**Summary**

{lalley2013aging}

Old age brings into play a variety of disparate physiological changes that affect memory, cognition, vital signs and the respiratory system. About 10–20% of elderly subjects, 65–75 years of age, experience mild cognitive impairment and memory loss \citep{decarli2003mild}, in association with reductions in brain volume and gray matter, and with lesions in transcallosal fiber tracts \citep{freye2004use, dickstein2007changes, bastin2010quantifying}. Deficits of memory and cognition can be of significance for the patient’s awareness and caretakers’ diagnosis of changes in vital signs and well-being. Vital signs (blood pressure, heart rate, temperature regulation) change notably in the elderly \citep(chester2011vital). Endothelial aging increases arterial wall stiffness with higher systolic and pulse pressures. Vascular sympathetic receptors desensitize, resulting in increased tendency toward postural hypotension. Maximum heart rate decreases and resting heart rate slows, probably due to $\beta\_1$ -adrenoreceptor desensitization, and compensatory modulation of heart rate in response to external stressors decreases. Core body temperature is lower and thermoregulatory responses are suppressed.

Respiratory performance begins to decline after year 30. The changes detected by spirometric measurements have been described in detail \citep{verbeken1992senile, stocks1995reference, colloca2010age} and summarized in this review in Table 1 and Fig. 3.

Most of the aging-associated changes in the respiratory system evolve from a decrease in chest wall compliance, a reduction in static elastic recoil of the lungs (Fig. 2), and decreasing strength of the respiratory muscles.

{zaugg2000respiratory}

Nonetheless, with advancing age a significant decrement in the functional capacity of the respiratory system occurs \citep{variakojis1997preoperative}. Longitudinal data show that even in older athletes, physiologic respiratory capacities progressively deteriorate with age despite continued vigorous endurance exercise (approximately 10% per decade) \citep{mcclaran1995longitudinal, mittman1965relationship}. Accordingly, the ability to deliver more oxygen to tissues than they require ("reserve capacity") decreases by a factor of four from the age of 20 to the age of 70 years in apparently healthy individuals \citep{gerstenblith1976age, smith1986respiratory}.

{janssens1999physiological}

ABSTRACT: Physiological ageing of the lung is associated with dilatation of alveoli, enlargement of airspaces, decrease in exchange surface area and loss of supporting tissue for peripheral airways ("senile emphysema"), changes resulting in decreased static elastic recoil of the lung and increased residual volume and functional residual capacity. Compliance of the chest wall diminishes, thereby increasing work of breathing when compared with younger subjects. Respiratory muscle strength also decreases with ageing, and is strongly correlated with nutritional status and cardiac index. Expiratory flow rates decrease with a characteristic alteration in the flow–volume curve suggesting small airway disease. The ventilation–perfusion ratio (V’ A /Q’) heterogeneity increases, with low V’ A /Q’ zones appearing as a result of premature closing of dependent airways. Carbon monoxide transfer decreases with age, reflecting mainly a loss of surface area. In spite of these changes, the respiratory system remains capable of maintaining adequate gas exchange at rest and during exertion during the entire lifespan, with only a slight decrease in arterial oxygen tension, and no significant change in arterial carbon dioxide tension. Ageing tends to diminish the reserveof the respiratory system in cases of acute disease. Decrease dsensitivity of respiratory centres to hypoxia or hypercapnia results in a diminished ventilatory response in cases of heart failure, infection or aggravated airway obstruction. Furthermore, decreased perception bronchoconstriction and diminished physical activity may result in lesser awareness of the disease and delayed diagnosis.

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 age-related functional changes described are related to these three phenomena. Also noteworthy are the decrease in the respiratory response to hypoxia and hypercapnia and a diminished awareness of increased airway resistance or elastance. The present review explores the age-related structural changes of the respiratory system and their consequences on respiratory mechanics and gas exchange.

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Physiological ageing of the respiratory system is associated with changes in the compliance of the chest wall and lung parenchyma, which result in static air-trapping, increased functional residual capacity and increased work of breathing. Expiratory flow rates decrease with ageing, With characteristic changes inthe flow–volume curvessug-gesting increased collapsibility of peripheral airways. Respiratory muscle function is affected by geometric changes in the rib cage and is strongly correlated with nutritional status (lean body mass, body weight), peripheral muscle mass and strength and cardiac index. In subjects aged >=80 yrs, values of maximal inspiratory pressure may reach critically low values, which may be associated with alveolar hypoventilation in circumstances such as left-sided heart failure or pneumonia. Gas exchange iswell preserved at rest and during exertion in spite of a reduced alveolar surface area and increased ventilation–perfusion heterogeneity. Infact, inelderly subjectswith regular training, the respiratory system can adapt to high levels of exercise. However, age-associated alterations of the respiratory system tend to diminish the subjects’ reserve in cases of infection or heart failure. Decreased sensitivity of respiratory centres to hypoxia or hypercapnia will result in a diminished ventilatory response in cases of acute disease such as heart failure, infection or aggravated airway obstruction. Furthermore, decreased perception of added resistive loads (i.e. bronchoconstriction) and diminished physical activity may result in less awareness of the disease and delayed diagnosis.

