THE HYPERVENTILATION SYNDROME IN PANIC DISORDER, AGORAPHOBIA AND GENERALIZED ANXIETY DISORDER*

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Summary—The symptom complex of panic disorder and generalized anxiety disorder suggests an etiological role for hyperventilation. The present study investigates the overlap between DSM-III-R panic disorder, panic disorder with agoraphobia and generalized anxiety disorder with hyperventilation syndrome (HVS). The anxiety disorder diagnoses were based on a structured interview, and HVS determined by the so-called hyperventilation provocation test (a brief period of voluntary hyperventilation with recognition of symptoms). The overlap rates with HVS were: 48% for panic disorder, 83% for panic disorder with agoraphobia and 82% for generalized anxiety disorder. However, a pilot study on transcutaneous monitoring of carbon dioxide tension leads us to question the validity of the voluntary hyperventilation method that we used to determine HVS-status. It is unclear whether hyperventilation plays an important role in panic and general anxiety, as our overlap findings suggest. For patients who recognize the symptoms induced by voluntary hyperventilation, the hyperventilation provocation procedure provides a therapeutic means of exposure to feared bodily sensations.

Two models explaining panic attacks currently dominate the research field—the biological model and the cognitive model. Both, however, ascribe a different role to hyperventilation in the genesis of panic attacks. Some proponents of the biological model suggest that patients with panic attacks may chronically hyperventilate in an attempt to maintain a low CO_2 level, to avoid triggering supposed hypersensitive central noradrenergic CO_2-receptors (Klein and Gorman, 1987). Thus, hyperventilation during panic attacks would be an unsuccessful way of reducing large noradrenergic discharges (van den Hout, 1988). On the other hand, the cognitive theory of panic proposes that panic attacks result from catastrophic interpretation of bodily symptoms, caused perhaps by hyperventilation or by other physiological changes such as those induced by exercise, caffeine or emotional states (Clark, 1986; Rapee, 1987). The cognitive model hypothesizes that hyperventilation *per se* does not cause panic and that panic occurs only when bodily sensations associated with it are perceived as unpleasant and interpreted catastrophically (Clark, 1986).

Preliminary evidence suggests that hyperventilation plays an important role in at least some panic attacks. For instance, there is a strking similarity between the symptoms of Panic Disorder in DSM-III-R (American Psychiatric Association, 1987) and the symptoms of Hyperventilation Syndrome (HVS; Weimann, 1968; Lum, 1976). In addition, it has been demonstrated that naturally occurring panic attacks can be accompanied by drops in pCO_2 (Hibbert and Pilsbury, 1988; Salkovskis, Warwick, Clark and Wessels, 1986). Also, treatments aimed at changing respiratory behavior have proved successful in treating panic and agoraphobic patients (Clark, Salkovskis and Chalkley, 1985; Rapee, 1985; Salkovskis, Jones and Clark, 1986). And, in a study of the diagnostic overlap between agoraphobia and the HVS, Garssen, van Veenendaal and Bloemink (1983) found that 61% of agoraphobic patients also suffered from the HVS. In a similar vein, Hoes, Colla, van Doorn, Folgering and de Swart (1987) found that 35% of patients meeting criteria for the HVS also met criteria for Panic Disorder, which was the case in only 5% of the non-hyperventilating patients.

The present study endeavors to investigate the diagnostic overlap between the HVS and the anxiety disorder categories of Panic Disorder (PD), Panic Disorder with Agoraphobia (PDA) and

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Generalized Anxiety Disorder (GAD). For PD and PDA patients overlap is expected to be in the range of 61%, found for agoraphobic patients in the earlier study of Garssen *et al.* (1983). The incidence of HVS in GAD patients is of particular interest, since the symptom profile of GAD suggests possible involvement of hyperventilation. GAD symptoms include trembling, paresthesias, shortness of breath, palpitations, dizziness and sweating which are also common among HVS-patients. Rapee's (1986) findings indicate a lesser role for hyperventilation in GAD than in PD. In comparison, PD patients responded to a brief period of voluntary hyperventilation with markedly greater distress and a greater number of symptoms than GAD patients. PD patients also showed lower resting end-tidal pCO_2.

