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Diet, absorption, and hormone studies in relation to body weight in obstructive airways disease

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ABSTRACT Sixteen male patients with stable chronic obstructive airways disease were separated into two groups of eight according to arterial carbon dioxide tensions. Hypercapnia was associated with lower arterial oxygen tensions, higher red cell volume, and increased weight, while normocapnic subjects were decidedly thin. The considerable difference in body weight between the two groups could not be explained by variation in calorie intake, and malabsorption was excluded as a cause of weight loss in the underweight subjects. Serum tri-iodothyronine, thyroxine, cortisol, and oestradiol concentrations were similar and normal in each group, but both groups had significantly low testosterone values as compared with controls, values in the hypercapnic being appreciably lower than in the normocapnic group. The adrenal androgen dehydroepiandrosterone was significantly high in the normocapnic group and low in the hypercapnic group compared with controls. Serum pituitary luteinising and follicle stimulating hormones were normal, but three hypercapnic individuals had high serum prolactin values. Early morning urinary aldosterone values were significantly higher in the hypercapnic than in the normocapnic group. Such hormone comparisons have not previously been made in subjects with chronic obstructive airways disease grouped according to arterial blood gas values, and it is concluded that major alterations in adrenal and testicular function may occur, possibly due to pituitary suppression from hypoxia. Such hormonal changes might in part account for the contrasting alterations in body habitus found in this condition.

Whereas patients with chronic obstructive airways disease (COAD) who are chronic bronchitics tend to be overweight, those with predominant emphysema lose weight and tend to be thin (Vandenbergh *et al*, 1967; Campbell *et al*, 1975; Semple, 1978; Thurlbeck, 1978). Depressed food intake has already been shown to occur only in a proportion of these thin emphysematous subjects (Wilson *et al*, 1964; Vandenbergh *et al*, 1967). Malabsorption is a possible factor as this has been described in emphysema with alpha$_1$-antitrypsin deficiency (Greenwald *et al*, 1975) and also in association with the weight loss of altitude hypoxia (Pugh, 1962) although in this condition appetite suppression does occur. A high prevalence of gastrointestinal disturbances in COAD has been cited as a possible cause of poor appetite (Vanderbergh *et al*, 1967), while yet another factor contributing to the weight loss may be the increased energy expenditure of dyspnoeic breathing (Cherniack, 1959). Depression of adrenal and gonadal function which occurs at altitude (Pugh, 1962; Guerra-Garcia *et al*, 1969) could contribute to weight loss by reducing anabolic steroid hormone production, and a similar type of hormone depression has already been noted in emphysema (Marmorston *et al*, 1966). As the reasons for weight loss in emphysema are far from clear, we have sought to determine the relation of diet and absorption of food to body habitus in COAD and have also studied the hormonal aspects of two groups of patients with obstructive airways disease—hypercapnic, hypoxic chronic bronchitic "blue bloaters" and their thin emphysematous normocapnic "pink puffer" counterparts.

Methods

Approval for the project was granted by the hospital ethical committee, and informed written consent obtained from all patients. Sixteen stable male chest clinic patients were chosen to represent a wide range of body habitus. All had grade 3 or 4 dyspnoea (MRC questionnaire on respiratory symptoms, 1966) and only one was a non-smoker. By spirometry (Vitalograph, sitting) forced expiratory volume in one second (FEV_1) was always less than 70% of predicted normal value and forced expiratory volume/forced vital capacity ratio (FEV_1/FVC%) was always less than 70%, signifying airways obstruction. Patients were selected by the above criteria, and their blood gas tensions were then measured. They were grouped according to arterial carbon dioxide tensions ($Paco_2$), those with a $Paco_2$ level greater than 5·8 kPa hereafter being referred to as the "hypercapnic group" and those with a level less than 5·8 kPa as the "normocapnic group."

