

Unexplained underventilation of the lungs

MARTIN W. McNICOL¹ AND N. B. PRIDE²

From the Department of Medicine, Hammersmith Hospital, London W.12

The lungs normally are ventilated with enough air to dilute the carbon dioxide produced by metabolism, so that the partial pressure of carbon dioxide (PCO_2) in the alveoli is kept remarkably close to 40 mm. Hg. It is the alveolar ventilation and not the total amount of air going in or out of the mouth (or 'minute-volume') that determines the PCO_2 because a varying proportion of the total ventilation goes to the dead space and takes no part in gas exchange. Alveolar ventilation will be inadequate when total ventilation is reduced but will also be inadequate when there is normal or even increased total ventilation if dead space ventilation is increased. Such an increase in dead space ventilation will occur if breathing is rapid and shallow and mainly into the upper anatomical dead space, or if there is ventilation of alveoli poorly supplied with blood. Little gas exchange takes place in poorly perfused alveoli, so that these alveoli can be regarded as additional 'functional' dead space. In all cases inadequacy of alveolar ventilation will result in a rise in alveolar PCO_2 ; and because of the high diffusibility of carbon dioxide the arterial and alveolar PCO_2 are virtually identical so that the arterial PCO_2 will also be increased.

CAUSES OF UNDERVENTILATION

Chronic alveolar underventilation has numerous causes which may be grouped as follows:

ABNORMALITY OF LUNGS OR THORACIC CAGE Underventilation may occur with any condition which impairs ventilatory capacity, and most commonly this impairment is due to airways obstruction, as in chronic bronchitis. It has been suggested that in patients with severe airways obstruction the respiratory centre becomes insensitive to carbon dioxide (Prime and Westlake, 1954), but more recent work (Cherniack and Snidal, 1956; Richards, Fritts, and Davis, 1958) suggests that the impaired movement of the chest and lungs as bellows and the increased alveolar dead space are sufficient to account for

carbon dioxide retention without postulating impaired sensitivity to carbon dioxide. Some cases of underventilation occur with a restrictive impairment of ventilatory capacity, such as kyphoscoliosis or pleural thickening, and underventilation may also occur when there is neuromuscular weakness, as in myasthenia gravis, motor neurone disease, or spinal poliomyelitis. All this common group have an impaired ventilatory capacity.

DISEASE OF THE CENTRAL NERVOUS SYSTEM There have been reports of underventilation in bulbar poliomyelitis (Sarnoff, Whittenberger, and Affeldt, 1951), after encephalitis (Efron and Kent, 1957; Garlind and Linderholm, 1958), and in bulbar syringomyelia (case 4 of Rodman, Resnick, Berkowitz, Fennelly, and Olivia, 1962), but these causes are all uncommon. Underventilation may also occur after the administration of drugs which depress the central nervous system. In this group the ventilatory capacity is not reduced.

OBESITY Since 1951 there have been numerous reports of underventilation in extremely obese patients; sometimes there has been some reduction in lung volumes and ventilatory capacity but this is usually slight.

UNEXPLAINED In 1959 Rodman and Close reviewed four previous reports (Ratto, Briscoe, Morton, and Comroe, 1955; Massachusetts General Hospital, 1956; Pare and Lowenstein, 1956; Richter, West, and Fishman, 1957) and described a fifth case in which there was underventilation in subjects of normal weight and without abnormality of the thoracic cage or lungs. This they called the 'primary hypoventilation syndrome'. Since then Laddom and Scherrer (1959), Lawrence (1959), Naeye (1961), and Rodman *et al.* (1962) have reported a further five cases. It is possible that the fifth patient of Newman, Feltman, and Devlin (1951), who was described as 'moderately obese', was another example.

During the last two years we have seen four patients, not grossly obese, who had chronic

¹ Present address: Central Middlesex Hospital, London, N.W.10

² Present address: Cardiovascular Research Institute, University of California Medical Center, San Francisco 22

alveolar underventilation not adequately explained by their lung disease. They form an interesting group who tended to have periods of drowsiness and episodes of apnoea. We here report their case histories and the results of some lung function tests to show how this condition may be distinguished from 'chronic bronchitis and emphysema' with which it can easily be confused.

CASE REPORTS

CASE 1 C.P., a 53-year-old policeman, had been overweight (90 to 100 kg.) from the age of 45 years. In December 1956 he was seen by Dr. M. O. J. Gibson at the Bow Arrow Hospital as a contact of a case of pulmonary tuberculosis. His only symptom then was a mild morning cough but he was noted to be polycythaemic (haemoglobin 19.2 g./100 ml.). A chest radiograph showed no sign of tuberculosis but there was a shadow at the right lower hilum which appeared on tomography to be an aneurysmal dilatation of the right lower lobe pulmonary artery. In June 1957 he had acute bronchitis and a comment was made on his 'astounding cyanosis'. He was admitted to the Bow Arrow Hospital in November 1957 with a further attack of acute bronchitis. Though his dyspnoea was only slight the acute bronchitis was followed by the rapid onset of right heart failure with gross oedema. He was

observed to be drowsy and admitted to undue sleepiness and nocturnal sweating in the preceding year.

On examination the hands were warm and there was central cyanosis. The pulse was regular and the blood pressure 110/85 mm. Hg; there was oedema of the legs and over the sacrum. The jugular venous pressure was raised, and the pulse wave showed a prominent 'a' wave. A prominent right ventricular impulse was palpable, and there was accentuation of the pulmonary component of the second sound and a loud right atrial sound but no murmurs. A few crepitations were present at both lung bases. There was no abnormality in the central nervous system.

Investigations The haemoglobin was 17.8 g./100 ml. A chest radiograph showed large pulmonary arteries and an increased right hilar shadow with an enlarged right ventricle (see Fig. 1). There was right axis deviation, P pulmonale and evidence of right ventricular hypertrophy on the electrocardiogram. Arterial blood analysis showed an oxygen saturation of 72% and a raised carbon dioxide content, but no measurement was made of the PCO_2 .

