Clinical features of polycythaemic patients with chronic obstructive non-specific lung disease

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Forty-five patients with chronic hypoxic lung disease were studied to ascertain whether those with polycythaemia had specific distinguishing features. Thirty-three patients had red cell volumes less than 120% of the predicted normal values, and 12 patients had red cell volumes greater than this level and were regarded as polycythaemic. The latter were found to have a higher incidence of the features associated with obstructive bronchitis, whereas the non-polycythaemic subjects had more emphysematous characteristics. These findings may facilitate the selection of those patients who may benefit from a therapeutic reduction of red cell volume.

There is evidence to suggest that patients with chronic obstructive non-specific lung disease who develop polycythaemia may have several features which differentiate them from those with normal red cell volumes. Thus they are hypoxic (Shaw and Simpson, 1961; Hume, 1968) and have been found to have a higher incidence of pulmonary hypertension, right heart failure, and hypercapnia (Baldwin, Cournand, and Richards, 1949; Harvey, Ferrer, Richards, and Cournand, 1951; Lewis, Samuels, Daines, and Hecht, 1952). Some authors have noted that polycythaemia is more likely to occur in patients with chronic obstructive bronchitis than in those with predominant emphysema (Burrows, Niden, Fletcher, and Jones, 1964; Mitchell, Vincent, Ryan, and Filley, 1964; Burrows *et al.*, 1966) although in these latter studies the degree of polycythaemia was only assessed by measuring venous haematocrit or haemoglobin concentration. In contrast, Platts, Hammond, and Stuart-Harris (1960) found that haemoglobin concentration remained normal after the onset of cardiac failure in hypoxic and hypercapnic patients with chronic bronchitis and emphysema.

This study was undertaken to ascertain if polycythaemic patients with chronic obstructive non-specific lung disease comprise a homogenous group which can be recognized by specific clinical features.

METHODS

CRITERIA OF PATIENT SELECTION Forty-three male and two female patients with chronic simple or

mucopurulent bronchitis, as defined by the Medical Research Council Committee on the Aetiology of Chronic Bronchitis (1965), were studied. Details of patient selection have been described previously (Cocking and Darke, 1972).

FURTHER INVESTIGATIONS A questionnaire on respiratory symptoms (MRC, 1966) was completed and a full clinical examination was carried out. Postero-anterior and lateral chest radiographs were examined by an independent expert (R.G.G.), who was unaware of the patient's clinical details, and were classified as normal or showing major or minor degrees of emphysema (Laws and Heard, 1962). An electrocardiogram was assessed for right ventricular hypertrophy or right bundle-branch block (Goodwin and Abdin, 1959). Sputum was collected over three days and examined (Medical Research Council Committee on the Aetiology of Chronic Bronchitis, 1965). TLC¹ and RV¹ were measured with a Godart Pulmometer and TF by the steady state method; TF measurements were also standardized for a haemoglobin concentration of 14.6 g/100 ml and an alveolar capillary tension of 110 mmHg using the formula of Cotes *et al.* (1972) described below in the discussion. The following investigations were also performed by methods described previously (Cocking and Darke, 1972)—arterial blood gases, venous haematocrit, red cell count, haemoglobin concentration, serum iron concentration and unsaturated iron binding capacity, daily dietary iron intake, alimentary blood loss, and red cell and plasma volume (expressed as a percentage of the predicted normal values). In addition blood gases were determined in 22 haematologically normal control subjects who were free of cardio-respiratory disease.

¹For abbreviations see Appendix, p. 394

STATISTICS Significance of the difference of means was determined by *t* testing and incidence differences by the χ^2 test.

RESULTS

Twelve patients had red cell volumes in excess of 120% predicted values and comprised the P group, while the remaining 33 patients were placed in the non-P group.

HISTORY AND CLINICAL FINDINGS (Tables I and II) The polycythaemic patients had several distinguishing features. They had a significantly higher incidence of previous right heart failure, 83% having been affected compared to 9% of the non-P group ($P < 0.001$); furthermore, electrocardiographic evidence of right ventricular hypertrophy or right bundle-branch block occurred in 58% of the P group but in only 3% of the non-P group ($P < 0.001$). The radiographic findings of the two groups were also different; normal lung fields were found in 42% of the P group but were not observed in any non-P subject ($P < 0.001$); in contrast, major emphysema was noted in 33% of the P group and in 85% of the non-P group ($P < 0.005$). There was also a difference in the smoking habits of the two groups, as 33% of the P group had never smoked compared to 3% of

