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Cardiopulmonary Outcomes of Extreme Prematurity

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Cardiopulmonary diseases dominate the early days after birth for very preterm babies, but most survive these disorders. However, a minority who survive remain oxygen-dependent for a prolonged period, including after discharge. For the remaining very preterm survivors, cardiopulmonary problems are not major health issues in early childhood, apart from higher rates of hospital readmission for respiratory illnesses in the first few years after the primary hospitalization. However, as they progress through childhood and into adulthood, it is clear that very preterm survivors have reduced lung function, higher blood pressure, and other cardiovascular abnormalities that may lead to adverse cardiopulmonary outcomes much earlier in adult life than would normally be expected. The contribution of these cardiopulmonary problems in early adulthood to morbidity in middle and old ages needs to be determined.

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Before the 1970s, survival rates for extremely low birth weight (ELBW, birth weight <1000 g or 500-999 g) or very preterm infants (<28 weeks' gestational age) were very low, usually <10%. However, with the advent of modern neonatal intensive care, the hallmark of which is the ability to support ventilation, long-term survival rates for ELBW infants began to rise, to approximately 1-in-4 in the late 1970s in geographical cohorts.¹ Following the introduction of corticosteroids before birth, exogenous surfactant after birth, and an increased willingness to offer treatment, survival rates were almost 3-in-4 by the late 1990s.¹ Survival rates for infants 23 to 27 weeks are similar to those for infants 500 to 999 g birth weight in population-based cohorts.²

Despite antenatal corticosteroids and exogenous surfactant after birth, cardiopulmonary problems dominate the early days after birth for very preterm babies, and remain the major cause of mortality in the most immature infants in the surfactant era.³ Among those who survive the neonatal period are some who develop bronchopulmonary dysplasia (BPD),⁴ occasionally remaining oxygen-dependent for many months, or even years. However, most very immature survivors have no ongoing cardiopulmonary problems in early childhood. On the other hand, their prospects for cardiopulmonary ill-health later in life are not well characterized. In

the general population, cardiopulmonary problems cause considerable morbidity and mortality in adulthood. Cardiovascular disease is the leading cause of death in many countries; in Australia, it is responsible for nearly 40% of all deaths.⁵

The purpose of this article is to review the rates of cardiopulmonary ill-health after discharge for very preterm infants. It will consider hospital readmissions for cardiopulmonary illnesses, and data on lung function, blood pressure, and other cardiopulmonary outcomes in later life, including, where possible, into adulthood. As data by gestational age are not commonly available, data for some outcomes by birth weight will be considered as a substitute.

Readmissions to Hospital

In most reported studies, the rates of rehospitalization of ELBW/very preterm infants approach or exceed 50%.⁶ In contrast, readmission rates for normal birth weight (NBW, birth weight >2499 g) controls, where reported in the same study, are much lower; at the Royal Women's Hospital, Melbourne, approximately two to three times as many ELBW infants were readmitted at least once in the first 2 years after discharge compared with NBW controls.⁶ As survival rates of smaller and more immature infants have increased over time, the proportion of ELBW survivors from the Royal Women's Hospital who have been readmitted at least once in the first few years after discharge has risen from just over one in two in the early 1980s, to two in three in the late 1990s.⁶

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Where the information is available, readmissions for medical indications generally outweigh surgical readmissions.⁷⁻⁹ Overall, respiratory illnesses are the most common cause of rehospitalization. Cunningham and coworkers,¹⁰ in their cohort of infants <32 weeks' gestational age, reported that two of three of rehospitalizations up to 2 years of age were for respiratory illnesses, and the rate of respiratory rehospitalization in preterm infants was significantly greater than in the term controls (36% versus 2.5%). In older very low birth weight (VLBW; birth weight <1500 g) children, Kitchen and coworkers⁹ found that the higher rate of respiratory rehospitalizations persisted in the VLBW group at 5 years of age (mean number of rehospitalizations for respiratory tract infection per study child; 0.24 VLBW, 0.12 controls).

