Endocrine and metabolic studies in unstable cor pulmonale

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ABSTRACT Serum testosterone, follicle-stimulating hormone, luteinising hormone, and dihydroepiandrosterone concentrations rose significantly in seven men studied during recovery from a severe exacerbation of chronic obstructive airways disease. Urinary 17-ketosteroids also rose significantly though serum androstenedione and prolactin concentrations did not. Our findings suggest that hypoxia in this condition suppresses the hypothalamus or pituitary or both and that such suppression is reversible. In view of previous reports of increase in total body potassium and intracellular water with recovery from cor pulmonale, we also carried out metabolic studies on our patients. Low body potassium concentrations in cor pulmonale fell further with recovery, in part reflecting a fall in lean body tissue. Intracellular water appeared to increase on recovery despite a fall in other lean body mass indices (the simplest and most reliable being skinfold thickness). We suspect this result to be spurious and due to problems with equilibration in isotope dilution. Alternatively it may reflect waterlogging of cells. A false figure for intracellular water could be responsible for an unexpectedly low estimated intracellular potassium concentration on recovery. Our results cast doubt on isotope dilution methods for measuring body water compartments in disease states likely to cause changes in cell permeability.

In a previous paper comparing underweight normocapnic "pink puffers" with overweight hypercapnic "blue bloaters"¹ we showed no difference between them in calorie intake, thyroid function, or corticosteroid production to explain differences in body build, and moreover showed that pink puffers had negative results in malabsorption studies. Serum testosterone, however, was profoundly reduced in blue bloaters and somewhat reduced in pink puffers, while blue bloaters had rather higher serum prolactin levels. Further studies showed a correlation between severity of hypoxia and degree of testosterone suppression.² This testosterone reduction was apparently caused by hypoxic suppression of the hypothalamus or pituitary,³ and sexual impotence was a feature.⁴ We also considered that such endocrine disturbances might cause changes in body habitus in chronic obstructive airways disease.¹ The weight loss and depressed gonadal function which occur at high altitude^{5,6} might be similarly associated.

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Campbell and associates⁷ suggested that body tissue is lost rapidly by patients during exacerbations of cor pulmonale. This tissue, sometimes called fat-free mass, was apparently restored as values of total body potassium and intracellular water, indirect measures of fat-free mass, tended to increase with recovery. Accumulation of oedema in cor pulmonale and dispersal of it during recovery were not accompanied by the expected changes in total body weight and might have been due to redistribution of fluid between intracellular and extracellular compartments.

We performed similar metabolic studies and compared hormone levels during acute cor pulmonale and again after recovery to discover whether hypothalamopituitary suppression varies with severity of disease and whether loss of fat-free mass is related to anabolic steroid suppression.

Methods

Approval for the project was granted by the hospital ethical committee and informed written consent was obtained. Seven men (age range 36-63) admitted in

Table 1 Laboratory results for the seven patients in acute cor pulmonale and after recovery

Clinical phase	FEV ₁ (l)	FEV (% predicted)	FEV ₁ /FVC (%)	PaO ₂ (kPa)	PaCO ₂ (kPa)	Serum potassium (mmol/l)	Serum sodium (mmol/l)
Acute cor pulmonale							
Mean	0.76	26	45	5.5	7.7	4.0	139
Range	0.45–1.0	17–32	29–61	4.9–6.5	6.4–9.2	3.3–4.9	135–143
Recovery							
Mean	0.88	29	48	7.3	7.6	4.1	137
Range	0.5–1.2	19–38	31–61	5.7–9.3	6.6–10.0	3.4–4.9	131–140
Significance of difference	NS	NS	NS	p = 0.02	NS	NS	NS

FEV₁—forced expiratory volume in one second; FVC—forced vital capacity; PaO₂ and PaCO₂—partial pressure in arterial blood of oxygen and carbon dioxide.

Conversion: SI to traditional units—Blood gases: 1 kPa = 7.5 mm Hg; sodium and potassium: 1 mmol/l = 1 m Eq/l.