TABLE II
CLINICAL FINDINGS

	Non-P Group		P Group		Significance of Differences
	No.	%	No.	%	
Sex					
Female	1	3	1	8	
Male	32	97	11	92	
Mean age (years)	59.4 $\pm$ 1.48		55.7 $\pm$ 3.54		ns
	S.E.M.		S.E.M.		
Mean height (cm)	170.1 $\pm$ 1.45		168.1 $\pm$ 2.19		ns
	S.E.M.		S.E.M.		
Mean weight (kg)	60.9 $\pm$ 2.00		62.2 $\pm$ 3.62		ns
	S.E.M.		S.E.M.		
Sputum production/day					
< 10 ml	25	76	6	50	} ns
> 10 ml	8	24	6	50	
Sputum purulence					
No sputum	1	3	0	0	} ns
M ₁ -P ₁	22	67	6	50	
P ₂ -P ₃	10	30	6	50	
Sputum mainly grew a single pathogen	6	18	4	33	ns
Chest radiographic findings					
Normal (N)	0	0	5 ¹	42	P < 0.001
Minor emphysema (e)	5 ¹	15	3	25	
Major emphysema (E)	28	85	4	33	P < 0.005
Grade II-IV right ventricular hypertrophy or right bundle-branch block on ECG	1	3	7	58	P < 0.001

¹ A patient with cardiomegaly.

the non-P group ($P < 0.05$); however, when those who had smoked at some time in their lives were considered separately, the incidence of heavy smoking, and the incidence of those who had given up the habit was similar in both groups.

The two groups did not differ in respect of length of history, severity of dyspnoea and wheeze, presence of nasal catarrh, sex incidence, and mean age, height, and weight. The incidence of those who had worked in a dusty atmosphere at some time was similar in both groups and in this category similar numbers had worked in the coal and steel industries. Although the P subjects tended to produce more sputum than the non-P subjects, the incidence of those producing either more or less than 10 ml sputum/day did not differ between the groups; nor were there differences in the incidence of those with sputum of grades P₂ and P₃, purulence or the incidence of those whose sputum cultured a dominant pathogenic organism.

RESPIRATORY FUNCTION AND BLOOD GASES (Table III) The means of FEV₁ and FEV₁/FVC% were all severely reduced. The mean FEV₁ value of 587.5 ml found in the P group was significantly lower than that found in the non-P group (727.3 ml), but the FEV₁/FVC% means were similar. TLC and RV/TLC tended to be lower and TF tended to be higher in the polycythaemic patients although there were no significant differences between the means of the two groups. The mean standardized TF of the P group was signifi-

TABLE I
HISTORY

	Non-P Group		P Group		Significance of Differences
	No.	%	No.	%	
Length of history					
< 10 years	20	61	8	67	} ns
> 10 years	13	39	4	33	
History of					
Simple bronchitis	12	36	5	42	} ns
Mucopurulent bronchitis	21	64	7	58	
Grade of dyspnoea ¹					
2	4	12	1	8	} ns
3	7	21	3	25	
4	22	67	8	67	
Wheeze					
None	4	12	1	8	} ns
Intermittent	9	27	4	33	
Permanent	20	61	7	58	
Nasal catarrh					
None	1 ¹	3	4	33	} ns
Intermittent or permanent	15	45	8	67	
Previous heart failure	3	9	15	83	P < 0.001
Cigarette consumption per lifetime					
Non-smoker	1	3	4	33	} P < 0.05
< 200,000	22	67	6	50	
> 200,000	10	30	2	17	
Given up smoking	8	24	4	33	} ns
Dust exposure at some time	18	55	8	67	
As coalminer	8	24	1	8	} ns
As steelworker	6	18	5	42	
In miscellaneous dusty jobs	4	12	2	17	

¹ Grade 2, breathless when hurrying on level or walking up a slight hill; 3, breathless when walking with others of similar age on level; 4, stops for breath on walking at own pace on level.

TABLE III

RESPIRATORY FUNCTION AND BLOOD GASES

	Non-P Group		P Group		Significance of Difference of Means
	Mean $\pm$ SEM		Mean $\pm$ SEM		
FEV ₁ (ml)	727.3	39.23	587.5	39.95	P < 0.05
FEV ₁ /FVC %	39.0	1.20	36.6	2.17	ns
TLC (ml)	6,082.0	252.0	5,183.0	370.4	ns
RV/TLC %	60.2	1.80	57.0	3.13	ns
TF rest (ml/min/mmHg)					
Observed	11.5	0.60	14.9	2.69	ns
Standardized	11.4	0.60	13.9	2.46	ns
Sao ₂ %					
Rest	90.7	0.78	77.1	2.40	P < 0.001
Exercise	85.1	1.46	68.3	2.49	P < 0.001
PaO ₂ (mmHg)					
Rest	78.4	1.94	58.3	5.31	P < 0.001
Exercise	67.3	2.29	44.6	5.36	P < 0.001
Paco ₂ (mmHg)					
Rest (rebreathing)	41.9	1.51	50.7	2.52	P < 0.01
Rest (arterial)	42.0	1.27	47.0	3.09	ns
Exercise (arterial)	44.2	1.62	47.8	3.52	ns
pH					
Rest	7.36	0.005	7.36	0.013	ns
Exercise	7.34	0.005	7.33	0.012	ns

