

Presence of hyperventilation in patients with asthma-like symptoms but negative asthma test responses: Provocation with voluntary hyperventilation and mental stress

Karin C. Ringsberg, PhD,^a and Ingemar Åkerlind, PhD, DMSc,^{a,b} Linköping and Norrköping, Sweden

Background: A group of patients reporting asthma-like symptoms but with negative asthma tests has been identified.

Objective: The objective of this study was to determine whether hyperventilation might explain these symptoms and whether the tests could be used as diagnostic tools.

Methods: A hyperventilation provocation test (HVPT), a mental stress test, and the Word Color Conflict Test (WCCT) were performed on 10 patients with asthma-like symptoms, 10 patients with asthma, and 10 healthy subjects. End-tidal P_{CO_2} ($PETCO_2$) was recorded 10 minutes after the HVPT and during the WCCT. Blood pressure, heart rate, and respiratory rate were also studied. The Nijmegen symptom questionnaire was used in the assessment of symptoms.

Results: After the HVPT, the $PETCO_2$ values recovered most slowly in the study group, the difference being significant compared with the healthy group ($P < .01$). During the WCCT, the study group had the lowest $PETCO_2$ values at the 10- and 15-minute measurements, the difference again being significant compared with the healthy group ($P < .05$). The study group more often experienced symptoms before the test than the group with asthma ($P < .05$) and the healthy group ($P < .001$). The study group recognized significantly more symptoms previously experienced during the HVPT than the group with asthma ($P < .05$) and the healthy group ($P < .01$) and during the WCCT than the healthy group ($P < .05$). The study group showed a negative correlation between the $PETCO_2$ level and the number of symptoms after the HVPT at 8 ($r = -0.72$; $P < .05$) and 10 minutes ($r = -0.76$; $P < .05$) and after the WCCT ($r = -0.59$; $P < .05$). Blood pressure, heart rate, and respiratory rate showed small differences between the groups.

Conclusion: Patients with asthma-like symptoms may experience hyperventilation when provoked. Mental stress might be 1 trigger factor. The HVPT and WCCT can be used as diagnostic instruments. (*J Allergy Clin Immunol* 1999;103:601-8.)

Key words: Asthma, asthma-like, hyperventilation, hyperventilation syndrome, mental stress

Among patients referred to asthma clinics for investigation of asthma, patients who reported asthma-like symptoms such as heavy breathing, increased sputum production, hoarseness, cough, and subjective hyperreactivity but in whom the results of asthma tests are negative have been identified.¹⁻⁴ They also do not fulfill the criteria for any other diagnosed disease. In spite of this, some patients have been treated for asthma and subjected to the secondary effects of medication with corticosteroids; others have been dismissed with insinuations that mental stress alone could be the explanation for the symptoms. The situation is perceived as stressful and distressing by the patients.² However, it is also a diagnostic problem for physicians in the allergology, pulmonary medicine, and primary care sectors. Therefore it is important to find diagnostic tools to diagnose and treat these patients correctly. The symptoms are often provoked by chemical irritants, mental stress, and physical exercise. In one study this group of patients was found to experience a variety of symptoms often associated with hyperventilation more frequently than patients with asthma.¹ It has been suggested that hyperventilation might explain some symptoms in these patients.^{1,4}

Hyperventilation is a physiologic term meaning "breathing in excess of metabolic requirements as reflected in carbon dioxide production."⁵ The hyperventilation syndrome (HVS) is another concept that has long been used to describe a state associated with various symptoms (eg, dyspnea, tingling fingers, palpitations, chest pain, dizziness, confusion, and paraesthesia) considered to be associated with hyperventilation. The issue has been investigated from the physiologic, psychosomatic, psychiatric, and psychologic perspectives.⁶⁻¹² Originally the diagnosis of HVS was made only on the basis of the patient's description of symptoms. However, the importance of additional provocation tests has been discussed.^{5,6,13-18} These are often based on the recognition of symptoms during voluntary overbreathing in a laboratory situation,¹⁹⁻²⁵ but physical provocation is also used.⁶ A slow recovery rate of end-tidal P_{CO_2} ($PETCO_2$) after discontinuing hyperventilation has also been considered to strengthen the diagnosis.^{20,21,25} The disorder usually is complex and multifactorial and caused by a wide range of organic, psychiatric, and physiologic dis-

From ^athe Department of Health and Environment, Division for Preventive and Social Medicine and Public Health Science, Linköpings Universitet, Linköping; and ^bthe Primary Health Care Research and Development Unit, County of Östergötland.

