Thyroid function and endocrine abnormalities in elderly patients with severe chronic obstructive lung disease

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ABSTRACT Serum pituitary and thyroid hormones, testosterone, and the response of pituitary hormones to thyrotrophin releasing hormone were measured in 20 inpatients (mean age 68, range 42-81 years) with severe chronic obstructive lung disease and in 15 control convalescent inpatients (mean age 73, range 57-83 years) who had normal respiratory function. No significant differences were found in total and free thyroid hormone concentrations and basal concentrations of thyrotrophin, growth hormone, and prolactin; and their increments after injection of thyrotrophin releasing hormone were similar in patients with chronic obstructive lung disease, and control patients. Three patients with chronic obstructive lung disease, however, had no thyrotrophin responses to thyrotrophin releasing hormone. In men, low testosterone concentrations were found both in patients with chronic obstructive lung disease and in controls. Luteinising hormone concentrations were higher in men with chronic obstructive lung disease ($p < 0.02$), whereas concentrations of follicle stimulating hormone in the two groups were not significantly different. There was no significant correlation between arterial blood gas tensions and these hormone measurements. General effects of age and illness may be more important than direct effects of hypoxia in determining hypothalamic-pituitary function in elderly patients with chronic obstructive lung disease.

It has been suggested that chronic hypoxia in patients with chronic obstructive lung disease can produce abnormalities of hypothalamic-pituitary function.¹⁻³ Raised serum prolactin, low serum testosterone, luteinising hormone and follicle stimulating hormone concentrations and delayed thyrotrophin (TSH) responses to thyrotrophin releasing hormone (TRH) have all been observed,^{1,2} and similar abnormalities have been found in hypoxic pulmonary fibrosis⁴ and in a case of hypoxia due to obstructive sleep apnoea.⁵ Diminished excretion of testosterone on acute exposure to the hypoxia of high altitude has also been reported,⁶ but the level became normal within seven days and the contributory effects of cold and stress to this finding have yet to be resolved.⁷ Abnormalities of

the hypothalamic-pituitary axis are known to occur in response to stress⁸ and calorie deprivation,⁹ in systemic illnesses such as chronic renal failure,⁹⁻¹¹ and as a result of normal aging.¹²

Abnormalities in thyroid function tests commonly occur in patients with various non-thyroidal illnesses;¹³ these include low concentrations of serum triiodothyronine (T3), thyroxine (T4), and free thyroid hormone concentrations (particularly when measured by analogue assay).¹⁴ Severe illness is associated with suppression of TSH secretion¹⁵ and blunting¹⁶ or even failure¹⁷ of responses to TRH in the elderly. In contrast, delayed responses to TRH have been observed in patients with either chronic obstructive lung disease or pulmonary fibrosis, hypoxia being implicated as a causative factor.^{2,4} We have therefore investigated the thyroid hormones and endocrine function of 20 patients admitted with severe chronic obstructive lung disease and compared them with a group of control patients of similar ages with normal respiratory function.

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Methods

PATIENTS

Twenty patients (16 men, four women; mean age 68, range 42–81 years) admitted to hospital with acute exacerbations of chronic obstructive lung disease were studied. The forced expiratory volume in one second (FEV₁) and the forced vital capacity (FVC) expressed as percentages of predicted normal values were less than 40% and 65% in all 20 patients, indicating severe respiratory impairment. The control group comprised 15 ambulatory patients (10 men, five women; mean age 73, range 57–83 years) about to be discharged from hospital. None of these patients had acute illnesses. They were convalescing from cardiovascular problems (angina, syncope, cardiomyopathy, deep vein thrombosis, small myocardial infarction) or minor cerebrovascular accidents that had occurred more than six months previously, or were suffering from dementia. All 15 had measurements of FEV₁ and FVC within 20% of predicted normal values^{18 19} and had no sign of respiratory illness. None of the 35 patients had clinical evidence of thyroid disease and none was receiving oral corticosteroids or any drug known to affect the hormone measurements. Informed consent was obtained from each patient.

LABORATORY MEASUREMENTS

Weight and ideal weight²⁰ were determined in all those studied and blood gas analysis was performed on arterial samples from the patients with chronic obstructive lung disease while they were breathing room air (table 1). An afternoon sample of venous blood was taken at the time of the intravenous injection of 200 µg TRH and 20 and 60 minutes afterwards. Samples were taken two to three days after hospital admission in the patients with chronic obstructive lung disease. Patients were relaxed and resting throughout the blood collection to minimise effects of the stress of venepuncture on growth hormone and prolactin measurements.