Control results (means $\pm$ SEM): Sao₂ 95.8 $\pm$ 0.44; Pao₂ 97.8 $\pm$ 2.44; Paco₂ 35.7 $\pm$ 1.53; pH 7.40 $\pm$ 0.006 (n = 22)

cantly lower than the mean observed TF of this group (paired *t* test, $P < 0.01$), whereas there was no significant difference between the means of the standardized and observed TFs of the non-P group.

Although both groups were, on average, more hypoxic than the controls ($P < 0.001$), as anticipated the polycythaemic group was significantly more hypoxic than the non-P group ($P < 0.001$).

Both groups were also more hypercapnic than the controls although the non-P patients had a mean that fell within the normal range. The P patients had a mean Paco₂ obtained by the rebreathing method that was significantly higher than that found in the non-P patients ($P < 0.01$); although the same trend was observed in the results obtained by arterial sampling, the mean values were not significantly different.

The patients were on average more acidotic than the controls ($P < 0.01$), but the mean pH values of the two subdivisions were not significantly different.

HAEMATOLOGICAL INVESTIGATIONS (Table IV) The mean red cell volume (% predicted) in the non-P group was 96.4 compared to 139.3 in the P group; these means are significantly different ($P < 0.001$). There was no significant difference between the mean plasma volumes which were 92.6% predicted in the non-P group and 95.3% predicted in the P group. The means of the venous haematocrits, red cell counts, and haemoglobin concentrations reflected the red cell volume findings, being

TABLE IV

HAEMATOLOGICAL INVESTIGATIONS

	Non-P Group		P Group		Significance of Difference of Means
	Mean $\pm$ SEM		Mean $\pm$ SEM		
RCV % predicted	96.4	2.25	139.3	6.50	P < 0.001 ns
PV % predicted	92.6	1.61	95.3	5.04	
Venous haematocrit %					
RBC (million/mm ³)	47.4	0.55	56.4	2.09	P < 0.001
Hb (g/100 ml)	4.79	0.075	5.75	0.269	P < 0.001
Serum iron (μ g/100 ml)	15.2	0.21	17.6	0.51	P < 0.001
UIBC (μ g/100 ml)	113.6	8.33	110.3	17.93	ns
Faecal blood loss (ml/3 days)	234.7	18.77	311.5	31.41	P < 0.05
	1.0	0.19	1.8	0.36	ns

lower in the non-P patients. The two groups did not differ in respect of MCV, MCHC, MCH, serum iron concentration or faecal blood loss.

Six patients (13.4%) had iron deficiency in that they had low serum iron concentrations (mean 44.5 μ g/100 ml $\pm$ 10.43 SEM) and total iron binding capacities (mean 438.8 μ g/100 ml $\pm$ 47.11 SEM) which were 16% saturated or less (Leading article, *Lancet*, 1968); however, their red cells were morphologically normal. This iron deficiency was apparently not accounted for by either inadequate dietary iron intake or excessive faecal blood loss; only one patient had a calculated daily iron intake below 12 mg, which Wintrobe (1967) considers to be the minimum daily requirement, and no patient lost more than 1.5 ml of blood in the faeces each day (Grossman, Matsumoto, and Lichter, 1961). Iron deficiency was found in four patients in the non-P group (12.1%) and two patients in the P group (16.7%) and therefore did not explain the difference in red cell volume in the two groups.

Seven further patients (15.6%) had low serum iron concentrations (mean 65.9 μ g/100 ml $\pm$ 2.44 SEM) with well saturated total iron binding capacities (mean 266.6 $\pm$ 27.80 SEM); none was anaemic and their red cells looked either normal or macrocytic. These findings are not indicative of iron deficiency (Verloop, Meeuwissen, and Blockhuis, 1958) but can occur in patients with chronic infection (Cartwright *et al.*, 1946; Cartwright and Wintrobe, 1949). These features also did not account for the difference in red cell volume in the non-P and P patients, as their incidence was similar in the two groups, 15.2% of the non-P group and 16.7% of the P group being affected.

CORRELATIONS In the patients as a whole, red cell volume was linearly correlated with Sao₂ ($r = -0.681$, $P < 0.001$) and Pao₂ ($r = -0.447$, $P < 0.01$) (Cocking and Darke, 1972). However, no signifi-

cant relationships were demonstrable between red cell volume and hypoxia when the non-P and P groups were considered separately.

