Postoperative Apnea in Former Preterm Infants after Inguinal Herniorrhaphy: A Combined Analysis
[Clinical Investigation]

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Abstract

Background: Controversy exists as to the risk for postoperative apnea in former preterm infants. The conclusions of published studies are limited by the small number of patients.

Methods: The original data from eight prospective studies were subject to a combined analysis. Only patients having inguinal herniorrhaphy under general anesthesia were included; patients receiving caffeine, regional anesthesia, or undergoing other surgical procedures were excluded. A uniform definition for apnea was used for all patients. Eleven risk factors were examined: gestational age, postconceptual age, birth weight, history of respiratory distress syndrome, bronchopulmonary dysplasia, neonatal apnea, necrotizing enterocolitis, ongoing apnea, anemia, and use of opioids or nondepolarizing muscle relaxants.

Results: Two hundred fifty-five of 384 patients from eight studies at four institutions fulfilled study criteria. There was significant variation in apnea rates and the location of apnea (recovery room and postrecovery room) between institutions (P < 0.001). There was considerable variation in the duration and type of monitoring, definitions of apnea, and availability of historical information. The incidence of detected apnea was greater when continuous recording devices were used compared to standard impedance pneumography with alarms or nursing observations. Despite these limitations, it was determined that: (1) apnea was strongly and inversely related to both gestational age (P = 0.0005) and postconceptual age (P < 0.0001); (2) an associated risk factor was continuing apnea at home; (3) small-for-gestational-age infants seemed to be somewhat protected from apnea compared to appropriate- and

http://gateway.ut.ovid.com/gw2/ovidweb.cgi
large-for-gestational-age infants; (4) anemia was a significant risk factor, particularly for patients > 43 weeks' postconceptual age; (5) a relationship to apnea with history of necrotizing enterocolitis, neonatal anemia, respiratory distress syndrome, bronchopulmonary dysplasia, or operative use of opioids and/or muscle relaxants could not be demonstrated.

Conclusions: The analysis suggests that, if it is assumed that the statistical models used are equally valid over the full range of ages considered and that the average rate of apnea reported across the studies analyzed is accurate and representative of actual rates in all institutions, the probability of apnea in non-anemic infants free of recovery-room apnea is not less than 5%, with 95% statistical confidence until postconceptual age was 48 weeks with gestational age 35 weeks. This risk is not less than 1%, with 95% statistical confidence, for that same subset of infants, until postconceptual age was 56 weeks with gestational age 32 weeks or postconceptual age was 54 weeks and gestational age 35 weeks. Older infants with apnea in the recovery room or anemia also should be admitted and monitored. The data do not allow prediction with confidence up to what age this precaution should continue to be taken for infants with anemia. The data were insufficient to allow recommendations regarding how long infants should be observed in recovery. There is additional uncertainty in the results due to the dramatically different rates of detected apnea in different institutions, which appear to be related to the use of different monitoring devices. Given the limitations of this combined analysis, each physician and institution must decide what is an acceptable risk for postoperative apnea.


A number of investigators have examined the problem of apnea after surgical procedures in former preterm infants. Malviya et al., [1] concluded that infants > 43 weeks postconceptual age (postconceptual age = gestational age + age after birth) have a "maximum long run risk" of less than 5% for apnea and that, after 50 weeks postconceptual age, they may be safely anesthetized as outpatients provided that they have a completely unremarkable anesthetic and recovery period (2 h). Other investigators have recommended overnight monitoring for infants < 44 weeks and up to 60 weeks postconceptual age. [2-10].

Prospective and retrospective studies of postoperative apnea have attempted to define the population at greatest risk. [1-14] Specific risk factors have been described: a young postconceptual age at the time of surgery, [1-10] history of respiratory distress syndrome and/or bronchopulmonary dysplasia, [10] anemia (hematocrit < 30%), [8] ongoing apnea at home, [10] neonatal anemia, [2] and necrotizing enterocolitis. [4] Possible therapies to reduce the risk of postoperative apnea have been proposed, including intravenous caffeine, theophylline, or doxapram [5,6,15-17]; withholding opioids and muscle relaxants [14]; and spinal or caudal epidural anesthesia without supplemental general anesthesia. [18-20] Postoperative apnea, however, can occur even with regional anesthesia. [21].

The decision to care for former preterm infants on an outpatient basis may be motivated by the desire to contain cost and to keep infants with their parents rather than in the hospital. [1,12,13] Is there a danger that undetected apnea, inadequately treated apnea, or even death may result from this decision? To address this clinical problem, we undertook the unique step of obtaining the original data from
authors of the published prospective studies for which such data were available. These data were used for a combined analysis so that a more meaningful interpretation of the accessible data for this relatively rare event may be made.

**Methods**

Because the issue of most concern to the practitioner is to know when it is safe to anesthetize former preterm infants on an outpatient basis, we limited our data analysis to a single procedure that is commonly performed and appropriate for outpatient surgery, i.e., inguinal herniorrhaphy. For this reason, the number of patients from any one study may differ from the published number.