{sprung2006age}

Age-related loss of the lung static recoil forces, stiffening of the chest wall and diminished alveolar surface area lead to a decrease in vital capacity, an increase in residual volume, decrease in expiratory flows and increased ventilation-perfusion heterogeneity. Respiratory muscle strength consistently declines with age further increasing the work of breathing. While gas exchange may be well preserved at rest and during exertion, pulmonary reserve is diminished, and under conditions of positive fluid balance, positioning for surgery, and increased metabolic demand, postoperative respiratory failure can occur. Increased sensitivity to respiratory depressants and muscle weakness pose additional risks for the development of postoperative respiratory complications in elderly patients. Regional anesthetic techniques provide for superior postoperative analgesia, without necessarily altering the frequency of postoperative pulmonary complications in the older surgical population.

Alterations in respiratory physiology associated with aging must be appreciated to anticipate and minimize potential complications associated with surgery and anesthesia in the elderly. Individualized care to optimize preoperative cardiorespiratory function, minimize intraoperative respiratory pertubations, and to gently restore postoperative pulmonary function are essential anesthetic goals for elderly patients who require surgery.

The lungs continue to develop throughout life, with maximal functional status achieved in the early part of the third decade \citep{janssens1999physiological}. Lung function gradually declines thereafter, even in athletes who attempt to maintain aerobic capacity \citep{pollock1997twenty, mcclaran1995longitudinal}. Aging is associated with multiple changes in respiratory physiology, including structural changes in both the lungs and chest wall leading to alteration in measurable mechanical properties of respiratory system, reduction of arterial oxyhemoglobin saturation, and impaired response to hypoxia (Table I).

**Respiratory pump muscles, chest wall and lungs**

{lalley2013aging}

Several morphological changes reduce the respiratory efficiency of the chest wall and diaphragm in the elderly. The cross sectional areas of the intercostal muscles start to decrease after the age of 50 years, the reduction being greater in the expiratory muscles. There appears to be no change in the thickness of the diaphragm with age, although structural changes in the chest wall reduce the curvature of the diaphragm and maximal transdiaphragmatic pressure \citep{zaugg2000respiratory, sprung2006age}. In addition, the width of the esophageal hiatus is greater after the age of 70 years. Maximal static inspiratory and expiratory pressures decrease with aging, reflecting a reduction in respiratory muscle strength \citep{wijesinghe2005effect}.

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Chest wall compliance decreases progressively with age. The stiffening is presumably related to calcification and other structural changes within the rib cage and its articulations, i.e. calcification of costal cartilage and rib-vertebral articulations and narrowing of intervertebral disk spaces \citep{murray1986normal, crapo1993aging}. Changes in the shape of the thorax also occur as a result of age-related osteoporosis resulting in partial (wedge) or complete (crush) vertebral fractures, leading to increased dorsal kyphosis and anteroposterior (AP) diameter ("barrel chest"). The reported prevalence of vertebral crush fractures in the UK is 2.5% for females aged 60 yrs and reaches 7.5% for those aged 80 yrs. Partial vertebral fractures are found in 60% of females aged >=75 yrs \citep{gunby1994epidemiology}. Males alsoshowanincreaseinvertebral fractures withage, but rates are approximately half those of females \citep{gunby1994epidemiology}. In a studyof100chestradiographsofnormalsubjectsaged75–93 yrs, 25% had severe kyphosis as a consequence of vertebral wedge or crush fractures (>50%), 43% had moderate kyphosis (35–50度) and 23% had a normal curvature of the spine \citep{edge1964radiographic}. These modifications of the chest wall not only alter its compliance but also modify the curvature of the diaphragm, with a negative effect on its force-generating capabilities.

