THE UNIVERSITY OF CALGARY

PANIC DISORDER AND CHRONIC HYPERVENTILATION

BY

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ABSTRACT

The study examined evidence for chronic hyperventilation in Panic Disorder subjects relative to normal controls. Physiologic indices of chronic hyperventilation included blood bicarbonate levels, medullary CO2 chemoreceptor sensitivity, and recovery times for End-tidal CO2 following both upward and downward manipulation of blood CO2 levels.

Continuous measure of Tidal Volumes, Breathing Frequency, End-tidal CO2, and Heart Rate were recorded during steady-state CO2 inhalation tests at four levels of CO2 concentration (0%, 1%, 3%, 5%), during recovery from 5% CO2 inhalation, and during recovery from hyperventilation. In addition, each subject's somatic, cognitive, and anxiety reactions to each stimulus condition were recorded. Between and within comparisons were made on the hyperventilation and psychologic indices.

Chemoreceptor sensitivity was assessed through examination of the change in Minute Ventilation (litres of air breathed each minute) from 3% to 5% CO2 in the two groups. Recovery of End-tidal CO2 was assessed by comparing the groups' time constants for CO2 recovery

following enriched and deprived CO2 stimuli. Where hypothesized group differences occurred on physiologic measures, covariance analyses were used to partial-out the influence of the psychological variables upon the physiologic responses.

Results indicated that the two groups had equivalent medullary CO2 chemoreceptor sensitivity, but that the Panic Disorder subjects had lower bicarbonate due to chronic hyperventilation, and also a slower recovery time for End-tidal CO2 following hyperventilation. Psychologic variables could not fully account for the slower CO2 recovery of Panic Disorder patients compared to Controls.

It was proposed that the lower bicarbonate and slower CO2 recovery of Panic Disorder patients reflect hyperventilation-proneness, and that further study of these variables may enhance our knowledge of both the mechanisms subserving the physical symptoms of panic and the ongoing vulnerability to experience these symptoms.

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DEDICATION

To the memory of my father,

Robert Bruce Lynch

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Introduction

Overview of the Research

Psychological theories of Panic Disorder (PD) and Agoraphobia with Panic Attacks have emphasized the personality, cognitive, and learning aspects of these syndromes, with little attention being given to the underlying physiological processes mediating between these factors and the dramatic physical symptoms of these disorders (c.f. Chambless & Goldstein, 1982; Guidano & Liotti, 1983; Mathews, Gelder, & Johnston, 1981). A biophysiological literature on PD developed separately from the psychological literature, however the two literatures have been bridged in a number of important respects by recent findings which have implicated a partly psychological/behavioral, partly biological process in the production of panic attacks. Hyperventilation (HV), long considered merely a symptom of anxiety (Rice, 1950), is now being identified as a likely physiological foundation for the somatic symptoms of panic attacks (Gorman, Liebowitz, Fyer, & Stein, 1989). From the psychological literature, cognitive-behavioral researchers have contributed conceptual models which can link the physiological symptoms

of HV to the emotional 'panic' reaction (e.g., Clark, 1988; Salkovskis, 1988).

The purpose of the current research was to extend our understanding of the hyperventilation-panic linkage by focussing measures upon the chronic form of hyperventilation, which could explain features of Panic Disorder that acute hyperventilation alone cannot. For example, if it were shown that PD patients have chronic HV syndrome, this could explain not only the physiological underpinnings of individual panic attacks, but also the gradual development and chronic course of Panic Disorder. In this view, gradually increasing frequency and severity of panic attacks may be due to increasing chronicity of HV breathing patterns. Initial panic attacks would be conceived of as "acute" episodes of stress-induced HV occurring in the context of otherwise normal breathing patterns. Repeated episodes of acute stress-induced HV/panic, representing an increase in the severity of panic disorder, may be mediated by bodily homeostatic mechanisms to produce mild, habitual overbreathing patterns referred to as "chronic" HV. Panic attacks would then become even more frequent and severe because the acute episodes of HV were superimposed upon a facilitative chronic overbreathing pattern. In this way, HV/panic would gradually become more

severe and also more autonomous from psychological triggers.

Three measures associated with chronic HV were examined in the current study. First, blood bicarbonate levels were taken since low blood bicarbonate is a clear marker for habitual overbreathing/chronic HV. Second, since there have been suggestions that medullary CO2 chemoreceptors may increase their sensitivity as a homeostatic bodily adjustment for chronic HV, measures of CO2 chemosensitivity were employed. Third, since a strong tendency for delayed recovery of CO2 has been identified in some chronic hyperventilators, two tests of end-tidal CO2 recovery were carried out in the current study.

Historical Review of the Relationship between Hyperventilation and Panic Disorder

In their historical review, Hardonk and Beumer (1979) credit Da Costa's (1871) study of three hundred Civil War patients as the first major investigation of individuals who would today be classified as having Panic Disorder. Although Da Costa preferred the terms "Irritable Heart Syndrome", "Irritable Heart of Soldiers", or "Effort Syndrome", for many years thereafter the disorder carried his name. Many other names were subsequently given to this

disorder, so that by 1918 it had also become known as Valvular Heart Disease, Disordered Heart Action, Constitutional Physical Asthenia, Neurocirculatory Asthenia, and Neurasthenia. To this point, all investigators apparently attributed the condition to organic pathologies and their complications, although in 1919 Cahn noted a subgroup of these patients for whom neurotic anxiety and fear seemed to be the cause. Interestingly however, Hardonk et al. did not compile this as a history of Panic Disorder, but rather as a history of the "Hyperventilation Syndrome". As they point out (1979, p. 311), as early as 1929 a connection had been identified between Da Costa's Syndrome and excessive ventilation and by 1938 some were proposing that all of the aforementioned disorders be called "Hyperventilation Syndrome" due to the presence of excessive ventilation in the symptom pictures of these patients.

The term "Hyperventilation Syndrome" outlived its progenitors, siring a line of research of its own. From 1938 through 1968, research seems to have concentrated either on subjects selected as probable hyperventilators (with few attempts to assess the possible phobic status of subjects), or on agoraphobics (with, at most, passing references to increased ventilation which was considered a symptom secondary to anxiety), despite the re-iterated

suspicion by Lewis' (1953) that some or all of the symptoms of "neurocirculatory asthenia", "cardiac neurosis", and "anxiety reaction" were due to the pathophysiology of over-breathing. It has only been very recently that the attention of researchers has returned to the possible role of excessive ventilation in the production of panic attacks and phobic symptoms (e.g., Clark, Salkovskis, Chalkley, & Hemsley, 1983; Clark, Salkovskis, & Chalkley, 1985; Garssen, van Veenendaal, & Bloemink, 1983; Gibson, 1978; Gorman, Askanazi, Liebowitz, Fyer, Stein, Kinney & Klein, 1984; Grossman, de Swart, & Defares, 1985; Hibbert, 1984; Lazarus & Kostan, 1969; Ley 1985, 1987, 1988a; Lowenstein 1968; Rapee, 1985; Salkovskis, Clark, & Chalkley, 1983; Salkovskis, Jones & Clark, 1984; van den Hout & Griez, 1985a; Van Dis, 1975).

Physiological Effects of Acute Hyperventilation and their Similarity to Panic Attacks

Acute hyperventilation (HV) is the state in which ventilation temporarily exceeds cellular metabolism, so that more carbon dioxide is exhaled than is produced by the body, resulting in lower blood CO2 levels (Bullock, Boyle, & Wang, 1984).

The physiological and psychological consequences of HV-induced low blood levels of CO2 are numerous and complex. Although the exact nature of the neuro-biological, mechanical, and psychologic chains of events leading to each of the many possible symptoms of HV are not fully understood in many cases, it is generally agreed that a rapid rise in blood pH, occasioned during HV via the rapid loss of CO2 via the lungs, can cause symptoms of fatigue, weakness, and exhaustion, and changes in cardiovascular, neurologic, respiratory, gastrointestinal, musculoskeletal, and psychologic functioning (Lewis, 1953; Missri & Alexander, 1978). Ley (1988a) has pointed out that the twelve DSM-III (ref) panic attack symptoms may be found in most lists of the possible symptoms of HV. The prominence of HV symptoms in the DSM-III diagnostic criteria for panic attacks (American Psychiatric Association, 1980) invites a brief review of the physiological processes by which HV is thought to produce them. To facilitate the comparison of these disorders, Table 1 provides a list of common hyperventilation symptoms (adapted from Lum, 1976) and the corresponding symptom picture for Panic Attacks (as outlined in DSM-III; American Psychiatric Association, 1980).

Beginning with the "Cardiac" category in Table 1, the symptom of heart palpitations, which regularly accompanies

Table 1

Symptoms of Hyperventilation and Panic Disorder

Hyperventilation Symptoms (adapted from Lum, 1976):	DSM-III Panic Attack Symptoms (as numbered therein):
CARDIAC:	
palpitations, precordial pain, 'angina', chest pain	2. palpitations 3. chest pain or discomfort
RESPIRATORY:	
shortness of breath, 'asthma', excessive sighing	1. dyspnea (shortness of breath) 4. choking or smothering sensations
NEUROLOGICAL:	
dizziness, faintness, lack of concentration, migrainous headache, numbness, 'pins and needles' in face and limbs	5. dizziness, vertigo, or unsteady feelings 10. faintness 7. paresthesias (tingling in hands or feet)
MUSCULAR:	
cramps, fibrositic pains, tremors, rarely tetany	11. trembling or shaking
PSYCHIC:	
tension, anxiety, 'unreal' feelings, depersonalisation, occasionally hallucinations	6. feelings of unreality 12. fear of dying, going crazy, or doing something uncontrolled during an attack
GENERAL:	
weakness, exhaustion, sleep disturbance, nightmares, emotional sweating (armpits and palms)	9. sweating 8. hot and cold flashes

both HV episodes and panic attacks, can be explained in terms of the influence that lower CO2, due to HV, has on increasing heart rate (George, Nutt, Walker, Porges, Adinoff, & Linnoila, 1989; Freeman, Conway, & Nixon, 1986a; Grossman, 1983; Thyer, Papsdorf, & Wright, 1984). Chest pain is another cardiac symptom common to panic attacks and hyperventilation, and it leads many PD patients to believe they are having heart attacks. There is a considerable literature on the relationship of chest pain to both hyperventilation and Panic Disorder, and a comprehensive review will not be attempted here. Instead, a brief review of the relationship of chest pain and Panic Disorder will be followed by a description of the possible link between hyperventilation, chest pain, and panic.

The physiological origins of chest pain in PD patients are unknown, however cardiovascular disease does not appear to be implicated. Instead, research has shown a strong connection between the diagnosis of Panic Disorder and normal coronary arteriograms. In several large groups of chest-pain patients who presented to cardiologists but whose coronary arteriograms were found to be normal, psychological examination has revealed exceptionally high incidence figures for Panic Disorder. For example, Mukerji, Beitman, Alpert, Hewett, & Basha (1987) found 49 of 123 (40%) met criteria for Panic Disorder, Katon, Hall,

Russo, Cormier, Hollifield, Vitaliano, and Beitman (1988) identified 12 of 28 (43%) as having Panic Disorder, and Beitman, Basha, Flaker et al. (1987) found Panic Disorder in 43 of 165 (26%). Kane, Harper, and Wittels (1988) contacted 260 patients who had received normal results on coronary arteriograms eight to eighteen months prior, and reported that:

> "Of the 216 patients (83% of total sample), 130 were female and 86 male. Sixty-three percent of the women and 50% of the men satisfied the criteria for Generalized Anxiety Disorder, and 20% met the criteria for panic attacks" (p. 1412).

The incidence figure for Panic Disorder in this population is exceptionally high compared with the 1.0% PD morbidity estimate in community studies (Myers, Weissman, Tischler et al. 1984; Weissman & Merikangas, 1986) or the 6.5 to 13.0% estimate (Katon, Vitaliano, & Russo, 1986) in patients presenting to primary care physicians, The high incidence of panic disorder in chest pain patients with normal coronary arteries may even have been underestimated in some studies because they excluded subjects whose chest pain might have been due to esophogeal spasms (c.f., Beitman, Mukerji, Flaker, & Basha, 1988), since an abnormally high

co-morbidity between esophogeal spasms and Panic Disorder has also been identified (Clouse & Lustman, 1983).

These studies show that Panic Disorder is over-represented in chest-pain samples. There is reason to believe that hyperventilation may be the cause of both the panic attacks and the chest pain in many of these patients. The specific link between HV and chest pain may be the relatively recent discovery that HV often induces painful coronary artery spasms (Bouras, Kartsounis, & Bridges, 1987; Chelmowski & Keelan, 1988; Crea, Davies, Chierchia, Romeo, Bugliardini, Kaski, Freedman, & Maseri, 1985; Elbaz-Rostykus, Baylac-Domengetroy, Coisne, Gallimard, Allal, & Barraine, 1987; Falstie-Jensen, Engby, Rasmussen, Bagger, Thuesen, & Tagehoj-Jensen, 1987; Freeman, 1986; Freeman & Nixon, 1985a; Freeman & Nixon, 1985b; Freeman & Nixon, 1985c; Freeman & Nixon, 1985d; Freeman, Nixon, Legg, & Timmons, 1987; Heckerling & Hanashiro, 1985; Kruyswijk, Jansen, & Muller, 1986; Kaski, Crea, Meran, Rodriguez, et al., 1986; Lisker & Leff, 1983; Mortenson, Nielsen, & Grossman, 1986; Rasmussen & Bagger, 1985; Rasmussen & Henningsen, 1987; Rasmussen, Svend, Bagger, & per Henningsen, 1987; Takaoka, Yasue, & Horio, 1988; Wright, Engler, & Maisel, 1988).

At least one study has shown that the abnormally high incidence of Panic Disorder in coronary-healthy chest-pain

patients may be due to the presence of hyperventilation in these same patients. Bass, Cawley, Wade, Ryan, Gardner, and Hutchison (1983) studied ninety-nine consecutive patients referred to a chest clinic due to chest pain. The patients were divided into three groups corresponding to normal coronary arteries, moderately obstructed arteries, and severely obstructed arteries. Hyperventilation was diagnosed through a combination of measures including a symptom questionnaire, observation of breathing patterns, and end-tidal CO2 measurements, while psychiatric morbidity was assessed by a standard interview yielding a diagnosis according to the International Classification of Diseases (Edition 9). Seventy-four percent of Group 1 (physiologically healthy) patients were diagnosed as having an "Unexplained Breathing Disorder" (UBD) which would correspond to a diagnosis of hyperventilation. By comparison, only 47% of Group 2 (moderate coronary disease) and 13% of Group 3 (severe coronary disease) patients were hyperventilators. Thus the less cardiac disease the patients had, the more likely they were to be hyperventilators. In light of this information, it is interesting to note the results of the psychiatric interviews. In chest pain patients with no or only moderate coronary disease (Groups 1 and 2):

> "anxiety neurosis was the most common diagnosis, the patients having a wide variety of anxiety and phobic symptoms...common phobic themes included fear of crowds and of being confined" (p. 608).

In contrast, the most common psychiatric diagnosis for patients who subsequently received the diagnosis of significant coronary disease (Group 3) was Depressive Neurosis. To summarize this study, chest-pain patients who were found to have healthy hearts had a high incidence of HV, and HV was significantly associated with symptoms strongly suggestive of PD and Agoraphobia.

Under the "Respiratory" heading in Table 1, dyspnea (shortness of breath, respiratory difficulty) is listed as a symptom for both HV and panic. Ley (1985) has proposed a hyperventilation explanation for the dyspnea experienced by Panic Disorder patients. Under normal circumstances, breathing (minute ventilation, the number of litres of air breathed each minute) is chemically-driven by the CO2 produced by metabolism. However acute stressors may increase minute ventilation (i.e., cause hyperventilation), overriding the regulatory influence of blood CO2, and drive blood CO2 levels down. The tendency of PD's to react to symptoms of low CO2 with fear or frank panic may increase the stress on the person, acting to maintain the

hyperventilation in the manner of a vicious cycle. Ley's (1985) hypothesis is that fatigue during hyperventilation increases until the person finds it difficult to breathe even at normal levels, and PD patients may experience this progressive difficulty with breathing as dyspnea. The end of an HV/Panic attack would occur when fatigue eventually results in a sufficiently reduced minute ventilation that metabolic production of CO2 begins to exceed CO2 loss via the lungs, ending the symptoms caused by low CO2. Despite the appeal of this hypothesis, a typical hyperventilation episode is unlikely to require the level of effort known to fatigue respiratory muscles (c.f., Lambertson, 1960), and the mechanisms behind hyperventilation dyspnea and panic dyspnea remain unknown.

Two very common neurological symptoms of panic attacks are dizziness and faintness, and Table 1 shows that these are also known consequences of HV. HV causes a state of relative cerebral hypoxia. HV-induced low blood levels of CO2 cause cerebral vasoconstriction which markedly reduces blood flow to the brain, and also results in the Bohr effect (van Dis, 1975), in which the amount of oxygen transfer to tissues is reduced by a shift to the left in the oxyhemoglobin dissociation curve (i.e., the reduced blood supply that does reach the brain during HV releases proportionally less of its oxygen to brain tissues). It

may be this state of HV-induced relative cerebral hypoxia which causes PD's to experience dizziness and faintness during attacks.

The muscular symptoms listed in Table 1 (e.g., tremulousness, tetany, carpopedal or other muscle spasms) sometimes associated with panic attacks are also well-known consequences of HV (Brown, 1953; Lum, 1976; Van Dis, 1975) and may be the consequence of hyperventilation shifting the membrane potential of neurons towards the firing threshold (Lum, 1983; Stoop, de Boo, Lemmens, & Folgering, 1986).

Table 1 also indicates that the psychic manifestations of hyperventilation and panic attacks are very similar. Hyperventilation may exert its influence on panic attacks by providing a pattern of bodily sensations which are then given frightening interpretations by PD patients.

To recapitulate, there is considerable overlap between the respiratory (e.g., dyspnea), neurological (dizziness, faintness, numbness, paresthesiae, motor tremulousness) and cardiac (heart palpitations, chest pain) symptoms of panic attacks and those of hyperventilation episodes, leading to the suggestion that the relatively well-known physiology of hyperventilation may be the somatic foundation of panic attacks.

Support for the hyperventilation theory of panic comes from a number of diverse sources within the medical and

psychological literatures. The first and most important line of evidence to be reviewed concerns whether there are similar causes for hyperventilation and panic attacks. To hold the view that many panic attacks are actually hyperventilation episodes, one must be able to demonstrate that those stimuli which are known triggers for panic are also triggers for hyperventilation. Evidence bearing on this issue is reviewed in the following two sections. First, research on the overlap between naturally-occurring physiological and psychological triggers for panic and hyperventilation is reviewed, followed by evidence that the two most common laboratory-based methods of provoking panic may do so by inducing hyperventilation.

Physiological and Psychological Triggers for Hyperventilation

Naturally-occurring physiological triggers for increased (or hyper-) ventilation include heat and humidity (Pfeffer, 1978), intractable pain (Glynn, Lloyd, & Folkhard, 1981), direct or indirect stimulation of the medullary respiratory centers, hypoxemia, the influence of hormones or drugs on metabolism or on the central nervous system,

orgasm and trance states (Clark & Hemsley, 1982), and certain medical conditions, for example, asthma, liver cirrhosis, chronic obstructive pulmonary disease, chronic encephalitis lethargica, and pulmonary embolus (Bass & Gardner, 1985a; O'Donovan, 1943; Van Dis, 1975). A number of the more common triggers for physiological alteration and hyperventilation (e.g., changes in humidity, mild exercise, sexual relations, and sudden temperature changes) have also been cited as triggers for so-called "spontaneous" panics (Barlow, Vermilyea, Blanchard, Vermilyea, di Nardo, & Cerny, 1985).

Psychological factors are also widely recognized as potent triggers for panic, and many have been shown to trigger hyperventilation as well (Bass & Gardner, 1985b). For example, emotional states have been linked to hyperventilation at least as far back as the 16th century (Pfeffer, 1978). HV has been found in otherwise healthy normals exposed to situational stressors (Conway, Freeman, and Nixon, 1988; Garssen, 1980; Suess, Alexander, Smith, Sweeney, & Marion, 1980), when experiencing various emotions (Bass and Gardner, 1985b; Lum, 1976) such as anger (Stevenson & Ripley, 1952), and even when one is predisposed to wear tight clothing about the abdomen, forcing thoracic as opposed to diaphragmatic breathing (O'Donovan, 1943). Nixon & Freeman (1988) have shown that

merely thinking about emotive topics, or remembering the sensations accompanying symptom attacks, are reliable ways to induce hyperventilation in chest pain patients. Freeman, Conway, and Nixon (1986b) reviewed nineteen studies which found that emotional stimuli were capable of provoking hyperventilation, and confirmed these findings using their own procedure consisting of providing emotionally-oriented psychological challenges to subjects while they were under hypnosis.

The fact that emotional and situational stressors can provoke HV provides a possible explanation of the onset of Panic Disorder, since a great number of studies have shown that initial panic attacks are closely preceded by a number of emotionally-laden situational stressors (Buglass, Clarke, Henderson, Kreitman, & Presley, 1977; Doctor, 1982; Faravelli, 1985; Finlay-Jones & Brown, 1981; Hibbert, 1984; Kleiner & Marshall, 1987; Mathews, Gelder, & Johnston, 1981; Roth, 1959; Snaith, 1968; Shafar, 1976; Sheehan, Sheehan, & Minichiello, 1981; Solyom, Beck, Solyom, & Hugel, 1974; Uhde, Boulenger, Vittone, Siever, & Post, 1985).

The idea that HV is caused by stress, and that stress-induced HV may predispose to panic attacks, is consistent with Ottiviani and Beck's (1987) cognitive theory of Panic Disorder in which an important role is

played by emotional stressors in the PD patient's life, which are seen as sufficient causes for somatic symptoms, misattribution, and panic. They propose that the somatic symptoms of panic are misattributed by the patient to serious disease or mental illness, and that even autonomic excitement arising from positive life events may be catastrophically misattributed and result in panic.

Although psychological/emotional stress is known to be a precipitant of hyperventilation, the variability in emotional reactions to hyperventilation has never been given a full explanation. There are studies suggesting that expectations (van den Hout & Griez, 1982) and personality characteristics (Bass & Gardner, 1985; Clark & Hemsley, 1982) mediate between HV and symptom manifestations, and individual symptom-reporting biases probably play a role (Compernolle, Hoogduin, & Joele, 1979). Wientjes, Grossman, and Defares (1984) also point out the possibility that there are biological factors which determine the degree of hyperventilatory response to stressful situations. PD patients may be those at the high response end of the continuum of hyperventilatory responsiveness to stress, and those who are more biologically vulnerable to hyperventilate severely in response to stress may be more vulnerable to the development of HV syndrome and Panic Disorder.

Experimental Inductions of Panic: Relationship of Hyperventilation to Sodium Lactate Infusion and 35% CO2 Inhalation

Following Pitts' and McClure's (1967) pioneering study of sodium lactate infusion in anxiety neurotics and normal controls, many studies confirmed that lactate induces panic in about 70% of PD patients and in a much lower percentage of normal controls (Griez, 1984). The validity of lactate as an experimental model of panic was further enhanced by studies showing that antidepressant medications known to be effective in blocking naturally-occurring panic attacks were also effective in blocking the lactate attack (e.g., Kelly, Mitchell-Higgs, & Shermann, 1971; Rifkin & Siris, 1985; Rifkin, Klein, & Dillon, 1981). Although subsequent studies demonstrated that subjects' anxiety levels prior to lactate infusion can predict which PD patients will panic under lactate (e.g., Margraf, Ehlers, & Roth, 1986; and also which normal controls will panic with lactate (Yeragani, Poh, Balon, Weinberg, Berchou, & Rainey, 1987), the biophysiological mechanism(s) by which lactate produced the dramatic physical symptoms of panic still required explanation. This need increased with the ascendance of another panic-induction paradigm, 35% CO2 inhalation (Griez, 1984), since this procedure had no obvious

physiological processes in common with lactate infusion. Hyperventilation may be the physiological bridge between the lactate- and 35% CO2-panic.

Hyperventilation explanations of lactate- and CO2-panic presuppose an understanding of how lactate infusion and CO2 inhalation affect the blood, and an understanding of the chain of events leading from these effects to hyperventilation. To facilitate an explanation of these processes, Equation 1 below outlines the bi-directional metabolic sequence of events which has directed most of the research in this area (adapted from van Dis, 1975):

Equation 1

$$CO_2 + H_2O \;\langle===\rangle\; H_2CO_3 \;\langle===\rangle\; H^+ + HCO_3^-$$

Carbon Dioxide + Water <===> Carbonic Acid <===> Hydrogen Ion + Bicarbonate

The interrelationship between blood pH, bicarbonate ion, and carbon dioxide is expressed by the Henderson-Hasselbalch equation:

Equation 2

$$pH = 6.1 \log \frac{[\text{Bicarbonate Ion}]}{0.03\ pCO2}$$

which is also represented graphically in Figure 1. Since sodium lactate is metabolized, mole for mole, into bicarbonate (Grosz & Farmer, 1972), a sodium lactate infusion weights the right side of the scale in Figure 1, causing an increase in blood pH (alkalinizes the blood). Inhalation of a high concentration of CO2, on the other hand, weights the left-hand side of the scale in Figure 1, resulting in a decrease in blood pH (acidifies the blood). At first glance, it is difficult to see how lactate- or CO2-panics could be due to hyperventilation. First, although hyperventilation and lactate both alkalinize the blood, hyperventilation reduces CO2 (left side of Equation 1 and Figure 1) whereas lactate acts by increasing bicarbonate on the right side of Equation 1 and Figure 1. Second, unlike CO2 inhalation, hyperventilation reduces rather than increases CO2. A review of panic-induction studies and their relationship to alkalinization and

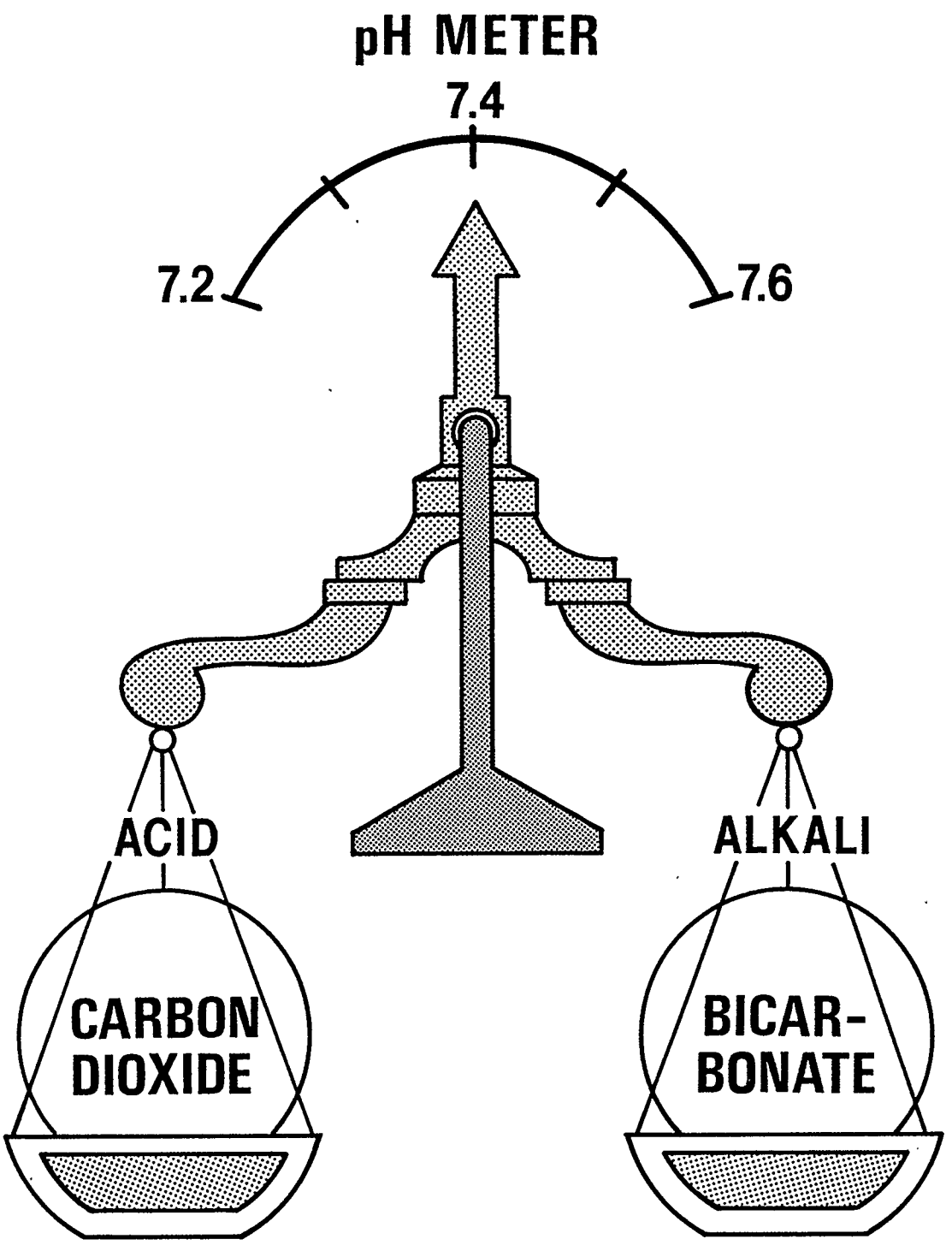


Figure 1

Loss of Carbon Dioxide by hyperventilation is compensated for by renal excretion of Bicarbonate ion to restore pH towards normality.

