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Life-threatening Perioperative Apnea in the Ex-"premie"

THE SURVIVAL RATE for preterm infants has increased steadily during the past few years, because of improvement in all aspects of neonatal care.[1] However, along with this increased survival has come a variety of new problems. One of these is the increased incidence of surgical disease (*e.g.*, inguinal hernia) and another is a predisposition to perioperative apnea, associated with relatively minor surgical procedures.[2,3] In this issue, Liu and associates report on the incidence of apnea occurring in preterm infants, following anesthesia and surgery.[4] This has become a hot topic in pediatric anesthesia. Despite this interest, there is little known about which patients are at risk and what care should be provided for those who are at risk. Dr. Liu and her associates have helped enlighten us on these subjects.

The Incidence of Apnea

Apnea is defined as a cessation of breathing that lasts 20 s or more and results in cyanosis and bradycardia. It occurs in 20–30% of preterm infants during the first month of life.[5] The more premature the infant, the more likely is the occurrence of apnea. There are many predisposing factors to the development of apnea, including hypoglycemia, hypoxia, hyperoxia, sepsis, anemia, hypocalcemia, and environmental temperature changes.[6]

There have been two previous reports of apnea in preterm infants undergoing anesthesia and surgery. In one,[2] Gregory reported that 75% of preterm infants (36 ± 2 weeks) had apnea develop during the induction of anesthesia, and 25% had apnea during the first 12 h after surgery. Three of the latter required mechanical ventilation in the recovery room for 2–6 h. Eight per cent of term infants had apnea during the induction of anesthesia, but none had postoperative apnea. In the second study,[3] Steward found that 12% of preterm infants developed apnea during and up to 12 h following anesthesia. None required mechanical ventilation postoperatively.

Control of Respiration

The control of ventilation in the preterm infant is less efficient than that of older infants. It is unclear whether this is due primarily to immaturity of the central nervous system or to inability of the respiratory system (chest wall, lungs) to respond effectively to respiratory stimuli. The ventilatory response of preterm neonates to changes in inspired oxygen and carbon dioxide is less than that of term infants. Infants with apnea have altered control of respiration. Their resting Pa_{CO_2} is higher, and their CO_2 response curve is slightly flattened. Hypoxia reduces ventilation in preterm infants, rather than increasing it, as occurs in adults.[6] Preterm infants are more prone to sudden infant death syndrome (SIDS) than term infants, and those studied following near-miss SIDS show a decreased response to hypoxia and failure of arousal with this stimulus.[7] Preterm infants with apnea have prolonged brain stem conduction times for auditory evoked responses.[8] As the infant grows, these conduction times tend to shorten to those of normal infants, at which time apnea disappears. This suggests that apnea of prematurity may be due, at least in part, to incompletely developed neural function of the brain stem.

Chest Wall and Diaphragm

Much attention has been directed toward the role of the chest wall and lungs as a cause of the apnea of the preterm infant.[9,10] Their rib cage is significantly more compliant, and a less effective distending force for the lung, than it is in older infants and children. The soft rib cage tends to distort during inspiration and fails to oppose totally the action of the diaphragm. As a consequence, much of the force generated by the diaphragm is expended in distortion of the chest wall, rather than in producing a tidal volume.

The diaphragm is the major muscle of ventilation in preterm infants, as it is in older patients. The resistance of this muscle to fatigue depends upon the proportion of high oxidative type I muscle fibers present.[11] Up to 30 weeks gestation, the diaphragm is made up of about 10% type I fibers. Full term infants have 25% and adults 55% of these fibers. The number of type I muscle fibers in the intercostal muscles also increases with age. Infants whose conceptual ages are less than 37 weeks have only 19% type I fibers, while term infants have 46%, and those over 48 weeks, 65% type I fibers in their intercostal muscles. These data indicate that the oxidative capacity of both sets of ventilatory muscles increases from midgestation to early childhood. In preterm infants, this lack of high oxidative fibers in the muscles of respiration predisposes them to respiratory fatigue and reduces their ability to sustain ventilation, especially during periods of stress.

