HYPERVERVENTILATION AND PANIC DISORDER: A PSYCHOPHYSIOLOGICAL CONNECTION

Jürgen Margraf
Department of Psychology, Free University of Berlin, Germany

Abstract — Hyperventilation is probably the most frequently discussed correlate of panic attacks. Although some authors see it as the main or even unique cause of panic attacks, there have been numerous reviews with contradictory conclusions. Recent research, however, provides some more clarity. After a short overview of the characteristics of hyperventilation, the present article discusses (1) indirect measures of the overlap between panic and hyperventilation, (2) direct measures of hyperventilation at rest and during naturally occurring panic, (3) the influence of cognitive variables, and (4) the major theories attempting to explain the relationship between hyperventilation and panic. The results indicate a substantial overlap between panic and hyperventilation, but by far no one-to-one relationship and no chronic hyperventilation in panic patients if anticipatory anxiety is ruled out. In addition, cognitive studies firmly support the relevance of perceptive and associative processes. Theories that consider hyperventilation as a necessary or sufficient condition for panic attacks are clearly discarded by the imperfect relationship between the two phenomena. The central chemoreceptor sensitivity theory of panic is consistent with the physiologic effects of both hyperventilation and CO₂ inhalation but has to face inconsistent results on ventilatory characteristics of panic patients. Furthermore, it can neither explain the weak responses to hyperventilation or CO₂ in some panic patients nor the influence of cognitive variables. Only a psychophysiological theory that takes cognitive, conditioning and physiologic factors into account is consistent with the total body of research accumulated to date. According to this approach, hyperventilation is related to panic in two ways: First, it is one of many processes that can lead to the perception of bodily sensations which may trigger positive feedback loops between sensations and anxiety responses. Second, because of the circular nature of such feedback processes, hyperventilation can also be a response to anxiety. In conclusion, hyperventilation is not uniquely relevant for panic, but the degree of overlap between the two phenomena gives it a prominent role as a trigger for panic and a vehicle for successful psychological treatment.

INTRODUCTION

In spite of the flood of publications following the introduction of panic disorder as a separate diagnostic category in DSM-III (American Psychiatric Association, 1980), the etiology of panic attacks remains controversial. A particularly intriguing problem for researchers and clinicians alike is the apparent "spontaneity" of many attacks. Most patients
insist that at least some of their attacks come “out of the blue” without any danger or sufficient reason to panic. This fact has posed a major challenge to basic research and clinical management. An important strategy in trying to respond to this challenge has been to investigate correlates of “spontaneous” panic attacks. Probably the most frequently discussed correlate is hyperventilation. Some authors go as far as to suggest that panic attacks are entirely due to hyperventilation and, accordingly, prefer the diagnostic label “hyperventilation syndrome” over “panic disorder” (cf. Lum, 1981; Magarian, 1982; Ley, 1985a, 1987). Over the years, numerous reviews of the overlap between hyperventilation and anxiety or emotional disorders have appeared, usually quite sympathetic to the idea of a causal relationship (e.g., Lum, 1976, 1981; Dalessio, 1978; Missri & Alexander, 1978; Magarian, 1982; Brashear, 1983; Grossman, 1983; Bass & Gardner, 1985b) although some critical views were also expressed (e.g., Dent et al., 1983). More specifically, a number of authors have addressed the specific relationship between hyperventilation and panic disorder (e.g., Hibbert, 1984; Bass, Kartsounis, & Lelliott, 1987; Bass & Lelliott, 1989; Cowley & Roy-Byrne, 1987, 1989; Gorman & Papp, 1990). If one compares the frequently contradictory conclusions of the publications quoted above, one is led to the impression that many of the central questions about the relationship of panic disorder and hyperventilation are unresolved and no general consensus has been reached. The purpose of the present article is to show that recent research allows some more definite conclusions. Specifically, the following issues will be discussed in the light of recent research:

1. Indirect measures of the overlap between hyperventilation and panic.
2. Direct measures of hyperventilation at rest and during naturally occurring panic.
3. Cognitive variables and hyperventilation.

The review of these topics provides a firm basis for an evaluation of some of the major theories currently proposed to explain the relationship between panic and hyperventilation. These theories place different emphasis on physiological processes such as respiratory alcalosis or central chemoreceptor sensitivity and on psychological processes such as the interpretation of the bodily sensations produced by hyperventilation. It will be argued that only a psychophysiological approach is consistent with the total body of research accumulated to date. The central assumption of psychophysiological models of panic is that seemingly “spontaneous” panic attacks result from a positive feedback loop between bodily sensations, their perception and association with danger and the resulting anxiety which in turn influences sensations, perception, and associative processes
(Ehlers & Margraf, 1989). According to this approach, hyperventilation is related to panic in two ways: First, it is one of many processes that can lead to the perception of bodily sensations which may serve as triggers for positive feedback loops. Second, because of the circular nature of such feedback processes, hyperventilation can also be a response to anxiety. Before beginning with the review of findings and theories that will substantiate this conclusion, however, a short overview of the characteristics of hyperventilation is in place.

DEFINITION AND CLINICAL CHARACTERISTICS OF HYPERVENTILATION

Hyperventilation can be defined as a degree of respiration that exceeds metabolic demands. It can be easily overlooked in oneself or others. Although respiration rate can be readily counted this is only one of several determinants of ventilation. Another important determinant is the depth of breathing. Because of differences in body constitution the depth of breathing cannot simply be detected by observation of chest movements. In addition, hyperventilation depends on other factors that exert their influences over periods of time longer than single breaths. Even if the amount of ventilation exceeds metabolic demands only slightly, the effects of excessive breathing can be accumulated over minutes or hours. In the same vein, Okel & Hurst (1961) and Salzman, Heyman, and Sieker (1963) have shown that once hyperventilation is established, a few deep breaths per hour are enough to maintain this state. The most reliable and important measure of hyperventilation is therefore not respiration rate or minute volume but rather the partial pressure of carbon dioxide (pCO₂) in the arterial blood. In healthy humans, the arterial pCO₂ can be inferred from the pCO₂ at the end of expiration (endtidal pCO₂) with sufficient certainty. Normal values of pCO₂ vary around 40 mm Hg. The partial pressure of oxygen is of little interest because the symptoms of hyperventilation are related to the fall in pCO₂ and the rise in blood pH that this entails.

