Sex hormone suppression and sexual impotence in hypoxic pulmonary fibrosis

P D'A SEMPLE, GH BEASTALL, TM BROWN, KW STIRLING, RJ MILLS, WS WATSON

From the Chest Unit, Inverclyde Royal Hospital, Greenock; Department of Steroid Biochemistry and Centre for Respiratory Investigation, Royal Infirmary, Glasgow; and Department of Clinical Physics and Bioengineering, Southern General Hospital, Glasgow

ABSTRACT Eight men with hypoxia associated with idiopathic pulmonary fibrosis were studied. Serum testosterone concentrations were low in two subjects and fell to subnormal levels in two others as the clinical condition and arterial oxygen tension deteriorated. There was a significant correlation between serum testosterone concentrations and arterial oxygen tensions ($p < 0.05$). Three patients showed evidence of suppression of luteinising hormone secretion at the pituitary level. Only occasional abnormalities of thyroid and prolactin concentrations were noted. Most of the men suffered from organic sexual impotence, which is considered to be due at least in part to endocrine disturbance. These findings are similar to observations in patients with hypoxic chronic obstructive airways disease and support the hypothesis that hypoxia of lung disease suppresses the hypothalamo-pituitary-testicular axis.

While studying metabolic aspects of chronic obstructive lung disease we found reduced serum testosterone values in affected men¹ and were able to show an association between severity of hypoxia and degree of testosterone suppression.² In subsequent studies we showed suppression of the hypothalamus or pituitary or both and not of the testes themselves to be responsible³ and other aspects of endocrine function to be comparatively normal. Such changes were reversible, improving with a rise in arterial oxygen tension in patients recovering from acute exacerbations with cor pulmonale.⁴ These hormone abnormalities had not previously been described in such patients, although low levels of urinary 17 ketosteroids had been noted at high altitude, indicating reduced testosterone production in the hypoxia of altitude,⁵ and also in emphysema.⁶ We have shown that organic sexual impotence can be a consequence of such low anabolic steroid production.⁷ As there have been no reported studies of the hypothalamo-pituitary-testicular axis or sexual function in other clinical conditions characterised by hypoxia we set out to study a group of men with hypoxia secondary to pulmonary fibrosis.

Address for reprint requests: Dr P D'A Semple, Chest Unit, Inverclyde Royal Hospital, Greenock PA16.

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Methods

Approval for the project was granted by the hospital ethical committee and informed written consent was obtained from all patients. Eight men attending a chest clinic who were considered to have radiographic evidence of pulmonary fibrosis were invited to participate. All had fine late inspiratory crackles and in no case was an aetiological factor incriminated. Severity of breathlessness was gauged with the help of the Medical Research Council questionnaire on respiratory symptoms⁸ and the six married patients under the age of 70 were asked questions relating to their sexual function. Lung function studies included measurement of FEV₁ and forced vital capacity (FVC), residual volume and total lung capacity (TLC) (helium dilution method), and single breath transfer factor (TLCO). The results obtained were compared with predicted normal values.^{9,10} Arterial blood samples for gas analysis were taken from the radial artery after the patient had been lying down resting for 15 minutes and breathing room air. Patients found to have an arterial carbon dioxide tension greater than 6.0 kPa (45 mm Hg) were excluded.

Within one week of these baseline investigations the patients had a pituitary stimulation test performed, all at about the same time of day (10.30 am-12 noon). Gonadotrophin releasing hormone

(100 µg) and thyrotrophin releasing hormone (20 µg) (Relefact LH-RH/TRH, Hoechst) were injected intravenously. Blood samples were taken at standard time intervals and stored at -20°C before assay. All serum hormone measurements were made by radioimmunoassay methods. Serum follicle stimulating hormone and luteinising hormone concentrations were obtained according to procedures recommended by the supraregional assay service, prolactin was measured by the method of Cowden *et al*,¹¹ and thyroid stimulating hormone was measured by a modification of the method of Hall *et al*,¹² a rabbit antihuman thyroid stimulating hormone serum kindly donated by Professor WR Butt being used. The reference standards for follicle stimulating hormone, luteinising hormone, prolactin, and thyroid stimulating hormone assays were MRC 69/104, 68/40, 75/504, and 68/38 respectively. Thyroxine and triiodothyronine were measured with semi-automated radioimmunoassays¹³ using second antibody separation. Testosterone was measured in diethyl ether extracts of serum with an antibody that has about 20% cross reactivity with 5α dihydrotestosterone.