Review of the literature found 14 papers, [1-14] 10 of which were prospective in nature, [1-10] that studied postoperative apnea in former preterm infants. We limited our analysis to prospective studies because we believed that prospective studies would likely provide the most useful information. Even in the published prospective papers, there was insufficient information, particularly with regard to specific risk factors and historical and demographic information, to permit a standard metaanalysis. For this reason, we took the unusual step of asking the authors of all published prospective studies to participate in this analysis. Data from eight of ten published prospective studies are therefore the subject of this combined analysis, [1,4-10] We were unable to obtain the original data from two prospective studies, because the authors no longer had it available; these were excluded. [2,3] We obtained missing information from those authors able to provide it. We excluded patients who received special treatments, such as caffeine or spinal anesthesia, or patients who underwent surgical procedures other than herniorrhaphy. [5-7] Patient data from 255 of 384 patients collected over 6 yr in eight studies at four institutions fulfilled inclusion criteria and were combined into a single database, [1,4-10] For purposes of comparison, we pooled data across studies collected at any one institution, e.g., two studies by Kurth et al. [4,9] and four studies by Welborn et al. [5-8] Eleven risk variables of interest were examined: postconceptual age, gestational age, anemia (hematocrit < 30% for all studies), use of muscle relaxants, use of opioids, birth weight, home apnea monitor, history of necrotizing enterocolitis, neonatal apnea, and respiratory distress syndrome or bronchopulmonary dysplasia. In our analysis, we used a uniform definition of apnea for all patients, i.e., cessation of breathing or detection of air flow for greater or equal to 15 s or < 15 s with bradycardia (heart rate < 80 beats/min). Despite multiple definitions of apnea reported in the published papers, only patients with apnea events fulfilling this definition were included in this analysis.

In our analysis, we combined information from two locations (recovery room and postrecovery room), defining the outcome of interest as occurrence of apnea in either location. We postulated that the effect of each risk factor (increasing or decreasing the probability of apnea) would be similar between institutions despite the differences in the overall incidence of apnea between institutions. Because criteria for intervention to terminate apparent apneic events most likely varied across institutions, we could not determine which of these apnea episodes would have resolved spontaneously. Therefore, all apnea spells (defined above) were regarded as clinically important.

**Data Analysis**

Relationships between apnea and various individual risk factors or combinations of risk factors were
modeled by logistic regression (SAS PROC CATMOD, SAS Institute, Cary, NC), and the importance of each variable for prediction was assessed by the Wald and likelihood ratio tests. We used logistic regression because it allows one to specify and test multivariate models for prediction of outcomes (in this case, apnea). In particular, it allows testing the effect of one variable (e.g., the effect of gestational age) after controlling for other variables (e.g., institution, postconceptual age). Logistic regression models the logit of the probability $P$ of an event, $\log \left[ \frac{P}{1 - p} \right]$, as a linear function of predictors. In each model of combined risk factors, we represented the differing overall incidences of apnea by institution by including a separate intercept term for each institution and a single coefficient for each risk factor across institutions. The significance of the bivariate relationships between apnea and the individual dichotomous risk factors controlling for institution was confirmed using an exact test (StatXact, Cytel) for a common odds ratio in several two-by-two tables. Aggregated risks were analyzed by calculation of an exact binomial upper confidence bound. For each analysis, cases with missing data for a variable required in that analysis were omitted. Therefore, all 255 cases were included for any analysis with the variables of institution, postconceptual age, gestational age, and anemia. Analyses involving birth weight or respiratory distress syndrome, for example, excluded the 67 patients from Welborn's studies.

Results

Monitors used for data acquisition and definitions of apnea were not uniform by study or by institution (Table 1). Some risk variables of interest (postconceptual age, gestational age, anemia) were collected in all eight studies, but the remaining variables (birth weight, home apnea monitor, and history of necrotizing enterocolitis, neonatal apnea, respiratory distress syndrome, bronchopulmonary dysplasia, use of nondepolarizing muscle relaxants, or use of opioids during surgery), despite efforts to fill in the missing information, were each missing from at least one study's data (Table 2 and Table 3). We were unable to determine the time of the first or last apneic event after the anesthetic/surgical procedure because these data were not available for most studies.

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Year</th>
<th>n</th>
<th>Nasal Thermistry</th>
<th>Pulse Oximetry</th>
<th>Continuous Recording</th>
<th>Electrocardiogram</th>
<th>Impedance Pneumography</th>
</tr>
</thead>
<tbody>
<tr>
<td>Welborn</td>
<td>1988</td>
<td>11</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Welborn</td>
<td>1989</td>
<td>16</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Welborn</td>
<td>1990</td>
<td>16</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Welborn</td>
<td>1991</td>
<td>24</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Kurth</td>
<td>1987</td>
<td>26</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Kurth</td>
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<td>45</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Warner</td>
<td>1992</td>
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<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Malviya</td>
<td>1993</td>
<td>57</td>
<td>No</td>
<td>No</td>
<td>No</td>
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<td>Yes</td>
</tr>
</tbody>
</table>

Table 1. Monitors Used for Each Study
Table 2. Historical Data Available for Most Patients in Each Study