(Adapted from Lum (1976))

acidification of the blood will clarify the role of hyperventilation in lactate- and CO2-panics.

Sodium Lactate infusion, Blood Alkalosis, and Panic

A brief overview of the mechanics of Figure 1 will serve to introduce studies of blood alkalosis in inducing panic. As depicted in Figure 1, there is an acid-alkali 'balance' in the blood, corresponding to a normal blood pH of 7.40, and this normal pH balance is defended by the body (Bullock, Boyle, & Wang, 1984). Blood alkalosis can be induced either by increasing available alkali in the blood (e.g, by infusing an alkali like lactate into the blood) or by decreasing available acids (e.g., by hyperventilating and losing blood acid, CO2, to the atmosphere) tipping the scale in Figure 1 in the direction of higher blood pH. Since the body defends blood pH, physiological reactions follow which operate to re-establish normal pH (e.g., by excreting alkali from the blood or by conserving blood acids).

As noted above, both lactate infusion and hyperventilation alkalinize the blood. However HV alkalinizes the blood by decreasing an acid, CO2, in the blood (reducing the weight on the left hand side of the scale in Figure 1), whereas lactate alkalinizes the blood

by increasing an alkali, bicarbonate, in the blood (increasing the weight on the right hand side of the scale in Figure 1). Although both procedures alkalinize the blood (i.e., raise blood pH level) they should result in markedly different CO2 levels in the blood. During sodium lactate infusion, the alkali load of the blood increases, and the body reacts by attempting to restore the acid-alkali balance in the blood by conserving blood acids, the most important one being CO2. The primary mechanism by which blood CO2 is conserved is a slowing of respiration (hypo-ventilation), which causes less CO2 to be lost to the atmosphere via the lungs (Cohen, 1976). Thus, one would expect sodium lactate infusion to result in lower respiration than normal and higher than normal blood CO2 levels. From the point of view of the hyperventilation theory of panic then, the most important differentiating factor between sodium lactate-induced blood alkalinity and hyperventilation-induced blood alkalinity would be that blood CO2 levels should be higher than normal in the former, and lower than normal in the latter. The empirical results, however, contradict this expectation. Instead, there have now been a number of studies which have shown that: 1) lactate induces hyperventilation, and 2) the degree of HV occurring under lactate predicts which PD subjects will panic. During infusion of sodium lactate to

normal controls and PD patients, Liebowitz et al. (1985) observed that hyperventilation routinely accompanied the lactate-panic, accounting for the fact that panicking patients' CO2 levels at the point of panic were significantly lower than those of both normal controls and PD patients who did not panic under lactate. Gorman, Cohen, Liebowitz, Fyer, Ross, Davies, & Klein (1986) also studied normal controls and PD patients using lactate infusions. All three groups (controls, PD panickers, and PD non-panickers) were observed to hyperventilate during lactate infusion. At the point in time when PD patients panicked under lactate, the only variable which differentiated them from the other two groups was the greater magnitude of their hyperventilation-induced CO2 loss.

Even more important for the hyperventilation theory of panic, it has also been shown that in the two minutes prior to the patient reporting a panic attack during lactate infusion, a significant increase in the ongoing hyperventilation occurs, resulting in a dramatic drop in blood CO2 just before the attack (Gorman, Goetz, Uy, Ross, Martinez, Fyer, Liebowitz, & Klein, 1988).

Although these studies strongly suggest that hyperventilation can account for lactate panic, both procedures result in an alkalinization of the blood. It

remained to be determined whether blood alkalosis, per se, was the panicogenic factor common to both, irrespective of the different CO2 levels involved in the two procedures. In this context, it is important to recall that lactate is an indirect and therefore relatively slow way of alkalinizing the blood. Lactate must be metabolized to an alkali, bicarbonate, before it will alkalinize the blood. Reason suggests, therefore, that if blood alkalosis alone is the agent responsible for panic, infusion of a pure alkali instead of a substance like lactate which requires a conversion process before alkalinizing the blood, should result in a more rapid induction of panic. In a recent study comparing sodium lactate infusion to direct infusion of an alkali (bicarbonate) in PD subjects however, bicarbonate was found to take significantly longer to induce panic, and it also induced significantly fewer panic attack symptoms compared to lactate (Gorman, Battista, Goetz, Dillon, Liebowitz, Fyer, Kahn, Sandberg, & Klein, 1989). There was also a trend for bicarbonate to induce fewer panic attacks overall (9 of 20; 45%) than lactate (13 of 22; 59%), although this result only approached significance, perhaps due to the small sample size. Taken together, these results argue against the theory that metabolic alkalosis is the mechanism by which sodium lactate infusions induce panic, since a procedure which

maximized this factor was less effective than lactate in inducing symptoms and panic. Their finding that blood alkalosis of the metabolic type, caused by infusion of an alkali to the blood, does not cause panic is also supported by Gorman, Cohen, Liebowitz, Fyer, Ross, Davies, & Klein (1986), who noted that lactate panickers did not achieve a higher metabolic alkalosis under lactate than non-panickers. Instead, the results of the Gorman et al. (1989) study supported the idea that alkalosis of the respiratory type (hyperventilation) causes panic. Both lactate and bicarbonate infusions caused hyperventilation in the PD subjects, and that the degree of CO2 loss during HV differentiated panickers from nonpanickers; i.e., bicarbonate and lactate panickers developed lower CO2 due to HV, than did bicarbonate and lactate non-panickers. Therefore blood alkalosis of the metabolic type (i.e., that induced by adding bicarbonate to the blood) alone was not panicogenic, but the respiratory alkalosis superimposed upon it by hyperventilation was found to be a potent predictor of experimental panic.

Hyperventilation during lactate-panic has also been identified using computerized axial tomography. Stewart, Devous, Rush, Lane, and Bonte (1988) found that

> "Sodium lactate produced a 20%-23% increase in whole brain blood flow in normal controls subjects and in patients with panic disorder who did not panic, but led to only a 2.2% increase in whole brain blood flow in patients with panic disorder who panicked with lactate infusion" (p. 449).

The authors concluded that the considerably lower increase in whole brain blood flow exhibited by panicking subjects compared to non-panickers and normal controls reflected their hyperventilation at the time of panic, which follows from the knowledge that hyperventilation acts to decrease cerebral blood flow. Therefore, PD patients' tendency to hyperventilate during lactate-panic substantially attenuated the opposing influence of lactate, which acts to increase cerebral blood flow.

In summary, it has been demonstrated that, at the point of lactate panic, and at the point of panic during the infusion of a metabolite of lactate (bicarbonate), what differentiates panickers from nonpanickers is the panickers' lower CO2 level, which reflects a greater degree of hyperventilation in the panickers compared to the nonpanickers at the point of panic (Gorman, Battista, Goetz, Dillon, Liebowitz, Fyer, Kahn, Sandberg, & Klein, 1989). Hyperventilation, therefore, appears to supply an

adequate explanation of sodium-lactate panics in the laboratory.

35% CO2 Inhalation, Blood Acidosis, and Panic

Carr & Sheehan (1984) hypothesized that lactate, through its action in alkalinizing the blood, may lead to a counter-reaction in which certain brain regions experience cerebral ischemia which would increase both acid production and conservation. Specifically, decreased blood flow to these brain regions would enhance anaerobic metabolism thereby increasing the production of lactic acid, and the decreased blood flow would also result in less CO2 being carried away from the region. Together, these factors would result in blood acidosis in certain brain regions, and this was considered a possible cause of the lactate-panic. This theory, although not specific regarding which brain regions would be affected by vasoconstriction and acidosis to cause panic, had the advantage that it was consistent with findings that another procedure which also acidifies the blood, brief inhalations of 35% CO2, also causes panic. This hypothesis conflicts with the hyperventilation theory of panic, since HV is thought to induce panic through its action in lowering the blood level of CO2, not raising it.

In the most innovative study relating to the hypothesis that a high blood level of CO2 is responsible for panic, Griez & van den Hout (1985b) had normal subjects

inhale a gas mixture consisting of 35% CO2 and 65% O2. The high oxygen content of the mixture was irrelevant, since it is known that inhalation of high concentrations of oxygen does not induce panic in PD patients (van den Hout, Griez, van der Molen, & Lousberg, 1987). Subjects were required to fill their lungs to capacity, once, with 35% CO2, 65% O2. Inhalation of high CO2 gas concentrations induces two opposing conditions in rapid succession to one another. First an abnormally high blood CO2 level is induced as CO2 in the lungs is taken into the blood. Second, the high blood CO2 level stimulates CO2 chemoreceptors, resulting in rapid breathing which drives blood CO2 levels down quickly. van den Hout et al.'s (1985b) study was designed to investigate which of these blood CO2 levels, the initial high or the subsequent low level, was capable of generating the somatic symptoms associated with panic. Ten normal subjects underwent three gas inhalation sessions. In the first session, they were asked to exhale the gas mixture immediately after filling their lungs with it, and then to breathe freely, while in Sessions two and three they held the gas mixture in their lungs for 4 or 8 seconds, respectively, prior to exhaling it and breathing freely. The dependent measure was the timing of the onset of DSM-III peripheral somatic symptoms of panic during each of the sessions. Contradicting the high CO2 level/blood

acidosis theory of panic induction, it was found that no peripheral symptoms of panic occurred while blood CO2 levels were abnormally high, even when the high CO2 state was prolonged by the gas mixture (containing more than 1000 times the concentration of CO2 found in room air) being held in their lungs for up to 8 seconds. When free-breathing was permitted, all subjects showed the expected rapid decline in their artificially raised blood CO2 levels, and it was during this rapid CO2 decline, such as occurs during HV, that significant somatic symptoms of panic occurred. Moreover, the timing of the onset of somatic symptoms was temporally related to the breath-holding time. That is to say, panic symptoms were brought on only by HV-induced decreases in blood CO2 that followed exhalation of the gas mixture, and delaying the hyperventilation by breath-holding resulted in a parallel delay in the presentation of symptoms. The delayed presentation of symptoms was interpreted as indicating that a certain amount of HV and CO2 loss had to occur before symptoms were produced. The finding that decreases in CO2, not high levels of CO2, result in the somatic symptoms of panic was also reported by van den Hout (1988). However, it remains unclear from the end-tidal CO2 results in these studies what the brain levels of CO2 may have been at the time of panic. Taken together, the lactate infusion and 35% CO2 inhalation studies provide support for the hyperventilation theory of panic inasmuch as both

involve a drop in CO2 which is the defining characteristic of acute hyperventilation episodes.

To summarize the above literature review, it is known that the three most common methods to experimentally induce panic have at least one factor in common: they lower blood CO2 levels via hyperventilation, and the magnitude of the CO2 decrease is a strong predictor of which PD subjects will panic. It is now known that hyperventilation occurs immediately prior to the onset of lactate-induced panic attacks, with such regularity that it may be considered a "marker" for the lactate panic attack (Gorman, Cohen, Liebowitz, Fyer, Ross, Davies, & Klein, 1986). Of course, panic patients are not naturally inundated with surges of lactate, nor are they regularly exposed to exceptionally high levels of CO2 in their day-to-day environments. Therefore more naturalistic correlates of the lactate panic and the 35% CO2 panic must be explicated in order to explain panic attacks in the normal environment of the PD patient. It is argued here that the most likely explanation of low blood CO2 levels occurring outside the contrived situation of the laboratory, is hyperventilation. Falling CO2 levels are the defining characteristic of hyperventilation, and HV is known to have numerous triggers that <u>are</u> present in the PD patient's day-to-day environment, and these triggers (e.g., stress, emotional

states) have been implicated as causal factors in the genesis of Panic Disorder. To the extent that hyperventilation is the cause of most of most naturally-occurring panic attacks, both biophysiological theories (regarding a biophysiological lesion which may predispose subjects towards hyperventilation) and psychological theories (regarding the role of non-physiological triggers of HV) are relevant to an understanding of Panic Disorder.

Hyperventilation: Symptom or Cause of Panic?

For hyperventilation to be considered a cause of panic attacks, it must be shown that: 1) hyperventilation closely precedes panic (placing it in a temporally correct position to be hypothesized as a causal factor in panic production); and, 2) hyperventilation accompanies naturally-occurring panic attacks, not just experimental analogues of panic.

Regarding the first question, there are several lines of evidence which indicate that significant hyperventilation closely precedes panic attacks. To begin with, there is the analogue evidence provided by van den Hout & Griez (1985b) that dropping CO2 levels, as occur during hyperventilation, precede onset of the somatic

symptoms of panic attacks in normal controls. It is also now known that mild hyperventilation occurs throughout a sodium lactate infusion and that significant additional hyperventilation, resulting in a dramatic drop in blood CO2, occurs in the two minutes prior to the onset of the lactate panic attack (Gorman, Goetz, Uy, Ross, Martinez, Fyer, Liebowitz, & Klein, 1988). Ley (1985) has also presented presented evidence from intensive interviews with PD subjects concerning the order in which their symptoms occurred with respect to the experience of fear during the panic attack. With few exceptions, subjects reported that the symptoms typical of hyperventilation-induced low CO2 preceded the onset of fear in their panic attacks, and endorsed the view that the symptoms were the cause of their fear during attacks.

The second question concerns evidence that hyperventilation occurs during naturally-occurring panic attacks, not just during experimental analogs of panic attacks. Two studies have reported on serendipitous observation of CO2 levels during naturally-occurring panic attacks, and a third has monitored ambulatory PD patients to measure panics occurring in their natural environment. Griez, Pols, & van den Hout (1987) and Salkovskis, Warwick, Clark, & Wessels (1986) observed that significant hyperventilation, indexed by rapidly dropping CO2 levels,

accompanied each of the two unexpected panic attacks that they observed. In a prospective study of panic, Hibbert and Pilsbury (1988) used a skin sensor on the forearm of four PD patients to estimate blood levels of CO2 while the subjects were freely ambulatory and carrying on their daily activities, and during which time they had one or more panic attacks. In evaluating the results of this study, one must consider that the long time-constant of the measurement equipment (imposed by the time required for CO2 to migrate through the skin to the sensor), the equipment's inability to detect hyperventilation episodes lasting less than three minutes, and finally the overall "blunting" of the CO2 signal by the skin which results in underestimation of blood CO2 changes during hyperventilation (Hibbert et al., 1988), made this a very conservative test of the hypothesis that naturally-occurring panic attacks are accompanied by hyperventilation-induced drops in CO2. Despite these countervailing influences, Hibbert et al. were able to report definite physiological evidence of hyperventilation during patients' panic attacks. Given the limitations of the equipment, it was not possible to determine whether all panic attacks were accompanied by hyperventilation. A preliminary study by Hibbert (1986) using using the same methodology with only two subjects yielded comparable results to his 1988 study.

To summarize, it is known that both lactate infusions and hyperventilation act to alkalinize the blood through HV-induced CO2 losses, and that this same process occurs during panic attacks recorded in the natural environment. Therefore there is substantial evidence that a pivotal event in the lactate-, CO2-, and naturally-occurring-panic attack is the hyperventilation which immediately precedes it.

Co-Morbidity Studies of Hyperventilation and Panic Disorder/Agoraphobia

If hyperventilation is the cause of the somatic symptoms of panic attacks, it should be possible to identify a high incidence of PD in samples selected as hyperventilators; conversely, there should be a high incidence of HV syndrome in samples selected for Panic Disorder.

In several patient samples selected on the basis of being hyperventilators, a high incidence of Panic Disorder has been identified. Researchers from the Mayo Clinic (Herman, Stickler, & Lucas, 1981) conducted a rare long-term follow-up of children (modal age 13-15 years) who had been diagnosed as psychogenic hyperventilators (i.e., absence of medical causes for their hyperventilation), and

40% of their 34 cases reported having hyperventilation episodes well into adulthood. Symptom questionnaires during follow-up assessed many of the DSM-III criteria for Panic Disorder. Thirty-three percent reported attacks of sweating, 27% had light-headedness, 20% had chest pain, 17% had marked fear of dying, and choking sensations were present in 17%, heart palpitations in 13%, and paresthesias in 13%. The authors concluded that

> "for some children, the hyperventilation syndrome seems to presage years of anxiety-related disorders..." (p. 186).

In another study, Bass and Gardner (1985a) reported on psychiatric interviews given to 21 unequivocal chronic hyperventilators. The findings were that:

> "nine reported panic, which occurred either spontaneously, in relation to circumscribed situations such as crowds, or in response to disagreeable symptoms such as palpitations. Seven had clinical phobic neuroses with limitation of activities. Another eight reported mild phobic symptoms but without avoidance behaviour. Thus all but six of the

21 patients reported phobic symptoms of some description" (p. 1389).

An association between hyperventilation and Panic Disorder has also been identified in psychiatric populations. For example, Garssen, van Veenendaal, & Bloemink (1983) studied several hundred consecutive psychiatric outpatients who were given a questionnaire to assess the most common somatic symptoms of hyperventilation, a voluntary hyperventilation test to verify the diagnosis of HV, and a questionnaire measure of agoraphobia. One hundred sixty-two of these patients had scorable questionnaires, for a response rate of 60 percent. There was considerable overlap between the HV and Agoraphobia diagnoses, with sixty-five percent (17 of 26) of the definite hyperventilators meeting DSM-III criteria for Agoraphobia, and 61% (17 of 28) of those meeting DSM-III criteria for agoraphobia being classified as 'definite hyperventilators'. Hoes, Colla, van Doorn, Folgering, & de Swart (1987) did a similar study in a diagnostically-undifferentiated psychiatric group. Questionnaires were used to assess the presence of DSM-III criteria for Panic Disorder and also the symptoms of hyperventilation in a sample of 274 patients presenting to an outpatient psychiatric clinic. Of these 274 patients,

170 were diagnosed as hyperventilators and 35% of this group, and only 5% of those not diagnosed as hyperventilators, met criteria for Panic Disorder.

A co-morbidity link between HV and PD/Agoraphobia has also been demonstrated in samples which have been selected specifically for PD or Agoraphobia. Van Dis (1975) found that between 50 and 60% of a mixed group of agoraphobic and social phobic patients were hyperventilators. Ley (1985) found higher than normal breathing rates in six of 10 agoraphobics studied, suggesting hyperventilation.

Using positron emission tomography, Reiman, Raichle, Robins, Butler, Herscovitch, Fox and Perlmutter (1986) studied eight PD subjects who had earlier demonstrated a vulnerability to lactate-induced panic. In comparison with 25 normal control subjects, blood gas results showed pre-infusion CO2 to be significantly lower in the PD than the control group, indicating the presence of hyperventilation prior to re-infusion with lactate. Since PD subjects were aware that lactate was about to be used again, and since they had all had previous panic attacks provoked by lactate, their lower CO2 level probably reflected their tendency to hyperventilate in response to the stress of having lactate re-infused.

To summarize, experimental evidence linking HV to lactate- and CO2-induced panic attacks buttresses the

hyperventilation theory of Panic Disorder. This theory also receives support from findings that high proportions of subjects selected for hyperventilation suffer from Panic Disorder and/or Agoraphobia, and that clinical samples selected for Panic Disorder have a high incidence of hyperventilation.

Anti-Hyperventilation Treatment: Impact on Panic Disorder

The hyperventilation theory of panic attacks is also supported by studies which have assessed the impact on Panic Disorder of therapies designed to counter hyperventilation. Respiratory control training procedures have been investigated with the idea that, if a lower level of ventilation could be taught to PD hyperventilators, their blood CO2 level would be higher on a chronic basis (and thus farther from the low CO2 panic symptom threshold) resulting in fewer panic attacks.

Clark, Salkovskis & Chalkley (1985) reported on the use of breathing re-training to reduce panic attack frequency in "situationals" who had panic attacks (n = 11) and "non-situationals" (n = 7) who suffered from panic attacks. The situational/non-situational distinction corresponded roughly to DSM-III diagnoses of Agoraphobia

with panic attacks, and Panic Disorder, respectively (Clark, personal communication). PD subjects who identified a high degree of correspondence between their symptoms during panic attacks and symptoms produced during a voluntary hyperventilation test were selected for the study. Treatment was provided for both groups, consisting of a re-attribution component, which taught patients to attribute panic attack symptoms reproduced by voluntary hyperventilation as normal consequences of stress-induced HV, and a breathing re-training component. All subjects were asked to refrain from increasing their exposure to feared situations above baseline levels during treatment in order not to confound the effects of exposure with those of breathing re-training. Results indicated no change during baseline in the frequency of panic attacks for either group, but both groups showed a significant decrease in panic frequency by the second week of respiratory control treatment. For the "situationals" (the patients for whom behavioral avoidance tests are meaningful), there was also a significant pre- post-treatment decline in subjective anxiety during behavior avoidance tests, suggesting that exposure therapy for phobics could be made less stressful by pre-training in respiratory control.

While this was an interesting pilot study on the potential usefulness of breathing re-training with

hyperventilator panic patients, the lack of a panic patient control group offered a "neutral" but equally credible treatment procedure leaves their results open to interpretation as a placebo, demand characteristics (Orne, 1962), or non-specific treatment effect. Measures of the process they assumed to underlie improvement (i.e., increases in patients' blood CO2 levels) would also have improved their study. Six month and 2 year follow-ups of these patients showed continued improvement, although it was not clear whether this effect could be attributed exclusively to the breathing re-training therapy since one week after treatment the patients were told to increase their exposure to feared situations.

Salkovskis, Jones, & Clark (1986) did a replication and extension of the study by Clark et al. (1985). The most important difference in this study compared to the previous investigation was the addition of a measure of the process thought to underlie breathing re-training's success in reducing panic attacks, i.e., increases in blood levels of CO2. Nine PD patients who had three or more symptoms that could also be explained by HV were selected. Patients were taught to breathe their expired air in and out of a bag to ameliorate the symptoms of low CO2, practised deliberate HV and used bag re-breathing to alleviate the resulting symptoms, were given instruction in attribution

of panic symptoms to HV, and practised audio-tape coached breathing.

A comparison of resting CO2 in PD's compared to that of 23 age-and sex-matched normal controls showed the patients to have lower resting CO2 at baseline, indexing hyperventilation. Results showed that panic frequency was stable during four weeks of baseline, however panic frequency declined over four weeks of breathing re-training treatment. Questionnaire measures of phobic avoidance and depression showed significant improvement after treatment, as did measures of general anxiety and severity of panic attacks. Within one week of breathing re-training, PD patients' CO2 had risen significantly, reaching the level of normal controls by the end of week 2 and stabilizing for the remainder of the four weeks' treatment. Perhaps the most interesting results of this study were the correlates of this Breathing Re-training-induced PCO2 increase:

> "A relationship between clinical outcome and success in increasing PCO2 is indicated by the significant correlation ($r = 0.65$, $p < 0.05$) between improvement in the M&M [Marks and Mathews' Fear Questionnaire] global rating of phobic distress and the change in PCO2 at the end of the pure respiratory treatment; a related finding is the association between

> pre-treatment resting PCO2 levels and good clinical outcome following respiratory control (M&M Global rating $r = -0.74$, $p < 0.05$; rating of General Anxiety $r = -0.62$, $p < 0.05$. Change in PCO2 following respiratory control treatment correlated with pretreatment resting PCO2 ($r = 0.80$, $p < 0.01$)." (p. 9)

While the results suggest that raising CO2 through respiratory control treatment is effective in reducing panic frequency and severity, agoraphobic avoidance, and depression, methodological features of this study complicate the conclusions which can be drawn. There are at least two plausible alternative explanations of the results of this study. First, Salkovskis et al. (1986) correctly point out that the lack of control groups does not permit analysis of which aspects of their treatment package were influential. There are two distinguishable components of the therapy provided in this study, and it is unclear which of these might be primarily responsible for improvement in the patients' symptoms. Regarding the 're-attribution' component of therapy for example, patients simply may have responded to therapist reassurance, in this case the reassurance that their panic attacks were nothing more than harmless HV episodes. As Rapee (1987) has

pointed out, reassurance that symptoms are benign consequences of HV may reduce anxiety about panic attacks, resulting in a reduction in anxiety-driven hyperventilation. This could have caused the observed increase in CO2 and the observed reductions in panic and phobic symptoms, quite apart from any effect of training in slow breathing. This interpretation receives support from a recent study by Hibbert & Chan (1989). PD patients were divided into "hyperventilator" (n=13) and "non-hyperventilator" (n=8) groups on the basis of their response to a voluntary hyperventilation test. The results relevant to this discussion were that Breathing Re-Training (which included both the re-attribution of panic symptoms to HV, and the training in slow breathing) was just as effective in alleviating symptoms in the non-hyperventilator as in the hyperventilator group. Since improvement in the non-hyperventilator group cannot easily be attributed to anti-hyperventilatory slow-breathing training, these results suggest that the improvement in both groups may have been due to the anxiolytic effects of re-attribution of panic symptoms to HV. Rapee (1985; 1987) has noted that this criticism applies to other studies in which a combination treatment consisting of re-attribution of symptoms to HV and training in slow breathing have been used to successfully treat PD patients.

A second explanation of Salkovskis et al.'s (1986) results follows from the argument that there was an artifact in their experimental procedure which led to inaccurate estimates of subjects' CO2 levels as treatment proceeded. Breathing re-training treatment may have affected CO2 levels only during the laboratory tests, leaving chronic hyperventilation breathing patterns and a chronically low blood CO2 level unchanged. It will be recalled that Salkovskis et al.'s (1986) interpretation of their results was that breathing re-training resulted in a chronic anti-hyperventilatory change in breathing patterns which resulted in higher blood levels of CO2, the latter viewed as the proximal cause of symptom reduction. Although this view was supported by correlations between CO2 change and symptom improvement, it is important to consider the "demand characteristics" (Orne, 1962) of this experiment. Subjects became aware, during slow breathing training, that slower breathing was expected of them. Under such circumstances, subjects would likely try to please the experimenters by breathing slower during experimenter-supervised CO2 measurements, which would result in artifactually high CO2 readings as this expectation was implicitly re-affirmed via repeated CO2 testing. Since subjects' end-tidal CO2 could easily have been temporarily raised by breathing slower during the CO2

measurement sessions, it is possible that subjects' extra-experimental breathing patterns remained hyperventilatory in nature, and that the observed improvement in symptoms resulted entirely from the anxiolytic effect of re-attributing these symptoms to HV.

These two studies by Clark and colleagues point out the importance of using measures of hyperventilation 1) which are less susceptible to voluntary change by patients; 2) which index the chronic ventilation status of patients rather than their status only during measurement sessions; and, 3) which are unobtrusive and therefore less easily intuited by subjects, reducing their tendency to try and confirm the experimenter's expectations.

Hyperventilation, Expectations, and Panic

CO2 inhalations and voluntary hyperventilation were used in the current study to investigate several physiological hypotheses. An understanding of the role that expectations and instructional sets play in influencing responses to these stimuli led to the adoption of a particular instructional set for the current study.