Our laboratory's normal data for all of these methods have been obtained from appropriate volunteer hospital inpatient populations. The correlation between serum testosterone and arterial oxygen tension was tested by a least sum of squares linear fit.

Results

The results of pulmonary function tests and resting blood gas tensions are shown in table 1. In all cases the FEV₁/FVC ratio was 70% or greater, excluding significant airways obstruction. In all patients both TLC and TLCO were less than 80% of predicted

normal values, in keeping with a diagnosis of pulmonary fibrosis. In addition, all subjects were hypoxic and normocapnic. Subjects 2 and 8 were each studied a second time several months later, when clinical deterioration accompanied by a drop in arterial oxygen tension (PaO₂) was observed. Subject 2 was not sufficiently well to have his TLC and TLCO measured on the second occasion. Dyspnoea at rest (grade 4) was present in most of the patients (table 2). The only patient with minimal dyspnoea (No 7) had the highest PaO₂.

Of the six married men under 70, four admitted that they had had diminished libido for periods of six months to three years accompanied by infrequent or absent early morning penile erections, while subject 3 had had normal libido despite absence of early morning erections for years (table 2). In those with suppressed libido coitus was infrequent and, when achieved, it tended to be unsatisfactory, with either unsatisfactory or absent orgasm. The prospect of dyspnoea induced by coitus often played some part in suppressing libido.

Two subjects (Nos 1 and 4) had frankly subnormal serum testosterone concentrations, while the values for two others (Nos 2 and 8) became subnormal (2b and 8b) with clinical deterioration (table 3). There was a significant correlation ($p < 0.05$) between serum testosterone and PaO₂ (fig). Serum hormone binding globulin values were slightly raised in four of the six patients in whom it was measured. The serum luteinising hormone and follicle stimulating hormone response to injected gonadotrophin releasing hormone was not tested in subject 1. Three of the other subjects (Nos 2b, 3, and 4) had subnormal luteinising hormone responses, and two of these (Nos 3 and 4) also had subnormal follicle stimulating hormone responses. An initial high basal luteinising hormone concentration was noted in sub-

Table 1 Results of pulmonary function tests and resting arterial blood gas tensions

Patient No	Age (y)	FEV ₁ (% pred)	FEV ₁ /FVC (%)	TLC (% pred)	TLCO (% pred)	PaO ₂ (kPa)	Paco ₂ (kPa)
1	35	39	83	40	20	6.1	4.7
2a	45	47	70	79	19	8.3	4.1
b	45	30	84	—	—	6.1	4.3
3	59	68	82	56	74	9.9	4.5
4	72	90	73	78	29	7.2	4.4
5	50	34	92	39	49	7.6	3.8
6	41	61	73	69	67	10.1	5.2
7	53	83	83	66	67	10.3	6.0
8a	56	44	72	43	56	7.7	4.8
b	56	44	80	44	44	4.4	4.3

FEV₁—forced expiratory volume in one second; FVC—forced vital capacity; TLC—total lung capacity; TLco—single breath transfer factor; PaO₂, and Paco₂—partial pressure in arterial blood of oxygen and carbon dioxide; % pred—percentage of predicted normal value;* 2a, b and 8a, b—patients studied on two separate occasions.

