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Effects of nutrition, growth hormone disturbances, training, altitude and sleep on lung volumes

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CONTENTS

Various modulating factors have been shown to affect postnatal lung growth and development in humans and other mammalian species. Therefore, normative pulmonary function data should ideally indicate the environmental conditions of life. This paper will review current knowledge on the effects of nutrition, growth hormone disturbances, training and altitude on lung volumes in children and adults. Furthermore, the impact of sleep states on lung volumes is considered. The present review is a background paper of a consensus document on measurements of lung volumes in humans.

Effect of nutrition on lung volumes

Our knowledge of the effect of disturbances in nutrition, either inadequate nutrition or overnutrition, on lung growth has been provided mainly by animal studies.

Inadequate nutrition and lung growth in animals

The effects of inadequate nutrition on lung volumes have been studied in two species with differing lung maturity at birth: in rats, which have immature lungs at birth; and guinea-pigs, in which lung growth is advanced at birth.

In rats, the adverse effects of inadequate foetal nutrition can be summarized as follows: nutritional status during pregnancy affects foetal lung growth, with a greater effect in late pregnancy resulting in small and hypocellular lungs at birth [1]. Inadequate nutrition during the first 21 days of life is associated with a decrease in cell division [2], diminished alveolar formation, smaller lung volumes, and decreased accumulation of elastin [3, 4]. This is especially marked with insufficient protein nutrition [3, 4]. Late postnatal nutritional insufficiency after weaning affects cell size, but not cell division [5]. The structure of the lung parenchyma of rats restricted in protein during early and late postnatal periods has been studied after refeeding for 11 weeks. All parenchymal subcomponents grew consistently with normal volume and surface densities [6, 7] as compared to controls, indicating that recovery occurs after refeeding.

In guinea-pigs, the greatest effects of nutritional insufficiency occur prenatally. Prenatal starvation is associated with a dramatic decrease in neonatal survival rate, and airspace volume is significantly reduced in live neonates [8]. Despite normal postnatal feeding, residual reductions in alveolar surface area persist. The effects of neonatal and weaning starvation on lung growth are less marked; and after refeeding, full recovery in lung dimensions is noted in adulthood [9].

Vitamin D deficiency in dams and pups induces rickets in young rats, and rachitic rats have low lung weight and lung compliance [10]. These data raise the question of the role of vitamin D deficiency in respiratory disorders accompanying fat soluble vitamin malabsorption syndromes.

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Inadequate nutrition and lung growth in humans

Conflicting data have been reported on the effect of intrauterine growth retardation on lung volumes in children. CHAN *et al*. [11] found that vital capacity (VC) was normal in children of low birth weight, whereas RONA *et al*. [12] reported that forced vital capacity (FVC) was decreased after adjustment for gestational age, parental smoking, and social factors.

To the best of our knowledge, no functional and/or postmortem lung volume data are available for insufficiently nourished infants during the postnatal active period of alveolar multiplication and elastin accumulation, *i.e*. the first 2 yrs of life [13–16]. We may speculate that adverse effects will be greatest in humans when nutritional insufficiency occurs during late gestation and the first 2 yrs of life. Adverse effects of inadequate nutrition on the development of lung function in the growing human lung may be expected to be associated with low lung volumes and low lung compliance, and an increased ratio of maximal expiratory flow rate to lung volume. This speculation is supported by functional data reported in postnatally inadequately nourished hamsters, in which maximum expiratory flow at 50% of the VC ($\dot{V}'_{max,50}$) was half that found in control animals. However, since VC was dramatically diminished in inadequately nourished hamsters, when $\dot{V}'_{max,50}$ was expressed in relation to VC, it was much greater in inadequately nourished animals than in controls [17]. Thus, when postnatal alveolarization is suppressed, relative airflows are high. The lung growth pattern related to nutritional insufficiency is the direct opposite of the lung growth disorders caused by hypoxia at high altitudes, where alveolar growth is increased [18] and associated with disproportionate lung-to-airway size [19].

