Management of Respiratory Failure: Oxygen Therapy

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Joseph Priestley, who discovered oxygen in 1794, soon recognised its therapeutic potential, and suggested that it might be 'peculiarly salutory to the lungs in certain morbid cases'. These proposals were put into practice by Dr Thomas Beddoes, who described the physiological effects of the gas in his book Medicinal Uses of Factitious Airs, which aroused sufficient interest to allow him to establish his Pneumatic Institution in Clifton, Bristol, in 1798, oxygen being used as one of the new treatments. Beddoes carried out extensive experimental work on his factitious airs, and clearly describes a pneumonic-like infiltration in the lungs of a cat who had been exposed to high concentrations of oxygen for some days.

Pulmonary Oxygen Toxicity

This effect on the lungs, later rediscovered by Lorrain-Smith in 1897, has now been dignified by the term pulmonary oxygen toxicity, although the French generously term it the Lorrain-Smith effect. The problem was rarely of much consequence in clinical medicine until it became possible to ventilate patients by a cuffed endotracheal tube with high concentrations of oxygen for prolonged periods[1]. It now seems probable that continued inhalation of over 40 per cent oxygen for more than 24 hours can reduce the vital capacity, and cause substernal distress and breathlessness with cough, even in normal healthy subjects. If the exposure continues without any reversion to lower concentrations of oxygen, the alveolar epithelium and endothelium of alveolar capillaries are both damaged, producing the adult respiratory distress syndrome[2, 3].

Characterised by severe breathlessness, cyanosis refractory to oxygen, and diffuse infiltrates on chest X-ray, this syndrome can arise from numerous pulmonary insults, including pneumonia, septicaemia, non-thoracic trauma (shock lung), fat embolism, aspiration of gastric juice or near-drowning, and following exposure to drugs and poisons, including heroin, smoke from fires, paraquat and oxygen. The term adult respiratory distress syndrome (ARDS), coined to describe the common clinico-pathological entity resulting from these different lung insults, is coming into wider use in Britain, although obviously many will prefer to retain older diagnostic terms such as pneumonia, when the cause of the pulmonary lesion is known.

The syndrome is characterised pathologically by a protein-rich alveolar oedema completely flooding many alveoli. The oedema arises from disruption of the pulmonary endothelial junctions and the tight junctions between alveolar endothelial cells. In patients kept alive by mechanical ventilation, the continued ventilation into the few alveoli left open in this disastrous process results in the formation in these open air spaces (Fig. 1a, b) of a 'hyaline membrane', and the similarity to the respiratory distress syndrome of the newborn led to the term adult respiratory distress syndrome[2].

Fig. 1. Postmortem histological appearances of two separate areas from the lungs of a 14-year-old boy who died of ARDS following septicaemia and peritonitis. (a) the alveoli are completely filled with a protein-rich exudate; (b) some air spaces remain open lined by the hyaline membrane.
Although oxygen may itself produce the syndrome, the role of oxygen toxicity in ARDS is more complicated. These patients are hypoxaemic by definition, as blood continues to perfuse the alveoli that are filled with the protein-rich oedema fluid, so that much of the cardiac output passes through the lungs without being oxygenated. This large shunt can amount to 30 per cent to 50 per cent of the cardiac output, hence even increasing the inspired oxygen concentration towards 100 per cent can produce little rise in arterial oxygen tension (Fig. 2). This

poses a therapeutic dilemma, for the patient is dying of hypoxaemia, yet attempts to relieve the condition by giving a high concentration of oxygen worsen the damage to his lungs, with eventual progression of the hypoxaemia, which becomes even more refractory to oxygen. In those patients in whom some of the alveoli are still open (see Fig. 1), Lamy et al. [4] were able to show that in some of them increase in the positive end expiratory pressure (PEEP) during mechanical ventilation could reduce the shunt, so increasing the arterial oxygen tension without necessarily having to use 100 per cent oxygen. Nonetheless, ARDS still carries a very high mortality. A recent controlled trial of extra-corpectral membrane oxygenation by the US National Heart, Lung and Blood Institute showed that even this, probably the most sophisticated and costly of all life support systems used in medicine, did not improve the prognosis over that obtained with conventional treatment by mechanical ventilation and PEEP.

