Polycythemia Associated with Disturbed Function of the Respiratory Center

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THE PATIENT described in this report is presented as an example of absolute polycythemia with hypoxemia, in which there was no cardiac or pulmonary disease per se, but in which there was a decreased ventilatory function consequent to an impaired respiratory centrogenic drive.

In the strictest sense, polycythemia should be restricted to those conditions in which the volume of circulating red cells is increased above normal. In practice, however, the term polycythemia is applied to those conditions in which the numbers of red cells per unit volume of blood is increased as well as to those conditions in which the total red cell volume is increased. Thus, relative polycythemia may be present when the plasma volume is less than normal.

The determination of the arterial oxygen saturation in polycythemia has served to separate this condition into two groups on the basis of the presence or absence of hypoxemia. In our experience, patients having increased total red cell volume and showing normal arterial oxygen saturation have normal ventilatory function with slightly decreased blood CO_2 content. The majority of these patients have a palpable spleen and are diagnosed as having polycythemia vera.

On the other hand, the vast majority of adult patients (other than high altitude dwellers) having polycythemia and hypoxemia show an abnormality of pulmonary function including a raised blood CO_2 content and have clinical findings characteristic of advanced emphysema.

Secondary polycythemia associated with hypoxemia occurs in high altitude dwellers, in chronic lung disease, in congenital heart disease and, to a lesser degree, in certain acquired cardiac conditions. Exposure to certain chemical agents, especially aniline and its derivatives, may change the hemoglobin molecule so that it is no longer capable of carrying oxygen and consequently polycythemia may develop. A relatively mild polycythemia is found in some of the endocrine states such as in Cushing's syndrome. The cause of polycythemia vera is still unknown. A working classification on a physiopathologic basis is depicted in table 1.

Case Report

A 35 year old white male was admitted to the Royal Victoria Hospital February 6th, 1954, complaining of fatigability, pounding in the head (particularly the occipital region), anorexia and vomiting of six weeks duration. About two years previously he was hospitalized for similar complaints which disappeared after brief hospitalization. A month before admission he was diagnosed as polycythemia vera in another hospital. His local physician noted a deepening of his color about eight months before his admission to the Royal Victoria Hospital.

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Submitted April 2, 1956; accepted for publication May 19, 1956.

We wish to thank Dr. W. Fyles and Dr. D. Chu for their assistance, and Mrs. E. V Harkness and Mr. J. Nowaczek for their technical help.

TABLE 1.—*A Classification of Polycythemia on Basis of Arterial Oxygen Saturation and Blood Volume*

Type	Pathologic Physiology
I. HYPOXEMIC ABSOLUTE POLYCYTHEMIA (ERYTHROCYTOSIS)	Absolute increase in blood volume with lowered arterial oxygen saturation. May be due to—
A. HIGH ALTITUDE RESIDENCE	1) Lowered alveolar pO_2 without pulmonary disease.
B. PULMONARY DISEASE a) Emphysema b) Diffuse Granulomatoses or Fibrosis c) Arterio-venous Shunts	2) Abnormal pulmonary distribution of ventilated air (e.g., emphysema) or diffusion defect (e.g., alveolar-capillary block due to Ayerza's syndrome, granuloma, fibrosis or oedema).
C. HEART DISEASE a) Congenital b) Acquired—particularly mitral stenosis	3) a) Shunting of venous blood into arterial channels (e.g., congenital heart disease, A-V aneurysm). ? ? Alveolar diffusion defect.
D. RESPIRATORY CENTER DYSFUNCTION	4) Hypoventilation leading to low alveolar pO_2. May include syndrome of obesity with polycythemia.
E. CHRONIC METHEMOGLOBINEMIA OR SULFHEMOGLOBINEMIA, IDIOPATHIC OR ACQUIRED (e.g., anilines)	5) Altered hemoglobin decreases oxygen-carrying capacity of blood and O_2 dissociation curve shifts to the left.
II. NON-HYPOXEMIC ABSOLUTE POLYCYTHEMIA	Arterial O_2 saturation normal.
A. POLYCYTHEMIA VERA (ERYTHREMIA)	Possibly on basis of erythropoietic hormone—pathology unknown.
B. NEUROGENIC POLYCYTHEMIA	Associated with brain lesions such as subtentorial tumors. Observations of arterial oxygen saturation not reported.[19]
III. RELATIVE POLYCYTHEMIA	Decreased plasma volume leading to polycythemia with normal oxygen saturation. Observed in—
A. ACUTE	
B. CHRONIC a) Adrenal Insufficiency b) Idiopathic (Stress) Polycythemia	1) Sudden excessive loss of fluid from body as in prolonged vomiting or diarrhea. 2) Extravascular and intracellular fluid shifts as in "Shock." 3) Pathophysiology of chronic "Stress" type is unknown.
C. OTHER ENDOCRINE DISEASE (e.g., Cushing's Disease)	Only a few blood volumes reported; most of these showed relative polycythemia.

