■ CLINICAL INVESTIGATIONS

Anesthesiology
82:809–822, 1995

J. B. Lippincott Company, Philadelphia

Postoperative Apnea in Former Preterm Infants after Inguinal Herniorrhaphy

A Combined Analysis

Charles J. Coté, M.D., Alan Zaslavsky, Ph.D.,† John J. Downes, M.D.,‡ C. Dean Kurth, M.D.,§ Leila G. Welborn, M.D.,‖ Louise O. Warner, M.D.,# Shobha V. Malviya, M.D.***

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 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**

This article is accompanied by an editorial. Please see: Fisher DM: When is the ex-premature infant no longer at risk for apnea? ANESTHESIOLOGY 82:807–808, 1995.

* Vice Chairman, Director of Research, Children's Memorial Hospital; Professor of Anesthesia and Pediatrics, Northwestern University Medical School, Chicago, Illinois.

† Associate Professor of Statistics, Harvard University, Cambridge, Massachusetts.

‡ Anesthesiologist-in-Chief and Director, Department of Anesthesiology and Critical Care Medicine, The Children's Hospital of Philadelphia; Professor of Anesthesia and Pediatrics, University of Pennsylvania, Philadelphia, Pennsylvania.

§ Assistant Professor of Anesthesia, Physiology, and Pediatrics, University of Pennsylvania School of Medicine, Department of Anesthesiology and Critical Care Medicine, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania.

‖ Professor of Anesthesiology and Pediatrics, George Washington University, The Children's National Medical Center, Washington, D.C.

Clinical Assistant Professor of Anesthesiology, The Ohio State University College of Medicine, and Director of Anesthesia Research, Children's Hospital, Columbus, Ohio.

** Assistant Professor of Anesthesiology, University of Michigan, The C. S. Mott Children's Hospital, Ann Arbor, Michigan.

Received from the Department of Anesthesiology, Children's Memorial Hospital, Chicago, Illinois. Submitted for publication July 6, 1994. Accepted for publication December 19, 1994.

Address reprint requests to Dr. Coté: Department of Anesthesiology, Children's Memorial Hospital, 2300 Children's Plaza, Chicago, Illinois 60614.

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. (Key Words: Anesthesia, pediatrics: prematurity. Complications: apnea. General anesthesia: complications. Monitoring: capnography; impedance pneumography; pulse oximetry. Statistics: metaanalysis/combined analysis.)

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 apnea,[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 ≥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.

Table 1. Monitors Used for Each Study

Investigator	Year	n	Nasal Thermistry	Pulse Oximetry	Continuous Recording	Electrocardiogram	Impedance Pneumography
Welborn	1988	11	No	No	Yes	Yes	Yes
Welborn	1989	16	No	Yes	Yes	Yes	Yes
Welborn	1990	16	No	No	Yes	Yes	Yes
Welborn	1991	24	No	No	Yes	Yes	Yes
Kurth	1987	26	No	No	Yes	Yes	Yes
Kurth	1991	45	Yes	Yes	Yes	Yes	Yes
Warner	1992	60	No	No	No	Yes	Yes
Malviya	1993	57	No	No	No	Yes	Yes

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

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

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

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

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 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.

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

Risk Factor	Number with Risk Factor	Population with Data Available
NEC	6	143
RDS	84	188
BPD	20	131
Opioids	4	188
Relaxant (nondepolarizing)	121	188
Birth weight		175
Home apnea	63	198
Neonatal apnea	86	215
Anemia	35	255
GA		255
PCA		255

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

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 addi-

Table 4. Percentage of Patients with Detected Apneic Episodes in Recovery Room, Postrecovery Room, or Either Location by Investigator

Investigator	Patients (n)*	Apnea Rate in Recovery Room	Apnea Rate Postrecovery Room	Overall Apnea Rate for All Patients	Apnea Rate for All Nonanemic Patients†	Apnea Rate for All Patients without Anemia or Recovery Room Apnea‡
Kurth[4,9]	71	31.0	7.7§	31.0	31.1	0.0
Malviya[1]	57	5.3	0.0	5.3	4.3	0.0
Warner[10]	60	5.0	6.7	10.0	7.6	3.9
Welborn[5–8]	67	0.0	49.3	49.3	45.0	45.0
Combined	255	21.0	18.6	25.1	20.4	16.8

