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Age-related changes in the respiratory system

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ABSTRACT: This article summarises the main structural and physiological changes which take place in the lung from young adulthood to senescence. An understanding of these changes helps the clinician to correctly interpret some results of radiology and pulmonary function frequently seen in clinical practice. An appreciation of the altered physiology and the consequent reduction in pulmonary reserve should alert the physician to the need for a more critical evaluation of the various respiratory parameters measured during illness in an older patient.

Rhythmic breathing occurs virtually continuously over a lifetime and the alveolar gas-exchanging surface is brought into contact with more than 270 million litres of air, which may contain harmful particulate matter and noxious gas elements. Thus to separate changes in the respiratory system caused by ageing itself from those caused by environmental or work-related factors is extremely difficult and sometimes impossible. Chronic obstructive pulmonary disease (COPD) is possibly the most important disease entity related to age and environment.

Epidemiological studies show that the prevalence of COPD is increasing[1]. In the 1990's prognostic models of COPD were developed. These have shown that age, ventilatory function, gender and smoking were the major determinants for the development of COPD. Other important factors were outdoor air pollution and occupation.

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Structural changes

Changes in small airways and alveoli.

Increasingly after the age of 50 years, throughout the lung, a proportion of the elastic fibres in the region of the respiratory bronchiole and alveolus degenerate, appear ruptured and coiled[2]. These changes are most marked in elastic fibres around the alveolar ducts. As a consequence, dilatation of the alveolar ducts occurs and this is followed by enlargement of the airspaces. In some individuals this is exaggerated so that the external surface of the lung has a similar appearance to emphysema. It is possible to discriminate this from emphysema, since microscopically there is no evidence of destruction of the alveolar walls or inflammation within the small airways. Furthermore these appearances occur uniformly throughout the lung. A consequence of this process is the finding of openings or "fenestrae" in the alveolar membranes at the point where elastin fibres are degenerating[3]. Occasionally such openings fuse with those in neighbouring alveolar membranes creating larger airspaces. Although these changes are histologically different from emphysema, they result in similar physiological abnormalities.

It is unclear what causes age-related degeneration of elastin fibres. There is considerable variation from person to person in a way similar to the variation seen in susceptibility to emphysema. Imbalance of proteases - antiproteases may be important[4], but low intensity exposure to noxious gases and elements over many years may also contribute to a decline in reparative processes.

Collagen, the other main protein in the lung parenchyma, exceeds elastin on a quantitative basis[5]. Within lung and elsewhere it is a long-lived molecule which, as a part of normal maturation, undergoes cross-linking[6]. The cross-linked collagen does not function as well, in terms of pliability - in tendons and artery walls it is stiffer[7] and it is likely that this alteration contributes to a loss of elasticity and stiffening of the chest wall.

Changes in large airways

There is a reduction in mucociliary function and inefficient clearance of bronchial secretions in elderly persons[8]. These secretions mix with bacteria and other particles and are removed from the airway forming part of the complex host defence system of the lung. A reduction in mucociliary function contributes to the susceptibility of elderly people to respiratory infections.

Changes in pulmonary vessels

The pulmonary arterial wall becomes thicker through collagen deposition within the media, fibrosis within the intima and laying down of occasional atheromatous plaques[9]. In the smaller vessels there is loss of elastin. Pulmonary arterial pressures and resistance do not alter much with age, but the vessels become less distensible. It is unclear what changes occur in the pulmonary veins. Total pulmonary capillary volume falls with age.

Changes in the chest wall

The radiographic features of ageing in the ribs, sternum and vertebral column include calcification of rib articulations and costal cartilages and demineralisation of the ribs and vertebrae[10]. There is loss of vertebral disc space and a decrease in vertebral height. In some individuals there is osteoporosis of the vertebrae and ribs

with a marked kyphoscoliosis. The barrel-shaped appearance of the thorax in some elderly people takes place because of the shortening of the vertical height and consequently increased anterior-posterior diameter.

Changes in respiratory muscles

The respiratory muscles are made up of different fibres with differing myofibrillar ATP activity: Type 1 (slow), Type IIA (fast-fatigue resistant) and Type IIB (fast-fatigueable). The three major fibre types have characteristic histochemical, biochemical and physiological properties. During life the proportion of different fibre types found in respiratory muscles alter. This is particularly prominent in the abdominal muscles. Older individuals show Type IIA fibre atrophy, there being a predominance of Type 1 and Type IIB fibres, indicating de-conditioning of this muscle[11].