Acute Exacerbations of Respiratory Failure

Established ARDS is relatively rare, but all British physicians will be familiar with the problem posed by treatment of patients with chronic bronchitis and emphysema who are admitted to hospital with an exacerbation of their pre-existing chronic hypoxaemia and CO₂ retention. In normal healthy adults this combination of hypoxaemia and an elevated arterial PCO₂ would provide a powerful respiratory stimulus, acting through both the peripheral chemoreceptors (mainly sensitive to hypoxia), and the central chemoreceptor, probably on the lateral border of the medulla, which is principally sensitive to cerebrospinal fluid acidity, and thus dependent upon the arterial PCO₂. However, in these patients this mechanism has failed, and the therapeutic dilemma here is to prevent the patient dying of hypoxaemia, without at the same time removing a ventilatory drive from the hypoxaemia, so that he will accumulate sufficient CO₂ to die of the ensuing respiratory acidosis. This dilemma, first described by Donald in 1949 [5], led to the introduction of controlled oxygen therapy [6], which aims to give just enough oxygen to prevent hypoxic death, yet not sufficient to remove completely the ventilatory stimulus from the oxygen want, with resultant death from respiratory acidosis. This endeavour requires that the patient should be steered between these twin dangers, and so criteria must be defined that will allow safe navigation of this relatively narrow channel.

We have recently carried out a retrospective analysis of blood gas measurements and their changes during controlled oxygen therapy in 157 exacerbations of acute-on-chronic respiratory failure occurring in 135 such patients. These measurements were related to the outcome in each case, so as to determine these guidelines in terms of blood gas tensions. On the basis of our previous experience [7], we had proposed that controlled oxygen therapy for these patients should aim to achieve an arterial oxygen tension above 8.0 kPa (50 mmHg) while at the same time not allowing the arterial hydrogen ion activity (H⁺) to rise above 56 nmol/litre (pH below 7.25). This emphasis upon the importance of acidity of the blood rather than absolute values of PCO₂ alone, depends upon recognition of the difference between acute and chronic CO₂ retention in man. The in vivo relationships between the (H⁺)(or pH) and arterial PCO₂ of the arterial blood during experimental acute CO₂ retention are known [8]. If such CO₂ inhalation continues for some days, an experiment that has obviously never been carried out in healthy normal men, the reabsorption of bicarbonate in the distal renal tubule increases, so that the arterial (H⁺) falls for a given level of PCO₂. The limits of this relationship in chronic CO₂ retention are also known, and these two significance bands of PCO₂/(H⁺) relationships can be utilised in an acid base diagram (Fig. 3) [9, 10].

When these arterial (H⁺) and PCO₂ values in our patients were plotted on this diagram, it became apparent that those in whom the (H⁺)/PCO₂ relationships lay within or above the acute respiratory band were at greater risk of death during that admission than were patients in whom the relationships tended towards the chronic band. The age of the patient was also an important predictor of prognosis, but a combination of age of the patient with the level of arterial (H⁺) at the point of highest PCO₂ during controlled oxygen therapy were together the best indicators of the prognosis during
that episode of acute respiratory failure.

The level of arterial oxygen tension on admission to hospital when breathing air, which for inclusion in the series was required to be below 50 mmHg (8.0 kPa), did not prove to be of great importance in determining the prognosis, although values as low as 19 mmHg (2.5 kPa) were recorded in one patient. The concepts of chemical control of ventilation outlined above indicate that as controlled oxygen therapy increases the arterial PO₂ (initially by 2 litres oxygen/minute by nasal prongs) there will at the same time be a small increase in PCO₂. This classical response was indeed usually seen, but in some patients the PCO₂ either fell, or showed no further rise, when the controlled oxygen therapy gave a moderate but satisfactory rise in arterial PO₂. This abnormal response, at least as far as the theory of chemical control of ventilation is concerned, does not appear to be adequately explained by postulating a central depression of ventilatory neuronal activity by hypoxia, which was then reversed by controlled oxygen therapy, so that the increase in ventilation prevented any further rise in PCO₂.

Although this phenomenon remains unexplained, it may be that fatigue of the respiratory muscles[11] contributes to this response. Nonetheless, at present it seems that in practical terms the proposed guidelines of a PO₂ of about 50 mmHg (8.0 kPa) without the (H⁺) rising above 56 nmol/litre (pH below 7.25) are useful, although continued monitoring of arterial blood gas tensions until the patient is out of danger appears wise, for in our experience failure of PCO₂ to rise with oxygen did not always mean that the patient survived.

