The Red Cell Mass–Arterial Oxygen Relationship in Normal Man

APPLICATION TO PATIENTS WITH CHRONIC OBSTRUCTIVE AIRWAY DISEASE

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ABSTRACT The normal relationship between red cell mass measured, with ^{51}chromium-labeled red cells, and arterial oxygen saturation (Sa_{O_2}) over the range from 97.3 to 83.4% was examined by studying 73 normal men residing at sea level and altitudes of 1600 and 3100 m. A simple, linear relationship between Sa_{O_2} and red cell mass was found over the entire range ($r = -0.7524$, $P < 0.001$). In contrast, a correlation between red cell mass and arterial O_2 tension was found only over the lower half of the range of O_2 tensions where Sa_{O_2} was also decreased ($r = -0.7731$, $P < 0.005$). This suggested that O_2 saturation rather than tension is the more important determinant of the erythropoietic response to chronic hypoxia. If this response is regulated by tissue O_2 tension, then it will be influenced by O_2 transport, which, in turn, is a function of blood flow and arterial O_2 content, and hence Sa_{O_2}. In nine patients with chronic obstructive airway disease the relationship between red cell mass and Sa_{O_2} was also determined and was found to be steeper than in the normal subjects ($P < 0.05$).

INTRODUCTION

That chronic hypoxia stimulates red cell production in normal man is well recognized, but the effects of hypoxia on erythropoiesis in certain pathological states has remained in question. It has, for example, been commonly observed that in patients with chronic obstructive airway disease, hypoxemia is often not associated with a significant increase in hemoglobin concentration or hematocrit (1, 2). This apparent absence of polycythemic response in these patients has led to some speculation regarding possible mechanisms of bone marrow suppression in chronic pulmonary disease. However, Shaw and Simpson (3) and Vanier, Dulfano, Wu, and Desforges (4) demonstrated that hypoxemia in chronic obstructive airway disease is in fact generally accompanied by an increase in red cell mass. They also pointed out that these increases in red cell mass are often not reflected in a rise in hematocrit or hemoglobin concentration because of an associated and variable plasma volume expansion.

Although red cell mass is increased in these patients, Ratto, Briscoe, Morton, and Comroe (5) pointed out the difficulty in determining the appropriateness of an observed increase in red cell mass in relation to the associated level of hypoxemia. Quantitative information concerning the effect of hypoxemia on red cell mass in normal man, free from complicating disease processes, would be required to resolve this question. Shaw and Simpson (3) approached this problem by collecting data from the literature on red cell mass in high altitude natives and combining this information with published values for normal arterial oxygen

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saturations at those altitudes. Such data, however, constituted a collection of results of different workers who used different methods in a variety of ethnic groups. In addition, the arterial blood gas data were from individuals other than those in whom the red cell mass measurements were made.

To establish more firmly the normal relationship between arterial oxygenation and red cell mass, we undertook the present study. Normal men residing at sea level, 1600 m (5300 ft) and 3100 m (10,200 ft), who provided a range of values of arterial oxygenation and red cell mass suitable for this purpose, were studied by a single team of investigators who used identical methods throughout.

METHODS

Subjects. The subjects participating in this study were normal males residing in Los Angeles, Calif. (sea level); Denver, Colo. (1600 m), and Leadville, Colo. (3100 m). All had lived at their respective altitudes of residence for at least 2 yr. The Los Angeles subjects comprised a group of 15 male volunteers of mean age 40 yr, who were selected from the medical and technical staffs of the pulmonary disease sections of the University of Southern California and the UCLA medical school. All were in good health. The 19 Denver subjects, mean age 42 yr, were selected from the executive staff of a large manufacturing firm in Denver and were subjected to a general clinical and laboratory examination by the company within the last year, the results of which were entirely normal. The Leadville subjects comprised a group of 39 men of mean age 39 yr. These were selected from a larger group of men, who had volunteered for a previous study (6), and their clinical histories, physical examinations, chest x-rays, pulmonary function studies, and electrocardiograms done in the course of that study were found to be normal. Serum iron determinations were done in all Denver and Leadville subjects; any individual with an abnormally low value was excluded. In addition, a separate group of nine men with obstructive airway disease, documented by history, physical examination, chest x-ray, and pulmonary function tests was studied for purposes of comparison with the normal group. The nature and purpose of our study was explained to the subjects and informed consent was granted by all participants.

Procedures. The studies were performed in the pulmonary laboratories of the Los Angeles County Hospital and the UCLA medical center, in the Cardiovascular Pulmonary Research Laboratory of the Colorado General Hospital (Denver), and in the University of Colorado High Altitude Research Laboratory established at St. Vincent's Hospital in Leadville.

Blood volume measurements were performed with autologous ^{51}chromium-labeled red cells in all subjects. With the subject supine, an 18-gauge needle was placed in a large antecubital vein and kept patent throughout the procedure with a small syringe containing heparinized saline. A 12 ml sample of unheparanized blood was drawn and added to 50 μc of ^{51}sodium chromate and 2.5 ml of strumia-ACD solution in a sterile, plastic centrifuge bag.[1] After a 3 min incubation at room temperature the red cells were centrifuged and washed twice with normal saline. This technique results in the binding of about 85% of the originally added chromium by the red cells with less than 0.1% unbound isotope left in the system after the second wash. Serial counting in six subjects indicates that red cells treated in this fashion have an initial disappearance rate of 0.72 ± 0.13 (SEM) %/hr. The labeling procedure requires about 20 min, at the end of which time 5-ml of packed, labeled cells containing 20–25 μc of ^{51}Cr was drawn into a disposable 5-ml syringe and the total radioactivity content measured in a semiautomatic, flat-field counting apparatus (7).[2] This aliquot was then injected intravenously in the arm contralateral to the sampling site. A single venous blood sample was taken from the indwelling needle without stasis 15 min after injection of the labeled cells, i.e., after a total of 45 min of recumbency. The radioactivity of this blood sample, which is a function of the dilution of the originally injected activity by the total circulating blood volume, is expressed by the counting apparatus directly as blood volume. This directly measured blood volume was partitioned into red cell mass and plasma volume by using the hematocrit of the 15 min blood sample. Hematocrits were done in duplicate using the microcapillary method. No correction for trapped plasma was made, since this is very small (8). In addition, no correction for body-venous ratio was used in the calculation of plasma volume. Plasma and blood volumes measured in this fashion are consistently smaller than those derived from the use of albumin labels such as T-1824 or radioactive iodine-labeled serum albumin.