It was concluded that he had emphysema with chronic respiratory failure and cor pulmonale. The heart failure responded to digoxin and mersalyl and he remained relatively well except for a bout of paroxysmal tachycardia with anginal pain in February 1958 and two further attacks of acute bronchitis in March 1958 and January 1959. In July 1959 he was admitted to Hammer-

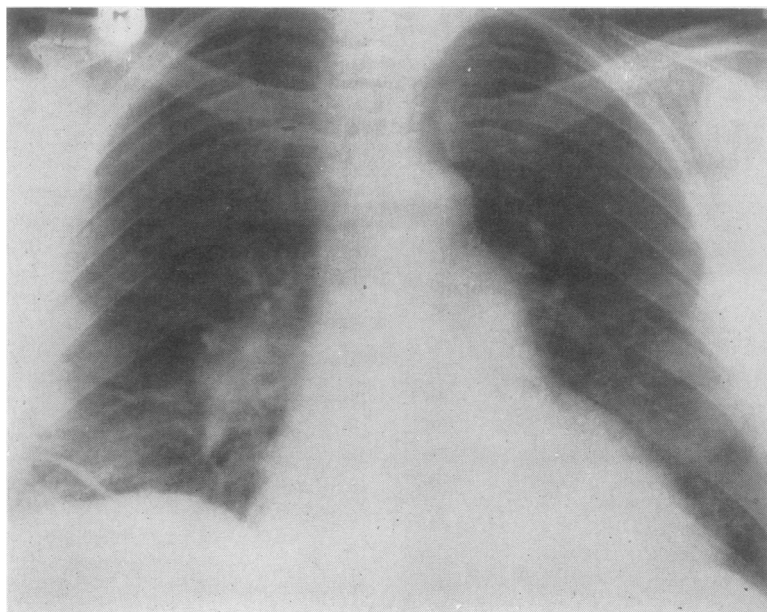


FIG. 1. Case 1. Postero-anterior chest radiograph showing an enlarged heart, large main pulmonary arteries, and an opacity at the lower part of the right hilum.

smith Hospital with a recurrence of right heart failure; dyspnoea was still slight.

Examination showed no change in the physical signs.

Further investigations then revealed a red blood cell volume of 7,000 ml. and a plasma volume of 3,400 ml. At this time the haemoglobin was 21 g./100 ml. and the white blood cell and platelet counts were normal. The venous plasma total carbon dioxide content (TCO_2) was 38 mM./l., and arterial blood analysis showed that the oxygen saturation was 74%, the pH was 7.29, and the PCO_2 80 mm. Hg.

He again responded to digoxin and mersalyl. As his oedema-free weight was 97 kg. he was placed on a reducing diet.

In October 1959 he had a further attack of acute bronchitis followed within 24 hours by gross underventilation and coma. On admission he was very deeply cyanosed and was sweating profusely, and there was widespread muscle twitching. Heart failure had not recurred. An intravenous infusion of nikethamide was started and tracheostomy was performed; oxygen and antibiotics were given and digoxin and mersalyl were continued. He made a rapid recovery. Nine days later, however, there was a further sudden episode of virtual apnoea and coma; this relapse was not associated with infection. The tracheostomy was re-opened and a further nikethamide infusion was given, but there was little response and he required intermittent positive pressure respiration from a Radcliffe respirator for the next four days. He again recovered and was reasonably well until April 1960 when he had a recurrence of right heart failure. In October 1960 he had an episode of syncope on effort. In December 1960 he had a left basal pulmonary infarct and was noted to have an ill-sustained nystagmus on looking to the right; this sign disappeared within a week and at no other time have there been abnormal neurological signs. In January 1962 he had a right lower lobe pneumonia, a recurrence of heart failure, and a left femoral vein thrombosis. Clubbing of the fingers and toes, previously absent, had developed. On three occasions during this illness he became very drowsy but responded to intravenous infusion of nikethamide. He remains chronically cyanosed and has a mixed venous PCO_2 between 80 and 95 mm. Hg (the normal value is less than 54 mm. Hg) despite which he feels relatively well and remains at work. A pulmonary systolic murmur has appeared, but the opacity at the right hilum on the chest radiograph has remained unchanged over the last five years.

Treatment Treatment has been directed to correcting the heart failure, obesity, polycythaemia, and underventilation.

The heart failure has responded well to digoxin and mersalyl.

His weight was reduced by 9 kg. to 88 kg. without a change in the PCO_2 .

The polycythaemia was at first treated by repeated venesection but by April 1960 he had a mild iron deficiency anaemia with a grossly elevated packed cell volume (P.C.V.) and he was treated with radioactive

phosphorus (6 mc ^{32}P) and oral iron. A further dose of ^{32}P was given in December 1960. The haemoglobin and P.C.V. have been reduced but are still above normal.

It was thought that thrombosis in the right lower pulmonary artery associated with the polycythaemia might have accounted for the radiological opacity but no local alteration in blood flow was shown by regional studies using radioactive gases. In addition he has had a probable left external jugular vein thrombosis, a pulmonary infarct, and a femoral vein thrombosis. For these incidents he has been treated with phenindione and is now being maintained on long-term anticoagulant treatment. Treatment of the polycythaemia has not reduced the PCO_2 .

Many central nervous system stimulants and respiratory stimulants have been tried but only nikethamide has been of benefit. Five intravenous infusions of nikethamide have been given. On two occasions tracheostomy was also performed; the other three infusions of doses between 25 and 40 mg./minute resulted in improvements in consciousness and sustained falls of mixed venous PCO_2 of 9, 26, and 19 mm. Hg. No reduction in PCO_2 followed maintained oral treatment with caffeine, dexamphetamine, salicylates, amiphenazole, or the carbonic anhydrase inhibitors, acetazolamide and dichlorphenamide. He proved a resistant subject to hypnosis, and daily periods of voluntary overventilation did not help. With intermittent positive pressure respiration (I.P.P.R.) by a Radcliffe respirator the mixed venous PCO_2 was maintained at 50 to 55 mm. Hg for several days, but, despite gradual weaning, the PCO_2 soon regained its former level of over 80 mm. when I.P.P.R. was discontinued. An attempt at I.P.P.R. with a patient-triggered apparatus failed to increase the ventilation as he closed his glottis against the machine.

CASE 2 A. A., a 56-year-old master bricklayer (this case is being reported in more detail elsewhere by Dr. V. Wynn), was first seen at St. Mary's Hospital at the age of 51 when he complained of breathlessness on effort. He admitted to cough and phlegm for several years but had not noticed the gross ankle oedema then present. He was obese (95 kg.). The family history of obesity was striking; his father was about 95 kg. and died of heart failure, and his mother weighed 140 kg. The patient has five brothers and two sons and all of these are heavier than he but without symptoms. Despite the right heart failure, the heart sounds then were normal and there were no murmurs. A diagnosis of cor pulmonale on a basis of chronic bronchitis and emphysema exacerbated by obesity was made and he made an excellent response to mersalyl and a low salt and low calorie diet. In January 1957 he was free of all symptoms except cough. There were no abnormal signs on examination and his weight had fallen 7 kg. to 88 kg.; but the haemoglobin was 20.8 g./100 ml., arterial blood pH 7.30, and PCO_2 69 mm. Hg. In January 1958 he had an attack of acute bronchitis followed by heart failure, and this sequence of events recurred in March 1959; each episode responded well to antibiotics, digoxin, and diuretics. He was well and at work until November 1960 when

heart failure recurred. On recovery from this some further investigations were made at Hammersmith Hospital in December 1960.

