

COPD and Thyroid Dysfunctions

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Abstract

Background Chronic obstructive pulmonary (COPD) is one of the major causes of morbidity and mortality in the world. COPD is characterized by chronic inflammation in the pulmonary compartment and in the systemic circulation. This disorder is associated with clinically significant alterations in biochemistry and organ function; thyroid dysfunctions are common in chronic diseases, such as COPD. Several characteristics of COPD patients could increase their likelihood of developing hypothyroidism or hyperthyroidism. The purpose of our study was to assess the impact of thyroid dysfunction in patients with COPD. **Methods** We evaluated the pulmonary function tests, arterial blood gases, maximal inspiratory pressure (MIP), maximal expiratory pressure (MEP), and thyroid functions in patients with COPD, recruited between admissions in Respiratory Diseases Unit, Policlinico Umberto I, Rome, Italy, from June 2012 to May 2013. We selected patients with subclinical hypothyroidism (ScH), overt hypothyroidism, and hyperthyroidism, and a control group without thyroid disturbance.

Results Our results indicate that patients with overt hypothyroidism have lower levels of pO_2 , MIP, and MEP compared with subjects with ScH, hyperthyroidism, and the control group. We also found a substantial tendency towards pCO_2 levels increase in patients with hypothyroidism ($p = 0.06$).

Conclusions Patients with thyroid dysfunctions have a greater impairment of MIP and MEP and a negative correlation was observed between hypoxemia and TSH. Further studies are needed to investigate whether the treatment of thyroid dysfunction could have a beneficial effect on COPD patients' lung function and prognosis.

Keywords Chronic obstructive pulmonary disease · Thyroid dysfunction · Maximal expiratory pressure · Maximal inspiratory pressure · Hypoxemia · Hypercapnia

Introduction

Chronic obstructive pulmonary disease (COPD) is one of the major cause of morbidity and mortality in the world, leading to a worsening of quality of life and to premature death because of its complications [1]. It is characterized by chronic bronchitis or emphysema and progressive air-flow obstruction. Patients with COPD have a chronic illness; they are commonly hypoxemic, hypercapnic, and have increased levels of systemic inflammatory markers. Although it is not a systemic disease, COPD is characterized by a systemic chronic inflammation that is associated with impairment of organs function [2, 3].

Alterations in thyroid function tests are commonly observed in COPD. Thyroid diseases were very common disorders, with a prevalence of 4.3 % in adult population of United States [4]. The secretion of thyroid hormones, triiodothyronine (T3) and thyroxine (T4), is regulated by thyroid-stimulating hormone (TSH), which is produced by pituitary gland. The thyroid hormones are critical determinants of metabolic activity in adults, regulating the metabolism of proteins, lipids, and carbohydrates and

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controlling the activity of membrane-bound enzymes [5]. They can also regulate the transcription of numerous genes encoding both myofibrillar and calcium-regulatory proteins in myofibres, enhance mitochondrial oxidation, and increase metabolic rate [6]. Particularly, the effects on metabolic rate are probably an important link between the thyroid hormones and respiratory drive [7].

The most common thyroid diseases are hypothyroidism and hyperthyroidism. Thyroid disorders may be classified according to international guidelines on the basis of TSH as subclinical hypothyroidism (ScH) (TSH levels between 4.5 and 10 $\mu\text{UI/ml}$ values with normal values of free T4), overt hypothyroidism (TSH values >10 $\mu\text{UI/ml}$, with low values of free T4), subclinical hyperthyroidism (TSH <0.02 $\mu\text{UI/ml}$ with normal values of free T4), and overt hyperthyroidism (TSH <0.02 $\mu\text{UI/ml}$ with high values of free T4) [8, 9].

