VARIATION IN RESPIRATORY FUNCTION WITH AGE

The respiratory system undergoes various anatomical, physiological and immunological changes with age.

- **The structural changes includes–**

1. **Chest wall and thoracic spine deformities:** It impairs the total respiratory system compliance leading to increase work of breathing. The respiratory system comprises primarily the thoracic cage, lungs, and diaphragm. Total respiratory system compliance includes lung and chest wall compliance. Compliance is change in volume relative to change in pressure. Lung compliance determines the rate and force of expiration and the thoracic compliance determines the elastic load during inspiration. With aging there are structural changes to the thoracic cage causing reduction in chest wall compliance. Age-related osteoporosis results in reduced height of the thoracic vertebrae. Stiffening of the thoracic cage from calcification of the rib cage and age-related kyphosis from osteoporosis reduces the ability of the thoracic cage to expand during inspiration and places the diaphragm at a mechanical disadvantage to generate effective contraction.
2. **Decrease in respiratory muscle strength with age:** It can impair effective cough, which is important for airway clearance. The diaphragm is the most important respiratory muscle and plays an essential role during inspiration. Likely explanation for reduced diaphragmatic strength with age is related to muscle atrophy and age-related decrease in fast twitch fibers, responsible for generating higher peak tensions. This age-related decline in diaphragmatic strength may predispose older individuals to diaphragmatic fatigue and ventilatory failure during increased ventilatory load on the respiratory system.
3. **Senile emphysema:** The lung parenchyma loses its supporting structure causing dilation of air spaces: "senile emphysema" There is homogeneous degeneration of the elastic fibers around the alveolar duct starting around 50 years of age resulting in enlargement of airspaces. Reduction in supporting tissue results in premature closure of small airways during normal breathing and can potentially cause air trapping and hyperinflation, hence "senile emphysema".

- **The Physiological changes-**

1. The lungs undergo a phase of growth and maturation during the first two decades of life and achieve maximal lung function around age 20 years in females and 25 years in males. Lung function remains steady with very minimal change from age 20 to 35 years and starts declining thereafter.
2. The decline in pulmonary function tests depends on peak lung function achieved during adulthood, the duration of the plateau phase, and rate of lung function decline. Studies on lung function are done either to establish the reference values for the pulmonary function laboratories or to determine the age-related decline (Knudson 1981; Janssens et al., 1999; Zeleznik 2003). The lung matures by age 20–25 years, and thereafter aging is associated with progressive decline in lung function.

3. The alveolar dead space increases with age, affecting arterial oxygen without impairing the carbon dioxide elimination. The airways receptors undergo functional changes with age and are less likely to respond to drugs used in younger counterparts to treat the same disorders.
4. Older adults have decreased sensation of dyspnea and diminished ventilatory response to hypoxia and hypercapnia, making them more vulnerable to ventilatory failure during high demand states (ie, heart failure, pneumonia, etc) and possible poor outcomes.

- **The Immunological changes-**

1. Bronchoalveolar lavage (BAL) fluids in healthy older subjects have consistently shown an increased proportion of neutrophils and lower percentage of macrophages compared with younger adults.
2. There is age-associated increase in immunoglobins IgA and IgM in the BAL fluid. Ratio of CD4+/CD8+ lymphocyte increases with age in the BAL fluid, suggesting the presence of primed T-cell from repeated antigenic stimuli of the lower respiratory tract mucosa (Meyer et al 1996).
3. Moreover, there is increased ability of alveolar macrophages to release superoxide anion in response to stimuli in the elderly. These changes likely represent the combined affect of repetitive antigenic stimuli from environmental exposure and age-related decline in down regulatory response to antigenic exposure.
4. Persistent low grade inflammation in the lower respiratory tract can cause proteolytic and oxidant-mediated injury to the lung matrix resulting in loss of alveolar unit and impaired gas exchange across the alveolar membrane seen with aging. The clinical implication of immune deregulation with age is yet to be determined.