The symptoms of hyperventilation are quite diverse. Prominent are dizziness and lightheadedness which the patients often describe as vertigo (however, this is not the neurologic rotatory or vestibular vertigo). Paresthesias are frequent whereas tetany (tonic stiffness of the muscles in hands and feet, twitching of the facial muscles, tremor of the fingers) is relatively rare. Cardiovascular changes regularly occur and often have subjectively noticeable consequences such as palpitations, sweating, hot flushes or chest pain. Frequent psychic symptoms are anxiety, nervousness and derealization. It is not surprising, then, that the "total clinical picture appears to be a composite of symptoms produced not only by the
physiologic derangements caused by hyperventilation itself but often more prominently by underlying anxiety" (Missri & Alexander, 1978, p. 2093). The physiologic mechanisms that produce the symptoms of hyperventilation are a still uncertain combination of the direct effects of alkalosis on the excitability of nerves and muscles, a pH-dependent fall in blood calcium ions and (primarily cerebral) vasoconstriction (Missri & Alexander, 1978; Magarian, 1982). Maddock and Mateo-Bermudez (1990) recently showed that hyperventilation elevates serum lactate but found no correlation of this effect with the anxiety produced by hyperventilation. A substantial attenuation of vagal tone was reported by George, Nutt, Walker, Porges, Adinoff, and Linnoila (1989).

For many authors, hyperventilation can be more than a physiologic abnormality. Proponents of this approach see hyperventilation as the core element of an independent syndrome that may cause massive disability. According to Magarian (1982), the hypothesis that the symptoms of what used to be called DaCosta syndrome were due to hyperventilation was first published by Goldman (1922). Patients such as the ones described by DaCosta (1871) still find their way to cardiologists. Evans and Lum (1977) argued that hyperventilation is an important cause of "pseudoangina". They observed that physiotherapy aimed at restoring normal breathing patterns dramatically reduced these patients' complaints. Bass et al. (1983) studied 99 patients who had been referred for coronary arteriography because of angina-like chest pain. Almost two thirds of the 46 patients without significant coronary pathology reported symptoms of hyperventilation in combination with lowered endtidal pCO₂ and heightened anxiety as compared to patients with coronary pathology. The term hyperventilation syndrome (HVS) was probably coined by Kerr, Dalton, and Gliebe (1937) who also introduced a brief period of voluntary hyperventilation as a diagnostic test ("hyperventilation test") for the syndrome. HVS is conceived as a psychosomatic disorder that affects a large proportion of the patients seen in somatic medicine as well as in clinical psychology and psychiatry (e.g., Lum, 1976, 1981; Magarian, 1982). The syndrome may manifest itself in recurrent acute attacks or in chronic, but usually milder symptoms. The psychic symptoms of HVS are more or less those of panic disorder and even the subsequent development of phobias has been described (Lazarus & Kostan, 1969). Estimates of the prevalence of HVS range from about 6% of outpatients with gastrointestinal or cardiovascular complaints to over 10% of the patients in general medicine. For the latter group even higher estimates have been published (see Magarian, 1982; Brashear, 1983). These estimates are hampered, however, by the uncertainty that surrounds the diagnosis of HVS (Bass et al., 1987). Grossman and de Swart (1984) have shown that the diagnosis solely on the basis of reported complaints is not
reliable. In the same vein, the hyperventilation test has recently been criticized (Hibbert & Pilsbury, 1989) for yielding a large proportion of false positive as well as false negative results. This diagnostic uncertainty makes all statements about the syndrome preliminary. In the present article, hyperventilation is not seen as an independent syndrome. Instead, hyperventilation is regarded as a physiologic mechanism and a behavioral habit whose relationship to panic disorder as a diagnostic entity will be reviewed.

INDIRECT MEASURES OF THE OVERLAP BETWEEN HYPERVENTILATION AND PANIC

Studies of the relationship between panic disorder and hyperventilation have typically relied on indirect measures of hyperventilation as these were relatively easy to obtain and quite unobtrusive compared to, for instance, arterial blood samples. Most frequently investigated were the following four phenomena: (1) the degree of overlap in the symptoms of the two conditions, (2) the anxiety responses to voluntarily induced hyperventilation, (3) the effects of anxiety or stress on respiratory variables, and (4) the effects of supposedly “respiratory” treatments on the patients’ wellbeing. The results of these studies are reviewed in this section.

Respiratory symptoms are among the most frequent and distressing symptoms of panic attacks (Barlow, Vermilyea, Blanchard, Vermilyea, Di Nardo, & Cerny, 1985; Margraf, Taylor, Ehlers, Roth, & Agras, 1987). This appears to be the case across different cultures although some transcultural variation has been found. Based on the data of the Upjohn Cross National Study, Katschnig and Amering (1990) reported that choking or smothering sensations are more prevalent in Latin America and Southern Europe compared to North America and Northern Europe. Interestingly, these authors obtained similar results for fear of dying which apparently was highly correlated with choking or smothering sensations. Garssen, van Veenendaal, and Bloemink, (1983) and Pollard (1986) found that the majority of agoraphobic patients show symptomatic overlap with hyperventilation and that over 60% of these patients rate the effects of voluntary hyperventilation as similar to their naturally occurring panic attacks. Taking the opposite approach, Bass and Gardner (1985a; see also Gardner, Meah, & Bass, 1986) found that most chronic hyperventilators (defined by pCO₂ under 30 mm Hg) are somatically healthy, but that many suffer from psychological disorders (primarily emotional or somatoform disorders). However, eleven out of their 21 patients showed no psychiatric morbidity. In the same vein, Hoes, Colla, van Doorn, Folgering and de Swart (1987) reported a seven times higher prevalence of panic
disorder in hyperventilators compared to non-hyperventilators but even the 35% prevalence found in the hyperventilators was far from the 100% relationship claimed by some authors.

