The Pulmonary Toxicity of Oxygen

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A CONCISE REVIEW of oxygen toxicity by Dubois[1] appeared five years ago in this journal. This was one mark of a rising level of clinical concern with complications of oxygen therapy. Interest was stimulated, and continues to be, by several parallel developments in medicine, respiratory physiology, and technology. Two of these, aerospace life-support systems and modern hyperbaric medicine, although not part of everyday medical practice, have contributed information about ambient-pressure oxygen toxicity. Less dramatic but also important are the increasingly common applications of prolonged mechanical ventilation with high concentrations of inspired oxygen, and a surge of interest in the surface properties of the layer lining the lung and its possible relevance to the mechanism of pulmonary oxygen toxicity.

Although the present review emphasizes some of the more recent information about oxygen toxicity, the basic facts are older than the present century. There are four general manifestations of oxygen toxicity: systemic effects of hyperbaric oxygen; local pulmonary toxicity of oxygen; absorption atelectasis; and the metabolic effects of oxygen at ambient pressure, including retrolental fibroplasia and hematologic changes. At least two of these were described in detail before 1900. Paul Bert's *La Pression Barometrique* appeared in 1878.[2] J. Lorrain Smith made a detailed investigation of oxygen as a potentially lethal pulmonary irritant at partial pressures near atmospheric; his published description appeared in 1899.[3] Smith's first intention had been to study the effect of increased oxygen tension on infection by anaerobic organisms but, in his words, "It soon became apparent that the oxygen at a tension of over 100 per cent of an atmosphere produced pneumonia in the normal animal. It was therefore necessary to carry out a preliminary research in regard to this." He proceeded to expose a series of mice and other animals to oxygen in a small chamber. Two mice showed no adverse effects from continuous exposure to oxygen at 41.6 per cent of an atmosphere for eight days. After four days' exposure to oxygen at 73.6 per cent of an atmosphere, one of two mice died with "congestion and consolidation of the lungs." The same result was obtained at 79.9 per cent of an atmosphere. At tensions near 130 per cent, death occurred in 90 hours. In all animals there was intensive congestion and exudative change in the lungs. These experiments demonstrated a local pulmonary toxicity of oxygen, distinguished from Bert's production of tetany in animals by the lower oxygen tension required to induce it, the longer time to onset and, of course, its different primary manifestation. The direct pulmonary toxicity of oxygen at ambient pressure has since been called "the Smith effect" or "the Lorrain Smith effect." He also demonstrated what has since been noticed repeatedly in studies of oxygen toxicity: a conspicuous interindividual and interspecies variation.

A great deal of information about oxygen toxicity was gathered in the following decades. Bean's selective review of 1945 listed more than 350 references in the bibliography.[4] Much of this work was concerned with the general biologic problem, medical applications being limited to humans in chambers of some kind—the hyperbaric environment, divers and caisson workers, or infants in incubators. Most

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patients continued to be protected by the relative inefficiency of masks, catheters, and oxygen tents as methods of long-term oxygen administration.

Five years ago a major trend in patient care was under way. The key problem in postoperative care, and care of the critically ill, began to be found more and more frequently in the respiratory area.[5] Newer antibiotics, effective management of renal failure, and increased understanding of volume and electrolyte replacement left pulmonary function the major factor determining survival in many of these patients. This shift in emphasis was concurrent with rapid advances in cardiac surgery, leading to improved hemodynamic operative results, and survival of more patients in whom pulmonary sufficiency after cardiac surgery became a controlling issue.

Tracheostomy and mechanical ventilation, often undertaken reluctantly in these patients when other approaches to hypoventilation or hypoxia have been unsuccessful, have become commoner. There is a strong impression that these measures, immediately life-saving, are often followed by secondary pulmonary deterioration in spite of physiotherapy, adequate humidity, and other conventional adjuncts. The role played by necessarily increased oxygen tension needs better definition. The pertinent questions are the time-dose factors in oxygen toxicity; the mechanism through which tissue damage occurs, and conversely, the factors underlying protection against development of oxygen toxicity in some species and individuals; and the possibility of protection by drugs. Information about all of these areas is incomplete; it is the purpose of this paper to review briefly some of the background and current work in the field of oxygen toxicity and to describe experiments which demonstrate the effect of oxygen on extractable surface-active components of the lung.