Griez (1982) and Clark & Hemsley (1982) have pointed to the importance of the psychological context in which HV occurs, citing the important role that Schachterian

cognitive labelling of emotional states may play in determining emotional responses to hyperventilation. A number of studies have examined this issue, with uniformly corroborative findings. For example, in a study by Rapee (1986), 20 PD patients and 13 Generalized Anxiety Disorder patients were given 90 seconds of voluntary hyperventilation. No subjects panicked during this test, with patients indicating that they did not panic because it was obvious to them that hyperventilation accounted for their symptoms and that they had viewed the laboratory setting as a safe one where the experimenter would not allow any harm to befall them. These same factors may explain why only 25% of a group of Panic Disorder patients panicked during voluntary HV in a study by Gorman et al. (1984), since patients may have viewed the hospital-based laboratory session as a safe context for HV. Similarly, Griez, Zandbergen, Lousberg, & van den Hout (1988) hyperventilated 11 PD patients and 8 normal controls, reducing blood CO2 levels to less than half of their initial values. There was no significant increase in subjective anxiety during the low-CO2 hyperventilation challenge in either group, and this was explained by Griez et al. (1988) in terms of the neutral experimental instructions used. No subjects were led to expect anxiety during the tests, instead they were led to expect only a

physiological study of their CO2 levels. These instructions must be contrasted with those used in sodium lactate infusion studies, where PD patients are informed prior to the study that the procedures may induce a panic attack, and panic rates of 70% or more are observed in PD patients (e.g., Gorman, Cohen, Liebowitz, Fyer, Ross, Davies, & Klein, 1986; Liebowitz, Gorman, Fyer, Levitt, Dillon, Levy, Appleby, Anderson, Palij, Davies, & Klein, 1985; Reiman, Raichle, Robins, Butler, Herscovitch, Fox, & Perlmutter, 1986).

The role of expectations in facilitating panic during symptom-producing procedures was also demonstrated in a study by Compernolle, Hoogduin, and Joele (1979) in which they induced the expectation that the context was not a safe one. By raising patients' anticipatory anxiety a week in advance by informing them that an attack would be induced next session, and by commenting on the patient's symptoms during the hyperventilation (e.g., pointing out their increased heart rate) they were successful in inducing panic attacks in the majority of their PD patients.

Further evidence of the role of expectations in inducing panic was provided by Rapee, Mattick, & Murrell (1986). Inhalation of 50% CO2 was preceded either by no explanation of the probable symptoms that would occur, or

by description of the likely sensations that would occur during the test. PD subjects who received no explanation had more intense somatic symptoms, more panic-related cognitions, and reported the 50% CO2 inhalation experience to be more similar to their naturally-occurring panic attacks than did PD patients who had been told what symptoms to expect. Social phobics, on the other hand, did not respond differentially to the explanation/no-explanation manipulation. In another study of manipulated expectations, van den Hout and Griez (1982) induced expectations of either relaxation or of unpleasant tension in normal controls regarding an upcoming 35% CO2 inhalation test. During the inhalation of 35% CO2, the relaxation-expectation group showed a confirming change in this direction, and the unpleasant tension-expectation group showed a non-significant change towards increased tension.

Taken as a group, these studies indicate that panic anxiety can be markedly reduced in the laboratory by informing subjects that there is no intention to induce panic attacks, by advance explanation of the most likely symptoms to be produced by the experimental stimuli, and by conducting laboratory sessions in a context viewed as safe by the subjects.

Rationale and Objectives for the Current Study

Tests of the chronic HV model of Panic Disorder require identification of persistent ventilation and ventilation-related changes in PD subjects. Both biophysiological and psychological formulations of panic would benefit from the identification of indices of chronic HV that are unique to PD's and which contribute to our understanding of PD's sensitivity to biological and psychological challenge. The three indices of chronic HV that were chosen for investigation in the current study were 1) blood bicarbonate level, 2) medullary CO2 chemoreceptor sensitivity, and 3) slow recovery of End-tidal CO2. The rationale for each of these measures is outlined below.

Blood Bicarbonate as a Measure of Chronic HV

Lewis (1953) was among the first psychologic researchers to propose that a chronic from of HV exists:

> "I believe that many predisposed subjects...tend to develop a chronic psychophysiologic state characterized by fluctuating hyperpnea, borderline CO2 deficit and variable impairment of consciousness.

> Diverse symptomatic patterns accompany these basic changes, and the chronic course is punctuated by recurring acute episodes. As the respiratory component is often camouflaged by more prominent features, the resultant clinical picture is particularly confusing" (p. 920).

The development of chronic hyperventilation syndrome may be explained by reference to Figure 1. A low CO2 state resulting from an acute episode of HV (lifting the left-hand side of the scale) results in a higher blood pH. This hyperventilation can be triggered by stress (Garssen, 1980; Jellinek, Goldenheim, & Jenike, 1985; Suess, Alexander, Smith, Sweeney, & Marion, 1980), and can be maintained almost indefinitely and effortlessly by an occasional deep breath or sighing respiration (Balke, Ellis, & Wells, 1958; Okel & Hurst, 1961; Saltzmann, Heyman, & Sieker, 1963). Given a prolonged low CO2 state lasting as little as several hours, significant renal compensation (excretion of bicarbonate in urine, lightening the weight on the right hand side of the scale, restoring normal pH) occurs (Gledhill, Beirne, & Dempsey, 1975). Bicarbonate loss is well known in studies of altitude acclimitization (Balke, Ellis, & Wells, 1958) in which hyperventilation is an adaptive response to the relative

scarcity of oxygen at higher altitudes. The new, lower bicarbonate level is then defended by the body (Gennari, Goldstein, & Schwartz, 1972; Missri & Alexander, 1978) through a continuation of HV. As Cohen (1976) puts it:

> "The more important response to any change in HCO3- [bicarbonate] (whether or not due to a renal abnormality) is that of the lungs, which make a corresponding change in CO2 [increasing or decreasing respiration], rather than reverse the primary change in HCO3-" (p. 9).

Thus a lower bicarbonate level, induced by prolonged acute HV, may cause a lower level of CO2 to be maintained on a chronic basis by a compensatory increase in ventilation (chronic hyperventilation). The possible implications of low bicarbonate and chronic HV for panic disorder were outlined by Van Dis (1975):

> "If hyperventilation is sustained for longer than ten days [i.e., becomes chronic], a condition of chronic hyperventilation can develop. The homeostatic mechanisms of the body will try to adapt to the non-physiological state of overbreathing. An important coping mechanism of the body is the attempt

> to restore the acid-base balance by the excreting of bicarbonate by the kidneys, thus changing an important biochemical buffer system. The next episode of acute overbreathing, as a result of this change in buffer capacity, will give rise still more quickly to changes in pH and ionic balance. The state of chronic hyperventilation will therefore produce physiological changes and psychological symptoms more and more rapidly following even a short episode of acute hyperventilation" (pp. 372-373, italics added).

After acknowledging the probable role that acute hyperventilation probably plays in the production of the somatic symptoms of many panic attacks, Salkovskis (1988) has also summarized how bicarbonate reduction maintaining chronic overbreathing in PD's can explain a number of facets of their disorder:

> "Renal excretion of bicarbonate results in a reduced buffering capacity and greater susceptibility to pH challenge (for instance, lactate infusion, hyperventilation). That is, a given amount of respiratory change, will result in more symptoms occurring with a shorter latency. This increased sensitivity is also associated with an enhanced

exercise response, reduced breath-holding capacity, and is maintained at the cost of chronically elevated respiration and associated fatigue, chest pain and breathlessness (which appear inexplicable to the patient, further fueling their anxiety)" (p 126).

In this view, acute attacks of overbreathing form the somatic foundation of many panic attacks, and if bicarbonate compensation develops (chronic HV), the acute attacks may require less stress and less over-breathing to produce the somatic symptoms of panic. Acute panic attacks would therefore develop more rapidly and more frequently in the presence of an underlying chronic HV syndrome. In addition, the homeostatic balance which maintains chronically elevated respiration/HV would produce a chronic vulnerability to the acute attacks until the person met criteria for the diagnosis of Panic Disorder.

To recapitulate, chronic HV could provide at least partial explanations for the rapidity with which panic attacks develop, the progression from initial isolated panic attacks to the frequent attacks required for a diagnosis of Panic Disorder, and the chronic course of Panic Disorder. At least one study has found a lower blood bicarbonate level in PD patients compared to normal controls (Gorman, Cohen, Liebowitz, Fyer, Ross, Davies &

Klein, 1986), and others have shown nonsignificant trends for lower bicarbonate in PD's compared to normals (e.g., Liebowitz, Gorman, Fyer, Levitt, Dillon, Levy, Appleby, Anderson, Palij, Davies, & Klein, 1985; Gaffney, Fenton, Lanke & Lake, 1988). One study has also found that a combination of behaviour therapy and pharmacotherapy used to successfully treat a group of PD subjects also led to normalization of their low bicarbonate and CO2 levels (Gorman, Fyer, Ross, Cohen, Martinez, Liebowitz, & Klein, 1985).

Medullary CO2 Chemoreceptor Sensitivity as a Measure of Chronic HV

Lum (1976) and Salkovskis (1988) have noted that chronic HV is the physiological basis of acclimitization to living at high altitude where HV compensates for the relative scarcity of oxygen. The bicarbonate excretion characterizing chronic HV at altitude may also result in the setting of a new, lower CO2 chemoreceptor threshold. Magarian (1982) has proposed that this adjustment helps to maintain the chronic overbreathing, a process which has been described by Brown (1953, p 451):

> "An increased sensitivity to carbon dioxide of the chemosensitive cells of the respiratory center takes place during the prolonged hyperventilation, so that a reduced carbon dioxide tension will maintain the same respiratory [over-] ventilation that previously required a larger [CO2] stimulus. It is indeed generally found that increased ventilatory response to inhalation of carbon dioxide does follow passively imposed hyperventilation, and similar results have been obtained with hypoxic hyperventilation produced by a 3-week stay at 9500 feet altitude".

Physiologically then, chronic HV might be measurable through its effect in increasing CO2 chemoreceptor sensitivity. Therefore if PD subjects are chronic hyperventilators, CO2 inhalations applied to them in the present study may produce greater ventilation increases than the same procedures applied to normal controls. Enhanced sensitivity of central CO2 chemoreceptors in Panic Disorder patients remains a disputed finding however, with some researchers reporting in the affirmative (Gorman, Fyer, Goetz, Askanazi, Liebowitz, Fyer, Kinney, & Klein, 1988; Lousberg, Griez, & van den Hout, 1988), and others in the negative (Woods, Charney, Loke, Goodman, Redmond, & Heninger, 1986). Methodological features of the confirming

and disconfirming studies have complicated the conclusions which can be drawn from them. For example a number of the studies have used the Read Rebreathing method for assessing CO2 chemoreceptor sensitivity (Lousberg et al., 1988; Woods et al., 1986), which involves a shorter period of breathing measurement than the steady-state method adopted in the current study. The disadvantages of shorter measurement periods include the fact that the data points plotted to assess the slope for chemoreceptor sensitivity each contain information on only a few breaths, whereas in the current study it was possible to include breathing data for a full minute at each of two different levels of CO2 to estimate slopes. Second, since PD's are known to have greater variability in their breathing than NC's (Gorman et al., 1988), there is a distinct advantage in including data from as many breaths as possible, making the steady-state method more sensitive to differences in chemoreceptor sensitivity than the Read rebreathing technique. The method used by Gorman et al. (1988) was to use half-minute averages of breathing at five intervals in a five minute 5% CO2 inhalation run and calculate rate-of-change as an index of chemoreceptor sensitivity. Theirs was a provocation paradigm however and 39% of their PD patients had a panic attack, causing premature termination of measurement for these subjects. Their use of a clear plastic box

completely enclosing the subjects' heads as a means of delivering CO2 may have contributed to the high panic rate observed in PD subjects, and the role of high anxiety and panic in producing higher ventilation confounds their chemoreceptor sensitivity tests. While other investigators have acknowledged the possible confounding influence of anxiety on tests of chemoreceptor sensitivity in PD patients, psychological measures were not taken (e.g., Lousberg et al., 1988). To provide a more controlled test of the hypothesis, the current study 1) employed the steady-state method, 2) used instructions designed to minimize anxiety during the test, 3) used a mouthpiece and noseclip rather than a plastic head canopy to deliver CO2, and 4) measured subjective anxiety, physical symptoms, and frightening cognitions during the tests so that these influences, if significant, could be controlled for in statistical analyses. To test specifically for the sensitivity of central (medullary) as opposed to the sensitivity of peripheral CO2 chemoreceptors located in the lungs and the carotid and aortic arteries, each CO2 gas mixture used in the current study was mixed with high concentrations of oxygen (minimum O2 content 95%). As Clark (1968) has shown, the contribution of peripheral CO2 chemoreceptors is minimized when hyperoxic CO2 gas mixtures are used, so that the response to CO2 is determined almost

exclusively by the sensitivity of the medullary chemoreceptors.

Slow Recovery of CO2 as a Measure of Chronic HV:

The link between slow recovery of End-tidal CO2 and chronic HV syndrome is empirical, deriving originally from the work of Hardonk and Beumer (1979) who found a slower return to baseline of blood CO2 after voluntary hyperventilation in chronic hyperventilators compared to normal controls. A similar finding was reported by Folgering & Durlinger (1983), who showed that the slow CO2 recovery phenomenon was present in normal subjects who were hyperventilated. This occurred under isocapnic conditions, i.e., when peripheral aortic and carotid CO2 receptor input was minimized by keeping CO2 constant, which argues for central (medullary) control of this phenomenon. That the phenomenon was CO2-regulated at the central level was shown by the differential time constants of CO2 recovery at three different levels of maintained CO2. One recent study has given evidence that during recovery from voluntary hyperventilation some PD patients continue to hyperventilate, keeping their arterial CO2 lower longer than normal controls. Interestingly, it was only the

patients who had a panic attack in response to hyperventilation who continued to hyperventilate in the recovery period (Gorman, Fyer, Goetz, Askanazi, Liebowitz, Fyer, Kinney, & Klein, 1988), while PD non-panickers and normals quickly recovered the CO2 they had lost during hyperventilation.

In the present study, slow recovery of End-tidal CO2 was investigated not just following voluntary hyperventilation, but also following a high (5%) CO2 stimulus. Should PD subjects show a slower recovery of their end-tidal CO2 after these breathing stimuli compared to NC's, it could argue for a disturbance in the regulation of their breathing which predisposes them to HV, the effect of psychological arousal on maintaining acute hyperventilation, or a combination of these factors. In the present study, both psychological and physiological measures were collected to explore these possibilities.

To summarize the theoretical position taken in the present research, many somatic symptoms accompany an HV-induced low CO2 state (Lewis, 1953; Missri & Alexander, 1978), and these symptoms may be experienced as panic by those suffering from Panic Disorder. It is well-known that acute episodes of HV, like panic attacks, may be triggered by stress. The more prolonged or chronic that the HV becomes, the more that blood levels of bicarbonate should

fall (within physiological limits), and the more that chemoreceptor sensitivity to CO2 should increase. The current study attempts to confirm the presence of chronic hyperventilation syndrome in PD patients (i.e., bicarbonate compensation, heightened respiratory sensitivity to CO2 inhalation, and slow recovery of End-tidal CO2).

METHOD

Instructional Sets used in the Study

This study was primarily concerned with the identification of respiratory physiological differences between PD patients and normal controls. A number of procedures standarly used in physiological assessment of anxious patients to reduce the influence of anxiety upon the physiological results were used in the current study. First, to minimize the influence of psychological anxiety upon the physiological results, every effort was made to reduce PD patients' anxiety throughout the study. This was accomplished in a number of ways. We did not induce the expectation that panic would occur during the laboratory session, whereas in provocation studies (e.g., lactate infusion studies) PD patients are told that the infusion will likely cause panic. Subjects were led to expect only a study of carbon dioxide levels in expired breath during a series of respiratory maneuvers. Subjects were also told to expect some symptoms ("possibly you will experience breathing harder, as in physical exercise) as a natural consequence of breathing the gas mixtures, in order to reduce PD subjects' tendency to catastrophize about

symptoms. Similarly, prior to the voluntary hyperventilation test, subjects were led to expect some of the most common symptoms of hyperventilation (e.g., dizziness, tingling sensations in the fingers, and fatigue) to minimize PD subjects' tendency to catastrophize about these common symptoms.

Subject Recruitment

Women patients referred to the Foothills Hospital Panic and Agoraphobia Clinic by physicians in Southern Alberta were assessed for possible participation in this study. Additional subjects with Panic Disorder or Agoraphobia with Panic Attacks were recruited by a newspaper advertisement which described some of the symptoms of these disorders and requested sufferers to volunteer for the research project. Normal women volunteers were recruited primarily from employees of the University of Calgary.

Diagnosis of Panic Disorder

To be included in the experimental group, the subject had to be female, and had to meet DSM-III criteria for

Panic Disorder or Agoraphobia with Panic Attacks. Prospective PD and normal control subjects were given a series of standardized Panic and Agoraphobia questionnaires and then interviewed individually by a clinical psychologist to determine if they met DSM-III criteria for Panic Disorder or Agoraphobia with Panic Attacks. The twelve symptoms of a panic attack used in DSM-III to diagnose Panic Disorder were a subset of the larger set of common Panic Attack symptoms rated by all subjects when they filled out the Body Sensations Questionnaire and the Agoraphobic Cognitions Questionnaire (Chambless, Caputo, Bright & Gallagher, 1984). Questionnaire ratings corresponding to the DSM-III diagnostic symptoms of Panic Disorder were queried extensively during the clinical interview to ensure that subjects understood the questionnaires and responded accurately. Normal control subjects received the same clinical interview and psychometric tests as the patient group. Normal control subjects were excluded from the study if they admitted on questionnaire or interview assessment to ever having experienced a full-blown panic attack.

All subjects of the study were also given a medical interview by a specialist in internal medicine prior to their participation in the laboratory measurement session. Exclusion criteria for all subjects included any medical

contraindications for participation (e.g., history of significant cardiac or respiratory disease), the presence of any metabolic or other organic pathology which could compromise interpretation of blood test results, or the presence of any medical condition which could provide an explanation of the somatic symptoms of their panic attacks (e.g., thyroid dysfunction). Volunteers for the normal control group were also excluded if they had clinically significant symptoms of anxiety or depression.

Psychometric Measures

Four brief questionnaire measures of panic and agoraphobic symptomatology, and one questionnaire measure of depression, were used as part of the subject screening process. The Mobility Inventory for Agoraphobia (Chambless, Caputo, Jasin, Gracely, & Williams, 1985) provided two measures of agoraphobic avoidance behavior. It contains a wide range of questions regarding situations that may provoke anxious avoidance by the person, either when they are alone or when they are accompanied by a trusted companion.

Assessment of the verbal-cognitive system of agoraphobia consisted of the Agoraphobic Cognitions

Questionnaire (Chambless, Caputo, Bright & Gallagher, 1984). This scale provides ratings of the frequency with which certain catastrophic ideas (e.g., "I'm having a heart attack") occur during panic attacks. Cognitive awareness and fear of the most common somatic symptoms of panic attacks were measured by the Body Sensations Questionnaire (Chambless et al., 1984). The Beck Depression Inventory (Beck, Ward, Mendelsohn, Mock & Erbaugh, 1961) was used to assess depression.

Procedure

Subjects had the experimental procedures explained to them verbally, signed a Consent for Participation in Research form which explained the study procedures (Appendix A), completed questionnaire assessment of their symptoms, and received a clinical interview to determine if they met DSM-III criteria for Panic Disorder or Agoraphobia with Panic Attacks. Subjects then received their medical interview.

A laboratory measurement session was held for each subject within one week of having completed their psychological and medical interviews. During the laboratory measurement session, subjects were first

required to provide a small sample of venous blood from their chosen forearm. Measures of Forced Vital Capacity (FVC) and Forced Expiratory Volume in one second (FEV1) were then conducted. The subject was then directed to a washroom and asked to attempt to void, to reduce the discomfort of urinary urgency during the subsequent two hour measurement period. Follwing this, subjects were attached to EKG leads and inductance plethysmograph bands. Care was taken to loosen any tight clothing which might restrict the abdominal or chest muscle excursions that accompany breathing.

Instrumentation

A Model 713 pH/Blood Gas analyzer manufactured by Instrumentation Laboratory Inc. was used to analyze venous blood samples. Forced Expiratory Volume in one second (FEV1) and Forced Vital Capacity (FVC) were measured by a Breon Inc. Model 2400 Spirometer.

Five analog signals, corresponding to ribcage plethysmographic signal, abdomen plethysmographic signal, EKG, end-tdial CO2, and expired respiratory flow, were collected during the experiment. Computer control of the data acquisition process was provided by CODAS software

(Dataq Instruments, Inc.) and by proprietary software written for this project. Plethysmographic signals were calibrated before the data collection began by having the subject breathe a volume of 800 cubic centimetres in and out of a Stead-Wells Model P-1400 spirometer (Warren E. Collins Inc.). CO2 measurement equipment was calibrated before data collection using room air and a calibration-grade medical gas mixture containing 5.02% carbon dioxide, 94.98% oxygen. During data collection, plethysmographic signals from the ribcage and abdomen were harvested from two Respitrace Corporation Respibands, routed through an oscillator and then through a Respitrace Calibration Unit which output two voltage signals corresponding to the excursion (increase and decrease in diameter) of the ribcage and abdomen during each breath. EKG was collected using a standard five lead (left arm, right arm, left leg, right leg, chest) configuration, with the signals routed through a Hewlitt-Packard Bioelectric Model 8811A EKG amplifier, which produced a voltage signal corresponding to the electrical activity of the heart. CO2 in expired breath was continuously collected from a sample tube connected to the mouthpiece through which the subject breathed. The air sample was then sent to either a Beckman LB-II Infra-Red Gas Analyzer or a Mass Spectrometer, which output a voltage signal respresenting the percentage of CO2

in each exhalation. Expired flow was measured at the outlet of a one-way, modified Otis-McKerro valve (manufactured by Warren E. Collins, Inc.) by a Fleisch Pneumotach (Type # 2, Model # 137861; Gould Instruments Inc.) and Differential Pressure Transducer (Model MP45-1-871; Validyne Engineering Corporation), which sent their signal to a Hewlitt-Packard Carrier amplifier (Model 8805-B) which output a voltage signal corresponding to the rate of flow of expired breath.

Each of the five voltage signals was then routed through a Coulborn Instruments Lablink System Analog Input board, which transferred the signals to a Dataq Corporation Waveform Scroller board in an IBM PC-AT computer. The Waveform Scroller performed an analog to digital conversion at the rate of 1000 samples per second on each of the five signals, and stored the digitized waveforms in binary format on hard-disk for later analysis.

Proprietary software written for this project analyzed the five digitized analog signals on an IBM PS/2 Model 60 computer to provide breath-by-breath values for tidal volume, peak end-tidal CO2, breathing count, and heart rate. The reduced, breath-by-breath and heart-rate data was modemed to the University of Calgary NOS/VE supercomputer where it was further reduced to 15 second averages for each measure and each phase of the experiment.

Physiological Assessment

Subjects were seen individually in the Pulmonary Function Laboratory at the Foothills Hospital for a series of physiological tests. After having a sample of venous blood taken and analyzed for PvCO2, PvO2, Base Excess, pH, and HCO3-, the subject was led into a room where she was fitted with the EKG electrodes and Respitrace inductance bands. Next, using a spirometer, the subject's Forced Expiratory Volume (FEV1; maximum litres of air the subject could force from their lungs in one second), and Forced Vital Capacity (FVC; a measure of maximum lung capacity in litres) were determined. To calibrate the Respitrace Unit, the subject was then required to provide about twelve breaths in and out of either a spirometer (limited to 800 cc excursions) or a spirobag (with a total capacity of 800cc) first while standing, then while lying down. This having been completed, the subject was instructed to remain lying down on the bed, while their EKG electrodes and Respitrace bands were connected to the amplification equipment. The subject was then familiarized with the use of the mouthpiece affixed to the Otis-McKerro valve, and had a noseclip affixed so that they would breathe entirely through the mouthpiece.

Baseline Phase

With the subject lying down and breathing in and out through the mouthpiece, a five minute baseline of resting breathing was commenced. The subject was instructed merely to "relax", and was informed that CO2 measures would be taken over the next five minutes. At the end of five minutes, the subjects were detached from the noseclip and mouthpiece. At this time they completed a slightly modified set of the screening questionnaires as well as a likert-type scale which asked them to rate their subjective anxiety from 0 to 10 (Appendix B).

Carbon Dioxide/Oxygen Inhalations

Throughout the four CO2 inhalation tests, calibration-grade CO2-O2 gas mixtures were used to ensure that an accurate 0, 1, 3, or 5% CO2 mixture was being used. Before this first CO2 inhalation phase, the subject was informed that their breathing "might, or might not" increase while breathing the gas mixtures, and that either response was normal. A controlled gas flow was sent to a large rubber reservoir, which was connected to the intake

of the Otis-McKerro valve through which the subject breathed. The subject was connected to the mouthpiece, had a noseclip applied so that they would breathe exclusively through the valve, and breathed the gas mixture through their mouths for five minutes. At the end of five minutes, the subject was briefly detached from the mouthpiece and noseclip while they completed the same questionnaires as before. This procedure was repeated for 3% C02 in 97% 02. The procedure was also repeated for 5% CO2 in 95% 02, with the change that when the subject stopped receiving the gas mixture after five minutes, this time they were asked to stay on the mouthpiece and noseclip while breathing room air for a further five minutes. Questionnaires were administered while the subject was still on the mouthpiece, with the subject pointing to her responses on a card which reproduced the ten-point likert scale for each questionnaire.

Voluntary, Paced Hyperventilation

The subject was again placed on the mouthpiece and noseclip, breathing room air, and was verbally coached to breathe as quickly and deeply as possible for three minutes. At the end of three minutes of hyperventilation,

the subject was told to "breathe normally now", and was left on the mouthpiece and noseclip for a further seven minutes, during which time they filled out the standard questionnaires.

De-Briefing from the Experiment

After being detached from all equipment, the subjects were seen individually by a psychologist who explained the hypotheses of the experiment in relation to the measures taken during the laboratory test session. Each subject was explicitly reassured that any breathing increases or somatic sensations experienced during the gas inhalation tests was due entirely to the CO2 content of the gases, not the oxygen content.

RESULTS

Organization and Statistical Plan for the Results

The results of the current investigation primarily concern three hypotheses: 1) that PD's have lower blood bicarbonate than NC's, which would indicate the presence of chronic hyperventilation in the PD group; 2) that PD's have greater ventilatory responses to CO_2 stimulation than NC's, pointing to a higher sensitivity of their medullary chemoreceptors; and 3) that PD's overbreathe more after cessation of breathing stimuli such as 5% CO_2 or hyperventilation, i.e., that PD's have a slower recovery of their End-tidal CO_2 than NC's. The results sections are presented in the order of these hypotheses.

The first hypothesis was evaluated with a t-Test comparing blood bicarbonate levels in the two groups. For physiological hypotheses 2 and 3, a Pearson product-moment correlation matrix of all possible pairings of the physiological dependent variables was generated. Given the the functional relationship between end-tidal CO_2 and Minute Ventilation, and the arithmetic relationship between Minute Ventilation and its Breathing Frequency and Tidal Volume components, significant inter-correlations were expected to occur between the ventilatory measures.

Repeated measures Multivariate Analyses of Variance (MANOVAs) were then carried out and only the significant effects emerging from a MANOVA were investigated in univariate ANOVAs for each dependent variable. Where analyses revealed the presence of heterogeneity of variances in univariate ANOVA data matrices, conservative F-tests were performed on the affected sources of variance using Greenhouse-Geisser adjusted degrees of freedom (Winer, 1971). Significant correlations between dependent variables can produce inflated type 1 error rates (Harris, 1975), therefore in all univariate F-tests, simple main effects tests, and all post-hoc Newman-Keuls analyses a probability level of .01 was used for rejection of the null hypothesis. The statistical procedures used for evaluation of the physiological results were repeated for the psychological measures.

Two subjects from the PD group were excluded from the experiment. The first exclusion occurred when a subject's diagnosis changed from Panic Disorder to a dual diagnosis of Post-Traumatic Stress Disorder and Major Depression. The change in diagnosis followed a lethal suicide attempt, after which time the patient shared new historical information about the circumstances surrounding the onset of her anxiety symptoms. The second exclusion was a subject who showed no ventilation increase whatsoever in

response to CO2 inhalation. This was the only subject in either group not to respond even minimally to chemical stimulation of breathing. It is unclear what may have produced her highly unusual readings.

Thirty-seven subjects completed the first five phases of the experiment, corresponding to the four CO2 gas inhalations and the recovery from 5% CO2 inhalation, with complete physiologic data. Technical problems arising in later phases resulted in 33 and 35 subjects being valid for the hyperventilation and recovery from hyperventilation phases, respectively. The original 37 subjects were used in the analyses of psychological variables across the experiment.

