Respiratory Medicine (2000) **94,** 1221–1228
doi:10.1053/rmed.2000.0953, available online at http://www.idealibrary.com on IDEAL®

Impact of hypoxaemia on neuroendocrine function and catecholamine secretion in chronic obstructive pulmonary disease (COPD). Effects of long-term oxygen treatment

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The aim of the study was to investigate the effects of chronic hypoxaemia on neuroendocrine function in hypoxaemic chronic obstructive pulmonary disease (COPD). The stress level was assessed by measurement of daytime plasma catecholamine and nocturnal urinary catecholamine levels and endocrine function was assessed by measuring serum gonadotropins, peripheral sex hormones and peripheral thyroid hormones, and by measuring thyroid stimulating hormone (TSH), prolactin and growth hormone before and after thyroid releasing hormone challenge in 12 male, stable, hypoxaemic COPD patients before and after at least 4 months of long-term oxygen treatment (LTOT). Mean pre-treatment PaO_2 was 7·39 ± 0·78 kPa and mean nocturnal arterial oxygen saturation ($MSaO_2$) was 86·6 ± 3·2%. Plasma norepinephrine (NE) levels were higher than normal, while all other pre-treatment hormone levels were within normal range. Low forced expiratory volume in 1 sec (FEV_1) was associated with low basal and stimulated TSH ($P<0·01$). Urinary NE excretion correlated positively to nocturnal time spent with $SaO_2<85\%$ ($P<0·05$). In similarity with normal controls, positive correlations were found between sex hormone binding globulin and testosterone both before and after LTOT ($P<0·01$). No significant hormonal changes were noted following an average of 8 months of LTOT for the entire study group. However, in a subgroup ($n = 6$) with an increase in $MSaO_2$ exceeding 7% points following LTOT, nocturnal excretion of NE and epinephrine were reduced by 30% ($P<0·05$) and S-free thyroxin by 20% ($P<0·05$).

In conclusion, patients with chronic hypoxaemia secondary to COPD exhibit elevated plasma NE levels but otherwise normal endocrine levels, including a normal hypothalamic–pituitary–testicular axis. The severity of airway obstruction is associated with reduced basal and stimulated TSH. The endocrine function is not significantly changed following LTOT except for a subgroup with severe nocturnal hypoxaemia, where elevated nocturnal NE excretion was noted, which was reduced only if whole night oxygenation was normalized during oxygen therapy.

Key words: chronic obstructive pulmonary disease; hypoxaemia; stress; thyroid stimulating hormone; thyroxin; norepinephrine; epinephrine; testosterone; sex-hormone binding globulin; follicle stimulating hormone.

Respir. Med. (2000) **94**, 1221–1228

Introduction

There is an apparent clinical resemblance between a hyperthyroid state and advanced chronic obstructive pulmonary disease (COPD). In both conditions tachycardia, weight reduction and loss of muscle mass may be found. In COPD complicated by hypoxaemia these traits may be aggravated, since chronic or intermittent hypoxaemia may trigger a hypermetabolic state causing depletion of fat-free mass (1). Hyperthyroidism increases work of breathing by elevating the chemosensitivity and respiratory drive (2). Early detection of thyroid disturbances may therefore be clinically important in COPD.

In studies of animals as well as of healthy human subjects a close anatomical and functional relationship has been found between catecholamine secretion and thyroid hormone secretion, whereas an inverse relationship has been noted in primary thyroid abberrations (3–5). Chronic nocturnal hypoxaemia such as in obstructive sleep apnoea (OSA) is associated with increased catecholamine secretion, which is reduced by long-term continuous positive airway

Received 10 April 2000 and accepted in revised form 17 August 2000.

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0954-6111/00/121221+08 $35·00/0

pressure (CPAP) treatment (6–8). We have recently shown that such a reduction in nocturnal urinary NE excretion in OSA patients is associated with an altered thyrostat (8). However, to our knowledge, the effects of elevated catecholamine secretion induced by chronic hypoxaemia due to COPD on thyroid secretion have not been studied.

Most alterations of the thyrostat are easily demonstrated by measurement of thyroid stimulating hormone (TSH) employing ultrasensitive methods (9), but primary disturbances of the hypothalamic–pituitary–thyroid axis at the pituitary level are best revealed by thyroid releasing hormone (TRH) challenge (10). As well as the pituitary–thyroid axis, other parts of the frontal pituitary lobe may be affected by chronic hypoxaemia. Reduced as well as increased serum gonadotropins are reported in COPD complicated by hypoxaemia (11,12).

