in individual members of the control group was unrelated to their gastric acidity. This degree of blood loss has been shown to be remarkably constant for any individual (Croft and Wood, 1967). It would appear that the control patients with the greater blood loss possess some factor or factors absent in almost all patients with pernicious anaemia as well as in the remaining control patients. Differences in the rate of gastric emptying, gastric mucosal characteristics, or in systemic effects of aspirin may be responsible for the variation in blood loss between individuals.

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# Effect of Controlled Oxygen Therapy on Arterial Blood Gases in Acute Respiratory Failure

D. A. WARRELL,* B.M., M.R.C.P. ; R. H. T. EDWARDS,* M.B., PH.D., M.R.C.P. ; S. GODFREY,*‡ M.B., PH.D., M.R.C.P.
N. L. JONES,† M.D., M.R.C.P.

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**Summary: Seven patients in acute exacerbation of chronic respiratory failure were given 24·5% and later 28% oxygen through Ventimasks. The mean increases in arterial $P_{O_2}$ were 11 and 21 mm. Hg while breathing 24·5% and 28% oxygen respectively compared with control values while breathing air. Associated increases in arterial $P_{CO_2}$ were 4 and 8 mm. Hg, respectively. In five of the patients these increases in inspired oxygen concentration resulted in useful increases in tissue oxygen supply without significant deterioration in ventilation, but in two patients arterial $P_{CO_2}$ rose excessively and artificial ventilation was required.**

## Introduction

An essential part of the management of respiratory failure occurring in patients with chronic airway obstruction is the relief of hypoxia by increasing inspired oxygen concentration. Campbell (1965) suggested that the continuous administration of 24·5% or 28% oxygen might be expected to increase arterial oxygen saturation and tissue oxygen supply by a useful amount with less risk of decreasing ventilation than would be incurred by the use of higher concentrations of oxygen. The present paper reports a study of the effect of 24·5% and 28% oxygen administration to patients admitted to hospital with acute respiratory failure. The object was to document the improvement in arterial $P_{O_2}$, study the time course of any changes, and examine the effect on arterial $P_{CO_2}$.

## Methods

*Patients.*—The seven patients were chronic bronchitics (Medical Research Council, 1965). In five of them, who had been attending an outpatient clinic for cases of respiratory disease, previous values for forced expired volume in the first second ($F.E.V._1$) had been less than 50% of predicted normal (Cotes, 1965), indicating chronic severe airway obstruction, and rebreathing mixed venous $P_{CO_2}$ ($P\bar{v}CO_2$) (Campbell and Howell, 1960) had been persistently raised, indicating chronic respiratory failure (Table I). They were admitted to hospital during an exacerbation of symptoms associated with evidence of acute worsening of respiratory failure; $P\bar{v}CO_2$ was above 65 mm. Hg and at least 15 mm. Hg higher than the values obtained in the outpatient clinic.

## Management

None of the patients had received oxygen therapy on their way to hospital; they were seen in the emergency department, being accepted into the study on the basis of a clinical assessment and measurement of $P\bar{v}CO_2$. The patients were moved to the ward and standard treatment with antibiotics, bronchodilators, and diuretics was instituted. Their co-operation in the study was obtained by informed consent. A Teflon cannula was inserted percutaneously into a radial artery and flushed at 15-minute intervals with small amounts of heparinized saline. Blood was sampled for the measurement of arterial gas tensions ($Pa_{O_2}$, $Pa_{CO_2}$) and lactate concentration, plasma bicarbonate and electrolyte concentrations, blood urea, serum lactic dehydrogenase activity, haemoglobin, packed cell volume, and leucocyte count. After 30 minutes blood gas tensions were again measured. The patients were then started on oxygen through a 24% Ventimask (Vickers Medical) (Campbell and Gebbie, 1966). Blood gas tensions were measured 15, 30, 60, 120, and 150 minutes later and lactate was measured at 60 minutes. A 28% Ventimask was substituted at 150 minutes and measurements were repeated 15, 30, 60, and 120 minutes later.

