

Controlled Oxygen Therapy in Respiratory Failure*

D. C. S. HUTCHISON, M.A., B.M., B.CH. ; D. C. FLENLEY, M.B., CH.B., B.S.C., M.R.C.P.ED.

K. W. DONALD, D.S.C., M.A., M.D., D.S.C., F.R.C.P., F.R.C.P.ED., F.R.S.ED.

Brit. med. J., 1964, 2, 1159-1166

One of the most common medical emergencies in this country is the development of acute respiratory failure in patients with chronic generalized obstructive lung disease who suffer an acute pulmonary infection or develop further serious airway obstruction due to asthma, smog-irritation, or exacerbation of bronchitis. Hypoxia may be profound during these episodes, and its relief by the administration of oxygen is urgently necessary. However, this often leads to further depression of ventilation and the development of "carbon-dioxide narcosis" (Donald, 1949; Comroe, Bahnson, and Coates, 1950; Westlake, Simpson, and Kaye, 1955; Sieker and Hickam, 1956). The therapeutic problem in these patients is to relieve the hypoxia without producing a dangerous rise in arterial carbon dioxide tension (PCO_2).

Barach (1938) was the first to report the onset of mental changes following oxygen therapy. He suggested that oxygen should initially be given at fairly low concentrations and be gradually increased as the situation allowed. Donald (1953) suggested the administration of oxygen by tent (approximately 35-40%) with intermittent brief periods breathing air. Campbell (1960a) elaborated Barach's original concept and suggested that the continuous administration of an oxygen mixture controlled with an accuracy of $\pm 1\%$ in the range 24 to 35% would allow relief of hypoxaemia without running the risk of a serious rise in PCO_2 .

Other workers have favoured early tracheostomy and mechanical ventilation, but the difficulties of this approach could be avoided if control of the inspired-oxygen concentration alone could be shown to be a safe method of treatment in a large number of cases. Many questions, however, remain unanswered. It is not known whether hypoxaemia can be adequately relieved by this method without producing a dangerous rise in arterial PCO_2 and fall in pH , or whether an upper limit of 35% in the inspired-oxygen concentration will always prevent the PO_2 from falling to a dangerous level. Likewise, it is not known what degree of control of the inspired-oxygen concentration is needed to prevent further CO_2 retention. It is not known at what point of recovery accurate control can be discontinued and oxygen given at high concentrations. There are no reliable clinical criteria regarding when oxygen therapy can be discontinued altogether. Many workers have stressed the difficulty of predicting from the initial levels of PO_2 , PCO_2 , or pH how the patient will respond when given oxygen.

In the present study a number of patients have been treated by controlled oxygen administration without assisted ventilation, and an attempt has been made to answer some of the above questions. A working approach to the treatment of such patients by accurate control of the inspired-oxygen concentration is suggested.

Throughout the text the terms PO_2 , PCO_2 , and pH will refer to the PO_2 and PCO_2 (mm. Hg) and to the pH in the arterial blood, unless otherwise stated.

Patients

Nine patients suffering from acute respiratory failure were studied—one patient on two occasions. The clinical features

in each case are summarized in Table I. On admission to hospital the haemoglobin ranged from 12.7 to 16.7 g./100 ml., with P.C.V. between 43 and 63%, except in one patient (Case 7) who had an iron-deficiency anaemia with a haemoglobin of 9.5 g./100 ml. and P.C.V. of 37%. The E.C.G. showed right-sided changes (P pulmonale, R ventricular strain, partial R.B.B.B.) except in Case 5, where it was normal, and in Case 9, which showed evidence of an old myocardial infarction. Lung volumes were measured just before discharge from hospital (except in Case 7, who died). The vital capacity ranged from 0.8 to 2.3 litres. The ratio of residual volume to the total lung capacity varied between 58 and 82%, the highest predicted normal value for these patients being 47%. The $F.E.V_{0.75}$ varied between 400 and 800 ml., with a mean of 590 ml. These results are all compatible with a diagnosis of chronic bronchitis and emphysema. The chest x-ray films satisfied the criteria of Laws and Heard (1962) for "emphysema" in all but two cases. In Case 3 cardiomegaly and pulmonary congestion were the only findings in the x-ray examination, and Case 5 showed generalized fine pulmonary fibrosis.

TABLE I.—Clinical Condition of Patients on Admission

Case No.	Age and Sex	History		Physical Examination				B.P.
		Symptoms* (Years)	Present Illness (Days)	Dyspnoea†	Finger-clubbing	Congestive Failure‡	Auscultation of Chest	
1	69 M	15	3	+	+	+	R.C.	150/80
2	56 M	8	7	—	—	—	D.	180/90
3	58 M	6	7	+	—	+++	R.C.	140/80
4	59 F	6	7	—	+	—	R.	140/100
5	72 F	Nil	21	—	—	—	D.R.	150/80
6	39 M	3	14	+	+	—	R.	120/60
7	63 F	1	14	+	—	+++	R.	180/50
8	43 M	7	7	+	—	—	R.	160/80
9	73 F	15	4	+	—	—	R.C.	150/90

* Winter cough, sputum, and dyspnoea; † Tachypnoea and use of accessory muscles. R = Rhonchi. C = Crepitations. D = Diminished breath sounds. ‡ Congestive failure: + = elevated jugular venous pressure; ++ = above + peripheral oedema; +++ = above + hepatomegaly.

Plan of Study

The patient's response to variations in the concentration of inspired oxygen was examined in detail, giving a total of 10 studies since Case 2 was studied during the two separate episodes. Arterial blood samples were taken from a small indwelling nylon catheter introduced into the brachial or radial artery by the Seldinger technique, thus avoiding repeated arterial puncture (Bernéus, Carlsten, Holmgren, and Seldinger, 1954); the PO_2 , PCO_2 , and pH of each sample were estimated. The catheter lumen was kept filled with a heparin solution, and a tap closed off the system between the periods of sampling.

In all but one of these 10 studies (Case 5) the catheter was introduced shortly after admission and either two or three arterial blood samples were taken during a period of 20 to 30 minutes while the patient was breathing air, before oxygen or any other treatment had been given. Following this, oxygen was adminis-

* From the Department of Medicine, University of Edinburgh, at the Royal Infirmary, Edinburgh.

tered, in Case 1 by the Venturi mask (Campbell, 1960b), and in subsequent studies by a blower system of our own design (Flenley, Hutchison, and Donald, 1963) which was capable of controlling the inspired-oxygen concentration with an accuracy of $\pm 1.8\%$ (95% confidence limits). After the initial period of air-breathing, the inspired-oxygen concentration was increased to 30–35% and maintained at this level during the next hour. The exact inspired-oxygen concentration was determined by analysis of an inspiratory sample from the oxygen mask of the blower system. If the PCO_2 rose by more than 6 mm. Hg the oxygen concentration was reduced in the next hour, but if the rise in PCO_2 was less than 6 mm. Hg the inspired-oxygen concentration was increased. This routine was followed in most cases, but the exact procedure varied from case to case as shown in Table II. In some cases the blood gases were

estimated on a number of days after the "acute study," and, where possible, estimations were carried out when the patient had recovered from the acute infection (Table II). Lung volumes were also measured at this time.