Chronic hypoxaemia in stable COPD is associated with a very slow increase in pulmonary pressures and deterioration of blood gases (13,14). Only minor acute effects on pulmonary hypertension were induced by oxygen supplement in the NOTT study and these effects could not predict the effects of 6 months of long-term oxygen therapy (LTOT) (15). In the present study, the hormonal impact of chronic hypoxaemia in COPD was evaluated before treatment and the possible hormonal effects of oxygen therapy were therefore evaluated after on average 8 months of LTOT and the patients were used as their own controls.

Patients and methods

SUBJECTS

The patient group comprised 12 male COPD patients aged 69·5 (30–79) years and with severe airway obstruction and daytime hypoxaemia ($PaO_2 < 7{\cdot}3$ kPa) or with daytime PaO_2 of 7·3–8·7 kPa, but with substantial nocturnal hypoxaemia associated with oedema of the lower extremities. All patients were ex-smokers and they were clinically stable and none had had an exacerbation of their respiratory disease within the 3 weeks prior to the study. LTOT was thus given according to the guidelines of the European Society of Pneumology (16). The study was approved by the ethical committee of Huddinge University Hospital and all patients gave their informed consent.

Chest radiographs and electrocardiograms showed that no patient suffered from uncontrolled left heart failure. None of the patients had a history of heavy snoring or witnessed apnoeas. One patient had well controlled insulin-dependent diabetes mellitus. Two patients were treated continuously with oral corticosteroids (10 mg of prednisolone) and one by repeated courses. No additional hormonal treatment was given to the patients. Ten patients were given theophylline preparations and seven were receiving oral β_2-agonists. All patients used inhaled β_2-agonists and inhaled steroids. Ten patients were treated with furosemide (40–160 mg) and four with spironolactone (50–100 mg). Medication was kept essentially unchanged during the study period. Twenty age-matched [68 (29–80) years] healthy males served as controls regarding serum gonadotropin and testosterone levels. All other hormonal variables were compared to the reference limits of our laboratory.

PHYSIOLOGICAL AND LABORATORY INVESTIGATIONS

The patients were admitted to the pulmonary department for assessment of their need for LTOT. Forced expiratory volumes were measured by dynamic spirometry (Vitalograph®, Buckingham, U.K.) in the afternoon about 30 min after β_2-stimulation. The best of three trials of forced expiratory volume in 1 sec (FEV_1) was used for statistical analysis and forced vital capacity (FVC) was taken from the same measurement. Urine for catecholamine assays was collected (from about 22.00 hours in the evening until 07.00 hours the following morning) simultanously with a finger pulse oximetry (Radiometer A/S, Copenhagen, Denmark). The mean arterial oxygen saturation for the whole night ($MSaO_2$) was calculated and the cumulative percentage of the nocturnal recording time with a SaO_2 level $< 90\%$ and $< 85\%$ ($\%t\,SaO_2 < 90\%$ and $\%t < 85\%$, respectively) was estimated. All oximetry tracings were scrutinized manually by the same observer (TB) without knowledge of the hormonal results. Arterial blood gases (ABL 520, Radiometer A/S) were drawn with the patient seated and resting at around 08.00 hours in the morning following the nocturnal pulse oximetry. Venous blood for hormone analyses was drawn with the patient supine and resting between 07.00 – 08.00 hoursthe same morning.

A TRH stimulation test was then performed after breakfast by use of an i.v. injection of 200 μg of TRH (Thyrefact®, Hoechst A.G., Frankfurt, Germany). Venous blood samples were drawn immediately before and 20 and 60 min after the injection of TRH for analysis of thyroid stimulating hormone (TSH), prolactin (PRL) and growth hormone (GH). A normal TRH response in males above 40 years of age is characterized by an increase in TSH and PRL levels by $\geq 100\%$ and an increase in GH levels by $\leq 100\%$ (10,17). The response to TRH stimulation is expressed as the Δ-value (i.e. the maximum value following TRH injection minus the basal level prior to injection).