Perhaps the most frequently used approach has been to study the effects of voluntary hyperventilation. As early as 1937 Kerr et al. advocated this as a diagnostic test for what they termed hyperventilation syndrome. Depending on the criteria used, the proportion of panic patients that report panic attacks as a consequence of such a test (usually 2–3 min duration) ranges from 18 to 82%, with most studies yielding values from 25 to 50% (Garssen et al., 1983; Gorman et al., 1984, 1988a; Rapee, 1986; Bass, Lelliott, & Marks, 1989; Holt & Andrews, 1989; Lakatos, Margraf, Lutz-Tappeser, & Zapotoczky, 1989; Brown, Rapee, Antony, & Barlow, 1990; Craske & Barlow, 1990; Maddock & Mateo-Bermudez, 1990; Rapee, Brown, Antony, & Barlow, 1990; Margraf, Ehlers, Herber, Meisner, & Wrobel, 1991). Patients with other anxiety disorders typically reported a lower proportion of panic attacks or a smaller subjective anxiety response, but still higher values than normal controls (Rapee, 1986; Gorman et al., 1988a; Holt & Andrews, 1989; Lakatos et al., 1989; Rapee et al., 1990; Margraf et al., 1991). However, in all of these studies hyperventilation produced at least some anxiety even in normal control subjects, a finding that has also been reported by Thyer, Papsdorf, and Wright (1984). In several studies the hyperventilation test was compared to prolonged CO₂ inhalation which typically resulted in higher proportions of “panicking” patients (Gorman et al., 1984, 1988a; Craske & Barlow, 1990; Holt & Andrews, 1989; Brown et al., 1990; Rapee et al., 1990). Nocturnal panickers and patients who only experienced daytime panic attacks did not differ with respect to respiratory measures or response to hyperventilation or prolonged CO₂ inhalation (Craske & Barlow, 1990). In contrast to the results on subjective measures reported so far, physiological differences between the responses of panic patients and clinical or normal control subjects to hyperventilation were typically absent (Gorman et al., 1984, 1988a; Rapee et al., 1990; Margraf et al., 1991). In an excellent study, Holt and Andrews (1989) analyzed the responses to hyperventilation in greater detail. They found few differences between panic/agoraphobic patients and patients with other anxiety disorders with respect to measures of somatic and psychic anxiety. The only prominent difference was that hyperventilation produced more fear of impending doom in panic and agoraphobia patients than in social phobics, patients with generalized anxiety disorder or normals. It is important to note that even if panic patients show a stronger subjective response to hyperventilation, this does not necessarily identify hyperventilation as a cause of panic. For instance, it is also possible that panic patients have become sensitized to the sensations produced
by hyperventilation by their panic attacks. If this interpretation were true, then persons who have the vulnerability for panic but have so far experienced only few attacks should not show specific responses. In the study quoted above, we compared such “non-clinical panickers” with persons with social fears that were also recruited from a non-clinical population by means of screening questionnaires (Margraf et al., 1991). At least in this study, there were no significant differences in the subjective and cardiovascular responses of non-clinical subjects with panic attacks or with social fears.

Even before interest in panic disorder arose, a number of studies had shown that hyperventilation is a common response to stress or anxiety-provoking stimuli (Dudley, Martin, & Holmes, 1964; Garssen, 1980; Suess, Alexander, Smith, Sweeney, & Marion, 1980; cf. Bass & Gardner, 1985a). More specifically with respect to panic, Salkovskis, Clark, and Jones (1984) reported on four patients who responded with hyperventilation to panic prone situations. However, such case reports cannot be generalized as was recently shown by Bass et al. (1989). These authors induced panic attacks by “fear talk” (imagery of feared situations) and found that such panics were only rarely associated with marked physiological (and respiratory) changes. Moreover, the pCO₂-responses to fear talk were similar in panic patients and normal controls.

The notion that hyperventilation was responsible for the problems of many anxious patients led to early therapeutic attempts with “respiratory” treatments. If patients were breathing faultily, they should benefit from correcting this bad “habit” (Rice, 1950; Lum, 1976, 1981). Reports such as the one by Lum (1981) who claimed that twelve months after breathing therapy 75% of his over 1000 patients were symptom free and another 20% were left with occasional untroubling symptoms have to be regarded with caution because of the lack of research design and control groups (Bass et al., 1987). However, a number of more systematic studies reported less overwhelming but still substantial therapeutic successes with such treatment approaches in more or less well defined groups of panic disorder patients (Lum, 1981; Bonn, Readhead, & Timmons, 1984; Grossman, & de Swart, 1984; Clark, Salkovskis, & Chalkley, 1985; Rapee, 1985; Salkovskis, Jones, & Clark, 1986a; de Beurs, Van Dyck, & Koele, 1990). No effect of breathing retraining in reducing panic frequency and no difference compared to exposure treatment was reported by de Ruiter et al. (1989a, b) in agoraphobic patients. However, this study obtained overall untypically low levels of success even with exposure treatment. Together with the very short duration of therapy this casts doubt on the validity of the treatment application. In general, the effectiveness of “breathing-related” treatments is well established by the studies quoted above. Nevertheless, severe doubts remain about...
the degree to which they support the notion of a causal relationship between hyperventilation and panic. The treatments typically involved more components than simple breathing retraining. Giving the patients the hyperventilation rationale in my own experience already constitutes a simple but often powerful cognitive intervention. In addition, some studies combined breathing techniques with exposure or relaxation methods. Most studies did not collect measures of respiration. Of the two studies that did, one reported normalization of pCO₂ with treatment (Salkovskis et al., 1986a) while the other did not find such an effect (de Ruiter et al., 1989a,b). Thus, it is unclear whether the therapeutic success was in fact related to changes in respiratory functioning. On the other hand, de Ruiter et al. (1989) may not have found changes in pCO₂ because of the overall low efficacy of their treatments. Data from drug treatments provide some additional support for changes in respiratory parameters with successful therapy. Gorman et al. (1985, 1986b) found that all items of their Acute Panic Inventory (a symptom questionnaire containing sensations frequently associated with panic attacks) that could be related to hyperventilation as well as venous pCO₂, pH and bicarbonate were normalized after successful drug treatment of panic. It is important to note, however, that what was normalized with respect to the physiological variables were primarily the variances and not the means which were often normal even before treatment.