The accuracy of the counting apparatus was tested by measuring in vitro volumes of water with ^{51}Cr. On five occasions the difference between known and measured volumes, ranging between 4000–6000 ml, averaged 10 ± 42.4 (SD) ml or 0.26 ± 0.88%. Three separate counting units were used in the course of this study and each was calibrated against in vitro volumes before use.

Brachial arterial blood samples were taken with the subject supine. Disposable 20-gauge needles were used to minimize trauma. Blood samples were drawn anaerobically into heparinized syringes and analyzed within 5 min for P_{O_2}, pH, and P_{CO_2} directly using the appropriate electrodes.[3] In Leadville, Sa_{O_2} was measured within 10 min with a reflection oximeter.[4] We have compared this oximeter with the Van Slyke method by analyzing 48 blood samples with both methods and found the standard deviation of the difference to be 1.64% saturation. The Sa_{O_2} was also calculated from Pa_{O_2} and pH using the Severing-

[1] Unitag, Abbott Co., Oak Ridge, Tenn.

[2] Volemetron, Ames Atomium Co., Bellerica, Mass.

[3] Radiometer, Copenhagen, Denmark.

[4] American Optical Co., Buffalo, N. Y.

TABLE I

Sea Level Normal Residents

Subject	Age	Height	Weight	BV	RCM	PV	Sa_{O_2}	Pa_{O_2}	*pH*	Pa_{CO_2}	Hct
	yr	*cm*	*kg*	*liters*	*liters*	*liters*	%	*mm Hg*		*mm Hg*	%
B. A.	47	178	81.8	4.88	2.10	2.78	95.5	71.0	7.43	37.0	43.0
L. G.	55	163	74.3	4.65	1.98	2.67	96.2	74.5	7.45	36.0	42.5
R. E.	27	174	69.8	4.20	2.02	2.18	96.1	80.0	7.42	40.0	48.0
W. B.	36	170	72.1	4.70	2.19	2.51	96.0	82.0	7.40	40.0	46.6
J. M.	34	183	90.9	4.90	2.28	2.62	96.8	83.0	7.42	39.0	46.6
R. W.	46	169	68.0	3.20	1.54	1.66	95.6	85.3	7.40	—	48.1
L. G.	55	175	72.7	4.65	2.00	2.65	96.6	86.0	7.41	46.0	43.0
D. V.	48	186	83.1	5.61	2.54	3.17	96.6	86.0	7.42	40.0	45.2
G. H.	47	182	88.5	4.52	2.13	2.39	96.1	86.7	7.43	—	47.1
R. M.	44	178	88.5	4.98	2.24	2.74	95.9	86.7	7.41	—	45.2
B. G.	30	178	78.6	4.90	2.17	2.73	96.9	89.0	7.43	39.0	44.3
S. Y.	20	186	73.6	4.92	2.03	2.89	96.9	90.0	7.43	39.0	41.3
H. H.	33	175	72.8	3.68	1.64	2.04	96.6	91.9	7.44	—	44.6
J. M.	39	194	81.8	4.40	2.06	2.34	97.0	95.6	7.43	—	46.7
R. J.	35	189	84.1	6.65	2.97	3.68	97.3	96.0	7.39	42.0	44.7
Mean	39.7	179	78.7	4.72	2.13	2.60	96.4	85.6	7.42	39.8	45.1
SEM	2.6	2.12	1.91	0.20	0.09	0.12	0.35	1.78	0.004	0.87	0.53

BV, blood volume; RCM, red cell mass; PV, plasma volume; Sa_{O_2}, arterial oxygen saturation; Pa_{O_2}, arterial oxygen pressure; Pa_{CO_2}, arterial carbon dioxide pressure; Hct, hematocrit.

haus slide rule (9). The subject's Sa_{O_2} was taken as the average of the calculated and oximeter figures. In Los Angeles where Pa_{O_2} falls on the flat portion of the oxygen hemoglobin dissociation curve, Sa_{O_2} was calculated from pH and Pa_{O_2}. Pa_{O_2} and pH on each arterial blood sample were measured on two separate electrode units in two separate laboratories and the mean of the two values was used. In Denver, Sa_{O_2} was taken as the mean of

TABLE II

1600 m Normal Residents

Subject	Age	Height	Weight	BV	RCM	PV	Sa_{O_2}	Pa_{O_2}	*pH*	Pa_{CO_2}	Hct
	yr	*cm*	*kg*	*liters*	*liters*	*liters*	%	*mm Hg*		*mm Hg*	%
G. M.	42	166	62.7	3.80	1.81	2.00	91.5	60.8	7.41	34.2	47.5
J. R.	36	174	71.9	4.62	2.00	2.62	92.5	61.8	7.44	32.8	43.3
E. P.	51	182	87.3	4.40	1.96	2.44	92.5	62.5	7.43	36.3	44.5
J. M.	38	183	91.8	5.00	2.48	2.53	93.2	63.2	7.43	31.0	49.5
C. H.	57	184	90.0	5.42	2.41	3.01	92.4	63.2	7.42	35.9	44.5
B. P.	51	174	73.0	3.98	1.77	2.21	93.0	63.9	7.43	36.9	44.5
L. L.	41	172	72.8	4.80	2.12	2.68	93.2	64.2	7.41	36.6	43.1
C. H.	43	184	81.6	4.88	2.29	2.59	92.3	64.3	7.39	38.8	47.0
R. D.	43	192	94.5	4.60	2.14	2.46	93.2	68.2	7.41	39.7	46.5
F. R.	61	178	82.5	4.50	1.96	2.54	94.5	69.0	7.42	37.8	43.5
W. K.	43	185	95.0	5.82	2.53	3.29	93.2	70.8	7.40	39.8	43.5
J. T.	35	183	85.5	5.50	2.56	2.94	95.4	70.9	7.45	32.9	46.5
C. B.	48	181	81.4	5.00	2.28	2.73	93.6	71.0	7.40	38.0	45.5
H. C.	42	183	80.5	4.65	2.05	2.60	94.8	72.0	7.41	36.2	44.0
W. H.	45	183	87.3	4.48	2.11	2.38	94.4	72.3	7.42	35.8	47.2
G. J.	45	178	80.0	4.62	2.10	2.52	93.9	72.6	7.42	35.0	45.5
L. F.	26	177	69.8	4.40	2.02	2.39	95.3	73.2	7.43	35.6	45.8
E. C.	45	174	80.0	4.00	1.82	2.18	95.8	77.8	7.46	36.7	45.5
R. C.	33	177	91.4	5.80	2.40	3.40	96.5	81.9	7.46	31.0	41.5
Mean	42.1	180	81.3	4.77	2.18	2.59	93.9	69.0	7.42	35.6	45.2
SEM	2.01	1.44	1.99	0.12	0.06	0.07	0.31	1.2	0.004	0.57	0.45