- **Despite these changes the respiratory system is capable of maintaining adequate oxygenation and ventilation during the entire life span. However, the respiratory system reserve is limited with age and diminished ventilatory response to hypoxia and hypercapnia makes it more vulnerable to ventilatory failure during high demand states (i.e., heart failure, pneumonia, etc) and possible poor outcomes.**

SEX-WISE VARIATION IN RESPIRATORY FUNCTIONS

Structural Differences-

- **Sex differences in lung size-** On average, men are taller than women and since lung size is closely related to standing height, men typically have larger lungs than their female counterparts. However, sex-differences in lung size cannot simply be explained by allometry; even when matched for standing height or sitting height (a surrogate for chest volume), women still have smaller lungs than men. The effect of sex on lung size is thought to be related to women having fewer alveoli as opposed to men having larger alveoli, although evidence supporting this notion is sparse.
- **Difference in shape and size of rib-cage-** Recently, morphometric analyses have revealed that not only do men and women's rib-cages and lungs differ in size, but also in shape. Using high-resolution computed tomography, García-Martínez *et al.* found sex-differences in the geometry of the rib-cage, confirming an earlier finding based on chest radiographs. Specifically, men typically have shorter rib-cages with a wider base compared to those of women. Since the lungs fill the space within the rib-cage, it follows that men and women would also have different shaped lungs. Using similar methods (i.e. high-resolution computed tomography), Torres-Tamayo *et al.* found that men have 'pyramidal' lung geometry, with the base of each lung being larger than its apex, whereas women have 'prismatic' lung geometry, with the base and apices of each lung being relatively similar in size.

