3. PATHOPHYSIOLOGY OF RESPIRATION

The biological function of respiration is not simply ventilating the lungs, but securing normal gas tensions (ca. 100 mmHg pO_2 and 40 mmHg pCO_2) for the alveolar air and consequently for the arterial plasma through the aid of ventilation. When the oxygen-need of the tissues changes (e.g. during exercise) the circulation, and consequently the pulmonary perfusion is altered, and ventilation must adapt in a way to secure normal gas tensions in the increased amount of perfusing plasma. *Respiration is globally insufficient* if – due to ventilation abnormality – the alveolar gas tensions are shifted: the arterial pO_2 becomes lower, pCO_2 higher than normal (simultaneously causing respiratory acidosis). On the basis of severe disproportionality regarding alveolar ventilation and perialveolar perfusion (V/Q), global insufficiency may also develop. In cases of smaller V/Q mismatching or an abnormality of the diffusion between the alveoli and the arterial plasma, only the arterial pO_2 will be lower, i.e. *partial insufficiency* develops.

While the overall respiration may be sufficient, occasionally this is reached through compensatory steps, such as altered respiratory mechanics, altered minute ventilation, etc., which steps, themselves, may induce clinical symptoms (e.g. dyspnea).

Although at the tissue level gases are exchanged by diffusion between the plasma of the capillary blood and the interstitial fluid, the gas transport is still not connected directly to the physically bound gases in the plasma (gas tension): mainly the hemoglobin (Hb) is responsible for the **transport** between the tissue and pulmonary capillaries.

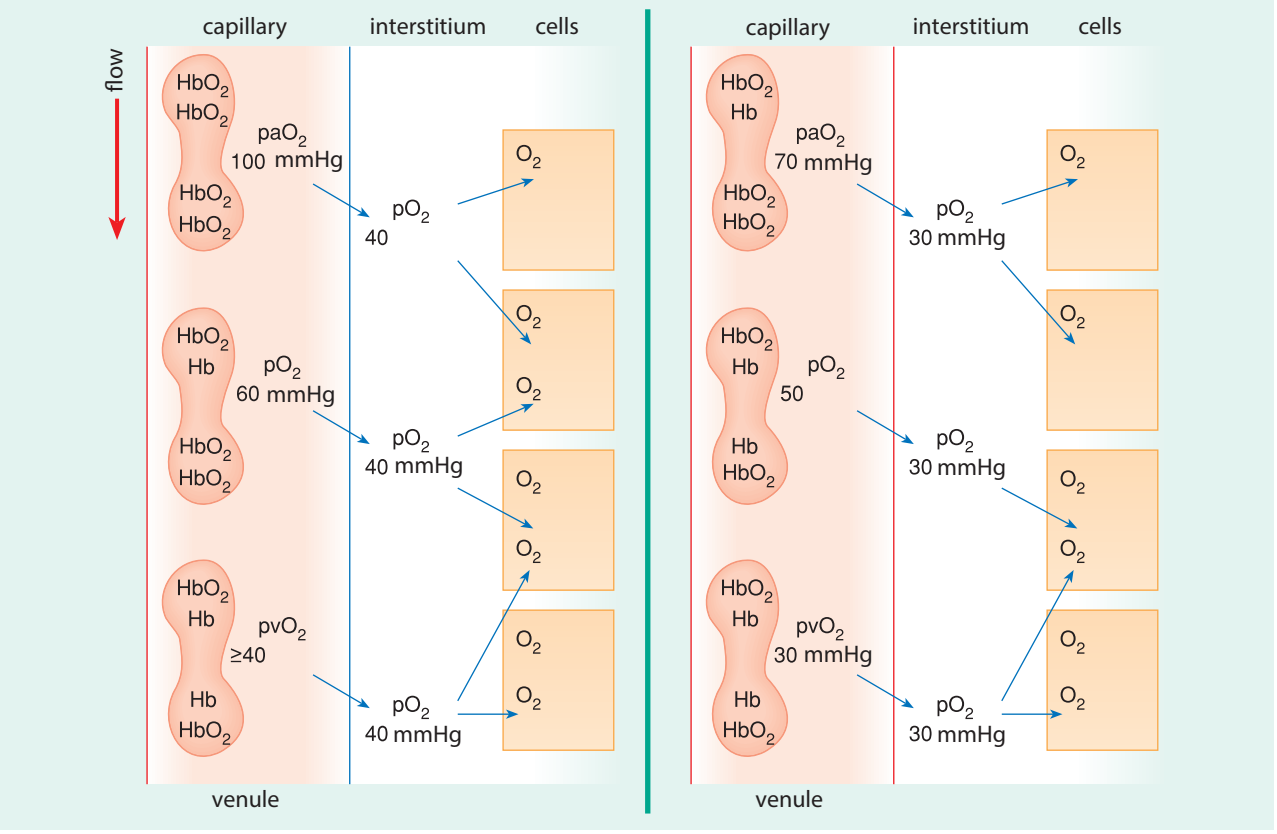

Fig. 3.1.: The route of O_2 from hemoglobin to the cells. The first part of the Fig shows the normal (interstitial pO_2 40 mmHg), the second one the hypoxic state (interstitial pO_2 30 mmHg).

The oxygen bound to Hb, i.e. the amount and saturation of Hb (the latter is determined by the plasma pO_2, according to the oxygen-dissociation curve) together establish the oxygen content of the blood. This is normally ca. 20 vol% in the arterial blood (the Hb is fully saturated). From the plasma of the tissue capillaries oxygen diffuses to the lower oxygen tension of the interstitium – in the plasma this oxygen is replaced by oxygen dissociating from the Hb, therefore the Hb-bound oxygen decreases, the oxygen content of the blood decreases and finally the oxygen content of the mixed venous blood will be ca. 15 vol% (i.e. the oxygen utilization is 5%). Thereby the O_2-saturation of the blood decreases by 25% (from ca. SaO_2 100 to SvO_2 75, i.e. one quarter of the O_2 content of the arterial blood is used up. The O_2-utilization expressed in vol% shows the O_2 amount *de facto* used by the tissues, even in cases of variable arterial O_2-content and O_2-saturation. In the case of known Hb content, from the saturation it is possible to calculate the O_2-content. In clinical practice pulsoxymeter (on the tip of a finger) can continuously measure the O_2-saturation of the blood, regarded as arterial.

The Hb also has a role in the transport of CO_2 in the opposite direction. The CO_2 produced in tissues in the red blood cells (RBC) is transformed by a carboanhydrase enzyme to H_2CO_3, which dissociates to H^+ and HCO_3^- ions. By the RBC membrane anion-exchanging antiporter (band 3 protein, cf. ch. 4.) the HCO_3^- is exchanged for Cl^- while the H^+ binds to deoxyhemoglobin. In the lungs these processes happen in the opposite direction.

Cells/tissues take up oxygen directly from the interstitium. Oxygen utilization within the cells is so good that the mitochondrial oxygen tension may be below 1 mmHg, (e.g. in the mitochondria of the myocardium this may be 0.3 mmHg, and in similar organella of the liver 0.4 mmHg).

Tissue hypoxia originates mainly from the decrease in interstitial pO_2 and insufficient oxygen-uptake or -utilization by the cells. This may develop either due to respiratory failure (hypoventilation, V/Q mismatch, diffusion abnormalities), or to abnormalities of transport (anemia), to defective tissue perfusion (ischemia), or to the inability of the cells to make use of the oxygen (intracellular enzyme blockades).

To fulfill the biological role of respiration, several of its processes must function in a sufficient and coordinated manner. These processes are:

- ventilation (regulation, mechanics and work of respiration)
- alveolo-capillary diffusion of gases, adequate ventilation/perfusion ratio
- transport of gases in the blood to tissues and back to the lung
- oxygen uptake and utilization of cells

Each of these individual processes may have some abnormalities even without severe complex respiratory failure, and they can elicit clinical symptoms, such as disturbances of the mechanics of breathing with the consequent rise in effort of respiration causing dyspnea.

3.1. VENTILATION

3.1.1. REGULATION OF RESPIRATION AND ITS DISTURBANCES

Ventilation is regulated by complex central neural mechanisms. Apart from the voluntary influences, the respiratory centers of the brainstem continuously

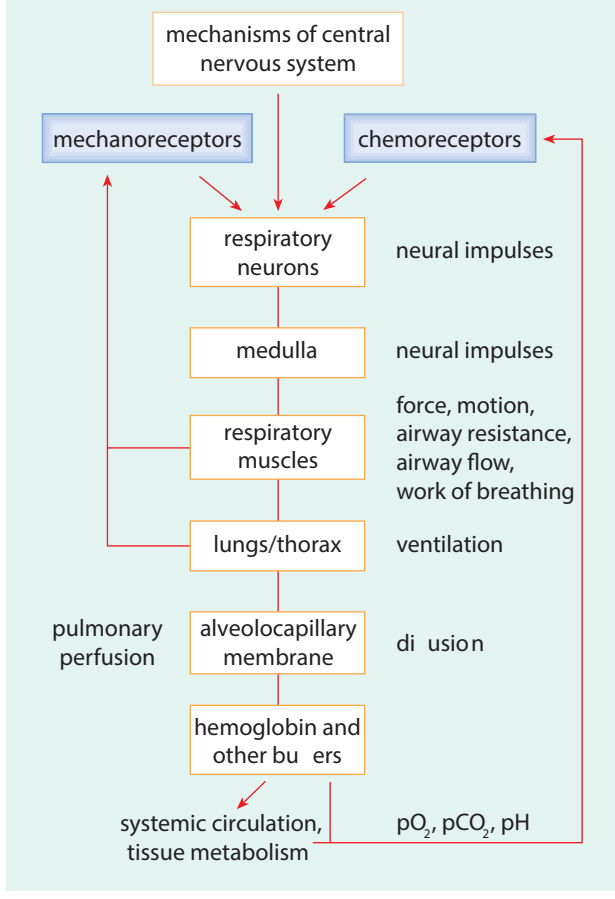

Fig. 3.2.: Components and interactions of the respiratory system / regulation of respiration.

receive information from the peripheral chemo-, and mechano-receptors, thereby adjusting the autonomic regulation of respiration to the varying external influences and internal needs. Since the most fundamental role of the respiratory system is the maintenance of arterial gas tensions at the normal levels (ca. 100 mmHg for p_aO_2 and 40 mmHg for p_aCO_2) these are just the factors regarded as adequate signals in the regulation. Most important are the CO_2- (and H^+)-sensitive receptors of the brain, the hypoxia-sensitive chemoreceptors of the carotid and the aortic glomus may be of secondary importance. Non-specifically other chemical substances may excite (e.g. ammonia) or inhibit (e.g. morphine) the respiratory center – lasting high levels of p_aCO_2 also decreases the activity of the center. Additional and important signals reach the respiratory centers from the mechanoreceptors of the respiratory system, or from the neural receptors sensitive for stretch and irritation of the lung itself (e.g. juxtaalveolar J receptors), but in a non-specific way. Signals influencing the respiratory centers are also derived from the cortex (speaking, singing, etc.), the skin (e.g. cold shower) and other regions (pain). The fast rise of ventilation during exercise or passive movements of the extremities (NB: without any shift in the arterial pO_2 or pCO_2) suggests that signals may originate from the active muscles and joints, which may be important in the adaptation of respiration to the actual needs.

It is a great achievement of the respiratory control that the arterial gas tensions do not change more than a few mmHg, since apart from adaptation to the tissue metabolism, respiratory functions must be adjusted to many other needs of the everyday activity. According to the actual need, the breathing of even depth and rate observed during rest (eupnea) is significantly altered during speaking, singing, crying, laughing, swimming – to mention just a few activities, and some special occupations (playing on pipe, glass-blowing) may produce yet even more extreme situations. During intensive exercise the large changes in metabolic rate and respiration must be coordinated. Normally the arterial gas tensions usually remain within normal limits even during maximal exercise (there is a respiratory reserve; ch. A3.), and upon exhaustion the further increase in muscle activity and circulation rather than the respiratory capacity is the limiting factor.

It is characteristic for the autonomic control of respiration that it may participate in the modification of several physiological parameters. For example, among panting species the high-frequency breathing is a tool of heat loss. In other cases, the CO_2-excretion may serve purposes of pH-regulation.

Common disturbances of the respiratory control usually affect the regularity, the rate or the depth of breathing or they may alter the minute-ventilation (total and/or alveolar ventilation) at the same time. Even in the case in which the respiration appears to be continuous and eurhythmic, it may be abnormal: according to the relationship between the tidal volume and the dead-space, the alveolar ventilation may be inadequate or the breathing may exceed what the body needs (hypo- and hyper-ventilation).

Hypopnea means that the size (depth) of the breath is smaller than needed, *hyperpnea* means the opposite, while in *apnea* there is no air flow (breathing stops after expiration). A pause of breathingat full inspiration is named *apneusis*. *Tachypnea* is more frequent than normal breathing, the rarer one is *bradypnea*. Apnea may appear periodically in Cheyne-Stokes breathing: the size of breath increases, then decreases, followed by an apneic period (crescendo – decrescendo – stop), afterwards everything starts from the beginning. It is regarded as physiological variant in sleeping neonates, originating from a relative immaturity of the chemoreceptor system, but may also be observed later in other situations.

Cheyne-Stokes breathing may be common during a stay in high mountainous regions (low atmospheric pressure, low alveolar pO_2 and also low pCO_2): the

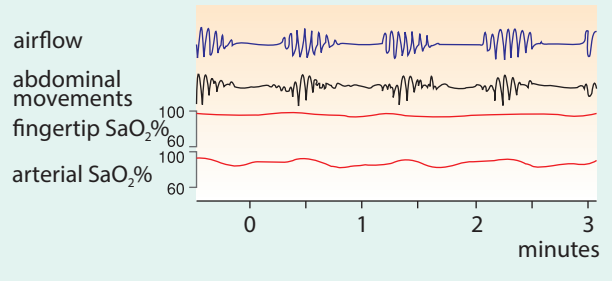

Fig. 3.3.: Cheyne-Stokes periodic breathing. Air flow is parallel with the abdominal movements. Lower curves: "arterial" O_2-saturation (pulsoxymetry method). The arterial saturation follows changes of ventilation with some delay, the pulsoxymetric sensor on the fingertip follows the alveolar/arterial changes with further delay (and with smaller amplitude). The saturation waves follow the changes of ventilation by 15-20 sec (in congestive heart failure even by 30 sec) (in the clinical practice frequent slow/lasting changes of saturation have no practical importance).

hyperventilation develops to improve oxygen supply also induces hypocapnia, therefore – instead of pCO_2 – hypoxia dominates in the central regulation of respiration. This is always a less accurate regulation and does not allow maintenance of even breathing, since ventilation normalizes pO_2, causing decrease or stop of breathing (hypopnea or apnea). The rising pO_2 will suppress again ventilation, causing hypoxia, which transiently re-initiates or enhances breathing (hyperpnea) until the normalized pO_2 does not suppress ventilation again. The undulating or periodic breathing is particularly pronounced during sleep.

Further mechanisms may also lead to periodic breathing, such as injury (mainly of vascular origin) of the basal ganglia, injury or dysfunction of the connection between the brainstem respiratory centers and the prefrontal cortex, or more often the late stage of congestive heart failure (it is present in 50% of patients with EF<40%). In such heart failure, due to the slowing perfusion, the information for gas tensions from lung capillaries reaches the peripheral/central chemoreceptors slowly, extending their reaction time. In the meantime, the pulmonary congestion due to backward failure of the left ventricle activates irritant pulmonary receptors, leading to enhanced CO_2-sensitivity of the respiratory center and to hypocapnia. Thus, the CO_2 tension decreases below the "apnea threshold" and the respiration is stopped. During apnea the pCO_2 rises, but the signal reaches the peripheral/central chemoreceptors with delay, and the duration of apnea is extended. Finally, this hypercapnia induces hyperventilation again, and the process is repeated. Without CO_2 the hypoxia would regulate respiration, but less precisely and slowly. These mechanisms may explain the undulating or periodic character of breathing, particularly during sleep (NREM). In patients of severe congestive heart disease, short episodes of periodic breathing may also appear during the daytime, what is – according to observations – a very poor prognostic sign regarding life expectancy of the patient (only a few months of survival without heart transplantation). Such patients are treated with theophylline, acetazolamide, or *minimal CO_2* (to exceed apnea threshold) or *careful oxygen inhalation* may be attempted to help.

Oxygen inhalation in some cases (particularly in congestion-induced disorders of diffusion and maintained CO_2-sensitivity) may attenuate the nighttime periodic breathing. However, in other cases (extreme chronic congestion, or simultaneous severe chronic obstructive respiratory disorder with decreased CO_2-sensitivity) oxygen administration switches off the actual signal (hypoxia) which regulates the respiration, and severe hypoventilation may develop. Consequently, severe hypercapnia develops and the necessary ventilation of the patient can only be secured by artificial breathing (assisted ventilation), otherwise acutely life-threatening CO_2-narcosis and coma may follow.

The method of artificial breathing is oro-nasal positive pressure (continuous positive airway pressure = CPAP) is most effective in two levels: higher inspiratory pressure (inspiratory positive airway pressure = IPAP) with lower positive expiratory pressure expiratory pressure (expiratory PAP = EPAP) in order to leave the pharynx open also during expiration.

Sleep apnea syndrome (SAS)

During sleep, respiration is slightly modified even among healthy individuals. The originally even respiration – with deepening of sleep (slow wave sleep, non-rapid eye movements = NREM 1-4 phases) – some changes regarding rhythm and apnea lasting for few seconds may appear. The arterial pCO_2 may increase by 4-8 mmHg, the pO_2 decreases by 3-10 mmHg, the pH decreases by 0.01-0.02 units. The explanation is probably based on a minute (tiny) decrease in the CO_2-sensitivity of central chemoreceptors. Another feature is a relaxation of muscles around the upper airways. In REM (rapid eye movement) phase, these phenomena become more pronounced, however, in healthy individuals they cause neither arterial hypoxemia nor hypercapnia.

In contrast, in pathological cases severe apneic-hypopneic periods may develop during sleep. Sleep apnea syndrome is diagnosed if hourly 5, or during the night 30 apneic periods occur, each of which lasts for at least 10 sec. Recently, those disorders are also regarded important in which the O_2-saturation decreases by min 4% - these may follow not only apnea but also milder hypopnea. Therefore, the original name was modified for sleep apnea/hypopnea syndrome. Most often, an upper airway obstruction (obstructive type SAS) is found in these patients. Relatively rarely, a disorder of the central regulation (decreased CO_2-sensitivity in 5% of cases, central type of SAS) causes the sleep apnea/hypopnea syndrome, but a combined etiology is also possible (mixed type of SAS). In these pathological cases, pronounced alveolar hypoxia, arterial hypoxemia (strong decrease of pO_2 with moderate decrease of saturation) with simultaneous significant hypercapnia develop.

Central sleep apnea

Idiopathic apnea: Cheyne-Stokes breathing is also known among neonates/infants, suggesting that, in this age, the central autonomic regulation of respiration may be insufficient. In pathological cases, the newborn breathes normally when awake, but during sleep the breathing is severely insufficient or stops completely. The daytime healthy looking child may die unexpectedly during sleep (one form of sudden infant death, SID), or may suffer a severe, lasting hypoxic brain injury. Today the phenomenon is referred to as congenital central hypoventilation syndrome, which is more common among infants or small children, but may also occasionally occur in a mild form among adults. According to the American Thoracic Society, the basic abnormality is the presence of a specific genetic mutation. Earlier, such phenomenon was referred to as the „curse of Ondine" (in a French folk tale, an Ondine fairy cursed her mortal husband because of his infidelity).

In milder forms of the syndrome the decreased central CO_2-sensitivity becomes more severe with aging, due to development of an insufficient function of brainstem regulation of respiration. In addition to the age-related changes in sensitivity various medications (sleeping-pills, sedatives), drugs (morphine), or a lasting high (!) pCO_2 (e.g. chronic respiratory failure) may be in the background.

In case of central sleep apnea, *polysomnography* (used for the complex analysis of physiological parameters) demonstrates that the thoracic and abdominal extensions are also absent during the apneic periods, i.e. the central regulatory function is missing or insufficient (Fig. 3.4.).

