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Review

Respiratory outcomes for the tiniest or most immature infants

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SUMMARY

Extremely low birth weight (<1000 g birth weight) or extremely preterm (<28 weeks of gestation) infants are surviving in greater numbers as neonatal care advances. Many of these survivors, especially those who develop bronchopulmonary dysplasia, have more respiratory ill health in the first years after discharge home, reduced respiratory function and impaired exercise capacity throughout childhood and into adulthood compared with term-born controls. It is important to establish the long-term respiratory outcomes for the tiniest or most immature survivors as they grow older, since they may contribute disproportionately to rates of chronic obstructive pulmonary disease and respiratory ill-health in adulthood.

1. Introduction

Perinatal care for the tiniest and most immature infants advanced rapidly towards the end of the twentieth century, including treatments such as antenatal corticosteroids from the 1970s to accelerate fetal lung maturation [1], and exogenous surfactant after birth from the late 1980s and early 1990s to reduce respiratory distress [2,3], combined with an increased willingness to offer care [4]. Consequently more extremely low birth weight (ELBW; <1000 g at birth) [5] or extremely preterm (EP; <28 weeks of gestation at birth) [6] infants survived, despite many requiring substantial respiratory support early in the newborn period. Some survivors developed bronchopulmonary dysplasia (BPD), a disease characterised by lung injury and arrested alveolar development [7]. Given their early breathing problems, ELBW/EP survivors may be more prone to respiratory ill-health later in life.

The purpose of this article is to review the long-term respiratory outcomes for the tiniest or most immature survivors. We consider respiratory symptoms and lung function data in ELBW/EP survivors compared with term controls, and in ELBW/EP survivors who did and did not develop BPD in the newborn period. Not all studies have included only ELBW or EP survivors, so we have reviewed any studies of preterm or low birth weight children that have reported lung function data later in childhood.

2. Normal lung growth and function with age

Lung volume and function increase in healthy children, reaching a maximum in late adolescence/early twenties, and then begin to decline steadily with age (Fig. 1). Despite these changes, in the absence of lung disease, the respiratory system remains capable of maintaining adequate gas exchange for the entire lifetime [8]. However, early lung injury or maldevelopment may mean that peak lung growth is reduced, and hence respiratory symptoms might appear earlier in life, even in the absence of other lung diseases. Furthermore, toxic agents that cause lung disease, such as cigarette smoking, may lead to an earlier decline in lung function in ELBW/EP survivors.

3. Bronchopulmonary dysplasia – a changing picture

Despite the advances in the intensive care provided to ELBW/EP infants in the modern era, the fact remains that a small proportion will develop respiratory failure, and many will go on to develop BPD with an continuing requirement for oxygen at and beyond 36 weeks of corrected gestational age. Some may even require supplementary oxygen at home [9]. Prolonged periods of exposure to oxygen, even in low concentrations, and to mechanical ventilation can lead to inflammatory and other biochemical and histological changes to the lungs at a time when they should not be exposed to such insults [10]. Today the lungs of infants with BPD tend to have less fibrosis and more uniform inflation than in the past [11–13]. However, they have simplified gas exchange structures with fewer, larger alveoli, indicating disruption with alveolarisation in the developing lung [11–13]. Severe cases of BPD are also associated

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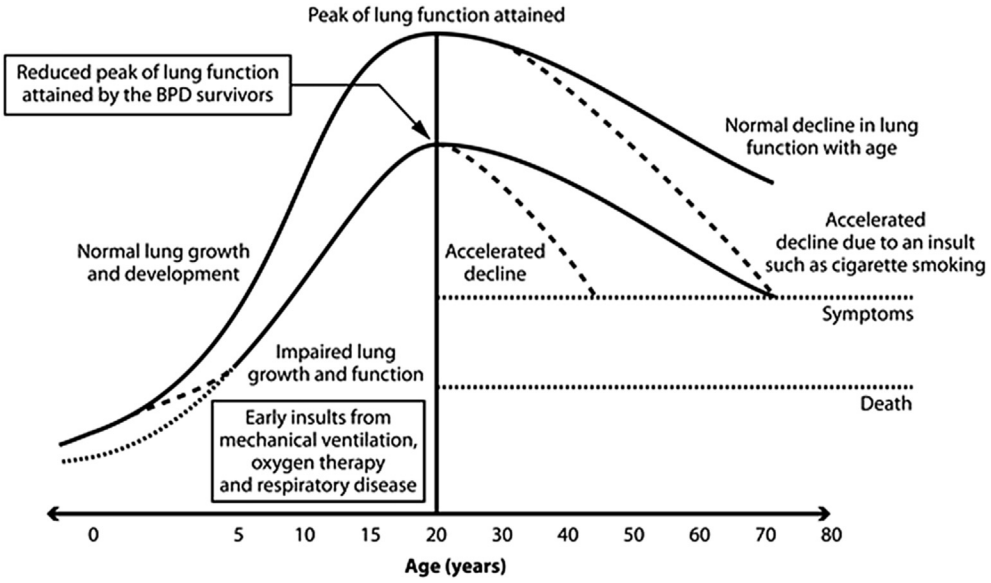