Taken together, results from the four research strategies reviewed in this section show that hyperventilation is not only a common response to stress or anxiety-provoking stimuli but that panic patients may show this response more than normal controls when confronted with certain stimuli (e.g., lactate infusion). In conclusion, there is significant overlap between panic and hyperventilation, but this is by far not a one-to-one relationship. In spite of the very clear-cut overlap, it is an important observation that many panic patients do not exhibit more hyperventilation symptoms or a stronger anxiety response to voluntary hyperventilation than control subjects and that many patients with established symptomatic hyperventilation do not suffer from panic attacks. While the methods employed in the studies reviewed here have produced some important findings, they can be criticized because they yielded only indirect information about hyperventilation. Thus, even if there is overlap in symptom ratings, perceived similarity between the effects of hyperventilation and panic attacks, or reduction of panic attacks with “breathing therapy”, this does not prove that hyperventilation really does occur during panic attacks. Their results therefore have to be validated by looking at direct measures of hyperventilation.
DIRECT MEASURES OF HYPERVENTILATION AT REST AND DURING NATURALLY OCCURRING PANIC

Studies using direct measures of hyperventilation such as pCO₂ and respiratory volume or rate have usually addressed (1) whether panic patients hyperventilate under resting conditions (often searching for signs of chronic hyperventilation) or (2) whether they do so during naturally occurring panic attacks.

With respect to the first question, a number of studies have reported indications of hyperventilation in panic patients. Compared to normal controls, Bonn et al. (1984) reported a higher respiration rate in agoraphobics and Salkovskis et al. (1986a) found lower pCO₂ resting values in panic patients who had rated the effects of an HV test as similar to their naturally occurring panic attacks. In the same vein, Bass et al. (1989) reported lower pCO₂ in agoraphobics (but no difference in respiration rate). Rapee (1986) found lower resting pCO₂ in panic patients compared to patients with generalized anxiety disorder (but no differences in resting minute volume). A relatively normal pCO₂ level of 37 mm Hg was found in a sample of agoraphobics studied by de Ruiter et al. (1989a,b). Unfortunately, this study did not include a control group. In the same vein, Roth et al. (1992) found no respiration rate or minute volume differences between panic patients and controls or between patients who did or did not “panic” in response to prolonged CO₂ inhalation. Biddle, Tiller, and Pain (submitted), on the other hand obtained similar values for resting pCO₂ and respiration rate in panic patients and normal controls, but higher tidal and minute volumes in the patients. A higher tidal volume and lower pCO₂ in panic patients were also found by Gorman et al. (1988b) who interpreted their results as signs of chronic hyperventilation. Gorman et al. (1986a) identified a group of questionnaire items that were responsive to lactate-induced “panic” and were normalized after successful drug treatment. All of these items turned out to be hyperventilation symptoms. In two other studies, Gorman, Liebowitz, Fyer, Fyer, and Klein (1986b) using venous bloods and Papp et al. (1989) using arterial bloods found low pCO₂ and high pH in those panic patients that subsequently “panicked” in response to lactate infusion. These findings were interpreted as chronic respiratory alkalosis in the venous study, but acute HV in the more recent arterial study. The authors speculated that maybe some degree of acute baseline HV is necessary for lactate-induced panic to occur. In both studies, lactate induced panic was accompanied by acute hyperventilation. Interestingly, even non-panicking patients hyperventilated more than normal controls. Studies of laboratory models of panic such as lactate infusion, however,
may have limited validity (Margraf, Ehlers, & Roth, 1986a) and therefore have to be validated by studies of naturally occurring panic attacks.

In looking at these results, two problems emerge. First, the findings are quite inconsistent with respect to the exact nature of the respiratory parameters affected. Thus, in some studies differences were obtained for respiration rate, but in others for respiratory volume or pCO₂. Most consistent was the result of lowered pCO₂. Second, most of the studies collected their respiratory data in subjects that were about to undergo some kind of stressor or panic provocation procedure (e.g., lactate infusion, hyperventilation test or exposure treatment). Since subjects were aware of the procedures and their possible panicogenic consequences, it is possible that the group differences do not represent trait differences, but reflect a transient anticipatory response to the test. Panic patients may show a larger anticipatory response to panic induction procedures than controls. In order to determine whether the effects observed so far represent chronic hyperventilation it is necessary to study patients without the threat of anything more unpleasant than having to give an arterial blood sample. Margraf (1989) studied 60 inpatients of a psychosomatic hospital who were diagnosed as having either panic disorder, depression, or bronchial asthma. Blood gases were measured during the first week after admission. In contrast to previous studies, patients did not anticipate any stress tests when the blood samples were taken. Other possible confounds such as room temperature, air pressure, time of day, age, and sex were controlled. The results showed no differences between the groups for partial pressures of oxygen and carbon dioxide, pH and base excess. The means of all groups were in the normal range. Thus, if the influence of anticipatory anxiety is ruled out, there is no support for the hypothesis of chronic hyperventilation in panic disorder. The interpretation of the hyperventilation obtained in the earlier studies as an anticipatory response is supported by the fact that the patients in these studies typically also showed heightened baseline anxiety and cardiovascular arousal (e.g., higher heart rate in Rapee’s 1986 study).

