Postoperative Apnea in Preterm Infants

C. D. Kurth, M.D.,* A. R. Spitzer, M.D.,† A. M. Broemmle, M.D.,‡ J. J. Downes, M.D.§

Preterm infants may become apneic during the immediate postoperative period. To define this risk, the authors studied prospectively the breathing patterns of 47 preterm infants less than 60 weeks postconception with pneumocardiograms before and after general inhalational anesthesia. Eighteen infants (37%) had prolonged apnea (>15 s) postoperatively, and an additional seven infants (14%) had short apnea (6–15 s) postoperatively. An infant’s risk of prolonged and short postoperative apnea was related to a young postconceptional age (P < 0.05) and to a history of necrotizing enterocolitis (P < 0.01). Furthermore, as the postconceptional age of the infant increased, the risk of postoperative apnea decreased proportionately (P < 0.025). Among the 18 infants with prolonged apnea, 85% experienced multiple apneic episodes. Manual stimulation was required in order for breathing to return in 13 (72%) of the infants. Breathing resumed spontaneously in four (22%) of the infants, and one infant required mechanical ventilation due to repeated prolonged apnea. The first apneic event occurred within 2 h postoperatively in 13 of the infants (72%); the remaining five infants (28%) had their initial apneic episode as late as 12 h after operation. The postoperative time to the last prolonged apneic event was inversely related to the postconceptional age (P < 0.01, r = −0.70) and extended up to 48 h postoperatively. The preoperative pneumocardiogram was not a reliable test for predicting postoperative apnea (sensitivity 56%, specificity 83%). Four infants with normal preoperative breathing pattern and no preoperative history of apnea experienced prolonged apnea after operation. These results confirm that, in preterm infants, apnea is a common problem following anesthesia. The authors conclude that preterm infants younger than 60 postconceptional weeks of age should be monitored continuously for at least 12 h postoperatively in order to prevent apnea-related complications. (Key words: Age factors. Anesthesia: pediatric. Complications. Lung: pneumocardiography. Monitoring. Surgery: pediatric. Ventilation: apnea.)

Prolonged Apneic Episodes (>15 s) occur in approximately 60% of young preterm infants during the first few weeks of life. The frequency of apnea subsequently decreases with advancing postconceptional (PC) age. Full-term infants, by comparison, rarely experience prolonged apnea.

As a consequence of improved neonatal care, greater numbers of young preterm infants are surviving, and many require anesthesia and operation. Life-threatening apnea has been identified recently in young, formerly premature infants after they have received anesthesia. Full-term infants, in contrast, rarely experience postanesthetic apnea. One study suggests that the risk of apnea in preterm infants during emergence from anesthesia is related to the PC age. The greatest risk occurs in infants with a history of apnea and a PC age less than 46 weeks. Postanesthetic apneic episodes may persist for up to 12 h in preterm infants recovering from inguinal herniorrhaphy. Whether this was a consequence of anesthesia, the herniorrhaphy, or an inherent abnormal preoperative pattern of breathing is unclear. These observations, however, have led to the recommendation that preterm infants less than 44 weeks postconception be monitored for 18–24 h after anesthesia in a hospital that can provide intensive respiratory care to young infants.

To more precisely access the risk of postoperative apnea and to describe breathing patterns that might assist perioperative management, we prospectively studied a series of young preterm infants with pneumocardiograms before and after anesthesia.

Materials and Methods

We recruited infants who were less than 61 PC weeks of age from the surgical clinics and in-patient wards of the Children’s Hospital of Philadelphia. Infants were eligible for study if they were born prematurely (less than 37 weeks gestation), as determined by Dubowitz exam at birth. Infants were excluded if they were in the intensive care unit on the day of operation or if postoperative admission to the intensive care unit was planned. This study was approved by this institution’s committee for the protection of human subjects, and informed consent was obtained for each infant.

The 47 eligible infants had anesthesia for 49 operations (table 1); for 35 operations (71%), infants were ASA physical status 1 or 2 and, for 14 (29%), physical status 3. Prior to operation, the infants had a preoperative baseline impedance pneumocardiogram. The pneumocardiogram (Heathdyne 16900 monitor and trend event recorder) was performed in the infant’s crib or isolette for at least 2 h, with a minimum of 30 min of sleep. The pneumocardiograms were done within 48 h of the operation on the 23 in-patients, and within 1 week of the operation for the 26 out-patients admitted on the day of operation. Six infants had their baseline pneumocardiograms...
Table 1. Operations

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Infants (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herniorrhaphy, circumcision, or both</td>
<td>26</td>
</tr>
<tr>
<td>Laparotomy</td>
<td>7</td>
</tr>
<tr>
<td>Ventriculoperitoneal shunt</td>
<td>7</td>
</tr>
<tr>
<td>Central line placement</td>
<td>4</td>
</tr>
<tr>
<td>Miscellaneous minor procedures</td>
<td>5</td>
</tr>
</tbody>
</table>

programs as part of the Apnea Screening Program at the Children’s Hospital of Philadelphia. These recordings were at least 6 h in duration, and were obtained from 1–4 months before operation. These infants were healthy, slightly older out-patients with normal pneumocardiograms, and their breathing patterns would not be expected to change during the interim. According to hospital policy, patients younger than 52 PC weeks were scheduled for overnight hospitalization following operation, and infants older than 52 PC weeks were evaluated for day surgery on an individual basis.

