Interval hypoxic training improves autonomic cardiovascular and respiratory control in patients with mild chronic obstructive pulmonary disease

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Objectives **Chronic obstructive pulmonary disease (COPD) is associated with cardiac autonomic nervous system dysregulation. This study evaluates the effects of interval hypoxic training on cardiovascular and respiratory control in patients with mild COPD.**

Methods **In 18 eucapnic normoxic mild COPD patients (age 51.7 ± 2.4 years, mean ± SEM), randomly assigned to either training or placebo group, and 14 age-matched healthy controls (47.7 ± 2.8 years), we monitored end-tidal carbon dioxide, airway flow, arterial oxygen saturation, electrocardiogram, and continuous noninvasive blood pressure at rest, during progressive hypercapnic hyperoxia and isocapnic hypoxia to compare baroreflex sensitivity to hypoxia and hypercapnia before and after 3 weeks of hypoxic training. In double-blind fashion, both groups received 15 sessions of passive intermittent hypoxia (training group) or normoxia (placebo group). For the hypoxia group, each session consisted of three to five hypoxic (15–12% oxygen) periods (3–5 min) with 3-min normoxic intervals. The placebo group inhaled normoxic air.**

Results **Before training, COPD patients showed depressed baroreflex sensitivity, as compared with healthy individuals, without evident chemoreflex abnormalities. After training, in contrast to placebo group, the training group showed increased ($P<0.05$) baroreflex sensitivity up to normal levels and selectively increased hypercapnic ventilatory response ($P<0.05$), without changes in hypoxic ventilatory response.**

Conclusion **Eucapnic normoxic mild COPD patients already showed signs of cardiovascular autonomic abnormalities at baseline, which normalized with hypoxic training. If confirmed in more severe patients, interval hypoxic training may be a therapeutic strategy to rebalance early autonomic dysfunction in COPD patients.** ***J Hypertens*** **27:1648–1654 © 2009 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Keywords: autonomic nervous system, baroreflex sensitivity, chronic obstructive lung disease, hypoxia, intermittent hypoxic training, ventilatory control

Abbreviations: BRS, baroreflex sensitivity; CO_2-et, end-tidal carbon dioxide; COPD, chronic obstructive pulmonary disease; HCVR, hypercapnic ventilatory response; HRV, heart rate variability; HVR, hypoxic ventilatory response; IHT, interval hypoxic training; SaO_2%, arterial oxygen saturation

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Introduction

The chronic obstructive pulmonary disease (COPD) is an internationally important cause of morbidity and mortality generating great health and economic burden around the world [1]. COPD is known to be a systemic disease showing, apart from lung limitations, systemic inflammation, cachexia, skeletal muscle dysfunction, cardiovascular, and also osteoskeletal changes [2].

There is rising evidence suggesting an important role of cardiovascular autonomic dysfunction in patients with COPD, even at mild stages of the disease, however, with weak relationship to the severity of airflow limitation [3,4]. In COPD patients, baroreflex sensitivity (BRS) is decreased [5] and heart rate variability (HRV) is reduced at rest and also during exercise [6,7], and a marked sympathetic activation as measured by muscle sympathetic nerve activity (MSNA) was observed in patients with chronic respiratory failure [8]. In addition, peripheral and central chemoreflexes are also depressed by severe COPD, whereas in mild COPD, findings are controversial [9–12]. All these findings have been shown to be major risk factors for cardiac morbidity and mortality [13].

Although the more severe autonomic disturbances have been attributed to a frank autonomic neuropathy [14], there is no comprehensive evaluation of cardiovascular and respiratory control abnormalities in COPD, and so far

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there is no evidence indicating whether such abnormalities occur at a similar stage of the disease and whether these have a functional origin at least at an early stage of the disease.