Several characteristics of COPD patients could potentially increase their likelihood of developing hypothyroidism or hyperthyroidism [10]. Impaired thyroid function in COPD may present as ScH, overt hypothyroidism, and nonthyroidal illness syndrome [11, 12]. It is well known that severity of airway obstruction, hypoxemia, and systemic inflammation may predispose to not only nonthyroidal illness syndrome, but also ScH and overt hypothyroidism [13–15].

In subjects with severe COPD who develop hypoxemia and hypercapnia, various endocrine organs are involved. Hypothyroidism can decrease respiratory drive, respiratory muscle function, exercise capacity, and increase risks for sleep disordered breathing in COPD; particularly hypothyroidism is associated with inspiratory and expiratory weakness in patients with COPD [16] that may be due to decreased expression of Type IIb myosin heavy chains, phrenic nerve neuropathy [17], or decreased neuromuscular transmission secondary to a decrease in the planar areas of nerve terminals and end-plates of type I and IIa fibres. Weakness correlates with the severity of hypothyroidism and is reversed by replacement therapy. Probably impaired muscle energy metabolism, resulting from a defect in glycogen breakdown or mitochondrial function and hypothyroid myopathy, contributes to the reduced exercise capacity in COPD patients.

Also hyperthyroidism may impair respiratory muscle function and exercise in COPD patients [18]. In fact, both maximal inspiratory and expiratory pressures (MIP and MEP) decrease, with increasing severity of hyperthyroidism [18]. Abnormalities in pulmonary function also may be observed because of decreased respiratory muscle performance, decreased lung compliance, and increased ventilatory requirements [19].

The purpose of our study was to assess the impact of thyroid dysfunction in COPD patients.

Methods

In this study, we evaluated the pulmonary function tests, arterial blood gases, MIP and MEP, and thyroid function in COPD patients. From June 2012 to May 2013, 189 consecutive individuals who were referred to Respiratory Diseases Unit, Respiratory Outpatients Ambulatory, and Respiratory Day Hospital, Policlinico Umberto I, Rome, Italy, were enrolled in the study. COPD patients, stage GOLD II and III, were enrolled [1]. The evaluation of the thyroid function was performed during hospitalization, and no patient was on treatment for thyrotoxicosis at baseline evaluation. All patients with diagnosis of hypothyroidism underwent therapy with levothyroxine, and all patients with hyperthyroidism received methimazole, but not β -blockers. All patients were smokers or ex-smokers. Stable COPD patients were receiving inhaled bronchodilator therapy (long-acting β_2 agonist and/or anticholinergic agents); antibiotics and systemic steroids were added to therapy during exacerbations (increased dyspnea, sputum production, and sputum purulence).

We excluded from the study patients with neuromuscular diseases, other respiratory diseases, and endocrine system diseases other than thyroids disorders. We also excluded from the study subjects undergoing treatments that could interfere with serum hormone levels (such as amiodarone).

In all patients, a clinical history was taken, physical examination was performed, body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2), and comorbidities were identified on the basis of concomitant therapy and/or investigations performed at hospital admission. Arterial blood gas analysis was performed in all participants; hypoxemia was defined by a $\text{pO}_2 <60$ mmHg and hypercapnia was defined by a $\text{pCO}_2 >45$ mmHg. Pulmonary function tests were performed at baseline using a spirometer (Cosmed, Quark PFT, Pavona, Rome, Italy), which had measurement accuracy within 5 % of volume. According to GOLD guidelines, subjects with $50 \% \leq \text{FEV}_1 < 80 \%$ predicted were described as moderate COPD, patients with $\text{FEV}_1 <50 \%$ predicted were described as having severe airflow obstruction. Diffusing capacity for carbon monoxide (DLCO) and DLCO/alveolar volume ratio (DLCO/VA) were measured using single breath method. MIP and MEP were measured using a portable mouth pressure meter (Spirovis—COSMED—Pavona, Italy); this had a disposable mouthpiece and a small leak to prevent glottic closure. MIP was obtained at the level of RV and MEP was measured at the level of TLC. The measurements were made in standing position. The subjects were encouraged to achieve maximal strength. The measurements were repeated until five values varying by less than 5 % and sustained for at least 1 s were obtained; the best value achieved was considered in the data analysis. PFTs were performed by a study blinded technician