Physiological changes

Altered lung volumes

Changes in lung elasticity affect lung volume[12]. With the respiratory muscles at rest (both inspiratory and expiratory) and not actively contracting, lung volume is determined by the balance between the elastic recoil of the lung tending to collapse and the opposing elastic recoil of the thoracic cage tending to expand. This resting lung volume, the volume at the end of a normal quiet exhalation, is termed the functional residual capacity (FRC). Because the elasticity of the lung decreases with age, FRC is larger in the elderly than in the young[13]. This increase in volume would be greater were it not for the decrease in thoracic wall elasticity that also occurs with ageing[14]. Lung compliance increases with age, but the decrease in the chest wall compliance is proportionately greater. Thus, overall compliance is decreased in old age[15].

Altered resistance of peripheral airways

The small intrapulmonary airways are essentially tethered to the parenchymal lung tissue. The elastic recoil of lung tissue pulls outward on the airway keeping it open. Any loss of this lung elastic recoil with age decreases the tethering effect, resulting in a narrowing of peripheral airways particularly as the lung deflates. Airway resistance increases. The resistive properties of the airways are commonly assessed from measurements of rates of airflow during rapid, forceful expiratory manoeuvres. The forced expiratory volume in one second (FEV_1) declines with advancing age at the rate of about 30 ml/year from age 25 to 65 years. FEV_1 continues to fall after age 65 years, but at a somewhat reduced rate of 20 ml/year. The annual rate of decline in FEV_1 is considerably accelerated in cigarette smokers. Forced vital capacity and peak expiratory flow also decrease for the same reasons[16].

Changes in ventilation/perfusion matching

A consequence of the reduction in supporting tissues around the airways is that the walls of the small airways (less than 2 mm in diameter) have an increased tendency to collapse in on themselves as the lung deflates during expiration. "Premature" closure of the airways is found to occur at higher lung volumes in the elderly than in younger individuals and occurs in the dependent parts of the lungs even during normal breathing in the older adult. Since these alveoli remain relatively full at the end of expiration, the volume of air in the next breath which is required to re-expand them is proportionately less, with the result that ventilation is reduced. Since perfusion remains relatively unchanged there results a decrease in ventilation/perfusion matching and therefore a drop in arterial oxygenation, manifested as a lower PaO_2 and a higher alveolar-arterial oxygen difference.

Changes in lung elastic properties with advancing age are not uniform in alveoli throughout the lung. This non-uniformity of pulmonary mechanical properties results in unevenness in the distribution of ventilation usually without adequate compensatory readjustments in the distribution of pulmonary blood flow. As a result there is a mismatch in the ratio of ventilation to perfusion in some gas-exchanging areas of the lung, and blood leaving those alveoli may not be fully oxygenated[17]. Overall, arterial O_2 saturation falls with age, and at the age of 85 years normal PO_2 can be 75 mmHg instead of 96 mmHg as in a younger person.

Ageing is also associated with a reduction in the number of small airways and flattening of the internal surface of the alveoli. The alveolar surface area of 75 m^2 at age 30 years reduces to 60 m^2 by the age of 70 years[18]. The loss in surface area seen in the healthy individual is unlikely, on its own, to be of functional significance. However, it does reduce the respiratory reserve so that in association with all the other age-related changes hypoxia is more likely to arise in situations of stress when conditions such as pneumonia or heart failure develop or during exercise.

Effects on exercise capacity

The ability to exercise as measured by maximal O_2 uptake decreases progressively with age in adults. In the elderly there is greater stress on the respiratory system to accommodate the increase in metabolic rate during exercise. There is greater increase in ventilation for a given increase in exercise workload in the elderly as compared to young adults. This is the result of a compensation for age-related increases in physiological dead space. Additionally, the force-generating capacity of the respiratory muscles is reduced in the elderly due to a loss of muscle strength. Increased FRC in the elderly, particularly at high levels of ventilation required during severe exercise, may place the respiratory muscles at a mechanical disadvantage such that a greater level of central respiratory motor output is required to achieve a given muscle force. On the other hand, the increase in FRC stretches the expiratory muscles and allows them to expire air with greater force.

However, the decrease in the ability of the elderly to achieve as high levels of exercise as young people is largely due to changes in the cardiovascular system and in the fibre composition of the skeletal muscles rather than to changes in the elasticity of the respiratory system. Both the maximal heart rate and maximal cardiac output that can be achieved during exercise fall with advancing age. The kinetics of changes in cardiovascular variables and O_2 consumption as well as maximal ventilation decline with age. However, the elderly may be able to perform for long periods of time at a higher percent of maximum O_2 consumption than the young.