Serum measurements of T4, T3, TSH, prolactin, growth hormone, luteinising hormone, follicle stimulating hormone, and testosterone were performed by in house radioimmunoassay methods.^{11 21} Serum free T4 (fT4) and free T3 (fT3) were measured by an analogue radioimmunoassay method (Amerlex, Amersham International). Serum TSH was also measured in basal samples with a sensitive immunoradiometric assay (Boots-Celltech), which can reliably distinguish the suppressed (undetectable) levels of TSH in hyperthyroidism from those in euthyroidism.²² Interassay coefficients of variation for these methods ranged from 4% to 12%.

Reference ranges for the thyroid function tests,

Table 1 Details of patients (values are means with ranges in parentheses)

	COAD group (n = 20)	Control group (n = 15)
Age (y)	68 (42–81)	73 (57–83)
Men only	69 (42–81)	71 (57–80)
Weight (kg)	55 (44–70)	68 (32–102)
Ideal weight (%)	81 (67–110)	95 (53–122)
Men only	80 (67–97)	97 (74–122)
FEV ₁ (% pred)	26 (12–40)	100 (80–120)
FVC (% pred)	44 (25–65)	100 (80–120)
PaO ₂ (kPa)	7.1 (4.3–12.6)	ND
Men only	7.1 (4.5–10.9)	
Paco ₂ (kPa)	7.3 (4.3–10.5)	ND
[H ⁺] (nmol/l)	42 (32–60)	ND

COLD—chronic obstructive lung disease; ND—not done.

prolactin, and growth hormone were derived from middle aged euthyroid men and women attending an outpatient endocrine clinic. Reference ranges for luteinising hormone, and follicle stimulating hormone, and testosterone in men were derived from middle aged healthy men attending for sterilisation or vasectomy.

STATISTICS

Statistical comparisons were made with the Mann-Whitney test for unpaired data.

Results

THYROID HORMONES AND BASAL THYROTROPHIN

Concentrations of total and free thyroid hormones and basal thyrotrophin were similar in chronic obstructive lung disease and in control patients (table 2). In the patients with chronic obstructive lung disease, two had low T4 concentrations and two had low fT4 concentrations. Low T4 concentrations, however, were also found in three control patients and low fT4 in one. Low T3 and fT3 concentrations were found in 11 and 10 patients with chronic obstructive lung disease and seven and six control patients respectively.

Two patients had marginally raised basal TSH, one patient with chronic obstructive lung disease (8.2 mU/l) and one control patient (7.2 mU/l); total and free thyroid hormone concentrations were within normal limits in both patients. All other patients had a

Table 2 Serum hormone concentrations and increments 20 minutes after injection of thyrotrophin releasing hormone (Values are means with ranges in parentheses)

Test	Reference ranges†	COLD	Controls
TT4 (nmol/l)	70–150	86.7 (63–116)	82.3 (65–116)
TT3 (nmol/l)	1.1–2.8	1.0 (0.5–1.5)	1.2 (0.8–2.0)
fT4 (pmol/l)	10–22.5	14.8 (9.5–21.7)	13.6 (8.0–22.7)
fT3 (pmol/l)	4.0–8.0	3.8 (2.2–5.0)	4.3 (3.1–5.4)
TSH (mU/l)			
Basal (RIA)	< 5.7	2.3 (< 0.9–8.2)	2.0 (< 0.9–7.2)
Basal (IRMA)	0.14–5.9	1.8 (0.3–9.8)	2.1 (0.5–8.9)
Increment	3.9–30	6.2 (0.8–30.6)	5.6 (1.4–16.3)
Men only		5.8 (1.0–30.6)	2.8 (1.4–4.6)
Prolactin (mU/l)			
Basal	60–390	212 (< 32–961)	302 (73–856)
Increment		589 (103–2584)	634 (183–1739)
Men only		487 (103–1191)	476 (183–943)
Growth hormone (mU/l)			
Basal	Often < 1.0 but variable	2.1 (< 0.6–11.2)	1.5 (< 0.7–7.9)
Increment	No response	2.1 (0–9.5)	5.9 (0–45)
Men only		1.9 (0–9.5)	1.2 (0–4.7)
Testosterone (nmol/l) (men)	10–30	10.7 (3.0–19.5)	11.0 (1.8–21.9)
LH (U/l) (men)	1.5–9.0	9.8 (2.3–14.9)	9.1 (2.1–34.1)
Excluding one patient*		9.8 (2.3–14.9)	6.3 (2.1–9.1)
FSH (U/l) (men)	1.5–9.0	8.8 (2.7–30.5)	5.4 (1.8–7.6)

*A significant difference ($p < 0.02$) was found for luteinising hormone after exclusion of one control patient (see text). No significant differences were found for the results of the other tests.

†Derived from middle aged euthyroid male and female outpatients.