Table 1 Patients demographics and clinical characteristics (data expressed as mean \pm SD)

Variables	COPD (<i>n</i> = 50)	COPD and hypothyroidism (<i>n</i> = 33)	COPD and ScH (<i>n</i> = 22)	COPD and hyperthyroidism (<i>n</i> = 50)	<i>p</i> value
Gender: male (<i>n</i> %)	32 (64)	19 (57.5)	13 (59)	28 (56)	0.32 ^a
Age (year)	72.32 \pm 10.34	71.66 \pm 12.12	76.23 \pm 7.8	69.78 \pm 11.66	0.27 ^b
BMI (kg/m ²)	22.46 \pm 2.16	22.15 \pm 2.38	22.57 \pm 2.03	22.06 \pm 2.18	0.82 ^b
SBP (mmHg)	128.6 \pm 10.34	120.8 \pm 11.7	125.8 \pm 16.82	130.92 \pm 14.91	0.34 ^b
DBP (mmHg)	82.4 \pm 9.2	88.5 \pm 7.3	86.69 \pm 9.24	90.2 \pm 6.3	0.19 ^b
Fasting blood glucose (mg/dl)	90.3 \pm 8.7	107.6 \pm 9.8	104.78 \pm 8.72	89.5 \pm 10.23	0.764 ^b
Current smokers (%)	46 (92)	24 (72)	15 (68)	44 (88)	0.962 ^a

BMI body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *COPD* chronic obstructive pulmonary disease, *ScH* subclinical hypothyroidism

^a Chi square test

^b Student's *t* test for unpaired data

and analysed by experienced pulmonologists. After interview and thyroid physical examination, serum levels of TSH, FT3, and FT4 were assessed by Chemiluminescent Competitive Enzyme Immunoassay method. Also, all patients underwent assay thyroglobulin (normal range between 1.40 and 78 ng/ml), anti-thyroperoxidase antibodies (normal range between 0 and 34 IU/ml), anti-thyroglobulin antibodies (normal range between 0 and 115 IU/ml), and anti-TSH antibodies (normal range between 1 and 1.5 IU/ml) assays. We stratified patients into three subgroups: ScH, overt hypothyroidism, and hyperthyroidism. As a control group, we also evaluated a subset of individuals with COPD, but without thyroid disturbance. Written, informed consent was obtained from all participants.

Statistical Analysis

Continuous variables were presented as mean \pm standard deviation (SD), and differences were evaluated by the paired Student's *t* or Wilcoxon test, depending on the shape of the distribution curve. Categorical variables were expressed by count and percentage and compared by chi square or Fisher's exact test when appropriated.

The Spearman coefficient was used for measuring linear correlation between variables.

The probability values are two-sided; a probability value <0.05 was considered to indicate statistical significance.

Statistical analyses were performed by using software SigmaStat (San Jose, CA, USA). Power analysis was performed using STATA v.11 (College Station, TX, USA).

Results

Among the 189 patients recruited in our study, 21 individuals were excluded at initial evaluation due to their

comorbidities [8 congestive heart failure, 9 paroxysmal arrhythmia, 4 obstructive sleep apnoea syndrome (OSAS)], and 14 during hospitalization (3 for cancer diagnosis, 4 for severe kidney failure, 5 for sepsis, 2 for valvulopathy).

The study group was stratified into 3 subsets according to TSH concentrations: 33 subjects with hypothyroidism, 22 patients with ScH, and 48 patients with hyperthyroidism. As control group, we evaluated 51 patients without thyroid dysfunction. Baseline characteristics are summarized in Table 1. Age, BMI, blood pressure, blood glucose, and tobacco consumption did not significantly differ between subjects with and without thyroid dysfunction.

