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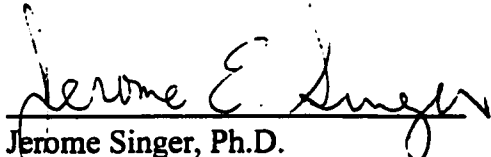


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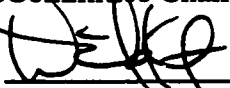
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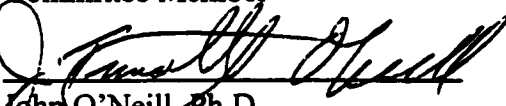
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## **ABSTRACT**

**Title of Dissertation: Cardiovascular Reactivity and Heart Rate Variability in Panic Disorder**

**Helen T. Santiago, Ph.D., 1999**

**Dissertation directed by Norman B. Schmidt, Ph.D., Assistant Professor  
Department of Medical and Clinical Psychology**

Evidence links panic disorder to cardiovascular disease and a greater than two-fold risk of hypertension, myocardial infarction and sudden death. Investigations of this association suggest that panickers have increased cardiac risk because of underlying autonomic dysregulation. Because previous studies of cardiovascular reactivity and heart rate variability have been inconclusive, these factors were re-examined in panickers and controls during physiological challenge in the laboratory and in panickers during naturalistic panic.

Forty-nine patients meeting DSM-IV criteria for panic disorder and 24 non-clinical controls underwent orthostatic, Valsalva and CO<sub>2</sub> challenge while heart rate, blood pressure, vagal tone, and anxiety symptoms and distress were recorded. Panickers then exposed themselves to panic-provoking situations in daily life during ambulatory monitoring of heart rate, blood pressure and heart rate variability.

Panickers at baseline and during challenge had higher systolic and diastolic blood pressure and heart rate, but lower vagal tone than controls, but only baseline vagal tone differed significantly. Repeated measures ANCOVAs of Group and Time effects, covaried for Age, revealed significant covariate effects significantly greater heart rate in

panickers upon standing, and lower vagal tone during Valsalva compared to controls. A Group x Trial interaction occurred upon standing with significantly increased vagal tone in panickers and decrease in controls. No main Group effects were found during CO<sub>2</sub> but Group x Trial effects were observed for systolic and diastolic blood pressure, while heart rate and vagal tone displayed trends toward significance. Four significant Group x Trial interactions occurred, characterized by systolic and diastolic blood pressure increases in controls with decreases in panickers, decreased heart rate in panickers with no change in controls, and vagal tone increases in panickers with decreases in controls.

Panickers compared to controls reported significantly more anxiety symptoms (API) and distress (SUDS) during baseline and challenge. Patients panicking to CO<sub>2</sub> versus those who didn't, had significantly higher baseline API and SUDS, suggesting anticipatory anxiety.

Repeated measures ANCOVAs, covaried for Age, demonstrated significantly increased systolic blood pressure and decreased heart rate variability during 21 panic versus non-panic episodes with similar activities in 15 patients. Reactivity during CO<sub>2</sub> and panic correlated well, but achieved only marginal significance because of the small sample size.

This study confirmed previous reports of decreased vagal tone in panickers versus controls but failed to find significant differences in stress reactivity. In a context not previously examined, significantly decreased heart rate variability and increased systolic blood pressure were found during monitoring of naturalistic panic. Because decreased heart rate variability is correlated with baroreceptor sensitivity loss, its decrease during

panic accompanied by increased blood pressure reactivity may have implications, not only for reactivity during panic, but over time, for the higher risk of hypertension and left ventricular hypertrophy reported in panickers. In addition, the linkage between decreased heart rate variability and sudden cardiac death warrants its further study in panic disorder.

**CARDIOVASCULAR REACTIVITY AND HEART RATE  
VARIABILITY IN PANIC DISORDER**

by

**Helen T. Santiago**

**Dissertation submitted to the Faculty of the  
Department of Medical and Clinical Psychology Graduate Program  
of the Uniformed Services University of the Health Sciences  
in partial fulfillment of the requirements for the degree of  
Doctor of Philosophy, 1999**

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## Table of Abbreviations

|              |                                                                      |
|--------------|----------------------------------------------------------------------|
| API.....     | Acute Panic Inventory                                                |
| SUDS.....    | Subjective Units of Distress Scale                                   |
| PD.....      | Panic Disorder                                                       |
| NC.....      | Non-clinical Control                                                 |
| ECG.....     | Electrocardiogram                                                    |
| HR.....      | Heart Rate                                                           |
| HRV.....     | Heart Rate Variability                                               |
| DBP.....     | Diastolic Blood Pressure                                             |
| SBP.....     | Systolic Blood Pressure                                              |
| VT.....      | Vagal Tone                                                           |
| RR.....      | Interbeat Interval                                                   |
| NN.....      | Interbeat Interval                                                   |
| pNN50.....   | Percent of Consecutive NN Intervals differing by >50 ms              |
| SDNN.....    | Standard Deviation of NN Intervals                                   |
| HF.....      | High Frequency                                                       |
| LF.....      | Low Frequency                                                        |
| LF/HF.....   | Low Frequency/High Frequency Ratio                                   |
| DSM-IV.....  | Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition |
| DSM-III..... | DSM-Third Edition                                                    |
| ANCOVA.....  | Analysis of Covariance                                               |
| MVA.....     | Microvascular Angina                                                 |
| BPM.....     | Beats per minute                                                     |

## INTRODUCTION

### Panic Disorder and Cardiovascular Disease: Evidence for an Association

Panic disorder, with a population prevalence of about 2%-4%, is a debilitating condition which, because of its overlapping symptomatology with cardiovascular disease, causes many patients to present initially to an emergency room or physician's office upon onset of a panic attack (Beitman, Mukeiji, Flaker & Basha et al., 1988). Routine electrocardiographic assessment frequently fails to find a physical basis for symptoms such as chest pain or shortness of breath and physicians often do not recognize the presence of panic. Further complicating this situation is evidence suggesting that chest pain and microvascular angina, both of which can occur in patients with angiographically normal coronary arteries, may have a higher than expected prevalence in panic disorder patients.

Despite being referred for psychological or psychiatric evaluation, many panic disorder patients continue to rely on emergency medical facilities when they have panic attacks. Although there is evidence that concerns about over-utilization of medical resources, coupled with the realization that panic disorder can present as impending myocardial infarction, may discourage physicians from further follow-up of patients whose initial cardiac evaluation is negative, awareness of the possible comorbidity of cardiovascular disease and panic disorder should encourage caution when dismissing a panic disorder patient's cardiac symptoms (Carter et al., 1994). Furthermore, recent studies suggest that panic disorder, overlooked or untreated, may lead not only to the development of cardiovascular disease but may exacerbate existing cardiovascular

disease (Katon, 1990).

The possibility of an association between panic disorder and cardiovascular disease was proposed by Coryell, Noyes and Clancy (1982) and Coryell, Noyes and House (1986). That association has since been strengthened by several epidemiological and cross sectional studies that have found an increased, at least two-fold, prevalence of cardiovascular disease in individuals with panic disorder compared to those without (Chignon, Lupine & Ades, 1993; Goldberg et al., 1990; Weissman, Markowitz, Ouellette, Greenwald & Kahn, 1990).

Recent investigations into the nature of the relationship between panic disorder and cardiovascular disease have focused on two lines of research primarily, one of which suggests that panic disorder patients are predisposed to cardiovascular disease because of an underlying autonomic dysregulation and one that suggests that panickers are predisposed because they have more cardiovascular risk factors than non-panickers.

In regard to the first line of reasoning, it has been observed that panic disorder patients often display greater heart rate and blood pressure reactivity than non-panickers and may differ in circulating catecholamine levels. The finding that vagal tone, or heart rate variability, which reflects the balance between the parasympathetic and sympathetic branches of the autonomic nervous system, may be abnormal in panic disorder, is also strongly suggestive of autonomic dysregulation. The second line of research has looked for evidence that established cardiovascular disease risk factors, e.g., hypertension, hypercholesterolemia and smoking, as well as accepted, but less established, risk factors, e.g., alcohol abuse, and lack of physical fitness, may be elevated in panic disorder

patients.

Several mechanisms could be proposed to explain the link between panic disorder and cardiovascular disease. In some cardiovascular disease patients, panic disorder onset occurs after the diagnosis of heart disease (Goldberg et al., 1990), suggesting that cardiovascular disease could cause panic disorder because of the heightened anxiety associated with a feared diagnosis, and subsequent cardiovascular arousal. Other studies indicate that cardiovascular disease frequently occurs long after the onset of panic disorder (Chignon et al., 1993) and that subtle preclinical changes may be found in panic disorder patients prior to diagnosis of full-blown cardiovascular disease (Kahn et al., 1990). Factors believed to be associated with panic disorder, such as cardiovascular hyperreactivity, diminished vagal tone and lack of physical fitness, have been proposed as mediating between panic disorder and subsequent functional changes such as hypertension, structural changes such as left ventricular hypertrophy and outcome, e.g., sudden cardiac death. Alternatively, neither panic disorder nor cardiovascular disease may be caused by the other, but may merely co-occur because of an underlying physiological dysregulation common to both disorders.

Interestingly, although panic disorder occurs more frequently in women, men with panic disorder have been reported to be at higher risk of sudden cardiac death. This observation may reflect the earlier onset of heart disease in men when compared to women but fails to take into account women's eventual similar cardiac mortality at later ages.

The following sections will examine recent investigations that have studied the

association between panic disorder and cardiovascular disease, in particular, those examining cardiovascular risk factors and evidence of autonomic dysregulation in panic disorder. Because untreated panic disorder may have grave consequences for cardiovascular health and quality of life, treatment outcome studies will also be reviewed.

### Epidemiological Studies

Studies by Coryell and colleagues (Coryell et al., 1982; Coryell et al., 1986) are frequently cited as supportive of a relationship between panic disorder and cardiovascular disease. In the earlier study, 113 psychiatric inpatients whose records were retrospectively reviewed after 35 years, were found to have reported history and symptoms that met DSM-III criteria for panic disorder and to be free initially of medical illness likely to increase mortality. Of 30 deaths in this group, 15 were due to "circulatory disease" (not otherwise specified) and occurred in 3 women and 12 men compared to an expected 1.4 and 6 deaths respectively, resulting in a significantly increased, two-fold mortality risk for both men and women. The second study, also retrospective and a replication of the first, followed 155 outpatients whose histories and symptoms met DSM-III criteria for anxiety neurosis, and of whom, 88% reported anxiety attacks. Although no cardiovascular deaths occurred in age and sex matched surgical patients within 12 years, 3 men with anxiety disorder died of cardiovascular disease (pulmonary embolism, congestive heart failure after a myocardial infarction and ruptured aneurysm secondary to hypertension). Although these studies suggest an increased cardiovascular risk among men with panic disorder, the authors have described the results as tentative because of the relatively small sample sizes and findings based on only 15 cardiovascular deaths. Furthermore,

although the majority of the anxiety disorder patients in the second study reported having anxiety attacks, the study results may not generalize to a panic disorder group.

The Epidemiological Catchment Area survey used the NIMH Diagnostic Interview Schedule (based on DSM-III criteria) to identify 60 subjects with a lifetime diagnosis of panic disorder from a large random sample in the New Haven area (Weissman et al., 1990). Comparing subjects with panic disorder to more than 3700 subjects with no psychiatric diagnosis, panic vs. no disorder was significantly associated, after controlling for demographic characteristics, with an increased risk of hypertension (OR = 1.9) and of myocardial infarction (OR = 4.5). However, whether the onset of panic disorder preceded or followed that of cardiovascular disease was not reported.

During a two year follow-up study (Kawachi, Colditz et al., 1994) of almost 34,000 men who were initially free of cardiovascular disease, 128 nonfatal MIs and 40 cases of fatal heart disease occurred. The Crown-Crisp index, an eight item self-report measure of phobic anxiety, identified men with the next to the highest and highest levels of phobic anxiety who, when compared to men at the lowest level of anxiety, had relative risks of 1.9 and 2.2 respectively for fatal heart disease and relative risks of sudden death of 7.7 and 4.3. Risk of fatal heart disease was most strongly associated with subjects reporting being "panicky in crowds", "more relaxed indoors" and "worrying ....when relatives are late coming home". Higher anxiety levels were also associated with hypertension, hypercholesterolemia and diabetes mellitus, but not with alcohol use or smoking.

A similar study (Kawachi, Sparrow, Vokonas & Weiss, 1994) examined the

relationship between scores on an anxiety scale, drawn from the Cornell Medical Index and validated against the Crown-Crisp index, consisting of 5 items: "Do strange people or places make you afraid?"; "Are you considered a nervous person?"; "Are you constantly keyed up and jittery?"; "Do you often become suddenly scared for no good reason?"; and "Do you often break out in a cold sweat?" and subsequent cardiovascular disease. In this 32 year follow-up of 2271 men in the Normative Aging Study, men reporting two or more anxiety symptoms had significantly increased risk of fatal heart disease (OR = 3.2) and of sudden cardiac death (OR = 5.7) when compared to men with no reported symptoms. However, when adjusted for risk factors common in anxiety, such as smoking and alcohol use, the odds ratio for fatal heart disease was no longer significant but a role for sudden cardiac death remained. The two studies conducted by Kawachi and colleagues support an association between anxiety and subsequent cardiovascular disease, particularly sudden cardiac death. A serious limitation of the self-report indices used in these studies is their lack of a clear relationship with a panic disorder diagnosis. Some items such as "Do you suddenly become scared for no good reason?" appear to support a panic diagnosis while an endorsement of "worrying.... when relatives are late coming home" suggests generalized anxiety disorder.

### Cross Sectional Studies

Panic disorder in patients with cardiovascular disease. Several studies have investigated the prevalence of panic disorder in patients with cardiovascular disease and some have tried to identify the temporal relationship between the onset of panic disorder and the development of heart disease. Using 24 items modified from an NIMH Anxiety

Disorders Research Section screening questionnaire, Goldberg et al. (1990) identified panic disorder in 16 of 52 cardiovascular patients (prevalence of 31%). Seven of these patients had panic disorder of long duration (average of 33 years) whereas 9 had panic disorder of short duration (4 years) and with an onset after diagnosis of heart disease. These findings suggest that in some patients a heart disease diagnosis might precipitate panic disorder onset. In another study of 197 patients referred for ambulatory electrocardiographic monitoring, 31 (16%) met DSM-III criteria for panic disorder when interviewed with the Schedule for Affective Disorders and Schizophrenia - Lifetime Version Modified for the Study of Anxiety Disorders (Chignon et al., 1993). Of these patients, 12 had positive electrocardiograms (ECGs) when monitored and a history of pre-existing panic disorder with a 10 year average duration. The prevalence of panic disorder was similar in patients with and without positive ECGs, suggesting that the presence of panic disorder does not rule out organic disease.

Kahn, Drusin and Klein (1987) reported that of 35 patients with idiopathic dilated cardiomyopathy who were awaiting heart transplant, 18 (51%) met DSM-III criteria for panic disorder. In contrast, none of 7 patients with rheumatic or congenital disorders met panic disorder criteria and only 4 of 18 patients with post-infarction cardiac failure, also awaiting transplant, were diagnosed with panic disorder (1 definite, 3 probable).

Cardiovascular disease in panic disorder patients. More recently, Kahn et al. (1990) found echocardiographic evidence of subclinical increases in left ventricular chamber size in 8 of 35 (23%) patients who met DSM -III criteria for panic disorder and in 1 of 35 (3%) non-clinical controls, in addition to subclinical increases in left

ventricular mass in 7 of the panic patients and none of the controls. These findings were believed to be suggestive of subtle premorbid changes associated with idiopathic dilated cardiomyopathy.

### The Significance of Chest Pain in Panic Disorder

Chest pain is a frequently reported symptom that accounts for many emergency room visits and referrals for cardiology evaluations among patients with and without panic disorder (Wulsin et al., 1988; Carter et al., 1992). It has been suggested that, even in patients with normal coronary arteries, chest pain and ST-segment depression imply the occurrence of myocardial ischemia (Chambers & Bass, 1990). However, in a study of 50 patients referred for radionuclide imaging during stress test evaluation of chest pain, only one of 28 who met criteria for panic disorder had a positive test (Carter et al., 1994). It has been suggested that although panic disorder may occur with, and contribute to, cardiovascular disease, there may be a bias against further evaluation if initial tests, i.e., ECG, rule out a cardiovascular basis for chest pain in a patient diagnosed with panic disorder (Carter et al., 1992).

It has been proposed that at least some panic disorder patients who experience chest pain with angiographically normal coronary arteries may suffer from microvascular angina (MVA) that results from constriction (possibly due to catecholamine release secondary to anxiety and arousal) of small resistance vessels within the heart wall that are not visualized during angiography (Chambers & Bass, 1990). In a study that examined the relationship between MVA and panic disorder, 4 patients diagnosed with MVA who met criteria for panic disorder and 2 patients with panic disorder only, were evaluated for

chest pain or panic response during a lactate infusion challenge. MVA was diagnosed during cardiac catheterization if patients experienced chest pain with atrial pacing, small artery constriction with ergonovine effusion and limited coronary flow increase with dipyridamole. Of the MVA patients, 3 who met criteria for panic disorder reported both extreme chest pain and panic, while the 2 known panickers without MVA reported only panic symptoms without chest pain. While acknowledging the small size of the sample, the authors suggested the possibility that the results reflect either comorbidity of panic and MVA or two types of MVA, one primarily cardiac and the other secondary to the autonomic arousal of panic. These patients were part of a larger group of 15 MVA patients of whom 6 (40%) met criteria for panic disorder. Whether the onset of panic order preceded or was subsequent to the diagnosis of MVA was not reported (Roy-Byrne, Schmidt, Cannon, Diem & Rubinow, 1989).

#### Hyperventilation: Implications for Microvascular Angina

Hyperventilation, which frequently accompanies panic attacks, is defined as excessive minute ventilation due to increased respiratory rate and/or increased depth of ventilation (tidal volume) which results in hypocapnia, a less than normal arterial CO<sub>2</sub> partial pressure ( $\text{Pa CO}_2 < 35 \text{ mm Hg}$ ). This alteration leads to an increased blood pH  $> 7.45$ , an increase in alkalinity, which shifts the oxygen dissociation curve so that oxygen is more tightly bound to hemoglobin (West, 1985, p.69-72), somewhat reducing cerebral and pulmonary oxygenation. Some symptoms, e.g., lightheadedness, dizziness and sense of unreality, that often occur during panic-related hyperventilation may be the result of reduced cerebral oxygenation. Hyperventilation's role in panic disorder has been

controversial and viewed variously as (1) chronic, but metabolically compensated so that pH is normalized, (2) panicogenic in some patients (Maddock & Carter, 1991), or (3) merely an accompaniment to, or symptom of panic (Papp, Klein & Gorman, 1993).

It has been proposed that chest pain in panic disorder patients with angiographically normal coronary arteries is related to the mechanical effects of musculoskeletal work on the chest wall or is due to microvascular spasm and angina secondary to hyperventilation during panic attacks (Chambers & Bass, 1990).

Hyperventilation during provoked panic is associated with chest pain in 50% of panic disorder patients and it has been suggested that microvascular angina may be secondary to the decreased mean oxygen content in the coronary sinus and decreased coronary blood flow which has been observed in normal subjects during voluntary hyperventilation (Rowe, Castillo & Crumpton, 1980). After observing ST-segment depression and elevation during coronary spasm induced by hyperventilation in patients with variant angina and normal or near normal coronary arteries, Fugii et al. (1988) proposed that coronary spasm is probably caused by respiratory alkalosis which results in hydrogen ions competing with the calcium ions that are necessary for contraction of vascular smooth muscle. Simultaneous multivessel spasm may be associated with prolonged, severe ischemia, arrhythmia and, possibly, sudden cardiac death.

Katon (1990) has also raised the question of whether microvascular spasm might not cause myocardial ischemia and eventually result in myocardial (heart muscle) injury and disease. Hyperventilation has also been associated with increased myocardial contractility, stroke volume and cardiac output, in addition to ECG changes in the ST-

segment and T-wave (Katon, 1990).

Although hyperventilation may be associated with panic in panic disorder patients, for example, a study in which 7 of 12 panickers and 1 of 12 non-clinical controls experienced panic during hyperventilation (Maddox & Carter, 1991), a more recent investigation has questioned the role of hyperventilation in panic disorder. In a study of 28 panic disorder patients who underwent ambulatory monitoring of transcutaneous arterial CO<sub>2</sub> partial pressure during spontaneous panic, Garssen, Buikhuisen and van Dyke (1996) found a decrease, small and non-significant, in transcutaneous PCO<sub>2</sub> during only one of 24 panic attacks experienced by 14 patients. It was proposed that these findings eliminated hyperventilation as an important mechanism for producing symptoms.

#### Evidence for a Physiological Predisposition to the Development of Cardiovascular Disease in Panic Disorder

If anxiety is associated with the development of cardiovascular disease, recurrent cardiovascular activation has been suggested as being implicated in that relationship (Manuck & Krantz, 1986). Many, but not all, panic attacks are accompanied by blood pressure and heart rate elevations, and some panic disorder patients have been reported to experience elevated resting heart rate and blood pressure during panic free periods. There is evidence that recurrent episodes of increased blood pressure can raise the set point of the baroreceptors that buffer acute pressure changes, thus setting the stage for hypertension, and possibly, leading to kidney injury and chronic impairment of renal blood pressure regulation (Guyton, 1997).

An underlying autonomic nervous system dysfunction, i.e., an imbalance between the sympathetic and parasympathetic branches of the autonomic nervous system resulting in increased adrenergic tone, decreased cholinergic tone and elevated serum catecholamines, has been proposed as a basis for the decreased heart rate variability, elevated resting heart rate and blood pressure and cardiovascular hyperreactivity that have been observed in many panic disorder patients (Yeragani, Balon et al., 1990). These alterations in arousal, when chronic, could provide a mechanism for the development of cardiovascular disease such as hypertension and left ventricular hypertrophy. However, investigation of differences in resting or reactive heart rates or blood pressure or of differences in epinephrine and norepinephrine serum levels between panickers and non-panickers, has revealed few consistent patterns. Furthermore, it has been suggested that the palpitations and arrhythmias reported during panic attacks are misperceptions of the panicker and that panic disorder patients do not differ significantly in physiological reactivity from non-panickers (Cameron et al., 1990). Addressing the lack of consistent findings among panic disorder patients, it has been proposed (Bystritsky & Shapiro, 1992) that panickers are not a homogeneous group and that they experience a variety of response patterns that can lead to different outcomes.

### Cardiovascular and Sympathetic Reactivity in Panic Disorder

#### Is there evidence that serum catecholamine levels are altered in panic disorder?

Plasma epinephrine and norepinephrine levels were measured in 10 panic disorder patients and 10 normal controls before and during a sodium lactate challenge (Gaffney, Fenton, Lane & Lake, 1988) and were found not to differ between the two groups even

though 8 of the 10 patients experienced severe panic during the infusion. Although it has been reported (Stein, Tancer & Uhde, 1992) in an exercise endurance study that resting levels of epinephrine and norepinephrine were similar in 16 panic patients and 15 normal controls, epinephrine in patients increased significantly during submaximal exercise.

To evaluate adrenergic function, Cameron et al. (1990) examined plasma epinephrine and norepinephrine in panic disorder patients and normal controls, and found no resting differences, but did find significantly decreased  $\alpha_2$ -adrenergic binding sites on platelets, suggestive of receptor down-regulation in the panickers. Similarly, Braune, Albus, Frohler, Hohn and Scheibe (1994) reported that panickers had decreased  $\alpha_2$ -adrenergic binding sites during a study of mental stress effects. However, they were also reported to have higher norepinephrine, but similar epinephrine, levels when compared to normal controls.

Because the baroreceptor reflex is mediated by sympathetic activation and its effectiveness is correlated with heart rate variability, orthostatic challenge has been used to elicit this reflex and to examine catecholamine responses and heart rate increases in panickers. In an investigation of responses to postural change (Stein, Tancer et al., 1992), similar levels of serum norepinephrine were found in panic disorder patients and normal controls, although heart rates after 75 seconds and after 5 minutes of standing were significantly higher in panickers than in the controls. Although heart rate increases upon standing are due to baroreflex-mediated sympathetic activation, the failure to find differences in epinephrine levels led to the authors' attributing the panic patients' heart rate increase to parasympathetic (vagal) withdrawal rather than sympathetic activation.

This attribution is supported by a study of endurance training in borderline hypertensives (Somers, Conway, Johnston & Sleight, 1991) which reports an association between increased baroreflex sensitivity and enhanced heart rate variability. Middleton, Ashby and Robbins (1994) reported significantly lower supine and standing norepinephrine levels, but similar heart rates in panic disorder patients versus normal controls. The significantly decreased heart rate variability in the panic disorder patients was proposed to reflect an altered baroreflex consistent with their abnormal epinephrine levels.

These and other similar studies were based on the assumption that sympathetic arousal was the cause of panic (despite the ineffectiveness of beta blockers in panic prevention). Their failure to find a significant difference in catecholamine levels between panickers and non-panickers suggested to George et al. (1989) that parasympathetic withdrawal might be contributing to panic.

In a more recent attempt to resolve the question of sympathetic activation in panic, Wilkinson et al. (1998) proposed that the standard sampling of antecubital venous blood to compare cardiac sympathetic tone in panickers and non-panickers was flawed because it primarily reflected muscle and nerve activity in the forearm. Assessing catecholamines at rest and in response to mental arithmetic in 13 panickers and 14 controls with radial and brachial artery, and coronary sinus samples, they reported no increase in whole-body and regional catecholamines in panickers at rest, or when compared to controls during mental arithmetic, but they did find significantly greater release of epinephrine from the heart at rest ( $p = .01$ ) which they conjectured was taken up and stored from plasma during panic. Arterial samples from 3 patients who panicked

in the laboratory revealed a 15% increase in norepinephrine and 153% increase in epinephrine. A coronary sinus sample from a fourth patient who panicked demonstrated a marked increase in cardiac epinephrine release. It was concluded that panickers did not differ from non-panickers in sympathetic cardiac tone at rest and that there was no evidence of global sympathetic activation during panic.

In summary, despite use of more sensitive methods in the latter study (Wilkinson et al. 1998), no consistent differences in epinephrine or norepinephrine levels have been reported between panic disorder patients and normal controls in this small group of studies that examined resting values and responses to a variety of challenges. However, some responses to postural challenge, although also inconsistent, have been suggestive of baroreflex abnormalities and/or decreased heart rate variability. Because of the variety of challenges and laboratory assessments employed it is difficult to evaluate the conclusions of this group of studies. Furthermore, it is not clear in some cases whether the reported adrenergic responses to stressors are central or peripheral effects.