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Chest wall compliance decreases with age due to structural changes of the intercostal muscles, intercostal joints and rib-vertebral articulations \citep{murray1986normal}. In addition, age-associated osteoporosis may increase in both dorsal kyphosis and anteroposterior chest diameter resulting in changes in the geometry of the thorax. This, together with increased chest wall stiffness, shifts the chest wall pressure-volume curve to the right (Figure 1, lower panel).

The “remodelling” of the chest wall with aging flattens the curvature of the diaphragm, which leads to a reduction in maximal transdiaphragmatic pressure ($P\_di $) \citep{zaugg2000respiratory}. Reductions in respiratory muscle mass may also contribute to a decrease in the force produced by respiratory muscle activity. A reduction of skeletal muscle electromyographic activity by as much as 50% in the 70-yr-old individual is attributed to the loss of type II fast-twitch muscle fibres \citep{larsson1983histochemical}. Indeed, in an electrophysiologic study, the electromyographic signal produced by twitch stimulation of the phenic nerve was modestly reduced in the elderly (mean age 73) compared to younger subjects (mean age of 29) \citep{polkey1997contractile}. As a result, during voluntary maximal inspiratory effort P di is lower in elderly than in younger patients and this may predispose to diaphragmatic fatigue \citep{tolep1995comparison} in clinical settings this may translate into difficulties in weaning a patient from the ventilator.

**Structural basis for changes in pulmonary mechanics ---- Lung parenchyma**

{sprung2006age}

With aging, structural alterations in the lung parenchyma occur such that there is a gradual reduction in lung elastic recoil, the inward force that promotes decreases in lung volume, at an average rate between 0.1 and 0.2 cm H 2 O per year \citep{turner1968elasticity}. Factors contributing to this reduction include changes in the spatial arrangement and/or cross-linking of the elastic fibre network. This becomes more pronounced after 50 yr of age, and may result in a homogenous enlargement of air-spaces causing the reduction of alveolar surface area from 75 m 2 at age 30 to 60 m 2 at age 70. Although histologically these changes are not associated with evidence of destruction of alveolar walls, they functionally resemble emphysema \citep{campbell1978aging, verbeken1992senile}. This loss of parenchymal elasticity with aging increases lung compliance; i.e., the lung static pressure-volume curve is shifted to the left and has a steeper slope (Figure 1, lower panel) \citep{turner1968elasticity}.

**Changes in respiratory muscle function**

{janssens1999physiological}

Respiratory muscle performance is impaired by the age-related increase in functional residual capacity (FRC) (fig. 1), the decrease in chest-wall compliance and the geometric changes in the rib cage. Both the kyphotic curvature of the spine and theAP diameter of the chest increase with ageing, thereby decreasing the force-generating capacity of the diaphragm \citep{edge1964radiographic}. Furthermore,P OLKEY eta \citep{polkey1997contractile} have shown a significant decrease in the strength of the diaphragm of elderly subjects (mean age 73, range 67–81 yrs) compared with a younger control group (mean age 29, range 21–40 yrs): -13% for transdiaphragmatic pressure (P di ) during a maximal sniff and -23% during cervical magnetic stimulation. T OLEP et al \citep{tolep1995comparison} also reported values of P di of fit elderly subjects (aged 65–75 yrs) which were 25% lower than values obtained in young adults (aged 19–28 yrs).

Respiratory muscle strength is related to nutritional status, which is often deficient in the elderly. E NRIGHT et al \citep{enright1994respiratory} showed significant correlations between maximal inspiratory (MIP) or expiratory (MEP) pressures and lean body mass (measured by bioelectrical reactance) or body weight. A RORA and R OCHESTER \citep{arora1982respiratory} showed the deleterious impact of undernourishment on respiratory muscle strength or maximal voluntary ventilation (MVV): the decrease in respiratory muscle strength and MVV was highly significant in undernourished subjects (7166% of ideal body weight (IBW)) compared with control subjects (104610% of IBW). Necropsy studies have confirmed the correlation between body weight and diaphragm muscle mass \citep{arora1982effect}.

Age-associated alterations in skeletal muscles most probably affect respiratory skeletal muscle function \citep{tolep1993effect}. Peripheral muscle strength declines with ageing: a 2% annual decrease in handgrip strength was described in 620 healthy subjects aged >65 yrs by B ASSEY and H ARRIES \citep{bassey1993normal}. Furthermore, MIPand MEPinelderly subjectsare strongly and independently correlated with peripheral muscle strength (handgrip) \citep{enright1994respiratory}.