The oxygen treatment was titrated over the following days, aiming to reach a daytime PaO_2 level of at least 8·0 kPa and $SaO_2 > 90\%$ during a whole night without causing the morning $PaCO_2$ to be raised above 8·0 kPa. Patients were treated for an average of 16 (range 14–18) h day^{-1} by a mean oxygen dose of $1{\cdot}8 \pm 0{\cdot}8$ l min^{-1}. After a mean treatment time with LTOT of $8{\cdot}25 \pm 2{\cdot}34$ months all measurements were repeated. The nocturnal urinary catecholamine collection and concurrent pulse oximetry as well as blood gas sampling were this time performed during ongoing oxygen therapy. In addition to the whole-night oximetry, the breathing pattern of the patient was assessed using a static-charge sensitive bed (SCSB) (Bio-matt, Biorec, OY, Finland) (18). Adherence to the prescribed oxygen treatment was assessed by open questionning and by examination of the counters of the oxygen compressors by medical technicians.

HORMONE ASSAYS

Serum concentrations of prolactin (PRL), TSH, triiodothyronine (T_3), free thyroxine (fT_4) and growth hormone (GH) were measured by time-resolved fluorescence immunoassay using commercial kits from Wallac OY, Turku, Finland (Delfia®, Autodelfia®). Serum concentrations of luteinizing hormone (LH), follicle stimulating hormone (FSH), testosterone (T) and sex-hormone binding globulin (SHBG) were determined by radioimmunological or immunoradiometric methods using commercial kits from Diagnostic Products Corp., Los Angeles, CA, U.S.A. (LH, FSH, T) and Orion OY, Turku, Finland (SHBG). NE and E in plasma and urine were determined using a modified high pressure liquid chromatography technique (19,20).

Practical detection limits and within and between assay coeffecients of variation were: for PRL $0{\cdot}04\,\mu g\,l^{-1}$, 4% and 5%; for TSH $0{\cdot}4\,mU\,l^{-1}$, 5·0% and 7·2%; for T_3, $0{\cdot}3\,nmol\,l^{-1}$, 4·1% and 4·1%; for fT_4 $2\,pmol\,l^{-1}$, 9·8% and 7·0%; for GH $0{\cdot}01\,\mu g\,l^{-1}$, 2·5% and 4·9%; for LH $1{\cdot}2\,U\,l^{-1}$, 7% and 10%; for FSH $1{\cdot}2\,U\,l^{-1}$, 7% and 11%; for T $0{\cdot}1\,nmol\,l^{-1}$, 6% and 10% and for SHBG $6\,nmol\,l^{-1}$, 5% and 11%. Total coefficients of variation for plasma catecholamines were 18% at about $2{\cdot}5\,nmol\,l^{-1}$ and for urinary catecholamines 5% at the upper reference level (see Table 2).

Apparent concentrations of free testosterone (fT) were calculated from values for total T, SHBG and a fixed albumin concentration of $42\,g\,l^{-1}$ by successive approximation using a computer programme based upon an equation system derived from the law of mass action (21).

STATISTICAL ANALYSIS

Normally distributed values were expressed as arithmetic mean ± SD, otherwise as median and range. Results before and after LTOT were compared by paired Student's *t*-test if normally distributed, otherwise by Wilcoxon's signed-rank test. Differences between subgroups were compared using unpaired Student's *t*-test or Mann–Whitney *U*-test and correlations between variables were assessed by linear regression or by Spearman's rank test according to distribution. The contribution of several parameters to the variability of a dependent variable was evaluated by stepwise regression. *P*-values below 0·05 were considered significant.

Results

BEFORE LTOT

Anthropometric and physiological data are given in Table 1. All patients suffered from severe irreversible airway obstruction with a FEV_1 in percentage predicted (%P) of 34·3 ± 13·1% (range: 18–65%) and all had FEV_1/FVC below 70%. Five patients had pre-treatment daytime PaO_2 below 7·3 kPa, five had PaO_2 values ranging between 7·6 and 7·8 kPa and in two cases PaO_2 ranged between 8·3 and 8·7 kPa. Two patients had $PaCO_2$ above 6·0 kPa and the remaining patients had normal values (Table 1). All but one of the patients had mean nocturnal SaO_2 ($MSaO_2$) below 90% and no patient had nadir nocturnal SaO_2 above