Do panic disorder patients have elevated resting heart rates or increased heart rate reactivity? Several laboratory studies have demonstrated the presence of significantly elevated resting heart rates in panickers versus normal controls at rest or prior to psychological or physiological challenge. Klein, Cnaani, Harel, Braun and Ben-Haim (1995) reported that resting heart rates in 10 panic disorder patients were significantly higher, possibly because of subclinical anxiety, than in 14 non-clinical controls. Yeragani, Meiri et al. (1990) found significantly higher supine, resting heart rates prior to an orthostatic challenge in 30 panickers when compared to 30 non-clinical controls and

Hoehn-Saric, McLeod and Zimmerli (1991) also reported higher resting rates in 18 panickers prior to a psychomotor task. Similarly, Roth, Margraf, Ehlers, Taylor et al. (1992) found significantly higher heart rates in 52 panickers compared to controls prior to mental arithmetic, cold pressor and CO<sub>2</sub>. In contrast, Stein, Tancer et al. (1992) and Cameron et al. (1990) failed to find significant supine heart rate differences between panickers and controls prior to orthostatic challenge, while Taylor et al. (1987) reported no heart rate differences prior to treadmill exercise. Bystritsky, Craske, Maidenburg, Vapnik and Shapiro (1992) found greater variability in resting heart rates in panickers than in normal controls, as well as during and after CO<sub>2</sub> inhalation.

Significantly higher heart rate responses to treadmill exercise in panickers versus sedentary and non-sedentary controls have been reported (Taylor et al., 1987) to orthostatic challenge (Stein, Tancer et al., 1992) and to a psychomotor task (Hoehn-Saric et al., 1991), while a lack of significant differences in heart rate reactivity to cold pressor, CO<sub>2</sub> and mental arithmetic (Roth et al., 1992) and orthostatic challenge (Yeragani, Meiri et al., 1990; Cameron et al., 1990) has also been documented.

Clearly, the results of investigations of tonic and reactive heart rates in panic disorder are inconsistent. The decreased heart rate responses to commonly used stressors, such as cold pressor, may indicate that these stressors fail to elicit a pattern of emotional/physiological arousal relevant to panickers, while the lack of marked heart rate increases during physiological challenge may be the result of decreased baroreceptor sensitivity. Increased heart rate responses to exercise, on the other hand, could be attributed to decreased fitness in panickers compared to the other groups. It has been

suggested (Clark et al, 1990) that higher baseline heart rates reported in some laboratory studies of panickers may result from their anticipatory anxiety. However, several studies have failed to find elevated baselines. These inconsistent findings may be due not only to different methods used in these studies but to the heterogeneity of panic disorder patients as a group with varying degrees of severity and varying responses to challenge.

Ambulatory electrocardiographic monitoring in panic disorder. Holter monitoring of panic disorder patients during non-panicky periods has been inconclusive in regard to baseline heart rate. Clark et al. (1990) found no heart rate differences at baseline between panickers and normal controls during ambulatory electrocardiography (ECG) while asleep or awake and proposed that differences during laboratory studies are due to anticipatory anxiety. In contrast to these findings, higher mean daily awake and sleeping heart rates have been reported in panic disorder patients versus non-clinical controls (Taylor et al., 1987). Ambulatory ECG monitoring in patients referred for cardiology evaluations revealed significantly higher maximum heart rates and lower minimum P-R interval in patients with panic disorder than in those without panic disorder (Chignon et al., 1993). ECG abnormalities were equally prevalent, however, in both groups of patients. Shear et al. (1987) reported higher than normal heart rates during non-panic, asymptomatic periods in 23 panic disorder patients. However, Bystritsky et al. (1995) compared the mean heart rates of 10 panic patients to 10 non-anxious controls during 8 hour Holter monitoring and found differences of only borderline significance.

Ambulatory electrocardiographic monitoring during panic has provided evidence of heart rate increases during panic (White & Baker, 1987; Taylor, Telch & Havvik,

1983), near-panic and non-panic, anxious periods (Shear et al. 1987) that were significantly different from non-anxious periods. Gaffney et al. (1988) analysed the Holter recordings of 8 patients during 31 panics and found 8 attacks with increased heart rate, 6 with increased rate but during increased activity and 17 with no change. Taylor et al. (1983) found significantly increased heart rates, disproportionate to activity, during 19 of 33 Holter recordings of panic when compared to non-panic times 24 hours previous or subsequent. Of 3 panic attacks recorded during 8 hour Holter monitoring by Bystritsky et al. (1995), 2 recordings revealed heart rate increases of 4 beats per minute and 1 a decrease of 5 beats.

Although the results of ambulatory monitoring of baseline heart rate are as inconsistent as those of laboratory studies, most studies, however, have documented heart rate increases, although not controlling for activity or age, during panic and near panic.

Is there evidence of elevated resting blood pressure or increased reactivity in panic disorder? Evidence, although limited, of an increased risk of left ventricular hypertrophy in some panic disorder patients (Kahn et al, 1990) suggests that precursors of hypertrophy such as hypertension or subtle early signs of hypertension might be present in panic disorder patients. There is evidence (Smith et al. 1985) that even in mild hypertensives who do not meet criteria for left ventricular hypertrophy, subtle abnormalities in left ventricular function, e.g., rapid ventricular filling rates, may be discerned. However, the failure to find evidence of hypertension in most studies of panic disorder patients may be due to exclusion criteria which permit only healthy individuals without hypertension or other cardiovascular disease, without cardioactive medication or without medical

complications to participate (Gaffney et al, 1988; Bystritsky et al., 1995; White & Baker, 1987; Yeragani et al., 1993). Presumably then, treated and untreated hypertensives and borderline hypertensives are excluded from many, if not most, studies. There is limited evidence, in laboratory-based studies, however, of elevated blood pressure baselines. For example, higher systolic blood pressures were reported in 18 panic disorder patients compared to 18 healthy controls prior to and during a mental stress task that involved divided attention and risk taking (Hoehn-Saric et al., 1991). In a study that found no significant differences between 30 panic patients and 30 normal controls in blood pressure response to postural challenge and hand grip, higher diastolic blood pressure in panickers at rest and while standing has been demonstrated (Yeragani, Meiri et al., 1990). Bystritsky & Shapiro (1992) found significant elevations of diastolic blood pressure at rest and in response to a CO<sub>2</sub> challenge in 6 panic disorder patients when compared to normal controls. In addition, panickers demonstrated greater blood pressure fluctuations before, during and after CO<sub>2</sub> inhalation than did controls.

In contrast, Taylor et al. (1987) found no significant diastolic or systolic blood pressure differences between 40 panic disorder patients and 20 sedentary and 20 non-sedentary normal controls during treadmill exercise. Similarly, Cameron et al. (1990) also failed to find significant group differences in supine or standing heart rate or blood pressure in 24 panic patients, 8 patients with generalized anxiety disorder and 32 normal controls.

The lack of consistent evidence of significant blood pressure changes during laboratory studies may result from the failure to choose challenges relevant to panic

disorder. CO<sub>2</sub> inhalation challenge is panicogenic in panic patients and an effective stressor when used in laboratory studies of physiological differences between panic patients and control subjects. In contrast, mental stressors frequently used in cardiovascular reactivity research, such as mental arithmetic and simulated public speaking, are associated with increased anxiety, but not with significant physiological reactivity in panic disorder patients and may not effectively discriminate between panickers and non-panickers. Braune, Albus, Frohler, Hohn & Scheibe (1994) found no differences between 20 panic patients and 10 controls in cardiovascular reactivity to mental stress, i.e., mental arithmetic and public speaking, although plasma epinephrine and anxiety were significantly higher in the panickers. A lack of significant differences between 52 panic patients and 26 age and sex-matched controls was reported by Roth, Margraf, Ehlers and Taylor (1992) in a study that examined physiological reactivity to mental arithmetic, CO<sub>2</sub> inhalation and a cold pressor, although 46% of the patients reported panic during CO<sub>2</sub> inhalation. This study also found evidence of greater anticipatory anxiety in the patients who experienced panic during CO<sub>2</sub> inhalation, suggesting that anticipatory anxiety may be a factor in panic provocation. It has also been suggested that in studies utilizing multiple stressors, exposure to the first stressor may attenuate responses to later ones.

Ambulatory blood pressure monitoring. If anticipatory anxiety in the laboratory is a potentially confounding factor in baseline reactivity measures and contributes to panic provocation in panic disorder patients, ambulatory monitoring of spontaneous panic in a naturalistic setting may provide a more accurate assessment of the physiological changes

before, during and after panic. Three studies have assessed ambulatory blood pressure in panic disorder.

Twelve normotensive patients with frequent panic attacks were monitored for 24 hours and demonstrated significant systolic and diastolic blood pressure increases during 13 panic attacks that were associated with low activity in most instances (White & Baker, 1987). Shear et al. (1992) monitored 22 panic disorder patients for 12 to 24 hours during which 11 full-blown panic attacks occurred that were associated with low activity, and with statistically, but not clinically significant (i.e., not exceeding normotensive limits) mean systolic blood pressure elevations when compared to both anxious, i.e., non-panic, and non-anxious periods. A trend toward higher 24 hour mean blood pressures on panic versus non-panic days was also found. In the third study, significant group-wise diastolic pressure elevations discriminated between 10 panickers who experienced 3 panic or near-panic episodes and 10 normal controls during 8 hours of ambulatory monitoring (Bystritsky et al., 1995). Diastolic blood pressure was the only measure showing consistent change during panic or near-panic.

Although the third ambulatory study was weakened by its short duration and small sample size, the previous studies provided evidence of significant blood pressure reactivity, associated with low levels of activity, in normotensive samples without elevated baselines. The consistency of the results of panic monitoring in a naturalistic setting, although preliminary, suggests that physiological reactivity during panic provoked in a sheltered or protective laboratory environment may be buffered by a feeling of safety and may result in the inconsistent cardiovascular reactivity measures reported in

many studies.

**Baroreceptor Sensitivity, Heart Rate Variability and Fitness: Evidence for an Association with Cardiovascular Reactivity and Disease**

There is increasing evidence that baroreceptor sensitivity, heart rate variability and aerobic fitness are interrelated and interactive factors that contribute to cardiovascular health. There is also evidence that these factors may be abnormal and/or decreased in panic disorder patients and may predispose these patients to an increased risk of cardiovascular disease, in particular, to an increased risk of hypertension, left ventricular hypertrophy and sudden cardiac death. This evidence will be reviewed.

**Baroreceptor Sensitivity**

Baroreceptors are spray-like stretch receptors that are located throughout the vasculature, but are most densely concentrated in the carotid sinus and aortic arch. These receptors function primarily to detect and buffer blood pressure surges and to limit their range of fluctuation (Guyton, 1997). The baroreflexes are baroreceptor-mediated responses to alteration of blood pressure due to physiological or emotional stressors such as postural change, e.g., supine to standing, or to a pharmacological challenge, e.g., phenylephrine (a vasoconstrictor) or nitroprusside (a vasodilator). Standing from a supine position results in an immediate blood pressure decrease in response to gravity and a brief compensatory heart rate increase to maintain cardiac output, followed by a gradual blood pressure increase and slight heart rate decrease. A blood pressure surge, on the other hand, activates vagal reflexes associated with the baroreflex and results in a heart rate decrease. Loss of baroreceptor reflex control of heart rate has been found to increase

susceptibility to ventricular fibrillation and sudden cardiac death (Billman, Schwartz & Stone, 1982; Billman & Hoskins, 1989).

Baroreceptor sensitivity is a measure of the effectiveness of the baroreflexes in restricting the range of blood pressure variability. In a clinical setting, baroreceptor sensitivity is often assessed by passively tilting a patient from a supine to an upright position (60 to 90 degrees) on a mechanical tilt-table and measuring the change in blood pressure (mm Hg) with change in R-R interval (ms) (Conway, Boon, Davies, Jones and Sleight, 1984). Effective baroreflexes are characterized by small blood pressure variations and large heart rate variations while ineffective baroreflexes are marked by large blood pressure variations and small heart rate variations (Mancia et al., 1986). The net effect of baroreflex activity is the alteration of cardiac output in order to stabilize blood pressure. The baroreflexes are most effective in the short term maintenance of blood pressure range because chronically wide fluctuations tend to lead to an upward adjustment of the receptor set-point and tolerance of higher blood pressure limits. Upward alterations of receptor set-point, as measured by mean blood pressure over time, may, however, be implicated in injury to pressure sensitive renal tubules and result in chronic hypertension (Guyton, 1997). Decreased baroreceptor sensitivity has been reported to be associated with systolic hypertension and combined diastolic and systolic hypertension in the elderly and did not appear to be caused by age-related increased arterial wall stiffening (James, Robinson, Panerai and Potter, 1996). Decreased baroreceptor sensitivity has been reported in borderline hypertensives as well (Somers et al., 1991) and might account for the significant blood pressure elevations above baseline reported during ambulatory

monitoring of panic attacks (White & Baker, 1987; Shear et al., 1992; Bystritsky et al., 1995).

Blood pressure variability shows marked increases during emotional behavior (Mancia et al., 1986) suggesting that the increased blood pressure reactivity recorded during panic and panic-like episodes in the laboratory is associated with the emotional responses to physiological arousal.

It has been demonstrated (Somers et al., 1991) that baroreflex sensitivity can be increased by endurance training and result in decreased daytime blood pressure in borderline hypertensives. The finding (Billman, Schwartz & Stone, 1984; Billman & Hoskins, 1989) that daily exercise decreases the susceptibility of dogs to ventricular fibrillation and increases their parasympathetic (vagal) tone, i.e., heart rate variability, also supports the role of aerobic fitness in maintaining baroreflex control of blood pressure since heart rate variability and baroreceptor sensitivity are known to be correlated (Somers et al., 1991; Mancia et al., 1986).

#### Heart Rate Variability

Note: when referring to measurements of heart rate variability based on Porges' method of estimating the amplitude of respiratory sinus arrhythmia, particularly in conjunction with the patented Vagal Tone Monitor (Porges, 1985), the term *vagal tone* will be used. Otherwise, the term *heart rate variability* will be employed.

Heart rate variability is the beat to beat variation in heart rate, synchronous with respiration as a result of rhythmic discharges of the vagus, and is also known as respiratory sinus arrhythmia. Heart rate variability reflects the interaction between the

parasympathetic branch of the autonomic nervous system, under control primarily of the vagus, and the sympathetic branch, the latter being largely enhanced by the humoral control of the neurotransmitters epinephrine and norepinephrine. Sympathetic activation results in the increased heart rate and blood pressure associated with physiological arousal while vagal activation is associated with buffering arousal. Vagal fibers to the sino-atrial node provide the basic tonic heart rate apparent during quiet sleep when sympathetic tone is lowest (Somers et al., 1991) while waking heart rate results from the interaction between sympathetic activation and vagal activation or withdrawal.

As has already been discussed, heart rate variability correlates with baroreflex sensitivity (Somers et al., 1991; Mancia et al. 1986) and is an intrinsic factor in baroreflex regulation of blood pressure. Heart rate variability decreases with age and poor health and, like baroreceptor sensitivity, appears to be positively correlated with physical fitness (Billman, Schwartz & Stone, 1984; Hull et al., 1994). Some measures of heart rate variability may differ by gender in younger men and women, women having higher heart rates and a circadian component which is reflected in lower heart rate variability in most measures, except at night (Stein, Kleiger & Rottman, 1997). Heart rate variability has been shown to have a cardioprotective effect and a recent report suggests that decreases in high frequency power (0.15 to .4 Hz and believed to be of parasympathetic origin) may be associated with a predisposition to ischemic onset, arrhythmia and sudden cardiac death (Fei et al., 1994; Casolo et al., 1992). Because older men ( $67 \pm 3$  years) have been reported to have increased heart rates and lower heart rate variability indexes at night than women of comparable age (Stein et al., 1997), a gender-based circadian variation may

account for the increased risk of sudden cardiac death reported in men with panic disorder.

Measurement of heart rate variability. Scientific interest in heart rate variability began with the earliest observations of respiratory sinus arrhythmia and recent investigations have focused on either the physiological mechanisms underlying this phenomenon or its relevance to clinical issues. Initially, quantification of sinus arrhythmia was concerned with heart rate measures over time, either instantaneous beat-to-beat changes in rate or the differences in interbeat interval or heart period over a designated time period or epoch. This approach to measurement of heart rate variability, constitutes a *time* domain method and utilizes time units such as milliseconds. Increased understanding of the roles played by the parasympathetic and sympathetic branches of the autonomic nervous system has led to analyses of the frequency components of heart rate variability to tease apart not only the influences of these systems but those of other physiological cycles, such as circadian rhythms, as well. This approach is referred to as a *frequency* domain method and the units of measurement are most often expressed in cycles per second or hertz when referring to individual frequency components. Although an analysis of heart rate variability could be described as employing a *time* or *frequency* domain approach, most are not purely time or frequency based.

Time series analysis of heart rate variability. A time series can be used to describe physiological data such as respiration or heart period that can be measured sequentially at successive time periods. Heart periods occur as unevenly spaced discrete events triggered by heart beats, which because they are due to continuous cellular humoral and neural

processes, may be viewed as continuous data. A respiratory rate of 12 (0.2 Hz) with a periodicity of 5 seconds could be sampled every 0.5 seconds (2 Hz) and would require 5 seconds to describe an complete respiratory cycle. Physiological processes such as heart period are assumed to fit a family of sine waves which makes it possible to describe the frequencies (F) and amplitudes (A, height of wave) of the process. This assumption also allows variance ( $A^2/2$ ), i.e., the total power of spectral analysis to be calculated (Porges & Bohrer, 1990).

Time domain measures of heart rate variability can be easily determined from the continuous electrocardiogram either by measuring the time in milliseconds between successive R waves, the interbeat (or NN) interval, or by calculating the instantaneous heart rate at each R wave. Frequently used time domain estimates of heart rate variability include the SDNN, the RMSSD, NN50 and pNN50. The SDNN, expressed in milliseconds, is the standard deviation of the NN intervals and is also the square root of the variance. The RMSSD is the mean squared differences of NN intervals. The NN50 is the number of successive intervals that differ by more than 50 milliseconds while the pNN50 is the percentage of these intervals (Task Force, 1996).

Frequency components of heart rate variability. The normal heart rate in healthy adults ranges from 60 to 80 beats per minute or 1.0 to 1.2 Hz. Periodic perturbations in the interbeat interval, or heart period, occur, resulting in an alternately lengthening and shortening of the heart period that corresponds in frequency to the respiratory cycle, i.e., 9 to 24 breaths per minute or 0.15 to 0.4 Hz, designated as *high frequency* (Task Force, 1996). The *low frequency* range of heart period oscillations is defined as 0.04 to 0.15 Hz

and includes Mayer waves, associated with blood pressure fluctuations, with a frequency of about 0.1 Hz. It has been suggested that the low frequency components are primarily of sympathetic origin while the high frequency components are primarily of vagal (parasympathetic) origin. It has been proposed that the high frequency components are due to activation of atrial stretch receptors during inspiration which results in changes in the frequency of sino-atrial node discharge (Porges & Bohrer, 1990).

A time series composed of two or more periodic components of differing frequency can be decomposed mathematically into its constituents. Autocorrelation examines the correlation between a time series and a time-shifted, i.e., later, version of itself. The autocovariance, which, loosely speaking, describes the degree to which the time series changes over time, is derived from the autocorrelation. The latter, when subjected to a Fourier transform, is the spectral density function. The Fourier transform is a commonly used mathematical technique that decomposes the time series into waves of differing frequencies. The amplitude and/or variance of each component can then be used to estimate spectral density and power (Porges & Bohrer, 1990). Low (LF) and high frequency (HF) power, expressed in milliseconds squared ( $\text{ms}^2$ ) and the low to high frequency ratio (LF/HF) are frequently used to study heart rate variability in short-term recordings (5 minutes). Analysis of long-term recordings (24 hours) examines the total power of all NN intervals and power in the low and high frequency ranges (Task Force, 1996).

Stationarity in measures of heart rate variability. The increased use of heart rate variability as a measure of interest in recent cardiovascular, psychophysiological and

other studies has led to concerns about a lack of uniformity in this variable's application, measurement and analysis. Stationarity, which has been defined as a "property of a time series when the mean and the variance remain constant with respect to time" (Gottman, 1990, p.838), has been an area of contention particularly in the time series analysis of heart rate periodicity (Porges & Bohrer, 1990; Jorna, 1992; Weber, Molenaar & van der Molen, 1992; Grossman, 1992). Physiological data tend to be dynamic and therefore not stationary because experimental manipulations often alter heart rate means and variances. Time series analyses of periodic functions, on the other hand, are based on the assumption of their predictability, or stationarity, during the time of measurement. Oscillations in the heart period are due to periodic influences such as respiration (respiratory sinus arrhythmia) in a high frequency band, a mid-frequency band (0.07-0.14 Hz) due to blood pressure feedback (Traub-Hering-Mayer waves) and a low frequency band (0.02-0.06 Hz) related to thermal regulation, and non-periodic influences such as alterations in metabolic demand (Porges & Bohrer, 1990). Baroreflex influences on heart rate can be substantial, have a short latency of about 0.25 seconds, peak in about 2.5 seconds and persist for another 2.0 seconds.

Spectral analysis also requires that the data be stationary for analysis to be reliable (Jorna, 1992; Porges & Bohrer, 1990). Filtering and statistical techniques have been developed, such as Porges' proprietary moving polynomial filter (Porges, 1985) which filters out periodic influences other than respiration, and the recursive procedure of Weber et al. (1992) which selects for analysis only the stationary intervals in the data. A frequently used estimate of heart rate variability, the peak-to-valley statistic (Grossman,

1992), is selective for respiratory sinus arrhythmia by measuring the mean difference between the maximum heart period during inspiration and the minimum heart period during expiration.

It has been argued (Grossman, 1992) that even two-fold changes in heart rate which result in decreased stationarity lead only to small overestimations of spectral density, less than 4%, while restricting spectral analysis solely to stationary segments may lead not only to rejection of an estimated 40-80% of recorded data (Grossman, 1992) but to the overlooking of important changes in levels of respiratory sinus arrhythmia which may be of primary interest in experimental studies (Committee Report, 1997).

In comparison to short term recordings of about 5 minutes, stationarity is a greater issue during long-term recordings (24 hours) because the length of sampling increases the probability of nonstationarity. Large changes occur, e.g., during sleep versus awake times, but averaging of high frequency and low frequency spectral components during long recordings leads to a flattening of these modulation levels and to loss of detail. It was recently recommended (Committee Report, 1997) that multiple short segments which satisfy stationarity be analyzed and the dynamics of the signal be examined by comparing these results over time. In addition, it was suggested that testing and subject conditions be made as stable as possible, that testing segments be made as brief as possible and that filtering be used to eliminate slow trends. It was conceded that violations of stationarity may be common and that moderate nonstationarity may not seriously affect measures of respiratory sinus arrhythmia.

Clinical applications of measures of heart rate variability. Heart rate variability

has been found to have value in, and is frequently employed in studies of cardiovascular function. Heart rate variability has been found to be decreased in cardiac failure (Kienzle et al., 1992; Casolo, Balli, Taddei, Amuhasi & Gori, 1989; Nolan et al., 1992) and may have value in predicting survival after myocardial infarction (Casolo et al., 1992; Bigger, Fleiss, Rolnitsky, Kleiger & Rottman, 1992; Lombardi et al., 1987; Lombardi et al., 1992; Bigger, Fleiss, Rolnitsky, Steinman & Schneider, 1991; Cerati & Schwartz, 1991) or heart transplant (Mortara et al., 1994).

Heart rate variability has been studied in the evaluation of diabetic neuropathy (Pagani et al., 1988; Freeman et al., 1991), in relationship to aerobic fitness and exercise (Stein, Papp et al., 1992; De Meersman, 1993; Goldsmith, Bigger, Steinman & Fleiss, 1992; Somers et al., 1991) and as predictor of developmental outcome in neonates (Fox & Porges, 1985; DePietro, Larson & Porges, 1987; DeGangi, DiPietro, Greenspan & Porges, 1991).

A growing awareness among investigators of panic and anxiety of a possible association between autonomic dysfunction and cardiac risk factors with panic disorder has resulted in studies of heart rate variability in panic disorder patients. Evidence of this linkage will be examined below.

### Aerobic Fitness

There is evidence of a association between both baroreflex sensitivity and heart rate variability, and aerobic fitness. Endurance training has been found to enhance heart rate variability and its cardioprotective effect in dogs who have undergone induced myocardial infarction (Hull et al., 1994), and several recent studies have demonstrated a

relationship between aerobic fitness and increased heart rate variability in humans as well (Stein, Papp et al., 1992; De Meersman, 1993; Goldsmith et al., 1992) even in the elderly (Yataco, Fleisher & Katzel, 1997). Furthermore, endurance training has also been shown to improve baroreceptor sensitivity in borderline hypertensives (Somers et al., 1991).

The evidence to date suggests that heart rate variability, baroreflex sensitivity and aerobic fitness are interactive, mutually dependent factors that contribute to physiological homeostasis and cardiovascular health. Evidence that these factors are abnormal or decreased in patients with panic disorder will be reviewed.

### Heart Rate Variability, Baroreceptor Sensitivity and Fitness in Panic Disorder

#### Evidence of Decreased Heart Rate Variability in Panic Disorder

There is evidence that decreased heart rate variability is associated with the onset of cardiac arrhythmias and with sudden cardiac death (Hull et al., 1994; Martin et al., 1987; Fei et al., 1994), as well as with the onset of myocardial ischemia (Verdino et al., 1996). Evidence of decreased heart rate variability in panic disorder would support the linkage between panic disorder and cardiovascular disease, particularly sudden cardiac death.

Postural challenge has been used in a number of studies to demonstrate decreased heart rate variability in panic disorder patients when compared to normal controls (Yeragani, Balon et al., 1990; Yeragani et al., 1993; Rechlin, Weis, Spitzer & Kashka, 1994). Normally, a postural change from a sitting or supine position to standing causes a brief fall in blood pressure which is compensated for by a baroreflex mediated, compensatory heart rate increase and moderate blood pressure increase. Significantly

decreased R-R variance, a measure of heart rate variability believed to be suggestive of vagal withdrawal, has been reported in panic disorder patients compared to normal controls, while at rest and during postural challenge (Yeragani, Balon et al., 1990; Yeragani et al., 1993). Studies employing spectral analysis techniques that examine high and low frequency components of heart rate variability (Yeragani et al., 1993; Middleton, Ashby & Robbins, 1994; Rechlin et al., 1994) have found decreased heart rate variability in panickers compared to non-panickers, believed to be suggestive of decreased cholinergic and increased adrenergic response, during controlled ventilation and postural challenge.