Perhaps most interesting of all the questions about the overlap between panic and hyperventilation is whether naturally occurring panic attacks are accompanied by measurable respiratory changes. In two early case reports of adventitiously recorded panic attacks, Griez, Pols, and van den Hout (1987) and Salkovskis, Warwick, Clark, and Wessels (1986b) observed substantial pCO₂ changes. However, such adventitious recordings may represent a biased selection of panic attacks. Systematically gathered data from ambulatory monitoring are therefore more reliable. With the advent of ambulatory monitoring equipment for transcutaneous pCO₂ (tpCO₂) measurement, such studies have become feasible as was first demonstrated by Hibbert (1986). In his case series of eight normals and
two panic patients, panic attacks were accompanied by tpCO₂ changes. In
two subsequent publications, however, Hibbert and Pilsbury (1988, 1989)
found that only some and by far not all panic attacks were accompanied
by changes in tpCO₂. Moreover, Hibbert and Pilsbury (1988) showed that
agoraphobic patients may be "positive" on the hyperventilation test but
have no ambulant tpCO₂ changes during their panic attacks, while others
may reveal such tpCO₂ changes but be "negative" on the hyperventilation
test. These results demonstrate a lack of validity of "traditional" methods
for identifying hyperventilators. In their largest study, Hibbert and
Pilsbury (1989) employed ambulatory tpCO₂ monitoring in fifteen panic
patients. All but one patient reported breathlessness during panic, but only
7 patients were hyperventilators as defined by abnormal falls in tpCO₂. In
these cases as well as in three of the remaining eight patients the panic
attacks occurred at the time of the maximum fall in tpCO₂. For the otherive patients there was no correspondence between maximum falls and
panic attacks. The comparison with the data from ambulatory tpCO₂
monitoring casted severe doubts on the validity of the hyperventilation
test, because this test was unable to distinguish between ambulatorily
defined hyperventilators and non-hyperventilators. In fact, five patients
in each of the two groups had shown a "positive" response to this
test. Hyperventilators tended to have lower resting pCO₂ levels and
a slower recovery of pCO₂ after the hyperventilation test. While this
confirmed earlier assumptions it was surprising that hypocapnic subjects
were less psychiatrically disturbed than normocapnics. Hyperventilation
was neither associated with a particular cluster of symptoms nor acted as
an important component of all panic attacks. The authors concluded that
hyperventilation is better understood as a consequence rather than as a
cause of panic. Although this interpretation can and has been criticized
(Bass & Lelliott, 1989), the finding that clearly not all panic attacks are
accompanied by tpCO₂ changes is important and has been replicated by
an independent group of researchers. Buikhuisen and Garssen (1990)
studied seventeen panic patients using ambulatory tpCO₂ monitoring.
Eight of their patients had panic attacks during the recording period.
None of these panic attacks occurred with tpCO₂ changes. Thus, the
findings on direct measures of hyperventilation lend further support to
the conclusion drawn form the previous section: Hyperventilation and
panic attacks do not form a one-to-one relationship. In addition, it seems
highly questionable whether panic patients hyperventilate chronically (i.e.
without the anticipation of panic or stress).

COGNITIVE VARIABLES AND HYPERVENTILATION

The studies on the relationship between panic attacks and hyperventila-
tion reviewed so far leave it an open question whether hyperventilation induces anxiety automatically by some physiologic mechanism, or whether cognitive variables such as perception and appraisal of the symptoms induced by hyperventilation play a major role. In addition, experimental studies need to control possible cognitive confounds such as expectancy and demand characteristics (Orne, 1962). A number of findings support the notion that cognitions have a major influence on the relationship between hyperventilation and panic. Thus, the Anxiety Sensitivity Index (Reiss, Peterson, Gursky, & McNally, 1986), a questionnaire that attempts to measure the cognitive predisposition to interpret arousal as threatening, has been shown repeatedly to predict the response to hyperventilation in non-clinical populations including non-clinical panickers (Holloway & McNally, 1987; Donnell & McNally, 1989). As mentioned previously, Holt and Andrews (1989) recently showed that only catastrophic cognitions differentiate the responses of panic/agoraphobic patients to hyperventilation and CO₂ from those of other anxiety patients or normals. The idea that anxiety results from the cognitive processing of perceived hyperventilation symptoms is further consistent with the observation that in most panic patients breathlessness precedes fear rather than follows it (Ley, 1985b; Bass et al., 1989). In addition, the fact that anxious patients’ perceptions of inspiratory resistive loads are less sensitive than those of controls (Tiller, Pain, & Biddle, 1987) may make them more likely to misinterpret respiratory sensations. As with the other findings reviewed so far, these results do not apply to all subjects: Bass et al. (1989) observed that a subgroup of 30% of their agoraphobic patients reported breathlessness after fear. In any case, subjective reports of perceived sequences of events are far from being perfect psychometric measures and can only be taken as preliminary indications that require more rigorous experimental confirmation. Several such experiments have been conducted with normal volunteers.

Salkovskis and Clark (1990) manipulated the interpretation of the somatic sensations of hyperventilation. They gave their non-clinical subjects instructions that either described these sensations as being indications of risk of fainting or as signs of good adjustment and a higher state of consciousness. A subsequent hyperventilation test produced the same bodily sensations and physiological changes in both groups (heart rate, pCO₂), but the experience was rated as pleasant or unpleasant depending on the instruction. Moreover, the number of bodily sensations experienced correlated with positive affect when a positive interpretation was given and with negative affect when a negative interpretation had been induced. A few years earlier, van der Molen, van den Hout, Vroemen, Lousberg, and Griez (1986) and van der Molen and van den Hout (1988) had used the manipulation of instructions to show that the
expectation of anxiety due to lactate infusion not only leads to anxiety but also to increased respiration rate in normal controls, whereas the expectation of pleasant excitement leads to decreased respiration rate and prevents anxiety from occurring. Similarly, van den Hout and Griez (1982) had successfully altered the affective responses to two single breath inhalations of CO₂ in normal volunteers. Somewhat related is the finding that rebreathing to cope with hyperventilation has a large placebo component. Although rebreathing indeed normalizes alveolar CO₂ quicker, this is independent of its symptom reducing effect as was shown by van den Hout, Boek, van der Molen, Jansen, and Griez (1988). These authors used a rebreathing apparatus that was constructed in such a way that the experimenters could open it up without the subjects' knowledge. Subjects that were breathing through the covertly opened apparatus showed a slower normalization of alveolar CO₂ but equal symptom reduction as subjects who were really rebreathing. Taken together, these studies clearly show the relevance of cognitive variables in normal volunteers. Can these results be generalized to clinical patients with panic disorder?