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Year</th>
<th>n</th>
<th>RDS</th>
<th>BPD</th>
<th>Neonatal Apnea</th>
<th>Home Apnea</th>
<th>Birth Weight</th>
<th>Relaxant (Nondepolarizing)</th>
<th>Opioid</th>
<th>NEC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Welborn</td>
<td>1988</td>
<td>11</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Welborn</td>
<td>1989</td>
<td>16</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
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<td>No</td>
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<td>Welborn</td>
<td>1990</td>
<td>16</td>
<td>No</td>
<td>No</td>
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<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
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<tr>
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<td>1991</td>
<td>24</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>Kurth</td>
<td>1987</td>
<td>26</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Kurth</td>
<td>1991</td>
<td>45</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Warner</td>
<td>1992</td>
<td>60</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Malviya</td>
<td>1993</td>
<td>57</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

RDS = respiratory distress syndrome; BPD = bronchopulmonary dysplasia; NEC = necrotizing enterocolitis.

Table 3. Risk Factors Examined, Number of Patients with Risk Factor, and Total Population Base with Data Available

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Number with Risk Factor</th>
<th>Population with Data Available</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEC</td>
<td>6</td>
<td>143</td>
</tr>
<tr>
<td>RDS</td>
<td>84</td>
<td>188</td>
</tr>
<tr>
<td>BPD</td>
<td>20</td>
<td>131</td>
</tr>
<tr>
<td>Opioids</td>
<td>4</td>
<td>188</td>
</tr>
<tr>
<td>Relaxant (nondepolarizing)</td>
<td>121</td>
<td>188</td>
</tr>
<tr>
<td>Birth weight</td>
<td>63</td>
<td>198</td>
</tr>
<tr>
<td>Home apnea</td>
<td>86</td>
<td>215</td>
</tr>
<tr>
<td>Neonatal apnea</td>
<td>35</td>
<td>255</td>
</tr>
<tr>
<td>Anemia</td>
<td></td>
<td>255</td>
</tr>
<tr>
<td>GA</td>
<td></td>
<td>255</td>
</tr>
<tr>
<td>PCA</td>
<td></td>
<td>255</td>
</tr>
</tbody>
</table>

NEC = necrotizing enterocolitis; RDS = respiratory distress syndrome; BPD = bronchopulmonary dysplasia; GA = gestational age; PCA = postconceptual age.

There were dramatic differences between institutions in the frequencies of events overall and in how the events were distributed between recovery and postrecovery. This is true when the institutions were compared ignoring other variables (Table 4; P < 0.001 for each variable, i.e., apnea in recovery or postrecovery) and remained true in logistic regression models controlling for gestational age and postconceptual age (Figure 1; P < 0.001). In some studies no apneic episodes were recorded in the recovery room. In others, none were recorded after discharge from the recovery room either because apnea did not occur, because the monitor failed to detect, alarm, and record the apneic event, or simply because it was not collected.
Table 4. Percentage of Patients with Detected Apneic Episodes in Recovery Room, Postrecovery Room, or Either Location by Investigator

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Patients (n)</th>
<th>Apnea Rate in Recovery Room</th>
<th>Apnea Rate Postrecovery Room</th>
<th>Overall Apnea Rate for All Patients</th>
<th>Apnea Rate for All Nonanemic Patients†</th>
<th>Apnea Rate for All Patients without Anemia or Recovery Room Apnea‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kurth⁴⁻⁵</td>
<td>71</td>
<td>31.0</td>
<td>7.7§</td>
<td>31.0</td>
<td>31.1</td>
<td>0.0</td>
</tr>
<tr>
<td>Malviya¹</td>
<td>57</td>
<td>5.3</td>
<td>0.0</td>
<td>0.0</td>
<td>4.3</td>
<td>0.0</td>
</tr>
<tr>
<td>Warner⁶⁻⁷</td>
<td>60</td>
<td>5.0</td>
<td>6.7</td>
<td>10.0</td>
<td>7.6</td>
<td>3.9</td>
</tr>
<tr>
<td>Welborn⁸⁻⁹</td>
<td>67</td>
<td>0.0</td>
<td>49.3</td>
<td>49.3</td>
<td>45.0</td>
<td>45.0</td>
</tr>
<tr>
<td>Combined</td>
<td>255</td>
<td>21.0</td>
<td>18.6</td>
<td>25.1</td>
<td>20.4</td>
<td>16.8</td>
</tr>
</tbody>
</table>

* Number of patients for some columns is less than the total because of selection criteria and missing data (see methods section).
† Apnea in either location (recovery room or postrecovery room) limited to patients without anemia.
‡ Apnea on floor limited to patients without anemia and without apnea in recovery room.
§ Based on 26 patients with available data.

Figure 1. Predicted probability of apnea in recovery room and postrecovery room by weeks postconceptual age for all patients for each investigator. Bottom marks indicate the number of data points versus postconceptual age. The curves for the Kurth et al. and Welborn et al. studies are nearly identical in the upper range, and for the Malviya et al. and Warner et al. studies, in the lower range. There was significant institution-to-institution variability. The reasons for this are unclear but may represent differences in monitoring technology as well as patient populations, because the studies with the highest rate of apnea were also those that used continuous recording devices. See text for further discussion.