Table 2 shows significantly lower pO₂ levels in patients with hypothyroidism compared with subjects with ScH, hyperthyroidism, and the control group (60.48 mmHg \pm 6.61 vs. 63.3 mmHg \pm 9.25 and 69.38 mmHg \pm 7.87 and 67.6 mmHg \pm 8.97 respectively; *p* = 0.05; Fig. 1). We also found a negative correlation between the pO₂ and TSH values (*p* = 0.01, *r* = -0.62; Fig. 2). Interestingly, we demonstrated higher levels of PaCO₂ in hypothyroid patients, although this finding did not reach a statistical significance (Fig. 3). In addition, we observed a significant decrease of the respiratory muscle strength measured by MEP. Patients with hypothyroidism had lower MEP values compared with other participants (63.58 cmH₂O \pm 10.41 vs. 73.62 cmH₂O \pm 13.46 Sch patients and 75.52 cmH₂O \pm 11.44 hyperthyroid patients and 74.82 cmH₂O \pm 10.91 control group; *p* = 0.05; Fig. 4).

Similarly, also the MIP was significantly reduced in hypothyroid patients (-34.9 cmH₂O \pm 17.03 vs. -41.1 cmH₂O \pm 13.17 Sch patients and -57.63 cmH₂O \pm 15.04 hyperthyroid patients and -59.56 cmH₂O \pm 16.02 control group; *p* = 0.05; Fig. 5). In line with these observations, a negative correlation between MEP and TSH was observed (*p* = 0.01, *r* = -0.69; Fig. 6). Conversely a positive relationship was found between MIP and TSH (*p* = 0.01, *r* = 0.52; Fig. 7).

Table 2 Patients main clinical and instrumental parameters (data expressed as mean \pm SD)

Variables	COPD ($n = 50$)	COPD and hypothyroidism ($n = 33$)	COPD and ScH ($n = 22$)	COPD and hyperthyroidism ($n = 50$)	p value
FEV ₁ (%)	56.18 \pm 15.57	54.15 \pm 17.3	54.8 \pm 15.4	57.36 \pm 14.75	0.2 ^a
FEV ₁ /FVC ratio	68.85 \pm 7.33	70.28 \pm 9.24	69.87 \pm 6.86	71.91 \pm 5.59	0.47 ^a
DLCO (ml/min/mmHg)	66.72 \pm 9.87	67 \pm 11.1	63 \pm 9.58	67.9 \pm 9.53	0.08 ^a
DLCO/VA (ml/min/mmHg/l)	72.46 \pm 8.49	72.21 \pm 9.73	70.61 \pm 6.87	73.92 \pm 7.93	0.073 ^a
MIP (cmH ₂ O)	-59.56 \pm 16.02	-34.9 \pm 17.03*	-41.1 \pm 13.17	-57.63 \pm 15.04	0.05 ^{a*}
MEP (cmH ₂ O)	74.82 \pm 10.91	63.58 \pm 10.41*	73.62 \pm 13.46	75.52 \pm 11.44	0.05 ^{a*}
pH	7.41 \pm 0.04	7.4 \pm 0.043	7.42 \pm 0.04	7.4 \pm 0.047	0.9 ^a
pO ₂ (mmHg)	67.6 \pm 8.97	60.5 \pm 6.61*	63.3 \pm 9.25	69.38 \pm 7.87	0.05 ^{a*}
pCO ₂ (mmHg)	49.44 \pm 12.64	52.04 \pm 13.42	49.46 \pm 11.6	49 \pm 12.61	0.06 ^a
HCO ₃ ⁻ (mmol/l)	29.03 \pm 7.7	28.07 \pm 8.46	30.77 \pm 8.18	28.75 \pm 7.18	0.71 ^a
Lactate (mmol/l)	1.29 \pm 0.48	1.12 \pm 0.5	1.21 \pm 0.44	1.14 \pm 0.46	0.975 ^a
SpO ₂ (%)	94.4 \pm 2.1	93.43 \pm 1.92	94.27 \pm 1.5	95.23 \pm 1.98	0.24 ^a