See Table I for explanation of abbreviations.

the values obtained from Van Slyke analysis and calculated from Pa_{O_2} and pH.

RESULTS

Anthropometric data, arterial blood gases, blood volume and its components, and hematocrits shown individually for all normal subjects grouped according to altitude of residence are presented in Tables I, II, and III.

Correction for body size. In order to study the effects of oxygenation on red cell mass, it is necessary to somehow normalize the data for body size. Several methods employing height-weight data have been proposed. These include expressions of red cell mass per kilogram of body weight, red cell mass per square meter of body surface area (10), red cell mass expressed as per cent of pre-

TABLE III
3100 m Normal Residents

Subject	Age	Height	Weight	BV	RCM	PV	Sa_{O_2}	Pa_{O_2}	*pH*	Pa_{CO_2}	Hct
	yr	*cm*	*kg*	*liters*	*liters*	*liters*	%	*mm Hg*		*mm Hg*	%
E. K.	61	173	58.9	4.48	2.35	2.13	83.5	46.4	7.46	34.4	52.5
R. K.	34	172	66.4	4.82	2.75	2.07	83.4	47.5	7.43	34.0	57.0
E. K.	34	175	83.2	5.98	2.66	3.32	85.9	51.0	7.43	33.7	44.5
H. S.	63	170	83.4	5.73	2.58	3.15	85.3	51.1	7.44	32.3	43.0
J. F.	37	177	76.4	5.19	3.08	2.11	87.1	53.2	7.43	27.0	59.5
M. C.	44	179	64.5	5.48	2.52	2.96	86.8	53.8	7.41	41.0	46.0
L. K.	29	160	55.5	3.72	1.82	1.90	88.2	54.0	7.46	34.0	49.0
R. O.	33	183	78.0	5.62	2.86	2.76	87.0	54.0	7.41	33.0	51.0
H. K.	33	180	70.7	4.60	2.07	2.53	89.5	54.8	7.42	35.3	45.0
M. D.	32	180	75.5	4.28	1.90	2.37	88.5	55.0	7.43	34.7	44.5
D. W.	38	182	70.9	5.85	2.49	3.36	89.0	55.3	7.47	30.9	42.5
T. F.	52	175	83.6	6.09	2.59	3.50	87.0	52.4	7.41	36.8	42.5
W. G.	51	180	73.4	4.54	2.29	2.25	87.5	55.9	7.40	37.8	50.5
J. D.	26	177	67.0	4.26	2.09	2.17	89.5	56.1	7.41	32.9	49.0
G. S.	48	180	78.8	5.41	2.49	2.92	88.8	56.1	7.45	29.3	46.0
A. P.	31	181	92.3	5.50	2.79	2.71	88.2	56.2	7.39	38.8	50.8
M. R.	36	175	70.2	5.10	2.32	2.78	88.8	56.3	7.44	33.7	54.5
L. J.	26	178	64.1	4.76	2.38	2.38	89.7	56.8	7.41	33.2	50.0
C. W.	38	172	62.3	5.19	2.36	2.83	89.1	57.0	7.45	33.0	45.5
W. M.	51	169	67.5	4.22	2.11	2.11	88.8	57.8	7.43	32.2	50.0
C. T.	32	172	63.0	4.01	1.85	2.16	88.7	57.9	7.41	33.8	45.5
C. G.	33	182	75.9	5.00	2.40	2.60	90.9	58.0	7.44	33.8	48.0
L. C.	30	183	94.5	4.82	2.41	2.41	90.0	58.0	7.41	29.9	50.0
E. I.	56	170	68.4	4.93	2.22	2.71	88.6	58.2	7.39	39.5	45.0
R. R.	44	179	88.9	4.60	2.19	2.41	90.0	58.4	7.43	33.7	47.5
T. F.	33	184	79.6	4.69	2.58	2.11	89.5	58.5	7.42	27.2	55.0
J. K.	28	188	87.3	5.43	2.69	2.74	92.0	58.7	7.43	30.6	49.5
R. W.	34	184	83.4	5.66	2.66	3.00	89.0	59.3	7.40	37.8	47.0
P. V.	32	175	74.8	5.39	2.35	3.05	90.1	59.9	7.41	32.3	43.5
C. R.	44	170	66.8	4.51	1.98	2.53	91.0	61.0	7.46	33.7	44.0
R. F.	55	180	84.3	5.05	2.40	2.65	90.8	61.0	7.43	34.7	47.5
G. D.	38	180	70.9	4.88	1.95	2.93	90.8	61.3	7.46	32.2	39.8
R. M.	38	188	79.1	5.16	2.43	2.74	90.9	61.7	7.46	33.9	47.0
T. B.	45	183	70.7	5.22	2.35	2.87	91.4	62.3	7.45	31.7	45.0
R. C.	32	160	63.9	4.18	1.92	2.26	90.7	62.5	7.43	33.4	46.0
N. N.	34	170	70.0	4.06	1.97	2.09	91.6	62.7	7.44	28.3	48.5
D. M.	42	180	80.5	5.19	2.34	2.85	91.5	62.8	7.45	29.9	45.0
D. J.	40	172	63.9	4.25	2.04	2.21	91.8	63.5	7.44	33.1	48.0
B. H.	37	178	75.2	4.92	2.24	2.68	92.1	64.8	7.42	32.2	45.5
Mean	39	176	73.9	4.94	2.35	2.60	89.1	57.2	7.43	33.3	47.7
SEM	0.49	1.02	1.49	0.09	0.05	0.06	0.34	0.68	0.004	0.47	0.66

