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Blood volume studies in chronic obstructive non-specific lung disease: a comparison of the bronchitic and emphysematous patients

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Summary

Blood volume measurements were made on forty-five patients with chronic obstructive non-specific lung disease. Thirty patients were considered to have the features of predominant emphysema, and fifteen had more bronchitic characteristics. Mean red cell volume was 100·8% of the predicted normal volume in the emphysematous group, whereas that of the bronchitic patients was 121·8% predicted. The emphysematous patients were not on average polycythaemic, because they were both less hypoxic and also had a subnormal polycythaemic response to hypoxia; in constrast a quantitatively normal response occurred in the more bronchitic subjects. The pathogenesis of the subnormal response occurring in the emphysema group is discussed. Mean plasma volume was similar but slightly reduced in both groups, being 92·1% predicted in the emphysema patients and 95·7% predicted in the remainder.

Introduction

Mitchell *et al.* (1964) and Burrows *et al.*, (1964, 1966) have shown that those patients with chronic obstructive non-specific lung disease who have the features of predominant emphysema are less likely to be polycythaemic than those with the features of chronic obstructive bronchitis. This observation may be attributable to the greater hypoxia that is more commonly found in the latter subgroup, but could also be partly the result of differences in the respective polycythaemic responses to hypoxia. There is only one study in which the relationships between red cell volume and the degree of hypoxia applicable to the bronchitic and emphysematous types have been compared; this was limited to nine patients but showed that the former had a more normal linear correlation between these variables whereas in the latter it was markedly subnormal, so that the red cell volume was less than expected for the degree of hypoxia (Weil *et al.*, 1968). If this observation were to be confirmed in a larger number of subjects it might partly explain the conflicting reports concerning the nature of this relationship in chronic obstructive non-specific lung disease, as discussed below.

In this paper we compare the relationships between red cell and plasma volume and the blood gases in thirty patients who—in our opinion—have the features of predominant emphysema, and fifteen with more bronchitic characteristics. Our results proved to be in accord with those of Weil *et al.* (1968) described above.

Methods

Criteria of patient selection and investigations performed

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 and the investigations performed have been described elsewhere (Cocking & Darke, 1972a, b).

Selection of patients with predominant emphysema

In view of the observations of Burrows *et al.* (1966), patients were considered to have predominant emphysema if they had the radiographical features of generalized emphysema and at least three of the following criteria:

(1) Sputum production less than 10 ml/day.
(2) No history of cor pulmonale.
(3) †TLC (per cent predicted of 100% or more).
(4) RV/TLC of 50% or more.
(5) TF less than 15 ml/min/mmHg.
(6) Arterial $Paco_2$ less than 50 mm/Hg.

The thirty patients who satisfied these criteria were placed in the Emphysema (E) Group and the remaining fifteen patients without the features of predominant emphysema became the Non-E Group.

Statistics

Standard statistical methods were employed; the significance of the difference of means was determined by '*t*' testing, regression lines by the method

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† For abbreviations, see appendix.

of least squares and incidence difference by the χ^2 test (Moroney, 1956).

Results

Clinical comparability of the two groups (*Table* 1)

The groups did not differ in respect of mean age, height and weight, FEV_1, FEV_1/FVC, RV/TLC or TF. However, radiological signs of major emphysema were noted in all the E Group but only 13% of the Non-E Group. The respective incidences of right heart failure were 7% and 73%. Seventeen per cent of the E Group produced more than 10 ml of sputum per day, whereas this was a feature of 60% of the Non-E Group. Mean TLCs were 6183 ml in the former and 5160 ml in the latter ($P < 0.05$).

Haematological investigations (*Table* 2)

The mean red cell volume of the E Group was 100·8% of the predicted normal value, whereas that of the Non-E subjects was 121·8% predicted; these means were significantly different ($P < 0.01$). The means of the venous haematocrit, red cell count and haemoglobin concentration all tended to be greater in the Non-E than the E Group, but only the venous haematocrit means were significantly different. Mean plasma volumes were similar in both groups and tended to be slightly diminished.

Blood gases (*Table* 2)

Both groups were more hypoxic than our controls ($P < 0.001$), but the Non-E Group had significantly lower mean values of Sa_{O_2} and Pa_{O_2} than the E Group ($P < 0.001$). Although both groups had significantly higher mean Pa_{CO_2} values than our controls, those of the E patients fell within the normal range quoted by Cotes (1965). However, both the mean rebreathing and arterial Pa_{CO_2} measurements of the Non-E Group were significantly higher than the corresponding means in the E subjects ($P < 0.001$ and $P < 0.05$). Both groups were more acidotic than our controls ($P < 0.001$) but their mean pH values were not significantly different.

