Extension of oxygen tolerance by interrupted exposure.

Hampson and Atik (1) recently reported a 0.03% incidence of oxygen-induced convulsions in a large patient population during routine administration of hyperbaric oxygen (HBO_2) therapy. Although this incidence is very low, it represents a three-fold increase with respect to the 0.01% incidence previously reported by Davis et al (2). As indicated by Dr. Zwart, the apparent inconsistency in convulsion incidence may be explained at least in part by the fact that different profiles for intermittent oxygen exposure were used in the two patient populations. In addition, Dr. Yildiz speculates that the type of equipment used to deliver the oxygen may have an effect on CNS O_2 toxicity occurrence. The following comments are provided in response to an invitation to summarize the available scientific information regarding effects of interrupted oxygen exposure on oxygen tolerance.

Early Studies

In what appears to be the first study of tolerance to interrupted hyperoxia, Soulie (3) found that exposure of rats to alternating 24-hour periods of O_2 and air at 1.0 ATA for three cycles did not decrease survival time during subsequent continuous exposures to the same O_2 pressure. Paine et al (4) also found that survival time in dogs breathing O_2 at 1.0 ATA could be greatly prolonged by changing the inspired gas from oxygen to air for a single 45-min or three 15-min periods each day. Although oxygen toxicity affects all living cells, prolongation of life in animals breathing O_2 at 1.0 ATA is considered to represent extension of pulmonary oxygen tolerance more than any other manifestation. Direct studies of pulmonary tolerance to continuous and interrupted oxygen exposure were carried out by Comroe et al (5) in normal men who breathed O_2 at 1.0 ATA continuously or intermittently for periods of 24 hours. During the intermittent exposures, periods of normoxia of 1, 5, or 15 min were inserted every 3 hours for a total duration that accumulated 24 hours of O_2 breathing. Although the total incidence of pulmonary symptoms was similar in all 4 groups, the group with 15-min interruptions had the least severe symptoms and the smallest average decrease in vital capacity.

Operational Applications

In World War II, undersea operational activity related to the evolution of open-sea oxygen diving, Lambertsen (6) found that the onset of CNS oxygen poisoning, as manifested by diaphragmatic and facial twitching, could be reversed by ascending to a shallower depth for a period of time before returning to deeper water. This observation led to a series of experiments in which guinea pigs were exposed to O_2 at 3.0 ATA either continuously or intermittently (7). The intermittent exposures alternated 30-min O_2 periods with 10-min normoxic (7% O_2) periods. The exposure duration within which 50% of the animals displayed early signs of oxygen poisoning (spasmodic movements) increased from 4.8 hours for continuous exposure to 15.3 accumulated oxygen hours for intermittent exposure. Hall (8) later extended these studies by evaluating several additional patterns of intermittent exposure at 3.0 ATA. Selected indices of oxygen poisoning included spasmodic movements, generalized convulsions, and death. Onset

times for all indices were extended most efficiently (maximum gain in total O_2 time for minimum increase in total exposure time) by an exposure pattern that alternated 20-min O_2 periods with 5-min air intervals. This pattern was later selected for evaluation of pulmonary tolerance to interrupted oxygen exposure in humans.

Optimization of Oxygen Tolerance Extension

In order to define general principles of oxygen tolerance extension by interrupted exposure for later evaluation in humans, Clark and Lambertsen (9) exposed rats systematically to varied patterns of intermittent O_2 exposure at pressures of 1.5, 2.0, and 4.0 ATA. Oxygen exposure periods of 20, 60, and 120 min were each alternated with at least 3 normoxic intervals selected to provide oxygen:normoxic ratios of 1:1, 2:1, and 4:1. When duration and pressure of the O_2 exposure were held constant while the normoxic interval duration increased progressively, there was a nearly linear increase in survival time. In general, oxygen:normoxic exposure patterns with the same ratio provided equivalent extensions of survival time at both 2 and 4 ATA. At both pressures, however, a 5-min normoxic interval was too short to extend survival time even when combined with a 20-min O_2 exposure, while recovery from a 120-min O_2 period was inadequate even during a 30-min normoxic interval. Neither of these exceptions was observed during intermittent exposure to O_2 at 1.5 ATA where oxygen poisoning develops more slowly than at higher pressures. It is possible that failure to extend survival time with a 5-min normoxic interval applies only to the rat. In guinea pigs exposed intermittently to O_2 at 3 ATA, survival time was increased by alternation of 5-min normoxic intervals with O_2 exposure periods of 10, 20, and even 30 min (8). Harabin et al (10) also found that survival time in guinea pigs exposed intermittently to O_2 at 2.8 ATA could be extended by alternating O_2 periods of 10-30 min with 5-min periods of air breathing (0.59 ATA O_2).