See Table I for explanation of abbreviations.

dicted blood volume (11), and red cell mass as per cent of predicted red cell mass (12). To determine which of these techniques most successfully minimized the influence of body size in the present study, these indices were tested by measuring the effect of each on the scatter about the rell cell mass–Sa_{O_2} regression line. The results of this analysis are shown in Table IV. These data represent the calculated regressions of standardized variates, i.e, $\frac{X-\overline{X}}{sX}$. Therefore, the standard errors of estimate (SEE) calculated for each regression and shown in the table are independent of the original units and, hence, may be compared directly with each other. The SEE was lowest for red cell mass expressed as per cent of predicted red cell mass, which indicated that this index represented the most successful means for correction of body size in the present data. However, the SEEs all were so similar in magnitude that no method had any substantial advantage over any other. This probably is due to the fact that this group of subjects contained very few individuals with unusual height-weight relationships (12). We, therefore, elected to use the most common correction, i.e., volume per kilogram of body weight.

TABLE IV
Effect of Various Indices of Body Size on RCM–Sa_{O_2} Regression

RCM as % of predicted RCM (12)	RCM = 422–3.4 Sa_{O_2} r = 0.7580 SEE = 0.0753 P = <0.001
RCM/kg of body weight	RCM = 124.96–1.037 Sa_{O_2} r = −0.7524 SEE = 0.0761 P <0.001
RCM/m² of body surface area (10)	RCM = 0.450–0.0063 Sa_{O_2} r = −0.7401 SEE = 0.0776 P <0.001
RCM as % of predicted blood volume (11)	RCM = 370–2.82 Sa_{O_2} r = −0.6979 SEE = 0.0827 P <0.001

See Table I for explanation of abbreviations.

Red cell mass and arterial oxygenation. Table V presents a summary of the data in Tables I, II, III, with red cell mass, blood volume, and plasma volume expressed as volumes per kilogram of body weight. Between sea level (P_B =

TABLE V
Hematologic and Arterial Oxygen Values in Normal Men at Various Altitudes

Elevation	P_B	BV	RCM	PV	Hct	Sa_{O_2}	Pa_{O_2}
	mm Hg	*ml/kg*	*ml/kg*	*ml/kg*	%	%	*mm Hg*
Sea level (n = 16)	760						
Mean		60.0	27.1	33.0	45.2	96.4	85.6
SD		8.62	3.72	5.27	2.01	0.54	6.91
SEM		2.21	0.93	1.31	0.50	0.14	1.78
1600 m (n = 19)	625						
Mean		58.7	26.8	31.9	45.2	93.9	69.0
SD		5.78	3.24	3.35	1.91	1.38	5.66
SEM		1.32	0.70	0.72	0.45	0.21	1.22
3100 m (n = 39)	530						
Mean		66.8	31.8	35.2	47.7	89.1	57.2
SD		8.54	6.65	5.27	4.12	2.15	4.22
SEM		1.31	1.04	0.84	0.66	0.34	0.68
Difference:							
1600 m–sea level		−1.3	−0.3	−1.1	00	−2.5	−16.6
P		NS	NS	NS	NS	<0.005	<0.005
3100 m–1600 m		+8.1	+5.0	+3.3	2.5	−4.8	−11.8
P		<0.005	<0.005	<0.01	<0.01	<0.005	<0.005

NS, not significant. See Table I for explanation of other abbreviations.

760) and 1600 m ($P_B = 625$), there was a substantial fall in Pa_{O_2} of 16.6 mm Hg from 85.6 ± 1.8 mm Hg to 69.0 ± 1.2 (SEM) ($P < 0.005$). Because of the minimal slope of the oxygen-hemoglobin dissociation curve in this range, the associated change in Sa_{O_2} was quite small, 2.5% from 96.4 ± 0.14 to 93.9 ± 0.21% ($P < 0.005$). Red cell mass, plasma volume, blood volume, and hematocrit were not significantly different at these two altitudes. Between 1600 m ($P_B = 625$) and 3100 m ($P_B = 530$) Pa_{O_2} again fell by about the same amount, 11.8 mm Hg from 69.0 ± 1.2 to 57.2 ± 0.68 mm Hg ($P < 0.005$). Here, however, the steeper slope of the dissociation curve produced a greater fall in Sa_{O_2} of 4.8% from 93.9 ± 0.21 to 89.1 ± 0.34%. Associated with this, the red cell mass was significantly higher at 3100 m by 5.0 ml/kg, 31.8 ± 1.04, as compared with 26.8 ± 0.70 ml/kg ($P < 0.005$). Hematocrit was also 2.5% higher, 47.7 ± 0.66%, as compared to 45.2 ± 0.44 ($P < 0.01$). In addition plasma volume was slightly but significantly higher at 3100 m by 3.3 ml/kg, 35.2 ± 0.84, as compared with 31.9 ± 0.72 ml/kg ($P < 0.01$). Thus blood volume was accordingly 8.1 ml/kg higher, 66.8 ± 1.31, as compared with 58.7 ± 1.32 ml/kg ($P < 0.005$).

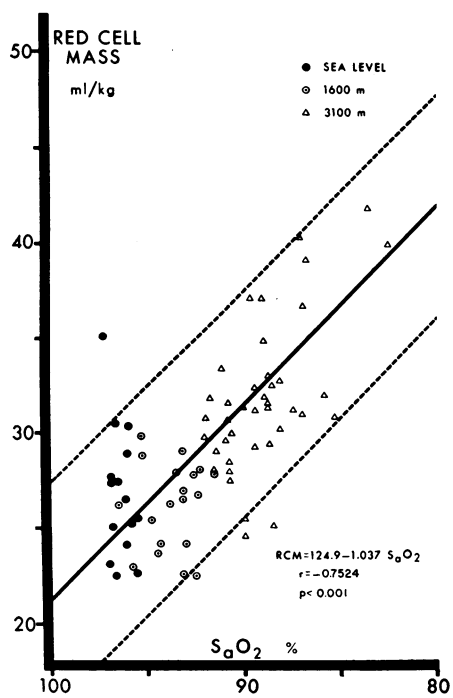

FIGURE 1 Red cell mass–Sa_{O_2} relationship in normal men residing at sea level, 1600 and 3100 m. Broken lines represent 95% confidence limits on individual estimates.