Correlations (*Table* 3; *Figs.* 1–4)

The correlations between red cell or plasma volume and the resting blood gases applicable to the

TABLE 1. Clinical findings

	E Group		Non-E Group		Significance of difference of means
	Mean	SEM	Mean	SEM	
Mean age (years)	59·5	1·54	56·1	3·02	NS*
Mean height (cm)	170·3	1·60	168·2	1·70	NS
Mean weight (kg)	60·1	2·24	63·7	2·65	NS
FEV_1 (ml)	733·3	42·97	603·3	33·26	NS
$FEV_1/FVC\%$	37·4	1·21	40·3	2·01	NS
TLC (ml)	6183	271·3	5160	291·1	$P<0.05$
TLC% predicted	99·0	3·37	85·2	4·95	$P<0.05$
RV/TLC%	59·3	1·83	59·4	2·99	NS
TF (ml/min/mmHg)	11·7	0·64	13·9	2·22	NS

* NS, not significant.

TABLE 2. Haematological investigations and blood gases

	E Group		Non-E Group		Significance of difference of means
	Mean	SEM	Mean	SEM	
RCV% predicted	100·8	2·76	121·8	8·75	$P<0.01$
PV% predicted	92·1	2·26	95·7	2·76	NS
Venous haematocrit %	48·4	0·73	52·5	2·16	$P<0.05$
RBC ($\times 10^6$/cm)	4·94	0·129	5·26	0·198	NS
Hb (g/100 ml)	15·5	0·22	16·5	0·63	NS
$Sa_{O_2}\%$	91·1	0·73	78·9	2·25	$P<0.001$
Pa_{O_2} (mmHg)	79·1	2·21	60·5	3·93	$P<0.001$
Pa_{CO_2} (mm/Hg)					
Rebreathing	40·1	1·20	52·3	2·38	$P<0.001$
Arterial	41·3	1·23	47·4	2·67	$P<0.05$
pH	7·36	0·005	7·35	0·104	NS

Control results (mean±SEM, $n=22$); Sa_{O_2}, 95·8±0·44; Pa_{O_2}, 97·8±2·44; Pa_{CO_2}, 35·7±1·53; pH, 7·40±0·006. * NS, not significant.

TABLE 3. Correlation and regression co-efficients

	Intercept	±SE	Slope	±SE	r	n	P
RCV–Sa_{O_2}							
E Group	244·6	2·6	–1·58	0·65	–0·416	30	<0·05
Non-E Group	334·3	6·5	–2·69	0·78	–0·694	15	<0·01
All patients	285·1	2·7	–2·04	0·33	–0·681	45	<0·001
Normals	346·3	1·4	–2·56	0·39	–0·616	73	<0·001
RCV–Pa_{O_2}							
E Group	127·9	2·7	–0·34	0·23	–0·274	30	NS*
Non-E Group	165·6	8·6	–0·72	0·58	–0·325	15	NS
All patients	159·2	3·3	–0·70	0·21	–0·447	45	<0·01
Normals	150·4	1·5	–0·59	0·12	–0·490	73	<0·001
RCV–rebreathing Pa_{CO_2}							
E Group	85·1	2·8	0·39	0·43	0·171	30	NS
Non-E Group	20·2	7·7	1·94	0·86	0·528	15	<0·05
All patients	47·6	3·2	1·36	0·34	0·519	45	<0·001
Normals (no data available)							
RCV–arterial Pa_{CO_2}							
E Group	119·0	2·8	–0·44	0·42	–0·196	30	NS
Non-E Group	58·7	8·3	1·33	0·83	0·406	15	NS
All patients	71·1	3·6	0·85	0·43	0·290	45	<0·05
Normals	146·0	1·7	–0·95	0·46	–0·246	68	<0·05

* NS, not significant.

patients of this study, and to the normal subjects investigated by Weil *et al.* (1968), are shown in Table 4; unstandardized variates were used in each case. In their original article, Weil and his colleagues used standardized variates to compute their correlations, which therefore differ from the values of their normal subjects appearing in Table 4. An unstandardized variate is any particular measurement on which a number of readings is made, e.g. RCV and Sa_{O_2}, whereas a standardized variate of, say, RCV is

(RCV – mean RCV)/standard deviation RCV.