Table 2 Hormone levels in acute cor pulmonale and after recovery

Clinical phase	Serum						Urinary 17-KS (μmol/24 h)
	17-OHA (nmol/l)	FSH (U/l)	LH (U/l)	DHAS (μmol/l)	A-dione (nmol/l)	Prolactin (mU/l)	
Acute cor pulmonale							
Mean	8.0	2.8	5.0	1.1	3.1	196	11
Range	4.0–14.0	0.4–7.3	0.7–12.1	0.3–1.9	1.2–6.3	160–240	3–22
Recovery							
Mean	17	4.7	7.8	2.2	4.0	226	23
Range	9–28	1.5–13.1	1.4–16.0	0.6–3.9	2.5–6.1	100–420	7–66
Normal range	11–36	0–23.5	0–33	2.0–9.0	2.0–11	60–360	Age dependent
Significance of difference	p = 0.02	p = 0.02	p = 0.02	p = 0.05	NS	NS	p ≤ 0.05

17-OHA—17-hydroxyandrogens (testosterone); FSH—follicle-stimulating hormone; LH—luteinising hormone; DHAS—dehydroepiandrosterone sulphate; A-dione—androstenedione; 17-KS—17-ketosteroids.

cor pulmonale failure were studied. All had chronic bronchitis (cough and sputum production on most days of the year for more than three years) and all had had grade 3 or 4 dyspnoea for several years.⁸ Patients with additional, unrelated disease were excluded. All had peripheral oedema and raised jugular venous pressures on admission and were hypoxic and hypercapnic (table 1). Standard treatment was with oxygen, antibiotics, diuretics, bronchodilators and physiotherapy.

Investigations were started three or four days after admission when oedema had largely subsided and patients were sufficiently well to be studied. Spirometry was performed in the sitting position with a Vitalograph dry spirometer. The forced expiratory volume:forced vital capacity ratio (FEV₁/FVC%) was less than 70% in all cases, signifying airways obstruction (table 1). Radial arterial blood gas samples were taken in heparinised (5000 units/ml) glass syringes after the patients had been off oxygen and lying resting for 15 minutes. Specimens were ice cooled and analysed within 10 minutes. Body weight was measured in pyjamas. Blood for hormone and electrolyte measurements was taken at 1100 hours.

Serum levels of all hormones were assessed by radioimmunoassay and urinary 17-ketosteroids were measured spectrophotometrically. Hormone reference ranges were derived by the department of steroid biochemistry, Glasgow Royal Infirmary. Total body potassium was measured by whole-body monitor⁹ and results were compared with predicted normal values.¹⁰ Total body water and extracellular water were measured by administering firstly tritium (³H)-labelled water and later bromine-77 or bromine-82 intravenously and analysing venous samples four hours after injection.¹¹ Intracellular water was deduced by subtraction, levels being compared with predicted normal values.¹² Dry body weight was deduced by subtracting total body water from body weight. Fat-free mass was estimated by four different methods: (a) from triceps and subscapular skinfold thickness¹³; (b) from total body water¹⁰; (c) from total body potassium¹⁰; and (d) predicted from height and weight.¹⁴ Statistics were applied using the Wilcoxon test for paired differences.

After recovery, some months later, these investigations were repeated.

Table 3 Body weight and body compartment estimates in acute cor pulmonale and after recovery

Clinical phase	Weight (kg)	TBW (l)	TBW measured TBW predicted	Dry body % weight (kg)	ECW (l)	ECW measured ECW predicted	ICW % (l)	ICW measured ICW predicted	TBK (mmol)	TBK measured TBK predicted	ICK (mmol/l)
Acute cor pulmonale											
Mean	70.5	36.9	100	33.5	17.5	100	19.4	93	2757	89*	142
Range	50–104	29–47	88–114	21–57	15–22	86–134	14–24	74–107	2094–3773	79–100	125–155
Recovery											
Mean	68.2	38.0	104	30.2	15.7	99	22.3	109	2569	83**	116
Range	47–97	28–52	96–113	19–45	13–21	81–113	16–31	85–122	1945–3378	71–95	106–130
Significance of difference	NS	NS	NS	NS	NS	NS	p ≤ 0.05	p ≤ 0.02	NS	p = 0.05	p ≤ 0.02

TBW—total body water; ECW—extracellular water; ICW—intracellular water; TBK—total body potassium; ICK—intracellular potassium. *Significantly low ($p \leq 0.005$); **significantly low ($p \leq 0.001$).

Conversion: SI to traditional units—Potassium: 1 mmol = 1 mEq.

