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Editorial Views

The Pulmonary Toxicity of Oxygen

BLESSINGS are characteristically mixed, and oxygen appears to be no exception. Because oxygen is so obviously essential, and often so immediately beneficial, its more subtle and seemingly somewhat theoretical pulmonary toxicity at high concentrations is easily overshadowed. A recent renewal of interest in this toxicity, and in its possible role in the pulmonary insufficiency that occurs after shock, hemorrhage, and trauma, has brought with it an important conceptual change: a more general willingness to consider supplemental oxygen as a drug like any other, to be prescribed in a dose selected to give maximum therapeutic effect with minimum toxicity. To those responsible for administration of oxygen to neonatal patients, where retrolental fibroplasia is a well-established hazard, this is an old story.

Many current investigations of oxygen are, in effect, studies of its pharmacology, for the safe and effective use of any drug requires knowledge of its actions, and the relationship of dose to response. For oxygen, these data are a part of basic respiratory physiology. It is equally necessary to be informed about toxicity, side effects, mechanisms of toxicity, and the likelihood of synergism with or antagonism to other therapies. DeLemos *et al.* examine the latter question in their report in this issue of ANESTHESIOLOGY.

The authors designed an experiment to ask whether lung damage from high inspired concentrations of oxygen is made worse or better by mechanical ventilation. A perfectly plausible formulation could be constructed to predict either outcome. In fact, no major effect was observed, a result which should be reassuring to all who treat sick humans with respirators. It is always possible to question the sensitivity of a measurement yielding a negative result, but there would be general agreement that the indices chosen are both sensitive and significant, and they certainly demonstrate a dramatic difference between the animals exposed to oxygen and the controls which breathed air. Measurements were made of static pressure–volume curves, tissue histology, and surface activity of lung extracts.

Some problems do exist in evaluating these kinds of data, as discussed by the authors. Their most dramatic finding, and the one least subject to interpretive quibbling, was the spontaneous death of animals after breathing oxygen for about two days. Of course, the outcome is the same for many other warm-blooded animals. There is some variation among individuals, and according to experimental design: species, age, ambient humidity, whether fed or fasted, and so forth; but even so, the effect is so general that it seems unlikely that man is uniquely resistant to pulmonary oxygen toxicity, a reason for realistic concern.

Finding the oxygen-poisoned lungs to be heavy is almost equally objective. A minor reservation here is the considerable uncertainty of predictions of lung weight at the extremes of body size; for man, weight is best predicted by a regression based on height and age, be-

cause the ratio of lung to total-body weight is influenced so strongly by the amount of body fat, the most variable component of body composition. (One might expect lung weight to be most accurately described by a measurement of body cell mass, either as exchangeable potassium or erythrocyte volume.) However, for a homogenous group of young animals without chronic illness, lung-to-body weight should be reasonably close to constant, and the experimental changes in question here are large.

Heavy lungs add some problems in interpretation of volume data, which have to be expressed as a ratio to allow comparisons to be made. If the ratio is volume-to-weight, this becomes larger for both increased weight and decreased volume, at a given transpulmonary pressure. But, when volumes are normalized by plotting percentage of maximum volume, changes in elastic properties can be seen. In the authors' data, lungs from animals exposed to increased oxygen concentrations behave as would smaller, but still normal, lungs. Some respiratory units have dropped out and apparently contribute venous admixture to the arterial desaturation observed in the second halves of the experiments. It is particularly interesting that there is little change in lung recoil measured this way because no change was seen in the surface tension of lung extracts. Other data do suggest that surface properties of lungs in oxygen are abnormal for some animals under some circumstances, even with due allowance for uncertainties inherent in methods available for measurement of extractable surface activity. An important question would seem to be whether surface changes, when they occur, are a metabolic result of oxygen exposure or a secondary, more mechanical, effect of pulmonary edema.

Even though the normalized pressure–volume curves are quite similar, there was an intriguing change, at low lung volume, for lungs from animals in the oxygen-alone group, where there was a tendency for air trapping in the deflated lung. This argues for increased airway closure, perhaps a significant variation in oxygen effect.

The list of unanswered questions in this field remains long. Other drug interactions are possible. Catecholamines, agents producing alpha blockade, various antioxidants, and agents affecting acid–base equilibrium have been found to influence oxygen toxicity in animals, but their importance in man is unknown. The effect of veno–arterial admixture, with abnormally desaturated pulmonary arterial blood, on the tissue effects of increased alveolar oxygen tension is, again, still a question. New causes for concern continue to appear. Long-term changes in the lungs of survivors of hyaline-membrane disease are being found, and similar chronic sequelae in adult survivors of intensive care may be identified in the future. The early occurrence of increased lung water in oxygen toxicity, with morphologic evidence of an endothelial leak, dictates caution when plasma volume is replaced by non-colloid solutions. Most important, the fundamental cause of pulmonary oxygen toxicity, as well as its pharmacologic interactions with many of the common concomitants of oxygen administration, remains unknown; where one asks what changes should be made in the conventions of oxygen therapy as the result of recent work, the answer would still appear only to be to use as little supplemental oxygen as is consistent with safe tissue oxygenation.

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