

Factors affecting growth of FEV₁

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ABSTRACT: *Factors affecting growth of FEV₁. P.S. Bakke.*

There is an increasing awareness that also growth in FEV₁ may be of importance to development of chronic obstructive lung disease in later life. This paper reviews current knowledge on factors in foetal and childhood life that may reduce lung growth. Passive smoking as well as malnutrition in foetal life is related to impaired lung function in later life. Birth weight is a risk factor to lung growth independent of gestational age and maternal smoking. Active and passive smoking in childhood and adolescence reduces growth. Girls seem to be more vulnerable than boys to the effect of smoking. Also host characteristics like atopy, bronchial hyper responsiveness and asthma are related to impaired growth of FEV₁. Lower respiratory tract

infections before the age of seven are also related to impaired lung growth in adult life. Although several studies have found socioeconomic status among adults related to chronic obstructive lung disease, it is not known to what extent low socioeconomic status affects growth of lung function after adjusting for risk factors like active and passive smoking and lower respiratory tract infections. Normal lung growth varies with age and between male and female. The importance of the various risk factors may differ depending at what point in the lung growth they come into play. Limited data is available about the interrelationship between the risk factors and the mechanisms through which they work.

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Introduction

Studies on risk factors to chronic obstructive pulmonary disease (COPD) have traditionally focused on the decline of lung function, primarily in terms of the forced expiratory volume in one second (FEV₁). However, there is an increasing awareness and focus on early life. Also growth of FEV₁ can influence the risk of developing COPD. An impaired growth of FEV₁ will result in a reduced maximal attained lung function. A subsequently smaller fall in FEV₁ is then required before the subject develops COPD. Risk factors to a reduced growth in FEV₁ may also work to reduce the length of the period with stable lung function in early adulthood, the so-called plateau phase, and to increase the subsequent decline in FEV₁ [1].

Factors related to growth of FEV₁ may come into play in foetal life, childhood and adolescence. The objective of this paper is to review current knowledge of factors that might influence growth of lung function. First the normal lung development will be described. Lung growth is an ongoing process and the paper is based mainly on data obtained from longitudinal studies in which at least two measurements on the same individual have been performed.

Normal lung development

Embryonic development

During the earliest embryonic stages, the lung develops as an out growth from the ventral wall of

the primitive foregut endoderm [2]. Following the formation of the trachea and the main bronchi the five lobes and 18 major lobules are formed. By the end of the 16th week of gestation airway division down to the level of the terminal bronchioles is completed. Between the 17th and 20th week of gestation there is a rapid lung growth during which the lungs are twice as large relative to body weight as at term. The first alveoli appear at the 30th week of gestation. At birth about 50% of the adult number of alveoli is formed [3]. Postnatally, the number of alveoli is completed by two years of age. But during this period there is a rapid increase in alveolar size and complexity. About 95% of the adult alveolar surface is formed postnatally [3].

Postnatal development

The newborn lung is not an adult lung in miniature, and considerable remodelling occurs [2]. Data on development of lung function before the age of 6 years is limited [4]. From the age of 6 to the age of ten years the growth of FEV₁ seems to be linear. At about this age there is an increase in the velocity of the growth of FEV₁ in both boys and girls.

The s-shaped velocity curves indicate a rapid and non-linear growth during adolescence (figure 1).

The growth velocity for girls peaks about 2 years earlier than for boys and at a lower level (figure 1). The growth velocity for girls decreases to zero at about the end of the teens, while for boys it continues into the mid twenties [5, 6]. Then they have reached the plateau phase. It is worth noting

