Journal of Clinical Investigation
Vol. 42, No. 7, 1963

PULMONARY DIFFUSING CAPACITY AND ITS SUBDIVISIONS IN POLYCYTHEMIA VERA

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(Submitted for publication July 23, 1962; accepted February 28, 1963)

Polycythemia vera is characterized by a greatly increased red cell mass, and patients with the disease have an increase of both hemoglobin concentration and total blood volume. The purpose of the present study was to observe the effect of these two variables, and their changes with treatment, on pulmonary diffusion.

The rate of chemical reaction with hemoglobin is an important factor in the over-all rate of gas uptake from the lung. Roughton and Forster (1) proposed the equation $1/D_L = 1/D_M + 1/\theta Vc$ (Equation 1) and showed that by its use it was possible to subdivide the total diffusing capacity of the lung. D_L is the total pulmonary diffusing capacity for CO from the alveolus to the interior of the red cell. D_M is the membrane diffusing capacity and relates to the movement of gas from the alveolus to the surface of the red cell. θ, often referred to as the rate of uptake of CO by the red cells, is actually the product of the rate at which CO replaces O_2 in oxyhemoglobin and the concentration of hemoglobin (2). Vc is the pulmonary capillary blood volume at any instant. McNeill, Rankin, and Forster (3) have related these parameters in terms of resistances. $1/D_L$ may be considered as the total resistance to gas uptake, which is composed of the sum of $1/D_M$, the membrane resistance, and $1/\theta Vc$, the red cell resistance.

In polycythemia vera one would expect the increased hemoglobin concentration to result in an increase in θ, thus lowering the red cell resistance and so producing an increase in D_L. Previous observers, however, have not found an abnormally high D_L in this disease.

Harrop and Heath (4) in 1927, using Krogh's original CO technique, reported a subnormal diffusing capacity in seven patients with polycythemia vera; further measurements in one patient after treatment showed no significant change. There have since been several reports stating that CO uptake is normal, but none has given values for D_L or compared pre- and posttreatment results. Ratto, Briscoe, Morton, and Comroe (5) reported a normal CO uptake in four patients. Rankin, McNeill, and Forster (6), and Forster (7), briefly mentioned that D_L, D_M, and Vc were normal in polycythemia vera. Fishman (8), quoting work from his laboratory with a steady state CO technique, concluded that diffusion was normal. Newman, Feltman, and Devlin (9) report a normal A-a (alveolar to arterial) difference for oxygen in four out of five patients with polycythemia vera.

People acclimatized to high altitude show features similar to polycythemia vera, as they have both an increased red cell mass and total blood volume (10). Barcroft and his colleagues (11) in 1920 measured D_L by Krogh's technique and found slightly but not significantly higher values for 13 newly acclimatized subjects, as compared with values at sea level. They noted that the natives permanently resident at high altitudes had significantly higher values for D_L than those of the party.

There have been several studies of O_2 transfer in the lungs in acclimatized subjects. Houston and Riley (12) found a decrease in the A-a difference in O_2 tension under conditions of prolonged simulated altitude and calculated that the D_L for O_2 was increased. Velasquez (13) reported that the maximal D_L for O_2 during exercise was greater than normal in subjects acclimatized to an altitude of 4,540 m.

The plan of the present study was to measure

* Part of this work was done while holding a Nuffield Dominion Traveling Fellowship in medicine and part was supported by a fellowship from the Endowment Research Fund of the United Birmingham Hospitals. Present address: Montreal General Hospital, Montreal, Canada.

D_L, D_M, and Vc in ten patients with polycythemia vera *a*) before treatment when both hemoglobin concentration and total circulating blood volume were abnormally high, *b*) 1 week later following several venesections when hemoglobin concentration was approximately normal, but blood volume usually still raised, and *c*) at least 3 months after treatment with P^{32} when both hemoglobin concentration and blood volume were close to normal.

METHODS

Ten patients were studied, in all of whom the diagnosis of polycythemia vera was established on clinical and hematological grounds and with the confirmatory evidence of pulmonary function tests. There were eight men and two women, ranging in age from 45 to 66 years.

Patient 6 had essential hypertension, and Patient 10 had a history of mild chronic bronchitis. Patient 8 had had a pulmonary infarction one month previously, but no other patient gave a history or had clinical or radiological evidence suggestive of such an event. The remainder had no history of cardiopulmonary disease, and physical examination, chest X ray, and electrocardiogram were normal. The spleen was palpably enlarged in all except Patient 9.

Each patient was studied before treatment and again 1 week later, after three or four venesections of about 500 ml each. The third occasion of study was from 3 to 9 months (mean 5) after treatment with P^{32}. Patient 4 died of gastrointestinal hemorrhage before the effect of P^{32} could be observed.