Obstructive sleep apnea

This disorder may be attributed mainly to a decreased tone of the pharynx and the soft palate, with the simultaneous narrowing of the bigger airways. As sleep becomes/grows deeper, the apneic periods become longer and more frequent, while the thoracic-abdominal respiratory efforts continue (Fig. 3.4.). Temporarily, the airway obstruction may be complete and the air flow may stop. Since the central drive is maintained, it may even enhance the thoracic/abdominal movements. However, the sensitivity of the central regulation often exhibits a slight decrease, due to the repeated hypercapnia.

In young healthy individuals even a mild airway obstruction leads to arousal due to a hypoxia/hypercapnia-induced dyspnea. In obstructive sleep apnea, however, the frequent arousals and fragmented sleep exhaust the patient and the threshold hypercapnia that causes arousal becomes higher and higher, and more severe hypoxia and hypercapnia develops. The air passing through the obstruction will give a snoring sound. In extreme cases the apneic period may exceed one minute. The severity of the clinical picture can be characterized by the "apneic index" which shows how many of the (at least 15 sec. long) apneic periods can be observed within one hour of sleep. Interestingly, even values of 50-70 are possible – leading to severe respiratory failure associated with acute and chronic consequences.

The pathophysiological and clinical changes occurring in the course of repeated sleeping and awakening cycles, and the chain of possible acute and chronic events are shown in Fig. 3.5. and in Table 3.1. Apnea induces a fall in arterial pO_2 and a rise in pCO_2 (global respiratory failure), which enhance sympathetic activity (vasoconstriction, rise of blood pressure, tachycardia). The alveolar hypoxia causes constriction of pulmonary vessels and leads to pulmonary hypertension. As a compensation of repeated hypoxia the erythropoietin production increases and leads to polycythemia.

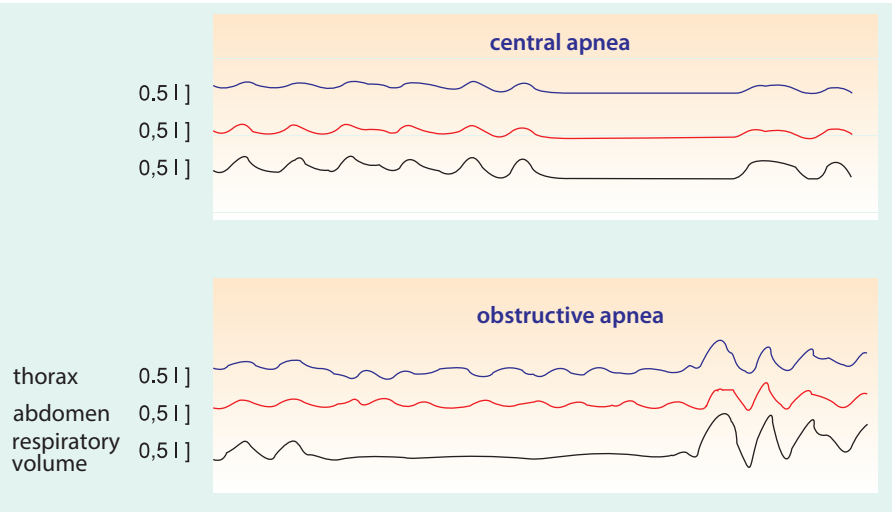

Fig. 3.4.: Interaction between thoracic/abdominal movements and airway flow in central and obstructive types of sleep apnea syndrome.

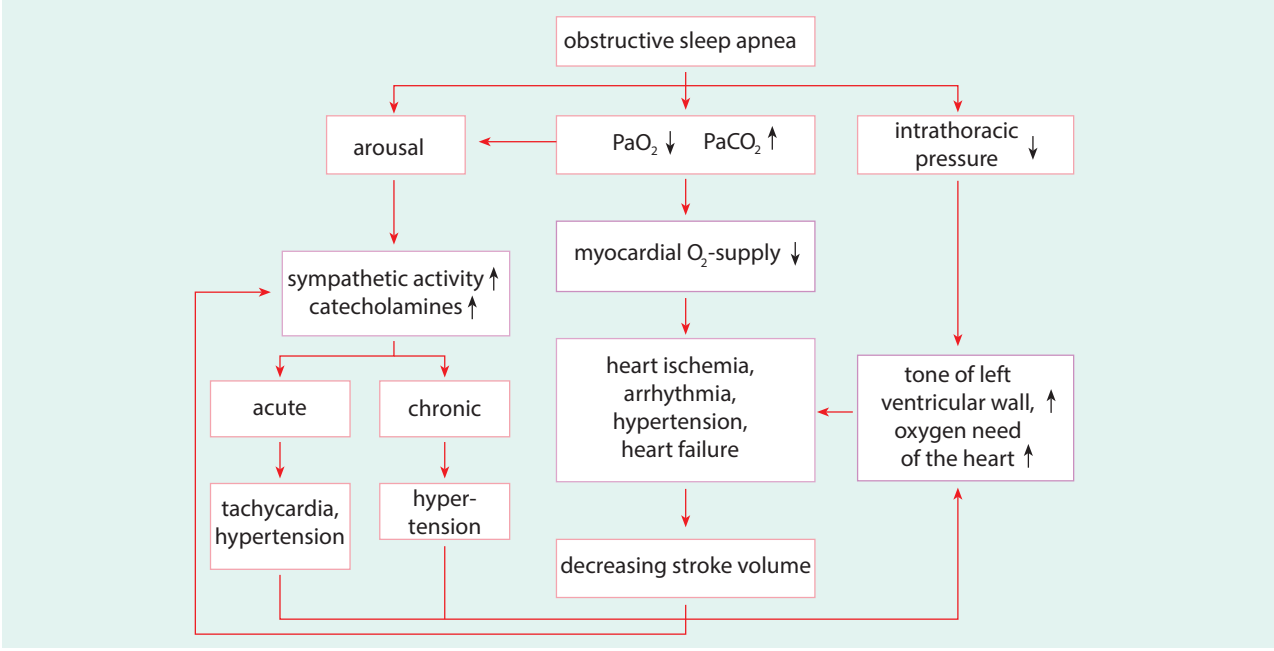

Fig. 3.5.: Obstructive sleep apnea and its consequences.

Table 3.1.

Characteristics of sleep-apnea-syndrome

Primary event	Mechanisms	Consequences	Clinical signs
Sleep starts	Oro-pharyngeal pressure↓ Upper airway tone↓ narrow, but plastic pharynx High inspiratory resistance	Intrapleural pressure↓ Vagus bradycardia Extrasystolia	Unexpected nocturnal death
Apnea			
Hypoxemia	Pulmonary vasoconstriction Erythropoietin production↑	Pulmonary hypertension Right ventricle overload Polyglobulia (RBC ↑)	Chronic cor pulmonale Right ventricular failure Blood viscosity ↑ —BP ↑ venous congestion, thrombosis
Hypercapnia	Reflex systemic vasoconstriction Brain vasodilation	Sympathetic tone, TPR ↑ Cerebral pressure ↑	Systemic hypertension Cushing reflex BP rise, bradycardia headache at arousal
	On the long run CO_2-sensitivity ↓	Chronic hypoventilation	In airway infection, or in pneumonia it develops earlier
	Chemoreceptor excitation	Motor restlessness	Tired at morning awakening
Acidosis	Reflex systemic vasoconstriction Myocardial contractility ↓	Sympathetic tone, TPR Ischemic CMP	Systemic hypertension Left ventricular failure VES, rhythm disorders
Awakening		NREM sleep insufficient	Daytime sleepiness on the long run behavioral/intellectual & personality changes, productivity ↓
Breathing starts again……sleep starts…. . . then again apnea…. . .			

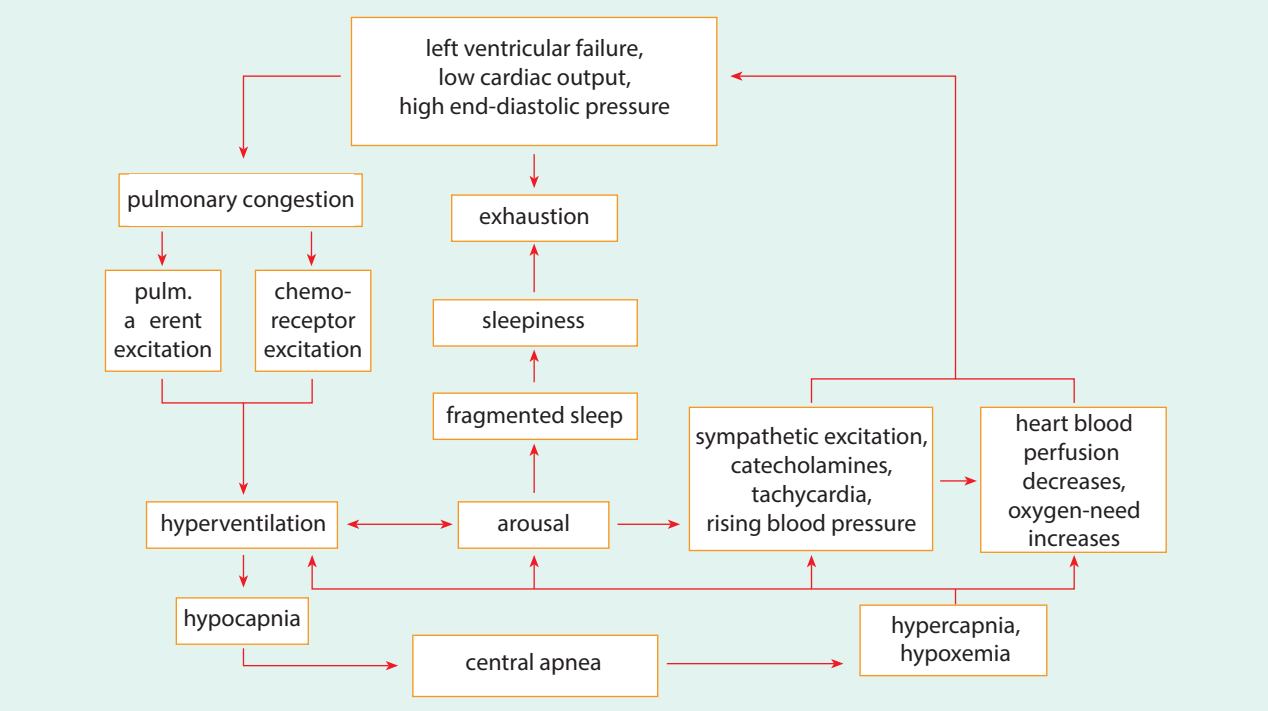

Fig. 3.6.: Interaction between left-ventricular failure and central sleep apnea.

The blood of higher viscosity increases the peripheral resistance and the systemic blood pressure. Due to high levels of pCO_2, the perfusion of the brain and the intracranial pressure increase – causing headache and further hypertension by the Cushing reflex. The systemic hypertension is further aggravated by the systemic vasoconstriction reflex elicited by hypercapnia and metabolic acidosis. During obstruction of the upper airways, the negative intrathoracic pressure is more pronounced, the venous filling and the diastolic ventricular wall tension (strain) increase, thereby also the O_2-need of the myocardium becomes higher. This may elicit acute coronary insufficiency, or in the chronically hypertrophic heart ischemic failure may develop. Eventually, the dangerous arrhythmias are more frequent. At the same time, the respiratory acidosis decreases the myocardial contractility, and this, combined with the higher peripheral resistance, may lead to heart failure. The risk of pulmonary edema is increased by the high vascular permeability evoked by the acidosis. The fragmented sleep causes next-day exhaustion, sleepiness, danger of accidents (e.g. falling asleep during driving). The repeatedly pronounced negative intrathoracic pressure enhances the atrial filling, thereby the production of ANP, causing nocturia upon arousals.

Similar symptoms may appear in cases when the process starts not with SAS, but with severe left-ventricular failure. In such cases, mainly a central type of apnea (Fig. 3.6.) is elicited by the slow circulation. The pulmonary congestion induces transient hyperpnea and this – in addition to a slight decrease in oxygen supply due to the impaired diffusion (wet-lung) – leads to CO_2 loss (corresponding to hyperventilation) since diffusion disorders do not affect the CO_2 diffusion. The consequent (hypocapnia-induced) apnea leads to respiratory failure. Apneas alternate with periods of hyperpnea (hyperventilation), but the hypoxemia is constant even during hyperpnea. Other late complications are similar to those in other forms of SAS.

With regard to the prevalence of different forms of SAS, they are more frequent in males and become more pronounced with increasing age and body weight (cf. Pickwick syndrome). Some antropometric features (e.g. short neck, large tongue) and lying on the back promote their development with or without preceding snoring. Alcohol consumption prior to sleep, exhaustion, or narcotics may also be risk factors.

Other abnormalities of regulation:

- *Biot-type of breathing:* Both the frequency and depth of breaths are chaotic. *Apnea* (respiratory arrest during expiration) may be mixed with *apneusis* (respiratory arrest during inspiration); the

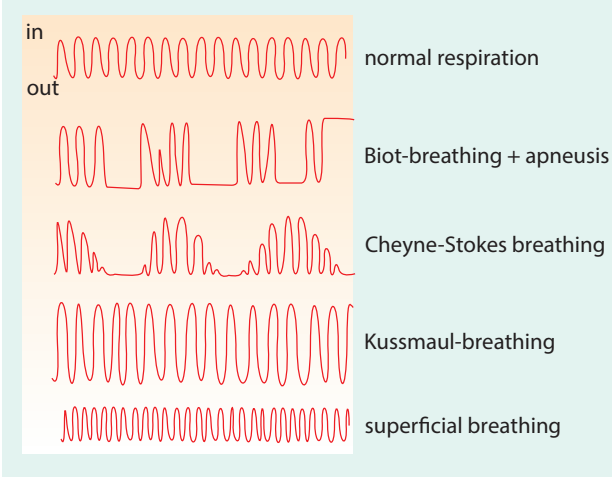

Fig. 3.7.: Abnormal breathing patterns.

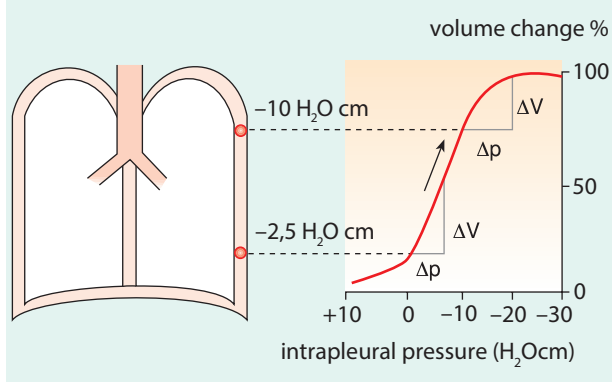

Fig. 3.8.: Due to the greater negative pressure at the start of inspiration the apical alveoli are wider than the basal ones with less negative pleural pressure. During inspiration, as shown by sections of the pressure/volume curve, similar pressure-changes cause smaller expansion of the apical than the basal alveoli (the ΔV/Δp ratios are altered).

latter suggests presence of a brain stem lesion. This is often a premortal symptom (gasping).

Inhibition of the respiratory centers, decrease of their sensitivity (narcotics, too high /!/ CO_2-level, extreme work of respiration) may cause hypoventilation of central origin; while decreasing pH (Kussmaul breathing = high amplitude normo/tachypnea, which enhances mainly the alveolar ventilation, and as a respiratory compensation of metabolic acidosis leads to the decrease of pCO_2 and consequently that of the extracellular carbonic acid), enhancement of CO_2-sensitivity (pregnancy, medications), excitement, anxiety, pain, or the subjective feeling of dyspnea (e.g. in chronic heart failure) are the most frequent factors in the background of central hyperventilation. The mechanics of breathing can be altered by reflexes or pain (e.g. fast superficial respiration accompanies rib fractures) and this easily decreases the volume of ventilation per minute.

3.1.2. MECHANICS OF VENTILATION AND THE WORK OF BREATHING

Elastic resistance

During expansion of the thorax the intrapleural and intraalveolar pressures lag behind the atmospheric pressure (negative pressure) and inflow of air through the airways to the alveoli serves reestablishment of equal pressures. (The air flows in until pressure equilibrium is reached.) In the course of the active process of inspiration the ribs are lifted forwards and upwards by the intercostal muscles. A 1-cm increase of the thoracic diameter results in an inflow of 200 ml air into the lungs. In addition, a 1-cm lowering of the diaphragm (by pressing down the abdominal organs) also increases the intrathoracic volume and leads to inflow of 350 ml air. Accordingly, the diaphragm functions more effectively than the intercostal muscles.

The intrapleural negative pressure is about -4 cm of water (cmH_2O) during inspiration (its changes may be assessed by a catheter introduced into the lower third of the esophagus). In the upright position the value is at or about -10 cmH_2O at the apical and -2.5 cmH_2O at the basal part of the lung: the difference can be ascribed mainly to the gravitation. (The lower lobes are relatively compressed by the weight of the tissues above, while the apical regions are relatively over-expanded by the pull of the weight of the lung.) As a result, at the end of the normal expiration (in mid-position, when the functional residual capacity /FRC/ equals the amount of air that is found in the lungs) the apical alveoli are wider than the basal alveoli, yet their further expansion needs more work: consequently, a greater part of the inspired air moves to the easily distensible basal alveoli. Fig. 3.8. demonstrates connections between the intrapleural pressure and changes of the pulmonary volume. The limited distensibility of the apical alveoli is demonstrated in the upper part of the sigmoid curve, the better mechanical characteristics of the basal alveoli can be seen in the lower part of the curve. Apparently, ventilation does not show a completely equal distribution even in healthy individuals.

As known from both old studies and fiction-literature the „apicitis" (referring mainly to tuberculot-

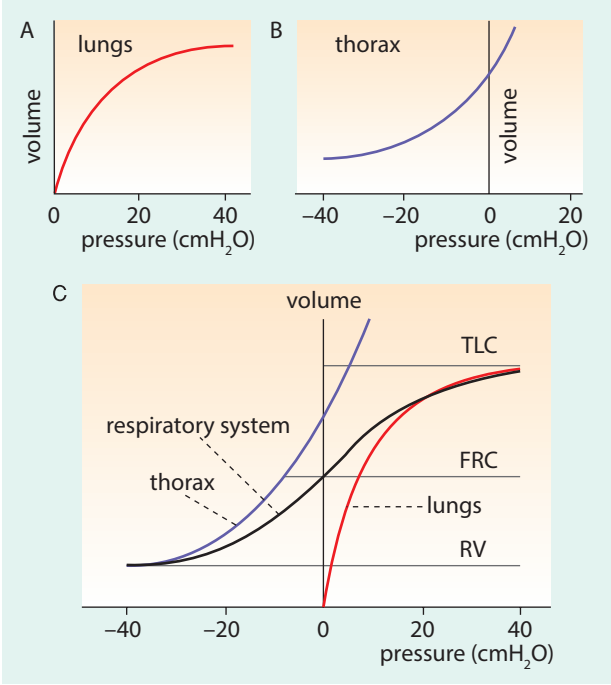

Fig. 3.9.: Part A shows the compliance curve of the lung, part B that of the thorax, part C demonstrates the unified volume changes of the ventilation pump as a function of pressure (expressed in cm-H_2O). In mid-position, at the end of quiet expiration, the distension tendency of the thorax and the retraction force of the lung may reach a balance and the lung contains gases corresponding to FRC.

ic infection of the apical alveoli) can be explained by the diminished apical ventilation. Similar mechanisms participate in the so-called "hypostatic pneumonia". In immobilized (mainly elderly) bedridden patients the ventilation of the dorsal lung regions is poor, infections can develop easier here.

Apart from these, in a given segment of the lung similar distension can be evoked by very different pressure-changes, depending on the elastic resistance of the lung (and the entire thorax): small elastic resistance means good distensibility and a high value of compliance.

In the respiratory system *compliance* refers to the volume change per unit change in pressure: normally about 2 liters/kPa (150-450 ml/cmH_2O). Larger compliance means easier distensibility, while a smaller one implies more difficult distensibility. If the pulmonary volumes are small, the pulmonary compliance is determined primarily by the surface tension of the alveoli and small airways. This tension is decreased by the surfactant. If the pulmonary volumes are large, the compliance depends mainly on the collagen and elastic fibers of the lung tissue.

With regard to the ventilation, not only the pulmonary compliance is important but that of the whole respiratory system, including components of the thorax. The compliance value depends on the initial and final volumes (the compliance value is greater for the first 100 ml than for the last one), but it does not depend on the speed of volume changes. Its reciprocal value is *elastance*, which refers to the elastic resistance against expansion.