* 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.

tional 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 (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 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-

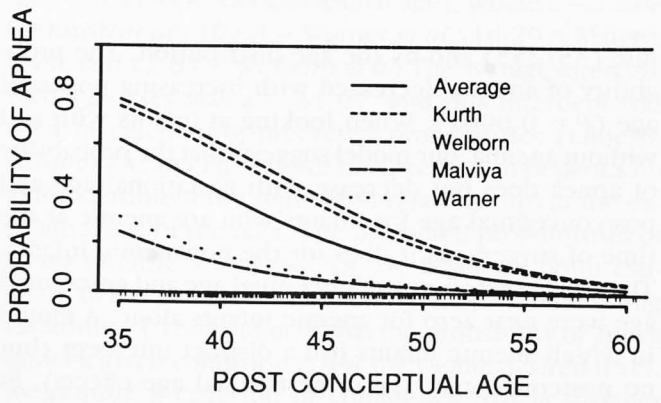

Fig. 1. Predicted probability of apnea in recovery room and postrecovery room by weeks postconceptual age for all patients for each investigator. Bottom marks indicate the number of data points *versus* postconceptual age. The curves for the Kurth *et al.* and Welborn *et al.* studies are nearly identical 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.

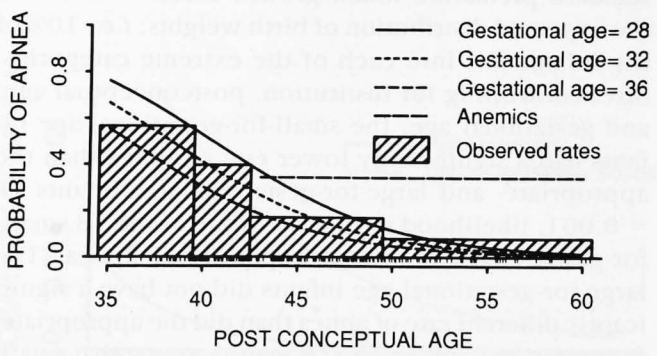

Fig. 2. Predicted probability of apnea for all patients, by gestational age and weeks postconceptual age. Patients with anemia are shown as the horizontal hatched line. Bottom marks indicate the number of data points by postconceptual age. The risk for apnea diminishes for infants born at a later gestational 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.

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

		Model 1: All Patients (n = 255)*		Model 2: All Nonanemic Patients (n = 220)*		Model 3: Nonanemic No Recovery Room Apnea (n = 172)*	
		1A	1B	2A	2B	3A**	3B
PCA (weeks)	GA (weeks)	Point Estimate	95% UCB	Point Estimate	95% UCB	Point Estimate	95% UCB
40	28	51	61	53	63	53	68
40	32	40	49	41	51	38	51
40	36	31	44	30	46	25	48
44	28	34	43	32	42	14	30
44	32	25	30	23	29	8	17
44	36	18	26	15	24	5	13
48	28	20	30	17	28	2	13
48	32	14	20	11	17	1.2	7
48	36	10	16	7	13	0.7	4
52	28	11	22	8	18	0.3	5
52	32	8	14	5	11	0.2	2.5
52	36	5	10	3	7	<0.1	1.4
56	28	6	15	3.5	12	<0.05	1.8
56	32	4	10	2	7	<0.05	0.9
56	36	3	7	1.4	4	<0.05	0.5
60	28	3	11	1.5	7	<0.05	0.7
60	32	2	7	1	4	<0.01	0.3
60	36	1	4	0.6	3	<0.01	0.2

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

* All herniorrhaphy 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.

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 (fig. 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

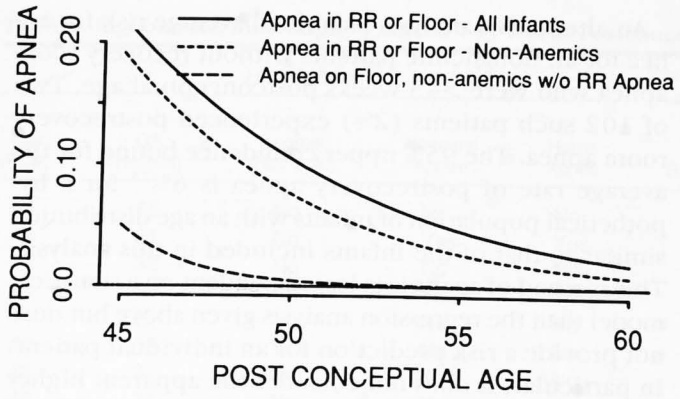

Fig. 3. Predicted probability of apnea by weeks postconceptual age for all three models: model 1 (solid line) = all infants; model 2 (irregular line) = all nonanemic infants; and model 3 (broken line) = patients who were not anemic and did not experience apnea in recovery room. The risk for apnea decreases 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 (>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 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.* 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