Time-dose Factors in Oxygen Toxicity

There is a large body of data from experiments in animals relating duration of exposure to hyperbaric oxygen (OHP), oxygen at ambient pressure (OAP), or oxygen at less than ambient pressure, to some observed end-point: usually convulsions or death. Experience with

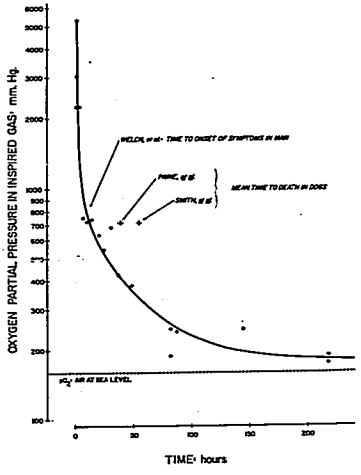

FIG. 1. Time-dose relationship in oxygen toxicity. Inspired P_{O_2} *vs.* time to appearance of symptoms in man from various series collected by Welch *et al.*[8] Added points are mean survival times for dogs breathing near-100 per cent oxygen at atmospheric pressure.

man is, of course, less, but more minute observations of functional and subjective change can be made. In one of the first experiments in human subjects, Becker-Freyseng and Clamann subjected themselves to 90 per cent oxygen for 65 hours[6]; both investigators had symptoms after 24 hours, and one experienced dyspnea, fever, vomiting, and a 40 per cent reduction in vital capacity. Individual variation is a characteristic of human response to oxygen at ambient pressure, and possibly because of it Becker-Freyseng and Clamann did not observe the substernal symptoms—pain or a less specific discomfort—that are usual with oxygen inhalation. Some of these early symptoms (which occur even sooner when oxygen inhalation is combined with accelerative force and restriction of chest motion, as in aviation) probably are caused by absorption atelectasis rather than by the Lorrain Smith effect. Dolezal,[7] in a more recent chamber experiment, exposed twelve subjects to an atmo-

sphere of over 96 per cent oxygen, maintaining CO_2 below 1 per cent. All had symptoms (chest pain, cough, anorexia, weakness) and half discontinued the experiment after 72–74 hours. One subject was able to continue for 110 hours; this period may well be the limit of voluntary tolerance of humans for ambient-pressure oxygen.

A curve relating oxygen partial pressure to time of appearance of symptoms in humans has been constructed by Welch *et al.*,[8] from data gathered in 1963 (fig. 1). The form of the symptoms, of course, depends upon the particular partial pressure of oxygen: at pressures below about 2 atmospheres, seizures do not occur and pulmonary toxicity dominates. Some conditions of the various studies are not identical, and the line through the points is drawn only to satisfy the eye. The curve is necessarily inexact for prediction of individual response. Nevertheless, the general form of the curve is useful, and it can be seen that tolerance to small increases of oxygen tension over that of sea level may be prolonged. This is the segment of the curve most interesting to those concerned with choice of space-capsule atmospheres. The selection of a 5 p.s.i. pure-oxygen environment for "Project Mercury" was supported by several studies made in this concentration range. The subjects were healthy young men, and the negative findings do not necessarily apply to patients in hospitals. For example, Robertson[9] maintained four subjects for 30 days in an atmosphere of pure oxygen at 258 mm. Hg total pressure, without development of symptoms and without changes in pulmonary function not attributable to decreased density of the breathing mixture. In the corresponding NASA studies by Coburn and many collaborators[10] who observed the effects of 100 per cent oxygen at 258 mm. Hg total pressure for 20 days, nothing is said about occurrence of respiratory symptoms. Lung volumes and carbon-monoxide-diffusing capacity were unchanged; in fact, retinal vasoconstriction was the only abnormality found. Earlier, Morgan *et al.*,[11] at an even lower oxygen tension of 176 mm. Hg total pressure, did observe substernal pain in one subject, beginning on the ninth day of exposure. Although these data suggest that small increases in oxygen concentration are safe in normal man for many days, for larger increases in inspired oxygen concentration in the range often used therapeutically, symptoms can be expected to appear on the second or third day, and symptoms are accompanied by functional changes. Caldwell[12] has shown that volunteers breathing 98 per cent oxygen undergo a significant, progressive fall in vital capacity, total lung capacity, and diffusing capacity.

