ANATOMY & PHYSIOLOGY OF RESPIRATION

FROM BRAIN TO BREATH

MAQUET
GETINGE GROUP

CRITICAL CARE

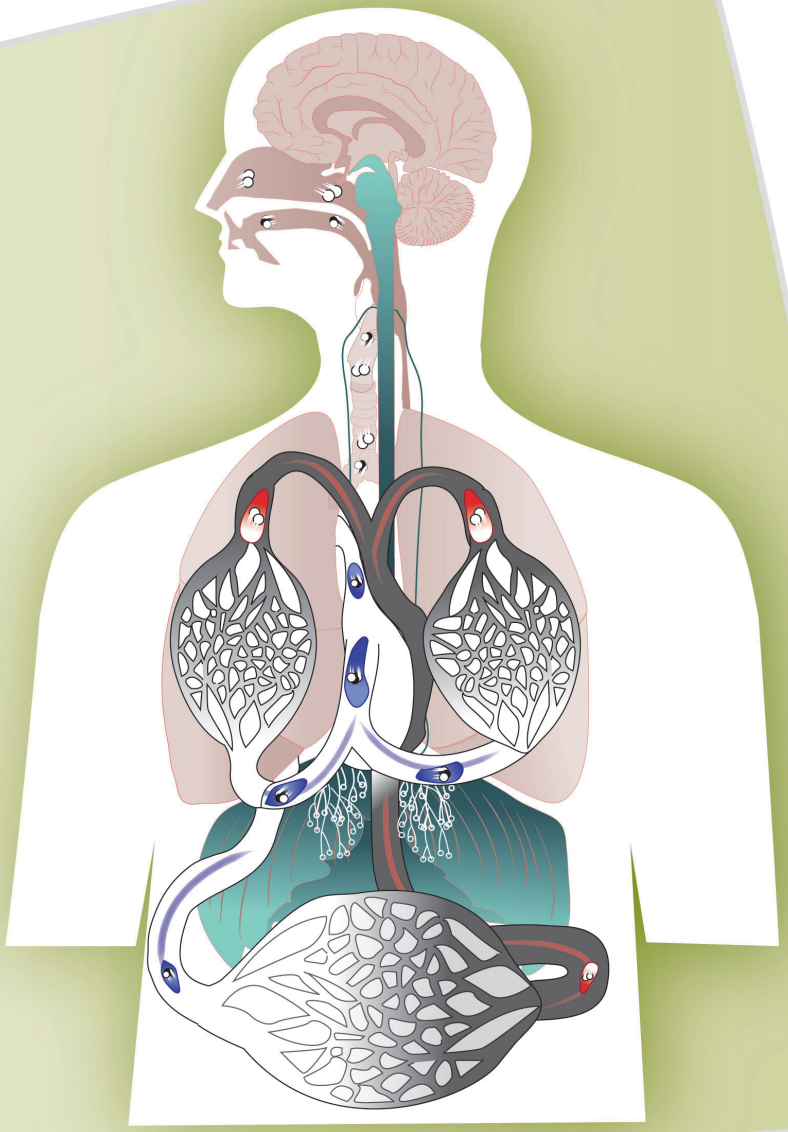


TABLE OF CONTENTS

1	Introduction	|	4
2	Anatomy	|	8
3	Physiology I - Spontaneous Breathing	|	19
4	Physiology II - Respiratory mechanics and gas exchange	|	37
5	Acid base balance	|	52
6	Clinical interpretations of the diaphragm electrical activity	|	57
7	Glossary	|	62
8	Suggested reading/References	|	66

1 INTRODUCTION

TABLE OF CONTENTS

1.1	Scope and purpose	|	5
1.2	Introduction	|	5
1.3	Neural control of breathing: From brain to breath	|	6
1.4	Feedback to the brain	|	7

1.1 SCOPE AND PURPOSE

This book will hopefully serve as a practical aid to those involved in pulmonary and critical care, even though it does not cover the entire field of respiratory anatomy and physiology and critical care medicine.

In this new updated version of the textbook, the concept of neural control of breathing has been developed and brought up to date. New sections have been added to describe the electrical activity of the diaphragm (**Edi**), and its clinical interpretation.

Readers who have experience in the field of respiratory and critical care and who are more interested in the neural aspects of breathing may focus their attention on the chapters "Anatomy", "Physiology I" and "Clinical interpretations".

Respiratory mechanics and gas exchange are included in the chapter "Physiology II", and the chapter on "Acid base balance" is included for those readers who need an introduction to the topic.

TERMINOLOGY

The terms requiring explanation are printed in **bold blue** text (at their first occurrence) and explained at the end of the book under "Glossary".

MAQUET wishes to thank everyone who has contributed to updating the original Physiology of Respiration textbook.

Our special thanks goes to Dr. Jennifer Beck who has updated the book to include the new aspects of diaphragm electrical activity, and its interpretation, with regards to the anatomy and physiology of respiration.

1.2 INTRODUCTION

Breathing is a complex process and is often oversimplified as being only involved with movement of air in and out of the lungs. Breathing is actually neurally controlled by specialized centers in the brainstem, a part of the central nervous system sitting at the base of the brain. The brainstem automatically regulates the rate and depth of breathing depending on the respiratory demand and the feedback it receives from various organs in the body.

Measuring the neural activity of the **respiratory centers** proposes quite a challenge, but is essential to the understanding of the pathophysiology of breathing since it initiates the entire process of respiration.

1.3 NEURAL CONTROL OF BREATHING: FROM BRAIN TO BREATH

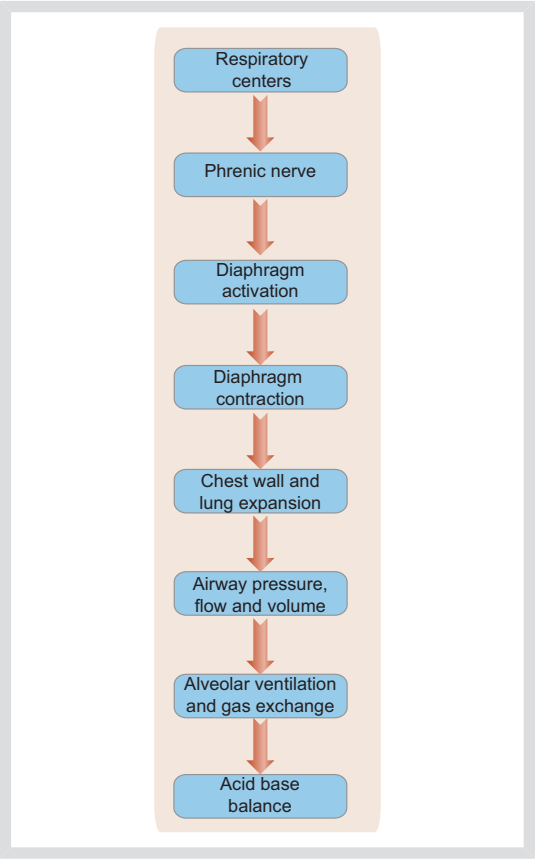


Fig. 1 - Schematic representation of the chain of events involved with spontaneous breathing

Spontaneous breathing begins with neural signals generated by the respiratory centers in the brainstem.

This chain of events can be simplified to involve the following course, beginning with a signal transmitted from the respiratory centers via the phrenic nerves, which then electrically activates the diaphragm.

After electrical activation, the diaphragm contracts, resulting in chest wall and lung expansion, lowered thoracic pressures, and generation of flow and volume.

Depending on the respiratory rate and the amount of **dead space**, alveolar ventilation and gas exchange will occur. This in turn affects the acid base balance of the arterial and venous blood.

Each of these steps is defined and described throughout this book.

1.4 FEEDBACK TO THE BRAIN

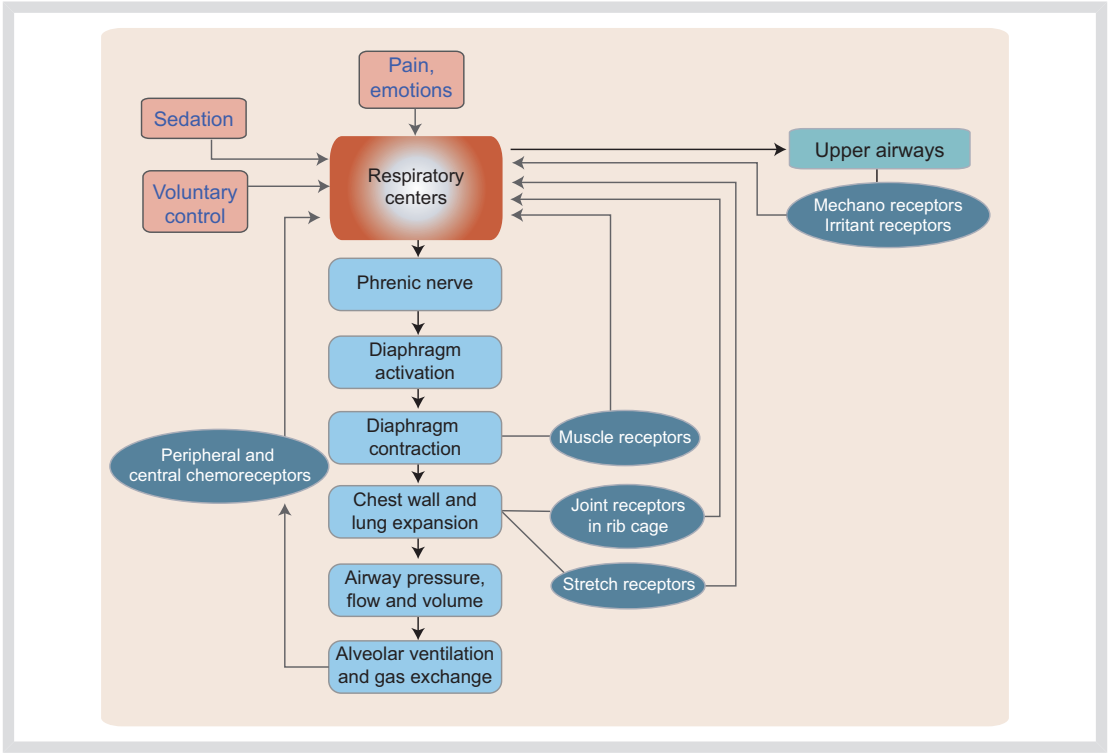


Fig. 2 - Schematic representation of the chain of events involved with spontaneous breathing, and the feedback the respiratory centers receive continuously.

The respiratory centers in the brain continuously receive information from receptors sensitive to the amount of oxygen and carbon dioxide in the arterial blood (**Chemoreceptors**), and receptors sensitive to mechanical factors (**Mechanoreceptors**) such as lung stretch, and muscle tension.

Feedback from other parts of the central nervous system (e.g. voluntary control of breathing, emotional state, and pain) and pharmacological factors (e.g. **sedation**, analgesia) also influence the respiratory output from the central nervous system.

2 ANATOMY

TABLE OF CONTENTS

2.1	The respiratory centers	9
2.2	The upper and lower airways	10
	2.2.1 The upper airways: the nasal cavity	11
	2.2.2 The upper airways: the pharynx	12
	2.2.3 The upper airways: the larynx	12
	2.2.4 The lower airways: the trachea	13
	2.2.5 The lower airways: the bronchial tree	13
2.3	The lungs and pleural cavity	14
2.4	The respiratory muscles	15
	2.4.1 The diaphragm	15
	2.4.2 Other respiratory muscles	17
	2.4.3 Structure of skeletal muscle	18

2.1 THE RESPIRATORY CENTERS

Breathing is regulated by the central nervous system. The respiratory centers in the central nervous system are located in the pons and in the medulla oblongata of the brainstem.

The medulla contains both a dorsal respiratory group (of neurons responsible for inspiration) and a ventral respiratory group (of neurons responsible for expiration). The pons, which is responsible for the depth and rate of breathing, contains the pneumotaxic center (inhibits inspiratory centers) and the apneustic centre (stimulates inspiratory centers).

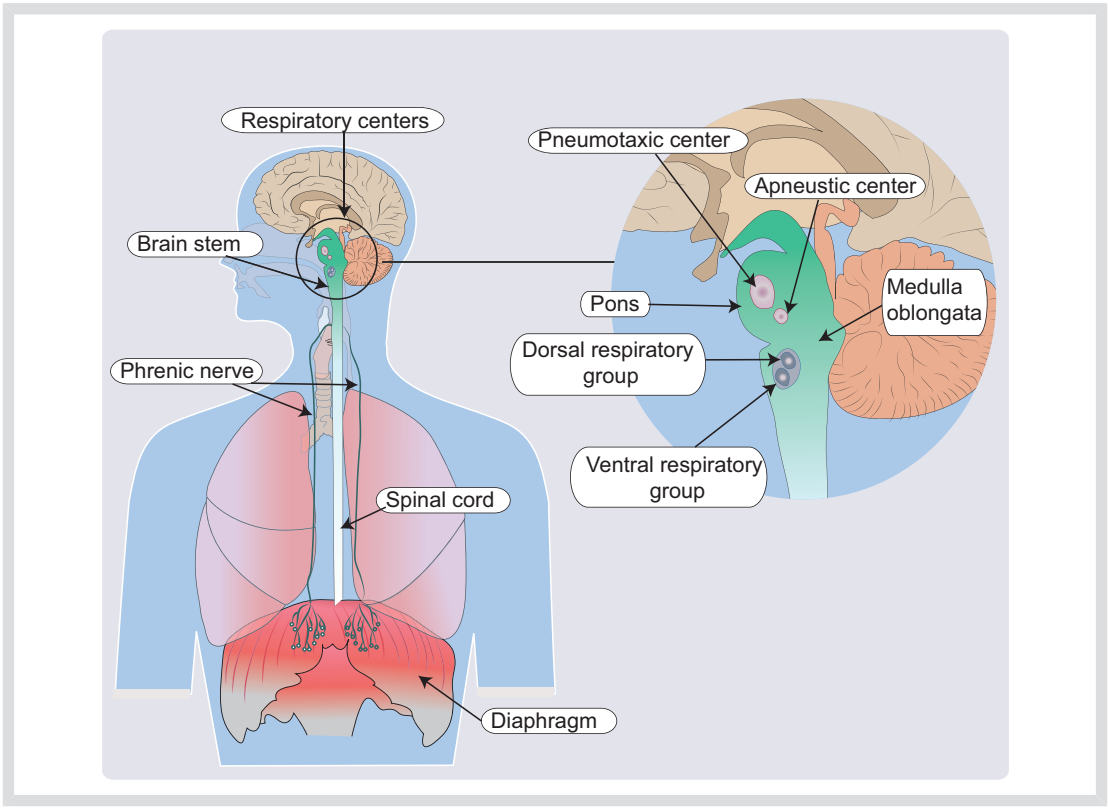


Fig. 3 – Anatomy of the respiratory centers, focusing on the brainstem and the different respiratory groups

2.2 THE UPPER AND LOWER AIRWAYS

To reach the lungs, air flow follows the pathway through the upper and lower airways. Here, we define the upper airways as comprising the nasal cavity, the pharynx and the larynx.

Here, we define the lower airways as comprising the **trachea** and the bronchial tree which branches off into the lungs.

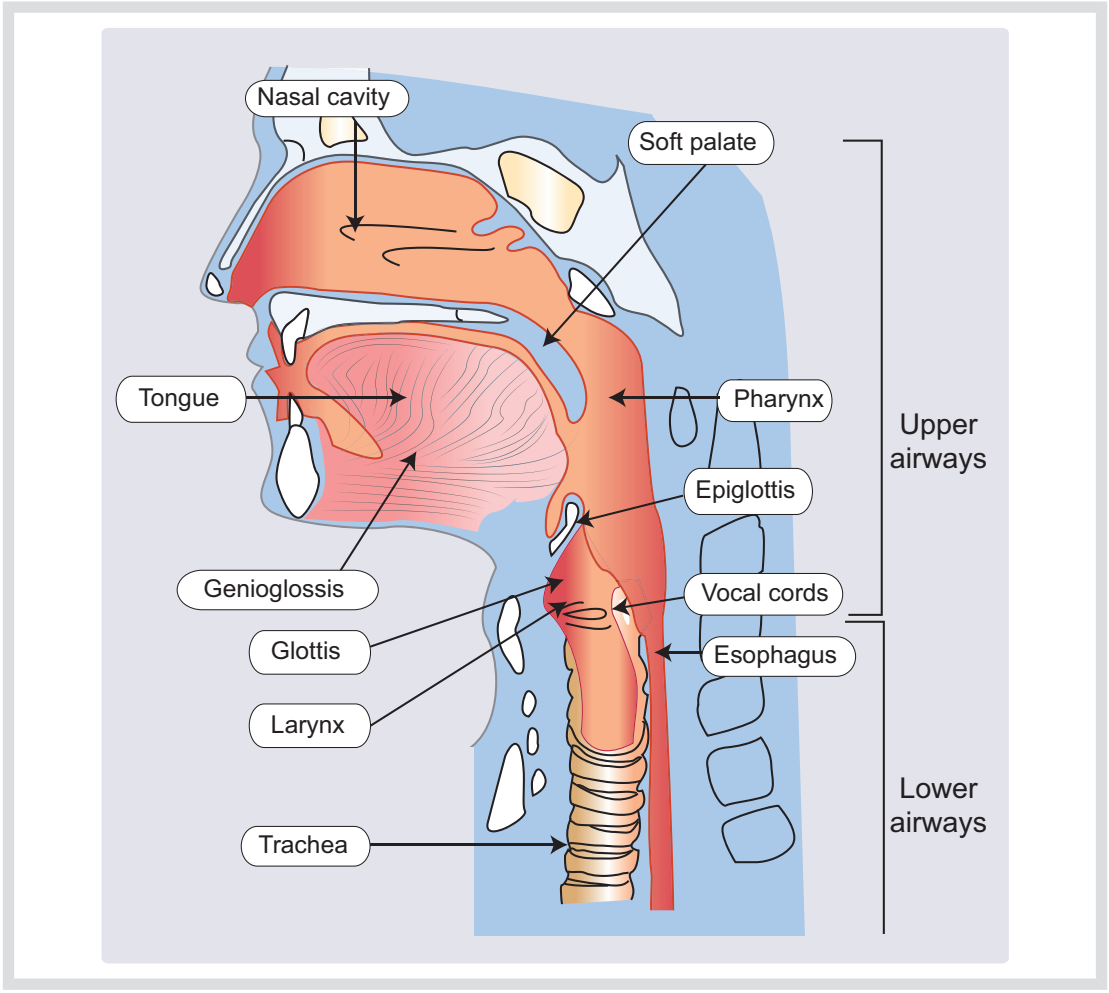


Fig. 4 - The anatomy of the upper airways (nasal cavity, pharynx and larynx) and lower airways (trachea and bronchi).