In bivariate analyses of the entire population, controlling for institution effects, the following variables were found to be related independently to the probability of apnea: postconceptual age (P < 0.0001), gestational age (P = 0.0005), and continued use of a home apnea monitor (P = 0.002). There was a weak relationship with the presence of anemia (P = 0.103; Figure 2); the clinical importance of this observation warranted more detailed analysis (see below). No significant relationship was found with a
history of neonatal apnea, necrotizing enterocolitis, respiratory distress syndrome, bronchopulmonary dysplasia, or use of opioids or nondepolarizing muscle relaxants. Because the use of pancuronium and d-tubocurare has been cited as a possible risk factor, [14] we compared the 40 patients who received these agents to the 81 patients who received vecuronium or atracurium, and we compared these patients against those who had not received relaxants. No specific risk was found to be associated with long-acting relaxants by themselves (P = 0.58) or compared to the intermediate acting relaxants (P = 0.58, exact test). There was no relationship with the use of any nondepolarizing muscle relaxant (P = 0.50). There was very little within-institution variability in the use of relaxants; all but three infants who received relaxants were in the Kurth et al. studies, and in those studies, all patients received relaxants. Only four children received opioids, and only six had a history of necrotizing enterocolitis. Because of the small amount of within-institution variability in these risk factors, these negative findings do not demonstrate that these factors have no effect on apnea risk.

Figure 2. Predicted probability of apnea for all patients, by gestational age and weeks postconceptual age. Patients with anemia are shown as the horizontal hatched line. Bottom marks indicate the number of data points by postconceptual age. The risk for apnea diminishes for infants born at a later gestational age. The shaded boxes represent the overall rates of apnea for infants within that gestational age range. The probability of apnea was the same regardless of postconceptual age or gestational age for infants with anemia (horizontal hatched line). See text for details.

Because postconceptual age was the most important variable predicting the probability of apnea, postconceptual age was included in all models examining the importance of other covariates. Gestational age is the next most important variable (P = 0.04). Home apnea monitoring was not significant after controlling for postconceptual age (P = 0.10). Therefore, all further models included postconceptual age, gestational age, and institution as covariates.

Using logistic regression analysis, both postconceptual age and gestational age bear an inverse
relationship to risk of apnea. As postconceptual age increases, probability of apnea decreases, holding gestational age constant. Likewise, as gestational age increases, probability of apnea decreases, holding postconceptual age constant, but the effect of each additional week of gestational age is slightly more than half that of each additional week of postconceptual age. The prediction equation for probability of apnea in the whole population (N = 255) is Model 1: logit P (apnea) = a - 0.176 (weeks postconceptual age) - 0.104 (weeks gestational age), where a is an intercept that differs by institution. This intercept ranged from a high of 10.77 (Welborn et al.) to a low of 8.34 (Malviya et al.). The incidence of detected apnea in this population was highest in the institutions that used continuous recording devices compared to those that used impedance pneumography with alarms but without recorders (Figure 1). Because there was considerable variation between institutions, we chose to calculate predictions using the intercept that predicts the average across studies (a = 9.96; see Appendix) to calculate predicted probabilities of apnea (Table 5, column 1A). We are 95% confident that the predictions are no greater than the values in Table 5, column 1B (see Appendix), subject to caveats in the discussion of Model 2 (see below).

Table 5. Probability of Apnea Using Three Models: All Patients, All Nonanemic Patients, All Nonanemic Patients and Those without Recovery Room Apnea

<table>
<thead>
<tr>
<th>Model 1: All Patients</th>
<th>Model 2: All Nonanemic Patients</th>
<th>Model 3: Nonanemic No Recovery Room Apnea</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 255)*</td>
<td>(n = 220)*</td>
<td>(n = 172)*</td>
</tr>
<tr>
<td>PCA (weeks)</td>
<td>GA (weeks)</td>
<td>Point Estimate</td>
</tr>
<tr>
<td>40</td>
<td>28</td>
<td>51</td>
</tr>
<tr>
<td>40</td>
<td>32</td>
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<td>40</td>
<td>36</td>
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<td>60</td>
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</table>

PCA = postconceptual age; GA = gestational age; UCB = 95% upper statistical confidence bound.
* All hemorhapy patients; calculated using parameter estimates presented in test.
† Excludes patients with missing data; calculated using parameter estimates presented in text.
‡ Duration of stay in the recovery room was variable and usually < 2 h.

After controlling for postconceptual age and gestational age, birth weight was related to the probability of apnea, although we had birth weights for only 175 infants. We divided patients into small-for-gestational-age (less than 10th percentile, N = 18), appropriate-for-gestational-age (N = 139), and large-for-gestational-age (greater than 90th percentile, N = 18) using a standard premature infant growth chart. [22] We found the expected distribution of birth weights, i.e., 10% of the infants fell into each of the extreme categories. After controlling for institution, postconceptual age, and gestational age, the small-for-gestational-age infants had a significantly lower rate of apnea than the appropriate- and
large-for-gestational-age infants (P = 0.001, likelihood ratio test). None of the 18 small-for-gestational-age infants experienced apnea. The large-for-gestational-age infants did not have a significantly different rate of apnea than did the appropriate-for-gestational-age infants. It would appear that small-for-gestational-age infants were somewhat protected from postoperative apnea.