In contrast to previous studies of diagnostic overlap which used self-ratings of agoraphobic and panic symptoms (Garssen *et al.*, 1983; Hoes *et al.*, 1987), the present study employs a structured interview for the differential diagnosis of anxiety disorders—the Anxiety Disorders Interview Schedule-Revised—to increase diagnostic reliability (DiNardo, O'Brien, Barlow, Waddell and Blanchard, 1983; de Ruiter, Garssen, Rijken and Kraaimaat, 1987). Diagnosis of the HVS is determined using the same procedure as employed by Garssen *et al.* (1983).

Anxiety disorder patients are also compared on two respiratory variables, i.e. alveolar pCO_2 and respiratory rate, to further explore differences between patient groups. This will enable us to cross-validate Rapee's (1986) finding of lower resting end-tidal pCO_2 in PD patients compared with GAD patients.

METHOD

Subjects

Patients participating in our research on anxiety disorders were judged by a referring professional as possibly suffering from an anxiety disorder. Most patients were referred by psychiatric residents of the outpatient clinic of the Psychiatric Department of the University Hospital of Utrecht; some were referred by other outpatient clinics in the area, and others were self-referred. Patients were diagnosed using the Anxiety Disorders Interview Schedule-Revised (ADIS-R; DiNardo *et al.*, 1983; Dutch version: de Ruiter *et al.*, 1987). Diagnoses were determined through consensus agreement between two clinicians experienced with anxiety disorder patients. *S*s were included if they met DSM-III-R criteria (American Psychiatric Association, 1987) for a primary diagnosis of panic disorder, panic disorder with agoraphobia or generalized anxiety disorder.

Of the 176 patients participating in the research project, 21 were diagnosed PD, 88 PDA, and 11 GAD. The remaining 56 patients received other DSM-III-R diagnoses, and were subsequently dropped from the study. Table 1 shows demographic characteristics of PD, PDA and GAD patients. The Dutch educational system is stratified and level of intelligence is generally well represented by the level of education a person attains. The patient groups did not differ significantly

Table 1. Sample characteristics

	Diagnosis		
Variable	PDA (*N* = 88)	PD (*N* = 21)	GAD (*N* = 11)
Age in years, Mean (SD)	34.3	33.0	47.7
	(9.7)	(8.4)	(17.7)
Sex	36M, 52F	9M, 12F	8M, 3F
Duration of disorder			
in months, Mean (SD)	61.2	50.2	56.3
	(59.0)	(69.6)	(67.1)
Educational levels*			
level 1	17	3	4
level 2	34	9	1
level 3	20	6	4
level 4	14	3	2
level 5	3	0	0

PDA = Panic Disorder with Agoraphobia.
PD = Panic Disorder without Agoraphobia.
GAD = Generalized Anxiety Disorder.
*Level 1 = primary school, level 2 = middle level high school, level 3 = higher level high school, level 4 = highest level high school, preparatory to university, and level 5 = university education.

from each other on sex, educational level (χ^2 tests) and duration of disorder (F-test). However, GAD-patients were significantly older than both PDA and PD patients [$F_{(2,117)} = 8.65$, $P < 0.001$].

Assessment

Respiratory measures. All Ss were assessed on respiratory rate (RR) and alveolar carbon dioxide pressure (pACO$_2$). RR was measured using a Godart pneumotachograph. A large Fleish head (No. 4) was used, which is prescribed for accurate measurement of high flow rates occurring during hyperventilation. pACO$_2$ was measured with a Godart capnograph, which was calibrated before each session with a gas mixture (4.0% CO$_2$ in air), previously analyzed by the Lloyd method. The pneumotachograph and capnograph signals were fed into an amplifier and traced on a polygraph.

Respiratory measurements were taken during three phases: rest (3 min), 90 sec of voluntary hyperventilation, and recovery from hyperventilation (3 min). Mean RR was determined from the last 30 sec of each measurement phase. Mean pACO$_2$ were determined from the last 30 sec of resting and recovery phases, and from the three lowest values in the last 30 sec of the hyperventilation phase.

Procedure

Patients were provided with written information describing the purpose of the research and the assessment procedure. On a first visit the Anxiety Disorders Interview Schedule-Revised (DiNardo *et al.*, 1983; de Ruiter *et al.*, 1987) was administered. The ADIS-R is a structured interview protocol designed for differential diagnosis among the anxiety disorders (DiNardo *et al.*, 1983). The ADIS-R also provides screening for affective and somatoform disorders, substance use and psychotic symptoms.