Table 4 Fat-free mass assessed by various techniques and indirect measurement of potassium concentration in fat-free mass in acute cor pulmonale and after recovery

Clinical phase and patient No	FFM(SFT) (kg)	FFM(TBW) (kg)	FFM(TBK) (kg)	FFM (predicted) (kg)	Δ TBK/ Δ FFM(SFT) (mmol/kg)
Acute cor pulmonale					
1	54.8	50.0	49.4	59.0	106
2	39.2	39.4	43.8	41.2	71
3	65.3	63.6	56.5	68.6	208
4	53.1	54.4	48.6	50.6	59
5	48.5	49.5	45.8	51.1	—
6	46.1	46.7	47.3	47.4	—
7	54.9	50.7	50.3	59.3	64
Mean	51.7	50.6	48.8	53.9	
Recovery					
1	50.7	50.8	46.2	55.3	
2	37.1	38.5	42.7	40.2	
3	63.4	70.7	53.5	65.7	
4	45.5	44.4	45.2	49.4	
5	48.2	51.0	45.2	50.0	
6	47.8	51.2	47.1	48.6	
7	57.9	58.1	51.7	61.0	
Mean	50.1	52.1	47.4	52.9	
Significance of difference	NS	NS	NS	NS	

FFM(SFT), FFM(TBW), FFM(TBK), and FFM (predicted)—fat-free mass assessed from skinfold thickness, total body water, and total body potassium and predicted from height and weight; Δ TBK/ Δ FFM(SFT)—change in total body potassium between cor pulmonale and recovery divided by change in fat-free mass.

Conversion: SI to traditional units—Potassium: 1 mmol = 1 mEq.

Results

Initially all patients had grade 4 dyspnoea (dyspnoea at rest) and five of the seven had improved to grade 3 (dyspnoea on minimal exertion) during the recovery study period. There was no significant improvement in degree of airways obstruction or hypercapnia after recovery but arterial oxygen tensions increased in all patients (table 1).

Serum testosterone (17-OHA), follicle-stimulating hormone and luteinising hormone rose significantly (table 2) when clinical recovery took place ($p = 0.02$). Both follicle-stimulating hormone

and luteinising hormone levels normally fluctuate but the rise accompanying clinical improvement, together with our earlier finding of low follicle-stimulating hormone and luteinising hormone in chronic obstructive airways disease compared with controls,³ confirms that these hormones are indeed further suppressed in the acutely hypoxic state. Serum dehydroepiandrosterone sulphate and urinary 17-ketosteroids also rose significantly ($p \leq 0.05$), though serum androstenedione and prolactin did not.

Though mean values for body weight did not significantly change (table 3) five out of the seven

patients continued to lose weight on recovery, especially two who were on reduction diets. Group mean total body water and dry body weight did not change significantly, though the latter fell in six men. A similar pattern was observed for extracellular water, while intracellular water increased significantly with recovery ($p \leq 0.05$). The group's mean total body potassium remained unaltered, though when expressed as a percentage of predicted normal the values were low ($p \leq 0.005$), with a further fall on recovery ($p = 0.05$). Intracellular potassium values, which were normal in the acute phase, fell significantly ($p \leq 0.02$) to subnormal with recovery. Serum potassium and sodium remained normal throughout (table 1).

Table 4 lists values for fat-free mass obtained by the four different methods—skinfold thickness, total body potassium, total body water, and “predicted.” The value obtained from the total body potassium was the lowest, but none of the mean fat-free mass values for the group obtained by these various techniques differed significantly from the others. When the changes in fat-free mass between the acute phase of the illness and recovery determined by each of the four methods were compared, the skinfold thickness method agreed closely with the total body potassium and “predicted” methods but the total body water method correlated poorly with each of the other three methods. Comparison of predicted fat-free mass values with those obtained by the skinfold method never showed more than an 8% discrepancy, whereas there were differences of up to 15% between predicted values and those obtained by the total body water and total body potassium methods.

For the five subjects (Nos 1, 2, 3, 4, and 7) who showed a significant change ($> \pm 7\%$) in total body potassium the ratio $\Delta \text{TBK} / \Delta \text{FFM}$ (SFT) (change in total body potassium between cor pulmonale and recovery divided by change in fat-free mass) derived from the skinfold thickness method is included in table 4. The accepted value for potassium concentration in fat-free tissue is 69 mmol (mEq)/kg. For subjects 2, 4, and 7 good agreement with this value was recorded, while subjects 1 and 3 showed potassium loss exceeding that which could be accounted for by loss of fat-free tissue.