In a recent study of the anxiogenic effects of prolonged CO₂-inhalation, we found that expectancy was an important mediating variable in panic disorder patients (Margraf, 1989). In this study, panic patients became anxious already when anticipating the CO₂-inhalation. The anticipatory anxiety was reflected in increases in self-report measures as well as in physiological measures of anxiety. In contrast, normal control subjects did not show an anxiety response while waiting for the CO₂-inhalation. The fact that patients show a specific anticipatory response is important in evaluating the findings of previous studies on hyperventilation. It can be assumed that all of these studies induced very negative expectations in patients because informed consent forms for legal reasons described the possible consequences of hyperventilation in a dramatic form. We studied the effects of hyperventilation in a series of three studies while attempting not to induce any specific expectation of panic (Margraf, 1989; Margraf et al., 1991). In this "neutral expectancy" condition, panic patients and non-clinical subjects with panic attacks showed stronger responses to hyperventilation (60 cycles/min for 2 min) than controls on self-report measures of discomfort, but not on physiological measures. However, subjects reported little similarity between the effects of voluntary hyperventilation and naturally occurring panic attacks. Since subjects with social fears showed responses similar to those of subjects with panic attacks, the specificity of the findings for panic disorder is questionable. The results indicate that in the absence of high anxiety expectancy, hyperventilation is not sufficient for the induction of panic or strong physiological responses in panic disorder patients.
In two further studies, conducted in collaboration with Drs Anke Ehlers, University of Göttingen and Walton T. Roth, Stanford University School of Medicine, the subjects’ anxiety expectancy was manipulated directly by giving different instructions (Margraf, 1989). In the first study, 48 panic patients and 48 controls participated in a hyperventilation test (30 cycles/min for 6 min). Half of the subjects received the instruction that the test was a “biological panic attack test” which was likely to induce panic attacks in vulnerable individuals (high anxiety expectancy). The other subjects were informed that the test was a “fast paced breathing” task which might temporarily induce some harmless symptoms (low anxiety expectancy). The results showed that panic patients were more affected by anxiety expectation. In the “biological panic attack test” condition, panic patients showed larger increases in self-report measures of anxiety and physiological arousal (heart rate, blood pressure, electrodermal activity) and more often terminated the hyperventilation early in contrast to controls in both conditions and patients in the “fast paced breathing” condition. More interesting than the patients’ larger response in the high anxiety expectancy condition, however, is the finding that patients showed similar responses as controls in the low anxiety expectancy condition. A simple cognitive experimental manipulation reduced the patients’ responses to the level shown by control subjects. All groups were exposed to the same physiological stressor because analyses of respiratory parameters showed identical increases in respiration rate and volume. Therefore, the differential physiological (and subjective) responses could not have been due to different degrees of hyperventilation, but must have been mediated by the subjects’ cognitions. It is important to note that controls were not “vulnerable” to the expectancy effects in this study. This could explain why in some studies using high anxiety expectancy instructions, reactivity differences between panic patients and controls to hyperventilation, CO₂-inhalations, sodium lactate infusions, or similar provocations were found.

A possible criticism of the above study is that expectancy effects were only shown for mild hyperventilation and less severely disturbed patients because the majority of patients had a diagnosis of panic disorder without agoraphobia. We therefore investigated the effects of differential instructions on the responses of patients with severe agoraphobia to pronounced hyperventilation (Margraf, 1989). For three minutes, patients had to hyperventilate at 60 cycles/min which is about the maximum frequency that can be maintained for more than a few breaths. Patients were 34 severely disabled agoraphobics with panic attacks who had all failed to complete a test walk through a shopping mall. Patients had to breathe through a modified spirometer ensuring a respiratory minute volume of 46 l/min. The results of this second experiment replicate the
importance of expectancy effects. Expectancy ratings confirmed that patients anticipated higher anxiety in the "biological panic attack test" condition than in the "fast paced breathing" condition. As in the first experiment, patients in the high anxiety expectancy condition showed stronger self-reported and physiological responses to the hyperventilation task. They also rated the effects of hyperventilation as being more similar to their naturally occurring panic attacks. Thus, the experiment replicated expectancy effects using extreme hyperventilation in severely disabled agoraphobics. Our results are in line with those of Sanderson et al. (1989) who found that the illusion of control attenuates the patients' anxiety response to CO₂-inhalation.

Additional indirect support for the role of cognitive variables comes from treatment studies. There are at least two studies now that show that cognitive-behavioral treatment reduces the rate of panic induced by hyperventilation or CO₂ (Brown et al., 1990; Göbel, Margraf, & Schneider, 1990). In both of these studies, interoceptive exposure had no specific effect on the response to the challenges, but end state functioning did. Subjects with high functioning after treatment responded much less to hyperventilation or CO₂ than did subjects with low functioning. Overall, the studies reviewed in this section very clearly show that the anxiety response to hyperventilation is mediated by cognitive variables. Differences in the responses of panic patients and controls disappear with adequate cognitive interventions. The specific vulnerability that panic patients have is most likely a stronger response to the expectation of anxiety and not an enduring physiological characteristic. These results have direct implications for our understanding of the relationship between hyperventilation and panic. In the following section I will discuss the most important theories that have been proposed to account for this relationship in the light of the empirical support they received.

