

ORIGINAL ARTICLE

Ventilation in Extremely Preterm Infants and Respiratory Function at 8 Years

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ABSTRACT

BACKGROUND

Assisted ventilation for extremely preterm infants (<28 weeks of gestation) has become less invasive, but it is unclear whether such developments in care are associated with improvements in short-term or long-term lung function. We compared changes over time in the use of assisted ventilation and oxygen therapy during the newborn period and in lung function at 8 years of age in children whose birth was extremely premature.

METHODS

We conducted longitudinal follow-up of all survivors of extremely preterm birth who were born in Victoria, Australia, in three periods — the years 1991 and 1992 (225 infants), 1997 (151 infants), and 2005 (170 infants). Perinatal data were collected prospectively, including data on the duration and type of assisted ventilation provided, the duration of oxygen therapy, and oxygen requirements at 36 weeks of age. Expiratory airflow was measured at 8 years of age, and values were converted to z scores for age, height, ethnic group, and sex.

RESULTS

The duration of assisted ventilation rose substantially over time, with a large increase in the duration of nasal continuous positive airway pressure. Despite the increase in the use of less invasive ventilation over time, the duration of oxygen therapy and the rate of oxygen dependence at 36 weeks rose, and airflows at 8 years of age were worse in 2005 than in earlier periods. For instance, for 2005 versus 1991–1992, the mean difference in the z scores for the ratio of forced expiratory volume in 1 second to forced vital capacity was -0.75 (95% confidence interval [CI], -1.07 to -0.44 ; $P < 0.001$), and for 2005 versus 1997 the mean difference was -0.53 (95% CI, -0.86 to -0.19 ; $P = 0.002$).

CONCLUSIONS

Despite substantial increases in the use of less invasive ventilation after birth, there was no significant decline in oxygen dependence at 36 weeks and no significant improvement in lung function in childhood over time. (Funded by the National Health and Medical Research Council of Australia and the Victorian Government's Operational Infrastructure Support Program.)

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RESPIRATORY PROBLEMS ARE COMMON after birth in extremely preterm infants (<28 weeks of gestation), and most of these infants require assisted ventilation until they are sufficiently mature and strong enough to breathe by themselves. However, immature lungs are not meant to be exposed to higher concentrations of oxygen than the very low levels provided in the uterus or to the airway pressure that is provided by ventilators to assist breathing. Such exposure can injure the lungs, and injury may arrest pulmonary development.¹ Some extremely preterm infants become oxygen dependent for many weeks and are subsequently subject to the development of bronchopulmonary dysplasia.¹

Assisted ventilation has changed substantially since the 1970s, when ventilation delivered through an endotracheal tube predominated.² Less invasive forms of ventilation, including nasal continuous positive airway pressure (CPAP), have evolved over time and in some medical centers have become the most common means of assisting ventilation after birth. Less invasive ventilation is considered to be “gentler” — easier on the lungs — and therefore potentially less injurious. The introduction of antenatal glucocorticoids³ in the 1970s and exogenous surfactant⁴ in 1991 has also modified the risk of postnatal lung disease, and fewer infants now have the severe atelectasis caused by a lack of surfactant.

Although assisted ventilation has become less invasive during the past 25 years, it is unclear whether assisted ventilation has been associated with improvements in short-term or long-term respiratory function. The aim of our study was to compare changes in assisted ventilation and oxygen therapy administered during the newborn period and in lung function at 8 years of age in children in Victoria, Australia, whose birth was extremely premature over three distinct periods, all of which followed the introduction of exogenous surfactant into clinical practice. We hypothesized that respiratory outcomes would have improved over time, with less oxygen dependence and improved lung function at 8 years of age.

METHODS

STUDY POPULATION AND OVERSIGHT

Perinatal care in the state of Victoria has been centralized since the 1970s. There have been only

four neonatal intensive care units in the state since that time. These neonatal units have collaborated with governmental data-collection agencies and the statewide transport service since the late 1970s to obtain population-based data on long-term outcomes for discrete cohorts of the smallest and most immature surviving infants in the state. Initially, data were collected only for infants with a birth weight of less than 1000 g; from the 1990s onward, data were collected for these infants as well as those born at less than 28 weeks of gestation. Data on all births (including home births, which are rare) are recorded.