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

Table 2 Clinical, sexual, and drug histories of patient with pulmonary fibrosis

Patient No	Dyspnoea grade	Sexual history			Drugs
		Diminished libido	Early am erection	Time since last coitus	
1	4				Prednisolone 40 mg
2a	3	Yes—3 y	No—2 y	1 m	None
b	4	Yes—3½ y	No	6 m	Prednisolone 10 mg, digoxin 0.25 mg, frusemide 40 mg, spironolactone 200 mg
3	3	No	No—? duration	1 m	None
4	4				None
5	4	Yes—7 m	No—6 m	7 m	Prednisolone 10 mg, cyclophosphamide 60 mg
6	4	Yes—1 y	No—1 y	1 m	None
7	1	No	Yes	<1 w	None
8a	4	Yes—6 m	Less regular	2 w	None
b	4	Yes—9 m	No	>3 m	Prednisolone 40 mg, azathioprine 200 mg, bendrofluazide 10 mg

Table 3 Anterior pituitary function in men with hypoxic pulmonary fibrosis: basal testosterone values and gonadotrophin concentrations after injection of gonadotrophin releasing hormone

Patient No	Basal serum 17 OHA (nmol/l)	Basal SHBG (nmol/l)	Serum LH (mU/l): minutes after GnRh			Serum FSH (mU/l): minutes after GnRh		
			0	30	60	0	30	60
1	9.0	—	6.6	—	—	2.7	—	—
2a	18	—	5.2	> 30	27	4.5	25	24
b	4.0	13	3.0	12	11	4.9	17	15
3	15	46	4.5	14	17	2.4	3.4	3.4
4	4.0	18	6.9	12	11	3.1	4.2	4.3
5	20	55	20	>100	>100	20	>30	>30
6	18	—	15	27	11	3.1	5.4	5.3
7	19	—	4.6	> 30	> 30	3.2	13	13
8a	22	54	6.1	20	23	5.2	6.9	9.2
b	5.2	50	5.2	22	19	4.1	7.4	6.5
Normal values	11–36	5–45	UD–9.0	20–42	20–38	UD–7.0	4–18	4.5–21

GnRH—gonadotrophin releasing hormone; 17 OHA—17 hydroxyandrogens (testosterone); SHBG—serum hormone binding globulin; LH—luteinising hormone; FSH—follicle stimulating hormone; UD—undetectable.

Correlation between arterial oxygen tension and serum testosterone in patients with hypoxic pulmonary fibrosis (closed circles, solid line; $n = 10$, $r = 0.682$, $p < 0.05$). Measurements from previously reported studies of patients with chronic obstructive lung disease¹⁻³ have been superimposed (open circles, dotted line; $n = 45$, $r = 0.473$, $p < 0.01$). Conversion: SI to traditional units—Arterial oxygen tension 1 kPa = 7.5 mm Hg.

Table 4 Anterior pituitary function in men with hypoxic pulmonary fibrosis: basal thyroid function and thyroid stimulating hormone and prolactin response to injection of thyrotrophin releasing hormone

Patient No	Basal serum T_3 (nmol/l)	Basal serum T_4 (nmol/l)	Serum TSH (mU/l): minutes after TRH			Serum prolactin (mU/l): minutes after TRH		
			0	30	60	0	30	60
1	2.4	130	3.4	6.9	4.6	410	990	560
2a	1.8	110	1.9	9.9	5.3	110	220	110
b	1.7	55	5.9	31	20	590	820	690
3	2.1	90	2.1	11	9.4	78	350	230
4	1.4	75	1.2	5.8	4.3	250	530	450
5	2.3	72	2.1	14	8.9	250	840	520
6	2.1	108	1.6	6.1	4.4	110	260	150
7	1.7	82	2.3	16	17	98	440	2600
8a	1.6	70	3.7	12	11	200	760	630
b	1.6	123	2.6	12	8.9	300	580	380
Normal range	0.9–2.8	55–144	UD–8.0	Increment >3.6 30 > 60 min	Increment >3.6 30 > 60 min	60–360	Increment >65% of basal 30 > 60 min	

TSH—thyroid stimulating hormone; TRH—thyrotrophin releasing hormone; T_3 —triiodothyronine; T_4 —thyroxine; UD—undetectable.

jects 5 and 6 and a high basal follicle stimulating hormone concentration in subject 5. Normal serum triiodothyronine and thyroxine values were obtained in all subjects (table 4). Rather flat thyroid stimulating hormone response curves between 30 and 60 minutes after injection of thyrotrophin releasing hormone were observed in subjects 7 and 8a. The basal serum prolactin concentration was moderately raised in subjects 1 and 2b. There was a delayed prolactin response to injected thyrotrophin releasing hormone in subject 7.