A temporary data adjustment was necessary in carrying out the MANOVAs for each of the two tests for slow recovery of CO2. Memory limitations of the University of Calgary Honeywell Multics mainframe computer made it necessary to reduce the number of levels of the repeated measures factor (time intervals). This was accomplished by using 30 second averages rather than 15 second averages for these two MANOVAs. It was not possible to measure tidal volumes during the high flows that characterized the hyperventilation provocation, and therefore this phase has no Tidal Volume or Minute Ventilation dependent variable.

Pre-Experimental Group Comparisons:

Psychotropic Medications:

Medications that are most commonly prescribed for Panic Disorder were queried for all subjects. For the PD group, 18.2% (4 of 22) had taken a minor tranquilizer (e.g., Ativan, Valium, Xanax) and 13.6% (3 of 22) had taken a tricyclic antidepressant (e.g., Tofranil, Anafranil) in the 24 hours prior to being tested, while none had taken Monoamine Oxidase Inhibitors or Beta-Blockers. No member of the NC group had taken any of the above drugs.

Diagnostic Separation of the PD from the NC Group:

Two standardized questionnaires designed to measure the symptomatology of Panic Disorder, one of agoraphobic avoidance, and one questionnaire measure of depression were given to all subjects prior to the experiment. Independent sample t-Tests comparing PD patients and controls were computed for total scores on the Body Sensations Questionnaire, Agoraphobic Cognitions Questionnaire, and Beck Inventory, and for the three subscale scores of the Mobility Inventory for Agoraphobia. Inspection of Table 2 shows that the PD group had significantly higher scores on

Table 2

t-Tests on Initial Assessment Questionnaires

Variable	Group	Mean	S.D.	t	df	Prob. (2-Tail)
Sensations	Normal	22.27	6.25	7.85	32.6	.0001
	Panic	46.73	12.50			
Cognitions	Normal	17.67	4.07	7.57	31.5	.0001
	Panic	34.05	8.87			
# Panics	Normal	0.00	0.00	7.59	21.0	.0001
	Panic	4.95	3.06			
Phobias (Alone)	Normal	32.30	7.21	5.61	25.3	.0001
	Panic	65.73	26.56			
Phobias (Accomp)	Normal	27.27	3.79	5.43	22.7	.0001
	Panic	53.91	22.53			
Beck	Normal	3.93	2.71	6.09	24.5	.0001
	Panic	19.18	11.28			

Note:

Sensations = Total Score on Body Sensations Questionnaire

Cognitions = Total Score on Agoraphobic Cognitions Questionnaire

Panics = Number of Panic Attacks last 7 days (subscale of the Mobility Inventory for Agoraphobia)

Phobias (Alone) = Total Phobia score when Alone (subscale of the Mobility Inventory for Agoraphobia)

Phobias (Accomp) = Total Phobia score when Accompanied (subscale of the Mobility Inventory for Agoraphobia)

Beck = Total Score on the Beck Depression Inventory

the Sensations measure ($t(33) = 7.85$, $p < .0001$), on the Cognitions measure ($t(31) = 7.57$, $p < .0001$), on the two measures of phobic avoidance (Phobic Avoidance when Alone Score: $t(25) = 5.61$, $p < .0001$; Phobic Avoidance when Accompanied Score: $t(23) = 5.43$, $p < .0001$), and on the number of panic attacks they experienced in the last week ($t(21) = 7.59$, $p < .0001$). PD subjects also had higher scores on the Beck Depression Inventory ($t(24) = 6.09$, $p < .0001$).

Test for Group Differences on Physical Characteristics:

Breathing is known to be influenced by certain physical characteristics. Table 3 shows that the two groups were comparable in terms of age ($t(38) = .24$, $p > .05$), height ($t(36) = .55$, $p > .05$), weight ($t(36) = .67$, $p > .05$), Forced Vital Capacity ($t(35) = .81$, $p > .05$), and Forced Expiratory Volume in one second ($t(34) = .53$, $p > .05$).

Blood Bicarbonate Levels

The first test of the hyperventilation hypothesis involved a comparison of blood bicarbonate levels.

Table 3

t-Tests on Physical Characteristics of Subjects

Variable	Group	Mean	S.D.	t	df	p (2-Tail)
Age	Normal	33.72	8.43	.24	38.07	.815
	Panic	33.08	9.05			
Height (cm.)	Normal	161.33	7.21	.55	35.54	.585
	Panic	160.13	6.80			
Weight (Kg.)	Normal	64.28	13.74	.67	36.39	.505
	Panic	61.42	13.48			
FVC (litres)	Normal	4.09	.61	.81	35.09	.421
	Panic	3.94	.56			
FEV1 (litres)	Normal	3.51	.55	.53	33.90	.597
	Panic	3.42	.48			

Note: FVC = Forced Vital Capacity
FEV1 = Forced Expiratory Volume in 1 second

Difficulty taking blood samples from a number of the subjects, and problems with missing data due to equipment failure in one or more of the phases of the experiment led to the exclusion of some subjects from data analyses. A combination of these two factors reduced the number of subjects for this comparison to nine NC's and fifteen PD's. The PD group showed lower bicarbonate than the NC's (Means = 23.31 and 25.91, $t(22) = 2.11$, two-tail prob.: $< .05$), indicating the presence of chronic hyperventilation syndrome in the PD group.

Medullary Chemoreceptor Sensitivity

Medullary chemoreceptor sensitivity was tested by the ventilatory response to inhalation of a graded series of CO2 gas concentrations. The magnitude of the ventilatory response to CO2 was taken as an index of the sensitivity of the central CO2 chemoreceptors. The first four phases of the experiment presented 0% (i.e., room air), 1%, 3%, and 5% CO2 inhalation, respectively. CO2 inhalation chemically stimulates breathing, and the magnitude of the breathing increase at various concentrations of CO2 was determined by looking at breathing during the final minute of each of these phases. Four indices of breathing were studied in this fashion during each of the four levels of administered

CO2: Minute Ventilation, Tidal Volume, Breathing Frequency, and End-tidal CO2. Psychological measures (subjective Anxiety, body Sensations, and anxiety-related Cognitions) were taken immediately after each of the four CO2 inhalations, and total scores for these questionnaire measures were entered into the correlational analyses. In addition, heart rate was taken as a general measure of autonomic arousal.

Correlations for the eight dependent variables are presented in Table 4. The three psychological variables were highly intercorrelated with one another (range of r's .64 to .81, $p < .0001$). The highest correlations between the psychological measures and the physiological measures occurred with heart rate (range of r's .40 to .51, $p < .0001$). The Cognitions score did not correlate with any of the ventilation measures. The Anxiety and Sensations measures correlated with the Minute Ventilation and Breathing Frequency measures (range of r's .22 to .24, $p < .01$).

A MANOVA was performed on the five physiological variables, with Groups (Panic, Control) and level of administered CO2 (0%, 1%, 3%, and 5% CO2) as between-subject and within-subject factors, respectively, and the results are presented in Table 5. The only significant multivariate source of variance was Phases

Table 4

Correlation Matrix for Psychological and Physiological Variables: Last Minute data for each Level of Administered CO2

	SEN	COG	ANX	MV	BF	TV	CO2	EKG
Sensations	-	.81**	.79**	.24*	.21*	.05	.07	.51**
Cognitions		-	.64**	.08	.05	.01	-.09	.40**
Anxiety			-	.22*	.12	.12	.09	.48**
Minute Ventilation				-	.35**	.63**	.27**	-.06
Breathing Frequency					-	-.42**	.21*	.02
Tidal Volume						-	.00	-.05
etCO2							-	.14
EKG								-

* $p < .01$

** $p < .001$

Table 5

Multivariate Analysis of Variance Summary Table:
Last Minute Data from each Level of Administered CO2:
Summary Scores for Physiological
and Psychological Variables

SOURCE	MANOVA STATISTIC	df	F
Groups (G)	T-squared = .1669	5/31	1.035
Phases (P)	T-squared = 10.6696	15/299	70.894
G x P	T-squared = .1368	15/299	.909

(T-squared = 10.6696, F(15,299) = 70.894, p < .0001). This effect signified that one or more of the dependent variables changed as a function of the level of CO2 that was administered.

The primary hypothesis being tested during CO2 inhalations was that PD patients may have a greater sensitivity of their medullary CO2 chemoreceptors. A standard test of this hypothesis (Rousso & Macklem, 1977) involves comparing the slopes of breathing increases for the two groups between two different levels of administered CO2 when Minute Ventilation is plotted against end-tidal CO2. In the current study, the two highest levels of administered CO2, 3% and 5%, were used for the comparison, and these results are plotted in Figure 2. Under this hypothesis, the PD group should show a steeper increase in their breathing increases between 3% and 5% CO2 compared to NC's. The slopes of the breathing increases for the two groups are compared with an independent samples t-Test in Table 6. Although the PD group had a slightly higher Minute Ventilation increase per unit increase in end-tidal CO2, there was no significant group difference (t = 1.02, p > .05).

Previous literature had indicated that depression could blunt the respiratory sensitivity to CO2. This introduced the possibility that the lack of a slope

Figure 2

Minute Ventilation as a function of End–Tidal CO2
at 3% and 5% CO2 Inhalations

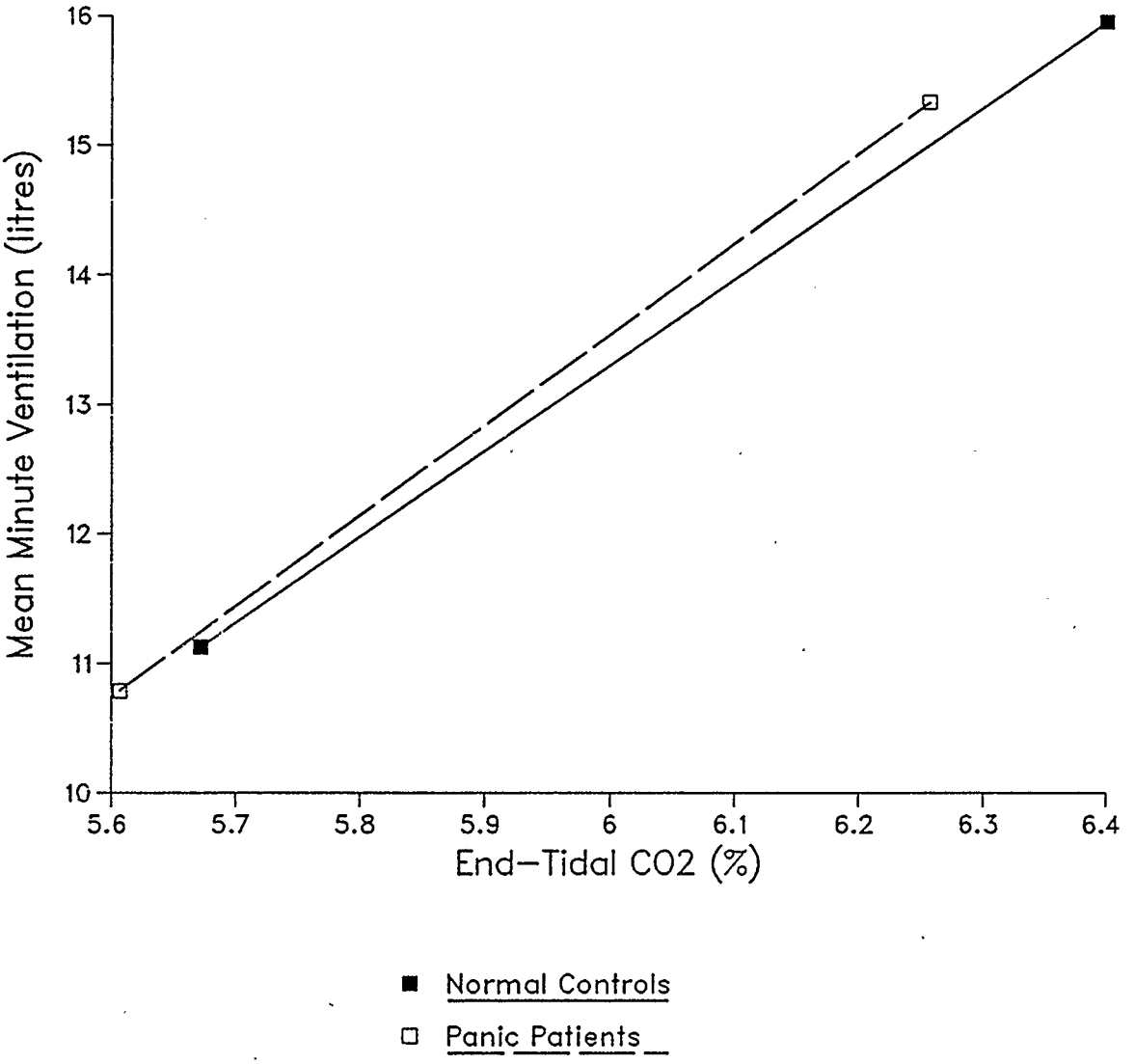


Table 6

t-Test for Group Differences in the Slope of Minute Ventilation vs. level of End-tidal CO2 in the last minute of 3% and 5% of Administered CO2

Variable	Group	Mean	S.D.	t	df	2-tail Prob.
Slope	Normal	7.012	3.79	-1.02	31.33	.315
	Panic	9.084	8.35			

difference between the two groups might be due to the higher depression scores of the PD group (see Table 2). Each subject's Beck Depression Inventory score was correlated with the slope of their Minute Ventilation increase between 3% and 5% CO2 to test this possibility. The obtained r of .23 ($p > .05$) was nonsignificant.

The behavior of the five physiological variables across the four CO2 inhalations were examined in univariate repeated measures ANOVAS. The ANOVA for Minute Ventilation is presented in Table 7. The significant effect for Level of CO2 ($F(3,105) = 111.69$, $p < .01$), depicted in Figure 3, demonstrates that the CO2 manipulation was effective in raising Minute Ventilation. A Newman-Keuls analysis used to isolate the means responsible for the significant increase in Minute Ventilation across levels of CO2 is reported in Table 8, where it can be seen that 1% CO2 did not increase breathing significantly compared to 0% CO2. However all other means comparisons were significant at the .01 level, indicating that the higher two levels of CO2 concentration (3% and 5%) were associated with higher Minute Ventilation responses compared to both 0% and 1% CO2.

During the four CO2 inhalations, the two groups experienced equivalent enrichment of their End-tidal CO2 ($F(1,35) = .05$, $p > .01$; Table 9). End-tidal carbon

Table 7

Groups X Phases Repeated Measures Analysis of Variance Summary Table: Minute Ventilation in the last minute of each Level of Administered CO2

Source	df	Mean Square	F
Groups (G)	1	4.854	.21
Error	35	22.939	
Phases (P)	3	440.741	111.69 ***
G X P	3	.552	.14
Error	105	3.946	

*** p < .0001

Figure 3

Minute Ventilation During
CO2 Inhalations

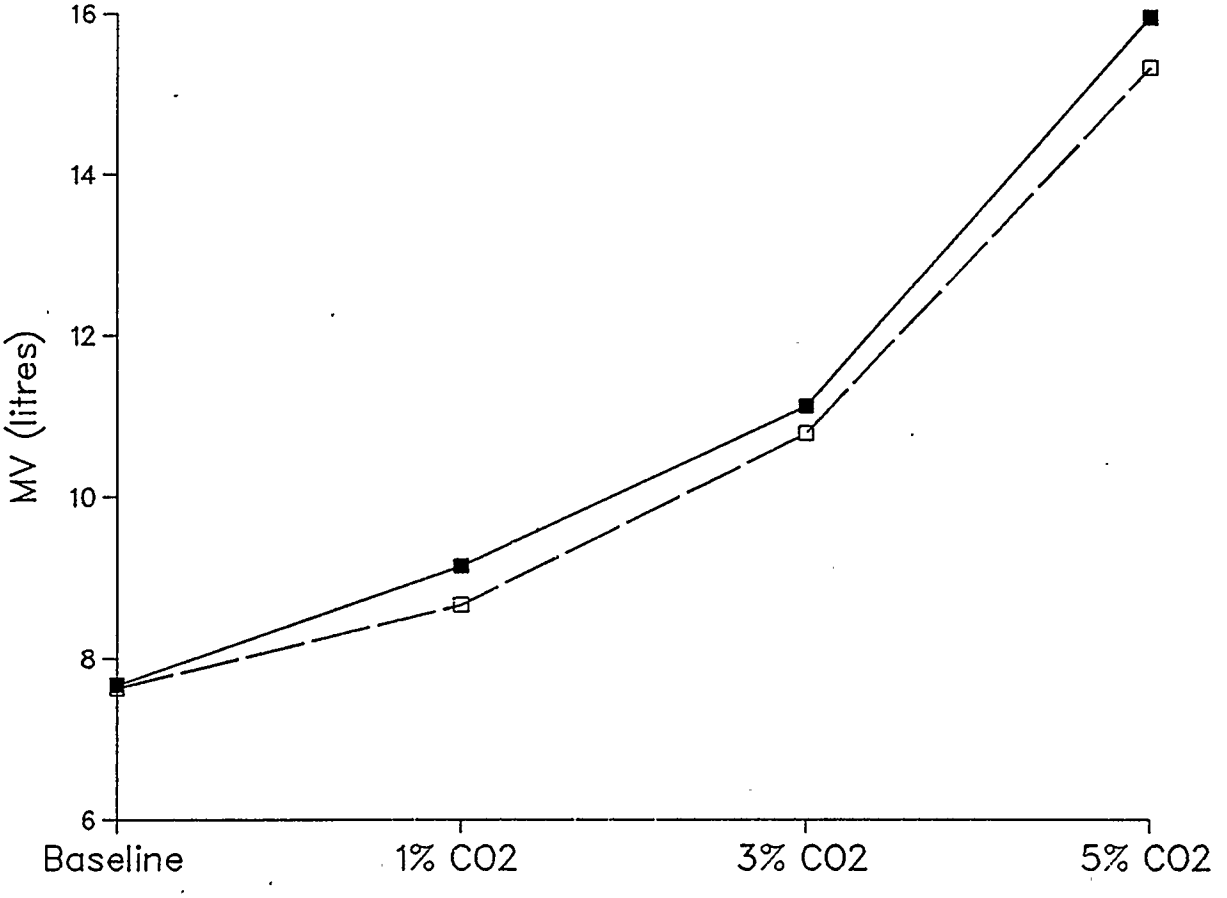


Table 8

Newman-Keuls Summary Table: Minute Ventilation in the last Minute of each Level of Administered CO2, Collapsed across Groups

Phase:	0% CO2	1% CO2	3% CO2	5% CO2
Mean:	7.644	8.854	10.926	15.587
0% CO2	-----	1.210	3.282 **	7.943 **
1% CO2		-----	2.071 **	6.733 **
3% CO2			-----	4.662 **
5% CO2				-----

** $p < .01$

Table 9

Groups X Phase Repeated Measures Analysis of Variance Summary Table:
End-Tidal CO2 during the last minute of each Level of Administered CO2

Source	df	Mean Square	F
Groups (G)	1	.087	.05
Error	35	1.936	
Phases (P)	3	16.359	94.55 **
G X P	3	.226	1.31
Error	105	.173	

** $p < .01$

dioxide levels differed markedly according to the percentage of CO2 that was given ($F(3,105) = 94.55$, $p < .01$), which reflects the fact that increasingly higher dosages of CO2 were given to subjects. Consistent with the Newman-Keuls analysis for the significant phase effect for Minute Ventilation (Table 8), Table 10 and Figure 4 show that End-tidal CO2 did not change between the 0% CO2 and 1% CO2 inhalation phases, while it did rise significantly with both 3% and 5% CO2 inhalation.

Neither of the main effects for the ANOVA on Breathing Frequency were significant (Group: $F(1,35) = .18$, $p > .01$; Levels of administered CO2: $F(3,105) = .3.22$, $p > .01$; Table 11). Figure 5 shows Breathing Frequency during CO2 inhalations to have been very stable around 3.75 breaths every 15 seconds for both groups. The ANOVA for Tidal Volumes in Table 12 on the other hand reveals that Tidal Volumes did increase during the CO2 inhalations ($F(3,105) = 57.03$, $p < .01$), which accounts for the previously noted Minute Ventilation increase. Therefore, the CO2 stimuli produced Minute Ventilation increases that, for both groups, were due to an increase in the depth rather than the frequency of their breathing. Newman-Keuls analysis for Tidal Volumes, summarized in Table 13 and the means portrayed in Figure 6, shows that 0%, 1%, and 3% CO2 were not different from one another, however Tidal Volumes at 5%

Table 10

Newman-Keuls Summary Table: End-tidal CO2 in the last minute of each Level of Administered CO2, Collapsed across Groups

Phase:	1% CO2	0% CO2	3% CO2	5% CO2
Mean:	4.815	5.059	5.634	6.316
1% CO2	-----	.2435	.8184 **	1.501 **
0% CO2		-----	.5749 **	1.257 **
3% CO2			-----	.6822 **
5% CO2				-----

** p < .01

Figure 4

End–Tidal CO2 During
CO2 Inhalations

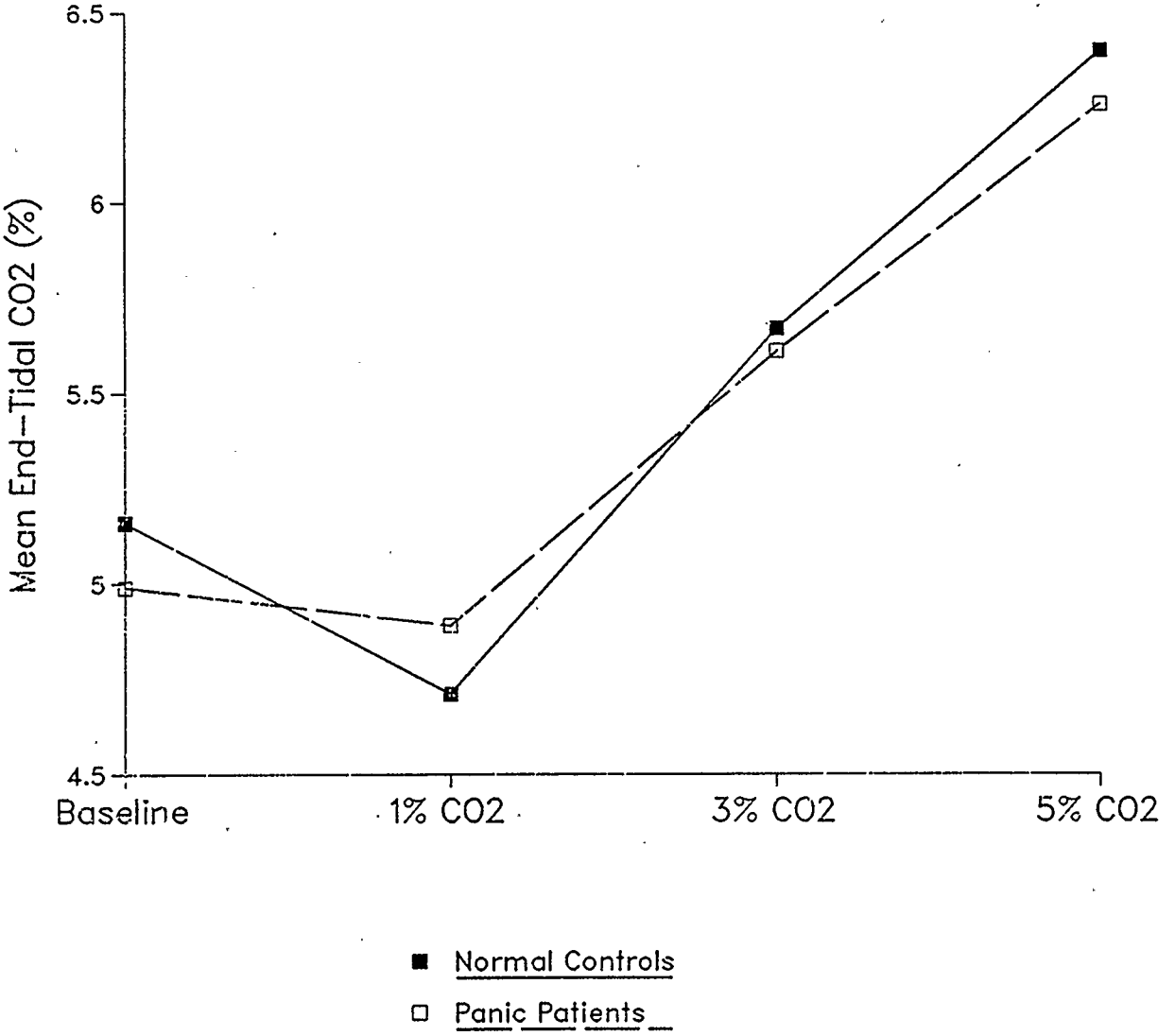


Table 11

Groups X Phases Repeated Measures Analysis of Variance Summary Table: Breathing Frequency in the last minute of each Level of Administered CO2

Source	df	Mean Square	F
Group (G)	1	.921	.18
Error	35	5.245	
Phase (P)	3	.947	3.22
G X P	3	.432	1.47
Error	105	.294	

** $p < .01$

Figure 5

Breathing Frequency During
CO2 Inhalations

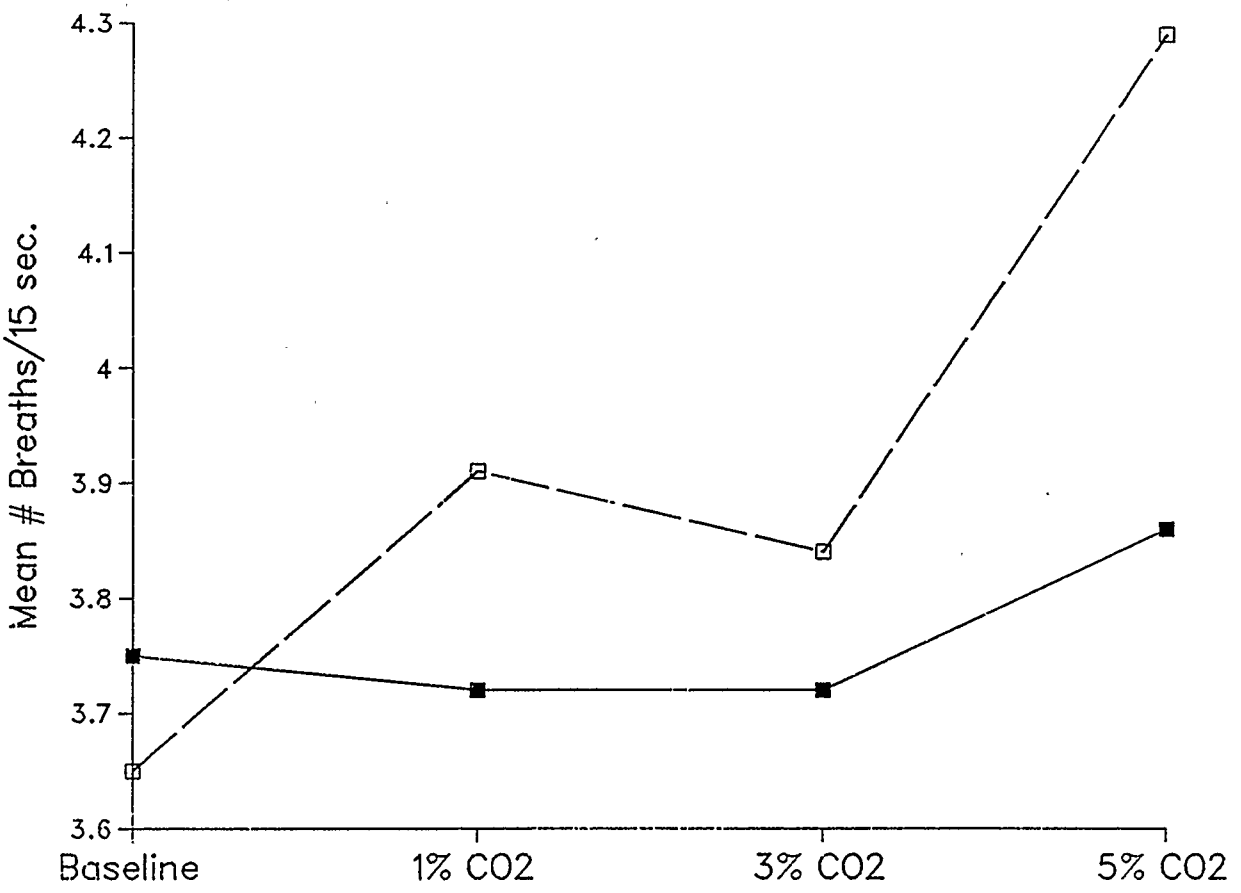


Table 12

Groups X Phases Repeated Measures Analysis of Variance Summary Table:
Tidal Volumes during the last minute of each Level of Administered CO2