All extremely preterm surviving infants born in Victoria in three periods (1991–1992, 1997, and 2005) were recruited at birth and followed longitudinally. Perinatal data, including data on the duration of assisted ventilation of all types and subtypes (intermittent positive-pressure ventilation and high-frequency oscillatory ventilation, both delivered through an endotracheal tube, and nasal CPAP), were collected prospectively. In the periods studied, high-flow oxygen therapy delivered by nasal cannula was not used. Oxygen dependence at 36 weeks of age was documented.

All aspects of the study were approved by the Human Research Ethics Committees at the Royal Women's Hospital, Mercy Hospital for Women, Monash Medical Centre, and the Royal Children's Hospital, Melbourne. Parents provided written informed consent for the participation of children in the 2005 cohort; follow-up assessments for the earlier cohorts were considered to involve routine clinical care. The first author designed the study, gathered and analyzed the data, vouches for the data and the analysis, wrote the article, and made the decision to submit the manuscript for publication. The funders of the study had no role in its design, in the collection, analysis, or interpretation of data, in the writing of the report, or in the decision to submit the manuscript for publication.

STUDIES OF RESPIRATORY FUNCTION

Respiratory function was measured in accredited respiratory-function laboratories in children approximately 8 years of age, with correction for preterm birth; most children from all periods were assessed in the Department of Respiratory Medicine at the Royal Children's Hospital in Melbourne, but some were assessed at Monash Medi-

cal Centre (all periods) or at the Austin Hospital (2005 cohort only) in Melbourne. Spirometry was performed in accordance with guidelines from the American Thoracic Society⁵ by respiratory scientists who were unaware of the clinical details regarding the participants. Maximum expiratory flow–volume curves were recorded with the child sitting in a body plethysmograph, with the door open. Flow was measured with a pneumotachograph as volume per unit time, and volume was obtained by calculating the area under the curve of the flow-versus-time relationship. Variables reflecting airflow included the forced expiratory volume in 1 second (FEV₁), forced vital capacity (FVC), and forced expiratory flow from 25 to 75% of vital capacity (FEF_{25–75%}). Results at body temperature and pressure saturated with water vapor were expressed as z scores and as percent of predicted value for height, sex, ethnic group, and age.⁶ Data on respiratory function at 8 years of age have been reported previously for the 1991–1992 cohort⁷ and the 1997 cohort,⁸ not only for children born at less than 28 weeks of gestation but also for those who weighed less than 1000 g at birth. No data on the respiratory function of the 2005 cohort have been reported previously. Parents also completed a questionnaire on the respiratory health of their child.⁹

STATISTICAL ANALYSIS

Data were analyzed with the use of Stata software, version 14.1 (StataCorp). Data were compared between periods by means of linear and logistic regression and were fitted with the use of generalized estimating equations, with robust error estimates used to account for clustering within multiple births. The major interest was in comparing the outcomes for the latest cohort (2005) with each of the preceding cohorts (1991–1992 and 1997). Differences between periods were first calculated without adjustment and were then calculated with adjustment for perinatal variables, including use of antenatal glucocorticoids, multiple births, gestational age, sex, the z score for birth weight, and the use of exogenous surfactant and postnatal glucocorticoids for the treatment or prevention of lung injury. For the data on lung function, we also adjusted for age and the z score for height when the children were tested at 8 years of age. Mean differences or odds ratios and 95% confidence intervals were calculated, where appropriate.