COPD patients with low ventilatory drive to carbon dioxide are at risk of developing hypercapnia, nocturnal hypoxemia [15], and elevated pulmonary artery pressure [16,17]. In addition, COPD patients with a blunted central drive to chemical stimuli (less chemosensitivity to hypoxia and hypercapnia) are at higher risk of near fatal episodes [12].

Therefore, it would be of great clinical importance to find new treatments to rebalance the cardiorespiratory control toward normal values.

The interval hypoxic training (IHT) was originally developed in the former Soviet Union and consisted of repeated 5–7 min of steady (9–12%) or progressive hypoxia (down to 5–7%), interrupted by equal periods of recovery [18]. It was reported that moderate intermittent hypoxia induces changes on the hypoxic ventilatory response (HVR) [19,20]. IHT appeared to reduce sympathetic activity, without significant changes in blood pressure [19]. Potentially, these effects may have a positive influence on cardiovascular autonomic imbalance and disturbed ventilatory response in patients with COPD.

For this purpose, we performed a comprehensive evaluation of cardiovascular and respiratory control function in patients with mild COPD, before and after a 3-week-IHT training to test whether there was already impairment in cardiovascular and/or respiratory control; and whether possible abnormalities could be modified by a simple nonpharmacological technique in a favorable way.

Methods

Participants

The present double-blind, placebo-controlled study was carried out at the Institute of Sports Science, University of Innsbruck, Austria in 18 patients with mild COPD symptoms (chronic cough, sputum production, wheezing and/or dyspnea that occurs on a frequent basis for at least 3 months) and evidence of impaired lung function (GOLD 0 to 2 according to the Global Initiative of Chronic Lung Disease from 2001) [21]. The participants were randomly assigned either to the training group or placebo group (nine participants in each group). We also obtained baseline data from 14 age-matched healthy individuals, as healthy controls. The anthropometric and main clinical data of the participants in each group are presented in Tables 1 and 2. All participants were volunteers from the same village (Mieming, Tyrol, Austria, 864 m asl) and gave written informed consent to participate in the study; they were unaware of specific aims of the study. The participants were advised not to change medications, smoking habits, nutrition, and physical activity during the entire study period.

Table 1 Chronic obstructive pulmonary disease patients (training, placebo) and healthy controls (control)

Parameters	Training	Placebo	Control
N	9	9	14
Sex (M/F)	5/4	5/4	5/9
Age (years)	51.0 ± 2.8	52.4 ± 4.1	46.7 ± 2.9
Height (cm)	174.0 ± 2.2	173.1 ± 2.9	174.7 ± 1.7
Weight (kg)	79.2 ± 5.1	75.9 ± 3.9	70.4 ± 2.8
BMI (kg/m^2)	26.4 ± 1.9	25.4 ± 0.9†	22.9 ± 0.7
Smoking history			
Total (*N*)	7	4	–
Former (*N*)	1	2	–
Current (*N*)	6	2	–
Lung function			
FEV_1 (l)	2.54 ± 0.20†	2.32 ± 0.18†	3.96 ± 0.20
FVC (l)	3.53 ± 0.30§	3.50 ± 0.26§	4.65 ± 0.25
FEV_1pred (%)	78.2 ± 3.6	72.9 ± 1.9†	83.1 ± 2.2
FEV_1/FVC (%)	72.3 ± 1.9*,†	66.2 ± 1.5†	85.8 ± 2.7

Baseline values of different groups on anthropometric data, smoking history, and lung function (mean ± SEM). FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; FEV_1pred, predicted value of FEV_1. $^{*}P < 0.05$ vs. placebo. $^{\S}P < 0.01$ vs. control. $^{\dagger}P < 0.05$ vs. control.