Source	df	Mean Square	F
Groups (G)	1	.303	1.57
Error	35	.194	
Phases (P)	3	1.196	57.03 *
G X P	3	.034	1.61
Error	105	.021	

** $p < .01$

Table 13

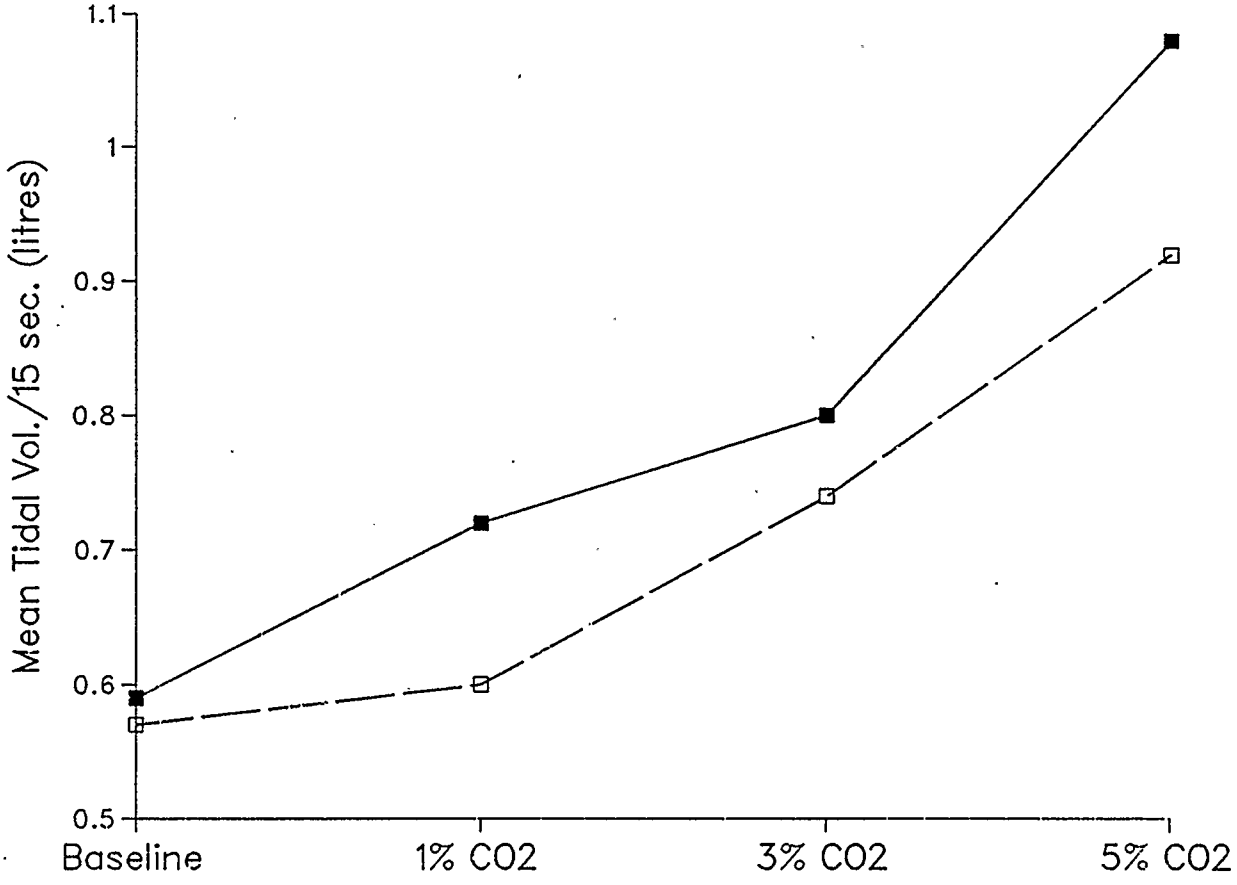
Newman-Keuls Summary Table: Average Tidal Volumes in the last Minute of each Level of Administered CO2, Collapsed across Groups

Phase:	0% CO2	1% CO2	3% CO2	5% CO2
Mean:	.574	.650	.764	.984
0% CO2	___	.076	.190	.410 **
1% CO2		---	.114	.334 **
3% CO2			___	.220
5% CO2				___

** $p < .01$

Figure 6

Tidal Volumes During
CO2 Inhalations



CO2 were significantly higher than those at 0% and 1%. The fact that the Minute Ventilation Newman-Keuls results showed significant mean differences between 3% and 5% administered CO2, while neither Breathing Frequency or Tidal Volume did, must be accounted for by the fact that Tidal Volumes and Breathing Frequencies increased slightly but not significantly between 3% and 5% CO2 inhalation, and these increases reached significance only when their combined effect in Minute Ventilation was tested.

Figure 7 shows that the PD group had a slightly higher heart rate across the CO2 inhalations, however this difference was not significant ($F(1,35) = 1.87$, $p > .01$; Table 14). Heart rate changed over the course of the four CO2 administrations ($F(3,105) = 19.39$, $p < .01$), and the Newman-Keuls analysis summarized in Table 15 reveals that this was due to a significant drop in heart rate from 0% to 1% CO2, which remained at this lower level through 3% CO2, and then rose significantly during inhalation of 5% CO2. The initial drop in heart rate between 0% and 1% CO2 was apparently cancelled out by the later rise in heart rate between 3% and 5% CO2, resulting in no difference between the heart rate at 0% and the heart rate at 5% CO2.

In summary, the results of a specific test of ventilation responses to two different levels of CO2 failed to support the hypothesis that PD subjects have a higher

Figure 7

Heart Rate During
CO2 Inhalations

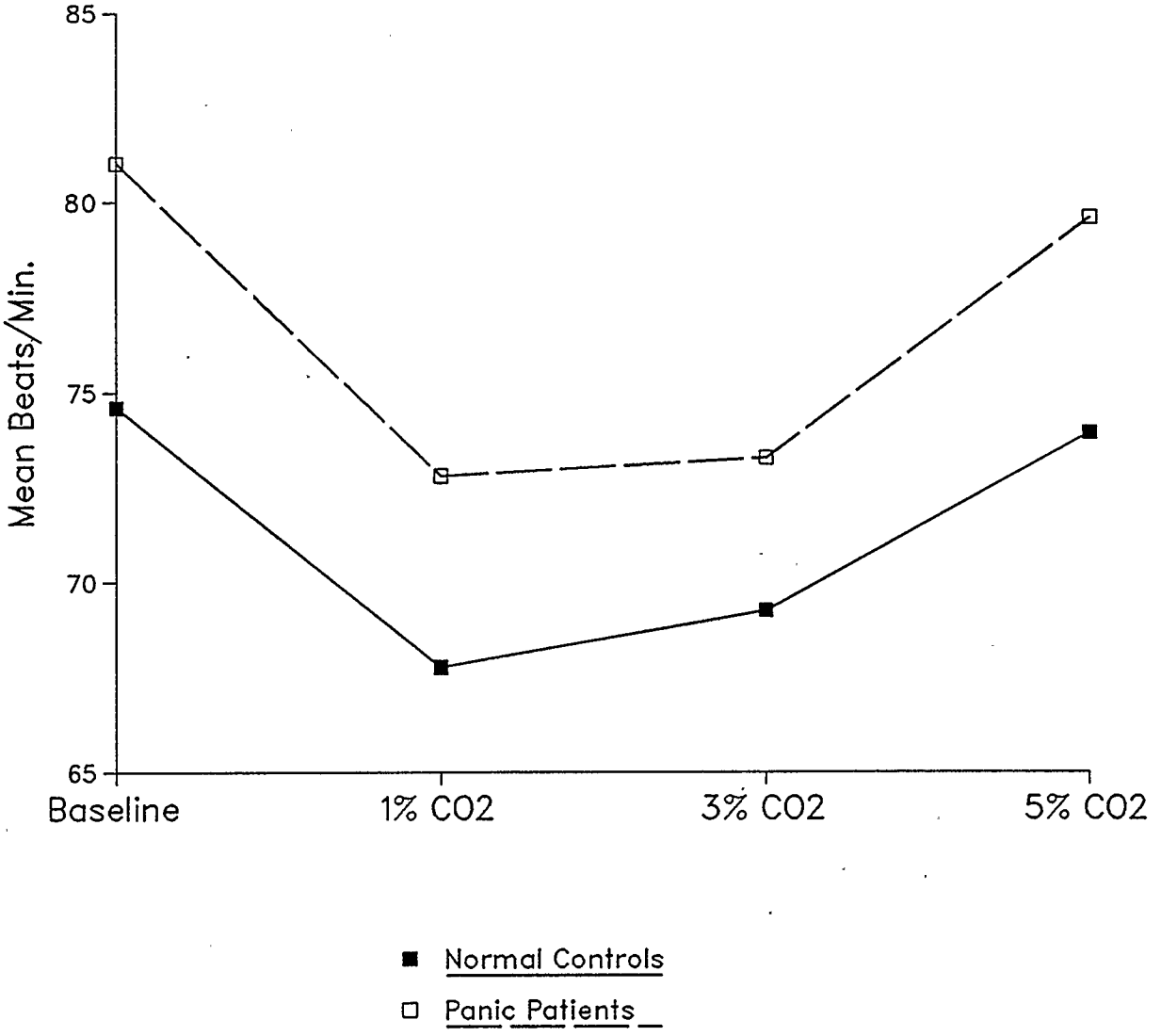


Table 14

Groups X Phases Repeated Measures Analysis of Variance Summary Table:
Heart Rate in the last minute of each Level of Administered CO2

Source	df	Mean Square	F
Groups (G)	1	996.562	1.87
Error	35	531.734	
Phases (P)	3	517.836	19.39 **
G X P	3	9.347	.35
Error	105	26.706	

** p < .01

Table 15

Newman-Keuls Summary Table: Heart Rate in the last minute of each Level of Administered CO2, Collapsed across Groups

Phase:	1% CO2	3% CO2	5% CO2	0% CO2
Mean:	70.755	71.643	77.304	78.424
1% CO2	-----	.8876	6.548 **	7.668 **
3% CO2		-----	5.661 **	6.781 **
5% CO2			-----	1.120
0% CO2				-----

** $p < .01$

sensitivity of their central CO2 chemoreceptors than NC's. Not only was there no chemoreceptor sensitivity difference between the groups, but the two groups also were equivalent on all breathing parameters throughout the four CO2 inhalation phases.

Slow Recovery of End-tidal CO2

The third hyperventilation hypothesis tested was that PD patients might show a slower recovery of End-tidal CO2 than NC's following offset of a breathing stimulus. The recovery from two different breathing stimuli, 5% CO2 and hyperventilation, were monitored continuously for five and seven minutes respectively to determine respiratory recovery within these time periods.

A) Slow Recovery of CO2 after termination of 5% CO2 inhalation

Immediately following termination of the 5% CO2 breathing stimulus, subjects were monitored for five minutes to determine the time course of the two groups' recovery on breathing measures.

The four breathing measures plus heart rate were highly intercorrelated with one another during the recovery

from 5% CO2. Comparing Table 16 to Table 4 shows that the most noteworthy difference in the correlations between physiological variables during CO2 inhalations compared to the correlations occurring in recovery from 5% CO2 was that heart rate during recovery from 5% CO2 came to be correlated with all breathing measures except End-tidal CO2. By comparison, during the four CO2 inhalation sessions heart rate did not correlate with any of the breathing variables.

MANOVA results for the five physiological variables are presented in Table 17. The groups did not differ on any of the physiological dependent measures ($F(5,31) = .9897$, $p > .05$). There was a highly significant Time effect ($F(45,1547) = 15.0232$, $p < .0001$) however, indicating that at least one of the physiological variables did change over the course of this recovery phase. There was no Group X Time interaction ($F(45,1547) = 1.1876$, $p > .05$), indicating that the two groups paralleled one another in the physiological changes which took place during recovery from 5% CO2.

Both groups decreased their Minute Ventilation during this recovery phase ($F(19,665) = 48.15$, $p < .01$; Table 18 and Figure 8). End-tidal CO2 changed as a function of Time during recovery from 5% CO2 ($F(19,665) = 4.03$, $p < .01$; Table 19). One might expect that this time effect for CO2

Table 16

Correlation Matrix for Physiologic Variables: Recovery from 5% CO2 Inhalation

	BF	TV	MV	CO2	EKG
Breathing Frequency	--	-.467***	.307***	-.085**	.123***
Tidal Volumes		--	.625***	-.112***	.172***
Minute Ventilation			--	-.250***	.235***
End-Tidal CO2				--	.018
Heart Rate					--

* p < .05

** p < .01

*** p < .001

Table 17

Groups X Time Repeated Measures Multivariate Analysis of Variance Summary Table: Physiological Variables during Recovery from 5% CO2 Inhalation

SOURCE	MANOVA STATISTIC	df	F
Groups (G)	T-squared = .1596	5/31	.9897
Time (T)	T-squared = 2.1850	45/1547	15.0232 ***
G X T	T-squared = .1727	45/1547	1.1876

*** $p < .001$

Table 18

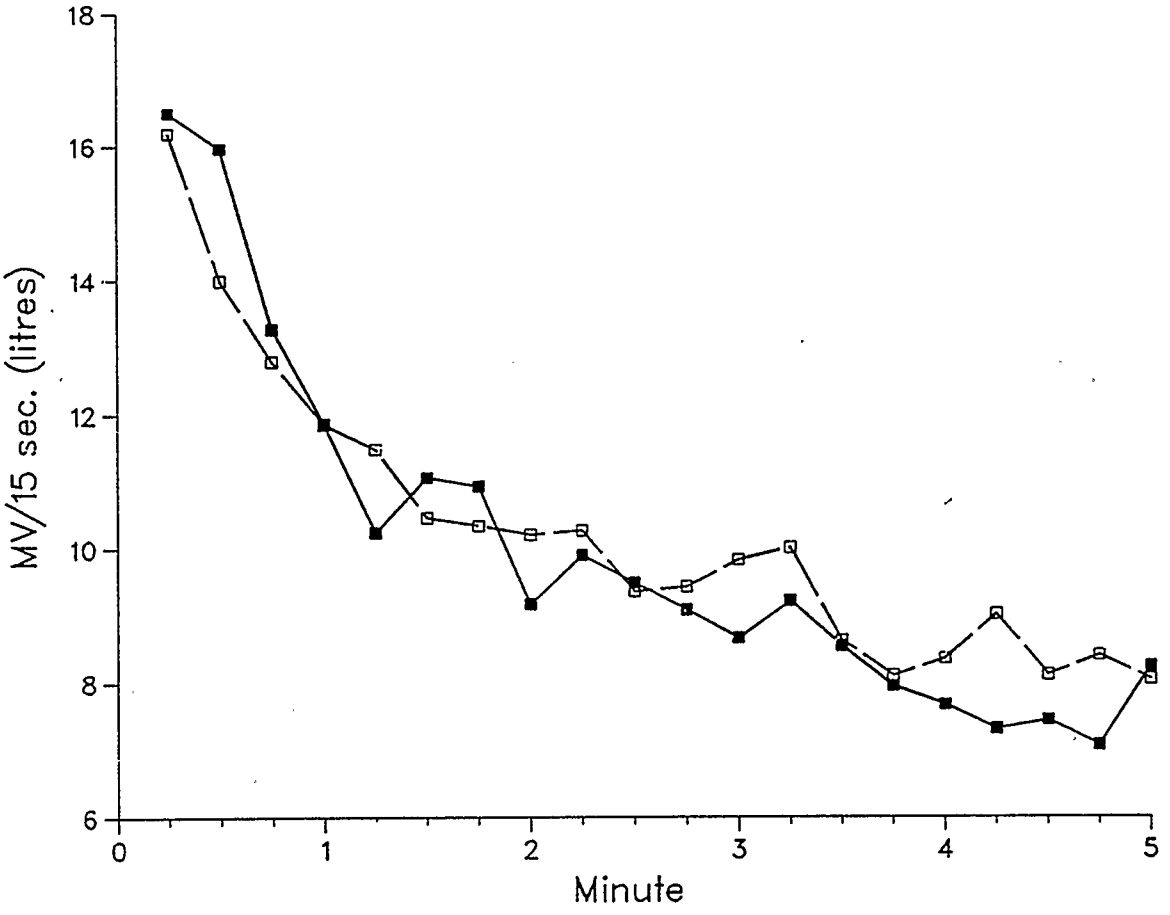
Groups X Time Repeated Measures Analysis of Variance Summary Table: Minute Ventilation during Recovery from 5% CO2 Inhalation

Source	df	Mean Square	F
Group (G)	1	12.697	.02
Error	35	64.821	
Time (T)	19	201.806	48.15 **
G X T	19	6.597	1.57
Error	665	4.190	

** $p < .01$

Figure 8

Minute Venilation During Recovery
from 5% CO2 Inhalation



■ Normal Controls

□ Panic Patients

Table 19

Groups X Time Repeated Measures Analysis of Variance Summary Table: End-Tidal CO2 during Recovery from 5% CO2 Inhalation

Source	df	Mean Square	F
Group (G)	1	5.562	.60
Error	35	9.294	
Time (T)	19	.580	4.03 **
G X T	19	.256	1.78
Error	665	.144	

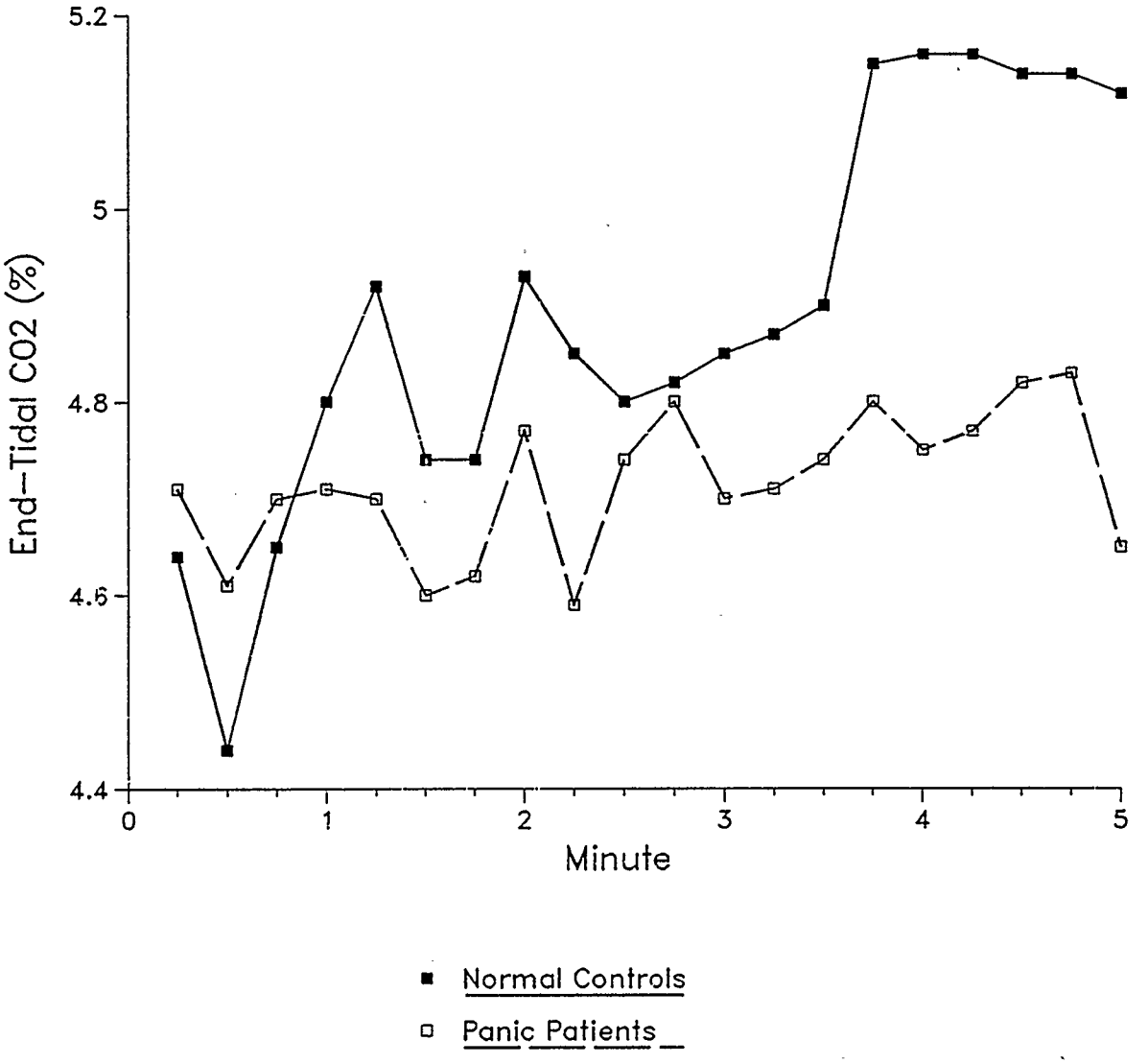
** $p < .01$

would consist of a decline in CO2 over time in this phase, since in the immediately preceding phase subjects had been administered a 5% concentration of CO2 and therefore had achieved high end-tidal CO2 readings in the last minute of that phase (NC's = 6.4%; PD's = 6.26%). However Figure 9 shows that in the beginning of the recovery period after 5% CO2 inhalation end-tidal CO2 levels for both groups' were considerably lower (NC's = 4.64%; PD's = 4.71%). This apparent contradiction can be explained by the 15 second time lag between each phase during which time no data were recorded. This time lag corresponds to the time required by the data acquisition computer to save the data from the previous phase, open a new data file for the next phase, and re-load the data acquisition software. In this 15 second time lag between the end of the 5% CO2 inhalation phase and the beginning of data collection for the Recovery from 5% CO2 inhalation phase, subjects 'blew off' a portion of their excess CO2. By the beginning of data collection for the Recovery from 5% CO2 inhalation phase their CO2 levels had already dropped considerably. End-tidal CO2 then proceeded to rise slowly over the course of the next five minutes.

The previously-noted decline in Minute Ventilation over the course of recovery from 5% CO2 inhalation was accomplished by a decrease in its components. Tidal Volume

Figure 9

End-Tidal CO2 During Recovery
from 5% CO2 Inhalation



dropped ($F(19,665) = 17.83$, $p < .01$; Table 20 and Figure 10) as did Breathing Frequency ($F(19,665) = 5.51$, $p < .01$, Table 21 and Figure 11). To summarize regarding the four physiological indices of breathing following cessation of 5% CO2 stimulation, the two groups had equivalent levels of and parallel changes in end-tidal CO2, Minute Ventilation, Tidal Volume, and Breathing Frequency over the course of recovering from the 5% CO2 breathing stimulus. These results do not support the hypothesis that PD's have a slower recovery of End-tidal CO2 than NC's after termination of a 5% CO2 breathing stimulus. General physiological arousal, as indexed by heart rate, was also equivalent between the groups during recovery from 5% CO2 ($F(1,35) = 2.48$, $p > .01$; Table 22 and Figure 12).

B) Slow Recovery of CO2 after termination of Voluntary Hyperventilation

A respiratory stimulus, maximal voluntary hyperventilation, was applied to all subjects. The respiratory dependent variables were directly manipulated by the experimenter with the goal of significantly reducing each subject's end-tidal CO2 level. To accomplish this, subjects were exhorted continuously for three minutes to breath as quickly and deeply as they could.

Table 20

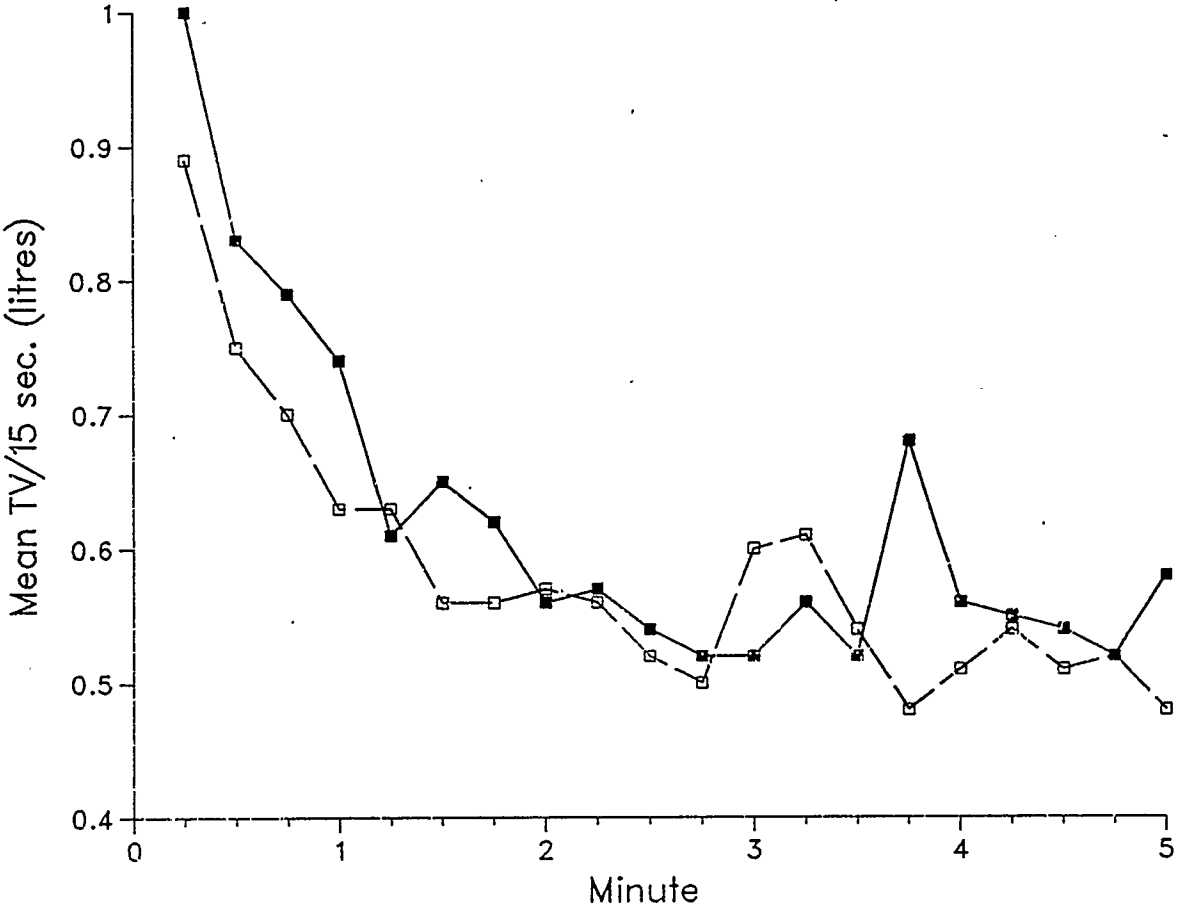
Groups X Time Repeated Measures Analysis of Variance Summary Table: Tidal Volumes during Recovery from 5% CO2 Inhalation

Source	df	Mean Square	F
Group (G)	1	.278	.57
Error	35	.492	
Time (T)	19	.428	17.83 **
G X T	19	.039	1.63
Error	665	.024	

** $p < .01$

Figure 10

Tidal–Volumes During Recovery
from 5% CO2 Inhalation



■ Normal Controls

□ Panic Patients

Table 21

Groups X Time Repeated Measures Analysis of Variance Summary Table: Breathing Frequency during Recovery from 5% CO2 Inhalation

Source	df	Mean Square	F
Groups (G)	1	32.311	1.28
Error	35	25.225	
Time (T)	19	3.421	5.51 **
G X T	19	.846	1.36
Error	665	.621	