T4—thyroxine; T3—triiodothyronine; T—total; f—free; TSH—thyrotrophin; RIA—radioimmuno assay; IRMA—immunoradiometric assay; COLD—chronic obstructive lung disease; LH—luteinising hormone; FSH—follicle stimulating hormone.

normal basal TSH level measured by immunoradiometric assay.

THYROTROPHIN RESPONSE TO THYROTROPHIN RELEASING HORMONE

There was no significant difference in the TSH increment after injection of TRH between patients with chronic obstructive lung disease and controls. In general, larger increments were found in women than in men ($p < 0.05$). Comparison of the TSH increment in the men only still showed no difference between the groups (table 2).

Three patients with chronic obstructive lung disease (two men, one woman) had no TSH responses to TRH (< 1.0 mU/l increment). The female patient with no response died suddenly with acute respiratory failure three days after the study. Eight other patients with chronic obstructive lung disease (seven men, one woman) had reduced responses (< 3.9 mU/l increment). In the control group reduced responses were found in eight male patients. A delayed TSH response to TRH (60 minute greater than 20 minute level) was seen in two patients with chronic obstructive lung disease and five controls.

PROLACTIN

There was no significant difference in basal prolactin levels or in the prolactin response to TRH between

patients with chronic obstructive lung disease and control patients (table 2). Abnormally high basal levels (> 700 mU/l) were recorded in two men with chronic obstructive lung disease (748 and 961 mU/l) and in two control patients; one man (766 mU/l) and one woman (856 mU/l). Basal prolactin levels did not differ significantly between men and women but the peak response after injection of TRH was higher in women ($p < 0.05$). Exclusion of women from the data analysis still showed no differences between the groups.

GROWTH HORMONE

Basal growth hormone levels and the response of growth hormone to TRH were similar in patients with chronic obstructive lung disease and controls (table 2). Two female control patients had large increments in growth hormone after injection of TRH (21 and 47 mU/l), contributing to the higher responses seen in women ($p < 0.05$). Comparison of the growth hormone response to TRH in men with chronic obstructive lung disease and male control patients still showed no difference.

TESTOSTERONE AND GONADOTROPHINS

Serum testosterone concentrations were not significantly different in men with chronic obstructive lung disease and control patients (table 2). Seven men

with chronic obstructive lung disease had testosterone concentrations below the reference range; four had slightly increased luteinising hormone concentrations, and one (patient 7) also had a raised follicle stimulating hormone concentration (table 3). Five control patients had low concentrations of testosterone. Control patient 4 (table 3) had the lowest testosterone (1.8 nmol/l) and the highest luteinising hormone level (34.1 U/l), indicating primary gonadal failure.

Exclusion of this patient from statistical analysis showed a significantly higher luteinising hormone concentration in men with chronic obstructive lung disease than in controls, but serum testosterone concentrations remained similar (table 2). Eleven men with chronic obstructive lung disease had luteinising hormone concentrations above the reference range, but only the one control (No 4) described above. Although four men with chronic obstructive lung disease had raised FSH concentrations, the mean levels did not differ significantly between the men in the two groups.

CORRELATIONS BETWEEN HORMONE MEASUREMENTS AND BLOOD GAS TENSIONS, RESPIRATORY FUNCTION, AND PERCENTAGE IDEAL WEIGHT IN PATIENTS WITH CHRONIC OBSTRUCTIVE LUNG DISEASE

There was a positive correlation between the basal growth hormone concentration and the arterial hydrogen ion concentration ($r = 0.578$, $p < 0.01$). The correlation based on logarithmic transformation of both axes to normalise the distribution of data points was still significant ($r = 0.523$, $p < 0.05$ —see figure). The percentage ideal body weight correlated with the basal TSH measured by immunoradiometric

Basal growth hormone/(mU/l)

Correlation between basal serum growth hormone and arterial hydrogen ion concentration in patients with chronic obstructive lung disease (based on logarithmic axes); ($r = 0.523$, $p < 0.05$).

assay ($r = 0.724$, $p < 0.001$) and the increment in thyrotrophin after injection of TRH ($r = 0.675$, $p < 0.001$). None of the hormone measurements correlated significantly with arterial oxygen (P_{aO_2}) or carbon dioxide tensions (P_{aCO_2}), %FEV₁, or %FVC.