Laboratory Methods

Arterial blood carbon dioxide tension was estimated with a Severinghaus electrode (Severinghaus and Bradley, 1958). Arterial blood oxygen tension was estimated with a Clark cell (Bishop and Pincock, 1959) and pH with a glass electrode (Electronic Instruments Ltd.). Arterial oxygen saturation was derived from the line-chart of Severinghaus (1958) and buffer-base from the nomogram of Singer and Hastings (1948). Estimations were carried out as soon as possible after the samples had been withdrawn, and in any case within 20 minutes.

The oxygen concentration in the samples of inspired gas was measured with the Clark cell by a method already described (Flenley *et al.*, 1963).

The total lung capacity and its subdivisions were measured by the closed-circuit helium-dilution method (Meneely and

TABLE II

Case and Day of Study	Hours	Inspired O ₂ Conc. %	Arterial Blood					
			PO ₂ mm. Hg	PCO ₂ mm. Hg	pH	SO ₂ %	Buffer Base mEq/l.	
Case 1 Day 1 (acute)	0	20.9	36	72	7.33	64	55	
	3/4	V = 31	38	68	7.36	69	55	
	1 1/2	V = 27	70	63	7.38	92	56	
	2 1/2	V = 23	65	57	7.38	91	54	
	2 3/4		61	53	7.40	90	54	
			43	47	7.43	79	—	
Discharge ..		20.9	42	47	7.38	89	50	
Case 2 (Study 1) Day 1 (acute)	0	20.9	23	79	7.32	38	56	
	1 1/2	36.4	26	86	7.28	42	54	
	1 3/4		46	90	7.25	74	55	
	3	29.2	56	93	7.24	82	54	
	3 1/2		48	77	7.31	79	56	
	5 1/2	27.4	48	75	7.29	78	54	
	5 3/4		42	78	7.30	72	55	
	6	46.0	40	71	7.30	71	55	
	6 1/2		92	78	7.30	96	62	
			97	78	7.33	96	58	
Day 2 ..		20.9	46	72	7.35	79	57	
		52.6	156	94	7.25	99	58	
Case 2 (Study 2) Day 1 (acute)	0	20.9	33	71	7.39	64	61	
	1/2		34	72	7.38	64	61	
	1	33.8	31	73	—	—	—	
	1 1/2		61	82	7.33	88	60	
	2		66	—	7.32	90	—	
	2 1/2	30.2	69	83	7.31	93	60	
	3		46	75	7.34	81	58	
	3 1/2		56	81	7.33	85	60	
	4 1/2	25.0	60	81	7.33	88	60	
	5 1/2		45	82	7.36	78	63	
	6 1/2		44	74	7.35	78	58	
	7 1/2		45	79	7.35	78	60	
	17 1/2	29.7	71	70	—	—	—	
			71	70	7.38	93	60	
	18	40.0	66	70	—	—	—	
		93	72	7.38	97	61		
		95	73	7.37	97	61		
19	20.9	90	74	7.35	96	60		
		34	68	7.41	65	61		
		36	67	7.39	69	59		
Discharge ..		20.9	38	67	7.39	72	59	
			67	—	—	—	—	
Case 3 Day 1 (acute)	0	20.9	39	100	7.35	71	73	
	1 1/2	36.0	40	93	7.35	72	68	
	1 3/4		67	115	7.33	90	76	
	2 1/2	29.9	74	118	—	—	—	
	3		54	122	7.23	81	66	
	3 1/2		59	118	7.25	84	67	
	4 1/2	24.4	45	107	7.25	73	61	
	5 1/2		49	107	7.25	77	61	
	6	29.5	52	103	7.34	83	72	
	Discharge ..		20.9	60	62	7.34	88	54
Case 4 Day 1 (acute)	0	20.9	39	58	7.43	75	57	
	1		40	58	7.43	76	57	
	2	34.5	74	62	7.39	94	57	
	2 1/2		79	64	7.38	95	57	
	3 1/2	42.0	81	61	7.42	95	59	
	4 1/2		87	63	7.38	96	57	
	4 3/4		78	77	7.26	92	52	
	Day 2 ..		Polymask	57	59	7.42	89	58
	Day 3 ..		V = 29	59	59	7.41	89	58
	Day 4 ..		V = 29	56	59	7.41	88	58
	Day 5 ..		V = 29	60	57	7.39	88	56
	Case 5 Day 1 (acute)	0	Polymask	—	86	7.28	—	58
		2		114	90	7.27	97	58
		2 1/2	28.9	47	86	7.34	79	63
		3 1/2		52	77	7.38	84	63
4 1/2		29.5	52	65	—	—	—	
6			53	65	7.39	86	59	
7		32.2	62	65	7.44	92	64	
Day 2 ..			32.5	57	64	7.45	89	64
Day 3 ..			Polymask	67	71	7.38	92	62
Day 3 ..			28.7	53	57	7.44	87	59
Day 4 ..				56	65	7.40	87	60
Day 6 ..			30.1	63	63	7.39	90	58

TABLE II.—(Contd.)

Case and Day of Study	Hours	Inspired O ₂ Conc. %	Arterial Blood					
			PO ₂ mm. Hg	PCO ₂ mm. Hg	pH	SO ₂ %	Buffer Base mEq/l.	
Case 6 Day 2 (acute)	0	20.9	55	51	—	—	—	
	1 1/2	35.9	52	50	—	—	—	
	2 1/2		85	55	—	—	—	
	3 1/2		86	56	—	—	—	
Discharge ..	1 1/2	58.9	193	65	—	—	—	
	1 3/4		188	66	—	—	—	
	2 1/2	20.9	74	41	7.42	94	—	
Case 7 Day 2 (acute)	0	20.9	36	72	7.26	60	49	
	2 1/2		36	69	7.26	60	48	
	3 1/4	34.2	39	70	7.26	65	48	
	3 3/4		60	77	7.24	85	50	
	4 1/2		65	76	7.23	87	49	
	5 1/2	61.6	64	78	7.23	86	49	
	6 1/2		122	89	7.21	97	51	
	Day 3 ..			116	93	7.22	97	54
				130	92	7.22	98	54
			30.0	60	86	—	—	—
				48	91	7.22	74	54
				48	91	7.22	74	54
				60	89	7.19	83	49
	Day 4 ..		30.0	58	90	7.19	82	49
				68	92	7.19	87	50
			71	94	—	—	—	
			76	91	—	—	—	
		30.5	40	91	7.19	63	48	
			34.8	46	104	7.06	63	42
Case 8 Day 1 (acute)	0	20.9	56	56	7.39	87	54	
	1 1/2	34.4	55	55	7.42	88	56	
	2		89	60	7.39	87	54	
	2 1/2	50.2	91	61	7.38	96	55	
Discharge ..			89	61	7.38	96	55	
			143	65	7.35	99	55	
			146	63	7.36	99	55	
			153	66	7.36	99	56	
		31.6	77	66	7.36	94	56	
			67	66	7.36	92	56	
			64	64	—	—	—	
			64	64	—	—	—	
			74	51	7.35	94	48	
	Case 9 Day 1 (acute)	0	20.9	33	72	—	—	—
1 1/2		34.5	31	67	—	—	—	
2 1/2			31	70	—	—	—	
3 1/2			57	67	—	—	—	
4 1/2			58	68	—	—	—	
5 1/2		29.6	52	69	—	—	—	
6 1/2			43	72	—	—	—	
7 1/2			46	74	—	—	—	
8 1/2			49	74	—	—	—	
9 1/2		25.0	47	72	—	—	—	
10 1/2			47	75	—	—	—	
11 1/2			42	75	—	—	—	
12 1/2			41	74	—	—	—	
13 1/2		30.6	49	71	—	—	—	
14 1/2			100	91	—	—	—	
Day 2 ..		Polymask	91	96	—	—	—	
			46	77	7.31	77	55	
			43	69	7.33	74	55	
			43	68	7.33	74	55	
			55	77	7.31	84	56	
			52	75	7.33	83	57	
Day 3 ..		29.0	46	77	7.31	82	60	
			43	69	7.33	74	55	
			43	68	7.33	74	55	
			55	77	7.31	84	56	
Day 4 ..			52	75	7.33	83	57	
		36.4	49	68	7.38	82	60	
		35.0	55	62	7.38	86	57	
	Discharge ..		20.9	69	45	7.42	93	51