**Hypoxaemia during Sleep in Chronic Bronchitis and Emphysema**

Disturbances of breathing during sleep have received increasing attention in the last few years, following the studies of Guilleminault et al.[12], who described sleep apnoea syndromes, particularly in obese patients without respiratory disease, characterised by many apnoeic episodes lasting for 10 seconds or longer, occurring in the rapid eye movement (REM) and non-REM phase of sleep, and associated with daytime somnolence, mild hypertension, and headaches. Many patients were brought to the doctor only because of their bed partners, who complained of their abnormal behaviour during sleep. These workers have extended earlier definitions[13] of obstructive sleep apnoea (where chest wall movement continues, yet air-flow at nose and mouth ceases, indicating obstruction to the upper airway), and central apnoea, where the chest wall and nasal and mouth airflow cease. Apnoeic episodes occur particularly during REM sleep, can occur occasionally in normal subjects, and increase in frequency in older subjects.

Flick and Block[14] have described similar episodes in patients with pre-existing chronic bronchitis and emphysema, particularly noting transient hypoxaemia during sleep, and we[15] have recently extended these observations. Severe transient hypoxaemia, with arterial PO₂

![Fig. 3. Acid base diagram showing the observed relationships between arterial (H⁺) (or pH) and arterial PCO₂ in life. The dotted lines indicate the 95 per cent confidence bands of these relationships in the single disturbances of acid base balance, as observed in clinical practice[10].](image)

![Fig. 4. (From top to bottom) Ear oxygen saturation, chest wall movement, nostril air flow, and pulmonary arterial pressure, during an episode of transient hypoxaemia during the REM phase of sleep in a 'blue and bloated' patient with chronic bronchitis and emphysema. Note the mixed central and obstructive apnoea causing the hypoxaemia which, in turn, seems to further increase the pulmonary arterial pressure[15].](image)
levels falling as low as 26 mmHg (3.5 kPa), occurred recurrently throughout the night in patients with the 'blue and bloated' pattern of chronic bronchitis and emphysema. In some of these patients, who are characterised by severe irreversible airways obstruction with hypoxaemia and CO₂ retention when awake, and pulmonary hypertension and secondary polycythaemia, the episodes of transient hypoxaemia during sleep are associated with further rises in the already elevated pulmonary arterial pressure (Fig. 4). We suggest that this phenomenon may account in these patients for the development of the sustained pulmonary hypertension and cor pulmonale. In contrast, in 'pink and puffing' patients with chronic bronchitis and emphysema, who despite equally severe irreversible airways obstruction, have relatively normal blood gas tensions when awake, and show no evidence of cor pulmonale or secondary polycythaemia, we have found such transient hypoxaemia to be rare.

Long-term Oxygen Therapy

The recognition of the recurrence and severity of transient hypoxaemia during sleep in the 'blue and bloated' bronchitics lends support to the current attempts to prolong the life of these patients by long-term domiciliary oxygen therapy. This is given for at least 15 hours a day and thus during sleep. An MRC controlled trial of this treatment has been undertaken in three British centres (Birmingham, Edinburgh and Sheffield) over the last 5 years. The treatment is expensive, and if the controlled trial does indeed establish its therapeutic value in terms of prolongation of life, it seems that the means of administering the treatment in the patient's home, over what may prove to be many years, will have to be reviewed. Current evidence suggests that the supply of oxygen in 48" ft (size F) cylinders, from the contracting chemist in the British NHS, available on the Drug Tariff on the recommendation of a hospital consultant, is costly and relatively inconvenient for the contracting chemist and the patient.

It seems probable that the oxygen concentrator[16] will prove to be the most economical method of providing such long-term domiciliary therapy, although this is not currently available on the NHS Drug Tariff. Recent figures from the DHSS indicate that over 50,000 patients in Great Britain aged less than 65 years are currently receiving long-term disability payments as a result of chronic bronchitis and emphysema, and suggests that this problem of rehabilitating the chronic respiratory cripple, in which long-term oxygen therapy will play an important part, is by no means insignificant.

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