RESULTS

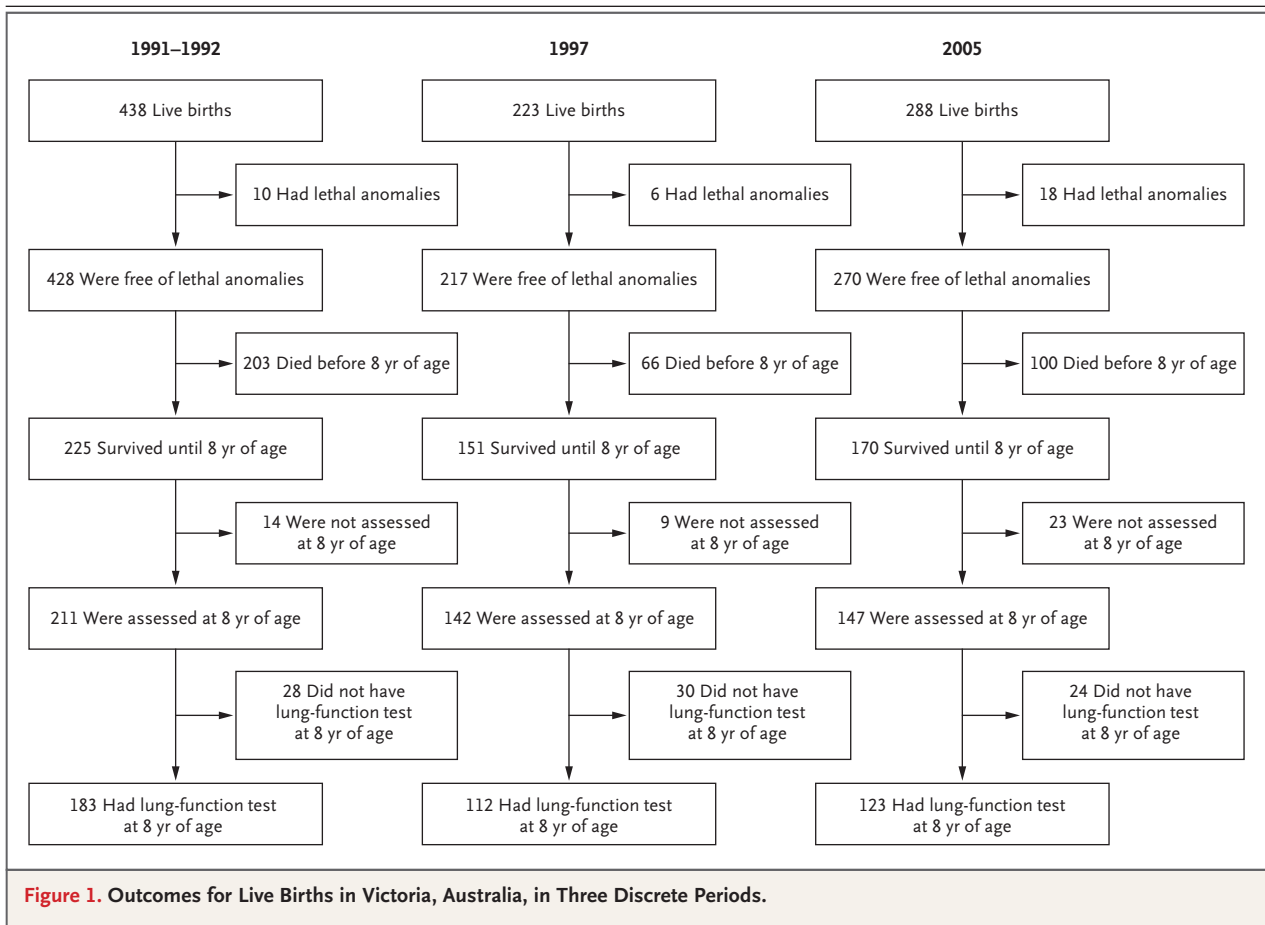
OUTCOMES AND SURVIVAL RATES

The flow chart in Figure 1 outlines the outcomes for all live births with a gestational age of 22 through 27 weeks in the state of Victoria in three discrete periods: 1991–1992, 1997, and 2005. The number of infants who underwent lung-function testing is also shown. The survival rates to 8 years of age for infants born free of lethal anomalies between 22 and 27 completed weeks were as follows: 53% (225 of 428) for the 1991–1992 group, 70% (151 of 217) for the 1997 group, and 63% (170 of 270) for the 2005 group.¹⁰