Interval hypoxic training protocol

All participants performed either 3 weeks of IHT (training group) or 3 weeks of sham training (placebo group). The IHT consisted of daily training, five sessions per week (a total of 15 sessions). For the training group, each session consisted of three to five hypoxic periods (15–12% inspired fraction of oxygen; HypoxyComplex $HypO_2$, HypoMed, Moscow, Russia), each lasting 3–5 min with 3-min normoxic intervals. The protocol is shown in Table 3. Hypoxic and normoxic air were inhaled via facial mask in sitting position. The placebo group performed the breathing program in the same way, but inhaled normoxic air. Start and termination of breathing periods were announced and controlled by instructors. Arterial oxygen saturation and heart rate were monitored by a pulse oximeter attached to a fingertip, and blood pressure was checked by two physicians who did not

Table 2 Medication of chronic obstructive pulmonary disease patients (training, placebo)

Agents	Training	Placebo	P^a
Sympathomimetics	4	6	0.637
Anticholinergics	5	5	1.000
Theophyline	1	–	1.000
Corticosteroids[b]	4	5	1.000
Antidepressants	1	2	1.000
ACE inhibitors	1	4	0.294
Thyroxine	–	2	0.471
ß-Blockers	1	–	1.000
Diuretics	1	–	1.000
Ca^{2+} antagonists	1	–	1.000
Angiotensin inhibitors	1	–	1.000
Proton pump inhibitors	5	2	0.335

ACE, angiotensin-converting enzyme. [a] Fisher's exact test. [b] Only prescribed for usage in certain critical circumstances such as acute worsening of lung function or acute exacerbations.

Table 3 Three-week-breathing program (training group[a])

Week	Hypoxia		Normoxia		Number of cycles Hypoxia/normoxia per session
	O_2 (%)	Duration (min)	O_2 (%)	Duration (min)	
1	15	3	21	3	3
2	13	4	21	3	4
3	12	5	21	3	5

[a]There were five sessions per week (one session/day); the placebo group performed the same program breathing only normoxic air (21% of inspired oxygen fraction).

participate in the data recording sessions and analysis in order to guarantee blindness of the study. The protocol assumed that whenever symptoms occurred or oxygen saturation dropped below 80%, hypoxia would be interrupted until saturation levels recovered 80% or greater. The breathing protocol had been adapted from the Clinical Research Laboratory of the Hypoxia Medical Academy in Moscow and was based on their previous long-term clinical experience in IHT [22]. The protocol complied with the declaration of Helsinki and was approved by the local Ethics Committee. A steady-hypoxia protocol was preferred in order to reduce the subjective perception of hypoxia and thus guarantee blindness.

Measurement session protocol

Two measurement sessions were performed, within 2 days before and after the completion of the IHT protocol. All participants were examined in sitting position at a comfortable temperature/humidity. They were connected to a rebreathing circuit through a mouthpiece, similarly to previously described and validated work [23,24]. In each condition, we continuously measured end-tidal CO_2 ($etCO_2$) by a capnograph connected to the mouthpiece (COSMOplus, Novametrix, Wallingford, Connecticut, USA) and oxygen saturation (SaO_2) by a pulse oxymeter (3740 Ohmeda, Englewood, Colorado, USA). Airway flow was continuously measured by a heated Fleish pneumotachograph (Metabo, Epalinges, Switzerland), connected to a differential pressure transducer (RS part N395-257; Corby, UK), connected in series to the expiratory part of the rebreathing circuit. In addition, we recorded the electrocardiogram (by chest leads) and continuous noninvasive blood pressure by the cuff method (Portapres; Finapres Medical Systems, Amsterdam, The Netherlands). In each participant, we recorded the data during 4 min of spontaneous breathing as baseline. During this recording, the participants remained connected to the rebreathing circuit, but this was left open to allow inspiration and expiration of air in the room. We also randomly performed the following rebreathing tests: progressive normocapnic hypoxia (SaO_2 from baseline to 80%, et-CO_2 maintained at a standard level of 38 mmHg); and progressive hyperoxic hypercapnia (et-CO_2 from baseline to +15 mmHg, SaO_2 > 98%).