Examination then showed moderate obesity (78 kg.). There was no clubbing. The only abnormalities in the cardiovascular system were accentuation of the pulmonary component of the second sound and a grade 2 systolic murmur, increasing on inspiration, at the left sternal edge. The blood pressure was 90/60 mm. Hg and no abnormalities were found in the rest of the examination.

Investigations The haemoglobin was 17 g./100 ml. with a packed cell volume of 53%. The venous plasma total carbon dioxide content was 36 mM./l. A chest radiograph showed a large heart and main pulmonary arteries. There was incomplete right bundle branch block on the electrocardiogram.

Course His weight has been reduced by 17 kg. in the last five years but the PCO_2 has always been abnormal except for a period when he was treated with dichlorophenamide.

CASE 3 L. W., a 51-year-old painter and decorator, had developed at the age of 40 a winter cough with frequent episodes of purulent sputum. For seven years he had noticed slight but slowly progressing dyspnoea of effort. He had had no ankle swelling. For at least four months he had had frequent but mild headaches. On direct questioning he admitted to undue drowsiness and frequent night sweats during the past year.

On 10 November 1960 he was found unconscious at home and was admitted to the Central Middlesex Hospital under the care of Dr. R. Asher. He was then semiconscious and cyanosed and had early papilloedema; lumbar puncture revealed a normal cerebrospinal fluid at a pressure of 230 mm. H_2O . The mixed venous PCO_2 was 75 mm. Hg. In the next few days he complained of headache and he had several further episodes in which apnoea was followed by coma. He invariably recovered from these episodes when given intravenous nikethamide. After 10 days he had no further episodes of coma nor any headache. The papilloedema regressed completely and the only abnormal finding remaining in the central nervous system was diplopia on looking to the left and upwards. An electrocardiogram showed non-specific changes; bilateral carotid angiography was normal. The mixed venous PCO_2 however remained persistently high.

He was admitted to Hammersmith Hospital for investigation in early January 1961; his only complaint then was of diplopia.

On examination there was no cyanosis or clubbing. He weighed 80.5 kg. The blood pressure was 150/80 mm. Hg and no abnormality was found in the cardiovascular system. The sputum was mucopurulent and there were occasional basal wheezes. There was weakness of the left medial rectus, superior oblique, and inferior oblique muscles.

Investigations The haemoglobin was 15.1 g./100 ml. with a packed cell volume of 51%. The venous plasma urea and electrolytes were normal except for a total

carbon dioxide content of 33 mM. There was patchy consolidation in the right middle and lower zones on the chest radiograph but no increase in heart size. An electrocardiogram showed slight clockwise rotation but no evidence of right ventricular hypertrophy. An electroencephalogram was normal but the mixed venous PCO_2 was still raised to 60 mm. Hg.

Course In the 18 months since first being seen he has had no further episodes of coma and has returned to work. The mixed venous PCO_2 varies between 50 and 59 mm. Hg; nevertheless, although he was quite free of symptoms when he was seen as an out-patient in September 1961, he still rapidly became cyanosed on exercise and was able to hold his breath for one and three quarter minutes without discomfort but with the development of cyanosis. The diplopia has resolved and no other neurological signs have developed. It seemed probable that the episodes of coma had been precipitated by acute underventilation with consequent hypoxia, CO_2 retention, and acidaemia.

CASE 4 W. N., a 48-year-old man, had had a chronic winter cough with mucoid sputum for many years, but he had never lost time from his work as a heavy labourer. In April 1961 he noticed the development of ankle swelling; he was admitted to Bethnal Green Hospital and was subsequently transferred to the London Chest Hospital under Dr. J. Smart. He denied having breathlessness prior to the ankle swelling, although he complained of it while he was in hospital. There had been no haemoptysis or chest pain and no evidence of a respiratory infection. For some months he had suffered from morning headaches. He was transferred to Hammersmith Hospital in June 1961.

Examination showed a tall, spare man weighing 59 kg. with long fingers, large facial features and feet, and a high arched palate. There was central cyanosis, worse when he was asleep when he also showed sweating. The hands were warm but there was no clubbing. There was ankle oedema, and the jugular venous pulse was elevated to 3 cm. above the sternal angle and showed a prominent 'a' wave. The blood pressure was 150/70 mm. Hg, there was an obvious right ventricular impulse and a pulmonary ejection click and grade 2 systolic murmur with accentuation of the pulmonary component of the second sound. There were wheezes all over the chest but no abnormality in the central nervous system.

Investigations The haemoglobin was 13 g./100 ml., and the packed cell volume was 47.5%. The white blood cell and platelet counts were normal as were the venous plasma electrolytes and urea except for a total carbon dioxide content of 39 mM. The chest radiograph showed pleural thickening on the right side in the fissures and at the costophrenic angle. There was also gross enlargement of the right side of the heart and of the main pulmonary arteries (Fig. 2). An electrocardiogram showed incomplete right bundle branch block, grade 1 right ventricular hypertrophy, and inversion of the T waves in leads II, III, and aVf. There was a moderately

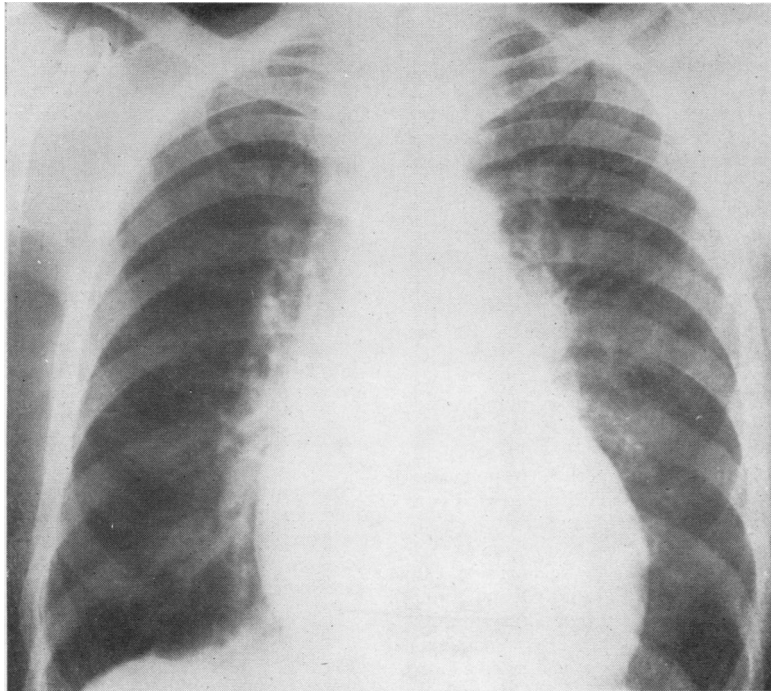


FIG. 2. Case 4. Postero-anterior chest radiograph showing enlarged heart and large main pulmonary arteries with right-sided pleural thickening.

severe generalized abnormality of the electroencephalogram. The mixed venous P_{CO_2} was 78 mm. Hg.