PERINATAL CHARACTERISTICS AND USE OF VENTILATION RESOURCES

Among survivors, rates of treatment with antenatal glucocorticoids and exogenous surfactant increased over time, but postnatal glucocorticoids were prescribed less frequently in 2005 than in either of the earlier periods (Table 1). Other perinatal characteristics were similar among the three periods, with the following exceptions: there were fewer multiple births in 2005 than in 1991–1992, and birth weight and the z scores for birth weight were lower in 1997 than in 2005. The mean durations of all assisted ventilation rose substantially over time, primarily because of a large increase in the mean duration of nasal CPAP given the declining duration of endotracheal ventilation.

On univariate analysis, the mean durations of assisted ventilation and nasal CPAP alone were substantially higher in 2005 than in 1991–1992, whereas only the mean duration of nasal CPAP was higher in 2005 than in 1997 (Fig. 2). The mean durations of assisted ventilation, endotracheal ventilation, and nasal CPAP fell and the rate of oxygen dependence at 36 weeks declined with increasing gestational age, whereas the mean durations of all these interventions and the rate of oxygen dependence were higher among infants treated with postnatal glucocorticoids (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). The mean durations of assisted ventilation and endotracheal ventilation declined with increasing z score for birth weight. The mean duration of endotracheal ventilation was longer in male children, and the mean duration of oxygen therapy was longer in children who received surfactant treatment (Ta-



ble S1 in the Supplementary Appendix). When adjusted for all perinatal variables listed in Table S1, the mean durations of assisted ventilation and nasal CPAP were substantially higher in 2005 than in either 1991–1992 or 1997, and the mean duration of oxygen therapy was higher in 2005 than in 1997 (Fig. 2). Rates of oxygen dependence at 36 weeks were higher in 2005 than in either of the earlier periods (Table 1), but the strength of the association was greater in the comparison with the 1997 cohort (adjusted odds ratio, 2.67; 95% confidence interval [CI], 1.60 to 4.46; $P < 0.001$) than in the comparison with the 1991–1992 cohort (adjusted odds ratio, 1.44; 95% CI, 0.85 to 2.42; $P = 0.18$).

OUTCOMES AT 8 YEARS

In all three cohorts, most survivors were assessed at 8 years of age. The remainder were either lost to follow-up or declined assessment; data from three children born in 2005 were unavailable, because the children were living in other states

or countries at the time of the study (Table S2 in the Supplementary Appendix). Some of the children assessed at 8 years of age were unable to have lung-function tests because they were too disabled to participate. The age at lung-function testing was lower in the 2005 cohort than in the earlier cohorts. The perinatal characteristics among the children for whom there were no lung-function data at 8 years of age were similar to the perinatal characteristics of those for whom there were lung-function data, although in the 2005 cohort there were fewer multiple births and more children who had been treated with postnatal glucocorticoids among the children who did not provide lung-function data than among those who did.

Summary values for raw expiratory flows, z scores, and percentages of predicted values are shown in Table 2. The distributions of z scores for participants in each group are shown in Figure S1 in the Supplementary Appendix. The mean z scores for all variables related to expiratory

Table 1. Perinatal Characteristics and Mean Duration of Assisted Ventilation and Oxygen Therapy among Children Who Survived to 8 Years of Age in Each Period.*

