REVIEW ARTICLE

Aging and the respiratory system

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ABSTRACT. All the components of the respiratory system are affected by aging, though at different rates: i) the lung elastic recoil decreases; ii) PaO_2 decreases and the $D(A\text{-}a)O_2$ increases; iii) the chest wall becomes stiffer; iv) the inspiratory muscles loose strength; and v) the respiratory centres are less sensitive. Residual volume, closing volume and function residual capacity increase, whereas vital capacity and FEV_1 progressively decrease. The flow volume curve becomes more convex to the volume axis at low lung volume. Whether these changes are due to aging or associated with aging is a matter of debate. However, the aging lung is more fragile in the face of respiratory and systemic diseases than the respiratory system of young adults. Nutrition, smoking habits and sleep-related disorders also affect the respiratory system. Although bronchial asthma may also appear in the elderly, chronic obstructive pulmonary disease is one of the most common respiratory diseases in advanced life and is a major cause of respiratory failure and ICU admission. Age in itself is not a risk factor of respiratory failure, but elderly patients have an increased risk of mortality for both acute respiratory failure (the failing lung), and exacerbated chronic ventilatory failure (the failing pump). Although advanced age can influence the final outcome of elderly patients from the intensive care unit (ICU), admission to the ICU as well as the institution of mechanical ventilation should not be denied on the basis of age alone, since the severity of illness, prior health status and admitting diagnosis have more weight than age in the final outcome.
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BACKGROUND

The aging of the respiratory system is the result of many factors: i) natural aging process, ii) prior diseases (pulmonary and systemic), iii) life-style (smoking, nutrition and exercise fitness), iv) socioeconomic status, v) occupational and environmental exposures, and vi) selection survival. Thus, it seems more appropriate to consider the age-related alterations of the respiratory system as changes associated with rather than due to aging (Fig. 1). The flimsy assumption that biological and chronological ages run parallel becomes more improbable for the respiratory system (1). Indeed, the lungs are massively challenged by the external environment; more than 20 000 litres of air have daily contact with the airways and alveolar wall, while the entire cardiac output crosses the pulmonary circulation.

Longitudinal assessment of lung performance by means of pulmonary function tests that reflect response or adaptation to a given stimulus may represent, within limits, a good marker of overall aging (2).

Differences between young and old subjects can be wide (today's elderly persons suffered from illnesses in their youth that are currently a rarity), or even small (elderly individuals represent survivors), depending on the complex variety of past events. Such differences are not constant, and may change with time without necessarily reflecting the aging process.

This article consists of two parts: the first discusses the morphological, biological, and physiological respiratory system modifications associated with age; Part two focuses not only on frequent respiratory diseases, such as chronic airflow obstruction at different clinical stages, but also on the access of old patients to aggressive therapeutic support.

PART ONE

INTRODUCTION

The aging lung is a non-uniform entity regarding its

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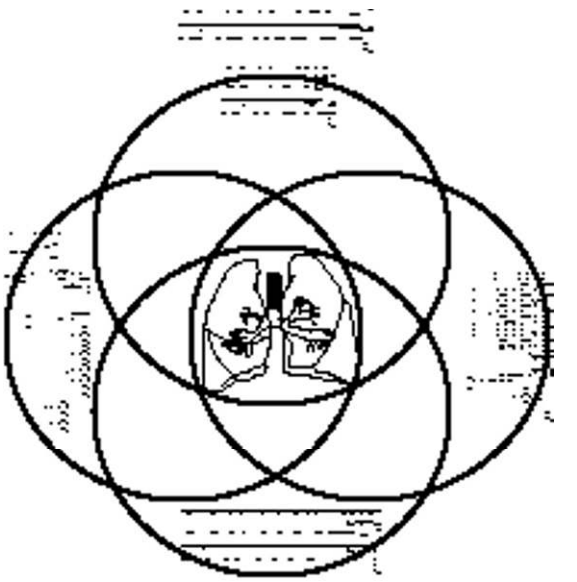

Figure 1 - *Factors interacting in, and contributing to the aging lung.*

anatomic structure and physiologic function, as well as the structure-function relationship. Each respiratory system component, namely lung, chest wall and control of breathing apparatus, declines in function at a rate determined by the interaction between internal and external factors. It can be advanced that lung function decline is the fastest process because of this organ's continuous exposure to environmental pollutants. However, even for the lung it is difficult to separate the effect of natural aging from the subliminal damage caused by external factors. Nonetheless, for the respiratory system as well as other systems of the body, the notion of aging and "old age" should be based on the assessment of performance, rather than time.

We share the view that the entire respiratory system is made up of two separate, but integrated entities, namely the lungs, including the intrapulmonary airways and vessels, and the ventilatory pump, comprehensive of the respiratory centres, the respiratory muscles and the thorax with its chest wall and diaphragm-abdominal compartments (3). The lungs are the pure gas exchange organ, whereas the ventilatory pump sustains alveolar ventilation. Both the lungs and the ventilatory pump are affected by aging. This distinction has important clinical implications, particularly when the respiratory system fails as a consequence of either acute or exacerbated chronic respiratory diseases, and causes severe, potentially life-threatening abnormalities in the arterial blood gases and pH. Indeed, while hypoxemia is mainly due to intrapulmonary factors, such as ventilation-perfusion mismatching and shunt (hypoxemic respiratory failure) (4, 5), hypercapnia is instead mainly the consequence of the ventilatory pump's diminished capability to sustain alveolar ventilation (hypercapnic ventilatory failure) (6, 7). Indeed, the unimpaired ventilatory pump can maintain a stable $PaCO_2$ even in the presence of severe ventilation-perfusion abnormalities (6). Therefore, the literature on the effect of aging on the lungs and ventilatory pump will be analyzed and discussed separately.

THE AGING LUNG

Whether the morphological and physiological changes observed in the lungs and airways with advancing age are due to aging, or associated with aging is a matter of debate (8).

The lungs

Morphological changes in the lungs have been widely observed in the elderly (9). A decrease in alveolar surface area with age has been consistently reported, from about 70 m^2 at age 20 to about 60 m^2 at age 70, and reflects a possible reduction in the number of alveoli per unit of lung volume (10). Indeed, Thurlbeck demonstrated a progressive loss of alveolar wall tissue, which decreases from about 11% of the total lung tissue at age 20 to about 8% at age 80 (10). In normal life-long non-smokers, this reduction is associated with a linear decrease of the ratio between airspace wall surface area and unit volume of lung tissue with aging, indicating an increase in airspace size with advancing age, that is more evident in men than in women (11). Furthermore, because of the age-related increase in the size of the respiratory bronchioles, alveolar sacs and alveolar ducts, the proportion between alveolar air and alveolar duct air diminishes with age (Fig. 2).

For years, the terminal airspace enlargement occurring with age has been called "senile emphysema"; an official NHL statement in 1985 recommends the term of "aging lung" rather than "emphysema" (12). Recent data from Verbeken et al. (13, 14) indicate that the lungs of the elderly are characterized by a homogeneous enlargement of the terminal airspaces without fibrosis, and differ from emphysema by the absence of alveolar wall destruction.