At the age of 16 he had rheumatic fever for three to four months. At no time since then had he been found to suffer from rheumatic heart disease. He had always been nervous and was subject to intermittent depression with crying spells and obsessive tendencies. For three years before admission he had been exposed to yellow phosphorus. His job required him to pack this phosphorus into large drums for shipping purposes. At the same time there was some questionable exposure to lead in paint and to paint thinners and removers. Otherwise, his past and functional histories were irrelevant.

On physical examination he was a stocky man, mildly overweight, with a plethoric face. The sclerae, conjunctivae and oral mucous membranes were injected. The right fundus showed some distention of retinal arteries and veins. The left fundus showed a thrombosis of the central retinal vein with multiple hemorrhages. He was in no respiratory distress. There was no glandular enlargement. He was comfortable when supine. His blood pressure varied from 145 to 150 over 85 to 90. The lungs were normal to examination. The heart was

not enlarged. Its rate and rhythm were normal and there were no murmurs. The abdomen was essentially negative. The liver and spleen were not palpable and no abdominal masses were present. Genital, neuromuscular and skeletal examinations were negative. The gums showed no lead line.

Hematologic examination showed a hemoglobin of 19.9 Gm. per cent, a packed cell volume of 68 per cent, a red cell count of 6,400,000, M.C.V. 106 cu. microns, M.C.H. 31 $\mu\mu g$ and M.C.H.C. 29 per cent. Reticulocytes were less than 1 per cent. Sedimentation rate was 0 (Wintrobe) in one hour. The total white count was 9,200 with 2 per cent (184) band forms, 70 per cent (6440) neutrophils, 4 per cent (368) basophils, 1 per cent (92) eosinophils, 8 per cent (736) monocytes and 15 per cent (1380) lymphocytes. Platelets, bleeding time, clotting time, prothrombic activity and the Rumpel Leedes test were normal. Fragility of the red cells to hypotonic saline was normal. In the differential smears a few red cells were seen which seemed slightly larger than normal, but no oval well-hemoglobinated macrocytes were present. No target cells were found. Sternal bone marrow aspiration revealed normal cellularity and the only abnormalities were the presence of a slight increase of reticulum cells and possibly a slight increase of eosinophilic granulocytes.

Laboratory investigations showed the serum potassium, calcium, alkaline phosphatase, A.C. blood sugar, N.P.N., total protein, albumin and globulin, the cephalin cholesterol and thymol flocculation tests and thymol turbidity to be within normal limits. The urinalysis was entirely normal. The direct serum bilirubin was 0.7 mg. per cent and total serum bilirubin was 1.3 mg. per cent. A twelve-lead electrocardiogram was entirely normal. X-ray of the chest suggested a slight increase of density of the skeletal structures including the ribs, clavicles and thoracic vertebrae. Otherwise the chest X-ray was negative. Because of the history of exposure to phosphorus further X-rays were taken of the long bones including the area from the portion of the pelvis immediately above the hip joints to the distal third of the leg on each side. The shaft of the femur presented a heavy cortex on the medial aspect with some relative reduction of the medullary portion of the bone. A full dental series was taken and the only abnormality was an area of rarefaction around the root of the right upper central incisor. X-rays of the jaws, the hands and both feet were entirely normal. The Wassermann test was negative.

Detailed pulmonary function studies were performed on several occasions and are depicted in table 2.

A detailed neurologic examination was completely negative.

An electroencephalogram, including selected basal leads, was normal.

On February 6, the blood volume as determined by the P_{32} tagged erythrocyte method was found to be 5760 ml. (71.4 ml./Kilo). The red cell mass was 3917 ml. (48.5 ml./Kilo) with a hematocrit of 68 per cent and the plasma volume was 1843 ml. (22.8 ml./Kilo). The normal values according to Berlin et al.[1] are: 69.0 ml./Kilo for total blood volume, 29.9 ml./Kilo for red cell mass and 38.7 ml./Kilo for plasma volume.