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Reprint requests: Karin Ringsberg, PhD, Department of Health and Environment, Division for Preventive and Social Medicine, and Public Health Science, Linköpings Universitet, S-581 85 Linköping, Sweden.

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Abbreviations used

HVPT:	Hyperventilation provocation test
HVS:	Hyperventilation syndrome
NQ:	Nijmegen questionnaire
PEFR:	Peak expiratory flow rate
PETCO ₂ :	End-tidal PCO ₂
WCCT:	Word Color Conflict Test

orders or a combination of these.^{5,26} Therefore it is no longer useful to label a patient as having HVS. We have adopted Gardner's⁶ definition of hyperventilation: "Hyperventilation is breathing in excess of metabolic requirements and is associated with reduction in PaCO₂, respiratory alkalosis and a wide range of symptoms." It has been reported not only that hyperventilation is often present in patients with asthma²⁷ but also that asthma could be misinterpreted as HVS.²⁸ Therefore it is very important to investigate the role of hyperventilation in patients with asthma-like symptoms but negative asthma tests, comparing them with patients with asthma and healthy subjects.

When studying hyperventilation, PETCO₂ can be recorded instead of measuring arterial PCO₂. A fundamental difficulty when diagnosing the presence of hyperventilation is the uncertainty about the lower limits of PETCO₂, which has been discussed by Bass and Gardner²⁹ and Gardner et al.³⁰ The same authors concluded that there are 2 types of chronic hyperventilation: persistent or provoked. Furthermore, when investigating hyperventilation they recommended clinicians to study recording of symptoms and recovery of PETCO₂ during and after different provocations.

The aim of this study was to determine whether patients with asthma-like symptoms but negative asthma test responses display signs of hyperventilation by means of provocation with voluntary hyperventilation and whether mental stress may be one trigger for such hyperventilation by comparing them with healthy control subjects and patients with asthma. The aim was also to determine whether the tests presented in this study could be used as diagnostic tools in these patients.

METHODS

Subjects

The study group consisted of 10 patients with asthma-like symptoms but negative asthma test responses. Ten patients with asthma and 10 healthy subjects served as control subjects. All patients were consecutively drawn from those who had, before the study, been referred to an outpatient clinic for the investigation of asthma. The healthy control subjects were recruited from female health care staff students. All subjects were to be between the ages of 18 and 60 years and nonsmokers for at least 1 year before the study. For further details of the subjects' age, duration of the disorder/disease, and results of lung function tests see Table I.

For inclusion in the study group, the patients were required to have negative asthma test responses. This means that the following 6 criteria had to be met: (1) lack of reversibility defined as an increase of FEV₁ or peak expiratory flow rate (PEFR) values after inhalation of a β_2 -stimulant of less than 10%; (2) normal FEV₁ or

PEFR values before inhalation of a β_2 -stimulant defined as 95% or more of the predicted normal value; (3) a negative methacholine test response defined as a PC₂₀ of 8 mg/mL or more³¹; (4) variability of less than 20% of the PEFR values; (5) no wheezing reported or heard by auscultation; and (6) negative skin prick test responses (2 patients had an allergy to birch and rat excrement). To be included in the asthma group, at least 2 of the following 4 criteria had to be met: (1) reversibility defined as an increase of the FEV₁ or PEFR values after inhalation of a β_2 -stimulant of 15% or more (32); (2) FEV₁ or PEFR values of 80% or less of predicted normal before and of 90% or more after inhalation of a β_2 -stimulant; (3) a positive methacholine test response defined as a PC₂₀ of 4 mg/mL or less³¹; and (4) variability of the PEFR values of 20% or more.³² The inclusion criteria for the healthy individuals were the same as for the patients with asthma-like symptoms, except for the absence of history of asthma-like symptoms or any known allergy.