V = Reading on Venturi gauge. Hours : indicates time after admission.

Kaltreider, 1941). The 0.75-second fast expiratory volume (F.E.V._{0.75}) was measured with a Bernstein spirometer. Normal values were obtained from the simplified equations of Needham, Rogan, and McDonald (1954).

Results

The values of the arterial blood PO_2 , PCO_2 , and pH , at the various concentrations of inspired oxygen, are shown in detail in Table II together with the derived oxygen saturations (SO_2) and buffer-base values.

All patients had a raised PCO_2 and decreased PO_2 when breathing air at the start of the studies. The pH was below normal in five of the seven studies in which measurements were made during the initial phase of air-breathing.

Cases 1, 4, 5, 6, and 8 suffered from moderate respiratory failure, but their condition during treatment did not cause anxiety and they all survived. Cases 2, 3, and 9 were in more severe respiratory failure; all were gravely ill on admission and the outcome of treatment was uncertain for some days, but they all recovered. One patient (Case 7) died from respiratory failure with progressive acidosis. The clinical progress of each case is summarized below.

Clinical Progress

Case 1 (Fig. 1).—This man was comatose when breathing air, with severe hypoxaemia (PO_2 36) and hypercapnia (PCO_2 72), and a pH of 7.33. He responded rapidly to oxygen given by the Venturi mask, with a persistent fall in PCO_2 from 70 to 53, irrespective of the inspired-oxygen concentration.

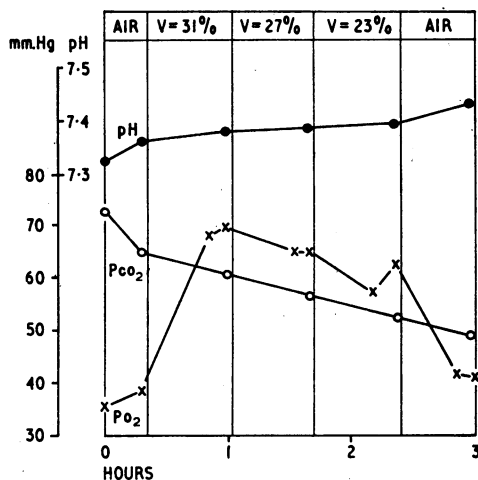


FIG. 1.—Arterial carbon dioxide tension (PCO_2), arterial pH , and arterial oxygen tension (PO_2) in Case 1, breathing air and during early stages of oxygen therapy. Oxygen was given by the Venturi mask, $V=31$, being the Venturi gauge set at 31% oxygen.

Case 2, Study 1 (Fig. 2).—This patient was unconscious on admission with profound hypoxaemia while breathing air (PO_2 26, and considerable carbon-dioxide retention and acidosis (PCO_2 86, pH 7.28). The hypoxaemia was partially relieved (PO_2 56) by administration of 36% oxygen, but this led to a further rise in PCO_2 to 93 and a fall in pH to 7.24. The inspired oxygen concentration was then reduced in two stages to 27%, leading to a fall in PCO_2 , but only at the expense of persistent severe hypoxaemia (PO_2 40). However, after six hours of controlled oxygen therapy he could tolerate 46% oxygen with no further increase in PCO_2 and a near normal pH . The next day his PO_2 was only 46 while breathing air and his PCO_2 rose to 94 (pH 7.25) while breathing 53% oxygen (PO_2 156). This respiratory acidosis was reversed once more by giving a lower concentration of oxygen, and he finally recovered.

Case 2, Study 2.—This was carried out during a further attack 18 months later. When breathing air he had less severe hypoxaemia

(PO_2 33) and a PCO_2 of 72 but a normal pH . The PCO_2 rose by 10 with 34% oxygen, but this rise was not readily reversed when 30% and 25% oxygen were substituted. However, owing to the presence of a high buffer base the pH never fell below 7.31. One day later he could tolerate 40% oxygen with little rise in PCO_2 . He again recovered.

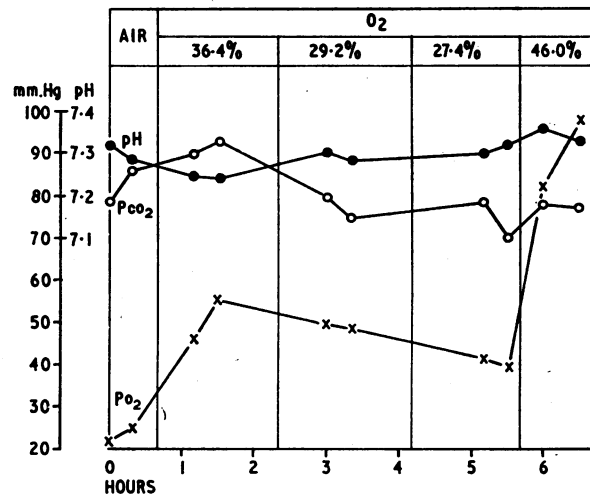


FIG. 2.—Arterial PCO_2 , pH , and PO_2 in Case 2, Study 1, when breathing air and during the early stages of controlled oxygen treatment. Oxygen concentrations in the inspired gas are also shown.

Case 3 (Fig. 3).—This patient with marked congestive failure had moderate hypoxaemia (PO_2 40), with a PCO_2 of 100. As the buffer base was also very high (73–68 mEq/l.) the pH was no lower than 7.35 when he was breathing air. A further serious rise of PCO_2 developed with 36% oxygen, and this rise was not reversed until 24% oxygen was given. He later tolerated 30% oxygen (PO_2 52) without further rise in PCO_2 and survived the episode.

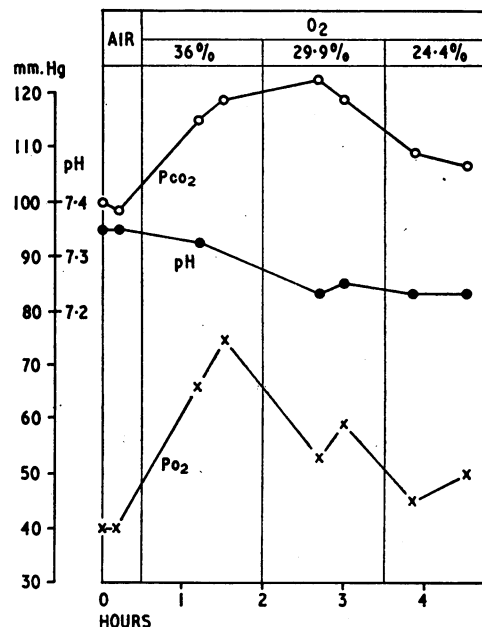


FIG. 3.—Arterial PCO_2 , pH , and PO_2 in Case 3 when breathing air and during the early stages of controlled oxygen therapy. Oxygen concentrations in the inspired gas are also shown.