The oxygen concentrations produced by Ventimasks were measured in the laboratory with a mass spectrometer (Campbell and Gebbie, 1966). Nominally 24% masks delivered a mean inspired concentration of 24·3 (S.D. 0·3)% oxygen, and 28% masks a mean of 28·2 (S.D. 0·4)% oxygen; values of 24·5% and 28%, respectively, were assumed in the present study. During the study routine observations of clinical state were made and recorded; these included the ability to cough and produce sputum either spontaneously or with help, a measure of the mental state, blood pressure, and heart rate. A portable chest radiograph and an electrocardiogram (E.C.G.) were taken as soon as possible after admission.

*Medical Registrar, Hammersmith Hospital. London W.12.
†Honorary Lecturer, Royal Postgraduate Medical School, London W.12. Present address: St. Joseph's Hospital, Hamilton, Ontario.
‡Present address: Institute for Diseases of the Chest, Brompton Hospital, London S.W.3.

## Analytical Techniques

Arterial blood was sampled anaerobically in heparinized glass syringes and was analysed within five minutes. $P_{O_2}$ was measured with a Beckman macroelectrode and $P_{CO_2}$ with a Severinghaus electrode, calibrated with gases previously analysed in the Lloyd-Haldane apparatus. The S.D. of duplicate measurements was 0·3 mm. Hg. Tonometry experiments were performed during the period in which the studies were made; the 95% confidence limits for measurements of $P_{O_2}$ were ± 1·5 mm. Hg and of $P_{CO_2}$ ± 1 mm. Hg. Values for arterial oxygen saturation ($Sa_{O_2}$) were derived from $P_{O_2}$ and $P_{CO_2}$ by means of the computer table prepared by Ball and Shephard (Denison, 1968). Ideal alveolar to arterial $P_{O_2}$ difference ($PA-a_{O_2}$) and pulmonary venous admixture ($\dot{Q}va/\dot{Q}t$) were calculated (see Table III), assuming values of 0·8 for respiratory exchange ratio and 5 ml./100 ml. for arteriovenous oxygen content difference. Plasma bicarbonate was measured with a Natelson microgasometer (Scientific Industries, Model 600), and arterial *p*H was then derived by use of the Henderson–Hasselbalch equation, assuming a value of 6·10 for p*K'* (Sinclair *et al.*, 1968). Arterial lactate concentration was measured by an enzymatic method (Boehringer and Soehne, Mannheim, West Germany); the S.D. of duplicate estimates was 0·17 mM/1. Haemoglobin was measured by the cyanmethaemoglobin method; plasma electrolytes, blood urea, and lactic dehydrogenase were measured with an autoanalyser.

## Results

Severe hypoxaemia was present during the initial period of air-breathing; the range of $Pa_{O_2}$ was between 25 and 38 mm. Hg (Fig. 1). There was a moderate degree of hypercapnia, $Pa_{CO_2}$ ranging from 55 to 76; all but one patient had values for $Pa_{CO_2}$ of over 65 mm. Hg. The patients were in a steady state before the administration of oxygen, $Pa_{O_2}$ and $Pa_{CO_2}$ changing less than 2 mm. Hg over the first 30 minutes in most cases. $Pa_{O_2}$ increased after 15 minutes of 24·5% oxygen but little further change at 30 minutes. The values for $Pa_{O_2}$ obtained from each patient 60 and 120 minutes after starting oxygen were compared with the average of the two control values breathing air. The mean increase in $Pa_{O_2}$ for the group of seven patients with 24·5% oxygen was 10·9 mm. Hg (range 6·7-17·9, S.D. 4·0 mm. Hg) (Fig. 2, Table II). The corresponding increase in $Sa_{O_2}$ was 16·4% (range 12 to 25, S.D. 4·6). The $Pa_{CO_2}$ increased in all but one patient, the average rise being 4·3 mm. Hg (range −1·2 to +9·3, S.D. 3·42 mm. Hg) (Table II).