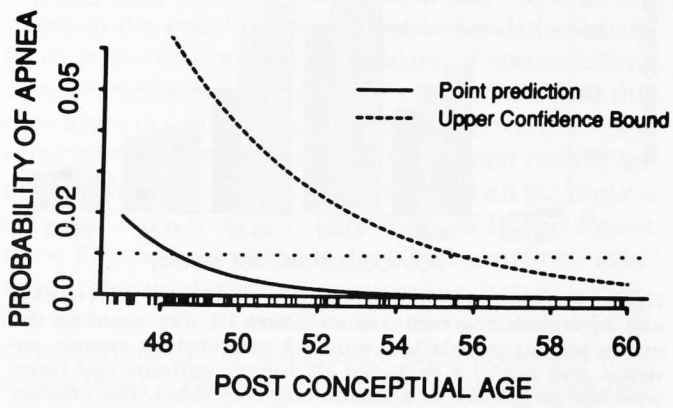

Fig. 4. Predicted probability of apnea after leaving recovery room by weeks postconceptual age (weeks) for infants who did not have apnea in recovery room or anemia (model 3). Bottom marks indicate the number of data points by postconceptual age. The risk does not fall below 1% with 95% statistical confidence until 56 weeks postconceptual age.

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.

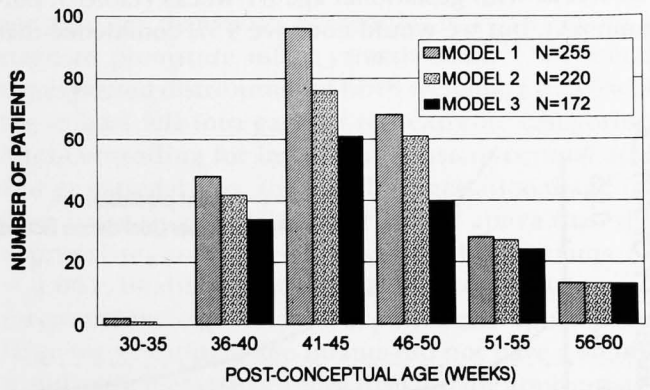

Fig. 5. Distribution of patients by postconceptual age (weeks) and by logistic regression model. Model 1 was based on the entire patient population, model 2 excluded all anemic patients, and model 3 excluded all anemic patients and those who had an episode of apnea in recovery room. The number of patients 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.

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

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

Historic Data					Outcomes			
Age (PCA)	GA (weeks)	Anemia (Hct < 30)	Neonatal Apnea	Home Apnea	Apnea Recovery Room	Stimulation Recovery Room	Apnea Postrecovery Room	Stimulation Postrecovery Room
44	28	No	No	No	Yes	No	?	?
44	31	No	Yes	Yes	Yes	No	?	?
44	32	No	No	No	Yes	No	?	?
44	34	No	Yes	Yes	Yes	No	?	?
44	35	Yes	No	No	Yes	No	?	?
44	36	Yes	No	No	Yes	No	?	?
45	31	No	Yes	No	Yes	No	No	No
45	31	No	Yes	Yes	Yes	?	No	No
45	33	Yes	No	No	Yes	?	No	No
45	33	No	No	Yes	No	?	Yes	Yes
46	34	No	Yes	Yes	Yes	Yes	?	?
47	31	No	Yes	No	No	?	Yes	Yes
47	34	No	Yes	Yes	Yes	No	No	No
48	24	No	No	No	Yes	No	?	?
48	36	Yes	?	No	No	No	Yes	No
49	33	No	Yes	Yes	Yes	Yes	No	No
49	35	No	No	No	Yes	No	Yes	No
51	28	Yes	?	No	No	No	Yes	No
52	32	No	No	No	Yes	No	No	No
54	32	No	No	No	Yes	No	No	No
54	32	No	Yes	Yes	Yes	No	No	No

