PULMONARY OXYGEN TOXICITY

A Review of the Evidence for Acute and Chronic Oxygen Toxicity in Man

BY

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During the last few years there has been growing concern that chronic pulmonary oxygen toxicity might result from the administration of high concentrations of oxygen with intermittent positive pressure ventilation (IPPV) during the management of respiratory failure. This concern was fostered by Nash, Blennerhassett and Pontoppidan (1967) who reported an association between the duration and concentration of oxygen administered to patients receiving IPPV, and the appearance of a series of pathological changes characterized by an early exudative phase and a late proliferative phase. Northway, Rosan and Porter (1967) observed in neonates with hyaline membrane disease, who had received IPPV and oxygen, a prolongation of the healing phase and the appearance of an apparently new chronic pulmonary syndrome. They associated this syndrome with IPPV and the administration of high concentrations of oxygen.

Although these studies have provided evidence of an association between the prolonged administration of oxygen and the functional and pathological features which have been described, they do not provide evidence of a cause-and-effect relationship. Moreover, as illustrated by the papers of Brewis (1969), and Soloway, Castillo and Martin (1968) there has been a tendency to attribute functional, radiological and histological changes to oxygen toxicity without a consideration of other possible mechanisms for these changes.

In addition to the possible direct toxicity of oxygen on alveolar cells, capillaries, and the surface lining of alveoli, there are several other distinctly different mechanisms whereby high concentrations of oxygen could alter pulmonary function. These include the rapid absorption of gas in the absence of nitrogen if airway closure or obstruction is present (Dale and Rahn, 1952; Rahn and Farhi, 1963); impairment of mucociliary transport (Laurenzi, Yin and Guarneri, 1968; Marin and Morrow, 1969); and the indirect effect of high partial pressures of oxygen on

the control of ventilation and the adequacy of gas exchanges when the ventilatory response to carbon dioxide is impaired. The primary purpose of this review is to examine the evidence for pulmonary oxygen toxicity in man, when oxygen is administered at normobaric conditions or the equivalent partial pressure. However, because of the obvious limits to experimental evidence in man the effects of prolonged administration of high concentrations of oxygen in experimental animals and primates will also be discussed, where this is relevant to the evaluation of the evidence of pulmonary oxygen toxicity in man.

EVIDENCE OF ACUTE PULMONARY OXYGEN TOXICITY IN MAN

In man, the majority of studies of the effect of breathing oxygen at high concentrations for several hours to a few days have been limited to measurement of vital capacity, changes in the pulmonary diffusion capacity for carbon monoxide, and to demonstration of radiological changes in the lung fields.

Effect of oxygen on the vital capacity and the mechanical properties of the lungs.

Breathing 100 per cent oxygen at 1 atmosphere has been shown by several investigators to produce a fall in vital capacity (table I). These studies have also shown a wide variation in the time of onset, the severity of changes in the vital capacity and radiological changes in the lung fields.

Several mechanisms may be proposed to account for the fall in vital capacity. The first is

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TABLE I

Lung volume, and chest X-ray changes in man during the inhalation of high concentrations of oxygen at 1 atmosphere.

Reference	Number of subjects	Inspired oxygen conc. (%)	Duration (hrs)	Vital capacity	Residual volume	Chest X-ray
Becker-Freyseng and Clammann (1939)	2	100	65	Decrease		
Comroe et al. (1945)	90	100	24	Majority decrease 200–1400 ml		No change in 6 subjects
	9	75	24	Decrease in some subjects		
	10	50	24	No change		
Ohlsson (1947)	6	78–88	53–77	Decrease		No change
Dubois et al. (1966)	7	100	72	In 4 subjects, decrease of 400–1300 ml		"Plate-like atelectasis" in 2 of 4 subjects
Caldwell et al. (1966)	4	100	30–74	Decrease 200–800 ml	Decrease in 2 subjects Increase in 1, and no change in 1	

a direct toxic effect of oxygen on the cells of the alveoli or their lining, resulting in a change in the elastic properties of the lung; the second is that if airways closure or obstruction is present, absorption atelectasis in the absence of nitrogen will be more rapid. The third is that the pain which was experienced by some of the subjects may have prevented them from making a maximal effort. The evidence for the first two mechanisms will now be discussed.