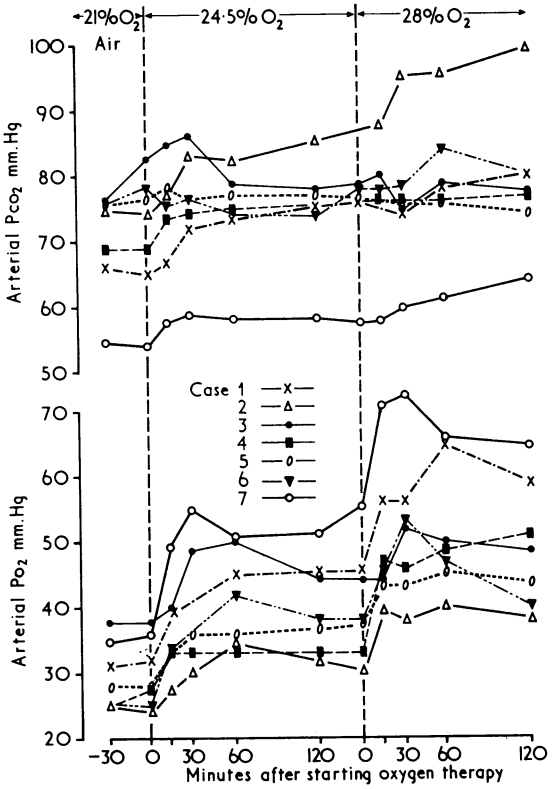


Fig. 1.—Values for arterial blood gas tensions during the first five hours of hospital admission in seven patients with acute respiratory failure breathing air and 24·5% and 28% oxygen by Ventimask.

TABLE I.—*Clinical Information About Seven Patients with Acute Respiratory Failure*

| Case No. | Age | Sex | Pulmonary Function before Exacerbation of Symptoms. Time of Measurement (Months) before Admission in Parentheses | | | | | Clinical Course |
|---|---|---|---|---|---|---|---|---|
| | | | F.E.V.$_1$ (1.) B.T.P.S. | V.C. (1.) B.T.P.S. | F.E.V.$_1$/V.C. (%) | TLco* (ml./min./mm. Hg) | $P\bar{v}co_2$ (mm. Hg) | |
| 1 | 54 | F. | 0·32 | 1·53 | 21 (6) | 3·3 (1) | 57 (6) | Artificial ventilation 8 hours after admission. Developed surgical emphysema. Died 6 days after admission |
| 2 | 65 | F. | | | No values available | | | Artificial ventilation 6 hours after admission. Discharged after 2 weeks: $Pa_{O_2}$ 51·5, $Pa_{CO_2}$ 47·5 mm. Hg |
| 3 | 56 | F. | 1·08 | 2·25 | 48 (5) | 18·9 (8) | 43 (5) | Discharged after 2 weeks: $P\bar{v}co_2$ 50 mm. Hg |
| 4 | 66 | M. | 0·50 | 1·70 | 29 (1) | 9·2 (20) | 66 (1) | Discharged after 3 weeks: $P\bar{v}co_2$ 63 mm. Hg |
| 5 | 71 | M. | 0·55 | 1·70 | 32 (4) | 20·0 (6) | 61 (4) | Discharged after 3 weeks: $Pa_{O_2}$ 49, $Pa_{CO_2}$ 45 mm. Hg |
| 6 | 58 | M. | 0·90 | 2·10 | 43 (7) | 13·8 (24) | 66 (7) | Discharged after 3 weeks: $P\bar{v}co_2$ 72 mm. Hg |
| 7 | 70 | M. | | | No values available | | | Discharged after 10 days: $P\bar{v}co_2$ 61 mm. Hg |

*Carbon monoxide uptake (single breath method).
B.T.P.S. = Body temperature, pressure, and saturation.