On February 15, a repeat total blood volume of 5798 ml. (71.8 ml/Kilo) confirmed the finding of February 6. At this time there was a normal circulation time of 12 seconds. On February 19, 20 and 24, phlebotomies of 500 ml. each were performed. On March 1, 1954, the total blood volume was 4922 ml. (61 ml./Kilo) with a hematocrit of 54 per cent, a hemoglobin of 15.6 Gm. per cent and R.B.C. of 5,100,000; the red cell mass was 2658 ml. (32.9 ml./Kilo) and the plasma volume was 2264 ml. (28.0 ml./Kilo). Thus, the phlebotomies reduced the red cell mass from 162 per cent of expected average to 110 per cent; they raised the plasma volume from 59 per cent to 72.5 per cent of expected average, while the total blood volume was lowered only from 103 per cent to 88 per cent of expected average. Concomitantly, the patient improved clinically and became asymptomatic.

After the phlebotomies the arterial oxygen saturation and the carbon dioxide content of the blood failed to show a significant return toward normal.

While in hospital, an effort was made to train him to breathe more deeply and deliberately. On discharge, from Hospital March 3, reassessment at the end of six months was recommended to his physician, particularly as regards the desirability of P_{32} therapy. On May 19, 1954, his doctor wrote that he still complained of easy fatigability, that his hematocrit on March 18 was 50 per cent and on May 19 was 56 per cent.

TABLE 2

A. LUNG VOLUMES:	PREDICTED NORMAL	ACTUAL VALUE
Total Capacity	5,340 ml.	6,266 ml.
Vital Capacity	4,090 ml.	4,913 ml.
Inspiratory Capacity		3,201 ml.
Expiratory Reserve Vol.		1,500 ml.
Residual Volume	1,250 ml.	1,353 ml.
$\frac{\text{Residual Volume}}{\text{Total Capacity}} \times 100$	23.4	21.6
Dead Space	150 to 200 ml.	166 ml.
Tidal Volume	500 to 600 ml.	265 ml.
B. VENTILATION STUDIES:	PREDICTED NORMAL	ACTUAL VALUE
Respiratory rate/min.	11 to 14	23.8
Ventilation at rest/min./M^2 Body Surface	3 to 4 L.	3.3 L.
Alveolar Ventilation at rest/min./M^2 B.S.	2 to 2.5 L.	1.24 L.
Maximum Breathing Capacity	130 L/min.	137.5 L/min.
Index of Intrapulmonary Mixing	2.5%	5.8%

C. BLOOD GAS STUDIES:

Date	Conditions	Results				
		Alveolar Ventilation L min/M^2 B.S.	Art. O_2 Sat. %	CO_2 Content Vols. %	P_{CO} MM_{HG}	pH
11/2/54	At rest breathing room air	1.24 L.	86.2	59.8	58	7.38
11/2/54	At rest hyperventilating room air	—	100.	47.	34	7.53
16/2/54	At rest breathing room air	1.3 L.	85.4	64.5	60	7.40
16/2/54	At rest breathing 100% O_2	0.4 L.	95.	68.	72	7.33
16/2/54	At rest breathing 30% O_2 + 5% CO_2					
	1st to 5th min.	1.3 L.				
	9th to 13th min.	2.3 L.	94.2	66.	69	7.35
24/2/54	At rest breathing room air after 1 L phlebotomy.	—	89.3	63.	63	7.36

Respiratory Function Studies

METHODS: A 9-liter Collins respirometer was used to determine the vital capacity and its subdivisions and the maximum breathing capacity. The residual volume was obtained from the functional residual volume by the nitrogen dilution method of Baldwin, Cournand and Richards.[2] The index of intrapulmonary mixing, which is the percentage of nitrogen in an alveolar air sample after breathing oxygen for seven minutes, was also obtained by this method. The physiologic dead space was calculated by using Bohr's formula[3] and substituting arterial for alveolar pCO_2. Ventilation studies were done, unless otherwise stated, while breathing room air from a plastic bag in a rigid air-tight box. With a Benedict-Roth spirometer in the circuit continuous readings of ventilation can be made by this method as described by Donald and Christie.[4] Determinations of the volume of ventilation while breathing room air, oxygen, and oxygen and carbon dioxide gas mixture, were made over a five minute period when the patient had reached a steady state.

Expired air was collected in a Douglas bag during a 5 minute period, breathing room air. Analyses of CO_2 and O_2 content of this expired air were used to calculate the respiratory quotient.