D_L was measured in the sitting position by the single-breath method, as modified by Ogilvie, Forster, Blakemore, and Morton (14). This was repeated three times at each of three different alveolar O_2 tensions in order to calculate D_M and Vc. Alveolar O_2 tensions of approximately 100 and 400 mm Hg were obtained by having the patient inspire approximately 0.3% CO, 8% He in air or 0.3% CO, 8% He in O_2. A third level of alveolar O_2 tension of approximately 600 mm Hg was achieved when the patient inspired the latter mixture after having breathed O_2 for the previous 2 minutes.

Breath-holding times were kept close to 10 seconds (range 9 to 11) and were measured by the method of Jones and Meade (15). This consists of measuring from the beginning of inspiration to the mid-point of expiration and subtracting 0.3 of the inspiratory time to allow for diffusion occurring over these two periods. In the patients studied the use of this technique gave values for D_L that differed little from those obtained by the more normal method of measuring breath-holding time. Residual volume was measured separately by a closed circuit He technique (16). Inspired volume was near maximum and kept as constant as possible for a given patient. The variation of alveolar volume from one stage of the study to another was never more than 400 ml, except in Patient 1, in whom the mean values in the second and third studies differed by 1,200 ml.

The expired samples were collected after 1 L of expired air had washed out the dead space. The sample was then dried by passage over calcium chloride and analyzed for CO in an infrared analyzer. The instrument gave different readings for CO in air and CO in O_2, so that separate calibration curves were used for the two circumstances. The sample then passed through a CO_2 absorber and was analyzed for He with a katharometer. Absorption of CO_2 was complete as judged by a zero deflection of the katharometer when gas mixtures containing no He were similarly treated. This instrument was also calibrated for different O_2 tensions, and the absorbed CO_2, which on the basis of previous experiments was assumed to be 4%, was allowed for in the final calculation of percentage of He. Expired O_2 tensions were measured polarographically with a polythene-covered platinum electrode (17).

An allowance was made for back pressure of CO, which was measured by a rebreathing technique (3). This was done at the start of the series and again after each three measurements of D_L. The value for a single D_L estimate was interpolated and proportioned to the O_2 tension of the sample. This back pressure estimate was then subtracted from both the initial and final CO concentrations.

Expired O_2 tension was converted to the intracapillary O_2 tension by allowing for the A-a difference for O_2 as described by McNeill and associates (3). An assumed O_2 uptake of 250 ml per minute was divided by $1.23 \times D_L$ to give the O_2 tension difference from alveolus to mean pulmonary capillary. This value was subtracted from the mean alveolar O_2 tension, the latter being taken as 5 mm Hg greater than that of the expired sample.

D_M and Vc were obtained from the graphical solution of Equation 1. Values for θ were taken from the data of Roughton and Forster (1), assuming $\lambda = 2.5$. As these values for θ were derived for blood of normal O_2 capacity (or hemoglobin concentration), a correction had to be applied in the case of polycythemic blood. This could be done either by changing θ in direct proportion to the O_2 capacity (2), or by calculating D_M and Vc using θ as given and then multiplying calculated Vc by $20/O_2$ capacity of patient's blood at the time of study (18). The latter method is simpler in practice and gives the same result as the former.

This correction for Vc assumes that the hemoglobin concentration of pulmonary capillary blood is the same as that of peripheral venous blood. If pulmonary capillary hematocrit is less than peripheral venous, Vc will be underestimated by a proportionate amount. It is also assumed that the rate of uptake of CO by the individual red cells is normal in polycythemia vera.

Physiological dead space and A-a O_2 tension difference were measured in the supine position by using techniques described elsewhere, and values were compared with normal values at comparable age (19). Lung volumes, expiratory flow rates, and the FEV 1.0/FVC ratio (forced expiratory volume at 1 second as a percentage

TABLE I

Details of patients and results of pulmonary function tests before treatment

Patient	Sex	Age	Height	Weight	BSA	VC*	RV	TLC	MEFR†	$FEV_{1.0}/FVC$‡	N_2 Elimination§	O_2 Saturation	
												Rest	Exercise
		yrs	*cm*	*kg*	m^2	*L*	*L*	*L*	*L/min*	%		%	%
1	M	53	174	79	1.95	3.30 (76)	1.25 (57)	4.55 (69)	278	82	2.8	96.0	96.2
2	M	58	160	72	1.74	3.80 (109)	1.90 (93)	5.70 (101)	312	92	2.3	98.6	95.6
3	M	64	183	59	1.74	4.25 (94)	2.36 (107)	6.61 (89)	193	72	1.5	96.2	95.9
4	M	60	173	62	1.73	3.52 (85)	2.14 (80)	5.66 (90)	179	69	2.9	95.6	96.1
5	M	45	167	55.5	1.63	4.18 (101)	2.27 (95)	6.45 (103)	271	78	2.0	96.6	94.1
6	M	66	175	75.5	1.90	3.57 (119)	2.85 (93)	6.42 (94)	180	70	2.8	97.9	98.1
7	F	60	150	59	1.54	2.03 (88)	1.80 (116)	3.83 (94)	182	66	3.2	96.2	97.5
8	F	63	175	60	1.72	2.58 (88)	2.20 (125)	4.78 (89)	157	77	5.8	95.4	95.3
9	M	57	170	56	1.65	3.96 (99)	3.02 (111)	6.98 (108)	396	73	2.3	96.2	96.3
10	M	61	170	59	1.68	3.20 (80)	2.70 (100)	5.90 (92)	125	62	2.0	96.9	95.1