2.2.1 THE UPPER AIRWAYS: THE NASAL CAVITY

The inside of the nose nearest the nostrils contains hairs which clear the air from larger particles. In the nasal cavity there are a great number of superficial, thin-walled blood vessels, which radiate heat and warm the inhaled air. As well as being an organ of smell, the nose has the important functions of cleaning, warming and humidifying the inhaled air.

The nasal cavity is kept moist by glandular secretions, which also humidify the air. The inspired air, which passes through the nose, is thus fully humidified and has a temperature of 32°C, no matter what the outside temperature.

If the inhaled air does not pass through the nose, (e.g. when breathing through the mouth), then partial drying of the lower airways´ mucous membranes occurs, making them more prone to infection and **bronchospasm**. During invasive ventilation it is important to ensure correct humidification and warming of the inspired gas, as the gas is supplied through an **endotracheal tube** or tracheal cannula which inhibits the physical function of the upper airway.

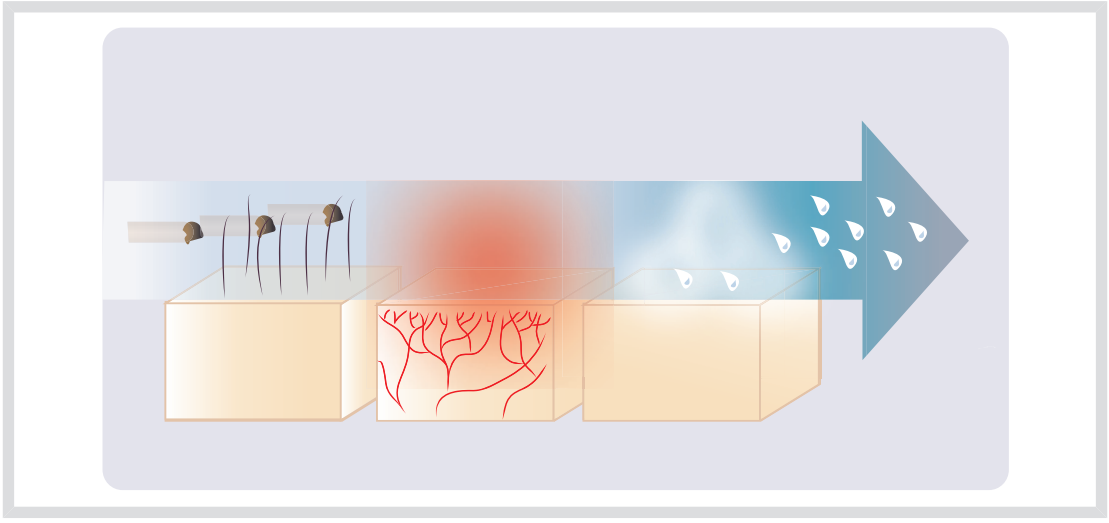


Fig. 5 – Schematic representation of the trajectory of inhaled air through the nasal cavity.

2.2.2 THE UPPER AIRWAYS: THE PHARYNX

The pharynx is situated under the nasal cavity and posterior to the mouth. Because both food and air pass through the pharynx, food is prevented from entering the nasal cavity by a closing upward motion of the soft palate in the roof of the mouth. The **epiglottis** (a flap of connective tissue) closes over the glottis when food is swallowed to prevent aspiration into the larynx.

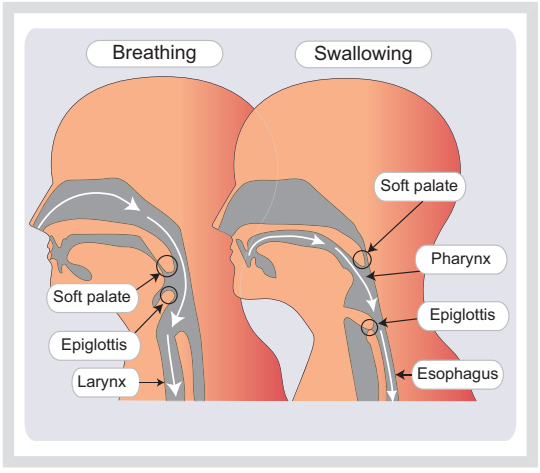


Fig.6 – Anatomy of the pharynx, demonstrating its position in relation to the epiglottis. Note the different epiglottis positions for breathing and swallowing.

2.2.3 THE UPPER AIRWAYS: THE LARYNX

The inhaled air reaches the larynx after passing through the nasal cavity and the pharynx. Below the pharynx, there is a bifurcation into respiratory (larynx) and digestive (**esophagus**) pathways. The larynx hosts numerous sensory receptors and a set of highly co-ordinated muscles which can open or narrow the space between the vocal cords, thus playing a role in: protecting the lower airways, vocalization (via regulation of the vocal cords), respiration (dilating and constricting the lower airways), and expulsive maneuvers.

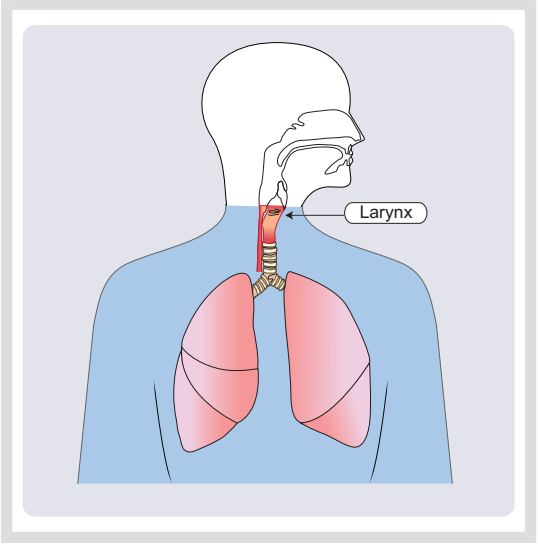


Fig. 7 – Anatomy of the larynx.

The extrapulmonary airway is at its narrowest at the vocal cords, and further narrowing at this point can cause considerable respiratory distress. For example, either during or after **intubation** the vocal cords can become swollen causing respiratory obstruction or hoarseness (after **extubation**).

2.2.4 THE LOWER AIRWAYS: THE TRACHEA

After passing the vocal cords, the air stream enters the trachea, which in the adult is 10-12 cm long and 20-25 mm in diameter. The trachea is kept open by horseshoe-shaped rings of cartilage (opening facing backwards).

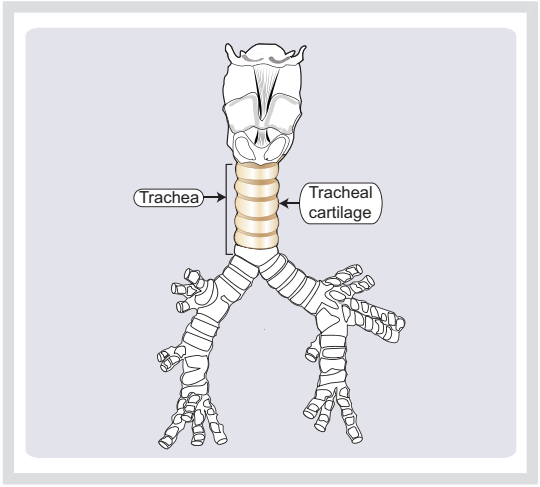


Fig 8 – Anatomy of the trachea

The mucous membrane in the trachea is covered with microscopic hairs (**cilia**). The cilia transport mucus and inhaled foreign material continuously upward towards the laryngeal opening, where it is either coughed up or swallowed into the esophagus, behind the trachea.

2.2.5 THE LOWER AIRWAYS: THE BRONCHIAL TREE

Within the chest, the trachea divides into two main bronchi, one to the right lung and one to the left lung. The right main bronchus is positioned slightly more vertically than the left. This means that any inhaled foreign body is more likely to enter the right lung. The main bronchi branch off into smaller and smaller bronchi (lobar bronchi, segmental bronchi, and **bronchioles**), until after 23 divisions they terminate in the alveoli.

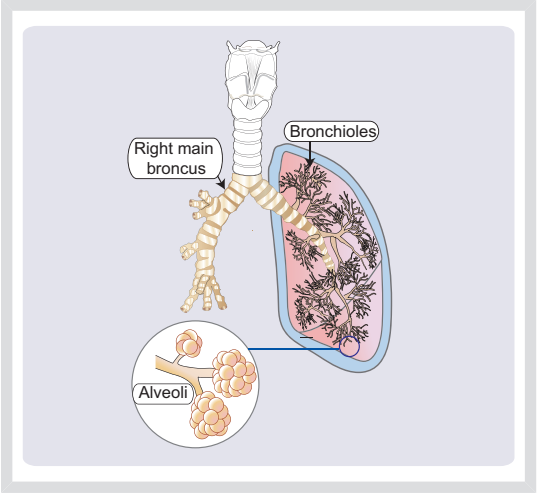


Fig 9 – Anatomy of the bronchial tree.

The bronchi and the bronchioles are, as is the trachea, covered with cilia. In contrast to the larger bronchi, distal bronchi lack cartilage plates in their walls and consequently can close if pressure outside the airway is higher than inside it. Air reaching the alveoli delivers its oxygen to the erythrocytes (red blood cells) in the neighboring capillaries, and at the same time takes up carbon dioxide (see Chapter 4).

2.3 THE LUNGS AND PLEURAL CAVITY

The lungs are divided into lobes; the left lung has two and the right lung three. The lobes are divided into bronchopulmonary segments which in turn are divided into lung lobules. These lung lobules are the smallest sub-division visible to the naked eye.

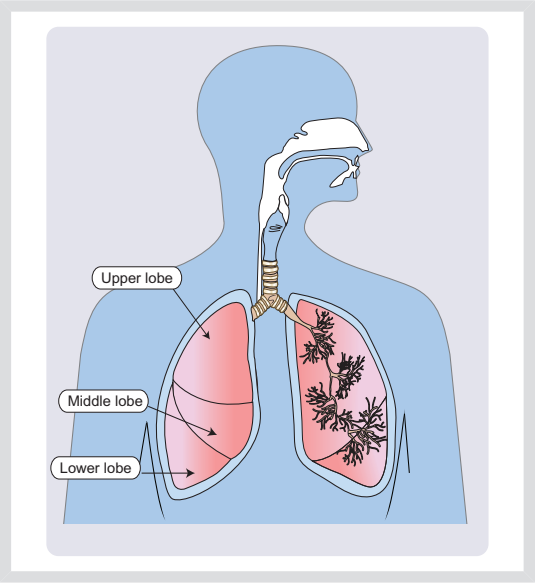


Fig. 10 - Anatomy of the lungs

Each lung is enveloped in its pleural membranes, an inner and an outer which are in intimate contact with each other. The inner membrane (the visceral pleura) closely envelopes the lungs´ surface while the outer membrane covers the inside of the chest wall and the diaphragm.

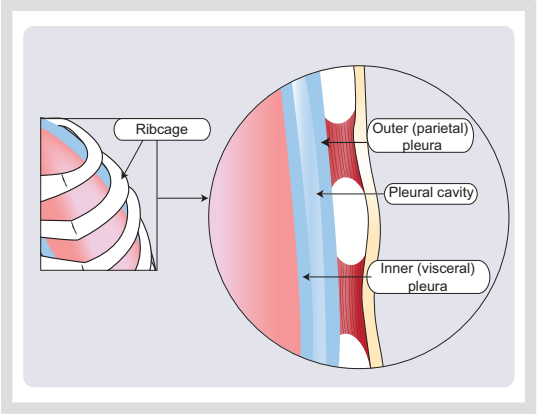


Fig. 11 - The pleural cavity identifying the outer and inner pleuras.

In the space between the pleural membranes, the pleural cavity, the pressure is negative. The negative pressure is maintained by the rib cage, which pulls the outer, parietal **pleura** outward. During inspiration, muscle activity increases the negative pressure in the pleural cavity, thus causing the lungs to expand and air to be sucked into them.

2.4 THE RESPIRATORY MUSCLES

2.4.1 THE DIAPHRAGM

Inspiration is an active process. The main inspiratory muscle is the diaphragm. It is a thin dome-shaped muscle that inserts into the lower ribs, thereby separating the thorax from the abdomen.

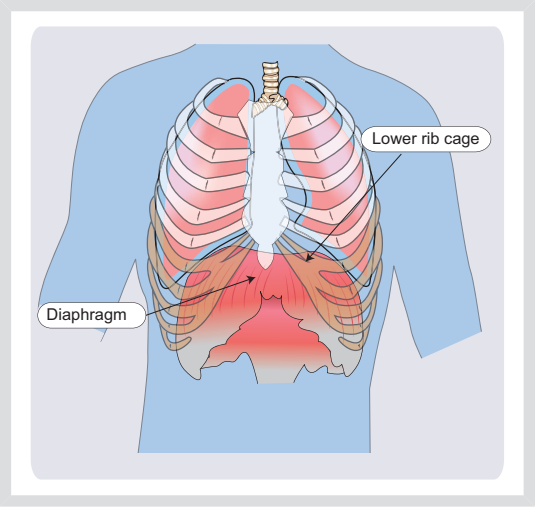


Fig. 12 - Anatomy of the entire diaphragm, identifying its position within the chest wall.

The diaphragm is pierced by the aorta, the esophagus, and the inferior vena cava.

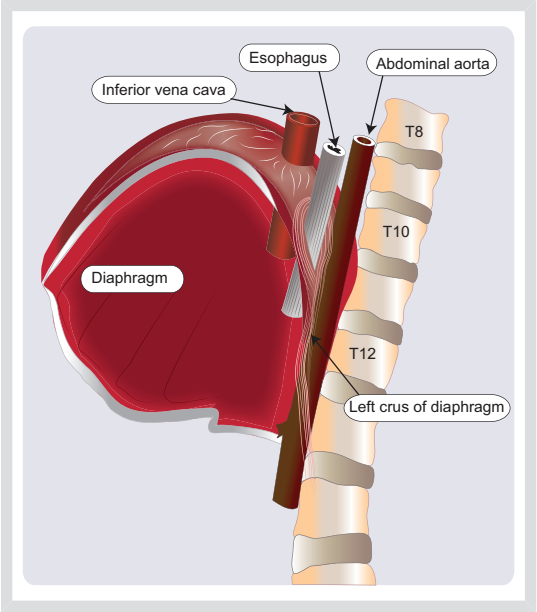


Fig.13 - Side view of the human diaphragm showing entry points of the esophagus, inferior vena cava, and abdominal aorta, with respect to the thoracic vertebrae (T8-T12).

When seen from below, it can be seen how the diaphragm consists of two parts, the **costal** portion and the **crural** portion.

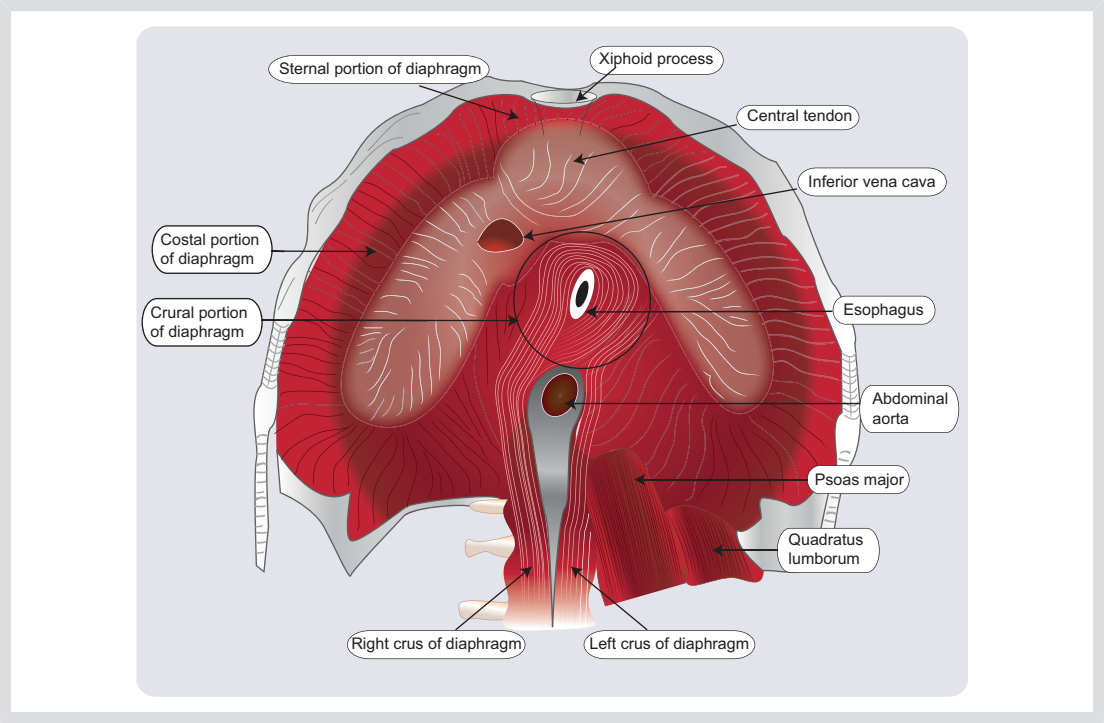


Fig 14 – Anatomy of the entire diaphragm, as seen from below. Note the costal portion (outer) and the crural portion (more central) of the diaphragm surrounding the esophagus.

The left and right portions of the crural diaphragm have their origin in the lumbar vertebrae, extend superiorly and anteriorly, and surround the esophagus in a scarf-like fashion. This is important when considering esophageal measurements of diaphragm electrical activity.

Although anatomically distinct, the costal and crural portions of the diaphragm are activated simultaneously during inspiration. Non-respiratory maneuvers (such as vomiting) may demonstrate dissociated activation between the two parts of the diaphragm.