Course The heart failure was treated with salt restriction, digoxin, and chlorothiazide, and a 7 kg. diuresis resulted. The mixed venous P_{CO_2} fell from 78

to 66 mm. Hg. He became considerably more alert (it was evident that he had previously been unduly drowsy despite his denial of this); he was no longer dyspnoeic and had no further headaches.

The clinical features of the four cases are summarized in Table I.

TABLE I
CLINICAL FEATURES

Patient	Age (Yr.)	Weight		History				Examination				Chest Radiograph	Electro- cardiogram	Electro- encephalogram	Blood			
		kg.	% pred.	Headache	Somnolence	Blackouts	Night Sweats	Heart Failure	R.V. Impulse	Increased P_2	Right Atrial Sound				Pulmonary Systolic Murmur and Click	Venous Plasma TCO_2 (mM/l)	Hb (g./100 ml.)	P.C.V. (%)
C.P.	53	88.5	123	+	+	+	+	+	+	+	+	+	Large rt. ventricle; large main pulm. art., especially to right lower lobe	Rt. ventricular hypertrophy grade 3	Mild generalized abnormality	34	18	67
A.A.	56	78	119	-	+	-	-	+	-	+	-	-	Large rt. ventricle; large main pulm. art.	Incomplete rt. bundle branch block	-	36	17	53
L.W.	51	80.5	108	+	+	+	+	-	-	-	-	-	Normal	Normal	Mild generalized abnormality	33	15	51
W.N.	48	59	93	+	+	-	+	+	+	+	-	+	Large rt. atrium and ventricle; large main pulm. art.	Rt. ventricular hypertrophy grade 1	Moderately severe generalized abnormality	39	13	47

LUNG FUNCTION TESTS

METHODS All gas volumes were measured at ambient temperature and pressure (ranging from 18 to 23° C. and 746 to 770 mm. Hg) with the patients seated at rest unless otherwise stated. No patients had oedema or a raised jugular venous pressure when tested. Predicted weights were obtained from the tables given by Kemsley (1952), and the grading of signs of right ventricular hypertrophy on the electrocardiogram was by the criteria of Goodwin and Abdin (1959).

Ventilatory tests The forced expiratory volume in 1 second (F.E.V._{1.0}) was measured from a tracing obtained on a low resistance spirometer (Bernstein, D'Silva, and Mendel, 1952) with a drum speed of 2 cm./sec. Normal values used were from an unpublished series. The slow expiratory vital capacity (V.C.) was also measured. Both the F.E.V._{1.0} and V.C. were repeated after five minutes' inhalation of a 1% isoprenaline aerosol in oxygen. The F.E.V._{1.0} was expressed also as a percentage of the expiratory V.C. (F.E.V. % V.C.). Maximal voluntary ventilation (M.V.V.) was measured on the low resistance spirometer by persuading the patient to breathe as deeply and as rapidly as he could for 15 seconds and repeating this on five occasions; the highest value was accepted. The indirect maximal breathing capacity (ind. M.B.C.) was obtained in litres/minute by multiplying the F.E.V._{1.0} by 35; normal values were those of Needham, Rogan, and McDonald (1954) for M.V.V. The forced inspiratory volume in 1 second (F.I.V._{1.0}) was measured after maximal expiration. Maximal expiratory and inspiratory flow rates (M.E.F.R., M.I.F.R.) were measured as described by Comroe, Forster, DuBois, Briscoe, and Carlsen (1962). The resting ventilation (V_E) was measured at the mouth using the respirometer designed by Wright (1955). The subjects had been at rest semirecumbent for at least 20 minutes before this measurement. The normal values used were those of MacLeish (1960).

Total lung capacity and subdivisions These were measured by the closed-circuit helium dilution method (Gilson and Hugh-Jones, 1949). Normal values were predicted from the simplified regression formulae derived by Needham *et al.* (1954).

Carbon monoxide uptake The whole lung diffusing capacity (D_{LCO}) was measured by the single-breath method of Ogilvie, Forster, Blakemore, and Morton (1957). Normal values were predicted from the regression formula on surface area given by these authors. The results are the mean of at least three and usually five tests on the same day. The 'permeability' (K_{CO}) of Krogh (1915), which is a measure of carbon monoxide uptake per unit of lung volume, was calculated from the same data; the predicted normal figures used were those of McGrath and Thomson (1959).

Distribution of ventilation, blood flow, and ventilation-blood flow ratios These were measured by two methods.

The single-breath test devised by West, Fowler, Hugh-Jones, and O'Donnell (1957 a, b) was used with the modifications of the original authors described by Read (1959). In this test a mass spectrometer is used as a rapid gas analyser. Results for inequality of ventilation ($\frac{\dot{V}_A}{\dot{V}_A}$), inequality of blood flow ($\frac{\dot{Q}_C}{\dot{V}_A}$), and inequality of ventilation-blood flow ratios ($\frac{\dot{V}_A}{\dot{Q}_C}$) were compressed as rate of change (%) per 500 ml. of expirate.

In addition, at the time of arterial blood sampling the resting ventilation was measured and a three-minute collection of expired gas was made. The O₂ and CO₂ content of this gas was analysed with the micro-Scholander apparatus. The physiological dead space (V_D) was measured by use of the Bohr equation for CO₂:

$$V_D = \frac{P_{aCO_2} - P_{eCO_2}}{P_{aCO_2}} \times V_T,$$

where V_T = tidal volume in ml., P_{aCO₂} = arterial carbon dioxide tension, and P_{eCO₂} = carbon dioxide tension in mixed expired gas, both in mm. Hg. The dead space was also expressed as a ratio of the tidal volume (V_D/V_T). The alveolar ventilation (V_A) in litres/minute (B.T.P.S.) was calculated from the equation

$$V_A = \frac{V_{CO_2} \times 0.863}{P_{aCO_2}}$$

where V_{CO₂} is the CO₂ output/minute (S.T.P.D.). The difference between the alveolar and the arterial oxygen tensions was also calculated, the alveolar oxygen tension (P_{AO₂}) being obtained by the alveolar air equation (Riley and Cournand, 1949):

$$P_{AO_2} = P_{iO_2} - P_{aCO_2} \left(F_{iO_2} + \frac{1 - F_{iO_2}}{R} \right)$$

where P_{iO₂} = inspired oxygen tension (moist), F_{iO₂} = fractional oxygen concentration in inspired dry gas, and R = respiratory quotient.