**Upper and lower airways**

{lalley2013aging}

Structural changes in nasal passages with aging are few \citep{edelstein1996aging}. Only the nasopharynx shows significant physical changes, and rhinomanometry demonstrates that nasal resistance increases. Histopathological studies show that there is an age-related decrease in cartilage cells with no alteration in the integrity of the mucosal lining. Status of the turbinates, nasal ciliary motility and nasal secretions are unaffected by age.

Differences in pharyngeal size and tone exist between young and older adults. The posterior pharyngeal wall is thinner and does not constrict to the same extent in older subjects as in young adults \citep{aminpour2011pharyngeal}. The pharyngeal dilator genioglossus muscles (GGM) exhibit inspiratory phased activity, which during wakefulness is higher in older than in younger men \citep{fogel2003control}. The higher wakeful muscle activity might be compensatory. With age-related reduction in muscle mass, the pharyngeal airway tends to become more collapsible, leading to increased airway resistance, whereas a reflexive increase in GGM activity would serve to maintain airway patency. Airway structural volume in general increases with age, particularly in men, in association with increased soft tissue \citep{chan2010obstructive}, while upper airway size decreases \citep{martin1997effect}.

{zaugg2000respiratory}

With advancing age, structural changes occur both in the upper and lower airways including the adjacent tissues. Loss of muscular pharyngeal support predisposes the elderly to upper airway obstruction \citep{allen1987seventy, berry1987sleep}. In addition, loss of protective reflexes of coughing and swallowing-presumably owing to an age-related peripheral deafferentation together with a decreased central nervous reflex activity-increases the risk of aspiration \citep{pontoppidan1960progressive}. More profound morphologic changes occur in the lung tissue itself. A decline in the volume of the pulmonary capillary bed results in a marked increase of the mean pulmonary artery pressure by 30%, and an increase of the pulmonary vascular resistance by up to 80% \citep{davidson1990influence}. Also, the increased total tension in the alveolar sheet of the aged lung increases pulmonary vascular resistance (see next section). A progressive concomitant loss of alveolar surface area by at least 30% occurs from the age of 20 to the age of 70 mainly owing to intra-alveolar fenestration \citep{mauderly1979effect}. This process, in contrast to alterations typically observed in the emphysematic lung, is non-inflammatory, without septal destruction and is related to the enlargement of the pores of Kohn citep{shimura1986effects, verbeken1992senile}.

**Pulmonary blood vessels**

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Beyond age 30–35 years, there is a gradual increase in the stiffness of the pulmonary vasculature, likely caused by an increase in muscle content and thickness \citep{taylor2010pulmonary}. In association with structural remodeling, pulmonary arterial pressure and pulmonary wedge pressure increase gradually after 45 years, becoming significantly elevated beyond 50 years. In addition, gas exchange capability of the lungs is compromised in association with reduced pulmonary capillary volume and number.

**Respiratory mechanics and lung volumes**

{zaugg2000respiratory}

The elastic properties of the lung tissue and thoracic wall gradually change by aging. The lung parenchyma loses elastic recoil and becomes more compliant, while the chest wall becomes stiffer (calcification of the ribs and vertebral joints) \citep{mittman1965relationship , turner1968elasticity}. The volume-pressure curve of the lung itself shows a shift to the left, whereas the volume-pressure curve of the thorax itself shifts to the right. The volume-pressure curve of the aged total system (lung and thorax) is flatter and shows less compliance.

The tidal volume slightly decreases, while the respiratory frequency slightly increases. Also, the abdominal contribution to tidal breathing increases. Although the divergent changes of chest wall and lungs do not considerably affect total lung capacity, when corrected for the age-related decrease in height, this leads to a barrel-like appearance of the chest and a flattened diaphragm. Related changes in the respiratory mechanics are schematically shown in Figure 2.

The diaphragmatic efficiency in the elderly is also impaired by a significant loss of muscle mass. A reduction of electromyogram activity by as much as 50% normally occurs in skeletal muscles of the 70-year-old individual, mainly owing to the loss of fast-twitch muscle fibers (type II) \citep{ larsson1983histochemical}. The reduction in diaphragm strength may be smaller (10%-20%) \citep{ polkey1997contractile}. Nonetheless, maximum pressures generated by full inhalation and expiration are significantly decreased, and with increasing age the FEVl/FVC ratio may be as low as 65%:55% in apparently healthy individuals \citep{ enright1993spirometry}. The rule of thumb that 70% represents the lower limit of the normal range for the FEVl /FVC ratio is not applicable in the elderly. Although age itself does not relevantly increase airway resistance at rest, the work of breathing may be elevated by 30% during exercise \citep{ turner1968elasticity}.