Discussion

We have shown that in hypoxic pulmonary fibrosis hormone changes are essentially similar to those we have already reported in chronic obstructive lung disease.^{1–3} In both conditions serum testosterone tends to be low in proportion to the degree of hypoxia (fig) and is not related to the concentration of hormone binding globulin, which is normal or modestly raised. Elevation of hormone binding globulin concentration may be secondary to low serum testosterone concentrations and this would tend to reduce the free testosterone values even further. Suppression of the hypothalamo-pituitary-testicular axis has again been demonstrated but in some patients with pulmonary fibrosis the disturbance appears to originate at pituitary rather than hypothalamic level, as evidenced by a diminished response of both luteinising hormone and follicle stimulating hormone to injected gonadotrophin releasing hormone in patients 3 and 4.

Subject 5, a comparatively young man, had high basal luteinising hormone and follicle stimulating hormone values (table 3) in the presence of normal serum testosterone, a picture seen in primary testicular failure as in Klinefelter's syndrome and

sometimes in elderly men.¹⁴ This is not a feature we have noticed previously in hypoxic lung disease. Possibly cyclophosphamide treatment was responsible for the high gonadotrophin concentrations in this patient as this drug damages testicular germinal (Sertoli) cells with consequent oligospermia,¹⁵ although normal endocrine function is usually preserved.¹⁶ Acute exposure to hypoxia at high altitude is known to induce changes in the testicular germinal epithelium of animals¹⁷ and produce oligospermia in rams¹⁸ and men¹⁹ and urinary output of testosterone after injection of human chorionic gonadotrophin is decreased in natives of high altitude regions.²⁰ All this evidence supports the possibility of testicular suppression in those circumstances. A fall in luteinising hormone, however, has also been noted in acute exposure to high altitude²¹ and so it seems possible that either the hypothalamus, the pituitary, or the testis alone may on occasion be the primary organ to fail in conditions of hypoxia.

In both of the chronic lung conditions we have studied, serum testosterone levels tend not to fall below normal until the PaO_2 drops below 7.3 kPa (55 mmHg)^{1–4} (fig). The four patients with pulmonary fibrosis who had the lowest testosterone and lowest PaO_2 values had died by the time of writing so it appears that a low serum testosterone concentration, like a low arterial oxygen tension, is an unfavourable feature. This was also our impression in our patients with chronic obstructive lung disease.

Unlike subject 2, subject 8 retained normal luteinising hormone and follicle stimulating hormone responses as his condition deteriorated with falling PaO_2 but by this time he was in hospital receiving intermittent oxygen treatments, which may have improved hypothalamo-pituitary-testicular function. It will be of some interest to find out

whether oxygen treatment can prevent or even reverse these hormone changes.

In our studies so far we have found nothing to contradict the hypothesis that hypoxia is the offending agent accounting for the hormone changes. Hypercapnia, which was present in many of our patients with chronic obstructive lung disease with suppression of the hypothalamo-pituitary-testicular axis, cannot be incriminated as it was absent in all of the patients with pulmonary fibrosis. Reviewing those of the seven patients with recovery from exacerbations of chronic obstructive lung disease with cor pulmonale in which serum testosterone and PaO_2 values rose,⁴ we found that arterial carbon dioxide tension fell in four but rose in three, which again makes hypercapnia an unlikely culprit. Although arterial pH tended to fall with recovery, values were within or near the normal range and pH therefore seems unlikely as a factor. Conceivably acid-base changes could influence the hypothalamo-pituitary-testicular axis as base excess did fall significantly with recovery. Hypothalamo-pituitary-testicular abnormalities are not, however, recognised features of acid-base changes in other clinical conditions. Corticosteroid suppression of the hypothalamo-pituitary-testicular axis has been described in Cushing's disease²² but we have no reason to believe that steroid treatment is responsible in hypoxic chest disease. Our own unpublished observations suggest that patients with non-respiratory disease retain normal testosterone values even when taking a 50 mg daily dose of prednisolone. Moreover, subject 4 in the present study had a low serum testosterone concentration but was taking no drugs, and few among our hypoxic patients with chronic obstructive lung disease who had low serum testosterone concentrations were taking oral steroids. Furthermore, we have noted an appreciable increase in serum testosterone in patients recovering from cor pulmonale,⁴ commensurate with the rise in PaO_2 , despite the fact that such patients were often taking no drugs on admission in the acute phase but on recovery were taking several drugs, including spironolactone—which has been alleged to cause a reduction in serum testosterone.²³