Case 4.—This woman was hypoxaemic (PO_2 40), with moderate carbon-dioxide retention (PCO_2 58) and a normal pH . No important rise in PCO_2 developed on 35% oxygen or 42% oxygen. For this reason oxygen was given by the Polymask for the next 24 hours. PCO_2 had risen by 15 at the end of this time with a severe fall in pH to 7.26. She was then given oxygen by the Venturi mask set at 29% (PO_2 57), the PCO_2 falling to 57, and she recovered without further incident.

Case 5.—As this woman had no history of chronic bronchitis she was initially treated with oxygen by Polymask. Twenty-four hours of this treatment (PO_2 114) produced coma, with a PCO_2 of 90 and a pH of 7.28. Carbon-dioxide retention improved slowly after the inspired oxygen was reduced to 29.5% and 32%, with the pH increasing to 7.44 as the PCO_2 fell to 65. Chest x-ray examination on recovery showed evidence of generalized fine pulmonary fibrosis.

Case 6.—This man had mild hypoxaemia (PO_2 54) and carbon-dioxide retention (PCO_2 50), with an increase in PCO_2 to 66 as 59% oxygen was given; this rise was reversed with lower levels of oxygen and he recovered.

Case 7 (Fig. 4).—This woman was grossly obese, uraemic (blood urea 200 mg./100 ml.), in severe congestive heart failure, and was also suffering from iron-deficiency anaemia (Hb 9.5 g./100 ml.). She was hypoxaemic (PO_2 36) and hypercapnic (PCO_2 70), with a pH of 7.26, when breathing air. After breathing 34% oxygen her PO_2 rose to 65, with a rise of 6 mm. Hg in PCO_2 ; 62% oxygen caused a serious rise of PCO_2 to 93, the pH falling to 7.22. This rise in PCO_2 was not reversed by lowering the inspired oxygen to 30%, and the pH continued to fall to 7.06, the PCO_2 being 104. Sodium lactate intravenously increased the pH to only 7.17 and she died shortly afterwards. Throughout the three days of her stay in hospital she remained in severe heart failure, with marked skin-vasodilatation, and a blood-pressure of 180/60. Necropsy showed bilateral apical fibrosis and emphysema, lower-lobe oedema, and patent major airways. There was right ventricular hypertrophy and the kidneys were congested but otherwise normal.

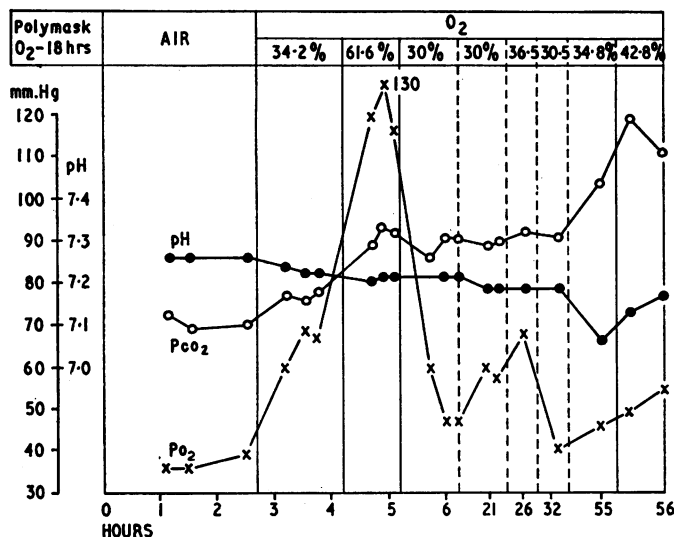


FIG. 4.—Arterial PCO_2 , pH , and PO_2 in Case 7 when breathing air and during controlled oxygen therapy. Oxygen concentrations in the inspired gas are also shown.

Case 8.—In this man the PO_2 was 56 and PCO_2 56 when breathing air. The PCO_2 rose to 66 when 50% oxygen was given and the pH dropped to 7.36; he was maintained in a satisfactory condition on a lower level of inspired oxygen (32%) and soon recovered.

Case 9.—This woman was in severe respiratory failure with an initial PO_2 of 33 and PCO_2 of 72 when breathing air, but pH estimations were not available for the first day. The PCO_2 showed little rise with 35% to 25% oxygen, but when oxygen was given by the Polymask, producing a PO_2 of 100, the PCO_2 rose to 91. This rise in PCO_2 was slowly reversed when 29% oxygen was given.

In the introduction various questions of the control of oxygen therapy were posed. An attempt is made to provide answers to these questions from the results in Table II.

1. Can Hypoxia be Relieved Without a Dangerous Rise in PCO_2 or Fall in pH ?

It is proposed later that a PO_2 of 50 will prevent death from hypoxia, and that the pH should be maintained above 7.25 during therapy (see Discussion). In Case 1 there was no danger of the pH falling below 7.25 irrespective of the level of PO_2

(between 58 and 70). In Case 2 (Study 1, Fig. 2) the above criteria could not be completely achieved, but a PO_2 of 48 was obtained with a pH of 7.29 when breathing 29% oxygen. In Case 2 (Study 2) administration of 34% oxygen kept the PO_2 above 50 and the pH between 7.31 and 7.33. Case 3 (Fig. 3) illustrates that increasing carbon-dioxide retention (PCO_2 rising from 100 to 122) on oxygen therapy could be reversed only by lowering the PO_2 to 45 (24% oxygen required), when the pH was 7.25. Our criteria of PO_2 over 50 and pH over 7.25 were therefore not satisfied in this case. Values obtained in Case 7 also failed to meet these criteria, and artificial ventilation would have been started earlier if the scheme of treatment which is proposed later had been adopted. Case 9 shows that a rise in PCO_2 from 70 to 75 could be reversed only by lowering the PO_2 to 47 and subsequently to 41, but unfortunately pH measurements were not available during the first day's treatment.

Controlled oxygen therapy therefore failed to provide a PO_2 over 50 and a pH over 7.25 in three of the 10 studies.

2. Is it Safe to Assume that an Inspired Oxygen Concentration of 35% will Always Prevent a Dangerous Level of Hypoxaemia in These Patients?

Again a PO_2 of 50 is proposed as the minimum safe level (see Discussion). An inspired-oxygen concentration of 35% ($\pm 1\%$) failed to produce a PO_2 over 50 in Cases 2, 7, and 9.

3. Do Moderate Changes (5%) in Inspired-oxygen Concentration in the Range 21–35% Produce Changes in Carbon-dioxide Retention?

