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Original articles

Medically unexplained dyspnea: psychophysiological characteristics and role of breathing therapy

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Background Medically unexplained dyspnea occurs commonly in medical settings and remains poorly understood. This study was conducted to investigate the psychophysiological characteristics of medically unexplained dyspnea and the efficacy of breathing retraining for these patients.

Methods A group of patients with medically unexplained dyspnea were compared to patients with a variety of organic lung diseases and healthy subjects. In another group of patients, the influence of breathing therapy on complaints, anxiety, and breath-holding was evaluated for an average of 1.5 years.

Results Patients with medically unexplained dyspnea reported more intense dyspnea than patients with a variety of organic lung diseases. Additionally, they were anxious and presented a broad range of symptoms in daily life and under challenge, for instance voluntary hyperventilation. More than one third of them qualified for panic disorder. They had shorter breath-holding time at rest, less increase in breath-holding time and higher chances of showing a "paradoxical" decrease of breath-holding time after hyperventilation. A combination of PaO2, forced expiratory volume in one second (FEV_1), and anxiety measures distinguished them from organic dyspnea. Breathing retraining profoundly improved their symptoms and decreased the level of state and trait anxiety. Moreover, they better tolerated the voluntary hyperventilation and the symptoms induced were also markedly decreased after therapy. Breath-holding time was prolonged and PetCO2 in a representative group of patients increased.

Conclusions Patients with medically unexplained dyspnea appear to have the feature of a "psychosomatic" patient: an anxious patient with a wide variety of symptoms of different organ systems that do not have an organic basis. They can be distinguished from organic dyspnea using a small set of physiological and psychological measures. Breathing retraining turns out to be an effective therapy for those "difficult to treat patients".

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Dyspnea is a common complaint prompting the patient to seek medical care. Based on the medical history and the results of physical examination, physicians often develop a list of possible causes for dyspnea in his/her mind, for instance pulmonary diseases, cardiovascular diseases, anemia, thyroid diseases, neuromuscular disorders, etc. The latter list directs to a further series of laboratory tests focusing on suspected causes and hoping to uncover the underlying pathology of organs and/or cellular derangement. The corresponding therapy is generally oriented on the underlying pathology, rather than on symptoms. This approach of medical model of disease has

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been quite successful in the majority of patients with dyspnea. However, about 14% of patients with presenting breathlessness are left undiagnosed[1] because the presence of structural alterations of organs is not confirmed even after thorough examinations. As a result, a label of "medically unexplained dyspnea" is used to classify the patients.[1] Patients appear very difficult to manage after the diagnosis is clinically established.[2]

Recent studies have suggested that dyspnea without identified pathology might be caused by psychophysiological or mind-body mechanisms.[3-5] In a group of patients labeled with "behavioral breathlessness", Howell[3] observed a high overlap of psychiatric disorders and a high prevalence of obsessional personality. In previous studies, we found that the "psychosomatic" patients demonstrated anxiety and somatoform disorders, characterized by a variety of psychological and somatic symptoms and a high level of anxiety.[4,5] Breathing instability leading to episodic hyperventilation correlated with the patients' dyspnea.[5] Breathing retraining appeared to be effective for those patients.[6]

We wondered whether patients with medically unexplained dyspnea are different from patients with organic dyspnea in psychophysiological aspects. If so, what are the diagnostically relevant differences? Is breathing retraining effective for patients with medically unexplained dyspnea? The present study was designed to answer these questions.

METHODS

STUDY ONE

Subjects

Patients with medically unexplained dyspnea

One hundred and eleven patients with medically unexplained dyspnea were grouped in this category. Organic diseases as a cause of dyspnea were excluded on the basis of (1) complete medical history and physical examination; (2) hemoglobin determination; (3) chest X-ray; (4) lung function tests: lung volumes, maximal expiratory flows, airway resistance and diffusion capacity for CO; (5) arterial blood gases; (6) ECG and echocardiography. When indicated, bronchoprovocation test, $\dot{V}/\dot{Q}$ scan, thyroid function tests and others were performed.