In most studies, higher rehospitalization rates are reported in infants with BPD than in infants without BPD, with rates varying from 40% to 60% in the first 2 years of life in infants with BPD.¹⁰⁻¹⁸ As children with a history of BPD reach school age, it appears that the risk of rehospitalization may be similar to their non-BPD peers. In the study of VLBW children at ages 8 to 10 years by McCormick and coworkers,¹⁹ the risk of rehospitalization in the preceding year was similar for BPD (6%) and non-BPD (7%) groups. Infants with BPD, as well as having higher rehospitalization rates, are also more likely to require multiple rehospitalizations and longer hospital stays. Cunningham and coworkers¹⁰ reported that 26% of infants with BPD versus 5% of controls without BPD had multiple rehospitalizations. Similarly, Chye and coworkers,¹⁷ in a case-control study, reported higher rates of multiple readmissions in the BPD group (53% versus 35%). Infants with BPD also require longer hospital stays than those with no BPD (median 10 days versus 3 days).¹⁸ Infants with BPD are more likely to be rehospitalized early in childhood with a respiratory illness than infants without BPD.^{13,17} However, as the rate of hospital readmission declines later in childhood, those who had BPD are no more likely to be readmitted to hospital, for respiratory or other reasons.²⁰

Respiratory Health Problems

ELBW children in cohorts from the Royal Women's Hospital, born during the 1980s and 1990s, had more frequent illnesses during the first 2 years of life, particularly upper and lower respiratory illnesses.⁶ O'Callaghan and coworkers²¹ reported that 55% of their ELBW cohort had wheeze or bronchitis in the first 2 years after discharge compared with only 36% in NBW controls. Bowman and Yu⁸ reported that 55% of ELBW infant had otitis media, 48% had wheezing, and 29% had lower respiratory tract infections in the first 2 years of life.

ELBW survivors with BPD in cohorts from the Royal Women's Hospital generally had more frequent respiratory illnesses (otitis media, lower respiratory tract infection, wheezing) than ELBW children who had not had BPD. Others have reported higher rates of ill-health in survivors who had BPD and who were very low birth weight or very preterm at birth.^{12,22,23}

Asthma is reported to be more prevalent among the smallest or most premature infants at birth than in those born full term or with NBW in some²⁴⁻²⁶ but not all studies.^{20,27} Those who had BPD have even higher rates of asthma in some studies.²⁸

Respiratory Function

Standard respiratory function tests include variables that reflect airflow, including the forced expired volume in 1 sec (FEV₁), the FEV₁/forced vital capacity (FVC) ratio, instantaneous flows at various % of vital capacity (VC), such as the flow rate at 75% of VC ($V_{EMAX75\%}$), at 50% of vital capacity ($V_{EMAX50\%}$), or at 25% of vital capacity ($V_{EMAX25\%}$), the maximum forced expiratory flow between 25% and 75% of vital capacity (FEF_{25-75%}), or the peak expiratory flow rate (PEFR). Other respiratory function variables predominantly reflect air trapping, including the residual volume (RV) or the RV/total lung capacity (TLC) ratio.

Several studies have reported respiratory function data in subjects with BPD in the late teens or early 20s.^{25,29-31} Northway and coworkers²⁹ described the respiratory function at 18 years of age of 26 unselected subjects who had BPD and who were born between 1964 and 1973. BPD was diagnosed in those who had been ventilated for respiratory distress, who were oxygen-dependent at 28 days, and who had Northway stages 3 or 4 on chest radiograph.⁴ Results were compared with 26 age-matched controls of similar birth weight and gestational age who had not been ventilated as infants, and 53 age-matched normal subjects who were not born prematurely, who had no history of chronic lung disease, and who were nonsmokers. The preterm subjects were relatively heavy (mean birth weights 1894 g and 1978 g, respectively) and mature (mean gestational ages 33.2 weeks and 34.5 weeks, respectively) compared with BPD survivors from more recent eras. Northway and coworkers found that 68% of BPD subjects had airway obstruction; this was reversible in most, but fixed in 24%. Those with BPD had reductions in variables reflecting airflow (lower FEV₁, FVC, FEF_{25-75%}, $V_{EMAX50\%}$, and PEFR) and increased gas trapping (higher RV/TLC) compared with both the preterm controls and the normal controls; 24% had one or more severe abnormalities in respiratory function. Values for FEV₁ in the BPD group, the non-BPD preterm group, and the normal controls are shown in Table 1.