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With increasing age, as mentioned previously, the chest wall becomes stiffer, i.e. less compliant, but the lungs become more distensible (diminished elastic recoil). As a result, residual volume (RV) increases (air trapping) by approximately 50% between 20 and 70 yrs of age and, during the same period, vital capacity (VC) decreases to about 75% of best values (fig. 1). Increased elastic recoil of the chest wall and diminished elastic recoil of the lung parenchyma (fig. 2) also explain the increase in FRC, i.e. elderly subjects breathe at higher lung volumes than younger subjects. Because of the shape of the static pressure–volume curve of the respiratory system (fig. 3), the increase in FRC is associated with an increased elastic load from the chest wall, placing an additional burden on the respiratory muscles. During normal resting tidal breathing, the increase in breathing-related energy expenditure in a 60-yr-old male is estimated at 20% compared with that of a 20-yr-old subject.

The closing volume (CV), i.e.the volumeatwhich small airways in dependent regions of the lung begin to close during expiration, increases with age. Premature closure of terminal airways is related to a loss of supporting tissues around the airways. CV may reach 55–60% of total lung capacity (TLC), and equal FRC; as such, normal tidal breathing may occur with a significant proportion of peripheral airways not contributing to gas exchange (low ventilation–perfusion ratio (V’ A /Q’) zones). This is the major reason for diminished arterial oxygen tension (P a,O 2 ), increase in alveolar–arterial difference for oxygen, and diminished carbon monoxide transfer with age.

TLC does not change significantly throughout life. The age-related diminished elastic recoil of the lungs is counterbalanced by an increased elastic load from the chest wall.

**Static lung volumes**

{sprung2006age}

The overall effect of loss of inward elastic recoil of the lung with aging is somewhat balanced by the decline in chest wall outward force such that the total lung capacity (TLC) remains unchanged. However, at relaxed end-expiration, the rate of decrease in lung recoil with aging exceeds that of the chest wall, such that functional residual capacity (FRC) increases by 1 to 3% per decade (Figure 2). Because TLC remains unchanged, an increase in residual volume (5 to 10% per decade) results in a decrease in vital capacity (VC). After age 20, VC decreases 20 to 30 mL per year. The ratio of RV to TLC increases from 25% at 20 yr to 40% in a 70-yr-old subject.

**Dynamic lung volumes**

{sprung2006age}

Longitudinal spirometric studies demonstrate progressive decreases in both forced vital capacity (FVC) (14–30 mL per year) and forced expiratory volume in one second (FEV 1 ) (23–32 mL per year) with aging in both men and women (Figure 3A) \citep{knudson1976maximal}. After age 65, the decrease of FEV 1 is on average 38 mL per year \citep{brandstetter1983aging}. Chronic smoking dramatically intensifies these age-related changes \citep{griffith2001predictors}. In healthy elderly subjects from 65 to 85 yr of age, the normal FEV 1 /FVC ratio may be as low as 65% to 55%, and the rule of thumb that 70% represents the lower limit of the normal range for the FEV 1 / FVC ratio is not applicable \citep{enright1993spirometry}. Lung function gradually deteriorates with aging even in individuals who attempt to maintain aerobic capacity over the sixth and seventh decades of life \citep{pollock1997twenty, mcclaran1995longitudinal}. Surprisingly, in these individuals a greater decrease in FVC compared to FEV 1 results in a significant increase in the FEV 1 /FVC ratio.

**Spirometry**

{janssens1999physiological}

Forced expiratory volume in one second (FEV1 ) and forcedvital capacity (FVC) increaseup to~20 yrs of age in females and 27 yrs of age in males, then diminish with advancing age (fig. 6) \citep{ knudson1976maximal}. Cross-sectional and long-itudinal studies both show an accelerated decline in FEV 1 and FVC with age, with the rate of loss being greater in males than in females and more rapid in patients with increased airway reactivity \citep{crapo1993aging}. The annual decrease in FEV 1 is approximately 20 mL in subjects aged 25–39 yrs, rising to 38 mL in subjects aged >=65 yrs \citep{brandstetter1983aging}.

