Postoperative Apnea in Former Preterm Infants after Inguinal Herniorrhaphy

A Combined Analysis

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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 havinginguinal 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, age, 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 < 0.001); (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 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 apnea, 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 nonanemic 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 dif-
f erent 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. (Key
Words: Anesthesia, pediatrics; prematurity. Complications:
apnea. General anesthesia: complications. Monitoring: cap-
gnography; impedance pneumography; pulse oximetry. Statis-
tics: metaanalysis/combined analysis.)

A number of investigators have examined the problem
of postoperative apnea after surgical procedures in former
preterm infants. Malviya et al., concluded that infants > 43
weeks postconceptual age (postconceptual age = gesta-
tional 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 anes-	hesthetized as outpatients provided that they have a com-
pletely unremarkable anesthetic and recovery period
(2 h). Other investigators have recommended over-
night 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 a history of
respiratory distress syndrome and/or bronchopulmonary
dysplasia, 10 anemia (hematocrit < 30%), 9 ongoing apnea at home, 10 neonatal apnea, 2 and
necrotizing enterocolitis. 9 Possible therapies to reduce
the risk of postoperative apnea have been proposed,
including intravenous caffeine, theophylline, or
doxapram, 5,6,16,17 withholding opioids and muscle
relaxants, 1 and spinal or caudal epidural anesthesia
without supplemental general anesthesia. 10-20 Post-
operative apnea, however, can occur even with regional
anesthesia. 31

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. 1,12,15 Is there a danger that
undetected apnea, inadequately treated apnea, or
even death may result from this decision? To add-
ress 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.

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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 anal-
ysis 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 num-
ber.

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 histor-
ical and demographic information, to permit a standard
metaanalysis. For this reason, we took the unusual
step of asking the authors of four institutions published
prospective studies to participate in this analysis. Data from eight
ten published prospective studies are therefore the subject of this combined analysis. 1,10 We were unable
to obtain the original data from two prospective studies,
because the authors no longer had it available; these
were excluded. 2,5 We obtained missing information
from those authors able to provide it. We excluded
patients who received special treatments, such as caff-
eine or spinal anesthesia, or patients who underwent
surgical procedures other than herniorrhaphy. 5,7 Patient data from 255 of 384 patients collected over 6
years in eight studies at four institutions fulfilled inclu-
sion criteria and were combined into a single database.
1,10 For purposes of comparison, we pooled data
cross studies collected at any one institution, e.g., two
studies by Kurth et al., and four studies by Welborn
et al. 5-8 Eleven risk variables of interest were examined:
postconceptual age, gestational age, anemia (hemato-
crit < 30% for all studies), use of muscle relaxants,
use of opioids, birth weight, home apnea monitor, his-
tory 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 ≥ 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.

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Table 1

Investigator

Welborn et al. 5,6,17
Welborn et al. 5,6,17
Welborn et al. 5,6,17
Kurth et al. 7
Kurth et al. 7
Waner et al. 8
Malviya et al. 9

In one paper, the location of the authors' institution
was not specified. Although 12 different institutions
in either the United Kingdom or USA were included,
a single risk factor or series of risk factors was
analyzed in both. Therefore, the listing of risk factor
terms in Table 1 is not intended to indicate the
degree to which a particular risk factor was
studied across these institutions; rather, individual
institutions were reviewed.

Data analysis

Relational variables and risk factors were evaluated
by multiple logistic regression analysis. To determine if
it allowed us to predict which infants were at risk for
proven postoperative apnea, we compared our particu-
lar risk factor analysis with others (e.g., bivariate
analysis, multiple logistic regression analysis).

Logistic regression analysis was performed with
P of a = 0.05 as the significance level. All predic-
tive variables were forced into the regression
model by inclusion and evaluated for each risk factor.
Bivariate analysis was performed to determine which
variables were associated with postoperative
apnea. Only data from those risk factors that had a
significant relationship (P < 0.05) with postoperative
apnea were included in the multivariate analysis.