The major age-related physiological change in the lungs is the loss of elastic recoil (8, 15, 16). Following earlier studies (17, 18), most published data show that the volume-pressure curve of the lung is displaced left, i.e., lower distending pressure with advancing age (8, 16). While a definite explanation for the pulmonary elastic recoil decline in the elderly has not yet been reached, this modification has been ascribed almost

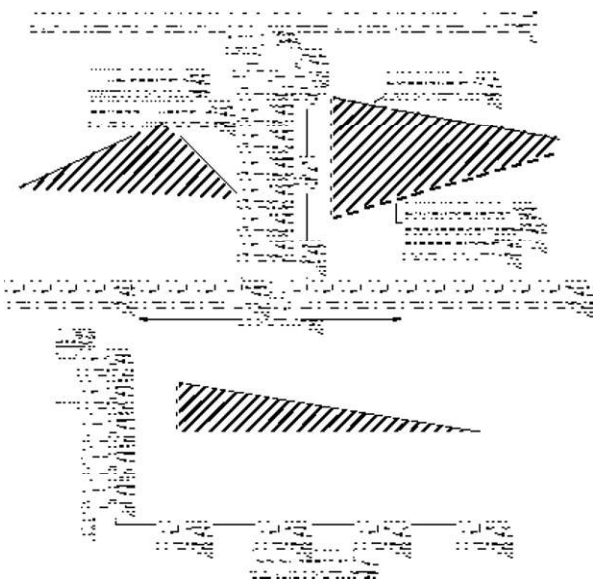

Figure 2 - *Relationship between changes in the surface alveolar area (top, left panel), alveolar and terminal airspaces area (top, right panel), and alveolar parenchyma with age. Data extrapolated from Ref. 10.*

exclusively to lung connective tissue alterations, particularly structural changes in elastin and collagen (19). Total pulmonary elastin and collagen contents do not change appreciably with aging when they are expressed per mg of dry lung weight (20). Pleural and septal elastins, however, increase while airway and vessel elastins decrease with advancing age. Moreover, a soluble form of collagen was found to decrease with age; collagen also becomes more stable, likely due to an increased number of intermolecular cross-links (21). Thus, changes in the spatial arrangement or cross-linking of both elastin and collagen fibres are thought to be involved in the loss of elastic recoil with increasing age. It was shown that the reduction in elastic recoil is greater at higher than lower volumes, averaging -0.2 and -0.1 cm H_2O/yr at 90% and 60%, respectively, of the total lung capacity (TLC) (19), and is negligible below 50% TLC (22). However, Knudson et al. (23) found that the loss of lung recoil with age in both sexes amounted to half the value reported by Turner et al. (19); this difference likely reflects the more rigorous selection criteria applied to the population examined in the Tucson epidemiologic study (22). Static lung compliance above the functional residual capacity (FRC) was found to either increase slightly with age or remain the same (16).

The airways

Both the central and peripheral airways are affected by age. A slight increase in diameter is probably the only effect of aging on the large, central airways (24). Due to the interrelationship between the lung parenchyma and the intrapulmonary airways and vessels, the decrease in recoil can affect the stability and diameter of the airways and vessels, because support is lost. The diameter of the small airways (< 2 mm) decreases with increasing age after 40 years (25). Due to the combination of different changes in the diameter of the central and peripheral airways, total flow resistance either increases slightly, or remains essentially unchanged with aging (26).

Pulmonary circulation

The little data available from retrospective and cross-sectional studies suggest that a slight decrease in pulmonary artery blood flow may occur in some, but not all, healthy old subjects (8). However, Davidson and Fee (27) found a linear increase in the mean pulmonary artery pressure from the age of 20 to 60 years.

Pulmonary gas exchange

Arterial blood gases. It was reported that in normal non-smoking subjects PaO_2 declines, and the room air alveolar-arterial oxygen gradient, i.e., $D(A-a)O_2$, increases with age, at least up to 70-75 years (Fig. 3) (16, 28). A meta-analysis of >2 200 published reports indicated an age-related decrease in PaO_2 amounting to about 0.33 mmHg/yr (29). The

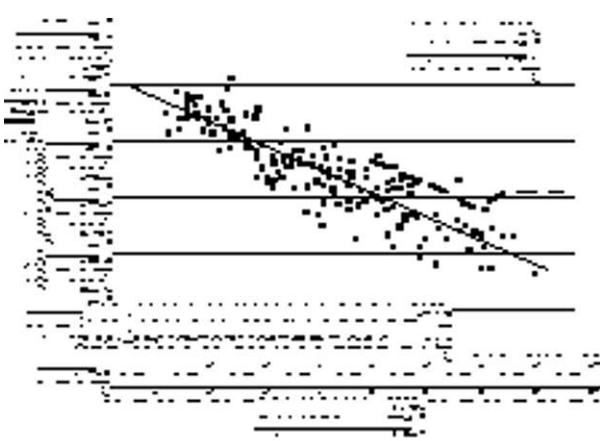

Figure 3 - *Relationship between arterial PO_2 and age. The continous line represents the regression line from the experimental data points (dots). The dashed line was drawn using average values from Ref. 30.*

PaO_2 decline may be explained by extrapulmonary and mostly intrapulmonary factors, and in older individuals was ascribed to living at about 1800 mt. above sea level. However, more recent work indicates that in healthy subjects >75 years, PaO_2 tends to plateau without any correlation with age (30). Similar results were found in elderly patients with mild chronic obstructive pulmonary disease (COPD) (31). The apparent discrepancy between previous (28) and recent (30) studies could reflect differences not only in the characteristics of the populations examined, but also between the aged population in the '60s and '90s due to a sort of natural selection that enabled the elderly to survive.

Age-related changes in $PaCO_2$ were not found in healthy subjects, and $PaCO_2$ remains virtually constant for the life span (16, 28). It was reported that minute ventilation is not diminished in older adults at rest, and that the unchanged $PaCO_2$ is due to a decreased body metabolism. This adjustment is required in view of the fact that physiological dead space increases progressively, from about 20% of the tidal volume at 20 years to 40% at 50 years, and thus determines a decrease in alveolar ventilation with age. However, other workers reported that the decrease in alveolar ventilation with age is compensated by a slight increase in minute ventilation to keep $PaCO_2$ essentially unchanged (32, 33). Indeed, an increase in resting minute ventilation with advancing age has been reported.

Intrapulmonary factors. The loss of lung elastic recoil has been claimed to be the main mechanism leading to lower distending pressures of the airways; there is an age-related increase in the closing volume, and hence a lack of preferential distribution of ventilation to the lower (or dependent) zones of the lungs in subjects older than 65 years. Indeed, due to the vertical gradient of pleural pressure (more negative at the top than at the bottom), the dependent airways are exposed to a positive regional pleural pressure during deflation, and tend to narrow or collapse more easily in the presence of reduced lung elastic recoil pressures (34). Airway narrowing or closure affects the distribution of ventilation to the distal gas exchange units, but does not necessarily influence their perfusion. In contrast, there is an increase in perfusion to the higher lung regions which receive less ventilation in the elderly (34). Although the VA/Qc ratio distribution need more extensive study in the elderly, a few anecdotal measurements show more dispersion and less symmetry in the ventilation and perfusion curves of older individuals than young subjects (35). Thus, ventilation/perfusion (VA/Qc) mismatching accounts for most of the decrease in PaO_2, and the increase in $D(A\text{-}a)O_2$ that are detectable with advancing age.

Single-breath carbon monoxide diffusion capacity (DLCO), and DLCO normalized for alveolar volume (DLCO/VA) have been uniformly reported to decrease with age, at rates of -0.21 and -0.16 mL/min/mmHg/yr for men and women, respectively, in a linear model regression (8). However, the decrease in DLCO with age is likely non-linear as it is most evident after 40 years. The magnitude of the reduction in the surface area of the terminal air spaces with age corresponds fairly well to the age-related decline observed in DLCO (36). Even though DLCO decreases with aging, its diminution does not contribute measurably to the $D(A\text{-}a)O_2$ increase and the PaO_2 drop observed in resting old subjects at sea level.

Extrapulmonary factors. For a given intrapulmonary gas exchange, PaO_2 can be significantly influenced by the age-related reduction in resting cardiac output and mixed venous O_2 content and pressure (PvO_2).

THE AGING PUMP

Apparently, all the components of the ventilatory pump, namely the thorax, the respiratory muscles, and the respiratory centres are affected by advancing age.

The chest wall

The stiffness of the rib cage increases with age, perhaps due to other age-related changes including: i) rib decalcification, ii) rib cartilage calcification, iii) changes in rib vertebral articulations, iv) changes in the shape of the chest, and v) narrowing of the intervertebral disk spaces (26, 37). These anatomical changes shift the chest wall volume-pressure relationship to the right, and determine a reduction in chest wall compliance at the age of 50 years and over, so that at the age of 60, the chest wall recoil would amount to 30-40% of the recoil of the respiratory system at full inflation (38). During normal breathing, rib cage expansion accounts for about 40% of the change in lung volume in young persons, and about 30% in the elderly.