Both portions of the diaphragm are stimulated by the phrenic nerves originating in cervical segments C3, C4, and C5.

2.4.2 OTHER RESPIRATORY MUSCLES

Also playing a role in inspiration are the external intercostal muscles and the accessory muscles (scalene, sternomastoid, and serratus anterior muscles). Their insertion directly into the ribs allows lifting of the rib-cage upon their contraction.

The intercostal muscles are stimulated by the intercostal nerves originating in thoracic segments T1-T11.

Expiration is normally passive by the inward recoil of the lungs and chest wall. If needed, the abdominal muscles (rectus abdominis, external and internal obliques) and the internal intercostal muscles can participate in expiration.

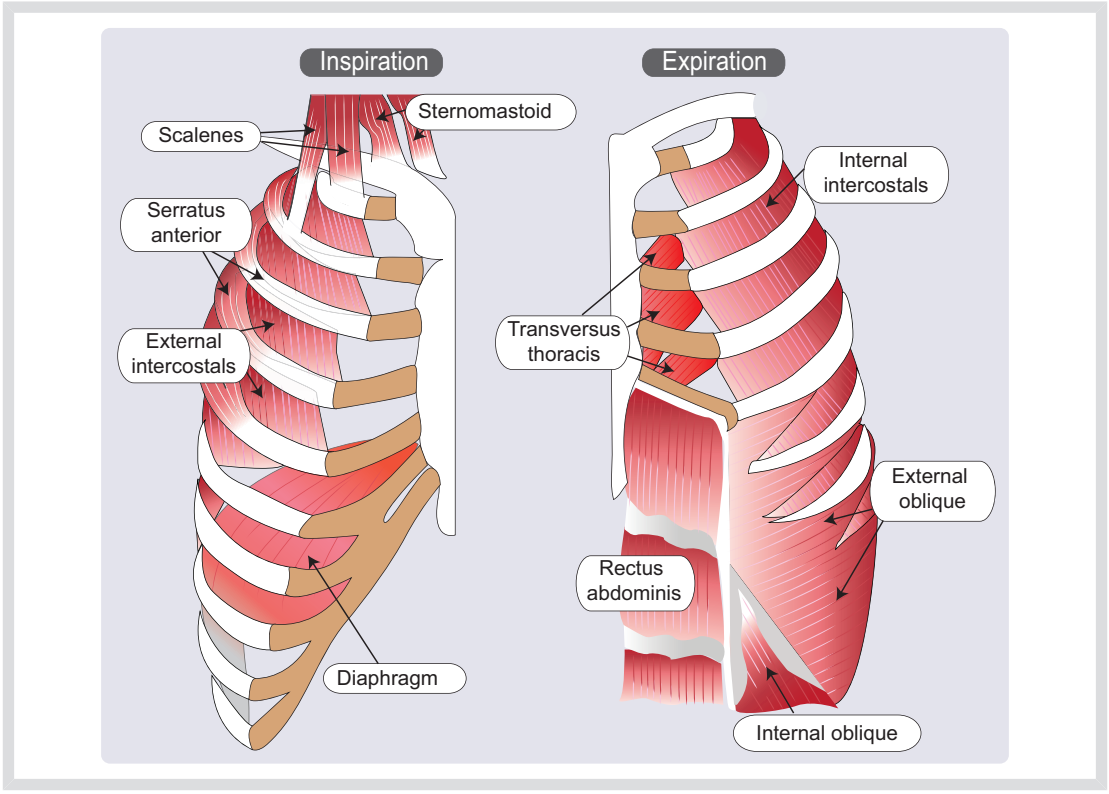


Fig 15 – Anatomy of the respiratory muscles involved with inspiration (left) and expiration (right).

2.4.3 STRUCTURE OF SKELETAL MUSCLE

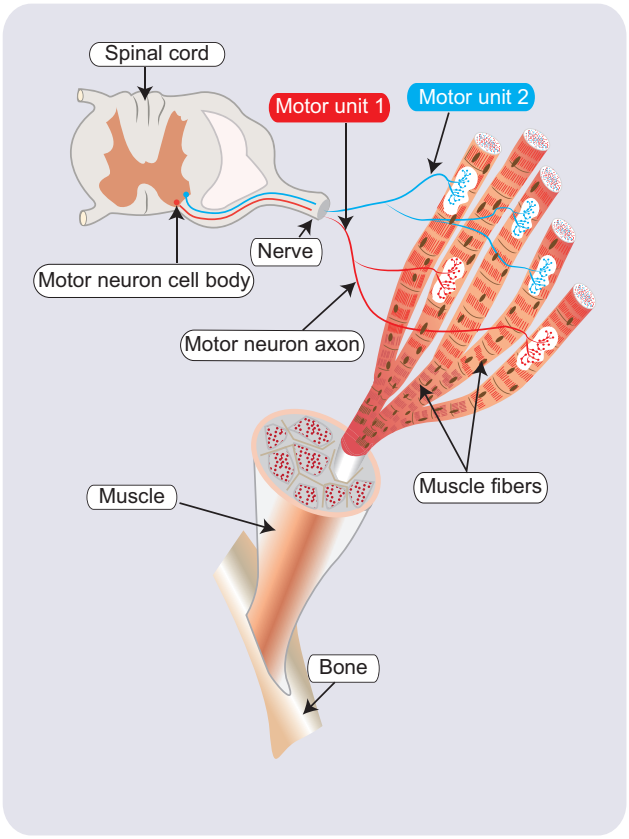


Fig. 16 – Structure of skeletal muscle, showing two different motor units (Motor unit 1 in red, Motor unit 2 in blue).

The diaphragm is a skeletal muscle. Skeletal muscle is made up of many motor units. A motor unit is a single motor neuron and all of the muscle fibers it innervates. In the figure, two motor units are demonstrated for simplicity.

The motor nerve fibers that innervate skeletal muscle arise in the spinal cord. In the case of the diaphragm, the motor nerves are the left and right phrenic nerves, arising from cervical segments C3, C4, and C5.

3 PHYSIOLOGY I - SPONTANEOUS BREATHING

Respiration is the uptake of oxygen by the body and the elimination of carbon dioxide. Respiration can be divided into:

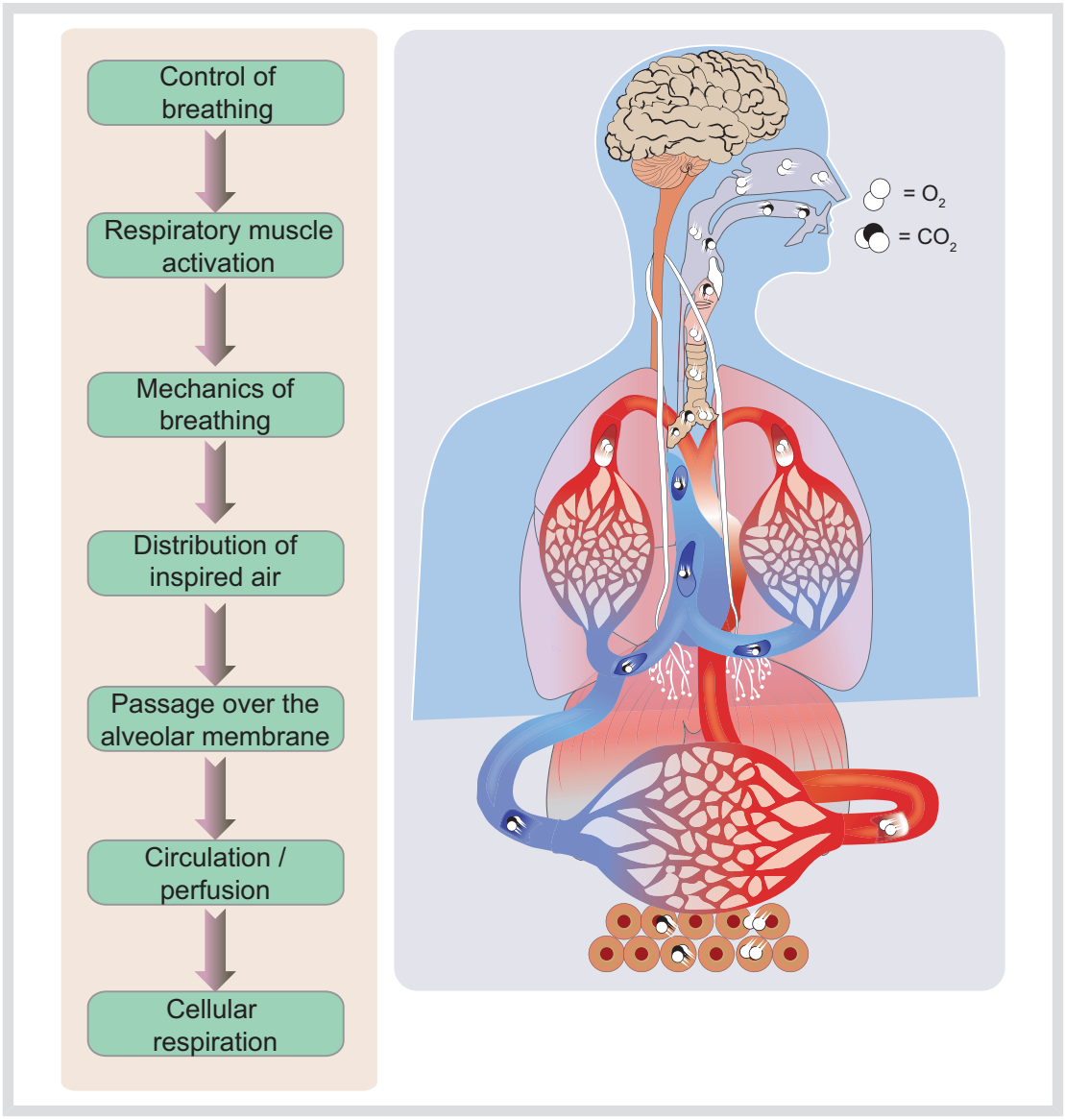


Fig. 17 - Schematic representation of the chain of events involved with spontaneous breathing from the control of breathing to the level of cellular respiration. CO_2 is produced during cellular respiration and is eliminated via circulation/perfusion to the alveolar gas and expired.

3.1 CONTROL OF BREATHING

The depth and rate of breathing is determined by neural signals arising in the pons and medulla of the brainstem ("the respiratory centers") that extend down to the diaphragm and other inspiratory muscles.

Under resting conditions, the diaphragm is the main muscle of inspiration. With increasing respiratory demand, other inspiratory muscles play more important roles and become activated.

The neural output from the respiratory centers is governed by information from different receptors in the body. Below is a description of some of the important feedback provided to the respiratory centers.

In healthy subjects, the order of inspiratory muscle recruitment is nearly simultaneous, with a slightly earlier activation of the upper airway dilator muscles to allow a patent airway.

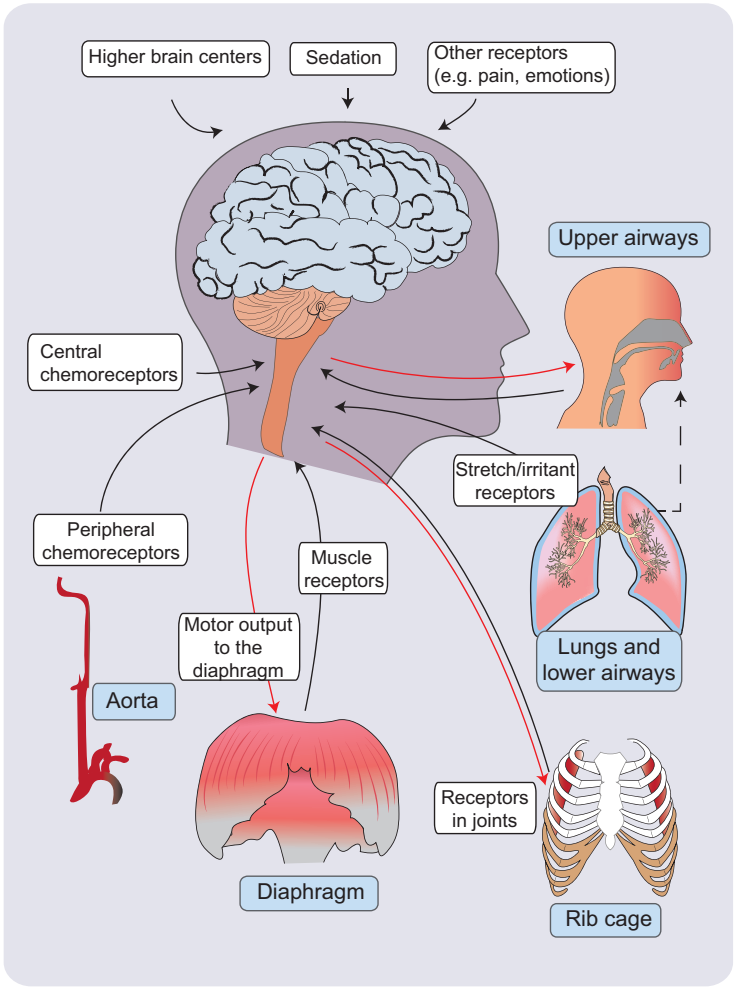


Fig 18 - Illustration demonstrating the different feedback systems to the respiratory centers. Black arrows indicate the afferent feedback from the organs to the brainstem. Red arrows indicate efferent output to the various respiratory muscles.

3.1.1 FEEDBACK FROM THE LUNGS

The lungs host receptors sensitive to stretch and respond to both lung distension and deflation. Lung distension modulates breathing pattern by shortening inspiration, or prolonging expiration, the so-called **Hering-Breuer** inspiratory-sensitive **reflex**. Deflation of the lungs at end-expiration shortens exhalation and stimulates inspiration, the Hering-Breuer deflation-sensitive reflex. These reflexes are due to the slowly adapting receptors, and the rapidly adapting receptors, respectively.

The rapidly adapting receptors are also stimulated by chemical stimuli and changes in lung compliance. When stimulated the rapidly adapting receptors cause tachypnea, cough, and augmented breaths. Pulmonary edema, mediators of inflammation and immune responses, inhaled irritants, and direct tissue damage stimulate the bronchial C-fiber receptors, causing **apnea** and/or rapid shallow breathing, and cough.

The above-described reflexes are mediated by the vagal nerves.

3.1.2 FEEDBACK FROM THE RESPIRATORY MUSCLES

Afferent feedback from the respiratory muscles affects neural drive to the different individual muscles. Golgi tendon organs and muscle spindles (types of muscle receptors) are sparsely present in the diaphragm and may provide feedback related to muscle tension and length, respectively.

3.1.3 JOINT RECEPTORS

Reflex responses mediated by receptors in the costovertebral joints may also facilitate responses to respiratory loads.

3.1.4 CHEMORECEPTORS

Receptors sensitive to the concentration of arterial oxygen, carbon dioxide, and the **pH** in the arterial blood (subsequently, when referring to arterial concentrations, the subscript "a" will be used), are constantly feeding back to the respiratory centers to alter breathing pattern in order to maintain homeostasis. The peripheral chemoreceptors in the carotid bodies respond primarily to hypoxemia (low P_aO_2), but a significant part of the ventilatory response to hypercapnia also originates in the peripheral chemoreceptors.

Central chemoreceptors in the brainstem also respond to hypercapnia (High **P_aCO_2**). Thus, hypercapnic stimulation of ventilation seems to depend jointly on both peripheral and central chemoreceptors.

Activation of either the hypoxic or hypercapnic chemoreflex elicits hyperventilation (increased respiratory drive), and therefore increased electrical activity of the diaphragm (Edi).

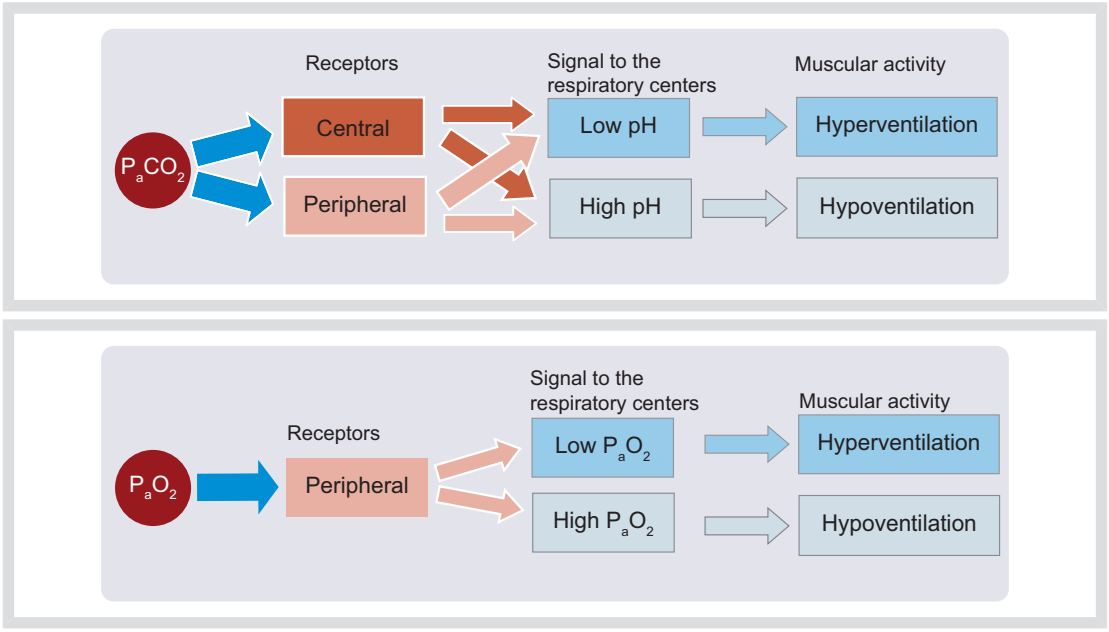


Fig. 20 – Impact of arterial O_2 on regulation of breathing

3.1.5 FEEDBACK FROM THE UPPER AIRWAYS

The larynx contains several types of receptors sensitive to pressure, temperature, and irritants (C-fiber receptors or J receptors), that when stimulated, cause cough, apnea, bronchoconstriction and mucus secretion.

The pharyngeal and laryngeal reflexes may be more important during the application of non-invasive ventilation, when an endotracheal tube is not present.