Sleep Pattern

Preterm infants spend as much as 40% of their time in rapid eye movement (REM) sleep. During REM sleep, there is increased chest wall distortion and increased dia-

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phragmatic work.[9] It is not surprising, therefore, that apnea occurs more commonly in these patients during REM sleep than at any other time.

The Lung

The lung of preterm infants also differs from that of older patients. As a consequence of these differences, preterm infants are more prone to develop atelectasis than term infants and adults. There are several reasons for this. First, their chest wall is very compliant, and fails to maintain a functional residual capacity (FRC) as effectively as occurs in older patients. Secondly, gas exchange units of preterm infants are smaller (75 μm diameter) and therefore much more prone to collapse than those of term infants (150 μm diameter) or adults (250 μm diameter), according to the LaPlace equation, all else being equal.[12]

Neonates normally breathe 30–60 times a minute to meet their increased metabolic needs. An important by-product of this high respiratory rate is maintenance of the FRC. This occurs because the time constant of the lungs of infants, the time during which two-thirds of a tidal volume is exhaled, is short (0.25 s). Assuming that the inspiratory and expiratory times are equal, which they usually are, at a respiratory rate of 60/min, there is time for approximately two time constants to pass during exhalation. At 30 breaths/min, four time constants will pass during exhalation and a larger volume will escape from the lung. Thus, the slower the respiratory rate, the more gas escapes from the lung, and the smaller is the FRC. During apnea the FRC decreases to very low levels.[13]

Residual Lung Disease

A varying amount of residual lung disease is common in infants who were born prematurely, and may persist for years.[14] The respiratory rate is higher, the compliance of the lungs reduced, and their Pa_{O_2} is below normal when breathing room air, due to mismatching of ventilation and perfusion.

If preterm infants are allowed to breathe spontaneously through an endotracheal tube without a positive end-expiratory pressure, their FRC decreases, and they have atelectasis develop. Atelectasis causes apnea in infants, either by changes in lung mechanics or by hypoxemia. Dr. Liu and her associates have not told us how much chronic lung disease was present or whether they applied a positive end-expiratory pressure when the patients were allowed to breathe spontaneously. Both would influence the likelihood of developing atelectasis and apnea.

Temperature Changes

Changes in environmental and body temperature also may cause apnea in some infants.[15] Changes in environmental temperature, such as those that occur with moving from the warmth of the operating room table and surgical drapes to a relatively cold recovery room, can cause apnea. Hypothermia (<35.5° C) is associated with apnea and hypoventilation in preterm infants. However, body temperatures between 35.5 and 36.5° C usually stimulate respiration and decrease apnea. Apnea is much more common when the body temperature is at 36.8° C than at 36.2° C.[15] It has been demonstrated that when the blower in the isolette comes on and warm air is blown across the body, infants have apnea more often.[16]

Anesthetic Drugs

Anesthetic drugs affect the ventilatory control mechanisms.[17] They depress the tidal volume and minute ventilation of adults. Robinson *et al.* demonstrated that 0.75 MAC halothane depressed the minute ventilation and FRC of spontaneously breathing lambs 50% and 40%, respectively, and increased Pa_{CO_2} 100%.* These changes are greater than those reported in adults. Froese and her associates showed that low concentrations of halothane inhibit intercostal muscle activity in older children.[18] We know of no similar studies in human neonates, but similar effects reasonably might be expected. Anesthesia decreases the ability of healthy lambs to increase their respiratory intercostal muscle activity, which increases diaphragmatic work. Low concentrations of volatile anesthetics depress the ventilatory response in humans to hypoxia,[17] and presumably also in infants.

Discussion

The Liu *et al.* study helps define which infants are at risk for developing apnea. Only the six infants with a history of apnea and a conceptual age below 44 weeks had apnea develop after anesthesia and surgery. The seven infants who also had a preoperative history of apnea, but whose conceptual age was 46–80 weeks, did not have apnea develop postoperatively. No full-term infant or infant without preoperative apnea had apnea develop postoperatively. However, it is probable that more infants would have had apnea develop postoperatively, but for the fact that the authors mechanically ventilated a large number of patients for other reasons.