Halvorsen and coworkers²⁵ reported the pulmonary outcomes for 46 subjects of birth weight <1001 g or gestational ages <29 weeks at a mean age of 17.7 years from a geographically based cohort of births between 1982 and 1985 in Western Norway. Twelve (26%) of the subjects had moderate or severe BPD based on oxygen requirement at 36 weeks' postmenstrual age, 24 (52%) had mild BPD based on oxygen requirement at 28 days but not 36 weeks, and 10 (22%) had no BPD. They compared results with 46 controls with similar ages who were born at term and of the same gender; the controls were not randomly selected, however, as they had to ask 40% more controls to participate to get the required number of 46, raising the possibility that volunteer bias in-

Table 1 Forced Expired Volume in 1 second (FEV₁ - % predicted) for Four Studies with Respiratory Function Reported in Late Adolescence/Early Adulthood

Study	Preterm Groups		Controls	Mean Difference (95% CI)		
	BPD	No BPD		BPD vs No BPD	BPD vs Controls	No BPD vs Controls
Northway ²⁹	74.8 (14.5) n = 25*	96.6 (10.2) n = 26	100.4 (10.9) n = 53	-21.8 (-28.8, -14.8)	-25.6 (-31.5, -19.7)	-3.8 (-8.9, 1.3)
Halvorsen ²⁵	87.8 (13.8) n = 12†	97.7 (12.9) n = 34	108.1 (13.8) n = 46	-9.9 (-18.8, -1.0)	-20.3 (-29.3, -11.3)	-9.9 (-18.8, -1.0)
Doyle ³⁰	81.6 (18.7) n = 33*	92.9 (12.8) n = 114	99.4 (9.5) n = 37	-11.3 (-16.9, -5.7)	-17.8 (-24.8, -10.8)	-6.5 (-11.0, -2.0)
Vrijlandt ³¹	90.1 (19.8) n = 8‡	99.2 (17.9) n = 12	109.6 (13.4) n = 48	-9.1 (-27.0, 8.8)	-19.5 (-30.5, -8.5)	-10.4 (-19.7, -1.1)

Abbreviations: BPD, bronchopulmonary dysplasia; CI, confidence interval.

*BPD determined by ventilator dependency, oxygen requirement >28 days and chest x-ray consistent with Northway Stage 3 or 4 changes.⁴

†BPD group had oxygen requirement at 36 weeks; the remainder in this table are considered to have no BPD, although 24 of the preterm group with no BPD had oxygen dependency at 28 days.

‡BPD defined as need for oxygen at 28 days and chronic changes (not specified) on chest x-ray; data only for males in both preterm groups.

fluenced the results. In their study, the preterm group had reductions in variables reflecting flow, and these were worse with increasing severity of BPD. Within the preterm group, the FEV₁ was lower in the moderate/severe BPD subjects compared with the remainder (Table 1). Rates of asthma were higher in the preterm cohort compared with the controls, but rates were not reported separately for BPD and non-BPD preterm subjects.

Doyle and coworkers³⁰ studied 147 survivors of birth weight <1500 g from the Royal Women's Hospital, Melbourne, who were born during 1977 to 1982 and who had respiratory function tests at a mean age of 18.9 (SD 1.1) years. Thirty-three (22%) had BPD in the newborn period, defined as in the original Northway study.⁴ There were also 37 NBW controls with respiratory function tests. All respiratory function variables reflecting airflow were substantially diminished in the BPD group, but lung volumes were not significantly different. Within the preterm group, the FEV₁ was lower in the BPD subjects than in preterm controls, and both groups were lower than NBW controls (Table 1). More preterm subjects in the BPD group had reductions in airflow in clinically important ranges (eg, FEV₁ <75% predicted, BPD 30.3%, no BPD 7.9%, $\chi^2 = 11.4$, $P = 0.001$; FEV₁/FVC <75%, BPD 42.4%, no BPD 15.8%, $\chi^2 = 10.7$, $P = 0.001$).