In the course of passive expiration, retraction of the elastic fibers of the lung and thorax decreases the lung volume. The positive pressure (exceeding the outer atmospheric pressure by about 3 cmH_2O) developing in the alveoli leads to exhalation of the air. At the end of a quiet (passive) expiration, the lung and the thorax reach a medium position (mid-position=FRC). Further tendency of lung-retraction is antagonized by the distension tendency of the thorax. The combined compliance curve from various elements of the ventilation pump (Fig. 3.9.) demonstrates the development of this medium position.

Non-elastic resistance of the airways

Apart from overcoming the elastic resistance, the airway resistance from shear stress and turbulence must also be conquered during active inspiration. The parameter of airway resistance (Raw) shows the pressure difference needed to produce a unit flow of air. Normally, this is less than 0.3 kPa/liter/sec. The airway resistance is significantly increased during tachypnea, due to the frequent change of flow direction and to the increasing turbulence.

Work of breathing

Fig. 3.10. demonstrates components of the work (effort) of breathing. It is clear that the elastic resistance changes disproportionally with alterations in volume. Inspiration of 1000 ml produces not twice but at least up to 3 to 4 times greater elastic resistance than the inspiration of 500 ml. In the case of several small breaths, the total of elastic resistance is smaller than in the course of inhalation of the same total volume in a single breath, i.e. a rapid-shallow respiratory pattern needs less effort to overcome the elastic resistance, while in case of rare-deep breaths this type of effort markedly increases. While the elastic resistance depends on the *extent of the volume change*, but not on the speed of this change, the airway resistance is determined primarily by the *speed and turbulence of air flow*. Rapid-shallow breathing steeply increases the airway resistance (Fig. 3.10.). During expiration, effort is used only as an exception,

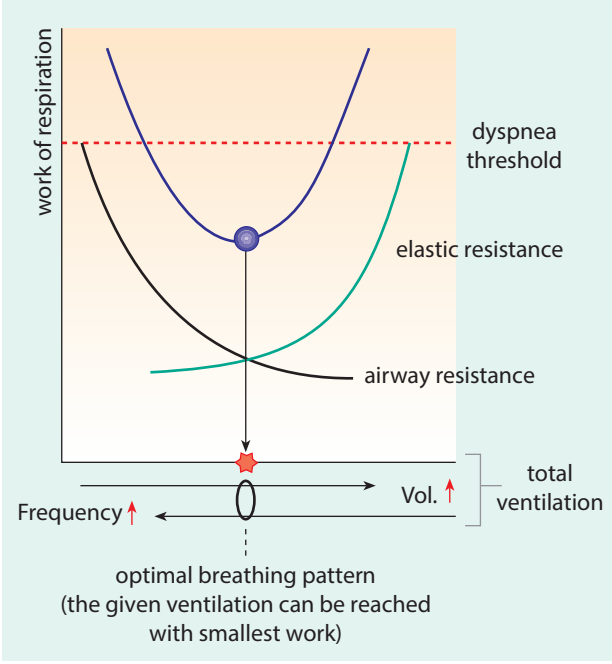

Fig. 3.10.: Components of the work of breathing. The upper parabola shows the sum of respiratory work at a given total ventilation (Vol x Freq.), optimum is indicated by the arrow.

in normal expiration the retraction of elastic elements (stretched by inspiratory work) leads to regaining the pre-inspiration volume.

The *summarized work of breathing* consists of the sum of effort used to overcome the elastic and non-elastic (airway) resistances during inspiration, and in exceptional cases the work of active expiration is added. At rest, more than 60% of the work of respiration is used to overcome the elastic, less than 40% the non-elastic resistance. At rest, the oxygen requirement of respiratory work is at or about 1 ml O_2 per 1 liter ventilation (i.e. at rest, the 8 ml/min O_2-consumption of the respiratory muscles is only 2-3% of the 250 ml/min oxygen requirement of the body).

Ventilation, alveolar ventilation

Ventilation is also referred to as *total ventilation*, or minute ventilation. The resting ventilation of 6-8 liters (12-16 × 500 ml) may be increased up to 120-170 liters by elevating the respiratory rate and the depth of breathing. Gas exchange is enhanced more by increasing the size (depth) of breath, since it allows greater elevation in alveolar ventilation. Not all of the total ventilation can reach the alveoli: the dead-space (physiologically ca. 150 ml) should be deducted from each breath and thus, the *alveolar ventilation* is about 12-16-times 350 ml, i.e. ca. 4.2-5.6 liters. Accordingly, by increasing the dead-space the alveolar ventilation decreases, while decreasing it may relatively improve the alveolar ventilation (e.g. Kussmaul breathing, or cricothyrotomy, tracheostomy in patients with narcotic intoxication).

Deviations from the normal resting pattern of respiration are coupled with dissimilar changes in the total and alveolar ventilations: in the case of superficial shallow breathing, the alveolar ventilation decreases despite the fact that the total ventilation is normal. In contrast, in the case of deep breaths, the alveolar ventilation is relatively enhanced, therefore the gas exchange is improved even if total ventilation is normal. For example, in patients with fractured ribs, the alveolar ventilation and gas exchange are poor, while in Kussmaul breathing they increase remarkably. With regard to the alveolo-capillary gas exchange (and fulfillment of the final biological goals of respiration) only the alveolar, not the total ventilation counts. At the same time, the work of breathing is proportional with the total ventilation.

Understandably, adaptation of ventilation to the actual needs refers to the alveolar ventilation. This is how the stability of the gas composition in the alveoli (p_AO_2, p_ACO_2) and the arterial blood (p_aO_2, p_aCO_2), can be secured: the partial pressure of O_2 is ca. 100 mmHg, and that of the CO_2 is ca. 40 mmHg. In the alveoli, other gases of the surrounding air and vapor tension (47 mmHg) elevate the pressure to the atmospheric level. In practice, most often the arterial O_2 and CO_2 tensions are both measured.

A given ventilation (respiratory minute-volume) can be reached by different rates of breath and corresponding respiratory volumes: e.g. instead of the normal 14 × 500 ml breathing, patterns of 7 × 1000 ml or 28 × 250 ml provide the same total ventilation. However, the work of breathing changes with the pattern. Rare-deep breaths cause a steep rise in the work for elastic resistance (whereas the airway resistance decreases only minimally). Rapid-shallow breathing steeply increases the effort required to overcome airway resistance, while that necessary to overcome elastic resistance shows only a little decline. The effort of breathing increases in both cases of abnormal respiratory pattern. The work of breathing can be kept optimal (minimal) only with appropriate mechanics of ventilation, any deviation (e.g. rare deep breaths in obstructive, or rapid shallow breathing in restrictive types of ventilatory disorders) results in a rise of the sum of the work of breathing. Naturally, if the ventilation increases (e.g. during exercise), the work of breathing rises, but even in these cases there is an optimal pattern of ventilation, with the least rise of effort.

3.1.2.1. CHANGES OF ELASTIC RESISTANCE (COMPLIANCE)

RESTRICTIVE VENTILATORY DISORDERS – DECREASED COMPLIANCE: Apart from the injury and fibrosis of the lung tissue, the rigidity of the thorax, or weakness of the respiratory muscles can also be an important factor. In cases of severe, multiple rib-fractures, the pain may prevent/discourage the patient to take optimally deep breaths.

Causes of restrictive ventilatory disorders

I. Decreased respiratory surface (disorders of the lung tissue)

- Interstitial pulmonary diseases

Pneumonia, idiopathic interstitial pneumonitis, granulomatoses (TBC, sarcoidosis), fibroses (e.g. extrinsic allergic alveolitis or systemic autoimmune diseases, e.g. progressive systemic sclerosis /PSS/, Raynaud syndrome, pulmonary manifestations of rheumatoid arthritis), pneumoconiosis, silicosis, hemochromatosis, tumor (primary lung carcinoma, metastases of other tumors), and any forms of RDS.

- *Pneumothorax, resection of lung segments* (e.g. due to tumor), *right-ventricular congestion* (backward failure of left-ventricular failure), *pulmonary edema* (severe acute left-sided failure, heart failure combined with stroke, toxic gas inhalation) also cause restrictive disorders corresponding to the decreased respiratory surface.

II. Impaired expansion of the lungs and chest

- Thoracic wall abnormalities

Thoracic deformities (progressive kyphoscoliosis), ankylopoietic spondylitis, thoracoplastic operations, pneumothorax, pleural fluid accumulation, pleural diseases (fibrothorax), obesity (Pickwick syndrome)

- Neuromuscular diseases

Amyotrophic lateralsclerosis (ALS), Guillain-Barré syndrome, myasthenia gravis, myopathies (dermatomyositis, polymyositis)

ACUTE RESTRICTIVE DISORDERS:

Impaired elasticity of the lung can be caused by a lack of surfactant (a detergent which lines the alveoli and small bronchioles and decreases the surface tension). This substance is normally produced by the type II pneumocytes. In the immature fetal lung, the surfactant production is missing or insufficient and in premature babies – due to the high surface tension – some alveoli collapse (atelectasis), the compliance decreases, the whole lung is rigid-nonelastic, even the open alveoli are difficult to expand. Severe dyspnea is characteristic. Severe mismatching of ventilation and pulmonary perfusion further deteriorates the situation (shunt-formation in the regions with atelectasis, increased dead-space ventilation in other regions). The full clinical picture is referred to as the ***respiratory distress syndrome (RDS)*** (originally described in neonates, therefore it is also named as „infantile RDS" = IRDS). The mechanics of breathing is altered: due to the rapid, shallow, superficial breaths, the utilization of surfactant becomes faster and the gas exchange will soon be insufficient, the patient is cyanotic, and due to alveolar hypoxia, pulmonary hypertension develops. Hypoxia, acidosis and pulmonary vasoconstriction predispose patients to capillary endothel damage, the permeability increases and plasma proteins get into the alveoli to produce fibrin precipitates ("hyaline membrane") and to worsen the alveolo-capillary diffusion. The high permeability also predisposes to pulmonary edema. In this type of pulmonary edema, the pulmonary capillary pressure (wedge pressure) does not rise, in contrast to the pulmonary edema developing in acute heart failure. The high protein-content of this edema-fluid is the basis of interstitial fibrosis which develops later on. Thyroxine and corticosteroids are needed for surfactant production, while insulin has an inhibitory effect; therefore, among the neonates of diabetic mothers (with high level of fetal insulin) RDS appears frequently. Preventive measures include pretreatment of steroids to the mothers.

The syndrome may also develop in an acute form in adults (ARDS). Its most frequent causes include: shock (Figs 2.23, 3.19), particularly in septic shock (ch. 2.2.2.5. and A.10.), but also infections, emboli of the lung, water aspiration (near drowning), inhalation of toxic gases (e.g. chlorine), endogenous toxicoses (diabetic ketoacidosis, uremia, acute pancreatitis), DIC. Additionally, damage to the pneumocytes and decreased production of surfactant, or faster destruction of the surfactant (due to local or blood-borne phospholipase A_2) may contribute to the development of the disease. Afterwards, the process resembles that seen in neonates. Substances derived from accumulating macrophages and leukocytes (mainly neutrophil granulocytes), i.e. lysosomal enzymes, cytokines (TNF-α, IL-1, 6, 8), activation of the complement system, products of fibrinolysis, local vasoactive substances (serotonin, bradykinin, histamine), growth factors, etc. elicit increased permeability and enhance the development of

pulmonary edema and further local damage, as well as, fibroblast proliferation and development of fibrosis, later on.

During the development of ***pneumonia***, the cellular-edematous infiltration of the affected lung regions elicits atelectasis (collapsed alveoli without gas exchange) or a decrease of the compliance (the distensibility of the inflamed, infiltrated, wet tissue is smaller). In the case of ***bronchopneumonia,*** the bronchial inflammation adds an obstructive component to the primarily restrictive disorder. Inflammations/injuries of the lung evoked not by infective agents (bronchial tumors, toxic gases, hot smoke, aspirations, immune processes, etc.) are collectively referred to as ***pneumonitis*** – the pathophysiological changes are similar. The inflammatory changes of the lungs, depending on their extent/severity, may cause acute respiratory failure, but may also be cured without residual abnormalities. However, repeated inflammations may cause residual/progressive damage of the lung tissue (bronchiectasis, pulmonary abscess, etc.).

The chronic inflammation-induced fibroblast activation, enhanced collagen synthesis and angiogenesis lead to the development of fibrosis. Among its mediators, certain growth factors are responsible for the fibroblast activation, for enhancement of collagen synthesis (transforming growth factor-ß /TGF-ß/, platelet-derived growth factor /PDGF/, fibroblast growth factor /FGF/, etc.), others are responsible (vascular endothelial growth factor /VEGF/, FGF) for the angiogenesis.

Pneumothorax (PTX): Air accumulates in the pleural space. This may be closed or open PTX. There are spontaneous and traumatic forms. It is characterized by various abnormalities of the lungs and the chest: increase of the elastic resistance, decrease of ventilatory movements (and of alveolar ventilation) and of the diffusion surface. It is a characteristic form of acute restrictive respiratory failure.

Closed PTX most often develops following rupture of an emphysemic bulla (e.g. following a coughing attack = spontaneous type), when due to the high alveolar pressure the air leaves through the ruptured alveolar wall to the pleural space instead of the bronchi and the external environment. The situation is similar if and when a broken rib injures the alveoli (traumatic type). If the injured bulla-surface is lifted from the lung, air enters the pleural space during inspiration, while during expiration the injured surface is stuck to the outer layer of the pleura, inhibiting the expiration of this air (= tension pneumothorax) and the pressure increases between the layers of the pleura. This dislocates the heart, the lung and the intrathoracic tissues/organs. Inflation of the lung becomes increasingly difficult, and a new inspiration should start from a larger thoracic volume: the elastic resistance of the thorax rapidly increases. The consequently increased respiratory effort evokes (induces) a severe acute dyspnea (with breathing-synchronous sharp pain /painful respiration/ due to the pleural damage). The hypoventilation first causes a partial respiratory failure, which may soon turn into a global one. The high intrathoracic pressure compresses the big veins, simultaneously decreases the venous return and filling of the heart, acutely decreases the cardiac output. The acute maldistribution of the low cardiac output affects in the short run mainly the muscles, the hypoperfusion of which causes muscle weakness, collapse (but loss of consciousness is seen only in very severe cases). The most severe circulatory consequence may be an obstructive type of circulatory shock. The fast decrease of the high intrapleural pressure (transthoracic cannulation with sucking) is a lifesaving intervention. In the case of closed PTX without ventil (one-way valve) the lung cannot follow the respiratory movements of the thorax, and with the arrest of alveolar ventilation acute respiratory failure develops.

In the case of open PTX (e.g. transthoracic injury) the pressure is equal between the pleural cavity and the outside world, movements of the thorax are not followed by equal changes of the lung, i.e. on the affected side the ventilation stops.

Pleural fluid accumulation: Exsudatum or transudatum accumulate in the pleural cavity mainly in various forms of pleuritis (infection, tumor, etc.), in cases of hydrothorax due to cardiac decompensation (in inflammations it may eventually be purulent). Similarly, blood accumulation is referred to as hemothorax due to vascular injury or hemorrhagic pericarditis/pleuritis. Independent of the type of fluid, its accumulation drastically decreases the compliance.

Pulmonary edema: This also results in a restrictive type of acute respiratory failure. Causes: end-stage failure of the left heart (ch. 2.1.4.1.), pulmonary embolism and pathological factors enhancing the permeability of pulmonary capillaries (anaphylaxis, chlorine-intoxication, war-gases, water-aspiration /near-drowning/, stroke, acidosis, etc.).

CHRONIC RESTRICTIVE DISORDERS:

Granulamatous and ***fibrotic*** diseases or ***hemochromatosis*** can increase the elastic resistance by causing parenchymal cicatrization (accumulation of scar tissue).

Silicosis is the oldest known occupational disease. Long-lasting inhalation of silicium-dioxide (dust of quartz) induces this progressive fibrosis with a latency of 20-30 years. The <5 μm dust particle-deposits in the alveoli are phagocyted by resident macrophages, which causes local inflammatory processes. The cytotoxic environment destroys the macrophages and the quartz particles are released to activate new macrophages, inevitably causing widespread, progressive tissue damage and fibrosis. This vicious circle remains active for years after the end of the dust exposition. Miners (metal mines and e.g. the coal-mines around Pécs), sand-blasters, employees of foundries or ceramic factories, limestone and granite processing employees are at the highest risk for silicosis.

Prolonged inhalation of other powders (asbestos, anthracite, beryllium, talcum, kaolin, graphite, aluminum) cause another type of fibrosis: ***pneumoconiosis***.

Kyphoscoliosis refers to the enhancement of the dorsal kyphosis with some scoliosis (lateral curvature) of the spine. The spinal compressions (e.g. in osteoporosis of the elderly) limit the distensibility of the thorax.

Spondylitis ankylopoietica (Bechterew's disease) is an autoimmune inflammation of the small joints of the spine. The thorax becomes rigid, and the ventilator movements are severely restricted.

Thoracoplastic surgery (surgical removal or translocation of ribs) had earlier been used in the collapse-treatment of severe (cavernous) tuberculosis (TBC): the iatrogenic collapses of the affected lung regions were associated with some clinical improvements. Nowadays, it is used only for closing persisting pleural cavities.

In severe obesity (Pickwick syndrome) the thoracic compliance is decreased by the subcutaneous fat layer on the chest wall and the abdominal breathing is also limited by fat accumulation. (Whales use lungs for respiration, but when washed ashore they die in respiratory failure, because they cannot lift the huge thoracic fat /they could do it in water, according to the rule of Archimedes/).

Amyotrophic lateralsclerosis (ALS) progressively destroys the anterior (motor) neurons of the spinal cord. In addition to a paralysis of the skeletal musculature, the respiratory muscles also become weaker, the lung volumes (vital capacity) become restricted and gradually respiratory failure develops. Over time, the patient continuously needs assisted ventilation.

Guillain-Barré syndrome: is a rare autoimmune neurological disorder, in which the motor system is affected. The paralysis gradually reaches the respiratory muscles. In 10-20% of cases, the restrictive disorder causes severe respiratory failure.

Myasthenia gravis is also a disease of immunological origin. Circulating antibodies appear, which can bind to acetylcholine receptors. The muscle weakness fluctuates: it affects the palpebral muscles, the muscles of chewing and swallowing, the muscles of the extremities, but in severe forms (crisis) dyspnea and progressive weakness of respiratory muscles may also be observed. In case of paralyzed diaphragm, in supine position (what limits the thoracic movements) soon dyspnea and respiratory failure develops.

A *painful rib-fracture* may also evoke a superficial frequent respiration characteristic for restrictive ventilatory disorders. In this case, pain relief may improve the pathological respiratory pattern.

In restrictive disorders the inspiration is labored, the respiratory pattern is characterized by superficial, frequent breaths and enhanced dead-space ventilation. Among the spirometric parameters VC and FEV_1 decrease proportionally (the Tiffeneau index is normal), eventually, the TLC, FRC and RV may also decrease. (Detailed description of spirometric parameters are found in ch. A2).

Abnormal decrease of elastic resistance – increased compliance:

It becomes easy to expand the lung, but the defective retraction force makes passive emptying difficult during expiration. As a consequence, the residual volume increases, making it more difficult to maintain a standard normal gas composition in the alveoli and soon respiratory failure may develop. This picture is characteristic for emphysema.

3.1.2.2. CHANGES OF AIRWAY RESISTANCE, OBSTRUCTIVE VENTILATORY DISORDERS

Pathological changes in the airway resistance result in *obstructive* ventilatory abnormalities, which develop on the basis of enhanced non-elastic resistance.