TABLE II.—*Mean Values (and 1 S.D.) for Measured Blood Gas Tensions ($Pa_{CO_2}$, $Pa_{O_2}$), Derived Oxygen Saturation ($Sa_{O_2}$) and Calculated Alveolar to Arterial $P_{O_2}$ Difference ($PA-a_{O_2}$) and Pulmonary Venous Admixture ($\dot{Q}va/\dot{Q}t$) in Seven Patients with Acute Respiratory Failure*

| Variable | | Air (20·9% $O_2$) | | 24·5% $O_2$ | | | | | 28% $O_2$ | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Time (minutes) | | −30 | 0 | +15 | 30 | 60 | 120 | 150 (0) | +15 | 30 | 60 | 120 |
| $Pa_{CO_2}$ (mm. Hg) | Mean | 70·2 | 71·2 | 73·7 | 75·2 | 73·8 | 70·0 | 75·6 | 76·2 | 76·4 | 78·5 | 78·9 |
| | 1 S.D. | 7·7 | 9·4 | 8·6 | 8·7 | 8·3 | 10·6 | 8·9 | 9·1 | 10·3 | 10·3 | 10·5 |
| $Pa_{O_2}$ (mm. Hg) | Mean | 29·8 | 29·8 | 36·7 | 40·3 | 43·0 | 44·4 | 40·6 | 49·7 | 51·6 | 51·9 | 49·7 |
| | S.D. | 4·9 | 5·3 | 6·8 | 8·8 | 7·1 | 6·9 | 8·7 | 10·8 | 11·4 | 9·9 | 9·8 |
| $Sa_{O_2}$ (% sat.) | Mean | 48·0 | 48·0 | 59·7 | 63·4 | 68·0 | 71·0 | 64·1 | 74·1 | 76·3 | 76·7 | 74·3 |
| | S.D. | 10·4 | 11·3 | 10·5 | 12·0 | 9·5 | 9·5 | 12·2 | 9·6 | 9·5 | 8·9 | 10·0 |
| $PA-a_{O_2}$ | Mean | 34·5 | 33·3 | 48·7 | 43·7 | 43·6 | 45·9 | 42·8 | 58·9 | 56·6 | 53·9 | 55·9 |
| | S.D. | 8·3 | 10·4 | 7·0 | 9·1 | 8·1 | 6·8 | 5·1 | 5·9 | 7·7 | 8·6 | 10·8 |
| $\dot{Q}va/\dot{Q}t$ (%) | Mean | 61 | 60 | 57 | 52 | 51 | 48 | 52 | 46 | 44 | 43 | 46 |
| | S.D. | 7 | 9 | 8 | 12 | 9 | 10 | 10 | 12 | 12 | 11 | 12 |

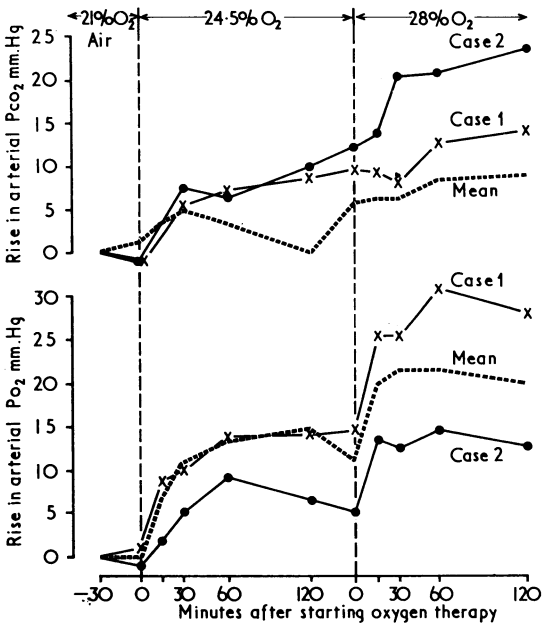


FIG. 2.—Changes in arterial blood gas tensions from initial values (at −30 minutes) during the first five hours of hospital admission in the two patients who eventually required artificial ventilation compared with the mean values for the whole group of seven patients.