TABLE 1. Anthropometric and physiological data presented as mean ± SD or median and range according to distribution. Blood gases and oxymetry measurements after LTOT were performed during ongoing oxygen therapy

	Before LTOT	After LTOT
BMI, ($kg\,m^{-2}$)	25·0 ± 3·8	24·9 ± 4·8
FEV_1 of % predicted	34·3 ± 13·1	33·3 ± 13·9
FVC of % predicted	56·5 (39–92)	42·0 (35–108)
FEV_1FVC(%)	45·5 (23–75)	45·5 (22–76)
Pulse (bpm)	78·6 ± 14·4	76·7 ± 12·6
Systemic BP, (mm Hg)	119·2 ± 13·6	122·0 ± 9·8*
Diastolic BP, (mm Hg)	71·7 ± 7·2	76·0 ± 11·5
PaO_2 (kPa)	7·39 ± 0·78	9·03 ± 0·76**
$PaCO_2$, (kPa)	5·65 ± 1·11	5·34 ± 1·00
$MSaO_2$ (%)	86·6 ± 3·2	93·6 ± 2·6**
Nadir SaO_2 (%)	76·1(62·5–85·0)	80·0 (75·0–90·0)*
$\%t\,SaO_2 < 90\%$	93·3 (1·5–100)	7·5 (0·0–53·0)**
$\%t\,SaO_2 < 85\%$	8·2 (0–89·9)	0·0 (0·0–0·0)**
Hb, $g\,l^{-1}$	154·5 (124–176)	157·5 (120–167)

Abbreviations: BMI: body mass index; FEV_1: forced expiratory volume in 1 sec; FVC: forced vital capacity; $MSaO_2$: mean arterial oxygen saturation during the whole night; Nadir SaO_2: the lowest SaO_2 during the nocturnal recording;$\%t$-$SaO_2 < 90\%$ or $< 85\%$: cumulative time of the nocturnal recording spent below a SaO_2 of 90% or 85% respectively. Significant differences induced by treatment are denoted by $^*P < 0{\cdot}05$ and $^{**}P < 0{\cdot}01$.

85%. The two patients with a PaO_2 above 8·0 kPa had $\%tSaO_2 < 90\%$ exceeding 80% of the night and both had signs of right heart failure. A quarter of the patients spent at least 25% of their time in bed with $\%tSaO_2 < 85\%$. Mean BMI was normal, five subjects had a body mass index (BMI) in the lower range of normal i.e. below 23 $kg\,m^{-2}$. Pulse rate was above 75 beats per min in half of the patients, yet systemic blood pressure was normal or low in all subjects.

Endocrine data are given in Table 2. Median P-NE was above and 9-h nocturnal urinary (U) NE was slightly below the upper limit of normal. Values for thyroid hormones, basal levels and increments following TRH challenge test for TSH, PRL and GH were within the normal ranges of our laboratory. Patients and controls did not differ with respect to LH, FSH, total and free testosterone and SHBG.

Group comparisons between the three patients treated with oral corticosteroids and the nine patients treated with only inhaled corticosteroids showed no significant difference regarding any hormonal parameter.

AFTER LTOT

Eight months of LTOT significantly increased mean values of PaO_2, $MSaO_2$ and nadir SaO_2, and significantly reduced percent $t\,SaO_2 < 90\%$ and percent $t\,SaO_2 < 85\%$ (Table 1). All of these variables were measured during ongoing oxygen therapy. PaO_2 was raised to at least 8·0 kPa in all subjects and $MSaO_2$ was elevated to above 90% in all but one patient. In one patient $MSaO_2$ could not be determined before treatment. Following LTOT there was a slight but significant increase in systolic blood pressure but no significant change in lung function, although there was a trend towards reduced FVC ($P = 0{\cdot}07$) (Table 1). In none of the cases did SCSB measurements reveal a breathing pattern compatible with OSA [i.e. five or more apnoeas per hour, periodic breathing $\geq 20\%$ of time in bed (18)]. No significant endocrine changes occurred following treatment in the entire patient group (Table 2).