3.1.6 SEDATION AND ANALGESIA

Mechanical ventilation often goes hand in hand with sedation and/or analgesia, and both can have an impact on the respiratory center's ability to stimulate ventilation.

3.2 RESPIRATORY MUSCLE ACTIVATION

Skeletal muscles receive electrical stimulation from a motor nerve (the phrenic nerve in the case of the diaphragm).

The junction between the terminal tip of the nerve fiber, and the motor end-plate of each muscle fiber is called the neuromuscular junction. Transmission across the neuromuscular junction requires the release of Acetylcholine (ACh) by the ACh transporter (vesicle), and its acceptance by ACh receptors on the muscle fiber membrane.

Once ACh has bound to receptors in the muscle fiber end-plate region, it opens channels in the muscle fiber membrane that are permeable to sodium (Na+) and potassium (K+) ions. Movement of ions across the muscle fiber membrane causes a change in electrical current. This current flow can be measured as a voltage difference over time, and when displayed as a waveform, is known as the **action potential.**

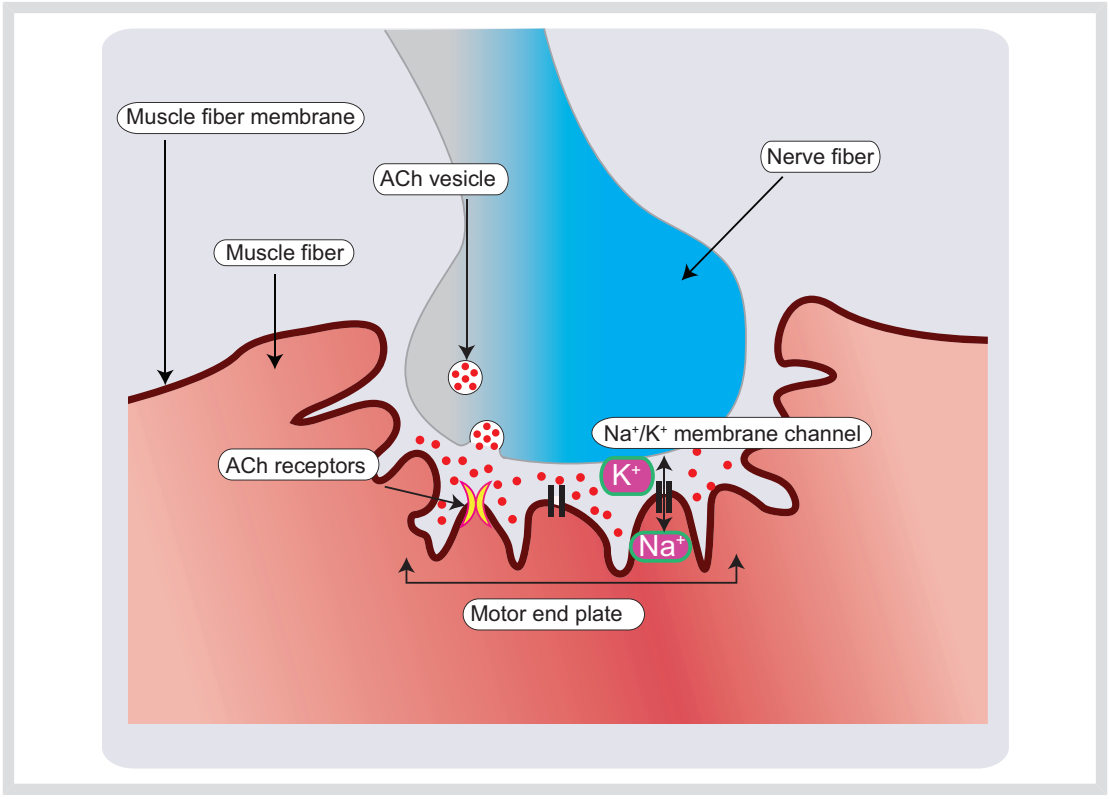


Fig. 21 – Schematic representation of the neuromuscular junction of skeletal muscle demonstrating the pathway of Acetylcholine molecules (ACh) between the nerve terminal and the motor end plate of the muscle fiber.

3.2.1 ACTION POTENTIALS AND THE DIAPHRAGM ELECTROMYOGRAM (EMG)

A single fiber action potential is the extracellular potential generated by movement of ions across the sarcolemma (muscle fiber membrane - see section 3.4) during depolarization of a single muscle fiber.

When a motor unit is activated, the single muscle fiber action potentials are summed for all fibers in the motor unit, resulting in a single motor unit action potential.

During spontaneous breathing, activation of the diaphragm motor units is achieved by increases in the discharge frequency of phrenic motor units and/or by recruitment of new motor units. When several motor units are recruited, and/or their firing rate increases, this yields a summation of the motor unit action potentials (in amplitude and in time), resulting in an interference pattern **electromyogram** (EMG) signal.

This chaotic-like, "noisy" EMG signal can be processed with filters and signal conditioning techniques to yield a waveform. Note that in order for the waveform to be reliable for physiological interpretation, the EMG signal of the diaphragm must be recorded with electrodes of an appropriate configuration, maintenance of electrode positioning and orientation with respect to the muscle fiber direction, and avoidance of signal disturbances, such as motion artifacts.

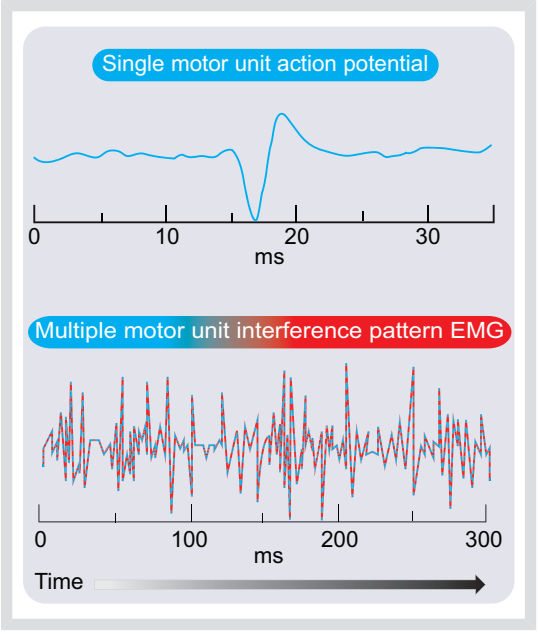


Fig. 22 – Schematic representation of a single motor unit action potential (top blue tracing) and the interference pattern electromyogram (EMG) consisting of the summation of multiple motor unit action potentials (mixed colors)

3.2.2 THE ELECTRICAL ACTIVITY OF THE DIAPHRAGM (Edi) WAVEFORM

After signal filtering and processing, the diaphragm EMG signal is transformed into a waveform, referred to as the electrical activity of the diaphragm (Edi) waveform. The waveform represents the neural respiratory drive (final output of respiratory centers) as a continuous function over time. The Edi waveform has the units of microvolts (μV).

When the Edi waveform is increasing (upwards deflection), it is representative of neural inspiration, and when the waveform is decreasing back to baseline, it is representative of neural expiration. Both the highest value reached (**Edi peak**) and the lowest value (**Edi min**) can be quantified for each breath, and given a numerical value. Because of the distinct pattern of the waveform increasing and decreasing, the Edi peak is often referred to as the phasic Edi, whereas the baseline (between breaths) is often referred to as the tonic Edi.

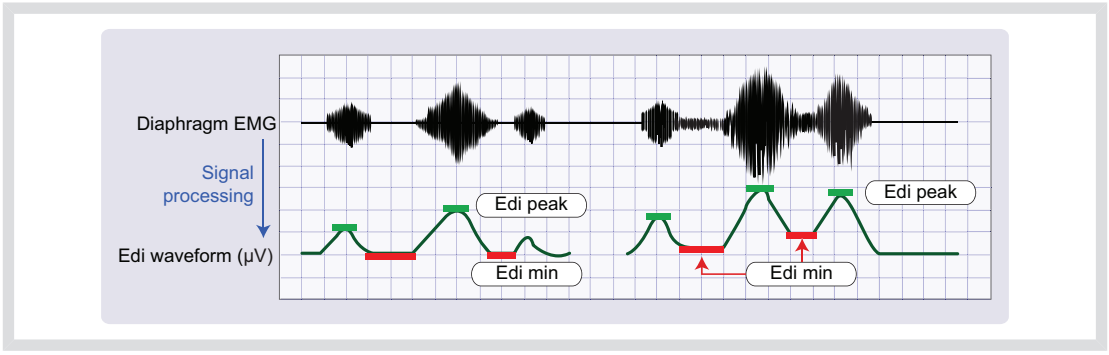


Fig. 23 - The EMG signal is presented schematically for a period of spontaneous breathing. Note the intermittent "bursts" of activity, indicative of breathing efforts (top tracings). After signal processing, the EMG signal is transformed into a waveform, representative of diaphragm electrical activity, known as the Edi waveform. From the Edi waveform, for each cycle (breath) the highest value reached (Edi peak indicated by green horizontal line) and the lowest value (Edi min indicated by red horizontal line) can be quantified. In the example on the left, there is very little diaphragm activity in between breaths (low Edi min) - indicative of low tonic Edi. On the right, the Edi min is elevated - indicative of increased tonic Edi.

The Edi waveform can be characterized by its timing to calculate **neural respiratory rate**, i.e. the number of neural respiratory efforts per minute. The **neural inspiratory time** can be defined as the period from onset of the increase in Edi to the peak Edi. The **neural expiratory time** can be defined as the time from the peak Edi to the onset of the next increase in Edi.

The Edi waveform in adults is generally less variable with low and stable Edi min.

The Edi waveform in infants can be characterized by larger variability in timing and Edi peak, with a distinct amount of changes in the Edi min value.

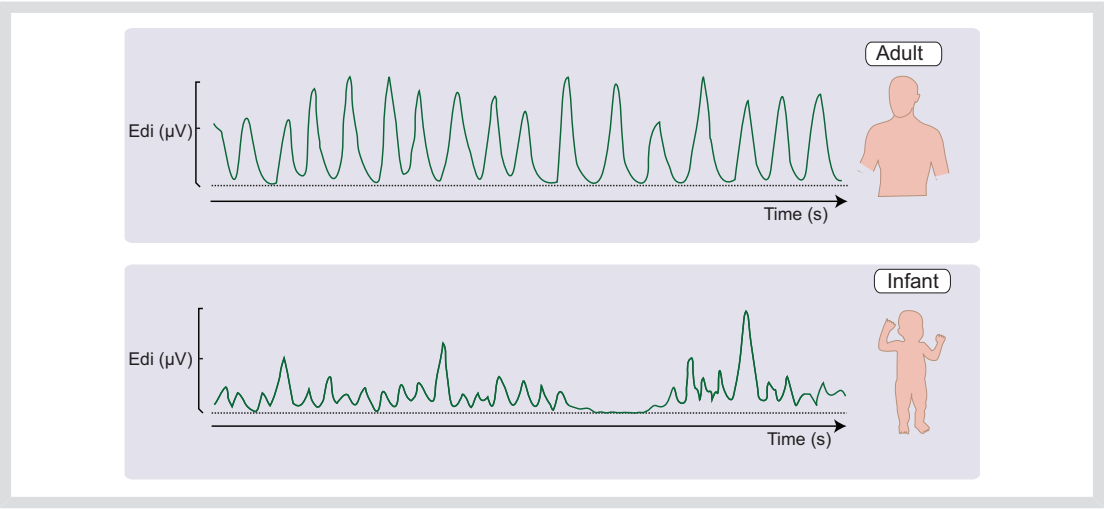


Fig.24 - Typical Edi waveform observed in adult patient (top tracing) and infant patient (bottom tracing).

3.2.3 MEASUREMENT OF Edi IN HUMANS

There are several possibilities for measuring the diaphragm EMG in humans. Insertion of needles or applications of electrodes on the body's surface are two options, although the former methodology may be considered painful and rather invasive; the latter is prone to artifacts (motion, subcutaneous tissue, cross-talk from other muscles).

Because of the anatomy of the human diaphragm, it is possible to measure the electrical activity of the diaphragm inside the esophagus, at the level of the **gastro-esophageal junction** where the EMG signals from the crural portion of the diaphragm can be picked up. Small sensors can be mounted on a regular naso/oro gastric feeding tube and positioned to record the Edi waveform.

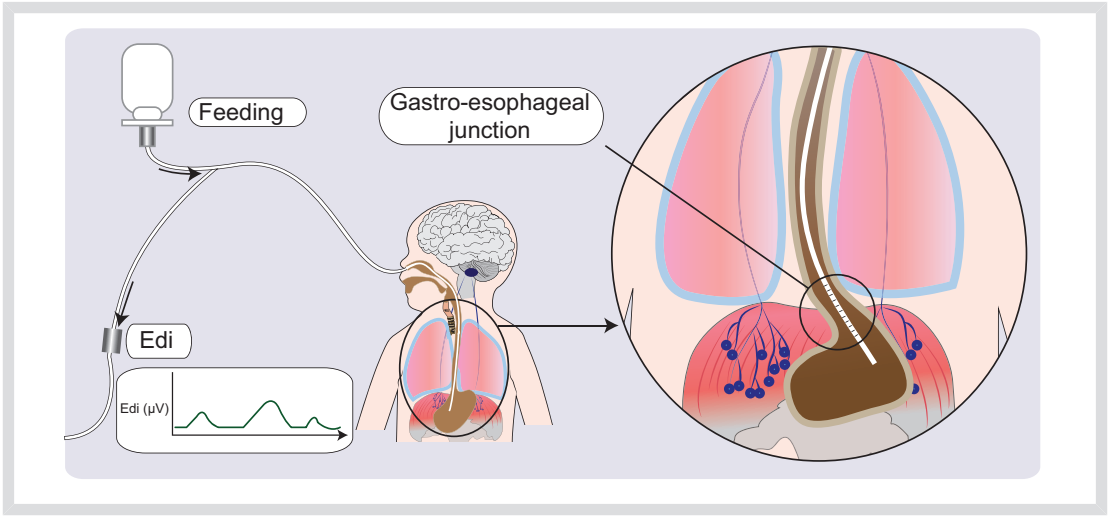


Fig.25 - Method for esophageal recordings of the Edi waveform.

3.2.4 Edi PEAK

When a subject's ability to generate a tidal breath decreases due to disease, this may increase the demand for increased diaphragm activity, and therefore will demand a higher Edi peak.

Other factors which can result in increased Edi peak include worsening of respiratory status, dynamic hyperinflation (shortened diaphragm), reduced ventilator assist, reduced sedation, increased demand for ventilation such as exercise, and increased dead space. The opposite holds true: Edi decreases within a given subject with respiratory improvement, increased sedation, increasing levels of ventilator assist, and reducing arterial CO_2.

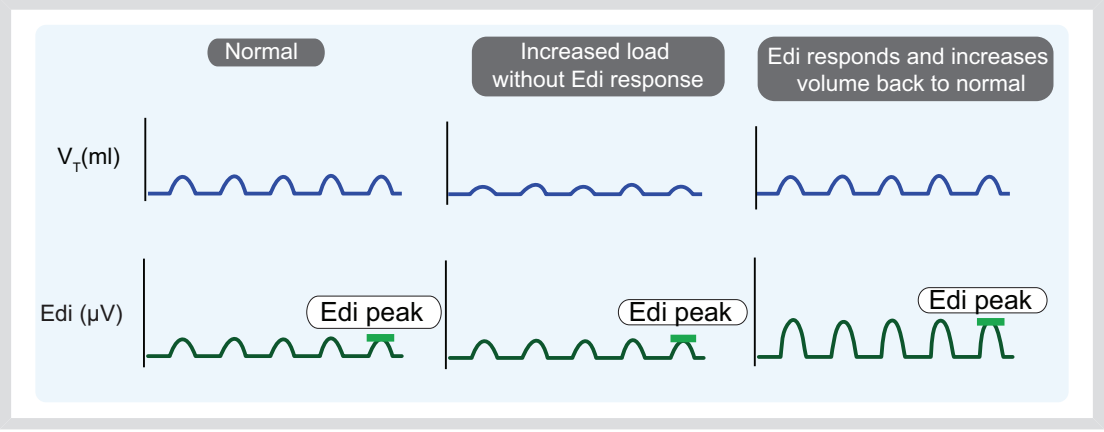


Fig. 26 - Schematic demonstration of the Edi waveform obtained in a healthy subject breathing spontaneously at rest (left panels). If a resistive load is applied (middle panels), the immediate result, if neural respiratory output does not change, is a reduction in tidal volume (amplitude of blue waveform is reduced). After several breaths (right panels), the respiratory centers will compensate for this reduced tidal volume by increasing respiratory drive, and hence the Edi peak, restoring tidal volume.

3.2.5 Edi MIN

The Edi waveform can sometimes remain elevated at the end of neural expiration (does not return to baseline), sometimes referred to as “tonic Edi”. The tonic Edi can be quantified by the Edi min value.

In intubated infants, application of positive end-expiratory pressure helps to keep the lung recruited, and minimizes the tonic Edi.

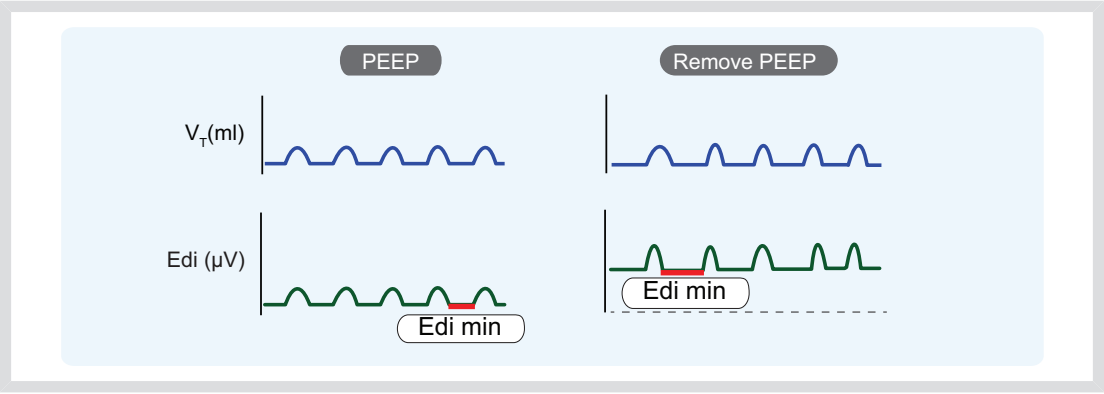


Fig. 27 - Schematic representation of a subject breathing spontaneously at rest. If end-expiratory lung volume is lowered artificially (e.g. removing **PEEP** while intubated), the deflation-sensitive receptors in the lungs will send signals to the respiratory centers about the de-recruitment of lung units, and will stimulate activation of the diaphragm. Even during neural expiration, the diaphragm remains active so as not to “relax” in between respiratory cycles. The maintained diaphragm activity (elevated Edi min indicated by red lines) prevents further de-recruitment or even recruits lung units to restore end-expiratory lung volume.