Discussion

There were no significant differences in thyroid hormone concentrations or basal TSH secretion between

Table 3 Details of male patients with low serum testosterone concentrations

Reference range	Age (y)	Testosterone (10–30 nmol/l)	LH (1.5–9.0 U/l)	FSH (1.5–9.0 U/l)	P_{aO_2} (12.0–15.0 kPa)	P_{aCO_2} (4.5–6.1 kPa)
COLD patient No.						
1	81	8.2	5.6	8.8	8.1	6.0
2	71	8.2	12.6	7.2	7.5	5.3
3	76	8.3	10.0	4.1	9.0	4.2
4	42	3.1	2.3	2.9	4.5	9.9
5	70	8.9	8.1	2.9	5.7	7.1
6	72	3.0	13.4	7.2	6.9	6.7
7	63	6.2	9.6	19.4	7.1	10.0
Control patient No.						
1	77	8.1	7.1	6.7	—	—
2	73	5.7	4.6	7.0	—	—
3	75	9.6	8.6	5.1	—	—
4	68	1.8	34.1	6.8	—	—
5	73	5.8	2.1	1.8	—	—

COLD—chronic obstructive lung disease; LH—luteinising hormone; FSH—follicle stimulating hormone; P_{aO_2} and P_{aCO_2} —arterial oxygen and carbon dioxide tensions.

Conversion—SI to traditional units: Blood gas tensions—1 kPa = 7.5 mm Hg.

our group of 20 patients with severe chronic obstructive lung disease and control patients of similar age with normal respiratory function. Delayed and reduced TSH responses to TRH also occurred in both groups, indicating that these changes in the hypothalamic-pituitary-thyroid axis were not specific to hypoxic patients in this study. Reduced responses have been described as an age related effect, particularly in men,¹⁶ whereas delayed responses are thought to indicate hypothalamic damage.²³ Absence of TSH responses to TRH occurred only in patients with chronic obstructive lung disease but this has been described in elderly patients with various acute illnesses.¹⁷ The severe illness and possible malnourishment of the chronic obstructive lung disease group (all but one patient was underweight) is likely to have had an additional suppressive effect on the TSH response to TRH.²⁴ The correlation observed between the percentage ideal weight and the basal TSH as measured by immunoradiometric assay or the TSH increment after injection of TRH would support this interpretation. The pituitary response to TRH recovers after illness,¹⁷ suggesting that the hypothalamic-pituitary axis is "reset" during the acute phase. This may present difficulties in assessing thyroid function since serum thyroid hormone concentrations may be diminished and, as found in our study, the TSH response to TRH may be completely absent. Basal TSH concentrations measured by a sensitive immunoradiometric assay are generally unaffected by non-thyroidal illness,¹⁴ and in this study all 20 patients with chronic obstructive lung disease had normal TSH results in this assay, confirming the clinical impression of euthyroidism. In chronic obstructive lung disease, as in other systemic illnesses, basal TSH by immunoradiometric assay may offer advantages for assessing thyroid function over the measurement of thyroid hormone concentrations or the performance of a TRH test.

The secretion of TSH, prolactin, growth hormone, and follicle stimulating hormone in the patients with chronic obstructive lung disease was no different from that in control patients with normal respiratory function. This suggests that hypoxia is not a cause of the disturbances of hypothalamic-pituitary function in chronic obstructive lung disease. Basal growth hormone concentrations in serum are known to fluctuate widely, reflecting episodic secretion of the hormone. Levels are increased by calorie restriction, low body weight, and stress,^{8,9} which makes their interpretation difficult. The correlation we observed with hydrogen ion concentration, however, suggests that increased growth hormone secretion may be associated with severe illness.

In agreement with an earlier study but in contrast with more recent reports,^{2,3} reduced gonadotrophin

secretion was not found in our patients with chronic obstructive lung disease, who had degrees of hypoxia and hypercapnia similar to those described previously. Although testosterone concentrations were lower than the reference range derived from younger men, they did not differ from those of the age matched controls, and luteinising hormone concentrations tended to be high. These features may be part of normal aging,²⁵ with stress and malnutrition also playing a contributory part.^{26,27}

It is known that during the acute phase of severe illness—for example, myocardial infarction or traumatic head injury—and after elective surgery patients may develop temporary hypogonadotrophic gonadal insufficiency.²⁸ Although this may occur in cor pulmonale,³ it is unlikely to account for the endocrine changes reported in patients with stable chronic obstructive lung disease.^{1,2} The fact that our patients with chronic obstructive lung disease had testosterone concentrations similar to those of controls and, in contrast to other reports,^{1,2,4} no correlation with P_{aO_2} was found, is most likely to be due to the greater age of our patients—only one was less than 60 years old, and he had a low testosterone concentration and severe hypoxaemia (table 3). Overall, the men with chronic obstructive lung disease were significantly older ($p < 0.01$) and more underweight ($p < 0.01$) than those in previous studies;^{1,2} any effect of hypoxia is likely to be obscured in the elderly patient with chronic obstructive lung disease by the wider range of endocrine changes that occur as a result of stress, old age, and malnourishment.

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