The oxygen treatment increased $MSaO_2$ by at least 7% points in six patients (good responders) and by less than 7% points in five patients (poor responders). Data for the two subgroups are given in Table 3. Compared to the poor responders, the good responders had significantly lower $MSaO_2$ before treatment and a tendency to higher FEV_1 %P (40.5 ± 13·2% *vs.* 25·8 ± 10·0%, $P = 0{\cdot}07$). The good responders had significantly lower FSH and higher basal TSH and ΔTSH values than the poor responders before and after treatment. Serum FSH before and after treatment and serum LH after treatment were significantly lower in the good responders than in the controls. Prior to treatment the good responders had significantly higher U-NE values than the poor responders. After treatment U-NE, U-E and serum fT_4 levels decreased ($P < 0{\cdot}05$ for all) within the good responder subgroup. These parameters became significantly lower and $MSaO_2$ tended to become higher in the good responder subgroup compared to the poor responders. In the poor responders urinary catecholamines tended to increase after LTOT. No significant difference with regard to medication or oxygen dosage was noted between the two subgroups.

CORRELATIONS

Reduced pretreatment FEV_1%P was accompanied by reduced basal and ΔTSH both before and after LTOT

TABLE 2. Endocrine variables before and after LTOT. Data are presented as mean ± SD or median and range according to distribution. For abbreviations see text

	Controls	Before LTOT	After LTOT
S-TSH ($mU\,l^{-1}$)	0·4–4·0*	1·2 (0·4–4·0)	1·0 (0·3–5·5)
S-T_3 ($nmol\,l^{-1}$)	<2·0*	2·04 ± 0·44	1·91 ± 0·28
S-fT_4 ($pmol\,l^{-1}$)	8–20*	18·0 (11–22)	15·0 (10–23) ·
ΔTSH ($mU\,l^{-1}$)		5·0 (1·0–16·8)	5·0 (1·0–15·4)
S-PRL ($\mu g\,l^{-1}$)	<11*	4·2 (2·0–10·0)	6·0 (3·0–13·0)
ΔPRL ($\mu g\,l^{-1}$)		16·6 ± 10·0	18·1 ± 8·5
S-GH ($\mu g\,l^{-1}$)	<5·60*	0·20 (0·04–1·1)	0·40 (0·04–0·90)
ΔGH ($\mu g\,l^{-1}$)		0·45 (−0·3–3·95)	0·40 (−0·30–2·2)
S-T ($nmol\,l^{-1}$)	17·9 ± 6·9†	14·3 ± 6·9	15·6 ± 6·5
S-SHBG ($nmol\,l^{-1}$)	43·4 ± 14·4†	38·0 ± 22·9	39·7 ± 25·3
fT ($pmol\,l^{-1}$)	372·5 ± 143·3†	304·3 ± 111·1	334·8 ± 117·7
S-LH ($U\,l^{-1}$)	7·0 (3·0–16·0)†	7·8 (0·9–22·0)	4·4 (0·9–20·9)
S-FSH ($U\,l^{-1}$)	6·0 (1·0–28·0)†	6·5 (2·0–22)	4·0 (2·0–17)
P-NE ($nmol\,l^{-1}$)	0·7–2·3*	3·2 (2·0–6·8)	3·9 (1·6–8·2)
U-NE ($nmol\,l^{-1}$)	<178*	160·5 (72–271)	144·0 (124–422)
P-E ($nmol\,l^{-1}$)	<0·70	0·10 (0·06–0·40)	0·10 (0·10–0·50)
U-E ($nmol\,l^{-1}$)	0–30*	7·50 (4·0–19·0)	7·00 (4·0–23·0)

*Reference levels of our laboratory. †Healthy controls.
Regarding reference levels for Δ values — see text.

TABLE 3. Significant differences between patients with an increase in nocturnal mean arterial oxygen saturation ($MSaO_2$) of $<7\%$ points (poor responders) *vs.* of $\geq 7\%$ points (good responders) following 8 months of oxygen treatment

	Δ $MSaO_2 < 7$ %	Δ $MSaO_2 \geq 7\%$
Before LTOT		
$MSaO_2$(%)	89·2 ± 2·5	84·5 ± 2·4*
FSH (Ul^{-1})	9·0 (5·0–22·0)	3·1 (2·0–4·0)**
TSH (mUl^{-1})	0·5 (0·4–1·3)	1·5 (1·0–4·0)*
ΔTSH (mUl^{-1})	1·4 (1·0–5·9)	8·0 (4·3–16·8)*
fT4 ($pmol l^{-1}$)	17·5 (17–18)	19·0 (11–22)
U-NE ($nmol^{-1}$)	136·0 (72–208)	195·5 (150–271)*
U-E ($nmol^{-1}$)	7·0 (4–10)	8·5 (6–19)
After LTOT		
MSaO2(%)	92·0 ± 3·2	94·9 ± 1·0[a]
fT4 ($pmol^{-1}$)	17·0 (15–23)	13·0 (10–17)*
U-NE ($nmol^{-1}$)	191·5 (144–422)	135·5 (124–175)*
U-E ($nmol^{-1}$)	15·5 (9–23)	6·0 (4–13)*