Subjects were admitted to a metabolic unit for three days. Height and weight were measured, and the latter value was compared with that predicted for sex, age, and height (Society of Actuaries, Chicago, 1959). Arterial blood samples for blood gas estimation were taken from the radial artery, the subject having rested breathing room air for 30 minutes. Red cell volume was performed by administering ^{51}Cr labelled red cells and measuring the radioactivity in samples 10, 20, and 30 minutes after injection. Predicted normal values were calculated using the equation developed by Nadler *et al* (1962) and modified by Hume and Goldberg (1963).

Food consumption was assessed by experienced dieticians and converted to a caloric value (McCance and Widdowson, 1960), that was then compared with the individual's predicted normal value (DHSS Report No 120, HMSO 1969). Similar dietary assessments for comparison were made in 18 men admitted with various traumatic orthopaedic problems but who were otherwise healthy. In addition the eight underweight subjects underwent jejunal biopsy, estimation of serum iron, B_{12}, and folate as well as d-xylose excretion test and three-day faecal fat estimation to assess intestinal absorption.

Blood was taken at midday from patients on the second day of admission. Serum tri-iodothyronine (T_3), thyroxine (T_4), 17 hydroxyandrogens (testosterone), dehydroepiandrosterone (DHA), luteinising hormone (LH), follicle stimulating hormone

Table 1 *Laboratory results of patients with chronic obstructive airways disease grouped according to* $Paco_2$ *values*

Subjects	*Age (yr)*	*Height (m)*	*Weight (% predicted)*	*FEV_1 (% predicted)*	*FEV_1/FVC (%)*	*Pao_2 (kPa)*	*$Paco_2$ (kPa)*	*Red cell volume $\left(\frac{\text{measured}}{\text{predicted}}\ \%\right)$*
Hypercapnic ($Paco_2$ > 5·8 kPa)								
1	69	1·81	64·2	25·0	25·7	6·3	7·6	103
2	70	1·55	108·5	68·0	61·8	8·1	5·9	143
3	53	1·70	133·3	26·6	40·5	7·2	6·4	157
4	66	1·59	132·5	30·9	41·5	7·2	6·0	134
5	66	1·65	111·8	28·6	38·8	5·3	9·0	165
6	78	1·59	161·1	40·1	50·8	5·6	11·9	167
7	59	1·58	104·2	34·0	68·0	6·2	7·9	159
8	52	1·69	110·0	54·8	54·0	7·4	5·9	141
MEAN	64·1	1·65	115·7	38·5	47·6	6·7	7·6	146·1
Normocapnic ($Paco_2$ < 5·8 kPa)								
9	38	1·83	70·7	24·4	42·2	7·7	5·1	96
10	70	1·61	57·9	28·3	44·2	9·8	4·7	86
11	56	1·55	65·4	26·0	30·9	8·4	4·7	124
12	53	1·64	79·7	48·4	40·0	7·5	5·3	118
13	52	1·69	64·0	29·7	47·6	8·2	5·3	107
14	56	1·64	61·6	20·0	33·7	9·8	5·1	110
15	61	1·64	81·0	22·6	48·7	8·0	5·2	120
16	57	1·73	106·2	66·7	51·9	9·6	5·3	105
Mean	55·4	1·67	73·3	33·3	42·4	8·6	5·1	108·3
Significance of difference	NS	NS	P < 0·01	NS	NS	P < 0·01	P < 0·01	P < 0·01

FEV_1 = Forced expiratory volume in 1s; FVC = Forced vital capacity; Pao_2 and $Paco_2$ = Partial pressure in arterial blood of oxygen and carbon dioxide; NS = Not significant.

(FSH), and prolactin as well as urinary aldosterone values were measured by radioimmunoassay and serum cortisol by a fluorimetric method.

Control values for these hormones were taken from a group of 14 male patients without chest disease matched for age attending either an anticoagulant clinic or with treated pernicious anaemia at a haematology clinic. Statistical comparisons were made with Wilcoxon's rank test.