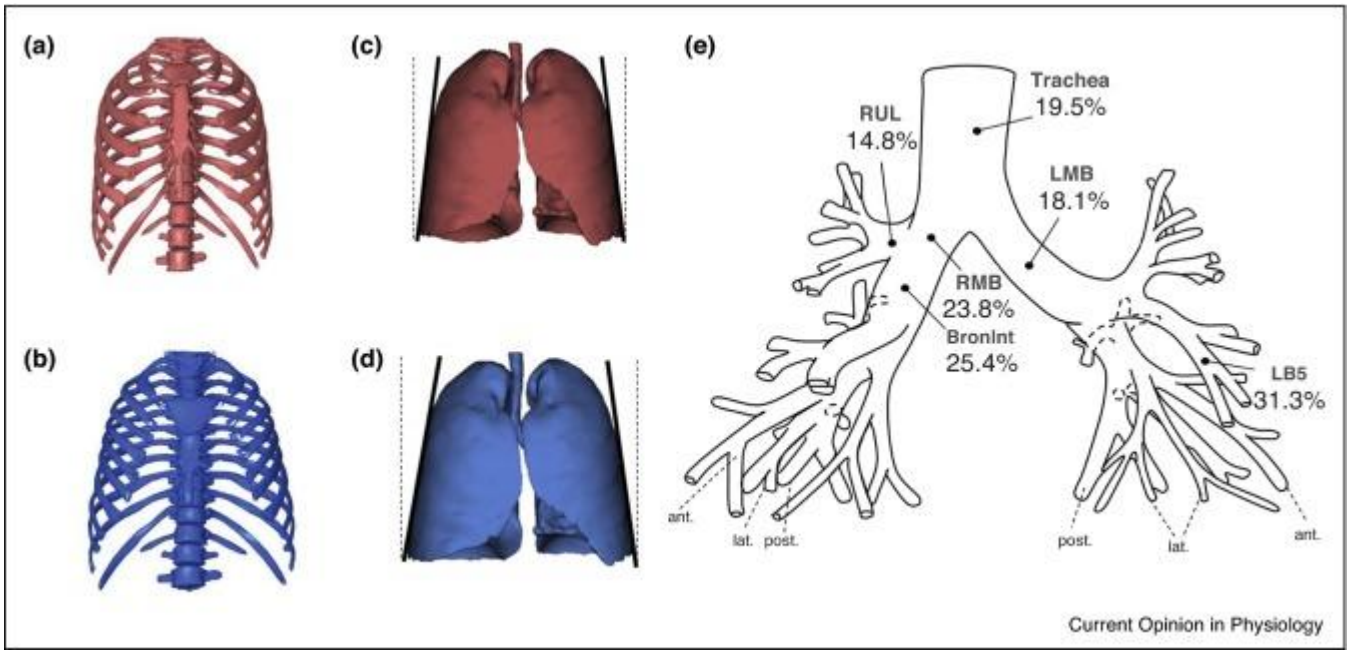

Figure1. **(Panels a and b)** Frontal view of lung mean forms derived from high-resolution computed tomography scans of women (Panel a) and men (Panel b) during in forced inspiration. **(Panel c and d)** Frontal view of surface warps associated to mean shapes based on regression residuals derived from high-resolution computed tomography scans of the rib-cages of women (Panel c) and men (Panel d). The angle formed by the thick black lines and thin dotted black lines on Panels c and d illustrates the sex-differences in lung shape. **(Panel e)**: Airway tree with assigned labels denoting the airway segments that are significantly smaller in women relative to lung size-matched men as well as the magnitude of the sex-difference.

- **Sex-differences in airway size-** Since women generally have smaller lungs than men, it is unsurprising that they also have smaller large conducting airways (i.e. >5th generation). Although it is tempting to assume that lung size and airway size are directly proportional to one another, their growth trajectories are unequal; a concept known as dysanapsis. In fact, even when matched for total lung capacity, the airway luminal area of the large conducting airways is 14–31% smaller in women.

➢ **Overall, the sexual dimorphism of the human respiratory system can be summarized as follows: the anatomy of the lungs, airways, chest wall, and respiratory muscles do not appear to differ based on sex, however; women have proportionally smaller lungs and airways than do men, and the shape of the rib-cage and lungs differs between the sexes.**

Physiological changes-

- **Sex-differences in resting pulmonary function-** The effect of sex on resting pulmonary function have been well characterized. Due to their smaller lungs and airways, women have lower maximum expiratory flows than do men. On average, women also have a lower maximal respiratory pressure, which is likely related to sex-differences in respiratory muscle mass.

- **Differences in haemoglobin concentration**, women have a lower diffusion capacity for carbon monoxide than do men, which is partially due to women having both a lower pulmonary capillary blood volume and alveolar-capillary membrane diffusing capacity than man. However, there is no sex-difference when diffusion capacity for carbon monoxide is expressed as a function of alveolar volume, suggesting that the difference in diffusion capacity for carbon monoxide is driven by sex-differences in lung size. At rest, sex-differences in the structure of the respiratory system do not influence the mechanics of breathing nor blood gas homeostasis; however, when the demand on the respiratory system increases, such as during exercise, several important sex-differences emerge.
- **Gas exchange tends to decrease with age** due to the loss of alveolar surface and reduced blood volume. [33] During childhood, PAO_2 and $PACO_2$ do not change significantly, but PaO_2 increases gradually during adolescence. Ventilatory response to hypercapnia and hypoxia is highest in early childhood and fall gradually until adulthood.

VARIATION IN RESPIRATORY FUNCTIONS WITH ENVIRONMENT

- The lungs are the first interface between oxygen in the environment and the metabolic machinery of the body. Both at rest and at high levels of work, successful gas exchange at the alveolar–capillary membrane is necessary to achieve an adequate supply of oxygen to the tissues and for the elimination of carbon dioxide.

- To achieve this goal, the mechanical function of the lungs, chest wall and respiratory muscles must move a large enough volume of air to supply oxygen to the body. Furthermore, gas exchange at the alveolar–capillary membrane must allow transfer of oxygen to the blood, which includes diffusion of oxygen from the air to the hemoglobin in the red blood cells. In addition, the drive to breathe from the central nervous system must be finely tuned to increase ventilation instantaneously as metabolic demand increases.