During progressive hypoxia, the CO_2 levels were clamped by passing a variable part of the expired air into a reservoir filled with soda lime, under continuous visual control of et-CO_2. When the expired air was passed through the soda lime, et-CO_2 decreased, whereas when expired air was sent directly into the rebreathing bag, et-CO_2 increased. This allowed the levels of et-CO_2 to be continuously adjusted in order to reach and maintain it at the desired level. At the same time, by effect of rebreathing, the oxygen content of the rebreathing bag progressively decreased, hence inducing a reduction in SaO_2. When the hypercapnic response had to be tested, oxygen was supplied to the rebreathing bag at very low flow, in order to maintain SaO_2 above more than 98%, whereas the expired air was sent directly to the rebreathing bag, thus inducing a progressive rise in et-CO_2.

Data acquisition and analysis

All signals were continuously acquired on a personal computer (Macintosh Powerbook; Apple, Cupertino, California, USA) at 600 samples/channel. The respiratory flow signal was integrated by software and each breath was identified by an automatic and interactive program written in BASIC by one of our members of group (L.B.). The chemoreflex sensitivity to hypoxia or hypercapnia was obtained from the slopes of the linear regression of minute ventilation vs. SaO_2 or et-CO_2, respectively, for each breath. The response to et-CO_2 was considered as predominantly an index of central chemoreflex, whereas the response to hypoxia was considered as predominantly an index of peripheral chemoreflex. The arterial BRS was calculated from the sequences of R–R interval and systolic blood pressure by the so-called 'alpha index', obtained by autoregressive power spectral analysis of R–R interval and systolic blood pressures [24,25], during the recordings obtained at baseline.