Using 24-hour Holter electrocardiography to record heart rate variability in 29 panic disorder patients and 23 non-clinical controls, Yeragani et al.(1998) examined low and high frequency during awake and sleep periods. Panickers were found to have significantly higher low frequency power during sleep and a significant increase in low power from awake to sleep periods when compared to controls suggestive of higher sympathetic drive during sleep. It was proposed that a nocturnal decrease in relative and total ultra-low frequency power may increase risk for arrhythmia and sudden death during a cardiac event.

Hyperventilation, i.e., rapid, shallow breathing, a common symptom of panic, has been shown to decrease heart rate variability, although no correlation was found between heart rate variability, heart rate and end-tidal CO<sub>2</sub> and symptom severity within or between panic disorder patients and social phobics (Asmundsen & Stein, 1994). Furthermore, decreased heart rate variability, suggestive of an increased risk of sudden

cardiac death, was associated with phobic anxiety in 581 men (aged 47-86 years) who were free of coronary artery disease (Kawachi, Sparrow, Vokonas & Weiss, 1995).

Although most studies employing physiological challenges to study panic disorder have reported a decrease in heart rate variability, a study of lactate-induced panic (Gorman et al., 1987) found no change in heart rate variability. The authors suggested that these results might be secondary to the cardiac effects of lactate infusion, i.e., excessive volume loading during lactate infusion may decrease heart rate.

Although conducted with 6 normal volunteers, a study of vagal tone after a sodium lactate infusion demonstrated a significant decrease ( $p < .009$ ) from baseline values (George et al., 1989) while hyperventilation produced a smaller significant decrease ( $p < .018$ ). Sodium lactate infusion elicited an increase in anxiety, as measured by Spielberger's state ratings, that showed a trend toward significance ( $p < .1$ ).

A more recent study of heart rate variability during sodium lactate infusion compared high frequency, and mid-frequency/ high frequency ratios in 6 panic disorder patients vs. 9 non-clinical controls and reported significant cardiac vagal withdrawal in the panickers (Yeragani, Srinivasan, Balon, Ramesh & Berchou, 1994).

Pharmacologic treatment appears to potentially enhance heart rate variability. After initial findings of decreased heart rate variability when compared to non-panickers, panickers who underwent pharmacological treatment with alprazolam or clonidine (Klein, Cnaani et al., 1995), or paroxetine (Tucker et al., 1997) were found not to differ significantly from non-panickers in respect to heart rate variability, a normalization possibly attributable to a decrease in anxiety.

These investigations provide evidence of decreased heart rate variability compared to non-clinical controls during postural, hyperventilation and sodium lactate challenges in the laboratory. In addition, ambulatory monitoring of daily life is suggestive of mechanisms that might contribute directly to risk of sudden cardiac death in panickers.

### Baroreceptor Sensitivity in Panic Disorder

Although several studies have found significant differences in systolic and diastolic blood pressure responses to orthostatic challenge in panic disorder patients compared to normal controls (Yeragani, Balon et al., 1990; Yeragani, Meiri et al., 1990), only one (Yeragani et al., 1993) has attributed these differences to decreased baroreceptor sensitivity in panic disorder. Somers et al. (1991), in a study that examined the effects of endurance training on baroreceptor sensitivity in borderline hypertensives, concluded not only that exercise improved baroreceptor sensitivity, but that baroreceptor function was correlated with heart rate variability.

Laboratory studies examining blood pressure reactivity in panic disorder patients have provided equivocal data and it has been suggested that anticipatory anxiety may have confounded the results (Clark et al., 1990). Ambulatory blood pressure studies of panic in a naturalistic setting (White & Baker, 1987; Shear et al., 1992; Bystritsky et al., 1995), however, have found more consistent evidence of significant blood pressure elevations during panic.

The use of orthostatic, or postural, challenge to evaluate blood pressure reactivity and heart rate variability in some of these studies of panic disorder patients is fortuitous

because orthostatic challenge is also the “gold standard” for investigations of the baroreflex. Although, to date, only one study (Yeragani et al. 1993) has proposed an association between increased blood pressure reactivity during orthostatic challenge and decreased baroreceptor sensitivity, the reports of decreased heart variability during orthostatic challenge, and the known correlations among these three variables, suggests a dysregulation of these factors in panic disorder.

### Aerobic Fitness in Panic Disorder

The evidence of an association between heart rate variability and panic disorder and between heart rate variability and physical fitness suggests that perhaps the decreased heart rate variability observed in panic disorder patients is the result of decreased physical fitness, secondary, perhaps, to avoidance of exercise and the associated cardiovascular arousal. Significantly decreased fitness, defined as lower maximum O<sub>2</sub> uptake, higher mean arterial blood pressure and lower maximum heart rate during exercise testing, in panickers vs. normal controls has been reported (Gaffney et al., 1988; Schmidt, Lerew & Santiago, 1998). Higher heart rates at sub-maximal effort have been found in panickers vs. normal controls or non-exercising normal controls, while panickers and non-exercising controls achieved significantly lower peak workloads than normal controls (Taylor et al., 1987). In contrast, Stein, Papp et al. (1992) found no physiological differences between panic disorder patients and normal controls during exercise although panickers terminated exercise non-significantly earlier than normal controls, possibly because of decreased conditioning. In addition, physical fitness may be associated with lower levels of cardiovascular arousal (Holmes & Cappel, 1987), suggesting that

increased heart rate and blood pressure reactivity in panic disorder may be related to decreased fitness.

The association among fitness, heart rate variability and baroreceptor sensitivity in normal controls suggests that a similar relationship might pertain to the same factors in panic disorder and could explain how decreased heart rate variability, possibly impaired baroreceptor sensitivity and decreased fitness observed in many panic disorder patients could predispose them to the development of cardiovascular disease.

#### Persistence of Cardiovascular Dysregulation after Treatment

Although two studies (Klein et al. 1995; Tucker et al., 1997) have reported normalization of heart rate variability after pharmacologic treatment of panic, other studies have found evidence of the persistence of cardiovascular dysregulation after pharmacological or behavioral interventions suggestive of an underlying autonomic dysfunction in panic disorder. Treatment with tricyclic antidepressants, particularly imipramine, has been shown to be related to increased resting heart rates and diastolic and systolic blood pressures and to orthostatic hypotension in panic disorder patients (Roth, Margraf, Ehlers, Haddad et al., 1992; Taylor & Hayward, 1990; McLeod et al., 1990; Louie, Louie & Lannon, 1992) despite patients' subjective reports of improved cardiovascular symptoms. Treatment with tricyclics has also been associated with increased cardiac conduction times resulting in first and second degree blocks which may increase the risk for sudden cardiac death (Taylor & Hayward, 1990). These alterations in cardiovascular physiology have been attributed to vagal withdrawal which permits unopposed sympathetic activation (Roth, Margraf, Ehlers, Haddad et al., 1992) and/or the

anticholinergic effects of imipramine (Yeragani et al., 1992). In a study in which 6 of 43 panic disorder patients but none of 71 depressed patients developed hypertension when treated with imipramine, desipramine and nortriptyline, it was proposed that hypertension was the result of either an underlying cardiovascular dysregulation or susceptibility to tricyclics (Louie et al., 1992).

Middleton et al.,(1990) observed lower average resting heart rate and elevated resting systolic blood pressure in a group of 12 panic disorder patients compared to 12 normal controls a minimum of 4 months after completion of successful cognitive therapy. The panic disorder patients also had abnormal orthostatic responses, suggestive of a baroreflex abnormality and characterized by a gradual decrease in systolic blood pressure upon standing, in contrast to the moderate increase seen in the controls.

The reports of persistent cardiovascular symptoms after both pharmacological and cognitive treatment for panic disorder suggest that autonomic dysregulation may be an intrinsic characteristic of panic disorder. Successful treatment may relieve the subjective distress triggered by physiological symptoms/sensations without altering their underlying cause. Clearly, more pharmacological and cognitive treatment outcome studies are warranted to resolve this issue.

#### Other Cardiovascular Risk Factors in Panic Disorder

Several well established cardiovascular risk factors including hypertension, cigarette smoking and hypercholesterolemia have been investigated because of their possibly increased prevalence in panic disorder as have some less established risk factors, i.e., cardiovascular reactivity, lack of physical fitness, and excessive alcohol use. To this

date, none of these risk factors have been clearly established as contributing to what appears to be an excessive risk of cardiovascular disease associated with panic disorder.

Smoking and panic disorder Although there appears to be an increased prevalence of cigarette smoking, alcohol use and, possibly hypercholesterolemia among panic disorder patients, few studies have examined the effects of these risk factors in panic disorder. Panic disorder patients who smoke were compared to non-smoking panic patients and non-smoking controls (Yeragani, Pohl et al. 1990) and found to have significantly higher supine heart rates, standing diastolic and mean arterial blood pressure, and standing and supine cardiac load (product of mean arterial blood pressure and heart rate). The authors suggested that cigarette smoking may be a significant confounding factor in baseline and reactive physiological measures in panic disorder studies. More recently Pohl, Yeragani and Balon (1992) reported that patients with early panic disorder onset (before 14 years of age) were unlikely to be smokers while 50% of patients with later onset of panic were prior smokers. The prevalence of smoking was significantly higher among female panickers than among controls and it was suggested that smoking might be a risk factor for panic disorder in women and that the deleterious adrenergic effects of smoking, i.e., increased heart rate and blood pressure might exacerbate the disorder. Levin et al. (1993) have proposed that smoking increases cardiovascular risk by increasing heart rate, decreasing heart rate variability and lowering the threshold for ventricular fibrillation, thus increasing the likelihood of sudden cardiac death.

Cholesterol levels in panic disorder Although total and low density cholesterol

levels were found to exceed the 75th percentile of the National Reference level in 50% of 74 female panic disorder and agoraphobia patients in one study (Hayward, Taylor, Roth, King & Agras, 1989), Yeragani, Pohl et al. (1990) reported finding that total, high density and low density cholesterol levels in panic disorder patients did not present an increased cardiovascular risk. In addition, total cholesterol was measured in 80 panic disorder patients and found not to differ from that of 80 gender and age matched controls (Tancer, Stein, Moul & Uhde, 1990). In contrast to the latter two studies, Bajwa, Asnis, Sanderson, Irfan and van Praag (1992) reported that 30 panic disorder patients had significantly higher serum cholesterol levels than either 30 depressed patients or 30 normal controls matched for gender and age. The authors hypothesized that the elevated cholesterol levels resulted from increased adrenergic activity associated with anticipatory anxiety. However, it has been proposed that because of evidence that serum cholesterol has a genetic basis as may panic disorder, any relationship between panic and cholesterol may be due to a common underlying genetic factor (Feder, 1993).

Alcohol use and alcoholism in panic disorder. Chronic excessive alcohol use is associated with increased risk for cardiomyopathy, cardiomegaly, decreased contractility, atrial arrhythmias and increased atherosclerosis (Knochel, 1983). Katon (1984) found increased alcohol use in 9% and alcoholism in 15% of panic disorder patients referred for psychiatric evaluation of somatic complaints and Schuckit and Hesselbrock (1994) estimate the prevalence of alcohol abuse in panic disorder to be about 14%, similar to that in the general population. The prevalence of panic disorder among alcoholics has been variously estimated at 6% (Schuckit & Hesselbrock, 1994) or to range from 2% to 13%

(Kushner, Sher & Beitman, 1990).

A recent study (Kushner et al. 1996) demonstrated that alcohol ingestion significantly reduced self-reported anxiety before, during and after CO<sub>2</sub> inhalation and also decreased physiological responding, although not significantly. Anecdotal evidence has suggested that patients with anxiety disorders self-medicate with alcohol and other drugs to relieve anxiety. However, because somatic symptoms associated with alcohol intake overlap with panic symptoms and increase anxiety, many, if not most, panic disorder patients may actually avoid alcohol use (George, Nutt, Dwyer & Linnoila, 1990). In fact, alcoholics may be unable to distinguish between withdrawal symptoms and panic symptoms (George, Zerby, Noble & Nutt, 1988). Many studies investigating panic disorder in alcoholics have interviewed hospitalized alcoholics experiencing withdrawal or detoxification (Hesselbrock, Meyer & Keener, 1985), a period of heightened anxiety, during which up to 80% of alcoholic men report a history of recurrent lifetime panic. Examination of previous medical records indicates that many of these patients erroneously date panic onset prior to alcohol use (Schuckit & Hesselbrock, 1994). It has been proposed that panic onset may be "kindled" by central nervous system hyperexcitability secondary to repeated alcohol withdrawal, resulting in the apparent co-occurrence of panic disorder and alcohol abuse (George et al., 1990). This view is supported by evidence of reduced anxiety during abstinence (Schuckit, Irwin & Brown, 1990). Clearly, the temporal and causal relationship between panic disorder and alcohol abuse is not yet understood.

### Summary

Although epidemiological studies provide evidence of an association between panic disorder and cardiovascular disease, studies of possible cardiovascular risk factors in panic disorder provide inconsistent findings. It has been suggested that panic disorder patients are a heterogeneous group whose reactivity to physiological challenge varies on a spectrum of response. There is some evidence of autonomic dysregulation in panickers, e.g., decreased or abnormal heart rate variability, and suggestions of subclinical increase in left ventricular mass that could be a precursor to hypertrophy and might result from chronic hypertension, a factor for which panickers are reportedly at increased risk (Weissman et al. 1990). Although heart rate variability, baroreceptor sensitivity and aerobic fitness are interrelated in non-clinical subjects, and there is evidence linking them in panickers, studies of cardiovascular reactivity in panickers have failed to demonstrate causal mechanisms for functional and structural changes that could account for the observed adverse cardiovascular outcomes. Furthermore, although baroreceptor sensitivity has been suggested, in a single study, as a contributor to anomalous blood pressure responses in panickers, no additional investigations of baroreceptor sensitivity in either a laboratory or naturalistic setting have been undertaken, despite the prognostic value of baroreceptor sensitivity in cardiovascular outcome. Despite the growing interest in the role of heart rate variability in panic disorder, only one study to date, comparing panic disorder patients to non-clinical controls (Yeragani et al., 1998), has examined heart rate variability in an ambulatory setting.

### Study overview

This study is an extension of an ongoing investigation that has been examining

whether panic disorder patients differ from non-clinical controls in cardiovascular reactivity and compares cardiovascular reactivity during physiological challenge (orthostatic and carbon dioxide inhalation) in panickers and non-clinical controls in an effort to delineate and quantify how heart rate variability might be related to measures of reactivity in these patients. In addition, ambulatory electrocardiographic and blood pressure monitoring provided a comprehensive record of recurrent cardiovascular activation and heart rate variability during naturalistic anxiety and panic. Specific hypotheses to be tested included:

**Hypothesis 1:** Panic disorder patients will demonstrate significantly greater cardiovascular reactivity during carbon dioxide inhalation and postural challenge than will non-clinical controls.

**Hypothesis 2a:** Panic disorder patients will show significantly decreased heart rate variability during carbon dioxide inhalation and postural challenge when compared to normal controls.

**Hypothesis 2b:** Decreases in heart rate variability will be negatively correlated with, and predictive of, systolic and diastolic blood pressure changes during carbon dioxide and postural challenge.

**Hypothesis 3a:** Panic disorder patients will experience significant decreases in heart rate variability during ambulatory electrocardiographic monitoring of panic and near-panic episodes in daily life when compared to non-panic periods with similar heart rate.

**Hypothesis 3b:** Panic disorder patients will experience significant systolic and

diastolic blood pressure increases above baseline during ambulatory monitoring of panic and near-panic episodes in daily life.

Hypothesis 3c: Decreases in heart rate variability during monitored panic and near-panic episodes in daily life will be significantly and negatively correlated with blood pressure changes during these episodes.

## METHODS

### Subjects

Thirty-four non-clinical controls without history of an Axis I disorder (DSM-IV criteria) and fifty-five subjects who meet DSM-IV criteria for panic disorder were recruited through advertisements in local newspapers. Prospective subjects were screened initially during a brief preliminary telephone interview to determine eligibility based on availability for the study, age between 18 and 64 years, absence of significant current medical illness, e.g., history of renal, cardiovascular, gastrointestinal, neurological, endocrine or pulmonary disease, and adequate ability to speak and read English. Borderline or moderate hypertension were not exclusionary criteria if the subject was determined by his/her physician to be capable of safely completing the assessment. Non-clinical controls were paid for their participation and panic disorder subjects were offered the opportunity to receive treatment in a cognitive behavioral therapy group after completion of laboratory and ambulatory assessment.

### Procedure

#### Overview.

After baseline cardiovascular measures were obtained all non-clinical control and panic disorder subjects underwent an evaluation of their cardiovascular responses to a series of physiological challenges, e.g., postural change, Valsalva maneuver and 35% carbon dioxide inhalation to evaluate cardiovascular reactivity and vagal tone for examination of group differences. Pencil and paper self-reports provided measures of anxiety symptoms and cognitions prior to and after each intervention. All subjects then

attempted to exercise on a stationary bicycle to provide an estimate of their  $\text{VO}_2$  max, a measure of aerobic fitness.

Table 1.1  
Overview of Methods

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|                                                                        |
|------------------------------------------------------------------------|
| <b>Laboratory Study: measures dependent variables:</b>                 |
| <b>SBP, DBP, HR, VT during</b>                                         |
| <b>baseline</b>                                                        |
| <b>postural challenge</b>                                              |
| <b>Valsalva maneuver</b>                                               |
| <b><math>\text{CO}_2</math> inhalation</b>                             |
| <b>Ambulatory study: measure dependent variables:</b>                  |
| <b>SBP, DBP, HR (ambulatory BP)</b>                                    |
| <b>HRV (Holter)</b>                                                    |
| <b>Activity/anxiety (activity diary) during 24-hour monitoring of:</b> |
| <b>non-anxious periods (baseline)</b>                                  |
| <b>naturally occurring panic</b>                                       |

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To examine cardiovascular reactivity and heart rate variability during panic and non-panic episodes panic disorder patients were encouraged to undergo ambulatory monitoring after completion of laboratory studies. Panic disorder patients who were willing to expose themselves to panicogenic situations were fitted with an ambulatory blood pressure monitor and a Holter electrocardiographic monitor for 24 hour cardiovascular assessment of spontaneous (unexpected) and situational panic (under circumstances in which panic has occurred previously). Subjects were instructed in the use of an activity diary provided for the recording of activity, subjective anxiety ratings and anxiety sensations (Table 1.1).

### Laboratory Studies.

All subjects underwent laboratory testing at 9:00 AM. Prior to their arrival in the laboratory, they had been instructed to wear comfortable clothing, suitable for exercising, and to complete and bring to the laboratory a medical history questionnaire and the following self-report measures which had been previously mailed to them:

Self-report screening measures. Most of following measures have been, and continue to be, widely used and have been reported to have acceptable levels of reliability and validity.

The Anxiety Sensitivity Index (ASI), which measures sensitivity to and discomfort with physical symptoms associated with anxiety, is a 16 item list of symptoms which are rated according to the degree to which they are endorsed by the subject on a five-point Likert scale, ranging from “very little” (0 points) to “very much” (4 points) (Reiss, Petersen, Gursky and McNally, 1986).

The Beck Anxiety Inventory (BAI) is a 21 item list of anxiety symptoms which are rated by the subject according to the degree of distress they experience with each symptom on a 4-point scale on which 0 = not at all and 3 = severely. Internal consistency of this inventory has been shown to be high ( $\alpha = .92$ ) and the test-retest reliability has been .75 after a week.

The Beck Depression Inventory (BDI) is a list of 21 sets of 4 statements in which items in a set correspond to an increasing severity of depression. The subject selects the item in each set which best describes his/her experience of that symptom (Beck, Ward, Mendelson, Mock & Erbaugh, 1961). Internal consistency has ranged from .73 to .95 and

test-retest reliability in non-psychiatric samples has had a range of .60 to .90.

The Fear Questionnaire-Agoraphobia Subscale (FQ-Ago) assesses the degree of phobic avoidance of situations on a 5-item scale (Marks & Mathews, 1979). This scale is widely used to assess agoraphobia in treatment outcome studies and has been shown to have adequate psychometric properties (Jacobsen, Wilson & Tupper, 1988).

The Mobility Inventory for Agoraphobia (MI) assesses the relative frequency of avoidance of 27 items or situations, such as tall buildings or public transportation, when alone or accompanied (Chambless, Caputo, Jasin, Gracely & Williams, 1985). This scale is reported to be reliable ( $r = .90$ ) and internally consistent ( $\alpha = .94$ ).

The Panic Appraisal Inventory (PAI) is a 3-part inventory which evaluates the perceived likelihood of panic in 15 situations, specific panic related threat appraisals, e.g., physical, social and loss of control, and panic-related coping self-efficacy (Telch et al. 1989). Likelihood is rated on a 0 to 100 scale of increasing likelihood of panic, degree of threat is rated on a 0 to 100 scale of increasing threat and coping self-efficacy is rated on a 0 to 100 scale of increasing self-confidence in the ability to effectively cope with panic.

The Sheehan Patient Rating Anxiety Scale (SPRAS) rates the intensity of 35 anxiety symptoms on a 5-point scale ranging from 0 (not at all distressing) to 4 (extremely distressing) (Sheehan, 1983).

The State-Trait Anxiety Inventory (Forms X-1, X-2) (STAI) is a list of anxious and non-anxious feelings which subjects endorse on a 4-point scale as more or less applicable to them either at that time or usually (Spielberger, Gorsuch & Lushene, 1970).

Upon arrival in the laboratory, subjects were asked to provide informed, written

consent to participate in the studies. Subjects were informed that they could withdraw from the study at any time. Subjects then completed questionnaires pertaining to tobacco, caffeine and medication intake within the previous 72 hours. Panic disorder patients also provided information about the number and severity of panic attacks during the last month, and about the degree of work and/or social impairment and avoidance associated with the attacks.

Diagnostic interview. The Structured Clinical Interview (SCID-I/P) which employs DSM-IV diagnostic criteria for Axis I disorders was administered by a graduate student trained in its use. Diagnoses were reviewed on a weekly basis by a licensed clinical psychologist. Interviews were videotaped, with the subject's consent, to ensure diagnostic validity and interrater reliability.

Self-report measures. The following self-report measure were administered at the end of each baseline and after each of the compressed air and carbon dioxide inhalations to determine whether subjects experienced a panic attack during the procedure:

The Acute Panic Inventory (API) is a 24 item check list of symptoms that occur during panic such as feeling faint or confused. Subjects rated each item according to severity on a 4 point scale from 0 (absent) to 3 (severe). A 25th item rated the subject's highest level of fear on a 100 point scale from 0 (no fear) to 100 (extreme fear). The 26th item on the API administered after the inhalation challenge required a Yes/No response to the question "Did you panic (i.e., have a sudden surge of intense anxiety) at any time during or after the compressed air/CO<sub>2</sub> inhalation?"

Physiological measurements. Using an automatic blood pressure monitor

(Critikon Dinamap Vital Signs Monitor, Model 1846 SX) systolic, diastolic, and mean arterial pressure and heart rate were recorded at intervals determined by the stage of the protocol throughout the laboratory procedure, except during bicycle exercise.

(Although mean arterial pressure was recorded, it was not included in the data analysis in an effort to reduce the number of dependent variables, and hence, Type I error.)

Cardiac vagal tone, a frequency domain estimate of heart rate variability, and heart rate were recorded continuously using a patented (Porges, 1985) Vagal Tone Monitor (VTM II, Bethesda, Maryland), a computerized monitor capable of a frequency analysis of the low, and high frequency components of the electrocardiogram (George et al., 1989). The VTM II requires a single channel, three lead, signal from an electrocardiographic pre-amplifier (Scope Services). The VTM II was calibrated initially using a standardized signal, but not thereafter on regular day to day basis.

The Porges method is widely accepted, is one of the two most commonly used techniques for evaluation of vagal tone and has been validated in clinical research settings (Billman & Dujardin, 1990; Dellinger, Jansen, Zaber & Birnbaum, 1988; Litvack, Oberlander, Carney and Saul, 1995). The author of this paper received instruction in the use of the VTM II in the laboratory of its developer, Dr. Stephen W. Porges, who made recommendations regarding equipment set-up, selection and use of a pre-amplifier, and placement, selection of epoch length and characteristics of a optimal signal. In addition, Dr. Porges provided assistance by telephone during the initial stages of the monitor's use.

Baseline 1. Subjects were asked to rest quietly, without speaking, in a seated position in a comfortable chair. Electrodes and chest leads for continuous single channel

electrocardiographic recording and heart rate variability monitoring were placed on the subjects in a standard three-lead configuration and an automatic blood pressure cuff was be placed on the non-dominant upper arm for diastolic and systolic blood pressure measurements. Recordings of blood pressure were obtained at 2 minute intervals during an 8 minute supine resting baseline while heart rate and heart rate variability were recorded continuously. Self-reports of anxiety symptoms and cognitions were obtained at the end of the baseline.

Orthostatic challenge. After completion of baseline physiological measures and a self-report measure of anxiety (The Acute Panic Inventory), subjects were asked to stand from a sitting position as smoothly as possible and to remain standing, facing forward for 5 minutes. Immediate diastolic and systolic blood pressure recordings were made upon completion of positional change and at 2 minute intervals while heart rate and heart rate variability were recorded continuously. After 5 minutes, subjects were instructed to sit down again and immediate blood pressure readings were recorded. Subjects then rested, without speaking, in a seated position for 5 minutes to allow physiological parameters to return to baseline values.

Valsalva maneuver. Subjects were instructed to inhale as deeply as possible and to perform a breathhold while simultaneously “bearing down” for 5 seconds (Sartory & Olajide, 1988). The examiner then demonstrated the maneuver. An immediate reading was acquired of blood pressure and heart rate, while heart rate variability was continuously recorded. The vagal tone record was marked when the reading was initiated. Vagal tone and heart rate were observed and subjects were instructed to repeat the

maneuver, after a 2 minute rest, if a heart rate increase followed by an immediate heart rate decrease accompanied by vagal tone increase did not occur.

Baseline 2. The subject rested quietly for 9 minutes, seated in a comfortable chair, while blood pressure was recorded at 3 minute intervals and heart rate and heart rate variability were recorded continuously. At the end of the baseline, the subject was asked to complete a self-report measure of anxiety symptoms.