Dubois and associates (1966) investigated the predisposing factors to changes in vital capacity and radiological appearances induced by breathing 100 per cent oxygen; they compared the pre-exposure lung volume of three subjects in whom there was no change in these features, with the lung volumes of four subjects in whom there was a fall in vital capacity, and in two of which there were radiological changes in the lung fields (table I). The greatest changes occurred in a subject in whom there appeared to be mechanical abnormalities of the lungs as evidenced by low lung volumes, including a small expiratory reserve volume. In this subject the vital capacity reduction and radiological changes could be prevented by breathing mixtures of oxygen and nitrogen. The fall in vital capacity, the changes in airway conductance which were also reported, and the radiological changes in the lung fields are most simply explained by absorption atelectasis. This

view is supported by the finding that the changes were prevented by breathing mixtures of oxygen and nitrogen. It is of clinical importance that these changes were most marked in subjects with pre-existent mechanical abnormalities of the lungs.

The role of mechanical abnormalities of the lungs in predisposing to lung volume, mechanical, radiological or blood-gas changes consistent with atelectasis during oxygen breathing has been confirmed by Nunn and associates (1965), and by Burger and Macklem (1968) who studied subjects breathing 100 per cent oxygen at low lung volumes. Nunn and associates (1965) observed gross radiological changes in the lung fields in one subject and a decrease in Pa_{O_2} in another. Burger and Macklem (1968) observed mechanical changes consistent with airways closure when the subjects breathed 100 per cent oxygen at 20 per cent of their vital capacity.

Burger and Mead (1969) extended these studies and obtained evidence of the relative importance of atelectasis and the direct toxic effect of oxygen on the elastic properties of the lung. The static pressure-volume curves of the lung in five normal subjects after breathing 100 per cent oxygen (at 0.39, 0.50, 1.0 and 2.0 atmospheres) for 3 hours differed from the control curves only at high lung volumes. Both the symptoms and the mechanical changes were reversed by deep breaths; these changes were not observed after the subjects

breathed 50 per cent oxygen in nitrogen at 2.0 atmospheres. These results are also consistent with the view that absorption atelectasis is the cause of the functional changes induced in the lungs by breathing 100 per cent oxygen.

The effect of oxygen breathing on the pulmonary diffusion capacity.

Ernsting (1961), using a breath-holding technique to measure the pulmonary diffusion capacity, observed a reduction in the pulmonary diffusion capacity after exposure to 100 per cent oxygen for 3 hours. Caldwell and associates (1966), also using a single-breath technique, demonstrated a fall in the pulmonary diffusion capacity of 30 per cent after 48 hours exposure to 100 per cent oxygen. Rosenberg and MacLean (1967), however, using a single-breath technique, were unable to demonstrate a reduction in the pulmonary diffusion capacity for carbon monoxide after a 3-hour period of exposure to 100 per cent oxygen.

The pulmonary diffusion capacity for carbon monoxide may be measured by several methods, and it is now recognized that there is no simple interpretation of the measurement obtained by any method (Bates and Christie, 1964). Moreover, the complexity of the possible effects of oxygen breathing on the distribution of ventilation and blood flow, lung volume, diffusion of carbon monoxide across the alveolar capillary membrane, and the rate of combination of carbon monoxide with the haemoglobin molecule, and the interaction of all these factors on the measurement of the pulmonary diffusion capacity for carbon monoxide, further emphasizes the difficulties in the evaluation of measurements of diffusion capacity.

Conclusion on the evidence of acute pulmonary oxygen toxicity.

It is concluded, on the basis of the studies on the mechanical properties of the lungs and the supporting evidence of Dale and Rahn (1952) and Rahn and Farhi (1963) that absorption atelectasis is the most important factor in the genesis of lung volume and radiological changes whilst breathing 100 per cent oxygen for periods of up to 70 hours. It is suggested that pre-existent or induced mechanical abnormalities of the lungs predispose to

absorption atelectasis by causing airways closure or obstruction. Burger and Mead (1969) were unable to demonstrate a direct toxic effect of oxygen on the elastic properties of the lungs in normal adults exposed to 100 per cent oxygen for 3 hours.