** $p < .01$

Figure 11

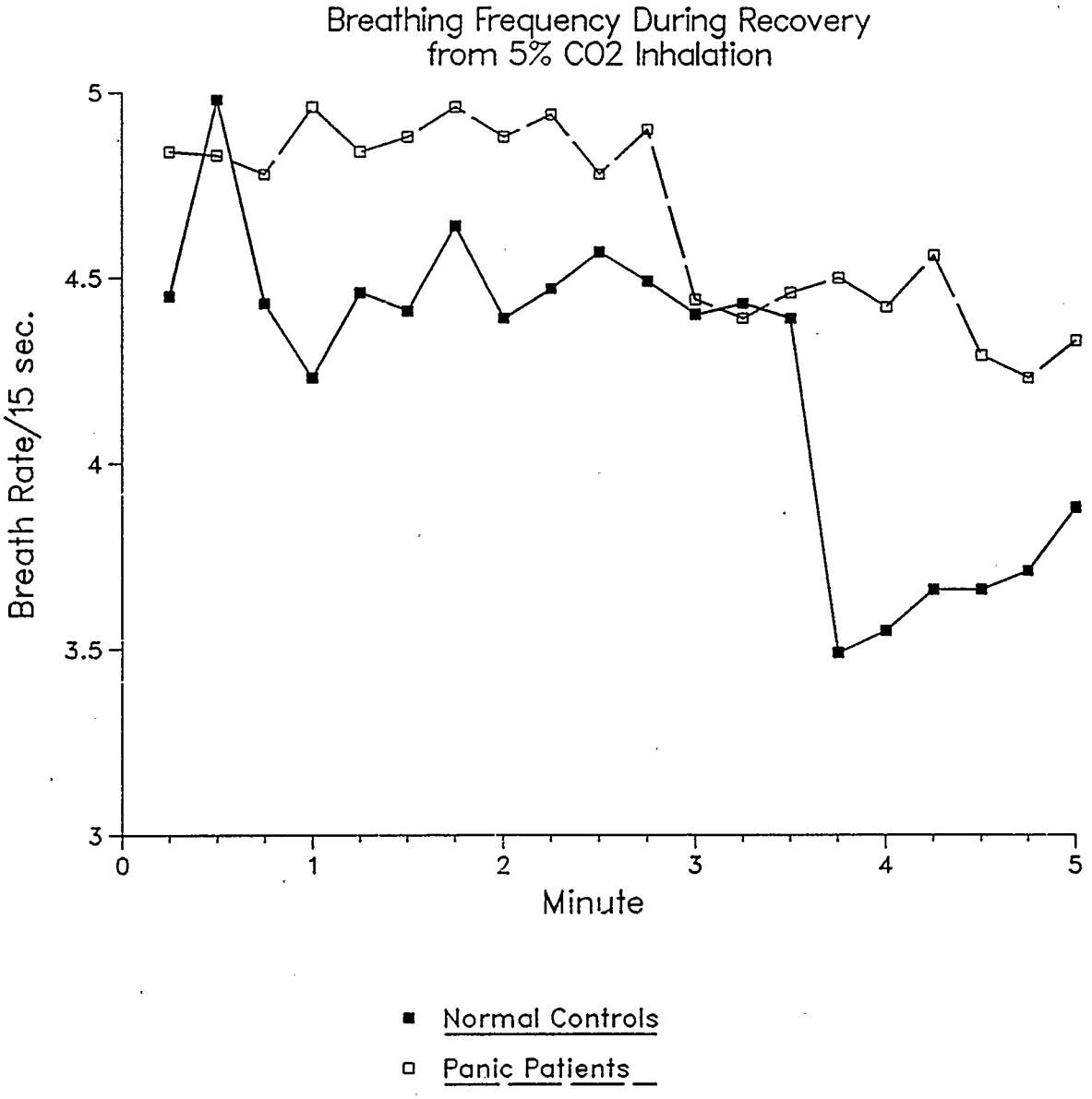
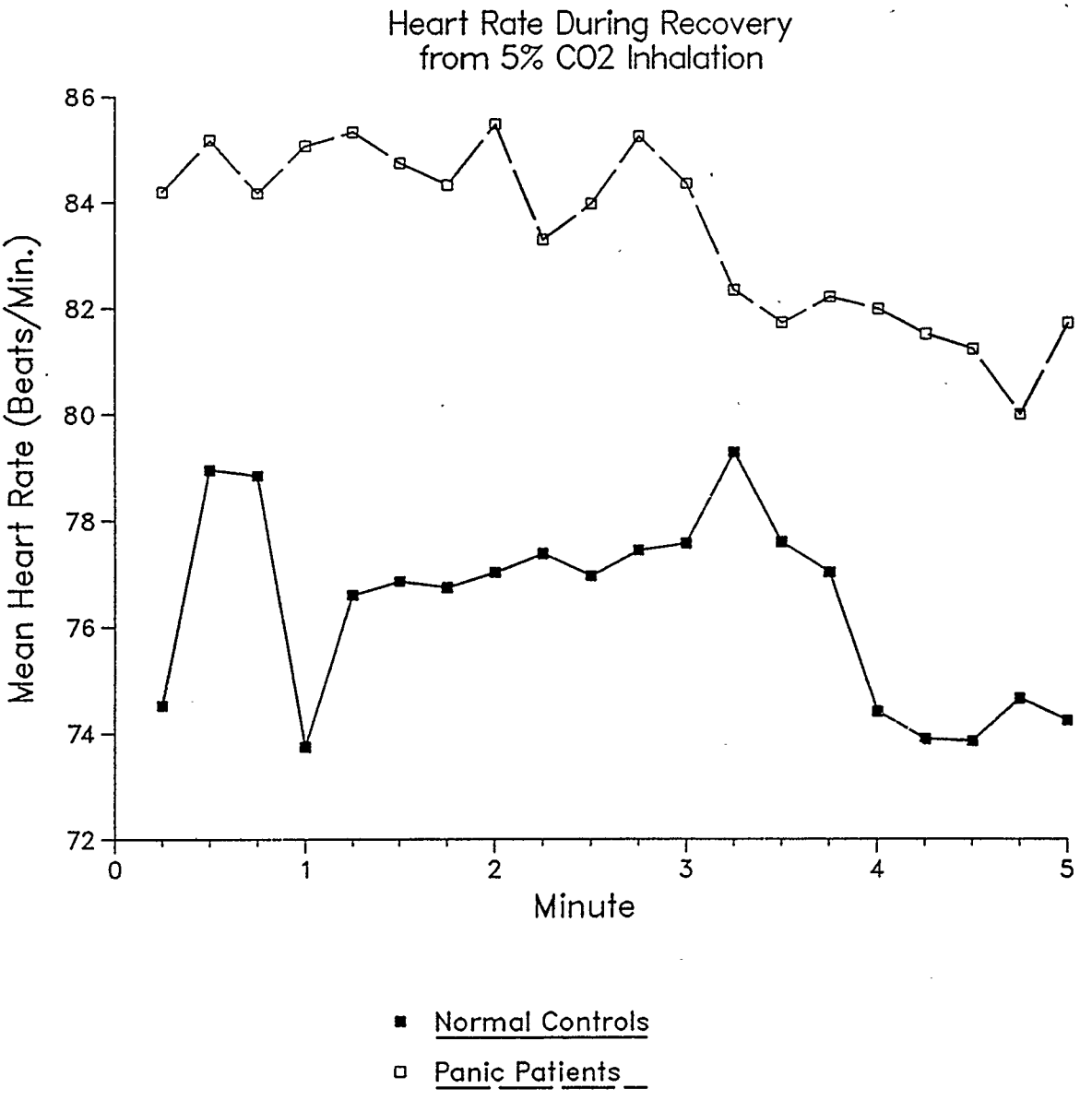

Breathing Frequency During Recovery
from 5% CO2 Inhalation
Breath Rate/15 sec.
5
4.5
4
3.5
3
0
1
2
3
4
5
Minute
Normal Controls
Panic Patients

Table 22

Groups X Time Repeated Measures Analysis of Variance Summary Table:
Heart Rate during Recovery from Hyperventilation

Source	df	Mean Square	F
Group (G)	1	8805.538	2.48
Error	35	3545.737	
Time (T)	19	75.717	3.38
G X T	19	32.128	1.43
Error	665	22.431	

Figure 12


Heart Rate During Recovery
from 5% CO2 Inhalation
Mean Heart Rate (Beats/Min.)
86
84
82
80
78
76
74
72
0
1
2
3
4
5
Minute
Normal Controls
Panic Patients

The hyperventilation manipulation was effective in reducing end-tidal CO2 as evidenced by the significant effect for time ($F(11,341) = 58.86$, $p < .01$; Table 23). This effect is graphed in Figure 13. There was neither a Group effect ($F(1,31) = 3.27$, $p > .01$) nor a Group X Time interaction ($F(11,341) = .93$, $p > .01$) for End-tidal CO2, these results satisfying the experimental requirement that both groups lose an equivalent amount of CO2 during HV.

Immediately after termination of the voluntary hyperventilation, a seven minute recovery phase was recorded. As in all previous phases, the five physiologic dependent variables were highly intercorrelated. Table 24 shows that, similar to the correlations during recovery from 5% CO2 inhalation (Table 16), heart rate entered into significant correlations with some of the ventilation measures. Specifically, during recovery from hypeventilation heart rate correlated significantly with Minute Ventilation and Breathing Frequency. With the exception of nonsignificant relationships between Anxiety and End-tidal CO2, and Cognitions and Tidal Volumes, psychological measures correlated significantly with all the physiological measures.

The overall MANOVA for the five physiologic dependent variables revealed that at some time during this recovery phase, the two groups differed in their response to one or

Table 23

Groups X Time Repeated Measures Analysis of Variance Summary Table:
End-Tidal CO2 during Hyperventilation Provocation

Source	df	Mean Square	F
Group (G)	1	9.079	3.27
Error	31	2.777	
Time (T)	11	2.570	58.86 **
G X T	11	.040	.93
Error	341	.044	

** $p < .01$

Figure 13

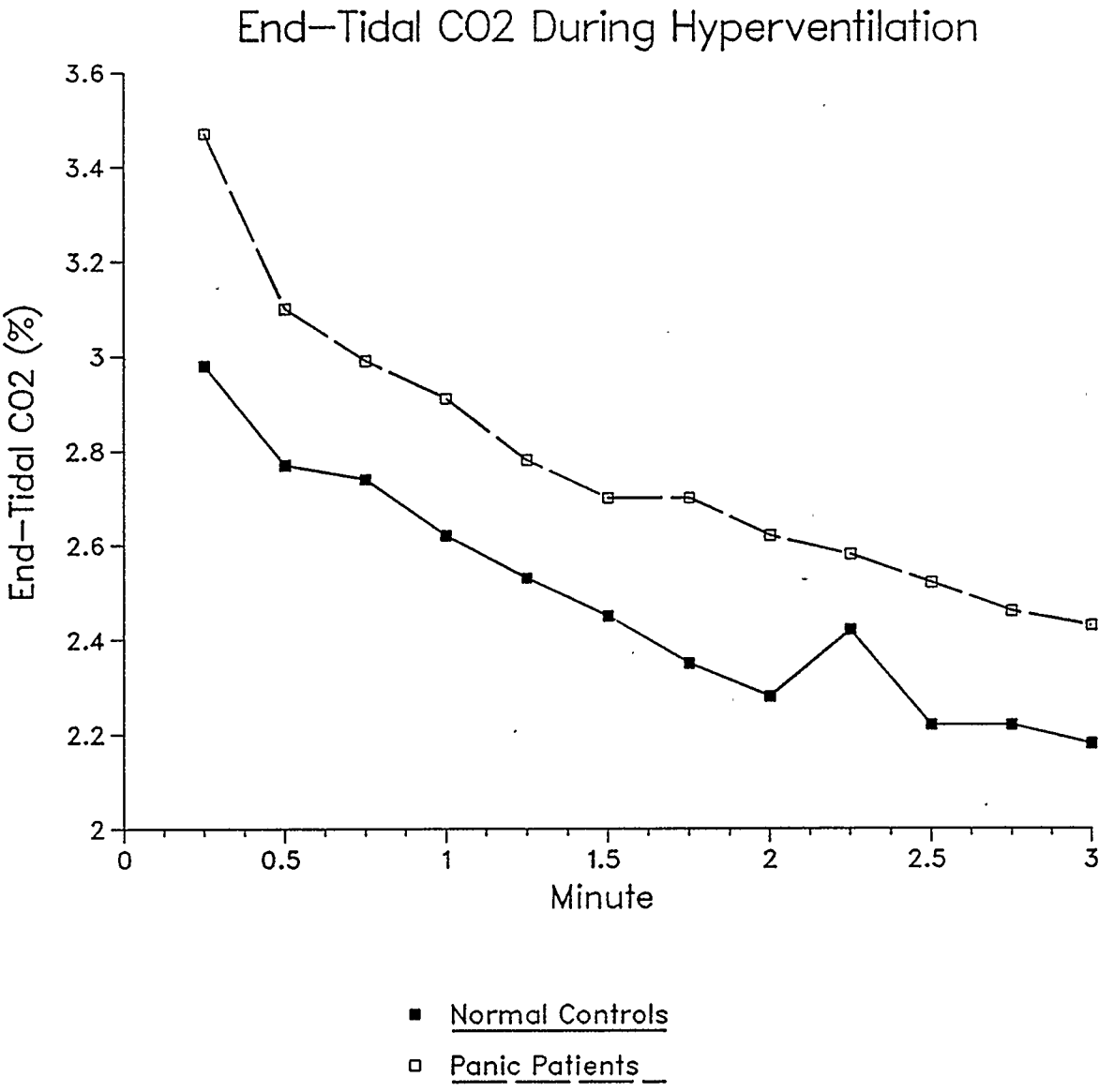

End–Tidal CO2 During Hyperventilation
End–Tidal CO2 (%)
3.6
3.4
3.2
3
2.8
2.6
2.4
2.2
2
0
0.5
1
1.5
2
2.5
3
Minute
Normal Controls
Panic Patients

Table 24

Correlation Matrix: Physiological Data in the last minute and Psychological Data at the start of the Recovery from Hyperventilation Phase

	ANX	SBN	COG	CO2	MV	BR	TV	EKG
Subjective Anxiety	-	.78***	.67***	-.20	.47**	.37*	.25	.50***
Sensations Total Score		-	.79***	-.51***	.58***	.40**	.34*	.47**
Cognitions Total Score			-	-.40**	.47**	.33*	.26	.55***
end-Tidal CO2				-	-.58***	-.31*	-.32*	-.10
Minute Ventilation					-	.46**	.62***	.47**
Breathing Frequency per 15 seconds						-	-.33*	.35*
Tidal Volume							-	.16
Heart Rate/Minute								-

* $p < .05$

** $p < .01$

*** $p < .001$

more of the dependent variables (Group X Time interaction: $F(65,2117) = 2.065$, $p < .00001$; Table 25). The Groups X Time interaction in the overall MANOVA was due to the PD group having a slower recovery of their End-tidal CO2 after hyperventilation ($F(27,837) = 5.42$, $p < .01$; Table 26). Figure 14 shows that this interaction consisted of the PD group maintaining a lower level of CO2 in the latter part of this phase compared to NC's, i.e., the PD's had a slower recovery of their end-tidal CO2 than the NC's.

Both groups' Minute Ventilation decreased significantly during this phase ($F(27,837) = 11.45$, $p < .01$; Table 27 and Figure 15). Tidal Volumes did not change significantly over time in this phase ($F(31,837) = 1.93$, $p > .01$; Table 28 and Figure 16), instead it was the decline in Breathing Frequency ($F(27,837) = 5.07$, $p < .01$; Table 29 and Figure 17) that accounted for the decline in Minute Ventilation during the recovery from hyperventilation. Heart rates in both groups also declined during recovery from hyperventilation ($F(27,891) = 13.94$, $p < .01$; Table 30 and Figure 18).

To summarize, there was evidence for significantly slower recovery of End-tidal CO2 in PD than NC subjects after hyperventilation. By comparison, after offset of the 5% CO2 breathing stimulus the PD group showed a nonsignificant trend for slower recovery of End-tidal CO2

Table 25

Groups X Time Repeated Measures Multivariate Analysis of Variance Summary Table: Physiological Variables during Recovery from Hyperventilation

SOURCE	MANOVA STATISTIC		df	F	
Groups (G)	T-squared =	.148	5/29	.859	
Time (T)	T-squared =	3.309	65/2117	21.552	***
G X T	T-squared =	.317	65/2117	2.065	***

*** $p < .0001$

Table 26

Groups X Time Repeated Measures Analysis of Variance Summary Table:
End-Tidal CO2 during Recovery from Hyperventilation

Source	df	Mean Square	F
Group (G)	1	48.148	2.86
Error	31	16.833	
Time (T)	27	5.881	60.26 **
G X T	27	.529	5.42 **
Error	837	.098	

** $p < .01$

Figure 14

End–Tidal CO2 During Recovery
from Hyperventilation

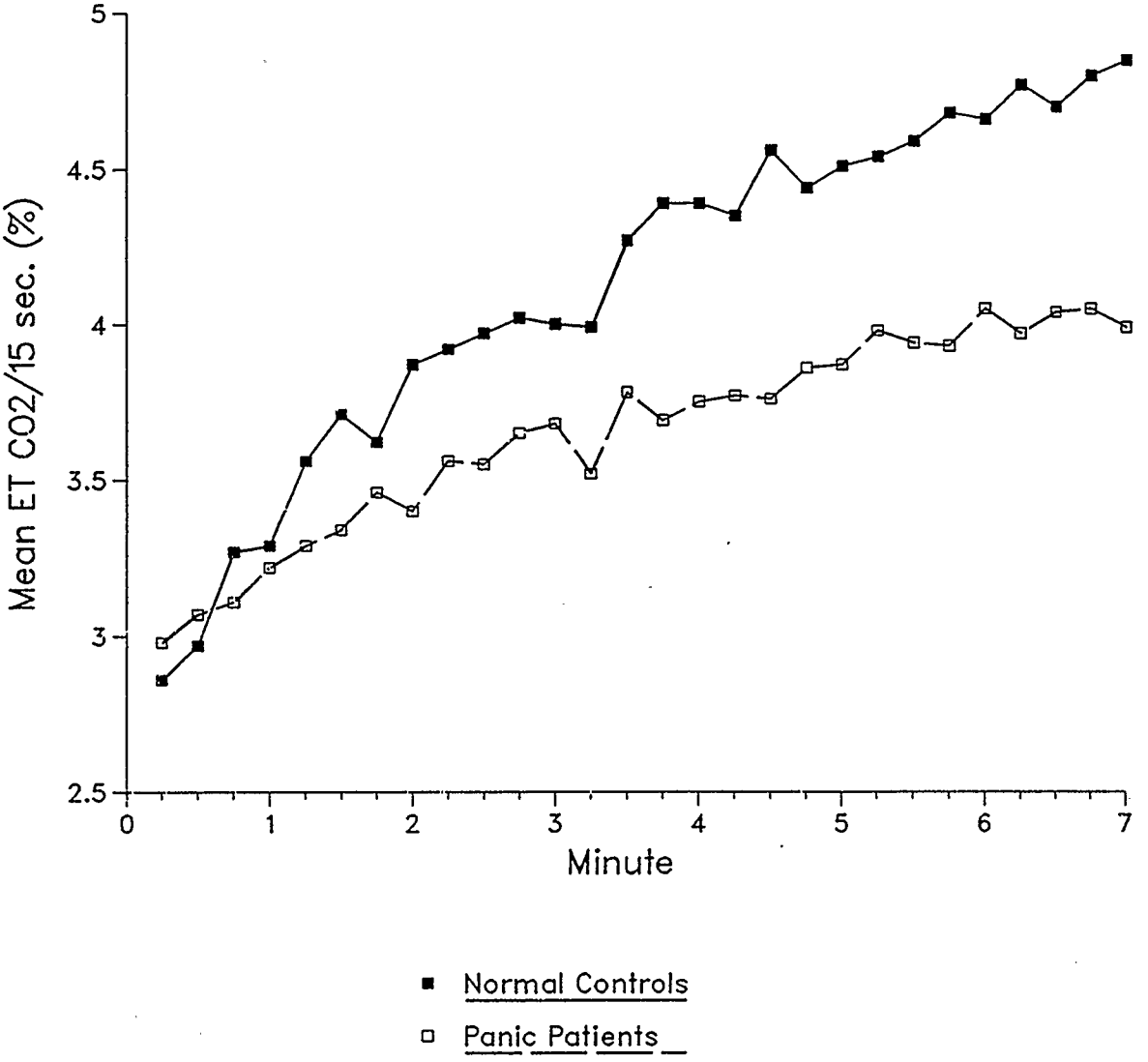


Table 27

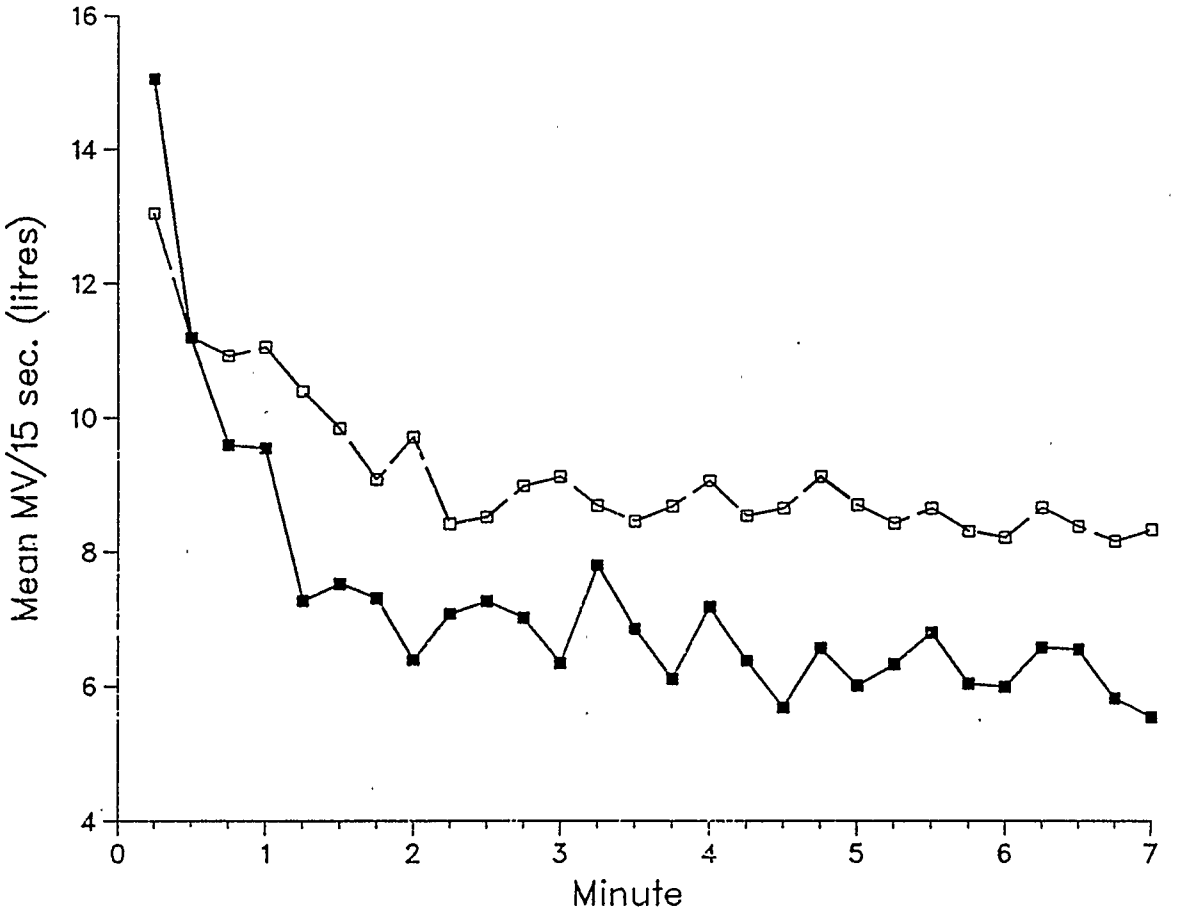
Groups X Time Repeated Measures Analysis of Variance Summary Table: Minute Ventilation during Recovery from Hyperventilation

Source	df	Mean Square	F
Group (G)	1	779.981	2.67
Error	31	292.176	
Time (T)	27	71.716	11.45 **
G X T	27	8.400	1.34
Error	837	6.263	

** $p < .01$

Figure 15

Minute Ventilation During Recovery
from Hyperventilation



■ Normal Controls

□ Panic Patients

Table 28

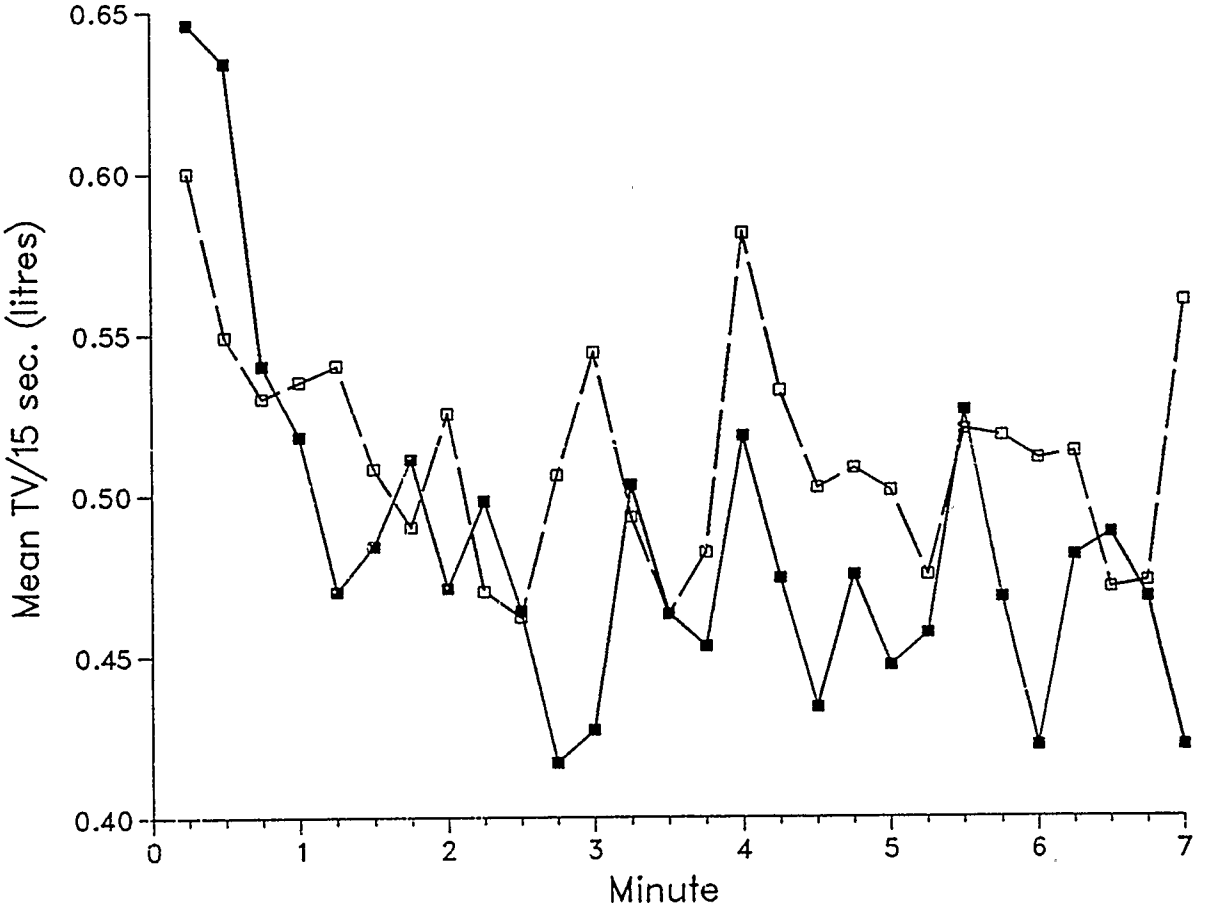
Groups X Time Repeated Measures Analysis of Variance Summary Table:
Tidal Volumes during Recovery from Hyperventilation

Source	df	Mean Square	F
Group (G)	1	.169	.14
Error	31	1.212	
Time (T)	27	.045	1.93
G X T	27	.019	.82
Error	837	.023	

** $p < .01$

Figure 16

Recovery from Hyperventilation:
Tidal Volume per 15 Second Interval



■ Normal Controls

□ Panic Patients

Table 29

Groups X Time Repeated Measures Analysis of Variance Summary Table: Breathing Frequency during Recovery from Hyperventilation

Source	df	Mean Square	F
Group (G)	1	197.748	2.02
Error	31	98.120	
Time (T)	27	5.706	5.07 **
G X T	27	.912	.94
Error	837	.973	