Anemia (hematocrit < 30%) was the only variable that had a significant effect above and beyond the relationship to gestational age and postconceptual age (Figure 2). Analysis of this risk factor was somewhat confounded by the small number of infants who were anemic (35/255) and by the age distribution. The probability of anemia decreased with increasing postnatal age (P = 0.0001). When looking at infants with and without anemia, our model suggests that the probability of apnea does not decrease with gestational age and postconceptual age for infants who are anemic at the time of surgery, as it does for the nonanemic infants. The coefficients for postconceptual age and gestational age were near zero for anemic infants alone. A model in which anemic infants had a distinct intercept (but no postconceptual age or gestational age effects), fit the data better than a model with common coefficients regardless of anemia as a risk factor (P = 0.065). Twelve of 35 anemic infants experienced apnea, including 5 of 19 anemic infants who were > 43 weeks postconceptual age. This effect of anemia is consistent with the nonsignificant effect of anemia alone (P = 0.103), because in the univariate model, young infants whose probability of apnea is high regardless of anemia were mixed with older infants whose probability of apnea would be low were they not anemic. Anemia appears to be a prominent risk factor for the older infants (> 43 weeks postconceptual age).

Therefore, because of these differences between anemic and nonanemic infants, a second model was fitted to the 220 patients (255-35) without anemia: Model 2: logit P (apnea) = a - 0.214 (weeks postconceptual age) - 0.118 (weeks gestational age), where a = 12.88 for Kurth et al., 10.33 = Warner et al., 10.29 = Malviya et al., and 12.64 = Welborn et al. The average intercept across studies was a = 11.97, and this intercept was used in calculating predicted probabilities (Table 5, column 2A, and Figure 3), but this prediction depends on extrapolation of the regression relationships at the extreme range of the data. The predicted probabilities of apnea in Table 5, column 2A, are based on point estimates of the parameters, which are subject to sampling variability. To be confident that the probability of apnea under a given condition is less than some desired level, we require a criterion of confidence that is stronger than simply obtaining a point estimate. We are 95% statistically confident that the predictions are no greater than the values in Table 5, column 2B (see Appendix). We found that, even after eliminating infants with anemia, we would not have 95% confidence that the probability of apnea is less than 1% anywhere within the range of the data (up to postconceptual age 60 weeks). We are confident that the probability of apnea is less than 5% at postconceptual age 56 weeks with gestational age 36 weeks or at postconceptual age 58 weeks with gestational age 33 weeks. It must be emphasized that the confidence bounds in Table 5 allow only for pure statistical uncertainties, assuming that the statistical models we used are equally valid over the full range of ages we considered, so that relationships based on infants throughout the entire age distribution of our data may be extrapolated to the upper end of the age range. Furthermore, they assume that the average rate of apnea reported across the studies we analyzed is accurate and representative of rates in all institutions. Uncertainty about these assumptions would lead to extension of these limits, as described in the Discussion.
Figure 3. Predicted probability of apnea by weeks postconceptual age for all three models: model 1 (solid line) all infants; model 2 (irregular line) all nonanemic infants; and model 3 (broken line) patients who were not anemic and did not experience apnea in recovery room. The risk for apnea decreases markedly when patients with anemia (model 2) are eliminated, and the risk diminishes further if patients with apnea in recovery room (model 3) also are eliminated. See text for discussion.

With the above considerations in mind, we fitted a third model that examined the probability of apnea in patients who were not anemic and who did not have any apnea in the recovery room (N = 172; Figure 3 and Figure 4): Model 3: logit P (apnea) = a - 0.495 (weeks postconceptual age) - 0.151 (weeks gestational age), where a = 24.14 average across studies: a = 25.36 for the Welborn et al. studies; a = 21.77 for the Warner et al. study; and a was inestimable (negative infinity) for one of Kurth et al.'s studies (no data available in one of two studies) and Malviya et al, (negative infinity, no cases reported in this group). By eliminating anemic patients and those with demonstrable apnea in the recovery room, we have 95% confidence that probability of apnea is less than 5% at postconceptual age 48 weeks with gestational age 35 weeks or at postconceptual age 50 weeks with gestational age 31 weeks (Table 5, column 3A), but we would not have 95% confidence that the probability of apnea is less than 1% until postconceptual age was 54 weeks with gestational age 35 weeks or postconceptual age was 56 weeks with gestational age 32 weeks (Table 5, column 3B), again extrapolating the model to the extreme range of the data and assuming the validity of the model and the average rates from these studies.
Figure 4. Predicted probability of apnea after leaving recovery room by weeks postconceptual age (weeks) for infants who did not have apnea in recovery room or anemia (model 3). Bottom marks indicate the number of data points by postconceptual age. The risk does not fall below 1% with 95% statistical confidence until 56 weeks postconceptual age.

(Figure 5) presents the number of patients included in each model by postconceptual age.