The respiratory muscles

The respiratory muscles are the only skeletal muscles that must contract with a regular rhythm throughout the life span, and like limb and other skeletal muscles, they are not spared by the effects of advancing age (39, 40). Indeed, inspiratory muscle strength, measured by means of maximum inspiratory pressure (MIP) and transdiaphragmatic pressure (Pdi,max) (39), appears to decrease with age. Black and Hyatt (41)

reported that after 55 years of age, MIP decreases by 2.3 and 1.1 cmH_2O/yr in men and women, respectively. Similar results were obtained by Chen and Kuo (42). However, McElvaney et al. (43) failed to find any age-related MIP change over 55 years. In addition, they observed a wide interindividual variability. Pdi,max averaged 128 and 171 cmH_2O in normal young (<32 yr) and elderly (>65 yr) persons, respectively. This difference was not explained by the age-related increase in FRC, nutritional factors, differences in fitness, or insufficient recruitment from the respiratory centres and motoneurons (39). To explain age-related changes in skeletal muscles, it was advanced that the process of selective denervation, atrophy and degeneration of the motor nerves to the muscle fibres might underlie type II fibre atrophy, the loss in fibre number, and the decrease in muscle mass and hence, strength (40).

The decrease in the pressure generating capacity of the respiratory muscles with advancing age, particularly after 55 years, does not seem to affect breathing at rest, nor exercise performance, nor the ability to maintain or initiate a physically active lifestyle during old age (40). However, it is worth noting that the oxygen consumption of the respiratory muscles increases linearly with age (44), and this may render them more susceptible to fatigue when stressed by pulmonary and chest wall diseases (45).

The respiratory centres

A depressed ventilatory response of almost 50% to both hypoxic and hypercapnic stimuli was reported in the elderly, compared to young normals (46). It is unclear whether the underlying mechanism is related to abnormal processing, or to reduced perception of chemical stimuli.

Dyspnea, defined as "an uncomfortable sensation of insufficient breathing", is the result of multifactorial mechanisms, which can all contribute to the sensation of breathlessness. Stimuli from different peripheral receptors, such as chemoreceptors, upper airway and lung mechano-receptors, chest wall receptors, particularly those travelling from the inspiratory muscle fibres, play a role, which has not yet been fully elucidated. Our present understanding has not reached the point where we can conclusively link a specific disease to a specific mechanism of dyspnea (47). Although breathlessness is the most common symptom in respiratory diseases, it may also be due to extrapulmonary causes. Elderly patients frequently report breathlessness. This should not be attributed to aging in itself, and the primary cause of this symptom should be carefully investigated, as in younger patients (48).

LUNG VOLUMES

The total thoracic volume is usually divided into four volumes and four capacities coming from the sum of volumes: tidal volume (VT), inspiratory reserve volume (IRV), expiratory reserve volume (ERV) and residual volume (RV); inspiratory capacity (IC = VT+IRV), functional residual capacity (FRC = ERV+RV), vital capacity (VC = VT+IRV+ERV) and total lung capacity (TLC = VC+RV). Lung volumes and capacities vary with age, body size, sex and probably race.

Subdivision of lung volumes

The subdivision of lung volumes changes with age, mainly as a consequence of the loss of elastic recoil and increased thoracic stiffness. In contrast, TLC remains relatively constant throughout adult age, although a small reduction may be observed due to decreased inspiratory muscle strength and loss of height (16). RV increases with age mainly due to an earlier airway closure during expiration, likely caused by the reduced diameter and the loss of support of the small airways (49). The latter is a consequence of the decrease in the retractive forces of the lungs. As RV increases, ERV and VC decrease because the volume at which the small airways close during expiration (closing volume) increases progressively with age (49). FRC, which results from the opposing elastic forces of the lungs and chest wall, is displaced at higher lung volume by aging, mainly as a consequence of reduced lung recoil (Fig. 4).

VC is the most widely measured variable, and much information is available from cross-sectional as well as a few longitudinal studies. The pooled data suggest a VC decline of -26 mL/yr in men and -21 mL/yr in women after the age of 40 years (8, 16). In a classic cross-sectional study, the data indicated that over 40 years of age, VC declines by about 25%, RV increases by a similar amount, and TLC declines by 5-10% (50). Differences among studies are mainly related to the inclusion criteria for defining "normal subjects". Indeed, smokers, former smokers, and people with occupational exposure and/or living in polluted areas, were not excluded in all the studies.

Maximum expiratory flows

The forced expiratory vital capacity (FVC) maneuver, by far the most popular test of pulmonary function, can be graphically displayed as a maximum flow-volume curve (Fig. 4). The forced expiratory volume in the first second of expiration (FEV_1) is also a common measure. Peak expiratory flow (PEF) and instantaneous flow at different lung volumes (75%,

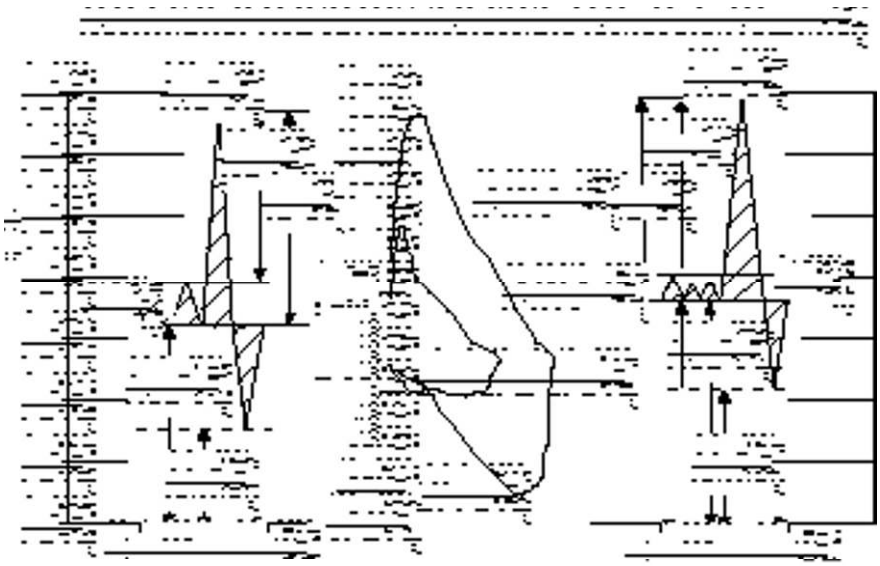

Figure 4 - *The subdivision of lung volumes in young (20-30 years) and in old people (70-80 years) is shown in the extreme left and right panels: residual volume and functional residual capacity increase with age, whereas vital capacity and inspiratory capacity decrease. In the middle panel, flow volume envelope in healthy 20- and 80-year-old individuals is shown: the reduction in FVC is associated with a marked reduction in maximal expiratory flows with age.*

50%, 25% of expired FVC) are also commonly assessed (38). Both FVC and VC decline with age. Maximum expiratory flows reduce with age at low lung volume more than at high lung volume. Elastic recoil is a major determinant of maximum expiratory flows, and this is in apparent contradiction with the well-known age-related loss of lung elastic recoil above and not below 50% VC. The reduction in maximum flows at 50% FVC and below is due to the progressive decrease in the mean diameter of the membranous bronchioles (16). It was reported that PEF is not affected by age (16). However, different studies found that PEF could also decrease slightly with age after 45 years at a rate of 4 L/min/yr in men, and 2.5 L/min/yr in women (51).

FEV_1 and its ratio to VC (FEV_1/VC%) is the main parameter for detecting airflow obstruction, and its value is influenced by aging (38). The physiological linear decline in FEV_1 was estimated to average 28 mL/yr after the age of 25 years from cross-sectional studies (16). However, longitudinal studies suggest that the FEV_1 decline starts only during the fourth decade of life, and is very small in the fifth, not approaching the -28 mL/yr even at a very advanced age, at least in non-smokers (8, 16).

The different rate of reduction in maximal flows, i.e., more prominent at lower lung volume, determines a change in the shape of the flow-volume curve (8, 16, 38), with the terminal portion becoming more convex to the volume axis with aging (Fig. 4). The "flow-volume envelope" provides the boundaries of the available functional reserve for increasing ventilation in the face of a greater metabolic demand, such as exercise, and respiratory and non-respiratory diseases. The age-related, progressive, decrease in maximum flows at low lung volume reduces the functional reserve, so with increasing ventilation, tidal expiratory flows will reach their maximum values earlier in elderly persons. Beyond that value, any further rise in ventilation will be associated with a rise in the end-expiratory lung volume, which will increase the elastic load, and decrease the inspiratory muscle pressure generating capacity (45). In addition, when tidal flows reach their maximum, abdominal muscle recruitment cannot further improve expiratory flows and ventilation. A recent study by Vitacca et al. (52) showed that forced expiratory flows and volume in the elderly are further reduced in the supine position, and that this change is associated with a lower tidal volume and a reduced lung compliance. This may be significant considering that diseases may keep old patients in bed, hence supine, longer than younger patients.