Carbon dioxide inhalation. Using a hand-held spirometer, the subject's vital capacity was determined. The subject was then instructed to inhale as deeply as possible from a 5 liter bag of compressed air and to perform a 5 second breath hold while 2 systolic and diastolic blood pressure measurements were made in rapid succession. The purpose of the compressed air inhalation was to provide a physiological control condition for subsequent carbon dioxide inhalation. Heart rate and heart rate variability were monitored continuously throughout this procedure and inhaled gas volumes were measured and recorded. The subject then completed an anxiety symptoms measure. The inhalation procedure was repeated three additional times in order to obtain a maximum response using a 5 liter bag containing a 35% carbon dioxide/65% oxygen mixture while blood pressure and heart rate recordings were made. Self-report measures of anxiety symptoms were completed after each inhalation. It had been observed during preliminary studies that most subjects have a stable response to second or third inhalations of carbon dioxide, while in others the response appears to be cumulative. Thus, to achieve a maximal response in most subjects three inhalations of carbon dioxide were administered.

Bicycle exercise. Because heart rate variability is correlated with physical fitness,

all subjects, after completion of physiological challenges and a 15 minute rest, underwent submaximal bicycle exercise to estimate their aerobic fitness. A computer programmed Air Force submaximal exercise protocol was utilized that provides an estimated  $\text{VO}_2$  max based on each subject's gender, age, weight, height, baseline and maximum heart rate, perceived level of exertion and exercise duration. Subjects provided informed, written consent prior to exercise. After determination of resting heart rate each subject pedaled at the rate of 100 strokes per minute, synchronous with a metronome beat, for up to eight or nine minutes and with a gradually increased workload, unless the test was prematurely terminated at the subject's request because of pain or exhaustion. The test program was also terminated if the maximum heart rate calculated by the program was exceeded by the subject's recorded heart rate. Heart rate and heart rate variability were continuously monitored throughout exercise and during post-exercise recovery until pre-exercise heart rate was achieved. Subjects were debriefed after recovery.

#### Ambulatory Studies.

Those subjects with panic disorder who were willing to expose themselves to panic provoking situations were monitored for twenty-four hours for assessment of heart rate variability and for physiological reactivity during spontaneous and situational panic during daily life. After completion of laboratory studies, and at least 30 minutes after completion of bicycle exercise, a Holter electrocardiographic monitor (Mortara) was applied to each subject's chest using a standard seven lead placement. In addition, a self-inflating cuff connected to an ambulatory blood pressure monitor (Spacelabs) was placed on the subject's non-dominant arm. The subject was instructed in the care of the Holter

monitor and care and placement of the blood pressure monitor. Each subject was asked to identify three situations known to the subject as likely to induce panic, such as exercising or attending a film presentation, and to record them in the activity diary. The subject was then asked to expose himself/herself to these panic-inducing situations during the 24 hour monitoring period. The blood pressure monitor was programmed to record heart rate and systolic and diastolic blood pressure at pre-set intervals determined by the subject's waking/sleeping routine (20 to 120 minute intervals). The subject was instructed in manual activation of the blood pressure monitor in the event of panic onset between scheduled recordings, and in the use of the activity diary. At the time of each cuff inflation, the subject was instructed to record in the diary, at the time of each cuff inflation, his/her perceived anxiety on a scale of zero to ten (ten corresponding to the highest anxiety level), i.e., his/her SUDS rating (Subjective Units of Distress). In addition the subject was instructed to note any activities, physical symptoms and feelings currently experienced and whether he/she was experiencing panic, either spontaneous or situational.

The activity diary was designed to provide a record of activities and subjective anxiety, in particular any panic episodes, which could then be matched according to real time to blood pressure and heart rate changes recorded by the blood pressure monitor. The Holter electrocardiographic recording tapes were analyzed by the AECG Core Laboratory (Brigham and Women's Hospital, Boston, Massachusetts) for heart rate variability during the 30 minutes preceding and subsequent to each identified panic or near-panic episode, using a patented computerized program (Zymed Corporation). The

computerized program has been widely used and validated for clinical research purposes (Rozanski et al., 1988; Blumenthal et al., 1995). Heart rate variability measures included pNN50 and high and low frequency power. This monitoring technique provided a comprehensive picture of heart rate, blood pressure and heart rate variability trends during panic in a naturalistic setting.

## STATISTICAL ANALYSIS

### Analytic Overview

Chi-square tests and t-tests, were used to test for between-group differences in demographic, clinical and physiological variables. Repeated measures analyses of variance and covariance were conducted to examine the effects of Group (panic disorder vs. non-clinical control) and Trial on systolic and diastolic blood pressure, heart rate and vagal tone at baseline and during orthostatic challenge, Valsalva maneuver, carbon dioxide inhalation and ambulatory monitoring of panic. Because age distribution was skewed toward younger ages in the non-clinical controls and toward older ages in the panic disorder group, and is known to have an effect on physiological variables, age was entered as a covariate. An SPSS repeated measures analysis of covariance, ANCOVA, was used to analyze these data. Because the SPSS program includes epsilon correction where appropriate, degrees of freedom will at times be reported as decimals. Pearson correlation analyses were performed where appropriate when examining laboratory and ambulatory data. The specifics of the data-analytic strategy will be addressed when presenting the results related to each of the hypotheses.

When presenting and discussing the laboratory data, the term *vagal tone* will be used because these data were analyzed by a Vagal Tone Monitor-VTM II, employing a patented method (Porges, 1985), and *vagal tone* is the terminology used by the patent holder. Although vagal tone is expressed as the natural logarithm of the variance/ ms<sup>2</sup>, the patent holder publishes vagal tone data without appended units (George et al., 1989). This practice will be continued in this study. When ambulatory data is presented in this study,

the term *heart rate variability* will be used to distinguish it from data gathered by the VTM-II. Furthermore, *heart rate variability* is recommended and used in guidelines issued by two groups providing standards for its measurement and interpretation (Committee Report, 1997; Task Force, 1996).

## POWER ANALYSIS AND SAMPLE SIZE DETERMINATION

### Overview

Preliminary data were used to estimate effect sizes and the number of additional subjects required to test the various study hypotheses. Analysis of preliminary data had suggested that moderate effect sizes could be expected. The sample of 75 subjects would generally permit all hypotheses to be examined at a power  $> .80$  ( $\beta < .20$ ) with a Type I ( $\alpha$ ) of  $< .05$ . Significance would be determined at  $p < .05$  and the Bonferroni inequality would be used to correct for Type I error.

Because initial results indicated that only one-half of panic disorder patients would experience panic during ambulatory monitoring, it was expected that ambulatory data might be limited to a sample  $\leq 20$ . The effect sizes associated with initial results were moderate to large and the sample ( $N = 10$ ), although small, provided power  $> 80\%$ .

Small effect size was based on  $d = .2$  to  $.4$ , for a moderate effect, size  $d = .5$  to  $.7$  and for a large effect, size  $d = .8$  to  $.9$  (Howell, 1992, p. 208).

Hypothesis 1: Panic disorder patients will demonstrate greater cardiovascular reactivity during physiological challenge than will non-clinical controls. A total sample size of 75 will permit examination of moderate effects at a power of .51 and large effects at a power of .95.

Hypothesis 2a: Panic disorder patients will exhibit significantly decreased heart rate variability during carbon dioxide inhalation and postural challenge compared to non-clinical controls. A total sample of 75 will allow this small to moderate effect size to be examined at a power of .80.

Hypothesis 2b: Decreases in heart rate variability will correlate inversely with blood pressure changes during physiological challenge. Based on previous studies, moderate effect sizes ( $r = .35$  to  $.40$ ) are expected to provide a power of  $.80$  with a sample size of  $75$ .

Hypothesis 3a: Heart rate variability will decrease significantly during ambulatory monitoring of panic compared to non-panic. Pilot data suggested that this effect would be moderate to large. A sample size of  $20$  could detect this effect at a power  $> .80$ . The Bonferroni inequality, with significance determined at  $p < .01$ , will be used to correct for Type I error.

Hypothesis 3b: Panic disorder patients will experience significant cardiovascular reactivity during panic episodes. Preliminary data predicted a moderate to large effect size requiring a sample of not more than  $20$  to detect power  $> .80$ . The Bonferroni inequality, with significance determined at  $p < .01$  will be used to correct for Type I error.

Hypothesis 3c: Decreases in heart rate variability will correlate inversely with systolic and diastolic blood pressure during panic. Preliminary data predicted  $r = .40$  to  $.45$ , which with a sample of  $.20$ , will be detectable at a power  $> .80$ , with a moderate to large effect size.

## RESULTS

### Subject Classification and Exclusion

Four panic disorder patients were excluded from the study for severe current major depression, primary diagnosis of social phobia and alcohol dependency/abuse revealed during the Structured Clinical Interview. In addition, three non-clinical control subjects were excluded from the study because of severe, previously undiagnosed and untreated hypertension and a possible right bundle branch block detected during the laboratory assessment. One non-clinical control was excluded because of current primary diagnosis of social phobia.

After completion of Structured Clinical Interviews and laboratory assessments 52 panic disorder patients and 28 non-clinical control subjects remained for inclusion in the study.

### Demographic characteristics of panic disorder patients and non-clinical controls

Panic disorder patients were found on t-test comparisons (Table 1) to be significantly older than the non-clinical controls (mean age of panickers = 37.47 years, mean age of controls = 30.59;  $t(78) = 2.8$ ,  $p = .006$ ). The distribution of ages in each group was skewed favoring younger subjects in the control group, i.e., 3 subjects < 20 years and none > 55 years, and older subjects in the patient group, i.e., no subjects < 21 and 3 subjects > 56 years,. Therefore, prior to data analyses to make the groups more comparable in age, which can influence physiological variables (e.g., systolic blood pressure and heart rate variability), the three youngest subjects in the control group (< 20 years) and the three oldest subjects (>56 years) in the panic disorder group were excluded

Table 1.  
Group Comparisons of Demographic Variables Among Panic Disorder Patients and Non-clinical Controls

|                                     | <u>Panic Disorder</u><br>(n=49) | <u>Non-clinical Controls</u><br>(n=25) |      |                              |
|-------------------------------------|---------------------------------|----------------------------------------|------|------------------------------|
| Demographic Variable                |                                 |                                        | (L)  | $\chi^2$ (df) p <sup>1</sup> |
| Age                                 |                                 |                                        |      |                              |
| <u>M</u>                            | 35.59                           | 31.56                                  | 1.86 | .07                          |
| <u>SD</u>                           | 8.39                            | 9.63                                   |      |                              |
| Gender                              |                                 |                                        |      | .08(1) .77                   |
| % Female                            | 67.3                            | 64.0                                   |      |                              |
| % Male                              | 32.7                            | 36.0                                   |      |                              |
| Ethnicity                           |                                 |                                        |      | 1.84(3) .61                  |
| % Caucasian                         | 79.5                            | 76.0                                   |      |                              |
| % African American                  | 12.2                            | 8.0                                    |      |                              |
| % Hispanic                          | 6.1                             | 8.0                                    |      |                              |
| % Asian                             | 2.2                             | 8.0                                    |      |                              |
| Marital Status                      |                                 |                                        |      | 4.04(2) .13                  |
| % Married                           | 44.9                            | 40.0                                   |      |                              |
| % Divorced/Separated                | 18.4                            | 4.0                                    |      |                              |
| % Never Married                     | 36.7                            | 56.0                                   |      |                              |
| Employment Status                   |                                 |                                        |      | 1.52(2) .47                  |
| % Employed                          | 84.7                            | 80.0                                   |      |                              |
| % Unemployed                        | 2.0                             | 8.0                                    |      |                              |
| % Student                           | 13.3                            | 12.0                                   |      |                              |
| Education                           |                                 |                                        |      | 7.32(4) .12                  |
| % High School or less               | 14.3                            | 0                                      |      |                              |
| % Some College                      | 28.6                            | 32.1                                   |      |                              |
| % Completed College                 | 30.6                            | 21.4                                   |      |                              |
| % Some Graduate/Professional School | 18.3                            | 32.1                                   |      |                              |
| % Graduate/Professional School      | 8.2                             | 14.3                                   |      |                              |

<sup>1</sup> two-tailed significance



Table 2.

**Group Comparisons of Self-report Measures**

| Variable                    | Panic Disorder<br>(n=49) |           | Non-clinical Controls<br>(n=25) |           |          |
|-----------------------------|--------------------------|-----------|---------------------------------|-----------|----------|
|                             | <b>M</b>                 | <b>SD</b> | <b>M</b>                        | <b>SD</b> | <b>t</b> |
| <b>Self-report Measures</b> |                          |           |                                 |           |          |
| BAI                         | 22.86                    | 14.21     | 2.04                            | 2.18      | 7.11*    |
| BDI                         | 15.85                    | 10.71     | 2.46                            | 3.05      | 5.99*    |
| ASI                         | 31.31                    | 9.78      | 9.83                            | 5.82      | 9.91*    |
| SPRAS-1                     | 54.33                    | 25.39     | 4.46                            | 4.34      | 9.52*    |
| SPRAS-2                     | 8.31                     | 7.40      | 1.26                            | 1.96      | 4.48*    |
| STAI-1                      | 37.51                    | 15.04     | 7.58                            | 7.20      | 9.22*    |
| STAI-2                      | 43.88                    | 11.96     | 11.33                           | 8.95      | 11.79*   |
| FEAR Q-1                    | 10.23                    | 9.17      | 1.50                            | 2.06      | 4.59*    |
| FEAR Q-2                    | 3.54                     | 2.18      | .50                             | .78       | 6.61*    |
| MIACCOM                     | 1.70                     | .60       | 1.03                            | .20       | 5.52*    |
| MIALONE                     | 2.12                     | .92       | 1.20                            | .20       | 5.80*    |
| DS-Work & Social            | 3.51                     | .96       | 1.17                            | .49       | 10.93*   |
| DS-Family Life              | 4.39                     | 2.78      | .59                             | 1.79      | 5.87*    |
| DS-Social Life              | 4.98                     | 2.85      | .77                             | 1.97      | 6.26*    |
| PAI-1                       | 534.53                   | 309.33    | 99.83                           | 149.13    | 6.51*    |
| PAI-2                       | 467.55                   | 354.71    | 23.54                           | 52.14     | 6.08*    |
| PAI-3                       | 515.10                   | 253.41    | 1328.83                         | 232.06    | -13.24*  |

**Note:** BAI = Beck Anxiety Inventory, BDI = Beck Depression Inventory, ASI = Anxiety Sensitivity Index, SPRAS = Sheehan Patient Rating Anxiety Scale, STAI = State-Trait Anxiety Inventory, MIACCOM and MIALONE = Mobility Inventory for Agoraphobia, Accompanied and Alone, DS = Disability Scale, PAI = Panic Attack Appraisal Inventory

\*  $p < .000$

from the remainder of the data analyses. This resulted in reductions in the age range of the combined group (from 18 to 63 years, originally, to 20 to 56 years) and the sizes of the groups (from  $N_p = 52$  and  $N_c = 28$  to  $N_p = 49$  and  $N_c = 25$ ) and a now marginally significant age difference between the panickers and controls (mean age of panickers = 36.04, mean age of controls = 31.56;  $t = 1.925$ ,  $p = .06$ ). Although the age difference was still marginally significant, to avoid further loss of statistical power additional reductions in the sample size were not undertaken. Instead, an analysis of covariance strategy, with age as a covariate, was employed. Chi-square comparisons of gender, ethnicity, employment, education and marital status, however, revealed no significant between-group differences (Table 1).

#### Self-report measures

As expected, panic disorder patients reported significantly higher levels of anxiety (state and trait), depression, anxiety sensitivity, phobic avoidance, and impairment of work, family life and social life than did non-clinical controls (Table 2).

#### Prevalence of DSM-IV Axis I disorders

All panic disorder patients met DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 1994) criteria for primary diagnosis of panic disorder either with agoraphobia (63.3%) or without agoraphobia (36.7%) (see Table 3). In addition, 8 (16.3%) of the panickers had co-occurring social phobia, 13 (26.5%) had generalized anxiety disorder and 6 (12.2%) met criteria for current (1 (2%)) or past posttraumatic stress disorder. Nine (18.4%) panic disorder patients had current major depression, 2 (4.1%) had dysthymia and 4 (8.2%) were past or current (1 (2%)) alcohol abusers (Table

3). None of the non-clinical controls met criteria for either past or current panic disorder, however, 1 (3.6%) had a history of an eating disorder (Table 3).

Table 3.

Current and Lifetime Prevalence of DSM-IV Axis I Disorders in Panic Disorder Patients and Non-clinical Controls

| Diagnostic Category | Panic Disorder  |                  | Non-clinical Controls |                  |
|---------------------|-----------------|------------------|-----------------------|------------------|
|                     | Current<br>%(n) | Lifetime<br>%(n) | Current<br>%(n)       | Lifetime<br>%(n) |
| Agoraphobia         | 63.3(31)        | 63.3(31)         | 0                     | 0                |
| Specific Phobia     | 0               | 0                | 0                     | 0                |
| Social Phobia       | 16.3(8)         | 16.3(8)          | 0                     | 0                |
| GAD                 | 26.5(13)        | 26.5(13)         | 0                     | 0                |
| PTSD                | 2.0(1)          | 12.2(6)          | 0                     | 0                |
| Major Depression    | 18.4(9)         | 38.8(19)         | 0                     | 0                |
| Dysthymia           | 4.1(2)          | 4.1(2)           | 0                     | 0                |
| Alcohol Abuse       | 2.0(1)          | 8.2(4)           | 0                     | 0                |
| Polydrug Dependence | 0               | 2.0(1)           | 0                     | 0                |
| Eating Disorder     | 0               | 2.0(1)           | 0                     | 3.6(1)           |

Note: GAD = generalized anxiety disorder, PTSD = posttraumatic stress disorder

### Aerobic fitness

All control subjects underwent bicycle exercise to assess their aerobic fitness. It was not possible, however, to adequately evaluate fitness in the panic disorder group.

Many patients either refused to attempt exercise because of pain, e.g., knee pain, or fear of panic onset, or discontinued exercise prior to becoming fatigued because cardiovascular symptoms, e.g., increased heart rate, rapid breathing, shortness of breath and sweatiness, which were similar to panic symptoms, made them fearful of a possibly impending panic attack.

### Laboratory Studies

**Hypothesis 1: When compared to non-clinical controls, panic disorder patients will demonstrate significantly greater cardiovascular reactivity during postural challenge and carbon dioxide challenge.**

### Overview

Cardiovascular reactivity, i.e., systolic and diastolic blood pressure, heart rate and vagal tone, was examined during each physiological challenge, i.e., postural change, Valsalva maneuver and carbon dioxide inhalation. Independent-sample t-tests were performed on baseline values of the dependent variables to examine group differences. Repeated measures ANCOVAs assessed the effects of group (panic vs. control) and trial on the dependent variables, and the effect of age as a covariate. As described above, all repeated measures analyses included age as a covariate because of the remaining skewed age distributions in the two groups and the known effects of age on the cardiovascular variables of interest in this study.

### Postural challenge

Although possibly redundant with the repeated measures analysis, independent-sample t-tests comparing non-clinical controls to panic disorder patients at baseline were performed and indicated that the panic patients consistently exhibited marginally significantly higher systolic ( $t(72) = 1.71, p = .09$ ) and diastolic ( $t(72) = 1.86, p = .07$ ) blood pressures and heart rates ( $t(72) = 1.88, p = .06$ ). Baseline vagal tone was significantly lower in panickers compared to non-clinical controls ( $t(55) = 2.25, p < .05$ ).

Repeated measures. A 2 x 5 repeated measures analysis (ANCOVA) was

conducted on physiological responses measured at five time points during the orthostatic challenge, i.e., (1) at baseline, (2) immediately upon standing, (3) after 2 minutes of standing, (4) after 4 minutes of standing and (5) immediately upon sitting. Group (panicker vs. control) was studied as a between-subjects effect and Age was used as a covariate. (Age was a covariate because age is known to influence physiological variables. The age distribution, although only marginally significantly different ( $p > .06$ ), was positively skewed with a median age of 28 years and mean of 31.6 years in the control group and approached a normal distribution with a median age of 35 years and mean of 35.6 years in the panic group. The range in the two groups was similar, i.e., 20 to 54 years in the controls and 21 to 56 in the panic group). Within-subjects effects on each dependent variable (systolic and diastolic blood pressure, heart rate and vagal tone) due to Trial, and Group and Trial were examined. In some instances, due to epsilon-correction, degrees of freedom are reported as decimals.

Summary. In general, significant effects of the age covariate affected blood pressure and vagal tone responses during the postural challenge. After controlling for age, a significant main effect for Group was seen only in heart rate responses which increased most markedly in the panic disorder group from baseline upon standing and remained higher. A Group x Trial interaction occurred immediately upon standing, notable for an increase in vagal tone from 5.93 at baseline to 6.34 on standing in the panickers accompanied by a decrease in vagal tone from 6.74 to 5.82 in the controls.

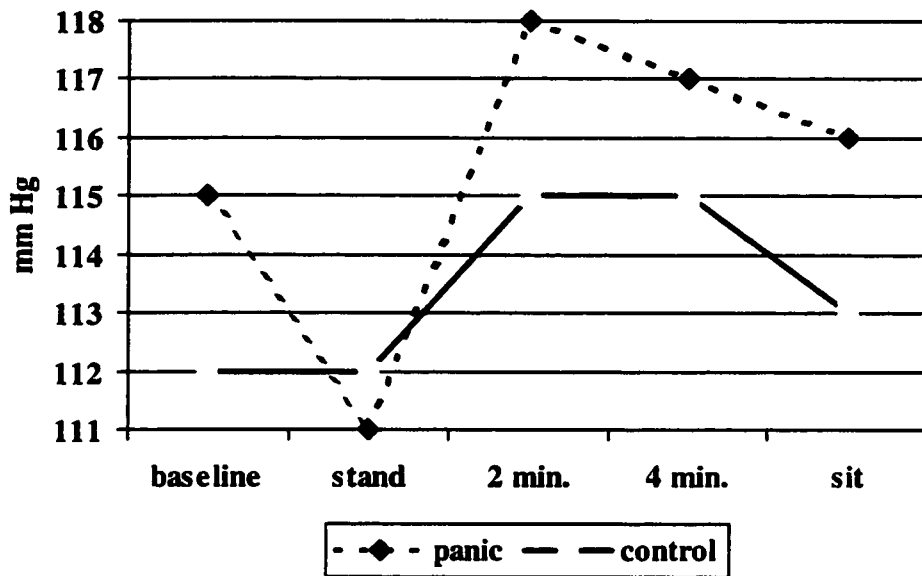


Figure 1. Adjusted means of systolic blood pressure during postural change.

Analysis of systolic blood pressure (Figure 1) revealed a significant main effect of the Age covariate,  $F(1, 70) = 11.87$ ,  $p < .001$ , but not for Group,  $F(1, 70) = .468$ ,  $p = .50$ . No significant within-subjects effects were found for Trial,  $F(3.32, 232.22) = .231$ ,  $p = .89$ , or Group x Trial,  $F(3.32, 232.22) = .672$ ,  $p = .59$ .

When diastolic blood pressure (Figure 2) was examined a significant effect was found for the Age covariate,  $F(1, 70) = 4.234$ ,  $p < .05$ , but not for Group,  $F(1, 70) = 1.47$ ,  $p = .23$ . A significant within-subjects main effect for Trial was revealed,  $F = (3.18, 222.43) = 4.51$ ,  $p = .004$ , as well as a non-significant effect for Group x Trial,  $F(3.18, 222.43) = 1.52$ ,  $p = .21$ .

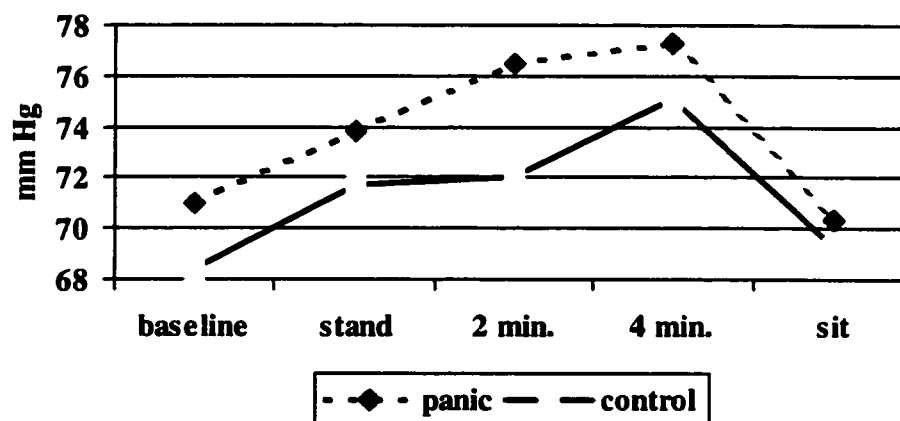


Figure 2. Adjusted means of diastolic blood pressure during postural change.

There was, however, a significant main effect on heart rate (Figure 3) of Group,  $F(1, 69) = 4.10, p < .05$ , but no effect for the Age covariate,  $F(1, 69) = .75, p = .39$ .

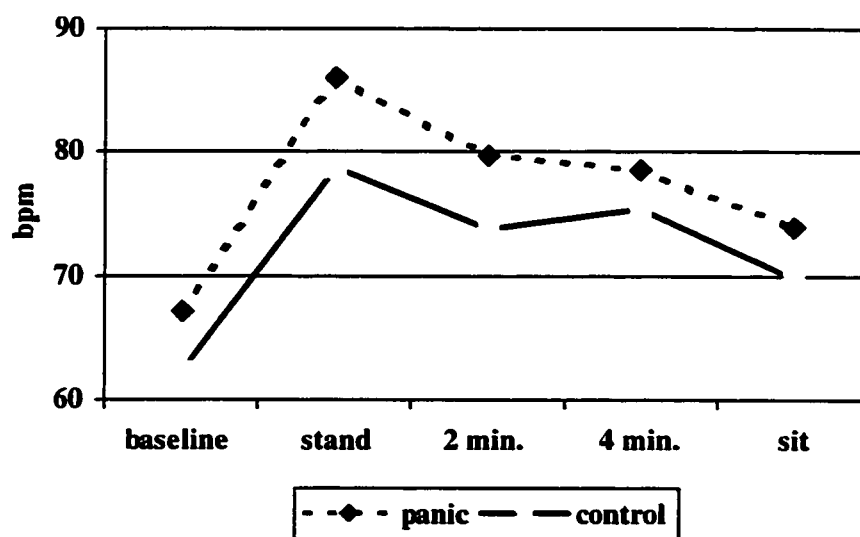


Figure 3. Adjusted means of heart rate during postural challenge.