Figure 5. Distribution of patients by postconceptual age (weeks) and by logistic regression model. Model 1 was based on the entire patient population, model 2 excluded all anemic patients, and model 3 excluded all anemic patients and those who had an episode of apnea in recovery room. The number of patients at each of the extremes of age is small explaining in part the necessity to extrapolate based on our assumptions. This also shows why conclusions reached at one institution or by a single study would be more subject to error given the small number of patients collected over so many years from four institutions.
There were 136 infants > 43 weeks postconceptual age who did not have the risk factors of anemia or apnea in recovery room, and only 113 of these were monitored after recovery room discharge. Of these, 21 experienced apnea in or after discharge from the recovery room; five of these were also anemic. None required bag-and-mask ventilation, but three required stimulation. Four infants did not have apnea in the recovery room but experienced apnea after discharge from the recovery room; two were also anemic. Two older infants who were not anemic developed apnea requiring stimulation after discharge from the recovery room (postconceptual age 45 and 47 weeks with gestational age 33 and 31 weeks, respectively). Table 6 presents historical data and outcomes of all infants > 43 weeks postconceptual age who experienced apnea. Table 7 presents the distribution of cases with and without apnea by institution and postconceptual age for the populations considered in each of the three models.

Table 6. Inguinal Herniorrhaphy Patients > 43 Weeks Postconceptual Age with Any Apnea (n = 21)

Table 7. Distribution of Cases with and without Apnea by Institution and Postconceptual Age for the Populations Considered in Each of the Three Models.
An alternative analysis examined average risk for apnea for all nonanemic patients without recovery room apnea who were > 43 weeks postconceptual age. Two of 102 such patients (2%) experienced postrecovery room apnea. The 95% upper confidence bound for the average rate of postrecovery apnea is 6% [23] for a hypothetical population of infants with an age distribution similar to that of the infants included in this analysis. This method of analysis is less dependent on a statistical model than the regression analysis given above but does not provide a risk prediction for an individual patient. In particular, it does not consider the apparent higher risk for apnea in patients at the lower end of the age range (postconceptual age close to 44 weeks) compared to those at the higher end of the age range (postconceptual age close to 60 weeks), because all cases are aggregated without regard to individual characteristics. This type of analysis may be useful for predicting average risk for this population of patients but not for individual patient risk.

Discussion

The anesthesia literature reveals that the number of former preterm infants from one institution, in any one study, and for any age range is small. Each study employed a slightly different protocol, including six separate definitions for apnea and three for bradycardia. [1-14] Diagnostic methods ranged from retrospective review of recovery room records analyzing nurses' visual observations of apnea in infants with routine electrocardiogram and impedance apnea monitors, [11-13] a method shown not to be particularly sensitive, [24,25] to prospective continuous recordings using nasal flow thermistors, impedance pneumography, and pulse oximetry. The time of initial apnea and duration of observation (recovery and postrecovery) varied between institutions and from study to study within institutions. The study of relatively rare events requires a large patient population, which is impossible to acquire at any one institution. Malviya et al. correctly point out that most incidents of clinically relevant postanesthetic apnea occur in infants < 44 weeks postconceptual age. However, observing no apnea in a study of moderate size of infants > 43 weeks postconceptual age [1] does not prove that the long-range probability of apnea is zero, [26] especially not for patients at the younger, more vulnerable end of the study group's age range (44-50 weeks postconceptual age) and for those with anemia. We sought to better define some risk factors with greater certainty by pooling data. For these reasons, we used only original data from prospective studies. Despite this, we were unable to eliminate all problems with the data analysis, and the small number of patients at the extremes of the age range necessitated
extrapolation of the fitted models.

Our analysis leads to several conclusions. First, there was considerable institution-to-institution variability in the incidence of apnea. The best explanation for this variability may be the sophistication of the apnea detection devices employed. The studies conducted by Malviya et al. [1] and Warner et al. [10] had the lowest incidence of events but also used the least sophisticated technology, i.e., impedance pneumography with alarm limits and nursing observation. The Welborn et al. studies [5-8] reported a similar overall incidence to the Kurth et al. studies, [4,9] and both investigators employed continuous recording devices with computer-assisted technology. Inexplicably, there was considerable variation between studies within one institution, and those studies reported no apnea events in the recovery room. [5-8] All other prospective studies reported recovery room apnea events. [1,2,4,9,10] Perhaps this difference in recovery room apnea may reflect a difference in threshold for intervention or a difference in population. The Kurth et al. studies employed the most sophisticated technology, and one of these is the only study to explore the value of pulse oximetry. [9] This institution-to-institution variability explains in part the wide disparity in the conclusions and recommendations made by each. For example, the incidence of postanesthesia apnea varied between institutions to such a degree that the curves in Figure 2 could be shifted forward or backward over a 12-week range. The predicted rates of apnea for older infants in the institution with the highest detected rates were 11 times those with the lowest rates. Even more striking is the fact that the two institutions that used continuous recording devices had apnea rates nearly identical to the two institutions that relied primarily on impedance pneumography with alarms (Figure 1). The continuous recording devices found more apnea; this is similar to the observations of several other investigators examining apnea events in the neonatal intensive care unit. [24,25] The confidence intervals reported in the results do not take into account the uncertainty due to differences between institutions. If continuous recording devices had been used by all institutions, the age limits in Table 5 might be shifted upward by as much as 6 weeks. Therefore, if one chooses impedance pneumography and nursing observation as a measure of clinically important apnea, our results may overestimate risk. However, if one chooses continuous recording devices as a measure of clinically important apnea, then our results may underestimate the risk.