A linear relationship was found between red cell volume and Sa_{O_2} in both groups of patients. In the emphysematous patients red cell volume increased subnormally in response to decreasing values of Sa_{O_2}, whereas the relationship in the Non-E subjects was quantitatively normal, when compared to the linear regression found in the healthy subjects of Weil *et al.* (1968) (Figs. 1 and 2). However, when all forty-five patients were considered together the slope of their red cell volume–Sa_{O_2} regression line proved to be shallower than that of the Non-E Group, but steeper than that of the E patients (Fig. 3). Sa_{O_2} was also significantly related to the venous haematocrit ($r = -0{\cdot}697$, $P < 0{\cdot}01$), red cell count ($r = -0{\cdot}627$, $P < 0{\cdot}05$) and haemoglobin concentration ($r = -0{\cdot}679$, $P < 0{\cdot}01$) in the Non-E group, whereas there were no corresponding significant relationships in the emphysematous patients.

Red cell volume, venous haematocrit, red cell count and haemoglobin concentration were not significantly related to Pa_{O_2} in either group, although there was a tendency for these parameters to increase as Pa_{O_2} decreased.

We also considered the possibility that exercise values of Sa_{O_2} and Pa_{O_2} might correlate with red cell volume better than the resting values, but in each case better correlation coefficients were obtained with the resting than the exercise values. Also the linear regressions obtained again showed that the emphysematous group had a shallower red cell volume–Sa_{O_2} regression line than the bronchitic group.

In the E Group red cell volume, venous haematocrit, red cell count and haemoglobin concentrations were not significantly related to Pa_{CO_2}. In contrast the red cell volumes in the Non-E patients tended to increase proportionately to Pa_{CO_2}. This trend was observed with the Pa_{CO_2} results obtained both from arterial samples and by the rebreathing methods, although only in the latter did the correlation coefficient reach a significant level (Fig. 4). Similar trends were observed between venous haematocrit, red cell count and haemoglobin concentration and Pa_{CO_2}, but the correlations were not significant.

When allowance was made for the correlations between Sa_{O_2} and Pa_{CO_2} in the two groups (E

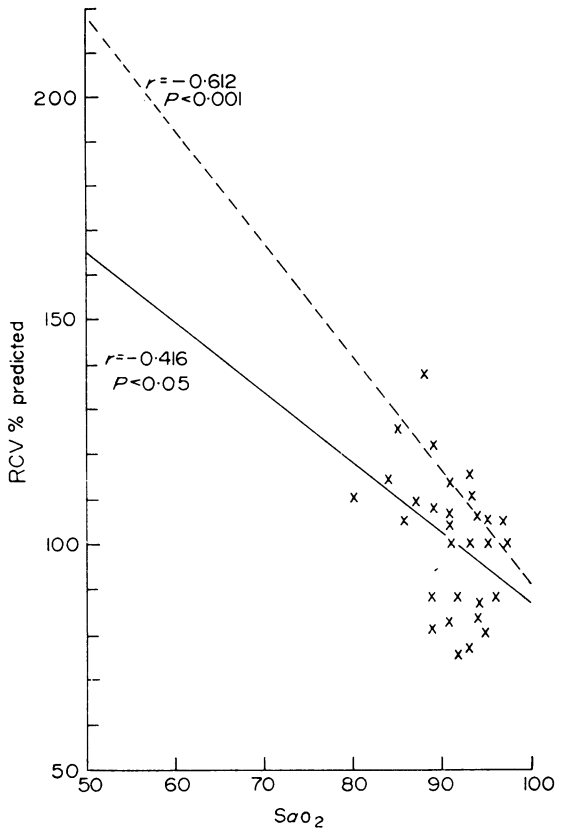

FIG. 1. Red cell volume % predicted—Sa_{O_2}) regressions in the E Group (solid line) and the normal subjects of Weil *et al.* (1968), (dashed line). Formulae: E Group, RCV=244·6 − 1·58×Sa_{O_2}; normals, RCV=346·3 − 2·56×Sa_{O_2}.