Trial had a significant within-subjects effect on heart rate,  $F(1.13, 216.04) = 6.721$ ,  $p < .001$ , while Group  $\times$  Trial,  $F(3.13, 216.04) = .615$ ,  $p = .61$ , did not.

Examination of vagal tone (Figure 4) revealed a significant covariate effect for Age,  $F(1,55) = 9.85$ ,  $p < .001$ , but no effect for Group,  $F(1,55) = .414$ ,  $p = .52$ . Analysis of within-subjects effects found a marginally significant effect for Trial,  $F(3.29, 181.05) = 2.471$ ,  $p = .06$ , a significant effect of Group  $\times$  Trial,  $F(3.29, 55) = 3.633$ ,  $p < .05$ , and a significant interaction between Group and Trial at Time 2 (immediately upon standing),  $F(1, 55) = 9.50$ ,  $p < .01$ , marked by an increase in vagal tone from 5.93 at baseline to 6.34 upon standing in the panic group and a decrease from 6.74 to 5.82 in the control group.

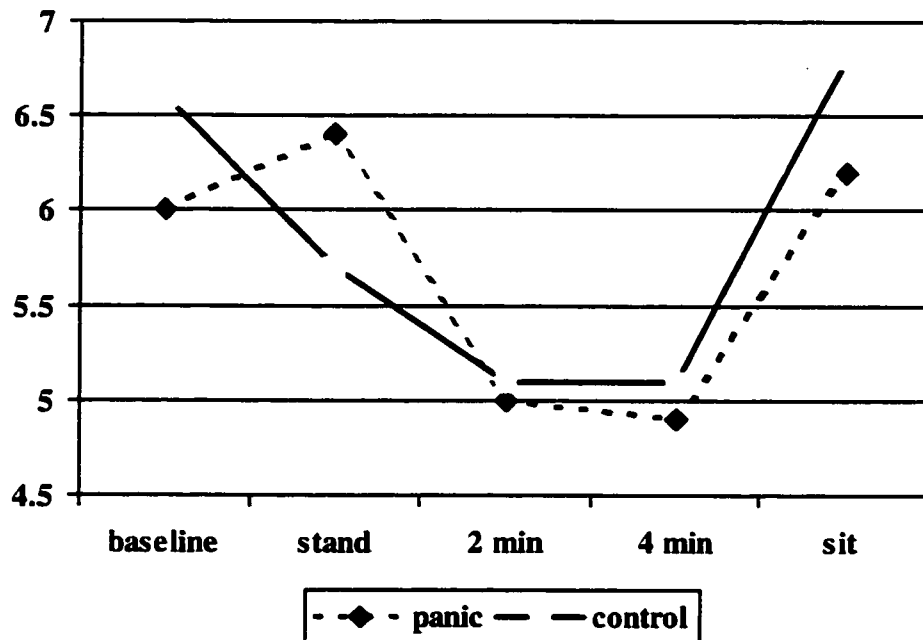


Figure 4. Adjusted means for vagal tone during postural change.

### Valsalva maneuver

Repeated measures. A 2 x 2 repeated measures ANCOVA was used to examine the between-subjects effect of Group with the Age as covariate, and the within-subjects effects of Trial (comparing the Valsalva maneuver to baseline) and Group x Trial on the following dependent variables: systolic and diastolic blood pressure, heart rate and vagal tone in response to the Valsalva maneuver. A significant between-subjects covariate effect on systolic blood pressure was revealed for Age,  $F(1, 71) = 13.96$ ,  $P < .001$ , but there was no effect for Group,  $F(1, 71) = .723$ ,  $p = .40$ . Examination of within-subjects effects indicated no significant tests for Trial,  $F(1, 71) = .400$ ,  $p = .53$ , or Group x Trial,  $F(1, 71) = .011$ ,  $p = .92$ .

Similarly, only the Age covariate had significant effects on diastolic blood pressure,  $F(1, 71) = 4.74$ ,  $p < .05$ , while there was no significant effect for Group,  $F(1, 71) = 1.098$ ,  $p = .30$ . There were no apparent within-subjects effects of Trial,  $F(1, 71) = .574$ ,  $p = .45$ , or Group x Trial,  $F(1, 71) = .018$ ,  $p = .89$ .

Analysis of heart rate responses revealed a trend toward significance in the between-subjects effect of Group,  $F(1, 71) = 2.943$ ,  $p = .09$ , but no effect was found for the Age covariate,  $F(1, 71) = .096$ ,  $p = .76$ . There were no significant within-subjects effects of Trial,  $F(1, 71) = 1.512$ ,  $p = .22$ ,  $F(1, 71) = 1.13$ ,  $p = .29$  or Group x Trial,  $F(1, 71) = .165$ ,  $p = .69$ .

When the between-subjects effects of Valsalva maneuver on vagal tone were analysed, both Group,  $F(1, 54) = 4.48$ ,  $p < .05$ , and the Age covariate,  $F(1, 54) = 7.14$ ,  $p = .01$ , were found to have significant effects. Tests of within-subjects effects, however,

revealed no statistical significance for Trial,  $F(1, 54) = .395$ ,  $p = .53$  or Group x Trial,  $F(1, 54) = .066$ ,  $p = .80$ .

Summary. Overall, these results are indicative of significant covariate effects of age on blood pressure and vagal tone responses during the Valsalva maneuver. A between-subjects effect of Group on heart rate that approached significance emerged, as did a significant effect of Group on vagal tone in which both panickers and controls experienced significant increases, but the increase in controls was significant larger than in the panickers.

#### Compressed air and carbon dioxide inhalation challenge

##### Subjective responses to the inhalation challenge.

Anxiety symptoms as reported on the Acute Panic Inventory (API) and subjective feelings of anxiety approaching panic on the Subjective Units of Distress Scale (SUDS), were significantly greater in panic disorder patients than they were in non-clinical controls. Independent sample t-tests revealed differences at baseline during which panickers reported significantly a greater number and intensity of anxiety symptoms (API) ( $t(68) = 4.38$ ,  $p < .001$ ) and anxious distress (SUDS) ( $t(68) = 4.28$ ,  $p < .001$ ) than did the non-clinical controls (Table 5). These differences were also apparent during compressed air inhalation ( $t(67) = 3.43$ ,  $p < .001$  (API);  $t(67) = 5.26$ ,  $p = .001$  (SUDS)). During the carbon dioxide inhalation the reported number and intensity of symptoms and level of distress increased for both panickers and controls, but remained significantly greater in panickers ( $t(67) = 2.79$ ,  $p = .001$  (API);  $t(67) = 4.57$ ,  $p < .001$  (SUDS)), 47% of whom responded positively to the question “Did you panic?” Although non-clinical

controls reported physical symptoms of anxiety on the API, similar to those of the panickers but generally of less intensity and accompanied by less anxious distress, there was only one report of panic in the control group.

Table 5.  
Between-group and Within-group Comparisons of Panic Symptoms and SUDS Ratings among Panic Disorder Patients and Non-clinical Controls at Baseline and During Inhalation Challenge

| Variable                  | <u>Panic disorder</u><br>(n=49) |           | <u>Non-clinical Controls</u><br>(n=25) |           | mean<br>difference | t <sup>3</sup> |
|---------------------------|---------------------------------|-----------|----------------------------------------|-----------|--------------------|----------------|
|                           | <u>M</u>                        | <u>SD</u> | <u>M</u>                               | <u>SD</u> |                    |                |
| Baseline API <sup>1</sup> | 6.22                            | 6.91      | .23                                    | .65       | 5.99               | 4.39**         |
| SUDS <sup>2</sup>         | 16.52                           | 18.62     | .77                                    | 2.72      | 15.75              | 4.28**         |
| Air API                   | 7.87*                           | 9.91      | 1.21                                   | 3.14      | 6.86               | 3.43**         |
| SUDS                      | 29.75**                         | 25.76     | 2.69                                   | 6.04      | 27.06              | 5.26**         |
| CO <sub>2</sub> 1 API     | 15.75**                         | 13.62     | 4.23*                                  | 4.40      | 11.52              | 4.19**         |
| SUDS                      | 42.29**                         | 26.84     | 9.23*                                  | 14.12     | 33.06              | 5.85**         |
| CO <sub>2</sub> 2 API     | 17.89*                          | 11.72     | 7.19*                                  | 6.74      | 10.70              | 4.28**         |
| SUDS                      | 48.30*                          | 27.77     | 14.62                                  | 21.02     | 33.68              | 5.38**         |
| CO <sub>2</sub> 3 API     | 17.77                           | 12.29     | 10.16**                                | 7.49      | 7.61               | 2.79**         |
| SUDS                      | 46.88                           | 29.97     | 15.80                                  | 20.29     | 31.08              | 4.57**         |

<sup>1</sup>Acute Panic Inventory

<sup>2</sup>Subjective Units of Distress Scale

<sup>3</sup>Between-group t-tests (independent samples), \*\* p <.001

means with asterisks: within-group t-tests (paired sample), \* p <.05, \*\* p <.001

### Cardiovascular responses to the inhalation challenge.

Repeated measures ANCOVAs examined the effects of Trials (time points of interventions, i.e., baseline, compressed air and three carbon dioxide inhalations), Group (panic vs. control) and Age as a covariate.

Overview. A 2 x 5 repeated measures ANCOVA was used to study the between-

subjects effect of Group covaried with Age and the within-subjects effects of Trials, and Group x Trials, measured at 5 time points (baseline, compressed air inhalation and 3 carbon dioxide inhalations), on the dependent variables, i.e., systolic and diastolic blood pressure, heart rate and vagal tone responses to compressed air and carbon dioxide. As indicated above, compressed air inhalation provided baseline measures to control for the effects of inspiratory effort.

In general, Age was found to have significant effects on systolic blood pressure and vagal tone. There were, however no significant between-subjects effects of Group. Four Group x Trial interactions occurred and included an interaction effect on systolic blood pressure at the last carbon dioxide inhalation, on diastolic blood pressure at the first carbon dioxide inhalation, on heart rate at the second carbon dioxide inhalation and on vagal tone at the first carbon dioxide inhalation.

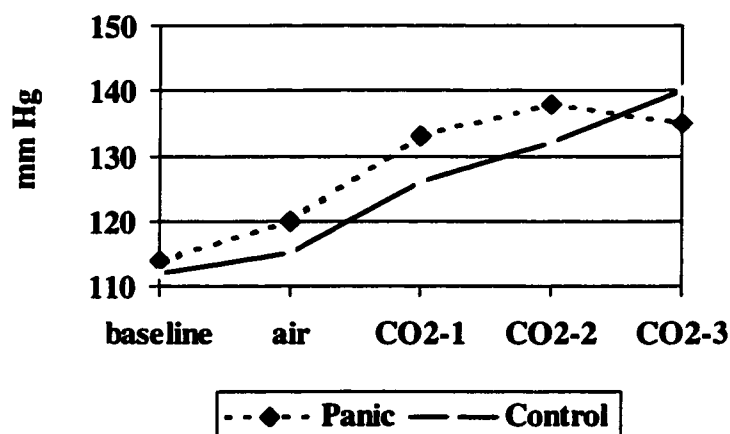


Figure 5. Adjusted means of systolic blood pressure during CO<sub>2</sub> inhalation.

Repeated measures. Although Age affected systolic blood pressure significantly,  $F(1, 61) = 5.86, p < .05$ , Group showed no significant effect,  $F(1, 61) = .740, p = .40$ . Analysis of within-subjects effects revealed an effect with a trend toward significance of Trial,  $F(2.46, 211.09) = 2.02, p = .11$ , and a significant effect for Group x Trial ( $3.46, 211.09) = 2.86, p < .05$ . A significant Group x Trial interaction effect occurred at Trial 5 (third carbon dioxide inhalation),  $F(1, 61) = 8.811, p < .01$ , such that systolic blood pressure (Figure 5) increased in the controls from 129.86 mm Hg at Time 4 to 137.32 mmHg while it decreased in the panic disorder patients from 139.44 mm Hg to 135.48 mm Hg.

Neither Age,  $F(1, 61) = .217, p = .64$  nor Group,  $F(1, 61) = .308, p = .58$ , were associated with significant effects on diastolic blood pressure. Trial, however, was linked

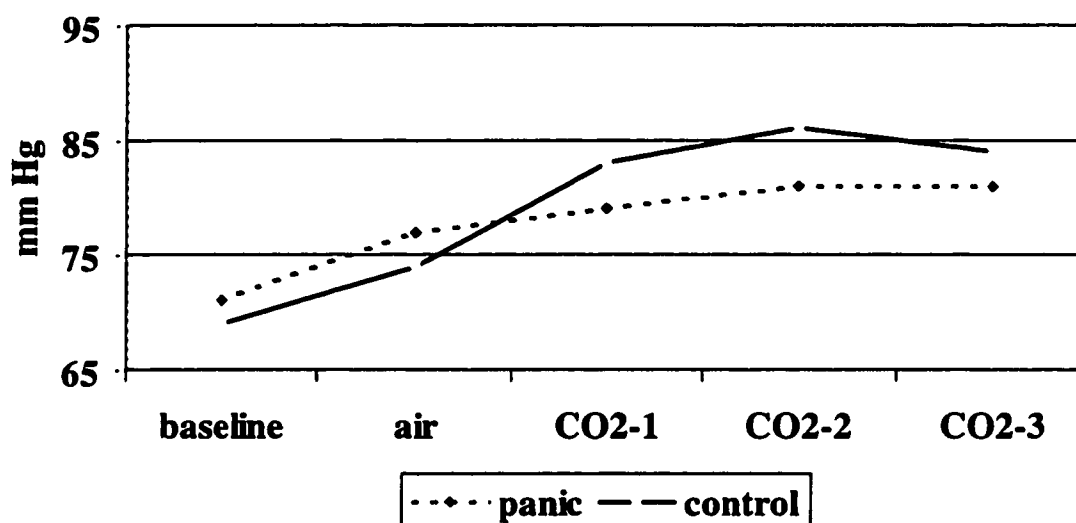


Figure 6. Adjusted means of diastolic blood pressure during CO<sub>2</sub> inhalation.

to significant within-subjects effects,  $F(3.48, 212.44) = 1.344$ ,  $p < .001$ , as was Group  $\times$  Trial,  $F(3.48, 212.44) = 2.09$ ,  $p < .05$ . There was, in addition, a significant Group  $\times$  Trial interaction,  $F(3.48, 212.44) = 5.738$ ,  $p = .02$ , at Trial 3 (the first carbon dioxide inhalation), marked by a marked increase in diastolic blood pressure (Figure 6) from 72.48 mm Hg to 83.00 mm Hg in the controls and a leveling-off in diastolic blood pressure from 81.17 mm Hg to 78.98 mm Hg in the panickers.

There was no significant between-subjects effect on heart rate for Group,  $F(1, 61) = .802$ ,  $p = .37$ , and no effect of the Age covariate,  $F(1, 61) = .343$ ,  $p = .56$ . Within-subjects effects of Trial were not significant,  $F(3.55, 216.28) = 1.574$ ,  $p = .15$ , although

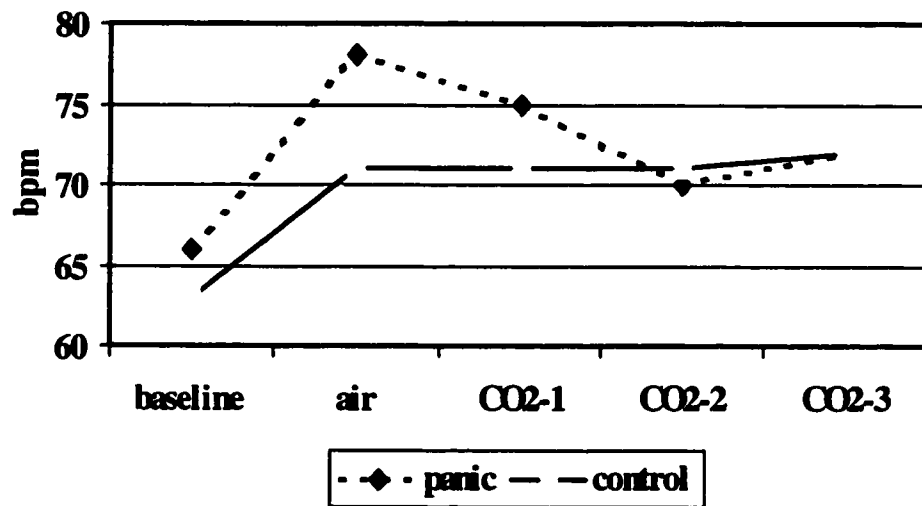


Figure 7. Adjusted means of heart rate during CO<sub>2</sub> inhalation.

Group x Trial showed a trend toward significance,  $F(3.55, 216.28) = 2.17$ ,  $p = .08$ . In addition, there was a significant Group x Trial interaction at Trial 4 (second carbon dioxide inhalation),  $F(1, 61) = 5.466$ ,  $p < .05$ , as heart rate decreased in the panickers from 76.21 bpm to 72.87 bpm and leveled-off in the controls from 72.38 bpm to 72.32 bpm (Figure 7).

The between-subjects effect of Group on vagal tone was not significant,  $F(1, 43) = .026$ ,  $p = .87$ , although the effects of the Age covariate,  $F(1, 43) = 5.061$ ,  $p < .05$ , were significant. Trial was without significant effects on vagal tone,  $F(3.43, 147.51) = .693$ ,  $p = .58$ , and Group x Trial demonstrated a trend toward significant effects,  $F(3.43, 147.51) = 2.53$ ,  $p = .08$ . Moreover, a Group x Trial interaction was revealed after Trial 3 (first carbon dioxide inhalation),  $F(1, 43) = 5.128$ ,  $p < .05$ , when vagal tone increased in panickers from 6.07 to 6.93 and decreased in the controls from 6.64 to 6.54 (Figure 8).

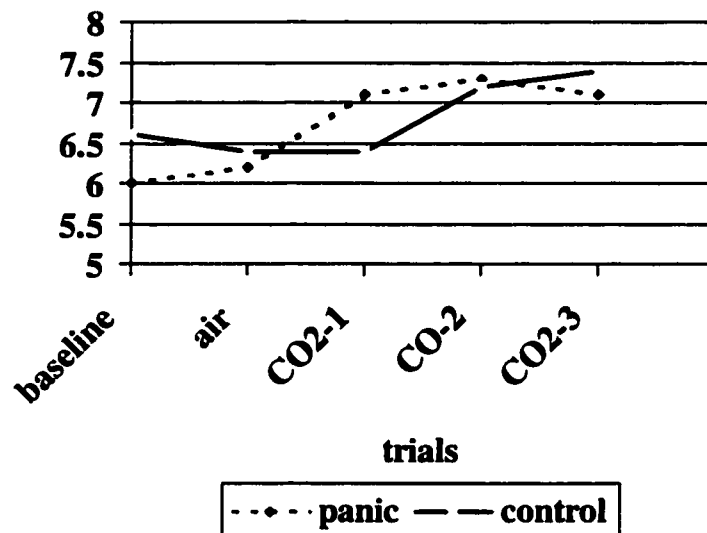


Figure 8. Adjusted means of vagal tone during CO<sub>2</sub> inhalation.

**Hypothesis 2a: Panic disorder patients will show significantly decreased heart rate variability during postural challenge and carbon dioxide when compared to non-clinical controls.**

Overview. At baseline vagal tone was significantly lower in panickers than in controls and appeared to demonstrate a generalized trend toward being lower in panickers throughout most of the physiological challenges. Repeated measures revealed that during the Valsalva maneuver vagal tone increase was significantly less in panickers than in non-clinical controls although both groups showed substantial increases above baseline levels. Group x Trial interactions occurred during the postural and inhalation challenges in which panickers' vagal tone responses were in a direction opposite to that of the controls and are suggestive of an abnormal or even paradoxical vagal response.

Postural challenge. Initially, results indicated that panic disorder patients had significantly lower vagal tone (VT) at baseline ( $t(55) = 2.25, p = .05$ ) than did the non-clinical controls. Repeated measures ANCOVA, however, found a significant covariant effect of Age,  $F(1, 55) = 9.85, p < .001$ , on vagal tone during postural challenge, and no significant effect of Group,  $F(1, 55) = .414, p = .52$ , suggesting that the apparent between-subjects differences in vagal tone were due primarily to age differences between the two groups. ANCOVAs revealed a significant Group x Trial interaction which occurred immediately upon standing and was marked by an increase in vagal tone in the panickers accompanied by a decrease in the non-clinical controls ( $VT_{\text{Panic}} = 5.93, VT_{\text{Control}} = 6.74$  at baseline;  $VT_{\text{Panic}} = 6.34, VT_{\text{Control}} = 5.82$  upon standing).

The Valsalva maneuver produced non-significant changes in blood pressure and heart rate but resulted in an increase in vagal tone above baseline measures ( $VT_{\text{Panic}} = 6.72, VT_{\text{Control}} = 7.46$ ). which repeated measures ANCOVAs revealed was a significant between-subjects effect of Group,  $F(1, 54) = 4.48, p < .05$ , and a significant covariant effect of Age,  $F(1, 54) = 7.14, p = .01$ .

Repeated measures ANCOVA found no significant between-subjects effect of Group on vagal tone during compressed air and carbon dioxide inhalation,  $F(1, 43) = .026, p = .87$ , although significant covariate effects of Age,  $F(1, 43) = 5.061, p < .05$  were found. At the first carbon dioxide inhalation, however, a significant Group x Trial interaction occurred during which vagal tone increased markedly in the panickers while it decreased in the controls.

**Hypothesis 2b: Decreases in heart rate variability will be negatively correlated with systolic and diastolic blood pressure changes during postural challenge and carbon dioxide inhalation.**

Overview. During postural challenge, systolic and diastolic blood pressures were, in general, marginally to significantly, inversely correlated with vagal tone when panickers and non-clinical controls were analyzed as a group. These correlations were less consistent and less often statistically significant when panic disorder patients and controls were analyzed as separate, smaller groups. No consistent correlations between blood pressure and vagal tone during the inhalation challenge were found.

Correlation analyses. Pearson correlation analyses were used to examine the correlation between vagal tone and systolic and diastolic blood pressure during postural and carbon dioxide inhalation challenge. When panic disorder patients and non-clinical controls were analyzed as a single group, vagal tone and both systolic and diastolic blood pressures were, for the most part, found to be significantly and negatively correlated during the postural challenge (Table 6). Upon standing, after two minutes and after four minutes correlations between vagal tone and systolic blood pressure ranged from significant to non-significant ( $r(58) = -.256, p = .053$ ;  $r(59) = -.387, p = .002$ ;  $r(59) = -.249, p = .06$ ) as did the correlations between vagal tone and diastolic blood ( $r(58) = .12, p = .36$ ;  $r(59) = -.249, p = .06$ ;  $r(59) = -.347, p = .007$ ). Upon sitting, systolic blood change was significantly negatively correlated with vagal tone ( $r(59) = -.311, p = .02$ ), but diastolic blood pressure, although negatively correlated with vagal tone, was no

Table 6.

Correlations Between Vagal Tone and Systolic and Diastolic Blood Pressure during Postural Challenge in Panic Disorder Patients and Non-clinical Controls

|    |     | Standing 1 |       | Standing 2 |       | Standing 3 |       | Sitting |       |
|----|-----|------------|-------|------------|-------|------------|-------|---------|-------|
|    |     | SBP        | DBP   | SBP        | DBP   | SBP        | DBP   | SBP     | DBP   |
| VT | r = | -.256      | -.123 | -.387      | -.249 | -.249      | -.347 | -.311   | -.101 |
|    | p = | .05*       | .05*  | .01*       | .06   | .06        | .01*  | .02*    | .45   |
|    | n = | 59         |       |            |       |            |       |         |       |

Table 6.1

Correlations Between Vagal Tone and Systolic and Diastolic Blood Pressure during Postural Challenge in Panic Disorder Patients

|    |     | Standing 1 |       | Standing 2 |       | Standing 3 |       | Sitting |       |
|----|-----|------------|-------|------------|-------|------------|-------|---------|-------|
|    |     | SBP        | DBP   | SBP        | DBP   | SBP        | DBP   | SBP     | DBP   |
| VT | r = | -.281      | -.205 | -.320      | -.266 | -.238      | -.334 | -.297   | -.124 |
|    | p = | .08        | .21   | .05*       | .10   | .14        | .04*  | .07     | .45   |
|    | n = | 39         |       |            |       |            |       |         |       |

Table 6.2

Correlations between Vagal Tone and Systolic and Diastolic Blood Pressure during Postural Challenge in Non-clinical Controls

|    |     | Standing 1 |      | Standing 2 |       | Standing 3 |       | Sitting |      |
|----|-----|------------|------|------------|-------|------------|-------|---------|------|
|    |     | SBP        | DBP  | SBP        | DBP   | SBP        | DBP   | SBP     | DBP  |
| VT | r = | -.234      | .009 | -.570      | -.139 | -.191      | -.341 | -.200   | .029 |
|    | p = | .33        | .97  | .01*       | .56   | .42        | .14   | .40     | .90  |
|    | n = | 19         |      |            |       |            |       |         |      |

SBP = systolic blood pressure, DBP = diastolic blood pressure, VT = vagal tone,

longer significant ( $r(59) = -.101, p = .45$ ).

When panic disorder patients were analyzed as a group (Table 6.1), vagal tone was consistently and negatively correlated with systolic blood pressure but was, on average, only marginally significant immediately upon standing, after two minutes and after four minutes ( $r(39) = -.281, p = .08$ ;  $r(39) = -.320, p = .05$ ;  $r(39) = -.238, p = .14$ , respectively). For diastolic blood pressure, correlations, although consistently negatively, achieved significance only after 4 minutes of standing ( $r(39) = -.205, p = .21$ ;  $r(39) = -.266, p = .10$ ,  $r(39) = -.334, p = .04$ , respectively). Upon sitting systolic blood pressure was marginally significantly correlated with vagal tone ( $r(39) = -.297, p = .07$ ) while diastolic blood pressure was not ( $r(39) = -.124, p = .45$ ).

In non-clinical controls, these correlations, while also consistently negative, were significant only for systolic blood pressure after two minutes of standing ( $r(19) = -.570, p = .009$ ), possibly because of the smaller sample size (Table 6.2).

During carbon dioxide inhalation, there was no evidence of a correlation between vagal tone and either systolic or diastolic blood pressure when panickers and controls were studied together or in separate groups.