The functional data available in humans concern inadequately nourished school children [20]. Thirty wasted children, with a weight less than 80% predicted for height, indicating acute nutritional insufficiency were studied. In addition, 135 stunted children, who had been inadequately nourished in the past, were studied. Peak expiratory flow (PEF) rate was the only mechanical parameter measured. PEF was not decreased in stunted children, indicating that previous nutritional insufficiency does not disturb growth-related increases of PEF, whereas PEF was decreased in wasted children, presumably because of muscle weakness. Future investigations, which compare normally and inadequately nourished growing infants and children of identical racial groups, should include lung function development with regards to lung volume, lung compliance, and relative flow rates. Furthermore, effects of refeeding in inadequately nourished children should be investigated.

The effects of nutritional insufficiency and refeeding on lung volumes and diaphragmatic contractile properties were studied in severely inadequately nourished patients with anorexia nervosa [21]. Fifteen female patients were studied at a mean (±SD) age of 24.9 (±8.7) yrs. FVC and forced expiratory volume in one second (FEV_1) were in the low normal range upon hospital admission, and increased significantly with a nutritional support of 30 days. Other lung volumes did not change. Diaphragmatic function was reduced initially and increased with nutrition.

Effect of nutritional changes on lung volumes

Information is scarce with regard to the potential effects of generational changes in diet, such as migrant populations. RAVEN *et al*. [22] have shown that third-generation Japanese-Americans have lung volume corrected for hei-ght more comparable to Caucasians than native Japanese. MASSEY and FOURNIER-MASSEY [23] studied Japanese-Ame-ricans aged 20–80 yrs. With regards to anthropometry and pulmonary function, they observed that younger Japan- ese-Americans resembled Caucasians more, and older Japanese-Americans resembled the Japanese from Japan. However, environmental factors other than changes in diet may occur in migrant populations to explain anthropome-tric and pulmonary function changes.

Overnutrition and lung growth in animals

Obesity induced by a high fat diet in male newborn rats alters biochemical properties of the lung and leads to structural changes [24]. At 8 weeks of age, obese rats display a significant increase in fixed lung volumes and in ratio of lung volumes to body weight and to body length^3, with enlarged alveoli compared to controls but a normal total number of alveoli [25].

Overnutrition and lung volumes in children

Few studies have addressed the question of the effects of obesity on pulmonary function in children. In obese children with 135–140% and 125–205% ideal body weight (IBW), lung volumes were normal [26, 27]. In more markedly obese children (147–300% IBW), a significant reduction in expiratory reserve volume was reported [28]. In the latter study, other lung volumes and maximal static pressure were normal, but expiratory flow rates and single breath diffusing capacity were decreased [28].

Effect of growth hormone disturbances on lung volumes

The effects of decreased growth hormone on lung volumes have been studied in children [29, 30] and adults [31, 32]. Studies in adults have related to excessive levels of growth hormone [32–34].

Lung volumes in growth hormone deficiency

In children who had a growth hormone deficiency, VC, functional residual capacity (FRC), and total lung capacity (TLC) were appropriate for the small statures of the patients [29, 30]. In children studied before and after treatment with human growth hormone, compensatory growth occurred, associated with increases in TLC and VC appropriate for the linear growth [29, 30].

In growth hormone deficient children, appropriate lung volumes for their small statures were associated with a low lung elastic recoil for their age [30], high carbon monoxide diffusion constants for their age [30], and closing volume and arterial partial pressure of oxygen in relation to their age [29].

Patients with adult onset hypopituitarism were found to have reduced lung volumes [31]. One study reported increased lung elastic recoil [31]. However, in another study, the pressure-volume relationship of the lung was normal when lung volume was related to the measured TLC [32]. Inspiratory muscle strength, airflows and gas exchange were normal [31, 32].

Lung volumes in patients with excessive growth hormone

In acromegalic adults, all lung volumes are increased in relation to standing height [32–34]. Despite the large lung volumes, diffusing capacity was normal [33, 34], suggesting an increase in the size of alveoli [33]. However, it has been argued that the transfer factor of the lung for carbon monoxide ($T_{L,CO}$) may not be reliable for the interpretation of the mechanisms of lung growth in cases of large lung volumes [34]. A recent study, confirming previous findings [32, 33] shows that pulmonary distensibility was normal [34] and suggests that large lung volumes of acromegalic patients should be achieved by an increase in alveolar number rather than an increase in size. However, only morphometric studies of the lungs of acromegalic subjects could answer the question of the mechanisms of alveolar changes, either hyperplasia or hypertrophy, related to excessive levels of growth hormone during adulthood.