** $p < .01$

Figure 17

Breathing Frequency During Recovery
from Hyperventilation

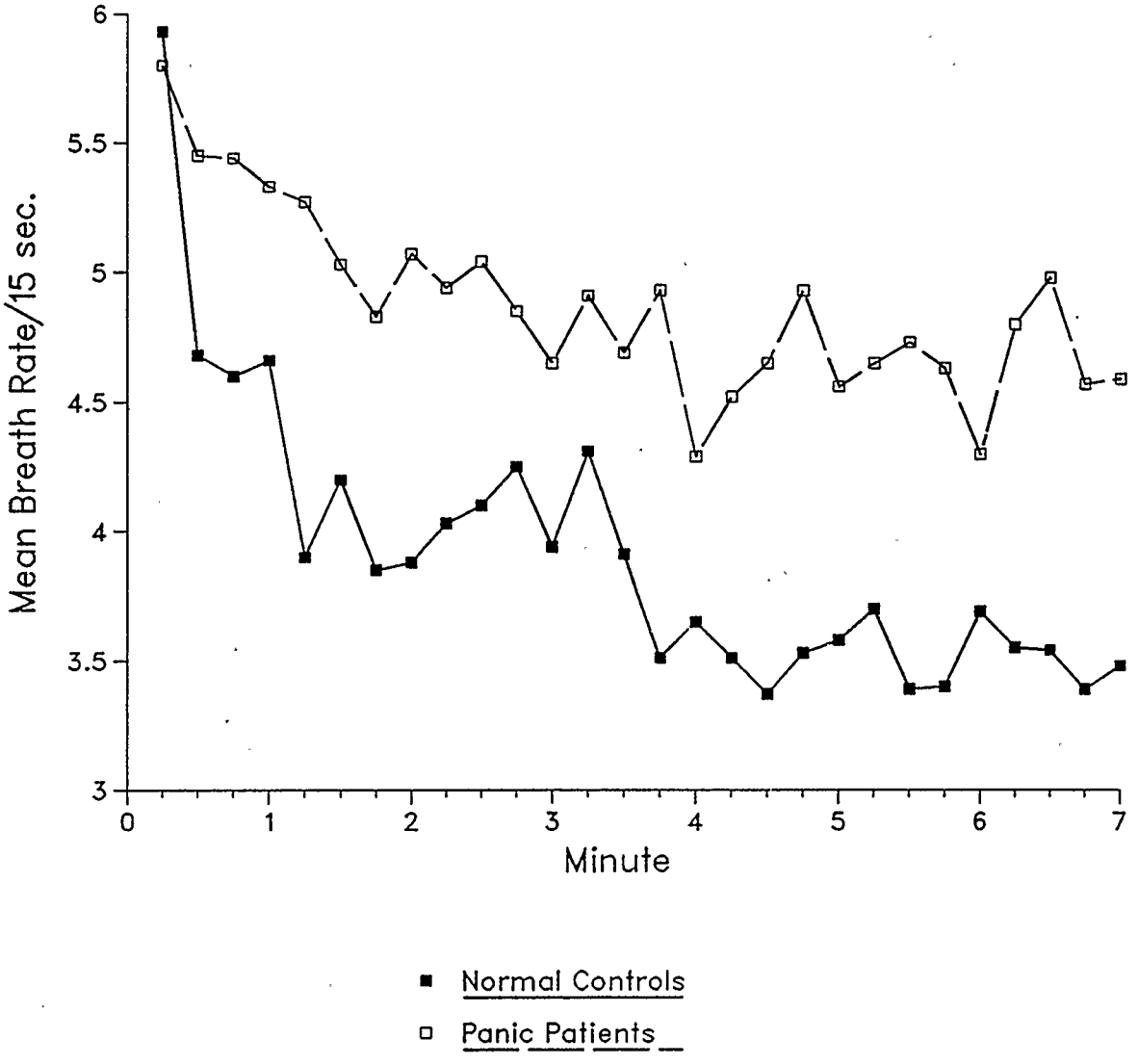


Table 30

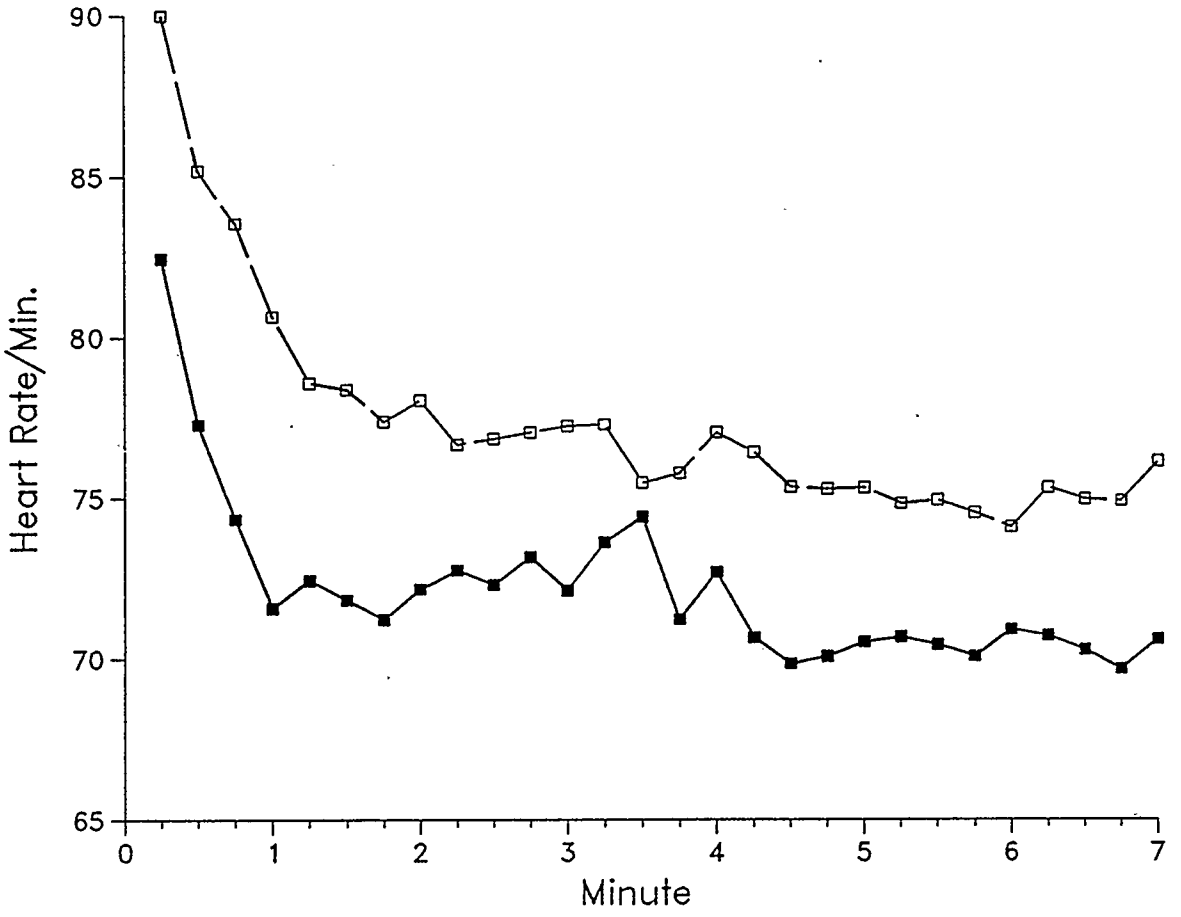
Groups X Time Repeated Measures Analysis of Variance Summary Table: Heart Rate during Recovery from Hyperventilation

Source	df	Mean Square	F
Group (G)	1	6485.073	1.26
Error	33	5166.824	
Time (T)	27	304.765	13.94 **
G X T	27	24.837	1.14
Error	891	21.863	

** $p < .01$

Figure 18

Heart Rate During Recovery
from Hyperventilation



than the NC group. Comparison of Figures 9 and 14 shows that recovery from 5% CO2 and recovery from hyperventilation produced very similar End-tidal CO2 recovery patterns for the two groups. Recovery from 5% CO2 was monitored for only five minutes, whereas recovery from hyperventilation was measured for seven minutes, and it is possible that the trend for a slower recovery of End-tidal CO2 in the PD group after 5% CO2 would have achieved significance had it been measured for the additional two minutes.

Anxiety, Sensations, and Cognitions Scores across all Stimulus Conditions in the Experiment

Although the current study focussed upon the measurement of biophysiological processes, an attempt was made to measure several psychological paramaters. Subjective Anxiety, somatic Sensations, and frightening Cognitions questionnaires were completed immediately at offset of each of the respiratory stimuli. Where there were significant ventilatory physiological differences between NC's and PD's, the psychological measures were entered into covariance analyses to rule out psychological interpretations of the results.

Table 31 shows that, with the exception of the correlation between Anxiety during baseline and Cognitions Score at 1% CO2 inhalation ($r(37) = .357$, $p < .05$) all correlations between psychological variables were significant at $p < .01$ or better. High mean correlations within each of the psychological measures (Anxiety: $r = .663$; Sensations: $r = .761$; Cognitions: $r = .773$) indicated that subjects tended to maintain their scores across the experimental phases.

The repeated measures MANOVA for the psychological measures is reported in Table 32. The Groups and Phases effects were qualified by a significant Groups X Phases interaction ($F(12,410) = 3.592$, $p < .0001$). Cognitions scores contributed to the significant MANOVA interaction (Groups X Phases interaction: ($F(4,140) = 4.97$, $p < .01$; Table 33), i.e., the groups' Cognitions responses to one or more of the experimental stimuli were different. Simple main effects calculated according to the procedures outlined by Winer (1971) revealed that group differences in Cognitions occurred only in response to hyperventilation ($F(1,59) = 15.57$, $p < .01$; Table 34) and that the group difference originated in an increase in PD's frightening Cognitions at hyperventilation ($F(4,140) = 13.85$, $p < .01$; Table 35 and Figure 19) that was not matched by the control group. Within-group comparisons showed that the NC's had

Table 31

Correlation Matrix: Psychological Measures across all Stimulus Conditions in the Experiment

	SEN0	SEN1	SEN3	SEN5	SENHV	COG0	COG1	COG3	COG5	COGHV	ANX0	ANX1	ANX3	ANX5	ANXHV
SEN0	—	.710***	.750***	.668***	.637***	.861***	.652***	.679***	.647***	.657***	.707***	.644***	.606***	.654***	.515***
SEN1		—	.809***	.859***	.719***	.650***	.835***	.687***	.760***	.760***	.451**	.799***	.579***	.705***	.588***
SEN3			—	.901***	.758***	.683***	.711***	.842***	.802***	.742***	.516**	.646***	.789***	.688***	.592***
SEN5				—	.795***	.602***	.688***	.706***	.778***	.720***	.545***	.647***	.728***	.809***	.649***
SENHV					—	.527***	.532***	.514***	.618***	.795***	.525***	.586***	.518**	.665***	.785***
COG0						—	.677***	.753***	.711***	.596***	.661***	.547***	.424*	.627***	.390*
COG1							—	.851***	.913***	.769***	.357	.618***	.491**	.661***	.436*
COG3								—	.930***	.711***	.404*	.506**	.589***	.600***	.406*
COG5									—	.821***	.434**	.559***	.562***	.736***	.505**
COGHV										—	.451*	.577***	.463*	.634***	.672***
ANX0											—	.636***	.560***	.710***	.530***
ANX1												—	.624***	.724***	.575***
ANX3													—	.687***	.590***
ANX5														—	.691***
ANXHV															—

* p < .01. ** p < .001. *** p < .0001

Note: SENx = Sensations Total Score
COGx = Cognitions Total Score
ANXx = Subjective Anxiety Rating

x = 0 during 0% CO2 Inhalation (Baseline)
x = 1 during 1% CO2 Inhalation
x = 3 during 3% CO2 Inhalation
x = 5 during 5% CO2 Inhalation
x = HV during Hyperventilation

Table 32

Repeated Measures Multivariate Analysis of Variance Summary Table: Psychological Measures across all Stimulus Conditions in the Experiment

SOURCE	MANOVA STATISTIC		df	F
Groups (G)	T-squared =	.618	3/33	6.799 ***
Phases (P)	T-squared =	1.197	12/410	13.634 ***
G x P	T-squared =	.315	12/410	3.592 ***

*** $p < .001$

Table 33

Repeated Measures Analysis of Variance
Summary Table:
Cognitions Scores across all Stimulus Conditions
in the Experiment

Source	df	Mean Square	F
Group (G)	1	4956.364	7.46 **
Error	35	664.105	
Phase (P)	4	331.904	6.36 **
G X P	4	259.607	4.97 **
Error	140	52.183	

** $p < .01$

Table 34

Simple Main Effects on Cognitions Scores:
Tests for Group differences at
each Level of Administered CO2 and at Hyperventilation

Source	df	F
Groups after 0% CO2 Inhalation (Baseline):	1/59	1.89
Groups after 1% CO2 Inhalation:	1/59	3.26
Groups after 3% CO2 Inhalation:	1/59	1.58
Groups after 5% CO2 Inhalation:	1/59	5.18
Groups after Hyperventilation:	1/59	15.57 **

** $p < .01$

Table 35

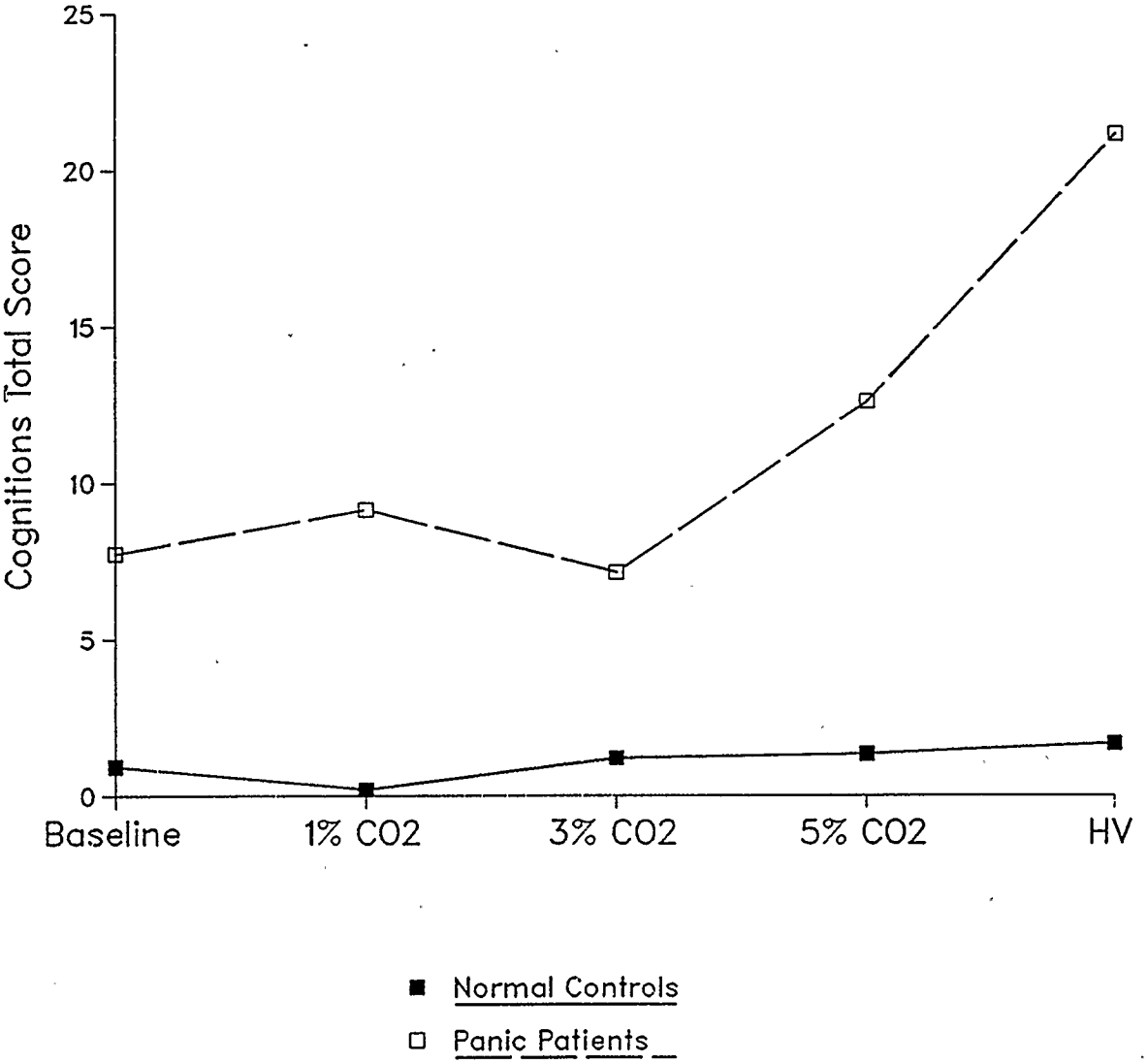
Simple Main Effects on Cognitions Scores: Test for Phase Differences for each Group

Source	df	F
Phase Difference for Normal Control Group:	4/140	.09
Phase Difference for Panic Group:	4/140	13.85**

** $p < .01$

Figure 19

Cognitions Scores across all Experimental Stimuli



low and stable Cognitions scores throughout the experiment ($F(4,140) = .09$, $p > .01$; Table 35), while the PD group had stable Cognitions scores across 0%, 1%, and 3% CO2 inhalations, but then increased their Cognitions in response to 5% CO2 and hyperventilation (Table 36). PD's hyperventilation Cognitions were higher than all other means in the interaction including those at 5% CO2, while their Cognitions at 5% were higher than their Cognitions at 3%, 1%, and 0% CO2.

Sensations symptom scores also contributed to the MANOVA interaction (Groups X Phases interaction: $F(4,140) = 8.61$, $p < .01$; Table 37). Groups differed on Sensations both at HV ($F(1,67) = 35.96$, $p < .01$; Table 38 and Figure 20) and at 5% CO2 ($F(1,67) = 11.93$, $p < .01$). Paralleling their Cognitions results, the NC's had stable Sensations scores across the experimental stimuli ($F(4,140) = 2.95$, $p > .01$; Table 39) while the PD group had different Sensations scores in response to some of the stimuli ($F(4,140) = 44.4$, $p < .01$). Specifically, the PD group significantly increased their symptoms in response to hyperventilation (Table 40).

The groups also had different subjective Anxiety levels across the experiment ($F(1,35) = 13.84$, $p < .01$; Table 41) The absence of a significant Groups X Phases interaction ($F(4,140) = 1.01$, $p > .01$) indicated that the

Table 36

Newman-Keuls Summary Table:
Panic Group Cognitions Scores at
each Level of Administered CO2 and at Hyperventilation

Phase:	0% CO2	1% CO2	3% CO2	5% CO2	HV
Mean:	31.59	31.59	34.45	53.86	90.23
0% CO2	-----	0.00	2.86	22.27**	58.64**
1% CO2		-----	2.86	22.27**	58.64**
3% CO2			-----	19.41**	55.78**
5% CO2				-----	36.37**
HV					-----

** $p < .01$

Table 37

Repeated Measures Analysis of Variance Summary Table: Sensations Scores across all Stimulus Conditions in the Experiment

Source	df	Mean Square	F
Group (G)	1	57790.703	19.17 **
Error	35	3015.036	
Phase (P)	4	9765.719	31.05 **
G X P	4	2709.167	8.61 **
Error	140	314.515	

** $p < .01$

Table 38

Simple Main Effects on Sensations Scores:
Tests for Group differences at each
Level of Administered CO2 and at Hyperventilation

Source	df	F
Groups after 0% CO2 Inhalation (Baseline):	1/67	4.78
Groups after 1% CO2 Inhalation:	1/67	6.08
Groups after 3% CO2 Inhalation:	1/67	5.50
Groups after 5% CO2 Inhalation:	1/67	11.93 **
Groups after Hyperventilation:	1/67	35.96 **

** $p < .01$

Figure 20

Sensations Scores across all Experimental Stimuli

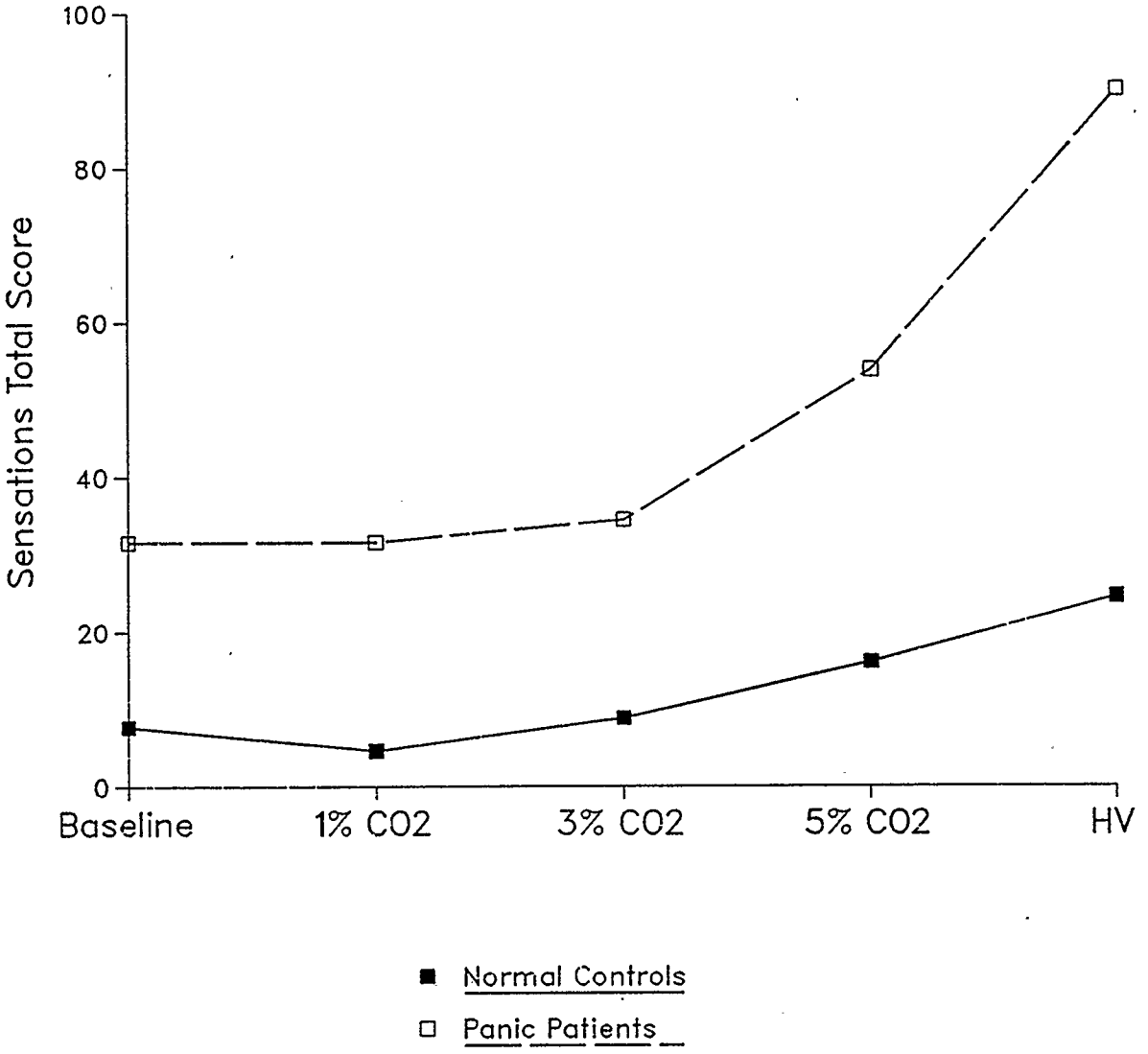


Table 39

Simple Main Effects on Sensations Scores:
Test for Phase differences for each Group

Source	df	F
Phase Difference for Normal Control Group:	4/140	2.95
Phase Difference for Panic Group:	4/140	44.40 **

** $p < .01$

Table 40

Newman-Keuls Summary Table:
Panic Group Sensations Scores at
each Level of Administered CO2 and at Hyperventilation

Phase:	3% CO2	0% CO2	1% CO2	5% CO2	HV
Mean:	7.41	7.73	9.14	12.59	21.18
3% CO2	----	.32	1.73	5.18	13.77**
0% CO2		----	1.41	4.86	13.45**
1% CO2			----	3.45	12.04**
5% CO2				----	8.59**
HV					----

** $p < .01$

Table 41

Repeated Measures Analysis of Variance
Summary Table:
Anxiety Ratings across all Stimulus Conditions
in the Experiment

Source	df	Mean Square	F
Group (G)	1	170.891	13.84 **
Error	35	12.347	
Phase (P)	4	47.032	25.70 **
G X P	4	1.842	1.01
Error	140	1.830	

** $p < .01$

groups had different Anxiety responses to all of the experimental stimuli. In addition, the two groups' Anxiety levels changed in a parallel fashion across the experiment ($F(4,140) = 25.7$, $p < .01$; Figure 21), increasing significantly at both 5% CO2 inhalation and HV (Table 42). Anxiety at hyperventilation was significantly higher than Anxiety to all other stimuli.

There were group psychological differences at the end of the hyperventilation phase (see Tables 34, 38, and 41), while in the immediately following phase, recovery from hyperventilation, a Group X Time interaction for End-tidal CO2 was observed. To evaluate the degree to which PD's slower recovery of End-tidal CO2 following hyperventilation might have been due to their higher psychological scores going into this recovery phase, an analysis of Covariance (ANCOVA) was used to statistically control for the group differences in Anxiety, Sensations, and Cognitions. Table 43 presents the ANCOVA summary table, where it can be seen that the combination of all three psychological covariates failed to account for a significant amount of the variance in End-tidal CO2 during recovery from hyperventilation ($F(3,28) = 3.13$, $p > .01$), and also that the Group X Time interaction for End-tidal CO2 remained significant ($F(27, 837) = 5.42$, $p < .01$). Nevertheless, two of the psychological covariates missed significance at the .01

Figure 21

Subjective Anxiety Ratings across
all Experimental Stimuli

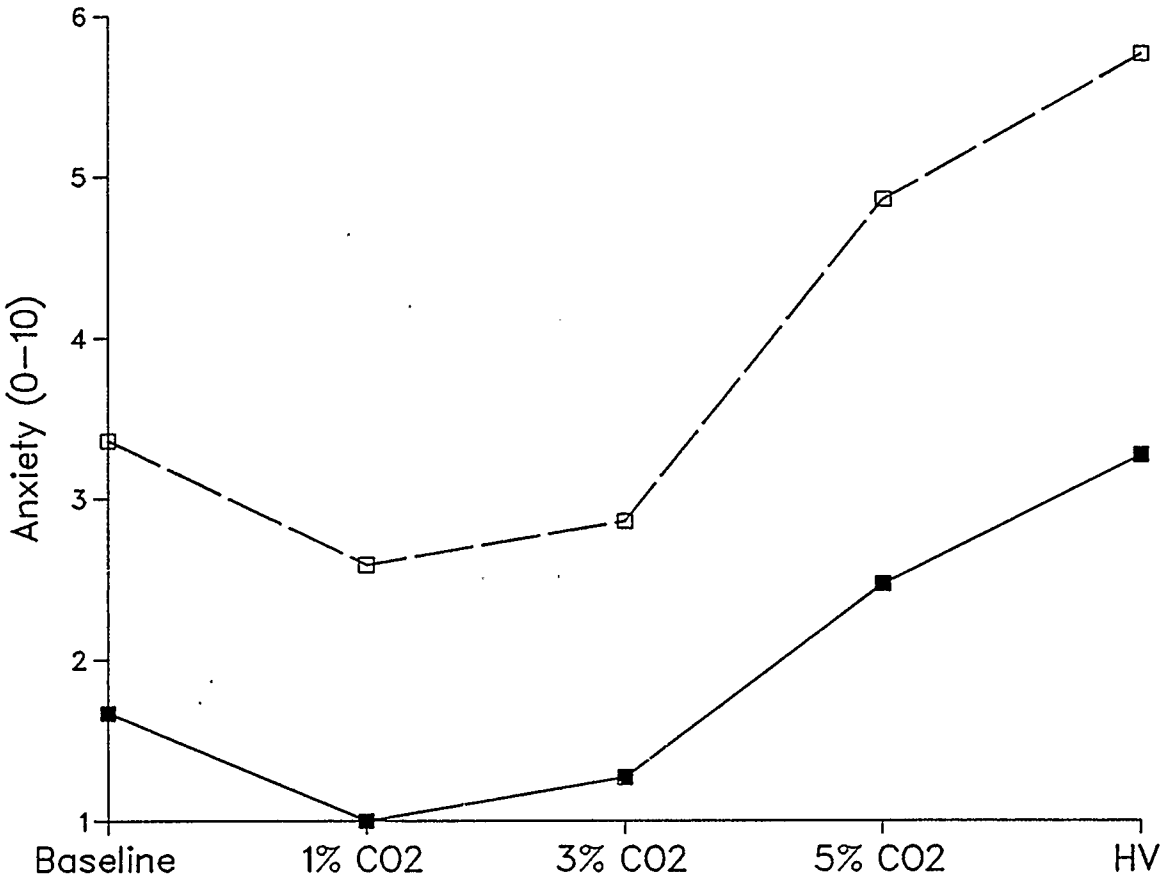


Table 42

Newman-Keuls Summary Table: Anxiety Ratings at each Level of Administered CO2 and at Hyperventilation, Collapsed Across Groups

Phase:	1% CO2	3% CO2	0% CO2	5% CO2	HV
Mean:	1.95	2.22	2.67	3.89	4.76
1% CO2	----	0.27	0.72	1.94**	2.81**
3% CO2		----	0.45	1.67**	2.54**
0% CO2			----	1.22**	2.09**
5% CO2				----	0.87**
HV					----

** $p < .01$

Table 43

Repeated Measures Analysis of Covariance Summary Table: End-tidal CO2 during Recovery from Hyperventilation, with Psychological Measures as Covariates

Source	df	Mean Square	F
Group (G)	1	1.040	0.07
Anxiety Covariate	1	75.598	5.42
Sensations Covariate	1	88.526	6.34
Cognitions Covariate	1	0.025	0.00
All Covariates	3	43.675	3.13
Error	28	13.957	
Time (T)	27	5.881	60.26 **
G X T	27	0.529	5.42 **
Error	837	0.098	

** $p < .01$

level by a small margin (Anxiety: $F(1,28) = 5.42$, recorded $p < .027$; Sensations: $F(1,28) = 6.34$, recorded $p < .018$). Since the individual significance levels of the covariates were partly determined by the order of their entry, correlational analyses were performed to determine the relationship between initial psychological status and End-tidal CO2 in the final minute of the recovery, when the separation of the groups was at its greatest. Table 44 shows that both Sensations ($r = -.51$, $p < .0001$) and Cognitions scores ($r = -.40$, $p < .01$) significantly predicted End-tidal CO2 recorded in the last minute of the recovery phase. In other words, the persistence of hyperventilation over this seven minute recovery phase was related to how many somatic symptoms and how many frightening cognitions were experienced as a consequence of the immediately preceding hyperventilation phase.