Changes due to altered respiratory muscles

The effects of ageing on the respiratory muscles may contribute to decrements in respiratory function. Respiratory muscle strength is less in the elderly reducing the maximal pressures that can be exerted during inspiration and expiration. Maximal inspiratory pressure decreases progressively after age 20 years, whereas the loss in maximal expiratory pressure accelerates past age 50 years[19,20]. These reductions, albeit small, in maximal respiratory pressures correlate with age-related reductions in the strength of other muscles, such as, trunk flexor and the hand grip muscles. Moreover, there is suggestive evidence that the respiratory muscles may be more fatigueable in the elderly than in the young. The diaphragm in mammals is the main inspiratory muscle. Studies show, that there are decreases in both rate of contraction and relaxation of the diaphragm with age. Tensions per cross-sectional area of the diaphragm are reduced and the velocity of its shortening is slowed.

The potential contribution of free radicals to age-related lung changes

Among the air pollutants, free radicals may be especially harmful. Experimental and clinical studies have provided evidence for the involvement of reactive oxygen species (ROS) in the development of acute and chronic lung disease. Some of the long term pathological effects are not easily distinguishable from "normal" ageing. Because life expectancy of the population is increasing in most parts of the world, even small amounts of environmental pollutants may contribute to lung injury because of the longer duration of exposure.

In an animal model of the senile lung it has been shown that ageing itself is associated with the increased formation of oxygen free radicals in the lungs[21]. Free radicals react with many cellular components, oxidising proteins, lipids, DNA bases, enzymes for intermediary metabolism and extracellular matrix components including collagen, elastin and hyaluronic acid[22].

The major sources of ROS in occupational and environmental exposure are asbestos, crystalline silica, coal, chromium, herbicides, and cigarette smoke[23]. ROS-induced lung injury at different target levels may contribute to similar patterns of cell injury and alterations at the molecular level by initiation, propagation and autolytic chain reactions. Intracellular signalling, activation and inactivation of enzymes, stimulation, secretion, and release of proinflammatory cytokines, chemokines, and nuclear factor activation and alterations are also common events.

Ozone and nitrogen oxides are potent toxic agents and they are common environmental pollutants both indoors and out, reaching especially high levels in smog. They are potent bronchial irritants and contribute to lung fibrosis and emphysema.

Oxidative reactions are often associated with accumulation of connective tissue in lungs, arteries, and nervous system[24, 25]. Many etiological factors of fibrogenesis stimulate free radical reactions either directly or through inflammatory stimuli. Free radicals appear to modulate the activity of phagocytes and extracellular matrix producing cells. Lipid peroxidation induces genetic overexpression of fibrogenic cytokines, the key molecules in the pathological mechanisms of fibrosis, as well as increased transcription and synthesis of collagen. Both these events can be downregulated, at least in experimental models, by the use of antioxidants. The effect of oxidative stress on cytokine gene expression appears to be an important mechanism by which it promotes connective tissue deposition[26].

Consequences of changes in respiratory system related to age and extrinsic factors

Increase in the prevalence of chronic obstructive pulmonary disease (COPD)

The increasing importance of COPD in the morbidity and mortality structure of the aged population is expected to have an impact on the health and social care structure. For example there will be an increased demand for wards specialised in pulmonary care, increased expenditure on investigations and hospital treatment and increased need for domiciliary oxygen therapy.

Reduced pulmonary function can lead to reduction in physical performance and in activities of daily living (ADL) thus resulting in increasing numbers of dependent people

Subjective factors limiting exercise performance and ability to perform the activities of daily living in the elderly with COPD are dyspnea[27] and fatigue[28]. Impaired lung mechanisms and gas exchange abnormalities are two major limiting factors to exercise. Unlike healthy subjects, COPD patients increase ventilation on exercise mainly by increasing respiratory rate (respiratory muscle work is approximately 12 times greater in COPD patients than healthy subjects at rest, let alone on exercise)[29]. An increased functional residual capacity contributes to greater respiratory muscle fatigue as the muscles work on a less favourable portion of their length-tension relationship. Increased oxygen consumption of skeletal muscle (and presumably also respiratory muscle) in the elderly compared to the young adds to this disadvantage[30]. Maximum oxygen uptake by respiratory muscles can be 10-15% higher in elderly healthy individuals, but it is often 35-40% higher in COPD patients.