3.2.6 Edi DURING MECHANICAL VENTILATION

Mechanical ventilation can be delivered with two extremes, one where the patient is neuro-muscularly paralyzed and the ventilator is fully in control (controlled ventilation).

The other extreme, is where the patient is breathing spontaneously and the patient and the ventilator share the work of breathing (supported ventilation).

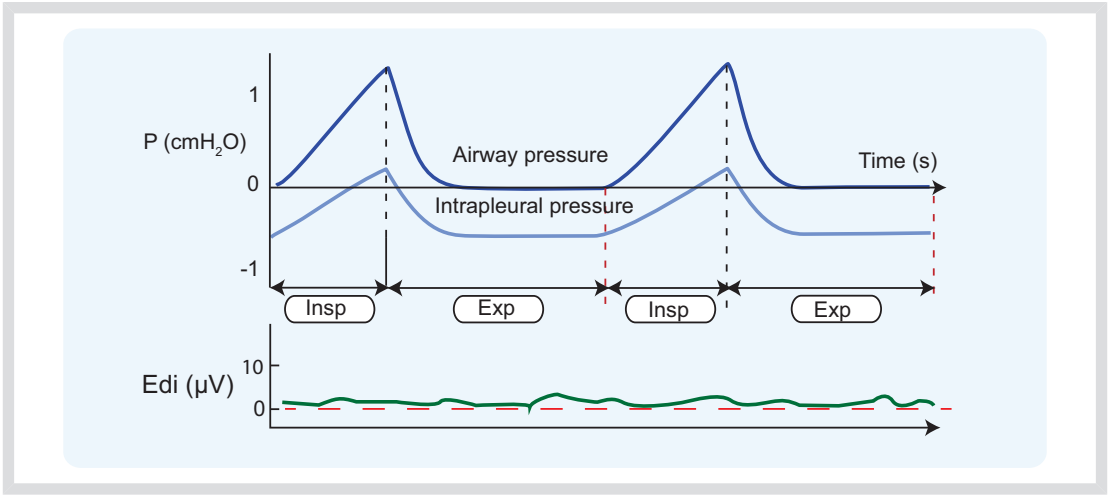


Fig. 28 - Controlled ventilation. Schematic representation of Edi and pressure waveforms during controlled ventilation. In a patient who is paralyzed and being supported with controlled ventilation, the characteristic waveforms are described. Note that the Edi curve will be flat at approximately 0 V because the neuromuscular junction is blocked pharmacologically, and no action potentials are initiated in the diaphragm muscle fibers. The airway and ***intrapleural*** pressure curves increase and decrease, as the positive pressure is applied intermittently to the patient's airways.

During spontaneous breathing, the Edi waveform is normally present.

In acute respiratory failure, the respiratory muscles require help by way of mechanical ventilation.

During **supported ventilation**, the patient is spontaneously breathing, and thus the ventilator should be synchronized to the patient's neural breathing efforts. The patient should not be over-assisted to the point where spontaneous breathing is abolished. This could potentially lead to ventilator-induced diaphragm dysfunction (VIDD).

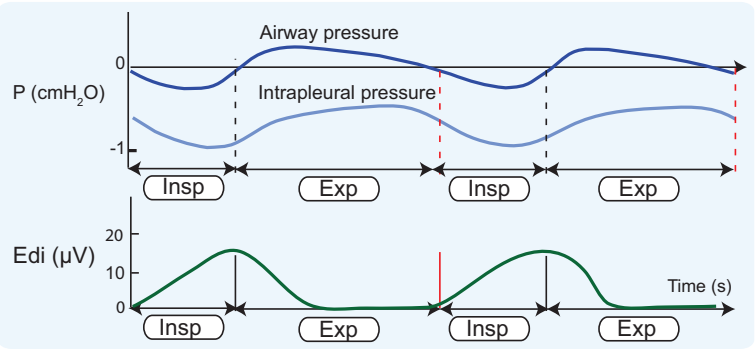


Fig. 29 - Spontaneous breathing. The Edi waveform and the airway pressure waveform are demonstrated for a healthy, non-ventilated subject during spontaneous breathing, no paralysis and no ventilator), and the waveforms show their characteristic phasic and intermittent activities.

3.3 SUMMARY OF EDI MONITORING

The Edi is a physiological signal representative of central respiratory output, and is normally present in spontaneously breathing subjects. The Edi waveform has a characteristic phasic pattern with quantifiable peak and minimum values. The Edi is essentially a vital sign, just like the electrocardiogram, and allows determination of neural breathing activity, and function of the diaphragm.

3.4 THE MECHANICS OF SPONTANEOUS BREATHING AND LUNG VOLUMES

3.4.1 SKELETAL MUSCLE CONTRACTION

Action potentials, once initiated, propagate over the surface of the muscle fiber membrane, and into the muscle fiber by way of the transverse tubules (or t-tubules). The action potential in the transverse tubules triggers the release of calcium ions from the sarcoplasmic reticulum. The presence of calcium ions initiates the contractile process, i.e. generation of force.

Electrical activation of skeletal muscle and its subsequent force production are distinct events. The process linking activation and force production is often referred to as excitation-contraction coupling or the **"neuro-mechanical coupling".**

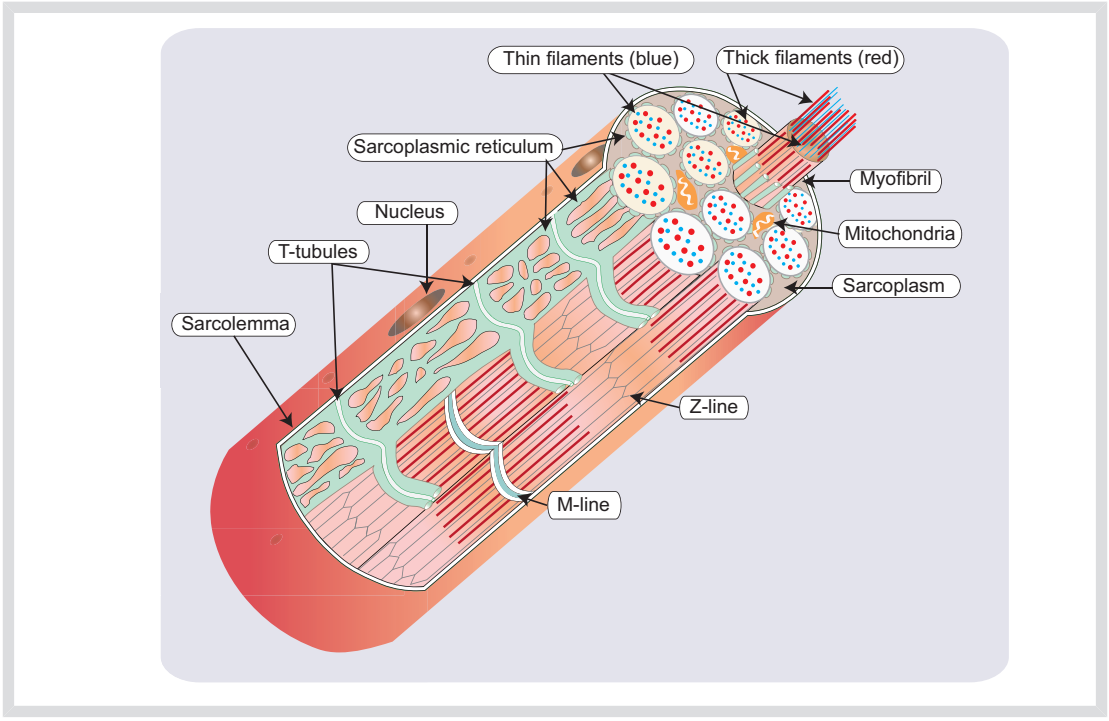


Fig. 30 – Anatomy of a skeletal muscle fiber. The cytoplasm of a skeletal muscle fiber contains the sarcoplasmic reticulum which is a structure storing the calcium ions required to intiate contraction. In contact with the muscle fiber membrane, the transverse tubules allow action potentials to propagate into the cell and activate the sarcoplasmic reticulum.

Whole muscle force is increased by the motor units increasing their firing rate and/or by the recruitment of additional motor units.

The amount of force generated by a skeletal muscle is dependent on its muscle length. For each skeletal muscle fiber, there is an optimal muscle length where the greatest tension is generated. If the muscle fiber is shortened or lengthened, the force generated for a given neural activation will be reduced (i.e. impaired neuro-mechanical coupling).

3.4.2 DIAPHRAGM CONTRACTION

Contraction of the human diaphragm results in its shortening and downward movement into the abdomen. The external intercostals muscles, if activated, contract and lift the chest upwards and outwards. These contractions of the diaphragm (and external intercostals) enlarge the dimension of the thorax, and cause a drop in pressure in the lung, thereby drawing air into the alveoli.

3.4.3 SPONTANEOUS BREATHING

INSPIRATION

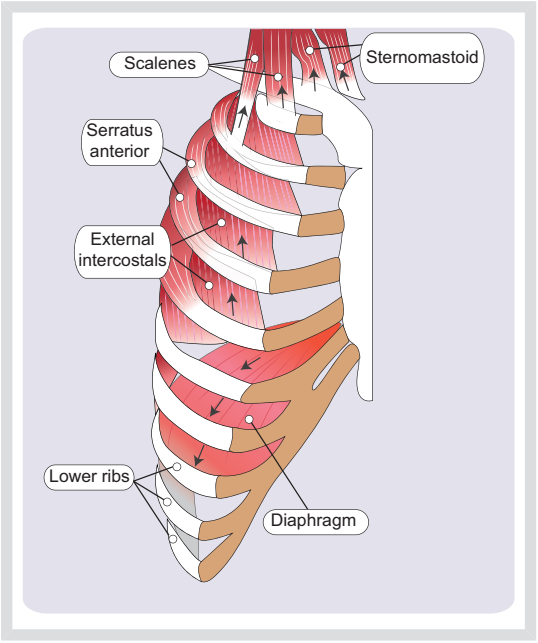


Fig. 31– Anatomy of the muscles of inspiration and their action when contracting (arrows).

Inspiration is an active process, i.e, the elasticity of the lungs, the chest wall and the flow resistance in the airways must be overcome. The most important inspiratory muscle is the diaphragm. During exercise or when airway obstruction is significant, the accessory breathing muscles (e.g. scalene muscles in the neck) and the abdominal muscles (serratus anterior and the external intercostals) are active to enforce breathing. On inspiration, the diaphragm moves downwards as it flattens out. It moves about 1 cm during a normal breath, but can move up to 10 cm in an adult.

Other muscles which contribute to inspiration are those which join the outside surface of the ribs. These muscles are called the external intercostal muscles and they lift the chest wall upwards and outwards. In addition, the accessory muscles, mentioned earlier, can help inspiration during strenuous breathing.

EXPIRATION

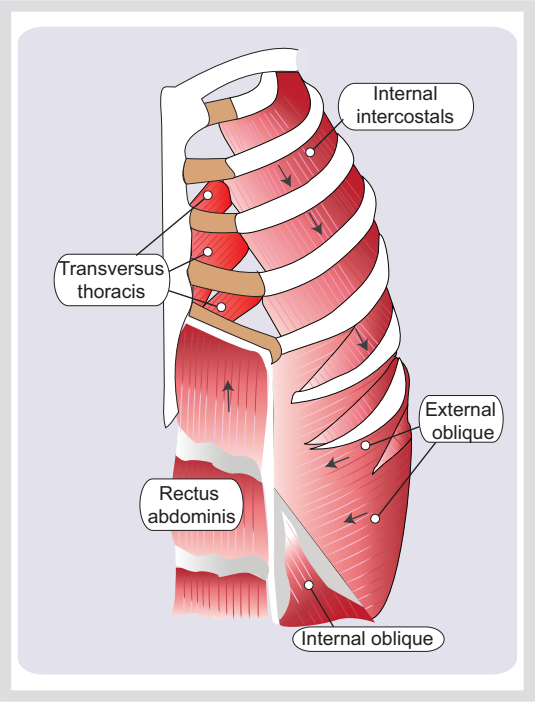


Fig.32 – Respiratory muscles – Expiration.

Expiration is normally a passive process i.e., air is driven out of the lungs by the elastic recoil of the lungs and chest wall as they return to their original position after inspiration. If expiration is difficult, e.g., by an obstruction in the airway, the abdominal muscles and muscles joining the inside surface of the ribs (internal intercostal muscles) help to draw the chest wall downwards and inwards and expel the air.

3.4.4 LUNG VOLUMES

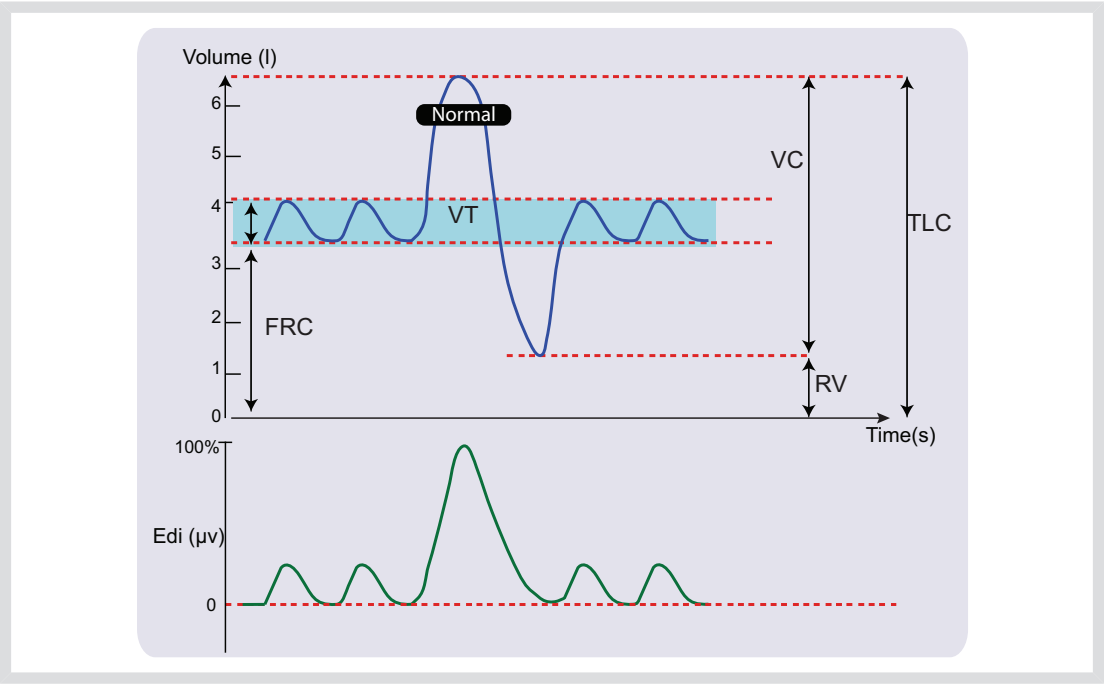


Fig 33 – Lung volumes during spontaneous breathing, Illustration of tidal volume, functional residual capacity, vital capacity and total lung capacity. The Edi waveform is also drawn schematically to show its relation to different inspired volumes.

The most commonly accepted terminology for different lung volumes is:

- VT = Tidal Volume (volume of gas passing in and out of the lungs during normal quiet breathing when no extra effort is needed).
- FRC= Functional Residual Capacity (the volume in the lung after a normal expiration)
- VC = Vital Capacity (max. volume of a breath)
- TLC = Total Lung Capacity (VC + RV)
- RV = Residual Volume (the volume remaining in the lungs after maximum expiration).
- The Edi waveform during a maximum inspiration (TLC) is considered to be at a maximal Edi amplitude (100%). Healthy subjects use about 8% of their maximum Edi during resting (tidal) breathing.

4 PHYSIOLOGY II - RESPIRATORY MECHANICS AND GAS EXCHANGE

4.1 AIRWAY CLOSURE AND COLLAPSE OF LUNG TISSUE

In the normal lung, all airways and alveoli are usually aerated and open throughout the breath cycle. However, with lower inspired tidal volumes (less inflation), a point may be reached when some of the smaller airways start to close during the subsequent expiration (airway closure). These airways may even remain closed during the next inspiration.

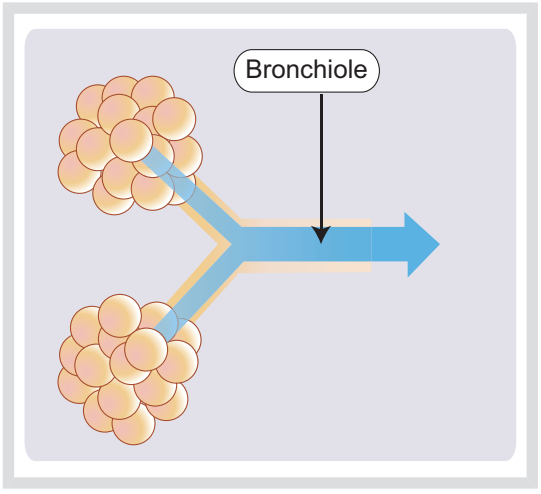


Fig. 34 - Expiration with open airways. No airway closure during normal tidal breathing in healthy young adults.

4.1.1 AIRWAY CLOSURE

Airway closure can be considered a normal phenomenon, and increases with age:

- In the newborn, airway closure may occur even at normal tidal volumes.
- In young, healthy individuals one can expect that all airways and lung tissues are aerated during normal breathing.
- As one gets older, airway closure occurs in normal individuals lying supine. Airway closure is frequently seen during anesthesia, particularly in obese patients, when a reduction of the resting volume takes place. However, during mechanical ventilation the use of the option Positive End Expiratory Pressure (PEEP) can help to avoid this problem. PEEP, as the name implies, is a pressure delivered continuously and constantly throughout expiration.