All the patients of the study group had asthma-like symptoms for at least 2 years and had been investigated before the study for asthma. They had all tried treatment with corticosteroids and β_2 -stimulants without success and were receiving no medication. All but one patient had also been provoked by a bicycle test.⁴ None of the patients had any other diagnosed disease that could have an impact on their respiratory function or any other vital function. Only women were included in the study because clinical observations had shown that few men consulted at the clinic for the disorder. We therefore chose to investigate a homogeneous group. In the asthma group, all the patients received inhalation therapy with a β_2 -stimulant; 5 patients received corticosteroid inhalation therapy on a regular basis, 2 patients received oral β_2 -stimulant therapy, and 1 patient received oral corticosteroid therapy. The healthy control subjects were receiving no medication. Lung function and reversibility tests were performed 1 week before the study and before and 15 minutes after inhalation of a β_2 -stimulant (2 mg terbutaline given with a Turbuhaler [Draco Ltd, Lund, Sweden]).

The study was approved by the Ethics Committee of Göteborg University.

Procedure

The subjects first completed the Nijmegen questionnaire (NQ).^{20,22,24} Thereafter they had a relaxation period of 20 minutes lying down listening from a tape recorder to the progressive muscle relaxation program of Jacobsson³³ modified by Uneståhl.³⁴ After this they were subjected to a mental provocation test, the Word Color Conflict Test (WCCT).³⁵⁻³⁶ Another relaxation period of 20 minutes followed, after which a hyperventilation provocation test (HVPT)^{21,37} was performed. The HVPT includes provocation with voluntary hyperventilation and recognition of symptoms during the provocation. Thus directly after the test the subjects were asked which of the symptoms listed in the NQ they had experienced during the test. This was also done after the WCCT. One day after the tests, the subjects were asked whether and for how long they had remaining symptoms listed in the NQ. The items in the NQ were presented in random order. The WCCT was performed as the first of the 2 provocation tests to avoid bias from the relatively stronger HVPT. However, the results are presented in reversed order. The HVPT was regarded as a base test, and the WCCT was regarded as a test that might explain any presence of hyperventilation.

Physiologic measurements (ie, PETCO₂, blood pressure, heart rate and respiratory rate) were recorded during the WCCT and during 10 minutes after the HVPT.

Provocation tests

WCCT. Mental stress was induced during 15 minutes by a video version of the WCCT.^{35,36} Immediately after the test, the subjects

TABLE I. Characteristics of the patients and healthy control subjects

Group	Age: median and range (y)	Duration of disease: median and range (y)	FEV ₁ *		Forced vital capacity*	
			-β ₂ (mean ± SD)	+β ₂ (mean ± SD)	-β ₂ (mean ± SD)	+β ₂ (mean ± SD)
Study group	44 (25-56)	9 (3-30)	114 (8.3)	113 (8.3)	110 (11.0)	108 (10.0)
Asthma group	41 (28-60)	8 (3-25)	83 (15.2)	98 (13.0)	99 (12.0)	107 (13.0)
Healthy group	41 (33-59)	—	112 (14.6)	114 (14.0)	112 (14.8)	112 (13.0)

*Percent of predicted normal value before (–) and after (+) inhalation of a β₂-stimulant.

were asked which of the symptoms listed in the NQ^{20,22,24} they had experienced during the test.

HVPT. Hyperventilation was provoked by voluntary hyperventilation.^{21,37} The subjects were asked to breathe rapidly and deeply until a recorder measuring PETCO₂ showed a value of 2.4 kPa and this value was maintained for 3 minutes. Thereafter they were instructed to breathe normally during a follow-up period of 10 minutes. Immediately after the test, they were asked which of the symptoms listed in the NQ^{20,22,24} they had experienced during the test.