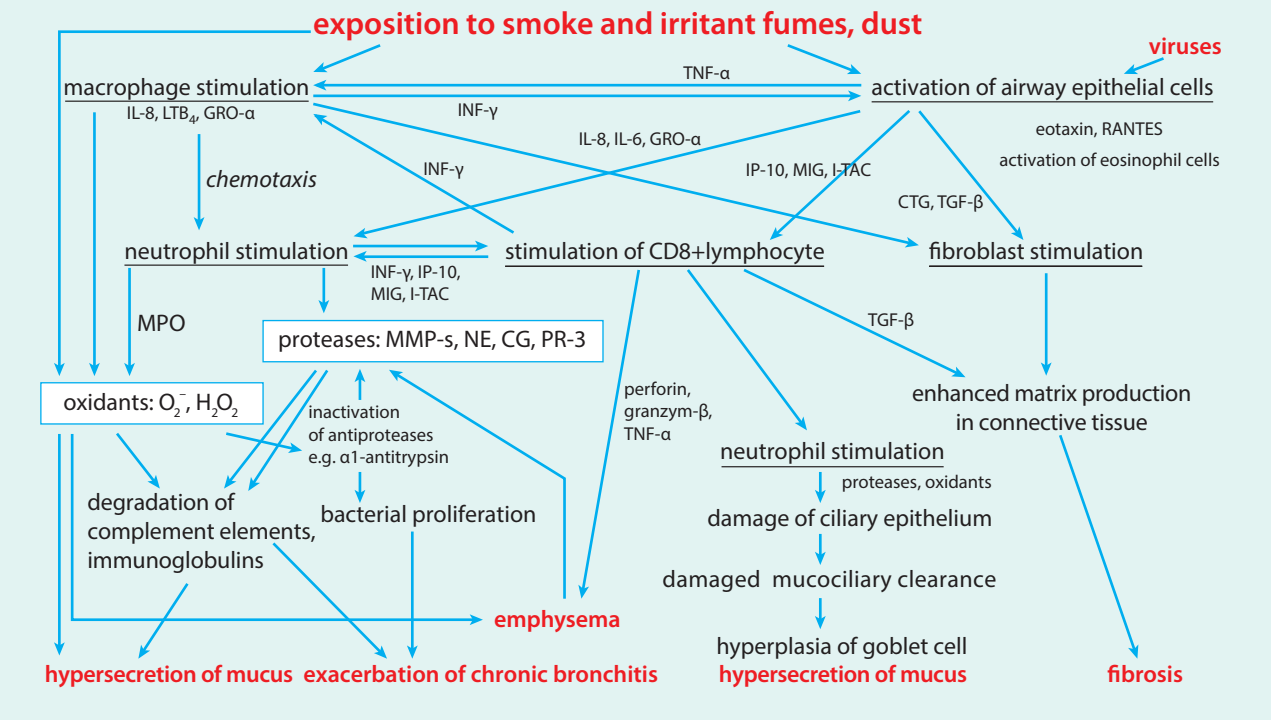

Fig. 3.11.: The role of smoking in the development of chronic bronchitis.

In the case of ***extrathoracic** stenosis* the inspiration is hampered (the intrathoracic negative pressure and the consequent subatmospheric intraluminal pressure in the upper airways augments the narrowing), but during expiration (particularly in forced expiration with high intrathoracic pressure) the obstruction is less pronounced. Stridor is a characteristic form e.g. in cases of laryngeal spasm or edema, yet there are many other causes: croup of diphtheria or viral infections, SAS, laryngeal or tracheal tumors, post-intubation tracheomalacia, post-tracheostomic stricture, aspiration, goiter compressing the trachea from the outside and destroying the cartilage, vascular ring in developmental abnormalities of the large vessels, or Wegener granulomatosis*.

The much more frequent ***intrathoracic** obstruction* leads to characteristic obstructive respiratory disorders. The mechanisms of airway narrowing: infiltration with inflammatory cells (e.g. ***acute bronchitis***), edema, increased mucus production, smooth muscle spasm, in the long run proliferation of smooth muscle and connective tissue elements of the bronchial wall.

Causes of obstructive respiratory disorders

1. Chronic bronchitis
2. Emphysema
3. Bronchial asthma

} Chronic Obstructive Pulmonary Disease (COPD)

COPD is a group of diseases with progressive, mostly irreversible intrathoracic airflow limitation, in which the narrowing of airways may be only partially reversible. (The FEV_1/FVC ratio cannot reach the 0.7 value even upon inhalatory $beta_2$-adrenergic bronchodilator treatment, and the improvement of FEV_1 is less than 12% of reference value, or remains below 200 ml.) More severe forms of the disease lead to global respiratory failure with hypoxia and hypercapnia. COPD affects an immense population, and now it is considered the 4^{th}-5^{th} most frequent cause of death in Hungary and throughout Europe, however, according to the tendencies it may reach the 3^{rd} position by 2020.

Chronic bronchitis is a chronic or periodically appearing state (minimum 3 months annually over a span of at least two consecutive years) consisting of enhanced bronchial secretion, expectoration, coughing at any time of the day, and dyspnea. In its *etiology* genetic and environmental factors participate. The most im-

* Wegener granulomatosis: vasculitis affecting small and medium-sized arteries all over the body. Its manifestations include bronchomalacia, subglottic stenosis, persistent cough with hemoptysis, pleural chest-pain, fibrotic thickening of the pleura, granulomatosis of the lung, recurrent bloody/purulent nasal fluid and necrotizing glomerulonephritis.

portant inherited, endogenous factor is *α_1-antitrypsin deficiency*, however, small birth-weight and/or atopic constitution (high IgE levels) are also more frequent in the history of patients with chronic bronchitis. Among the acquired factors *smoking* (present in 90% of cases) or lasting (usually) occupational dust/smoke exposure are unequivocally proven risk factors. Many observations suggest that air-pollution (SO_2), alcoholism, low socio-economic status and passive smoking in childhood are also predisposing factors of chronic bronchitis.

Smoking, which can be found in the overwhelming majority of chronic bronchitis cases (upon cigarette smoke exposition of 25-30 pack-years /1 pack-year is equal to smoking 20 cigarettes per day for 1 year/, COPD is expected to develop in the 15-20% of smokers showing an especially high sensitivity to cigarette smoke), is a challenging problem of national healthcare (over time, daily 30 cigarettes cause a 20-fold increase in the COPD-related mortality). The prevalence is high, on average ca. 22-28% of the adult population is a smoker. In Hungary, the situation is even worse: 23% of adult women and 38% of adult men are smokers. Sadly, even more youngsters are affected by active, and children by passive smoking. In the past 50 years, smoking-induced mortality rapidly increases, particularly in women. Recent evidence suggests that in individuals sensitive for cigarette smoke, with the appearance of COPD an adaptive immune-response is activated, which initiates autoimmune processes. Tobacco-smoke contains more than 4000 compounds, among them aromatic hydrocarbons, 40 known carcinogens, large amounts of free radicals (ca. 10^{17}/puff), and it damages the respiratory system by various mechanisms (Fig. 3.11.).

Tobacco-smoke:

1. transiently paralyzes the airway-cleaning mucociliary clearance;
2. causes airway inflammation with activation of tissue macrophages, which (by producing chemotactic and other inflammatory mediators) recruit and activate neutrophil granulocytes and other leukocytes – in the bronchoalveolar lavage fluid of COPD patients, the number of neutrophil/eosinophil granulocytes and other leukocytes is 4-5 times higher. This induces an inflammatory edema of the bronchiolar wall, in the long term with hyperplasia of the bronchial wall;
3. increases the number of mucus producing goblet cells (more mucus, productive cough);
4. causes mucous metaplasia of the serous glands that would normally produce protein-rich, less viscous fluid. The mucous glands produce more viscous mucus, which is difficult to excrete;
5. promotes the development of metaplasia of the mucosa (precancerous state, that may appear as leukoplakia in the oral cavity);
6. induces fibrosis by TGF-ß and connective tissue growth factor /CTGF/) activation;
7. inhibits the function of Lys-oxydase, therefore the production/synthesis of elastic fibers decreases, while the lysosomal elastase, the matrix metalloprotease and collagenase enzymes of the neutrophil granulocytes speed up the destruction of parenchymal elastic fibers, inevitably leading to emphysema;

After quitting smoking, the airway inflammation gradually decreases, the age-dependent annual rate of decrease of FEV_1 may even return to the normal value. However, lost functions cannot be regained. Unfortunately, in already manifested COPD, symptoms persist even after cessation of smoking, the inflammation does not stop completely, suggesting presence of persisting microbiological stimulus or autoimmune processes. Naturally, many of the established abnormalities (emphysema, hyperplasia of the bronchial wall) are irreversible.

Fig. 3.11. demonstrates the pathogenesis of smoking-induced chronic bronchitis. Free radicals and other irritant substances of the cigarette smoke activate the airway macrophage cells and also the epithelial cells of the airways. Both cell types produce inflammatory mediators (TNF-α, IL-1, IL-6, growth related oncogene-alpha /GRO-alpha/, chemotactic factors (IL-8, neutrophil chemotactic factor /NCF/, leukotriene B_4 / LTB_4/, hydroxy-eicosatetraenic acid /HETE/, RANTES /"Regulated upon Activation, Normal T cell Expressed and Secreted"/), which recruit neutrophil granulocytes and other leukocytes, and in loco activate them. Recent evidence suggest that epithelial cells of the airways produce further mediators (interferon-gamma-induced protein 10 /IP10/, interferon-inducible T-cell chemoattractant /I-TAC/, monokine induced by γ-interferon /MIG/, which activate CD8+ lymphocytes. The consequent perforin, granzym-B, TNF-α, and TGF-ß productions contribute to the development of emphysema and fibrosis. The neutrophil cells play a key role in the progression of the pathological changes by their lysosomal products (e.g. proteases, free radicals) and by production of further inflammatory cytokines, they promote the progression of inflammation. Proteases,

e.g. neutrophil elastase damages the ciliated epithelium and the mucociliary clearance resulting in variable alterations of the bronchial wall (inflammatory goblet cell proliferation and mucous metaplasia of glands leading to enhanced (viscous) mucus production, edema, hyperplasia of smooth muscle with enhanced tendency for cramping). Free radicals deactivate the antiproteases, including α_1-antitrypsin, which is responsible for 90% of the total antiprotease activity. The neutrophil elastase destroys also the elastic fibers, thereby contributing in later stages to the emphysema adjoining the chronic bronchitis. Oxidants (e.g. products of myeloperoxidase /MPO/) and proteases (e.g. matrix metalloproteases / MMP/, neutrophil elastase /NE/, cathepsin G /CG/, proteinase 3 /PR-3/) can also damage the immunoglobulins. Thus, the incidence of airway infections is high, despite the presence of activated leukocytes in the inflamed airways. Bacteria colonizing the upper airways spread downwards and colonize the lower airways. The weakened defense system of the lower airways is able to limit the number of bacteria, but it cannot completely exterminate them. Further weakening of the defense capacity allows propagation of new types of bacteria in the lower airways. As a result, frequent exacerbations of chronic bronchitis occur in COPD patients (up to 3-5 times a year), with increasing severity of coughing and expectoration, often with fever. (According to new data the colonization and exacerbations are caused by different types of bacteria). The color of the sputum is also altered: the former glassy-white mucus takes on a hue representative of yellowish or a green tint, depending on the bacterium.

The ***obstructive bronchiolitis*** (formerly ***chronic bronchiolitis with fibrosis***) is a complex form of COPD affecting the small (diameter < 1-3 mm) airways. Apparently, the chronic bronchitis in the beginning affects mainly the smallest airways and it expands only later to the bigger bronchi. It causes progressive narrowing of the small airways, with inflammation of the surrounding tissues, evoking fibrosis, and may contribute to the development of emphysema.

The structure of the smallest airways differs to some extent from that of the larger ones. For example, there are no goblet cells and normally there is no mucus production in the small ones. (From the trachea to the alveoli, on average, there are 23 distributions /generations/. The mucus of the sputum originates from at or about the 6th generation airways, the bronchioles represent the 14-16th generations). Apart from the ciliary epithelial cells, in the small airways basal cells, neuroendocrine cells, some mucinous cells and a large quantity of functionally important non-ciliary Clara cells (club cells or non-ciliated non-mucous secretory cells of the bronchiolar epithelium) can be demonstrated. These dome-shaped cells with microvilli produce the epithelial lining fluid (e.g. glucosaminoglycans) for the bronchioles, also some components of the surfactant, local antiproteases (antileukoprotease or bronchiolar mucosa protease inhibitor). In addition, these cells are responsible for the removal of mucus or toxic substances originating from the bigger bronchi. If necessary, these cells can be differentiated to ciliary cells to aid the regeneration of ciliary epithelium.

The oxidative stress, the pathological activities of proteases seen in chronic bronchitis initiate a mucinous transformation of Clara cells in the bronchioles. As a result, pathological mucus production develops in the small airways, what is making mucous clearance difficult to empty by coughing. Additionally, the surface tension increases in the bronchioles and this promotes the early collapse of small airways during expiration. It is also associated with the hyperplasia of smooth muscle, causing further narrowing of the lumen (there are many bronchioles with less than 400 μm diameter). Moreover, a damage of alveolar attachments (adhesion surface of the alveoli and the bronchioles) also develops. In addition to the bronchioles, the inflammation extends also to the alveoli, and it induces fibrosis in the peribronchial tissues (cf. inflammation vs. growth factors ch. A8.). These mechanisms explain the development of centrilobular emphysema characteristic for smokers.

Emphysema is a disease, characterized by destruction of the alveolar septa and elastic fibers, formation of bullae (damaged alveoli distend to form exceptionally large air spaces), permanent expansion of lung volumes (such as total lung capacity ch. A2), decreased surface of gas exchange and expiratory airway obstruction (Fig. 3.12.). In the *etiology* of the primary form, α_1-antitrypsin deficiency (bound to chromosome 14) is the most important factor, however, this enzyme activity also decreases in the secondary forms. In its pathomechanism, the shift in the ratio of protease/antiprotease activities leads to destruction of alveolar septa, fusion of alveoli, with a consequent decrease of the diffusion surface. Destruction of the elastic fibers also affects (diminishes) the elastic retraction (pulling) force exerted on the small airways and it also results in narrowing or even full collapse of small airways during expiration. (In healthy individuals, the normal network of elastic fibers keeps

small airways /without cartilage/ open, despite the positive intrapulmonary pressure during expiration. A loss of elastic fibers and alveolar attachments leads to a loss of support for the small airways and greater narrowing or collapse of the small airways during expiration) Lung compliance is increased. Smoking aggravates the symptoms of emphysema and shortens survival. Aging induces a decrease in the amount of elastic fibers, therefore among the elderly, particularly in association with smoking or dust exposition the emphysema is more frequent. Regarding morphology, in the case of genetic absence of α_1-antitrypsin, emphysema typically affects all alveoli of the lobule (panlobular, slightly more frequent on the base of the lung), while the form most often seen in smokers mainly affects alveoli in the middle of the lobule (centrilobular), that appears in the apical parts of the lungs. (Other forms of emphysema include paraseptal, bullous or scar-induced types.)

Bronchial asthma is characterized by suddenly developing bronchospasms appearing in attacks, with dyspnea, wheezing, coughing and the distinct feeling of thoracic pressure. It may cease spontaneously or may be reversed by medication. Worldwide, ca. 400 million patients are affected. The airway hyperreactivity is pertinent: inhaling cold air, dust, smoke (even passive), strong odors, or physical activity can induce a spasm (Fig. 3.13.). Since the obstruction is characteristically reversible, the asthmatic state developing in children, adolescents or young adults is not included in the COPD group. With the increase in age (particularly in boys showing only mild symptoms) it may ease, show remission (a symptom-free period of at least 12 months duration) or even disappear. In elderly people, the airway obstruction grows less and less reversible, and the clinical picture becomes more similar to COPD. There are intrinsic (unknown etiology) and extrinsic (triggered by known antigens) forms of asthma (Fig. 3.14.). In its *etiology* the genetic factors play a relatively small role (concordance is 20% in monozygotic and 5% in heterozygotic twins, although by now, regarding most chromosomes, genes were found, which exhibited connection of asthma or its mechanism). If both parents are asthmatic, the chances of bronchial asthma are 4-fold higher in their offsprings. With regard to the environmental factors, the increased appearance of aggressive pollens (e.g. ragweed, Artemisia /mugworts/), air pollution (SO_2, ozone), repeated (childhood, viral) respiratory infections are thought to be important. Recently, the contribution of overenthusiastic hygiene*, and formula feeding in neonatal age (instead of breastfeeding) has also been suggested. Obesity enhances the risk of asthma by 1.5-2-times via mediators produced by the fat tissue (leptin, IL-6, eotaxin, ch. 8.). In the *pathomechanism* eosinophilic airway infection, mucosal edema, bronchiolar smooth muscle hypertrophy and hyperplasia, viscous clear sticky mucus (with Charcot-Leyden crystals of eosinophil origin, ch. 4.3.1.1.), and reversible small-airway obstruction can be involved (Fig. 3.12.). Figs. 3.13. and 3.14. summarize the most important pathogenetic factors of extrinsic (allergic) bronchial asthma. Certain antigens, in individuals of special sensitivity exert a T_{H2} type immune system activation. This process initiates the IL-5 dependent activation of eosinophil granulocytes, and also the special IgE production of B lymphocytes. The IgE induces degranulation of mast cells, leading to a release of histamine, serotonin, leukotrienes, platelet activating factor (PAF),

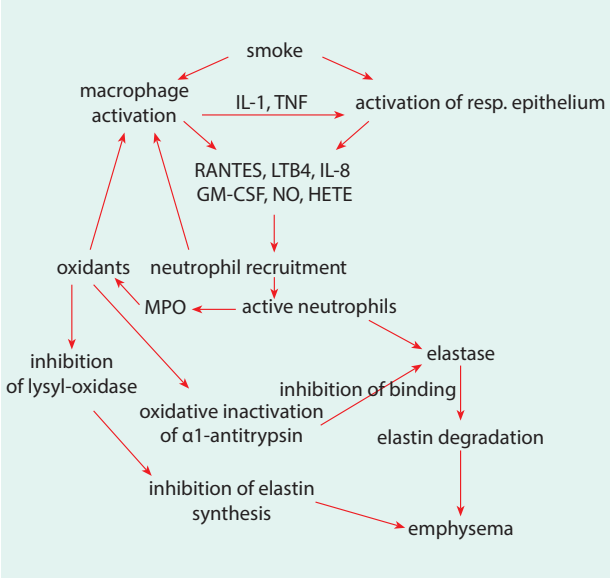

Fig. 3.12.: Factors participating in the development of emphysema.

* According to this "Hygiéne" theory, the decrease in childhood bacterial infections in a critical period of the development of the immune system promotes the development of type 2, T_{H2} cell-mediated processes that predispose individuals to autoimmunity, instead of the T_{H1}-type development, which is responsible for normal immune responses. Breastfeeding promotes the development of normal intestinal flora in early stages of childhood development and enhances the T_{H1} processes of normal immune responses, thereby suppressing the susceptibility to allergy and autoimmunity.

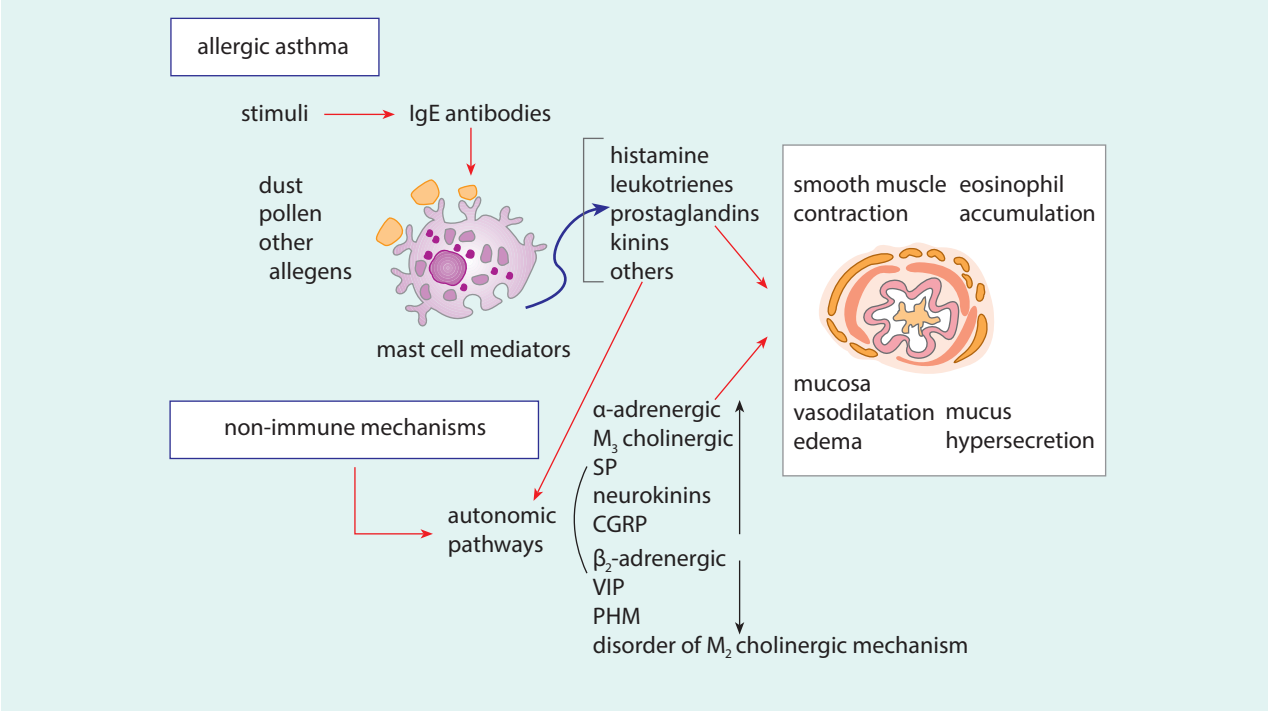

Fig. 3.13.: Important factors of the pathomechanism of bronchial asthma of allergic and non-immune origin.

prostaglandin $F_{2\alpha}$. Immediate bronchoconstriction develops, which is resolved within 20-30 min. Additionally, 2-6 hours following the exposure to the antigen, a more prolonged bronchoconstriction develops, due to an increase in the number and activity of eosinophil cells. In the intrinsic, non-allergic asthma there is no allergen, however, the airways are more sensitive to cold air, dust, smoke, etc. Between attacks, asthmatic patients breathe normally. Usually neither hypoxia nor hypercapnia develops. Even in severe acute asthma (stages I and II) hypocapnia/normocapnia joins the presence of hypoxia. Only in the most severe, stage III acute asthmatic attack develops global respiratory failure (probably due to the exhaustion of respiratory muscles). The asthma attacks require emergency treatment.