Vrijlandt and coworkers³¹ reported the results of respiratory function tests in 42 preterm (<32 weeks or <1500 g birth weight) subjects from 2 hospitals in The Netherlands at 19 years of age and compared the results with 48 nonrandomly selected, "healthy," term controls. The respiratory function of the preterm subjects was mostly in the normal range (eg, FEV₁ mean 95.4 [SD 15.9] % predicted) but the controls were better than expected (eg, FEV₁ mean 109.6 [SD 13.4%]), and hence the preterm subjects were significantly lower than the controls. In this study, the preterm group also showed some reductions in exercise capacity and diffusing capacity of carbon monoxide compared with the controls.

Contrasting the results for FEV₁ from these four studies, shown in Table 1, the sizes of the differences within the preterm groups between BPD and non-BPD subjects, and between both preterm groups and controls are similar. However, the largest differences between children with and without BPD were found in the Northway study,²⁹ which reflects survivors from a different era of intensive care than the other three studies.^{25,30,31} For the study of Vrijlandt and coworkers,³¹ data for preterm subjects with and without BPD were only reported for males (Table 1). The size of the difference between these two preterm groups in their study³¹ was similar to the other two contemporaneous studies,^{25,30} but not statistically significant because of the smaller sample size.

In another study of subjects who were not quite as old as the previous four studies (15 years of age), Anand and coworkers³² measured respiratory function of a cohort of 128 VLBW infants born in 1980 to 1981 from the region around Liverpool and compared the results with age-, sex-, and school-matched controls who were not VLBW (lowest birth weight 2098 g). FVC, FEV₁, FEF_{25 to 75%} were measured using a portable spirometer. They found significant differences between the groups for FEF_{25 to 75%} and the FEV₁/FVC ratio, but

not the FVC or FEV₁. In contrast with the results comparing older subjects with and without BPD in Table 1, Anand and coworkers³² did not find any substantial difference between the 83 VLBW subjects who had required respiratory support in the newborn period compared with the 45 VLBW subjects who had not required respiratory support, but they did not report results separately for the 8 children with BPD.

Changes Within the Same Cohort Over Time

There are few studies with longitudinal data in the same preterm subjects, and only one that has reported changes from early school age up to late adolescence/early adulthood.³⁰ In this study, data at 8 years and 18+ years of age in 129 subjects of birth weight <1500 g were described; 29 of the 129 subjects had BPD. Compared with respiratory function variables measured at 8 years, the only variable with a statistically significant difference over time in BPD subjects was a larger fall in the FEV₁/FVC ratio between 8 and 18 years of age compared with non-BPD preterm subjects (mean reduction 3.4%, 95% CI 0.2% to 6.7%). Active smoking was associated with a statistically significant reduction, and birth weight SD score was associated with a significant increase in the FEV₁/FVC ratio between 8 and 18 years. Adjusting for these variables increased the statistical significance of the difference in the reduction in the FEV₁/FVC ratio between BPD and non-BPD subjects (adjusted mean reduction 4.8%, 95% CI 1.7% to 7.9%).

Effect of Surfactant

With the introduction of surfactant in the 1990s, survival rates in ELBW/very preterm babies have increased dramatically.¹ In the small number of children enrolled in clinical trials who subsequently had respiratory function tests, the effect of surfactant administered soon after birth on respiratory function in childhood has been reported to be minimal,³³ or possibly beneficial.³⁴ Moreover, the nature of BPD has also changed in recent times, with the advent of the "new BPD,"³⁵ which is characterized more by alveolar arrest rather than by pulmonary fibrosis and cyst formation typical of BPD in earlier times.

Doyle and coworkers³⁶ reported the results of a geographical cohort study of 298 consecutive ELBW/very preterm survivors born in Victoria in 1991 to 1992. Exogenous surfactant was first used in Victoria in March 1991. Respiratory function was measured on 81% (240/298) ELBW/very preterm children at a mean age of 8.7 (SD 0.3) years; there were no substantial differences in respiratory function results between the 92 subjects treated and the 148 not treated with surfactant.