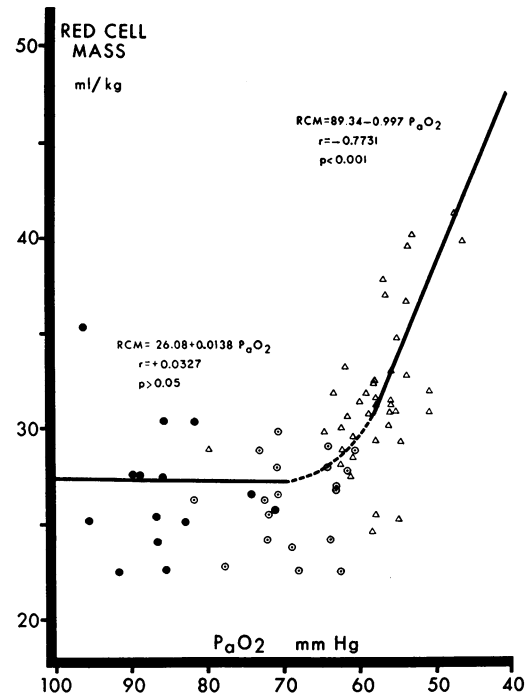

FIGURE 2 Red cell mass–Pa_{O_2} relationship in normal men residing at sea level, 1600 and 3100 m. Confidence limits could not be calculated due to the complex nature of the curve. Symbols have same significance as in Fig. 1.

Although these data were collected at three discrete altitudes they do in fact constitute a continuous spectrum of hematological and blood gas values. The range covered extends from an Sa_{O_2} of from 97.3 to 83.4% (Pa_{O_2}, 96.0–46.5) with an associated range of red cell mass from 22.4 to 41.8 ml/kg, and regression analyses of the entire collection of data were performed. The regression of red cell mass on Sa_{O_2} is shown in Fig. 1. This relationship appeared to be simple and linear ($r = -0.7524$ and $P < 0.001$). In contrast, the relationship between red cell mass and Pa_{O_2} was more complex and appeared to be biphasic with an inflection point at a Pa_{O_2} of about 67 mm Hg (Fig. 2). Consequently, the data were divided into two groups at this point and separate regressions were run on those values above and below this point. For Pa_{O_2} greater than 67 mm Hg no significant relationship between Pa_{O_2} and red cell mass was observed ($r = 0.0327$, $P > 0.005$),

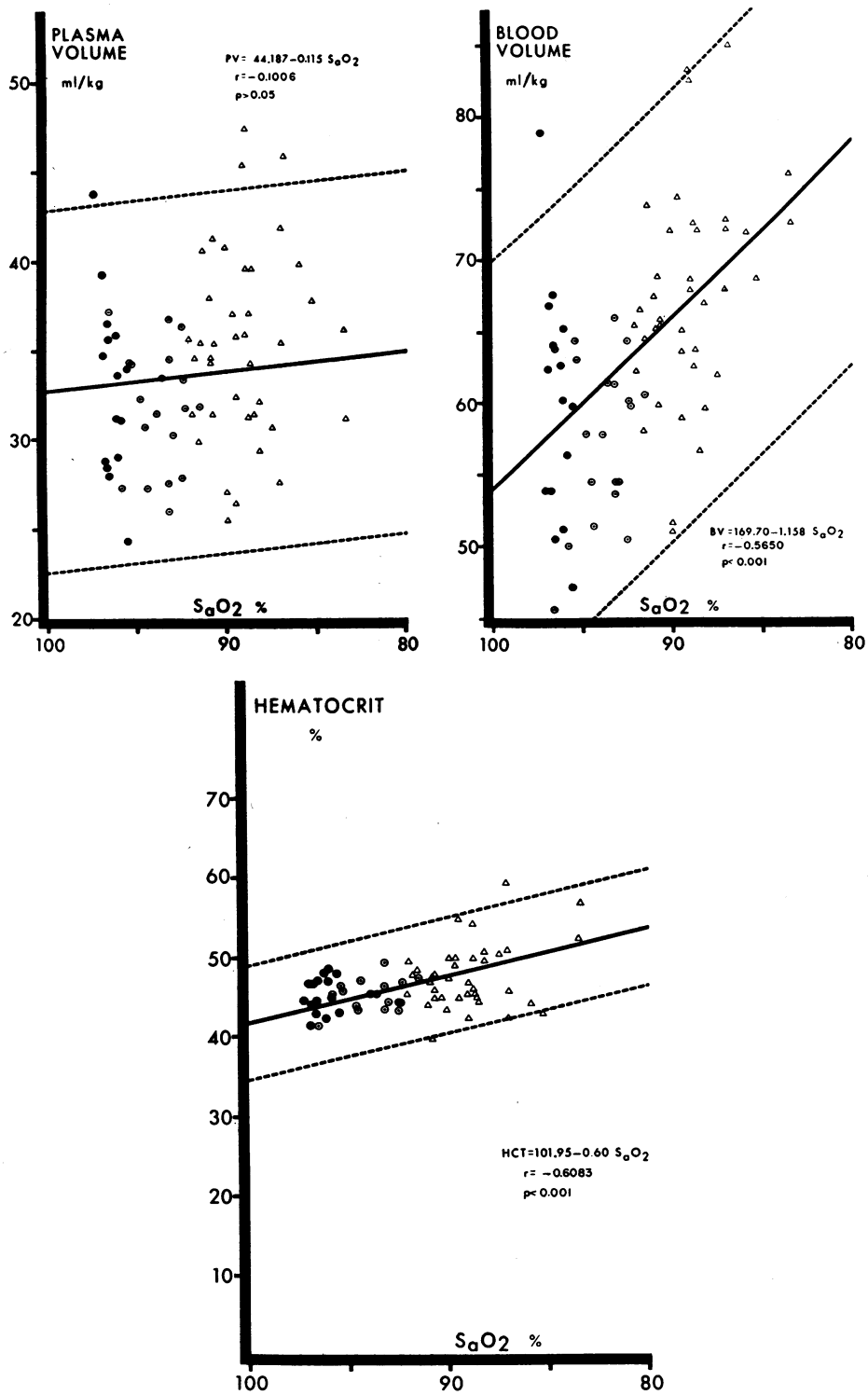

FIGURE 3 Relationship between Sa_{O_2} and plasma volume, blood volume, and hematocrit in normal men residing at sea level, 1600 and 3100 m. Broken lines represent 95% confidence limits on individual estimates.

