

特別講演

主催 埼玉医科大学 総合医療センター 新生児科, 後援 埼玉医科大学 卒後教育委員会
平成19年2月21日 於 埼玉医科大学 総合医療センター 5F 小講堂

THE LONG-TERM EFFECTS OF LOW BIRTHWEIGHT ON LUNG FUNCTION AND STRUCTURE: IMPLICATIONS FOR RISK OF LATER LUNG DISEASE

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Human lung development takes place from early embryonic life to infancy, after which the lung grows as chest dimensions increase. It is now apparent that the development and maturation of the lung's alveoli, airways and vascular bed are all influenced by environmental factors, and that changes in their development can persist throughout life. These developmental changes have the potential to increase the risk of later respiratory illnesses and accelerated lung aging. The lung has only a limited capacity for recovery from early alterations in its structural development, such that "tracking" of reduced lung function has been detected in individual subjects from early life to maturity.

Low birthweight affects 10-15 % of all births and has been shown in numerous studies worldwide to adversely affect lung function and increase the risk of lung diseases; however, the structural basis for these effects is largely unknown. We hypothesise that factors that cause low birthweight can induce persistent alterations in lung structure, such as a reduced number of alveoli, more reactive airways or accelerated lung aging. The major causes of low birthweight are intra-uterine growth restriction (IUGR) and preterm birth. We have used sheep to explore the separate effects of IUGR and preterm birth on lung structure and function from infancy to adulthood. We have shown that IUGR impairs alveolar development, which leads to reduced numbers of larger alveoli from infancy to adulthood, with thicker blood-air barriers and evidence of the early breakdown of alveolar walls. IUGR leads to reduced alveolar support for small airways in the lung, which would increase their susceptibility to narrowing

and obstruction. Preterm birth was induced in sheep at the earliest gestational age at which lambs could survive without the need for oxygen supplementation or ventilation; this removes the confounding effects of respiratory support and allows us to determine the effects of preterm birth per se. Preterm lambs were studied from infancy to maturity when their airway reactivity was tested and lung structure assessed. Preterm birth per se altered alveolar formation in infancy but did not have long term effects; however, there was evidence of more reactive airways in adult preterm sheep, especially in those that showed slow postnatal growth.

We conclude that low birthweight can alter lung development throughout life, but that the effects depend upon the causes of the low birthweight. IUGR likely affects lung development as a result of impaired fetal nutrition, hypoxia and/or corticosteroid exposure. These factors could also affect lung development in the early postnatal period, with long-term consequences. The changes in lung structure following IUGR would be expected to increase the risk of reduced lung function later in life. Mild preterm birth per se does not lead to persistent alterations in alveolar structure, but has an apparent effect on airway reactivity in adult sheep. Our studies suggest that perinatal factors leading to low birthweight have the potential to exert permanent alterations in lung structure and function, which would be expected to increase the risk for later obstructive lung diseases. Therefore preventing or reducing the severity low birthweight should be a priority for health delivery services.

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