[a] $P = 0{\cdot}06$, * $P < 0{\cdot}05$, ** $P < 0{\cdot}01$, regarding differences between subgroups.
For details of other abbreviations see Table 1 and text.

[Fig. 1 (a)]. Pre-treatment values of $MSaO_2$ correlated negatively to basal and ΔTSH before and after treatment [Fig. 1 (b) and Table 4]. The amount of nocturnal time spent with a $SaO_2 < 85\%$ before treatment correlated positively to pre-treatment U-NE levels as well as to basal and ΔTSH before and after treatment (Table 4). Four out of five patients with pre-treatment nocturnal U-NE above the upper normal limit (i.e. $>178\,nmol\,l^{-1}$) spent more than 10% of the night with a SaO_2 below 85%, whereas all but one of the subjects with nocturnal U-NE within normal limits spent less than 2% of the night with a $SaO_2 < 85\%$ (Fig. 2).

Stepwise regression analysis comparing the influence before treatment of age, PaO_2, $MSaO_2$, $\%tSaO_2 < 85\%$ and FEV_1%P on Δ TSH revealed that FEV_1%P remained the most significant variable, explaining 86% of the variability ($r^2 = 0{\cdot}86$) regarding Δ TSH, only $\%tSaO_2 < 85\%$ could further significantly contribute to the regression model (increasing r^2 to 0·95).

Plasma NE and serum fT_4 were positively correlated before treatment ($r = 0{\cdot}80$, $P < 0{\cdot}05$). Serum total testosterone and SHBG were positively correlated in the patients before and after LTOT ($r = 0{\cdot}75$ and $r = 0{\cdot}79$, $P < 0{\cdot}01$ for both) as well as in the controls ($r = 0{\cdot}49$, $P < 0{\cdot}05$).

Discussion

Our twelve patients differed considerably regarding age, degree of airway obstruction and hypoxaemia. Age may influence the secretion of gonadotropins or thyroid hormones (22,23). However, in our cohort, the effect of age did not over-ride other physiological factors such as oxygenation or lung function. The plasma NE levels were about three times higher in our study of resting elderly ex-smokers compared to those of elderly, healthy, active smokers (24). The elevated P-NE levels in our patients were thus, probably, mainly due to the impact of disease and not to previous smoking. Three of our patients were subjected to long-term oral corticosteroid treatment. Systemic corticosteroids may reduce testosterone levels (25) as well as exhibiting possible other hormonal effects. However, no significant difference regarding levels of sex hormones or other hormones were noted when these patients were compared with the nine patients without oral corticosteroid treatment.

Acute exposure (up to 4 h) of healthy subjects to severe hypoxia is reported to result in increased E- as well as NE-secretion, whereas chronic severe hypoxia (about 3 weeks) was followed by further increments in NE but by normalized E-secretion (26). Despite hypoxaemia the cellular machinery strives to maintain normal production of high energy phosphate compounds by increasing substrate turnover for these compounds. In an acute state this is achieved by glycogenolysis, which is mainly stimulated by E (26). A long-term energy supply in chronic severe hypoxic conditions is maintained by NE stimulated lipolysis (27). In accordance with these findings, the pre-treatment nocturnal levels of NE were higher than normal in our good responder subgroup who, in most cases, had severe chronic hypoxaemia ($MSaO_2 < 85\%$). The only significant correlation between hypoxaemia and catecholamines was noted between an index of severe nocturnal hypoxaemia (% time $SaO_2 < 85\%$) and nocturnal urinary NE excretion. Clear inverse correlations have been found between severe hypoxaemia and daytime plasma NE levels in COPD (28) but no changes in P-NE levels followed after inhalation of pure oxygen for 30 min (28) or after 8 months of LTOT as in the present study. However, nocturnal NE excretion was reduced in our good responder subgroup who, after LTOT,