TABLE VI

Male Patients with Chronic Obstructive Airway Disease

Subject	Class	Age	Height	Weight	BV	RCM	PV	Sa_{O_2}	Pa_{O_2}	*pH*	Pa_{CO_2}	Hct
		yr	*cm*	*kg*	*liters*	*liters*	*liters*	%	*mm Hg*		*mm Hg*	%
A. K.	PP	50	173	49.3	3.42	1.49	1.93	91.8	62.4	7.39	46.0	43.5
S. M.	PP	58	169	89.6	4.18	2.01	2.17	91.5	64.0	7.42	34.0	48.0
F. E.	PP	51	171	77.6	4.27	2.07	2.20	92.6	67.1	7.39	42.2	48.5
T. R.	PP	62	173	77.5	4.12	1.85	2.27	93.1	68.9	7.38	42.2	45.0
A. H.	Mixed	67	183	78.6	4.80	2.64	2.16	85.7	48.8	7.42	40.1	55.0
F. F.	Mixed	43	172	80.8	4.80	2.62	2.18	89.0	58.0	7.42	36.6	54.5
G. B.	BB	62	178	77.2	6.00	3.93	2.07	80.3	43.7	7.32	44.0	65.5
L. L.	BB	62	170	73.6	5.00	3.30	1.70	80.5	45.2	7.33	42.8	66.0
C. B.	BB	62	162	86.3	6.30	3.97	2.33	80.9	48.1	7.38	48.7	63.0
Mean		57.4	173	76.7	4.77	2.65	2.12	87.3	56.2	7.38	41.8	54.3
SEM		2.58	1.47	3.80	0.31	0.30	0.06	1.83	3.29	0.012	1.51	2.92

See Table I for explanation of abbreviations.

whereas for Pa_{O_2} less than 67 mm Hg, a significant relationship was found ($r = -0.7731$, $P < 0.005$). This biphasic relationship between arterial oxygen tension and red cell mass stands in marked contrast to the simple linear relationship between arterial oxygen saturation and red cell mass.

Plasma volume, blood volume, and hematocrit. The relationships between plasma volume, blood volume and hematocrit and Sa_{O_2} were examined in a fashion similar to that already described for red cell mass. The results are shown in Fig. 3. Plasma volume rose very slightly with decreasing Sa_{O_2}, but this relationship was not significant ($r = -0.01006$, $P > 0.05$). Blood volume, on the other hand, rose progressively with falling Sa_{O_2} due mainly to the rise in red cell mass ($r = -0.6560$, $P < 0.001$). Because the rise in red cell mass was greater than the rise in plasma volume there was an increase in hematocrit with decreasing Sa_{O_2} ($r = -0.6083$, $P < 0.001$).

Studies in patients with chronic obstructive airway disease. Red cell mass, plasma volume, blood volume, and hematocrit in relation to Sa_{O_2} were investigated in a group of patients with well-documented chronic obstructive airway disease. Four of these patients were of the "pink puffer" (PP) or class A variety (13, 14), in whom alveolar ventilation is typically well maintained with minimal derangement in blood gases, little elevation in hematocrit, and no history of cor pulmonale. Three patients were of the "blue bloater" (BB) or class B type (13, 14), in whom alveolar ventilation is typically reduced causing substantial hypoxemia associated with increased hematocrit and a history of past or present bouts of cor pulmonale. In addition, two patients had elements of both of the above types (mixed). None of these patients was receiving diuretic therapy. The results of the studies in these patients are presented in Table VI.

The individual values for these patients when plotted in relation to Sa_{O_2} fell almost entirely within the 95% confidence limits on individual estimates calculated in normal subjects. Because these patients all had in common the presence of severe airway obstruction, regression analyses have been calculated for red cell mass, plasma volume, blood volume, and hematocrit on Sa_{O_2}. The calculated regressions are shown in comparison with the corresponding regressions observed in the normal subjects in Fig. 4. The regression analysis of the patients' data suggests a steeper increase for red cell mass with falling Sa_{O_2} ($r = -0.9558$), which differed significantly from the curve for normals ($P < 0.05$). Plasma volumes were smaller than those observed in the normal group, but, as in the case of the normal group, no significant relationship between plasma volume and Sa_{O_2} was found ($r = -0.4520$, $P > 0.05$). These differences resulted in blood volumes slightly lower than those in the normal group. There was, however, an accentuation in the hematocrit rise ($r = -0.9713$), which was significantly steeper than that found in the normal group ($P < 0.005$).

When red cell mass was calculated in relation to the indices of body size listed in Table IV, the regressions on Sa_{O_2} differed from the normal in the