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POSTANESTHESIA APNEA IN FORMER PRETERM INFANTS

Table 1. Monitors Used for Each Study

<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>
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<td>24</td>
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<td>Yes</td>
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<td>No</td>
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<td>Yes</td>
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<td>1993</td>
<td>57</td>
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<td>No</td>
<td>Yes</td>
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</table>

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, \( \log [P/(1 - P)] \), 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 (tables 2 and 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.

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 (fig. 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.

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 ($P = 0.103$; fig. 2); the clinical importance of this observation warranted more detailed analysis (see below). No significant relationship was found with a history of neonatal 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, we compared the 40 patients who received these agents to the 81 patients who did not receive 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 one hospital in the study used one type of relaxant. Only one patient received relaxants, and only six had a history of necrotizing enterocolitis. Because the small amount of within-institution variability in these risk factors, these negative findings do not demonstrate that these factors have an effect on apnea risk.

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.
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>Kurth⁵⁹</td>
<td>71</td>
<td>31.0</td>
<td>7.76</td>
<td>31.0</td>
<td>31.1</td>
<td>0.0</td>
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<tr>
<td>Malviya¹</td>
<td>57</td>
<td>5.3</td>
<td>0.0</td>
<td>7.3</td>
<td>3.1</td>
<td>0.0</td>
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<td>Warner¹⁰</td>
<td>60</td>
<td>6.7</td>
<td>10.0</td>
<td>9.3</td>
<td>7.6</td>
<td>3.9</td>
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<td>Welborn⁶⁹</td>
<td>67</td>
<td>0.0</td>
<td>49.3</td>
<td>49.3</td>
<td>45.0</td>
<td>45.0</td>
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<tr>
<td>Combined</td>
<td>255</td>
<td>21.0</td>
<td>18.6</td>
<td>21.5</td>
<td>20.4</td>
<td>16.8</td>
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</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.

The prediction equation for probability of apnea in the whole population (N = 255) is Model 1: \( \text{logit} P(\text{apnea}) = a - 0.176 \) (weeks postconceptional 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 (fig. 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).

After controlling for postconceptional 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 groups. The relationship between anemia and probability of apnea is given in table 5 (columns 1C and 1D), but these associations were not significant (p = 0.10).

Fig. 1. Predicted probability of apnea in recovery room and postrecovery room by weeks postconceptional age for all patients for each investigator. Bottom marks indicate the number of data points versus postconceptional 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.

Fig. 2. Predicted probability of apnea for all patients, by gestational age and weeks postconceptional age. Patients with anemia are shown as the horizontal hatched line. Bottom marks indicate the number of data points by postconceptional 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 postconceptional age or gestational age for infants with anemia (horizontal hatched line). See text for details.
Table 5. Probability of Apnea Using Three Models: All Patients, All Nonanemic Patients, All Nonanemic Patients and Those without Recovery Room Apnea

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<th>PCA (weeks)</th>
<th>GA (weeks)</th>
<th>1A Point Estimate</th>
<th>95% UCB</th>
<th>1B Point Estimate</th>
<th>95% UCB</th>
<th>2A Point Estimate</th>
<th>95% UCB</th>
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<th>95% UCB</th>
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<tr>
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<td>4</td>
<td>0.6</td>
<td>3</td>
<td></td>
<td></td>
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</tbody>
</table>

PCA = postconceptual age; GA = gestational age; UCB = 95% upper statistical confidence bound.

* 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.

Table 5 continued...

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age (greater than 90th percentile, N = 18) using a standard premature infant growth chart. 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 (fig. 2). Analysis of this risk factor was somewhat confounded by the small number of infants who were anemic (55/255) 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...
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Fig. 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.

Apnea would be low were they not anemic. Anemia appears to be a prominent risk factor for the older infants (>45 weeks postconceptual age).

Therefore, because of the 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., 10.53 = Warmer 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 fig. 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.