TABLE 3

Respiratory Quotient 1.15	Alv. Vent. L/Min/M² B.S. 1.7
O_2 Absorption ml/Min/M² B.S. 124	Total Vent. L/Min/M² B.S. 3.8
CO_2 Eliminated ml/Min./M² B.S. 143	Ventilation Equivalent 3.1

Arterial blood was drawn during the steady state of ventilation and analyzed for oxygen content, oxygen capacity and carbon dioxide content by the method of Van Slyke and Neill.[5] Carbon dioxide tension was calculated from the nomogram or line chart for the acid-base balance of human whole blood at 37 C. by Singer and Hastings.[6] Whole blood pH was determined by using the Beckman pH meter with the glass electrode surrounded by water at 37 C.[7] An ear oximeter of the Wood type[8, 9] was used to show rapid changes in oxygen saturation while the patient voluntarily increased his tidal volume without increasing his minute ventilation.

RESULTS AND DISCUSSION

In polycythemia vera and in secondary absolute polycythemia the increase of red cell count, hematocrit, hemoglobin, total red cell volume and normoblastosis of the bone marrow, in the presence of normal red cell survival, provide evidence of increased erythropoiesis. In polycythemia vera the blood and bone marrow findings also indicate that there is an increased granulopoiesis and platelet production which is usually absent in absolute secondary polycythemia. An elevation of mean corpuscular volume such as found in this patient is rare in polycythemia vera. Macrocytosis and elevation of the mean corpuscular volume has been observed in individuals having prolonged decrease of arterial oxygen saturation.[10] Data are shown in table 4 from 10 patients with chronic pulmonary disease having elevated mean corpuscular volumes and hypoxemia. Half of the

TABLE 4.—*Red Cell Values in Patients with Hypoxemia and Hypercapnia*

Patient, No., Sex, Diagnosis	Red Cell Count millions/ Cu. mm.	Packed Cell Volume %	Mean Corp. Vol. Cu microns	CO_2 Content %	pCO_2 %	Arterial O_2 Saturation %
1. ♂ Pulmonary emphysema	6.6	77	117	55.6		82.9
	5.7	60	105	59.0		87.4
	6.06	64	106	57.9	64.2	79.5
2. ♂ Pulmonary fibrosis. Pulmonary emphysema ?	6.6	64	97	58.4		75.5
	5.3	57	108	64.1		81.5
	5.4	57	105	65.0	68.0	75.4
3. ♂ Pulmonary emphysema	5.0	52	104	55.4	47	89.0
4. ♂ Pulmonary emphysema	4.5	48	107	69.8		91.7
	4.5	51.5	114	72.5		88.3
	4.56	46.5	100	72.6	75.7	82.6
	4.04	46.5	116	69.4	69.0	83.6
5. ♂ Pulmonary emphysema	6.4	61.0	95.3	77.7		51.9
	5.3	51.0	96.0	69.1		83.7
6. ♂ Pulmonary emphysema	4.85	53.5	110	68.8		90.2
7. ♂ Pulmonary emphysema	6.24	63.5	102	57.6		69.2
	6.8	74	109	54.1	64	74.8
8. ♀ Pulmonary emphysema	4.8	54	112	64.4	67.8	55.0
9. ♂ Pulmonary emphysema	6.2	66	106	57.7		82.0
10. ♂ Pulmonary emphysema	3.6	48	131	68.8		77.5

patients had secondary polycythemia. The red cell counts and packed cell volumes were not above normal in the other half. From these data it is impossible to determine the possible relationship of elevation of the arterial CO_2 to increase of the M.C.V. nor did the degree of increase of the M.C.V. apparently parallel the degree of hypoxemia. Additional studies on this problem will be reported separately. The hematologic findings and the absence of splenomegaly in this patient suggested the presence of secondary polycythemia and consequently respiratory function tests were carried out.

The basic defect in respiratory function (see table 2) was a marked degree of alveolar hypoventilation. The very small tidal air of 265 ml. was calculated as an average over a 5 minute period with the patient in a steady state of rest. Since the dead space was found to be 166 ml., the calculated amount of air reaching the alveoli per breath was only 99 ml. Since the patient averaged 23.8 breaths per minute over the same 5 minute period, the total alveolar ventilation per minute was only 1.24 L./M.^{2}B.S. (liters per square meter of body surface). This theoretic estimation of the alveolar ventilation is probably not exact, since inspired gas is believed to travel through the bronchial tubes with a cone rather than a square front, but it serves to indicate quantitatively the inadequate alveolar ventilation. The hypoventilation was responsible for a moderate degree of hypoxemia (arterial oxygen saturation of 86 per cent) and a retention of carbon dioxide (CO_2 content = 59.8 vols. %; pCO_2 = 58 mm. hg.). The CO_2 excess was compensated by renal retention of base as is evidenced by the normal pH.