COPD chronic obstructive pulmonary disease, ScH subclinical hypothyroidism, FEV₁ forced expiratory volume in 1 s, FEV₁/FVC forced expiratory volume in 1 s to forced vital capacity, DLCO diffusing capacity for carbon monoxide, DLCO/VA diffusing capacity for carbon monoxide/alveolar volume, MIP maximal inspiratory pressure, MEP maximal expiratory pressure, PaO₂ partial pressure of oxygen, PaCO₂ carbon dioxide partial pressure, HCO₃⁻ bicarbonate ion, SO₂ oxygen saturation

* $p = 0.05$ versus COPD, COPD, and ScH, COPD, and hyperthyroidism

^a Student's t test for unpaired data

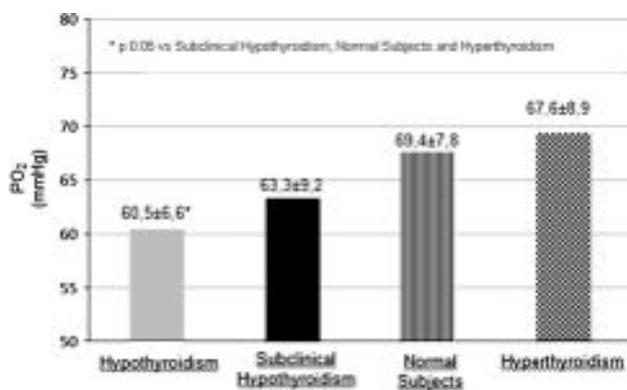


Fig. 1 Lower levels of pO₂ are present in patients with hypothyroidism compared to other patients

Discussion

The systemic manifestations of COPD include several endocrine disorders [20, 21]. The mechanism by which COPD alters endocrine, and particularly thyroid function, are not fully understood, but likely involve hypoxemia, hypercapnia, and systemic inflammation.

Our results indicate that patients with overt hypothyroidism have lower pO₂ levels compared with subjects with ScH, hyperthyroidism, and the control group. Furthermore, we found a significant decrease of MIP and MEP in patients with overt hypothyroidism, as compared to the other subsets of participants. Interestingly, we found a

tendency towards higher levels of pCO₂ in patients with hypothyroidism ($p = 0.06$).

Previous studies have reported that thyroid disturbance in COPD patients may cause lung function impairment: hypothyroidism has been associated with moderate reduction in vital capacity and lung volumes; hyperthyroidism may cause impairment in FEV₁ and vital capacity that improves with treatment [18]. In our study, we did not find a significant relationship between lung function and thyroid disorders in COPD patients.

In 32 patients with moderate-to-severe COPD, Okutan et al. [22] evaluated the relationship between thyroid hormones and pulmonary function: FT3 was lower in COPD group than controls. Moreover, the authors observed a negative correlation between pulmonary function tests, pO₂, and FT3 in COPD patients. In our study, we observed no significant differences in lung function of COPD patients with thyroid disease compared with the control group.

Dimopoulou et al. [12] demonstrated that serum thyroid hormone levels were within normal limits in 46 stable COPD patients with mild-to-severe disease, but they did not include a control group; they did not find any correlation between thyroid hormones and pulmonary function parameters in patients with mild COPD, but there was strong positive correlation between TT3/TT4 ratio and pO₂ in patients with severe COPD, so they concluded that severity of COPD could determine the peripheral metabolism of thyroid hormones. In our study, we did not observe