Second, the incidence of apnea is strongly related to postconceptual age and gestational age. A history of continued use of a home apnea monitor appeared to be a contributory risk factor, but when combined with the more important risk factors of postconceptual age and gestational age, one cannot distinguish the individual contribution it makes.

Third, when we divided patients, using standard growth charts, into infants who were small-, appropriate-, or large-for-gestational-age, there were no small-for-gestational-age infants who suffered apnea. The fraction of patients who were small-, appropriate-, or large-for-gestational-age appears to match that of the general population of premature infants, suggesting that we have a relatively balanced population. Small-for-gestational-age may be protective because the potential to develop apnea could be attributed, in part, to the accelerated maturation of infants who experience significant intrauterine stress. [27].

Fourth, after controlling for gestational age and postconceptual age, anemia was the only independent risk factor. Because 12 of 35 anemic infants suffered apnea spells, and 5 of these were
older than 44 weeks postconceptual age, this strongly supports the observation of Welborn et al. [8] At the younger end of the age spectrum, other factors override any additional influence that anemia may have, but it appears that, as the infant matures and the marked effects of young gestational age and postconceptual age diminish, the importance of anemia increases. For this reason, one should consider admitting and monitoring even the older infants (> 60 weeks postconceptual age) who are anemic. Because the probability of anemia decreases with increasing postconceptual age, anemia in an older infant may be a marker for a "sicker" infant who has had a more complex neonatal course. However, we would not want this observation to be over-interpreted to suggest transfusion before surgery. [28,29].

Fifth, analysis of the combined data base revealed that most apnea spells were pneumogram-diagnosed events that occurred in infants < 44 weeks postconceptual age; the majority resolved without intervention. This is consistent with the conclusions of most of the published studies. However, a small number of infants required more active intervention in the form of bag-and-mask ventilation in the recovery room. Two of 15 of the older infants without anemia or recovery room apnea experienced apnea and received stimulation after discharge from the recovery room. We do not know whether these infants would have suffered a fatal apnea spell had they not been stimulated, i.e., if they were in an unmonitored environment such as at home or in a car seat on the way home.

Despite the limitations, our analysis has defined what we know about the occurrence of apnea after general anesthesia file a single outpatient surgical procedure. To define risk factors, a standardized database with precise historical data collection is needed. In addition, standardized monitoring (nasal thermistry or capnogram, combined with electrocardiogram, impedance pneumography, and pulse oximetry), explicit criteria for intervention, and accurate record-keeping are essential to define the population at risk and the clinical effects of such apnea spells.

Neonatal apnea (apnea of prematurity) and apnea after general anesthesia seem to have a similar distribution of central (approximately 70%), obstructive (approximately 10%), and mixed (approximately 20%) origins. [9,30-32] Central apnea is often accompanied by upper airway obstruction. Upper airway obstruction, likely in the nasopharynx and/or aryepiglottic folds, often precedes obstructive apnea episodes and occurs during the central component of mixed apnea spells. [33-40] The propensity to respond to airway obstruction with apnea is common in infants with periodic breathing and decreases with increasing postnatal age. [33,39] Because upper airway obstruction appears to be important in the pathophysiology of apnea, it is reasonable to conclude that general anesthesia, which can decrease upper airway muscle tone, may contribute to the development of apnea after anesthesia, even in infants without a history of apnea. [33-48] This also explains in part the observed decrease in apnea in preterm infants with the application of nasal constant positive airway pressure [41-43] and the suggestion that the incidence of apnea may be less in patients receiving regional anesthesia. [18-21] The ability to switch from oral to nasal breathing is also age-dependent; some neonates are capable of oral breathing, but this ability may be impaired after general anesthesia. [44,45] We were unable to demonstrate any independent effects of nondepolarizing muscle relaxants or opioids, but all patients received general anesthesia.

We know little about the clinical importance of apnea, which lasts less than 15 s and is accompanied by bradycardia but which resolves spontaneously ("self resuscitation"). The most germane issue is, what
are the physiologic consequences of apnea and bradycardia even when the apnea is of brief duration? The incidence of bradycardia increases with duration of apnea and is directly correlated to decreases in hemoglobin oxygen saturation, [30,46] but desaturation does not usually precede apnea. [46-48] The baseline hemoglobin oxygen saturation tends to be less in patients who experience bradycardia, and the decrease in hemoglobin oxygen saturation tends to be greater in patients who also have bradycardia. [46,48] However, other studies suggest that the bradycardia may be reflexive in origin (the heart rate frequently slows precipitously before the onset of desaturation) [49]; the onset of bradycardia often coincides temporally with attempts at respiration against an obstructed airway. [48,50] Such a peripheral reflex (possibly vagal in origin) would explain the often observed precipitous decrease in heart rate that occurs even during brief apnea spells (< 15 s). Hypoxemia seems to reinforce laryngeal reflex bradycardia. [51].