The hypothalamo-pituitary-thyroid axis appears to be comparatively well preserved in pulmonary fibrosis as it is in patients with chronic obstructive lung disease,¹³ although we did find the occasional instance of delayed thyroid stimulating hormone response to injected thyrotrophin releasing hormone in both syndromes. Such delayed thyroid stimulating hormone and prolactin responses are thought to indicate hypothalamic damage,¹² but these fairly new tests of hypothalamo-pituitary func-

tion are still being evaluated and such results should be interpreted with caution. Occasional instances of non-drug-induced modest increases in serum prolactin were found in both respiratory conditions, but these changes are known to occur with any physical or emotional stress and the drugs used were not ones usually associated with increased prolactin concentrations.²⁴

It is not surprising to find evidence of reduced sexual function in this group of men with a tendency to testosterone deficiency. We had found evidence of loss of libido in nine of our 10 patients with chronic obstructive lung disease and it was a feature of most of our men with pulmonary fibrosis. This is clearly an unusual finding since 90% of men aged 50–60 years practise regular coitus or similar sexual activity and have regular early morning penile erections,^{25,26} and lack of such erections is generally taken as a guide in distinguishing organic from psychological causes of impotence.^{26–28} Most patients with chronic obstructive lung disease thought that diminished libido was not related to the prospect of dyspnoea during the exertion of intercourse, whereas in the patients with pulmonary fibrosis this factor did appear to accentuate the problem. Subjects 3, 5, and 6 had no early morning erections despite normal serum testosterone concentrations (table 2). We have shown that libido and sexual performance can fluctuate with the severity of disease and also with changes in arterial oxygen tension and serum testosterone.⁷ Possibly when they were studied patients 3, 5, and 6 were comparatively well from the respiratory standpoint and this may have been reflected in near normal endocrine activity. Previously we have indicated that organic sexual impotence may not be an "all or none" phenomenon²⁹ and normal serum testosterone concentrations do not necessarily reflect a normal hypothalamo-pituitary-testicular axis.³

In conclusion, low serum testosterone concentrations and sexual impotence occur in men with hypoxic pulmonary fibrosis as well as in hypoxic chronic obstructive lung disease. Significant correlations between PaO_2 and serum testosterone in both conditions suggest a causal relationship, particularly as there is no evident relationship between other arterial blood gas indices and serum testosterone. The hypothesis that hypoxia itself suppresses the hypothalamo-pituitary-testicular axis remains to be tested. Pituitary stimulation tests in pulmonary fibrosis suggest that pituitary suppression may be responsible for the deficient steroidogenesis in some cases whereas in chronic obstructive lung disease the suppression was apparently hypothalamic. One case of possible testicular suppression in pulmonary fibrosis was noted. Pituitary rather than

hypothalamic suppression of follicle stimulating hormone release occurs in both conditions, though we have no information on spermatogenesis or fertility. Minor suppression of the hypothalamo-pituitary-thyroid axis seems to occur in both conditions but in neither is it sufficient to cause clinical or biochemical hypothyroidism. Minor abnormalities of the hypothalamo-pituitary-thyroid axis and of prolactin concentration may indicate a degree of hypothalamic suppression in these conditions.

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