### Ambulatory Studies

**Hypothesis 3a: Panic disorder patients will experience significant decreases in heart rate variability during ambulatory electrocardiographic monitoring of panic and near-panic when compared to non-panic periods with similar heart rate.**

Fifteen panic disorder patients experienced 21 panic attacks or near-panic episodes

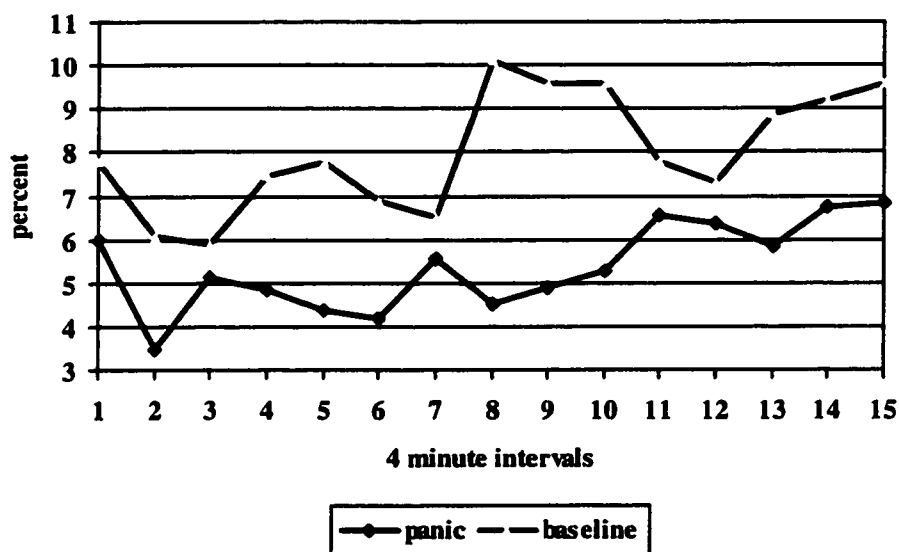


Figure 9. PNN50 at baseline and 30 minutes pre- and post-panic with the mid-point of panic at time 8.

(defined by the patients as “panic”, “almost panic” or “extremely anxious” and recorded as such in their activity diaries with Subjective Units of Distress  $\geq 6$ ) during ambulatory monitoring. Anxiety levels during reported panic, near panic and non-anxious periods were defined by the patients’ SUDS ratings (Subjective Units of Distress, a self-report measure of anxiety) recorded in their activity diaries. T-test analysis of data from electrocardiographic tape recordings (Holter) revealed significant decreases in pNN50 ( $t(19) = 3.14, p < .005$ ), an index of heart rate variability (Table 7). PNN50, the percentage of consecutive interbeat intervals differing by more than 50 ms., was derived from an analysis of 4 minute segments of Holter tapes during the 30 minutes prior to and 30 minutes after the peak of a reported panic or near panic episode and compared to non-

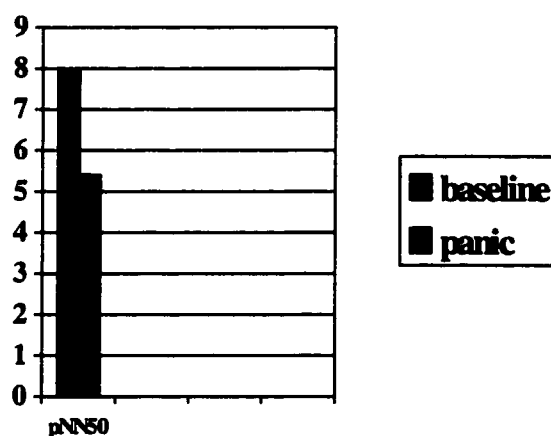


Figure 10. PNN50 during non-panic and panic.

anxious one hour baseline periods similarly analyzed in 4 minute segments (Figure 9).

A comparison of pNN50 (Figure 10) during non-anxious baseline periods with pNN50 during panic and near-panic, employing a repeated measures design, ANCOVA,

Table 7.

Physiological Measures and SUDS Ratings during Ambulatory Monitoring of Non-anxious and Panic Episodes

| Physiological measures   | Non-anxious<br>(n=21) |           | Panic<br>(n=21) |           | t     | p    |
|--------------------------|-----------------------|-----------|-----------------|-----------|-------|------|
|                          | <u>M</u>              | <u>SD</u> | <u>M</u>        | <u>SD</u> |       |      |
| Systolic blood pressure  | 122.84                | 14.00     | 131.74          | 17.63     | 4.66  | .001 |
| Diastolic blood pressure | 77.23                 | 11.06     | 85.16           | 10.66     | 4.61  | .001 |
| Heart rate               | 75.79                 | 13.93     | 85.20           | 15.14     | 4.40  | .001 |
| pNN50                    | 8.02                  | 8.33      | 5.36            | 7.48      | 3.14  | .005 |
| SUDS                     | 1.48                  | 1.13      | 6.04            | 1.65      | 10.55 | .001 |

with age entered as a covariate, revealed a significant main effect of Trial, i.e., non-anxious vs. panic periods, ( $F(1, 19) = 6.96, p = .02$ ).

**Hypothesis 3b: Panic disorder patients will experience significant systolic and diastolic blood increases above non-anxious baselines during ambulatory monitoring of panic and near panic episodes during daily life.**

Overview. Because Pearson correlation analysis had indicated that there was a significant relationship between age and cardiovascular reactivity in this sample, repeated measures, ANCOVAs, with Age entered as a covariate were performed. Results demonstrated that the effect of Trial (panic vs. non-anxious baseline) was significant only for systolic blood pressure and pNN50.

Heart rate and blood pressure reactivity during panic. Non-anxious control periods, matched to panic or near panic episodes by similar reported activity levels, were selected for comparison of physiological reactivity levels. T-tests indicated that patients experienced significantly higher systolic blood pressure ( $t(19) = 4.66, p < .001$ ), diastolic blood pressure ( $t(19) = 4.61, p < .001$ ) and heart rate ( $t(19) = 4.40, p < .001$ ) during panic and near panic periods compared to non-anxious baseline periods (Table 7).

Baseline systolic and diastolic blood pressure and heart rate were found to correlate inversely with age ( $r(21) = -.414, p = .06$ ;  $r(21) = -.487, p = .03$ ;  $r(21) = -.389, p = .08$ , respectively) (Table 9). Systolic and diastolic blood pressure and heart rate during panic also correlated inversely with age, but less robustly ( $r(21) = -.432, p = .05$ ;  $r(21) = -.329, p = .15$ ;  $r(21) = -.289, p = .20$ , respectively). Because age appeared to influence

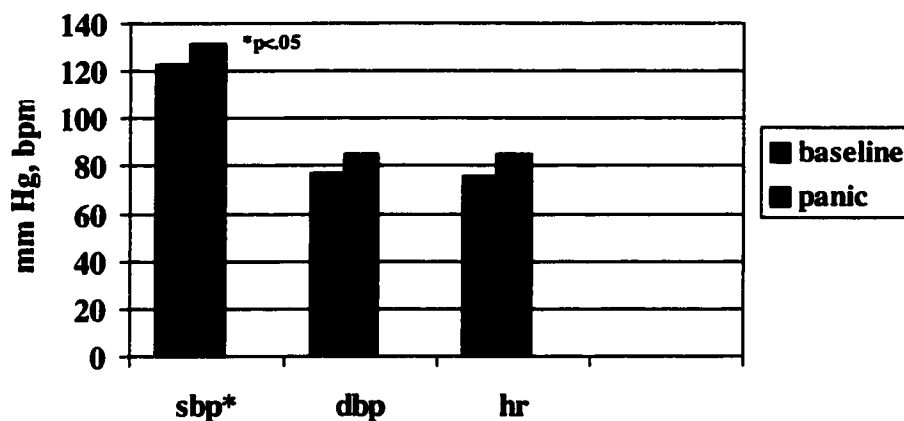


Figure 11. Systolic and diastolic blood pressure and heart rate during non-panic and panic.

cardiovascular responses to panic, a repeated measures ANCOVA was conducted to examine the effect of Trial (baseline versus panic) on systolic and diastolic blood pressure, heart rate and heart rate variability with Age entered as a covariate. Trial was found to have a significant within-subjects effect on systolic blood pressure,  $F(1, 19) = 4.47$ ,  $p < .05$ , and on heart rate variability,  $F(1, 19) = 6.96$ ,  $p < .05$  and non-significant effects on diastolic blood pressure,  $F(1, 19) = .035$ ,  $p = .86$  and heart rate,  $F(1, 19) = .474$ ,  $p = .50$  (Figure 11).

Although analysis of cardiovascular reactivity during carbon dioxide inhalation did not provide evidence of a significant difference between panic disorder patients and non-clinical controls, correlations between reactivity during carbon dioxide inhalation and naturally occurring panic were large but, because of the small sample size, achieved only weak or marginal significance. Correlations (Table 8) ranged from  $r(18) = .32$ ,  $p = .20$  for

systolic blood pressure,  $r = .34(18)$ ,  $p = .17$  for diastolic blood pressure to  $r(18) = .411$   $p = .09$  for heart rate. The correlation, moreover, between mean vagal tone during carbon dioxide inhalation and pNN50 was substantial ( $r(11) = .623$ ,  $p < .05$ ).

Table 8.

Correlations between Measures of Cardiovascular Reactivity and Vagal Tone during CO<sub>2</sub> Inhalation and during Panic

|       | SBP                                 | Carbon dioxide<br>DBP   | HR                      | VT                       |
|-------|-------------------------------------|-------------------------|-------------------------|--------------------------|
| Panic | $r = .320$<br>$p = .20$<br>$n = 18$ | $.340$<br>$.17$<br>$18$ | $.411$<br>$.09$<br>$18$ | $.623$<br>$.041$<br>$11$ |

SBP = systolic blood pressure, DBP = diastolic blood pressure, HR = heart rate, VT = vagal tone, pNN50

Subjective responses to panic episodes. T-tests compared anxiety levels as measured by SUDS ratings (Subjective Units of Distress) at non-anxious baselines and during panic episodes (Table 7) and revealed significantly increased anxious distress during panic ( $t(19) = 10.55$ ,  $p < .001$ ). SUDS ratings were not, however, significantly correlated with systolic pressure or heart rate during panic (Table 9). There was, however, a marginally significant *inverse* correlation between SUDS ratings and diastolic blood pressure during panic ( $r(21) = -.375$ ,  $p = .09$ ). Moreover, SUDS ratings during panic were significantly correlated with increasing age ( $r = .634$ ,  $p = .002$ ) and may reflect an association between the severity of the disorder and its duration.

**Hypothesis 3c: Decreases in heart rate variability during monitored panic and near panic episodes in daily life will be significantly and negatively correlated with**

### **systolic and diastolic blood pressure during these episodes.**

Systolic and diastolic blood pressures and heart rate variability at baseline (non-anxious periods) and during panic and near-panic episodes were evaluated with Pearson correlation analyses (Table 9). Although the correlation between pNN50 and systolic blood pressure was consistently negative, it was also consistently non-significant both during non-anxious periods ( $r(21) = -.249, p = .28$ ;  $r(21) = -.184, p = .43$ , respectively) and during panic ( $r(21) = -.08, p = .73$ ;  $r(21) = -.024, p = .92$ ). There was, however, a significant negative correlation between heart rate and pNN50 at during non-anxious baseline periods ( $r(21) = -.472, p = .03$ ) and during panic ( $r(21) = -.511, p = .02$ ).

Although there was a negative correlation that showed a trend toward significance between non-anxious SUDS ratings and heart rate variability ( $r(21) = -.375, p = .09$ ), non-anxious SUDS ratings failed to correlate with either blood pressure or heart rate (Table 9). There appeared to be no correlation between SUDS ratings, and pNN50, blood pressure and heart rate during panic.

### **Other Relevant Results**

#### **Tests of significance**

**Homogeneity of covariance.** Box's tests of equality of covariance matrices in the repeated measures ANCOVA of the inhalation challenge were not significant. Box's tests of homogeneity of covariance in the ANCOVA as applied to the postural challenge and Valsalva maneuver, however, indicate that dependent variables at three time points (Trials) were more affected by the age covariant than others. The affected dependent

variables and Trials were: panickers' heart rate at Trial 4 (after 4 minutes of standing), vagal tone in panickers at Trial 2 (upon standing) and diastolic blood pressure in panickers during the Valsalva maneuver.

Table 9.  
 Pearson Correlations Among Age, Physiological Variables and SUDS Ratings during Ambulatory Monitoring of Panic and Non-anxious (Baseline) Periods  
 (n = 21)

|        | BSBP       | BDBP           | BHR          | BSUDS       | BpNN50        | PSBP           | PDBP           | PHR            | PSUDS          | PpNN50        |
|--------|------------|----------------|--------------|-------------|---------------|----------------|----------------|----------------|----------------|---------------|
| Age    | r =<br>p = | -.414<br>.06   | -.389<br>.08 | .195<br>.40 | -.376<br>.09  | -.432*<br>.05  | -.329<br>.15   | -.289<br>.20   | .634**<br>.002 | -.217<br>.35  |
| BSBP   |            | .809**<br>.001 | .382<br>.09  | .117<br>.61 | -.249<br>.28  | .871**<br>.001 | .714**<br>.001 | .399<br>.07    | -.114<br>.62   | -.294<br>.20  |
| BDBP   |            |                | .416<br>.06  | .257<br>.26 | -.184<br>.43  | .689**<br>.001 | .737**<br>.001 | .348<br>.12    | -.359<br>.11   | -.262<br>.25  |
| BHR    |            |                |              | .023<br>.92 | -.472*<br>.03 | .246<br>.28    | .251<br>.27    | .776**<br>.001 | -.243<br>.29   | -.390<br>.08  |
| BSUDS  |            |                |              |             | -.375<br>.09  | .073<br>.75    | .314<br>.17    | .077<br>.74    | .021<br>.93    | -.274<br>.23  |
| BpNN50 |            |                |              |             |               | -.087<br>.71   | -.111<br>.63   | -.507*<br>.02  | -.292<br>.20   | .884<br>.001  |
| PSBP   |            |                |              |             |               |                | .858**<br>.001 | .297<br>.19    | -.271<br>.24   | -.080<br>.73  |
| PDBP   |            |                |              |             |               |                |                | .265<br>.25    | -.375<br>.09   | -.024<br>.92  |
| PHR    |            |                |              |             |               |                |                |                | -.061<br>.79   | -.511*<br>.02 |
| PSUDS  |            |                |              |             |               |                |                |                |                | -.061<br>.80  |

\* p < .05, \*\* p < .01

Note: BSBP, BDBP, BHR, BpNN50, BSUDS = systolic blood pressure, diastolic blood pressure, heart rate, pNN50 and SUDS at baseline.  
 PSBP, PDBP, PHR, PpNN50, PSUDS = systolic blood pressure, diastolic blood pressure, heart rate, pNN50 and SUDS during panic.

Effects of anticipatory anxiety on reactivity and self-reports of panic.

Roth et al. (1992) have proposed that anticipatory anxiety might increase the likelihood of panic, and Clark et al. (1991) have suggested that anticipatory anxiety might increase reactivity, during the carbon dioxide challenge. To determine whether anticipatory anxiety contributed to the likelihood of a panic, or to a panic-like, response to carbon dioxide inhalation, the baseline, pre-air and air inhalation SUDS (Subjective Units of Distress Scale) scores, presumably reflective of anxiety in anticipation of the carbon dioxide inhalation, of the panic disorder patients ( $n = 21$  (47%)) who panicked were compared to the SUDS scores of those who did not panic ( $n = 24$  (53%)). T-tests indicated that patients who panicked in response to carbon dioxide inhalation had significantly higher SUDS scores (Table 10) than did non-responders at baseline ( $t(43) = 2.44, p < .05$ ), prior to compressed air inhalation ( $t(43) = 2.73, p < .01$ ) and during compressed air inhalation ( $t(43) = 2.69, p = .01$ ). Panic responders also reported significantly higher scores, i.e., more anxiety symptoms of greater intensity, on the Acute Panic Inventory (API) at baseline ( $t(43) = 2.86, p < .01$ ) and throughout the inhalation challenge than did the non-responders. Panic responders and non-responders did not differ significantly in scores on the Anxiety Sensitivity Index (ASI) ( $t(43) = 1.17, p = .25$ ), however, which measures the tendency to respond fearfully to physical symptoms.

In addition, comparisons of blood pressure, heart rate and vagal tone during the postural and inhalation challenges found a significant difference between these subsets only in heart rate (HR) during air inhalation ( $HR_{\text{no panic}} = 77.54, HR_{\text{panic}} = 87.10; t(43) = 2.62, p < .05$ ), although diastolic blood pressure was higher in the non-responders than in

Table 10.

Comparisons of SUDS<sup>1</sup> Ratings at Baseline and during Air and Carbon Dioxide Inhalation in Panicking and Non-panicking Panic Disorder Patients

| Variable                 | No panic<br>(n = 23) |       | Panic<br>(n = 21) |       | mean<br>difference | t    | p     |
|--------------------------|----------------------|-------|-------------------|-------|--------------------|------|-------|
|                          | M                    | SD    | M                 | SD    |                    |      |       |
| Baseline SUDS            | 10.48                | 14.26 | 23.10             | 19.78 | 12.62              | 2.44 | <.05  |
| API                      | 3.65                 | 3.84  | 8.67              | 7.40  | 5.01               | 2.86 | <.01  |
| Pre-Air SUDS             | 25.96                | 17.49 | 45.24             | 29.09 | 19.28              | 2.73 | <.01  |
| API                      | 6.13                 | 7.58  | 12.62             | 10.82 | 6.49               | 2.36 | <.05  |
| Air SUDS                 | 22.00                | 17.75 | 41.43             | 29.88 | 19.43              | 2.69 | .01   |
| API                      | 5.00                 | 6.35  | 12.43             | 12.03 | 7.43               | 2.64 | <.01  |
| CO <sub>2</sub> (1) SUDS | 27.50                | 20.27 | 63.33             | 18.53 | 35.83              | 6.16 | <.001 |
| API                      | 10.42                | 10.38 | 23.19             | 14.14 | 12.77              | 3.48 | <.01  |

<sup>1</sup> Subjective Units of Distress Scale

the panic responders, achieved marginal significance upon standing (Trials 2 and 3) and showed a trend toward significance upon sitting and during air inhalation. Interestingly, diastolic blood pressure was higher in non-responders than panic responders at baseline and during each physiological challenge.

Repeated measures ANCOVAs re-examined the effects of group and trial on the dependent variables, i.e., systolic and diastolic blood pressure, heart rate and vagal tone, with baseline API and SUDS entered as covariates, and found no covariate effect.

Further exploration of differences in age and gender, factors known to influence cardiovascular reactivity, revealed no significant differences between these groups of patients, although 16 of 21(76%) of the panic responders were female compared to 14 of

24 (58%) non-responders, and were older than the males (36.9 years vs. 32.8 years).

#### Anticipatory anxiety during ambulatory monitoring

Although anticipatory anxiety plays a role in the development of panic in daily life, as it does in the laboratory, and is associated with situational panic attacks and agoraphobia, the mean baseline SUDS scores ( $1.48 \pm 1.13$ ) to which panic SUDS scores ( $6.04 \pm 1.65$ ) were compared were significantly lower ( $t(19) = 10.55, p < .001$ ) than during panic. These results do not rule out the possibility that anticipatory anxiety contributed to panic onset during deliberate exposure to panic-provoking situations.

#### The relationship between heart rate variability and heart rate.

Pearson correlation analysis (Table 9) indicated that heart rate and heart rate variability were significantly correlated during ambulatory monitoring at baseline ( $r(21) = -.472, p = .03$ ) and during panic ( $r(21) = -.511, p = .02$ ). Although it has been shown that heart rate increases can occur without a commensurate decrease in heart rate variability (Donchin, Feld & Porges, 1985; George et al., 1989) and observation of vagal tone in this study during the inhalation challenge indicated an increase in the controls while heart rate remained virtually unchanged, suggesting an uncoupling of these variables, it was not clear that changes in heart rate variability during ambulatory monitoring were not influenced by heart rate changes. To resolve the question of whether heart rate was a confounding variable during ambulatory monitoring of heart rate variability, a repeated measures ANCOVA was performed, with both heart rate and age entered as covariates, to examine their effects on heart rate variability at two measurement times, i.e., non-anxious baselines vs. during panic. A significant main effect

for Trial was found,  $F(1, 18) = 4.763$ ,  $p < .05$ , while Trial x Heart rate,  $F(1,18) = 1.13$ ,  $p = .30$  was not significant.

## DISCUSSION

### Study Overview.

It has been proposed that panic disorder patients may have an underlying autonomic dysfunction, or imbalance, that results in increased cardiovascular reactivity and decreased heart rate variability that is associated with increased cardiac risk (Yeragani, Balon et al., 1990; Tucker et al., 1997). To evaluate this proposal, this study examined a number of related hypotheses that predicted that patients with panic disorder would differ from non-clinical controls in having greater cardiovascular reactivity and decreased heart rate variability in response to physiological stressors in a laboratory setting. Furthermore, panickers would demonstrate marked increases in heart rate and blood pressure and decreased heart rate variability compared to their own non-anxious baselines in response to panic-provoking stressors in daily life. The following section will examine the extent to which the results support the predictions inherent in the hypotheses and the extent to which they confirm or disconfirm previous studies.

### Hypotheses 1 and 2a

Hypotheses 1 and 2a predicted that, compared to non-clinical controls, panickers would experience higher systolic and diastolic blood pressure and heart rate, and decreased vagal tone at baseline and during postural and carbon dioxide inhalation challenges, and during the Valsalva maneuver. These predictions are, to a moderate degree, supported by the results. Compared to controls, panickers had, at baseline, marginally higher systolic and diastolic blood pressures and heart rate, and significantly lower vagal tone. Although physiological responses to challenge were adjusted for age

effects, baseline measures were not. To further explore the effects of age on baseline measures correlation analyses were performed which indicated that systolic blood pressure was significantly correlated with age ( $R(74) = .469, p < .001$ ), as was diastolic blood pressure ( $R(74) = .362, p < .001$ ) while vagal tone was significantly, but inversely, correlated with age ( $R(59) = -.429, p = .001$ ) in panickers and controls. Heart rate ( $R(74) = .066, p = .58$ ) however, was not correlated with age. Tonic differences in systolic and diastolic blood pressure may be attributable to age, therefore, and cannot confirm previous reports of higher tonic blood pressures in panickers compared to non-clinical controls. Tonic differences in heart rate confirm previous findings. During postural challenge systolic and diastolic blood pressure were consistently, but not significantly higher, heart rate was significantly higher and vagal tone consistently lower, in panickers than non-clinical controls, but there were no other noteworthy group differences (Figures 1 to 4), with the following exception. Immediately upon standing the panickers experienced a significant increase in vagal tone and heart rate, in contrast to the controls who had a significant vagal tone decrease accompanied by a significant heart rate increase that was probably activated by the baroreflex. Simultaneously, there was a significant systolic blood pressure decrease in the panickers, but no change in the controls. The vagal tone increase in the panickers could have been the result of an effort-related deep inhalation which evoked a Valsalva response. Although instructed to rise *smoothly* to a standing position, panickers may have used greater effort during postural change.

Although the Valsalva maneuver evoked a vagal tone increase that was significant within the groups the response was greater in controls than in panickers and resulted in a

significant group difference.

Panickers exhibited consistently, but not significantly, higher systolic blood pressure and heart rate during the majority of the inhalation challenge trials. The inhalation trials were marked by four group x trial interactions affecting systolic and diastolic blood pressure, heart rate and vagal tone. It is proposed that these group differences in reactivity might have been the result of sympathetic activation in the panickers driven by anxious distress accompanied by simultaneous parasympathetic activation due to Valsalva-like respiratory efforts in the panickers which resulted in generally higher vagal tone in the panickers compared to the controls. Despite flaws in the procedure, the inhalation challenge produced marked group differences in reactivity (Figures 5 to 8) that support the proposal that panickers' responses to stressors are, at least, different from those of non-clinical controls.

In general, the results indicate that panickers and non-clinical controls differ in their cardiovascular responses to physiological challenge. Panickers in this study exhibited greater blood pressure increases, and heart rate increases which were significant during postural change, and decreased vagal tone, significant during the Valsalva maneuver, compared to the clinical controls. In addition, panickers exhibited marginally higher heart rate at baseline, in comparison to controls. The marginally higher systolic and diastolic blood pressure and significantly decreased vagal tone exhibited by panickers compared to controls at baseline may have been attributable to age.

Comparisons with previous studies. The marginally elevated systolic and diastolic blood pressure baselines found in this study may be attributable to age, and

cannot confirm several previous studies that have reported elevated, or significantly elevated systolic or diastolic blood pressures at baseline (Hoehn-Saric et al., 1991; Yeragani, Meiri et al., 1990; Bystritsky & Shapiro, 1992). While this study found only a trend toward higher systolic and diastolic blood pressure in panickers during postural and CO<sub>2</sub> challenge, higher diastolic blood pressure while standing, in panickers versus controls, has been reported (Yeragani, Meiri, 1990) while Bystritsky and Shapiro (1992) have found significant diastolic blood pressure responses to CO<sub>2</sub> in panickers compared to controls. In contrast, several previous studies have reported no significant group differences in blood pressures at baseline or during postural change (Cameron et al., 1990) or CO<sub>2</sub> challenge (Roth et al., 1992).

While baseline heart rate was only marginally higher in this study in panickers compared to controls, significantly elevated baseline heart rates in panickers have been demonstrated in previous reports (Klein et al., 1995; Yeragani, Meiri et al., 1990; Hoehn-Saric, McLeod & Zommerli, 1991; Roth et al., 1992 ). These laboratory results have been confirmed by Holter electrocardiographic studies that have found higher baseline heart rates in panickers than in controls (Taylor et al., 1987; Shear et al., 1987; Chignon et al., 1993). Other ambulatory studies have found no significant heart rate differences between panickers and controls (Clark et al., 1990; Bystritsky et al., 1995). This study found a significant main effect of group resulting in higher heart rates in panickers than in controls during postural change and only a consistent tendency toward higher rates in panickers during CO<sub>2</sub> challenge, although only one previous study has documented significant heart rate responses to postural change in panickers versus controls. A lack of

significant group differences has also been reported, however, during CO<sub>2</sub> (Roth et al., 1992) and postural challenge (Yeragani, Meiri et al., 1990; Cameron et al., 1990).