* VC is vital capacity; RV, residual volume; and TLC, total lung capacity. Values in parentheses are the percentages of predicted normal.
† MEFR is maximal expiratory flow rate measured from 200 to 1,200 ml of expired volume.
‡ $FEV_{1.0}/FVC$ is the forced expiratory volume at 1 second as a percentage of the forced vital capacity.
§ N_2 elimination represents the result of the single-breath N_2 elimination test. The figure for percentage of N_2 is the concentration difference between 750 to 1,250 ml expired gas after inspiration of 1 L of O_2. Normal for this age group is 3.5 to 4.5% (19).

of the forced vital capacity) were measured with a 6-liter low-resistance spirometer. Distribution of ventilation was assessed with the single-breath N_2 elimination test of Comroe and Fowler (20). O_2 saturations were measured spectrophotometrically. Red cell mass was estimated by using Co^{51}-labeled red cells, and plasma volume with I^{131}-labeled albumin.

RESULTS

Preliminary lung function tests. Table I gives the details of patients and the results of pulmonary function tests. Vital capacity and total lung capacity were slightly below predicted normal in all patients and increased 10 to 15% after treatment. Residual volume was within normal limits in all before treatment and showed little change after. FEV 1.0, expressed as a percentage of forced vital capacity, was above 65% in all except Patient 10, who had mild airways obstruction. The single-breath N_2 elimination test was within the normal limits given by Sandqvist and Kjellmer (21), except in Patient 8, who had had a previous pulmonary infarction. The arterial O_2 saturation at rest and on exercise was above 95% in all patients.

Hemoglobin and blood volume changes. Table III gives the packed cell volume, hemoglobin concentration, blood volume, diffusion and dead space data, and A-a differences for O_2 tension at the three stages of study. Blood volume data were not obtained for Patient 8 after venesection, and physiological dead space and A-a differences were not measured in Patient 7.

Packed cell volume was above 57% in all cases before treatment, with a correspondingly high hemoglobin concentration. Total blood volume was initially abnormally high, the mean 5,820 ml being 117% of predicted normal (22, 23), mostly as a result of the increased red cell mass. After venesection, red cell mass decreased but plasma volume usually increased slightly, the result being a decrease in total circulating blood volume. The mean total blood volume after venesection was 5,480 ml (107% of predicted) and after P^{32} it was 4,750 ml (97% of predicted).

Changes in D_L. Table II gives individual mean values for D_L at the three levels of alveolar O_2 tension at each stage of the study. The mean of three determinations of D_L in patients breathing air at each stage of the study is given in Table III and is expressed also as a percentage of the nor-

TABLE II

Individual values for diffusing capacity and oxygen tension in pulmonary capillaries before and after treatment

Patient		Diffusing capacity			Mean O_2 tension in pulmonary capillaries		
		a*	b	c	a	b	c
		ml/min/mm Hg			*mm Hg*		
1	Untreated	34.0	16.3	12.6	96	370	567
	After VS†	24.0	14.3	10.6	87	323	531
	After P^{32}	23.6	15.1	12.9	133	385	576
2	Untreated	26.8	14.0	13.7	101	353	435
	After VS	19.0	9.0	7.4	90	345	588
	After P^{32}	24.3	13.5	10.3	137	361	568
3	Untreated	33.5	19.3	15.8	95	404	590
	After VS	28.5	14.2	10.8	120	413	578
4	Untreated	28.5	14.6	13.8	98	345	469
	After VS	23.1	9.1	7.1	84	400	555
	After P^{32}	15.4	6.3	3.5	87	281	505
5	Untreated	27.4	11.2	9.1	102	432	568
	After VS	23.8	12.2	9.0	98	397	564
	After P^{32}	27.2	12.5	10.8	130	404	595
6	Untreated	33.3	19.5	12.2	122	315	565
	After VS	22.2	10.6	7.2	120	303	576
	After P^{32}	26.6	21.4	18.8	97	341	576
7	Untreated	40.4	25.0	18.3	92	373	542
	After VS	27.3	16.5	12.3	92	360	545
	After P^{32}	12.9	9.2	6.4	110	400	543
8	Untreated	23.6	17.0	10.0	102	234	554
	After VS	15.3	8.9	5.6	95	260	515
	After P^{32}	8.2	5.9	3.3	110	337	511
9	Untreated	19.8	7.2	3.2	135	379	497
	After VS	10.0	6.6	4.9	108	388	534
	After P^{32}	5.5	3.2		95	297	
10	Untreated	20.0	11.7	9.8	130	328	537
	After VS	9.0	4.1	2.5	110	283	516
	After P^{32}	7.3	3.2		105	310	