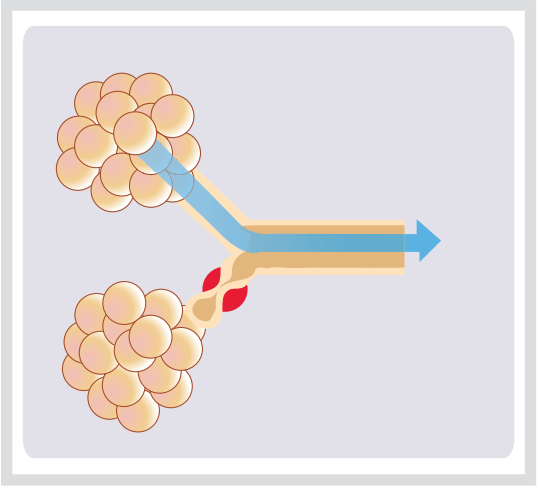


Fig. 35 – Airway closure occurs when the closing volume exceeds the end expiratory lung volume.

4.1.2 ATELECTASIS

Atelectasis, also known as collapse of lung tissue, is the collapse or closing of alveoli. During normal spontaneous breathing, this may occur without consequences and is a reversible occurrence.

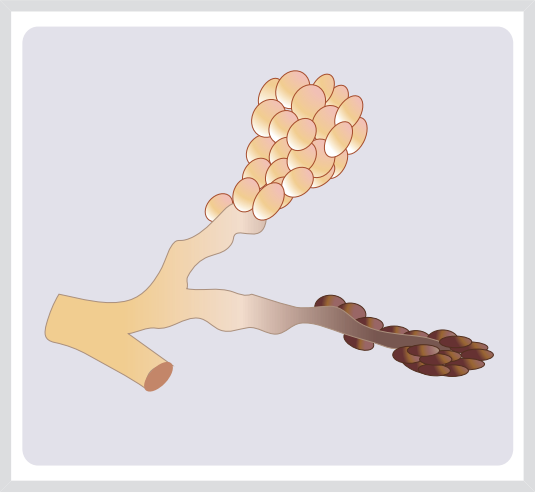


Fig. 36 – Alveolar collapse. Atelectasis occurs when part of the lungs collapse.

Even in patients with healthy lungs, **pulmonary** gas exchange is regularly impaired during general anesthesia with mechanical ventilation because of atelectasis. This results in decreased blood oxygenation, despite good **perfusion** (blood flow) of the alveoli.

Recruitment (vital capacity) manoeuvres, in combination with proper selection of PEEP levels and avoidance of excessive oxygen concentrations, are possibilities for opening and keeping the lung open for these patients.

In patients with healthy lungs who undergo anesthesia and surgery, the atelectasis will reverse itself spontaneously postoperatively. However, sometimes this may not happen for several days, especially after abdominal surgery and even more for obese patients. These patients could be at risk of postoperative lung complications if preventive measures are not taken to recruit the lung. Sustained atelectasis may promote infection because of stagnant secretions within the alveoli.

Airway closure, collapse of lung tissue and formation of atelectasis also frequently occur in intensive care unit (ICU) patients. Atelectasis is predominantly located in the more dependent part of the lungs due to gravitational forces.

Consequently, the dependent part of the lungs will have poor or no ventilation ($\dot{V}$) combined with good or excessive perfusion ($\dot{Q}$). The non-dependent parts of the lungs will be well or over ventilated, but poorly perfused, resulting in a mismatched $\dot{V}/\dot{Q}$ distribution and impaired oxygenation.

During mechanical ventilation, there is cyclic opening and closing of lung units with ventilator insufflations. This can create shear force and stress upon the lung tissue and the capillary membranes. This repeated stress with each breath, over a period of time, may lead to damage of the lung, so-called ventilator-induced lung injury (VILI).

ICU patients may also have other complications such as a variety of lung injuries and other conditions that may impair pulmonary gas exchange and effective ventilation of the patient's lungs. This will require more advanced methods to restore and improve the patient's lung function compared to the anesthesia-induced atelectasis described above. The current consensus for a lung-protective ventilation strategy, is to minimize over (tidal) distension of the lung, and apply an optimal PEEP setting to keep the lung open. The goal is to minimize tidal volume (to avoid **volutrauma**), to minimize pressures (to avoid **barotrauma**), and to keep the lung open (to avoid atelectrauma).

4.2 COMPLIANCE

Compliance is a measure of the elasticity of the lungs and the chest wall. It denotes the change in volume produced by a unit change in pressure. Patients with “stiff lungs” have a reduced compliance, meaning that more pressure is required for the lungs to be inflated. The diaphragm would compensate for this demand of increased pressure by increasing its force output, in turn requiring increased activation by the phrenic motor units. An increase in Edi peak values could be anticipated in this case.

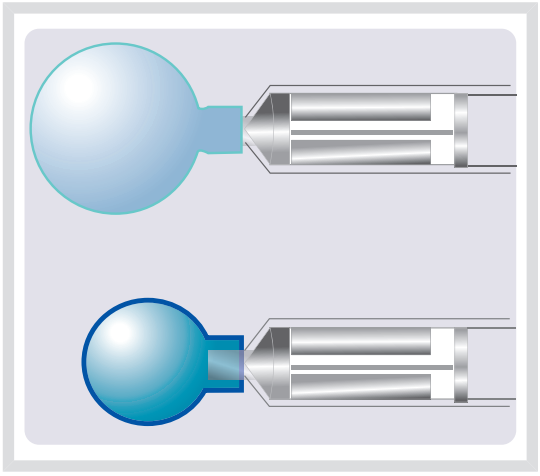


Fig. 37 –Schematic representation of the concept of compliance. The top balloon has a normal compliance, and for a given pressure applied, inflates quite well. The bottom balloon has a lower compliance (stiffer walls) and for the same applied pressure inflates much less.

STATIC COMPLIANCE

Static lung compliance (**C stat**) represents compliance during conditions of no flow. For a paralyzed or relaxed subject on a ventilator, it can be calculated according to the equation below. It comprises both lung and chest wall compliances.

$$C\ stat = \frac{VT}{Pplat - PEEP}$$

Normal static compliance is 50 to 100 ml/cmH_2O for adult patients.

DYNAMIC COMPLIANCE

As an alternative, compliance may also be measured as a dynamic parameter (**C dyn i**) on a breath-by-breath basis. It is then calculated in a similar fashion as the static compliance using the measured values of inspired tidal volume (VTi) divided by the difference between end inspiratory pressure (EIP) and positive end expiratory pressure (PEEP).

$$C\ dyn\ i = \frac{VTi}{EIP - PEEP}$$

Dynamic compliance can be a useful parameter to observe during recruitment procedures and PEEP titration when plotted together with measured EIP, PEEP, VTi and VTe on a breath-by-breath basis.

4.3 RESISTANCE

The airways have a tendency to hinder the passage of air so a certain pressure is required to deliver air to the alveoli. This airway **resistance** is determined by the properties of the airway and by the type and speed of airflow. Resistance is expressed as pressure divided by airflow. If airway resistance increases, additional pressure would be required to meet the ventilation needs of the subject. The diaphragm would require an increase in activation to compensate for the increased resistance, and the Edi peak values would be expected to increase.

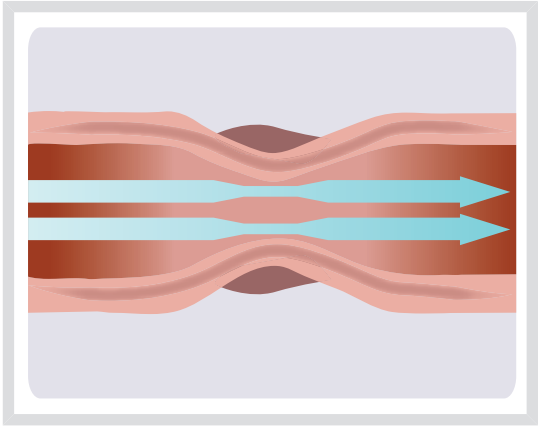


Fig. 38 – Resistance- Laminar flow. Schematic representation of the concept of resistance. As air passes through a tube, a narrowing of the tube's diameter (increased resistance) will hinder and reduce the air flow.

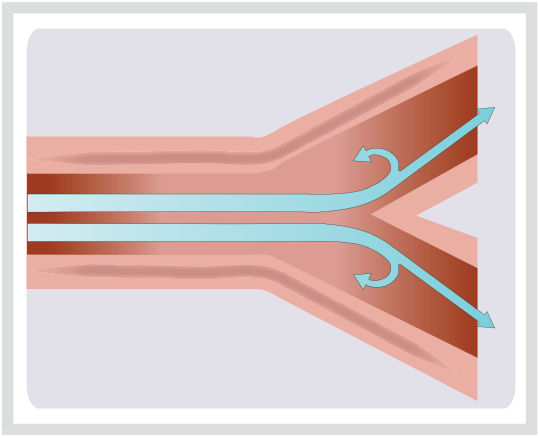


Fig. 39 – Resistance- Turbulent flow - eddies occur, caused by higher flow rates, uneven surfaces and branching. (Higher resistance than laminar flow).

4.3.1 CAUSES OF INCREASED RESISTANCE

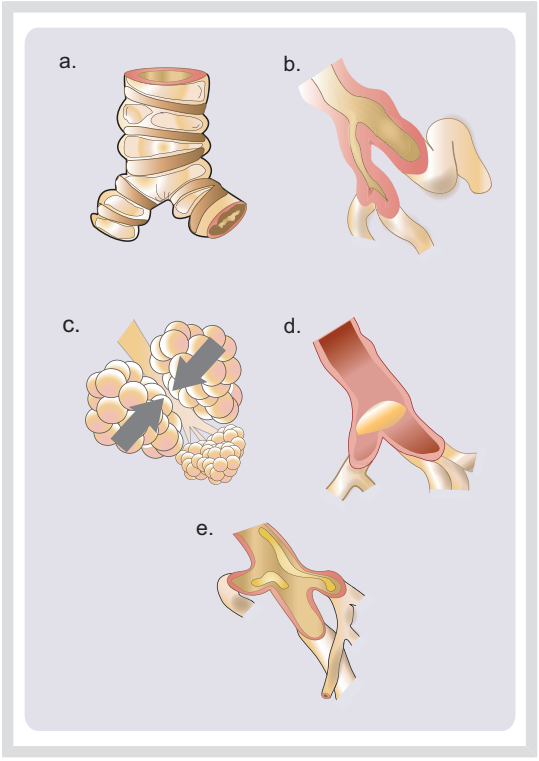


Fig. 40 - Increased resistance is found, for example, in **bronchospasm/asthma** (a), **pulmonary edema** (b), **emphysema** (c), foreign particles in the airways (d), and with excessive secretions (e).

4.4 RESTRICTIVE AND OBSTRUCTIVE LUNG DISEASE

Respiratory diseases can be restrictive and/or obstructive.

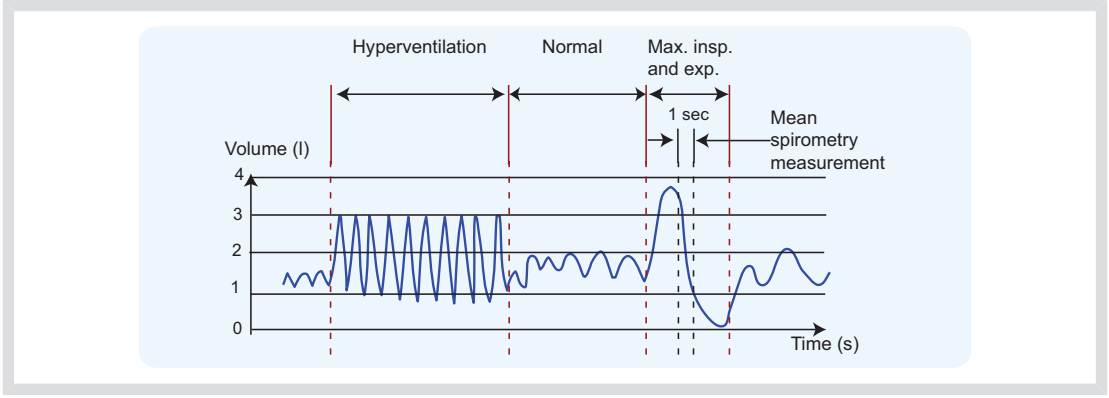


Fig. 41 - Normal ventilatory capacity. Volume waveform plotted as a function of time, beginning with normal (tidal) breathing, followed by hyperventilation, then a period of normal breathing, and a maximum inspiratory and a maximum expiratory maneuver. Waveform is provided for a healthy subject.

4.4.1 RESTRICTIVE LUNG DISEASE

In restrictive lung disease expansion of the lungs during inspiration is restricted in some way, which leads to a reduction in total lung capacity.

Restrictive respiratory disease is found, for example, in conditions producing "stiff" lungs (e.g. **silicosis**, tuberculosis), where air or fluid is present in the pleural cavity, chest wall is rigid or obesity (causing restriction in diaphragmatic movement).

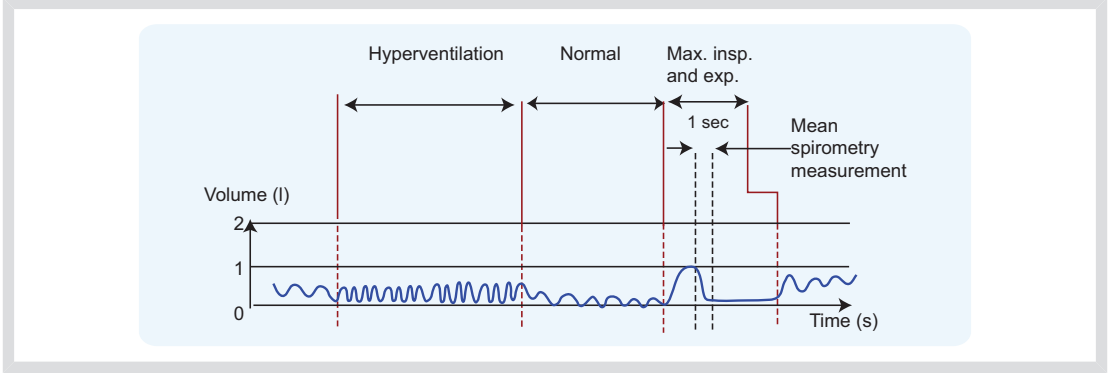


Fig. 42 – Restrictive lung disease. Volume waveform plotted as a function of time, beginning with normal (tidal) breathing, followed by hyperventilation, then a period of normal breathing, and a maximum inspiratory and a maximum expiratory maneuver. Waveform is provided for a patient with restrictive lung disease. Note the reduced volumes for all maneuvers but expiratory flow is still normal or can even be higher than in the normal subject.

4.4.2 OBSTRUCTIVE LUNG DISEASE

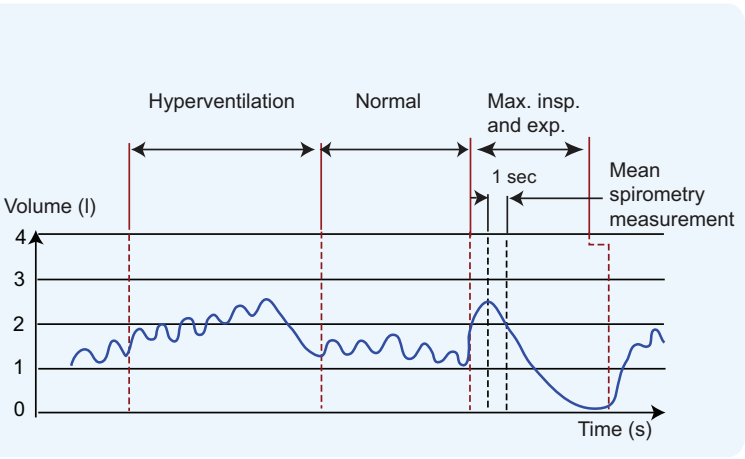


Fig. 43 – Obstructive lung disease. Volume plotted as a function of time, beginning with normal (tidal) breathing, followed by a period of hyperventilation, then a period of normal breathing, and a maximum inspiratory and a maximum expiratory maneuver. Waveform is presented for a patient with obstructive lung disease. Note the dynamic hyperinflation during the hyperventilation period and the slow expiratory flow during a forced expiration.

In obstructive lung disease the cross-sectional area of the smaller airways is reduced causing an increase in resistance to the flow of air. The resistance to flow is greater on expiration than during inspiration. The obstructive patient often adopts a low frequency of respiration, because prolonging expiration with low flow can reduce the work of breathing. Patients with obstructive lung disease usually show a certain degree of hyperinflation of the lungs due to air trapping. With hyperinflation, the diaphragm is likely to be shortened. This weakens the muscle, and will require a higher diaphragm activation (higher Edi) to maintain the same force production (i.e. reduced neuro-mechanical coupling).

The inner diameter of the airways is dependent on the dynamic lung volume. Both the bronchioles and the alveoli widen during inspiration. Obstructive lung disease can be caused by, for example, asthma, chronic **bronchitis**, or emphysema.

4.5 DISTRIBUTION OF INSPIRED AIR

One simple way of describing the effectiveness of ventilation is to divide the distribution of air into two parts:

- Alveolar ventilation (portion of air participating in gas exchange at the alveoli)
- Physiological dead space (portion of air not participating in gas exchange)

4.5.1 ALVEOLAR VENTILATION

Alveolar ventilation is that part of the total ventilation process in which gas exchange takes place. However, sometimes alveolar ventilation is insufficient and this may be due to:

- Insufficient breathing (low minute ventilation)
- Increased dead space (of patient and/or ventilator equipment)

The following factors can cause insufficient breathing:

- Depression of the respiratory center (e.g. due to anesthesia, sedatives, infection, brain **hypoxia**).
- Failing respiratory muscles (e.g. due to disease, trauma, **muscle relaxants**, fatigue).
- Improperly adjusted ventilator (e.g. in controlled modes, too small tidal volumes or too slow respiratory rate).