Discussion

From this study we can conclude that integrity of the hypothalamopituitary-testicular axis is compromised during severe hypoxia but recovers somewhat with improved oxygenation. The increase in urinary 17-ketosteroids, which are largely androgen metabolites, reflects increased testosterone produc-

tion with recovery. The rise in the adrenal androgen dehydroepiandrosterone sulphate and lesser increase in androstenedione, which is partly adrenal and partly testicular in origin, suggests that hypoxia may also influence their production, perhaps at the hypothalamic level.

Though total body weight showed no consistent changes, dry body weight decreased in six men on recovery, although the group mean did not change significantly. The lack of reduction in total body water might seem surprising but this was not measured until about the fourth day of the acute illness, when oedema had largely dispersed. A rise of intracellular water and fall of extracellular water during recovery is consistent with the finding by Campbell and colleagues⁷ of a fall in intracellular water with the onset of cor pulmonale oedema. They found no appreciable gain in weight at its onset and postulated that the fluid accumulation is due not to overall fluid retention but to a shift from the intracellular compartment. They suggested that this fall in intracellular water, which is usually accepted as an index of fat-free mass,¹⁵ might be related to loss of lean tissue. As a corollary to this, our finding of a 10% rise in intracellular water with recovery might reflect a gain in fat-free mass, perhaps caused by increased anabolic steroid production. We have reservations, however, about such a tidy explanation. The close relationship of intracellular water measured by isotope dilution to fat-free mass is accepted in healthy individuals,¹⁶ but we think it may not be applicable in the present context. The total body potassium method of assessing fat-free mass, also well tried in normal individuals,¹⁷ requires normal intracellular potassium values and as we have shown in this study that these may be less than reliable. The other indices—fat-free mass assessed by the skinfold thickness and by the “predicted” methods (table 4) and dry body weight (table 3)—all suggest that lean tissue is lost gradually despite clinical stabilisation, which is consistent with slowly progressive clinical deterioration—67% of these patients dying within five years of their first episode of oedema.¹⁸ The anomalous increase in fat-free mass assessed by body water radioisotope dilution might be explained by a waterlogging of cells, so that the increase in intracellular water on recovery may not reflect a true increase in fat-free mass. Alternatively, the inconsistent rise in intracellular water on recovery may be due to an altered cell permeability to isotopes in the acutely hypoxic phase that gives false values for water compartments. Isotope dilution studies should clearly be interpreted with caution in abnormal metabolic states.

Using an isotope dilution method considered by others to be unreliable,¹⁹ Campbell *et al* found inconsistent changes in total body potassium with recovery. Using the more reliable whole-body monitor method we found low total body potassium values during the acute illness with a further fall on recovery. Intracellular potassium concentrations assessed by dividing total body potassium by intracellular water fell to subnormal values, but this is a genuine fall only if the increased intracellular water accompanying recovery is genuine. If the main intracellular cation, potassium, were low, it would be replaced by sodium to a similar osmotic equilibrium. As the expected fall in serum sodium did not occur (table 1) it is difficult to explain low intracellular potassium in biochemical terms. Low intracellular potassium values therefore may result from spuriously high intracellular water measurements. Low total body potassium on the other hand could in part be due to reduction of fat-free mass, and this may apply to patients 2, 4, and 7 (table 4), in whom the loss of total body potassium was that expected from the degree of fat-free mass loss recorded. For the two patients 1 and 3 other, as yet unidentified, factors must contribute to the explanation of the excess potassium loss. This seems not to be due to diet¹ or solely to diuretic treatment.²⁰ The role of hyperaldosteronism here is unknown.

This study shows that suppressed hypothalamopituitary-testosterone function in acute cor pulmonale improves with clinical recovery and a rise in arterial oxygen tension. Most of the indirect measures of fat-free mass, however, suggest a persistent fall despite clinical improvement and increased anabolic steroid production. The apparent rise in intracellular water with recovery may have been due to poor isotope equilibration in acute cor pulmonale that gave falsely high extracellular water values and thereby falsely low initial intracellular water values. Even if the rise in intracellular water with recovery is genuine this apparently does not equate with increase in fat-free mass but may merely indicate waterlogged cells. Our finding of low total body potassium was confirmed and we believe that this is only in part due to loss of fat-free mass. Clearly further studies on this complex subject are indicated.

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