Animal data are consistent with this. With some variation in time to appearance of toxicity, all warm-blooded species that have been investigated eventually were killed by unanesthetized exposure to oxygen concentrations near 100 per cent at atmospheric pressure; at necropsy pneumonitis was found. Reptiles and amphibians, on the other hand, tolerate ambient-pressure oxygen indefinitely without development of pneumonitis[13]; they are similarly resistant to the systemic effects of OHP, unless warmed, when their tolerance is reduced to that of most homeotherms. The resistance of this group to development of pneumonitis in high oxygen atmospheres is specifically interesting in that extracts from their lungs are less surface-active than material extractable from mammalian lungs.[14]

Application of information obtained from experiments in animals to utilization of oxygen therapy in humans raises the question of interspecies variation. No fully adequate comparisons are available, but among mammals, at least as a first approximation, interspecies variation is not greater than individual variation. Table 1 is a summary of data from experiments in which dogs were exposed to partial pressures of oxygen at or near ambient pressure. The commonly-observed individual differences in apparent susceptibility can be seen, and for comparison with the time-to-symptoms curve for man, mean survival times from two of the larger dog groups are plotted on figure 1, on the same coordinates with Welch's collective human data.

Rats and mice sometimes are credited with the ability to withstand ambient-pressure oxygen for longer period than the larger animals, but morphologic changes in the lung occur as early as functional changes in man. Measure-

TABLE 1. Dogs Exposed to High Concentrations of Oxygen at Atmospheric Pressure: Summary of Reported Experience

Author and Reference	Number of Animals	Method of Exposure	Composition of Test Atmosphere	Observations
Paine *et al.*[15]	12	Chamber	95% O_2	10 died in 6–94 hours (avg. 39) 2 survived 52 hours
	3	Chamber	85–90% O_2	1 died after 72 hours 2 survived after 72 hrs and 118 hrs
	1	Chamber	75–80% O_2	1 survived after 170 hours
Ohlsson[16]	5	Chamber	80–88% O_2 0.1–0.8% CO^2	All died in 5–7 days
	3	Chamber	80–90% O_2 0.3–0.5% CO_2	All died in 5–8 days
	6	Chamber	80–90% O_2 3.0–3.5% CO_2	All died in 2–3 days
Smith *et al.*[17]	22	Tracheal cannula	97–99% O_2	All died in 32–83 hours (avg. 54.6)
Morgan *et al.*[18]	8	Chamber	P_{O_2} 550 mm. Hg P_{CO_2} 10 mm. Hg	Symptoms appeared within 44.5–48 hours All survived 52 hours
Caldwell *et al.*[19]	15	Chamber	98% ±0.5 O_2	7 survived 30–54 hours 1 survived 72 hours 7 died in 61–79 hours (avg. 67)
Spencer *et al.*[20]	9	Chamber	P_{O_2} 295–345 mm. Hg	No deaths due to oxygen in 8–14 days; negative necropsies
	17	Chamber	P_{O_2} 300–720 mm. Hg	16 died in 2–5½ days with atelectasis, pulmonary hemorrhage and edema
Brooksby *et al.*[22]	10	Chamber	50% O_2	35 days' exposure; progressively increased pulmonary vascular resistance with pulmonary hypertension

ment of alveolocapillary dimensions in rats exposed to 98.5 per cent oxygen, by Kistler, Caldwell, and Weibel,[21] showed interstitial thickening and endothelial damage, observed first after 48 hours of exposure, progressing to capillary destruction and a dramatic intra-alveolar exudative reaction in 72 hours. Still, death is delayed in comparison with larger animals: among rats exposed to oxygen at 760 mm. Hg, 57 per cent survived 34 days.[22]

Combining time to development of symptoms or to functional change in humans with time to death or morphologic change in animals makes it reasonable to suppose that high oxygen concentrations—say, above 80 per cent at ambient pressure—will cause significant pulmonary damage after 36 or 48 hours. Further, if the shape of the curve of figure 1 is correct (that is, falling steeply at high partial pressures, with inflection near the transition from OHP to OAP, and finally asymptotic to the P_{O_2} of air), then no increase in oxygen concentration is safe indefinitely.* Some con-