Recently, Singer and associates (1970) in a prospective study on patients following open heart surgery demonstrated no significant difference in intrapulmonary shunt, effective compliance, V_D/V_T ratio, or clinical course between two groups of patients who received different inspired oxygen concentrations. One group received 100 per cent oxygen for a mean duration of 24 hours, and the other group received an inspired oxygen concentration of not greater than 42 per cent and which maintained the arterial oxygen tension between 80 and 120 mm Hg. The mean duration of exposure to oxygen in this group was 21 hours.

CHRONIC PULMONARY OXYGEN TOXICITY IN MAN

Table II summarizes the clinical and histopathological features which have been associated with prolonged administration of high concentrations of oxygen. On the basis of a retrospective study of case records and autopsy results in a group of patients who had received intranasal oxygen for up to 19 days, Pratt (1958) considered that the capillary proliferation observed was the result of the oxygen administered. There was also positive correlation between the duration of administration of oxygen and the grading of capillary proliferation in children who received oxygen during a terminal illness (Pratt, 1965). Cederberg, Hellsten and Miörner (1965), in a retrospective study of patients from a respiratory care unit, observed a positive correlation between the concentration and the duration of administration of oxygen and the incidence of hyaline membranes. However, both capillary proliferation and hyaline membrane formation are frequently seen on histological examination of the lungs in the presence of pulmonary disease, and moreover the nature of these studies does not enable us to conclude that there is any causal relationship between oxygen administration and these lesions.

Nash, Blennerhassett and Pontoppidan (1967) undertook a clinical and pathological study to determine whether the progressive functional deterioration sometimes observed during the man-

TABLE II

Pulmonary pathology observed in man after prolonged administration of high concentrations of oxygen at 1 atmosphere.

Reference	Clinical diagnosis or investigation group	Number of patients	Age (yr)	Mode of administration of oxygen	Inspired oxygen conc. (%)	Duration (days)	Pulmonary pathology
Pratt (1958)	Group I[(1)] CVA	5	40–80	Nasal catheter	?	3–19	4 showed capillary proliferation
	MI + PE COLD Other	1 1 3	66 79			1 6 1	— — —
	Group II Terminal illness	22	2–78	Nasal catheter	?	0–7	Capillary proliferation present in 6 who received oxygen for 36 hours to 7 days
Pratt (1965)	Terminal illness	50	Children	?	?	0–4	Increasing capillary proliferation in those who received O₂ for 1 day or more
Cederberg, Hellsten and Miörner (1965)	Patients of a respiratory care unit (2)		Adults				Incidence of hyaline membranes
	I II III IV	19 84 28 19		IPPV volume cycled	21 21–29 40–49 49	1 2 4 7	— — 14% 37%
Nash, Blennerhassett and Pontoppidan (1967)	Experimental groups 1 2 3 4	70	Adults	IPPV pressure cycled	21–90 21–90 90–100 90–100	<10 >10 <10 >10	Average lung weight 1697 g; 46% lung weight >1800 g; prominent intra-alveolar fibrinous exudate, thickening of alveolar walls, with oedema or cellular proliferation and connective tissue; diffuse hyperplasia of alveolar lining cells
	Control group	70	Adults	—	21		Average lung weight 1176 g; 10% lung weight >1800 g; above features were infrequent
Castleman and McNeely (1967)	Multiple injuries	1	21	IPPV pressure cycled	85	26	Lung weight 1800 g; hyaline membranes in alveoli, alveolar ducts, and bronchioles; fibroblastic proliferation; hyperplasia of alveolar cells
Soloway, Castillo and Martin (1968)	See footnote (3)	6		IPPV	Up to 100	2–11	Consolidated lung; hyaline membranes, swelling of alveolar cells and detachment from basement membrane; interstitial oedema; fibroblastic proliferation
Brewis (1969)	Status epilepticus Anti-epileptic drugs Chloroform	1	33	IPPV pressure cycled	Up to 90	20	Clinical features. Day 1: normal chest X-ray. Day 4: opacity LL zone, and RU zone; subsequent extension of opacities; difficult to ventilate. Day 10: widespread soft opacities. Day 15: some clearing of lung fields

Notes:

(1) CVA = cerebrovascular accident.
   MI, PE = mitral incompetence and pulmonary embolism.
   COLD = chronic obstructive lung disease.
(2) Classification based on the inspired oxygen concentration and the duration of administration of oxygen.