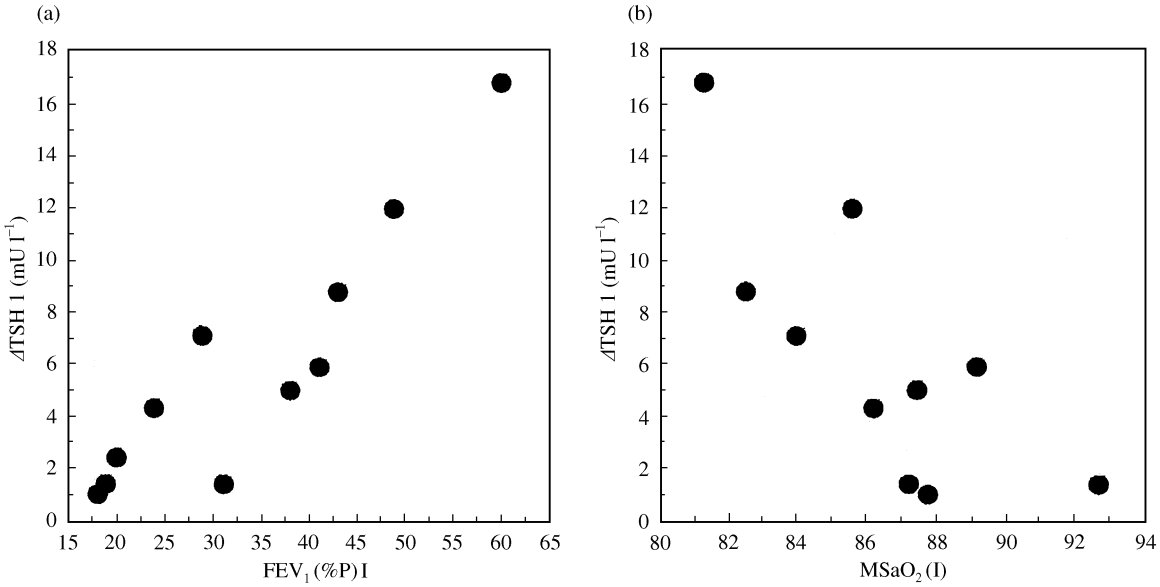

FIG. 1. (a) Association between stimulated TSH (ΔTSH) before LTOT and pre-treatment FEV_1%P ($r_s = 0{\cdot}88$; $P < 0{\cdot}01$). 1 (b) Association between pre-treatment-stimulated TSH (ΔTSH) and mean nocturnal SaO_2 ($MSaO_2$) before LTOT ($r_s = -0{\cdot}76$; $P < 0{\cdot}05$).

TABLE 4. Significant correlations (Spearman rank) between indices of pre-treatment nocturnal hypoxaemia and hormonal levels

	$MSaO_2(r_s)$	% Time $SaO_2 < 85\%$ (r_s)
S-TSH I	−0.69*	0.78*
S-TSH II	−0.69*	0.98**
Δ TSH I	−0.76*	0.78*
Δ TSH II	−0.72*	0.90**
U-NE I	−0.54 NS	0.67*

*$MSaO_2$: mean nocturnal arterial oxygen saturation;% time SaO_2 <85%: cumulative nocturnal time spent with SaO_2 below 85%; S: serum; U-NE: urinary norepinephrine; I: before LTOT; II: after 8 months of LTOT. For other details of abbreviations see Table 1 and text.
*$P < 0{\cdot}05$; **$P < 0{\cdot}01$; NS: not significant.

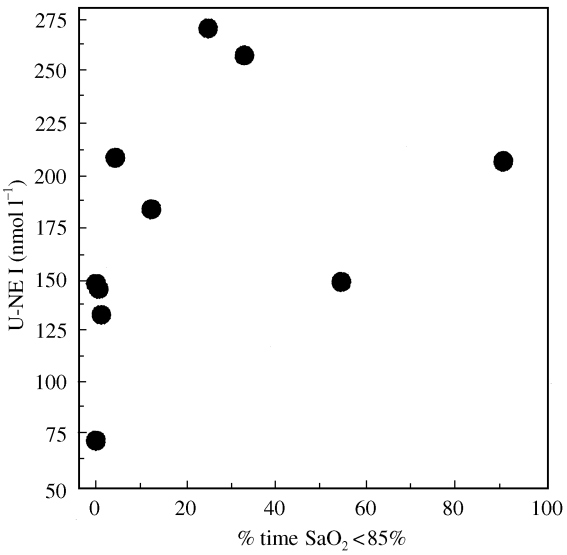

FIG. 2. Association between pre-treatment percentage of time in bed spent with SaO_2 <85% (% time SaO_2 <85%) and pre-treament nocturnal urinary norepinephrine excretion (U-NE) ($r_s = -0{\cdot}67$; $P < 0{\cdot}05$).