Physiologic measurements

PETCO₂ was recorded by means of a pulse-oxymeter and a capnograph (OSCAR oxy multigas monitor and pulse-oxymeter; Dansjö Medical AB, Bromma, Sweden). The baseline values before the 2 provocation tests were recorded after the relaxation periods. The values during the WCCT were recorded at 5, 10, and 15 minutes and calculated as the mean of the first 5 consecutive digital readings. During the recovery period after the provocation with voluntary hyperventilation, the values were recorded every minute. The cut-off point between normal and abnormal (ie, persistent chronic hyperventilation) of 4.0 kPa PETCO₂ was used after relaxation.³⁰

The following variables were registered by a vital-signs monitor (Critico Dinamap Adult/Pediatric Vital Signs Monitor; Tampa, Fla): systolic and diastolic blood pressure, taken in the left arm at baseline and every fifth minute during both tests, and heart rate and respiratory rate, measured at baseline and at 5, 10, and 15 minutes during the WCCT and every minute during the 10-minute follow-up after the provocation with voluntary hyperventilation.

Assessment of symptoms

A self-administered inventory of symptoms, the NQ, was used.^{20,22,24} It consists of a 16-item list of sensations described as symptoms provoked by hyperventilation (Table II). The frequency of symptoms previously experienced during daily life are graded on a scale from 0 to 4. A total NQ score of more than 23 is considered positive, indicating that hyperventilation might be present. Scores of 3 or more for individual items are considered to indicate major daily life complaints.

A model of reproduction of symptoms during provocation with hyperventilation is described.²⁴ According to that model, the HVPT is considered positive when at least 2 major daily life complaints (ie, ≥3 on individual items of the NQ) are reproduced and recognized during the test. The items related to dizziness and tingling fingers are not included as recognition criteria because these symptoms can occur in any subject after provocation with hyperventilation. This model is also used for the classification of the HVS.²⁴ To be classified as having HVS, the patient should have both a positive NQ score and a positive reproduction test. Absence of both of these is classified as non-HVS. Patients who fulfill only 1 criterion are

labeled possible HVS. In this study we used this model, although we did not label the condition HVS but labeled it *hyperventilation*, as mentioned in the introduction.

On the basis of the factor analysis of the items in the questionnaire (Table II), the symptoms can be divided into 3 components: shortness of breath, central tetany, and peripheral tetany.²² Shortness of breath consists of items 1 through 7; central tetany, items 7 through 11; and peripheral tetany, items 12 through 15. According to the model, item 7, chest pain, is included in both shortness of breath and central tetany. Item 16, anxious feelings, is not included in this analysis (Table III).

Statistics

Wilcoxon's signed ranks test was used for within-group comparisons, and the Mann-Whitney *U* test was used for between-group comparisons regarding heart rates, blood pressures, respiratory rates, and PETCO₂ during the WCCT. To describe the correlation between symptoms and PETCO₂, Pearson's correlation coefficient was calculated, and Pitman's test was used to test the significance.³⁸ Fisher's permutation test,³⁸⁻³⁹ which includes Fisher's exact test as a special case, was used for comparison between the groups regarding the symptoms. To compare the recovery of PETCO₂ after the HVPT, a regression coefficient between time after interruption of the voluntary hyperventilation and the PETCO₂ values was calculated for each patient for the period of 0 to 10 minutes. Fisher's test for paired comparisons³⁸ was applied to the coefficients to assess the rise of PETCO₂ in each of the 3 groups.

Comparisons between the groups with respect to the changes were made by Fisher's permutation test.³⁹ Two-tailed tests were used, and *P* values of .05 or less were considered significant.

RESULTS

PETCO₂

After relaxation and during quiet breathing (baseline), all groups had a mean PETCO₂ above 5.0 kPa (ie, within normal limits). The healthy control group had the highest value, the asthma group had the lowest value, and the study group took an intermediate position. The differences between the groups were not significant (Fig 1). When the provocation with hyperventilation was terminated and during the recovery period of 10 minutes, the study group had the slowest recovery rate of PETCO₂. The difference was significant between the study group and the healthy control group (*P* < .01) and between the asthma group and the healthy control group (*P* < .05). During this period of 10 minutes, the mean PETCO₂ of the study group never recovered to 4 Kpa, although it did so after 6 minutes in the asthma group and after 5 min-