THEORIES OF HYPERVENTILATION INDUCED PANIC

Hyperventilation produces symptoms in both normal volunteers and in panic patients. Before we discuss the possible explanation of the differences between patients and controls we therefore need to address the common physiological mechanism that underlies hyperventilation symptoms. In the past, many authors assumed that hypocapnia and alcalosis represent the physiologic mechanism by which the symptoms typical for panic attacks, hyperventilation and CO₂ are generated (cf. Bass et al., 1987). This hypothesis is consistent with the data from studies of voluntary hyperventilation and single breath inhalations of CO₂. As was shown by van den Hout and Griez (1985), one or two breaths of a mixture of 35% CO₂ and 65% O₂ produce only a transient hypercapnia that is
rapidly followed by a hypocapnic overshoot. However, these authors also noticed that the strongest anxiety was reported before this overshoot had occurred. Moreover, the typical hyperventilation and panic symptoms are also produced by inhalation of a mixture of 5% CO₂ and air over 10–20 min (Gorman et al., 1984, 1988a; Ehlers, Margraf, & Roth, 1988a; Roth et al., 1992). This mixture leads to a stable hypercapnia and acidosis. It seems, thus, that it is not alcalosis per se but any sufficiently strong and fast deviance in acid–base balance independent of the direction of change that is the relevant physiologic correlate of the symptoms of hyperventilation or CO₂-inhalation (Margraf, 1987). What theories have been proposed to account for the differences between panic patients and control subjects?

Theories that consider hyperventilation as a necessary or sufficient condition for panic attacks (e.g., Lum, 1981; Magarian, 1982; Ley, 1985a) are clearly discarded by the imperfect relationship between the two phenomena reviewed in the previous sections. These theories will therefore not be discussed here. Among the remaining theories, the two most important groups of approaches will be called here the central chemoreceptor sensitivity theory and the cognitive psychophysiological theory. Proponents of the first theory attempt to explain the often observed greater responsivity of panic patients to respiratory challenges as well as their stronger respiratory responses to other experimental panic induction procedures more or less exclusively by an assumed physiologic abnormality located in the brain stem areas that control respiration. Probably the first to propose greater sensitivity of the respiratory system in patients with the hyperventilation syndrome was Garssen (1980). Later, this notion was given two different concrete forms by Carr and Sheehan (1984), Gorman et al. (1986b, 1988a), Gorman, Liebowitz, Fyer, and Stein (1989) and Gorman and Papp (1990). Carr and Sheehan (1984) speculated that panic attacks result from acute decreases of intraneuronal pH in the brain stem. In their formulation of a “metabolic cause” of panic, the sensitivity is not due to increases in the concentration of CO₂ but rather of hydrogen ion. Panic is a consequence of a shift in the intraneuronal redox state that depends on the ratio of reduced to oxidized NAD which is proportional to the ratio of pyruvate reduced to lactate. While this model is consistent with the physiologic features of CO₂ inhalation and lactate infusion, it is less adequate for hyperventilation, because this challenge actually decreases the concentration of hydrogen ions.

More consistent with the hyperventilation data is the formulation by Gorman et al. (1986b). They assume that panic patients are hypersensitive to CO₂. Although there are also peripheral arterial and intrapulmonary chemoreceptors, they locate the assumed abnormality in the central
chemoreceptors situated in medullary brain stem centers. "Relatively low concentrations of CO₂ would trigger these centers to induce hyperventilation and other autonomic changes. Overwhelming the system with CO₂ produces such autonomic unrest that panic is provoked. In order to avoid triggering these hypersensitive receptors, patients with panic disorder chronically hyperventilate, thereby maintaining CO₂ concentration as low as possible. Medications that block panic may work directly on the hypersensitive chemoreceptors to normalize their reactions. This would obviate the need for hyperventilation as an adaptive response. While hyperventilation is not the cause of panic according to this theory, abnormal respiratory physiology assumes a place of critical importance." (Gorman et al., 1986b, p.800). The authors later stated that they consider the assumed central chemoreceptor hypersensitivity to be inherited and specified a second physiologic mechanism: "An additional potential mechanism is that the low CO₂ level maintained by chronic hyperventilation further sensitizes these CO₂ receptors according to a deafferentation hypersensitivity model. Blunting the exaggerated ventilatory response, either by antipanic drugs, which may reregulate the CO₂ receptors, or behavioral intervention, which teaches the patient not to overbreathe, could have the effect of blocking the full-blown attack" (Gorman & Papp, 1990, p.200).

This formulation of the chemoreceptor sensitivity theory is consistent with the physiologic effects of both hyperventilation and CO₂ inhalation. Support for the notion of hypersensitive chemoreceptors comes from the observation that patients who "panic" in response to 5% CO₂ inhalation show a more rapid increase in minute volume and inspiratory drive (defined as tidal volume divided by time in inspiration) than do non-panicking patients or normal control subjects (Gorman et al., 1988a). Furthermore, there is a circadian variation of chemosensitivity with minimal sensitivity at 5 a.m. (Raschke & Möller, 1988). This corresponds well to the circadian pattern in the occurrence of panic attacks that we recently reported (Margraf, 1990; Becker, Margraf, & Schneider, in press). On the other hand, Woods, Charney, Loke, Goodman, Redmond, and Heninger (1986), using the modified Read rebreathing method (Read, 1967) found no indication of heightened chemosensitivity in panic patients. The fact that Woods et al. measured the ventilatory response to CO₂ at levels between 5 and 9%, has led Gorman and Papp (1990, see also Gorman et al., 1990) to speculate that CO₂ hypersensitivity can only be found with lower CO₂ levels. Further doubts, however, are raised by the fact that in two other studies ventilatory responses to CO₂ were either normal or even less sensitive in patients with panic disorder (Biddle et al., submitted) or hyperventilation syndrome (Singh, 1984). Moreover, Biddle et al. (submitted) found no correlation between anxiety and
ventilatory responses and no panic attacks in response to inhalation of 6.9% CO₂ for four minutes (their instructions explained symptoms and did not create panic expectancy). In fact, there were negative correlations between anxiety measures and pCO₂ in panic patients.