Certain factors can result in increased dead space,such as connected equipment, emphysema and **pulmonary embolus.**

4.5.2 PHYSIOLOGICAL DEAD SPACE

Physiological dead space, are areas of the respiratory system where ventilation occurs (air passes through). It is the amount of volume where no gas exchange occurs.

Physiological dead space is the sum of the anatomical dead space plus the alveolar dead space - see below for more details.

The physiological dead space is about 2 ml/kg body weight or 80 ml/m^2 body surface for adult patients. (In an intubated patient it is about 50 ml/m^2 body surface).

ANATOMICAL DEAD SPACE

The portion of the ventilatory volume that does not take part in gas exchange (e.g. the nose, mouth, trachea and distal airways) - is known as anatomical dead space (or airway dead space).

Factors influencing anatomical dead space are:

- the height and weight of the individual
- position
- age
- lung volume
- tidal volume
- intubation/tracheotomy (reduces anatomical dead space)

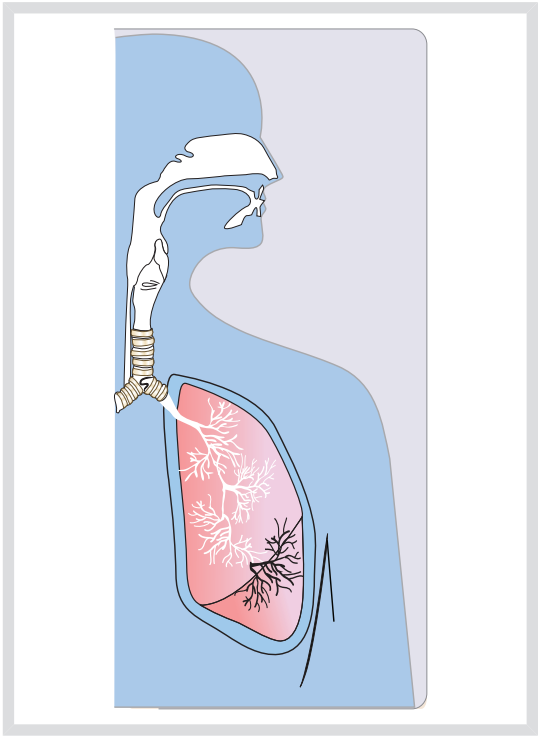


Fig. 44 – Schematic representation of anatomical dead space (white area). A zone of non-perfused airways is illustrated by the black area (alveloar dead space).

ALVEOLAR DEAD SPACE

Alveolar dead space is the amount of air reaching poorly perfused, or non-perfused alveoli.

The alveolar dead space is minimal in spontaneously breathing, healthy individuals. During mechanical ventilation, alveolar dead space increases markedly (even in healthy individuals) and can amount to 1/4 of the alveolar ventilation due to the undesirable effect of increased **intrathoracic pressure** (ventilation - perfusion imbalance). Anesthetic agents and pre-existing lung disease can further increase this effect. A large alveolar dead space is seen in the case of a pulmonary embolus, or emphysema.

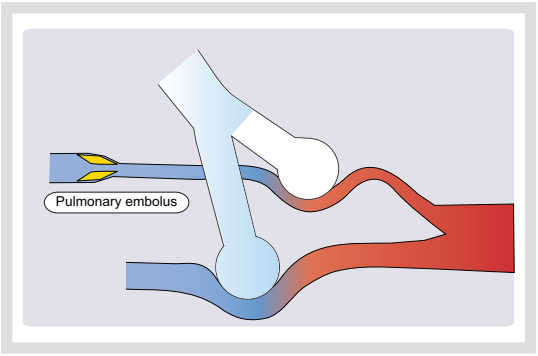


Fig. 45 - Alveolar dead space. An example of well ventilated but poorly perfused alveolus (thinner blood vessel) causing alveolar dead space (white in figure).

An increase in dead space decreases alveolar ventilation, and diminishes CO_2 elimination from the arterial blood. This increase in arterial CO_2 is sensed by the central and peripheral chemoreceptors as a signal to increase ventilation, which is accomplished by increasing the output of the respiratory centers, and therefore activating the diaphragm. An increase in the Edi peak values is anticipated with acute increases in arterial CO_2.

VENTILATION TO PERFUSION MISMATCH

The physiological dead space can increase due to changes in the pathophysiology of the lungs, such as changes in perfusion and/or changes in ventilation: a "ventilation to perfusion" mismatch.

A mismatch between ventilation and perfusion can also be observed in patients in lateral posture. The non-dependent lung will have well-ventilated compartments with insufficient perfusion, while the dependent lung will have poorly ventilated but well-perfused compartments during mechanical ventilation.

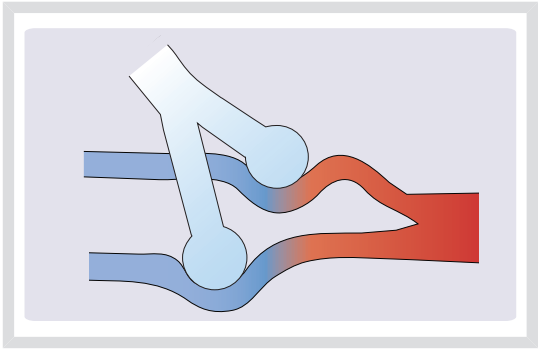


Fig. 46 – Example of normal perfusion to normally ventilated alveoli.

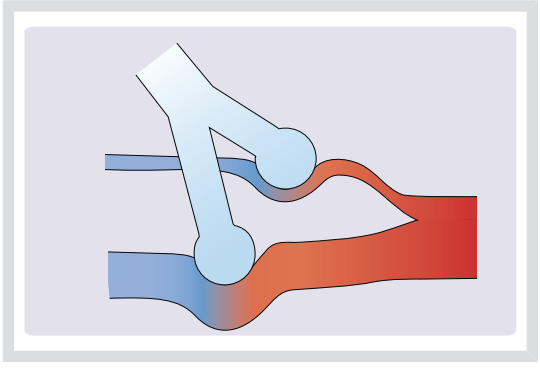


Fig. 47 - Ventilation to perfusion mismatch. Although ventilation is evenly distributed between the two lung compartments, perfusion is reduced in the upper lung and increased in the lower lung (see difference in vascular size in the figure), resulting in a mismatch between $\dot{V}$ and $\dot{Q}$.

LUNG COMPARTMENTS WITH DIFFERENT TIME CONSTANTS

Another cause of increased physiological dead space is the fact that lung compartments may require different times for filling and emptying, i.e. they have their own time constants. This is a common situation in patients with pulmonary diseases, e.g., obstructive lung disease. Lung compartments with low resistance and normal compliance are optimally ventilated while ineffective gas exchange occurs in lung compartments with high resistance and low compliance.

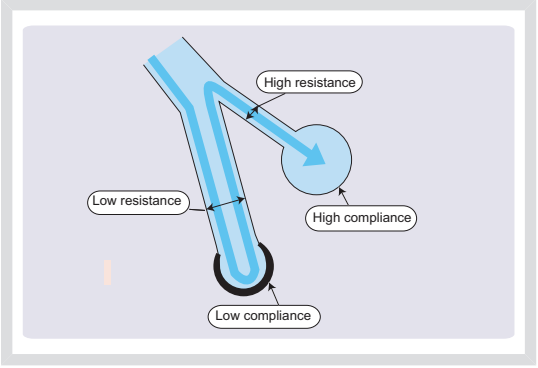


Fig. 48 – Schematic representation of lung units with different resistance and compliance, and hence with different time constants. The low-compliant and/or low-resistive compartment will fill faster during inspiration than a compartment with high compliance and/or high resistance. The slow compartment may not have completed its inspiration before expiration starts. Moreover, air may move from the fast to the slow compartment, adding to its inspiration ("pendel luft").

4.5.3 APPARATUS DEAD SPACE

When a patient is intubated and placed on a mechanical ventilator, the apparatus in itself adds to the dead space. This is the volume of the connection tubes, heat and moisture exchangers, and other accessories. The apparatus dead space, as the name implies, does not participate in gas exchange. On the other hand, an endotracheal tube reduces the anatomical dead space. The net effect of increased apparatus and reduced anatomical dead spaces has to be considered in order to achieve adequate alveolar ventilation when adjusting a ventilator in controlled modes.

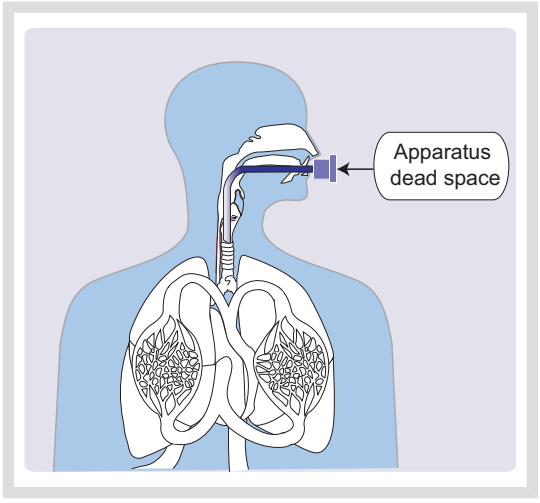


Fig. 49 – Apparatus dead space (highlighted in blue), in this case the endo-tracheal tube.

4.6 CIRCULATION – PERFUSION

4.6.1 VENTILATION – PERFUSION

The pulmonary circulation is a low pressure system. The blood flow is normally greatest in the most dependent parts of the lungs, due to the effect of gravity. When lying on one´s side the blood flow in the dependent lung (i.e. lower part of lung) is greater than that in the upper part of the lung. In the upright position the blood flow is greater in the bases of the lungs than in the apices.

The pulmonary blood vessels have a great capacity for dilation. If the flow of blood is cut off from one lung, then there will be twice the normal flow in the other lung, while the pressure in the pulmonary artery increases only marginally.

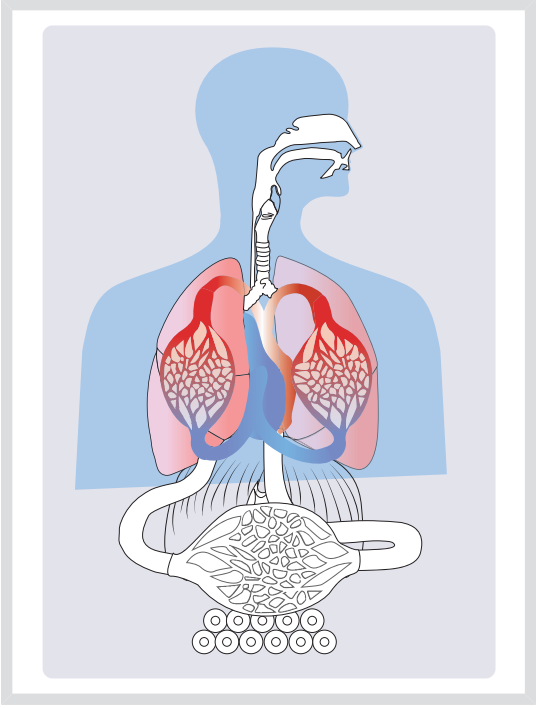


Fig. 50 - The pulmonary circulation, depicted schematically.

4.6.2 NORMAL VENTILATION – PERFUSION BALANCE

The ratio of the volume of ventilation (alveolar ventilation $\dot{V}$) to the pulmonary blood flow is normally 0.8 l/min.

With a normal alveolar ventilation of 4 l/min and a pulmonary blood flow of 5 l/min, the $\dot{V}/\dot{Q}$ ratio is 4/5=0.8.

If the ratio $\dot{V}/\dot{Q}$ is high, P_aO_2 rises and P_aCO_2 diminishes. If the ratio is low, P_aO_2 is markedly reduced and P_aCO_2 rises.

There are normally regional differences in the lungs: in the upright position the ratio in the lung apices is high. A typical value for $\dot{V}/\dot{Q}$ in the lung apices is thus 3.3, and in the lung base is 0.6.

4.6.3 IMPAIRED VENTILATION

Blood which supplies poorly ventilated alveoli (with low P_aO_2) cannot be adequately oxygenated.

Therefore a certain amount of incompletely oxygenated blood enters the arterial circulation and thereby reduces P_aO_2 (physiological shunt).

A large perfusion of under ventilated sections of lung results in a large difference between **P_AO_2** and P_aO_2 (large $P_{(A\text{-}a)}O_2$ difference).

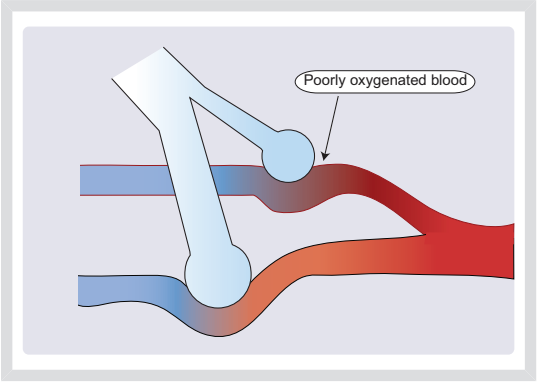


Fig. 51 - Schematic representation of impaired ventilation (smaller alveoili represented), resulting in poorly oxygenated blood.

4.6.4 COMPENSATORY CHANGES IN PERFUSION FOR IMPAIRED VENTILATION

A low alveolar PO_2 **(P_AO_2)** and a raised alveolar PCO_2 **(P_ACO_2)** initiates a blood vessel constrlction so that blood flow to under-ventilated alveoli diminishes and instead is redirected to well-ventilated alveoli.

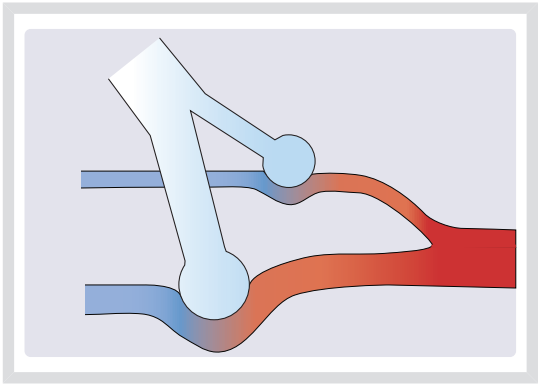


Fig. 52 - Compensatory changes in perfusion for impaired ventilation. Schematic representation to demonstrate the concept of hypoxic vasoconstriction

4.6.5 IMPAIRED PERFUSION

Good ventilation of poorly perfused sections of lung tissue, for example, in pulmonary embolus, gives rise to a large dead space. Blood flow is then unevenly distributed within the lungs without a corresponding redistribution in ventilation.

A small amount of de-oxygenated blood normally comes from the lungs and the heart to the left atrium (anatomical **shunt**). In the case of certain cardiac disorders, for example, **Fallot´s tetralogy,** there is a large shunt.

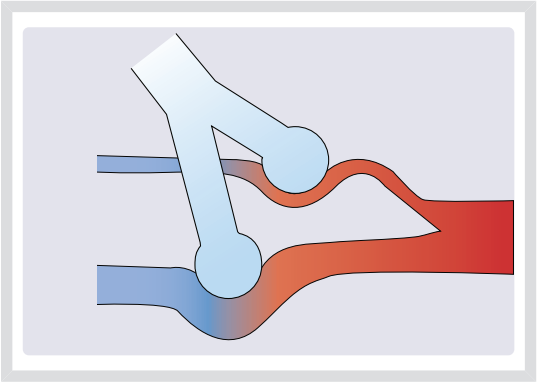


Fig. 53 - Impaired perfusion

4.6.6 HYPOXIA

Hypoxia (low arterial oxygen concentration) can be caused by a diffusion defect, physiological shunt, anatomical shunt, hypoventilation due to low minute ventilation, or a low PO_2 in the surrounding atmosphere, for example, at high altitude.

4.7 GAS EXCHANGE AND TRANSPORT

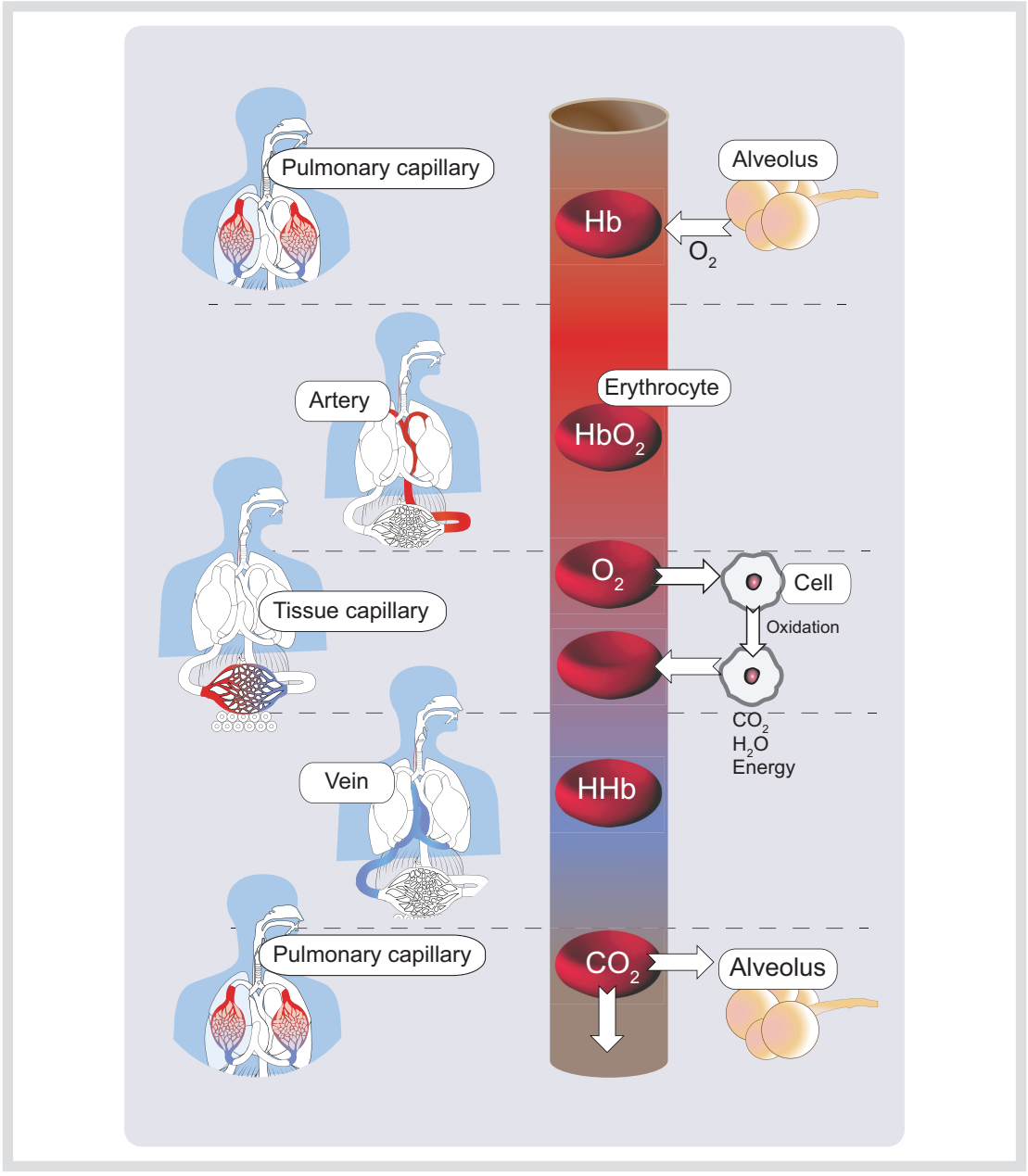


Fig. 54 - Overview of gas exchange and transport. See text for details. From top to bottom, is a description of oxygen (O_2) diffusion across the alveolar-capillary membrane, which then binds to a **hemoglobin** molecule (Hb) in the red blood cell (**erythrocyte**). Oxygen then diffuses out of the red blood cell and participates in cellular oxidation, releasing carbon dioxide (CO_2), water, and energy. The carbon dioxide diffuses to the capillaries and is expelled via the alveoli. HHb is hemoglobin without bound oxygen.