Administration of 28% oxygen led to a further increase in $Pa_{O_2}$ to an average of 21·4 mm. Hg above control levels while breathing air (range 12·9 to 33·3, S.D. 7·6 mm. Hg); the increase in $Sa_{O_2}$ averaged 26·3% (range 15 to 35, S.D. 6·2%) (Table II). In five patients there was little change in $P_{CO_2}$ above that obtained during the breathing of 24·5% oxygen; in the other two patients, both of whom had shown the highest increases during the 24·5% $O_2$ breathing, the $P_{CO_2}$ rose to 11·8 and 22·2 mm. Hg above control values. The average increase in $P_{CO_2}$ during 28% breathing was 7·7 mm. Hg above control values (range −0·6 to +22·2, S.D. 7·40 mm. Hg) (Table II). Calculated arterial *p*H on admission ranged between 7·23 and 7·39 at a time when arterial lactate concentration ranged between 1·02 and 1·67 mM/l. (Table III). After the patients had breathed 24·5% oxygen for 60 minutes, lactate had fallen by an average of 0·32 mM/l. (changes ranged from +0·08 to −0·71 mM/l.).

Serum lactic dehydrogenase and its heat-stable fraction were within the normal range in all cases. In four patients the haemoglobin concentration was above 16 g./100 ml. Radiographical changes consistent with bronchopneumonia were seen in four patients, and cardiac enlargement was seen in four. In three patients the main pulmonary arteries were prominent (Table III). There was E.C.G. evidence of right atrial or ventricular hypertrophy, or both, in four patients. Two patients had atrial arrhythmias (Table III).

*Clinical Course* (Table I).—The condition of five patients (Cases 3-7) improved so that they were fit to be discharged after 10 days to three weeks in hospital. Their blood gases on discharge indicated improved ventilation compared with the day of admission. In the two patients (Cases 1 and 2) whose $Pa_{CO_2}$ increased markedly during oxygen therapy the level of consciousness decreased progressively despite vigorous conservative measures, including physiotherapy and analeptic drugs. Assisted ventilation via endotracheal tube was required. One (Case 2) was discharged, well, after two weeks, but the other (Case 1) had a complicated clinical course and died six days after admission (Table I).

## Discussion

McNicol and Campbell (1965) found that patients with long-standing airway obstruction who presented with acute respiratory failure were severely hypoxaemic and moderately hypercapnic: $Pa_{O_2}$ was between 20 and 40 mm. Hg in 78% and $Pa_{CO_2}$ was between 60 and 80 in 74%. Blood gas tensions in our patients, before active therapy had been started, fell within these ranges. A major problem in such patients is the relief of hypoxaemia without worsening the degree of hypercapnia, which can lead to coma (Westlake *et al.*, 1955). Campbell (1960) pointed out that in these patients useful increases in arterial oxygen saturation result from small increases in arterial oxygen pressure. Such modest increases in arterial oxygen pressure can be achieved by relatively small increases in inspired oxygen concentration whose use should minimize the degree of respiratory depression asso-

TABLE III.—*Result of Investigations in Seven Patients with Acute Respiratory Failure on Admission to Hospital*