In this regard, it is worth recalling that the prediction equations for the modifications in physiological functions, lung volumes, maximal flows, pulmonary

Table 1 - *Age-related changes in the respiratory system.*

The aging lung
• reduction of lung elastic recoil
• reduction in PaO_2 and increase in $D(A\text{-}a)O_2$
• decrease in DLCO
The aging pump
• increased chest wall stiffness
• decreased respiratory muscle strength
• decreased respiratory center sensitivity
Lung volumes and maximal flows
• decreasing vital capacity
• increase in residual volume, closing volume, and functional residual capacity
• decreasing FEV_1 and forced expiratory flows

gas exchange etc. are based mainly on cross-sectional data (53). These equations can be appropriate for determining the prevalence of pulmonary function impairment, but are less well suited to determine age-related events, including the incidence or progression of impairment. However, a recent epidemiological survey that specifically addressed 65- to 85-year-old normal men and women reported a good agreement with the data from reference equations (54). Nevertheless, the use of normal values collected directly in elderly populations is encouraged, even though a reduced capacity to cooperate for spirometry in certain elderly populations, for example institutionalized patients, might constitute a major problem. Substitutive techniques, such as the measurement of respiratory impedance by means of the oscillation technique, may require less cooperation and might be more suitable under these conditions (55).

Age-related changes in the respiratory system are summarized in Table 1.

SPECIAL ASPECTS

This section addresses some aspects of individual life-style habits and biological events relevant to respiratory system function.

Nutrition in the elderly. Age-related decreases in lean body mass and total body metabolism have been reported (56). It is not clear whether this decrease is the primary event leading to a lower energy and protein intake, or whether the reduced intake determines the decrease in lean body mass. Protein-calorie malnutrition produces skeletal muscle atrophy, which is most significant in the fast-twitch fibres, and also involves inspiratory muscle contractility. In addition, the protein-calorie nutritional status has important effects on both cell-mediated and humoral immunity. Malnutrition can determine T-cell function and complement activity alterations, which may decrease the overall host defense mechanisms against infections (56).

Elderly subjects may experience a reduction in feeding drive, taste, and dentition, leadind to a minor food intake and difficulty in mastication. However, a multifactorial mechanism cannot be excluded, since changes in the nutritional status with aging can be determined by an interrelated collection of occurrences including physiological, phsychological, and socioeconomical factors. In this regard, it is noteworthy that the decline in the nutritional status of elderly patients is usually viewed as a normal event, due either to aging or the associated disease process; whether the nutritional status may play a role in the disease outcome is not fully considered.

Smoking cessation. It is well-known that smoking is a leading cause of chronic bronchitis, pulmonary emphysema, COPD, and lung cancer (57). Furthermore, it has been documented that cigarette smoking in the elderly is a major risk factor for: i) accelerated general physical decline, ii) pulmonary function deterioration, iii) progression of respiratory diseases in late life (58), and iv) even premature death (59). Smoking cessation represents the most effective measure to reduce the accelerated rate of FEV_1 decay in COPD (57). It was shown that smoking cessation slows the

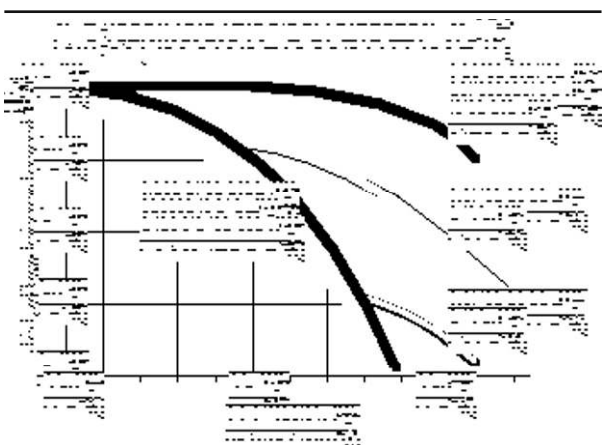

Figure 5 - *Relationship between FEV_1 decline and age in non-smokers or non susceptible smokers, and in regular or susceptible smokers. The FEV_1 decline in people who quit smoking at 45 and 65 years is also shown.*

rate of pulmonary function decline also in the elderly; however, the benefits of cessation on the respiratory system appear to be more gradual than those on the cardiovascular system (58). It was documented that smokers who quit, even after the age of 60, have a better pulmonary function than continuing smokers (57) (Fig. 5). In this context, it is worth recalling the concept of "lung age", i.e., the chronological age at which a person's measured pulmonary function is normal for the person's sex and height (60). For example, a 20-year-old smoker may have a "lung age" of more than 40 years. On the basis of the available evidence, smoking cessation should be strongly encouraged at any age; nonetheless, the psychological interactions of aging and smoking cessation should also be taken into account, since the "quality of life" and not only the "length of life" should be considered (61).

Sleep. The sleeping patient is still a patient. His disease not only continues while he sleeps, but indeed may progress in a fashion entirely different from that during the waking state (62). Extraordinary progress has been accomplished in sleep medicine (63).

Breathing during sleep. Sleep serves multiple covert functions, notably those associated with changes in neuronal activity. Sleep patterns vary during life; the most easily recognized age-related changes are an increase in nocturnal awakenings, and a decrease in stages 3 and 4 of slow-wave sleep (Fig. 6 and Table 2). Respiration is remarkably affected by sleep; REM sleep, which is characterized by the greatest instability of cardio-respiratory function, influences breathing in a totally different way, compared with non-REM sleep. i) Breathing becomes irregular predominantly at stages 1 and 2 of slow wave sleep (SWS or non-REM sleep), and during REM sleep. In contrast, in stages 3 and 4 of SWS, breathing appears even more regular than during wakefulness. ii) Minute ventilation decreases disproportionally with respect to the body metabolism, so that PaO_2 falls and $PaCO_2$ rises. In patients with COPD, this hypoventilation can greatly worsen arterial hypoxemia and hypercapnia. iii) The muscles of the upper airways and the diaphragm have a reduced input during non-REM sleep. The decrease in upper airway muscle drive and tone during SWS sleep leads to an increase in the airway resistance, because the upper airway walls are more floppy and prone to collapse nearly completely. This fact is believed to be responsible for snoring. iv) Throughout SWS sleep, breathing is essentially under metabolic control, whereas during REM sleep, multiple influences reflecting reticular and cortical activation can regulate respiration. In any case, minute ventilation drops by about 10%, and the ventilatory response to both hypoxia and hypercapnia is reduced by about 25% (64). Lung volumes fall during sleep; FRC drops by about 300 mL in healthy adults, and about 700-800 mL in asthmatics; this could be relevant to nocturnal asthma (65).