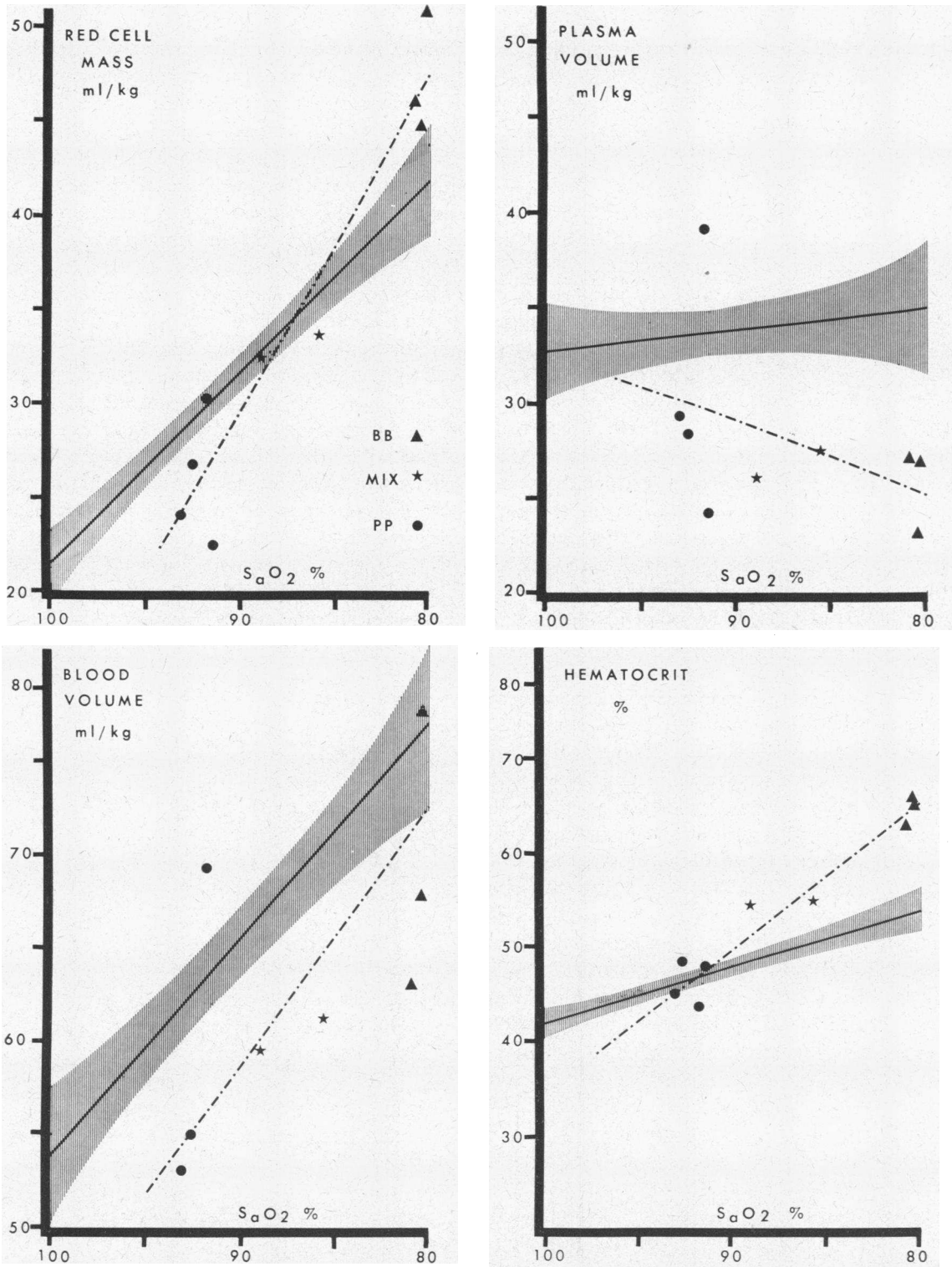

FIGURE 4 Red cell mass, plasma volume, blood volume, and hematocrit plotted against Sa_{O_2} in patients with chronic obstructive airway disease. Solid lines and shaded areas represent regressions found in normal subjects and the 95% confidence limits on the line. Broken line depicts the regression for the patients with chronic obstructive airway disease. The over-all pattern of response to hypoxemia in these patients appears to differ from the normal pattern of response.

same fashion described above, suggesting that differences in height-weight relationships between patient and normal groups were not responsible for the observed differences in regression lines.

DISCUSSION

In this study a method of measurement of red cell mass has been employed that greatly reduces the time required for this determination. We have made use of the fact that even a brief exposure of whole blood to ^{51}chromium results in the binding of substantial quantities of the isotope. That this binding is as firm as that which results from a longer incubation was demonstrated by Mollison and Veall (15) who showed that elution of ^{51}chromium from the red cells incubated for very brief periods with the isotope was no greater than that from red cells that had been incubated for much longer periods with ^{51}chromium. This permitted the use of a 3 min incubation period at room temperature which, in our experience, results in the uptake of about 85% of the isotope added to the system. The remaining unbound isotope was removed with two saline washings. Washing the cells does not seem to seriously affect subsequent in vivo red cell disappearance rates, as the experience of others has shown (16). 15 min is reported to be sufficient time for virtually complete mixing of the labeled cells in the circulation over a wide range of hematocrits. Use of a semiautomatic radioactivity counting apparatus abbreviated the procedure further and, in addition, proved to be quite accurate in in vitro tests, possibly because the procedure circumvents several volumetric operations that would ordinarily constitute additional sources of error. This method yielded a value of red cell mass at sea level of 27.1 ± 3.72 (SD) ml/kg, which is in good agreement with the results of others who have employed washed ^{51}Cr-labeled red cells in normal males at sea level–Huff and Feller, 28.3 ± 4.09 (SD) ml/kg (17); Eisenberg 27.8 ± 3.27 ml/kg (18); and Lertzman, Frome, Israels, and Cherniack, 26.2 ± 1.93 ml/kg (19).

Red cell mass, when viewed in relation to indices of arterial oxygenation, showed a strikingly different relationship to Sa_{O_2} than to Pa_{O_2} (Figs. 1 and 2). With falling Sa_{O_2} red cell mass rises in a simple and linear fashion over the entire range examined. In contrast, a falling Pa_{O_2} was associated with no rise in red cell mass until a "critical" value of about 67 mm Hg was reached. Below this point Pa_{O_2} and red cell mass were linearly related. It is noteworthy that this critical value falls on the shoulder of the oxygen-hemoglobin dissociation curve (Fig. 5). Hence, changes in Pa_{O_2} above this point result in very little alteration of Sa_{O_2} because of the minimal slope of the dissociation curve in this range. On the other hand, changes in Pa_{O_2} below 67 mm Hg fall on the steeper portion of the dissociation curve and accordingly result in substantial alterations in Sa_{O_2}. It would thus appear that only those changes in Pa_{O_2} which cause a change in Sa_{O_2} are associated with alterations in red cell mass. This would suggest that Sa_{O_2} is the more important determinant of red cell mass.