Results

There was no significant difference in age, height, or spirometric readings between the two groups of subjects separated according to $Paco_2$ values (table 1), but the hypercapnic group of eight subjects was significantly heavier (hypercapnic mean weight 78·0 kg; normocapnic 51·7 kg; $P<0.01$). Seven of the eight hypercapnic subjects were overweight and seven of the eight normocapnic subjects underweight. The hypercapnic group had lower arterial oxygen tensions and higher red cell volume expressed as a percentage of predicted normal.

Five of the overweight and seven of the underweight subjects ingested less than their predicted calorie requirement (table 2), and there was no significant difference between the two groups in mean daily calorie intake. On average both groups ingested more but not significantly more than the healthy men. Daily protein intake was normal and similar in each group as were the serum T_3 and T_4 values. The various investigations performed to exclude malabsorption in the eight underweight subjects produced normal results.

All but one of our 16 COAD subjects (No 1 had a modestly raised value) had normal values for serum cortisol (table 3). The hypercapnic group had a significantly lower mean testosterone level than the normocapnic group, and both study groups had significantly lower values than the control group. Seven of the eight hypercapnic and one of the eight normocapnic subjects had serum testosterone values below the lower limit of normal. Serum dehydroepiandrosterone was not significantly lower in the hypercapnic group than in controls but was higher in the normocapnic group than in controls. All individual values, however, were within the normal range except for subject 11 who had a raised value. Serum oestradiol, LH, and FSH were similar and normal in both groups. Serum prolactin concentrations were higher in the hypercapnic group than in both normocapnic and control groups, although the differences were not significant. However, three individual hypercapnic subjects (4, 5, and 6) had raised values. Early morning urinary aldosterone levels were higher in the hypercapnic group as compared with the normocapnic group.

Table 2 *Calorie and protein intake and thyroid function in patients with chronic obstructive airways disease grouped according to weight*

Subjects	*Weight (kg)*	*Weight (% predicted)*	*k calories (daily)*	*k calories (% predictea)*	*Protein (g/day)*	*Serum T_3 (nmol/l)*	*Serum T_4 (nmol/l)*
Overweight							
2	66·9	108·5	2409	102·5	74	2·0	72
3	98·0	133·3	4682	161·5	118	1·6	74
4	84·4	132·5	2304	98·0	68	1·8	62
5	76·0	111·8	2746	116·9	59	1·7	72
6	101·1	161·1	2108	81·1	83	0·9	81
7	67·7	104·2	1759	67·7	53	1·8	91
8	79·6	110·0	1799	69·2	53	1·9	132
16	80·0	106·2	1388	53·4	44	1·3	51
Mean	81·7	121·0	2399	93·7	69·0	1·63	79·4
Underweight							
9	57·4	70·7	2864	98·8	102	2·1	83
10	37·8	57·9	1434	61·0	54	2·1	90
11	41·2	65·4	1854	78·9	55	1·7	71
12	54·6	79·7	2304	88·6	47	1·8	74
13	46·3	64·0	3214	110·8	87	1·7	68
14	42·2	61·6	1939	74·6	73	1·6	89
15	54·4	81·0	2231	85·8	66	1·6	84
1	52·6	64·2	2081	88·6	67	1·6	80
Mean	48·3	68·1	2240	85·9	68·9	1·78	79·9
Significance of difference*	$P<0.01$	$P<0.01$	NS	NS	NS	NS	NS
Controls—Mean			2172	83·5	70·4		
Range			1400–4460	53·8–171·5	53–96		

*Statistics using Wilcoxon's rank test.
T_3=Tri-iodothyronine; T_4=Thyroxine.