In summary, three hypotheses related to chronic HV were investigated in PD and NC subjects. There was support for the idea that PD's may chronically hyperventilate, as indexed by their lower blood bicarbonate, and for the hypothesis that PD's have an impaired ability to recover CO2 lost during HV. There was also a trend for slower CO2 recovery following 5% CO2 inhalation. There was no support for the hypothesis that PD patients have enhanced medullary CO2 chemoreceptor sensitivity.

Table 44

Correlation Matrix: End-tidal CO2 in the last minute and Psychological Data at the start of the Recovery from Hyperventilation phase

	ANX	SEN	COG	CO2
Subjective Anxiety	----	.78***	.67***	-.20
Sensations Total Score		----	.79***	-.51***
Cognitions Total Score			----	-.40**
end-Tidal CO2				----

* p < .05
** p < .01
*** p < .0001

DISCUSSION

A considerable amount of research has implicated acute HV in the production of panic attacks. The acute HV model suffers from a number of limitations however, the major one being a difficulty in explaining ongoing susceptibility to HV and panic. The present research sought to provide empirical support for the role of chronic as opposed to acute HV in Panic Disorder. The medical-physiological literature on breathing indicates that chronic HV may be accompanied by a number of biophysiological changes, and the specific nature of these changes suggested several physiological hypotheses for the present investigation. The goal of this study was not to provoke panic, but to test these hypotheses by looking for differences between panic sufferers and normal controls in their response to high and low CO2 conditions.

The most direct and unequivocal measure of chronic HV is blood bicarbonate level, which declines after a prolonged period of overbreathing (Van Dis, 1975). The lower blood bicarbonate in our PD group provided evidence of chronic HV in the patient sample. Illness conditions which could cause such a result (e.g., those resulting in metabolic acidosis) were ruled out by the medical assessment done on all subjects. The magnitude of the

group bicarbonate difference, at 2.6 mEq/L, is comparable to group bicarbonate differences reported by other investigators (e.g., Gorman, Cohen, Liebowitz, Fyer, Ross, Davies & Klein, 1986: 2.0 mEq/L.; Liebowitz, Gorman, Fyer, Levitt, Dillon, Levy, Appleby, Anderson, Palij, Davies, & Klein, 1985: 2.02 mmol/L.; Gaffney, Fenton, Lane, & Lake, 1988: 1.0 mEq/L.). Overall then, lower blood bicarbonate in PD's compared to NC's appears to be a consistent but weak finding, both statistically and clinically.

There was a large overlap in the bicarbonate distributions of the PD and NC group in the current study, with two or three extreme values in the PD group accounting for the observed group difference. While it is true that the mean blood bicarbonate level observed in the current PD sample would not cause concern in a routine medical examination, when taken in the context of Panic Disorder it assumes some theoretical and clinical importance in terms of its origins in chronic HV breathing patterns. For example, low bicarbonate may promote a physiological tendency to maintain chronic overbreathing (Cohen, 1976), which could act as a maintaining factor for Panic Disorder. Future research might also test the hypothesis that the lower blood bicarbonate of some PD's increases the severity of their panic since less bicarbonate is available to

buffer the drops in CO2 that accompany attacks (Salkovskis, 1988; Van Dis, 1975). A low bicarbonate/chronic HV condition could also cause panic attacks to become more frequent. When the acute episodes of HV associated with panic are superimposed upon a facilitative chronic overbreathing pattern, less acute HV may be required to reach the low-CO2 symptom threshold.

Lower blood bicarbonate in the absence of metabolic disturbances is known in respiratory medicine to be the result of persistent overbreathing leading to renal excretion of bicarbonate. However there was no clear evidence of PD's overbreathing when they were compared to NC's at baseline. During quiet resting breathing of room air, there were no group differences on Minute Ventilation, Breathing Frequency, Tidal Volumes, or End-tidal CO2. The PD group was more aroused than NC's at baseline however, as evidenced by their higher Anxiety, body Sensations, and frightening Cognitions scores, and their higher heart rates. One explanation for the lack of group differences on the ventilation measures at baseline might be that differences were washed-out by a mild hyperventilation in both groups induced by the equipment used in the study. While the use of a mouthpiece and noseclip was the preferred method for conducting chemoreceptor sensitivity and CO2 recovery tests, this equipment arrangement is known

to induce an increase in Minute Ventilation and a corresponding drop in end-tidal CO2 (Perez and Tobin, 1985,) which could have masked group ventilation differences at baseline.

The lack of significant group differences in mean ventilation results at baseline should not be taken as a sign that the groups' breathing were the same. The breathing of PD's and NC's in the current study were not comparable in terms of variability indices. Not just at baseline, but during every stimulus condition in the experiment, there were statistically significant group differences in variability in all breathing measures and in heart rate. The pattern of breathing results in panic-provocation studies is quite different, where it is usual to find mean as well as some variance differences between PD's and NC's on breathing parameters (e.g., Gorman, Fyer, Goetz, Askanazi, Liebowitz, Fyer, Kinney, & Klein, 1988). PD's vulnerability to hyperventilate may be related to the high variability in their breathing that was observed in the current study, and this vulnerability may require a provocation paradigm before manifesting itself in observable mean ventilation differences. The attempts made in the current study to minimize anxiety during physiological measurement may have masked overt representations of PD's tendencies towards

hyperventilation. Other investigators have suggested that excessive variability in breathing parameters (e.g., Huey & West, 1983), and also possibly unusual muscular patterns associated with breathing (e.g., Lum, 1976, 1981) are related to hyperventilation proneness. These hypotheses suggest that PD subjects' vulnerability to hyperventilation might not have be easily detectable at baseline because of its idiosyncratic and transitory nature. Standard rate and depth measures may need to be supplemented by typologies which reflect the peculiarities of PD's breathing styles.

The second ventilatory hypothesis under investigation, that PD's have hypersensitive medullary CO2 chemoreceptors, is central to panic models espoused by Carr and Sheehan (1984) and Gorman, Liebowitz, Fyer, Fyer, and Klein (1986). A dysfunction in CO2 chemoreceptors, which are largely responsible for the regulation of breathing, would be an important finding which could account for PD's vulnerability to hyperventilation episodes. Under this hypothesis, PD's should breathe more than NC's in response to a high CO2 stimulus. While Gorman et al. (1988) found that PD's breathed more than NC's in response to CO2, this result was obtained in a provocation study where subjects were led to expect panic. Therefore PD's greater ventilation may have been due to their higher anxiety. A negative finding for this hypothesis (Woods, Charney, Loke,

Goodman, Redmond, & Heninger, 1986) and a second positive finding (Lousberg, Griez & van den Hout, 1988) are difficult to interpret due to limitations of the Read Rebreathing methodology used in their measurements.

The present study used data points which contained information on a full minute's breathing at each of two levels of administered CO2, using equipment and instructions designed to minimize anxiety during CO2 inhalations, and in which three components of anxiety were measured as a check on the instructional manipulations. With this improved methodology it was found that, contrary to the hypothesis, chemical stimulation of breathing with 3% and 5% CO2 produced nearly identical breathing increases in PD's and NC's. Replications of this result using the more reliable steady-state CO2 inhalation methodology and anti-anxiety instructional sets would shift the weight of evidence against the hypothesis that PD's have a physiologic disturbance of their CO2 chemoreceptors.

The lack of significant group differences on any of the physiological variables at baseline, during CO2 inhalations, or during hyperventilation made the use of change scores unecessary for group comparisons during tests of the third hypothesis, i.e., that PD's would have a slower recovery of end-tidal CO2 compared to NC's after blood CO2 had been experimentally manipulated upwards by

CO2 inhalation, and after it had been driven below normal by hyperventilation. As an empirical test of hyperventilation-proneness, slow recovery of End-tidal CO2 after hyperventilation was first investigated by the Dutch neurologists Hardonk and Beumer (1979), who found that hyperventilators took consistently longer to recover CO2 lost during HV than did normals. A test for slow recovery of CO2 after 5% CO2 inhalation was not performed by Hardonk et al. (1979). This procedure was included in the present study as an exploratory test due to theoretical interest in the possibility that high blood CO2 may induce hyperventilatory breathing patterns during recovery. Compared to NC's, PD's in the current study showed significantly slower CO2 recovery following hyperventilation, but only slightly and not significantly slower CO2 recovery following the 5% CO2 breathing stimulus. These slow recovery effects correspond to a stronger tendency on the part of PD patients to hyperventilate after offset of breathing stimuli. Both physiological and psychological explanations may apply to these findings.

Panic patients' continued hyperventilation during recovery may have been due to a physiological phenomenon known as "Respiratory After-Discharge" (RAD; Eldridge & Gill-Kumar, 1980). This effect corresponds to a tendency

to continue breathe more after exposure to and removal of a breathing stimulus. Analogies have been made between RAD and a self-sustaining "neural net" in the brainstem to account for the tendency to continue to overbreathe after offset of a breathing stimulus (Eldridge & Gill-Kumar, 1980). Not fully understood, the RAD phenomenon has been investigated in both the human (e.g., Swanson, Ward, & Bellville, 1976) and the animal literature (e.g., Eldridge et al., 1980), and there is some consensus that it is mediated by the medullary respiratory control centres. HV-induced CO2 losses, through their action in increasing neuronal firing rates, may account for the persistence of HV during recovery (Folgering et al., 1983), however since both groups in the current study were hyperventilated the same amount, this alone cannot explain the group difference during the recovery period.

Support for a physiological interpretation of the slower recovery of CO2 in PD's following hyperventilation comes from a comparison of the pattern of physiological results in the present study to two characteristics of the RAD phenomenon as observed in non-anxious subjects. First, Folgering et al. (1983) found that breathing frequency increases were a prime determinant of the RAD effect. This is consistent with the current findings in which a signficantly stronger RAD for PD's followed a stimulus for

high breathing frequency (HV at approximately 60 cycles/min.) but was not as strong, and failed to reach significance, following a stimulus which did not significantly increase breathing frequency (5% CO2 inhalation). Second, there is the consistent finding for RAD hyperventilation that, although it is stimulated by a high breathing rate, it manifests during the recovery period primarily as a persistently high Tidal Volume, while Breathing Frequency typically declines (Folgering et al., 1983; Swanson et al., 1976). This pattern of results was mirrored in the current study. Tidal volumes did not decrease significantly during recovery from HV for either group, while Breathing Frequency declined for both groups. It should be noted however that this RAD pattern was followed by both groups, and therefore does not account for the stronger RAD phenomenon in PD's.

There is likely a psychological component to the finding that PD's kept their CO2 lower than NC's in the recovery period following hyperventilation. PD subjects in the current study had higher anxiety, cognitions, and sensations scores going into recovery from hyperventilation than the NC group. When psychological scores were used as covariates in this phase however, the PD group still took significantly longer than NC's to recover their CO2. The composite of the three psychological covariates (Anxiety,

Sensations, and Cognitions) approached significance. Further examination of the influence of the psychological variables revealed that a considerable amount of the variance in the final-minute end-tidal CO2 data (i.e., when the separation of the groups was at its greatest) could be accounted for by subjects' initial psychological status. Given the tendency of PD subjects to react with high anxiety to certain somatic symptoms that have become "learned alarms" (Barlow, 1988), it is possible that the higher psychological arousal of the PD group at the beginning of recovery maintained their hyperventilation longer than that of the NC group during this phase. This interpretation is consistent with the results of Gorman, Fyer, Goetz, Askanazi, Liebowitz, Fyer, Kinney & Klein (1988) who found that the subjects who showed slower recovery of CO2 following hyperventilation were primarily those who panicked during hyperventilation. A study of normal college males, who presumably had no significant anxiety difficulties, found no relationship between their typical anxiety symptoms or their hyperventilation-reproduced symptoms and the rate of their CO2 recovery (Wientjes, Grossman, & Defares, 1984), and this might be taken as further evidence that it is anxious patients in particular who are susceptible to slow recovery of CO2 after HV.

This explanation may also apply to the results of the Hardonk et al. (1979) study. Given the high incidence of Panic Disorder that has been found in samples selected for hyperventilation, it seems likely that if Hardonk et al. had assessed the psychiatric status of their group of 100 hyperventilators they would have found a number of subjects with PD. If this is true, their hyperventilators may have had slower recovery of CO2 due to the psychological reactivity of their PD subjects.

Nevertheless, it should be noted that the relationship between slow CO2 recovery and prior psychological arousal is a correlational one in both the Gorman et al. (1988) and the current investigation, and so the existence, or the direction of causal connections between them, is unknown. While high psychological arousal could have caused a somatic-cognitive-HV spiral leading to slower CO2 recovery in PD's, it is equally possible that the PD subjects who have the greatest psychological and/or physiological susceptibility to symptom production during HV are the same subjects who have a disordered physiology causing a stronger RAD effect, with no direct causal connection between the two phenomena. It must also be noted that the current study compared PD's to normal controls and not to other anxiety-disordered patients, and so the phenomenon of

slow CO2 recovery may not be specific to PD but may be characteristic of other anxiety states as well.

To summarize regarding the somewhat complex pattern of CO2 recovery results, the significantly slower CO2 recovery of PD's in the current study may have been due to a physiological process arising in the brainstem known as Respiratory After-Discharge, psychological arousal, or, more likely, a combination of these two factors. Teasing apart the relative importance of physiological and psychological influences in producing this effect for PD subjects might be accomplished by studies a) in which psychological arousal is measured at intervals during recovery rather than just at the outset, and b) in which the stimulus for RAD given to PD's does not arouse significant psychological reactions. The psychological component of RAD may consist of symptomatic reactions to the preceding HV causing frightening interpretations and spiralling anxiety and HV throughout the recovery phase. Measurement of subjective anxiety at intervals during recovery, rather than just at the outset, would provide evidence for or against this hypothesis. If it was found that anxiety throughout recovery from HV was significantly related to PD's slower recovery of End-tidal CO2, it would would provide support for a cognitive-behavioral formulation of this phenomenon, but it would still remain

unclear whether psychological factors operated alone, or whether they were overlaid upon a physiological RAD effect that was still stronger for PD's than NC's. Demonstrating a physiological component as opposed to or in addition to a psychological process in slow CO2 recovery in PD patients would require control over PD's psychological reactions to the HV stimulus. This might be accomplished through isocapnic hyperventilation, i.e., by stimulating breathing while using equipment which prevents HV from lowering blood CO2 levels. If PD's psychological reactions to HV are, as a number of investigators have suggested (Cowley & Roy-Byrne, 1987; Huey & West, 1983; Ley, 1987; Rapee, 1987), primarily due to HV-induced CO2 losses, this procedure could be effective in nullifying most of the psychological reactions to HV. Since anxiety would be measured throughout recovery, this assumption could be examined empirically. If psychological factors were minimized by isocapnic HV, a cleaner comparison could be made between the strength of the physiological RAD effect between NC's and PD's, and provide important information regarding the physiological vulnerability of PD's towards hyperventilation.

If PD's were shown to have a stronger physiological tendency for RAD than NC's, it would also be important to determine if this is a physiological vulnerability factor

which antedates the onset of Panic Disorder. Measurement of RAD in groups judged to be at high risk of developing PD, for example infrequent panickers (Norton, Cairns, Wozney & Malan, 1988; Norton, Dorward, & Cox, 1986; Norton, Harrison, Hauch & Rhodes, 1985), could provide a partial answer to this question. RAD might also be investigated as a possible trigger for naturally-occurring panic. Naturalistic triggers for panic (e.g., emotional states, phobic stimuli) could be tested not only for their ability to trigger HV, but also RAD.

Whether it is primarily psychological or physiological in origin, the phenomenon of slow CO2 recovery for PD subjects remains an interesting finding which can be used to generate a number of hypotheses regarding Panic Disorder. For example, the greater hyperventilation of PD's than NC's during recovery from a hyperventilation provocation may play a role in the production of a chronic HV syndrome in PD patients. Development of chronic HV through reduction in blood bicarbonate levels requires that blood CO2 levels remain low over at least a period of hours (Gennari, Goldstein, & Schwartz, 1972). Acute hyperventilation episodes are time-limited events lasting a number of minutes, and unless one assumes a series of very closely spaced acute HV episodes, it is difficult to conceive how blood CO2 could be kept below normal long

enough for the bicarbonate loss to occur and convert the acute hyperventilation into chronic HV. The current RAD finding may provide at least a partial explanation of the process by which PD's keep their CO2 levels low for a sufficent period of time to undergo bicarbonate compensation. PD's in the current study showed a significant tendency to keep their CO2 low longer after hyperventilation compared to NC's, and the longer-lasting effects of acute hyperventilation episodes could make it more likely that the time required for bicarbonate compensation is exceeded. In this connection, it is interesting that Rapee (1988) has noted that PD subjects have significantly longer panic attacks than subjects who experience similar symptoms too infrequently to meet criteria for PD. It is possible that slow CO2 recovery/RAD, by prolonging the CO2 loss associated with acute HV episodes, prolongs panic attacks in PD's.

The second CO2 recovery test carried out in this study involved measuring CO2 over five minutes following five percent CO2 inhalation. Unlike the post-HV results, the two groups did not differ significantly after 5% CO2 in the time taken to recover towards normal end-tidal CO2 levels. It is of some interest however that there was a trend for the PD group to maintain a lower CO2 level in this recovery period much as they did during recovery from

hyperventilation, and if CO2 had been monitored for seven minutes instead of five, as it was after hyperventilation, it is possible that the effect may have achieved statistical significance. Preliminary results from Gorman, Fyer, Goetz, Askanazi, Liebowitz, Fyer, Kinney, and Klein (1988) suggest that even longer recovery periods of up to 15 minutes may be required to find this difference. Their results are not directly comparable to those of the current study, since a provocation paradigm was used. While they found that it was only those subjects who panicked in response to 5% CO2 who hyperventilated more than normals during recovery, in the current study non-panic levels of anxiety were observed with 5% CO2, and a trend for hyperventilation during recovery emerged. Future studies of slow recovery of CO2 following CO2 inhalation will need better control over subjects' anxiety levels.

Significantly slower recovery of End-tidal CO2 for PD's following high CO2 stimulation of breathing would be an important finding, with implications for exercise-induced panic, relaxation-induced panic, and nocturnal panic. Exercise increases CO2 production, which induces an increase in breathing rates and volumes, and if PD subjects could be shown to take significantly longer to recover normal breathing rates and volumes following exercise, this excess breathing could result in a

'hypocapnic overshoot', i.e., below normal blood CO2 levels and therefore the somatic symptoms about which PD's panic. This is an intriguing hypothesis inasmuch as nosological forerunners of Panic Disorder, especially studies related to "Effort Syndrome" (e.g., Soley & Shock, 1938), have long implicated exercise as a trigger for attacks. Indeed, exercise studies provided the original impetus for the lactate model of panic (Sheehan, Carr, Fishman, Walsh, & Peltier-Saxe, 1985), and current investigators believe mild exercise may be one of the more common triggers for so-called "spontaneous" panic attacks (Barlow et al., 1985). To investigate the connection between exercise, slow recovery of CO2, and panic, standard treadmill exercise tests for PD's and NC's could be followed by both physiological measurement of CO2 and psychological measures at intervals during recovery.

Relaxation-induced anxiety/panic (Barlow, Vermilyea, Blanchard, Vermilyea, Di Nardo & Cerny, 1985; Heide & Borkovec, 1984; King, 1988) and nocturnal panic (Craske & Barlow, 1989) also may be related to RAD/slow CO2 recovery effects following a raised blood CO2 level. Ley (1988b; 1988c) has given hyperventilation explanations for both of these phenomena, and although he does not refer to the literature on RAD, both of his hypotheses clearly implicate

slow CO2 recovery in the production of panic under these conditions.

Future studies of the physiology of Panic Disorder will have to take into account the presence of interactive thoughts and feelings which accompany the respiratory changes following provocation. Panic patients and controls showed very similar subjective anxiety patterns across the phases of the study, with PD's reporting greater anxiety throughout. Both groups showed similar increases in anxiety during the more intense provocations. However, the pattern of means for the two groups was quite different for the body Sensations and frightening Cognitions measures. The PD's were higher than NC's on these measures both during baseline and during the less intense (1% and 3% CO2) biologic provocations. With 5% C02 and HV, however, the PDs showed clear evidence of diverging psychologically from the controls. The PDs showed significant elevations in their already elevated sensations and cognitions scores whereas the controls showed no change from earlier levels. These observations are supportive of the fear of fear model of anxiety disorders (Chambless & Gracely, 1989) and need to be integrated into psychobiologic formulations (Rapee & Barlow, 1989) of Panic Disorder.

In conclusion, the findings of the present research are congruent with the rapprochement that is taking place

between biologic and psychologic formulations of Panic Disorder. While medical researchers are becoming more cognizant of the role of psychological variables (e.g., Yeragani, Poh, Balon, Weinberg, Berchou, & Rainey, 1987) and hyperventilation (Gorman, Goetz, Uy, Ross, Martinez, Fyer, Liebowitz, & Klein, 1988) in determining the panic response to biological challenges, psychological theorists have found it valuable to include the biophysiology of HV as an important component in their models of panic (e.g., Salkovskis, 1988). Salkovskis' model best exemplifies this approach. Individual differences in hyperventilatory responsiveness to stress are seen as a predisposing factor for panic, and low blood CO2, low bicarbonate, and the influence of hormones upon respiration are viewed as important moderators of the HV-induced physical symptoms associated with panic. The findings of the present study are consistent with this model and support the further study of hyperventilation-proneness in Panic Disorder.

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Appendix A

Research Participation Consent Form

Department of Psychology
University of Calgary

Name: _____

CONSENT FOR PARTICIPATION IN THE AGORAPHOBIA RESEARCH PROJECT
TO BE COMPLETED PRIOR TO PERFORMING ANY PROCEDURES ON THE ABOVE INDIVIDUAL

Procedure

The procedure involves completion of a set of questionnaires and an interview regarding the symptoms of agoraphobia, and the self-monitoring of daily activities relating to phobias and anxiety levels. A medical examination by a specialist in Internal Medicine will be carried out. Several physiological measures will be taken by a Pulmonary Function Technician. These measures will include a sample of venous blood, monitoring of the gas composition of expired air after brief voluntary hyperventilation, and measurement of breathing rates and volumes during inhalation of a series of three carbon dioxide-oxygen mistures. A clinical psychologist will be present at all times and will, if necessary, verbally administer relaxed breathing instructions to any person who experiences anxiety after brief hyperventilation. Instruction in the use of behavioral procedures for controlling agoraphobia will also be given as part of this study.

I, the undersigned, have had the above procedures explained to me. I understand that if I choose not to participate in this research project, other treatment options for my agoraphobia will be made available to me. I understant fully the nature of the project, and hereby agree to participate. I understand that I may withdraw from the project at any time.

_____
Signature of the individual

_____
Date

_____
Witness

I, _____, hereby certify that I have explained the above procedures to _____.
Name of individual

Appendix B

Subjective Anxiety Rating Scale, modified Agoraphobic Cognitions Questionnaire, modified Body Sensations Questionnaire

HOW ANXIOUS OR PANICKY ARE YOU RIGHT NOW ?

Pick a number from the scale below :

0	2	4	6	8	10
Completely Relaxed, Sleepy	Alert, Normal	Mild Anxiety	Moderate Anxiety	Severe Anxiety	Full-Blown Panic Attack

FOR EACH THOUGH LISTED BELOW, CHOOSE A NUMBER FROM THE SCALE TO INDICATE HOW PERSISTENT THE THOUGHT WAS DURING THE LAST PROCEDURE:

0	2	4	6	8	10
Not Present	Flashed Briefly in mind	Slightly Persistent	Moderately Persistent	Severely Persistent	Extremely Persistent

_____ I AM GOING TO THROW UP
_____ I AM GOING TO PASS OUT
_____ I MUST HAVE A BRAIN TUMOR
_____ I WILL HAVE A HEART ATTACK
_____ I WILL CHOKE TO DEATH
_____ I AM GOING TO ACT FOOLISH
_____ I AM GOING BLIND
_____ I WILL NOT BE ABLE TO CONTROL MYSELF
_____ I WILL HURT SOMEONE
_____ I AM GOING TO HAVE A STROKE
_____ I AM GOING TO GO CRAZY
_____ I AM GOING TO SCREAM
_____ I AM GOING TO BABBLE OR TALK FUNNY
_____ I WILL BE PARALYZED BY FEAR

NOW LIST AND DESCRIBE ANY OTHER FRIGHTENING THOUGHTS THAT YOU HAD DURING THE LAST TEST: (and give a rating from the scale above):

_____ _____
_____ _____

FOR EACH SYMPTOM LISTED BELOW, CHOOSE A NUMBER FROM THE SCALE TO INDICATE HOW INTENSE THE SYMPTOM WAS DURING THE LAST PROCEDURE:

0	2	4	6	8	10
Not at all	Slight Symptom	Mild Symptom	Moderate Symptom	Severe Symptom	Extreme Symptom

_____ HEART PALPITATIONS
_____ FEELING SHORT OF BREATH
_____ PRESSURE OR HEAVY FEELING IN THE CHEST
_____ NUMBNESS IN ARMS OR LEGS
_____ NUMBNESS IN ANOTHER PART OF YOUR BODY
_____ TINGLING IN THE FINGERTIPS
_____ DIZZINESS
_____ BLURRED OR DISTORTED VISION
_____ NAUSEA
_____ HAVING "BUTTERFLIES" IN YOUR STOMACH
_____ FEELING A KNOT IN YOUR STOMACH
_____ HAVING A LUMP IN YOUR THROAT
_____ WOBBLY OR RUBBER LEGS
_____ SWEATING
_____ A DRY THROAT
_____ FEELING DISORIENTED AND CONFUSED
_____ FEELING DISCONNECTED FROM YOUR BODY (PARTLY PRESENT)
_____ CHOKING OR SMOTHERING SENSATION
_____ FEEL INCREASED NEED TO URINATE
_____ TREMBLING OR SHAKING
_____ HOT AND COLD FLASHES
_____ BODY FEELS GENERALLY WEAK

OTHER SYMPTOMS: (DESCRIBE AND RATE): _____ ____