TABLE II. The mean frequency* of symptoms and number of subjects who experienced symptoms on the NQ before the tests

Item	Study group		Asthma group		Healthy group	
	Mean $\pm$ SD	n	Mean $\pm$ SD	n	Mean $\pm$ SD	n
1. Feelings of tenseness	2.0 $\pm$ 1.16	9	1.5 $\pm$ 0.71	9	1.3 $\pm$ 0.95	8
2. Shortness of breath	2.2 $\pm$ 0.79	10	2.0 $\pm$ 0.82	10	0.3 $\pm$ 0.48	3
3. Accelerated/deepened breathing	2.5 $\pm$ 0.53	10	2.1 $\pm$ 0.57	10	0.6 $\pm$ 0.80	6
4. Feeling unable to breathe deeply	2.6 $\pm$ 1.17	9	2.1 $\pm$ 0.74	10	0.1 $\pm$ 0.32	1
5. Palpitations	1.4 $\pm$ 0.70	9	2.0 $\pm$ 1.05	9	1.8 $\pm$ 1.03	9
6. Constricted chest	2.2 $\pm$ 0.79	10	1.2 $\pm$ 0.92	8	0.2 $\pm$ 0.40	2
7. Chest pain	1.8 $\pm$ 0.92	9	0.7 $\pm$ 0.68	6	0.4 $\pm$ 0.70	3
8. Dizziness	2.1 $\pm$ 0.99	10	0.8 $\pm$ 0.40	8	0.5 $\pm$ 0.53	5
9. Blurred vision	1.6 $\pm$ 1.43	7	0.8 $\pm$ 1.03	5	0.1 $\pm$ 0.32	1
10. Confusion	1.3 $\pm$ 0.95	8	0.4 $\pm$ 0.70	3	0	0
11. Sensation of bloated abdomen	2.7 $\pm$ 0.95	10	2.0 $\pm$ 1.33	8	1.4 $\pm$ 1.17	7
12. Stiffness of fingers or arms	1.1 $\pm$ 0.99	7	0.7 $\pm$ 0.68	6	0.1 $\pm$ 0.32	1
13. Cold hands or feet	3.2 $\pm$ 0.79	10	2.1 $\pm$ 0.88	10	2.1 $\pm$ 2.0	9
14. Tightness around the mouth	0.9 $\pm$ 2.00	5	0.1 $\pm$ 0.32	1	0	0
15. Tingling fingers	1.5 $\pm$ 0.85	8	1.2 $\pm$ 1.03	7	0.3 $\pm$ 0.68	2
16. Anxious feelings	1.8 $\pm$ 0.92	10	1.1 $\pm$ 0.74	8	1.4 $\pm$ 0.70	9

*Frequency: 0 = never occurring, 1 = rare, 2 = sometimes, 3 = often, and 4 = very often.

utes in the healthy control group. During the WCCT, the mean PETCO₂ values decreased below the baseline values in all groups. When the test was finished after 15 minutes, the mean values had decreased 10% in the study group, 2% in the asthma group, and 4% in the healthy control group. The difference was significant between the study group and the healthy control group at the 10- and 15-minute measurements ($P < .05$).

Blood pressure, heart rate, and respiratory rate

There were no significant differences between the groups at baseline regarding blood pressure and heart rate. During both provocation tests, the values of these parameters increased in all groups compared with baseline, but no significant differences between the groups were seen. All groups increased their respiratory rate during the HVPT. The increase remained for the study group during the recovery period, and the values were significantly higher than those for the asthma group at the measurements taken 2, 3, and 6 minutes after the test ($P < .05$). Likewise a tendency to significance was seen between these 2 groups at 4 minutes ($P = .057$). During the WCCT, all groups had a higher respiratory rate compared with baseline, but there were no significant differences between the groups except for the asthma group, which had a higher value compared with the study group at the 15-minute measurement ($P < .05$).