On a second visit, taking place a mean of 11.4 days (SD = 6.8) after the interview, a number of psychological questionnaires were administered. One was the Bodily Sensations Questionnaire (BSQ) which asks Ss to rate the frequency with which 32 bodily sensations have occurred during the past month. These sensations include most of the symptoms Weimann (1968) mentioned as characteristic of HVS-patients. Ratings are made on a 4-point ordinal scale (range = 0–3) consisting of the categories 'did not occur', 'one or more times a month', 'one or more times a week', and 'daily'. Only symptoms that received a score of 2 or 3 ('daily' or 'one or more times a week') were considered in the present study.

Patients were taken into the experimental room, seated in a reclining chair and were informed about the nature of the equipment. Patients were then asked to breathe normally through the mouthpiece for a period of 3 min (resting phase). After this, they were instructed to breathe as fast and as deeply as possible for a period of 90 sec. This voluntary hyperventilation procedure was demonstrated by the experimenter. During the hyperventilation phase pACO$_2$ had to decrease to 20 mmHg or less, and had to be maintained at this level for at least 90 sec. After the hyperventilation phase, Ss were instructed to relax and resume normal breathing. Measures were taken for a further 3 min (recovery phase).

After Ss had been disengaged from the equipment, they were asked to rate which one(s), if any, of the 32 symptoms of the BSQ had occurred during the phase of voluntary hyperventilation. If at least four of the symptoms which the patient had assigned a frequency score of 2 or 3 before the test, occurred during the hyperventilation phase, the patient was considered a possible HVS-patient. The final criterion for diagnosing a HVS-patient (HVS+) was his or her recognition of the symptoms as similar to those occurring in daily life, e.g. when having panic attack (in the case of PD and PDA patients) or when feeling very tense (in the case of GAD patients). If voluntary hyperventilation produced virtually no symptoms, or if they were not recognized, the diagnosis was negative (HVS−). When the patient was uncertain whether he/she recognized the symptoms, or only recognized them partially, the diagnosis HVS uncertain (HVS?) was assigned.

RESULTS

Diagnostic overlap between the HVS and the three anxiety disorder patient groups is shown in Table 2. Seventy (83%) out of 84 PDA-patients, 10 (48%) out of 21 PD-patients and 9 (82%) out

Table 2. Frequency of the diagnosis of Hyperventilation Syndrome in Patients with Panic Disorder with Agoraphobia (PDA), Panic Disorder (PD), and Generalized Anxiety Disorder (GAD)

Anxiety disorder category	HVS+	HVS−	HVS?	Total
PDA	70 (83%)	11 (13%)	3 (4%)	84
PD	10 (48%)	10 (48%)	1 (4%)	21
GAD	9 (82%)	2 (18%)	0 (0%)	11

HVS+ = Hyperventilation Syndrome positive.
HVS− = Hyperventilation Syndrome negative.
HVS? = Hyperventilation Syndrome uncertain.

of 11 of GAD-patients met criteria for Hyperventilation Syndrome. The difference between PDA- and PD-patients was significant [$\chi^2(2) = 12.89$, $P < 0.01$].

Mean values for respiratory variables in the three anxiety disorder patient groups are presented in Table 3. There were no significant differences on pCO_2 or RR between the three groups in any of the three measurement phases.

DISCUSSION

The present findings indicate a high degree of overlap between Hyperventilation Syndrome and three anxiety disorder categories. The overlap for PDA patients (83%) was higher than the 61% reported in an earlier study (Garssen *et al.*, 1983). Possibly, this is caused by differences in the method used for diagnosing agoraphobia. The incidence of HVS in PD patients was unexpectedly low (48%). Because PD and PDA are often considered as two different stages of a single underlying disorder (Zitrin, Klein, Woerner and Ross, 1983; Sheehan and Sheehan, 1982), one might expect to find similar overlap rates for the two disorders.

The overlap rate (82%) for GAD seems especially high. This finding is in disagreement with findings of Rapee (1986) who found that only 25% of 13 GAD patients reported that the symptoms produced by voluntary hyperventilation resembled their anxiety symptoms. However, these findings must be considered somewhat preliminary, since they are based on only 11 and 13 patients, respectively.

Respiratory rate and alveolar carbon dioxide tension were not significantly different in the three patient groups, in any of the three measurement phases (rest, hyperventilation and recovery). Rapee's (1986) finding of lower resting phase $pACO_2$-values for PD vs GAD patients was not replicated. However, in our study, major differences on these respiratory variables between groups are not expected, since all three anxiety disorder categories showed considerable overlap with the HVS. Moreover, a diagnosis of HVS does not necessarily imply low resting and/or recovery $pACO_2$ levels. HVS-patients may show normal breathing patterns and concomitant normocapnia between attacks. Indeed, the frequency distributions of resting $pACO_2$ levels of HVS-patients and normal control *S*s show considerable overlap (Lum, 1976).