Effect of Smoking

Respiratory function in ELBW subjects who smoke in early adulthood has been reported to be worse than in those who

do not smoke; Doyle and coworkers³⁷ reported the results of respiratory function at a mean age of 20.2 years of a cohort of 44 of 60 consecutive ELBW subjects born during 1977 to 1980 at the Royal Women's Hospital, Melbourne. Respiratory function had also been measured on 42 of the 44 subjects at 8 years of age. Respiratory function was compared between the 14 smokers and the 30 nonsmokers. Several respiratory function variables reflecting airflow (FEV₁/FVC, V_{EMAX75%}, V_{EMAX50%}, V_{EMAX25%} and FEF_{25-75%}) were significantly diminished in smokers. The proportion with a clinically important reduction in the FEV₁/FVC (<75%) was higher in smokers (64%) than in nonsmokers (20%; $\chi^2 = 8.3$, $P < 0.01$). There was a larger decrease in the FEV₁/FVC ratio between ages 8 and 20 years in the smokers compared with the nonsmokers (mean difference in rate of change: -8.2%; 95% CI -14.1% to -2.4). Given that the rate of deterioration in respiratory function is more rapid in ELBW smokers up to age 20 years, and the fact that cigarette smoking is detrimental to respiratory function in all subjects in adulthood,^{38,39} adults who were preterm and who smoke should have repeat respiratory function tests well into adulthood, to establish whether chronic obstructive airway disease develops more rapidly and at earlier ages.

Cardiovascular Health Problems

Blood Pressure

Very preterm survivors have higher blood pressure in late childhood and early adulthood. Pharoah and coworkers⁴⁰ measured blood pressure with an oscillometric device at 15 years of age of a cohort of 128 singletons of birth weight <1501 g born in 1980-1981 along with age-, sex-, and school-matched controls. They reported higher systolic blood pressure in VLBW subjects by 3.2 mm Hg (95% CI 0.4 to 6.0), but found no statistically significant difference in diastolic blood pressure.

In another study of 156 subjects <1501 g birth weight (mean gestational age 28.8 weeks) and 38 normal birth weight subjects (mean gestational age 40.0 weeks), at 18 or more years of age the preterm group had higher systolic blood pressure measured by a mercury sphygmomanometer by 8.6 mm Hg (95% CI 3.4 to 13.9) and higher diastolic blood pressures by 4.3 mm Hg (95% CI 1.0 to 7.6) than NBW subjects.⁴¹ In addition, ambulatory systolic blood pressure was also increased in the preterm group over a 24-hour period by 4.7 mm Hg (95% CI 1.4 to 8.0), and for both the awake (5.0 mm Hg; 95% CI 1.6 to 8.5) and asleep (3.6 mm Hg; 95% CI 0.05 to 7.1) periods. There were no significant differences between the birth weight groups for any ambulatory diastolic blood pressures. Among the VLBW subjects, there was no significant relationship between birth weight standard deviation score and any measure of blood pressure.

Hack and coworkers⁴² compared blood pressure at 20 years of age of 195 VLBW individuals with that of 208 NBW controls. After adjustment for gender, race, maternal education, and body size, the difference in systolic blood pressure between VLBW and NBW individuals was 3.5 mm Hg; the

differences were slightly larger in females than males. In their study, intrauterine growth also did not have a significant effect on systolic blood pressure within the VLBW group.

These differences in blood pressure observed in very preterm children are clinically important because, on a population basis, it has been estimated that a 2-mm Hg reduction in the diastolic BP would result in a 17% decrease in the prevalence of hypertension, a 6% reduction in the risk of coronary heart disease, and a 15% reduction in the risk of stroke or transient ischemic attack.⁴³

Other Cardiovascular Abnormalities

A range of assessments of vascular and endothelial function are associated with subsequent cardiovascular outcome in at-risk groups, and abnormalities in variables such as arterial stiffness and thickness, and pulse wave velocity may be present in early childhood.⁴⁴⁻⁴⁷ In one study of preterm girls, Bonamy and coworkers⁴⁸ investigated vascular function and structure, and blood pressure at 16 years of age in 34 subjects (mean gestational age 29 weeks and mean birth weight 1343 g) compared with 32 gender- and age-matched controls born at term (mean gestational age 40 weeks and mean birth weight 3602 g). Preterm girls had significantly higher brachial and aortic blood pressure, a narrower but less stiff abdominal aorta, and lower peripheral skin blood flow than did control infants. Although blood pressure and arterial stiffness increase with lower birth weight, and therefore presumably with lower gestational age, the rise in arterial stiffness seems to explain only some of the increase in blood pressure, and hence mechanisms other than arterial stiffness must contribute to the birth weight–blood pressure relationship.⁴⁹