Patients with asthma

Twenty patients who met GINA criteria of asthma were recruited. Pulmonary function tests were performed to demonstrate reversible airway obstruction. Prior to testing, the patients were not asked to refrain from their medications.

Patients with organic dyspnea

Thirty-seven patients with a variety of lung diseases other than asthma were classified in this group. Among them, 13 cases suffered from interstitial lung diseases, 7 chronic obstructive pulmonary diseases (COPD), 4 sarcoidosis, 3 lung cancer, 2 pulmonary tuberculosis, 2 pleural diseases, 2 alveolar proteinosis, 1 bronchiectasis, 1 pulmonary-hepatic syndrome, and 2 hypoxemia of unknown etiology.

Healthy subjects

One hundred and ninety-two healthy subjects were recruited from outside the hospital. They had neither history nor symptoms suggestive of respiratory diseases or anxiety disorders.

Experimental procedure

The subject first answered a Nijmegen questionnaire evaluating the prevalence of spontaneous complaints in daily life,[7] and State-Trait-Anxiety Inventory assessing the level of state (STAI-S) and trait (STAI-T) anxiety.[8] Subsequently, the subject graded the intensity of his/her dyspnea on a visual analogue scale (VAS),[9] followed by a breath-holding test. At the end of a deep inspiration the subject held his/her breath as long as possible, by closing the nose with his/her fingers. The number of seconds he/she refrained from breathing was noted. Then a hyperventilation provocation test (HVPT) was performed. The subject breathed as deeply as possible at a rate of 60 breaths per minute for 3 minutes. A metronome indicated the frequency. Immediately after HVPT, the dyspnea level was graded on VAS, followed by another breath-holding test. Finally, the subject answered a 29-item symptom checklist concerning the occurrence and intensity of the symptoms induced by HVPT.[4]

Statistical analysis

A variance analysis with Duncan test was performed to compare the 3 groups of patients and healthy subjects on the scores of symptoms and of anxiety, VAS, and breath-holding time. The same procedure was used to compare the 3 groups of patients on forced expiratory volume in one second (FEV_1), PaCO2 and PaO_2. Multiple regression was performed with progressive backward elimination of the non-or least significant factors to relate breath-holding time or VAS to various symptom factors. A discriminant analysis was employed to investigate which combination of psychological and physiological parameters seperated best medically unexplained dyspnea from organic dyspnea.

STUDY TWO

Patients

The inclusion criteria were (1) patients with medically unexplained dyspnea; (2) completion of at least 10 sessions of breathing retraining; (3) at least one year elapsed from the initial evaluation to the follow-up examination. Ninety-nine patients met the criteria and were informed to come back for follow-up. Sixty-five patients came back to the laboratory. One patient (PSQ, male, 65 years) was excluded because he developed episodes of chest pain with ischemic ST-T changes on ECG and was recently diagnosed with coronary heart disease. In total, 64 patients completed the follow-up examination. Eleven patients lived in provinces far from Beijing and were unable to come because of a high cost to travel and/or their job. One patient refused to come because of no benefit from breathing retraining. These 12 patients were interviewed by telephone. We lost contact with 22 patients because of house moving and/or job changes.

Before breathing retraining, 10 out of 76 patients had been on medication for 1 month to 10 years. During breathing retraining, 3 of them were able to taper the doses and were eventually free from medications. The other 7 patients kept on using medications until the follow-up examination. After breathing retraining, 9 patients resorted to medication therapy because their symptom relief was unsatisfactory. Four of them used medications temporarily. The medications used included Alprazolam, Diazepam, Clonazepam, Lorazepam, Doxepin, Ludiomil, Atenolol, Seroxat, Prozac, or traditional Chinese medicine.