Fig. 2 Negative relationship between the pO₂ and TSH

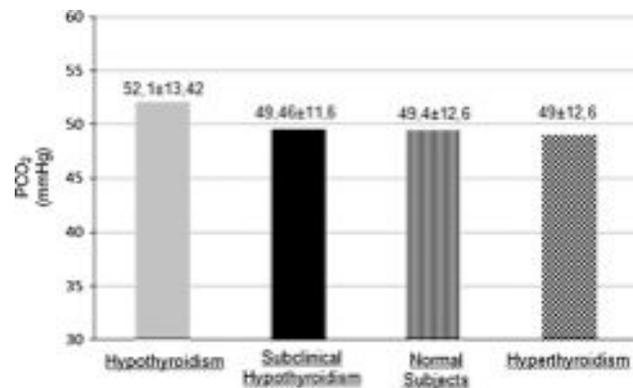
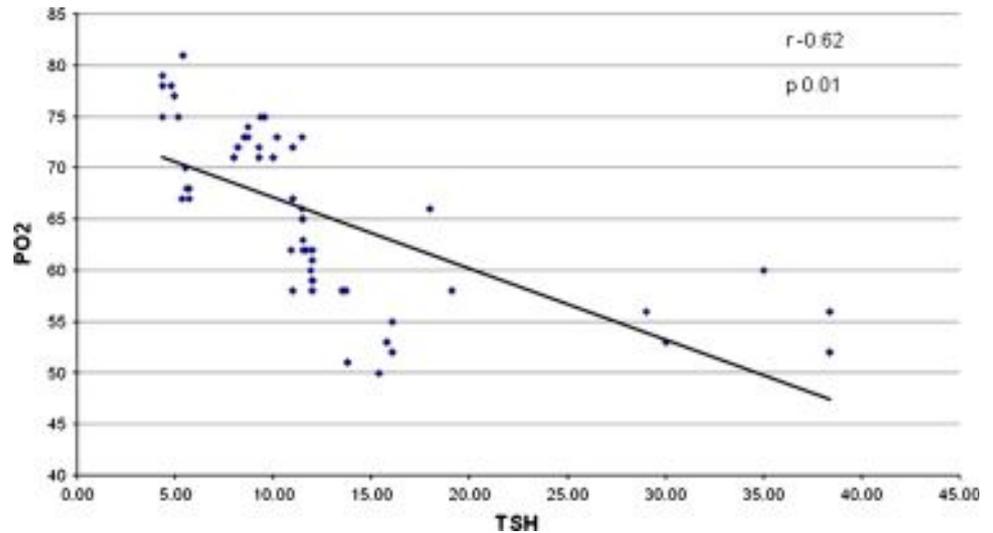