In Case 2 (Study 1, Fig. 2) lowering the inspired-oxygen concentration from 36% to 29% produced a fall in PCO_2 from 93 to 77, and a further decrease to 27% oxygen caused the PCO_2 to fall to 71 with a further rise in pH to 7.33. In Case 3 (Fig. 3) lowering the inspired oxygen from 30 to 24% was necessary to reverse a progressive rise in PCO_2 . These two cases are the only ones where changes of about 5% in oxygen concentration are shown to have caused significant changes in PCO_2 .

4. At What Stage of Recovery from Acute Respiratory Failure can Uncontrolled High Concentrations of Oxygen be Substituted?

Case 1 (Fig. 1) was given oxygen by the Venturi mask at various settings, and over the course of two hours PCO_2 fell irrespective of the setting of the Venturi gauges (Table II). Case 2 (Study 1) developed a serious rise in PCO_2 to 94 (pH 7.25) when given 52% oxygen after 24 hours' controlled oxygen therapy. This rise in PCO_2 was reversed by reducing the inspired-oxygen concentration. In Case 2 (Study 2) breathing 40% oxygen produced a rise in PCO_2 on the second day, the pH falling to 7.35, and this trend was reversed when breathing air. Case 4, who suffered from moderate respiratory failure (PCO_2 58) and tolerated 42% oxygen with no exacerbation of acidosis, nevertheless developed a pH of 7.26 and PCO_2 of 77 when the Polymask was used the day after admission. Case 5, who developed carbon-dioxide narcosis when breathing from a Polymask initially, showed a rise in PCO_2 from 64 to 71 when a Polymask was used a second time three days later. Case 7 (Fig. 4) showed a marked rise in PCO_2 from 78 to 93 when 62% oxygen was injudiciously given on the first day, and this rise could not be reversed when the oxygen concentration was reduced. In Case 9 a rise in PCO_2 from 71 to 91 occurred when a Polymask was used on the second day.

It can be concluded that high concentrations of oxygen, as produced by the Polymask when set at 6 l./min. (approximately

60% oxygen, Flenley *et al.*, 1963), can cause serious exacerbations of carbon-dioxide retention for at least three days after the start of carefully controlled treatment of an acute episode of respiratory failure.

5. When Can Oxygen Therapy be Discontinued ?

Case 2 (Study 1) developed a PO_2 of 46 when breathing air after two days in hospital, and in Study 2 the PO_2 fell to 34 when breathing air on the second day. Case 4 had a PO_2 of only 60 when breathing 29% oxygen from the Venturi apparatus five days after admission. Case 5 showed similar figures on the sixth day. Case 9 had a PO_2 of only 55 when receiving 35% oxygen on the fifth day.

In the light of these results controlled oxygen therapy may be required for at least one week, if not longer, in this type of case.

Discussion

The reasons for the onset of ventilatory depression during acute exacerbations of chronic bronchitis are not fully understood. According to one school of thought the most important factor is depression and abnormal behaviour of the respiratory centre, in addition to impairment of the function of the lungs themselves. An alternative view is that the respiratory centre is behaving normally, but that the increased airways obstruction associated with the acute infection leads to such an increase in the mechanical work of breathing that failure of the respiratory muscles themselves takes place, leading to underventilation. However respiratory failure is produced, hypoxia appears to be of increasing importance as a stimulus to respiration, and the syndrome of underventilation and carbon-dioxide narcosis following oxygen therapy is well recognized. There is considerable patient-to-patient difference in the response to oxygen therapy, and Comroe *et al.* (1950) were the first of a number of groups of investigators to stress the difficulty of predicting from the initial PCO_2 , PO_2 , or pH which patients would develop respiratory depression. We have attempted to elucidate some of the causes of this uncertainty and also to assess the relative importance of the actual level of arterial PCO_2 , PO_2 , and pH .

Control of Inspired Oxygen Concentration

The magnitude of the increase in PO_2 must be one of the most important factors in bringing about ventilatory depression during oxygen therapy. Even with modern methods of oxygen therapy there is still considerable uncertainty regarding the true inspired-oxygen concentration, and for this reason a blower system previously described (Flenley *et al.*, 1963) was used in the majority of the studies reported here. This system was shown to deliver an inspired-oxygen concentration which was predictable within $\pm 1.8\%$ (95% confidence limits) and to be capable of maintaining this in the face of a respiratory minute-volume of up to 10 litres per minute. It was then possible to study the patient's response to a precise inspired-oxygen concentration and to maintain this concentration for long periods.

Relation Between the Inspired-oxygen Concentration and the Arterial Oxygen Tension

The relation between the inspired-oxygen concentration (FIO_2 %) and the arterial PO_2 is shown in Fig. 5; for the sake of comparison between patients FIO_2 % has been plotted against the increment in PO_2 (ΔPO_2) rather than the absolute values of PO_2 . The appropriate data in Cases 1 and 5 are not available.

The slope of the regression line through these points ($\Delta PO_2 / \Delta FIO_2$) is 2.08. Campbell (1960a) has used an approximation

of the two-level method of Riley, Cournand, and Donald (1951) to predict the relation between the inspired-oxygen concentration and arterial PO_2 , but we have not felt justified in this study in making the assumptions necessary to the method and have chosen to derive a purely empirical relationship. In Fig. 5 it will be seen that there is, not surprisingly, variation of response from patient to patient, and these differences are another contributing factor towards the difficulty of predicting the changes in PO_2 and PCO_2 when oxygen is given.

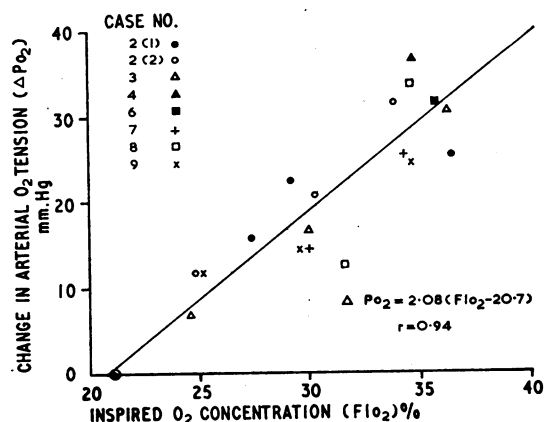


FIG. 5.—Relation between the inspired-oxygen concentrations (FIO_2) and the increment in arterial oxygen tension (ΔPO_2) above that obtaining when breathing air.

Relationship Between the Arterial Oxygen Tension and the Arterial Carbon Dioxide Tension

In the majority of patients with respiratory failure there is a further rise in PCO_2 when oxygen is given. If it is accepted that the rise in PO_2 is responsible for the depression of ventilation, then it is clearly of some importance to establish whether

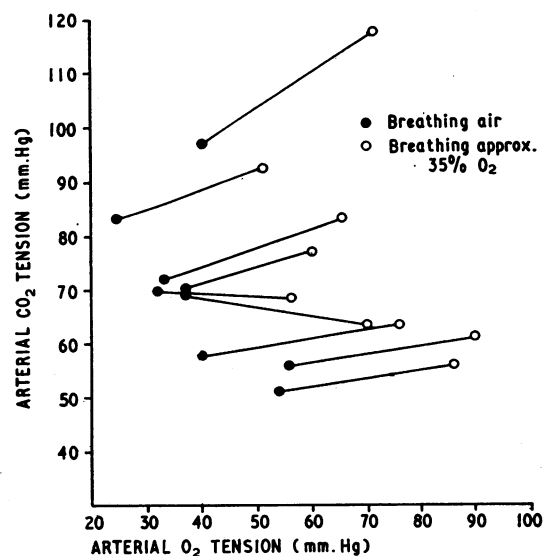


FIG. 6.—Mean arterial carbon dioxide tension (PCO_2) plotted against mean arterial oxygen tension (PO_2) when breathing air and after a period of 30 minutes' breathing 35% oxygen. All studies except Case 5.

there is any relation between the increase in arterial PO_2 (ΔPO_2) and the increase in arterial PCO_2 (ΔPCO_2).