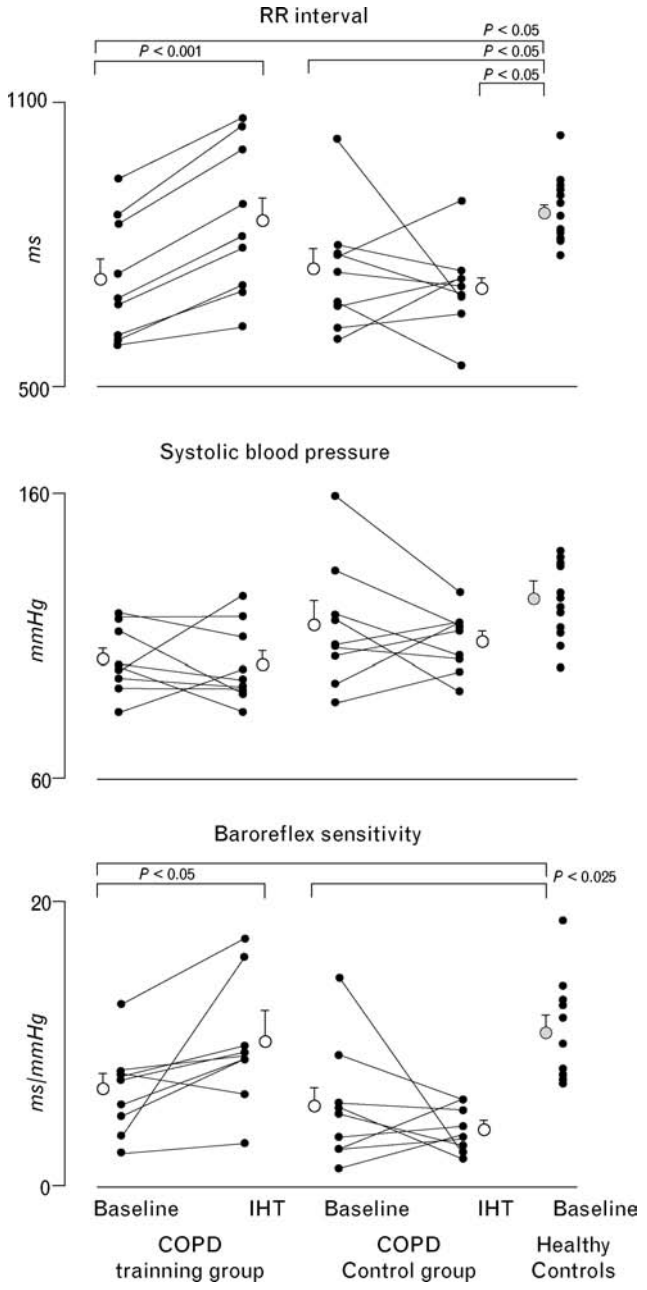
Statistical analysis

Data are presented as means ± SEM. Differences between different groups and different examination (before/after IHT) were assessed by a mixed-design analysis of variance. Differences between healthy controls and COPD patients at baseline or after IHT were assessed by factorial analysis of variance. If overall significances were found, *t*-test was used for comparisons. Due to the small number of participants, differences before and after training were tested also by nonparametric tests (Wilcoxon) and significances were reported only if both tests were significant. Correlations between resting respiratory parameters and cardiovascular and respiratory autonomic data were tested by linear regression analysis on baseline data.

Results

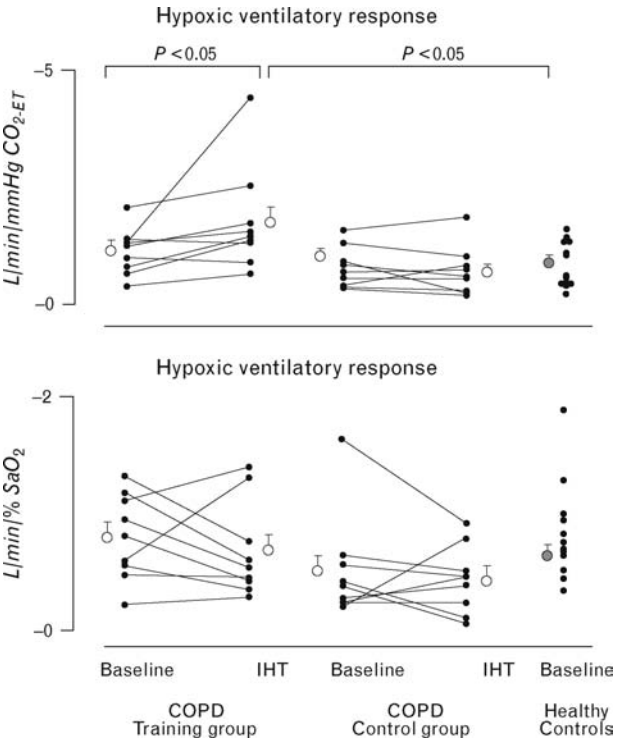
Results are expressed in Figs. 1 and 2 and in Table 4. All participants completed the IHT or the sham protocols successfully, and no clinical problems occurred.

Fig. 1



Changes in R–R interval, blood pressure, and baroreflex sensitivity before and after interval hypoxic training in the two groups of chronic obstructive pulmonary disease patients (training and control groups), and in the healthy controls. COPD, chronic obstructive pulmonary disease; IHT, interval hypoxic training.

Fig. 2



Changes in hypoxic and hypercapnic ventilatory responses before and after interval hypoxic training in the two groups of chronic obstructive pulmonary disease patients (training and control groups), and in the healthy controls. CO_2-et, end-tidal carbon dioxide; COPD, chronic obstructive pulmonary disease; IHT, interval hypoxic training; SaO_2, arterial oxygen saturation.