*a = Patient breathing air, test mixture containing 21% O_2; b = patient breathing air, test mixture containing 90% O_2; and c = patient breathing 99% O_2, test mixture containing 90% O_2.
† After VS = after venesection; after P^{32} = after treatment with P^{32}.

mal value predicted for that patient from the data of Burrows, Kasik, Niden, and Barclay (24). We did not have our own normal values in the appropriate age group, but in ten normal subjects, age 25 to 55 years, the measured values did not differ significantly from those predicted by the equation of Burrows and associates. The average standard deviation of the mean D_L, in the ten patients with polycythemia vera, when breathing air, was 1.4 ml per minute per mm Hg. The coefficient of variation for all measurements of D_L was 6.6%.

Figure 1 gives D_L as a percentage of predicted normal at the three stages of the study. Before treatment the value in all patients was greater than predicted. The mean value was 147% of the predicted value, a highly significant increase ($p < 0.01$). After venesection, the mean value fell to 103% of predicted normal, five patients falling within the normal range, two above, and three probably below. After P^{32}, the mean value was 81% of predicted normal; six patients were probably normal, but three were definitely subnormal.

Figure 2 shows D_L at the different stages plotted against hemoglobin concentration at the time of study. D_L decreased in every case after venesection, and this change was highly significant ($p < 0.001$). After P^{32}, D_L fell again, with a further decrease in hemoglobin concentration in most cases. In two cases hemoglobin increased, and D_L returned towards its original value.

Changes in D_L at raised O_2 tensions. The results presented in Table II show that D_L at the intermediate and high O_2 tensions decreased following venesection. The magnitude of the decrease was similar, 30% at the high O_2 tension, 32% at the intermediate level, and 35% at the highest O_2 tension.

The alveolar O_2 tensions at which the measurements were made are also shown in Table II, and they show no obvious trend from one stage of the study to another.

Figure 3 shows an example of the way in which D_M and Vc were determined from the values for D_L measured at three levels of alveolar O_2 tension. Since D_L at the highest O_2 tension was often small, especially following treatment, the reciprocal of

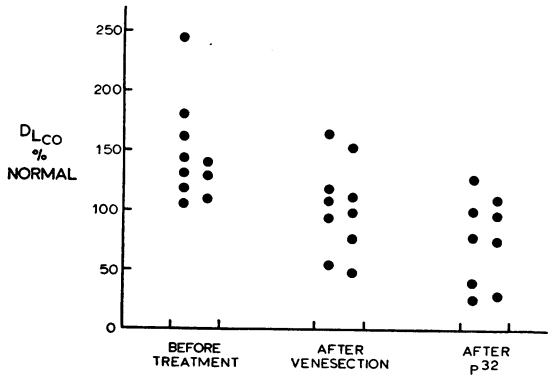

FIG. 1. TOTAL PULMONARY DIFFUSING CAPACITY FOR CO FROM THE ALVEOLUS TO THE INTERIOR OF THE RED CELL (D_L), EXPRESSED AS A PERCENTAGE OF NORMAL, BY USING THE PREDICTION FORMULA OF BURROWS AND ASSOCIATES (17), AT THE THREE STAGES OF STUDY. All estimates of D_L are the mean of three determinations. One patient died before study after P^{32}.

