

## Oxygen Therapy:

### *A Continuing Hazard to the Premature Infant*

RETROLENTAL FIBROPLASIA, an abnormal proliferation of the immature retinal vasculature of the prematurely born infant, can occur following exposure to hyperoxia. This may resolve with time or progress to fibrosis and variable loss of vision. In the most severe cases the infants are totally blinded. Susceptibility is highly variable, and, in general, inversely proportional to gestational age. Retrolental fibroplasia occurs mainly in infants who weigh less than 1,500 g or have gestational ages of less than 32 weeks at birth, but it can occur in any prematurely born infant.<sup>1</sup>

Until recently, retrolental fibroplasia was almost exclusively the concern of the pediatrician who used oxygen in the treatment of prematurely born infants with cardiorespiratory distress. The recent successes of neonatal intensive care have changed all this; now, anesthesiologists must concern themselves with this serious iatrogenic disease. In the past few years there has been a marked decrease in neonatal mortality among the very premature infants who are most susceptible to retrolental fibroplasia, *i.e.*, those of 1,000 g birth weight and 28 weeks' gestation or less. Such infants often require anesthesia and operation. Common procedures include ligation of a patent ductus arteriosus, laparotomy for intestinal obstruction or perforation, placement of cerebrospinal fluid shunts, and placement of intra-atrial catheters for parenteral nutrition. In the past, anesthesiologists used oxygen liberally; now they must realize they can blind such an infant with excessive oxygen during the few hours the infant is in their care!

The report by Betts and co-workers in this issue illustrates this important point. They describe a 1,140-g, 32-week-gestation twin in whom retrolental fibroplasia developed. The evidence strongly suggests that this resulted from hyperoxia produced by anesthesia with nitrous oxide and oxygen during laparotomy and oxygen given during the post-anesthesia recovery period. This experience is not unique.

Although the relationship between hyperoxia and retrolental fibroplasia was established in the mid 1950's, it was a decade later before frequent measurement of arterial oxygen tension ( $Pa_{O_2}$ ) could be applied routinely in the care of sick newborns receiving oxygen. When this was done, it was possible

to examine directly the relationship between severity and duration of hyperoxia and development of retrolental fibroplasia in man. Such comparisons confirmed what had been suspected from earlier clinical studies: the response of the premature eye to hyperoxia is extremely variable and, in the most sensitive, very brief hyperoxia can cause severe damage. The experience to date suggests the most susceptible infants can be blinded by a total exposure of just two or three hours to a  $Pa_{O_2}$  greater than 100 torr. Other infants of equivalent prematurity have tolerated documented exposures ten times as long without suffering permanent injury.<sup>2</sup>

Since safety standards must be designed for the most rather than the least susceptible, it is now recommended that whenever practical any premature infant (less than 38 weeks' gestation or 2,500 g) who needs an increased inspired oxygen concentration for more than a few minutes have the inspired oxygen concentration ( $F_{I_{O_2}}$ ) adjusted to maintain the measured  $Pa_{O_2}$  values between 60 and 100 torr (the range of normal for the newborn). This will provide adequate oxygenation and minimize, but probably not eliminate, the risk of retrolental fibroplasia. Maintaining  $Pa_{O_2}$  within this narrow range is often difficult and sometimes impossible even with very frequent measurements of  $Pa_{O_2}$ .

There are several practical points for consideration by the anesthetist who applies these recommendations in the operating theater and postanesthetic recovery room. First, the risk of retrolental fibroplasia persists until the retinal vasculature has matured. Thus, a 6-week-old infant who had had only 26 weeks' gestation at birth, has reached only 32 weeks, and may still be highly susceptible.

Second, regulation of  $F_{I_{O_2}}$  requires an oxygen:air blender that will reliably deliver any  $F_{I_{O_2}}$  between 0.21 and 1.0, as well as an oxygen analyzer, calibrated at least daily with room air and pure oxygen, to measure the concentration of oxygen actually delivered to the infant's airway.

Third, usually  $Pa_{O_2}$  values are measured in newborns by sampling from an umbilical arterial catheter with its tip in the descending aorta. This is downstream from the ductus arteriosus. When pulmonary arterial pressure is increased or aortic pressure is decreased, blood will shunt from pulmonary artery to aorta and

$Pa_{O_2}$  values measured in the descending aorta will be lower than those in blood going to the eyes from the ascending aorta. In practice this shunt is usually small in the very premature infants who are at greatest risk of retrolental fibroplasia unless they are severely hypotensive. Thus, when systemic pressure is maintained at a normal level and  $Pa_{O_2}$  in the descending aorta is kept at 80 torr or less, the  $Pa_{O_2}$  in the ascending aorta will rarely exceed 100 torr in infants of birth weight 1,500 g or less.<sup>3</sup> Right-to-left ductal shunting without systemic hypotension occurs with pulmonary hypertension syndromes. These usually occur in less premature infants, in whom the risk of retrolental fibroplasia is lower but still present if they are not fully matured. This is diagnosed by sampling blood simultaneously from the umbilical-artery catheter and the temporal (or right radial) artery and finding a significantly higher  $Pa_{O_2}$  in the latter. When such a shunt is present, repeated sampling from the temporal or right radial artery must be used to guide oxygen and ventilation therapy because the size of the shunt can change rapidly.

Fourth, preterm infants with cardiopulmonary disease are commonly in a very unstable state, so that changes in therapy often cause marked alterations in pulmonary perfusion and ventilation and, therefore,  $Pa_{O_2}$  values. This is particularly likely during surgical procedures. For example, ligation of a patent ductus arteriosus in an infant with a very large left-to-right shunt will produce an almost instantaneous improvement in compliance, necessitating changes in ventilation, pressure and rate, and  $F_{I_{O_2}}$ . Proper control of  $Pa_{O_2}$  can be achieved only by measurement soon after each change in the infant's condition and after any change in therapy that is likely to affect pulmonary function.

Fifth, the lungs of many preterm infants are easily hyperventilated during manually assisted ventilation;

in extreme cases, the effects of a low arterial carbon dioxide tension ( $Pa_{CO_2}$ ) on alveolar oxygen tension can cause significant changes in  $Pa_{O_2}$ . For example, at sea level an infant whose lungs are hyperventilated to a  $Pa_{CO_2}$  of 20 torr will have an alveolar  $P_{O_2}$  value of more than 120 torr. While the majority of premature infants have alveolar-arterial oxygen partial pressure differences of at least 20 to 40 torr, some do not. When this difference is small, the  $Pa_{O_2}$  will exceed safe levels during hyperventilation even when room air is inspired.

The American Academy of Pediatrics, Committee on Fetus and the Newborn, published a review of retrolental fibroplasia as a supplement to *Pediatrics* in 1976.<sup>1</sup> Those interested in the subject should read this. The same committee has published a manual, *Standards and Recommendations for the Hospital Care of Newborn Infants*, which contains detailed recommendations for the use of oxygen in newborns. The latest edition is now in press and will soon be available from the Academy (1801 Hinman Avenue, Evanston, Illinois 60204).

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