Fig. 3 Higher levels of PaCO₂ are present in hypothyroid patients

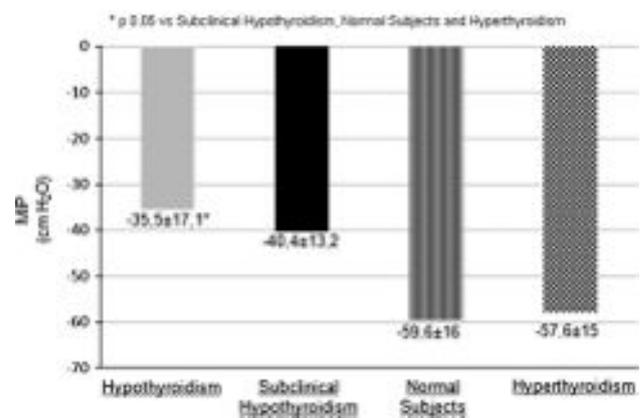


Fig. 5 MIP was significantly reduced in hypothyroid patients

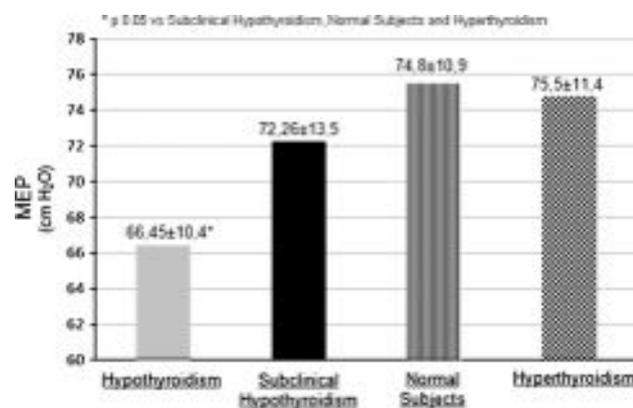


Fig. 4 Patients with hypothyroidism had values of MEP lower compared with other patients

an association between COPD severity and thyroid dysfunctions, but we found lower values of pO₂ in subjects with overt hypothyroidism compared with the control group and with patients with ScH and hyperthyroidism.

In our study, we found that MIP and MEP in patients with overt hypothyroidism were lower than other groups.

Many studies have demonstrated that respiratory muscle strength is reduced in patients with hypothyroidism and this reduction may be due to associated myopathy and neuropathy. Several alterations in muscle function have been reported in overt hypothyroidism; the rapid decline in energy reserves of exercising hypothyroid muscle have been attributed to reduced mitochondrial activity or to a defect in glycogen breakdown [23].

Ashtyani et al. [24] have demonstrated that MIP was reduced in subjects with overt hypothyroidism and improved with treatment. In our study, COPD patients with overt hypothyroidism had lower levels of MIP compared with other groups. In a study of 43 patients with overt hypothyroidism, Siafakas et al. [16] have demonstrated the relationship between respiratory muscle weakness and the degree of hypothyroidism.

Respiratory muscle weakness also can be found in hyperthyroidism [25]. Siafakas et al. [18] evaluated respiratory muscle strength in 20 patients with hyperthyroidism and in a control group of 20 healthy subjects, and they

Fig. 6 Negative relationship between MEP and TSH

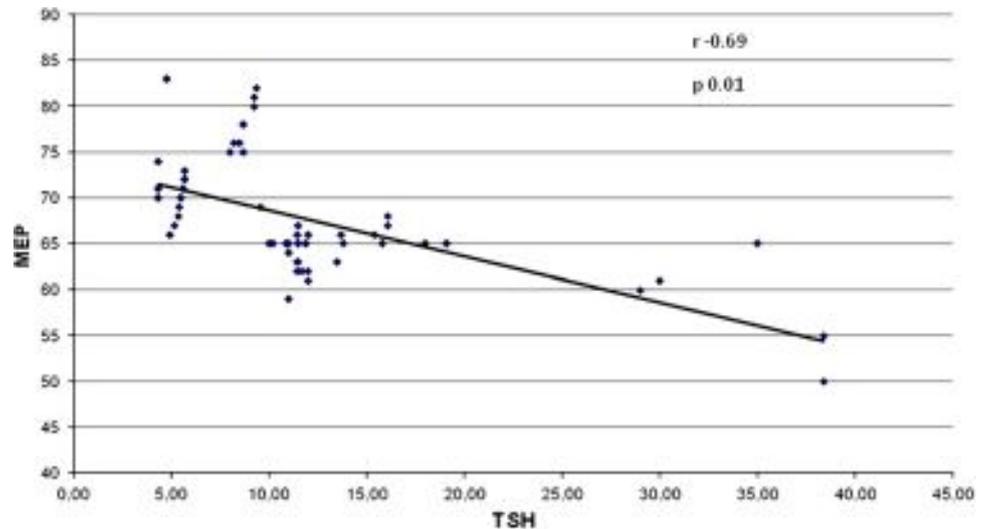
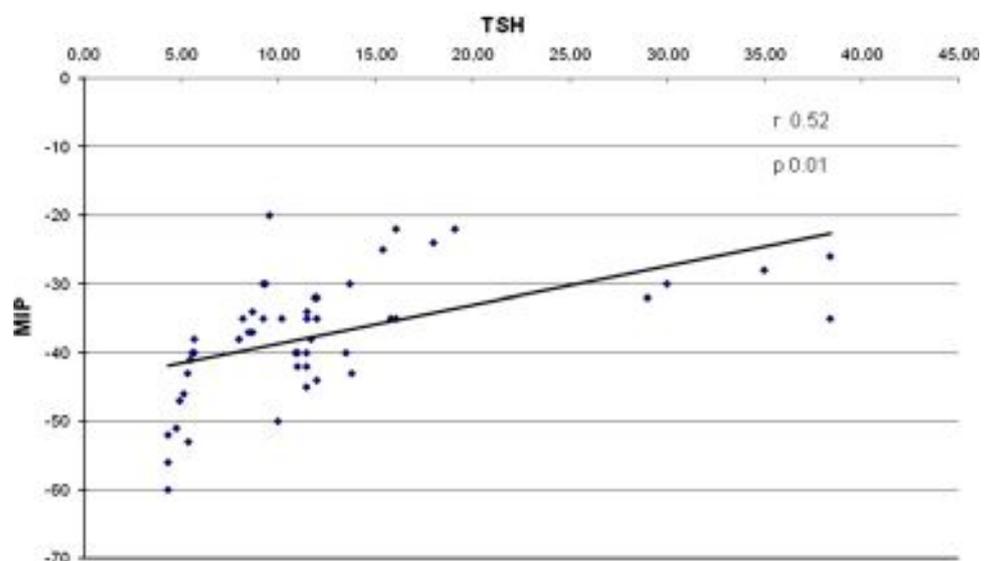