Is brief apnea harmful if accompanied by bradycardia? Cerebral blood flow during periods of apnea is directly related to heart rate (r = 0.86); a marked reduction in cerebral blood flow (20-70%) has been demonstrated in preterm infants when the heart rate slows below 80 beats/min. [52] We do not have cerebral blood flow information on the older population returning for inguinal hernia repair. Kurth and LeBard, observing postanesthesia apneic episodes longer than 6 s in former preterm infants, found hemoglobin oxygen saturation less than 80% in 67 of 556 spells (12%). [9] The same group, using near-infrared spectroscopy, found cerebral and peripheral desaturation to begin within 5 s of discontinuation of ventilation of premature infants. Cerebral resaturation lagged 15 s behind resaturation in peripheral arteries. [53] Because the rapidity of cerebral desaturation depends on oxygen-carrying capacity (hemoglobin value), cerebral blood flow (related to cardiac output and heart rate at this age), and cerebral oxygen consumption, one must assume that the anemic, borderline oxygenated infant who also experiences bradycardia would be at greatest risk for rapid cerebral desaturation. Consequently, we must assume these to be adverse events, despite our lack of neurodevelopmental studies in this particular cohort of infants. [16,46,52-55].

Apnea of prematurity and postanesthetic apnea appear to bear no relationship to sudden infant death syndrome. General anesthesia, however, can induce or unmask abnormalities of ventilatory control not previously noted in a former preterm or even a term infant. [11,56] Such abnormalities can be fatal; two of the authors have observed a death or near death in former preterm infants who were not admitted and monitored for apnea. These anecdotal cases illustrate that death can occur if this special population is not appropriately cared for postanesthesia.

Our analysis of the data across four institutions reveals that the incidence of apnea even in the older population of former preterm infants is low, but it is not zero. The majority of patients were observed for at least 2 h, and most who experienced apnea spells after discharge from the recovery room also had apnea in the recovery room. However, one older patient required stimulation after discharge from the recovery, and this infant did not have obvious risk factors such as clinically apparent apnea in recovery, anemia, or continuing apnea at home. We do not know whether the apnea event would have resolved spontaneously. A recommendation for 2 h of observation in recovery is somewhat arbitrary, because we only know that most of the infants in this analysis were observed for this amount of time; we also know that the first apnea event may not manifest for at least 12 h.
The incidence of apnea varied widely between institutions, which may reflect in part the technology used to detect apnea. At all institutions, the incidence of apnea was inversely related to gestational age and postconceptual age and markedly diminished after 43 weeks postconceptual age. Extrapolation of models based on our data suggests that it would be prudent to admit and monitor all preterm infants who manifest apnea in the recovery room or who are anemic (hematocrit < 30%). Our data further suggest that, even under strong assumptions about the generalizability of the available data, we can only conclude that the risk for preterm infants without anemia or recovery room apnea decreases to less than 5% (95% confidence) at postconceptual age 48 weeks with gestational age 35 weeks or at postconceptual age 50 weeks with gestational age 32 weeks, but we would not have confidence that the probability of apnea decreases to less than 1% (95% confidence) until postconceptual age was 54 weeks with gestational age 35 weeks or postconceptual age was 56 weeks with gestational age 32 weeks. Each practitioner and each institution must weigh the risks and benefits of admission and monitoring as well as what is an acceptable risk on a case-by-case basis.

Future Studies

Future definitions of clinically important apnea should include criteria for $Sp_O_2$ and heart rate, which are more important than simply a pause in respiration that often resolves spontaneously. Because of the importance of oxygen delivery to the brain, future studies must analyze the incidence and severity of concomitant desaturation ($Sp_O_2 < 85\%$) and bradycardia (< 80 beats/min). There is also a need for standardized data collection of historical risk factors. Because it is clear that patients < 44 weeks postconceptual age are at greatest risk for experiencing apnea, future studies should be directed at patients above this age.

The efficacy of prophylaxis with intravenous caffeine and its age-related kinetics need to be studied: a single dose of caffeine, because of age differences in drug kinetics, may not provide sufficient protection. [57,58] The advantages and practicality of spinal anesthesia compared with general anesthesia remain to be established in prospective, controlled studies with large numbers of infants. Even after such studies are completed, the occurrence of postanesthetic apnea in former preterm infants will likely never be eliminated. In our view, these infants will remain a special challenge to their anesthesiologist.

**Cote CC, Downes JJ: Unpublished observations. 1994.**

Appendix

Calculation of Mean Intercept. Each model was first fitted including a separate intercept for each institution. We then fixed the postconceptual age and gestational age coefficients that were obtained and calculated the new intercept "a" such that the predicted total number of apneas that would appear in all cases matched the observed number of cases with apneas. This value a is reported as the intercept that predicts the average across studies. In every model, similar results for postconceptual age and gestational age effects would have been obtained if institution effects had been ignored.

Calculation of Confidence Limits. For any selected values of postconceptual age and gestational age, the asymptotic sampling variance of the predicted logit, i.e., the linear predictor on the right side of the prediction equation, can be calculated as XVX, where X is the vector of covariates and V is the estimated
covariance matrix. For each line in Table 5, we calculated the 95% upper confidence bound of the linear predictor as point estimate + 1.645 (SE); the corresponding probabilities are reported in the 95% upper confidence bound columns.

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