Baseline: cardiovascular data

Before IHT, BRS was reduced in COPD in comparison with healthy controls (6.19 ± 1.05 vs. 10.66 ± 1.65 ms/mmHg, $P < 0.025$) and the R–R interval was significantly shorter (741 ± 33 ms in COPD vs. 870 ± 18 ms of healthy controls, $P < 0.05$). Systolic blood pressure was not significantly different. The extent of respiratory abnormalities correlated with BRS [forced expiratory volume in 1 s (FEV1): $r = +0.46$, $P < 0.01$; FEV1/forced vital capacity (FVC): $r = +0.38$, $P < 0.05$] and R–R interval (FEV1: $r = +0.56$, $P < 0.01$; FEV1/FVC: $r = +0.53$, $P < 0.01$; Fig. 1).

Baseline: respiratory control

Before IHT, the COPD patients had slightly lower CO_2-et levels (32.9 ± 1.2 vs. 36.3 ± 1.0 mmHg of healthy

Table 4 Resting respiratory data of different groups (training, placebo) before (baseline) and after the breathing program (interval hypoxic training) in comparison with healthy controls (control)

Variable	time	Training	Placebo	Control
VE	Baseline	11.2 ± 0.7	12.5 ± 1.4	10.1 ± 0.45
(l/min)	IHT	11.2 ± 0.8	12.8 ± 0.8	–
Vt	Baseline	850 ± 89	917 ± 80	877 ± 56
(ml)	IHT	938 ± 91	867 ± 71	–
Respiration rate	Baseline	14.4 ± 1.4	14.0 ± 1.2	12.1 ± 1.1
(breaths/min)	IHT	13.1 ± 1.6	15.2 ± 0.8	–
CO_2-et	Baseline	33.8 ± 1.6	31.8 ± 1.9	36.3 ± 1.0
(mmHg)	IHT	34.1 ± 1.8	33.2 ± 1.2	–
SaO_2	Baseline	96.6 ± 0.4	97.1 ± 0.5	97.2 ± 0.3
(%)	IHT	96.6 ± 0.2	97.4 ± 0.3	–

CO_2-et, end-tidal carbon dioxide; IHT, interval hypoxic training; SaO_2, arterial oxygen saturation; VE, minute ventilation; Vt, tidal volume.

controls, $P < 0.05$), whereas SaO_2 levels were similar as in healthy controls (96.8 ± 0.3 vs. $97.2 \pm 0.3\%$, *P*: NS). At baseline, both groups had similar HVR (-0.65 ± 0.09 vs. $-0.64 \pm 0.1\,l\,min^{-1}\%\ SaO_2^{-1}$, *P*: NS) and similar hypercapnic ventilatory response (HCVR; 1.08 ± 0.14 vs. $0.89 \pm 0.12\,l\,min^{-1}\,mmHg^{-1}\ CO_2\text{-}et^{-1}$, *P*: NS; Fig. 2).

Effects of interval hypoxic training on cardiovascular data

After 3-week-IHT, the training group showed significantly increased BRS (from 6.8 ± 1.47 to 9.87 ± 2.79 ms/mmHg, $P < 0.05$) up to nearly normal values of healthy individuals, in contrast to the placebo group, which showed an opposite trend (from 5.66 ± 1.57 to 4.04 ± 0.5 ms/mmHg, *P*: NS). The R–R interval significantly increased in the training group (from 729 ± 49 to 852 ± 62 ms, $P < 0.001$), almost to the level of healthy individuals, whereas it was slightly shortened in the placebo group (from 751 ± 48 to 711 ± 34 ms, *P*: NS). There were no significant changes in systolic blood pressure in both groups, apart from a slight decrease in the training group after IHT (Fig. 1).

Effects of interval hypoxic training on respiratory control

After IHT, we found a significant and specific increase in HCVR (from $1.17 \pm 0.18\,l\,min^{-1}\,mmHg^{-1}$ to $1.63 \pm 0.39\,l\,min^{-1}\,mmHg^{-1}\ CO_2\text{-}et^{-1}$, $P < 0.05$), whereas no changes were found in the HVR. Interestingly, there were slight changes in breathing pattern of the training group after the IHT: a slightly higher value in tidal volume (850 ± 89 ml before IHT vs. 938 ± 91 ml after IHT, *P*: NS) combined with a slightly reduced respiration rate (14.4 ± 1.4 vs. 13.1 ± 1.6 breaths min^{-1}, *P*: NS) after IHT, indicating a tendency of rearrangement toward a deeper and slower breathing (Fig. 2, Table 4).