Variable	1991–1992 (N=225)	1997 (N=151)	2005 (N=170)
Perinatal characteristic			
Antenatal glucocorticoids — no. (%)	160 (71)	134 (89)	145 (85)†
Multiple pregnancy — no. (%)	73 (32)	30 (20)	37 (22)†
Gestational age — wk completed	25.9±1.1	25.6±1.2	25.8±1.2
Birth weight — g	891±176	824±177	867±195‡
Male — no. (%)	113 (50)	82 (54)	86 (51)
Birth-weight z score	−0.26±0.88	−0.53±0.83	−0.33±0.86‡
Exogenous surfactant — no. (%)	97 (43)	127 (84)	148 (87)†
Postnatal glucocorticoids — no. (%)	91 (40)	70 (46)	39 (23)§
Duration of assisted ventilation or oxygen therapy — days			
Assisted ventilation			
Median	30	48	44†
Interquartile range	17–45	31–62	24.8–73†
Mean	33.3±26.1	49.1±26.0	53.2±43.2†
Endotracheal ventilation			
Median	21	19	10
Interquartile range	8–34	8–32	2.5–23.5
Mean	24.4±22.8	23.1±21.0	19.9±28.6
Nasal CPAP			
Median	5	24	31.5§
Interquartile range	0.5–12	14–36	16.8–42§
Mean	8.9±11.7	26.0±15.3	33.3±26.0§
Supplemental oxygen			
Median	42.5	45	53.5
Interquartile range	5–85	10.5–88	9.8–106
Mean	70.2±64.8	65.1±48.0	75.1±68.0
Oxygen dependence at 36 wk — no. (%)	104 (46)	65 (43)	96 (56)‡

* Plus-minus values are means ±SD. Assisted ventilation includes endotracheal ventilation and nasal continuous positive airway pressure (CPAP).

† P<0.05 for the comparison of the 2005 cohort with the cohort from 1991–1992.

‡ P<0.05 for the comparison of the 2005 cohort with 1997 cohort.

§ P<0.05 for the comparison of the 2005 cohort with the cohorts from both 1991–1992 and 1997.

flow were negative in all three periods (Table 2). This finding means that as a group the children had expiratory flows that were lower than expected. Although the mean z score for FEV₁ at 8 years improved between 1991–1992 and 1997, the score deteriorated again in 2005 (Table 2). In unadjusted analyses, z scores for FEV₁:FVC were substantially lower in 2005 than in 1991–1992, whereas z scores for both FEV₁ and FEV₁:FVC were lower in 2005 than in 1997 (Fig. 3). There were only a

few substantial independent relationships between expiratory flows at 8 years and either perinatal variables for age or the z score for height at 8 years (Table S3 in the Supplementary Appendix). Adjustment for all perinatal variables and for age and the z score for height at the time of testing had little effect on the differences in flow rates among the three periods and altered no conclusions (Fig. 3). Rates of wheezing in the 12 months preceding the 8-year assessment were

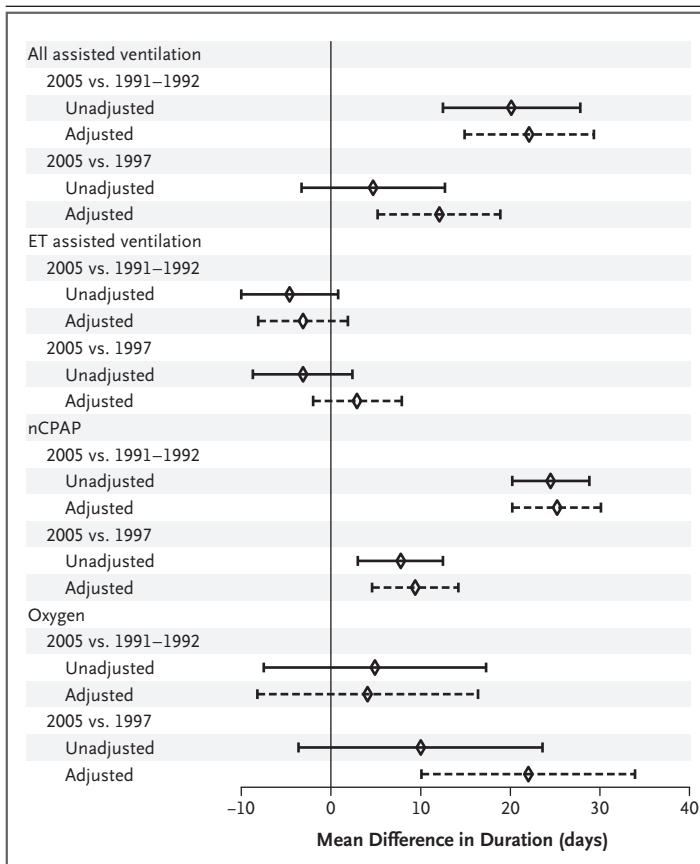


Figure 2. Mean Duration of Assisted Ventilation and Oxygen Use in Three Discrete Periods.