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

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 (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.[24,25] The confidence intervals reported in the results do not take into account the uncertainty due to differences between institutions. If

Table 7. Cases with Apnea and Total Number of Cases for Each Institution by 5-Week Ranges of Postconceptual Age and Each Model with Percent Apnea

	Kurth		Welborn		Malviya		Warner		Totals Combined		
PCA (weeks)	With (n)	Total	With (n)	Total	With (n)	Total	With (n)	Total	With (n)	Total	Percent
Model 1: All 255 Patients											
31–35	1	1	1	1	0	0	0	0	2	2	100
36–40	4	8	24	26	1	1	0	13	29	48	60
41–45	10	19	6	28	2	22	5	27	23	96	28
46–50	5	28	1	6	0	18	1	16	7	68	10
51–55	3	11	1	6	0	10	0	1	4	28	14
55–60	0	4	0	0	0	6	0	3	0	13	0
All ages	23	71	33	67	3	57	6	60	65	255	25
Model 2: 220 Nonanemic Patients											
31–35	1	1	0	0	0	0	0	0	1	1	100
36–40	4	7	21	22	1	1	0	12	26	42	62
41–45	7	12	6	28	1	15	3	21	17	76	22
46–50	5	25	0	5	0	15	1	16	6	61	10
51–55	3	11	0	5	0	10	0	1	3	27	11
56–60	0	4	0	0	0	6	0	3	0	13	0
All ages	20	60	27	60	2	47	4	53	53	220	24
Model 3: 172 Nonanemic Patients without Recovery Room Apnea											
31–35	0	0	0	0	0	0	0	0	0	0	0
36–40	0	0	21	22	0	0	0	12	21	34	62
41–45	0	0	6	28	0	14	1	19	7	61	11
46–50	0	4	0	5	0	15	1	16	1	40	2
51–55	0	8	0	5	0	10	0	1	0	24	0
56–60	0	4	0	0	0	6	0	3	0	13	0
All ages	0	16	27	60	0	45	2	51	29	172	17

PCA = postconceptual age.

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 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 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.[33–40] 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 in-

guinal 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.

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

References

1. Malviya S, Swartz J, Lerman J: Are all preterm infants younger than 60 weeks postconceptual age at risk for postanesthetic apnea? Anesthesiology 78:1076–1081, 1993

2. Liu LMP, Coté CJ, Goudsouzian NG, Ryan JF, Firestone S, Dedrick DF, Liu PL, Todres ID: Life-threatening apnea in infants recovering from anesthesia. Anesthesiology 59:506–510, 1983

3. Welborn LG, Ramirez N, Oh TH, Ruttimann UE, Fink R, Guzzetta P, Epstein BS: Postanesthetic apnea and periodic breathing in infants. Anesthesiology 65:658–661, 1986

4. Kurth CD, Spitzer AR, Broennle AM, Downes JJ: Postoperative apnea in preterm infants. Anesthesiology 66:483–488, 1987

5. Welborn LG, DeSoto H, Hannallah RS, Fink R, Ruttimann UE, Boeckx R: The use of caffeine in the control of post-anesthetic apnea in former preterm infants. Anesthesiology 68:796–798, 1988

6. Welborn LG, Hannallah RS, Fink R, Ruttimann UE, Hicks JM: High-dose caffeine suppresses postoperative apnea in former preterm infants. Anesthesiology 71:347–349, 1989

7. Welborn LG, Rice LJ, Hannallah RS, Broadman LM, Ruttimann UE, Fink R: Postoperative apnea in former preterm infants: Prospective comparison of spinal and general anesthesia. Anesthesiology 72:838–842, 1990

8. Welborn LG, Hannallah RS, Luban NLC, Fink R, Ruttimann UE: Anemia and postoperative apnea in former preterm infants. Anesthesiology 74:1003–1006, 1991

9. Kurth CD, LeBard SE: Association of postoperative apnea, airway obstruction, and hypoxemia in former premature infants. Anesthesiology 75:22–26, 1991

10. Warner LO, Teitelbaum DH, Caniano DA, Vanik PE, Martino JD, Servick JD: Inguinal herniorrhaphy in young infants: Perianesthetic complications and associated preanesthetic risk factors. J Clin Anesth 4:455–461, 1992