The other tests of lung function failed to reveal any evidence of pulmonary insufficiency. The lung volumes and maximum breathing capacity were within the expected range of normal. The increase in index of intrapulmonary mixing can be explained on the basis of inadequate alveolar ventilation as a whole, rather than on any localized impairment in distribution of inspired air. A very short period of voluntary hyperventilation succeeded in raising the arterial O_2 saturation and in lowering the CO_2 content to normal. The patient was also able to improve his alveolar ventilation voluntarily by simply increasing his tidal volume without increasing his total ventilation per minute. This was done by slowing the respiratory rate to 10–12 per minute. In this way the minute ventilation was not increased, but ventilation of the alveoli was considerably improved. The improved alveolar ventilation so produced resulted in a rise of arterial oxygen saturation to a normal value.

To determine the relationships of ventilation to oxygen absorption and of oxygen absorption to carbon dioxide exhaled, the volume and gaseous content of expired air collected over a 5 minute period were analyzed. During this study an ear oximeter recorded continuously O_2 saturation values of 87 to 88 per cent. The results are shown in table 3 and suggest that the patient was actually ventilating to a greater extent than he normally did, since the respiratory quotient is greater than one and the patient ventilated over 3 L./min., while absorbing 100 ml. of O_2 (ventilation equivalent—normally less than 3 L./min./100 ml. of O_2 absorbed). The minute ventilation and alveolar ventilation are also somewhat higher than had been previously recorded in this patient.

Studies were carried out to determine the patient's response to 100 per cent oxygen, and to a mixture of 30 per cent oxygen and 5 per cent CO_2. The subject

with a normal respiratory function responds on inhaling the former gas by little or no change in ventilation and by full oxygen saturation of arterial blood without significant alteration in CO_2 content or pH. Five per cent carbon dioxide, on the other hand, will produce in the normal individual a marked hyperventilation with a little rise in both arterial oxygen saturation and CO_2 content, and with a moderate drop in pH.

The normally functioning respiratory center is remarkably sensitive to even the slightest increase in blood pCO_2 and responds by initiating a vigorous hyperventilation. The response elicited in the patient under discussion (see table 2) was identical to that seen in patients with advanced emphysema showing hypoxemia and hypercapnia.[11, 12] In this advanced stage of pulmonary insufficiency a marked decrease in ventilation will occur on breathing high concentration of oxygen and further hypercapnia and respiratory acidosis result despite the correction of the hypoxemia. On the other hand, these patients show a very poor and delayed response to the inhalation of carbon dioxide.[13] These abnormal responses, so characteristic of severe emphysema, were observed in our patient when he was exposed to 100 per cent oxygen and to 5 per cent carbon dioxide.

How ventilation is impaired by inhalation of high concentrations of oxygen in hypoxemic patients is not known. A logical interpretation is that the hypoxemia serves as a stimulus to the carotid body, which in turn reflexly controls ventilation through the respiratory center in the medulla and pons. The respiratory center is itself depressed by the high level of carbon dioxide in the blood. The administration of oxygen removes the stimulus to the carotid body and a sudden decrease in ventilation with consequent further hypercapnia and acidosis results.

There can be no question that this patient has an abnormally functioning respiratory center. Despite a considerable degree of hypercapnia this patient showed a marked hypoventilation of his alveolar spaces. Somewhat similar cases have been reported by Newman et al.[14] who suggest that the respiratory center damage may be secondary to long-standing polycythemia vera. It would appear more reasonable in the cases reported by Newman et al., as well as in our case, to assume that the primary defect was in the respiratory center which caused alveolar hypoventilation, a lowered pO_2 and a raised pCO_2. The hypoxemia so produced in time resulted in a secondary form of absolute polycythemia.

More recently, reports have been appearing in the literature of a similar syndrome associated with obesity,[15-17] and Ratto et al. have published a case report of a patient with polycythemia and anoxemia which very closely resembles our own case.[18]

Summary

1. An unusual case of absolute polycythemia associated with hypoxemia, probably resulting from abnormal function of the respiratory center has been presented.

2. The mechanism of development of this type of polycythemia has been discussed.

3. A classification of polycythemia on the basis of blood volume and arterial oxygen saturation has been suggested.

SUMMARIO IN INTERLINGUA

1. Es presentate un caso inusual de absolute polycythemia associate con hypoxemia, resultante probabilemente ab un function anormal del centro respiratori.

2. Es discutite le mechanismo del disveloppamento de iste typo de polycythemia.

3. Es proponite un classification de polycythemia super le base del volumine de sanguine e del saturation oxygenic arterial.

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