On the day of operation, the infants received general endotracheal inhalational anesthesia with neuromuscular blockade (table 2). The only premedication was atropine. During anesthesia, the infant’s heart and breath sounds, electrocardiogram, systemic arterial pressure, temperature, and inspired expired gas concentrations were monitored. The neuromuscular blockade was reversed with atropine and neostigmine in infants who received a nondepolarizing relaxant. Adequacy of reversal was assessed with a twitch monitor or clinically. At the end of the operation, inhalational agents were discontinued, and patients were given 100% O₂ and extubated in the operating room when they met well-established criteria. Infants were subsequently observed for 2 h in the recovery room. A postoperative pneumocardiogram was performed for a minimum of 6 h postoperatively for 5-day surgery patients and 18 h for 44 in-hospital patients.

We used the following definitions for apnea and bradycardia, which were based on their adverse effects on infant arterial oxygenation, systemic oxygen delivery, and cerebral blood flow. Prolonged apnea is the cessation of breathing for greater than 15 s or less than 15 s if accompanied by bradycardia. Bradycardia is a decrease of heart rate greater than 40 beats/min below resting heart rate. Central apnea is the absence of chest wall movement on trend event recordings, whereas obstructive apnea was suspected when bradycardia was accompanied by increased thoracic impedance on trend event recordings. Short apnea was a respiratory pause greater than 6 s but less than 15 s. We noted short apnea only when the apnea density (total apnea > 6 s in min/100 min of sleep) was abnormally high (> 5). History of apnea referred to prolonged apnea noted clinically or with a pneumocardiogram at any time from birth until enrollment in the study. All the pneumocardiograms were read by one of us (ARS) without knowledge of the patient’s clinical status. Physicians and nursing staff caring for the patients were unaware of the results of the pneumocardiograms.

Data are expressed as the mean ± SEM for independent samples. For statistical analysis, we employed the chi square test, Fisher’s exact test, and a one-way analysis of variance test, which uses the least significant differences for multiple comparisons of significant F values. We utilized a specific chi square test for analysis of linear trends in proportions. Linear regression and correlation was calculated by the least squares method. Significance is defined as P < 0.05.

Results

We identified three groups of infants on the basis of their postoperative breathing patterns (tables 3, 4). One group of 24 infants had normal breathing postoperatively. Of these, 20 (84%) infants had normal preoperative breathing and four (16%) had episodes of short apnea, as shown by preoperative pneumocardiograms. The second group consisted of 18 infants who had episodes of prolonged apnea postoperatively. In 11 infants (61%), there was normal breathing preoperatively, while in five (28%), episodes of short apnea were detected preoperatively. In two babies (11%), prolonged apnea was seen on the preoperative pneumocardiogram, but the apnea was clearly more frequent and prolonged on the postoperative pneumocardiogram. The third group included seven infants who had episodes of short apnea postoperatively. These infants also had episodes of short apnea shown on their preoperative pneumocardiogram with similar frequencies noted before and after anesthesia.
The normal and abnormal (prolonged and short apnea) preoperative pneumocardiograms were not very specific (83%) or sensitive (56%) for predicting which infant would have postoperative apnea (table 3). Moreover, four infants with PC ages of 49, 52, 54, and 55 weeks had prolonged apnea postoperatively, in spite of a normal preoperative pneumocardiogram and no history of apnea.

In comparison with infants who had normal postoperative breathing, infants with prolonged postoperative apnea had significantly younger PC (P < 0.01) and postnatal (P < 0.01) ages, while infants with short postoperative apnea had significantly younger PC (P < 0.05) ages (table 4). Furthermore, significantly more infants in the prolonged and short postoperative apnea groups had histories of necrotizing enterocolitis (P < 0.01). The three groups did not differ significantly by gestational age, birthweight, duration and anesthesis, history of apnea, presence of neurological disease or bronchopulmonary dysplasia, physical status, preoperative hematocrit, type of operation, postoperative analgesic or anesthetic agent used, or body temperature while in the recovery room.

Infants experienced episodes of apnea after 25 of 49 operations (51%); after 18 (37%), the apnea was prolonged. By Armitage’s method, there was an inverse linear trend (P < 0.025) between the incidence of prolonged and short postoperative apnea and the infant’s PC age (fig. 1). Among the 13 infants 42 PC weeks of age or younger, prolonged postoperative apneic episodes occurred in eight (62%); another two infants (14%) had short postoperative apneic episodes. In contrast, at 55–60 PC weeks of age, only one infant (14%) had prolonged postoperative apnea; the remaining six (86%) had normal postoperative breathing.