The mean differences in the duration of assisted ventilation of different types and of oxygen use in 2005 are shown in comparison with the same data for 1991–1992 and for 1997. The data shown are mean differences and 95% confidence intervals, both unadjusted and adjusted for perinatal variables. Values to the right of the vertical line indicate that mean duration was longer in 2005 than in the earlier periods. AV denotes assisted ventilation, ET endotracheal tube, and nCPAP nasal continuous positive airway pressure.

similar in all three cohorts: 26% (48 of 182) in 1991–1992, 26% (29 of 112) in 1997, and 23% (28 of 123) in 2005.

DISCUSSION

The major findings in our study of survivors of extremely preterm birth that occurred during three discrete periods are that the mean duration of assisted ventilation, particularly nasal CPAP, increased substantially over time but that there were no parallel short-term or long-term improvements in respiratory function. Indeed, there were higher rates of oxygen dependence at 36 weeks of age

and more airflow obstruction at 8 years of age in the most recent period we reviewed (2005). These findings were contrary to our hypothesis.

Numerous studies of the lung function of preterm cohorts during childhood are available for the period in which surfactant has been available, and most report reductions in airflow relative to expectations or to controls born at full term.¹¹ Vollsæter et al.¹² reported that among children 11 years of age in Norway who were born before 28 weeks of gestation or whose birth weight was less than 1000 g, expiratory flow rates in 1999 and 2000 were higher than the rates in such children born in 1991–1992. Similarly, we previously reported that among children 8 years of age who were born preterm in 1997 and whose gestation was less than 28 weeks or whose birth weight was less than 1000 g had higher expiratory flows than similar children born in the state of Victoria in 1991–1992. However, the expiratory flows in the preterm group did not improve relative to the values measured in controls.⁸

The major strengths of the present study include the fact that the cohorts were from the same geographic region, which eliminated changes in referral patterns between eras as a possible source for differences between eras. All infants received their intensive care in one of only four neonatal units over the entire period, which allowed for excellent follow-up rates (through elementary school) and for the examination of serial cohorts covering the period during which surfactant treatment has been available for clinical use. Our study has certain limitations. Not all survivors in our cohorts have been able to undergo lung-function testing, primarily because some children were too disabled to meet the criteria for testing. Given the strict criteria for obtaining acceptable results on lung-function tests, it would have been almost impossible to obtain lung-function data on 100% of any childhood cohort, much less an extremely preterm cohort with a substantial proportion of disabled survivors. Another limitation is that our results may not apply to patients in countries with different demographic characteristics. Furthermore, we do not have data on hospitalizations for respiratory illnesses for all cohorts or on the need for medications. However, rates of wheezing were similar in all three periods.

What do the results of our study mean? Perhaps the assumption that nasal CPAP is less in-

Table 2. Expiratory Flows at 8 Years of Age in Each Period.*

Variable	1991–1992 (N=183)	1997 (N=112)	2005 (N=123)
FEV₁			
Raw value — liters	1.44±0.27	1.43±0.30	1.25±0.28
z score	-1.01±1.11	-0.65±1.30	-1.19±1.17†
Percent of predicted value	87.9±13.4	92.0±15.7	85.4±14.4‡
FVC			
Raw value — liters	1.67±0.37	1.65±0.34	1.50±0.33
z score	-0.89±1.28	-0.47±1.26	-0.75±1.17
Percent of predicted value	89.6±14.9	94.4±14.9	91.0±14.2
FEV₁:FVC			
Raw value	0.87±0.09	0.86±0.09	0.84±0.08
z score	-0.06±1.49	-0.30±1.33	-0.77±1.20‡
Percent of predicted value	98.3±10.0	96.8±10.1	93.4±9.2‡
	1991–1992 (N=177)	1997 (N=110)	2005 (N=110)
FEF_{25–75%}			
Raw value — liters/sec	1.43±0.46	1.42±0.46	1.35±0.45
z score	-1.45±1.04	-1.30±1.06	-1.27±1.08
Percent of predicted value	69.2±21.6	72.2±21.9	72.3±23.4

