Changes in arterial blood gases during and after a period of oxygen breathing in patients with chronic hypercapnic respiratory failure and in patients with asthma

M. RUDOLF*, J. A. McM. TURNER, B. D. W. HARRISON, J. F. RIORDAN AND K. B. SAUNDERS

Department of Medicine, The Middlesex Hospital Medical School, London

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Summary

1. Ten patients with chronic hypercapnic respiratory failure (group 1) and eight patients with asthma (group 2) breathed pure O₂ from an MC mask for 60 min. Blood gases were measured during this period and for the subsequent 45 min.

2. In nine of ten patients in group 1 and in all eight patients in group 2 arterial O₂ tension (PₐO₂) fell to values lower than had been obtained before O₂ was given.

3. These undershoots in PₐO₂ are unrelated to changing CO₂ stores or to hypoventilation, and are more likely due to persistence of altered ventilation-perfusion ratios associated with O₂ breathing.

4. Magnitude of the undershoots is usually small, and periods of less than 15 min off O₂ are unlikely to be harmful.

Key words: asthma, chronic hypercapnia, hypoxaemia, oxygen breathing, oxygen transients, respiratory failure, ventilation-perfusion ratios.

Introduction

In treating patients with acute exacerbations of chronic hypercapnic respiratory failure it may be difficult to increase arterial oxygen tension (PₐO₂) without an unacceptable rise in the arterial carbon dioxide tension (PₐCO₂). It is best to give a small but continuous increase in inspired O₂ concentration (Campbell, 1960b; Hutchison, Flenley & Donald, 1964; Campbell, 1967). Intermittent administration of O₂ (Cohn, Carroll & Riley, 1954) is illogical because it only intermittently relieves hypoxia (Massaro, Katz & Luchsinger, 1962).

Another disadvantage of intermittent O₂ therapy in such patients is that some become more hypoxaemic after supplemental O₂ than they were before they received it (Massaro et al., 1962; Cullen & Kaemmerlen, 1967) and thus intermittent O₂ administration may be dangerous. Two textbooks of respiratory disease state that O₂ therapy in patients with hypercapnic respiratory failure should be continuous (Cumming & Semple, 1973; Crofton & Douglas, 1975) and point out that hypoxaemia may worsen when O₂ therapy stops but give different explanations: the former ascribes the undershoot in PₐCO₂ to persistent hypoventilation induced during O₂ breathing, the latter to the different washout characteristics of large CO₂ and small O₂ stores (Campbell, 1960a).

Although continuous administration of O₂ may be intended, such therapy is often intermittent, either because the patient removes the mask or because the physician removes it so that arterial blood gases can be measured during air breathing. What then is the time course of PₐCO₂ and PₐO₂ after a period of O₂ breathing and, if there is a rebound fall in PₐO₂, what is the magnitude and the cause of it? We have studied these questions in
patients with chronic hypercapnic respiratory failure and in patients with asthma who were hypoxic but had a normal or low $P_{a, CO_2}$.

Methods

Patients

We studied two separate groups of patients.

**Group 1.** Ten patients (eight male, two female), mean age 65 years (range 45–78 years). All had been admitted to hospital with an episode of acute on chronic hypercapnic respiratory failure, but were clinically stable at the time of the study. All had chronic bronchitis (Medical Research Council, 1965), and nine were smokers or ex-smokers. All had chronic irreversible airflow obstruction (mean FEV$_1$ of 0.8 litre; range 0.5–1.35 litres). At the time of study, mean $P_{a, O_2}$ was 49.0 mmHg (6.53 kPa) with range 39.5–58.4 mmHg and mean $P_{a, CO_2}$ was 58.0 mmHg (7.74 kPa) with range 45.2–73.3 mmHg.

**Group 2.** Eight patients (five male, three female), mean age 51 years (range 18–69 years). All had recently been admitted to hospital with severe asthma with hypoxaemia ($P_{a, O_2} < 60$ mmHg) and normo- or hypocapnia ($P_{a, CO_2} < 45$ mmHg). All were clinically stable at the time of study. None had chronic bronchitis and all had evidence of reversible airflow obstruction. At the time of study, mean $P_{a, O_2}$ was 63.5 mmHg (8.47 kPa) with range 52.0–70.5 mmHg, and mean $P_{a, CO_2}$ was 35.3 mmHg (4.71 kPa) with range 25.4–40.8 mmHg.