Symptoms according to the NQ

Symptoms previously experienced during daily life. The study group reported a greater frequency and a larger

variety of previously experienced symptoms than the other 2 groups (Table II). Eighty percent of the patients (8 of 10 patients) in the study group and 40% of the patients (4 of 10 patients) with asthma had a positive questionnaire score (ie, a total NQ-score of more than 23; all the healthy control subjects had a score below that limit). The mean sum of all frequency scores was 31 (SD $\pm$ 8.9) in the study group, 21 (SD $\pm$ 5.2) in the asthma group, and 11 (SD $\pm$ 4.7) in the healthy control group. The difference between the study group and the asthma group ($P < .05$) and between the study group and the healthy control group ($P < .001$) was significant. Analysis of the complaints of the NQ divided into 3 components revealed that the study group had the highest mean frequency scores of all components (Table III). The differences were significant between the study group and the asthma group for shortness of breath ($P < .05$) and central tetany ($P < .01$) and between the study group and the healthy control group for all components ($P < .001$).

Reproduced and recognized symptoms during the provocations. During the HVPT, the study group recognized altogether 29 major daily life complaints (ie, ≥ 3 on individual NQ items), the asthma group had 7, and the healthy control group had 2. The study group differed significantly both from the asthma group ($P < .05$) and the healthy control group ($P < .01$). The corresponding figures during the WCCT were 25, 7, and 4, respectively. The difference was significant between the study group and the healthy control group ($P < .05$). When these recognized symptoms during the 2 provocation tests were divided into the 3 components,²² there was a significant difference in the number of symptoms between the study

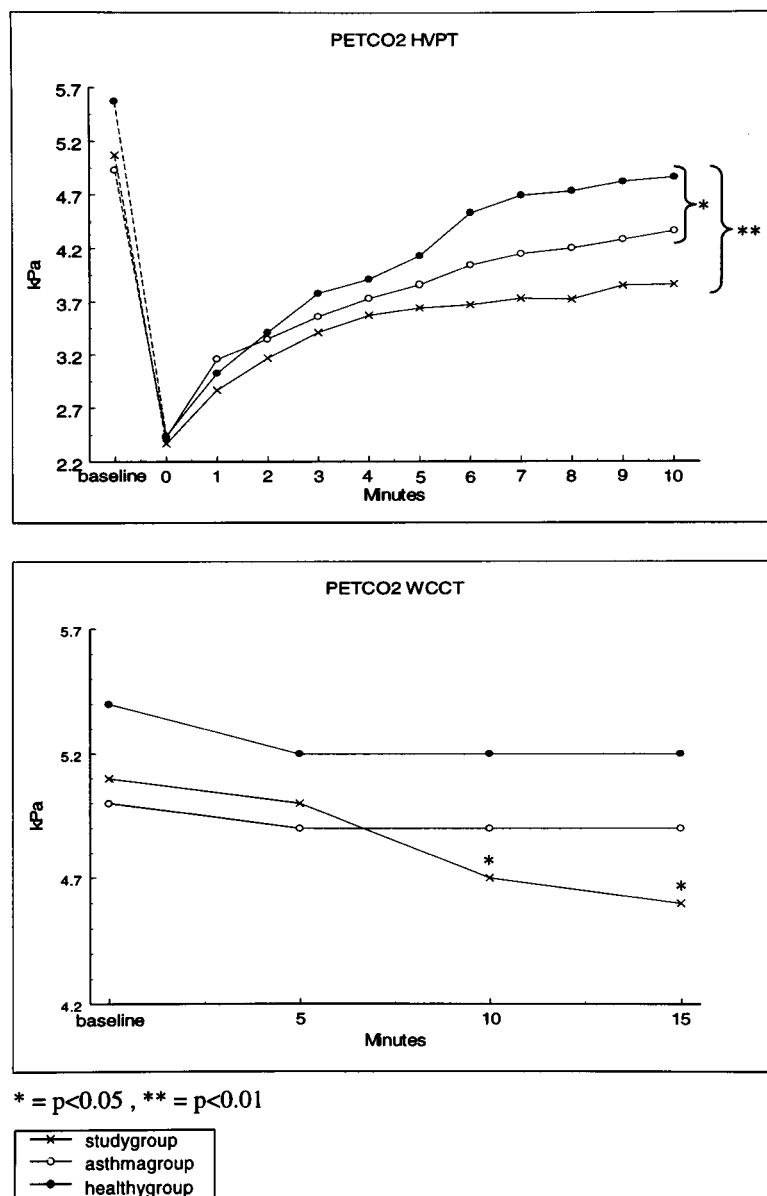


FIG 1. Mean values of PETCO₂ measured at baseline and during 10 minutes after provocation with HVPT and during provocation with mental stress (WCCT).