Arterial blood This was sampled from an indwelling needle in the brachial artery while the patients were at rest and semirecumbent. Ventilation was measured at this time at the mouth with a Wright respirometer, and blood samples were collected over a period of one minute after the needle had been in the artery for at least 20 minutes and the ventilation had been at previously obtained resting levels for at least five minutes. The pH was measured immediately at 38° C. with an E.I.L. glass electrode and 'Vibron' electrometer. Oxygen content and capacity and carbon dioxide content were measured by the methods of Van Slyke and Neill (1924), and the arterial P_{CO₂} was derived from the nomogram of Singer and Hastings (1948). The arterial oxygen and carbon dioxide tensions (P_{aO₂} and P_{aCO₂}) were also measured when the patients were breathing room air by the modification of the bubble equilibration technique described by Strang (1961). In this method a mass spectrometer is used for the gas analysis of the bubble.

Mechanics A 15 cm. balloon was passed through the nose into the lower third of the oesophagus, and the changes in oesophageal pressure were measured

TABLE IIa
LUNG FUNCTION TESTS

Case	Ventilatory Capacity						Total Lung Capacity and Subdivisions						Carbon Monoxide Uptake		
	F.E.V. ₁₋₁₀ (l.)	F.E.V. ₁₋₁₀ After Isoprenaline (l.)	F.E.V. V.C. %	F.I.V. ₁₋₁₀ (l.)	M.E.F.R. (l./min.)	M.I.F.R. (l./min.)	Indirect M.B.C. (l./min.)	M.V.V. (l./min.)	T.L.C. (l.)	V.C. (l.)	I.C. (l.)	E.R.V. (l.)	R.V. (l.)	R.V. T.L.C. %	Dlco (ml./mm. Hg/min.)
C.P.	1.40	1.55	54	1.55	76	114	38	4.11	2.82	2.17	0.65	1.29	31	26.3	4.65
A.A.	1.30	1.35	52	1.50	31	104	45	4.03	1.62	1.19	0.43	2.39	59	30.9	5.66
L.W.	1.60	1.60	54	2.20	71	150	54	7.35	2.73	2.17	0.56	4.62	63	33.5	3.84
W.N.	1.45	1.55	47	2.80	84	200	35	6.68	2.57	1.67	0.90	4.11	61	29.1	3.52
Range of mean pred. normals	2.16- 3.02	2.16- 3.02	>65	>3.20	400	300	103- 112	5.81- 6.89	3.43- 4.16	2.51- 3.59	1.00- 1.15	2.24- 2.40	37- 40.5	28.0- 32.5	3.65- 3.84

TABLE IIb
LUNG FUNCTION TESTS

Case	Distribution of Ventilation and Blood Flow										Mechanics		Ear Oximetry		Exercise			
	VE* (l./ min.)	Rate (per min.)	VT (ml.)	VD (ml.)	VD VT	VA (l./ min.)	PAO ₂ - PaO ₂ (mm. HG)	VA VA (% change per 500 ml. expirate)	VA QC	VA VA	Airways Resist- ance (cm. H ₂ O/ l./sec.)	Dynamic Com- pliance (l./ cm.H ₂ O)	Resting	Volun- tary Over- Breath- ing (points)	Dyspnoea	Sweating	Desat- uration (points)	Max. Exercise Vent. (l./min.)
C.P.	6.0	20	300	147	0.49	3.22	18	26	13	3.7	0.21	Labile	+9	Slight	++	-8	32	34
A.A.	5.3	12	442	145	0.33	3.77	15	18	17	Normal	0.36	Labile	+9	Slight	ml	-12	24	31
L.W.	7.0	12	583	408	0.70	2.22	3	14	10	3.0	0.19	Slightly labile	+6	Slight	+	-14	26	34
W.N.	13.0	24.5	530	408	0.78	3.03	17	18	18	1.8	0.26	Labile	+10	Slight	++	-9	28	35
Range of mean pred. normals	8.2	17.6	466	< 160	< 0.30	4.20- 5.40	< 10	< 12	< 9	1.0-3.0	0.150- 0.350	Steady	+3	—	—	0	26	26

* The figures for resting ventilation, tidal-volume, and dead space in C.P., A.A., and L.W. were obtained on a different occasion from the results shown in Table III.

with an electromanometer. Flow was recorded by a Lilly pneumotachometer of negligible resistance, and the volume was obtained by electrical integration of this flow signal. Pressure, flow, and volume were recorded on a Sanborn four-channel recorder. Dynamic compliance and airways resistance were calculated during quiet breathing (Mead and Whittenberger, 1953).

Voluntary overbreathing This was performed for two minutes and measured by a Wright respirometer; changes in oxygen saturation were followed by ear oximetry and in two cases were confirmed by arterial blood analysis.

Standardized exercise test The step test described by Hugh-Jones and Lambert (1952) was used with a work load of 350 kg.M/min. which was sustained for five or six minutes. During the test ventilation was measured at the mouth by the Wright respirometer and changes in arterial oxygen saturation were followed by ear oximetry.

Response to CO₂ inhalation The minute ventilation, arterial PCO₂, and hydrogen ion activity ([H⁺]_a) were compared with the subjects breathing 100% O₂ and a 5% CO₂, 95% O₂ mixture. Measurements were made after the appropriate gas had been breathed for 20 minutes. The arterial hydrogen ion activity was expressed as moles × 10⁻⁹/litre (or nanoNormal, nN) and is the antilog of (8 - pH). The measurement of CO₂ response was made with the patients breathing high oxygen mixtures so that the effect of an increase in ventilation on oxygen saturation and the consequent Christiansen-Douglas-Haldane effect on the PaCO₂ was eliminated. The results are expressed as follows:

- (i) \dot{V}_E/PaCO_2 is the rise in \dot{V}_E in l./min. divided by the rise in PaCO₂ in mm. Hg
- (ii) $\dot{V}_E/[\text{H}^+]_a$ similarly is the rise in \dot{V}_E in l./min. per 1×10^{-9} mol/l. in [H⁺]_a
- (iii) $\dot{V}_E/\text{PaCO}_2 \cdot \dot{V}_{ER} = \frac{\dot{V}_E \text{ on } 5\% \text{ CO}_2, 95\% \text{ O}_2}{\dot{V}_E \text{ on } 100\% \text{ O}_2}$

This proportionate rise in \dot{V}_E over resting levels is expressed per 1 mm. Hg rise in PaCO₂.

- (iv) $\dot{V}_E/[\text{H}^+]_a$ is similarly the proportionate rise of \dot{V}_E over resting values per 1×10^{-9} mol/l. rise in [H⁺]_a.

These methods are a combination of those of Alexander, West, Wood, and Richards (1955) and of Garlind and Linderholm (1958).

Mixed venous PCO₂ This was measured by the rebreathing method as described by Campbell and Howell (1960). In most cases the CO₂ content of the bag was measured with a simplified Haldane apparatus (Campbell, 1960) but in some cases the CO₂ tension during the second stage of the procedure was followed on the mass spectrometer.

RESULTS (see Tables II and III) Predicted normal values in some cases vary for each patient but as this variation is not great, the range of predicted values for the four patients is given.