Fig. 6 shows the mean PCO_2 and PO_2 in all cases except Case 5 during the initial period when breathing air and again after a period of at least 30 minutes breathing 35% oxygen. It will be seen that in two subjects (1 and 9) there was no rise in PCO_2 as PO_2 increased, although both patients evidently had severe respiratory failure; the other patients, however, developed a

rise in PCO_2 as is commonly described. The ratio between the increase in PCO_2 and the increase in PO_2 ($\Delta PCO_2/\Delta PO_2$) is equal to the slope of the lines in Fig. 6. This ratio appears to increase with increasing PCO_2 , and the highest value for the ratio was approximately 0.5 (Case 3) when the initial PCO_2 was 100. The exact ratio of $\Delta PCO_2/\Delta PO_2$ is of little value in practical management as these patients are in a changing state, and this ratio cannot be used to predict accurately the changes in PCO_2 which will follow changes in PO_2 later in the treatment.

Those subjects who decrease their PCO_2 and presumably increase their alveolar ventilation when given oxygen are of particular interest. Such patients may be examples of hypoxic but rapidly remediable depression of the respiratory centres. The relation between ΔPCO_2 and ΔPO_2 is clearly of clinical importance, and our results confirm that the danger of further rise in PCO_2 during oxygen therapy is greater when the PCO_2 is already at high level. The state of carbon-dioxide narcosis may then follow and is usually associated with a severe acidemia, which of itself may be of even more serious consequence.

Safe Level of Arterial Oxygen Tension

A rational approach to controlled oxygen therapy in these patients requires that a level of PO_2 be found which is high enough to prevent damage from hypoxia, and yet low enough to provide adequate respiratory stimulus, and thereby avoid severe respiratory acidosis. What is the lowest PO_2 which is safe in these patients?

Mental function is notoriously sensitive to hypoxia, and the effects in normal subjects are well documented. Boycott and Haldane (1908), experimenting on themselves in a decompression chamber, found a marked decline in mental powers, with loss of judgment and irrational behaviour as their alveolar PO_2 fell below 45. Hoffman, Clark, and Brown (1946) and Harboe (1957) found that consciousness is lost at a PO_2 of about 30. These results must be applied with caution to patients with chronic respiratory failure. In the first place the subjects in a decompression chamber have a low PCO_2 in addition to their hypoxia, for the hypoxia makes them hyperventilate. This low PCO_2 causes cerebral vasoconstriction, thereby potentiating the effects of hypoxaemia. The patients considered here have considerable cerebral vasodilatation due to hypercapnia, and this probably has a protective effect by producing a higher cerebral-tissue-oxygen tension for a given level of arterial PO_2 . In addition it is well known that man can acclimatize to low oxygen tensions. For example, West, Lahiri, Gill, Milledge, Pugh, and Ward (1962) demonstrated that mountaineers acclimatized at 19,000 ft. (5,790 m.) could exercise until their PO_2 fell to 25–35, and experienced only severe dyspnoea, without any adverse mental effects.

In our own cases mental changes due to hypoxia could not be clearly distinguished from those due to hypercapnia or acidosis. Hypoxia produces irrational and often aggressive behaviour, whereas hypercapnia leads to progressive drowsiness, but both ultimately cause stupor and finally unconsciousness. The lowest PO_2 we obtained was 23 (Case 2); this patient was unconscious on admission but suffered no neurological sequelae, and his mental faculties were normal on recovery. In a number of other cases the PO_2 when breathing air was less than 40. The PO_2 on discharge, when the patients were ambulant, was between 59 and 74 in the six cases where it was measured. We feel that many of these patients are partially acclimatized to hypoxaemia.

Changes in the ST segment and T waves of the E.C.G. were described by Patterson, Clark, and Levy (1942) when patients with myocardial ischaemia breathed low concentrations of oxygen. No such changes were seen in the eight E.C.G.s taken in our cases when the PO_2 was between 30 and 50, not even in Case 9 who had evidence of an old myocardial infarction.

Many patients continue to live for some time in a state of chronic respiratory failure, with persistent hypoxaemia and hypercapnia. Baldwin, Courmand, and Richards (1949) found a mean PO_2 of 50 (calculated from their values for oxygen saturation and pH) in their patients with chronic cor pulmonale. Aber, Bayley, and Bishop (1963) obtained similar results in eight such patients with congestive failure and oedema, but a mean PO_2 of 59 in 10 patients with chronic obstructive airways disease without heart failure. Platts, Hammond, and Stuart-Harris (1960) studied 16 patients who developed congestive failure while under observation; the oxygen saturation before the onset of failure averaged 79%, equivalent to a PO_2 of 47, assuming a pH of 7.35. After the onset of failure the mean saturation fell to 68%, equivalent to a PO_2 of 38 at the same pH. The patients in all of these studies appeared to be in a relatively stable phase and not suffering from acute exacerbations of chronic respiratory failure.

From this evidence, incomplete though it is, we suggest that a PO_2 of 50 will prevent immediate death from hypoxia in these patients, although congestive failure may develop, and we would propose that one aim of controlled oxygen therapy should be to provide a PO_2 of at least this level. We have been repeatedly impressed with the difficulty of estimating the level of PO_2 from clinical signs, such as the degree of cyanosis or mental condition, and we would emphasize that the only method at present available for ensuring that the PO_2 is above 50 is by direct measurements on arterial blood. Furthermore, in any patient with mental changes, due to either hypercapnia or hypoxia, it cannot be safely assumed that the PO_2 is over 50 if he is breathing approximately 30% oxygen (Case 2 (Study 1), Case 7, and Case 9). *The safe method is to measure the arterial PO_2 .* In the absence of an oxygen electrode the arterial blood-oxygen saturation is extremely useful, particularly in the range being considered.

Hypercapnia and Respiratory Acidosis

By definition, respiratory failure is associated with a raised PCO_2 , which in turn tends to cause a respiratory acidosis. The extent of this acidosis, as measured by the arterial pH, is determined by the buffering capacity of the blood and tissues.

1. *Pco₂ and pH.*—In addition to determination of a safe minimum level of PO_2 it is necessary to establish the levels of PCO_2 or pH which can be accepted during controlled oxygen therapy. The mental effects of hypercapnia are well known, these being dominated by drowsiness and coma; hence the term “carbon-dioxide narcosis.” Previous workers have found difficulty in establishing at what levels of PCO_2 or pH these changes occur (Comroe *et al.*, 1950; Westlake *et al.*, 1955; Sieker and Hickam, 1956), and our experience supports this view. For instance, in Case 2 (Study 2) and Case 7 drowsiness was the only feature, despite an initial PCO_2 of 70. Case 9 was mentally normal when the PCO_2 was 63, but she became confused when the PCO_2 rose to 100 with oxygen given by a Polymask.