Protocol

Diuretics and bronchodilators were withheld for 12 h before the study. A brachial artery cannula was inserted under local anaesthesia, and blood samples were taken 15 and 30 min later while the patient was breathing air; the mean $P_{a, O_2}$ and $P_{a, CO_2}$ values of these two samples provided control (pre-O$_2$) values. Pure O$_2$ was then given via an MC mask at a flow rate of 4 litres/min, giving an inspired O$_2$ concentration of about 60%. Blood samples were taken at 30 and 60 min of O$_2$ breathing, after which the patient again breathed air and further samples were taken at 2, 4, 6, 10, 20, 30 and 45 min. Throughout the study the patients maintained a constant semi-recumbent posture. Patients in group 2 took three deep inspirations at 45 min after O$_2$ breathing and further samples were then taken at 2.5, 5, 10, 15 and 20 min.

The experimental protocol had been approved by the Hospital’s Ethical Committee, and there were no adverse effects.

Blood-gas analysis

Blood samples were taken into heparin-treated glass syringes and analysed in duplicate with standard Radiometer electrodes (type E 5046, type E 5036 and type G297/G2, all with a standard PHM27 meter), calibrated with standard gases and buffers immediately before and after every sample. Arterial O$_2$ saturations were calculated with the Severinghaus blood-gas calculator (Severinghaus, 1966).

For each group changes in blood-gas data were assessed for statistical significance by Student’s paired $t$-test.

Results

Full data on individual blood-gas analyses are given in Clinical Science Tables 79/4 and 79/5, deposited with the Librarian, the Royal Society of Medicine, 1 Wimpole Street, London W1M 8AE, who will supply copies on request.

**Group 1**

Mean $P_{a, O_2}$ ($\pm$ 1 SD) increased from a control value of 49.0 ± 6.9 mmHg (6.53 ± 0.92 kPa) to 184 ± 68.6 mmHg (24.52 ± 9.15 kPa) at the end of the O$_2$ breathing hour, and mean $P_{a, CO_2}$ increased from 58.0 ± 8.0 mmHg (7.74 ± 1.07 kPa) to 66.8 ± 9.4 mmHg (8.91 ± 1.26 kPa); the increase in mean $P_{a, CO_2}$ was highly significant ($P < 0.001$), and a rise in CO$_2$ tension was seen in all ten patients (Table 1).

On cessation of O$_2$ breathing, both $P_{a, O_2}$ and $P_{a, CO_2}$ fell to values not significantly different from control values ($P > 0.05$) by 10 min. Mean $P_{a, CO_2}$ subsequently remained not significantly different from control, but mean $P_{a, O_2}$ continued to fall, being significantly lower than the control at 30 min, 45.5 ± 5.9 mmHg (6.07 ± 0.78 kPa), $P < 0.05$, and at 45 min, 44.2 ± 6.8 mmHg (5.90 ± 0.91 kPa), $P < 0.01$. $P_{a, O_2}$ fell below control values in nine of the ten patients. Calculated mean O$_2$ saturation at 45 min (74.2 ± 10.0%) was also significantly lower than the control value (79.0 ± 8.9%, $P < 0.05$). The largest individual fall in saturation was 16.3%.

The time course of these events is more clearly shown by plotting changes relative to the control
<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Control Pre-O₂</th>
<th>On O₂</th>
<th>After cessation of O₂</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>30</td>
<td>60</td>
<td>2</td>
</tr>
<tr>
<td>$P_aO_2$</td>
<td></td>
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<tr>
<td>(mmHg)</td>
<td>45.0</td>
<td>176.3***</td>
<td>183.9***</td>
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<td></td>
<td>(6.9)</td>
<td>(68.7)</td>
<td>(68.6)</td>
</tr>
<tr>
<td>$P_aCO_2$</td>
<td>57.0</td>
<td>65.9***</td>
<td>66.4***</td>
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<tr>
<td>(mmHg)</td>
<td>(8.0)</td>
<td>(9.9)</td>
<td>(9.4)</td>
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Mean values (±1 SD) are shown. Significance of difference from control value: *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$; † not significant ($P > 0.05$).
pre-O₂ values (Fig. 1), when the undershoot at 30
and 45 min is clearly demonstrated.