Pulmonary Oxygen Tolerance Extension in Humans

Using the 20:5 oxygen:normoxic pattern that was found to be most efficient in guinea pigs at 3 ATA, Hendricks et al (11) measured vital capacity as an index of pulmonary oxygen poisoning in 5 men exposed intermittently to O_2 at 2 ATA. Comparing rate of decrease in vital capacity during intermittent exposure with matched data from a different group of subjects who were exposed continuously to O_2 at 2 ATA (12), they found that the duration of O_2 breathing associated with a 4% decrease in vital capacity more than doubled during intermittent exposure. Subsequently, the concept that similar gains in oxygen tolerance are provided by intermittent exposure patterns that have the same oxygen:normoxic ratio was evaluated in humans by alternating 60-min O_2 periods with 15-min normoxic intervals in 6 men exposed to O_2 at 2 ATA (13). The rate of vital capacity reduction in 4 of 6 subjects on the 60:15 protocol was nearly identical to the average rate of fall in the 5 subjects previously exposed on the 20:5 pattern, while vital capacity fell more rapidly in the remaining 2 subjects. These results are consistent with the conclusion that 60-min O_2 exposure periods at 2 ATA are too long for optimal extension of pulmonary oxygen tolerance.

Extension of CNS Oxygen Tolerance

Following the early observation of Lambertsen (6) that signs of CNS oxygen poisoning could be rapidly aborted by reducing the inspired PO_2, related studies in guinea pigs (7,8) and later in rats (9) showed that the onset of generalized convulsions could be delayed by interrupted oxygen exposure with normoxic intervals as short as 5 min. Data analysis of small animal studies was complicated by the fact that convulsions did not always occur before death, and the incidence of convulsions often varied with different intermittent exposure patterns. For obvious reasons, comparable studies have not been performed in humans. During O_2 breathing at 2 ATA,

however, a reversible decrease in the amplitude of the electroretinographic (ERG) b-wave provides a pre-convulsive index of CNS oxygen poisoning. Comparing the rate of decrease in ERG b-wave amplitude during continuous exposure in one group of subjects with comparable data from another group of men exposed intermittently on a 60:15 oxygen:normoxic pattern indicates that the durations of O_2 breathing at 2 ATA associated with 10% or 20% decrements in b-wave amplitude are increased by about 46-51% during intermittent exposure (14). Although optimal patterns of intermittent exposure for extension of pre-convulsive periods during O_2 breathing at higher pressures have not been determined, it is likely that delay of convulsions during intermittent exposure should be qualitatively similar to that demonstrated for preservation of retinal response to a light flash. However, it is important to recognize that susceptibility to oxygen-induced convulsions varies widely among different individuals and even in the same individual on different days (15). It is also true that the increased brain blood flow and oxygen dose associated with relatively small elevations in arterial PCO_2 can abolish any protection provided by brief interruptions of oxygen breathing (16).

Relevance to Clinical Applications

The animal data show clearly that an intermittent exposure pattern with a relatively low oxygen:normoxic ratio is more effective than one with a higher ratio (relatively long O_2 exposure period with respect to the associated normoxic interval). They also show that a 10-min break is better than a 5-min break. These conclusions are best supported by survival time data, but the more limited convulsion data are consistent. Although the use of an "air" break (0.6 ATA O_2) rather than a normoxic interval may affect quantitative results, it is not likely to alter qualitative relationships. With regard to the reported difference in convulsion incidence (0.01% vs 0.03%), it is possible that the different intermittent exposure profiles are at least partly responsible, but the difference is not statistically significant in large patient populations as stated by Dr. Hampson. It is far more likely that convulsion incidence will be adversely affected by any source of CO_2 accumulation such as inadequate ventilation of an oxygen hood, excessive dead space in the oxygen delivery system, or narcotic respiratory depression in the patient.