* Plus-minus values are means ±SD. Expiratory flows are presented as raw values and expressed as z scores and as a percentage of the predicted value for age, height, sex, and ethnic group. Absolute values (in liters, percentages, or liters per second) have not been compared across periods because these values cannot be interpreted without knowledge of the age, height, sex, or ethnic group of the participants contributing the data. FEF_{25–75%} denotes forced expiratory flow from 25% to 75% of vital capacity, FEV₁ forced expiratory volume in 1 second, and FVC forced vital capacity.

† P<0.05 for the comparison of the 2005 cohort with the 1997 cohort.

‡ P<0.05 for the comparison of the 2005 cohort with both the 1991–1992 cohort and the 1997 cohort.

vative and less injurious to the lung than endotracheal ventilation was incorrect. Another possibility is that nasal CPAP is being overused. Over time, the threshold for commencing nasal CPAP has decreased substantially: it is administered to infants with minimal signs of respiratory distress after birth even though the condition of many of these infants might have improved without it. Nasal CPAP is also used for extensive periods to reduce the apnea of prematurity; physicians' threshold for tolerating apnea has probably decreased over time, making some infants subject to prolonged periods of nasal CPAP.

There was a halving of the use of postnatal glucocorticoids from 1997 to 2005. Although postnatal glucocorticoids are associated with adverse short-term and long-term neurodevelopmental outcomes, they also reduce the rate of bronchopulmonary dysplasia.^{13,14} Moreover, if glucocorticoids are given to infants at high risk for broncho-

pulmonary dysplasia, they may improve the likelihood of survival free from cerebral palsy.¹⁵ Adjustment for the administration of postnatal glucocorticoids, along with other perinatal variables, increased the odds of oxygen dependence at 36 weeks in 2005 as compared with 1997, although this increase had little effect on the point estimates for differences in expiratory flows between periods and did not alter any conclusions.

We speculate that prolonged periods of oximetry may be partly responsible for the increasing rate of oxygen dependence observed in 2005 and that this trend may translate into worse lung function when children reach the age at which they will attend school. We have unpublished data on the mean duration of oximetry over the first 6 weeks of life in extremely preterm infants cared for at the Royal Women's Hospital in Melbourne, where in 1992 the mean duration of oxygen monitoring was restricted owing to the lack