DISCUSSION

In this study the subjects with polycythaemia differed from the remainder in having a higher incidence of right heart failure and right ventricular hypertrophy, more normal lung fields radiographically, more severe hypercapnia and hypoxia, and a tendency to produce more sputum, to have lower TLCs and RV/TLC ratios and higher TFs. They were therefore characterized by many of the features which Burrows and his colleagues (1964 and 1966) associated with obstructive bronchitis. In contrast, the non-polycythaemic group had a much higher incidence of emphysema with little evidence of cardiac involvement. The groups, however, were not homogeneous as some polycythaemic patients undoubtedly had predominant emphysema. The greater red cell volumes and incidence of right heart failure of the polycythaemic group can be attributed to the more severe hypoxia that occurred in these patients. There were no other factors, such as iron deficiency, gastrointestinal bleeding or chronic infection, which would explain the differences in red cell volume between the groups.

The higher TF figures which Burrows *et al.* (1964 and 1966) noted in their bronchitic subjects compared to those with more emphysematous features may be attributable partly to the higher haemoglobin levels which were observed in the former. Roughton and Forster (1957) showed that TF can be related to haemoglobin concentration. This has been confirmed subsequently by several workers who demonstrated that TF was relatively low in anaemia and high in polycythaemia, but reverted to more normal levels if the haemoglobin abnormality was corrected (Rankin, McNeill, and Forster, 1961; Burgess and Bishop, 1963). Cotes *et al.* (1972) have recently produced a simple formula by which TF can be corrected for haemoglobin concentration and this was used in the present study: $TF (standardized) = TF (observed) (14.6\alpha + Hb) \div (1 + \alpha)$ Hb where TF (standardized) is the diffusing capacity of the lung for carbon monoxide at a haemoglobin concentration of 14.6 g/100 ml and an alveolar capillary oxygen tension of 110 mmHg, ' α ' is the Dm/Vc ratio and Hb is the haemoglobin concentration in g/100 ml. The authors found that ' α ' was approximately 0.7 in both anaemic and control patients,

and in this study it was also assumed to apply to polycythaemic subjects, although future work may invalidate this assumption. Cotes *et al.* (1972) made the point that in conditions where the Dm/Vc ratio is likely to be abnormal Dm and Vc should be measured separately. The effect of introducing the correction in the present study was to produce mean standardized TFs in the two groups which were closer than the mean observed TFs.

The observations made in this study may be of some practical value in the treatment of polycythaemic patients with chronic hypoxic lung disease, in whom it is sometimes the practice to reduce the red cell volume as a therapeutic measure. The justification for doing this is based on evidence which suggests that the development of polycythaemia can produce a poor prognosis in this condition (Mitchell, Webb, and Filley, 1964) due to the development of pulmonary hypertension and high blood viscosity producing heart failure and further hypoxia (Harvey *et al.*, 1951; Renzetti, McClement, and Litt, 1966; Segel and Bishop, 1966; Dintenfuss and Read, 1968; Agarwal, Paltoo, and Palmer, 1970). Furthermore, encouraging results have been obtained by those who have reduced the level of polycythaemia by, for example, using continuous oxygen (Chamberlain and Millard, 1963), venesection (Massaro and Katz, 1965; Rakita, Gillespie, and Sancetta, 1965), haemolytic drugs combined with marrow suppressants (Pengelly, 1966 and 1969), and, more recently, exchange transfusion with Dextran 40 (Harrison, Gregory, Clark, and Scott, 1971). However, the efficacies of these measures need further assessment, as all these observations were made on relatively few patients without matched controls. The selection of patients with polycythaemia for these various forms of therapy can be difficult, particularly as the venous haematocrit does not always give an indication of the size of the red cell volume, and it is obviously impractical to measure the red cell volumes of all subjects with chest disease indiscriminately. Hence the findings of this investigation may be helpful in so far as they draw attention to those patients in whom secondary polycythaemia is either likely to be present or liable to develop.

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APPENDIX

ABBREVIATIONS USED

FEV ₁	Forced expiratory volume in 1 second	TF	Transfer factor (diffusing capacity) for the lung for carbon monoxide
FEV ₁ /FVC	Percentage of forced vital capacity expired in 1 second	SaO ₂	Arterial oxygen saturation
TLC	Total lung capacity	PaO ₂	Arterial oxygen tension
RV	Residual volume	PaO ₂	Arterial carbon dioxide tension
		RCV	Red cell volume
		PV	Plasma volume
		RBC	Red blood count
		Hb	Haemoglobin concentration
		MCV	Mean corpuscular volume
		MCHC	Mean corpuscular haemoglobin concentration
		MCH	Mean corpuscular haemoglobin
		UIBC	Unsaturated iron binding capacity
		P	Probability
		n	Numbers of observations
		r	Correlation coefficient
		ns	Not significant at 5% level
		SEM	Standard error of mean