Few studies actually report results obtained in large samples of elderly subjects. E RICSSON and I RNELL \citep{ ericsson1969spirometric}, for instance, report data on 264 normal "elderly" subjects, none of whom was older than 71 yrs of age. F OWLER et al \citep{ fowler1987maximal } studied 182 Londoners aged >=60 yrs, but only 44 subjects were aged >75 yrs and 23 were >80 yrs. E NRIGHT et al \citep{ enright1997peak}. reported values obtained in 471 subjects aged >=65 yrs, but only 10 males aged >80 yrs were included in the study. The two largest studies reporting spirometric data for healthy elderly subjects were published by M ILNE and W ILLIAMSON \citep{ milne1972respiratory} and D U W AYNE S CHMIDT et al \citep{ schmidt1973spirometric}. D UWAYNE -S CHMIDT et al. \citep{ schmidt1973spirometric} showed that FEV1 , and FVC decrease uniformly with age. Values for FEV 1 /FVC were stable in young adults and then decreased for females aged >55 and males aged >60 yrs to the 70–75% range. However, M ILNE and W ILLIAMSON \citep{milne1972respiratory} noted a decrease with age for FEV 1 /FVC only in females, with values remaining stable throughout the 60–90 yrs age range in males.

Reported data show that previous regression equations, based on extrapolations from groups of younger subjects, tended to overestimate predicted values for FEV1 , FVC and FEV 1 /FVC in elderly subjects \citep{milne1972respiratory}.

**Total lung capacity (TLC)**

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The volume of gas in the lungs after a maximal inspiratory effort, is determined by the strength of the inspiratory muscles and the elastic recoil of the chest wall and lungs. TLC does not change significantly with age because decreased outward elastic recoil of the chest wall that accompanies loss of respiratory muscle strength is offset by decreased inward lung recoil associated with deterioration of elastic airway connective tissue.

**Residual volume (RV)**

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The volume of gas remaining in the lung after a maximal forced expiration, increases with age along with the ratio RV/TLC. RV is determined by two factors: (1) the strength of expiratory muscle that oppose outward chest wall recoil at low thoracic volumes, and (2) collapse of small airways and trapping of gas in alveoli during forced expiration. With loss of expiratory muscle strength, outward chest recoil is less opposed, thus RV increases.

**Vital capacity (VC)**

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The volume of gas expired by maximal expiration just after maximal inspiration, and equal to TLC-RV, decreases with age because RV increases while TLC is unchanged.

**Functional residual capacity (FRC)**

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The volume of gas at the end of normal tidal expiration when the respiratory muscles are relaxed, increases with age, by 1–3% per decade, along with the FRC/TLC ratio. At FRC, the elastic forces of lung and chest walls are equal and in opposite directions. The pleural surfaces link these two opposing forces; outward elastic chest wall forces are balanced by inward lung tissue elastic forces. With aging, Alveoli enlarge and coalesce, resulting in losses of elasticity and surface area and an increase in the fixed lung volume. Along with less efficient gas mixing and alveolar–capillary gas exchange, static pressure–volume relationships are shifted toward reduced elastic recoil with age. The rate of decrease in lung recoil exceeds that of the chest wall so that lung volume at the end of tidal expiration increases.

**Expiratory reserve volume (ERV)**

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The volume of gas expired by a maximal expiration made at the end of normal tidal expiration, is equal to FRC − RV. ERV decreases with aging because transmural pressure increases and causes dynamic compression of airways, which impairs expiratory airflow and prevents dependent alveoli from emptying. Although both FRC and RV increase with aging, RV increases more. The most likely structural factor for the increase in ERV is a loss of connective tissue around small airways that normally have a stenting effect.

**Dynamic lung compliance**

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Decreases with age largely because elastic tissue is lost from alveoli and smaller airways, increasing resistance to flow.

**Arterial PO2**

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Decreases progressively with age, however alveolar PO 2 in well-ventilated regions of the lungs doses not, therefore the alveolar–arterial oxygen difference, (A − a)DO 2 , increases progressively.

**Alveolar dead space**

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Regions of the lung that are ventilated but not adequately perfused, increases in association with reduced cardiac output.

**Ventilation–perfusion (V A /Q)**

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Inhomogeneity, or mismatch increases with age. There is a greater tendency toward airway closure in lower lung regions, where intrapleural pressure is higher and there is less elastic tissue in older humans to hold small airways open and resist airway collapse. CV may approach FRC, so that a substantial percentage of airways may be closed and produce a low V A /Q during normal tidal breathing \citep{janssens2005aging}.

**Pulmonary diffusing capacity (DFC)**

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The volume of gas that diffuses across the membranes between the alveoli and lung capillaries, decreases with age. Factors responsible for the reduction include loss of alveolar surface area, decreased capillary blood volume and decreased surface area for alveolar–capillary gas diffusion. The reduction in DFC, along with a small increase in physiological shunting (transfer of blood from the left cardiac ventricle to systemic circulation without undergoing pulmonary gas exchange) and increased V A /Q mismatching contribute to falling PaO 2 and increasing (A − a)DO 2 .