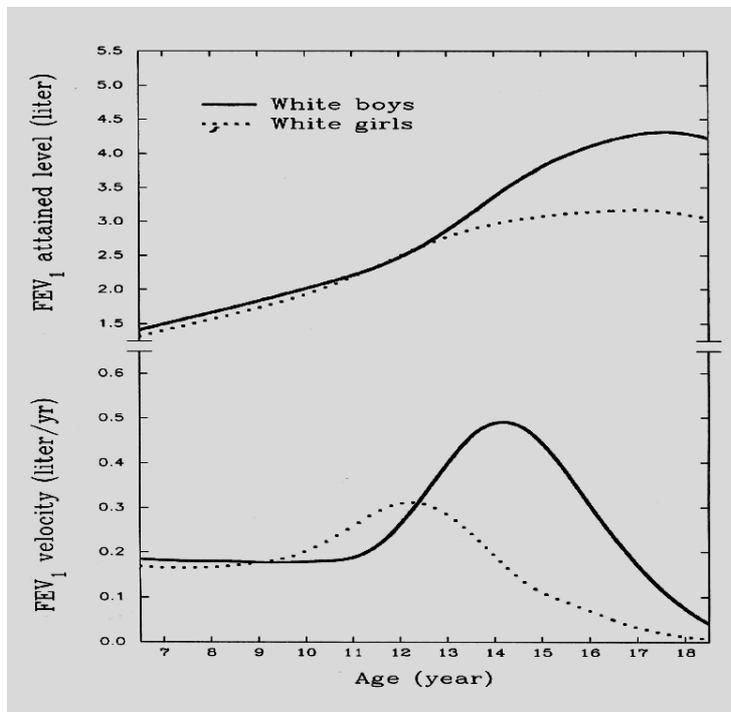


Fig. 1. - Sex specific mean FEV₁ and annual velocity as a function of age in white children 6 to 18 years of age [taken from reference 5].

that there are large inter individual differences in these patterns [5]. The configuration of the adult female lung is the result of proportional growth of its airways in relation to its parenchyma, but that of the male lung is the result of dyasynapsis that is the growth of airways that has lagged behind that of lung parenchyma [7].

Factors that might affect growth of FEV₁ in foetal life

There are a variety of diseases and malformations that can lead to reduced lung growth in foetal life [2]. In table 1 some examples are given. One requirement for normal lung growth is adequate intra-thoracic space. When abdominal contents move into this space it leads to pulmonary hypoplasia. Similarly, oligohydromnios is associated with narrow airways. The earlier the onset of the reduction in amniotic fluid the more severe the impaired lung function. Hence, an adequate amount

Table 1. - Factors that might affect lung growth in fetal life

Malformations
examples:

- Congenital diaphragmatic hernia
- Oligohydromnios
- Renal agenesis

Environmental factors

- Maternal smoking
- Malnutrition

Atopy

fluid within the airways seems necessary for optimal airway growth [8]. Foetal lung growth is also subject to hormonal influence. Surfactant production is stimulated by glucocorticosteroids and thyroid hormone and inhibited by testosterone. Hence, male human foetus lags behind female foetus by 1-2 weeks with respect to lung maturation [9].

These conditions are difficult to prevent. More preventable conditions that affect lung growth are maternal smoking and malnutrition.

Maternal smoking

It has been a debate on whether maternal smoking during pregnancy is an independent risk factor to reduced lung function as children exposed to parental smoke also tend to have been exposed in foetal life [10]. To avoid the potential confounding effect of postnatal tobacco exposure LØDRUP CARLSEN *et al.* examined lung function in 800 healthy newborn babies [11]. They observed that babies of smoking mothers had impaired flow volume curves compared to babies

of non-smoking mothers. Similar finding have also been reported by other studies [12]. Maternal smoking is also related to reduced birth weight, which is associated to reduced growth of FEV₁ [13]. Hence, the effect of maternal smoking could work through reduced birth weight. However, also after adjusting for birth weight was maternal smoking during pregnancy related to impaired lung function at birth [11].

In the foetal rat maternal smoking reduces the ratio of lung weight to body weight, total lung DNA and the number of alveoli, and the amount of parenchymal elastic tissue [14].