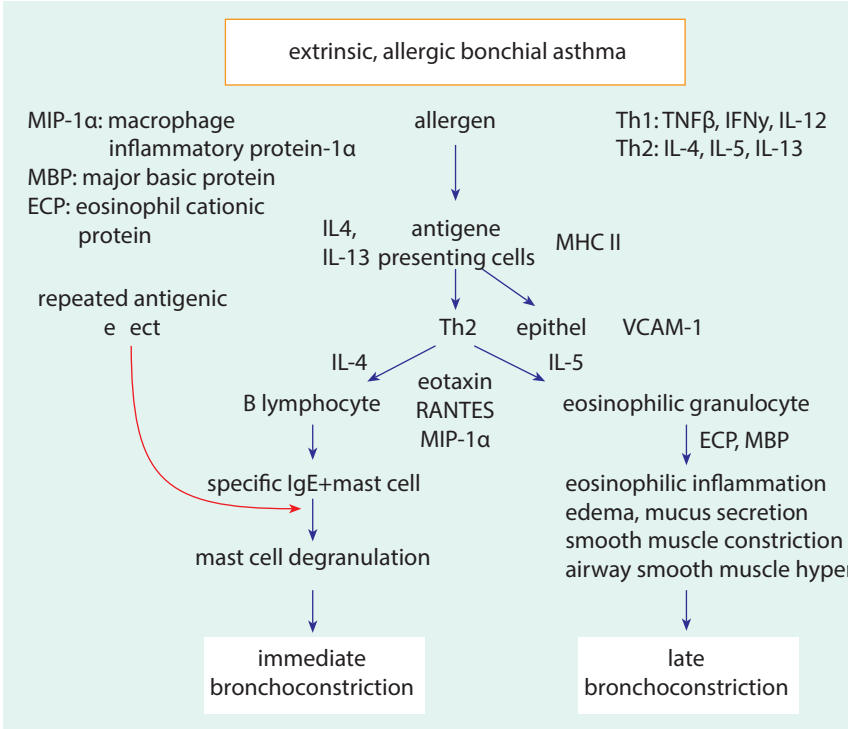

Fig. 3.14.: Factors and mechanisms of development of extrinsic bronchial asthma.

In the long run, the wall of the airways thickens due to chronic inflammation induced by eosinophil cells, underneath the basement membrane collagen is deposited (types III, V), the number of goblet cells increases, as seen

in chronic bronchitis, the smooth muscle hypertrophizes. Desquamative injuries develop on the mucosa, which enhances the hypersensitivity of the airways (the sensory nerve endings are too near to the surface). The hypersensitivity can be demonstrated by provoking tests, e.g. inhalation probe with KCl (98% specificity), metacholine, carbachol (stable acetylcholine derivatives).

***Bronchiolitis**: Acute bronchiolitis* is an acute viral (respiratory syncytial virus, influenza, adenovirus, etc.) infection of the airways, extending to the smallest bronchioles. The disease characteristically occurs prior to the age of 2-years, particularly in prematurely born, hospitalized children of low socioeconomical status and of smoking parents. It is possible that in extremely small airways, obstruction of inflammatory origin develops very easily. In the obstructed regions there is atelectasis, and in other regions, hyperinflation. In most cases, severe respiratory failure develops – the hypoxemia may also affect brain development. Breastfeeding may provide certain protection. The IgE level is often high, and there may be a connection with the later manifesting asthma.

Bronchiolitis obliterans is one of the phenomena in the organ rejection of transplanted lungs (another important one is the fibrosis/sclerosis of the vessels). Partly immune, and partly inflammatory/ischemic events lead to proliferation of granulation tissue, which occludes the lumen of small bronchioles, resulting in scarring and fibrosis. Characteristically, the bigger airways tend to dilate, become inflamed and fibrotic.

Bronchiectasis: It is an irreversible dilation of bronchi, mostly in the lower lung segments. It is mostly associated with chronic bronchitis or bronchiolitis – its development may be enhanced by drugs (pharmaceuticals) that inhibit mucus clearance and decrease coughing (e.g. codeine), but earlier pneumonia, bronchopneumonia, tuberculosis, fibrosis, mucoviscidosis, atelectasis may also be in the background: the bronchi are obstructed and infected. The infection affects the wall of the bronchus, the smooth muscles and elastic fibers are destroyed, cuboid cells or fibrosis replace the ciliated columnar epithelial cells. The mucociliary defense is insufficient, the elasticity of the bronchial wall decreases. A particularly severe form of the disease develops in hereditary primary ciliary dyskinesia (Kartagener syndrome), in which the mucociliary clearance is seriously damaged due to the genetic defect of cilia. The obstructed bronchi dilate due to the interior accumulation of inflammatory mass and increasing interior air-pressure. It is characterized by an obstructive type of coughing, with massive purulent expectoration, often accompanied with hemoptysis.

Cystic fibrosis: A systemic hereditary disorder of the exocrine glands, which very often affects the mucosa of the airways (usually this is the immediate cause of the early demise of patients at the age of 25-30 years), although the pancreas, liver, biliary tract, intestinal system, reproductive organs and sweat glands are also affected. Sticky mucus associated with high salt content obstructs the airways, promoting a tendency for repeated infections, in the long run, destroying the lung tissue. With regard to its diagnostics, the high salt content of the sweat is important.

General features of intrathoracic obstructive respiratory disturbances

The intrathoracic airway obstruction is relieved during inspiration and becomes more pronounced at expiration (since the airways lose elastic fibers, they dilate more easily, but collapse during expiration due to the positive intrapulmonary pressure). The elastic fibers of the lungs act not only to retract the lung at expiration but they also keep the small bronchioles, which have no cartilage, from collapsing. A decrease in their amount predisposes to collapse of the bronchiole. The FEV_1 value decreases below 70%, i.e. disproportionally, when expressed as a percentage of forced vital capacity (FVC). FRC rises, the respiratory mid-position is found at a high lung volume (hyperinflation), which contributes to the keeping of the small airways open. The drawback of such a compensation is the suboptimal length of the respiratory fibers at the onset of inspiration, leading to a decrease in the efficacy of their function and their early exhaustion.

The residual volume (RV) may significantly increase, its composition may become abnormal (hypoxic, hypercapnic), since the low inspiratory reserve and vital capacity limit the capacity of increasing the ventilation (Fig. 3.15.). The breathing pattern is altered: slow and deep breaths are characteristic. The effort of breathing is high mainly due to the the enhanced airway resistance, but partly also because of the higher elastic resistance of the thorax (in emphysema the thorax is rigid, the thoracic volume is permanently large – even the TLC may increase). Due to the enhanced elastic and airway resistance and to the rapid exhaustion of the respiratory muscles, dyspnea develops easily (ch. A.2. and ch. 3.7.)

Pathophysiological bases of the treatment of intrathoracic obstructive ventilation disorders

The airways react with a narrowing to parasympathetic cholinergic (muscarinic type 3 activation), and with dilation to sympathetic adrenergic (beta$_2$-adrenergic activation) effects. Accordingly, in the treatment of reversible airway obstruction in **bronchial asthma,** the administration of short/long-acting β_2 adrenergic drugs is important. These drugs are used in inhaled forms or orally, or in the case of acute asthmatic attack, parenterally (sc., im., iv.). Although these drugs are thought to be specific to the airways, unfortunately they may have cardiac side-effects (tachycardia, arrhythmia, etc.). In the case of **COPD**, which exhibits an only partially reversible airway obstruction, the muscarin$_3$ receptor antagonist anticholinergic drugs are used as bronchodilators (based on clinical observations). The effect of bronchodilators is enhanced by the phosphodiesterase-inhibitor theophylline – this extends the lifetime of cAMP in the cells and enhances the efficacy of bronchodilator drugs, although its own dilatory effect is moderate.

Among the antiinflammatory agents, the glucocorticoids are potent drugs in cases of eosinophilic airway inflammation, in **bronchial asthma** and in rare cases of chronic bronchitis. These drugs are preferably used in inhaled forms in order to avoid the systemic side-effects. In **COPD,** steroids are used only in moderately severe and severe cases, yet even then the effect is uncertain (COPD is a primarily neutrophil inflammation). In severe therapy-resistant asthma, antileukotrienes, anti IgE therapy or immunotherapy (antigen-specific therapy or administration of anti-IL-5 or anti-IL-4Rα) may be a possible choice.

In the treatment of **COPD,** it is of utmost importance to stop smoking and to avoid industrial dust/gas exposition or environmental smog. In addition to bronchodilators, mucolytic and expectorant substances (acetylcysteine, carbocysteine, ambroxol) can also be used. In cases of exacerbations, rapid and appropriate broad spectrum antibiotic treatment is necessary. The most severe cases may require lasting oxygen treatment.

In both diseases, it is important to follow the currently recommended stepwise treatment schemes, corresponding to the severity of the diseases. Such schemes imply the stepwise use of drugs and other therapeutic measures. In the case of bronchial asthma, the regularly renewed international guidelines and recommendations of GINA (Global Initiative for Asthma), while in the case of COPD, the actual GOLD (Global Initiative for Chronic Obstructive Lung Disease) guidelines must be followed.

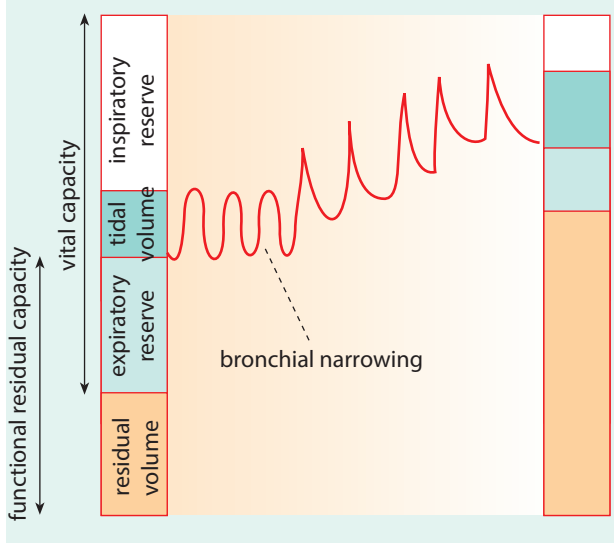

Fig. 3.15.: Effect of acute small-airway narrowing on breathing pattern and lung volumes.

3.1.2.3. CHANGES OF WORK (EFFORT) OF RESPIRATION – DYSPNEA

Elevation of the work (effort) of respiration causes symptoms, such as *dyspnea*: subjective feeling that breathing is difficult, shortness of breath, respiratory discomfort, and increasing awareness of unpleasant respiratory effort. In such cases the oxygen requirement of respiration increases: while at rest, 1 liter ventilation necessitates the consumption of 1 ml oxygen, and at higher ventilation this value may be 9 or even 15 ml. In cases (e.g. during very high-intensity physical exercise), all the extra oxygen obtained by the enhanced ventilation may be consumed by the respiratory muscles. Despite an optimal breathing pattern, the work of respiration may increase tremendously during physical exercise both in restrictive and obstructive respiratory disorders. (For further details see: ch. 3.6. and ch. 3.7.)

3.1.2.4. CHANGES OF THE ALVEOLAR VENTILATION

Decrease of alveolar ventilation below the actual need of the body, or its rise above this need is important if, consequently, this deviation does not allow the maintenance of standard normal alveolar-arterial gas composition. In assessment of alveolar ventilation, changes of p_aCO_2 are decisive, since these are brought about mostly by disturbances of ventilation. An elevation of the 40 mmHg pCO_2 to 44 mmHg, or its decrease to 36 mmHg, defines the limits of normal range. Although an elevation of

pCO_2 is always coupled with hypoxemia, pO_2 may be influenced by other factors, which are independent of ventilation and may not influence pCO_2 (e.g. high altitude, diffusion abnormality, mild forms of V/Q mismatching).

3.1.2.4.1. Alveolar hypoventilation

In alveolar hypoventilation, the alveolar ventilation is smaller than the actual need of the organism: this is shown by the arterial pCO_2 exceeding 44 mmHg.

FREQUENT CAUSES OF HYPOVENTILATION

I. Regulatory disorders of ventilation: functional (sleep, metabolic alkalosis, anesthetics (e.g. morphine, narcotics, sedatives); organic causes: bulbar poliomyelitis, encephalitis, tumors, infections, vascular diseases, sarcoidosis, central SAS, primary alveolar hypoventilation
II. Neuromuscular disorders: Guillain-Barré-syndrome (polyradiculitis), poliomyelitis, peripheral neuropathy, myasthenia gravis, polymyositis, muscle dystrophies
III. Disorders of the chest: kyphoscoliosis, spondylitis ankylopoietica, fibrothorax, thoracoplastic surgery, hypoventilation syndrome of obesity (Pickwick)
IV. Obstruction of upper airways: obstructive SAS, extrathoracic obstruction (e.g. stenosis or malacia of the trachea)
V. Pulmonary diseases: COPD, restrictive lung diseases (severe forms)

Overdose of morphine, narcotics or sedatives may cause lethal paralysis of respiration due to functional damage of brain stem respiratory centers.

Primary alveolar hypoventilation is a disease of unknown origin, which develops due to decreased CO_2-sensitivity of the brain stem respiratory centers. It may not evoke severe symptoms in itself, however, when it is associated with chronic bronchitis or obesity, the symptoms (hypoxia, hypercapnia, cyanosis) may be disproportionally severe. This disorder may be one of the mechanisms of the frequently observed ***"blue bloater"*** clinical form of chronic bronchitis. If the sensitivity of the respiratory center is maintained, the ***"pink puffer"*** clinical form of emphysema develops (without respiratory failure), in which – despite severe dyspnea – the gas tensions are closer to normal and usually there is no hypercapnia or cyanosis.

The virus of poliomyelitis destroys the neurons of the anterior horn. The symptoms vary according to which segment of the spinal cord is affected: it is possible that also the respiratory muscles become weaker or paralyzed. Since the use of effective widespread vaccination, epidemics do not occur even in developing countries.

In the case of alveolar hypoventilation, the main clinical feature is always global respiratory failure. *Laboratory* characteristics, without clinical symptoms: ***1)*** high p_aCO_2, ***2)*** low p_aO_2, and ***3)*** respiratory acidosis. The most pronounced *clinical* consequences are summarized in Table 3.4. (ch. 3.6.2.).

3.1.2.4.2. Alveolar hyperventilation

Comprehensively, this disorder is induced primarily by the disturbances of the central regulation of respiration and the decrease in atmospheric oxygen tension (high

Table 3.2.

Changes of the HbO_2 dissociation curve

Parameters	Air in Environment	Alveolus	Arterial Blood	Tissues	Mixed Venous Blood
pO_2	0,21 x 760 mmHg 150 mmHg	100 mmHg (Vapor 47 mmHg)	< 100 mmHg	40 mmHg	40 mmHg
Hb content			140–160 g/l		140–160 g/l
Hb o_2 saturation (Sao_2)			98%		75%
O_2 content			20 ml/ 100 ml vér (20 Vol%)		15 ml/ 100 ml blood (15 Vol%)
Δ av o_2					5 ml/ 100 ml blood (5 Vol%)
Pco_2	< 0.3% » 0 mmHg	40 mmHg	40 mmHg	46 mmHg	46 mmHg

altitude). It often has a psychological origin (anxiety, hysteria), or it is evoked by intense pain, however, mild cases of infiltrative lung diseases, obstruction of pulmonary vessels (microembolization) and pulmonary congestion of cardiac dyspnea cases may also lead to hyperventilation. By definition, enhanced ventilation is referred to as hyperventilation only in the case if the **alveolar ventilation exceeds the actual *need*** (i.e. the exercise-induced hyperpnea, tachypnea and any enhancement of ventilation serving physiological needs, do not belong here). In hyperventilation, hypocapnia and respiratory alkalosis is to be expected. At sea level, the p_AO_2 may exceed 100 mmHg, however, a rise in arterial pO_2 cannot increase (significantly) the saturation of the already almost fully saturated Hb (in the case of low initial p_AO_2, e.g. at high altitude, the saturation improves).

CAUSES OF ACUTE/LASTING ALVEOLAR HYPERVENTILATION

I. Hypoxemia: High altitude, pulmonary disease, cardiac shunt
II. Pulmonary disorders: Pneumonia, interstitial pneumonitis, fibrosis, edema, pulmonary embolism, pulmonary vascular disease, bronchial asthma
III. Cardiovascular abnormalities: Congestive heart failure, hypotension
IV. Metabolic abnormalities: Acidosis (diabetic, renal, lactate – Kussmaul breathing), liver failure (the accumulating ammonia stimulates the respiratory centers)
V. Neurological and psychological abnormalities: functional (anxiety, fear, stress, hyperventilation syndrome), organic (CNS lesions, infections, tumors, intracranial bleeding)
VI. Medications, drugs: Salicylates, methylxanthine derivatives (tea, coffee), progesterone
VII. Others: Conscious regulation (e.g. maximal voluntary ventilation), fever, sepsis (tissue ischemia and lactate acidosis), pain, pregnancy, assisted ventilation (inappropriately controlled)

Alveolar hyperventilation characterizes the respiration of mountaineers at high (>3000 m) altitude. At the low atmospheric pressure, the partial oxygen pressure of air decreases, leading to a fall in p_AO_2. For O_2-pressure, the gradient between the alveolar space and plasma decreases leading to a poor oxygenation of blood. Upon rest, and even more so during physical activity (faster circulation, shorter contact-time, ch. 3.3.), hypoxemia develops. Peripheral chemoreceptor (carotid glomus) activation enhances the activity of the respiratory center and leads to hyperventilation with hypocapnia. Respiration is driven by the hypoxia (the p_aCO_2 is low, p_aO_2 is below 60 mmHg), Cheyne-Stokes breathing appears frequently, particularly during sleep. By inducing constriction of the pulmonary vessels, alveolar hypoxia elevates the pulmonary pressure, in the long run resulting in pulmonary hypertension.

Upon rapid ascent to high altitude, during the first days the hypoxia-sensitivity of the carotid body increases and this persists for days following return to sea level. In the chronic adaptation of indigenous populations at high altitudes, the responsiveness to acute hypoxia decreases. This may be associated with the hypertrophy of the carotid body. Among the consequences of severe acute mountain sickness pulmonary edema (HAPE) and cerebral edema (HACE) may also develop, but the mechanisms have not been clarified yet.

Hyperventilation may also occur in *early phases* of certain ***pulmonary diseases***, e.g. pneumonia, microembolization, bronchial asthma. It is assumed that activation of stretch-receptors and irritant receptors of the lung (C-fibers and J-receptors, excited by pathological processes such as inflammation, edema) enhance the activity of the respiratory centers through vagal fibers. Chronic hypoxemia may also lead to chronic hyperventilation (ch. 3.6.2.). In *later phases* of these diseases, ventilation and/or diffusion become limited, therefore alveolar hypoventilation and various forms of respiratory failure are to be expected.