Significantly decreased baseline vagal tone in panickers compared to non-clinical controls in this study, was possibly attributable to age, and cannot confirm previous reports (Yeragani, Balon et al., 1990; Middleton et al., 1994; Rechlin et al., 1994; Kawachi et al., 1995; Klein et al., 1995; Tucker et al., 1997). Generally decreased vagal tone was found in panickers during most of the postural and inhalation challenges in this study, although there were no significant group differences. The Valsalva maneuver, however, produced not only significant increases in both panickers and controls, but resulted in significantly higher vagal tone in the controls. The majority of previous studies of vagal tone responses to physiological challenge, most often postural change, have also reported a decrease in panickers (Yeragani, Balon, et al. 1990; Yeragani et al., 1993; Rechlin et al., 1994), with the exception (Gorman et al., 1987) of a lactate-infusion study, which found no change in panickers. The latter study, however, may have been flawed because lactate-infusion has frequently been employed (Gaffney et al., 1988; Roy-Byrne et al., 1989) as an effective panicogenic agent in panickers and produces vagal tone changes even in non-clinical controls (George et al., 1989). A more recent lactate-infusion study (Yeragani et al., 1994) moreover, reported significant vagal withdrawal in panickers.

Evidence from previous laboratory studies demonstrating increased systolic or diastolic blood pressure at baseline or in response to physiological challenge has not been consistent or convincing and the present study cannot provide support for higher baseline

blood pressures, and only modest support for increased blood pressure reactivity in panickers compared to controls. The findings in this study of significantly higher heart rates, however, in panickers during postural change confirms previous reports of increased heart rate reactivity. Tonic vagal tone has most often been found to be decreased in panickers compared to controls, and this study supports that finding. Compared to other cardiovascular measures, vagal tone has been examined in a greater number of studies that have used a single challenge, i.e. postural challenge, which has provided fairly consistent evidence of decreased vagal tone in panickers and which is supported by the present study. The more consistent findings from vagal tone studies suggest that the failure of previous studies of blood pressure and heart rate to provide a similar level of consistent results is due to a relatively small number of studies utilizing a large variety of challenges, e.g., mental arithmetic, simulated public speaking, cold pressor, hand grip, lactate infusion, carbon dioxide inhalation etc.

#### Hypothesis 2b:

Hypothesis 2b predicted that decreased vagal tone would be inversely correlated with systolic and diastolic blood pressure during postural challenge and carbon dioxide inhalation. Correlation analyses of blood pressure measures and vagal tone were performed for panickers and controls combined and for each group separately. For the combined group during postural change inverse correlations between systolic blood pressure and vagal tone ranged from significant upon standing, after 2 minutes and upon sitting, and marginal after 4 minutes standing. Correlations between diastolic blood

pressure and vagal tone were consistently negative but achieved significance only upon standing and at 4 minutes of standing. When panickers were analysed as a group, correlations between systolic blood pressure and vagal tone were significant at 2 minutes of standing and marginal at other time points. Correlations between diastolic blood pressure and vagal tone were modest at best and significant only at 4 minutes of standing. In the control group correlations between vagal tone and diastolic and systolic blood pressure were weaker than in the panickers, although systolic blood pressure was strongly correlated with vagal tone after 2 minutes of standing. Correlation analyses of systolic and diastolic blood pressure and vagal tone during the inhalation challenge provided no evidence of a consistent correlation between these measures. This result may have been due to the flawed nature of the procedure (discussed below) or because the procedure may have altered baroreceptor function.

Vagal tone and blood pressure have been shown to be inversely correlated and both measures are utilized in estimations of baroreceptor sensitivity (Conway et al., 1984). Decreased vagal tone has been investigated as a contributor to mechanisms underlying panic disorder and, thus, may be implicated in the increased cardiac risk that is associated with panic disorder (Casolo et al., 1992; Fei et al., 1994). Vagal tone is also correlated with baroreceptor sensitivity whose loss is also associated with cardiac risk. Recently Yeragani et al. (1993), after observing differences in blood pressure responses in panickers and controls during postural change, speculated that the baroreflex may be dysfunctional in panic disorder. Postural change has been used frequently to provoke and examine changes in vagal tone in panic disorder, and could also be employed to assess

baroreceptor sensitivity. Other studies have not examined the correlation between vagal tone and blood pressure which might elucidate baroreceptor function in panic disorder. In this study, although vagal tone and diastolic and systolic blood pressure were moderately well correlated, the panic and control groups were too small and unequal in size for meaningful group comparisons.

#### Hypotheses 3a and 3b

Hypotheses 3a and 3b predicted that panic disorder patients would experience significant increases in systolic and diastolic blood pressure and heart rate, and decreases in heart rate variability during naturally occurring panic compared to non-anxious baselines with similar activities. These predictions were not fully supported by the results. Only systolic blood pressure was found to increase significantly during panic, and although diastolic blood pressure and heart rate increased substantially, these increases were not significant. The measure of heart rate variability which had been selected for analysis, the pNN50, decreased significantly during panic compared to baseline, but other heart rate variability measures which were also examined did not demonstrate statistically significant changes.

Comparisons with previous studies. Three previous studies have evaluated ambulatory blood pressure in panickers. White and Baker (1987) reported significant increases in diastolic and systolic blood pressure, associated with low activity, during 13 panic attacks in 12 patients. A study of 11 panic attacks, associated with low activity, in 22 panickers revealed statistically significant systolic blood increases (Shear et al., 1992).

In a third study of 10 panickers who experienced 3 panic attacks and who were compared to 10 non-clinical controls, there were significant group-wise differences in diastolic blood pressure. The present study confirms the findings of significant systolic, but not of diastolic, blood pressure increases during panic. Not all panic attacks recorded in this study occurred at low activity levels, but all were matched to similar baseline activities, e.g., driving on a non-anxiety-evoking freeway matched to driving on a panic-evoking freeway. Because activity was appropriately controlled, the systolic blood pressure increases occurring during panic may be attributable to increases in stroke volume and arterial tone secondary to the sympathetic arousal associated with fear and panic.

One study cited above (White & Baker, 1987) and other ambulatory (Holter electrocardiographic) studies have reported evidence of significantly increased heart rate during panic compared to non-anxious periods (Taylor et al., 1983; Shear et al., 1987). On the other hand, Gaffney et al. (1988) found 8 of 31 monitored panic attacks with increased heart rate, 6 with increased heart rate during increased activity and 17 without heart rate change. Of 3 panic attacks analysed by Bystritsky et al. (1995) none demonstrated significantly increased heart rate. Although most of these studies have documented heart rate increases during panic, the present study fails to confirm their results.

Although one ambulatory study has compared baseline heart rate variability in panic disorder patients and non-clinical controls (Yeragani et al., 1998) no studies to date have examined heart rate variability during panic.

Inconsistencies among measures of heart rate variability. The pNN50 had been

selected to measure heart variability during ambulatory monitoring for several reasons. Although the pNN50 is a time domain measure, it had been shown to be highly correlated with, and to approximate, high frequency spectral density measures representative of parasympathetic activation (Task Force, 1996). Furthermore, time domain measures have been recommended as more appropriate than frequency domain measures for longer term recordings, i.e., 24 hours, while frequency domain measures have been recommended for brief recordings, i.e., of not more than 5 minutes duration. In general, long recordings examine large trends in heart variability such as diurnal/ nocturnal differences or other circadian variations. Short term recordings, on the other hand, because they're often used to examine dynamic responses to physiological change, are susceptible to problems of non-stationarity. To avoid this problem, it has been recommended that recordings be made in segments of only sufficient duration to adequately sample the frequency of interest, e.g., about 2 minutes for high frequency, which could then be compared to later stable segments (Task Force, 1996). The current study required examination of heart rate variability recordings during panic and non-panic episodes that were intermediate in length between long and short term. Recordings were analysed in both the time and frequency domains in four minute segments that comprised an hour in total. Correlation analysis of high (HF) and low (LF) frequency spectral power, SDNN and pNN50 during panic yielded significant correlations between pNN50 and HF ( $r = .516$ ,  $p = .02$ ), LF ( $r = .503$ ,  $p = .02$ ), and SDNN ( $r = .872$ ,  $p < .001$ ). Contrary to previous reports (Task Force, 1996) correlations between pNN50 and HF at non-anxious baselines were weak and non-significant, although the correlation between pNN50 and SDNN at baseline was strongly

significant ( $r = .725$ ,  $p = <.001$ ).

Although low frequency power had been viewed as reflecting primarily sympathetic activation, a parasympathetic component of LF is now recognized (Committee Report, 1997). This suggests that both LF and the LF/HF ratio are not reliable measures of autonomic balance, and, moreover, that although high frequency power may adequately represent parasympathetic activation, an adequate spectral representation of sympathetic activation may not be available. Furthermore, the high frequency spectrum in panickers may also be altered and less representative of parasympathetic activation.

PNN50 and SDNN might be expected to be strongly correlated since each reflects variance in the respiratory component of heart period and each is usually correlated with high frequency power. Surprisingly, there was no mean difference between SDNN at baseline and SDNN during panic, although the mean difference between pNN50 at baseline and during panic was highly significant, suggesting that although both variables are sensitive to changes in heart period, these methods may produce disparate results. Hence, the pNN50 and SDNN may not be equivalent measures.

In summary, although several measures of heart rate variability were examined in this study, i.e., the low and high frequency spectral densities, SDNN and pNN50, only the latter showed significant change during panic compared to the non-anxious baseline. As discussed, the low frequency spectral density may not be a reliable measure of autonomic balance. Furthermore, the application of frequency domain analysis to recordings that are neither long nor short term may be inappropriate, suggesting that the

analysis of intermediate length recordings may require further study. However, the lack of change in the SDNN during panic compared to non-anxious baseline is difficult to explain. Although both the pNN50 and SDNN measure variation in the heart period, it may be possible for the standard deviation of the heart period to remain fairly constant even while the number of consecutive heart periods differing by  $> 50$  ms. decreases.

### Hypothesis 3c

Hypothesis 3c predicted that decreases in heart rate variability during panic in daily life would be significantly, inversely correlated with systolic and diastolic blood pressure during these episodes. The inverse correlations that were found for these measures were weak and non-significant at baseline with  $r$  ranging from  $-.249$  ( $p = .28$ ) for systolic blood pressure to  $-.184$  ( $p = .43$ ) for diastolic blood pressure. During panic correlations decreased further so that  $r = -.08$  ( $p = .73$ ) for systolic blood pressure and  $-.02$  for diastolic blood pressure ( $p = .92$ ). In the discussion of Hypothesis 2b, it was proposed that the correlation between heart rate variability and diastolic and systolic blood pressure might reflect baroreceptor function. Because heart rate variability and baroreceptor function are highly correlated, it has been proposed that decreased heart rate variability implies decreased baroreceptor sensitivity (Tucker et al., 1997). This line of reasoning suggests that the observed decrease in heart rate variability in this study may be associated with altered baroreceptor function and result in the observed significant systolic blood pressure increases and decreased correlation between blood pressure and heart rate variability during physiological challenge. Few studies, however, have proposed that baroreceptor function may be altered in panic disorder (Tucker et al., 1987;

Yeragani et al., 1993) and none to date have examined this issue.

### Experiment-wise Error

This study consists of a series of laboratory experiments which test group-wise differences in response to a series of stressors or challenges. Assuming that panic disorder patients have a greater risk for cardiovascular events such as sudden cardiac death than do non-clinical controls, this study tests the hypotheses that this risk is due either to increased cardiovascular reactivity and/or to decreased heart rate variability. In addition, this study replicates previous laboratory studies in an attempt to understand their inconclusive results. Lastly, as a separate experiment, cardiovascular reactivity and heart rate variability during naturally occurring panic are compared to each panicker's own non-anxious baseline levels.

The postural and inhalation challenges involved measurements of four dependent variables during five trials for each challenge within two groups of subjects, i.e.,  $2 \times 4 \times 5 = 40$  cells, or 20 between-subjects comparisons for each challenge. The number of comparisons increased the likelihood of type I error and decreased the probability of significant findings if Bonferroni corrections were applied. If each challenge were examined individually, at an  $\alpha = .05$ , the error rate per experiment would be 1 per individual experiment. In fact, few of the individual comparisons made during laboratory challenges resulted in significant between-subjects differences and some of these may be the result of type I error. A more liberal view of the results suggests, however, that trends within the data such as the consistently lower vagal tone in panickers

compared to controls, while not generally statistically significant, support the occasionally significant between-subjects differences in vagal tone.

### Importance of Ambulatory Monitoring in Panic Disorder

Ambulatory monitoring of panic attacks during daily life may be a more fruitful approach to understanding the physiological mechanisms underlying panic than laboratory simulations of panic. Ambulatory physiological measurements are automated and independent of subject effort, not confounded by either the demands or implied safety of the laboratory and are responses to stimuli that are personally relevant to the individual patient. Previous ambulatory blood pressure investigations have relied on the chance occurrence of panic in patients who experience frequent attacks. In the current study patients were asked to expose themselves to at least one of several situations identified by them as reliably eliciting panic. The recording of 21 panic attacks in 15 patients indicates that panic disorder patients are able to effectively elicit panic during daily life rather than depending on its chance occurrence.

This study used Holter electrocardiographic and ambulatory blood pressure monitoring to simultaneously record systolic and diastolic blood pressure, heart rate and heart rate variability during 21 panic periods matched by similarity of activities to 21 non-anxious periods in daily life. When panic periods were compared to non-anxious periods with similar activities, significant increases in systolic blood pressure and significant decreases in heart rate variability during panic were found. Heart rate and diastolic blood pressure were also elevated above baseline, but not significantly. SUDS ratings of subjective distress during panic were also significantly elevated. To test the comparability

of a laboratory simulation of panic during carbon dioxide inhalation to naturally occurring panic, blood pressure and heart rate reactivity during panic were compared to, and correlated substantially with, reactivity during carbon dioxide but achieved only weak or marginal significance because of the small size of the ambulatory sample. Heart rate variability during panic and vagal tone during carbon dioxide, however, were strongly and significantly correlated.

The finding that systolic blood pressure was significantly elevated and heart rate variability was significantly decreased during panic suggests that baroreceptor sensitivity, which has been shown to be correlated with heart rate variability, may have decreased during vagal withdrawal, resulting in or contributing to the observed increase in systolic blood pressure. It has been proposed in previous studies that vagal withdrawal (George et al., 1989; Wilkinson et al., 1998; Yeragani et al., 1994), rather than sympathetic activation, could account for the blood pressure reactivity observed in panickers during monitored panic and during physiological challenge in the laboratory. Vagal withdrawal without sympathetic activation could also account for failure of previous studies to demonstrate increased catecholamine levels in panickers during laboratory stress.

#### Study Limitations and Suggestion for Future Studies

The failure to find significant differences in cardiovascular reactivity between panic disorder patients and non-clinical controls during the inhalation challenge suggests that perhaps carbon dioxide inhalation is not as relevant to panic disorder patients as are the situations in daily life that elicit naturalistic panic. In fact, however, almost half of the panickers responded to inhalation challenge with high levels of anxiety and reported

feeling panicky. Even during compressed air inhalation 4 (19.1%) responders reported feelings of panic, and anxiety ratings of  $\geq 70\%$  on an anxiety scale of 0 to 100%, with 100% being the highest level of anxiety. That anticipatory anxiety might have contributed to panic is suggested by the significantly higher anxiety ratings and greater number and intensity of anxiety symptoms reported by panic responders even at baseline, about an hour prior to the inhalation challenge. Although carbon dioxide is panicogenic in some panickers, the results of this study suggest that even compressed air can be panicogenic. Furthermore, this study supports the notion that cognitive factors, i.e., anxiety-promoting beliefs elicited by physiological symptoms, might determine which symptom-provoking challenges are salient to panickers.

#### The Valsalva maneuver and the inhalation challenge.

The failure of this and, perhaps, of other investigations (Trakowski, 1996) to find significant reactivity in panickers compared to non-clinical controls during carbon dioxide inhalation may have resulted from the inspiratory effort required by the procedure. The deep inspiration and breath-hold required in the Valsalva maneuver have been shown, in this study and in others, to enhance vagal tone, and in fact, the Valsalva maneuver has been taught to panickers to forestall impending panic (Sartory & Olajide, 1988). Examination of reactivity data revealed that vagal tone was increased in response to the inhalation challenge in both panic disorder patients and normal controls, but the magnitude of the increase in the controls was significantly greater than in the panickers. Because this maneuver is similar to the deep inspiration and breath-hold required during the inhalation challenge, it appears likely that the inhalation challenge might also enhance

vagal tone. In fact, examination of vagal tone levels (Table 4 and 4.1) reveal large increases over baseline in both groups during the Valsalva maneuver, a return to near-baseline levels during the compressed air inhalation followed by gradual increases in vagal tone to greater than Valsalva levels during the carbon dioxide inhalations. There was one exception to this progression when vagal tone fell sharply in panickers after the second CO<sub>2</sub> inhalation, but continued to rise in the controls. At the first carbon dioxide inhalation, vagal tone decreased slightly in the controls but rose sharply in the panickers (Table 4.1), a result of a Group x Time interaction discussed earlier.

This pattern of paradoxical changes in vagal tone during the inhalation challenge suggests the presence of two simultaneous, conflicting autonomic responses; adrenergic activation due to the anxiety elicited by the inhalation coupled with a Valsalva-like, parasympathetic activating response to the respiratory maneuver. SUDS ratings in panickers indicate a sharp increase in anxiety with the air inhalation (Table 5), a peak at the first carbon dioxide inhalation and a leveling-off thereafter, suggestive of habituation over trials, which may have permitted greater expression of the vagal tone enhancing component. This mechanism could explain why the inhalation challenge was characterized by systolic blood pressure increases accompanied by increases in vagal tone although systolic blood pressure and vagal tone were inversely related during the postural challenge and are generally known to be inversely correlated.

It is suggested that if the carbon dioxide procedure continues to be used in panic assessment, that inhalation be made a more passive procedure utilizing a breathing mouthpiece fitted with valves permitting inhalation of a fixed volume of gas based on an

estimation of the subject's tidal volume, i.e., a fraction of the vital capacity.

Demographic differences in the study sample.

The effects of subjects' age on their cardiovascular responses reduced the significance of apparent differences in reactivity in the groups studied. The age distribution in the panic disorder group differed from that of the non-clinical control group even after making adjustments for significant mean age differences. Distributions of mean ages favored older subjects in the panic group, and younger subjects in the control group.

Differences in the education levels of the groups also approached significance due to the generally higher educational achievements of the control group, e.g., 14% of the panickers had, at most, a high school education compared to none of the controls, while only 8% of the panickers had completed graduate or professional school in comparison to 16% of the controls. This distribution may have resulted from the fact that most of the controls were employed or resided in the affluent Montgomery County area and adjacent District of Columbia, while the panickers were drawn from a broad geographic area surrounding the metropolitan area.

Differences in marital status also approached significance with more panickers being divorced or separated compared to controls, 18% vs. 4%, and fewer panickers being never married compared to controls, 37% vs. 56%. The younger age of the non-clinical controls may have contributed to these differences.

Because increasing age has also been shown to be associated with loss of heart rate variability (Parati et al., 1995), it was necessary to covary for age in the statistical

analysis. It was also found that age was highly correlated with SUDS measures ( $r(21) = .634, p = .002$ ) during panic (Table 9), possibly reflecting an association between duration of the disorder and/or severity. Differences in education could influence the cognitive components of panic disorder. That is, less educated panickers might, for example, be less willing to accept the fact that the physical symptoms associated with panic are less likely to be the signs of an impending cardiac emergency than they are to be the recurrence of a frightening, but essentially harmless panic response.

Improving demographic characteristics of subjects. Demographic characteristics such as age and education should have been more carefully controlled than they were in the current study. Matching on education, age, and gender might have improved the results from this study. Heart rate variability has been shown to diminish significantly with age, poor health (Yataco et al., 1997) and loss of physical fitness which has been reported to be decreased in panickers (Schmidt et al., 1998) and which could not be controlled for in this study. Efforts should be made in future investigations to control for this factor, but it is not clear how this can be accomplished if panic disorder patients are fearful of the cardiovascular symptoms associated with exercise, e.g., rapid heart rate, tachypnea, shortness of breath and sweatiness, and either avoid exercise or discontinue exercise upon the onset of symptoms

Effects of subject effort during physiological challenge.

It was observed during postural challenge that some subjects rose to a standing position with more effort than others, sometimes inhaling deeply or grasping the arms of the chair for support. A tilt-table that would have made the postural challenge a more

passive, and less effortful, procedure, was not available and it is not clear that this procedure was conducted without the confounding effects of subject effort. Similarly, as discussed above, the results of the carbon dioxide inhalation appear to have been confounded by the Valsalva-like effects of inspiratory effort and breath holding.

Suggested improvements to laboratory procedures. Baroreceptor sensitivity is strongly correlated with cardiac risk and should be carefully evaluated, preferably by utilizing a passive tilt-table procedure that would eliminate patient effort. Use of one of several recently introduced, non-invasive, but continuous and rapidly responding blood pressure monitors, or invasive monitoring, e.g., arterial catheter, in conjunction with continuous measurement of heart rate variability would provide an accurate measure of the baroreflex which has a response period of only several seconds.

Ambulatory monitoring as a safety-aid

Because the ambulatory blood pressure device provided a digital reading at each inflation that could be read by the patients, several patients stated that they found the visual readout reassured them that their symptoms were not dangerous (e.g., heart rate etc. were not excessive) which reduced their apprehensions about the possible catastrophic nature of their symptoms. They stated the belief that being monitored gave them a feeling of security that reduced the likelihood of panic. It was stated by at least one patient that a panic attack or heart attack could not possibly occur during Holter electrocardiographic monitoring. At the time these effects became apparent, numerous panic attacks had occurred during ambulatory monitoring and it didn't seem advisable to prevent visual readouts at that stage in the study. Data from subjects who for any reason,

e.g., infrequent attacks, inability to discontinue medications, or fear of an elicited panic, didn't panic during monitoring were excluded from analysis.

It is suggested that future studies of ambulatory monitoring of heart rate and blood pressure be conducted without allowing subjects access to digital readouts.

Implications of this study for diagnosis and treatment of panic disorder.

Carbon dioxide, as usually administered, may not be an useful physiological challenge in laboratory studies. Carbon dioxide has been used, however, as a reliable panic-evoking agent to identify panic disorder patients, to simulate panic symptoms and to study its physiological effects on behavior. Because cognitive-behavioral therapy seeks to uncouple physiological symptoms from their catastrophic interpretation, carbon dioxide inhalation has been utilized prior to cognitive-behavioral treatment as a baseline measure, and mid-way during treatment and after treatment to determine the effectiveness of treatment. Since their response to carbon dioxide inhalation is short-lived and occurs in a safe environment unlike actual panic, patients sometimes gain insight into how their interpretation of essentially harmless physical symptoms determines whether they will panic and how severe their panic will be. Carbon dioxide inhalation can be a useful introduction to cognitive-behavioral therapy and changes in response midway through and after therapy can reinforce the cognitive-behavioral lessons learned. In addition, patients learn which symptoms contribute most to their anxiety and will require the most exposure practice during treatment.

Ambulatory monitoring of panic during life could also provide clues about how each patient's panic develops, its severity, the nature of his/her symptom cluster and of

the precipitating events that contribute to panic, all of which can be adjuncts to therapy. A review of the ambulatory record has been enlightening to some patients when they discover how they've exaggerated the dangers associated with of their symptoms. Ambulatory monitoring could be used to identify the onset of anticipatory anxiety and symptoms in order to learn to halt the progression of anxiety to full-blown panic.

Ambulatory monitoring of symptoms could be a valuable tool in symptom recognition that could be effective in dissociating symptoms from catastrophic interpretations and replacing them with benign cognitions.

The findings from this study that are suggestive of the presence of increased cardiac risk factors, i.e., greater blood pressure reactivity, decreased heart rate variability and, possibly, decreased baroreceptor sensitivity in panickers compared to controls, emphasize the importance of early and effective treatment of panic disorder. Outcome studies that investigate the physiological benefits, i.e., reduction of cardiac risk factors, in addition to the stress-reducing benefits, of pharmacological and behavioral treatments for panic disorder should be undertaken to determine optimal treatment.

## CONCLUSIONS

Because panic disorder is associated with greater risk for adverse cardiac outcome, this study examined the effects of physiological challenge on cardiovascular reactivity and heart rate variability, possible correlates of cardiac risk, in panic disorder patients and non-clinical controls in a laboratory setting. In addition, cardiovascular reactivity and heart rate variability in panickers were studied during ambulatory monitoring of naturally occurring panic and non-anxious periods.

Results from the laboratory portion of this study confirm findings from previous studies that suggest that heart rate variability is tonically decreased in panic disorder patients, less enhanced by the Valsalva maneuver, and somewhat decreased in response to postural change compared to non-clinical controls. This study also provided modest support for increased heart rate and blood pressure at baseline and during challenge in panickers compared to controls. Decreased heart rate variability in conjunction with systolic blood pressure increases suggests that baroreceptor sensitivity may also be decreased. If heart rate variability is conclusively shown to be decreased in panickers, this finding would have important implications for the increased cardiac risk associated with panic disorder. Loss of baroreceptor sensitivity is also linked to increased cardiac risk and may contribute to the increased blood pressure reactivity during panic that has been observed in this and previous studies. Furthermore, a dysfunctional baroreflex in conjunction with recurrent blood pressure surges may be a precursor to the chronic hypertension for which panickers are at higher risk.

The ambulatory portion of this study revealed significant decreases in heart rate

variability during naturally occurring panic that were associated with significant systolic blood pressure increases. These results support findings from the laboratory portion of this study and other previous studies reporting increased blood pressure reactivity, decreased heart rate variability and, possibly, decreased baroreceptor sensitivity. In addition, the ambulatory results suggest that naturalistic panic may be more effective than laboratory challenges in eliciting physiological changes relevant to the study of panic disorder.

The combined results from the laboratory and ambulatory portions of this study suggest, at least tentatively, that increased blood pressure reactivity, decreased heart rate variability and, possibly, decreased or abnormal baroreceptor function may be linked to the greater cardiac risk associated with panic disorder and warrant further study.

## REFERENCES

- American Psychiatric Association (1994). Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition). Washington, DC, American Psychiatric Association.
- Asmundsen, G.J.G. & Stein, M.B. (1994). Vagal attenuation in panic disorder: An assessment of parasympathetic nervous system function and subjective reactivity to respiratory manipulations. Psychosomatic Medicine, *56*, 187-193.
- Bajwa, W.K., Asnis, G.M., Sanderson, C., Irfan, A. & van Praag, H.M. (1992). High cholesterol levels in patients with panic disorder. American Journal of Psychiatry, *149*, 376-378.
- Beitman, B.D., Mukeiji, V., Flaker, G. & Basha, I.M. (1988). Panic disorder, cardiology patients and atypical chest pain. Psychiatric Clinics of North America, *11*, 387-398.
- Bigger, J.T., Fleiss, J.L., Rolnitsky, L.M., Steinman, R.C. & Schneider, W.J. (1991). Time course of recovery of heart period variability after myocardial infarction. Journal of the American College of Cardiology, *18*, 1643-1649.
- Bigger, J.T., Fleiss, J.L., Steinman, R.C., Rolnitsky, L.M. Kleiger, R.E. & Rottman, J.N. (1992). Frequency domain measures of heart period variability and mortality after myocardial infarction. Circulation, *85*, 164-171.
- Bigger, J.T. & Hoskins, R.S. (1989). Time-series analysis of heart period variability during submaximal exercise. Circulation, *80*, 146-157.
- Billman, G.E., Schwartz, P.J. & Stone, H.L. (1982). Baroreflex control of heart rate: A predictor of sudden cardiac death. Circulation, *66*, 874-879.