**Gas exchange**

{lalley2013aging}

PaO 2 decreases progressively with age, from about 95 mm Hg at 20 years of age to about 75 mm Hg at 70 years \citep{cerveri1995reference}. The decrease in PaO 2 occurs in association with increased V A /Q heterogeneity in lower regions of the lung \citep{cardus1997increase}, where airway compression linked to loss of lung elastic recoil and reduced resistance to collapse result in airway closure, significant ventilation–perfusion impairment during quiet breathing and reduction in lung diffusing capacity \citep{holland1968regional, paoletti1985reference}. Lung perfusion can also be reduced with aging because of lower cardiac output \citep{levitzky1984effects}. Although PaO 2 declines with aging, PaCO 2 is maintained constant \citep{wahba1983influence, sprung2006age}. Various hypotheses have been offered to explain unchanging PaCO2 , including decreasing basal metabolic rate \citep{ sprung2006age} and greater diffusivity of CO2 through the alveolar–capillary barrier \citep{ levitzky1984effects}. The most likely explanation is that because the Hb–O 2 dissociation curve levels off at PaO2 values greater than 60 mmHg in lung regions with high V A /Q ratios, there is not much of an increase in the O 2 content of blood leaving these regions. In contrast, lung regions with low V A /Q ratios have low O 2 content (figs. 5–13). When blood from these different regions mixes in the pulmonary veins, the result is a lower than normal content with a resultant low PO 2 , which will not have much impact on breathing until PO 2 drops below 60 mmHg. On the other hand for CO 2 , the relationship between PCO 2 and CO 2 content does not flatten out. Thus, lung regions with high V A /Q have low CO 2 content that can offset the impact of low V A /Q in regions that have high CO 2 content. Furthermore, neural control of ventilation is more sensitive to elevated PaCO 2 than to reduced PaO 2. In situations where there is a residual increase in PCO 2 in older subjects with increased V A /Q heterogeneity, it is offset by increased minute alveolar ventilation.

{zaugg2000respiratory}

Arterial oxygenation is progressively impeded with increasing age \citep{smith1986respiratory}, whereas carbon dioxide elimination is unaffected by \citep{raine1963aa}. The impaired oxygenation is reflected by the progressively increasing alveolar-arterial oxygen gradient and the decreasing arterial oxygen tension (approximately 5 mm Hg per decade from the age of 20 years). A more recent study showed that the decrease in arterial oxygen tension is most significant from 40 to 75 years of age. Thereafter, arterial oxygen tension remains relatively stable at about 83 mmHg \citep{cerveri1995reference}. Impaired oxygenation is primarily owing to an increased ventilation/perfusion mismatch with shunt- and dead-space-like effects, rather than to a decrease in diffusing capacity \citep{cardus1997increase, donevan1959influence}. Uneven distribution of inspired gas is the most probable explanation for the increasing age-related deterioration in ventilation/perfusion match and results from early airway closure in small bronchioles owing to the uneven loss of elastic recoil in the aged lung. A close relationship between preoperative closing capacity, air trapping, and alveolar-arterial oxygen tension during anesthesia has been reported \citep{warner1989role}. Attenuation of the hypoxic pulmonary vasoconstriction and hypocapnic bronchoconstriction response owing to the stiffening of the vasculature and airways ("fine tuning of ventilation/perfusion ratio") additionally contributes to the observed ventilation/ perfusion maldistribution in the elderly and may become particularly evident during one-lung ventilation \citep{weenig1974relationship}.