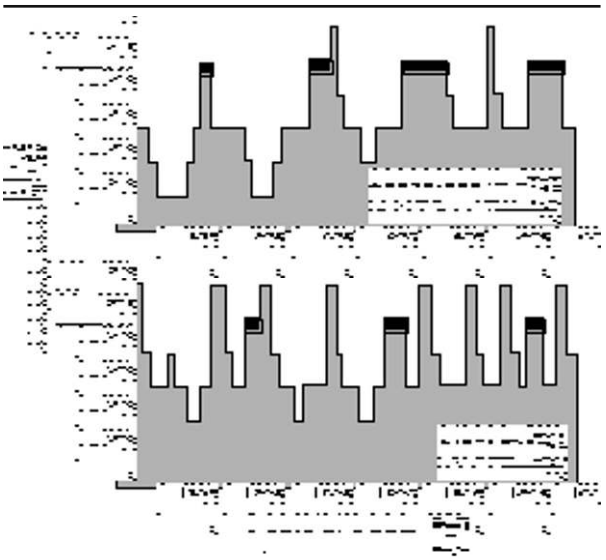

Figure 6 - *Relationship between sleep stages and hours of sleep in young adults and elderly persons. Note lighter sleep in old age with more frequent periods of waking and disappearance of the 4th stage.*

Sleep-Related Respiratory Disturbances (SRRD). Sleep problems in the elderly are very frequently encountered, and include sleep apnea syndromes (obstructive, central and mixed), dysrhythmic (periodic) breathing, and nocturnal alveolar hypoventilation. The obstructive sleep apnea syndrome (OSAS) is the most common organic sleep disorder, and

Table 2 - *Sleep architecture change in the elderly.*

• Total sleep time	decreased
• Daytime napping	increased
• Sleep efficiency (the ratio of time asleep to time in bed)	decreased
• Nocturnal awakenings	increased
• Sleep latency (time required to fall asleep)	unchanged
• REM latency (time to the first REM period during sleep)	decreased
• Slow-wave sleep (stage 3 and 4)	decreased
• Daytime sleep latency (time to sleep onset during attempts to fall asleep during defined daytime intervals)	decreased

Table 3 - *Respiratory tract defense mechanism.*

PHYSICAL AND PHYSIOLOGICAL	AIRWAY DEFENSES	ALVEOLAR DEFENSES
• Aerodynamic filtration • Humidification Absorption Dilution • Airway reflexes: cough - sneeze - bronchoconstriction • Mucociliary transport • Alveolar clearance mechanisms *Humoral* (non-specific soluble factors) • Alpha$_1$ - antitrypsin • Lysozym • Lactoferrin • Interferon • Surfactant • Complement • Immunoglobulins: IgA- IgG - IgM *Cellular* • Alveolar and interstitial macrophages • Dendritic cells • Neutrophils and Eosinophils • B and T lymphocytes • Mast-cells and Basophils	• Physical • Physiological • IgA	*Resident Defense Mechanisms:* alveolar macrophages- complement- surfactant *Pulmonary Inflammatory Responses:* macrophages - polymorphonuclear leukocytes *Specific Immune Responses:* • Accessory cells (interstitial macrophages - dendritic cells) • Lymphocyte populations • IgG

HOST DEFENSE IMPAIRMENTS in the ELDERLY

Aging of the Lung	**Aging of the Immune System**
• decreased elasticity • less effectiveness of cough • decreased mucociliary clearance *Concomitant Illness:* • COPD • Neurologic disease • Cardiac disease • Diabetes • Renal failure	*T-cell defects:* decreased proliferative response - decreased cytokine expression *B-cell defects*: decreased immunoglobulin (IgG, IgM) production - increased circulating autoantibodies Imperfect T-cell/β-cell interactions (with expression of abnormal immunoglobulins)

results in an excessive daytime somnolence. According to recent epidemiological studies, OSAS prevalence is about 2% in women, and 4% in men (66); however, in older men and women it ranged from 28% to 62% and from 20% to 62%, respectively (67). There is no question that the occurrence of S-RRD increases with increasing age, but its clinical significance is still unclear. Findings in a clinical population indicated that S-RRD in the elderly are minimally associated with mortality and morbidity, while cohort studies of older subjects suggested the opposite (68). COPD patients may become hypoxemic during sleep; the hypoxemia appears more marked during REM sleep, and is related to daytime PaO_2 and $PaCO_2$, and REM sleep duration (69). The underlying mechanisms are represented by alveolar hypoventilation (the most important), decrease of FRC, and ventilation/perfusion mismatching.

Exercise. Due to scientific and technological advances, cardio-pulmonary exercise testing has been gaining popularity in clinical settings over the last 20 years. Aging causes many subtle, albeit detectable, physiological changes in response to exercise; the major structural change appears to be the loss of lung elastic recoil, which reduces the capacity to increase expiratory flow rates with increasing ventilatory demand.

Maximal aerobic capacity ($V'O_2$ max) offers a measurable criterion to assess the influence of aging; its decline amounts to approximately 6-10% per decade. Although the older adult displays several alterations in the ventilatory response to exercise compared to the young adult, alveolar ventilation is adequate to maintain arterial blood gas homeostasis (70).

It seems clear that aging is associated with a decline in respiratory function, but aging of the cardiovascular system is more likely to limit physical perfor-

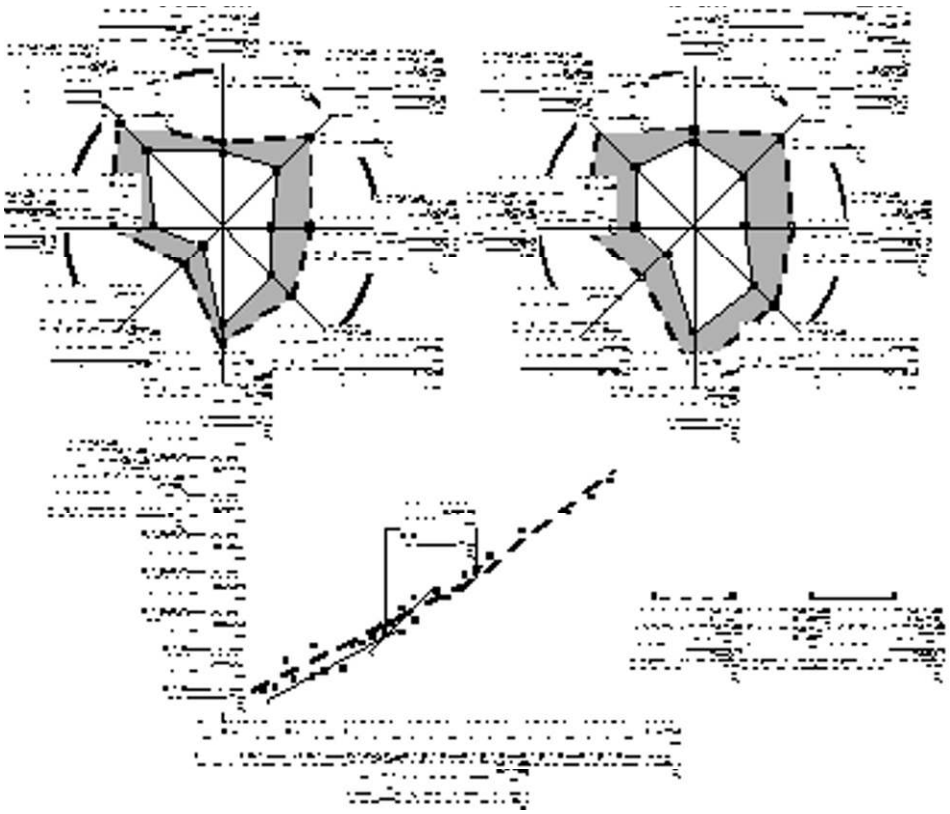

Figure 7 - *Cardio-pulmonary Exercise Test in a young (22 years) and an elderly (74 years) normal man. Data are reported at two levels of exercise: anaerobic threshold (AT) and maximal aerobic capacity (VO_2max). Cardiac and breathing reserve are within normal limits.*

mance than the aging respiratory system. Moreover, the rate of decline in cardio-pulmonary performance can be slowed down by avoiding a sedentary existence (71).

The question whether the pulmonary system limits exercise performance in the elderly is difficult to answer for a number of reasons, including the wide variability of responses in the aged compared to the young adult (Fig. 7). This is due to the different level of fitness in the aged and to a larger variability in the baseline pulmonary function that, in turn, represent the effects of aging on the lung and chest wall.

The major effect of aging on the metabolic demands consists in an increased work and cost of breathing: this would cause an increased whole-body oxygen consumption, at a given work rate (decreased efficiency). Even considering that the aging process causes a parallel decline in metabolic demand and pulmonary reserve, we could answer the above question suggesting that the lung function may play a role in limiting exercise performance.

Exercise testing seeks to assess the level of exercise tolerance as well as define the pathophysiological processes that limit exercise. Endurance training improves exercise tolerance mainly by inducing structural and biochemical changes in exercising muscles; these changes, in turn, improve oxygen delivery and its utilization at the muscular level. The interruption of training leads to prompt regression of the accumulated benefits.

Defense mechanisms of the respiratory system. In the elderly, both the physiological and humoral and cellular mechanisms of defense of the respiratory tract may be less effective. The main factors that are thought to induce an age-related impairment in the airway and alveolar host defenses are reported in Table 3 (72, 73). Age-related changes in respiratory mechanics, including a decrease in elastic recoil, structural alterations of the chest wall, and reduction of respiratory muscle strength, may weaken the airway physiological defenses.