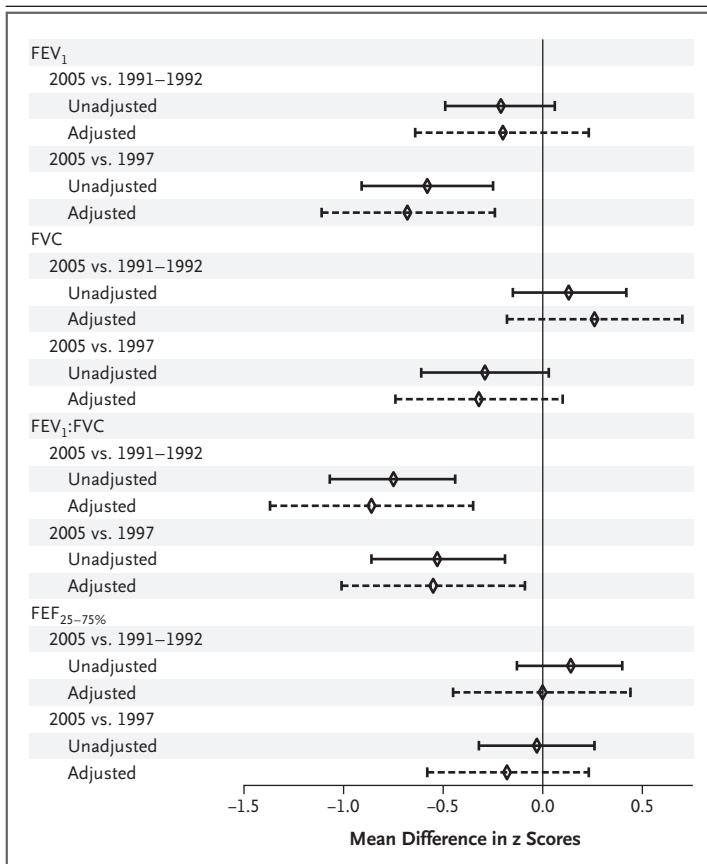


Figure 3. The z Scores for Expiratory Flows in Three Discrete Periods.

The z scores for expiratory flows in 2005 are compared with the scores from 1991–1992 and from 1997. The data shown are mean differences and 95% confidence intervals, both unadjusted and adjusted for perinatal variables, and the z scores for age and height when assessed at 8 years. Values to the left of the vertical line indicate that expiratory flows were lower in 2005 than in the earlier periods. FEF_{25–75%} denotes forced expiratory flow from 25 to 75% of vital capacity, FEV₁ forced expiratory volume in 1 second, and FVC forced vital capacity.

of oximeters but was unlimited by 2002, despite the fact that most infants were breathing ambient air from day 1 (Doyle LW, Fang AF: unpublished data). The problem with the continuous monitoring of oxygen saturation in infants breathing ambient air is that the fraction of inspired oxygen can only be increased, not decreased. Exposure to additional oxygen among infants who do not have substantial lung disease may cause pulmonary oxygen toxicity, which may impair lung growth. We speculate that such a scenario may have contributed to the prolonged oxygen dependence and worse lung function at 8 years of age that we observed in the current study.

Today several types of noninvasive assisted

ventilation other than nasal CPAP are available, including high-flow nasal cannulae, nasal intermittent positive-pressure ventilation, and even nasal high-frequency ventilation. Moreover, for infants who are intubated, the available variations in flow, pressure, rate, and patient triggering (i.e., response of a ventilator to an infant's inspiratory efforts) mean that many different options for invasive and noninvasive assisted ventilation are possible. Recent randomized trials^{16–18} that examined different types of ventilation have largely reported short-term outcomes (e.g., oxygen dependence at 36 weeks or failure to maintain extubation for a short period). However, such studies have not evaluated long-term lung function, with a few exceptions.^{19,20} In a report from the United Kingdom Oscillation Study Group involving children between 11 and 14 years of age who were born at less than 29 weeks of gestation, those randomly assigned to high-frequency oscillation in the newborn period had better lung function than those assigned to conventional ventilation,²⁰ although between 11 and 14 months of age oscillation provided no apparent advantage with regard to lung function.¹⁹ In our present study of extremely preterm survivors, the provision of high-frequency oscillatory ventilation through an endotracheal tube was rare in 1991–1992, and it was uncommon in the later periods, consuming only 3% and 5% of the resources used for assisted ventilation in 1997 and 2005, respectively.

It is important to note that abnormal lung function in childhood is a portent of chronic obstructive lung disease in adulthood; indeed, expiratory flows in the 1991–1992 cohort deteriorated between the ages of 8 and 18 years,²¹ suggesting that those children are unlikely to achieve the normal peak lung function expected by their mid-20s. If the lung function of the most recent cohort, born in 2005, also deteriorates in adolescence in a way that is similar to the earlier cohort, these children would be even more likely than earlier cohorts to have chronic obstructive lung disease as adults.

In conclusion, our data show that among our most immature newborn survivors, long-term respiratory function was no better among those born in 2005 than in the cohorts born in the 1990s. This observation applies despite the increased use of noninvasive ventilation in everyday neonatal intensive care.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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