TABLE III

*Blood volume and pulmonary diffusion measurements before and after treatment**

Patient	Date	PCV	Hb	RBC volume	Plasma volume	Total blood volume†	V_A	D_L	D_M	Vc	Corrected Vc‡	V_D/V_T§	A-aD§
		%	g/100 ml	ml	ml	ml	ml	ml/min/mm Hg	ml/min/mm Hg	ml		%	mm Hg
1	a) 5/ 9/61	65	20.3	4,240	2,306	6,546 (101)	3,400	34.0 (139)	143	53	37	24.3 (26.3)	17.4 (11.2)
	b) 5/17/61	48	16.7	2,944	3,750	6,694 (104)	2,900	24.0 (99)	55	50	44	26.1	35 (15.4)
	c) 2/ 1/62	49	16.3	2,400	3,230	5,630 (87)	4,000	23.6 (97)	44	71	65	24.0	7 (16.1)
2	a) 5/13/61	57	19.0	2,843	2,693	5,536 (94)	4,120	26.8 (133)	111	45	35	34.2 (28.3)	24 (17.0)
	b) 5/19/61	43	14.6	2,100	3,097	5,197 (88)	3,880	19.0 (95)	55	33	34	31.9	24 (12.2)
	c) 2/ 2/62	54	18.5	2,446	2,274	4,720 (80)	4,300	24.3 (121)	166	42	34	31.0	16 (15.9)
3	a) 5/26/61	61	18.3	3,317	2,631	5,948 (122)	4,930	33.5 (180)	66	85	68	21.2 (30.7)	19 (20.2)
	b) 7/17/61	52	15.6	2,600	3,200	5,800 (119)	5,200	28.5 (153)	143	47	45	27.3	12 (16.9)
4	a) 6/ 5/61	64	19.4	3,592	2,852	6,444 (127)	4,350	28.5 (145)	77	51	41	30.4 (29.1)	29 (18.0)
	b) 6/16/61	42	12.0	2,623	3,250	5,873 (116)	3,900	23.1 (118)	1,000	27	34	28.8	31 (17.5)
	c) 11/ 7/61	42	13.3	1,841	3,623	5,464 (107)	4,000	15.4 (79)	Infinite	11	12		
5	a) 6/13/61	62	19.1	3,277	2,676	5,953 (132)	4,750	27.4 (128)	250	38	29	16.4 (23.1)	29 (12.7)
	b) 6/21/61	45	12.0	2,381	3,200	5,581 (123)	4,800	23.8 (111)	87	40	40	20.5	27 (14.6)
	c) 1/30/62	46	16.1	1,954	2,398	4,352 (96)	4,600	27.2 (128)	143	46	42		
6	a) 7/11/61	58	17.0	4,037	3,178	7,205 (117)	4,350	33.3 (162)	250	51	40	18.2 (31.5)	5 (16.7)
	b) 7/19/61	48	15.3	2,840	3,400	6,240 (101)	4,370	22.2 (108)	Infinite	28	27	9.5	12 (20.1)
	c) 10/18/61	40	12.7	1,571	2,419	3,990 (65)	4,790	26.6 (130)	35	160	168	6.9	17 (22.8)
7	a) 10/20/61	69	20.3	3,234	1,500	4,734 (124)	3,030	40.4 (245)	100	87	64		
	b) 11/ 1/61	59	16.4	2,201	1,700	3,901 (102)	2,890	27.3 (165)	63	62	56		
	c) 3/ 8/62	34	12.0	1,343	2,657	4,000 (104)	2,720	12.9 (78)	29	32	39		
8	a) 10/27/61	68	18.5	3,121	1,529	4,650 (120)	3,120	23.6 (119)	84	45	36	24.2 (30.3)	23.3 (19.7)
	b) 11/14/61	46	14.0				3,270	15.3 (77)	72	21	23		
	c) 3/13/62	42	13.2	2,337	3,163	5,500 (141)	3,120	8.2 (41)	Infinite	16	18		
9	a) 12/19/61	62	20.5	2,763	3,216	4,979 (109)	4,870	19.8 (106)	Infinite	15	11	34.6 (28.1)	25.6 (16.2)
	b) 1/ 1/62	46	14.2	1,735	2,500	4,235 (92)	5,190	10.0 (54)	31	22	23	45.2	8.2 (14.7)
	c) 5/ 7/62	52	13.6	1,526	2,036	3,562 (78)	4,890	5.5 (29)	Infinite	10	11	46.5	14.2 (14.8)
10	a) 1/25/62	71	20.6	3,900	2,255	6,155 (126)	4,560	20.0 (109)	55	44	32	40.0 (29.5)	37 (19.1)
	b) 2/ 5/62	48	14.2	2,741	3,080	5,821 (119)	4,450	9.0 (49)	Infinite	8	9	34.7	42 (17.4)
	c) 5/ 8/62	40	12.3	2,043	3,466	5,509 (113)	4,470	7.3 (27)	Infinite	5	6	38.5	30.5 (16.5)

* Table gives data at three states of study: a) before treatment; b) after venesection 1 week later; and c) after P^{32} at least 3 months later. PCV = packed cell volume; V_A = mean alveolar volume; D_L = total pulmonary diffusing capacity when breathing air; D_M = membrane diffusing capacity; Vc = pulmonary capillary blood volume; V_D/V_T = ratio of physiological dead space to tidal volume when breathing air; and A-aD = difference in oxygen tension between alveolar gas and arterial blood when breathing air.

† Values in parentheses below those for total blood volume are percentages of predicted normal, taking 82 ml per kg as normal for men (20) and 65 ml per kg as normal for women (21).

‡ Corrected Vc was obtained by multiplying calculated Vc by $20/O_2$ capacity (16).

§ Values in parentheses below V_D/V_T and A-aD are predicted mean normal values (17).