Breathing retraining

A semi-structured interview was taken by one of the authors in order to inquire about the patient's complaints, life style and his (or her) own interpretation of the complaints. The doctor tried to achieve a re-attribution of the patient's symptoms to an inappropriate breathing leading to hyperventilation. Then, the rationale of breathing retraining was explained: reducing hyperventilation by acquiring an abdominal breathing pattern, with slowing down of respiration. Biofeedback equipment providing audible electromyogram (EMG) signals (Poda Biofeedback Systems JD-2A, Beijing, China) was used in breathing retraining. Breathing frequency was kept 8 to 12 per minute in most cases. Each session lasted for an hour.

Follow-up examination

For the 64 patients who came back, the procedures in the initial evaluation were repeated in the follow-up examination. These included Nijmegen questionnaire, STAI-state and STAI-trait anxiety, hyperventilation provocation test and 29-item symptom checklist, VAS and breath-holding time before and after HVPT. Additionally, the overall subjective improvement was rated by the patient as follows: 0 = not improved, 1 = slightly improved, 2 = markedly improved and feeling well.

End-tidal CO_2 partial pressure ($PetCO_2$)

In 28 patients, $PetCO_2$ during spontaneous breathing following the breath-holding and during the whole period of hyperventilation was recorded in the initial evaluation as well as in the follow-up examination. A Capnograph (Criticare Systems Poet TE, Waukesha WI, USA) was connected to patients via a small cannula inserted in one of the nostrils.

Statistical analysis

The null hypothesis test for within comparison was used to compare the data before and after breathing therapy. Student's *t*-test was used to compare the degree of subjective improvement and to compare patients who completed the follow-up examination with those reached by telephone. Chi-square test was used to compare the gender distribution between the two patient groups. Multiple regressions with backward elimination were performed to relate the changes in VAS, breath-holding time or STAI to the changes of symptom factors.

RESULTS

STUDY ONE

Level of anxiety and total scores of symptoms

As shown in Table 1, patients with medically unexplained dyspnea had highest anxiety on STAI-S and STAI-T. Additionally, they reported many symptoms in daily life

Table 1. Level of anxiety (STAI) and scores of symptoms in daily life and following HVPT

Groups	No. of subjects	Gender (female)	Age (years, range)	STAI-State	STAI-Trait	Nijmegen Questionnaire	29-symptom checklist
Nonorganic (A)	111	74	40.1 (23-66)	45.94 ± 12.33	51.20 ± 10.85	26.30 ± 11.23	22.58 ± 13.30
Asthma (B)	20	12	42.9 (21-66)	36.30 ± 13.38	43.30 ± 13.81	20.15 ± 9.24	14.45 ± 11.20
Organic (C)	37	15	49.5 (20-69)	37.30 ± 11.16	40.73 ± 10.18	16.22 ± 8.97	6.30 ± 5.56
Healthy (D)	192	97	41.4 (20-68)	32.72 ± 9.41	34.87 ± 9.11	4.68 ± 4.59	4.66 ± 5.07
P value			0.0004	0.0001	0.0001	0.0001	0.0001
Duncan test			C > (B, D, A)	A > (C, B, D)	A > (B, C) > D	A > B > C > D	A > B > (C, D)

Table 2. Symptom factors following hyperventilation provocation test and in daily life in four groups of subjects