Ventilatory tests The F.E.V._{1.0} was reduced to about 50% of the predicted in all cases with a reduced F.E.V. % V.C., indicating airways obstruction. The M.I.F.R. was less reduced than the M.E.F.R.

In two of the three patients who performed the test the maximal voluntary ventilation (M.V.V.) was less than the indirect maximal breathing capacity.

Resting ventilation is labile in these patients and tends to increase when efforts are made to measure it, but in three patients figures below normal were obtained. In the fourth (W.N.) the ventilation was 13.0 l./minute. We were reluctant to accept this as a true resting level but after 20 minutes breathing at this minute volume the arterial PCO₂ was 65 mm. Hg. A similar figure for ventilation was obtained on three further occasions. Despite the variation in minute volume none of the patients showed a gross irregularity of rhythm or depth of breathing.

TABLE III

MINUTE VENTILATION AND ARTERIAL BLOOD BREATHING AIR, 100% OXYGEN AND A MIXTURE OF 5% CARBON DIOXIDE AND 95% OXYGEN

Inspired gas	Minute Ventilation (l./min.)			Arterial Blood									Response to CO ₂ Inhalation*			
				pH			SaO ₂ (%)		PaO ₂ (mm. Hg)	PaCO ₂ (mm. Hg)			VE	VE	VER	VER
	Air	100% O ₂	5%CO ₂ 95%O ₂	Air	100% O ₂	5%CO ₂ 95%O ₂	Air	100% O ₂	Air	Air	100% O ₂	5%CO ₂ 95%O ₂	PaCO ₂	[H ⁺] _a	PaCO ₂	[H ⁺] _a
C.P.	3.8	4.0	16.5	7.31	7.29	7.13	77	105	52	83	99	123	0.52	0.53	0.13	0.13
A.A.	4.4	3.8	12.7	7.31	7.29	7.22	90	108	67	58	61	70	0.98	0.98	0.18	0.18
L.W.	5.9	8.3	21.0	7.32	7.31	7.24	89	109	66	55	56	66	1.27	1.47	0.15	0.18
W.N.	13.0	9.5	16.0	7.32	7.30	7.25	81	105	55	65	71	83	0.54	1.07	0.06	0.11
Normal	8.2	8.8	16.3	7.39	7.39	7.37	>95	>105	95	42	42	45	2.50	4.54	0.28	0.51

* See text for explanation of these symbols.

Total lung capacity and subdivisions The total lung capacity (T.L.C.) was normal in two patients and reduced in the two overweight patients. The inspiratory capacity (I.C.) was reduced in all patients, as was the expiratory reserve volume (E.R.V.). The two patients with a normal T.L.C. had an increased residual volume (R.V.); a third patient had a raised R.V./T.L.C.% but in his case this was due to the combination of a normal R.V. and a reduced T.L.C.

Carbon monoxide uptake This was not reduced whether expressed as carbon monoxide uptake for the whole lung (DLCO) or as uptake per unit of lung volume (Kco).

Distribution of ventilation, blood flow, and ventilation-blood flow ratios The single-breath test showed inequality of ventilation in all patients. In one patient (L.W.) there was no abnormality of the ventilation-blood flow ratios, and the alveolar-arterial oxygen tension difference was not increased, but the other three patients all showed some imbalance between ventilation and blood flow which contributed to the arterial oxygen desaturation. Alveolar ventilation was below normal in all, and two patients had considerably increased physiological dead space.

Arterial blood Resting samples showed arterial oxygen desaturation, elevation of PCO_2 , and a reduced pH in all four patients. In three there was an increased alveolar-arterial PO_2 difference, and the desaturation was greater than could be explained by underventilation alone. On breathing 100% oxygen, the arterial oxygen saturation in all patients rose to at least 105% excluding a significant right to left shunt.

Mechanics The dynamic compliance was normal in all patients. Airways resistance was increased in one patient (C.P.) and at the upper limit of normal in another (L.W.).

Voluntary overbreathing Oximeter readings at rest in these patients were very labile. Introducing a mouth-piece usually resulted in a rise in ventilation giving an increase in oximeter reading of several per cent which persisted for five or more minutes. A two-minute period of voluntary over-ventilation increased the saturation in all cases.

Standardized exercise test All four patients were able to complete five minutes of the relatively severe test without severe dyspnoea. In two patients there was profuse sweating. They showed a rapid desaturation in the first minute of exercise after which no further fall in oximeter reading occurred. Though the patients achieved a steady level of ventilation in the fourth and fifth minutes of exercise, which was considerably below their maximum breathing capacity (either M.V.V. or indirect M.B.C.), they all went into ventilatory debt. The standardized ventilation (which gives a measure of the overall ventilatory cost per minute of a given piece of exercise) was only slightly above normal in these four patients. In one patient (L.W.) the end-expiratory PO_2 and PCO_2 were measured at the mouth using a mass spectrometer while mild exercise was carried out on a bicycle. The oximeter reading fell 15% during this exercise and the end-expiratory PO_2 fell from 102 mm. Hg to 50 mm. Hg while the end-expiratory PCO_2 rose from 42 mm. Hg to 61 mm. Hg. These changes, combined with the poor ventilatory response, suggest that the desaturation on exercise was due to a worsening of the underventilation. These changes on exercise occurred at a time when the patient (L.W.) was maintaining a mixed venous PCO_2 of 53 mm. Hg and was symptom-free.

Response to CO_2 inhalation (Table III and Figs 3 and 4). For comparison we have assumed that the relationships between Paco_2 or $[\text{H}^+]_a$ and ventilation are linear. Figure 3 shows the rise in Paco_2 or $[\text{H}^+]_a$ required to double the resting ventilation, i.e., $\dot{V}_{\text{ER}}=2.0$. By all methods of assessment the

TABLE IV
SUMMARY OF ABNORMALITIES OF LUNG FUNCTION APART FROM THE CHANGES FOLLOWING ALVEOLAR UNDERVENTILATION

Patient	Ventilatory Capacity	Lung Volumes	Physiological Dead Space	Inequality of Ventilation	Inequality of Ventilation-blood Flow Ratios	Alveolar-arterial PO_2 Difference	Airways Resistance
C.P.	} 40-50% of predicted	Small T.L.C.; small R.V.	Normal	Moderate	Moderate	Increased	Increased
A.A.		Small T.L.C.	Normal	Moderate	Moderate	Increased	Normal
L.W.		Large R.V.	Large increase	Slight	Slight	Normal	Normal
W.N.		Large R.V.	Large increase	Large increase	Moderate	Moderate	Increased