Malnutrition

Animal studies have shown that malnutrition during critical periods of lung development has permanent effect on lung structure [2]. A study from India [15] comparing lung function in adults aged 38-59 years to hospital registers containing their birth weight, observed that FEV₁ as adults fell by decreasing birth weight. As smoking was practically non-existing among women in the study area, the reduced birth weight, affecting one third of the babies, was taken to reflect poor nutritional status. The study showed male foetus to be more vulnerable to malnutrition than female foetus. A recent, brief report from China noted a similar finding although no trend between lower birth weight and lower FEV₁ as adults was observed [16].

Factors affecting lung growth in childhood and adolescence

Several factors may affect lung growth after birth (table 2). They will be briefly discussed below.

Table 2. - Factors that might affect lung growth after birth

Low birth weight
Smoking
– Active
– Passive
Asthma
Bronchial hyper responsiveness
Atopy
Lower respiratory tract infections
Low socioeconomic status

Passive and active smoking

Several studies have examined the effect of passive smoking on lung growth. In a recent meta analysis of 21 studies it was concluded that children whose mothers smoke exhibit clear deficits in lung function [17]. The greatest effect is seen on the mid end expiratory flow rather than for FEV₁. This may indicate that passive smoking has a particularly negative effect on the small airways. The largest of the cohort studies examining the effect of passive smoking also found a small, but significant effect on FEV₁ growth in the order of –3.8 ml/year, in the age span of 6-18 years [18]. The authors also assessed retrospectively the relative contribution of the current passive smoking with that in the first 6 years of life. The authors concluded that in school age children the reduced growth in lung function was partly associated with earlier exposure and partly with current.

No data is available as to how change in passive smoking may affect the subsequent growth in lung function. Nor is the relative contribution of passive smoking in foetal life versus in childhood on growth of lung function clarified.

The effect of active smoking has been examined in 10 000 children examined with spirometry annually from the age of 6 to the age 18 years [19]. Girls were more susceptible to smoking than boys. This gender difference could be due to sex specific reporting bias or differences between the sexes in amount inhaled per cigarette. However, the effect of smoking in girls could also be modulated by hormonal changes reflected in the stage of the subject's menstrual cycle or to the onset of menarche during adolescence [20]. Finally, girls may be more vulnerable to smoking than boys as the FEV₁ growth peaks at an earlier age in girls than in boys.

Birth weight

BARKER *et al.* [21] compared adult lung function and death from COPD to birth certificates in men born between 1911 and 1930 in Hertfordshire, England. Of the 1174 men still alive at age 59-70, 73% participated in the study. The study showed that the FEV₁ increased with increasing birth weight after adjusting for age, height, smoking habits and social status. COPD death rate fell with

increasing birth weight. These findings may imply that there is a causal relationship between foetal growth and adult lung function. Alternatively babies with low birth weight may be more susceptible to lung damage and exposure to external agents, for instance infections, subsequently causing impaired lung function. Others [13, 22, 23] have observed a relationship between reduced birth weight and impaired lung function in children up to the age of 5-11, independent of gestational age and maternal smoking [13]. A recent Australian cohort study [24] of 210 pre term children also observed an association between low birth weight and reduced lung function at age 14 years. However, even in the cohort of children with very low birth weight (500-999 g) the mean (SD) level of FEV₁ in percent predicted was normal, being 93% (8%). The children with the very low birth weight had caught up with the children with birth weight above 2500g, and this had mostly happened between the age 8 and 14 years. This finding may imply that children with impaired lung function due to low birth weight may compensate with an increased growth in the period of rapid lung growth. Whether they later on as adults may experience an increased decline in FEV₁ is not clear.

Asthma, bronchial hyper-responsiveness and atopy

In a cohort of 600 children examined annually with spirometry for 13 years from the age of 5-9, a total of 67 children reported asthma during the course of the study [25]. Male asthmatic children showed a lung growth within the normal range, while female asthmatics showed a development of FEV₁ that was slower than non-asthmatic females. The authors estimated that a female who developed asthma at age 7 would experience a 5% reduction in FEV₁ by age 10 and a 7% deficit at age 15. A more severe influence of asthma in female lung growth has also been observed by others [26]. The reason for this gender difference is not clear. However, again, they may be related to hormonal and immunological differences by gender [20].