Among the 18 infants with prolonged postoperative apnea, 13 (72%) experienced their first episode within 2 h postoperatively, and five (28%) had their first apneic episode from 2–12 h postoperatively. Of these five infants, three had received acetaminophen for postoperative analgesia, but the other two did not receive any analgesic medications. The postoperative time to the last prolonged apneic event varied inversely (γ = 698e−0.1x, r = −0.70, P < 0.01) with the infant’s PC age (fig. 2). Infants younger in PC age had prolonged apnea for a significantly longer time postoperatively than infants older in PC age. Babies aged between 32 and 40 PC weeks continued to have prolonged apneic episodes from 12–48 h postoperatively, whereas infants aged 48–55 PC weeks had prolonged apneic episodes from admission to the recovery room to nearly 10 h postoperatively. Three infants aged 43, 52, and 54 PC weeks were healthy out-patients admitted for hernia repair. The 43-week-old infant had one prolonged apneic episode 12 h postoperatively, but normal breathing in the recovery room. The other two patients had prolonged apnea only in the recovery room.
The preterm infant’s breathing pattern after general inhalational anesthesia appeared to respond in two ways. One response consisted of breathing interspersed with episodes of prolonged apnea. Typically, these infants had multiple episodes, usually accompanied by bradycardia. In the majority of infants, the prolonged apnea began in the recovery room when the postoperative effects of anesthesia were the greatest. A few infants, however, had normal breathing in the recovery room, and did not become apneic until several hours later. Since postoperative analgesics could not have accounted for this delayed apnea, this suggested to us that, for some infants, the recovery room provided a nearly continuous source of stimulation by personnel and equipment; thus apnea occurred only when the infants were moved to a quieter location.22-23

Another respiratory response following anesthesia in preterm infants was a return to their preoperative pattern of breathing, which consisted of either normal breathing or breathing accompanied by episodes of short apnea. Thus, even though an infant may have had an abnormal baseline breathing pattern, anesthesia may not necessarily exacerbate this abnormality. Postoperative apnea may occur because of a weak central respiratory drive.23 As the preterm infant ages, the respiratory drive strengthens, and the threshold for apnea increases. Thus, infants of younger gestational age have flatter CO₂ response curves than infants of older gestational age24; preterm infants with apnea have flatter CO₂ response curves than those without apnea25,26; and the incidence of apnea decreases as the PC age increases.1,2

Accordingly, postoperative apnea may occur because the central respiratory drive and the threshold for apnea are temporarily decreased by such factors as residual anesthetics and postsurgical elevations of endorphins. Thus, the incidence of postoperative apnea was greater and the time to last apnea was longer in younger preterm infants with lower thresholds for apnea than in the older infant. Halogenated inhalational anesthetics decrease ventilatory responses to CO₂.27 Elevated levels of endorphins cause apnea during infancy that is reversible with the admin-
istration of naloxone. Since endorphins can be significantly elevated for 72 h postoperatively, they may cause apnea after the patient has been taken from the recovery room, when most halogenated inhalational anesthetics have been eliminated.

Among preterm infants, pharyngeal airway obstruction is another common cause of apnea. Residual anesthetics could aggravate the preterm infant's predilection for this obstructive apnea. Our postoperative trend event recordings, however, did not reveal any episodes of obstructive apnea.

Based on a retrospective study, Stewart reported that apnea was the most frequent postanesthetic complication for the preterm infant. Apneic episodes requiring manual stimulation occurred until 12 h postoperatively in 18% of the infants. Most of the infants with postanesthetic apnea did not have a preoperative history of apnea. Liu et al. described prolonged apneic episodes that required mechanical ventilation in 21% of their preterm infants on emergence from anesthesia. They found, as did we, that the risk of apnea is related to young PC and postnatal ages. However, in our study, we also found that prolonged apneic episodes that required manual stimulation may begin as late as 12 h postoperatively and may continue to occur for up to 48 h postoperatively in infants younger than 45 PC weeks, and up to nearly 10 h in infants from 45-55 PC weeks. A prospective design and the use of pneumocardiograms may have increased our detection of prolonged postoperative apnea. Furthermore, normal preoperative pneumocardiograms and the lack of a history of apnea did not provide reliable reassurance that apnea would not occur postoperatively.

Based on these observations, we recommened the following postoperative care for preterm infants who receive general inhalational anesthesia: infants younger than 60 PC weeks should be monitored continuously for at least 12 h postoperatively. If the infant has a postoperative apneic event, monitoring should be continued until at least 12 apnea-free hours have elapsed. For infants younger than 45 PC weeks, this will usually be at least 36 h postoperatively; infants older than 45 PC weeks will usually need to be monitored for 24 h postoperatively.

The authors thank Kathy Peeke, Patti Juliano, and Debbie Goldich for their technical assistance, and Lynn M. Carroll for editorial assistance.

References

4. Stewart DJ: Preterm infants are more prone to complications following minor surgery than are term infants. ANESTHESIOLOGY 56:304–306, 1982