Table 3 *Results of hormone analyses in patients with chronic obstructive airways disease grouped according to* $PaCO_2$ *values*

Subjects	*Serum cortisol (nmol/l)*	*Serum 17 OHA (nmol/l)*	*Serum DHA (nmol/l)*	*Serum oestradiol (pmol/l)*	*Serum LH (U/l)*	*Serum FSH (U/l)*	*Early morning urinary aldosterone (nmol/l)*	*Serum prolactin (μ/l)*	*Drugs*
Hypercapnic									
1	820	4·5	1·0	112	8·7	28·0	10	246	Frusemide, K, Franol
2	460	9·8	6·1	103	11·0	1·2	8	133	Nil
3	260	14·5	6·6	91	6·6	7·6	21	88	Frusemide, K, digoxin
4	400	6·7	3·5	100	8·5	3·5	7	606‖	Salbutamol inhaler
5	280	7·3	4·4	ND	8·0	0·3	33	>1500‖	Frusemide, K, Franol
6	460	5·0	2·1	ND	11·0	1·8	15	1030‖	Salbutamol, frusemide, K, digoxin
7	280	4·3	5·0	101	15·0	6·1	39	320	Frusemide, spironolactone, digoxin
8	300	9·2	1·4	94	5·0	0·3	3	83	Nil
Mean	407	7·7†	3·8	100·2	9·2	6·1	17	501	
Normocapnic									
9	350	14·0	7·6	42	9·2	1·9	3	73	Salbutamol, chromoglycate
10	490	14·0	7·0	64	11·0	2·0	6	349	Salbutamol, Moduretic
11	550	10·0	16·2	44	7·9	2·8	4	136	Nil
12	500	15·0	6·6	123	20·0	14·0	4	188	Salbutamol, nitrazepam
13	460	15·0	5·4	121	5·3	0·3	3	135	Benylin
14	270	12·1	9·9	112	15·0	0·5	13	100	Salbutamol, Franol
15	370	17·3	11·5	89	5·3	0·3	7	121	Salbutamol, thiazide, theophylline
16	340	11·0	8·4	73	2·8	0·3	8	128	Nil
Mean	416	13·6‡	9·1§	83·5	9·6	2·3	6	154	
Significance of difference*	NS	P<0·01	P<0·01	NS	NS	NS	P<0·01	NS	
Controls—Mean		18·7	5·6	97·8	11·2	3·9		173	
—Range		9·2–27	3·3–10·8	40–150	4·0–33	0·4–12		80–286	
Normal range	225–600	11–36	0·7–13	30–200	0–33	0–23·5		60–360	

*Statistics using Wilcoxon's rank test.
†Significantly lower than control group (P<0·01).
‡Significantly lower than control group (P<0·02).
§Significantly higher than control group (P<0·01).
‖Individual high values.
17 OHA=17 hydroxyandrosterone (testosterone); DHA=Dehydroepiandrosterone; LH=Luteinising hormone; FSH=Follicle stimulating hormone; ND=Not done.

Discussion

Interestingly, patients with COAD and with hypercapnia were overweight while those with normocapnia were decidedly underweight. While this finding may not be universal it supports the clinical impression of two groups of patients at the ends of a range, the hypoxic, hypercapnic, polycythaemic, overweight blue bloaters and the underweight emphysematous pink puffers with near normal arterial blood gas tensions. This study makes some new observations on the metabolic and endocrine aspects of these two groups.

Although diets have previously been assessed in emphysematous subjects losing weight, the food intake of the two groups defined here have never been compared. Within the limitations of skilled dietary assessment our results suggest that while appetite suppression may be present in individual subjects with COAD this is not universal, and indeed neither group shows a consistent alteration in eating habits (table 2). Our patients, however, were comparatively well when interviewed, and possibly dietary suppression contributes to the rapid loss of lean body mass noted during exacerbations of COAD (Campbell *et al*, 1975). Two previous studies (Wilson *et al*, 1964; Vandenbergh *et al*, 1967) showed a significant reduction in mean calorie intake in emphysematous subjects losing weight, but in both studies there was a wide range of calorie intake between individuals and indeed some weight-losing subjects ate much more than other weight-stable subjects. This suggests some other mechanism of weight loss; a view supported by Campbell and colleagues (1975) who noted from published reports that hypoxia in human altitude tests and also in laboratory animal experiments causes loss of tissue mass by an as yet unexplained process. From our investigation neither malabsorption nor abnormal thyroid function seem to be causative factors. Another hypothetical cause of weight loss is increased calorie expenditure from the work of breathing in emphysema (Cherniack, 1959). Weight loss, however, may be very rapid in