* Although it is evident that oxygen at the P_{O_2} of sea level can be tolerated for long periods—a lifetime—an intriguing proposal has been made: that the atmospheric oxygen fraction is unhealthily high.[23, 24] This idea is based on the fact that the atmosphere is in slow transition from a reducing state to an oxidizing one. The earliest phase of this change is attributed to photochemical reactions coupled with differential escape of hydrogen from the atmosphere, caused by its smaller mass. Later, it is supposed, a little elemental oxygen continued to appear through this mechanism, but most was formed photosynthetically. The relative abundance of oxygen may have oscillated somewhat, but over a long-time scale its concentration is increasing.[25] Advantageous as an energy source, but threatening to the incompletely-oxidized constituents of living organisms, biological antioxidant mechanisms were evolved, and their evolution permitted aerobic life, but they are being overwhelmed by the increasingly-oxidizing environment.

firmation for this is found in results from Brooksby's series of ten dogs exposed for five weeks to only 50 per cent oxygen at atmospheric pressure (table 1). Significant pulmonary capillary damage, demonstrable by angiography, with pulmonary hypertension and right ventricular hypertrophy, occurred.[26]

There is almost no information about the potential interaction of oxygen with other factors often present: anesthesia, positive-pressure breathing, concurrent pulmonary infection, or abnormalities of ventilation–perfusion ratio. Ohlsson's experiments showed that such additive effects are influential. Rabbits were subjected to high oxygen concentration after sublethal pulmonary injury by blast or exposure to a chemical irritant, and mortality in the traumatized group was decreased.[16] The data of figure 4 suggest that positive-pressure ventilation when combined with 100 per cent oxygen is at least nonprotective against physical changes. Interpretable clinical data from experience with humans are hard to come by. Undoubtedly, some patients do survive many days of high oxygen concentration; in those who do not, the pathologic anatomy seen in the lungs is far advanced. It is intellectually satisfying to attribute changes found in an organ at necropsy to a single disease process, but when a patient succumbs after a long period of intensive care, it is hardly ever possible to draw such a conclusion. Support for the concept of pulmonary oxygen damage in intensive-care patients is found in the observations of Nash,[27] correlating histologic changes attributable to pulmonary oxygen toxicity with the duration of oxygen therapy.

Mechanisms of Toxicity and of Chemical Protection

Although biochemical effects of high oxygen tension probably are not organ-specific, the functional and morphologic consequences of failure to maintain membrane integrity and ionic gradients will vary from organ to organ. For the lungs, the response to poisoning by oxygen is comprised of an increase in pulmonary vascular resistance and alveolo-arterial diffusion gradient, decreased compliance, atelectasis, and alveolar transudation. These toxic effects originally were explained by Lavoisier as oxygen's "incendiary" action, making the fires of life to burn brighter. Since the lungs were thought to be the site of biologic oxidations, it was reasonable that they should be damaged. Actually, evidence first appeared in 1932 that oxygen in excess has the opposite effect, irreversibly depressing respiration in all tissues.[28] The underlying mechanism may be one or several: the three that have been accorded most attention are enzyme inhibition, free radical formation, and peroxidation.

The all-important event in cellular respiration is electron transfer through the flavoprotein-cytochrome system, regenerating reduced pyridine nucleotides coupled with regeneration of ATP. Some of those investigators concerned with this fundamental biologic problem have examined the short-term effects of high oxygen pressures on respiratory-chain enzymes. Chance and his co-workers[29] applied fluorometric techniques to observation of inhibition of energy transfer in intact organs under hyperbaric conditions. The oxidation of DPNH, ubiquinone, and flavin was found to be increased. Other respiratory-chain components, which are either fully oxidized at normal oxygen tensions or do not react with oxygen, were unchanged.

The direct fluorometric data reflect effects that are mostly intramitochondrial; but Chance[29] also found changes in the ratios of oxidized and reduced substrate pairs, showing a change in the cytoplasmic redox state; these pairs were lactate:pyruvate, alpha-glycerophosphate:dihydroxyacetone phosphate, and malate:oxaloacetate; each ratio was decreased. This change could be a reflection of intramitochondrial redox alterations, but also of dehydrogenase inhibition in the cytoplasm. Chance favors the former, finding no accumulation of glycolytic intermediates on tissue analysis. Nevertheless, inhibition of many sulfhydryl-containing dehydrogenases by hyperbaric oxygen has been demonstrated in other preparations,[30, 31] notably succinic dehydrogenase and cytochrome C reductase.

