, or cognition [137]. These impairments are present in varying levels across disorders rather than being syndrome-specific. In this context, HRV measures of vagal tone and autonomic flexibility may be useful in assessing basic deficits in attention and emotion regulation by reflecting CNS organization of psychophysiological resources.

The functional approach is also consistent with evidence that anxiety and depression share a similar genetic background [138]. Further validation can be found in the "broadly patholytic" effects of antidepressants, which are effective in relieving a cluster of dysphoric symptoms across diagnostic entities [124]. A similar notion has been applied to pathophysiology; reduced HRV may be found in any "generally ill" patient and must be interpreted in a more detailed context [74]. Indeed, diminished HRV and low vagal tone have been implicated in a wide range of CVD states and neurologic dysfunctions [70–81]. As such, it is not surprising that low HRV has been found in PD, GAD, and depression, but not the highly specific anxiety disorder of blood phobia. The effects of learning and environment may explain why correspondences in autonomic constitution are differentially expressed as panic, persistent worry, and depression across individuals. This account is supported by the greater specificity of behavioral therapies in contrast to the diffuse efficacy of pharmacologic interventions [124, 139].

PANIC ANXIETY, HRV, AND CARDIOVASCULAR DISEASE (CVD)

The salience of CV symptoms in panic anxiety has long raised the specter of a relationship between this syndrome and cardiopathology. Cardiac arrhythmias were detected in some reports of NCA [12], but others found no ECG aberrations [140]. ST segment abnormalities, ventricular premature contractions (VPCs), and bouts of sinus tachycardia were found in a relatively recent study of NCA [141]; the presence of VPCs and sinus tachycardia was confirmed in ambulatory studies of PD but more serious arrhythmias were not observed [46, 47]. Findings of significant HR elevations in panic attacks [41, 45–48] support the association of sinus tachycardia, if not more pernicious arrhythmias, with PD.

Enhanced vagal tone can protect against malignant cardiac arrhythmias by buffering elevated sympathetic activity, and low vagal tone, limited spectral reserve, and diminished HRV have been cited as risk factors for sudden cardiac death [73, 142–144]. Minimally, low vagal tone in PD could potentiate the risk of palpitations *vis-à-vis* increased vulnerability to sinus tachycardia. However, psychological stress can be a potent elicitor of VPCs [142], which is consistent with findings of increased VPC's in panickers. VPC's can occur in healthy individuals, but when observed frequently may indicate underlying pathology [145]. It is conceivable that the stress of recurrent panic attacks coupled with low vagal tone could ultimately exacerbate the risk of dangerous arrhythmias in PD.

It is possible that PD bears a relationship with hypertension, which is also associated with low HRV and reduced vagal tone [75, 88]. Hypertension was reported to be prevalent in anxiety neurosis [146], and transient tachycardia has been linked with hypertension and CVD [50]. Hence, diminished vagal tone may be a common denominator among panic, hypertension, and CVD. In fact, several epidemiologic studies have suggested a link between panic anxiety and excess mortality. Elevated risk of premature death was found in men with neurosis and women with depressive neurosis [147], and excess mortality from CVD has been specifically linked with PD [148–150]. Finally, an association has been found between low HRV and an extensive list of pathological states including not only various forms of CVD, but also neurologic disorders, alcoholism, diabetes, and fetal distress [74–78]. It appears that low HRV can generally reflect CNS–ANS dysregulation, and indicate a generic "decomplexification" of physiologic dynamics that is common to many disease states [54, 70, 73].

On a more optimistic note, there is limited evidence that HRV measures can change following psychotherapy [151, 152]. Furthermore, techniques such as relaxation training and slowed respiration have been shown to increase vagal tone [89, 153]. Thus, therapeutic interventions may be advantageous in PD not only by raising the threshold for tachycardia and thereby reducing the risk of panic attacks, but also by providing general benefits for CV health.

SUMMARY AND CONCLUSION

The construct of autonomic balance has a long tradition in the investigation of anxiety. Panic syndromes have often been synonymous with autonomic imbalance [3, 92], and various forms of anxiety have often been portrayed as a sympathetic im-

balance [154–156]. However, the very notion of a central autonomic tendency expressed as "balance" has been criticized on theoretical and methodological grounds, and has never gained wide acceptance in psychophysiology [62]. HRV analysis provides fresh insights into this construct through the information it conveys regarding central regulation of autonomic cardiac control and the integrity of neural feedback mechanisms. Furthermore, HRV measures have a demonstrated relationship with vital self-regulatory processes such as attention and emotion. These attributes have led to the growth of HRV analysis in clinical research, as it yields a unitary view of ANS function that cannot be obtained with more segmental approaches [75].

The use of HRV measures has produced both specific and general insights into panic anxiety. Reduced HRV and low vagal tone in PD is consistent with the CV symptoms of panic attacks, and is further indicative of limited psychophysiological flexibility. This portrait of low resiliency in anxiety compels a reconsideration of the notion of excess autonomic lability and the traditional homeostatic framework from which it arises.

The principle of self-similarity from nonlinear dynamics expands upon the findings regarding HRV and anxiety. Phenomenologically, panic anxiety presents a severe constraint on the complexity of behavioral and emotional responding. Panic obstructs alternative reactions to fear and evokes a state that is almost invariably maladaptive [28]. PD is often associated with agoraphobia; in such cases, the loss of behavioral options is profound. It is notable that the German word *angst* has a parallel origin with *eng*, which is rendered as "narrow" or "restricted" [157]. Indeed, restricted response variability appears across biological, affective, and behavioral dimensions of panic anxiety.

The concept of "attractors," also drawn from nonlinear dynamics, may be heuristically useful in regard to panic. An attractor is a condition in the "state space" of an organism that has a high likelihood of occurrence [158]. Panic attacks have a wide "basin of attraction" in PD; they are likely to occur under a broad range of circumstances that lack a specific situational trigger. Furthermore, the threshold for tachycardia is reduced by low vagal tone, which helps to maintain the wide attractor basin. In contrast is a disorder such as blood phobia. Blood phobics only faint under highly circumscribed conditions, and so the basin of attraction for syncope is much narrower than the basin for panic in PD. The behavioral restrictions of blood phobia are relatively few, and interestingly, blood phobics appear to have relatively normal HRV. It may be that the specific phobias are not as likely to show impaired HRV as the more pervasive and debilitating anxiety disorders.

In sum, the analysis of HR variability holds great potential for the investigation of panic anxiety. This technique has revealed an autonomic substrate for the symptoms of panic that has long eluded researchers. Additionally, the HRV data converge with developmental findings that link panic susceptibility with attentional and emotional dysregulation. Functional differences in these areas reflect their CNS underpinnings, and are best viewed in a dimensional model of psychopathology. The HRV data also insinuate an association between PD and physical disease, although this connection requires closer scrutiny. Finally, from a systems perspective, these studies suggest compelling resemblances across psychosomatic levels of analysis in panic anxiety.

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