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; figs. 3 and 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. study; a = 21.77 for the Warmer 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 5 presents the number of patients included in each model by postconceptual age.

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.

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% to 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. 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, to prospective continuous recordings using nasal flow thermistor, impendence 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 does not prove that the long-range probability of apnea is zero, 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...
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Table 6. Inguinal Herniorrhaphy Patients >43 Weeks Postconceptual Age with Any Apnea (n = 21)

<table>
<thead>
<tr>
<th>Age (PCA) (weeks)</th>
<th>GA (Hct &lt; 30)</th>
<th>Neonatal Apnea</th>
<th>Home Apnea</th>
</tr>
</thead>
<tbody>
<tr>
<td>44</td>
<td>28</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>44</td>
<td>31</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>44</td>
<td>32</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>44</td>
<td>34</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>44</td>
<td>35</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>44</td>
<td>36</td>
<td>Yes</td>
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<td>33</td>
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<td>Yes</td>
</tr>
<tr>
<td>46</td>
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<tr>
<td>47</td>
<td>31</td>
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<tr>
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<td>34</td>
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<td>48</td>
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<td>No</td>
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<tr>
<td>48</td>
<td>36</td>
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<tr>
<td>49</td>
<td>33</td>
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<tr>
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<tr>
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<td>Yes</td>
<td>?</td>
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<tr>
<td>52</td>
<td>32</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>52</td>
<td>32</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>54</td>
<td>32</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

PCA = postconceptual age; GA = gestational age; Hct = hematocrit; ? = unknown.

The number of patients in one institution was too small to employ the method of separations. 

The 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. and Warner et al. 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 reported a similar overall incidence to the Kurfth et al. studies, 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. All other prospective studies reported recovery room apnea events. Perhaps this difference in recovery room apnea may reflect a difference in threshold for intervention or a difference in population. The Kurfth et al. studies employed the most sophisticated technology, and one of these is the only study to explore the value of pulse oximetry. 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 (fig. 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. The confidence intervals reported in the results do not take into account the uncertainty due to differences between institutions.
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.

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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.

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. A possible explanation of this observation is that anemia can lead to disturbances in the sleep-wake cycle, and that an infant maturing in utero may require a greater amount of oxygen. This brings into question the value of evaluating the behavior of older infants who are nonanemic. Because anemia is a condition that can vary with increasing age, the anemia of an older infant may not be a true anemia, but rather a nonanemic. Thus, it is possible that these infants would not have been able to develop their normal sleep-wake cycles, and to suggest that they may have a risk factor for apnea.

Fifth, anemia continues to be a major issue that most anesthesiologists face in the management of infants with anemia. This is a particularly important problem that requires major attention. It is possible that treatment and mask ventilation of the older infant with a nonanemic apnea may not be as effective as ventilation in a mask and mask ventilation in an unmonitored environment. This is an important finding, and one that needs to be evaluated further.

Despite these findings, we know that there is an association between anemia and the incidence of apnea. To define the association, we used a standardized measurement protocol, consisting of standardized sleep and apnea monitoring, using standardized monitoring protocols, and using standardized sleep and apnea monitoring. These findings are important for intervention and for understanding the effects of support on the developing brain.

Neonatal apnea is also more generally understood. In addition to the conditions listed in table 4, approximately 30% of infants have a congenital upper airway problem or a congenital heart problem, which are likely to be present during the course of pregnancy.
postconceptual age, this strongly supports the observation of Welborn et al.9 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 for a single outpatient surgical procedure. To define risk factors, a standardized database with precise historical data collection is needed. In addition, standardized monitoring (nasal thermist 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 appear 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.33–40 This also explains in part the observed decrease in apnea in preterm infants with the application of nasal constant positive airway pressure41–43 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.13–15 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 airflow.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 in-
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 < 50%). 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 $\text{SpO}_2$ 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 ($\text{SpO}_2 < 85\%$) 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. 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.
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References


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 number 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 VX, 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.