These observations help to explain the actions of some protective substances; the potential utility of an effective protective drug is obvious. Many of the suggested toxic mechanisms carry with them possibilities for protec-

tive maneuvers, and many have been tried. Sanders *et al.*,[32] noted that succinate oxidation had been observed to be relatively resistant to hyperbaric oxygen, that its oxygenation is not DPN-linked, and that L-glutamate oxidation, also somewhat resistant to oxygen poisoning, might proceed through conversion to succinate via gamma-aminobutyric acid. The latter has established protective properties. They, therefore, pretreated rats with sodium succinate, exposed them to OHP at 5 atmospheres, and observed protection both from death and from tissue ATP depletion. In the work of Felig and Lee, again in rats but at ambient-pressure oxygen, administration of sodium lactate was associated with increased survival and decreased pulmonary damage.[33] It had been found that an exogenous base, TRIS buffer, affords significant protection against both pulmonary and CNS effects, an effect usually explained as due to prevention of sympathomedullary stimulation by acidosis. Unfortunately, TRIS buffer does not prevent pulmonary damage at atmospheric pressure.[34] Of a series of alkalinizing agents, investigated by Felig, only lactate was significantly effective at ambient pressure. He suggests that the mechanism is not correction of acidosis, but rather reduction in DPN associated with lactate-pyruvate conversion, which restores the DPNH pool depleted by hyperoxygenation.

The well-recognized problem of extrapolation from one level of biologic integration to a higher one is particularly applicable to protection against oxygen toxicity. Enzymes in solution in cell-free systems tend to be more susceptible to oxygen poisoning than the same enzymes in particulate subcellular fractions, tissue slices, homogenates, or the whole animal.[35] At the whole-animal level, endocrine and metabolic variables modify the response to oxygen. This area has been explored by Bean,[36] who finds that both epinephrine and thyroid hormone potentiate toxicity of OHP, whereas corresponding endocrine ablation or pharmacologic blockade are protective. Chlorpromazine, as might be expected, is one of the effective protective drugs in hyperbaric oxygen, but does not prolong survival in 100 per cent oxygen at 1 atmosphere.[34]

Other potential mechanisms of oxygen toxicity involve nonenzymatic processes: free radical formation, lipid peroxidation, and surfactant denaturation. Gerschman proposed that toxic effects are mediated through free radical formation, analogous to and possibly additive to radiation injury to cells.[23] This idea fits well with the results from manipulations of naturally-occurring anti-oxidants and free-radical chain breakers. Glutathione and Vitamin E are two of these, and they do influence hemolysis in hyperbaric oxygen.[37]

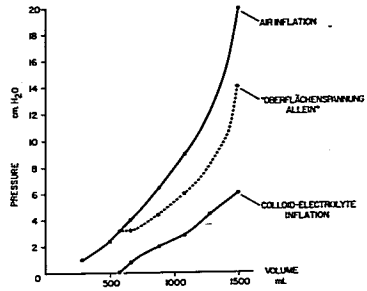

FIG. 2. Recoil due to surface forces. von Neergaard's observations of pressure-volume characteristics of lung with and without surface tension effects.[38]

The effects of oxygen on the surface-active layer lining the lung, and on its role in maintaining normal lung recoil and prevention of atelectasis, have been proposed as an explanation for the Lorrain Smith phenomenon. The general background is as follows: von Neergaard recognized the importance of surface forces in the lungs, in the 1920's.[38] Figure 2 shows the pressure-volume curves he obtained from hog lung, first with air, and then with a liquid which eliminated the air-tissue interface. The difference between the two curves, at a given volume, is due to the effects of surface tension, "Oberflaechenspannung." This observation was explained and amplified by Clements,[39] Pattle,[40] and others. It has been demonstrated that alveoli normally are lined with a material which lowers alveolar interfacial tension or the tendency to collapse as alveolar volume decreases. The material is a lipoprotein, the lipid component being mostly dipalmitoyl lecithin, probably, but not cer-