11. Steward DJ: Preterm infants are more prone to complications following minor surgery than are term infants. Anesthesiology 56: 304–306, 1982

12. Rescorla FJ, Grosfeld JL: Inguinal hernia repair in the perinatal period and early infancy: Clinical considerations. J Pediatr Surg 19: 832–837, 1984

13. Melone JH, Schwartz MZ, Tyson KRT, Marr CC, Greenholz SK, Taub JE, Hough VJ: Outpatient inguinal herniorrhaphy in premature infants: Is it safe? J Pediatr Surg 27:203–208, 1992

14. Mayhew JF, Bourke DL, Guinee WS: Evaluation of the premature infant at risk for postoperative complications. Can J Anaesth 34:627–631, 1987

15. Scanlon JEM, Chin KC, Morgan MEI, Durbin GM, Hale KA; Brown SS: Caffeine or theophylline for neonatal apnoea? Arch Dis Child 67:425–428, 1992

16. Peliowski A, Finer NN: A blinded, randomized, placebo-controlled trial to compare theophylline and doxapram for the treatment of apnea of prematurity. J Pediatr 116:648–653, 1990

17. Eyal F, Alpan G, Sagi E, Glick B, Peleg O, Dgani Y, Arad I: Aminophylline versus doxapram in idiopathic apnea of prematurity: A double-blind controlled study. Pediatrics 75:709–713, 1985

18. Harnik EV, Hoy GR, Potolicchio S, Stewart DR, Siegelman RE: Spinal anesthesia in premature infants recovering from respiratory distress syndrome. Anesthesiology 64:95–99, 1986

19. Gallagher TM, Crean PM: Spinal anaesthesia in infants born prematurely. Anaesthesia 44:434–436, 1989

20. Webster AC, McKishnie JD, Kenyon CF, Marshall DG: Spinal anaesthesia for inguinal hernia repair in high-risk neonates. Can J Anaesth 38:281–286, 1991

21. Watcha MF, Thach BT, Gunter JB: Postoperative apnea after caudal anesthesia in an ex-premature infant. Anesthesiology 71:613–615, 1989

22. Battaglia FC, Lubchenco LO: A practical classification of newborn infants by weight and gestational age. J Pediatr 71:159–163, 1967

23. Bickel PJ, Doksum A (eds): Mathematical Statistics Oakland, Holden-Day, 1977; p 180

24. Muttitt SC, Finer NN, Tierney AJ, Rossmann J: Neonatal apnea: Diagnosis by nurse versus computer. Pediatrics 82:713–720, 1988

25. Brouillette RT, Morrow AS, Weese-Mayer DE, Hunt CE: Comparison of respiratory inductive plethysmography and thoracic impedance for apnea monitoring. J Pediatr 111:377–383, 1987

26. Hanley JA, Lippman-Hand A: If nothing goes wrong is everything all right? JAMA 249:1743–1745, 1983

27. Perelman RH, Farrell PM, Engle MJ, Kemnitz JW: Developmental aspects of lung lipids. Ann Rev Physiol 47:803–822, 1985

28. DeMaio JG, Harris MC, Deuber C, Spitzer AR: Effect of blood transfusion on apnea frequency in growing premature infants. J Pediatr 114:1039–1041, 1989

29. Bifano EM, Smith F, Borer J: Relationship between determinants of oxygen delivery and respiratory abnormalities in preterm infants with anemia. J Pediatr 120:292–296, 1992

30. Henderson-Smart DJ, Butcher-Puech MC, Edwards DA. Incidence and mechanism of bradycardia during apnoea in preterm infants. Arch Dis Child 61:227–232, 1986

31. Dransfield DA, Spitzer AR, Fox WW: Episodic airway obstruction in premature infants. Am J Dis Child 137:441–443, 1983

32. Butcher-Puech MC, Henderson-Smart DJ, Holley D, Lacey JL, Edwards DA. Relation between apnoea duration and type and neurological status of preterm infants. Arch Dis Child 60:953–958, 1985

33. Ruggins NR, Milner AD: Site of upper airway obstruction in infants following an acute life-threatening event. Pediatrics 91:595–601, 1993