Type of the symptoms	Nonorganic (A)	Asthma (B)	Organic (C)	Healthy (D)	*P* value	Duncan test
Symptoms induced by HVPT						
Factor 1 (Central nervous system)	0.73 ± 0.62	0.62 ± 0.59	0.13 ± 0.27	0.10 ± 0.20	0.0001	(A, B) > (C, D)
Factor 2 (Respiratory)	1.52 ± 0.87	0.92 ± 0.97	0.58 ± 0.61	0.19 ± 0.29	0.0001	A > B > C > D
Factor 3 (Paresthesias)	0.70 ± 0.66	0.46 ± 0.60	0.15 ± 0.32	0.33 ± 0.48	0.0001	A > B > C; A > D
Factor 4 (Anxiety)	0.78 ± 0.80	0.18 ± 0.28	0.05 ± 0.15	0.07 ± 0.21	0.0001	A > (B, D, C)
Factor 5 (Cardiac)	0.88 ± 0.90	0.81 ± 0.72	0.30 ± 0.57	0.26 ± 0.44	0.0001	(A, B) > (C, D)
Symptoms in daily life						
Factor 2 (Respiratory)	1.67 ± 0.66	1.50 ± 0.68	1.18 ± 0.67	0.07 ± 0.17	0.0001	(A, B) > C > D
Factor 4 (Anxiety)	1.05 ± 0.97	0.66 ± 0.74	0.38 ± 0.61	0.09 ± 0.23	0.0001	A > B > C > D
Factor 6 (Central nervous system and paresthesias)	0.74 ± 0.66	0.49 ± 0.47	0.43 ± 0.45	0.10 ± 0.22	0.0001	A > (B, C) > D

Subjective gradation of the symptoms: from 0 (none) to 4.

Table 3. VAS (in cm on a 50 cm bar) and breath-holding time (in seconds) at rest and following hyperventilation in healthy subjects and patients

Groups	VAS (rest)	VAS (HVPT)	VAS (HVPT-rest)	Breath-holding (rest)	Breath-holding (HVPT)	Breath-holding (HVPT-rest)
Nonorganic (A)	18.88 ± 12.16	27.76 ± 12.99	8.80 ± 12.69	48.95 ± 20.56	75.40 ± 48.46	26.34 ± 38.90
Asthma (B)	10.94 ± 9.71	19.55 ± 13.95	8.61 ± 10.56	45.50 ± 23.68	82.60 ± 51.76	37.10 ± 31.35
Organic (C)	12.40 ± 8.85	14.62 ± 11.13	2.22 ± 8.75	34.54 ± 16.04	54.16 ± 31.27	19.62 ± 19.15
Healthy (D)	1.20 ± 2.83	6.13 ± 8.76	4.93 ± 8.60	57.28 ± 17.23	109.58 ± 34.20	52.3 ± 24.50
P value	0.0001	0.0001	0.0009	0.0001	0.0001	0.0001
Duncan test	A > (C, B) > D	A > B > C > D	(A, B) > C	D > (A, B) > C	D > (B, A) > C	D > B > C; D > A

VAS (HVPT-rest) = VAS following HVPT-VAS at rest; Breath-holding (HVPT-rest) = breath-holding following HVPT-breath-holding at rest.

as well as during HVPT. The intensity of their dyspnea reached at least grade III according to the criteria of Fletcher et al.[10] Panic disorder was present in 38% of these patients, based on the criteria of Diagnotic and Statistical Manual of Mental Disorders (DSM-IV).[11]

Types of the symptoms

In keeping with the results of a principal component analysis previously published,[4] the symptoms induced by HVPT were grouped into five factors and the daily life symptoms under three factors (Table 2). Patients with medically unexplained dyspnea had the highest intensity and prevalence of respiratory symptoms in daily life, followed by anxiety symptoms and symptoms of the central nervous system and paresthesias. Similarly the most frequent symptoms induced by HVPT were respiratory complaints, followed by cardiac and anxiety symptoms.

FEV_1 and arterial blood gases

Patients with asthma and with other organic lung diseases had significantly lower forced expiratory volume in one second (FEV_1) than patients with medically unexplained dyspnea (79.9%, 74.8% and 114.5%, respectively, $P = 0.0001$) and lower PaO_2 than those with medically unexplained dyspnea (79.39, 79.46 and 91.96 mmHg, $P = 0.0001$), whereas pH and $PaCO_2$ were not different in the three groups of patients (for pH: 7.42, 7.41, 7.42, $P = 0.19$; for PaCO2: 39.50, 37.91, 37.83 mmHg, $P = 0.55$).