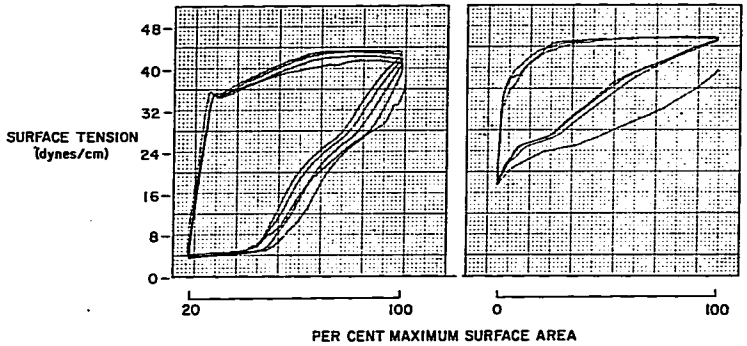

FIG. 3. Surface tension vs. area. Examples of surface tension-area curves from dog lung extracts. Left: normal lung. Right: after breathing 100 per cent oxygen (Dog CL 25).[42]

tainly, formed in the large alveolar cell, or corner cell, by a unique process of mitochondrial degeneration. The activity of the lung-lining layer can be interfered with directly by alveolar lavage with detergents or phospholipases; by interference with metabolic processes by way of pulmonary artery ligation; or developmentally, in hyaline membrane disease. More details of the work of many investigators in this area are available in current reviews.[41]

Oxygen concentration is one of the factors influencing the surface properties of lung extracts, at least in dogs.[15] Surface activity most commonly is assayed with a Wilhelmy surface balance, originally applied for the purpose by Clements. Figure 3 is an example of these kinds of data. As an illustration of this method, data from experiments in dogs exposed to 100 per cent oxygen at atmospheric pressure are described here; part of these results have been published.[42] As the surface area in the balance is reduced cyclically from maximum to minimum and re-expanded, surface tension is plotted against area as in figure 3. Minimum surface tension attained is used as an index of extractable surface activity. Normally, minimum surface tension would be 3.4 ± 0.7 dynes/cm., for measurements made this way. The significance of increased minimum surface tension cannot be interpreted as showing only a quantitative change in surface active material extracted, in that, within limits, variations in the weight of lung extracted do not influence minimum surface tension, which appears to reflect poorly-defined physical-chemical changes in the material. Beyond these limits, and with degassed lung which may be extracted incompletely,[43] quantitative factors are seen.

The effects of oxygen on extractable surface activity under four conditions are summarized in table 2. These dogs were anesthetized, the tracheas intubated, and they breathed humidified room air or pure oxygen, some spontaneously and some with a pressure-limited ventilator for 30 hours. The ventilator was set to assist respiration and to maintain normal Pa_{CO_2}. The animals were given two or three deep sighing respirations every 30 minutes. The assisted-respiration groups were included in this study because of the frequent use of mechanical ventilation and pure oxygen simultaneously. Changes in extractable surface activity have been observed after overinflation by mechanical ventilation,[44] but only in association with pulmonary edema and right heart failure.

The results are shown in figure 4. The minimum surface tension of extracts of lungs ventilated with room air is significantly lower, *i.e.*, "better," than that of lungs ventilated with oxygen, either spontaneously or mechanically ($P < 0.005$). There was no significant differ-

ence between spontaneous and mechanical ventilation with the same oxygen percentage. The change in surface activity with 100 per cent oxygen appeared sooner, that is, in 30 hours, than the changes observed by Caldwell [19] in unanesthetized, unrestrained animals, implying that anesthesia and immobility facilitate oxygen damage.

Although these results are derived from apparently-aerated lung, inclusion of liver-like samples from the same lungs did not increase the standard error of the data. In fact, in the oxygen groups, atelectatic specimens tended to have slightly lower surface tensions than the corresponding well-aerated samples. Although this difference was not significant, it suggests that underventilated portions of the lung, once collapsed, had been protected from further oxygen exposure, hence protected from further damage.