Because the infants who had apnea develop were younger conceptually, they would have fewer type I muscle fibers in their diaphragm and intercostal muscles, and, as a consequence, would be less able to sustain the increased respiratory work that occurs with atelectasis, hy-

* Robinson S, Gregory GA, Willis M: The effects of halothane anesthesia on pulmonary function in the newborn lamb. Abstr of Am Soc of Anes Meeting, 1978

percarbia, or hypoxemia. From the data presented, it is unclear whether the infants still were having apnea episodes up to the time of surgery. If so, their brainstem pathways may have been developed incompletely. By allowing the infants to spontaneously breathe 100% oxygen through an endotracheal tube at the end of the procedure, without adding positive end-expiratory pressure to the airway, Dr. Liu and her associates would increase the likelihood of atelectasis occurring in these patients.[19] In addition, breathing 100% oxygen without PEEP would increase the R-L shunt about 12–15%.[20] Thus, this rather common mode of getting older patients to resume spontaneous ventilation, breathing 100% oxygen through an endotracheal tube without applying a positive end-expiratory pressure, is unwise in preterm infants. However, it must be remembered that apnea also occurs, albeit less frequently, in preterm infants who have been recovered by more conventional means.[3]

It is of interest that five of the six infants who had apnea develop postoperatively were paralyzed with muscle relaxants during the procedure. All were less than 40 weeks gestation at the time of surgery. The three patients who received muscle relaxants and did not develop apnea were 59.8 ± 18 weeks of conceptual age. It is possible that the young infants had some residual neuromuscular block and because of the reduced percentage of type I muscle fibers, were less able to overcome the effects of the residual block than older, more mature infants. This possible association should be investigated further.

The authors have suggested quite strongly that infants of less than 46 weeks conceptual age should not have surgical procedures performed as outpatients because of greater risk for having apnea develop postoperatively. Based on the limited amount of information available, it is difficult to state with certainty that this is the correct conclusion. However, it is the conservative approach and least likely to cause difficulty for the patients. How long into the postoperative period the patient should be hospitalized is unclear. Postoperative apnea has been reported to occur as late as 12 h after the end of anesthesia. Therefore, it would seem advisable to monitor the patients for at least 18 h. It would also seem desirable that infants who are at risk for developing apnea should be operated upon only when absolutely necessary and only in hospitals with full facilities for neonatal respiratory care. Elective surgery should be avoided in these patients until they are beyond 44 weeks gestation.

While many surgical procedures can be deferred until the infant is older, some are considered relatively urgent: for example, inguinal herniotomy. Whether the preterm infant is actually at more risk from the presence of the hernia or from the potential complications of anesthesia for surgical repair has not been defined. The incidence of serious complications occurring during the conservative management of inguinal hernia in preterm infants never has been studied.

Day care surgery has many advantages for infants having relatively minor operations. Therefore, there is reluctance to advise admission to hospitals unnecessarily. However, it is apparent that a special group of infants at high risk of potentially very serious complications has been identified. Further prospective studies are needed to delineate more exactly those most at risk of having apnea develop. Until such information is available, extreme caution must be exercised, and it is probably best to do the following:

1. Delay nonessential surgery for preterm infants until they were beyond 44 weeks conceptual age.
2. Where such surgery cannot be delayed, the patient should be admitted to hospital and monitored on an apnea monitor for at least 18 h postoperatively. The hospital must be able to mechanically ventilate infants postoperatively.
3. Pediatric surgeons must reexamine the indications for surgery in the preterm infant and define these conditions that safely can be managed conservatively until the patient grows older and more mature.

GEORGE A. GREGORY, M.D.
Professor of Anesthesiology and Pediatrics
Department of Anesthesia
University of California, San Francisco
School of Medicine
San Francisco, California 94143

DAVID J. STEWARD, M.B.
Anaesthetist-in-Chief
Department of Anaesthesia
The Hospital for Sick Children
555 University Avenue
Toronto, Ontario
Canada M5G 1X8

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