In ***congestive heart failure,*** similar mechanisms may cause chronic hyperventilation on the basis of the wet-lung (it appears paradox that the patient complains about dyspnea and hyperventilates at the same time, the p_aCO_2 is low). Pulmonary congestion and hyperventilation may also develop in anemia. Naturally, in *severe* pulmonary edema, global respiratory failure develops.

Quite often, a functional (e.g. psychological) abnormality stands in the background of hyperventilation, e.g. fear, pain, anxiety, nervousness (***hyperventilation syndrome***). Particularly women and perfectionists tend to respond to stress with hyperventilation. According to some data, in outpatient units, nearly about 10% of all complaints may be ascribed to hyperventilation. The most frequent complaints are: dizziness, perioral (and extremity) paresthesia, shortness of breath. The condition of the patient may be variable, and the presence or severity of dyspnea is independent of physical exertion (in contrast to dyspnea of organic origin). The "20-deep-breaths test" provokes the symptoms; apart from its diagnostic value, in a sense it is therapeutic since it demonstrates to the patient the mechanism of the symptoms.

In *metabolic acidosis,* the H^+ ions accumulate in the EC and liquor spaces, in *hepatic failure* the ammonia stimulates the respiratory centers.

By stimulation of the respiratory centers, mild *salicylate intoxication* induces hyperventilation and respiratory alkalosis, while in more severe intoxication, the acidic metabolites cause metabolic acidosis.

Elevated *progesterone* levels, whether during pregnancy or due to anticoncipient treatment, enhance the activity of the respiratory centers.

The pathomechanism of hyperventilation associated with *sepsis* is complex. In addition to SIRS, severe and widespread tissue ischemia and consequent lactic acidosis, DIC also contribute to the development of this respiratory abnormality.

Consequences of alveolar hyperventilation

Hypocapnia → p_aCO_2 fall → brain vasoconstriction → dizziness, fainting tendency
Respiratory alkalosis
→ relative decrease of ionized Ca^{++} in plasma → neuromuscular excitability increases → consequent tetany with dangerous laryngospasm
→ EC K^+-concentration decreases → arrhythmias, muscle weakness develops
→ the O_2-saturation curve of Hb is shifted to the left → Hb binds O_2 too strongly → tissue oxygenation is diminished, despite high p_aO_2

The CO_2-tension decreases in the arterial blood, leading to brain vasoconstriction, decreased brain blood flow, brain ischemia and fainting. In more chronic cases (chronic anxiety, high altitude, anemia, cardiac dyspnea) such disturbances of brain perfusion –in addition to diffuse complaints and fainting – may appear in the form of poorly diagnosed psychosomatic symptoms (see *hyperventilation syndrome*).

CO_2-loss leads to respiratory alkalosis with decreased ionization of se-Ca: in an alkalotic milieu, proteins behave as proton donors, and they bind Ca^{++} instead of H^+. The low se-Ca^{++} results in tetany (prior Ca-deficiency or latent hypoparathyroidism probably promotes its manifestation – otherwise the fainting tendency dominates).

It is presumed that conformational change of cell membrane Na^+ channels is behind the tendency for **tetany**: this leads to enhanced neuromuscular excitability (the "0"-phase of action potential – fast Na^+ inflow – becomes enhanced and weak or non-specific stimuli become able to induce muscle contraction). Prodromal symptoms of tetany include tingling paresthesia of the lips or fingers of the hands and feet. The blockade of circulation of the upper arm (by blood pressure measuring cuff) provokes a characteristic spasm ("deer-head") of the hand (Trousseau sign also known as *main d'accoucheur* /French for "hand of the obstetrician"/); mechanical stimulation of the facial nerve or facial muscles induce involuntary twitches of mimic muscles (Chvostek sign). Acute tetany is characterized by ascending *tonic-clonic spasms* of the extremities (rigid forced position of the hands, gear-like jerking of the lower arms and legs). Mimicking and trismus (lockjaw) often develop, but laryngospasm (vocal cord and glottic spasm) is the real danger: this may cause suffocation. In the treatment of hyperventilation tetany, soothing the anxious patient is very important. The CO_2-loss can be minimized by rebreathing from a sack. Administration of oral or parenteral Ca or in worst cases laryngotomy, may be necessary.

3.2. VENTILATION/PERFUSION (V/Q) MISMATCHING

The effectiveness of ventilation is best in the event in which the gas exchange occurs in well-ventilated alveoli (V) of optimal perialveolar capillary blood flow (Q): V/Q=1. Indeed, the total alveolar ventilation is ca.

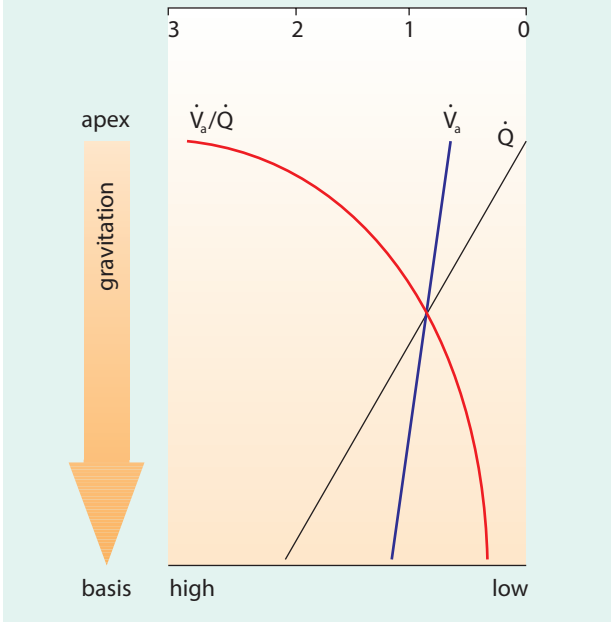

Fig. 3.16.: The ventilation/perfusion ratio (V/Q) in the apical and basal regions of the lung of healthy persons. Downwards both ventilation and perfusion increase, but the V/Q ratio is well above 1.0 in the apex and below it at the basis.

5-6.5 liter/min, the pulmonary blood flow (i.e. cardiac output) is ca. 5 liter/min, their ratio is near 1.0. At the alveolar level, the V/Q ratio is, however, not always ideal, even in healthy adults. It may be even less optimal under pathological conditions.

In an upright position, at the onset of inspiration, the apical alveoli of the lung are already wider than the basal ones (see ch.3.1.2.), however, their size cannot increase too much. Understandably, during inspiration the air flow to the alveoli is greater towards the basis (Fig. 3.16.). The perialveolar capillary perfusion exhibits an even greater shift towards the basis. Gravitation obviously contributes to such distribution of perfusion. Fig. 3.16. demonstrates the changes in the V/Q ratio from the apex towards the basis of the lungs: the V/Q ratio decreases, and there are only a few regions where its value is ideal.

Apart from such regional differences, even within one lobe, the ventilation of individual alveoli may be different. This phenomenon is normally compensated by perfusion changes: around the poorly ventilated alveoli the perfusion decreases (the alveolar hypoxia induces local vasoconstriction), while it increases around the hyperventilated ones – thereby a certain parallelism is maintained between the total ventilation and perfusion. During physical exertion, both perfusion and alveolar ventilation increase and the V/Q ratio improves, it becomes more even throughout the lung.

3.2.1. DECREASE OF V/Q – SHUNTING OF BLOOD

In most cases, a decrease in the V/Q ratio occurs due to a partial or complete bronchial obstruction, or in extreme cases, due to an atelectasis (no gases in the alveoli). If perfusion is maintained, the V/Q will be zero. Even if some alveolar ventilation remains, the gas tensions in these alveoli approach those of the systemic veins. The ventilation cannot replace the oxygen carried away by the perfusion, and cannot exhale the CO_2 delivered to the alveoli. After reaching this new balance, the pulmonary capillary blood is not oxygenated, its CO_2 content is not reduced, as if it was shunted through arterio-venous shunts (Fig. 3.17.).

In a unique way for the organism, the hypoxia within the poorly ventilated alveoli (and not the arterial hypoxia itself!) causes pulmonary vasoconstriction, thereby the blood is directed towards the better ventilated lung regions. Such adaptation of the perfusion allows that less blood perfuses the hypoventilated regions and, from there, a smaller amount blood (chatacterized by high CO_2- and low O_2-tension and -content) is mixed to the arterial blood (of the systemic circulation). Simultaneously, the large amount of blood from the hyperventilated alveoli shows low CO_2-pressure and CO_2-content and high O_2- pressure (but not much higher O_2-content). This mechanism results in a total compensation for CO_2 associated with mild hypoxemia. Without such adaptation, hypercapnia and hypoxemia would develop much earlier and in more severe forms. As the disorder becomes more severe, and some regions of the lung become grossly hypoventilated, such adaptation becomes less efficient and the aggravation of arterial hypoxemia is associated with the appearance of hypercapnia.

Anatomical shunt (bronchial circulation, real arterio-venous shunts) composes ca. 2-3% of the total pulmonary perfusion. This can explain that even during inhalation of 100% oxygen, some difference remains between the arterial blood and the alveolar gas tensions (the difference is proportional with the extent of anatomical shunts /e.g. bronchial perfusion/ within the pulmonary circulation). The blood perfusing the hypoventilated alveoli is not normally arterialized, contributing to formation of *functional shunts*, which is normally again ca. 2-3%. Thus, shunting normally refers to about 4-6% of the pulmonary circulation.

3.2.2. ABNORMAL RISE OF V/Q – DEAD-SPACE VENTILATION

Fig. 3.14. demonstrates that the V/Q ratio may be shifted in the other direction as well. In emphysema, not only the alveolar walls, but also the capillaries running in them are destroyed, in the newly formed bullas, the V/Q increases, and perfusion may also decrease due to microembolization. In extreme forms (total occlusion of capillaries with maintained ventilation), the V/Q is mathematically infinite. The alveolar gas composition approaches that in the exterior air (except that the vapor-pressure remains high in the alveoli), since perfusion cannot carry away the oxygen from and cannot supply CO_2 to the alveoli. With regard to the gas exchange, ventilation of these lung regions and alveoli is useless much like that of the trachea and the bronchi, therefore their ventilation is regarded as *enhanced dead-space ventilation*.

Under resting conditions, the *anatomical dead-space* is ca. 150 ml, i.e. 30% of the tidal volume. During

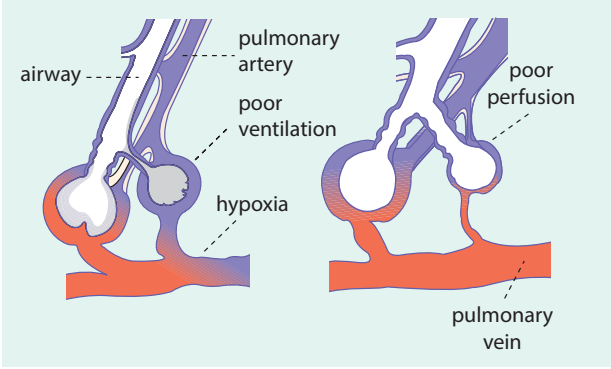

Fig. 3.17.: Deviation of V/Q ratio: perfusion of hypoventilated alveoli causes shunting (venous admixture to arterial blood), ventilation of hypoperfused alveoli results in a rise in functional dead-space ventilation.

physical activity, the deep breaths improve the ratio of dead-space ventilation, it may become as low as 10%. In pathologic states (increased dead-space, tachypnea) the dead-space ventilation may account for even 50% of the total ventilation.

Venous admixture (shunt circulation) and elevated functional dead-space may occur **together**, e.g. in pulmonary embolism, within the regions of occluded circulation the functional dead-space is elevated, while in other regions of fast perfusion venous admixture dominates.

On the one hand, abnormal changes in V/Q may cause abnormalities of arterial gas tensions and respiratory failure of various severities. At the onset, hypoxemia is accompanied by normo- or hypocapnia, i.e. the respiratory failure is partial, later the severe V/Q mismatching causes global respiratory failure with hypoxemia and hypercapnia. On the other hand, disproportional V/Q may result in an increase in the work of breathing and may elicit dyspnea.

3.3. ALVEOLO-CAPILLARY DIFFUSION AND ITS ABNORMALITIES

Oxygen reaches the perialveolar capillaries by diffusion from the alveolar space and a transport of opposite direction facilitates the excretion of CO_2 from blood to the alveoli.

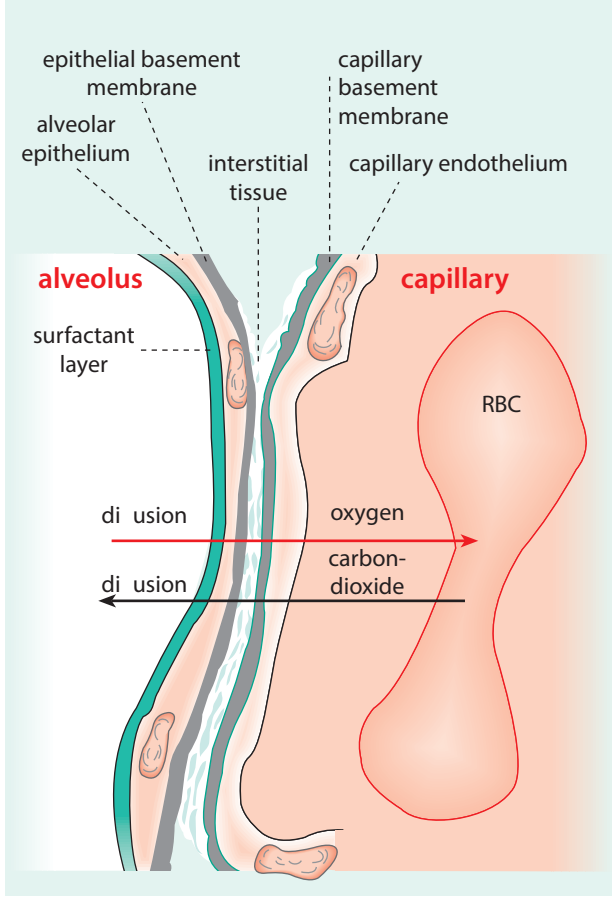

Fig. 3.18.: Components of the diffusion route.

Factors influencing diffusion (Fig. 3.18.)

1. The *route of diffusion* leads through the alveolar epithelial cell, alveolar basement membrane, interstitium, capillary basement membrane and endothelial cells to the plasma of the capillaries and to the red blood cells. The distance between the mid-point of the alveolus and the capillary mid-point is a few μm: unexpectedly small, much smaller than the diameter of a red blood cell.
2. On the two sides of the diffusion membrane the difference between the partial pressures is 60 mmHg for O_2 (100-40 mmHg) and 6 mmHg for CO_2 (46-40 mmHg). Since CO_2 is more diffusible, a smaller *pressure gradient* is enough for its transport. Pathological alterations of diffusion capacity affect exclusively the diffusion of oxygen, but not that of CO_2.
3. The size of the *diffusion surface* is normally 70-90 m^2.
4. The *contact-time* (diffusion time, Fig. 3.19.) between the alveolar air and capillary plasma, which time can be used for diffusion, is 0.75 sec at rest. During exercise, this decreases to about 0.25 sec, since more

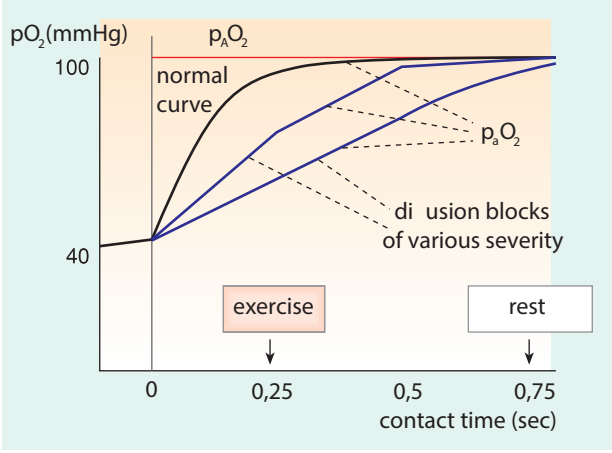

Fig. 3.19.: Changes of arterial oxygen tension during gas exchange, in function of the contact-time normally, and in patients with various levels of damaged diffusion capacity.

blood will perfuse the capillaries faster, but among healthy individuals this is still enough contact-time, since the greater part of diffusion happens in the first period.

Causes of diffusion disorders:

1. *The diffusion route is longer*, if the alveolar wall is thicker (e.g. hyaline-membrane, increased number of alveolar cells), if fluid accumulates in the lumen of the alveolus (pulmonary edema), if the capillary membrane is thicker or the interstitium is enlarged by fluid (severe congestive left ventricular failure, ARDS, inflammatory edema) or by fibrosis (autoimmune or other inflammatory processes affecting the lung, silicosis, sarcoidosis, TBC). These disorders may lead to temporary or irreversible decreases of the diffusion capacity. Enormous dilation of the pulmonary vessels also increases the diffusion route. In the hepatopulmonary syndrome (ch. 7.6.1.7.), the diameter of the pulmonary capillaries may increase from less than 15 μm to 50-80 μm, thereby the O_2-tension of the arterial blood will be smaller than the alveolar O_2-tension, it cannot be normalized even by inhalation of pure oxygen.
2. High altitude with low atmospheric pressure or low oxygen partial pressure of the air decreases the *alveolo-capillary pressure gradient*.
3. Resection of pulmonary lobes, lung tissue destruction (restrictive abnormalities accompanying fibrosis, inflammation, tumor), widespread atelectasis markedly decrease the diffusion surface. By destroying the interalveolar septa and forming large bullas, emphysema also *reduces the respiratory (diffusion) surface*.
4. In the case of widespread destruction or obstruction of capillaries, the flow-rate may be so rapid in the remaining capillaries that the *contact-time* becomes *insufficient* and arterialization of the blood is only partial. Mainly, the O_2 diffusion is affected. If the damage and the fall in diffusion capacity is severe enough (advanced stages of fibrosis), the contact-time may be so small that oxygenation becomes insufficient, first only during exercise (latent diffusion disorder), and subsequently even at rest (Fig. 3.19.).

In processes with limited diffusion capacity, exclusively the O_2 diffusion is affected and hypoxemic, partial respiratory failure develops.

3.4. DISORDERS OF OXYGEN-TRANSPORT

3.4.1. TRANSPORT OF GASES IN THE BLOOD

The oxygen taken up from the alveoli first appears in physically dissolved form (gas tension) in the plasma (Fig. 3.1.). Out of the 20.4 ml O_2/100 ml oxygen content of the arterial blood ca. 0.3 ml is physically dissolved, the remaining 20.1 ml O_2 is transported in hemoglobin-bound form. All alveolar gases are almost proportionally represented in the plasma, their total pressure equals the atmospheric pressure – from this, 95-100 mmHg is the partial oxygen pressure (p_aO_2). Although the amount of this physically dissolved oxygen is minimal, the partial pressure is an important determinant of the oxygen-binding of Hb. If the p_aO_2 is high (near 100 mmHg), practically all oxygen-binding places of all Hb molecules bind oxygen, i.e. the oxygen saturation of Hb is 100%. With decreasing p_aO_2, oxygen dissociates from Hb; not in a linear fashion, but according to the oxygen-dissociation curve: at the beginning, great falls in partial pressure lead to little oxygen dissociation, then the curve becomes steeper and even small decreases in partial pressure result in a release of a large amount of oxygen from Hb. The released oxygen first enters the plasma to replace whatever had been lost through the capillary wall to the interstitium (this is the source of oxygen for the cells). Increased cellular oxygen uptake reduces the interstitial pO_2, and induces faster replacement from the plasma and faster dissociation of oxygen from the Hb. At the tissue level, the pO_2 is only ca. 40

mmHg – on the venous side the oxygen saturation is only 75%, i.e. about one quarter of Hb is in "reduced" or "deoxygenated" form (i.e. about 35 g/liter is reduced out of the 140 g/liter Hb). The oxygen content of the blood depends on the amount of Hb in a unit of blood and on the saturation. Normally 20 ml oxygen may be released (mainly from Hb-binding) from each 100 ml of arterial blood, i.e. the oxygen content of the arterial blood is 20% - in the mixed venous blood, this value is about 15% (Fig. 3.20.). In cases of shifts of the dissociation curve, at 40 mmHg pO_2 the oxygen release may be much smaller than normal (e.g. in methemoglobinemia inducing a left shift), or much higher (e.g. in acidosis inducing a right shift) (Table 3.3.).