- Finally, the sense of breathlessness, or dyspnea, which may inhibit attempts to increase work, must achieve a compromise with the metabolic demand so that work is not impaired.

Impact of High altitude

- **At high altitude**, respiration extracts utilizes a high proportion of the overall energy expenditure. In spite of a slight decrease in the work of breathing resulting from the lower density of the ambient air at high altitude, much greater volumes of air are necessary to supply enough oxygen to the body from atmospheric air, in which the level of oxygen is reduced. Delivery of oxygen is further impaired by a diffusion limitation of oxygen from the air to the blood, which increases with altitude.

- **At extreme altitudes**, a disabling sense of dyspnea is compounded by cerebral hypoxia, which may further limit exercise. Climbers to these heights have reported taking as many as 10 breaths per step as the rate of ascent progressively and tortuously slows.

- **High altitude** imposes a diffusion limitation of oxygen from the air to the blood. This diffusion limitation is secondary to several factors: (i) a lower driving pressure for oxygen from the air to the blood, (ii) a lower affinity of haemoglobin for oxygen on the steep portion of the oxygen/haemoglobin curve, and (iii) a decreased and inadequate time for equilibration of oxygen as the red blood cell traverses the pulmonary capillary. As mentioned above, the decreased alveolar partial pressure of oxygen at high altitude is in part minimized by ongoing ventilatory acclimation.

- Thus, **lung function at high altitude** is accompanied by both impairment of gas exchange and diffusion limitation of oxygen from the air to the blood. The net effect is worsening hypoxemia, which is proportional both to the increase in energy expenditure and to high altitude.

- The lung is an elegant gatekeeper between environmental hypoxia and physical performance at high altitude. Because of the necessity of moving large quantities of air during exercise at altitude, the success of this task requires intact and functional lung mechanics, which are driven by central respiratory drive. An impairment of flow and a mechanical limitation may both be encountered, especially at extreme altitude. This process is facilitated by ongoing ventilatory acclimation, which is secondary to progressively increasing carotid body sensitivity to hypoxia. In spite of impressive lung mechanics and air flow, total body function is further impaired by arterial oxygen desaturation with increasing exercise and altitude, which is secondary both to the ventilation/perfusion heterogeneity and to the diffusion limitation of oxygen from the air to the blood. Further limitation is encountered from an extreme sense of dyspnea as well as depression of central nervous system output resulting from brain hypoxia.

Impact of Cold Environment

- Acute or chronic cold exposure elicits several effects on the respiratory system. Pulmonary mechanics are compromised by broncho-constriction, airway congestion, secretions and decreased mucociliary clearance. These responses are active in cold- or exercise-induced asthma, and are possibly responsible for decreased immune function and protection against airborne pollutants.

- The primary ventilatory effect of cold air is to decrease baseline ventilation and respiratory chemo-sensitivity. Although these responses provide significant protection against heat loss in many animals, the effect in humans is minimal.

- Cold exposure also elicits an increase in pulmonary vascular resistance. This stimulus is synergistic with hypoxia and may mediate pulmonary hypertension and edema at altitude.

- Chronic exposure to cold environments results in morphological changes such as increased numbers of goblet cells and mucous glands, hypertrophy of airway muscular fascicles and increased muscle layers of terminal arteries and arterioles. These latter two factors may play a role in the symptoms of chronic obstructive pulmonary disease and bronchitis, high altitude pulmonary hypertension and edema, and right heart hypertrophy.

Impact of Heat Stress

- Any increase in deep body temperature is associated with a rise in heart rate and tidal volume and a reduction in respiratory rate. An increase in pulmonary ventilation associated with a reduction in end-tidal carbon dioxide tension occurs only when deep body temperature increase reaches 1.5 degrees C. The apparently greater change in both pulmonary ventilation and end-tidal carbon dioxide tension during the more rapid increase in deep body temperature by 2 degrees C is not significant.