(3) Diagnosis = Septicaemia and shock.
   Toxaemia of pregnancy.
   Hypertension and pulmonary oedema.
   Septicaemia, neoplasia and renal failure.
   Multiple injuries.
   Complete correction of Fallot's Tetralogy.

agement of adult patients without obvious pre-existing pulmonary abnormalities, and the association of these functional abnormalities with unusual gross and histological appearance of lungs, was related to the administration of high concentrations of oxygen during intermittent positive pressure ventilation (table II). The control group of seventy adult patients were considered by the authors to be comparable in underlying disease to the experimental group of patients but they did not receive IPPV and oxygen. At autopsy a wide range of gross and microscopical abnormalities was encountered but there were definite features which distinguished the two groups. In the experimental group the lungs were much heavier than the control group (46 per cent were over 1800 g); the lungs were of solid consistency and the cut surface had the appearance of haemorrhagic consolidation. The lungs of the experimental group contained prominent intra-alveolar fibrinous exudate and often this was layered on the walls of alveoli, alveolar ducts, and the respiratory bronchioles to form hyaline membranes. In 33 per cent of the experimental group there was marked thickening of alveolar and interlobular septa by oedema, and cellular fibroblastic proliferation with reticulin and loose fibrillar collagen. This was associated with only mild to moderate lymphocytic infiltration, and there was no evidence of infection. In 24 per cent of the experimental group there was diffuse hyperplasia of the alveolar lining cells, with the formation of a cuboidal epithelial layer. The analysis of their data indicated that there was an association between the duration and the concentration of oxygen administered, and the incidence and severity of the lesions described. The lesions were unrelated to the duration of IPPV. Nash, Blennerhassett and Pontoppidan (1967) acknowledged that they were unable to present evidence of a cause-and-effect relationship between oxygen administration and the pathology.

The case record and the autopsy findings of a 21-year-old man with multiple injuries, including thoracic trauma, were reported by Castleman and McNeely (1967). He received IPPV and an inspired oxygen concentration of 85 per cent. He was also given multiple blood transfusions. From the sixth day there was a progressive fall in arterial oxygen tension and pul-

monary compliance, which was associated with widespread confluent radiological opacities in both lung fields. Although there was clearing of the lung fields on the fourteenth day, several days later the opacification of the lung fields recurred and he died on the twenty-sixth day of his admission. The autopsy findings were as decribed in the experimental group of Nash, Blennerhassett and Pontoppidan (1967).

The possible relationship between the prolonged administration of oxygen and the histological lesions described by Soloway, Castillo and Martin (1968) are not clearly defined. Moreover, the histories of these patients reveal a variety of major disorders; these, and the presence of hypotension, shock, septicaemia, and the administration of multiple blood transfusions and intravenous fluids, may have contributed to the genesis of some of the lesions described (Blaisdell, Lim and Stallone, 1970). Similarly, the case report of Brewis (1969) in which the author appears to have attributed most of the changes observed to "pulmonary oxygen toxicity" without evaluating the possible role, for example, of aspiration of gastric juice, the "polypharmacology" which the patient received, and the factors in the management which might have led to airways closure or obstruction, so predisposing to atelectasis.

Barber, Lee and Hamilton (1970) demonstrated that the administration of 100 per cent oxygen and IPPV for more than 40 hours to five adult patients with irreversible brain damage resulted in greater intrapulmonary shunts and higher V_D/V_T ratios than in another group of similar patients who received air and IPPV. All the patients who received oxygen showed definite radiological lesions with time. Although the lung weights of the patients who had received oxygen were greater than those who breathed air the difference was not statistically significant and the gross and histological features of the lungs of both groups were similar. The authors considered that the lack of conclusive pathological difference in lung tissue may have been due to the method of examination of the tissues by light microscopy. Kistler, Caldwell and Weibel (1967) showed by electron microscopy that widespread capillary endothelial destruction and interstitial oedema were early lesions in the development of pulmonary oxygen toxicity in rats. Many of these

changes were not visible by light microscopy. Barber, Lee and Hamilton (1970) concluded that the administration of oxygen with positive pressure ventilation resulted in an impairment of pulmonary function in patients with irreversible brain damage, but the mechanisms underlying these changes could not be defined.