Discussion

Main findings

To our knowledge, this is the first comprehensive evaluation of cardiovascular and respiratory functions in patients with mild COPD and also the first study testing the effects of IHT in such patients in a randomized double-blind, placebo-controlled study. In the present study, we found that

(1) despite mild clinical involvement, COPD patients already showed signs of sympathetic activation, presented by higher heart rate and depressed baseline BRS in comparison with healthy controls.
(2) IHT normalized heart rate and BRS and also produced a significant increase in HCVR.

We suggest that the changes induced by IHT could be clinically beneficial in COPD and potentially protective against development of hypercapnia.

Cardiovascular control abnormalities in chronic obstructive pulmonary disease

Autonomic abnormalities have been consistently found in COPD. Although Patakas *et al.* [5] were the first to demonstrate a decreased BRS in rather severe COPD patients in comparison with healthy controls, we found depressed BRS even in mild COPD patients at baseline in comparison with healthy controls. A decrease in BRS is associated with a higher risk of cardiovascular morbidity and mortality, cardiac arrhythmias, and stroke, which are frequently reported in severe COPD [26], together with possible development of pulmonary hypertension [5,27].

Several strategies and interventions were reported to improve depressed BRS, including oxygen supplementation [13] and exercise training [26]. Our findings in patients with mild COPD suggest an early BRS impairment. This BRS dysfunction and its reversibility are likely to be mainly functional, at least in early stages of the disease, probably in contrast with more severe COPD stages [28]. Overall, an altered BRS might be an early indicator of autonomic impairment in COPD patients and an early target for various medical and physical interventions that may possibly lead to a delay in COPD progression or other comorbidities. In the present study, we found a selective improvement in BRS by IHT in the training group, upto almost normal values of healthy individuals.

Heindl *et al.* [8] and Velez-Roa *et al.* [29] reported a marked sympathetic activation in patients with chronic respiratory failure compared with healthy controls by measuring the short-term oxygen-induced MSNA. Before IHT, our data also suggest sympathetic activation (faster heart rates and depressed BRS). An increased sympathetic activity was also found in pulmonary artery hypertension [29] and is frequently reported in COPD patients with poor prognosis [30]. Although hypoxic neuropathy is often described in COPD patients [14,31–33], our results suggest that in early stages of COPD, there is mainly a functional disturbance in the autonomic nervous system. This, in fact, was at least partly reversible by IHT upto normal values. This autonomic dysfunction in mild COPD stages may be an early indicator for the onset of COPD, even preceding more abnormal spirometric findings.

Respiratory control abnormalities in chronic obstructive pulmonary disease

The presence of an abnormal ventilatory drive in COPD remains controversial [12]; however, a blunted ventilatory drive to chemical stimuli (hypoxia and/or hypercapnia) is reported more frequently [9,10,34,35], particularly in severe COPD or in patients undergoing near fatal episodes of asthma [12]. Overall, these reports suggest a progression of abnormalities with the severity of the disease [35]. Accordingly, in our patients, we could not

find a blunted ventilatory drive, presumably due to the mildness of their disease. Abnormalities in respiratory control clearly have a major impact on severity and prognosis in COPD. In contrast to HVR, which was not related to nocturnal desaturation in COPD [15], patients with low HCVR were at risk of developing nocturnal hypoxemia [17]. The transient nocturnal hypoxemia increases pulmonary artery pressure, possibly leading to sustained pulmonary hypertension and ultimately right heart failure [36]. Overall, it has been suggested that hypercapnia may develop in patients with severe asthma and COPD by an alteration in chemosensitivity as the severity of the disease progresses [12]. In COPD patients, it may therefore be an advantage to have a high HCVR in order to delay the onset of hypercapnia.