VAS and breath-holding time

As shown in Table 3, patients with medically unexplained dyspnea graded highest on VAS at rest as well as immediately after HVPT, whereas patients with organic lung diseases graded markedly lower, particularly after HVPT. The breath-holding time before and after HVPT was shortest in patients with organic lung diseases, followed by asthmatics and patients with medically unexplained dyspnea. The increase of breath-holding time following HVPT was largest in healthy subjects. A decrease of breath-holding time following HVPT compared to the value at rest was observed in 42 out of 168 patients (35 with medically unexplained dyspnea, 4 with organic dyspnea, 3 asthmatics).

Correlation of breath-holding and VAS with symptoms

Multiple regressions between breath-holding time after HVPT with symptom factors 1 to 5 showed, for the total population, negative and positive relationships with factors 2 and 3 respectively. The partial correlation coefficient with factor 2 was statistically significant in the three groups of patients. The partial correlation with factor 3 was significant only in healthy subjects and in asthmatics (Table 4). With respect to VAS after HVPT, positive partial correlation was observed with factor 2 for the total population (also with factor 3) and the four subgroups. In addition, VAS positively correlated with factors 5, 4 and 3 in healthy subjects (Table 4).

Concerning the breath-holding time at rest, a negative correlation with factor 2 was observed in the total population, essentially due to the patients with medically unexplained dyspnea. Mainly because of the same group of patients, VAS at rest was positively correlated with factor 2 (Table 4).

Table 4. Multiple regression relating breath-holding or VAS to symptom factors

	Symptom factors	R^2	*P* value
Following HVPT			
Breath-holding = f (factors 1 to 5)			
Nonorganic	−2	0.20	0.0001
Asthma	−2, +3	0.38	0.02
Organic	−2	0.08	0.08
Healthy	+3	0.17	0.0001
All	−2, +3	0.24	0.0001
VAS = f (factors 1 to 5)			
Nonorganic	+2	0.45	0.0001
Asthma	+2	0.32	0.009
Organic	+2	0.21	0.004
Healthy	+5, +4, +2 +3	0.31	0.0001
All	+2, +3	0.59	0.0001
At rest			
Breath-holding = f (factors 2, 4 and 6)			
Nonorganic	−2	0.05	0.02
Asthma		0.15	0.09
Organic		0.08	0.08
Healthy		0.02	0.18
All	−2	0.09	0.0001
VAS = f (factors 2, 4 and 6)			
Nonorganic	+2	0.12	0.0002
Asthma	+2	0.16	0.08
Organic	+2	0.13	0.03
Healthy	+4	0.03	0.01
All	+2	0.51	0.0001

R^2: Relative contribution of symptom factor to overall variance of breath-holding time or VAS. The sign of the symptom factor indicates a positive or negative correlation.

Discriminant analysis

To investigate whether the observed differences could distinguish patients with medically unexplained dyspnea from patients with organic dyspnea and asthma, state and trait anxiety, symptom factors in daily life as well as during hyperventilation, VAS, breath holding time, pH, $PaCO_2$, PaO_2, FEV_1 were introduced in a discrimamt analysis. After backward elimination, FEV_1 and PaO_2 turned out to be the most discriminating variables with adjusted R^2 of 0.51. Adding Trait anxiety or anxiety symptoms induced by HVPT significantly increased the adjusted R^2 from 0.51 to 0.56 or 0.58.

STUDY TWO

General well-being of the patients after breathing retraining

Sixty-four patients were examined over a mean period of 19 months (range: 11 to 53 months). Among them, 44 were females with a mean age of 37.2 years (range 14 to 57 years) and 20 males (mean age: 43.7years, range 17 to 67 years). On the average, they completed 24.2 sessions of breathing retraining (range 8 to 60 sessions). 48 patients (75%) were feeling well based on subjective estimate, 11 patients (17%) got slightly improved and 5 patients (8%) were bad or not improved at the follow-up examination. Sixty percent of patients (38 out of 64) were able to adopt abdominal breathing to relieve their symptoms, whenever the symptoms occurred.