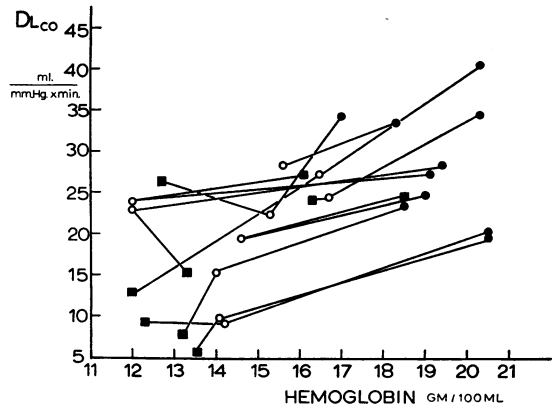

FIG. 2. THE DIFFUSING CAPACITY OF THE LUNG (D_L) PLOTTED AGAINST HEMOGLOBIN CONCENTRATION IN GRAMS PER 100 ML AT THE TIME OF STUDY. The black circles are before treatment, the open circles 1 week later after venesection, and the black squares 3 months after P^{32}. All points are the means of three determinations of D_L.

the individual values sometimes varied more than shown in this example, and the line of best fit was then less readily constructed.

Changes in D_M. It can be seen from Table III that the values for D_M were very variable. This is in keeping with our experience in normal subjects, in one of whom D_M ranged from 50 to 153 in eight measurements over a 10-month period. There was no systematic change from one stage of the present study to another.

Changes in Vc. The individual values for Vc, both uncorrected and after correction for hemoglobin concentration, are shown in Table III. Comparison has been made with the results of Hamer (25), who found a mean of 74.5 ml (SD, 32.2) in 25 normal subjects and no change in Vc with age. These agreed well with our finding of a mean Vc of 75.0 ml in six normal subjects whose average age was 30 years.

The uncorrected Vc in the untreated patients had a mean value of 51.4 ml, which was not significantly less than normal ($0.05 < p < 0.1$). After venesection there was a significant fall ($p < 0.01$), but there was no further change following treatment with P^{32}.

The mean Vc after correction for hemoglobin concentration was 39.3 ml, which was significantly less than normal ($p < 0.01$). In each patient the value was less than the mean normal value. Neither after venesection nor treatment with P^{32} was there any significant change in corrected Vc.

It will be noted that the three patients who had a definitely subnormal D_L after treatment (Patients 8, 9, and 10) also had the lowest values for corrected Vc (6, 11, and 18 ml, respectively). These patients were slightly anemic at the time of measurement, but the degree of anemia does not appear sufficient to explain the very low D_L.

Physiological dead space and A-a difference. The results obtained for the ratio V_D/V_T (physiological dead space to tidal volume) and A-a difference in patients breathing air are given in Table III. The value for A-a difference tended to be higher than normal, but was definitely above the normal range in only two patients before treatment. It remained abnormal after treatment in one of these (Patient 10, who had mild chronic bronchitis). Alveolar-arterial difference did not correlate with D_L, and there was no definite trend in the former with treatment. V_D expressed as a percentage of V_T was within normal limits in all patients except Patients 9 and 10. It was not measured in Patient 7 and only in the first stage in Patient 8. These high values for V_D were associated with the two lowest values for Vc.

DISCUSSION

The present results indicate that, as predicted, D_L was greater than normal in the group of patients with polycythemia vera before treatment. They differ from the results of most other workers, who have concluded that D_L was normal in

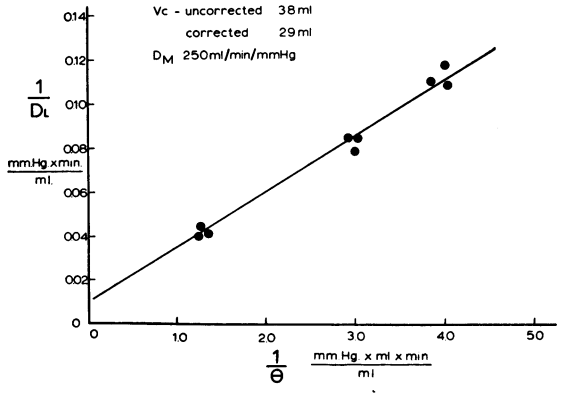

FIG. 3. EXAMPLE OF THE RELATIONSHIP BETWEEN $1/D_L$ AND $1/\theta$ (PATIENT 5, BEFORE TREATMENT). D_L is the total pulmonary diffusing capacity for CO from the alveolus to the interior of the red cell; θ is the product of the rate at which CO replaces O_2 in oxyhemoglobin and the concentration of hemoglobin.

this disease (5, 6, 8). One possible reason for this may lie in the rather wide range of D_L in normal subjects (24), which makes it difficult to state with certainty that a value for an individual is outside the normal limits. This difficulty was partly avoided in the present study by comparison of results before and after treatment.

The low results for D_L reported by Harrop and Heath (4) are more difficult to explain. Forster (7) has suggested that some of their patients were cases of secondary polycythemia, but as all were said to have had a palpable spleen, this explanation seems unlikely. They made no allowance for back pressure, however, which would have caused the results to be falsely low.