Animal studies, either in growing guinea-pigs [35] or adult rats [36] treated with growth hormone, did not show disproportionate enlargement of the lungs. Growth hormone might be active only in diseases in which secreting tumours deliver large amounts of hormones [33, 37].

Effect of training on lung volumes

The animal studies available have provided conflicting data with regards to the effects of sustained exercise on enhancement of lung growth [38, 39]. In humans, studies of the effects of training on lung volumes have been performed both in boys and girls, pre- and postpubertal, tested either cross-sectionally or longitudinally.

Among physical activities, swimming has been the most extensively studied and appears to be the only one associated with a marked increase in lung volumes.

Effect of swimming on lung volumes in children and young adults

Since the early 1960s, it has been repeatedly observed that lung volumes are larger in young swimmers [40–51]. This has been reported in all cross-sectional and longitudinal studies except one [50]. One study reported lung volume measurements at the start of swimming training in boys aged 10 yrs. Lung volumes were already increased, suggesting that large lungs may be a requirement for becoming a top swimmer [43].

All of the other studies have been performed after more than 1 yr of training. The youngest group, training for more than 1 yr included 7–8 year old girls [48]. In this group, VC, FRC and TLC were significantly greater than in an age-matched control group with similar residual volume (RV)/TLC and FRC/TLC ratios. The increase in lung volumes was more marked in older girls, who had trained longer [48].

Three longitudinal studies have been performed over 1 [49], 3 [40] and 5 yrs [42]. In the 1 yr study [49], the heights of the girl swimmers' were distributed throughout the normal range initially and 1 yr later. In contrast, the values for VC and TLC exceeded the normal range after 1 yr in 11 out of 17 subjects. In the 3 yr study [40], both boy and girl swimmers were taller at a given age, and the difference between groups became greater in the older children. Swimmers also had larger TLCs as a consequence of larger values for VC. In the 5 yr study [42], in girls with a mean age of 11.5 yrs at the start of the study, VC increased during continued training to a significantly greater extent than expected with regards to the normal growth in height. In this study, some evidence was found for a relationship between the degree and duration of training and the increase in VC.

A group of girl swimmers who had undergone 2.5 yrs of intensive swimming training were the subjects of a follow-up for 10 yrs [44]. When last examined 7 and 10 yrs after the original study, all the girls had given up swimming training. Interestingly, the increased values for VC observed at the first study remained unchanged.

In addition to lung volumes, other lung function parameters have been studied in young swimmers. Maximal static pressures were not significantly increased in prepubertal girl swimmers [48, 49]. Chest wall measurements were noted to be significantly larger in prepubertal girl swimmers compared to controls. Maximal expiratory flow rates (FEV_1, maximum mid-expiratory flow rate (MMFR)) were significantly increased both in boy and girl swimm-ers compared to controls, to a similar extent as were VC and TLC [40, 41, 47]. $T_{L,CO}$ at rest has been shown to be increased in trained swimmers compared to controls [46, 47], to a similar extent as was TLC. No study has measured alveolar distensibility in child swimmers, but normal alveolar distensibility was reported in young adult swimmers [52]. The finding of a normal alveolar distensibility suggests that large lungs in young adult swimmers could be achieved by an increase in alveolar number [52].

Effects of other sports and of enhanced physical education in children

The effect of running training on lung volumes has been studied during a short period (4 months) [53] and a long period (26 months) [54] in boys starting training at 11 yrs of age. The short period of running training did not influence TLC. In contrast, the longer period was associated with a significant increase in VC over that expected from the age-dependent increase in body height. Recently, a large controlled study was performed to test the impact of an enhanced physical education programme upon FVC in primary school children during 6 yrs of follow-up from 7–12 yrs of age [55]. Physical activity was enhanced by a vigorous experimental programme of 5 h of additional physical education per week, taught by a specialist. The enhanced physical education programme had a small positive effect upon the FVC, averaging 3.2% across all 6 yrs.