The difference of between the oxygen contents in the arterial and mixed venous blood ($\Delta A\text{-}VO_2$ 5%) indicates the oxygen utilization (extent of exhaustion) by the tissues. There are large deviations from this mean value of 5%, depending on the given tissue: e.g. in the coronaries, the utilization is greater (8-10% at rest, it may even reach 14% during exertion), in the kidney, it is smaller (ca. 2%). One way to satisfy an increased oxygen need of the tissues is to increase their oxygen utilization (if possible, although it may be limited e.g. in the coronaries) and – the ultimate condition for this is a decrease in the interstitial and plasma pO_2 (which also limits the applicability of this method). Alternative-

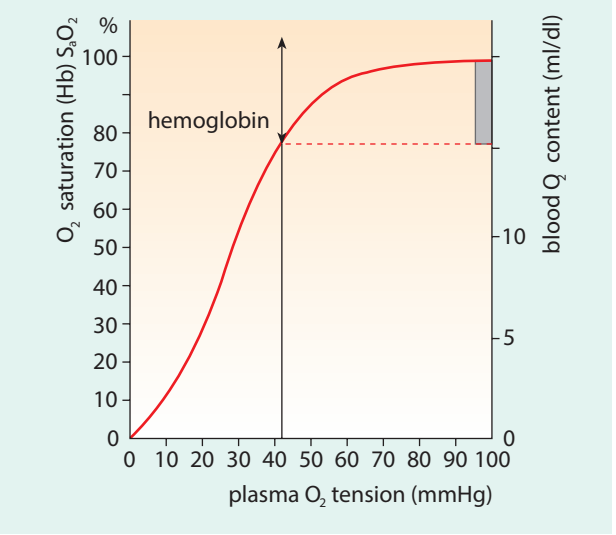

Fig. 3.20.: The oxygen tension (pO2) of the plasma (abscissa), the oxygen saturation of Hb, and oxygen content of the blood (%). Normally the tissue (mixed venous blood) pO_2 is ca. 40 mmHg, one quarter of Hb is "reduced" (arrow), out of the 20% oxygen content of the arterial blood 5% is taken up by the tissues (the oxygen utilization is 5% shown by the hatched area).

Table 3.3.

Changes of the HbO_2 dissociation curve

Leftward shift	Rightward shift (Bohr shift)
pH - increase	pH - decrease
pCO_2 - decrease	pCO_2 - increase
temperature - decrease	temperature rise
2,3-DPG - decrease	2,3-DPG - increase
1. pH - decrease	1. pH increase
2. stored blood	2. hypoxemia
3. ADP - increase	3. anemia
4. phosphate-deficiency	4. phosphate retention
5. pyruvate-kinase-increase in RBC-s	5. pyruvate-kinase deficiency in RBC
6. hexokinase deficiency in RBC-s	
7. chemical inhibition of glycolysis (e.g. monoiodo-acetate)	
8. diphosphoglycerate-mutase – deficiency	
Decreased binding of 2,3 - DPG to Hb	
1. fetal Hb	
2. diabetes mellitus	
Abnormal hemoglobins	Abnormal hemoglobin
Hereditary	Hereditary
Hb Rainier	Hb Kansas
Hb Barts	Hb Seattle
Hb H	Hb S
Acquired	
carboxyhemoglobin	
methemoglobin	

ly, without further change in the utilization, the tissue perfusion might be increased – this is limited by the capacity of the circulatory system.

In the transport of CO_2, mainly the red blood cells participate: from the interstitium, the CO_2 diffuses into the plasma, then to the red blood cells. Here, carbonic acid is produced, the H^+ binds to Hb, the bicarbonate anion diffuses back to the plasma (Cl^- enters the red blood cell), the bicarbonate is transported to the lung. In the lung, all these happen in the opposite direction, and from the carbonic acid of the plasma, CO_2 diffuses to the alveolar space. Some CO_2 is also transported to the lung in physically dissolved form and as carbamino-Hb (CO_2 bound to the amino-group of Hb).

3.4.2. FORMS OF HYPOXIA

The expression refers to disordered oxygen supply/utilization of tissues. The most important forms are demonstrated in Fig. 3.21.

Hypoxemic hypoxia: It may be evoked by low oxygen content of the inhaled air, defective ventilation or diffusion, V/Q mismatching (i.e. a wide scale of respiratory disorders), or by venous admixture to the arterial blood (right-to-left shunt). In the arterial blood the p_aO_2 is low (hypoxemia), as well as the O_2-saturation and the O_2-content. With no change in O_2-utilization and circulation, a fall in the pO_2 of the venous blood and the interstitium is unavoidable, this condition limits the O_2-supply for the cells. Compensatory steps to avoid these consequences include polyglobulia in chronic cases, since a larger amount of Hb, even if not fully saturated, may transport relatively more oxygen (the peritubular interstitial cells of the kidney produce more erythropoietin, consequently the bone marrow produces more red blood cells), while in acute cases, only an increase in tissue perfusion (higher cardiac output) is available for compensation.

Stagnation (ischemic) hypoxia: Arterial blood of normal gas composition reaches the tissues, however,

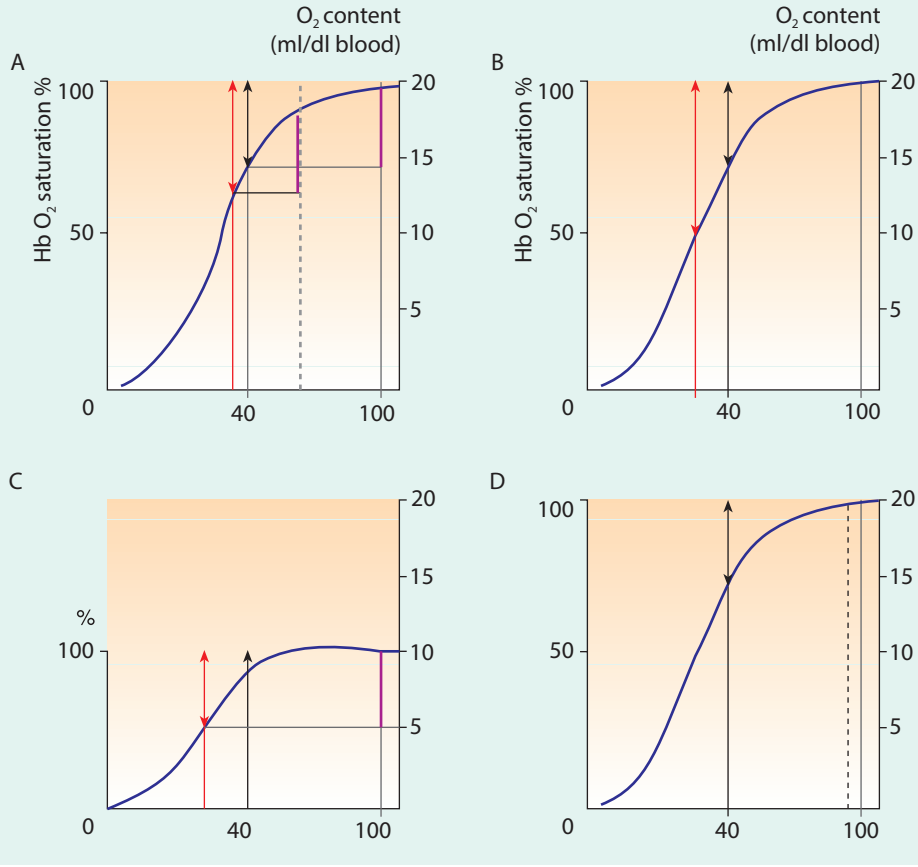

Fig. 3.21.: Types of hypoxia: **A**: in hypoxemic hypoxia: the arterial pO_2 is lower than normally, in order to maintain 5% O_2-utilization the amount of "reduced" Hb instead of the normal 3.5 g% (black arrow) may exceed 5 g% (red arrow). **B**: in stagnation hypoxia: the arterial blood is normal, but due to the stagnation the O_2 utilization is high and the tissue and venous pO_2 corresponds to that of hypoxemic hypoxia. **C**: anemic hypoxia: the oxygen content of the arterial blood is low because of the low Hb-content (although the available Hb is saturated due to normal plasma pO_2) – 5% O_2-utilization is possible only at extremely low tissue pO_2. **D**: histotoxic hypoxia: the tissues are incapable of O_2-utilization, and the venous blood resembles to the arterial one.

its further flow is limited due to stagnation. Oxygen utilization ($\Delta A\text{-}VO_2$) is forced to increase, tissue pO_2 decreases. This type of hypoxia is characteristic for slow peripheral circulation because of local (atherosclerosis, other arterial stenoses, venous occlusion, cold-induced vasoconstriction) or generalized (e.g. shock) circulatory abnormalities (ch. 2.2.2.4. and ch. A10).

Anemic hypoxia: Although in the arterial blood both p_aO_2 and Hb oxygen saturation are normal, due to the low Hb content, the oxygen content of the blood is not sufficient (ch. 4.2.1.). A utilization of 5% is possible only in the event in which a deeper point is reached on the Hb dissociation curve, which in turn is possible only at an abnormally low plasma/interstitium/tissue pO_2. Compensation is possible by enhanced tissue perfusion (ch. 2.1.4.5.) to decrease the need of enhanced utilization/dissociation. In red blood cells, the enhanced production of 2,3-diphosphoglycerate (2,3-DPG) leads to a shift of the Hb O_2-dissociation curve to the right, thereby the tissue oxygen uptake may be improved even by 40%. These are common compensatory features in all forms of anemia, but any acute/chronic decrease of any Hb-variant which is capable of O_2-transport, results in similar consequences (CO poisoning, methemoglobinemia, abnormal Hb-variants).

Carbon-monoxide (CO) is produced during incomplete burning. It is a gas of no color or smell. It binds to Hb by ca. 300-time greater affinity than O_2, additionally, upon one CO-binding. Hb becomes incapable of O_2 transport (although the skin color remains "healthy pink" because CO-Hb is red), since CO binding induces an allosteric change in the molecule that greatly diminishes the ability of the other three oxygen binding sites to off-load oxygen to peripheral tissues (strong left shift of the curve). The early non-specific anemic symptoms (ch. 4.2.1.2.) (headache, dizziness, nausea) are first followed by muscle hypoxia (CO shows an even higher affinity to myoglobin), which causes extreme weakness, collapse and immobilization, later on brain hypoxia causes unconsciousness. The binding of CO is not irreversible, high enough oxygen pressure (pure oxygen inhalation, hyperbaric oxygen treatment) may gradually push off CO from Hb binding sites. Simultaneously, ventilation must be enhanced to speed up excretion of this CO through the lung – ventilation can be increased by adding 5% CO_2 to the inhaled 95% oxygen. The danger of CO-poisoning is high in closed garages with working motors, in homes with chimneys of poor condition, in homes with gas-heating systems, and in cases the kitchen range hood is used in energy-conserving heat-insulated houses (it may suck back CO from the chimney). When the CO-concentration reaches 150-200 ppm (parts/million) the poisoning may be lethal. This emphasizes the importance of using appropriate CO sensors.

Methemoglobinemia: Hb containing oxidated ferric-iron (Fe^{3+}) is continuously produced in red blood cells. It has a brownish color. The Hb O_2-dissociation curve is shifted to the left and this Hb binds oxygen with greater avidity (strongly) than the normal Hb with ferrous-iron (Fe^{2+}) and it cannot release O_2 normally at the tissue level. Its accumulation in the blood causes tissue hypoxia. Among healthy adults the methemoglobin-reductase enzyme continuously regenerates methemoglobin to the normal variant. Dangerously high levels are found, if the water used for drinking or for watering the early-fresh vegetables is chemically contaminated with nitrate (dunghill or latrine too near to the well, artificial fertilizers, etc.). Among babies the danger is even greater, because the methemoglobin-reductase enzyme is not active as yet, and they also consume relatively more water (ca. 0.8 liter/day) as compared to their body weight and total water compartment (ca. 3.5 liter for a baby of 5-6 kg). Other oxidizing agents (nitrites of marinade), drugs (phenacetine, sulfonamides, lidocaine, nitroglycerine, nitroprusside-Na) may also induce methemoglobinemia. The skin of methemoglobinemic infants/babies is grayish-brown (also cyanotic above 10% methemoglobin), the severe brain hypoxia (exceeding 40%) causes apathy. The neural damage may be severe and may lead to death (70-80% methemoglobin ratio). These babies should be treated by i.v. methylene-blue (it accelerates the reduction of hemoglobin). Prevention is extremely important: in settlements without running water pregnant/lactating women, infants and children must be provided with safe bottled water. (Boiling kills bacteria, but does not influence nitrate!)

Abnormal hemoglobins: Most of these variants either cannot bind oxygen or they bind it too strongly (=shift of dissociation curve to left), therefore they cannot be used for oxygen-transport (Table 3.3.).

Histotoxic hypoxia: Normal arterial blood reaches the tissues, but intracellular toxicosis prevents the cells from oxygen uptake. The venous blood nearly corresponds to the arterial one, whilst in the tissues there is severe energy deficit due to lack of oxygen utilization. This is characteristic in cyanide poisoning, but in the medical practice there are several (less severe) causes of intracellular enzyme blockade: uremic toxins, ketoacidosis, osmotic changes, etc.

Cyanosis refers to livid/blue discoloration of the skin and mucosa. With regard to the mechanism, a rise in "reduced" Hb-level (from 35 to values exceeding 40 g/liter) occurs in the capillaries of the given tissue. Cyanosis may be local, due to a local stagnation without special pathological condition (e.g. cyanosis of the lips among individuals exposed to cold), but it may also occur systemically, particularly in hypoxemic and stagnation types of hypoxia (the "reduced" Hb can increase only in these forms). In various forms of polyglobulia, cyanosis develops rather frequently, while in anemias – despite the severe tissue hypoxia – the low Hb-content does not allow a rise of reduced Hb above 40 g/liter (in extreme cases, such as circulatory shock, anemia and local cyanosis may be present simultaneously).

3.5. DISORDERS OF CELLULAR OXYGEN UPTAKE

According to the example of histotoxic hypoxia it is obvious that the oxygen uptake of the cells may be defective irrespective of the question whether or not oxygen was transported to the cell. Anything disturbing the cellular oxygen utilization has similar consequences as if oxygen did not reach the cells. This most often can be explained by blocking intracellular enzymes. Specific inhibition of enzymes of tissue respiration is possible (e.g. in cyanide poisoning), but it is more frequent that the enzyme block is not, or only partially specific, either due to toxins (e.g. uremic toxins or ammonia in liver failure), or even more often due to disorders of salt- and water-balance or acid- base-balance. For example, a rising osmotic pressure leads to alteration of secondary/tertiary structure of intracellular enzyme-proteins, with consequent change in their metabolic functions (practically always to a decrease in these functions). Similar effects may be observed in pH-disorders: although in metabolic acidoses (e.g. uremia, diabetes mellitus) the pH of the plasma decreases, the H^+-ions entering the cells are neutralized by the buffer effect of cellular proteins, thus, the cytoplasmic pH remains practically unchanged. However, in this buffering the intracellular (enzyme)proteins play an eminent role – the cost of this compensation is that their electrical charge, fine structure and function are altered (their function decreases due to non-specific inhibition of enzymes). In all of these cases, the cellular oxygen utilization becomes insufficient, even if the oxygen transport to the cells is basically sufficient.

3.6. RESPIRATORY FAILURE

Respiration is regarded as sufficient if it is able to provide enough oxygen for and removes enough carbondioxide from the tissues. Although the tissue damage developing from histotoxic hypoxia, ischemia or stagnation, in many respects resembles the picture seen particularly in abnormalities of respiration, by its definition, respiratory failure is still bound more strictly to the insufficiency of the process of external respiration (e.g. disorders of ventilation, diffusion, V/Q mismatching).

In global respiratory failure the arterial gas tensions are pathological: in addition to hypoxemia ($p_aO_2 < 60$ mmHg), hypercapnia ($p_aCO_2 > 50$ mmHg) and concomitant respiratory acidosis are characteristic. It is often, but not necessarily accompanied by dyspnea.

3.6.1. FORMS AND ETIOLOGY OF RESPIRATORY FAILURES

Respiratory failure may appear in two clinical forms

Type-I, partial, hypoxemic, normo/hypocapnic, respiratory failure of non-ventilatory origin (due to the greater diffusibility of CO_2, only hypoxemia develops, the increased ventilation or V/Q ratio may even decrease the CO_2 level)

Type-II, global, hypoxemic and hypercapnic, ventilatory type of respiratory failure

Etiological factors

1. *alveolar hypoventilation* (always causes type-II respiratory failure);
2. *ventilation/perfusion mismatching* (moderate forms lead to type-I, very severe forms to type II respiratory failure);
3. *diffusion disorder* (the consequent respiratory failure first appears only during physical exercise, later also at rest, but the failure is always type-I, hypoxemic);
4. *right-to-left shunt* (Eisenmenger syndrome, leads to type-II, global respiratory failure)
5 *high altitude* (results in type-I respiratory failure).

The mechanisms of alveolar hypoventilation, V/Q mismatching, diffusion disorders and the anomalies developing at high altitude have been described earlier. The right-to-left shunt may develop in the lung or the heart, in the presence of abnormal direct an-

atomical connections between the arterial and venous systems (e.g. septal defect, Eisenmenger syndrome).

The speed of development

According to the speed of development of the pathological process of respiratory failure, *acute and chronic respiratory failures* are known.

3.6.1.1. ACUTE RESPIRATORY FAILURES

Acutely developing abnormalities of blood gas tensions occur in various acute disorders of the respiratory system, which disorders can be hardly or only partially compensated by the enhancement of circulation. Such disorders may affect the central nervous system (drug intoxication, stroke), the neuromuscular system (paralysis or spasm of respiratory muscles), injuries of the thorax or the diaphragm, pneumothorax, surgeries, airway obstructions (asthma, laryngospasm, aspiration, suffocation), damage of the lung tissue (RDS, extensive pneumonia, pulmonary edema), vascular abnormalities (pulmonary embolism, /thrombus, fat or air embolization/, pulmonary edema, shock).

ARDS (acute/adult respiratory distress syndrome): protein-rich pulmonary edema of non-cardiac origin characterized by "low pulmonary capillary pressure", enhanced capillary permeability (restrictive disorder and decreased diffusion capacity) and shunting of blood (V/Q mismatching). All these pathological changes develop in previously healthy lungs upon the effect of various injuring factors, and they lead to severe global respiratory failure.