| Case No. | $PvCO_2$ (mm. Hg) | Arterial Bicarbonate Conc. (mM/l.) | Arterial *p*H | Arterial Lactate Conc. (mM/l.) | | Plasma Electrolyte Conc. (mN) | | | Blood Urea (mg./100 ml.) | L.D.H. (i.u./100 ml.) | Hb (g /100 ml.) | P.C.V. (%) | Leucocyte Count (cells/ cu. mm.) | Chest Radiogram | E.C.G. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Breathing Air | After 1 hour of 24·5% oxygen | Na | K | Cl | | | | | | | |
| Laboratory Normal range: | | | | | | 136–149 | 3·8–5·2 | 100–107 | 14–38 | 50-170 (30-60%)* | | | | | |
| 1 | 77 | 33·8 | 7·32 | 1·49 | 0·90 | 135 | 5·3 | 89 | 98 | — | 18·6 | 61 | 5,000 | Cardiomegaly, prominent P.A., basal consolidation | R.A.H. R.V.H. |
| | — | 38·5 | 7·32 | 1·67 | 1·28 | 136 | 4·9 | 88 | 72 | 105 (50%) | 16·3 | 57 | 6,000 | Prominent P.A., basal consolidation | Atrial ectopic beats R.A.H. R.V.H. |
| 3 | 81 | 33·3 | 7·25 | 1·02 | 1·10 | 136 | 5·0 | 94 | 85 | 165 (60%) | 15·0 | 51 | 7,000 | Cardiomegaly | Atrial fibrillation |
| 4 | 81 | 42·1 | 7·39 | 1·54 | 0·83 | 141 | 2·8 | 82 | 52 | 125 (65%) | 12·2 | 43 | 9,000 | Cardiomegaly, pleural effusion | Normal |
| 5 | 81 | 31·3 | 7·23 | 1·25 | 1·10 | 137 | 4·0 | 88 | 27 | 120 (45%) | 16·5 | 53 | 8,000 | Basal consolidation | Normal |
| | 86 | 33·8 | 7·26 | 1·35 | 1·22 | 136 | 4·6 | 90 | 146 | — | 16·5 | 55 | 13,000 | Cardiomegaly, prominent P.A., lobar consolidation | R.V.H. |
| | 70 | 30·0 | 7·35 | — | — | 137 | 4·6 | 90 | 36 | 170 (40%) | 14·6 | 48 | 17,000 | Long-standing extensive fibrosis (old tuberculosis) | R.A.H. |

* Heat stable fraction.
P.A. = pulmonary artery. R.A.H. = right atrial hypertrophy. R.V.H. = right ventricular hypertrophy.

ciated with relief of hypoxaemia. We have confirmed these observations. In our patients an increase in the inspired oxygen pressure of 25 mm. Hg produced with 24·5% oxygen led to an average increase of 11 mm. Hg in $Pa_{O_2}$ and of 16% in $Sa_{O_2}$. This increase in oxygen saturation represents an increase of about 200 ml./min. in the oxygen available to the tissues at a cardiac output of 61 ml./min., an increase sufficient to supply the basal needs for oxygen (Campbell, 1967). A further increase of 25 mm. Hg in the inspired oxygen pressure by administration of 28% oxygen led to increases of 10 mm. Hg in $Pa_{O_2}$ and 10% in $Sa_{O_2}$ over and above those obtained while breathing 24·5% oxygen.

Though $Sa_{O_2}$ was on average less than 50% before the start of oxygen therapy there was little biochemical evidence of tissue hypoxia. Arterial lactate concentrations were only marginally raised, but they had fallen after administration of 24·5% oxygen for 60 minutes. Higher arterial lactate levels were reported by Penman (1962) in patients with acute exacerbations of chronic bronchitis. Values ranged between 0·8 and 6·2 mM/l. while breathing air and fell by an average of 0·5 mM/l. after 15 minutes of breathing 100% oxygen. Penman's patients were generally less hypoxaemic than ours. It is possible that the manometric method which he used to estimate lactate gave higher values than the enzyme method used by us. Serum lactic dehydrogenase levels were normal in our patients as in most of Refsum's (1963) patients who had acute exacerbations of chronic respiratory failure. Refsum found that serum aspartate and alanine aminotransferases were raised in some patients who had a normal lactic dehydrogenase.