showed a substantial improvement and normalization in mean nocturnal SaO_2($MSaO_2 > 93\%$) (29) (Table 1). NE-secreting neurons may thus react only to severe hypoxaemia ($SaO_2 < 85\%$) and reductions in nocturnal catecholamine excretion may be induced only following substantial long-term improvements in sleep-related oxygenation (7,8).

Despite oxygen therapy in hypoxic COPD patients for several months, NE levels are persistently elevated, which has been attributed to the strain caused by the severe airway obstruction in advanced COPD (30). In our poor responder subgroup who tended to have to the most severe airway obstruction, several months of LTOT was followed by a substantial increase in nocturnal catecholamine excretion, but only by a small improvement in nocturnal oxygenation. The impact of improved oxygenation on catecholamine excretion in this subgroup may have been outweighed by the continuously strenuous effects of chronic severe airway obstruction.

In accordance with previous studies of chronic hypoxaemia (8,11,12) the hypothalamic–pituitary–thyroid axis functioned normally in the present study. Nevertheless,

basal and stimulated TSH levels were reduced in our patients with severe airway obstruction and remained unaltered despite improved oxygenation following LTOT. Subnormal basal and stimulated TSH levels are reported in other critical non-thyroidal diseases and are considered to predict a poor prognosis (31,32). Thus, severe irreversible airway obstruction seems to have profound systemic effects comparable with those of other fatal non-thyroidal diseases.

Improved oxygenation had insignificant effects on the thyrostat at the pituitary level in the present study. However, a small reduction in free thyroxin was noted in our good responder subgroup, in which a reduced nocturnal NE excretion was also noted. *In vitro* studies show that reduced NE excretion is accompanied by reduced deiodination of T_4 to T_3 leading to increased T_4 levels (5). However, high altitude studies in healthy subjects imply that hypoxaemic stress decreases the pituitary or peripheral conversion rate of fT_4 to fT_3 (33). Relief of the hypoxaemic stress following LTOT in our good responder subgroup could have increased this conversion rate.

While low circulating concentrations of gonadotrophins in COPD patients with stable hypoxaemia or with acute exacerbations have been reported (11,34), quite normal values were found in our study group as a whole. However, our good responder subgroup with severe pre-treatment nocturnal hypoxaemia had subnormal FSH levels. Contrary to previous findings in stable hypoxaemic COPD patients (35), we found neither gonadotropin levels nor free and total testosterone to be significantly affected by LTOT. Thus, our study suggests that chronic hypoxaemia is not of major importance for determining gonadotropin levels in COPD. Furthermore, serum total testosterone and SHBG correlated positively in the patients before and after treatment as well as in controls, which demonstrates an intact hypothalamic–pituitary–gonadal axis in our patients. This positive correlation does not reflect an effect of testosterone binding to SHBG on androgen metabolism, but rather the attempt to maintain a constant androgenic/anabolic activity in a healthy organism with altered SHBG levels due to for example nutritional changes (36,37).

In conclusion, patients with chronic hypoxaemia secondary to COPD exhibit elevated plasma NE levels but otherwise normal endocrine values, including a normal hypothalamic–pituitary–testicular axis as judged from the positive associations between testosterone and SHBG. The severity of airway obstruction is associated with reduced basal and stimulated TSH. The endocrine function is not significantly changed following LTOT except for a subgroup with severe nocturnal hypoxaemia, where elevated nocturnal NE excretion was noted, which was reduced only if whole night oxygenation was normalized during oxygen therapy.

Acknowledgements

We are grateful to the nurses in the Department of Respiratory and Allergic Diseases for excellent assistance with the test protocol. This study was supported by grants from the Swedish Heart and Lung Foundation and from the Karolinska Institute, Sweden.

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