Causes of ARDS

Circulatory shock: hypovolemic, cardiogenic, distributive forms, severe burns

Infections of pulmonary origin or extrapulmonary sepsis

Hematological disorders: DIC, massive transfusion

Toxic gases, inhalation/aspiration of gastric content: Cl_2 (chemical weapon in WW-I, nowadays accidents occur, while mixing hypochlorous acid and HCl /Cl_2 is released/), NH_3, NO_2, gastroesophageal reflux disease (GERD)

Intoxications (poisons): paraquate (Gramoxone), barbiturates, aspirin, hydrochlorothiazide

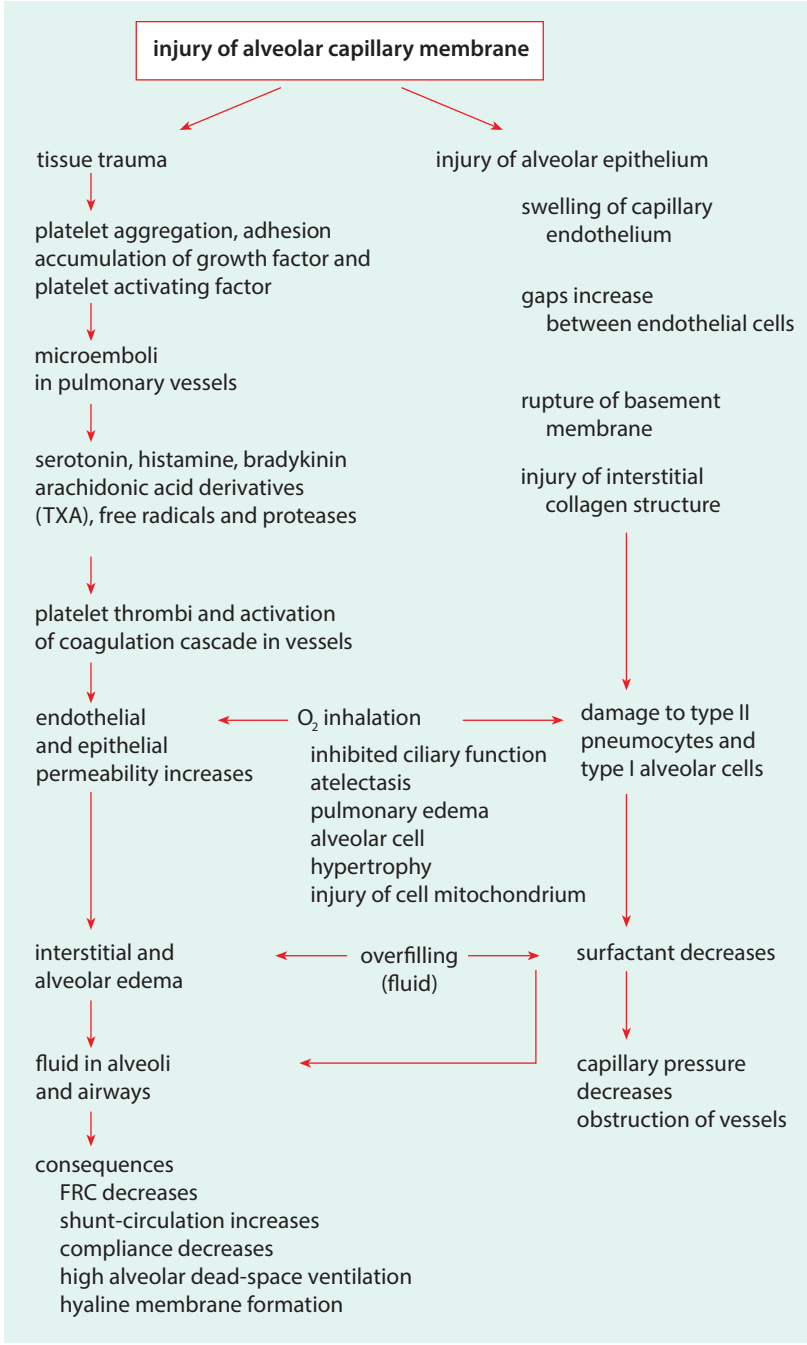

Fig. 3.22.: The pathomechanism of ARDS. Ventilation with high O_2-concentration may worsen the situation probably because it enhances free radical production.

- Pulmonary embolism
- *Metabolic disorders:* diabetic ketoacidosis, uremia
- *Others:* acute pancreatitis, irradiation, near-drowning (aspiration), mountain-sickness

The **pathogenesis of ARDS** is complex, not clarified in all details (Fig. 3.22.). At the onset tachypnea, normo/hypocapnic hypoxemia characterizes the blood gases. Upon the primary lung injury (e.g. endotoxinemia), complement, macrophages and a large number of neutrophil granulocytes are activated, these cells and their degranulation products can be demonstrated in the broncho-alveolar lavage fluid.

Among the degranulation products, *lysosomal enzymes* (proteases, phospholipases), *free radicals, arachidonic acid derivatives* (PGs, leukotrienes, PAF) and other inflammatory mediators, *cytokines e.g. TNF-α, IL-1, -6, -8* are released, which further enhance the inflammatory processes, they recruit and activate further neutrophils by chemotaxis. (In circulatory shock, in addition to the locally released products of neutrophils, lysosomal enzymes from other injured tissues may also reach the lungs.)

The free radicals and proteases damage capillary endothelial cells and increase the permeability, resulting in an accumulation of protein-rich interstitial and alveolar edema-fluid, which induces restrictive ventilatory disorder and diffusion abnormality.

The oxidants can damage the surfactant-producing cells, and by damaging lipid and apoprotein components of the surfactant, they weaken its action to decrease surface tension. Plasma proteins that come from capillaries may, by themselves, inhibit surfactant function, while the edema fluid dilutes and „washes off" the surface-active substances from the alveolar wall. Surfactant is also metabolized more quickly: the lysosomal phospholipase A_2 promotes its destruction. Regions of atelectasis develop in the lung and these can pathologically influence the V/Q ratio (shunting) and can decrease the compliance of the lung (restrictive component).

With further progression, alveolar cells are detached, they necrotize, hyaline-membrane formation and development of microthrombi follow. Severe ARDS is characterized by global, type-II respiratory failure. If the patient survives the acute phase, the edema fluid becomes organized and it is transformed into hyaline membrane, and pulmonary fibrosis develops, causing long-term problems. Alveolar hypoxia inducing release of leukotrienes (D_4, E_4) and PG-s may lead to pulmonary hypertension.

In the **treatment of ARDS,** in addition to the treatment of the initial disease, oxygen must be given, in most cases and positive pressure artificial ventilation (CPAP – continuous positive airway pressure) is needed. Among the possible supplementary treatments, steroids inhibit the inflammatory processes, transbronchial surfactant supplementation helps keeping the alveoli and small bronchioles open, antioxidants decrease the oxidative damage. Recently, the possible use of NO-inhalation is being investigated.

3.6.1.2. CHRONIC RESPIRATORY FAILURES

Chronic respiratory failure is a more frequent event than the acute one, it develops more slowly, it lasts longer, but the possibilities of its compensation are better: e.g. polyglobulia develops to compensate hypoxemia, the hypercapnic acidosis is counterbalanced by enhanced renal bicarbonate reabsorption. Among the possible causes, disturbances of the central nervous system (paralysis, thyroid hypofunction), those of the neuromuscular system (myasthenia), deformities of the chest (kyphoscoliosis, obesity), chronic airway obstructions (chronic bronchitis, bronchiolitis, COPD), damage of the lung tissue (emphysema, fibrosis), vascular abnormalities (severe congestion, pulmonary hypertension) can be detected. (Detailed description of the causes: see earlier)

Table 3.4.

Clinical signs and consequences of global respiratory failure

pO_2↓	pulmonary vasoconstriction → pulmonary hypertension → cor pulmonale chronicum → right ventricular failure
	erythropoietin ↑ → polyglobulia → high blood viscosity → BP ↑
pCO_2↑	reflex systemic vasoconstriction → total peripheral resistance ↑ BP ↑
	cerebral vasodilatation → cerebral pressure rise → Cushing reflex → BP ↑ hypertension, later: left ventricular failure
	CO_2 sensitivity decreases → defective reaction to hypercapnia (eventually hypoxia-directed, periodic breathing, hypoventilation tendency); O_2-inhalation may induce hypoventilation and CO_2-narcosis
respiratory acidosis	reflex systemic vasoconstriction → BP ↑
	myocardium contractility decreases → heart failure
	vascular permeability enhanced → danger of pulm. edema in heart failure

3.6.2. CONSEQUENCES OF RESPIRATORY FAILURE

The consequences of respiratory failure depend on the form of the failure. The consequences of global respiratory failure are summarized in Table 3.4. In chronic failures, the systemic and pulmonary hypertension, heart failure, polyglobulia and thrombophilia are the most important consequences. In acute failures, there is a high tendency for the development of pulmonary edema.

In partial (type-I) respiratory failure, hypoxemia of various severity can be expected, without disorders in the release of CO_2 of better capacity. Hypoxemia may induce hypoxic functional disorders of the tissues, while the enhanced production of erythropoietin leads to polyglobulia, increased viscosity, an increased risk for thrombosis and systemic hypertension. At the same time, the chronic hypoxia may also elicit chronic hyperventilation: the low pO_2 repeatedly enhances ventilation so much that the final result is hypocapnia and respiratory alkalosis, with all of their consequences.

3.7. DYSPNEA

Dyspnea (shortness of breath) is defined as the subjective feeling of difficulty to breathe. The symptoms may be variable: the patients complain of an unpleasant awareness of the increased respiratory efforts, shortness of breath (SOB), angina-like thoracic pressure/pain. In most cases, the **work (effort) of ventilation increases**. Dyspnea is NOT ALWAYS accompanied by respiratory failure, although the presence of respiratory failure promotes the development of this feeling. The importance of dyspnea can be understood from the fact that this single symptom, per se, can strongly influence the quality of life of patients with chronic respiratory diseases. In declaring various levels of invalidism among patients, dyspnea is a very frequent component, which disables them, decreasing working capacity. Clarifying the pathomechanism of dyspnea may help to improve the quality of life in these patients.

3.7.1. THE MOST FREQUENT PROVOKING FACTORS OF DYSPNEA

I. In healthy people: Intensive physical activity

II. Enhanced respiratory drive:

a) Hypoxemia

b) Metabolic acidosis

c) Intrapulmonary receptor stimulation (lung-infiltration, pulmonary hypertension, pulmonary edema)

III. Ventilatory disorders:

a) Obstructive ventilatory disorders (extrathoracic, intrathoracic): bronchial asthma, emphysema, bronchitis, endobronchial tumor, tracheal/laryngeal obstruction

b) Restrictive ventilatory disorders: pulmonary fibrosis, backward failure of the left ventricle, pneumothorax

c) Decreased thoracic/abdominal compliance: pleural callus, kyphoscoliosis, obesity, abdominal tumor, pregnancy

IV. Weakness of respiratory muscles:

a) Absolute (neuromuscular diseases, e.g. Guillain-Barré syndrome, muscle dystrophy, cachexia/sarcopenia).

b) Relative (decreased efficacy of muscles): hyperinflation (e.g. asthma, emphysema), extreme expansion of the thorax in case of pneumothorax, dynamic hyperinflation during physical exertion (chronic bronchitis, other obstructive ventilatory disorders)

V. Increased dead-space ventilation:

a) Damage of the pulmonary capillaries (emphysema, interstitial lung diseases)

b) Narrowing of pulmonary vessels (e.g. pulmonary embolism, pulmonary vasculitis)

VI. Psychological disorders: anxiety (e.g. hyperventilation syndrome), aggravation

Dyspnea often develops in healthy individuals, *intensive physical exercise* evokes the feeling even in fit, well-trained athletes. Possibly, the adaptation of the cardiovascular system is responsible for its occurence: the dynamic rise of the preload (EDV, EDp, CVP) causes congestion, decreases the lung compliance and increases the work (effort) of breathing. The unavoidable increase in ventilation during exercise (or even a similar rise in ventilation without exercise) eventually increase the work of breathing excessively, even without cardiovascular adaptation: the effort of breathing increases disproportionately (exponentially) with the rising ventilation.

The *enhanced respiratory drive* induces dyspnea in hypoxemia, metabolic acidosis and in some lung disorders (when excitation of intrapulmonary C-fibers /J-receptors/ enhances the activity of the respiratory centers). At a ventilation levels near the maximal voluntary ventilation, dyspnea regularly appears.

In *obstructive and restrictive ventilatory disorders,* the corresponding component of the effort of breathing increases, and it evokes SOB. The *absolute or relative weakness of respiratory muscles* influences the central nervous system: any disproportional-

ity between the respiratory drive and the ventilatory results also evokes this feeling of discomfort. Relative weakness is brought about in obstructive respiratory diseases by compensatory elevation of respiratory mid-position (this helps to keep small airways and alveoli open), since the respiratory muscles are slightly shortened already at the onset of the inspiration and the efficacy of contraction is poor. *Increased dead-space ventilation* leads to extreme ventilation to satisfy the oxygen requirement, therefore the work (effort) of breathing is high. *Psychological disorders* form an important group of pathological states causing dyspnea. Anxiety, per se, can induce dyspnea. The additionally evoked hyperventilation by fear and pain are common in the medical practice, all of these factors promote the development of dyspnea.

In *aggravation* the patient deliberately demonstrates more severe symptoms to reach various (e.g. financial: sick-pay, disability pension, compensation, etc.) benefits.

3.7.2. PATHOMECHANISM OF DEVELOPMENT OF DYSPNEA

The feeling of dyspnea is a result of a complex process, which integrates mechanisms from the periphery and the central nervous system (Fig. 3.23.).

Among the ***peripheral signals,*** *an* eminent role is played by the hypoxia-sensitive peripheral **chemoreceptors**. Oxygen inhalation in dyspnea following protracted intensive physical exercise leads to disproportional improvement of subjective complaints of dyspnea. The chemoreceptors of the thoracic wall are also sensitive to metabolites (e.g. CO_2) from other sources. This explains the finding that dyspnea develops very easily in respiratory failures associated with hypercapnia. Similar levels of enhanced ventilation (and respiratory work) are always coupled with more severe dyspnea if the enhancement is induced by CO_2-breathing as compared with that caused by exercise, since these chemoreceptors are stimulated not only by the CO_2 originating from the metabolism of the body.

Other peripheral signals come from **the lung's own receptors.**

1. Slowly adapting *stretch-receptors* embedded into the smooth muscle layer of airways: these are activated at the onset of inspiration and induce expiration; ***2.*** Fast-adapting stretch-receptors, or *irritant receptors* are located near the surface of the airway epithel: they react to mechanical irritation, to velocity of air-flow, to irritant gases, cigarette smoke; ***3.*** C-fibers located in the lung parenchyma near the alveoli and capillaries: they react to congestion, to release of histamine, bradykinin, PG-s, to the appearance of exogenous chemical substances, and they induce coughing or in severe cases, even laryngospasm. C-fibers are also named *J-receptors*, because of their location at juxta-alveolar pulmonary capillaries.

Another group of peripheral afferents involve *receptor-signals* coming from the stretched **muscle spindles of the respiratory muscles**. Their importance can be demonstrated by the finding that both a voluntary decrease of the tidal volume and setting the tidal volume to a low level in mechanically ventilated patients can induce dyspnea. Special excitation (by vibration) of these receptors can mitigate the feeling of severe dyspnea.

The **proprioceptive receptors** of the skeletal muscles and the joints also contribute to the regulation of res-

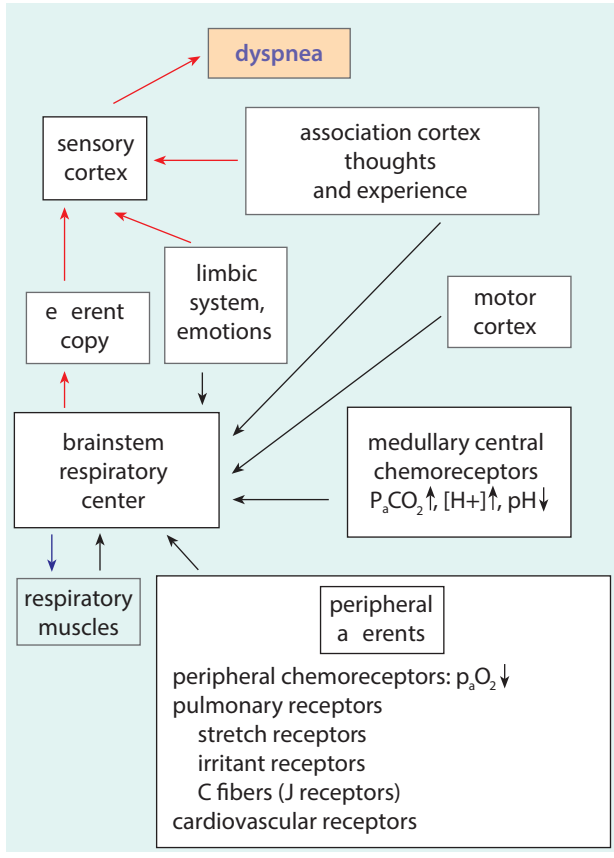

Fig. 3.23.: Peripheral and central mechanisms participating in the development of dyspnea. (Information by peripheral and central receptors to the cortex and "efferent copy" of the activity of brainstem respiratory center compared in the cortex and evaluate the efficacy of breathing efforts. In case of disproportionality between the respiratory drive and the peripheral result, respiratory discomfort, dyspnea develops.

piration and probably to the development of dyspnea, as well. Their activity explains that even passive movements of the extremities can increase the activity of the respiratory centers.

The role of peripheral afferents is not exclusive in evoking dyspnea. Even upon cooling or chemically blocking the vagus (the vagal nerve, the main path for afferent impulses), the subjects are capable of feeling respiratory discomfort, but the quality of dyspnea feeling is altered. Spinal cord transection or heart-lung transplantation does not exclude the possibility that dyspnea develops, it can happen e.g. by decreasing the tidal volume in assisted mechanical ventilation.

With regard to the ***central factors,*** the stimulation of *central CO_2-sensitive chemoreceptors* in the medulla is the most important. In reality, these receptors detect the *H^+-concentration* of the cerebrospinal fluid (liquor). An additional decrease in the medullary pH enhances the complaints in any forms of high respiratory work. A compensatory hyperpnea, per se, can evoke dyspnea in acidosis (Kussmaul breathing). An effective compensation of acidosis (abolishing acidemia) greatly improves the symptoms. With regard to the central factors, it is not the CO_2-rise, but rather the local pH, which seems to be important.

In interaction with the *association areas of the cerebral cortex and the limbic system, the motor and sensory cortex* is able to compare the respiratory drive/force and the reached ventilatory results, and their disproportionality leads to dyspnea. In completely paralytic, mechanically ventilated patients, administration of respiratory stimulant substances (which were without effect because of the machine-driven ventilation) still evoked dyspnea.

In **the prevention of dyspnea,** the *training state* is important. An identical physical exercise performed below the individual's own anaerobic threshold (no lactate acidosis, no need of buffering, no need of excess CO_2-disposal, i.e. no need of excess ventilation with the same oxygen uptake) causes a smaller rise in respiratory effort (and dyspnea) than a similar exercise in other individuals who exceed their anaerobic thresholds.

In *congestive heart failure,* the dyspnea induces hyperventilation, both can be attenuated by drugs (e.g. morphine, sedatives) *suppressing the activity of the respiratory centers*. Cave! Too severe suppression may frequently occur, causing respiratory failure!

In various ventilatory disorders with involving increased effort of breathing, *treatment of the primary abnormality* is the method to be used: e.g. discontinuation (cessation) of smoking, or use of bronchodilators helps decreasing the respiratory effort. In Pickwick syndrome, body weight should be reduced to alleviate dyspnea.

At present, it is rather of a theoretical importance that vibration-type excitation of respiratory muscles induces an illusion of respiratory movements and attenuates dyspnea.

3.8. AGE-RELATED CHARACTERISTICS OF THE RESPIRATORY SYSTEM

1. In elderly osteoporotic patients (women after menopause, in both sexes after the age of 70-y), the ventral compression of osteoporotic vertebrae causes dorsal kyphosis, and the thoracic compliance decreases.
2. In contrast, the compliance of the lung increases (loss of elastic fibers associated with emphysema), which means decreased capacity for retraction during expiration. A "barrel chest" may develop even without illness. The compliance may still decrease in cases of simultaneous late (severe) ischemic heart disease.
3. The total lung capacity does not change significantly, but the vital capacity, the FEV_1 (20-30 ml/year) and the Tiffeneau-index decreases. V/Q mismatching is more prevalent. The arterial O_2-content decreases. The p_aO_2 decreases (0.3% per year), since the regulation of respiration becomes less sensitive, the diffusion surface decreases, and the strength of respiratory muscles also decreases.
4. The COPD prevalence is greater and its progression is faster, mainly due to the prolonged exposition to cigarette smoke and/or air-pollution. The difference between asthma and COPD becomes minimal, and the so-far reversible asthmatic airway obstruction gradually becomes irreversible.
5. Special complications:
   - in severe osteoporosis coughing may cause rib fracture
   - during forced coughing, spontaneous PTX may develop (due to emphysema), with poor/nonspecific symptoms and difficult diagnosis
   - cardiopulmonary cachexia may develop: the patient must choose between the activities of everyday life and feeding/digestion – both induce a need of increased circulation
6. With aging, SAS occurs more frequently – this further enhances the tendency for hypertension and cardiac complications

7. Airway infections are frequent, there are many non-specific, poorly diagnosable forms of pneumonia (first symptoms are often: dizziness, incontinence). New tuberculotic infections or activation of old foci are frequent at old age (above 80-y).
8. Enhanced risk of deep venous thrombosis and pulmonary embolism is observable.
9. Occurrence of lung cancer increases.

Further readings:

GOLD 2017 Global Strategy for the Diagnosis, Management and Prevention of COPD
http://goldcopd.org/gold-2017-global-strategy-diagnosis-management-prevention-copd/

2017 GINA Report, Global Strategy for Asthma Management and Prevention http://ginasthma.org/2017-gina-report-global-strategy-for-asthma-management-and-prevention/

Harrison's Principles of Internal Medicine. I., II., 19th Edition. McGraw-Hill, 2015.

Hart S, Greenstone M: Foundations of Respiratory Medicine, Springer, 2018.

Shah PL, Herth FJF, Lee YCG, Criner GJ: Essentials in Clinical Pulmonology, CRC Press