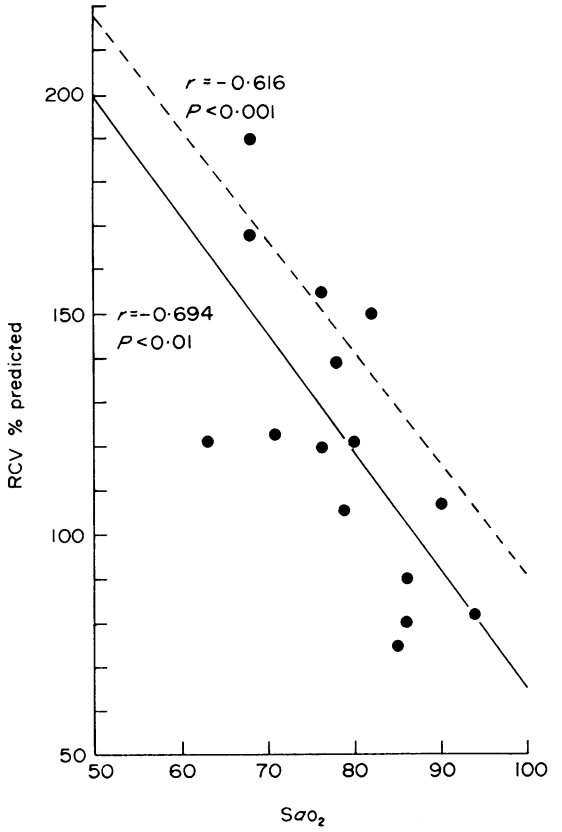

FIG. 2. Red cell volume % predicted—Sa_{O_2} regressions in the Non-E Group (solid line) and the normal subjects of Weil *et al.* (1968) (dashed line). Formulae: Non-E Group, RCV=334·3 − 2·69×Sa_{O_2}; normals, RCV= 346·3 − 2·56×Sa_{O_2}.

Group, $r = -0{\cdot}344$; Non-E Group, $r = -0{\cdot}493$) the partial coefficient of correlation between red cell volume and Sa_{O_2} was calculated to be −0.456 in the E Group and −0·581 in the Non-E Group. The corresponding partial coefficients of correlation with the rebreathing Pa_{CO_2} were 0·035 in the E Group and 0·302 in the Non-E Group. This suggests that red cell volume in the E patients was determined by Sa_{O_2} alone, whereas in the Non-E Group Pa_{CO_2} may have been an additional but less important determinant of change in red cell volume.

No significant correlations were demonstrated between red cell volume and pH or plasma volume, in either the patients studied in this series or in the normal subjects of Weil *et al.* (1968).

The response of plasma volume to hypoxia differed in the two groups. In the Non-E patients it was directly proportional to the Sa_{O_2} ($r=0{\cdot}514$, $P=0{\cdot}05$), whereas no significant relationships were found in either the E Group or in normal subjects. A similar pattern emerged in the plasma volume–Pa_{O_2} relationship in the Non-E Group, although the correlation coefficient did not reach a significant level. No significant relationships were found in either group or in the normal subjects between plasma volume and Pa_{CO_2} or pH.

Discussion

These results show that the emphysematous patients had a lower mean red cell volume than the remainder, not only because they were less hypoxic, but also because they had a subnormal polycythaemic response to hypoxia, whereas the more bronchitic subjects had a quantitatively normal marrow response. This confirms the preliminary work of Weil *et al.* (1968). The slope of the red cell volume–Sa_{O_2} regression line of all forty-five patients fell in between those of the two subgroups, being shallower than the linear regression applicable to the bronchitic subjects and steeper than that found in the

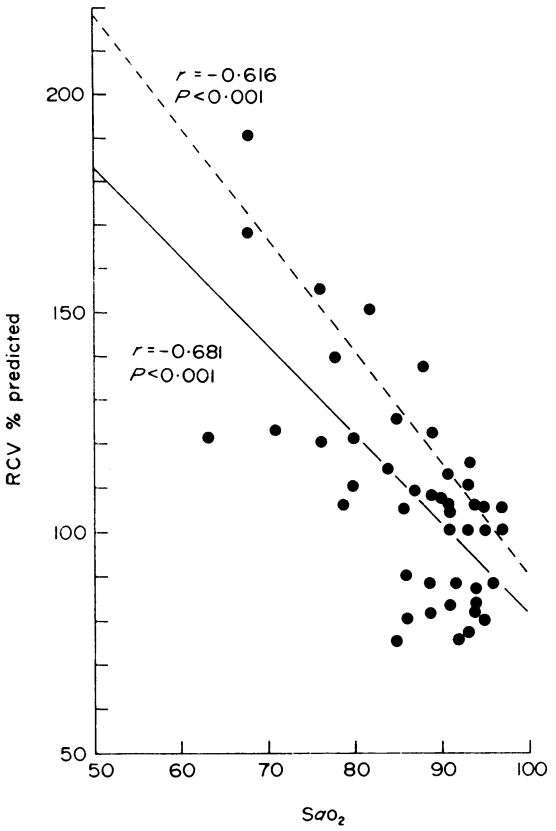

FIG. 3. Red cell volume % predicted—Sa_{O_2} regressions in the combined E and Non-E patients (solid line) and the normal subjects of Weil *et al.* (1968) (dashed line). Formulae: E and Non-E patients, RCV = 285·1 − 2·04 × Sa_{O_2}; normals, RCV = 346·3 − 2·56 × Sa_{O_2}.