EXPERIMENTAL EVIDENCE FOR CHRONIC PULMONARY OXYGEN TOXICITY

Although these clinical studies have provided evidence of an association between the prolonged administration of a high concentration of oxygen and the development of clinical, functional, radiological and histological abnormalities, it is necessary to provide unequivocal evidence for the role of oxygen in the genesis of these lesions. This evidence can only be provided by animal experiments.

Robinson and colleagues (1967) exposed monkeys to 99–100 per cent oxygen at total pressure of between 600 and 700 mm Hg for periods of up to 16 days. Histological examination of the lungs of monkeys killed on the third and fourth day of exposure showed a subacute proliferative lesion characterized by exudation into the alveoli, haemorrhage, and septal oedema. More prolonged exposure resulted in grey bloodless lungs, with an increase in fibroblasts, hypertrophy and hyperplasia of the alveolar lining epithelium. There was a dose-response relationship between the amount of oxygen administered and the severity of the clinical manifestations, and the histopathological features which were similar to those described by Nash, Blennerhassett and Pontoppidan (1967). In the surviving animals clinical recovery occurred after gradual reduction of oxygen concentration. At 32 days post-exposure the only pathological findings were focal areas of atelectasis, and mild septal fibrosis.

Influence of arterial oxygen tension on pulmonary oxygen toxicity and survival time.

Winter and associates (1967) considered that the clinical incidence of apparent pulmonary oxygen toxicity associated with the prolonged administration of high inspired oxygen concentrations was less than predicted from previous animal experiments. They suggested that low or normal arterial oxygen tensions in the presence of

high alveolar tensions may be partially protective against changes arising from the administration of oxygen. They created large venous to "arterial" shunts by side-to-side anastomosis of the inferior vena cava to the right inferior pulmonary vein in dogs. In the "shunted" animals the development of lung damage was delayed, and the survival time was nearly doubled on exposure to 100 per cent oxygen at 2.5 atmospheres. This evidence suggests that under hyperbaric conditions the low arterial oxygen tension does ameliorate the development of pulmonary structural changes. The arterial oxygen tension difference between the control and the "shunted" groups was large and the mean values were 1754 and 127 mm Hg respectively. Unfortunately it is not possible to extrapolate the results of this study directly to the development of pulmonary oxygen toxicity under normobaric conditions in animals and man. Moreover, the results of this study may be compared to the failure of large surgically created intracardiac shunts in dogs to prevent changes in pulmonary pathology arising from the administration of 100 per cent oxygen at 1 atmosphere for 2 days (Miller, Waldhausen and Rashkind, 1970).

PULMONARY OXYGEN TOXICITY IN NEONATES

Intermittent positive pressure ventilation, and the administration of high concentrations of oxygen may be required in the management of respiratory failure of the newborn. The commonest cause of respiratory failure of the newborn is hyaline membrane disease. Until recently it has been stated that if the infant survives the first 3 days of life it will recover, with the lung fields becoming radiologically normal in 7–10 days (Schafer, 1965). Northway, Rosan and Porter (1967), however, provided clinical, radiological and histological evidence of a prolongation of the healing phase of hyaline membrane disease, and the emergence of a hitherto undescribed chronic pulmonary syndrome which was associated with IPPV and administration of high concentrations of oxygen. Following the acute phase of 2–3 days, there was a period of regeneration which lasted 6 days and this was associated with complete radiological opacification of the lung fields, and hypoxaemia in the presence of high inspired concentrations of oxygen. Histological features included necrosis and coalescence of the alveoli, some repair of the

alveolar epithelium, focal thickening of the basement membrane, and the growth of pericapillary reticulin. There were also areas of bronchial necrosis, and squamous metaplasia of the bronchial epithelium. During the following 10–20 days there was a transition to the chronic disease and a honeycomb appearance of the lung fields on X-ray. The histological features of the lungs of those who died at this stage were dilated alveoli whose tributary bronchioles showed marked hyperplasia of the peribronchial smooth muscle and mucosal metaplasia. These were interspersed with atelectatic alveoli having normal bronchioles. There were early vascular lesions consistent with pulmonary hypertension, including medial hyperplasia. In their series there were infants who at 1 month still showed signs of respiratory failure. The term "bronchopulmonary dysplasia" was applied to this chronic lung disorder.