The 12 patients reached by telephone did not differ from the 64 patients examined with respect to age, gender proportion, breathing retraining sessions, subjective improvement, and coping strategy, except for the follow-up duration. The patients reached by telephone were followed over a longer period (25 months vs 19 months, $P = 0.04$).

Symptoms and anxiety after breathing retraining

As shown in Table 5, the total score of symptoms in daily life (Nijmegen questionnaire) and those induced by voluntary hyperventilation were markedly decreased after breathing therapy. A more detailed analysis on the types of symptoms showed a significant improvement on all symptom factors. The scores of state and trait anxiety were also significantly decreased.

Table 5. Scores of symptoms and anxiety (STAI) before and after breathing therapy in 64 patients with medically unexplained dyspnea

	Breathing therapy	
	Before	After
STAI-State	43.33 ± 11.99	33.46 ± 10.65***
STAI-Trait	50.80 ± 10.92	43.44 ± 11.25***
Symptoms in daily life (NVL)	29.63 ± 11.41	18.05 ± 10.05***
Factor 2 (Respiratory)	1.72 ± 0.62	0.80 ± 0.68***
Factor 4 (Anxiety)	1.24 ± 0.88	0.62 ± 0.76***
Factor 6 (CNS and paresthesias)	1.07 ± 0.79	0.54 ± 0.59***
29 symptoms in HVPT	25.58 ± 14.33	14.72 ± 10.46***
Factor 1 (CNS)	0.70 ± 0.51	0.53 ± 0.41*
Factor 2 (Respiratory)	1.60 ± 0.88	0.78 ± 0.68***
Factor 3 (Paresthesias)	0.96 ± 0.80	0.54 ± 0.60***
Factor 4 (Anxiety)	0.78 ± 0.81	0.35 ± 0.49**
Factor 5 (Cardiac)	0.93 ± 0.92	0.61 ± 0.74*

NVL: Nijmegen questionnaire; CNS: symptoms of central nervous system. Significance with respect to that before breathing therapy: * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

Influence of breathing therapy on VAS, breath-holding time and $PetCO_2$

As shown in Table 6, the ratings on VAS were markedly decreased after breathing therapy both at rest and

immediately after HVPT, and the breath-holding times increased.

Table 6. Influence of breathing therapy on VAS and breath-holding time in 64 patients with medically unexplained dyspnea

	Breathing Therapy	
	Before	After
VAS (rest)	17.89 ± 11.52	7.44 ± 8.87 ***
VAS (HVPT)	27.54 ± 12.63	14.83 ± 10.80 ***
Breath-holding (rest)	52.29 ± 22.81	62.14 ± 18.19 ***
Breath-holding (HVPT)	77.09 ± 51.26	96.38 ± 42.90 **

Significance with respect to that before breathing therapy: ** $P<0.01$; *** $P<0.001$.

In 28 patients, $PetCO_2$ was monitored during spontaneous breathing following breath-holding and during the whole period of hyperventilation. After therapy, PetCO2 was higher at rest (32.4 mm Hg before vs 37.4 mm Hg after therapy, $P=0.0001$) and tended to be slightly higher in the course of hyperventilation (Fig).

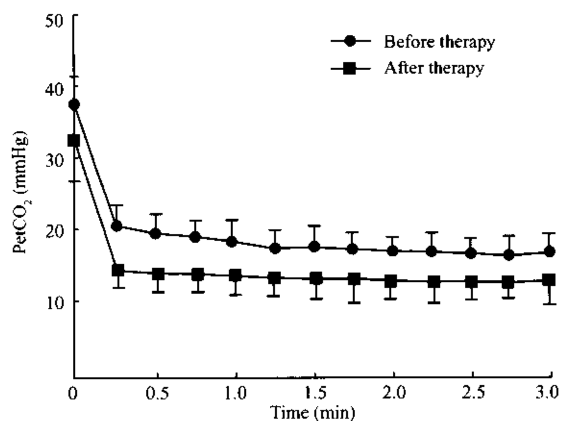

Fig. The values of $PetCO_2$ during spontaneous breathing (time 0) and during the whole period of hyperventilation (means of 15 s) before (closed circles) and after breathing therapy (closed squares). After therapy, $PetCO_2$ was higher at rest and tended to be slightly higher in the course of voluntary hyperventilation. The drop of $PetCO_2$ at the onset of hyperventilation was similar before and after breathing therapy.