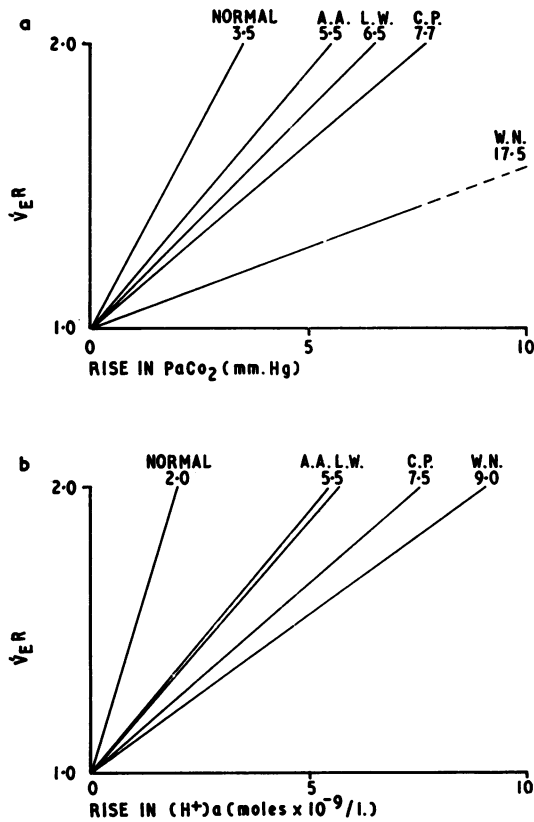


FIG. 3. (a) Rise in arterial P_{CO_2} (P_{aCO_2}) required to double the resting ventilation ($\dot{V}_E R = 2$); (b) rise in arterial hydrogen ion activity ($[H^+]_a$) required to double the resting ventilation ($\dot{V}_E R = 2$).

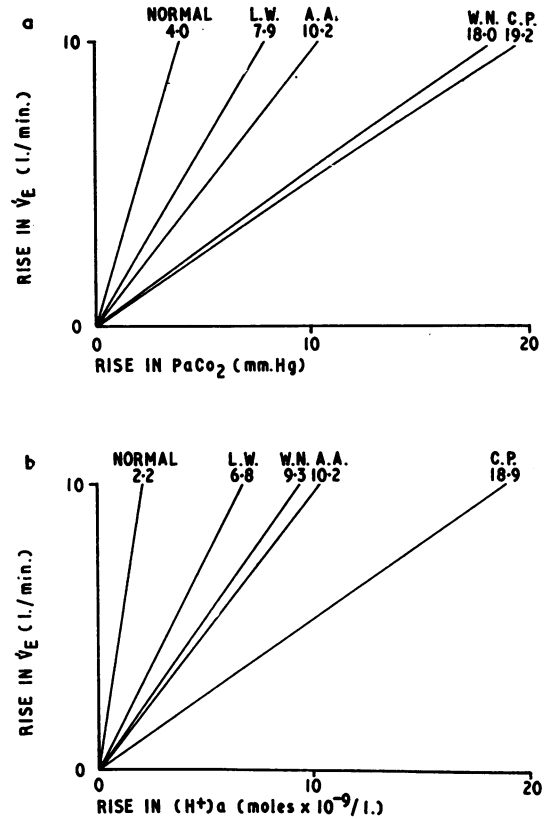


FIG. 4. (a) Rise in arterial P_{CO_2} (P_{aCO_2}) required to raise the resting ventilation (\dot{V}_E) by 10 litres per minute; (b) rise in arterial hydrogen ion activity ($[H^+]_a$) required to raise the resting ventilation by 10 litres per minute.

response to carbon dioxide inhalation can be seen to be impaired.

A summary of the abnormalities of lung function in these patients, other than the changes following underventilation, is given in Table IV.

DISCUSSION

The main abnormality in these four patients was inadequate alveolar ventilation at rest; this was associated with a poor ventilatory response to the inhalation of carbon dioxide and to the stress of exercise. These changes were out of proportion to those that we would expect in patients with airways obstruction of a corresponding degree. The headaches, somnolence, tremor, polycythaemia, and right heart failure which occurred in our patients were probably accounted for by the alveolar underventilation; they frequently accompany the under-

ventilation which occurs in the chronic bronchitic with severe airways obstruction, but in our patients they were much more prominent than the symptoms produced by the airways obstruction which was not severe. It also seems likely that worsening of the underventilation with increased acidity of the arterial blood led to the profuse sweating observed when the patients were asleep, exercising or breathing carbon dioxide mixtures.

Although the finding of underventilation satisfactorily explains many of the clinical features, we do not know why it occurred. Chronic bronchitis with airways obstruction probably accounted for the reduced $F.E.V_{1.0}$ and $F.E.V. \% V.C.$ and the inequalities of ventilation and blood flow that we found in all our patients, for the increase in residual volume in L.W. and W.N., and for the increase in airways resistance in C.P. However, we do not think that the reduction in $F.E.V.$ accounted for the

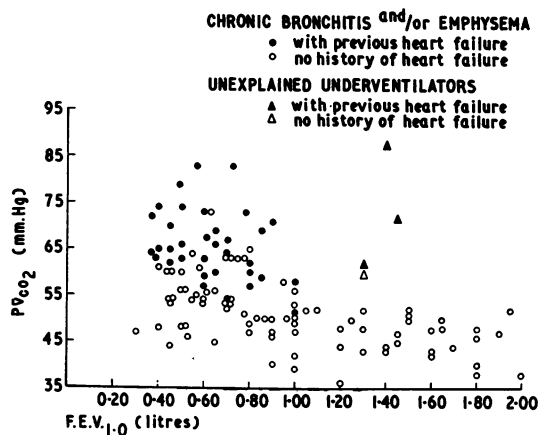


FIG. 5. The $F.E.V._{1.0}$ plotted against the mixed venous P_{CO_2} ($P\dot{V}CO_2$) in 113 cases of irreversible airways obstruction due to chronic bronchitis and/or emphysema and in four patients with unexplained underventilation. All measurements were made when the patients were in their 'chronic' state.

alveolar underventilation because we have not seen it occur in chronic bronchitis unless the $F.E.V._{1.0}$ is 1 litre or less (see Fig. 5), whereas our four patients had an $F.E.V._{1.0}$ of 1.3 litres or more. There were other points of distinction between these four patients and the majority of men with chronic bronchitis and airways obstruction. These may be considered under six headings:

DYSPNOEA Our patients, except when in heart failure, only admitted to very slight dyspnoea. For instance, A.A. claimed no difficulty in climbing 100 stairs to his work as a bricklayer, and L.W.'s breath-holding time was abnormally long.

EXERCISE TOLERANCE We have found very few patients with chronic bronchitis, airways obstruction, and an arterial PCO_2 over 60 mm. Hg who have been able to complete the exercise test we used, but these four men did so without difficulty. During this test men with chronic bronchitis usually achieve a maximum exercise ventilation at least as great as their indirect maximal breathing capacity, show an increased standardized ventilation and only slight desaturation. Our patients, while going into ventilatory debt, had a maximum exercise ventilation below their maximum breathing capacity; the standardized ventilation was only slightly elevated, yet severe desaturation occurred.