Effects of interval hypoxic training in chronic obstructive pulmonary disease

The effects of IHT are various and complex and depend on the protocol adopted. Modifications of total hypoxia, intensity and duration of the single hypoxic cycles, the duration of normoxic pauses, and the number of cycle repetitions may determine beneficial or even negative effects [18]. Acute hypoxia increases sympathetic activity and ventilation (by increase in tidal volume and breathing frequency) [19]. The IHT may, therefore, function as a form of interval stress training (increased sympathetic activity during hypoxic cycles), which may lead to an improved stress tolerance during daily life of COPD patients, as recently shown in patients with coronary artery disease [37]. The exercise limitation in COPD patients depends on many factors [38], including increased airway resistance and respiratory work [39], increase in physiological dead space, ventilation-perfusion mismatch, and reduced ventilatory efficiency [38]. The slight increase in tidal volume with concomitant decrease in respiration rate, only seen in the training group after IHT, may indicate a tendency toward an improved ventilation efficiency and may therefore be beneficial for COPD patients by the reduction of respiratory metabolic costs and probably also dyspnea.

Although it has been reported that intermittent hypoxia induces changes on the HVR in healthy individuals [20,40], we could not find increased HVR in our COPD patients. This may likely depend on different IHT protocols, rather than a different study population (COPD vs. healthy individuals). In fact, the present study confirms previous findings [19] of an increase in vagal activity after IHT also in healthy individuals. The lack of increase in HVR could be due to a much milder hypoxic protocol in our patients.

Clinical relevance

Patients with COPD who experienced a near fatal episode have reduced chemosensitivity to hypoxia and hypercapnia [12]. Thus, patients with a blunted central drive to chemical stimuli are apt to lapse into a critical condition. This, together with the disturbed autonomic reflexes, the increased sympathetic activity, the loss of vagal activity, and the altered BRS represents a major cardiovascular risk factor [13]. These findings are strongly supported by the result of the Lung Health Study of nearly 6000 persons with mild-to-moderate COPD [41], which showed that far more patients died of cardiovascular diseases than COPD.

The ventilatory drive can be affected by treatment with bronchodilators, oxygen administration, and lung volume reduction surgery (LVRS). Oral administration of β-2-agonists increases HCVR and slightly increases HVR [12]. Despite these possibilities, the cardiorespiratory abnormalities remain a major problem in COPD, so it would be of great clinical interest to find additional strategies to rebalance the disturbed autonomic nervous system and shift the different parameters toward normal values. Our present findings show a potential additional treatment.

Limitations of study

We selected only mild COPD patients for safety reasons, as IHT has never been tested before in COPD. Additionally, there was also an interest in testing the presence and the possible reversibility of early autonomic disturbances in COPD by IHT. The small number of observations in each group is due to the complexity of a double-blind placebo-controlled IHT protocol. Not surprisingly, this is the first study of this type ever performed in COPD. All patients were under medications and these were not discontinued during the study for ethical reasons. However, medications were equally distributed in the two COPD groups (Table 2), so an interference with IHT should not be expected. There was a small but significant difference in BMI between COPD patients and healthy controls. The higher BMI in COPD could have influenced the comparison with and healthy individuals [42,43], however, since the two COPD groups showed comparable BMI, it could not have influenced the effects of IHT. Although the present results are to be considered specific for the protocol adopted, we believe that other protocols could be used as well with positive results.

In conclusion, patients with even mild levels of COPD have some degree of autonomic dysfunction. The improvement in these indices with IHT suggests that these abnormalities are to a great extent functional and could be reversed, at least at an early stage of the disease. The autonomic improvement and the absence of adverse side reactions in our patients, together with the positive findings observed, suggest that IHT could be a potential therapeutic option in COPD and warrants further studies in more compromised patients.

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