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REFERENCES

1. Hampson N, Atik D. Central nervous system oxygen toxicity during routine hyperbaric oxygen therapy. *Undersea Hyperb Med* 2003; 30:147-153.
2. Davis JC, Dunn JM, Heimbach RD. Hyperbaric medicine: Patient selection, treatment procedures, and side-effects. In: Davis JC, Hunt TK, eds. Problem wounds: The role of oxygen. New York: Elsevier, 1988:225-235.
3. Soulie P. Modifications experimentales de la resistance individuelle de certains animaux a l'action toxique de l'oxygene. *CR Soc Biol* 1939; 130:541-542.
4. Paine JR, Lynn D, Keys A. Observations on the effects of prolonged administration of high oxygen concentration to dogs. *J Thorac Cardiovasc Surg* 1941; 11:151-168.
5. Comroe JH Jr, Dripps RD, Dumke PR, Deming M. Oxygen toxicity. The effect of inhalation of high concentrations of oxygen for twenty-four hours on normal men at sea level and at a simulated altitude of 18,000 feet. *JAMA* 1945; 128:710-717.
6. Lambertsen CJ. Extension of oxygen tolerance in man: Philosophy and significance. *Exp Lung Res* 1988; 14:1035-1058.

7. Lambertsen CJ. Respiratory and circulatory actions of high oxygen pressure. In: Goff LG, ed. Proceedings of the Underwater Physiology Symposium. Publication No. 377. Washington, DC: Natl Acad Sci-Natl Res Council, 1955:25-37.
8. Hall DA. The influence of the systematic fluctuation of PO_2 upon the nature and rate of development of oxygen toxicity in guinea pigs. Master's Thesis, University of Pennsylvania, 1967.
9. Clark JM, Lambertsen CJ. Principles of oxygen tolerance extension defined in the rat by intermittent oxygen exposure at 2.0 and 4.0 ATA. Undersea Biomed Res 1989; (supp) 16:99.
10. Harabin AL, Survanshi SS, Weathersby PK, et al. The modulation of oxygen toxicity by intermittent exposure. *Toxicol Appl Pharmacol* 1988; 93:298-311.
11. Hendricks PL, Hall DA, Hunter WH Jr, Haley PJ. Extension of pulmonary O_2 tolerance in man at 2 ATA by intermittent O_2 exposure. *J Appl Physiol: Resp Environ Exercise Physiol* 1977; 42:593-599.
12. Clark JM, Lambertsen CJ. Rate of development of pulmonary oxygen toxicity in man during oxygen breathing at 2.0 ATA. *J Appl Physiol* 1971; 30:739-752.
13. Clark JM, Gelfand R, Stevens WC, Lambertsen CJ. Extension of pulmonary oxygen tolerance in man at 2.0 ATA by intermittent exposure on a 60:15 oxygen:normoxic pattern in Predictive Studies VI. *Undersea Biomed Res* 1990; (supp) 17:25.
14. Clark JM, Gelfand R, Stevens WC, Lambertsen CJ. Comparison of human visual and pulmonary responses to continuous and intermittent oxygen exposure at 2.0 ATA in Predictive Studies V and VI. *Undersea Biomed Res* 1991; (supp) 18:86.
15. Donald KW. Oxygen and the diver. Harley Swan, UK: The SPA Ltd; 1992.
16. Lambertsen CJ, Ewing JH, Kough RH, Gould R, Stroud MW III. Oxygen toxicity. Arterial and internal jugular blood gas composition in man during inhalation of air, 100% O_2 and 2% CO_2 in O_2 at 3.5 atmospheres ambient pressure. *J Appl Physiol* 1955; 8:255-263.