34. Upton CJ, Milner AD, Stokes GM: Upper airway patency during apnoea of prematurity. Arch Dis Child 67:419–424, 1992

35. Ruggins NR, Milner AD. Site of upper airway obstruction in preterm infants with problematical apnoea. Arch Dis Child 66:787–792, 1991

36. van Someren V, Stothers JK: A critical dissection of obstructive apnea in the human infant. Pediatrics 71:721–725, 1983

37. Milner AD, Boon AW, Saunders RA, Hopkin IE: Upper airways obstruction and apnoea in preterm babies. Arch Dis Child 55:22–25, 1980

38. Mathew OP, Roberts JL, Thach BT: Pharyngeal airway obstruction in preterm infants during mixed and obstructive apnea. J Pediatr 100:964–968, 1982

39. Milner AD, Saunders RA, Hopkin IE: Apnoea induced by airflow obstruction. Arch Dis Child 52:379–382, 1977

40. Swift PGF, Emery JL: Clinical observations on response to nasal occlusion in infancy. Arch Dis Child 48:947–951, 1973

41. Mathew OP: Maintenance of upper airway patency. J Pediatr 106:863–869, 1985

42. Marshall TA, Kattwinkel J: Functional residual capacity and oxygen tension in apnea of prematurity. J Pediatr 98:479–482, 1981

43. Miller MJ, Carlo WA, Martin RJ: Continuous positive airway pressure selectively reduces obstructive apnea in preterm infants. J Pediatr 106:91–94, 1985

44. Miller MJ, Martin RJ, Carlo WA, Fouke JM, Strohl KP, Fanaroff AA: Oral breathing in newborn infants. J Pediatr 107:465–469, 1985

45. Rodenstein DO, Perlmutter N, Stanescu DC: Infants are not obligatory nasal breathers. Am Rev Respir Dis 131:343–347, 1985

46. Finer NN, Barrington KJ, Hayes BJ, Hugh A: Obstructive, mixed, and central apnea in the neonate: Physiologic correlates. J Pediatr 121:943–950, 1992

47. Hiatt IM, Hegyi T, Indyk L, Dangman BC, James LS: Continuous monitoring of PO_2 during apnea of prematurity. J Pediatr 98:288–291, 1981

48. Upton CJ, Milner AD, Stokes GM: Apnoea, bradycardia, and oxygen saturation in preterm infants. Arch Dis Child 66:381–385, 1991

49. Storrs CN: Cardiovascular effects of apnoea in preterm infants. Arch Dis Child 52:534–540, 1977

50. Vyas H, Milner AD, Hopkin IE: Relationship between apnoea and bradycardia in preterm infants. Acta Paediatr Scand 70:785–790, 1981

51. Wennergren G, Hertzberg T, Milerad J, Bjure J, Lagercrantz H: Hypoxia reinforces laryngeal reflex bradycardia in infants. Acta Paediatr Scan 78:11–17, 1989

52. Perlman JM, Volpe JJ: Episodes of apnea and bradycardia in the preterm newborn: Impact on cerebral circulation. Pediatrics 76: 333–338, 1985

53. Shah AR, Kurth CD, Gwiazdowski SG, Chance B, Delivoria-Papadopoulos M: Fluctuations in cerebral oxygenation and blood volume during endotracheal suctioning in premature infants. J Pediatr 120:769–774, 1993

54. Levitt GA, Mushin A, Bellman S, Harvey DR: Outcome of preterm infants who suffered neonatal apnoeic attacks. Early Human Dev 16:235–243, 1988

55. Tudehope DI, Rogers YM, Burns YR, Mohay H, O'Callaghan MJ: Apnoea in very low birth weight infants: Outcome at 2 years. Aust Paediatr J 22:131–134, 1986

56. Coté, CJ, Kelly DH: Postoperative apnea in a full-term infant with a demonstrable respiratory pattern abnormality. Anesthesiology 72:559–561, 1990

57. Le Guennec J-C, Billon B, Paré C: Maturational changes of caffeine concentrations and disposition in infancy during maintenance therapy for apnea of prematurity: Influence of gestational age, hepatic disease, and breast-feeding. Pediatrics 76:834–840, 1985

58. Pons G, Carrier O, Richard M-O, Rey E, d'Athis P, Moran C, Badoual J, Olive G: Developmental changes of caffeine elimination in infancy. Dev Pharmacol Ther 11:258–264, 1988

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 X′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.