Effects of sporting activity in adults

It was reported that lung volumes were not increased in young adult runners in contrast to observations in young adult swimmers [52]. Lung volumes were not affected by rowing activity in adults [56].

Effects of ventilatory muscle training in adults

Lung volumes have been studied after training programmes which were limited to the ventilatory muscles in young adults [57, 58]. Five weeks of ventilatory muscle strength training over the entire VC range led to only a small increase in VC, despite more than a 50% increase in maximal static inspiratory pressures at FRC [57]. The small increase in VC could be explained by lung stiffness at large volumes. Another study showed that normal subjects can increase their VC and TLC over a 6 week training period by performing multiple daily sustained inhalations to TLC [58]. The increase in lung volumes could be attri-buted to greater maximal shortening of the inspiratory muscles [58]. Such a mechanism could explain the in-crease in VC in breathholding divers [59].

Effect of altitude on lung volumes

No consistent differences in lung volumes (TLC, VC, FRC and RV) attributable solely to altitude have been uncovered in studies of residents at altitudes from sea level to 1,800 m [60–62]. Increases in lung volumes are, however, a part of the adaptive response to high altitudes (at Š3,000 m). The effects of altitudes between 1,800 and 3,000 m on lung volumes are unknown.

Hypoxia occurs at high altitudes because of the reduced partial pressure of oxygen in the atmosphere. The adaptive mechanisms used to compensate for this hypoxia are dependent on the altitude, on whether the exposure to high altitude is temporary or prolonged, and on whether the individual acclimatized during growth. Pulmonary adaptations in residents at high altitudes classically include hyperventilation, increases in $T_{L,CO}$, polycythaemia, and increases in lung volumes. Detailed reviews of all the adaptations to high altitude are available [63–66].

Studies consistently show larger measured lung volumes in natives of high altitudes, which are not explained by race or body size [63, 65, 67–69]. The most commonly reported volume in these studies is VC, but studies also show increases in TLC, FRC and RV in high altitude natives.

The magnitude of the increases in lung volume is hard to quantify because of differences in body size and race of the subjects and the variability between studies. Average increases in TLC in highland natives compared to lowland natives range 7–15%. Compared to the changes in TLC, the increases in VC are smaller and those of FRC and RV larger.

In residents of high altitude, the increase in lung volume varies depending upon when the acclimatization occurred and the duration of the exposure to high altitude. Increase in VC are about the same for individuals who acclimatized and lived at high altitude during growth regardless of whether or not they were born at high altitude [63, 65, 70]. Lowlanders who acclimatize to high altitude as adults have smaller VCs than highland natives.

High altitude children aged >5 yrs had larger VCs than lowlanders [70, 71]. The differences between VCs of highlanders and lowlanders increased until 21 yrs of age [70]. VC did not appear to change if the stay at high altitude was less than 3 yrs [70]. This information suggests that the larger lung volumes in native highlanders is acquired as a result of exposure to hypoxia during growth, rather than being genetically determined. One morphometric study of the lungs of five native highlanders found an increase in the number and size of the alveoli in comparison with sea level controls [72]. The larger lung volumes seen in high altitude natives are not accompanied by increased rates of airflow [16].

No measurement of lung volume is available in infants born at high altitude. Mortola *et al.* [73] reported increa-sed compliance of the respiratory system (C_{RS}) in healthy full-term infants born in La Paz, Bolivia. This increase was not found in an ethnically similar group of newborns living at low altitude. This increased in C_{RS}, reflecting changes in lung structural and mechanical properties found at birth in populations living at high altitude, is probably not a genetic characteristic, and is most likely the result of foetal hypoxia.

Studies in animals support the hypothesis that changes in lung volumes are acquired [65, 74]. In a study of the effect of high altitude on beagles, Johnson *et al.* [74] point out that the increased lung volumes in animals raised at high altitudes are associated with an increase in the fine septal tissue and the internal surface area of the lung (Johnson, 1992 personal communication). Studies of newborn rats exposed to hypoxia found an increase in the number and size of alveoli [17]. Thus, the larger lung volumes seen in high altitude natives appear to be the result of accelerated and/or prolonged lung growth in response to a hypoxaemic stimulus at an early age rather than over-inflation (stretching) of the lung. The finding that flows are not increased [16] and the information that only the fine septal tissues increased in beagles acclimatized during growth [74] are consistent with dysynaptic lung growth, in which the airways do not participate in the adaptation to altitude.