Billman, G.E., Schwartz, P.J. & Stone, H.L. (1984). The effects of daily exercise on susceptibility to sudden cardiac death. Circulation, 69, 1182-1189.

Braune, S., Albus, M., Frohler, M., Hohn, T. & Scheibe, G. (1994). Psychophysiological and biochemical changes in patients with panic attacks in a defined situational arousal. European Archives of Psychiatry and Clinical Neuroscience, 244, 86-92.

Bystritsky, A., Craske, M., Maidenberg, E., Vapnik, T. & Shapiro, D. (1995). Ambulatory monitoring of panic patients during regular activity: A preliminary report. Biological Psychiatry, 38, 648-689.

Bystritsky, A. & Shapiro, D. (1992). Continuous physiological changes and subjective reports in panic patients: A preliminary methodological report. Biological Psychiatry, 32, 766-777.

Cameron, O.G., Smith, C.B., Lee, M.A., Hollingsworth, P.J., Hill, E.M. & Curtis, G.C. (1990). Adrenergic status in anxiety disorders: Platelet  $\alpha_2$ -adrenergic receptor binding, blood pressure, pulse and plasma catecholamines in panic and generalized anxiety disorder patients and in normal subjects. Biological Psychiatry, 28, 3-20.

Carter, C., Maddock, R., Amsterdam, E., McCormick, S. & Billett, J. (1992). Panic disorder and chest pain in the coronary care unit. Psychosomatics, 33, 302-309.

Carter, C., Maddock, R., Zogho, M., Lutrin, C., Jella, S. & Amsterdam, E. (1994). Panic disorder and chest pain: A study of cardiac stress scintigraphy patients. American Journal of Cardiology

Casolo, G.C., Balli, E., Taddei, T., Amuhasi, J. & Gori, C. (1989). Decreased spontaneous heart rate variability in congestive heart failure. American Journal of Cardiology, 64, 1162-1167.

Casolo, G. C., Stroder, P., Signorini, C., Calzolari, F., Zicchini, M., Balli, E., Sulla, A. & Lazzerini, S. (1992). Heart rate variability during the acute phase of myocardial infarction. Circulation, 85, 2073-2079.

Cerati, D. & Schwartz, P. J. (1991). Single cardiac vagal fiber activity, acute myocardial ischemia and risk for sudden cardiac death. Circulation Research, 69, 1389-1401.

Chambers, J. & Bass, C. (1990). Chest pain with normal coronary anatomy: A review of natural history and possible etiologic factors. Progress in Cardiovascular Diseases, 33, 161 - 184.

Chignon, J.-M., Lupine, J.-P. & Ades, J. (1993). Panic disorder in cardiac outpatients. American Journal of Psychiatry, 150, 780-785.

Clark, D.B., Taylor, C.B., Hayward, C., King, R., Margraf, J., Ehlers, A., Roth, W. T. & Agras, W. S. (1990). Motor activity and tonic heart rate in panic disorder. Psychiatry Research, 32, 45-53.

Committee Report (1997). Heart rate variability: Origins, methods and interpretive caveats. Psychophysiology, 34, 623-648.

Conway, J., Boon, N., Davies, C., Jones, J. V. & Sleight, P. (1984). Neural and humoral mechanisms involved in blood pressure variability. Journal of Hypertension, 2, 203-208.

Coryell, W., Noyes, R. & Clancy, J. (1982). Excess mortality in panic disorder: A comparison with primary unipolar depression. Archives of General Psychiatry, 39, 701-703.

Coryell, W., Noyes, R. & House, J.D. (1986). Mortality among outpatients with anxiety disorders. American Journal of Psychiatry, 143, 508-510.

De Meersman, R.E. (1993). Heart rate variability and aerobic fitness. American Heart Journal, 125, 726-731.

DiPietro, J. A. & Porges S. W. (1991). Vagal responsiveness to gavage feeding as an index of pre-term status. Pediatric Research, 29, 231-236.

Donchin, Y., Feld, J. M. & Porges, S. W. (1985). Respiratory sinus arrhythmia during recovery from isoflurane-nitrous oxide anesthesia. Anesthesia and Analgesia, 64, 811-815.

Fei, L., Anderson, M. H., Katritsis, D., Sneddon, J., Staffers, D.J., Malik, M. & Camm, A. J. (1994). Decreased heart rate variability in survivors of sudden cardiac death not associated with coronary artery disease. British Heart Journal, 71, 16-21.

Fox, N.A. & Porges, S. W. (1985). The relationship between developmental outcome and neonatal heart period patterns. Child Development, 56, 28-37.

Freeman, R. Saul, J.P. Roberts, M.S., Berger, R. D. Broadbridge, C. & Cohen, R. J. (1991). Spectral analysis of heart rate in diabetic neuropathy. Archives of Neurology, 48, 185-190.

Fugii, H., Yasue, H., Okumura, K., Matsuyama, K., Morikami, Y., Miyagi, H. & Ogawa, H. (1988). Hyperventilation-induced simultaneous multivessel coronary spasm in

patients with variant angina: an echocardiographic and arteriographic study. Journal of the American College of Cardiology, 12, 1184-1192.

Gaffney, P.A., Fenton, B.J., Lane, L.D. & Lake, C.R. (1988). Hemodynamic, ventilatory, and biochemical responses of panic disorder patients and normal controls with sodium lactate infusion and spontaneous panic attacks. Archives of General Psychiatry, 45, 53-60.

Garssen, B., Buikhuisen, M. & van Dyke, R. (1996). Hyperventilation and panic attacks. American Journal of Psychiatry, 153, 513-518.

George, D.T., Nutt, D.J., Dwyer, B.A. & Linnoila, M. (1990). Alcoholism and panic disorder: Is the comorbidity more than the coincidence? Acta Psychiatrica Scandinavica, 81, 97-107.

George, D.T., Nutt, D.J., Walker, W. V., Porges, S. W., Adinoff, B. & Linnoila, M. (1989). Lactate and hyperventilation substantially attenuate vagal tone in normal volunteers: A possible mechanism of panic provocation? Archives of General Psychiatry, 46, 153-156.

George, D.T., Zerby, A., Noble, S. & Nutt, D.T. (1988). Panic attacks and alcohol withdrawal: Can subjects differentiate the symptoms? Biological Psychiatry, 24, 240-243.

Goldberg, R., Morris, P., Christian, F., Badger, J., Chabot, S. & Edlund, M. (1990). Panic disorder in cardiac outpatients. Psychosomatics 31 168-173.

Goldsmith, R. L., Bigger, J. T., Steinman, R. C. & Fleiss, J. L. (1992). Comparison of 24-hour parasympathetic activity in endurance-trained and untrained young men. Journal of the American College of Cardiology, 20, 552-558.

Gorman, J. M., Davies, M., Steinman, R., Liebowitz, M. R., Fyer, A. J., Coromilas, J. & Klein, D.F. (1987). An objective marker for lactate-induced panic. Psychiatry Research, 22, 341-348.

Gottman, J., (1990). Time-series analysis applied to physiological data. In J. T. Cacioppo & I.G. Tassinari (Eds), Principles of psychophysiology: Physical, social and inferential elements. New York: Cambridge University Press.

Grossman, P. (1992). Breathing rhythms of the heart in a world of no steady state: A comment on Weber, Molenaar, and van der Molen. Psychophysiology, 29, 66-72.

Grossman, P. (1992). Respiratory and cardiac rhythms as windows to central and autonomic biobehavioral regulation: Selection of window frames, keeping the panes clean and viewing the neural typography. Psychophysiology, 34, 131-161.

Guyton, A.C. & Hall, J. (1997). Textbook of Medical Physiology. Philadelphia: W.B. Saunders.

Hatch, J.P., Klatt, K., Porges, S. W., Schroeder-Jasheway, L. & Supik, J.D. (1986). The relationship between rhythmic cardiovascular variability and reactivity to orthostatic, cognitive and cold pressor stress. Psychophysiology, 23, 48-56.

Hayward, C., Taylor, C.B., Roth, W. T., King, R. & Agras, W. S. (1989). Plasma lipid levels in patients with panic disorder or agoraphobia. American Journal of Psychiatry, 146, 917- 919.

Hesselbrock, M. N., Meyer, R. E & Keener, J. J. (1985). Psychopathology in hospitalized alcoholics. Archives of General Psychiatry, 42, 1050-1055.

Hoehn-Saric, R., McLeod, D. R.& Zimmerli, W.D.( 1991). Psychophysiological

response patterns in panic disorder. Acta Psychiatrica Scandinavica, 83, 4-11.

Holmes, D.S. & Cappel, B.M. (1987). Prophylactic effect of aerobic fitness on cardiovascular arousal among individuals with a family history of hypertension. Journal of Psychosomatic Research, 31, 601-605.

Howell, D.C. (1992). Statistical Methods for Psychology (Third Edition).  
Duxbury Press: Belmont, CA.

Hull, S.S., Vanoli, E., Adamson, P.B., Verrier, R. L., Foreman, R. D. & Schwartz, P. J. (1994). Exercise training confers anticipatory protection from sudden death during acute myocardial infarction. Circulation, 89, 548-552.

James, M.A., Robinson, T.J., Panerai, R.B. & Potter, J.F. (1996). Arterial baroreceptor-cardiac reflex sensitivity in the elderly. Hypertension, 28, 953-960.

Jorna, P.G.A.M. (1992). Spectral analysis of heart rate and psychological state: A review of its validity as a workload index. Biological Psychology, 34, 237-257.

Kahn, J.P., Drusin, R.E. & Klein, D.F. (1987). Idiopathic cardiomyopathy and panic disorder: Clinical association in cardiac transplant candidates. American Journal of Psychiatry, 144, 1327-1330.

Kahn, J.P., Gorman, J. M., King, D.L., Fyer, A. J., Liebowitz, M. R. & Klein, D.F. (1990). Cardiac left ventricular hypertrophy and chamber dilatation in panic disorder patients: Implications for idiopathic dilated cardiomyopathy. Psychiatric Research, 32, 55-61.

Katon, W.J. (1984). Panic disorder and somatization. American Journal of Medicine, 77, 101-106.

Katon, W. J. (1990). Chest pain, cardiac disease and panic disorder. Journal of Clinical Psychiatry, 51, (suppl.5), 27-30.

Kawachi, I., Colditz, G.A., Ascherio, A., Rimm, E. B., Giovannucci, E., Stampfer, M. J. & Willett, W.C. (1994). prospective study of phobic anxiety and risk of coronary heart disease in men. Circulation, 89, 1992-1997.

Kawachi, I., Sparrow, D., Vokonas, P.S. & Weiss, S.T. (1994). Symptoms of anxiety and risk of coronary heart disease: The normative aging study. Circulation, 90, 2225-2229.

Kawachi, I., Sparrow, D., Vokonas, P.S. & Weiss, S.T. (1995). Decreased heart rate variability in men with phobic anxiety (data from the Normative Aging Study). American Journal of Cardiology, 75, 882-885.

Kienzle, M.G., Ferguson, D. W., Birkett, C.L., Myers, G.A., Berg, W. J. & Mariano, D.J. (1992). Clinical hemodynamic and sympathetic neural correlates of heart rate variability in congestive heart failure. American Journal of Cardiology, 69, 482-485.

Klein, E, Cnaani, E., Harel, T., Braun, S. & Ben-Haim, S.A. (1995). Altered heart rate variability in panic disorder patients, Biological Psychiatry 37, 18-24.

Knochel, J.P. (1983). Cardiovascular effects of alcohol. Annals of Internal Medicine 98, 849-854.

Kushner, M.G., Mackenzie, T.B., Fiszdom, J., Valentiner, D.P. Foa, E., Anderson, N. & Wangenstein, D. (1996). The effects of alcohol consumption on laboratory-induced panic and state anxiety. Archives of General Psychiatry 53, 264-270.

Kushner, M.G., Sher, K.J. & Beitman, B.D. (1990). The relation between alcohol

problems and the anxiety disorders. American Journal of Psychiatry 147, 685-695.

Lazoglu, A.H., Glace, B., Gleim, G. W. & Coplan, N. L. (1996). Exercise and heart rate variability. American Heart Journal 131, 825-827.

Lint, D. W., Taylor, C.B., Fried-Behar, L. & Kenardy, J. (1995). Does ischemia occur with panic attacks? American Journal of Psychiatry 15, 1678-1680.

Litvack, D.A., Oberlander, T.F., Carney, L.H. & Saul, J.P. (1995). Time and frequency domain methods for heart rate variability analysis: A methodological comparison. Psychophysiology, 32, 492-504.

Lombardi, F. Sandrone, G., Mortara, A., La Rovere, M.T., Colombo, E., Guzzetti, S. & Malliani, A. (1992). Circadian variation of spectral indices of heart rate variability and mortality after myocardial infarction. American Heart Journal, 123, 1521-1529.

Lombardi, F., Sandrone, G., Pernpruner, S., Sala, R. Garimoldi, M., Cerutti, S., Baselli, G., Pagani, M. & Malliani, A. (1987) Heart rate variability as an index of sympathovagal interaction after myocardial infarction. American Journal of Cardiology, 60, 1239-1245.

Louie, A. K., Louie, E. K. & Lannon R.A. (1992). Systemic hypertension associated with tricyclic antidepressant treatment in patients with panic disorder. American Journal of Cardiology, 70, 1306-1309.

Maddock, R. J. & Carter, C. S. (1991). Hyperventilation-induced panic attacks in panic disorder with agoraphobia. Biological Psychiatry, 29, 834-854.

Mancia, G., Parati, G., Pomidossi, G., Casadei, R., Di Rienzo, M. & Zanchetti, A. (1986). Arterial baroreflexes and blood pressure and heart rate variabilities in humans.

Hypertension, 8, 147-153.

Manuck, S.B. & Krantz, D.S. (1986). Psychophysiologic reactivity in coronary heart disease and essential hypertension. In K. A. Matthews, S.M. Weiss, T. Detre, T.M. Dembroskie, B. Falkner, S.B. Manuck & R. B. Williams, Jr. (Eds.) Handbook of stress, reactivity and cardiovascular disease. (pp. 11-34). New York: Wiley.

Martin, G. J., Magid, N.M., Myers, G., Burnett, P.S., Schaad, J. S., Lesch, M. & Singer D.H. (1987). Heart rate variability and sudden death secondary to coronary artery disease during ambulatory monitoring. American Journal of Cardiology, 60, 86-89.

McLeod, D. R., Hoehn-Saric, R., Zimmerli, W.D. De Souza, E. B. & Oliver, L. K. (1990). Treatment effects of alprazolam and imipramine: Physiological versus subjective changes in patients with generalized anxiety disorder. Biological Psychiatry, 28, 849-861.

Middleton, H.C. (1990). Cardiovascular dystonia in recovered panic patients. Journal of Affective Disorders, 19, 229-236.

Middleton, H.C., Ashby, M. & Robbins, T. W. (1994). Reduced plasma noradrenalin and abnormal heart rate variability in resting panic disorder patients. Biological Psychiatry, 36, 847-849.

Mortara, A., La Rovere, M.T., Signorini, M.G., Pantaleo, P., Pinna, G., Martinelli L., Ceconi, C., Cerutti, S. & Tavazzi, L. (1994). Can power spectral analysis of heart rate variability identify a high risk subgroup of congestive heart failure patients with excessive sympathetic activation? A pilot study before and after heart transplantation. British Heart Journal, 71, 422-430.

Mulder, L.J.M. (1992). Measurement and analysis methods of heart rate and

respiration for use in applied environments. Biological Psychiatry, 34, 205-236.

Mullaney, J. A. & Trippett, C.J. (1979). Alcohol dependence and phobias: Clinical description and relevance. British Journal of Psychiatry, 135, 565-573.

Nolan, J., Flapan, A.D., Capewell, S., MacDonald, T.M., Neilson, J. M.M. & Ewing, D.J. (1992). Decreased cardiac parasympathetic activity in chronic heart failure and its relation to left ventricular function. British Heart Journal, 69, 761-767.

Pagani, M, Malfatto, G., Pierini, S., Casati, R., Masu, A.M., Poli, M., Guzzetti, S., Lombardi, F., Cerutti, S. & Malliani, A. (1988). Spectral analysis of heart rate variability in the assessment of autonomic diabetic neuropathy. Journal of the Autonomic Nervous System, 23, 143-153.

Papp, L.A., Klein, D.F. & Gorman, J. M. (1993). Carbon dioxide hypersensitivity, hyperventilation and panic disorder. American Journal of Psychiatry, 150, 1149-1157.

Parati, G., Frattola, A., Di Rienzo, M., Castiglioni, P., Pedotti, A. & Mancia, G. (1995). Effects of aging on 24-hour dynamic baroreceptor control of heart rate in ambulant subjects. American Journal of Physiology, 268, H1606-H1612.

Pohl, R. Yeragani, V. K. & Balon, R. (1992). Smoking in patients with panic disorder. Psychiatry Research, 43, 253-262.

Porges, S. W. (1985). Method and apparatus for evaluating rhythmic oscillation in aperiodic physiological response systems. United States Patent No.4,510,944.

Porges, S. W. (1992). Vagal tone: A physiologic marker of stress vulnerability. Pediatrics, 90, 598-504.

Porges, S. W. & Bohrer, R.E. (1990). Analysis of periodic processes in

psychophysiological research. In J. T. Cacioppo & I. G. Tassinari (Eds), Principles of psychophysiology: Physical, social and inferential elements. New York: Cambridge University Press.

Porges, S. W. & Byrne, E. A. (1992). Research methods for measurement of heart rate and respiration. Biological Psychiatry, 34, 93-130.

Rechlin, T., Weis, M., Spitzer, A. & Kashka, W. P. (1994). Are affective disorders associated with alterations of heart rate variability? Journal of Affective Disorders, 32, 271-275.

Roth, W. T., Margraf, J., Ehlers, A., Haddad, J. M., Maddock, R. J., Agras, W. S. & Taylor, C.B. (1992). Imipramine and alprazolam effects on stress test reactivity in panic disorder. Biological Psychiatry, 31, 35-51.

Roth, W. T., Margraf, J., Ehlers, A., Taylor, C.B., Maddock, R. J., Davies, S. & Agras, W. S. (1992). Stress test reactivity in panic disorder. Archives of General Psychiatry, 49, 301-310.

Roy-Byrne, P.P., Schmidt, P., Cannon, R.O., Diem, H. & Rubinow, D. R. (1989). Microvascular angina and panic disorder. International Journal of Psychiatry in Medicine, 19, 315-325.

Sartory, G. & Olajide, D. (1988). Vagal innervation techniques in the treatment of panic disorder. Behavior Research and Therapy, 26, 431-434.

Schmidt, B. N., Lerew, D. R. & Santiago, H.T. (1998). Effects of heart rate feedback on estimated cardiovascular fitness in patients with panic disorder. (Under review).

Schuckit, M.A. & Hesselbrock, V. (1994). Alcohol dependence and anxiety disorders: What is the relationship? American Journal of Psychiatry. 151, 1723-1734.

Schuckit, M.A., Irwin, M. & Brown, S.A. (1990). The history of anxiety symptoms among 171 primary alcoholics. Journal of the Studies of Alcohol, 51, 34-41.

Shear, M. K. Kligfield, P., Harshfield, G., Devereux, R. B., Polan, J. J., Mann, J. J., Pickering, T. & Frances, A. J. (1987). Cardiac arrhythmias in panic patients. American Journal of Psychiatry. 144, 633-637.

Shear, M. K., Polan, J. J., Harshfield, G., Pickering T., Mann, J., Frances, A. & James, G. (1992). Ambulatory monitoring of blood pressure and heart rate in panic patients. Journal of Anxiety Disorders, 6, 213-221.

Smail, P., Stockwell, T., Canter, S. & Hodgson, R. (1984). Alcohol dependence and phobic anxiety states, I: A prevalence study. British Journal of Psychiatry. 144, 53-57.

Smith, V. E., Schulman P., Karimeddini, M. K., White, W.B., Meeran, M. K. & Katz, A.M. (1985). Rapid ventricular filling in left ventricular hypertrophy: II. Pathologic Hypertrophy. Journal of the American College of Cardiology, 5, 869-874.

Somers, V. K., Conway, J., Johnston, J. & Sleight, P. (1991). Effects of endurance training on baroreflex sensitivity and blood pressure in borderline hypertension. Lancet. 337, 1363-1368.

Stein, J. M., Papp, L.A., Klein, D.F., Cohen, S., Simon, J., Ross, D., Martinez, J. & Gorman, J. M. (1992). Exercise tolerance in panic disorder patients. Biological Psychiatry, 32, 281-287.

Stein, M. B., Tancer, M.E. & Uhde, T. W. (1992). Heart rate and plasma

epinephrine responsivity to orthostatic challenge in anxiety disorders. Archives of General Psychiatry, 49, 311-317.

Stein, P. K., Kleiger, R. T. & Rottman, J. N. (1997). Differing effects of age on heart rate variability in men and women. American Journal of Cardiology, 80, 302-305.

Tancer, M.E., Stein, M. B., Moul, D. E. & Uhde, T. W. (1990). Normal serum cholesterol in panic disorder. Biological Psychiatry. 27, 99-101.

Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. (1996). Heart rate variability: Standards of measurement, physiological interpretation, and clinical use. Circulation, 93, 1043-1065.

Taylor, C.B. & Hayward, C. (1990). Cardiovascular considerations in selection of anti-panic pharmacotherapy. Journal of Psychiatry Research. 24, 43-49.

Taylor, C.B., King, R., Ehlers, A., Margraf, J., Clark, D., Hayward, C., Roth, W. T. & Agras, S. (1987). Treadmill exercise test and ambulatory measures in panic attacks. American Journal of Cardiology. 60, 48J-52J.

Taylor, C.B., Telch, M. J. & Havvik, D. (1983). Ambulatory heart rate changes during panic attacks. Journal of Psychiatric Research. 17, 261-266.

Trakowski, J.H. (1996). Effects of attentional focus on emotional responding to a biological challenge in panic disorder. (Unpublished dissertation).

Tucker, P., Adamson, P., Miranda, R., Scarborough, A., Williams, D., Groff, J. & McLean, H. (19997). Paroxetine increases heart rate variability in panic disorder. Journal of Clinical Psychopharmacology, 17, 370-376

. Verdino, J., Gottdiener, J. S., Kop, W. J., O'Leary, S.T., Howell, R. J. & Krantz,

D.S. (1995). Decreased heart rate variability precedes daily life ischemia. (Abstract).

Journal of the American College of Cardiology, 31, 2A.

Weber, E. J. M., Molenaar, P. C.M. & van der Molen, M. W. (1992). A non-stationarity test for the spectral analysis of physiological time series with an application to respiratory sinus arrhythmia. Psychophysiology, 29, 55-65.

Weissman, , M.M., Markowitz, J. S., Ouellette, R., Greenwald., S. & Kahn, J.P. (1990). Panic disorder and cardiovascular/cerebrovascular problems: Results from a community survey. American Journal of Psychiatry. 147, 1504-1508.

West, J. B. (1979). Respiratory physiology: The essentials Baltimore: Williams & Wilkens.

White, W.B. & Baker, L.H. (1986). Episodic hypertension secondary to panic disorder. Archives of Internal Medicine, 146, 1129-1130.

White, W.B. & Baker, L.H. (1987). Ambulatory blood pressure monitoring in patients with panic disorder. Archives of Internal Medicine, 147, 1973-1975.

Wilkinson, D.J. C., Thompson, J. M., Lambert, G. W., Jennings, G. L., Schwarz, R. G., Jeffreys, D., Turner, A.G. & Esler, M.D. (1998). Sympathetic activity in patients with panic disorder at rest, under laboratory mental stress, and during panic attacks. Archives of General Psychiatry, 55, 511-520.

Wulsin, L.R., Hilliard, J.R., Geier, P., Hissa, D. & Rouan, G.W. (1988). Screening emergency room patients with atypical chest pain for depression and panic disorder. International Journal of Psychiatry in Medicine, 18, 315-323.

Yataco, A.R., Fleisher, L.A. & Katzel, L.I. (1997). Heart rate variability and

Yataco, A.R., Fleisher, L.A. & Katzel, L.I. (1997). Heart rate variability and cardiovascular fitness in senior athletes. American Journal of Cardiology, 80, 1389-1391.

Yeragani, V. K., Balon, R., Pohl, R., Ramesh, R., Glitz, D., Weinberg, P., & Merlos, B. (1990). Decreased R-R variance in panic disorder patients. Acta Psychiatrica Scandinavica. 81, 554-559.

Yeragani, V. K., Meiri, P.C., Pohl, R., Balon, R., Desai, N. & Golec, S. (1990). Heart rate and blood pressure changes during postural change and isometric handgrip exercise in patients with panic disorder and normal controls. Acta Psychiatrica Scandinavica. 81, 9-13.

Yeragani, V. K., Pohl, R., Balon, R., Ramesh, C., Glitz, D. & Sherwood, P. (1990). Risk factors for cardiovascular illness in panic disorder patients. Neuropsychobiology. 23, 134-139.

Yeragani, V. K., Pohl, R., Balon, R., Ramesh, C., Glitz, D., Weinberg, P. & Merlos, B. (1992). Effect of imipramine treatment on heart rate variability measures. Biological Psychiatry. 26, 27-32.

Yeragani, V. K., Pohl, R., Berger, R., Balon, R., Ramesh, C., Glitz, D., Srinivasan, K. & Weinberg, P. (1993). Decreased heart rate variability in panic disorder patients: A study of power-spectral analysis of heart rate. Psychiatry Research, 46, 89-103.

Yeragani, V. K., Sobolewski, E., Igel, G., Johnson, C., Jampala, V.C., Kay, J., Hillman, N., Yeragani, S. & Vempati, S. (1998). Decreased heart rate variability in patients with panic disorder: a study of Holter ECG records. Psychiatry Research, 78, 89-

99.

Yeragani, V. K., Srinivasan, K., Balon, R., Ramesh, C. & Berchou, R. (1994).

Lactate sensitivity and cardiac cholinergic function in panic disorder. American Journal of Psychiatry, 151, 1226-1228.