Relating the changes of breath-holding, VAS and STAI to those of symptoms

A multiple regression analysis showed that the decrease in respiratory complaints significantly contributed to the decline of rating on VAS both at rest and following HVPT, and to the prolongation of breath-holding time following HVPT (Table 7). The reductions in STAI-state or trait were influenced mainly by the decrease of anxiety symptoms (factor 4) in daily life. Following HVPT, the changes in STAI-trait correlated mainly with the changes in respiratory symptoms.

Table 7. Multiple regression relating changes of breath-holding, VAS or STAI-state and trait to the changes of symptom factors before and after breathing therapy

The difference before and after breathing therapy	Symptom factors	R^2	P value
Following HVPT			
Δbreath-holding = Δfactors 1 to 5 (following HVPT)	−2	0.11	0.0089
ΔVAS = Δfactors 1 to 5 (following HVPT)	+2	0.32	0.0001
ΔState = Δfactors 1 to 5 (following HVPT)	−	−	−
ΔTrait = Δfactors 1 to 5 (following HVPT)	+2	0.13	0.0043
At rest			
Δbreath-holding = Δfactors 2, 4, 6 (at rest)	−	−	−
ΔVAS = Δfactors 2, 4, 6 (at rest)	+2	0.13	0.0044
ΔState = Δfactors 2, 4, 6 (at rest)	+4	0.19	0.0008
ΔTrait = Δfactors 2, 4, 6 (at rest)	+4	0.20	0.0004

R^2: Relative contribution of symptom factor to overall variance of breath-holding time, VAS, state or trait. The sign of the symptom factor indicates a positive or negative correlation.

DISCUSSION

Patients with medically unexplained dyspnea reported more intense dyspnea than patients with a variety of organic lung diseases. Additionally, they were anxious and presented a broad range of additional symptoms in daily life and under challenge (voluntary hyperventilation, HVPT), for instance, cardiac symptoms, paresthesias, and symptoms of the central nervous system. More than one third of them were qualified for a diagnosis of panic disorder. These observed features fit the general features of the "psychosomatic" patient: an anxious patient with a wide variety of symptoms from different organ systems that are present with high frequency in daily life and in specific situations and do not have an organic basis. In addition, these patients also have a shortening of the breath-holding time and an increase of dyspnea recorded on a visual analogue scale (VAS). These features are not specific since these are observed also in patients with asthma and other organic lung diseases. The breath-holding time following HVPT appeared to be related to the main symptoms elicited by hyperventilation. There was a decrease in the breath-holding time with marked respiratory symptoms (factor 2) in the three groups of patients (also at rest in medically unexplained dyspnea), an increase in the breath-holding time with more pronounced symptoms of paresthesias and stiffness (factor 3) in healthy subjects and in asthmatics. As factor 3 was the largest symptom factor following HVPT in healthy subjects and factor 2 the largest among the patients (Table 2), the element mainly influencing the breath-holding time appeared to be determined by the dominant symptom factor: in healthy subjects it increases with the intensity of paresthesias, in patients it decreases with

respiratory complaints. At rest, the influence of symptoms on breath-holding appears to be minimal.

It is not unexpected that VAS was influenced mainly by respiratory symptoms. However, in healthy subjects other symptom factors contributed to VAS. At rest, anxiety symptoms influenced VAS. Following HVPT, anxiety, paresthesias and cardiac symptoms significantly added to VAS. VAS thus depends not only on the respiratory symptoms but also on the level of anxiety and other somatic symptoms. As an index of dyspnea, VAS reflects more than pure dyspnea in healthy subjects. It is only in patients that VAS is a good indicator of respiratory symptoms.