TABLE 2. Experimental Groups, Conditions, and Maximum and Minimum Surface Tensions of Lung Extracts

	Dog No.	ST (min.) d/cm.	ST (max.) d/cm.
Group I: Room air, spontaneous breathing	CL 9	4.8	39.2
	CL 16	2.0	42.8
	CL 24	2.4	34.5
	CL 34	3.3	36.8
	CL 36	8.8	44.1
	CL 38	1.6	39.6
	Mean	3.8±0.3	39.5±3.6
Group II: Room air, assisted ventilation	CL 13	8.0	40.0
	CL 20	10.2	46.4
	CL 30	4.8	41.6
	Mean	7.7±2.7	42.7±3.4
Group III: 100% oxygen, spontaneous breathing	CL 10	20.0	44.0
	CL 12	14.0	36.4
	CL 15	19.2	44.4
	CL 17	16.8	45.6
	CL 21	16.0	45.6
	CL 23	15.2	44.0
	CL 25	18.4	44.8
	CL 40	5.7	46.5
	CL 41	4.1	46.3
	CL 42	8.2	44.8
	CL 43	3.7	39.4
	Mean	12.8±6.2	43.8±3.1
Group IV: 100% oxygen, assisted ventilation	CL 7	18.6	42.0
	CL 11	15.2	37.6
	CL 22	8.0	40.8
	CL 26	23.5	33.6
	CL 28	21.6	39.2
	Mean	17.4±6.1	38.6±3.3

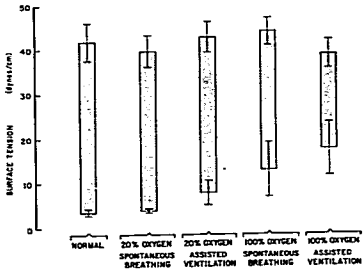

FIG. 4. Effect of increased oxygen tension and mechanical ventilation on surface activity of lung extract. Summary of mean values of maximum surface tension (top of bar) and minimum surface tension (bottom) for experimental groups. At left, results from fresh normal dog lung.[42]

Conclusions

It is probable that the direct pulmonary toxicity of oxygen contributes significantly to the mortality of the critically ill, the patients in whom its use is most necessary. There are basic questions about oxygen toxicity, in particular the mechanism through which it occurs, that are unanswered, largely because of the very fundamental character of the biologic problem. Nevertheless, some provisional conclusions are possible. One is that no toxic threshold exists. Any increase in the oxygen percentage of the inspired gas mixture is a threat, but when oxygen administration is limited to a few days, percentages over 70 per cent are dangerously high. Opportunities for unintended use of high concentrations have become more frequent with commoner use of mechanical ventilatory assistance. As demonstrated by Bosomworth,[45] pressure-limited ventilators with oxygen-driven nebulizers that depend on room air entrainment for 40 per cent oxygen may actually deliver concentrations

closer to 100 per cent, but this is avoidable by appropriate monitoring. There is need for the development of systems that will permit delivery of metered concentrations of oxygen.

Still, hypoxemia has to be treated with oxygen in the concentration necessary to maintain acceptable arterial P_{O_2}; what this must be is a matter of individual clinical judgment, but surely it seldom would be much above 100 mm. Hg. It can be expected that contributory factors, in themselves susceptible to treatment, will be identified in the future. The ultimate answer to the problem probably lies in the area of biochemical protection.

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Drugs

PARENTERAL IRON The rate of hemoglobin regeneration was measured in women with iron-deficiency anemia during treatment with iron sorbitex. Hemoglobin concentrations rose an average of 0.26 Gm./100 ml. per day, or 1.8 Gm./100 ml. per week. This hemoglobin regeneration rate was no higher than that previously found using oral iron or iron dextran parenterally. Since the amount of iron as iron sorbitex which can be injected in a single dose is limited by toxicity to 100 mg. per day, and since approximately one-third of the injected iron is lost in the urine, multiple injections of iron sorbitex are required to treat iron-deficiency anemia adequately. If other iron therapy has been given previously or if the patient is not iron-deficient, iron sorbitex may show increased toxicity. The multiple daily injections required, the local discomfort resulting therefrom, and the inability to achieve a more rapid response than that obtainable with other forms of iron therapy are significant disadvantages in the use of iron sorbitex. (*Scott, D. E., and others: Iron Sorbitex for Treating Iron-deficiency Anemia, Obstet. Gynec. 30: 679 (Nov.) 1967.*)