Fig. 1. Normal lung development and decline in lung function compared with abnormal or impaired development that may occur after mechanical ventilation and oxygen therapy, and development of bronchopulmonary dysplasia (BPD). (Adapted from Tager et al.[8]).

with pulmonary hypertension and abnormal pulmonary vascular development [14]. The development of BPD is now widely viewed as a consequence of lung inflammation, potentially arising from the exposure to intrauterine infection, or to mechanical ventilation and supplemental oxygen after birth [11,15].

In 1967, Northway and colleagues first reported the lung damage that occurred in infants with respiratory failure who had received mechanical ventilation [16]. They defined the impaired development that occurred after exposure of immature and vulnerable lungs to mechanical ventilation as BPD [16]. The repeated opening and closing of alveoli at higher pressures and volumes, alongside high concentrations of supplemental oxygen, resulted in cystic and fibrotic changes within the lungs of these tiny, immature infants [16,17]. As neonatal care has advanced since the 1960s, there have been improvements in the types and administration of assisted ventilation, including gentler ventilation techniques, antenatal corticosteroids and exogenous surfactant therapy that have led to changes in the epidemiology and definition of BPD. 'Old BPD' presented predominantly in the pre-surfactant era, and was characterised by alveolar septal fibrosis and inflammation, whereas 'new BPD', observed mainly in the post-surfactant era, is characterised by impaired alveolar growth, reflecting increasing prematurity of infants surviving with extremely low birth weights who have greater exposure to mechanical ventilation and supplemental oxygen [7,18].

4. Respiratory health problems

Children born very tiny or immature have more upper and lower respiratory illnesses than term-born children over the first few years of life [19,20], and more so in those who had BPD [20–23]. Asthma or recurrent wheezing are more prevalent later in life in those born very tiny or immature than in those not born very tiny or immature in some [24–26] but not all studies [27,28]. Those who had BPD sometimes have higher rates of asthma than those without BPD [29].

Children born very tiny or immature are more likely than term-born controls to require readmission to hospital for respiratory illnesses over the first few years of life, and rates of hospital readmission have risen as survival rates have increased over time [20]. Overall, respiratory illnesses are the commonest cause of rehospitalisation in the first few years [30,31], and occur more frequently in preterm survivors who had BPD in the newborn period [30]. 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 [28].

5. Respiratory function in preterm survivors

Respiratory function testing in common clinical practice primarily assesses airflow through spirometry, and lung volumes. Other tests can include diffusing capacity of the lungs for carbon monoxide, ventilation efficiency of the lung, or cardiopulmonary exercise testing, which provide additional details of lung pathophysiology.

Spirometry is generally the first clinical option because it is easily performed by most patients, with appropriate coaching by a respiratory technologist; however, children with a mental age of <5 years are less likely to produce reliable results [32]. A seated patient inhales maximally from tidal breathing to total lung capacity (TLC), and then rapidly exhales until no further volume is exhaled, which leaves a residual volume (RV) in the lung (Fig. 2) [32]. The initial high flow of gas emanates from the large airways, whereas the later flow of gas comes more from the smaller airways. If performed forcefully, a forced vital capacity (FVC) is generated. The most useful clinical value generated by a spirogram is the forced expired volume in 1 s (FEV_1) because it is easy to measure, and it is reproducible and sufficiently sensitive in detecting airway obstruction, the commonest lung function abnormality seen in children. Other measures of flow from the spirogram include the forced expiratory flow between 25% and 75% vital capacity ($FEF_{25-75\%}$), which is obtained from the slope of the spirogram when between 25% and 75% of the FVC has been expired; abnormalities in the $FEF_{25-75\%}$ reflect small airways disease. Lung volumes (TLC and RV) may be measured by body plethysmography, and the functional residual capacity (FRC) of the lung calculated. In asthma and other forms of lung disease, the RV:TLC ratio and the FRC typically rise, reflecting gas trapping within the lungs.