Even in the healthy aged population, mucociliary clearance rates appear to be slower than those observed in the young subjects (74). Previous smoking

habit further influences mucociliary clearance in older individuals. The effectiveness of the cough depends on the functional integrity of the respiratory system. In the elderly, inspiratory muscle weakness precludes a large end-inspiratory lung volume, thus preventing the weaker expiratory muscles from exerting their relative maximal force due to the mechanical disadvantage caused by the smaller initial volume. In addition, for a given thoracic volume, the lung elastic recoil is less, and hence, the driving pressure for cough is lower. With aging, however, many other factors, such as impaired alertness, glottal incompetence, increased airway compliance and obstruction, decreased sensitivity of the cough receptors and the more frequent occurrence of conditions denying stimuli access to these receptors (e.g., excess secretions), can contribute to limit cough effectiveness. Thus, the protective function of the upper airway may be compromised with advancing age, and thereby expose the lower respiratory tract to an increased burden of microbes, particulate matter, and noxious environment agents; this is particularly harmful because the likelihood of aspiration in people of advanced age is increased. Moreover, older subjects with bronchiectasis become prone to recurrent exacerbations and enter a vicious cycle in which decreased airway defenses, recurrent infections and worsening of bronchiectasis with further impairment of mucociliary clearance follow one another.

CONCLUSIONS TO PART 1

In order to answer a challenging question, how the aging respiratory system should be perceived, we reported and discussed the major age-related modifications in the respiratory system:

- morphological changes, which reduce the mechanical reserve;
- physiological modifications, which can impair the overall gas-exchange capability (Table 1);
- biological events, which make the aged respiratory system more fragile in the face of respiratory and systemic diseases (Table 3).

Moreover, the aging lung lives in an aging person who may have other clinical problems, including loss of cognitive function, which may limit the possibility of performing complete diagnostic procedures. Nevertheless, we believe that age should not be considered a limiting factor in the diagnostic and therapeutic decision-making process, and when possible, the primary cause of symptoms should be carefully investigated, as in younger patients.

Table 4 - *Distribution of diagnoses underlying respiratory failure.*

AGE	<45 years	45-65 years	>65 year
ARDS	18	12	13
Trauma	31	20	14
Pneumonia	16	29	13
Sepsis	10	8	10
Others	38	25	34
Sub-total	113	94	84
COPD	5	37	70
Total	118	131	154

ARDS: acute respiratory distress syndrome; Trauma: includes motor vehicle accidents; Others: burns, heart failure, surgery, hypothermia, shotgun and stab wounds; COPD: chronic obstructive pulmonary disease.

PART TWO

INTRODUCTION

There can be little doubt that the general population in developed western countries is aging, and thus generating a growing attention to advances in geriatric medicine in general, and respiratory medicine in particular (75). Indeed, the clinical features of many respiratory diseases are influenced by age, but a systematic review of geriatric respiratory medicine goes far beyond the objectives of this article. We will focus on the differential diagnosis and treatment of asthma and COPD in the elderly for the following reasons: i) asthma is often considered a disease of youth, and thus is frequently underdiagnosed and undertreated in the elderly; ii) in the fied of respiratory medicine, COPD not only is the most common, but also the most obvious example of age-dependent disease, the pathogenesis of which directly involves some aging processes, such as the "aging lung", and is associated with the cumulative effect of the environment and personal habits, in particular smoking; iii) international guidelines for the diagnosis and treatment of asthma (76) and COPD (77, 78) have recently been published; and iv) COPD is a major cause of ICU admission for old patients (see Table 4).

The growing magnitude of the COPD problem has determined its reappraisal, as documented by the recent publication of guidelines for the diagnosis and care of patients with COPD under the auspices of both the American and European Respiratory Societies (77, 78). In the past 15 years, COPD prevalence and mortality increased by 40% and >30%, respec-

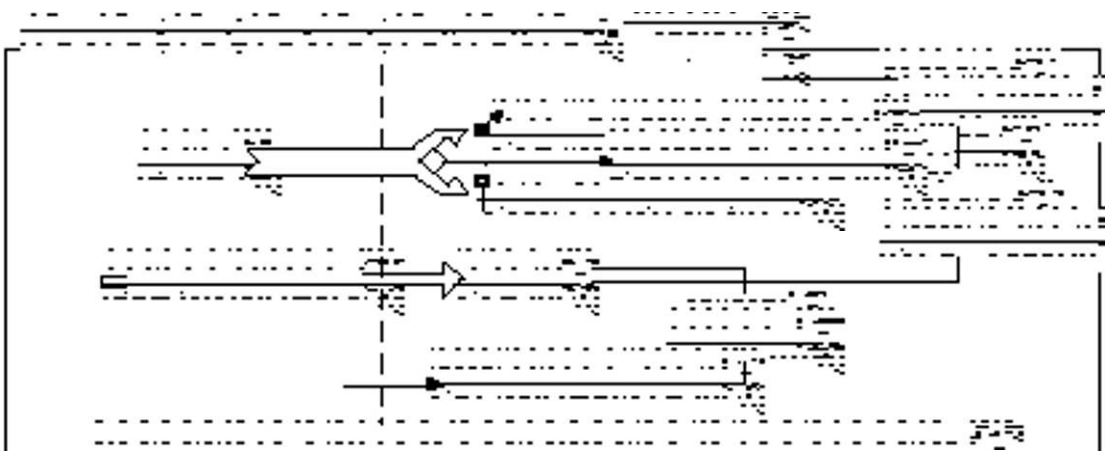

Figure 8 - *Prevalence of airflow obstruction (COPD: chronic obstructive pulmonary disease) in the elderly. The numbers in brackets indicate the prevalence of COPD and asthma after the age of 65 in part according to Ref. 79. As shown in the Figure, about 30% of COPD have partially reversible airflow obstruction.*

tively. Most of the mortality from COPD occurred in individuals over the age of 65 years. Furthermore, the incidence of COPD in the elderly has increased, while rates of heart disease and stroke have fallen.

Chronic obstructive pulmonary disease

COPD is defined as a disease state characterized by the presence of airflow obstruction due to chronic bronchitis and emphysema. Airflow obstruction is slowly progressive, can be partially reversible and may be accompanied by bronchial hyperresponsiveness. Increasing age is an extremely important risk factor, as it reflects the cumulative nature of smoke-induced lung damage. COPD is a complex and heterogeneous disorder where airflow obstruction is determined by irreversible factors, such as loss of elastic recoil and increased collapse of the airways, and by partially reversible components linked to inflammatory airway remodelling and airway smooth muscle contraction (77-79).

It is well recognized that bronchial asthma and COPD are frequent, possibly related disorders with marked similarities and distinct differences. Attention was recently focused on the reversibility of airflow obstruction which can reflect the presence of either bronchial asthma (of recent onset or long-lasting), or an "occult" asthmatic component occurring in COPD (80, 81). Although these two conditions are often difficult to differentiate, their distinction is clinically important because both will show functional improvement with appropriate therapy. To stress these combined features of chronic airway obstruction and bronchial asthma, the terms chronic asthmatic bronchitis (82) and asthmatic COPD (83) have been suggested. This terminology seems fairly appropriate in certain elderly patients who exhibit a significant reversibility of airflow obstruction in the presence of a clinical and functional COPD pattern (Fig. 8).

In the past, bronchial asthma was largely underestimated and hence undertreated in the elderly. According to current epidemiological data, however, bronchial asthma is much more frequent than previously thought (Fig. 9) (84-95). Based on the demonstration of a reduced β-adrenergic receptor responsiveness in normal elderly, it was recently advanced that late-onset asthma may represent the extreme end of a spectrum of age-associated β-adrenergic dysfunction (96).