D_L invariably decreased after treatment in the patients with polycythemia vera. In five patients the value after treatment was normal, but in Patients 4, 7, 8, 9, and 10 it was abnormally low. In three of these D_L before treatment had been only a little greater than normal. In all of the patients in whom D_L was abnormally low after treatment, the Vc was also less than normal.

It appears most probable that the increased D_L before treatment resulted from the increased hemoglobin concentration of the blood in those capillaries taking part in gas exchange in the lung. The Vc, when corrected for hemoglobin concentration, was less than normal and there is no evidence that D_M was increased. Although the precision of estimates of D_M is poor, the measurements of Vc are more reliable. Even when we accept the inaccuracy of the estimates of D_M, consideration of the number and shape of capillaries still makes it hardly possible for D_M to have been greater than normal, when corrected Vc was significantly less than normal. Furthermore, the changes in D_L following treatment are also explicable by the alteration in hemoglobin concentration; in only two instances did a change in D_L fail to follow the change in hemoglobin concentration. These changes in D_L are the converse of those reported by Rankin and associates (2) in anemia before and after treatment. They concluded that the change in D_L was due solely to a change in θ, and they found that Vc did not alter after treatment when this was allowed for.

Vc when corrected for hemoglobin concentration was significantly less than normal, and individual patients showed very low values. This is of interest, since the total blood volume was greatly increased. The radiological appearances suggested that the major pulmonary arteries and veins were distended, and these changes disappeared after treatment. In a group of seven other patients with polycythemia vera, Segel (26) measured the "central blood volume" by injection of I^{131}-labeled human serum albumin into the pulmonary artery. The mean value before treatment was 1,341 ml, which is greater than normal. In each patient there was a decrease following treatment, the mean then being 949 ml, and the change was highly significant ($p < 0.001$). The pulmonary capillary bed does not therefore share in the pulmonary vascular engorgement of this disease, and treatment had no significant effect upon Vc.

The values for D_M are even more variable than those previously found in normal subjects. Forster (7) has emphasized that D_M is a less reliable measurement than Vc, as it is more affected by small errors in D_L. This is especially true in the present series where D_L is low in several cases and therefore less exact. It can also be seen from the graphical solution of Equation 1 that when Vc is small, the slope of the line is steep, and therefore the intercept less reliable. D_M is also dependent on the value used for λ (the ratio of the permeability of the red cell membrane to that of the red cell interior). Lacking conclusive evidence of the true value, most workers at present use 2.5, as we have done. If we had taken $\lambda = \infty$ or $\lambda = 1.5$, all the values for D_M would have been decreased or increased, but the variability between them would remain. In view of these difficulties, no conclusions can be drawn from changes in D_M in this study.

In seeking an explanation for the reduction of Vc, it is first necessary to consider whether the measurements are valid. It has been assumed, as must always be done in estimating Vc by this method, that the pulmonary capillary hematocrit is equal to the venous hematocrit. This assumption is usually thought to be justifiable in healthy subjects, and there does not appear to be any further reason to doubt its validity in polycythemia. After treatment, these patients had blood of a normal composition, and Vc was still abnormally small in several of them. A further objection might be raised to the use of values for θ obtained from normal blood. It is true that θ has

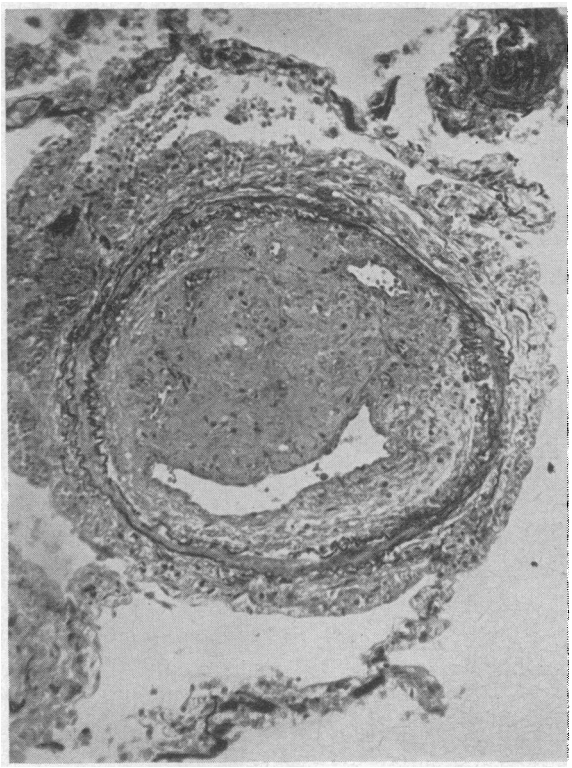

FIG. 4. TRANSVERSE SECTION THROUGH A SMALL PULMONARY ARTERY SHOWING AN ABNORMALLY THIN MEDIA WITH ATROPHY OF ELASTIC FIBERS. There is a large recent thrombus and below, a crescent of old organized thrombus; × 150. Elastic, Van Gieson stain.

not been determined for blood from polycythemic patients, but the red cells in this disease appear normal in size and shape, and the hemoglobin concentration within them is normal. It therefor seems unlikely that their rate of gas uptake will differ appreciably from normal.