The present study sought to investigate the hypothesis that hyperventilation plays a role in panic and anxiety symptoms, within a subgroup of anxiety disorder patients. To support this hypothesis,

Table 3. Mean scores and standard deviations (in brackets) for PDA, PD and GAD patients on Alveolar Carbon Dioxide Pressure ($pACO_2$) and Respiratory Rate (RR)

Respiratory variable	PDA	PD	GAD
$pACO_2$*—rest phase	36.5	35.6	35.7
	(5.1)	(5.0)	(5.1)
$pACO_2$—hyperventilation	17.0	16.9	16.1
	(3.1)	(3.3)	(4.3)
$pACO_2$—recovery phase	28.9	27.6	28.3
	(5.4)	(5.4)	(5.7)
RR†—rest phase	15.4	15.4	17.8
	(4.8)	(7.8)	(7.6)
RR—hyperventilation	35.6	37.7	36.6
	(8.4)	(8.2)	(11.5)
RR—recovery phase	16.1	16.1	19.9
	(5.4)	(6.9)	(9.0)

*$pACO_2$ measured in mmHg.
†RR measured in cycles per min.

one must, (1) demonstrate that (severe) hyperventilation occurs during panic or general anxiety, and, (2) that hyperventilation plays a *causal* role in the production of most of the somatic anxiety symptoms that accompany panic and general anxiety.

Only direct and continuous registration of arterial or alveolar CO_2 pressure would admit the co-occurrence of hyperventilation with panic and/or anxiety symptoms. Adequate technical equipment for such registration has only recently been developed by Pilsbury and Hibbert (1987). They have reported pilot data from four panic patients, using ambulatory monitoring of transcutaneous pCO_2 (Hibbert and Pilsbury, 1988).

Addition of the second requirement, i.e. proof of the *causal* role of hyperventilation in panic and/or anxiety symptoms, is essential. Although vigorous hyperventilation (leading to drops in arterial pCO_2 of 10 mmHg or more) causes changes in an number of physiological systems, symptoms do not always occur. Without further evidence, demonstration of the co-occurrence of hyperventilation and anxiety/panic does not exclude the possibility that hyperventilation is merely a sign of physiological activation. In that case, it would be comparable to other signs of arousal, such as tachycardia and increased electrodermal activity.

The hyperventilation provocation procedure employed in the present study was not aimed at examining co-occurrence of hyperventilation and panic/anxiety directly. However, the hyperventilation procedure was employed with the assumption that asking about recognition of symptoms during voluntary hyperventilation would provide plausible evidence for a causal role for hyperventilation in panic and anxiety symptoms. The provocation procedure is based on the assumption that recognition of induced symptoms implies that symptoms the patient experiences in daily life are also caused largely by hyperventilation. However, a recent pilot study leads us to question the validity of this basic assumption, underlying the provocation procedure (Hibbert and Pilsbury, 1988). In this study, one patient found symptoms produced by voluntary hyperventillation very similar to those of her panic attacks. However, ambulatory measurement of pCO_2 during panic attacks revealed no significant lowering of pCO_2. Another patient demonstrated considerable drops in transcutaneous pCO_2 during panic, but failed to recognize the symptoms induced by voluntary hyperventilation. Although these findings must be considered preliminary, they cast doubt on the validity of the provocation procedure. Thus, it remains unclear whether the proposition that hyperventilation plays an important role in panic and generalized anxiety is tenable on the basis of our findings.

Aside from the causal role of hyperventilation in panic and anxiety, the hyperventilation procedure itself may have clinical applications. Both in the present study and in the earlier study (Garssen *et al.*, 1983) a large percentage of anxiety patients recognized the symptoms produced by voluntary hyperventilation. For this subgroup of patients voluntary hyperventilation might provide a therapeutic means for exposure to feared bodily sensations. Exposure to bodily symptoms, induced by sodium lactate infusion (Bonn, Harrison and Rees, 1973) or CO_2 inhalation (Griez and van den Hout, 1986) has been shown to be effective in treating panic patients. If it could be shown that repeated voluntary hyperventilation has a similar effect, this would suggest it is a simple, inexpensive way of achieving exposure to bodily sensations.

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