RESTING VENTILATION Three of our patients had a reduced resting ventilation which is not often found

in chronic bronchitis or emphysema. In two of the men there was virtual apnoea at night; when awake there was great minute-to-minute variation in ventilation.

VOLUNTARY OVERBREATHING Two minutes of overbreathing in our patients raised their oxygen saturation by at least 6% (as measured with an ear oximeter), whereas in chronic bronchitis the average rise is less than 3% (Wilson, Borden, Ebert, Wells, and Johnson, 1950).

COMA Although coma associated with carbon dioxide retention is seen in chronic bronchitis with airways obstruction, it usually occurs in exacerbations of infection or after the use of oxygen or sedatives. Both C.P. and L.W., however, had episodes of apnoea and coma without an obvious precipitating cause.

RIGHT HEART FAILURE The appearance of heart failure as the presenting feature in three of our patients contrasts with its more usual appearance as a late complication of severe chronic bronchitis. This syndrome could be confused with the underventilation of 'chronic bronchitis and emphysema'. Because of this we have discussed at some length these points of distinction, which are summarized in Table V.

TABLE V

SUMMARY OF FEATURES DISTINGUISHING CHRONIC BRONCHITIS FROM UNEXPLAINED UNDERVENTILATION

	Chronic Bronchitis with Alveolar Underventilation	Unexplained Underventilation
Dyspnoea	Severe	Slight
Exercise	Poor tolerance, slight oxygen saturation	Good tolerance, gross oxygen desaturation
$F.E.V._{1.0}$	Less than 1.0 litre	More than 1.0 litre
Resting ventilation ..	Normal, or even increased	Labile, may be reduced
Voluntary overbreathing ..	Small rise in oxygen saturation	Considerable rise in oxygen saturation

We do not think that the underventilation in our patients could be accounted for by obesity or a defined neurological disease. Two of the patients (C.P. and A.A.) were overweight and had the small lung volumes often found in the obese, but their obesity was much less marked than in any of the reported cases, and they both failed to lower their PCO_2 on losing 9 and 17 kg. respectively. None of the four patients had a history of encephalitis; they had diffusely abnormal electroencephalograms (attributed to hypoxia and carbon dioxide retention) but the only local neurological abnormalities found

in our patients during many examinations were transitory nystagmus in C.P. and transitory diplopia in L.W. Both these patients had periods of complete apnoea, and it seems possible that these abnormalities were the result of hypoxia rather than related to the cause of the underventilation. Primary polycythaemia vera with a midbrain vascular lesion resulting in underventilation was considered as a possibility in C.P., but there has been no splenomegaly and no increase in the white blood cells or platelets.

Two patients (L.W. and W.N.) had very large physiological dead spaces. In W.N. the increase in dead space was such that an increased minute volume provided inadequate alveolar ventilation; the other features in this patient were identical with those of the rest of the group. In three previously reported cases (Ratto *et al.*, 1955; Richter *et al.*, 1957; and case 2 of Rodman *et al.*, 1962) there has been an increase in physiological dead space to between 220 and 280 ml. An increase of the physiological dead space is common in chronic bronchitis and emphysema but may also be found in pulmonary embolism. Thromboembolism can be an unsuspected cause of chronic right heart failure (Owen, Thomas, Castleman, and Bland, 1953), but in reported cases dyspnoea has been severe and carbon dioxide retention absent (Ehrner, Garlind, and Linderholm, 1959), so it seems unlikely to have been the cause in our patients. Nevertheless at necropsy in the case described by Lawrence (1959) there were numerous pulmonary infarcts; these were thought to be recent and to be a complication of polycythaemia.

The marked underventilation in our patients therefore remains unexplained; their clinical and physiological features resemble those of the 10 patients previously described, all but one of whom (a 36-year-old woman reported from the Massachusetts General Hospital in 1956) have been men between the ages of 30 and 60 years. The aetiology of the syndrome is probably diverse; chronic bronchitis may have played a part in its production in our patients similar to that played by obesity in other cases. But there must be another as yet unrecognized defect, and this probably lies in the central nervous system. Some neurological or psychiatric abnormality has been observed in eight of the 10 previously reported cases; three were of low intelligence, one had a positive Wassermann reaction in the cerebrospinal fluid, one was schizophrenic and had been treated with frequent insulin comas, one had persistent hiccough, one was 'depressed and obsessive', and in the probable case of Naeye (1961) focal loss of medullary cells with reactive gliosis was found *post mortem*. Of our

patients, apart from the diplopia in L.W., another (W.N.) was well below average in intelligence.

It is interesting to speculate on the role of underventilation in the aetiology of cor pulmonale in patients with airways obstruction. In emphysema the disturbance of alveolar and blood gases co-exists with anatomical loss of the pulmonary vascular bed, and the respective importance of each of these factors is not clear. Nevertheless alveolar underventilation appears to be the most consistent clinical association (Rossier and Bühlmann, 1954; Ferrer and Harvey, 1959; Campbell and Short, 1960), though there is doubt whether the changes in the alveolar gases or in the blood gases are the more important (Fishman, 1961). Our cases with their liability to right heart failure despite a lung function which is not greatly disturbed are like those occurring in obesity in having underventilation as the only obvious factor. They confirm our general experience that cor pulmonale in patients with irreversible airways obstruction is more common at any given level of F.E.V._{1.0} in those patients who have elevation of the PCO₂ (see Fig. 5).

Our experience does not allow us to assess the prognosis of this syndrome. Heart failure has responded to rest, digoxin, and diuretics, but attempts to produce a long-lasting increase in ventilation have been unsuccessful except for an apparently good response to dichlorphenamide in A.A. and a partial response to oral amiphenazole in L.W. The alarming apnoeic episodes are an obvious risk to life, but C.P. and A.A. are still at work five years after the first appearance of right heart failure, and when free from oedema they are only slightly disabled. Successful treatment would produce adequate ventilatory stimulation without side effects and would presumably greatly improve the prognosis. It is however not available.

SUMMARY

Four cases of unexplained underventilation are described. Clinically they were characterized by headache, somnolence, sudden episodes of unconsciousness, and a tendency to right heart failure. There was little dyspnoea. The dominant defect in lung function was alveolar underventilation, associated in three of the patients with low overall ventilation. In addition there were clinical and physiological features suggesting that all these patients had mild chronic bronchitis, but reasons are given for considering that this did not account for the underventilation.

The aetiology is unknown. Attempts to stimulate ventilation have been largely unsuccessful.

All these patients were originally seen at other hospitals, and we are most grateful to Dr. M. O. J. Gibson, Dr. V. Wynne, Dr. R. Asher, and Dr. J. Smart for permission to quote their findings in these cases. We should also like to thank Dr. C. M. Fletcher and Dr. P. Hugh-Jones, under whose care these patients were at this hospital, for their criticism and advice, and Miss E. Buchanan for help with the lung function tests.

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