Consequently, the reduction of Vc is a real one, and the evidence suggests a possible explanation. It is well known that patients with polycythemia are especially prone to both arterial and venous thrombosis in the systemic circulation. They not uncommonly also suffer pulmonary infarcts, although only one of the patients studied was known to have done so. It is suggested that widespread thrombosis in small pulmonary arteries may occur, leading to a substantial obliteration of the pulmonary capillary bed, without giving rise to clinically obvious pulmonary infarction.

We have not been able to find reports of histological examination of the lungs in this disease, nor have we had the opportunity of examining the lungs of any of the patients we have studied. We have, with the help of Dr. Donald Heath, studied sections of lung taken from two other patients who had died with polycythemia vera. In both, there was evidence of thrombus formation in many small pulmonary arteries, and in one case, large pulmonary arteries as well. The pulmonary veins were not affected, but thrombus was also present in bronchial arteries. The appearances in one patient are illustrated in Figures 4 and 5.

Additional evidence in favor of such an explanation is that indicating a disturbance of ventilation perfusion ratios in the lung. The A-a difference when the patients breathed air tended to be larger than normal, as also did the ratio V_D/V_T. The latter was definitely abnormal in the two patients with the smallest Vc. These patients had normally distributed ventilation as judged by the single-breath oxygen test, and the finding of a larger than normal V_D therefore suggests the presence of relatively underperfused alveoli.

The spleen was enlarged in all but one of the patients studied, and all fulfilled the other clinical and hematologic criteria for the diagnosis of polycythemia vera. From this point of view they were a homogeneous group. The considerable variability in D_L was an unexpected finding, and the possibility was considered that in some patients the impairment of gas exchange had caused a secondary polycythemia. Such an occurrence is very unusual in patients with a similar reduc-

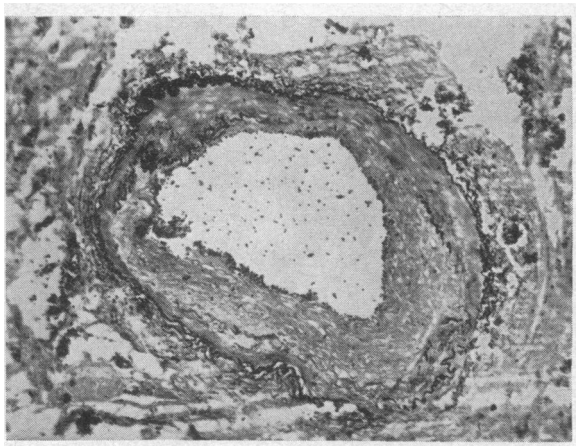

FIG. 5. TRANSVERSE SECTION THROUGH A BRONCHIAL ARTERY SHOWING DESTRUCTION OF THE INTERNAL ELASTIC LAMINA, WIDESPREAD ATROPHY OF THE MEDIA, AND AN EXTENSIVE ORGANIZED THROMBUS; × 100. Elastic, Van Gieson stain.

tion of D_L, due to the alveolar-capillary block syndrome, and even then the polycythemia is only slight. Furthermore, none of our patients had arterial unsaturation at rest or during exercise before (Table III) or after treatment. It is therefore concluded that the reduced D_L was not the cause of the polycythemia.

These data reinforce the view that hemoglobin concentrations cannot be ignored in the assessment of D_L, as measured at present. It has previously been shown that patients with severe anemia have a low D_L (2), and the present study indicates that the reverse is true in polycythemia vera. It remains uncertain, however, whether smaller deviations of hemoglobin from normal will significantly affect determinations of D_L for clinical purposes.

SUMMARY

Pulmonary diffusing capacity (D_L), membrane diffusing capacity (D_M), and pulmonary capillary blood volume (Vc) were estimated by a single-breath carbon monoxide method in ten patients with polycythemia vera before and after treatment.

D_L was greater than normal in all patients before treatment; after treatment it was normal or below normal. In the latter cases, Vc was very small, and physiological dead space (V_D) was sometimes increased.

Vc, corrected for hemoglobin concentration, was less than normal and did not change significantly after treatment. D_M varied widely both before and after treatment.

It is suggested that the increased D_L before treatment resulted from the increased hemoglobin concentration, and it is postulated that the reduction of Vc may have been due to thrombosis of small pulmonary arteries.

ACKNOWLEDGMENTS

We are much indebted to Dr. Nathan Segel, who is studying the hemodynamic effects of polycythemia vera, for the measurements of blood volume and to Dr. Donald Heath for advice about the histology of the pulmonary vessels.

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