**Group 2**

Table 2 shows the alterations in mean $Pa_{O_2}$ and $Pa_{CO_2}$ and Fig. 2 the data plotted as changes from control pre-O₂ values. Mean $Pa_{O_2}$ increased from a control value of $63.5 \pm 5.7$ mmHg ($8.47 \pm 0.76$

kPa) to $223.5 \pm 73.8$ mmHg ($29.80 \pm 9.84$ kPa) at the end of the O₂ breathing hour. Mean $Pa_{O_2}$
then fell to reach a value not significantly different from control by 6 min, came back to the control
level by 10 min, and fell further to $57.7 \pm 5.5$ mmHg (7.69 $\pm$ 0.73 kPa) at 45 min. Both the values at 30 and 45 min were significantly lower than the pre-O2 value ($P < 0.01$). An undershoot in $Pa_{O2}$ was seen in all eight patients.

There was a small but statistically insignificant rise in mean $Pa_{CO2}$ during the O2 breathing hour, from $35.3 \pm 5.7$ mmHg (4.71 $\pm$ 0.76 kPa) to $38.6 \pm 9.0$ mmHg (5.15 $\pm$ 1.20 kPa). None of the values of mean $Pa_{CO2}$ after cessation of O2 breathing was significantly different from control.

The three deep inspirations that patients in this group performed at 45 min after O2 breathing produced no significant changes in the arterial blood gases, and in particular this manoeuvre did not abolish the undershoots in $Pa_{O2}$.

**Discussion**

An undershoot in $Pa_{O2}$ below the control pre-O2 value was found in nine of the ten patients with chronic hypercapnic respiratory failure and in all eight of the asthmatic patients, which confirms the original observations of Massaro et al. (1962) and of Cullen & Kaemmerlen (1967). We believe that a rebound fall in $Pa_{O2}$ 30–45 min after cessation of O2 therapy is a common though usually unrecognized event.

What is the cause of this undershoot? One theory is that, in patients with chronic hypercapnia, the oxygen breathing may cause a fall in alveolar ventilation by removing the sole remaining drive to breathing. When supplementary oxygen is removed, hypoventilation persists while the patients are breathing air with an additional fall in $Pa_{O2}$ (Crofton & Douglas, 1975). If the metabolic production of CO2 remains constant, $Pa_{CO2}$ should then be elevated above the control value at the time that the $Pa_{O2}$ undershoot occurs, which is not so (Fig. 1).

A second hypothesis is that the $Pa_{O2}$ undershoot is due to the differing washout characteristics of large CO2 and small O2 stores after O2 breathing, with persistence of raised $PcO2$ in both blood and alveolar gas, which is responsible for a decreased alveolar $Po2$ and hence further arterial hypoxaemia (Campbell, 1960a; Cumming & Semple, 1973). But although washout is indeed slower for CO2 than for O2 (Fig. 1), the CO2 washout is nevertheless completed by the time the $Pa_{O2}$ undershoot occurs at 45 min.

In addition, as both the hypoventilation and the slow-washout hypotheses postulate the presence of elevated $Pa_{CO2}$, one would expect the largest $Pa_{O2}$ undershoots to be associated with the highest rises in $Pa_{CO2}$ produced during the O2 breathing hour. But in group 1 the largest $Pa_{O2}$ undershoot occurred in the patient who had the smallest increase in $Pa_{CO2}$ during O2 administration and the one patient who did not develop an undershoot in $Pa_{O2}$ at 45 min was the very patient who had the largest rise in $Pa_{CO2}$ brought about by O2 (Fig. 3).

Thus in group 1 the undershoot in $Pa_{O2}$ after O2 breathing cannot be explained by either of the conventional theories, for the production of this rebound hypoxaemia is unrelated to any changes that occur in $Pa_{CO2}$. Nor is the presence of chronic hypercapnia essential, for all patients in group 2 developed undershoots in $Pa_{O2}$ though $Pa_{CO2}$ was normal or low.