group and the asthma group regarding central tetany during the HVPT ($P < .05$), although a tendency to a significant difference was seen regarding shortness of breath during the WCCT ($P = .057$; Table III). The difference between the study group and the healthy control group was significant concerning shortness of breath during the HVPT ($P < .05$) and the WCCT ($P < .01$) and concerning central tetany during the HVPT ($P < .05$).

Altogether, 6 patients of the study group and 1 patient of the asthma group had positive reproduction tests during both provocation tests. These patients also had a positive total frequency score (ie, a total NQ score of more than 23). Furthermore, 2 patients of the study group and 3 patients of the asthma group had only a positive NQ

score. This indicates, according to the criteria of Vansteenkiste et al,²⁴ that the number of patients experiencing hyperventilation in the study group was higher than in the other groups. The difference was significant both in relation to the asthma group ($P < .01$) and versus the healthy control group ($P < .001$).

Remaining symptoms. No subject had symptoms remaining 20 minutes after the WCCT. Eight patients in the study group, 3 patients in the asthma group, and 2 patients in the healthy control group reported that they had experienced symptoms listed in the NQ up to 6 hours after the tests (Table III). One patient of the study group had symptoms that persisted for more than 1 day. The difference between the study group and the healthy con-

TABLE III. The items of the NQ divided into components

Component	Frequency of symptoms before testing			No of recognized major daily life complaints						No of symptoms reported 1 day after the test		
	S	A	H	HVPT			WCCT			S	A	H
	(mean ± SD)	(mean ± SD)	(mean ± SD)	S	A	H	S	A	H	S	A	H
Shortness of breath	2.1 ± 0.40	1.7 ± 0.36*	0.7 ± 0.63†	14	5	1*	16	5	0‡	4	6	1
Central tetany	1.9 ± 0.80	0.8 ± 0.31‡	0.5 ± 0.85†	12	1*	1*	7	1	4	9	1	1
Peripheral tetany	1.7 ± 0.72	0.7 ± 0.59	0.6 ± 0.70†	3	1	0	2	1	0	4	0	0

S, Study group; A, asthma group; H, healthy control group.

* $P < .05$.† $P < .001$.‡ $P < .01$.TABLE IV. Correlations between PETCO₂ and the number of symptoms 5, 8, and 10 minutes after the HVPT and after termination of the WCCT

Test	Study group (r)	Asthma group (r)	Healthy group (r)
HVPT			
5 min	-0.60	0.13	0.05
8 min	-0.72*	0.21	0.01
10 min	-0.76*	0.12	-0.11
WCCT	-0.59	0.12	-0.67*

* $P < .05$.

trol group was significant ($P < .05$), and a tendency to significance was seen between the study group and the asthma group ($P = .07$). The difference was most obvious for central tetany symptoms.

Number of symptoms in relation to level of PETCO₂. There was a negative correlation between the number of symptoms and the level of PETCO₂. For the study group, the correlation was significant at 8 minutes ($r = -0.72$; $P < .05$) and at 10 minutes ($r = -0.76$, $P < .05$) after the HVPT and almost significant at 5 minutes after the HVPT ($r = -0.60$; $P = .07$) and after the WCCT ($r = -0.59$; $P = .08$). In the asthma group, the correlations were positive and not significant. A negative significant correlation was also found in the healthy control group after the WCCT ($r = -0.67$; $P < .05$; Table IV).