Other factors contributing to increased ventilatory requirements include ventilation/perfusion mismatching and the high dead space volume, both of which contribute to an earlier accumulation of lactic acid[31].

Chronic respiratory diseases, especially those displaying an obstructive component (COPD, asthma) impair quality of life

Quality of life can be broken into the following components: (1) emotional functioning; (2) social role functioning; (3) ability to perform activities of daily living (ADL); and (4) ability to participate in enjoyable activities[32]. Several attempts to identify factors relating to quality of life and the negative impact of a chronic and progressive illness have met with varying success[33]. Whilst exercise limitation is an important factor in restricting quality of life in patients with respiratory disease,[34] other factors may also operate. Cough and sputum production may cause sleep disturbance and raise specific social and emotional problems in afflicted patients. Similarly, breathlessness during exercise and at

Table 1 - Age-related changes in the lung

primary cause	*structural effects*	*Physiological changes*	*altered functions*
degeneration of elastin	dilatation of alveolar ducts, more fenestrae in alveolar membranes, reduction in number of small airways	increased FRC, decreased static elastic recoil of the lung, increased lung compliance, increased dynamic airflow resistance	increased work of breathing, altered distribution of ventilation, hypoxaemia
increased collagen cross-linking	less pliable tendons, stiffer parenchyma, less distensible vessel walls	Decreased chest wall compliance, Decreased blood vessel compliance	increased work of breathing, greater tendency for pulmonary hypertension
unknown	*unknown*	Reduced mucociliary clearance From large airways	increased susceptibility to infection
atrophy of Type IIA muscle fibres	altered proportions of different fibre types	deconditioned respiratory muscles	increased susceptibility to respiratory failure

rest may produce increased levels of anxiety and lead patients to a loss of control or mastery over their disease and their health. It has been shown that up to 50% of the variance in a disease-specific quality of life score could be explained by cough, wheeze, walking distance disability and anxiety level. In other words, 50% of the variance in the health score was unrelated to these variables. Another recent study also investigated the relationship between physiological factors and quality of life in patients with COPD. It showed that quality of life in these patients was partly determined by airflow limitation, transfer factor of the lung, pack years smoking and age. However, these factors could not predict the whole spectrum of impaired quality of life[35].

Pulmonary rehabilitation can improve specific elements important to quality of life, such as psychological variables, including anxiety and depression, activity and self-confidence, and other elements, including endurance, strength, dyspnea and performance of ADL[36]. Thus, in the future, the proportion of pulmonary patients in geriatric rehabilitation wards can increase and so can the need of specialised pulmonary rehabilitation.

Although several elements of pulmonary rehabilitation are known or believed to improve survival of COPD patients (smoking cessation, improved nutrition, exercise and active life-style, avoidance and early treatment of exacerbations), yet no studies have convincingly demonstrated that pulmonary rehabilitation programmes lengthen survival[37]. Nevertheless, pulmonary rehabilitation is effective in improving the ability to perform ADL and thus overcoming dependency. It can therefore be expected that the demand for pulmonary rehabilitation facilities will increase.

In a global self-perceived scale[38] subjects were classified as having a poor opinion of their health status if they rated themselves in "bad" or "very bad" health

Patients with symptoms of respiratory failure, the most notable being dyspnea, more often rate their health status as poor than the control group. This reduces motivation and exacerbates mental ill-health. Thus, the proportion of elderly people with a low satisfaction in life will increase and result in more psychological problems. These need management, not only in their own right, but also as an adjunct to the management of co-existing illness or handicap.

Summary

The most important physiological changes associated with ageing are: a decrease in the static elastic recoil of the lung, a decrease in compliance of the chest wall and a decrease in the strength of respiratory muscles. Most of the changes described (Table 1) are related to these three phenomena[39]. Throughout life the lungs are constantly

exposed to injurious materials in the inspired air and the ageing process itself is associated with gradual deterioration of lung performance. Even so the healthy respiratory system of an octogenarian is still capable of gas exchange at a level that exceeds usual resting demands. Nevertheless, the morphological and physiological changes occurring during the process of ageing lead to a higher incidence and prevalence of acute and chronic respiratory diseases in the elderly as compared to young subjects. Environmental pollution and work-related noxious exposures can have an additional negative effect on the ageing respiratory system, accelerating the decline in pulmonary function. The consequences of this process, to some extent, can be predicted.

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