While we can dispose of previous hypotheses with some confidence, we have considerable difficulty in proposing a plausible new one. We felt it important to interfere with the subjects' breathing as little as possible, and particularly to avoid using a mouthpiece or hood. There is no information on the effect of breathing through a mouthpiece on ventilation in patients with chronic airways obstruction or with asthma, but in patients with heart failure either hyperventilation or hypoventilation may occur (Saunders, 1966), and it would certainly have been difficult in this study to attribute any blood-gas changes to the after-effect of O2 alone, rather than to the effect of a mouthpiece. This meant that we could not measure CO2.

![Figure 3. $Pa_{O2}$ undershoot at 45 min after cessation of O2 breathing plotted against increase in $Pa_{CO2}$ after 60 min of O2 in group 1 patients.](image-url)
output, and must assume it to be unchanging in our dismissal of one previous hypothesis, nor could we give an accurately controlled inspired concentration of $O_2$, or measure expired ventilation, which would have allowed a more precise analysis of gas exchange with the $O_2$–$CO_2$ diagram (Rahn & Fenn, 1955).

At the end of the study, $P_{a,o_2}$ was lower than control values, whereas $P_{a,co_2}$ was the same. Therefore, a change in ventilation–perfusion relations must have occurred. We now consider four possible mechanisms.

(1) Alveoli collapse faster if $N_2$ is replaced by $O_2$ (Burger & Macklem, 1968; Dantzker, Wagner & West, 1975). Possibly, then, $O_2$ breathing induced alveolar collapse with shunting which persisted when air-breathing was resumed. In some patients with heart failure and pulmonary oedema a few deep breaths may raise $P_{a,o_2}$, suggesting reopening of blocked airways or collapsed alveoli (Saunders, 1965, 1966). Deep breaths in subjects of the present study caused a small but non-significant increase in $P_{a,o_2}$ (Table 2). In normal subjects (Wagner, Laravuso, Uhl & West, 1974) and dogs with pulmonary oedema (Wagner, Laravuso, Goldzimder, Neumann & West, 1975) $O_2$ breathing increases shunt, but the same group found no increase in shunt on $O_2$ breathing in four asymptomatic asthmatic patients (Wagner, Dantzker, Iacovoni, Tomlin & West, 1978) and only small increases (mean 0.8% of cardiac output) in $P_{a,o_2}$ to return to baseline in patients with chronic obstructive pulmonary diseases (Wagner, Dantzker, Dueck, Clausen & West, 1977), with only minor changes in ventilation–perfusion distributions. All this work refers to the effect of 100% $O_2$ for 30 min, whereas we gave about 60% $O_2$ for 60 min. Assuming a respiratory quotient of 0.83, an arteriovenous difference in $O_2$ content of 5 ml/100 ml of blood, and by use of the Severinghaus blood-gas calculator (Severinghaus, 1966), the alveolar gas equation and a standard shunt equation (Rahn & Fenn, 1955) we calculate that an increase in anatomical shunt of about 8% would be required to decrease $P_{a,o_2}$ from 49 to 44 mmHg (Table 1), a very much larger change than those recorded by the inert-gas technique.

(2) Both in patients with chronic lung disease (Pain, Read & Read, 1965; Eiser, Jones & Hughes, 1977) and in asthmatic patients (Field, 1967; Valabhji, 1968) it has been shown that during $O_2$ breathing ventilation–perfusion matching is impaired, due to diversion of blood flow away from well-ventilated to poorly ventilated lung units, presumably because hypoxic vasoconstriction is abolished (Fishman, 1961; Cotes, Pisa & Thomas, 1963; Horsfield, Segel & Bishop, 1968). Could the undershoot be caused by reversal of hypoxic vasoconstriction, with less appropriate ventilation–perfusion matching which persisted on resumption of air breathing? This seems an unlikely explanation since the time course of onset and reversal of hypoxic vasoconstriction in animal preparations is rapid (see, for example, Fig. 8 of Grant, Davies, Jones & Hughes, 1976) and it seems quite unlikely that such an effect could persist for 45 min after $O_2$ breathing stopped.