Although clinical history and physical examination are often helpful, bronchial asthma and asthmatic COPD are not readily distinguished, because pulmonary function testing in older subjects can be difficult to perform properly, and the perception of symptoms and their severity is attenuated. Nevertheless, the available data indicate that reversible bronchial obstruction occurs at all ages (97), even though the response to bronchodilators is seldom assessed in elderly subjects. Moreover, despite the fact that a component of "occult" asthma is present in as many as 30% of the elderly COPD patients, bronchodilator medications are used in less than 10% (98-100). The differential diagnosis between bronchial asthma and COPD is important because different therapeutic strategies with two distinct goals may be followed. In the presence of a reversible airflow obstruction (asthma or asthmatic COPD), anti-inflammatory drugs (inhaled steroids) and β-2 agonists are indicated to gain full control of the

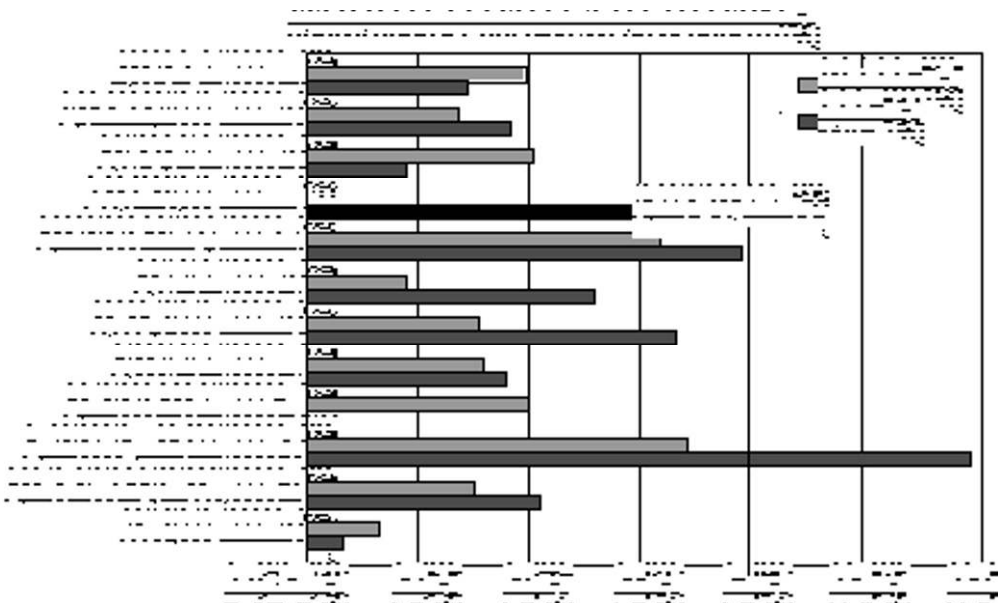

Figure 9 - *Data from 12 studies reporting the prevalence of bronchial asthma in the elderly.*

symptoms and improve lung function (76). Conversely, in the absence of a reversible airflow obstruction (fixed COPD), anticholinergic and β-2 agonists appear useful for improving the symptoms and quality of life (77, 78).

COPD is not only a widespread disease among the elderly, it is also one of the most common causes of respiratory failure. The latter constitutes a privileged area for the application of modern and aggressive medical techniques. These advances not only challenge the physician's scientific capabilities, but also his/her ethical commitment in the decision to withhold and/or withdraw costly and invasive, though potentially life-saving, aggressive procedures (101). We believe that this aspect of geriatric respiratory medicine deserves special attention.

RESPIRATORY FAILURE

Respiratory failure is defined by abnormal gas tension and pH in the arterial blood, with PaO_2 <60-55 mmHg and/or $PaCO_2$ >45 mmHg breathing room air (5). Therefore, the diagnosis of respiratory failure cannot be reached on the basis of clinical observation alone, but requires the examination of arterial blood. Respiratory failure may present either as a rapid, sudden event in a previously healthy respiratory system (acute respiratory failure: ARF), or an exacerbation of a chronic respiratory insufficiency (exacerbated chronic respiratory failure). The management of both acute and exacerbated chronic respiratory failure may require mechanical ventilation to: i) reverse the life-threatening hypoxemia and/or respiratory acidosis, and ii) "buy time" for the concurrent pharmachologic therapy to become effective, and the lungs to recover from the insult.

Mechanical ventilation is normally administered in the ICU as a part of a high-tech, high-cost aggressive management of critical illness (102). Within the context of increasing medical expenses in western countries, special concern has grown for the utilization of costly and aggressive life-preserving technology in the elderly (103, 104). Indeed, since advanced age may be predictive of poor outcome, especially in the ICU (105-107), age is often used as a barrier for ICU admission as well as aggressive treatment (103). Despite the suggestion that expensive life-support care should be denied to the very aged with a poor life expectancy as part of a strategy to conserve limited resources (108), persons over 65 years seem to represent a significant portion of the patients undergoing mechanical ventilation in the ICU, as shown by Table 4, which pools data from more than 30 recent clinical reports. In this uncontrolled series of about 400 mechanically ventilated patients for acute and exarcerbated chronic respiratory failure, patients over 65 years represent 38% of the total, and 46% of these required mechanical ventilation for acute exacerbation of COPD. This Table illustrates two concepts: i)

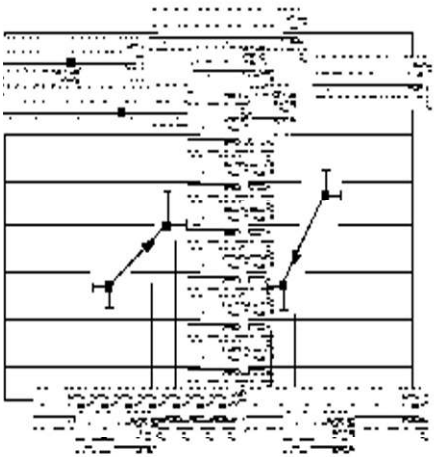

Figure 10 - *Relationship between $PaCO_2$ with $PvCO_2$ (left panel) and PaO_2 with PvO_2 (right panel) in stable COPD patients and in patients with acute exacerbations of COPD.*

severe respiratory failure requiring mechanical ventilation is not uncommon in the elderly; ii) though several causes of acute respiratory failure have been reported in the elderly, acute exacerbation of COPD is the most common. Therefore it seems worthwhile to analyze the role of age in the outcome of severe respiratory failure.

Acute Hypoxemic Respiratory Failure: the failing lung

In most instances, acute hypoxemic respiratory failure (ARF) is determined by an acute lung injury (ALI) which is defined by: i) presence of one or more risk factors, ii) acute onset, iii) diffuse, bilateral infiltration on standard chest X-ray, and iv) severe hypoxemia, namely PaO_2/FiO_2 <300. When PaO_2/FiO_2 is <200, ARF is generally referred to as acute respiratory distress syndrome (ARDS) (109). ALI or ARDS is not a single disease, but a syndrome with a common clinical picture due to the widespread lung injury in relation to groups of risk factors (110). Although the etiology and mechanisms eventually leading to the diffuse lung injury remain unknown, massive flooding of the alveolar spaces with extravascular lung water and inflammatory material, due to increased pulmonary capillary permeability, represents the common final picture of ALI/ARDS. This alveolar edema determines a marked intrapulmonary shunt, up to >50% of total lung perfusion, which profoundly challenges the gas exchange capability of the lungs, and causes a severe, life-threatening hypoxemia. Adequate oxygenation is a major problem in these patients, and positive pressure ventilation may be needed to optimize the recruitment of potentially ventilating airspaces (111). Sepsis, aspiration pneumonia, shock, and trauma, are the most common (about 75%) risk factors. It has been recognized that aging in itself is not an additional risk factor for the development of ALI/ARDS in patients with increased risk for other reasons (112), even though pneumonia and sepsis in elderly patients are often complicated by the development of ARDS (113).

Despite a great amount of basic and clinical research, at 30 years after its description the ARDS mortality rate is still very high (about 50-70% or more), mainly due to the development of multiple organ failure (MOF) (107). Based on the overall influences of coexisting medical problems related to a previous poor health status in older compared to younger patients, and age-associated changes in cardiorespiratory physiology, it was suggested that advanced age may worsen the prognosis for ARDS patients (113). The chances of survival are so small in patients >80 years that one questions withholding and withdrawing of mechanical ventilation (108). The causes of poor outcome associated with age in ARDS were specifically addressed by Gee et al. (114) who found that patients >60 years had a higher mortality rate (69%) than patients <60 years (12%). These workers speculate that cardiac output was reduced in the older patients because of deranged regulatory mechanisms, resulting in a reduced blood flow relative to tissue demands and contributing to a poor outcome. In summary, the overall prognosis of ARDS is influenced by advanced age together with other risk factors, pre-existent disease, other system failure, and the presence of an immunocompromised host (115).