DISCUSSION

The results show that the patients with asthma-like symptoms but negative asthma test responses did not experience persistent chronic hyperventilation during quiet breathing but that they might experience hyperventilation when provoked.³⁰ Their slower recovery rate of PETCO₂ after the HVPT and their greater reduction of PETCO₂ during the WCCT and their slightly higher respiratory rate after the HVPT in comparison with the other 2 groups support this conclusion. After the HVPT, the

asthma group also had a slower recovery rate of PETCO₂ than the healthy control group, indicating that hyperventilation might have been present in some patients with asthma too. The study group more frequently had a variety of symptoms often seen in hyperventilation, both in general and after the provocations compared with the other 2 groups. The differences between the study group and the healthy control group were salient. The asthma group took an intermediate position, which is not surprising because this group and the study group describe similar symptoms and consequently are difficult to separate clinically. However, the study group reported more tetany symptoms both during life before and during the HVPT, indicating that hyperventilation might be present more often in the study group, explaining some of the symptoms.^{6,21} The results are further underlined by the fact that significant negative correlations between the level of PETCO₂ and the number of symptoms were found in the study group during both tests. The study group and the asthma group differed thereby because the correlation between the level of PETCO₂ and number of symptoms was positive in the asthma group. However, the results must be interpreted with caution, considering the small group sizes and the risk of type II error.

What might cause this hyperventilation? The results from the WCCT support our idea that mental stress might be 1 trigger factor. The test caused a greater reduction of PETCO₂; it reproduced more symptoms in the study group than in the other 2 groups, and a significant negative correlation between the level of PETCO₂ and the number of symptoms was found in the study group. It is possible that the patients, because of a feeling of discomfort in certain situations, start to over-breathe, which causes a reduction of PETCO₂, resulting in different symptoms. If the patient is worried about these symptoms, secondary stress may further aggravate the over-breathing. This is in accordance with recent findings by Leznoff⁴⁰ in patients with multiple chemical sensitivity. Another explanation for the experience of symptoms might be that the patients with asthma-like symptoms but negative asthma

tests could be more sensitive than healthy subjects to small reductions in PETCO₂. It has been shown that the symptoms are experienced at different levels of PETCO₂ in healthy subjects and patients with asthma.^{27,30,41,42}

A slow recovery rate of PETCO₂ after discontinuing hyperventilation has been considered to be an important diagnostic criterion for hyperventilation.^{21,25} Recovery rate has usually been followed for not more than 5 minutes.^{21,25,30} Our study shows that follow-up periods for patients with asthma-like symptoms but negative asthma test responses should be longer, even longer than in this study. Ten minutes after the HVPT, the mean PETCO₂ of the study group had not recovered to 4 kPa, although it did so after 6 minutes in the asthma group and after 5 minutes in the healthy control group.

The validity and the reliability of the HVPT has been questioned.^{37,43-45} In patients with chest pain and healthy subjects, mental stress itself has been found to provoke the WCCT-induced symptoms without a concomitant hypocapnia, defined as PETCO₂ less than 4 kPa.³⁷ Considering this, although we have not studied the same category of patients, and to improve the discriminative power of the NQ, we have followed a stricter and more thoroughly evaluated model in the classification of reproduced symptoms.²⁴ We also suggest that the limits for hyperventilation should be further studied and discussed.

Another way to study the connection between symptoms and fluctuations in PETCO₂ could be a diary kept by the patients and long-term ambulatory monitoring of PETCO₂ during daily life situations.

In conclusion, the results from this study show that patients with asthma-like symptoms but negative asthma test responses do not experience persistent chronic hyperventilation during quiet breathing but that they might experience hyperventilation when provoked. The results from the WCCT support our idea that mental stress might be one trigger factor.

An HVPT, according to the method described in this study, could be a useful tool in the diagnosis of hyperventilation and separation of the patient with these symptoms from patients with asthma and healthy subjects. To find out whether mental stress might be one trigger factor, the patient should be subjected to a stress test. The tests should comprise recognition of symptoms, divided into different components, for analysis of the symptom profile of the patient and the study of recovery of PETCO₂ during at least 10 minutes after the provocations. The tests described in this study can be handled by a nurse with assistance from a doctor.

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