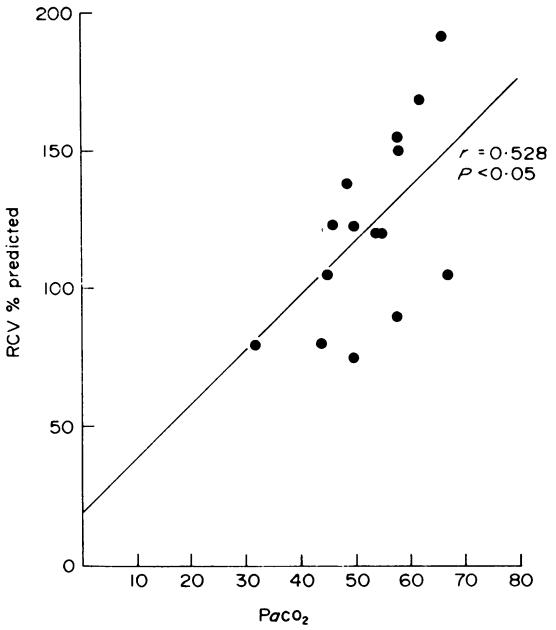

FIG. 4. Red cell volume % predicted—rebreathing Pa_{CO_2} regression in the Non-E Group. Formulae, RCV = 20·2 + 1·94 × Pa_{CO_2}.

emphysematous group. This observation implies that the nature of the polycythaemic response to hypoxia in any particular group of patients with chronic obstructive non-specific lung disease depends on the relative proportions of the emphysematous and bronchitic types of which it is composed. This conclusion offers one possible explanation for the conflicting results of previous blood volume studies in these patients, with come workers maintaining that the polycythaemic response to hypoxia is subnormal (Vanier *et al.*, 1963; Ayvazian, Richardson & Silber, 1969; Cocking & Darke, 1972a) and others that it is quantitatively normal (Shaw & Simpson, 1961; Lertzman, Israels & Cherniack, 1962; Hume, 1968). Other possible causes for these inconsistencies have been discussed previously (Cocking & Darke, 1972a).

The two subgroups not only differed in respect of red cell volume and its relationship with the blood gases, but there was also a difference in the correlations between plasma volume and the degree of hypoxia; in the emphysematous group the two were unrelated, whereas a significant correlation was found in the more bronchitic patients. However, there is no obvious explanation for these findings, as one would expect plasma volume to increase rather than decrease, as Sa_{O_2} diminishes, particularly if polycythaemia and heart failure supervene. In spite of these differences the mean plasma volumes proved to be similar but slightly reduced in both subgroups, thus confirming the observations of previous investigators (Hume, 1968; Weil *et al.*, 1968).

The criteria by which the emphysema group was selected were based on the findings of Burrows *et al.* (1966) which have recently been questioned by Thurlbeck *et al.* (1970). The latter showed that some patients with severe emphysema, particularly of the centrilobular type, can be difficult to distinguish clinically from those with predominant obstructive bronchitis, as they may have increased lung markings radiographically—in contrast to the radiotranslucent lung fields usually present (Laws & Heard, 1962)—and may also develop pulmonary hypertension and right heart failure. Furthermore, these workers also considered that most patients with chronic obstructive lung disease are not easily divisible into the two distinct categories of emphysema and obstructive bronchitis, but show a gradation of features

between these two extremes. However, we believe that we selected two clinically distinct groups of patients, one with emphysematous features, and the other—somewhat less homogeneous—composed mainly of patients with predominant bronchitis, but containing a few with intermediate characteristics who might fulfil the criteria of increased marking emphysema described above. Furthermore, our contention that the two groups were clinically distinct is supported by the differences that were observed in the relationships of the blood gases with the red cell and plasma volumes.

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Appendix

Abbreviations used

FEV_1	Forced expiratory volume in 1 sec.
FEV_1/FVC	Percentage of forced vital capacity expired in 1 sec;
TLC	Total lung capacity;
RV	Residual volume;
TF	Transfer factor (diffusing capacity) of lung for carbon monoxide;
Sa_{O_2}	Arterial oxygen saturation;
Pa_{O_2}	Arterial oxygen tension;
Pa_{CO_2}	Arterial carbon dioxide tension;
RCV	Red cell volume;
PV	Plasma volume;
RBC	Red blood count;
Hb	Haemoglobin concentration;
P	Probability;
n	Numbers of observations;
r	Correlation coefficient;
NS	Not significant at 5% level;
SEM	Standard error of mean.