Effects of Corticosteroids

Antenatal

Antenatal corticosteroid therapy substantially improves the survival rate of preterm infants and reduces many neonatal morbidities, with few side effects.⁵⁰ Higher blood pressure in adulthood has been described in several animal species after exposure to antenatal corticosteroids.^{51,52} In a cohort study of 177 preterm survivors with birth weights <1501 g from the Royal Women's Hospital, Melbourne, at age 14 years children exposed to antenatal corticosteroids ($n = 89$) had higher systolic and diastolic blood pressures than those not exposed to corticosteroids ($n = 88$) (mm Hg; mean difference [95% CI]: systolic, 4.1 [0.1 to 8.0]; diastolic, 2.8 [0.05 to 5.6]). However, few had blood pressures in the hypertensive range. Subsequently, reports from the original randomized controlled trial of antenatal corticosteroids from Auckland, New Zealand, did not find any substantial differences with antenatal betamethasone therapy in blood pressure at either 6 years of age (in 223 subjects; mm Hg; mean difference [95% CI]: systolic: -1.6 [-4.1 to 0.8]; diastolic: -0.3 [-2.5 to 1.8 mm Hg]),⁵³ or at 30 years of age (in 455 subjects; mm Hg; mean difference [95% CI]: systolic: 1 [-2 to 3]; diastolic: 0 [-2 to 1]).⁵⁴

Postnatal

Postnatal corticosteroids have acute respiratory effects in the newborn period; they help to get babies off ventilators and reduce the rate of BPD, whether used early,⁵⁵ moderately early,⁵⁶ or late.⁵⁷ However, there is much concern about their long-term effects, particularly neurological, especially when used in the first week of life rather than later.⁵⁸

In 1 study of 63 survivors at 8 to 11 years of age from a randomized controlled trial of postnatal dexamethasone, median values for FEV₁ and FVC were not statistically different between dexamethasone ($n = 35$) and placebo ($n = 28$) groups.⁵⁹ However, significantly fewer children in the dexamethasone group had an FEV₁ <5th centile (40% dexamethasone, 68% placebo, $P = 0.03$). Rates of asthma were similar in the 2 groups (29% dexamethasone, 33% placebo). In another smaller study, children treated with dexamethasone in the newborn period for 18 days ($n = 7$) had worse lung function at 15 years of age on some variables than either subjects treated for 42 days with dexamethasone ($n = 9$) or with placebo ($n = 4$).⁶⁰

From a cardiovascular viewpoint, postnatal corticosteroids are associated with cardiomyopathy in the newborn period.^{55,56} More long-term, postnatal corticosteroids seem to have little effect on blood pressure in later childhood, from ages 8 to 17 years,⁶¹⁻⁶³ despite exposure to blood concentrations that would be much higher and for much longer than would occur in a fetus of similar gestational age exposed to a course of antenatal corticosteroids. However, later cardiovascular effects of postnatal corticosteroids into adulthood are not known.

Conclusions

Very preterm survivors have an increase in hospital readmissions in the early years of life, particularly for respiratory illnesses; they have diminished airflow and airway trapping on respiratory function testing, particularly in those who had BPD in the newborn period, and in those who are actively smoking, and they have higher blood pressure and other cardiovascular differences that may lead to adverse cardiopulmonary outcomes much earlier in adult life than would normally be expected. Clearly the cardiopulmonary health of very preterm survivors should be followed later into adulthood, not only for those who are now adults, but those who will become adults in the next few decades to determine whether the changes in perinatal intensive care and the increasing number of very preterm survivors may be contributing disproportionately to the burden of adult cardiopulmonary disease in the future.

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