LONG-TERM RESPIRATORY OUTCOMES FOLLOWING PRETERM BIRTH

CONSECUENCIAS RESPIRATORIAS FUNCIONALES A LARGO PLAZO DEBIDO A LA PREMATUREZ

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ABSTRACT

Preterm birth interrupts the normal development of the respiratory system. Taken together with the lung injury that can occur antenatally such as from chorioamnionitis or postnatally by interventions such as mechanical ventilation and oxygen therapy, survivors are at risk of developing long term deficits of their respiratory system. Decrements of lung spirometry have been regularly reported in those born preterm across all gestational ages. Those who develop chronic lung disease of prematurity (also called bronchopulmonary dysplasia) are the most affected, but lung function decrements are also seen in those born at later gestation of between 33 and 36 weeks, a population that generally does not require respiratory support in the neonatal period. Besides spirometry, many other techniques have been used to assess the status of the respiratory system including measurement of static lung volumes, airway resistance and compliance, bronchial hyper-responsiveness, diffusing capacity, exhaled nitric oxide and newer imaging techniques including hyperpolarised 3-helium magnetic resonance imaging. Discussed in this review are the findings from such methods to delineate the respiratory outcomes that occur after preterm birth.

Key words: Preterm birth, lung physiology, broncho pulmonary dysplasia, chronic lung disease of prematurity, static lung volumes, imaging, multiple breath washout.

RESUMEN

El nacimiento prematuro interrumpe el desarrollo normal del aparato respiratorio. Los sobrevivientes tienen riesgo de desarrollar déficit en su función, debido a la injuria prenatal por corioamnionitis y postnatal por ventilación mecánica y oxigenoterapia. Consistentemente se ha reportado la disminución de valores espirométricos en prematuros nacidos a cualquier edad gestacional, siendo los más afectados aquellos con enfermedad pulmonar crónica del prematuro o displasia broncopulmonar. Esta alteración se observa inclusive en aquellos nacidos entre las 33 y 36 semanas de edad gestacional, una población que generalmente no requiere de soporte respiratorio en el período neonatal. Existen otras formas de evaluación de la función pulmonar además de la espirometría, tales como la medición de volúmenes pulmonares, resistencia y reactancia de la vía aérea, hiperreactividad bronquial, capacidad de difusión, óxido nítrico exhalado y nuevas técnicas de imágenes tales como la resonancia magnética con gases hiperpolarizados con 3-helio. En esta revisión se discuten los hallazgos de estos métodos para evaluar el impacto del nacimiento prematuro en el aparato respiratorio.

Palabras clave: Pretérmino, fisiología pulmonar, displasia broncopulmonar, enfermedad pulmonar crónica del prematuro, volúmenes pulmonares estáticos, imagenología, índice de aclaramiento pulmonar.

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ABBREVIATIONS:

ADC	*Apparent diffusion coefficient*
BPD	*Bronchopulmonary dysplasia*
BHR	*Bronchial hyper-responsiveness*
CLD	*Chronic lung disease of prematurity*
DL_{CO}	*Carbon monoxide diffusing capacity*
EIB	*Exercise induced bronchoconstriction*
ERV	*Expiratory reserve volume*
FeNO	*Fractional exhaled nitric oxide*
$FEV0._{5/1}$	*Forced expired volume in 0.5/1 second(s)*
FOT	*Forced oscillation technique*
FRC	*Functional residual capacity*
FVC	*Forced vital capacity*
Gaw	*Airway conductance*
IC	*Inspiratory capacity*
IRV	*Inspiratory reserve volume*
IVC	*Inspiratory vital capacity*
LCI	*Lung clearance index*
Raw	*Airway resistance*
Rrs	*Respiratory resistance*
RV	*Residual volume*
TLC	*Total lung capacity*
VT	*Tidal volume*
Xrs	*Respiratory reactance*

INTRODUCTION

Preterm (defined as less than 37 weeks' gestation) birth, a common occurrence, is associated with morbidity and mortality both in the neonatal period and beyond (1). Important long-term outcomes include neurodevelopment and respiratory health. The latter can be assessed in a variety of ways from outlining symptomology to health care utilisation to formal lung function testing. While spirometry is the most common respiratory assessment in follow-up of preterm children, increasingly more detailed testing is being used for preterm-born survivors. While previous focus has been on the extremes of prematurity, in particular those who develop chronic lung disease of prematurity (CLD), there is increasing evidence that even delivery at later gestations, including early term delivery, is associated with lung dysfunction in childhood (2). CLD is often also called bronchopulmonary dysplasia (BPD) and the terms are often used interchangeably. This review will discuss the impact of risk factors on the developing lung, including those which lead to the development of CLD, and the longer term respiratory outcomes of preterm birth with a particular focus beyond basic spirometry, the outcomes of which have been a frequent subject of recent reviews (3, 4).

EPIDEMIOLOGY

Preterm birth accounts for approximately 11% of all live births worldwide, with increasing rates in many countries (5). It is a leading worldwide cause of death in the under 5-year age group (6), accounting for over 1 million deaths in 2015. However, neonatal mortality as a result of being born preterm has decreased in both the developed and developing world, with the overall death rate decreasing from 10.5 per 1,000 live births 2000 to 7.6 in 2015 (7). Many of the deaths are due to respiratory diseases, which affect 2-3% of all newborn infants (8, 9); the rates of respiratory illness increase with decreasing gestational age. Significant progress has occurred in the management of preterm neonates including the use of maternal antenatal corticosteroid administration, exogeneous surfactant and gentler forms of mechanical ventilation (10). However, as survival improves, the longer-term outcomes including good quality of life for the survivors become increasingly important (11).

LUNG DEVELOPMENT

An understanding of lung development is key to understand why preterm infants may develop future respiratory deficits (12, 13). Normal lung development has been classified into 5 phases (14) (see Figure 1 (15)):

Embryonic gestational age 0-7 weeks.
Pseudoglandular weeks 7-17.
Canalicular weeks 17-27.
Saccular weeks 28-36 and
Alveolar weeks 36 to at least 2 years post natal age.

In extremely preterm-born infants, especially those born at <26 weeks' gestation, alveolar development has not yet commenced, thus the infant relies on respiratory saccules for their gaseous exchange. In addition, failure to produce adequate antioxidant, enzymes and surfactant, which reduces surface tension at the gas-exchanging units, often results in the development of neonatal respiratory distress syndrome (RDS) (16). The insults of extra-uterine life on the immature and fragile lungs occur at a crucial phase of lung development, resulting in subsequent abnormal alveolarisation and aberrant pulmonary vascular development (15).