(3) The subjects were rested and relaxed, and cardiac output may well have fallen during the course of the experiment. If $O_2$ uptake was constant, it is possible that the resulting fall in mixed venous $Po_2$ might itself cause a fall in $P_{a,o_2}$ (West, 1977).

(4) Finally, we may speculate whether simple maintenance of a constant semi-recumbent posture for 2 h might itself be accompanied by a progressive deterioration in ventilation–perfusion relations. We know of no mechanism whereby this might occur, but did not do the relevant air-breathing control experiment.

In summary, we cannot pin down an exact mechanism from measurement of gas tensions alone (and the first aim of this work was to demonstrate whether the phenomenon of $P_{a,o_2}$ undershoot after $O_2$ breathing was a constant one), but we find the second and fourth hypotheses above unlikely, and suggest that shunting at the alveolar level, perhaps with a progressive fall in cardiac output and mixed venous $Po_2$, could account for our findings.

How long should one wait after discontinuing supplemental $O_2$ before taking a sample of arterial blood? In our patients, it took on average 15 min for $P_{a,o_2}$ to return to baseline in patients with chronic hypercapnic respiratory failure and 10 min in patients with asthma, which agrees with the results of studies specifically designed to answer that question (Cugell, 1975; Howe, Alpert, Rickman, Spackman, Dexter & Dalen, 1975; Sherter, Jabbour, Kovnat & Snider, 1975). In patients with chronic airways obstruction (with or without chronic $CO_2$ retention) Sherter et al. (1975) found that after a short period of 100% $O_2$ breathing it took on average 20 min for $P_{a,o_2}$ to return to baseline. Howe et al. (1975), in patients with various cardiac diseases but no lung disease, found that $P_{a,o_2}$ values returned to control values within 7 min of stopping $O_2$. In neither of these studies was $P_{a,o_2}$ followed for as long as 45 min after $O_2$.
breathing, but their figures suggest that $P_{a}O_{2}$ was still falling and that with longer observation undershoots like those we have seen might have been observed.

Woolf (1959) suggested that the rate of fall of arterial $O_{2}$ saturation measured with an ear oximeter could be used to diagnose emphysema, and more recently concluded that it is reasonable to take a blood sample in patients without chronic airways obstruction after 10 min and in patients with this condition after 30 min (Woolf, 1976). We agree with the timing of 10 min for the first group of patients, but in the second $P_{a}O_{2}$ would probably have undershot at 30 min. Our practice is to take arterial blood samples 15 min after cessation of $O_{2}$ therapy in patients with chronic hypercapnia.

Apart from one patient in group 1 whose arterial $O_{2}$ saturation fell 16%, the undershoots we have observed are small and possibly not of clinical importance. All our patients were in a clinically stable state at the time of study and it cannot be assumed that our results necessarily apply to patients with acute exacerbations of respiratory failure, especially those with very low $P_{a}O_{2}$ and low pH, who seem particularly likely to get $CO_{2}$ narcosis (Bone, Pierce & Johnson, 1978). On the other hand, in such cases experimental manipulations of inspired $O_{2}$ tension of the type used in this study would be completely unethical. Perhaps in acutely ill patients who are more severely hypoxaemic and thus on the steep slope of the oxyhaemoglobin dissociation curve, small undershoots in $P_{a}O_{2}$ might be important, especially if the patients are unable to improve $O_{2}$ delivery to the tissues by increasing their cardiac output.

In conclusion, we have shown that the phenomenon of a rebound fall in arterial $O_{2}$ tension 30-45 min after cessation of $O_{2}$ breathing is a common occurrence, and takes place irrespective of the presence of $CO_{2}$ retention. We believe that it is due to the persistence of areas of low ventilation-perfusion ratio, brought about by the period of $O_{2}$ breathing. Short periods of up to 15 min off $O_{2}$ are not harmful, and indeed are recommended if it is necessary to obtain blood-gas data representative of the patient's condition breathing room air. The size of the undershoots is likely to be of major clinical importance only in acutely ill patients.

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