Comparison of the results of the present study with those reported by other authors is complicated by differences in the method of administering oxygen and in the clinical condition of the patients with chronic airways obstruction. Schiff and Massaro (1967) observed a mean increase of 11 mm. Hg in $Pa_{O_2}$ after changing from air to 24·5% oxygen by Ventimask in patients who were not acutely ill. Mithoefer *et al.* (1967) gave oxygen by Ventimask to patients who were clinically stable and also to those in respiratory failure. Their procedure was not standardized, however, and a wide range of $Pa_{O_2}$ changes were observed. Hutchison *et al.* (1964) administered oxygen by the Edinburgh mask to patients with acute respiratory failure. The inspired oxygen concentrations were generally higher than those used in the present study and no fixed sequence was employed. The overall relationship between $Pa_{O_2}$ and inspired oxygen concentration ($FI_{O_2}$) was an increase of 2·08 mm. Hg $Pa_{O_2}$ for each 1% increase in $FI_{O_2}$ which is less than the value of 3·3 mm. Hg/1% calculated from the maximum increase in $Pa_{O_2}$ after 24·5% and 28% oxygen in our patients. The increases in $Pa_{O_2}$ after oxygen administration were associated with increases in $Pa_{CO_2}$. With 24·5% oxygen these were small in degree, amounting on an average to less than 5 mm. Hg, an insignificant worsening in the degree of hypercapnia; this compares with an average value of 2 mm. Hg obtained by Schiff and Massaro (1967). The increases were more pronounced with 28% oxygen, amounting to about 8 mm. Hg above the $Pa_{CO_2}$ during air breathing. There was some variation in the response of individual patients; it is noteworthy that the two patients showing the greatest increases in $Pa_{CO_2}$ eventually required endotracheal intubation and intermittent positive-pressure breathing in order to counteract their worsening respiratory failure.

The presence of severe abnormalities in the distribution of ventilation and perfusion in the lungs of these patients limited the increase in $Pa_{O_2}$ to less than half of the increase in inspired $P_{O_2}$. If there was no change in the cardiac output and respiratory exchange ratio, we may calculate the change in venous admixture ratio, using the average values obtained in our studies. These calculations (Table II) imply that much of the total cardiac output, amounting to 60%, was effectively bypassing gas-exchanging parts of the lung while the patients were breathing air; this proportion fell to 50% during the breathing of 24·5% $O_2$ and to 44% during the breathing of 28% $O_2$. Though various factors, particularly the improved drainage of blocked bronchi, may have been expected to improve ventilation–perfusion relationships during the time of study, the administration of oxygen itself may have brought the improvements. Possibly the vascular reactivity of areas of the lung which are severely hypoxic may be improved by the administration of oxygen, so that the compensatory local vasoconstriction may become more effective. In contrast, Lee and Read (1967) found that inhalation of 100% oxygen by patients with chronic airway obstruction caused a deterioration in ventilation-perfusion relationships. Their patients differed from ours, however, in that they had fully recovered from episodes of respiratory infection or respiratory failure and were much less hypoxaemic ($Sa_{O_2}$ 73-97%).

Various methods for the administration of oxygen to patients in respiratory failure have been advocated in recent years. We prefer the Ventimask because it yields an accurately known concentration in spite of varying oxygen flow and variable breathing patterns (Campbell and Gebbie, 1966; Bethune and Collis, 1967; Green, 1967; McNicol, 1967). We have confirmed in this study that oxygen therapy needs to be accurately controlled in order to avoid increasing hypercapnia. The improvement in arterial oxygen saturation with 24·5% $O_2$ with little or no increase in $Pa_{CO_2}$ suggests that this regimen is effective, and is the one which should be used if serial blood gas determinations are not available. We should emphasize, however, that ideally the treatment of any patient in this situation should be controlled with measurements of mixed venous or arterial $P_{CO_2}$ so that any worsening of the respiratory failure can be detected early and the appropriate measures instituted.

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Requests for reprints should be addressed to Dr. D. A. Warrell, Department of Medicine, Hammersmith Hospital, Du Cane Road, London W.12.

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