In addition to the points already raised, there are several major problems with the central chemoreceptor sensitivity theory. First, as discussed in the previous sections of this article, there is no indication of chronic hyperventilation in panic patients if anticipatory anxiety is ruled out. Second, it cannot explain why not all panic patients show strong responses to hyperventilation or CO₂. Most importantly, however, it cannot explain the results of the studies that cognitively manipulated the response to these challenges. If there were indeed a lasting, inherited hypersensitivity in panic patients, then different expectations or the illusion of control should make no difference. As we have seen in the previous section on cognitive variables, these exert a strong influence on the responses to hyperventilation or CO₂. A valid theory has to be able to incorporate these findings and it is argued here that the cognitive psychophysiological approach, the second group of theories referred to at the beginning of this section, can do so.

Over the past decade, a number of authors have proposed theoretical models of panic disorder that explicitly take psychological factors into account. These models have been given a variety of names including behavioral, psychological, cognitive and psychophysiological (e.g., Barlow, 1986, 1988a,b; Clark, 1986, 1988; Margraf et al., 1986a; Margraf, Ehlers, & Roth, 1986b,c; Rapee, 1987; Ehlers, Margraf, & Roth, 1988b; van den Hout, 1988; Ehlers & Margraf, 1989). As I have argued elsewhere, I prefer the term “psychophysiological model” because it best describes the interaction of psychological and physiological factors that these approaches put at the core of panic disorder (Margraf & Ehlers, 1989). The central assumption of these models is that seemingly “spontaneous” panic attacks result from a positive feedback loop between bodily sensations, their perception and association with danger, and the resulting anxiety which in turn influences sensations, perception and associative processes. This “vicious circle” was specified by Lewis as early as 1950 in order to account for the “hyperventilation syndrome.” The association of specific bodily sensations with immediate threat of a mental or physical catastrophe is seen as both the necessary and sufficient condition for panic attacks to occur. The psychophysiological approach is consistent with the findings of earlier research on panic and has received additional support from studies carried out within this framework (for a review see Margraf & Ehlers, 1989). A frequent misunderstanding about the psychophysiological approach is that it precludes any physiologic or genetic predispositions for panic. From this it is then often deduced that the theory would
be falsified if such predispositions could be established. However, we (e.g., Margraf et al., 1986a,b; Ehlers & Margraf, 1989) as well as other proponents of psychological models (e.g., Barlow, 1986, 1988a,b; Clark, 1986, 1988; Rapee, 1987) have explicitly stated that positive feedback loops may depend on individual predispositions, may they be somatic or cognitive, inherited or acquired. The contrast to purely physiologic approaches lies in the fact that from a psychophysiological perspective such predispositions may be heterogeneous, that physiologic characteristics are not seen as necessary for panic attacks and that there is no assumption of a one-to-one relationship between the two types of phenomena.

This is also the case for the psychophysiological understanding of the relationship between panic attacks and hyperventilation. In this approach, the relationship is conceived in two ways: First, hyperventilation is seen as one of many processes that can lead to the perception of bodily changes that may then trigger the positive feedback loop considered central to the development of panic. Second, because of the circular nature of the process, hyperventilation can at the same time also be a response to anxiety. The data reviewed in the present article clearly support the psychophysiological position. While studies using indirect as well as direct measures showed a substantial overlap between panic and hyperventilation, they also shed strong doubts on the possibility that panic patients show chronic hyperventilation and very clearly established that there is no one-to-one relationship with acute hyperventilation. Just as many panic attacks occur without hyperventilation, overbreathing frequently is not accompanied by panic. The recent ambulatory tpCO₂ data and cognitive studies prove this point especially. The latter line of research at the same time firmly supports the relevance of perceptive and associative processes for the relationship between panic and hyperventilation.

The nature of the associative process that the psychophysiological model implies in the feedback between bodily sensations and panic lies on a hypothetical continuum ranging from interoceptive conditioning to purely cognitive interpretations. The various versions of psychophysiological models place different emphasis on the two poles of this continuum (Ehlers & Margraf, 1989). In this context, it is interesting that respiratory sensations may serve as unconditioned stimuli for classical conditioning processes. A particularly dramatic example was given by Campbell, Sanderson, and Laverty (1964). These authors were able to show in healthy volunteers that already a single pairing of a neutral tone with a pharmacologically induced respiratory paralysis produced a conditioned skin conductance response that was highly resistant to extinction or even seemed to increase over time. While respiratory paralysis is not part of the normal spectrum of human experiences, the fear of asphyxiation as
well as the sensation of breathlessness are frequent characteristics of panic disorder and hyperventilation. Furthermore, Jansen, van der Molen, and van den Hout (1987) demonstrated that hyperventilatory responses can be classically conditioned. In two studies healthy volunteers were breathing six times gas mixtures with a high concentration of CO₂ which led to hyperventilation. When subjects subsequently breathed normal air through the same apparatus, they showed hyperventilation in response to the inhalation although no CO₂ was given. On the other hand, there are limits to the relevance of conditioning processes. van der Molen, van den Hout, Merckelbach, van Dieren and Griez (1989) found that hypocapnia has no effect on the extinction of conditioned fear responses. More importantly, the results from the cognitive studies reviewed in the previous section cannot be explained by pure conditioning approaches.

In conclusion, hyperventilation is not uniquely relevant for panic, but the degree of overlap between the two phenomena gives it a prominent role as a trigger and a vehicle for successful psychological treatment. For example, our clinical experience shows that repeated exposure to voluntary hyperventilation is a fast and reliable way of reducing the anxiety response to hyperventilatory type sensations. Moreover, a hyperventilation test can be usefully included in the cognitive treatment of panic attacks. In this context, the test demonstrates to the patients that their seemingly mysterious symptoms can be easily explained by a harmless physiologic mechanism rather than by the typically feared severe disease. An excellent description of this treatment approach is given by Clark (1989). With respect to the explanation of the relationship between panic and hyperventilation, a number of important findings cannot be explained by purely physiologic or conditioning approaches. Instead, only a psychophysiological theory that takes cognitive, conditioning and physiologic factors into account is consistent with all the major results reviewed.

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REFERENCES


Hyperventilation and Panic Disorder