It is difficult to decide the relative importance of pH or PCO_2 levels in determining the danger of respiratory acidosis. The contrast between Cases 3 and 7 in our series impressed upon us the importance of the pH levels. Both cases suffered from similar degrees of hypercapnia (PCO_2 120), yet in Case 3, who survived, the lowest pH was 7.25 and in Case 7, who died, the lowest pH was 7.06. In three previous studies (Comroe *et al.*, 1950; Westlake *et al.*, 1955; Sieker and Hickam, 1956) no patient died so long as the pH remained above 7.25, although Sieker and Hickam report survival in a number of cases where the pH fell considerably below this level.

2. *Buffering Capacity.*—The degree of buffering capacity of the blood can be calculated as “buffer base” from the nomogram of Singer and Hastings (1948). This value represents both bicarbonate ion and buffer protein, including haemoglobin.

Patients who are chronically exposed to high levels of PCO_2 increase the renal reabsorption of bicarbonate and thereby increase their buffer base. The rate of bicarbonate reabsorption by the renal tubules can increase by 60% as the arterial blood PCO_2 is raised experimentally from 50 to 100 in the dog (Rector, Seldin, Roberts, and Smith, 1960). This maximal reabsorption rate is achieved only when a given level of hypercapnia is maintained for four days. *In our patients there is little change in the level of buffer base after the time of admission, suggesting that the maximal rate of bicarbonate reabsorption had already been reached* (Table II).

Gross and Hamilton (1963) have described the difficulty of assessing the absolute level of PCO_2 from physical signs, and they conclude that the increase in PCO_2 over the patient's normal level when ambulant is of more importance. This "pre-morbid" level is usually not known, but we feel that it can be assumed that the pH will be above 7.35 in any ambulant patient with chronic respiratory failure. The rise in PCO_2 due to an acute exacerbation will therefore be reflected in the fall in pH below 7.35. Again this supports our view that the arterial pH is of more immediate prognostic value than the level of PCO_2 in the management of these cases.

The importance of the level of buffer base in this context is also illustrated by comparing Case 3 and Case 7. In Case 3 the buffer base was between 61 and 76 mEq/l., well over the normal range of 44 to 52 mEq/l. In Case 7, where the pH fell to 7.06, the buffer base was only between 42 and 54 mEq/l. In this case the blood urea was 200 mg./100 ml., although at necropsy the kidneys were histologically normal. It must be pointed out that the buffer base also depends upon the degree of metabolic acidosis, which can occur owing to the anaerobic production of excess lactate in these hypoxic patients (Huckabee, 1958), in addition to the renal reabsorption of bicarbonate.

It is worth noting that in the series of Sieker and Hickam (1956) the mean pH was 7.12, but the mean buffer base remained within the normal range, there being on the average no significant rise to compensate for the acidemia. The mortality rate was 50% in this group of patients.

3. *Limits of pH.*—We would suggest that one aim of controlled oxygen therapy should be to maintain the pH over 7.25. It must be pointed out that arterial blood *must* be sampled if this measurement is to be made, and that rebreathing methods can only estimate the mixed venous PCO_2 (Campbell and Howell, 1960). This method can be invaluable in establishing the diagnosis of respiratory failure, but as it cannot provide information on either the PO_2 or the pH we feel that it is not advisable to rely only on rebreathing methods in the management of severe cases of respiratory failure. In any case where the PCO_2 is over 70 by the rebreathing method when the patient is breathing air the PO_2 cannot be much more than 30 (Fig. 6), and such a case requires arterial-blood-gas monitoring in order to ensure that controlled oxygen therapy provides a PO_2 of at least 50, while the pH is maintained above 7.25.

Oxygen Therapy in Respiratory Failure Due to Chronic Bronchitis and Emphysema

These patients can be treated conservatively with controlled oxygen therapy or by mechanical ventilation with intermittent positive-pressure respiration (I.P.P.R.). From the experience in the studies described above we would propose the following scheme of treatment.

Controlled oxygen therapy can be given with various degrees of sophistication both in administration of the oxygen and in monitoring of the patient's progress.

The simplest treatment requires that only slightly elevated concentrations of oxygen, approximately 30%, be given continuously to any patient in whom an exacerbation of chest infection with cyanosis is present, if that patient is known to suffer from chronic bronchitis and emphysema. The Venturi

mask (Campbell, 1960a) or the much cheaper Edinburgh mask (Flenley *et al.*, 1963) will give an oxygen concentration controlled within about 5% in the range 21 to 35%, and this alone will be adequate for many cases.

If such patients become drowsy, or show other evidence of excessive carbon-dioxide retention on oxygen therapy, the second line of treatment is indicated. This requires an estimation of the mixed venous PCO_2 by the rebreathing method (Campbell and Howell, 1960). This will confirm the diagnosis of respiratory failure and give a reasonable estimate of the arterial PCO_2 but it does *not* measure the degree of acidosis or the adequacy of oxygenation.

For reasons given previously, we would strongly advocate that all three factors— PCO_2 , PO_2 , and pH —should be measured in the arterial blood in any case of severe respiratory failure; for example, where a "rebreathing PCO_2 " is over 70. This then constitutes the third level of sophistication in treatment, with accurate control of the inspired-oxygen concentration and repeated arterial-blood-gas measurements, which are easily obtained if a fine-bore indwelling catheter is introduced into the brachial or radial artery by the Seldinger technique. The lumen of this catheter is kept filled with a weak solution of heparin and the catheter is closed with a tap.

We would propose that the aim of this controlled oxygen therapy should be to maintain a PO_2 of at least 50 mm. Hg without depressing the pH below 7.25.

Intermittent positive-pressure respiration is indicated in our view if controlled oxygen therapy cannot maintain the arterial-blood-gas tensions or pH at the levels suggested above. In this cautious approach to I.P.P.R. we differ from Massaro, Katz, and Luchsinger (1962), who state "the only safe way to administer oxygen to patients with acute respiratory failure is in conjunction with a mechanical respirator." It is important to realize that I.P.P.R. in these patients, who have severe obstruction of the airways and who often have heart failure, is a very different proposition from that in a young previously fit subject with normal heart and lungs who may suffer from a neurological disorder or thoracic trauma. The cardiac output falls even in normal subjects during I.P.P.R. (Kilburn and Sieker, 1960) and this fall in output can be very serious in patients with cor pulmonale (Roncoroni, Agrest, Roehr, and Grzesko, 1962). Sieker and Hickam (1956) had a mortality of 50% in their patients with very severe respiratory acidosis despite the use of I.P.P.R.

Tracheostomy is often advocated in the treatment of respiratory failure. In our view this procedure is required in two circumstances. Firstly, it is necessary when obstruction of the major airways with secretions recurs despite repeated physiotherapy or bronchoscopy. Tracheostomy allows more adequate tracheal toilet in the patient who will not cough. In the second place, of course, tracheostomy is necessary before instituting I.P.P.R. with a cuffed tracheostomy tube.

Other measures required in these cases include control of infection with antibiotics, control of heart failure with digoxin and diuretics, the avoidance of sedatives (unless the patient is on a respirator), and the use of respiratory stimulants.