exacerbations of COAD (Campbell *et al*, 1975), yet the proportion of the metabolic rate contributed by the work of breathing is quite small.

Altitude hypoxia has been shown to depress adrenal and gonadal function (Pugh, 1962; Guerra-Garcia *et al*, 1969), and Marmorston *et al* (1966) have drawn attention to abnormal urinary hormonal excretion patterns in emphysema. Although each of these conditions is associated with weight loss (Pugh, 1962; Campbell *et al*, 1975), apparently these two aspects, hormonal and metabolic, have not before been causally linked. In our study serum testosterone values were significantly low in both groups but considerably so in the hypercapnic overweight group where seven of the eight subjects had individually low values. We do not feel that age differences account for this, as appreciable reduction in testosterone does not occur till after the age of 70 (Stearns *et al*, 1974). It is known that low testosterone values in men may cause obesity in addition to impotence, female distribution of fat and hair, and soft small testes (Franks *et al*, 1978). Possibly, therefore, increased fat in these hypercapnic subjects is related to this hormonal imbalance. The reason for the normocapnic group being without excess fat is less easy to explain in such terms, although the significantly raised levels of the adrenal androgen DHA in this group compared to either the controls or the hypercapnic patients may be a factor.

The failure to show raised serum LH levels in the presence of low serum testosterone suggests that primary testicular failure is unlikely. Taking the 16 study subjects together there was a significant correlation between the degree of hypoxia and the reduction in serum testosterone ($n=16$, $r=0{\cdot}600$, $P<0{\cdot}05$) and also between the degree of hypercapnia and the reduction in testosterone values ($n=16$, $r=0{\cdot}681$, $P<0{\cdot}05$). Probably, therefore, hypoxia induces these changes by reducing the release of either the gonadotrophin releasing hormone from the hypothalamus or LH from the pituitary. Dynamic testing would be required to confirm this hypothesis, but interestingly in this regard hypoxia reduces antidiuretic hormone production from the human posterior pituitary (Claybaugh *et al*, 1978).

Prolactin secretion from the pituitary is under the control of the inhibitory factor dopamine. Hyperprolactinaemia may arise in men for various reasons and may be associated with hypogonadism though rarely gynaecomastia (Thorner, 1976). The observed rise of serum prolactin in the three hypercapnic subjects in this study (table 3) does not seem to have been induced by pharmacological agents such as methyldopa, metoclopramide, or the phenothiazines that are known to have antidopaminergic actions (Thorner, 1976). Thus it is tempting to speculate that the observed hyperprolactinaemia in these three individuals also arose as a result of hypoxia-induced interruption of the hypothalamic-pituitary axis.

Early morning urinary aldosterone values were higher in the hypercapnic group, and this might reflect the hyperaldosteronism known to occur with respiratory failure. Hyperaldosteronism might account in part for the fluid retention and reduction in total body potassium known to occur in cor pulmonale (Campbell *et al*, 1975; Semple *et al*, 1978).

In conclusion, though caloric intake values estimated from dietary histories must be viewed with caution, we have shown no evident alteration in calorie intake or absorption of food to account for changes in body habitus in COAD. There do appear to be profound changes in anabolic steroid output and in prolactin production, apparently as a result of hypoxia affecting the hypothalamic-pituitary axis. We postulate that such alterations in hormone production might be causally related to the fairly pronounced and contrasting changes in body habitus found in the two distinct clinical patterns in patients with chronic bronchitis and emphysema.

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