One may speculate that the impaired lung growth in asthmatics may also work through airway inflammation and atopy. However, a recent Danish study following 498 children, aged 7-17 years at enrolment, for 6 years found asthma related to impaired FEV₁ growth also after adjusting for bronchial hyper responsiveness and atopy to house dust mite [27].

Several longitudinal studies have found that bronchial hyper responsiveness to cold air [28] and to histamine [27, 29, 30] affects the growth of spirometric variables. The Danish study also found atopy associated to reduced lung growth after controlling for asthma and bronchial hyper responsiveness [27].

Hence, it seems that asthma, bronchial hyper responsiveness and atopy are independently related to impaired growth of pulmonary function. Whether they are casually related or act as markers for impaired lung growth is not clear. The Danish

study indicates that atopy predisposes susceptible individuals to reduced growth. The possibility that an inherited atopic status may affect lung growth already in fetal life cannot be ruled out [1].

Lower respiratory tract infection (LTRI)

Three types of studies have examined the effect LTRI on lung growth [31]; 1) follow-up studies of children with LTRI; 2) population studies of children and adults with retrospective ascertainment of LTRI; and 3) population studies of adults with independent ascertainment of LTRI. The second type of studies is obviously subject to recall bias and will not be reviewed further. The best controlled and largest of the first type of studies [32-34] have shown a deficit of FEV₁ of 4-9% and in FEV₁/FVC ratio of 2-3% 7-10 years after bronchiolitis due to respiratory syncytial virus. The largest of the third type of studies is based on a cohort of 18 000 persons born in 1957 and followed for 35 years [35]. Independent verification of pneumonia was obtained when subjects were 7 years old. After controlling for sex, height and smoking FEV₁ was reduced by on average 102 ml and FVC by 173 ml. There was no change in the FEV₁/FVC ratio indicating a reduction in lung volume rather than an obstructive defect. The study did not find any difference in reduced lung growth between those suffering from pneumonia below or above the age of 2 years. Other studies have found the greatest effect of pneumonia on reduced lung growth in those being under 2 years when the pneumonia occurred [21, 36].

Hence it seems clear that LTRI in childhood is related to lower lung function as an adult. However, it remains to be clarified whether the childhood pneumonia causes the observed deficit in lung function or the pneumonia occurs more frequently in children with a lower pre-morbid lung function.

Socioeconomic status

In adults low socioeconomic status has been found to be a risk factor of COPD and respiratory symptoms, after controlling for smoking habits and occupational airborne exposure [37, 38]. Low socioeconomic status may cause increased decline in FEV₁ in adults. However, as people tend to stay in the socioeconomic group they are born into, one may speculate that factors related to low socioeconomic status might work in childhood causing impaired growth and thereby increased risk of COPD in adult life. It is not known to what extent low socioeconomic status affects growth of lung function after adjusting for risk factors like active and passive smoking and lower respiratory tract infections. Diet low in antioxidants is related to low socioeconomic status and may be a risk factor to reduced growth of FEV₁ [39].

Conclusion

This brief review has shown that several factors both during foetal life and childhood may af-

fect growth of FEV₁. Host characteristics like atopy, bronchial hyper responsiveness and asthma are independent risk factors to reduced growth. Active and passive smoking are important preventable risk factor to reduced growth of FEV₁. In developing countries malnutrition during foetal seems to be of importance. Also lower respiratory tract infections before the age of 7 years is associated with reduced lung function in adult life. As the rate of lung growth is non-linear the importance of the risk factors to reduced growth may also vary with the point of time of the lung growth they occur. Limited data is available about the interrelationship between these risk factors and the mechanisms through which they work.

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