In summary, the management of these cases can be viewed as a therapeutic crescendo, from simple administration of slightly raised oxygen concentrations to full-scale repeated arterial blood sampling and close control of the inspired-oxygen concentration, with resort to I.P.P.R. if the suggested limits cannot be obtained by conservative measures.

The measurement of arterial PO_2 , PCO_2 , and pH has until recently been the province of specialized departments, but a strong case can now be made for the ready availability of such methods and of technical staff trained in their use. The insertion of a small-bore catheter into a peripheral artery is a simple procedure, and complications are extremely rare. The recent development of electrode methods for determining blood-gas tensions should be exploited more fully in the clinical field.

These measurements can now be made by a well-trained technician, the apparatus being mounted on a trolley for use in the ward area. While resistance to such arterial blood monitoring undoubtedly exists, it should be remembered that large-bore arterial catheters are now often used for radiological investigations in many conditions where life is not immediately threatened.

It is universally accepted that severe metabolic emergencies such as diabetic coma or acute renal failure require precise biochemical monitoring, and a different standard of observation and treatment for patients with severe respiratory failure is no longer acceptable. Both diabetic coma and advanced respiratory failure are serious emergencies which are nevertheless reversible in a large number of cases. Both emergencies require constant attention by an experienced physician supported by technical staff, and both demand frequent estimation of the appropriate blood chemistry over a number of hours or even days until a safe degree of recovery is assured.

Summary

Ten detailed studies of respiratory failure secondary to an acute exacerbation of chronic bronchitis are reported. The response of the patients to precisely defined variations in the inspired-oxygen concentration was studied by frequent analysis of the PO_2 , PCO_2 , and pH of the arterial blood, sampled from an indwelling catheter.

A wide variation in the response of the patients to oxygen was found and some of the factors which contribute to these variations have been investigated. These include: (a) the degree of control of the inspired-oxygen concentration, (b) the varying relation between the inspired-oxygen concentration and the arterial PO_2 , and (c) the varying relation between changes in arterial PO_2 and changes in the PCO_2 .

It is proposed that the aim of conservative management by controlled-oxygen therapy in these cases should be to maintain an arterial PO_2 of at least 50, without allowing the pH to fall below 7.25. A low arterial pH is thought to be of more value in assessing the severity of the condition than is the level of the arterial PCO_2 . A PCO_2 of 70 or more when breathing air suggests that severe respiratory acidosis is almost certain to occur if oxygen is given in high concentration.

Accurate control of the inspired-oxygen concentration has proved of great value even in severe cases of respiratory failure, for by this means adequate relief of hypoxia can be obtained without the production of severe respiratory acidosis. It is suggested that control of the inspired concentration within 5% in the 21 to 35% range is required, and that higher concentrations of oxygen may still be dangerous for at least three days after the start of controlled-oxygen therapy even if the response to this treatment is satisfactory. Oxygen therapy may well be required for at least one week.

Tracheostomy and mechanical ventilation are proposed as a second line of treatment if controlled oxygen therapy with antibiotics, bronchodilators, and respiratory stimulants cannot

maintain an arterial PO_2 over 50 without depressing the pH below 7.25.

A plea is made for a higher general standard of quantitative observation and treatment in respiratory failure. The levels of oxygen being administered should be known and the response in terms of arterial PO_2 , PCO_2 , and pH should be accurately determined.

One of us (D.C.F.) was supported by a grant from the Medical Research Council, and one of us (D.C.S.H.) was supported by the Scottish Home and Health Department.

REFERENCES

- Aber, G. M., Bayley, T. J., and Bishop, J. M. (1963). *Clin. Sci.*, **25**, 159.
- Baldwin, E. de F., Cournand, A., and Richards, D. W. (1949). *Medicine (Baltimore)*, **28**, 201.
- Barach, A. L. (1938). *Ann. intern. Med.*, **12**, 454.
- Bernéus, B., Carlsten, A., Holmgren, A., and Seldinger, S. I. (1954). *Scand. J. clin. Lab. Invest.*, **6**, 217.
- Bishop, J. M., and Pincock, A. C. (1959). *J. Physiol. (Lond.)*, **145**, 20P.
- Boycott, A. E., and Haldane, J. S. (1908). *Ibid.*, **37**, 355.
- Campbell, E. J. M. (1960a). *Lancet*, **2**, 10.
- (1960b). *Ibid.*, **2**, 12.
- and Howell, J. B. L. (1960). *Brit. med. J.*, **1**, 458.
- Comroe, J. H., Bahnon, E. R., and Coates, E. O. (1950). *J. Amer. med. Ass.*, **143**, 1044.
- Donald, K. W. (1949). *Lancet*, **2**, 1056.
- (1953). *Ibid.*, **1**, 495.
- Flenley, D. C., Hutchison, D. C. S., and Donald, K. W. (1963). *Brit. med. J.*, **2**, 1081.
- Gross, N. J., and Hamilton, J. D. (1963). *Ibid.*, **2**, 1096.
- Harboe, M. (1957). *Acta physiol. scand.*, **40**, 248.
- Hoffman, C. E., Clark, R. T., and Brown, E. B. (1946). *Amer. J. Physiol.*, **145**, 685.
- Huckabee, W. E. (1958). *J. clin. Invest.*, **37**, 264.
- Kilburn, K. H., and Sieker, H. O. (1960). *Circulat. Res.*, **8**, 660.
- Laws, J. W., and Heard, B. E. (1962). *Brit. J. Radiol.*, **35**, 750.
- Massaro, D. J., Katz, S., and Luchsinger, P. C. (1962). *Brit. med. J.*, **2**, 627.
- Meneely, G. R., and Kaltreider, N. L. (1941). *Proc. Soc. exp. Biol. (N.Y.)*, **46**, 266.
- Needham, C. D., Rogan, M. C., and McDonald, I. (1954). *Thorax*, **9**, 313.
- Patterson, J. E., Clark, T. W., and Levy, R. L. (1942). *Amer. Heart J.*, **23**, 837.
- Platts, M. M., Hammond, J. D. S., and Stuart-Harris, C. H. (1960). *Quart. J. Med.*, **29**, 559.
- Rector, F. C., Seldin, D. W., Roberts, A. D., and Smith, J. S. (1960). *J. clin. Invest.*, **39**, 1706.
- Riley, R. L., Cournand, A., and Donald, K. W. (1951). *J. appl. Physiol.*, **4**, 102.
- Roncoroni, A. J., Agrest, A., Roehr, E., and Grzesko, S. (1962). *Amer. Heart J.*, **64**, 207.
- Severinghaus, J. W. (1958). In *Handbook of Respiration*, edited by D. S. Dittmer and R. M. Grebe, p. 73. Saunders, Philadelphia.
- and Bradley, A. F. (1958). *J. appl. Physiol.*, **13**, 515.
- Sieker, H. O., and Hickam, J. B. (1956). *Medicine (Baltimore)*, **35**, 389.
- Singer, R. B., and Hastings, A. B. (1948). *Ibid.*, **27**, 223.
- West, J. B., Lahiri, S., Gill, M. B., Milledge, J. S., Pugh, L. G. C. E., and Ward, M. P. (1962). *J. appl. Physiol.*, **17**, 617.
- Westlake, E. K., Simpson, T., and Kaye, M. (1955). *Quart. J. Med.*, **24**, 155.