A possible mechanism which might explain this relationship involves the hypothesis that erythropoietin production is regulated by renal interstitial or intracellular Po_2 rather than by arterial Po_2 (20). Oxygen delivery, an important determinant of tissue Po_2 thus would be a major regulator of erythropoiesis. Oxygen delivery, in turn, depends

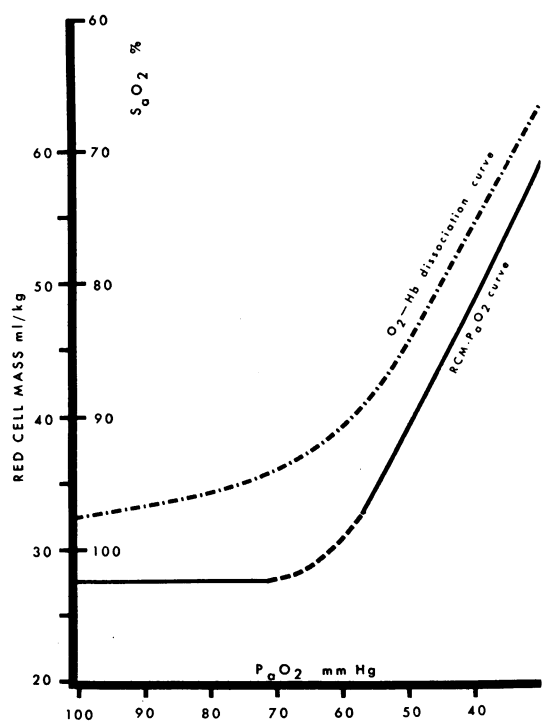

FIGURE 5 Comparison of Pa_{O_2}–red cell mass relationship with oxygen-hemoglobin dissociation curve (broken line). Note the similarity of the behavior of red cell mass and arterial oxygen saturation with changing oxygen tension.

upon blood flow and arterial oxygen content, and the latter is saturation dependent. Other factors that were not investigated in the present study, but which could be expected to affect oxygen delivery and, hence, erythropoiesis include fluctuations in arterial oxygenation, cardiac output, and pattern of regional distribution of blood flow, particularly during exercise or sleep. Oxygen delivery may also be influenced by variations between different individuals in the amount of 2,3-diphosphoglycerate within the red cell which would influence the affinity of hemoglobin for oxygen (21).

Plasma volumes in the present study were unrelated to Sa_{O_2} but tended to be slightly larger in those individuals with lower Sa_{O_2}. These findings are at variance with results of studies comparing plasma volumes in residents of Lima, Peru, (sea level) with those in natives of Morococha, Peru (4540 m) in which plasma volumes were found to be consistently smaller in the Morococha natives when measured with ^{59}Fe (22), vital red (23), and T-1824 (24). It has, however, been pointed out that natives of Morococha comprise an ethnically unique group which in addition, is very probably genetically different as well, a consequence of existence at high altitudes since prehistoric times (25). In fact, the cardiovascular responses of this group to hypoxia are in certain respects different from those seen in non-Indian, high altitude populations that have been established in more recent times (26). Reynafarje, Lozano, and Valdivieso (27) were able to provide a clearer picture of the effects of hypoxia on plasma volume uncomplicated by genetic and ethnic factors by conducting serial studies on sea level residents who were taken to Morococha for 1 yr. In these individuals plasma volume measured with T-1824 was reduced for 6–8 months, but by the end of 1 yr it had returned to sea level values.

Relative hematocrit changes associated with decreases in Sa_{O_2} were considerably smaller than the parallel changes in red cell mass in this study, as the experience of others has shown (3, 4). A fall in Sa_{O_2} which produced a 100% increase in red cell mass, produced a relative increase of only 28% in hematocrit. This is quite similar to the value of 33%, which is the theoretical relative change in hematocrit that would result from a doubling in red cell volume in the presence of a constant plasma volume. This is simply a consequence of the fact that hematocrit is the ratio of red cell volume to the sum of red cell volume and plasma volume.

This information regarding the pattern of hematological response to hypoxia in normal man provided a quantitative frame of reference with which to view the data of patients with chronic obstructive airway disease who were studied by the same methods. Although the number of patients studied was small, certain consistent patterns emerged that differed significantly from those observed in the normal group. These consisted of a steeper red cell mass–Sa_{O_2} relationship in association with lower plasma volumes which resulted in a greater rise in hematocrit with decreasing Sa_{O_2}. These variations from the normal patterns may be due in part to the possibility that the value of Sa_{O_2} measured at rest may not be representative of the average Sa_{O_2} throughout the day, particularly in those patients with a low Sa_{O_2}.

The above conclusions differ in some respects from those of other authors. Vanier et al. (4), for example, concluded that the response of red cell mass to hypoxia was less than that in high altitude dwellers, whereas Shaw and Simpson (3), on the other hand, concluded that it was similar. Plasma volumes were found to be increased in both the series of Vanier et al. (4) and Shaw and Simpson (3) who attributed these increases to the frequent existence of cor pulmonale or to a history of cor pulmonale in these groups. On the other hand, Hume and Goldberg (28) found lower plasma volumes in their patients with obstructive disease than in those of the control group. This latter finding is in agreement with that of the present study and is consistent with the reports of decreased plasma volume in other types of secondary polycythemia, such as cyanotic congenital heart disease (28–30). In our series, patients with past and present cor pulmonale (type BB) did not have larger plasma volumes.

These varying results may be due to differences in patient selection, differences in the size and composition of control groups, or may be due to systematic differences in methods of measurement. When red cell labels such as ^{51}Cr or ^{32}P are employed, the calculated values for plasma volume are always 10% smaller than the values obtained

with albumin labels like T-1824 or ^{131}I (31). The latter measurements may include a significant extravascular component (32) due to diffusion of labeled albumin molecules out of the vascular space. When progressively larger molecules are labeled, progressively smaller plasma volumes are found which approach those calculated from labeled red cells (33–35). Furthermore, hypoxia and chronic obstructive airway disease may alter the distribution of labeled albumin between intra- and extravascular spaces. The present study, employing exclusively a red cell label in both normal subjects and in patients, has avoided some of these pitfalls.

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