Several possible mechanisms for the development of bronchopulmonary dysplasia may be suggested, but Northway, Rosan and Porter (1967) reasoned that the most probable cause was oxygen-induced lesions of the respiratory mucosa with defective drainage, combined with lesions of the alveoli and capillaries induced by oxygen and the respiratory disease. In contrast to these reasonings, Shepard and associates (1964, 1968), who described similar histopathological lesions, attributed them to the reparative process of hyaline membrane disease. These features have also been described by Boss and Craig (1962) and Robertson, Tunell and Rudhe (1964). The nature of these studies does not enable a clarification of the genesis of bronchopulmonary dysplasia, and the role of IPPV and oxygen cannot be defined.

Shanklin and Wolfson (1967) associated the development of pulmonary haemorrhage with the treatment of premature infants with continuous oxygen enrichment of incubator air. This was a retrospective study and it was not possible to obtain evidence of a quantitative relationship between the incidence and the severity of the haemorrhage and the amount of oxygen administered. The design and analysis in this study do not therefore provide evidence of a causal relationship between the administration of oxygen and pulmonary haemorrhage and, as shown by Landing (1957), there is in any case a high incidence of pulmonary haemorrhage at autopsy in neonates.

Bruns and Shields (1954) observed that over a period of 5 years in which there had been a decline in the frequency of administration of oxygen to premature neonates there was a decline in the incidence of hyaline membranes seen at autopsy. The significance of the association between the two declining variables, oxygen administration and the incidence of hyaline membrane disease, is open to debate in view of the numerous additional factors that have influenced clinical practice in this field.

CONCLUSION AND CLINICAL CONSIDERATIONS

Short-term exposure to elevated partial pressures of oxygen has in adult man been shown in some subjects to cause a reduction in the vital capacity and, occasionally, radiological changes in the lung fields. The mechanical and lung volume changes suggest that absorption atelectasis is important in the genesis of these functional abnormalities, and pre-existing or induced changes in the mechanical properties of the lungs potentiate airways closure or obstruction, with the subsequent development of absorption atelectasis. In man there is no direct evidence of a toxic effect of oxygen on the elastic properties of the lungs, but it is recognized that adequate mechanical studies have been performed only during short-term exposure to high concentrations of oxygen.

The clinicopathological studies of Nash, Blennerhassett and Pontoppidan (1967) provided evidence of an association between the prolonged administration of high concentrations of oxygen and the development of a chronic pulmonary disease. Robinson and associates (1967) supported this clinical evidence by demonstrating similar pathological features in monkeys as a result of prolonged exposure to high concentrations of oxygen. On gradual withdrawal from high concentrations of oxygen some of these animals recovered clinically and were shown subsequently to have minimal pathological lesions. There is no evidence concerning the threshold or time-concentration relationship involved in the development of the chronic lesion, nor is there evidence relating modifying factors which could be directly applicable to the administration of oxygen at normobaric conditions.

The development of chronic pulmonary oxygen toxicity in man, as a result of the prolonged

administration of high concentrations of oxygen during the management of respiratory failure, is, therefore, a reasonable probability. Nevertheless it would be unreasonable to attribute all the functional, radiological and pathological changes observed during the management of these patients to oxygen toxicity without proper consideration of the other factors which may contribute to the abnormalities. Moreover, absorption atelectasis occurs on the basis of airways closure or obstruction and attention should be directed to the prevention and management of those factors which may lead to airways closure or obstruction. The clinical importance of the possibility of chronic pulmonary oxygen toxicity in man is that it becomes advisable to "titrate" the inspired oxygen concentration to the patients' requirements as judged by the arterial oxygen tension. Clearly, there will be many clinical situations where in the presence of gross pulmonary arteriovenous or intracardiac right-to-left shunting it will be necessary to administer high concentrations of oxygen until there is a resolution of the functional abnormalities and when it is possible to provide adequate arterial oxygenation at lower inspired oxygen concentrations.

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Further details can be obtained from Professor J. A. Thornton, University of Sheffield, Department of Anaesthetics, The Royal Infirmary, Sheffield S6 3DA. Tel. 0742 20977, Ext. 383.