Breathing is under considerable behavioral control of the higher brain. The cortical influence modulates the sensation of dyspnea and therefore the breaking point of breath-holding. Alpher et al[12] showed that distraction of the subject's attention by means of a mental task extended the breath-holds. Van der Does[13] observed an inverse correlation between breath-holding time and a score of somato-sensory amplification in patients with panic disorder or with symptoms of depression. It is likely that the symptoms appearing suddenly (in the course of the HVPT) attract the subject's attention more than his daily life complaints. This might explain why a link between breath-holding time and symptoms is observed primarily following hyperventilation.

Overall, medically unexplained dyspnea could be separated from organic dyspnea by a combination of PaO_2, FEV_1 and anxiety measures. Since the diagnosis of medically unexplained dyspnea was primarily based on the exclusion of organic dyspnea, it is logical that PaO_2 and FEV_1 were most influential in the discriminant analysis. However, adding anxiety measures significantly improved the discrimination: in a patient complaining of dyspnea, with normal spirometry and blood gases, the dyspnea is likely to be non-organic in origin if the patient is clearly anxious. Other tests, like VAS and breath-holding time, do not contribute to the specificity of the diagnosis.

Breathing retraining originated in ancient Buddhism traditions and has been widely used as meditation to reduce negative effects and to relieve anxiety in the Eastern world. In 1938, Soley and Shock[14] first applied it as a therapy for patients labeled with "anxiety state with hyperventilation syndrome". This was followed by extensive studies in patients with anxiety disorders and with so-called hyperventilation syndrome.[6,15-17] In these studies breathing retraining achieved a reduction of somatic complaints, level of anxiety, and frequency and intensity of the symptom attacks.

Up to now, there have been few studies focusing on a specific regimen for medically unexplained dyspnea. We submitted a group of patients to breathing retraining. After breathing therapy, the daily life complaints were markedly improved and significant improvement was observed not only with respiratory symptoms, but also with anxiety and symptoms of the central nervous system and paresthesia. Since respiratory symptoms mainly deal with aspects of dyspnea (chest pain, shortness of breath, unable to breathe deeply, discomfort in or around the chest and faster or deeper breathing), it is not unexpected that the rating on VAS was markedly decreased. The breath-holding time was accordingly prolonged. Additionally, the level of state and trait anxiety was reduced. The resting $PetCO_2$ in a representative group of patients was increased.

When the patients were submitted to hyperventilation provocation tests for the second time after breathing therapy, surprisingly, they tolerated the test quite well and the symptoms induced by voluntary hyperventilation markedly decreased. Accordingly, VAS following HVPT was decreased and the breath-holding time after HVPT increased.

It appears that breathing retraining works both on the mind and on the body, more specifically on anxiety as well as on breathing. It is likely that breathing retraining improves patients' symptoms not only by the direct action on breathing, shown by the improvement of end-tidal CO_2 (Fig), but also by modifying negative affectivity, evidenced by the decrease in STAI-trait. The link between the changes of trait anxiety and of respiratory symptoms induced by HVPT before and after breathing therapy (Table 7) might be causal. As trait anxiety is decreased after breathing therapy, the process of symptom perception might be modified. If patients are less introceptively orientated and less negative in their interpretation of bodily sensations, their somatic complaints will decrease. When facing a challenge, for instance HVPT, they will tolerate it much better.

One might question whether the patients treated with breathing retraining have recovered completely. We compared the patients with marked improvement with healthy subjects in study one. They still have more symptoms (daily life and following HVPT) and higher anxiety compared with healthy subjects. However, in view of its favorable influence on patients' symptoms, breathing retraining may be advocated as a therapy for

those "difficult to treat patients".

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