Changes in chest configuration are not as well-documented as the changes in lung volume. Peruvians native to high altitude regions are described as having larger and more prominent chests, with larger chest circumferences than Peruvian lowlanders [65]. These findings are, however, not consistent across high altitude populations and are specifically not seen in Asiatic highlanders [65]. Johnson *et al.* [74] found beagles raised in Leadville, CO, USA had larger lung volumes, at any given transpulmonary pressure, than beagles raised at lower altitudes, but saw no change in chest configuration. The larger lung volumes were accommodated by a lower diaphragm.

The findings concerning changes in lung volumes associated with acute exposure to high altitudes are variable. A reasonable summary is that, on average, VC decreases (about 200 mL in adults) and TLC and RV increase with the initial exposure to altitude but return to baseline values within a month [63, 75, 76].

Effects of sleep on lung volumes

The only comparative measurements of lung volumes during wakefulness and sleep concern FRC in supine adults and newborns.

Data available in adults

In eight healthy male adults (aged 21–41 yrs), FRC has been measured using the helium dilution technique. FRC fell significantly from wakefulness to non-rapid eye move-ment (NREM) (stage 3/4) and rapid eye movement (REM) sleep by 9.9 and 10%, respectively. No significant difference was observed between NREM (stage 3/4) and REM sleep [77].

In five healthy male adults, aged 23–33 yrs, FRC has been measured using a horizontal body plethysmograph [78]. FRC fell significantly from wakefulness to all states of sleep. FRC fell by an average of 13–15% in NREM, stage 2, 3/4 and 16.5% in REM sleep. In REM sleep, the fall in FRC was nonsignificantly different from that in NREM sleep, in contrast to that observed in asthmatic adult patients in whom FRC significantly decreased [78].

Data available in newborns

The potential influence of active (REM) *versus* quiet (NREM) sleep on the end-expiratory lung volume, FRC, remains controversial. Two studies have assessed changes in FRC in active as compared to quiet sleep, using inductance plethysmography to detect changes in anteroposterior diameters both of rib cage and abdomen in preterm infants [79], and alterations in the baseline signal from a respiratory jacket in term infants [80]. In both studies, FRC was found to fall slightly during the transition from quiet to active sleep, although in the healthy term infants FRC recovered to previous levels within 20–40 s [80].

Two studies using a body plethysmograph have reported a significant fall in FRC in active compared to quiet sleep in healthy full-term newborns [81, 82]. The mean fall in FRC was 31% in six infants and 12% in eight. There may be methodological rather than purely physiological explanations for these differences, including lack of support of the upper airways [81, 82]. Three studies have measured FRC using the helium dilution technique during active and quiet sleep assessed by neurophysiological criteria [83–86]. In healthy full-term newborns, no significant changes in FRC were observed, related either to sleep state or regularity of respiration; however, no attempt was made to measure rib cage and abdominal motion [83].

Two studies have concerned both preterm and full-term newborns, and showed no change in FRC in relation to change in sleep state, but a fall in FRC only when rib cage and abdominal motion were 180° out of phase, regardless of sleep state [84, 85].

Discrepancies between these different studies may be related to the method of measurement. Using body plethysmography, repeat measurements of FRC can be achieved over much shorter time periods than when using helium to wash out the lungs between repeat measurements. If there is a rapid recovery in FRC following any reductions during active sleep [80], any sleep-related changes in FRC may be detected by plethysmography but missed using helium dilution techniques. However, as stated above, the magnitude of changes during plethysmographic measurements may have been overestimated due to poor equilibration of airway pressures during airway occlusion in active sleep [81].

For routine practice, it is recommended that functional residual capacity be measured during quiet sleep, when breathing is regular and when rib cage and abdominal motion are in phase [86]. In preterm infants and neonates, who manifest periods of paradoxical rib cage motion during quiet sleep and a large proportion of active sleep, measurement of functional residual capacity when rib cage and abdominal movements are in phase is difficult.

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