Exacerbated Chronic Respiratory (ventilatory) Failure: the failing pump

A persistent abnormality in arterial blood gases during room air breathing defines chronic respiratory failure (CRF), which in the elderly can be caused by both lung and chest wall disorders. COPD is by far the most common cause of CRF, although chest wall abnormalities due to progressive kyphoscoliosis may not be uncommon. Neurologic disorders may also occur, but are rare as a primary cause of CRF. Exacerbated chronic respiratory failure develops when the respiratory impairment increases and the arterial blood gases further deteriorate, usually associated with a lower pH (<7.36) than in the stable condition.

The advanced stage of COPD is characterized by an extremely limited airflow, and the well recognized ventilation-distribution abnormalities leading to hypox-

emia and hypercapnia which are also the consequence of ventilatory pump failure, even though the mechanism underlying chronic CO_2 retention has not yet been completely elucidated (78). The etiology of exacerbation of COPD is still unknown, although viral and/or bacterial infections of the respiratory tract may play a role (116). In this regard, it should be recalled that influenza is a common viral disease in the cold season, and that elderly people are at higher risk for complications. Control measures should be implemented more vigorously in the elderly. Vaccination of persons at high risk each year before the influenza season, is currently the most effective measure for reducing the impact of this viral disease, although it was reported that elderly persons may develop lower postvaccination antibody titers than healthy young adults, and thus remain susceptible to influenza-related upper respiratory tract infection (117). However, it was shown that even in the case of influenza development despite vaccination, the vaccine is effective in preventing lower respiratory tract involvement, or other secondary complications (117).

The pathophysiologic mechanism determining the development of respiratory failure from the exacerbation of COPD was recently reviewed (118, 119). Figure 10 illustrates the deterioration in arterial and mixed venous PO_2 and PCO_2 in COPD patients, from the stable condition to the acute exacerbation. Briefly, ventilation-perfusion mismatching worsens. Furthermore, a remarkable increase in airflow resistance places a considerable load on the respiratory muscles whose pressure generating capacity is profoundly challenged by pulmonary hyperinflation. An additional load is provided by the intrinsic positive end-expiratory pressure (PEEPi), i.e., the end-expiratory elastic recoil due to the incomplete expiration determined by abnormal flow resistance and expiratory flow limitation (77, 78, 119). Indeed, PEEPi must be fully counterbalanced to generate a sub-atmospheric pressure in the central airway and start inspiration (120). Under these circumstances, not only does gas exchange deteriorate, but also respiratory muscle may fatigue, eventually leading to ventilatory failure. Therefore, in patients with acute exacerbation of COPD, the failing lung is complicated by the failure of the ventilatory pump which cannot maintain an adequate alveolar ventilation in the presence of severe VA/Q mismatching (78). However, whereas hypoxemia may be easily corrected by supplying oxygen-enriched air (through nose cannulas or face mask), which suffices to keep PaO_2 in the upper flat portion of the HbO_2 dissociation curve, the excessive hypercapnia and respiratory acidemia may require mechanical ventilation to sustain alveolar ventilation, and unload the respiratory muscles (105). Therefore, exacerbated chronic respiratory failure occurring in COPD is better referred to as "ventilatory failure", because the acidemia due to hypercapnia is the life-threatening condition which requires the more aggressive treatment (121).

A recent large scale study by Seneff et al. (105) showed that COPD patients admitted to the ICU for exacerbation have an overall high hospital mortality (24%); the rate is lower for patients <65 years (10.2%) compared to patients >65 years (32.9%), and rises to 59% one year after discharge in the latter. However, these workers report that the higher mortality was not due to aging in itself, but to the development of non-respiratory organ system dysfunction and the severity of the respiratory impairment, particularly a $PaCO_2$ >50 mmHg at admission. Nevertheless, age had a statistical weight for long-term survival. Since age was found to be not related to the short-term risk, it was concluded that age should not be used as a major criterion for treatment decision-making, even for institution of mechanical ventilation. Indeed, the nearly double mortality in the patients in whom mechanical ventilation was started on the 1st day of admission to the ICU was completely explained by the more severe physiological score (105). In a retrospective analysis of 105 COPD patients receiving intermittent negative pressure ventilation by means of an iron lung because of respiratory failure, age >65 years was associated with a significantly poorer outcome; however, it was not specified whether outcome was short- or long-term nor to what extent it was related to the pre-existing health status (106).

Mechanical ventilation and ICU management in the elderly

As mentioned above, advanced age can influence the short-term outcome of mechanically ventilated ARDS patients, and mainly the long-term outcome of ICU discharged COPD patients. However, some workers (122, 123) failed to find a real impact of age on the outcome of mechanical ventilation, while others (124) noted a significant influence of age, especially in patients requiring prolonged ventilatory support. A major problem in comparing different studies is that age is variably defined from 60 (125) to 85 years (122), and that diagnoses and duration of ventilation are quite different. A more recent analysis of the outcome after mechanical ventilation indicated that for the majority of elderly patients short-term survival was nearly as good as in younger patients, although a subgroup of patients ≥80 years with a limited chance for survival from respiratory failure was identified (108). A large scale study using a database (126) found a strong positive non-linear

relationship between mortality rate and aging in mechanically ventilated patients, suggesting that age has an important effect on outcome from mechanical ventilation, though other factors such as ICU duration and diagnosis also influence the final outcome.

In this regard, it should be mentioned that conventional mechanical ventilation through an endotracheal tube bypassing the upper airway may be associated with important, life-threatening complications, particularly barotrauma and infections (127). It was suggested that non-invasive mechanical ventilation, either through a face/nose mask (128-130) or by means of the iron lung (106), might be a powerful tool to reverse acute exacerbation of COPD or cardiogenic pulmonary edema (131), thus avoiding endotracheal intubation and ventilator related complications. Benhamou et al. (132) assessed the value of nasal mask ventilation (NMV) as first-line treatment for severe ARF in the elderly (age, 76+8.1 years). In their uncontrolled clinical study, they found that NMV successfully treated respiratory distress initially in 60% of the 30 patients. These results suggest that NMV could be a possible alternative in the treatment of ARF, even in very ill patients, when endotracheal ventilation is controversial or not immediately required.

On the basis of the available evidence (113), it seems that the decision to admit a patient to the ICU and institute mechanical ventilation should not be based on age alone, particularly as a cost-containment factor in evaluating the potential benefit of mechanical ventilation to an individual patient (104). ICU outcome is more a function of the severity of illness, prior health status, and admitting diagnosis (103). It was suggested that age accounts for only 3% of the explanatory power of the acute physiology and chronic health evaluation (APACHE) predictive index for survival of all ICU patients (133). In addition, once the older patient has been admitted to the ICU, life-support technological resources should not be withdrawn on the basis of age alone (103). It should also be considered that non-invasive ventilation is particularly attractive in the elderly, provided that patients are appropriately selected, adequate nursing is offered, and conventional ventilation is immediately accessible to avoid undue delay should non-invasive ventilation fail (134).

GENERAL CONCLUSIONS

For the first time in our history as a species, mankind as a whole is aging. As a result, medical science must face up to many challenges, among which not only a continuing search for new ways to postpone death, but also the development of new approaches to disabling diseases in those who live longer. Therefore, geriatric respiratory medicine is becoming an important growing field in the biological sciences. Respiratory diseases are increasing in western countries, and now represent the 3rd-4th leading cause of death. Knowledge of the age-related anatomic and functional changes involving the respiratory system in the absence of disease is essential for distinguishing what is normal from what is abnormal and may help to deal with respiratory problems in older individuals. Indeed, age-associated alterations influence disease presentation, symptom perception, treatment response, and possible complications.

The prevention of disability in elderly people poses a challenge to the public health care system and social services. In addition, geriatric respiratory medicine is confronting problems which can be adequately solved, at least in part, only by following a proper approach, in particular by keeping in mind that advanced age is a part of life and not the prologue of death.

We are probably in the condition to state that a classic phrase from our high-school desks, i.e., "senectus ipsa morbus est" (135), may be replaced by "diseases and not age can be the cause of death" (136).

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