Fig. 7 Direct relationship between MIP and TSH. * $p = 0.05$ versus ScH, normal subjects, and hyperthyroidism



demonstrated that both MIP and MEP decreased with increasing severity of hyperthyroidism, improving after treatment. In our study, we found a significant decrease of MIP and MEP in patients with hypothyroidism compared with other groups.

In the present study, we also demonstrated that patients with COPD and hypothyroidism have lower values of pO_2 than controls and a tendency towards higher pCO_2 levels.

Many studies have demonstrated that subclinical and overt hypothyroidism are associated with reduced ventilator drive than induced hypoxemia and hypercapnia. In fact, in induced hypothyroidism animal models a decrease in peripheral chemoreceptor response to hypoxemia and hypercapnia was observed [26]; in humans approximately one-third of the hypothyroid patients had a blunted ventilator response to hypoxemia and hypercapnia, particularly in severe hypothyroidism [27]. This relationship between

thyroid disease and reduced ventilator drive has been demonstrated in patients with OSA [28].

Banks et al. [29] measured thyroid hormones in 25 COPD patients with various degrees of hypoxemia and hypercapnia, but no correlation between thyroid hormones and pH, pO_2 , and pCO_2 was found. They concluded that several endocrinological alterations due to chronic pulmonary diseases might be related to variables other than hypoxemia and hypercapnia.

Gow et al. [30] did not find a correlation between arterial blood gas measurements and thyroid hormone concentrations in patients with COPD. In our study, we found lower levels of pO_2 in COPD patients with hypothyroidism and a significant correlation between pO_2 and TSH.

In conclusion, our results point out that patients with COPD and hypothyroidism have a reduced respiratory

drive with a substantial decrease of pO_2 and a tendency to increase pCO_2 . The greater impairment of hypothyroid and COPD patients also is shown by measuring respiratory muscle strength, which is significantly lower in this subset of individuals compared with other participants. These results may prompt future studies designed to evaluate whether the treatment of thyroid disease may lead to an improvement in functional impairment, quality of life, prognosis, and mortality in COPD patients.

Acknowledgments The experiments comply with the current law.

Conflict of interest The authors declare that they have no conflict of interest.

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