{janssens1999physiological}

W AGNER and coworkers \citep{wagner1974continuous, wagner1974measurement} have developed a technique measuring, in humans, the distribution of ventilation and perfusion, based on the simultaneous elimination by the lung of six inert gases of markedly different solubilities. This technique provides the best available over-view of the distribution of ventilation and perfusion in health and disease. Using this technique, W AGNER and co-workers \citep{wagner1974continuous, wagner1974measurement} have shown, with ageing, an increase in V’ A /Q’ imbalance, with a rise in units with a high V’ A /Q’ ratio (wasted ventilation or physiological dead space (V D )) and in units with a low V’ A /Q’ ratio (shunt or venous admixture). The decrease in P a,O 2 with age is a consequence of this increased heterogeneity of V’ A /Q’ ratios and, inparticular, ofthe increase inunits witha low V’ A /Q’ ratio (dependent parts of the lung, poorly ventilated during tidal breathing, as reflected by an increased closing volume) \citep{ wagner1974continuous}. Regressions proposed for the computing of P a,O 2 as a function of age vary widely, mainly in relation to the coefficient attributed to age \citep{ delclaux1994arterial}. Indeed, for an 82-yr-old male, predicted values for P a,O 2 range 8.4–11.3 kPa (63–84 mmHg). GUE´NARD and M ARTHAN [54] found no significant correlation between P a,O 2 and age in 74 subjects aged 69–104 yrs; mean values reported were 11.2+-61.0 kPa (84+-67.5 mmHg). D ELCLAUX et al. [53] measured arterial blood gases in 274 subjects aged 65–100 yrs (mean 82 yrs) with and without airway obstruction; mean P a,O 2 was 10 +- 1.4 kPa (75 +- 11 mmHg). The authors suggest accepting as normala P a,O 2 of10.6–11.3 kPa (80–85mmHg) for subjects >65 yrs of age \citep{ delclaux1994arterial}.

An increase in the alveolar–arterial pressure difference for oxygen (P A-a O 2 ) with age would be expected because of the increase in V’ A /Q’ heterogeneity, mostly related to the increase in closing volume. High values obtained by this equation (i.e. 4.8 kPa (36 mmHg) for 80 yrs of age) may be in part explained by the supine position of subjects at time of sampling. More recent studies found no significant relationship between age and P A-a O 2 ; however, values reported are well above normal values for younger adults, i.e.3.2 +- 1.4 kPa (24 +- 10 mmHg) \citep{ delclaux1994arterial} and 4.4 +- 0.6 kPa (33 +- 4.5 mmHg).

{sprung2006age}

Arterial oxygenation gradually declines with aging \citep{craig1971closing} whereas CO2 elimination remains unaffected despite an increase in dead space ventilation \citep{raine1963aa}, The latter is due at least in part to a decline in CO 2 production associated with a decrease in basal metabolic rate. Several equations have been proposed to predict the PaO 2 as a function of age. Between the ages of 40 and \citep{valentine1990preoxygenation}, the following equation provides a reasonable estimate, and takes into account changes in both PaCO 2 and the body mass index (BMI): PaO 2 (mm Hg) = 143.6 - (0.39 × age) - (0.56 x BMI) - (0.57 × PaCO 2 ). After 75 yr of age, arterial oxygen tension did not correlate with BMI and PaCO2, and remains relatively stable at around 83 mmHg.

Several factors contribute to this age-related decline in PaO 2 . In young seated subjects breathing air at rest the alveolar-arterial pressure difference for oxygen (A-aDO 2 ) is between 5 and 10 mmHg. An increase in the A-aDO 2 with age (Figure 5A) occurs because of an increase in ventilation/perfusion heterogeneity, thought to be caused by a decrease in alveolar surface area and the above mentioned premature closure of the small airways \citep{wahba1983influence}. In addition, increased body mass index (i.e., obesity), which frequently accompanies aging, can contribute to widening of the A-aDO 2

The diffusing capacity of the lungs for carbon monoxide decreases with aging \citep{guenard1996pulmonary}, The expected annual reduction in diffusing capacity approximates 0.3 and 0.2 mL·min –1 ·mmHg –1 in males and females, respectively \citep{murray1986normal}, and the changes are more pronounced after 40 yr of age. Women between the ages of 25 and 46 yr have the smallest annual decrease in diffusing capacity, suggesting a protective effect of estrogens, but after age 47 the yearly decline in diffusing capacity in women approaches that in men \citep{neas1996determinants}. The decrease in diffusing capacity is attributed to ventilation/perfusion mismatching, decline in pulmonary capillary blood volume \citep{guenard1996pulmonary} and the loss of the alveolar surface area \citep{thurlbeck1975growth}.

**Carbon monoxide transfer factor**

{janssens1999physiological}

Ageing is associated with a decline in the transfer capacity of the lungs for carbon monoxide (T L,CO ) \citep{guenard1996pulmonary}. The annual reduction in T L,CO is 0.2–0.32 mL . min -1 . mmHg -1 in males and 0.06–0.18 mL . min -1 . mmHg -1 in females \citep{murray1986normal}. This decrease is more evident after 40 yrs of age. Incriminated factors are increased heterogeneity in V’ A /Q’, reduction of the alveolar surface area \citep{verbeken1992senile, thurlbeck1975growth}, decreased density of lung capillaries \citep{butler1970capillary} and a decline in pulmonary capillary blood volume \citep{guenard1996pulmonary}.