4.7.1 HOW GAS IS EXCHANGED AND TRANSPORTED

Oxygen passes by **diffusion** over the alveolar membrane from the alveolar air to the blood in the pulmonary capillaries. Although oxygen has a relatively poor diffusing capacity, adequate diffusion takes place because of the significantly higher partial pressure of oxygen in the air than in the pulmonary artery.

In the erythrocytes, O_2 combines with hemoglobin (Hb) which is a compound containing iron and the result of this chemical reaction is oxyhemoglobin (HbO_2 - an oxygen-loaded form of hemoglobin).

O_2 is released from oxyhemoglobin and diffuses from the capillary into the cell. Diffusion, in this case, means that O_2 moves from capillaries with a high PO_2 to cells with a low PO_2. The amount of oxygen released depends on many different factors, such as CO_2 concentration, pH and temperature of the blood.

Cells obtain their energy by oxidation of nutritive substances, i.e. cellular respiration. Production of energy is primarily an aerobic process (consumption of oxygen). Oxidation takes place in several ways, when O_2 is consumed.

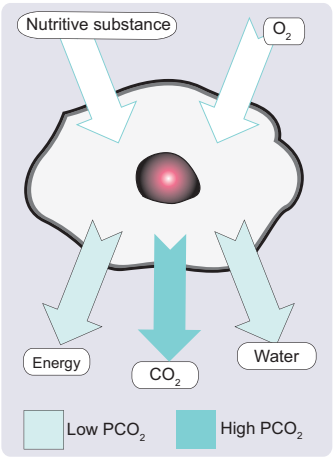


Fig. 55 - Oxidation of nutritive substances. Schematic representation of one cell and transport of products

CO_2 diffuses into the blood. Part of it is dissolved (P_aCO_2) and part is bound to protein in proportion to the P_aCO_2. In the lung CO_2 diffuses from the capillaries to the alveoli and is eliminated by the ventilation.

$$\text{Nutritive substances} + O_2 \xrightarrow{\text{Oxidation}} \text{Energy} + CO_2 + H_2O$$

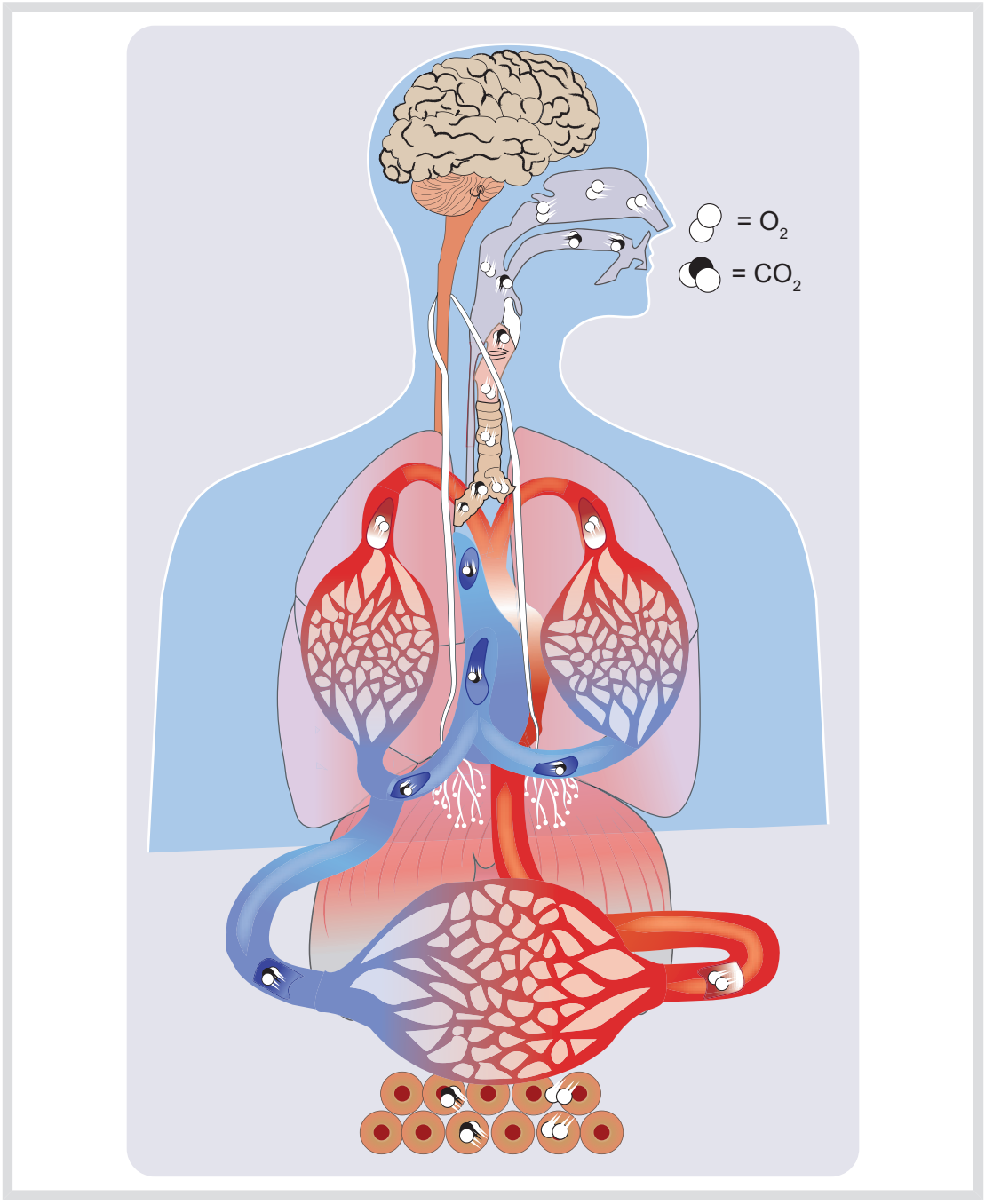


Fig. 56 - Schematic illustration of respiration process

5 ACID BASE BALANCE

5.1 GENERAL

The pH of the blood is maintained at a near constant value by three mechanisms:

1. *The buffer systems.* A buffer is a chemical mixture, which stabilizes pH in a solution when an acid or an alkali is added. The most important buffer system is the carbonic acid - bicarbonate system.
2. *Breathing*. By hypo/hyperventilation the P_aCO_2 value is changed and thereby the pH.
3. *The kidneys*. CO_2 is an acidic product that can be excreted via the lungs. Other acids, not related to respiration, can also be excreted via the kidneys.

The standard bicarbonate (St HCO_3) is a measurement of the amount of bicarbonate in the blood and measures the metabolic component. The bicarbonate concentration under standard conditions is PCO_2 5.3 kPa (40 mmHg), temperature is 37°C and saturated with oxygen.

Base Excess (B.E) is defined as the amount of strong acid that must be added to each liter of fully oxygenated blood in order to return the pH to 7.40 at a temperature of 37°C and a PCO_2 of 5.3 kPa (40 mmHg). A B.E of more than +3 equals metabolic alkalosis, and a B.E less than -3 equals metabolic acidosis.

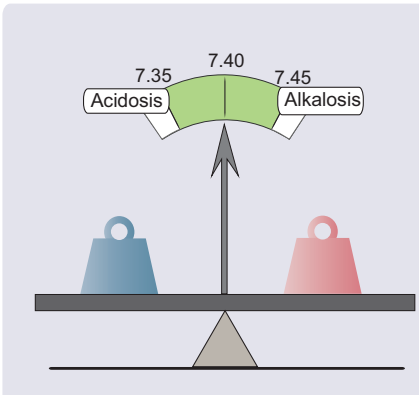
Water and CO_2 combine within the erythrocytes and are then divided up into hydrogen ions and bicarbonate ions.

$$CO_2 + H_2O \rightarrow H_2CO_3 \rightarrow HCO_3 + H$$

The hydrogen ions combine with hemoglobin and the bicarbonate ions (HCO_3) diffuse into the plasma.

CO_2 is essential for the acid-base balance of arterial blood. In acute respiratory disorders a mismatch in the production to elimination ratio leads to respiratory **acidosis** or **alkalosis.**

In a patient with chronic **hypercapnia**, however, the resorption of bicarbonate increases in the kidneys. This condition leads to a compensatory metabolic alkalosis. In the metabolic disorders of acid-base balance, the body tries to compensate for derangements by changes in ventilation. For example, the respiratory center tries to compensate for metabolic acidosis (e.g., in diabetic coma) by hyperventilation.



Normal values

pH of arterial blood	7.35 - 7.45
P_aO_2	11 - 13 kPa
P_aCO_2	4.7 - 6.0 kPa
St HCO_3	21 - 27 mmol/l
B.E.....	between +3 and -3 mmol/l
S_aO_2	95 - 99%

Fig. 57 - Normal acid base balance. Illustration demonstrating the concept of acid-base balance as a scale (acidity in blue, alkalosis in red).

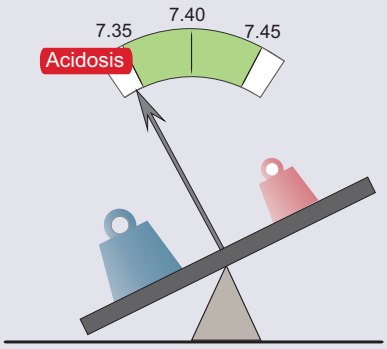
5.2 DISORDERS OF ACID BASE BALANCE

Changes in acid-base balance are reflected in the pH of arterial blood. It is important to ascertain the reason behind the change.

- With the respiratory acid-base disorders, CO_2 excretion via the lungs is either too little or too great (alveolar hypo- or hyperventilation) relative to the body´s CO_2 production.
- With the metabolic acid-base disorders, there is an imbalance between the body´s production and elimination of non-respiratory acids.

5.2.1 RESPIRATORY ACIDOSIS

Respiratory acidosis (low pH, high P_aCO_2) can arise as a result of hypoventilation in, for example, chronic bronchitis, deep unconsciousness, respiratory arrest, or hypoventilation on a ventilator. A very large shunt causes venous blood to pass through the lung without eliminating CO_2. This increases P_aCO_2, sometimes called "shunt dead space".



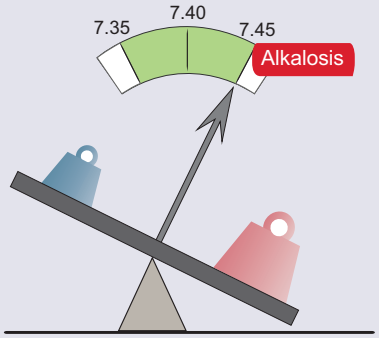
Example of respiratory acidosis

pH.....	7.20
P_aCO_2	9.0 kPa
St HCO_3.....	22 mmol/l
B.E	- 2.6 mmol/l

Fig. 58 - Respiratory acidosis

5.2.2 RESPIRATORY ALKALOSIS

Respiratory alkalosis (high pH, low P_aCO_2) arises as a result of hyperventilation due to, for example, pain, panic, or hyperventilation on a ventilator.



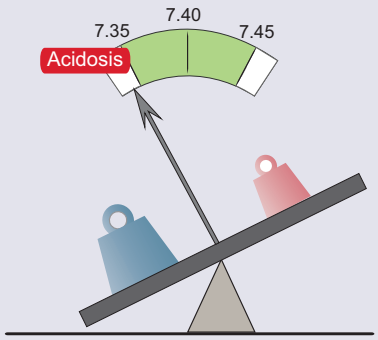
Example of respiratory alkalosis

pH.....	7.55
P_aCO_2	2.8 kPa
St HCO_3.....	24 mmol/l
B.E.....	+ 0 mmol/l

Fig. 59 - Respiratory alkalosis

5.2.3 METABOLIC ACIDOSIS

Metabolic acidosis (low pH, base deficit) is caused by reduced excretion or increased production of acids, loss of base via intestinal **fistulae** or through diarrhea, increased lactic acid levels following lack of oxygen in the cells (e.g., in cardiac arrest, hypoxia, reduced blood circulation), and renal insufficiency.



Example of metabolic acidosis

pH.....	7.24
P_aCO_2..... (the low value reflects the respiratory center´s compensation for acidosis e.g. increased CO_2 elimination)	2.8 kPa
St HCO_3.....	11.5 mmol/l
B.E	- 17 mmol/l

Fig. 60 - Metabolic acidosis

5.2.4 METABOLIC ALKALOSIS

Metabolic alkalosis (high pH, base excess) arises with loss of acid products as, for example, in repeated vomiting with subsequent loss of the stomach´s hydrochloric acid.

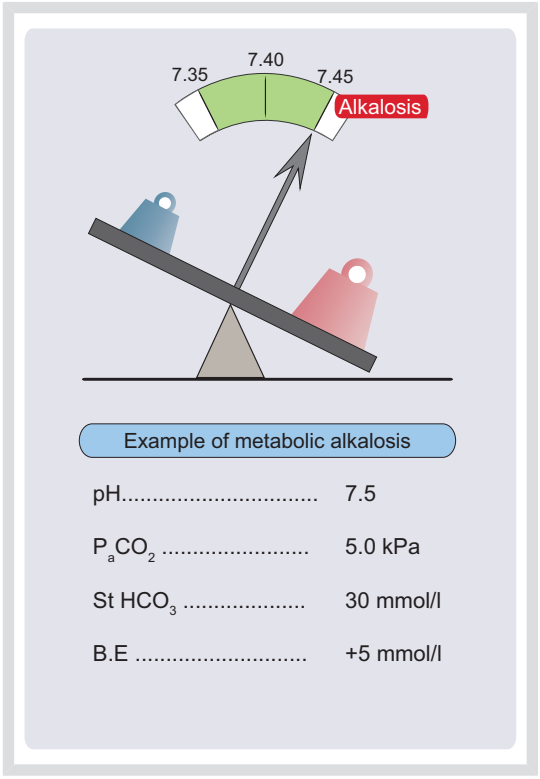


Fig. 61 - Metabolic alkalosis

5.2.5 COMPENSATORY CHANGES FOR DERANGEMENT IN ACID-BASE BALANCE

The body tries to compensate for metabolic derangement in acid-base balance by changes in ventilation. An example of this is when the respiratory center tries to compensate for metabolic acidosis (e.g., in diabetic coma) by hyperventilation. The body attempts to correct for ventilatory disorders in much the same way by metabolic compensatory mechanisms.

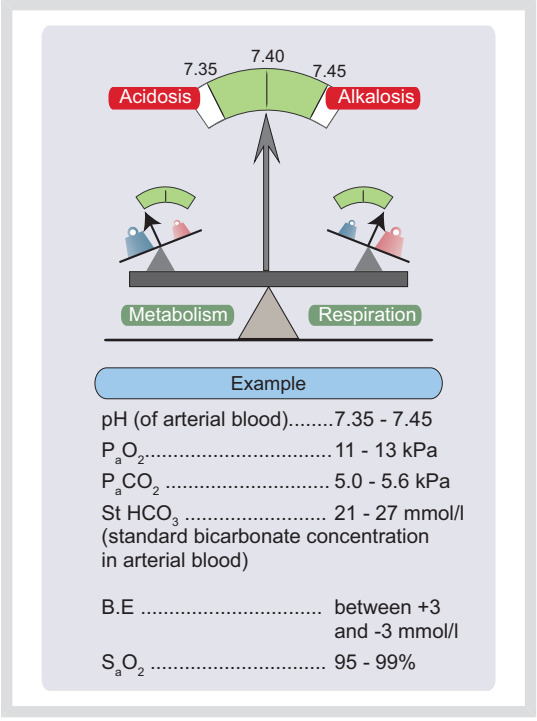


Fig. 62 - Compensatory changes in the acid base

5.2.6 BLOOD GAS CHANGES IN DISORDERS OF LUNG FUNCTION

Blood gas changes in different disorders of lung function

	Alveolar hypo-ventilation	Change in ventilation-perfusion	Diffusion impairment	Shunt
P_aO_2	Reduced	Reduced or unchanged	Reduced	Reduced
P_aCO_2	Increased	Unchanged (or reduced/ increased)	Unchanged (or increased)	Unchanged (or reduced/ increased)

Fig. 63 - Blood gas changes in different disorders of lung function

6 CLINICAL INTERPRETATIONS OF THE DIAPHRAGM ELECTRICAL ACTIVITY

The Edi signal allows for monitoring and interpretation of the neural breath in conjunction with the ventilator-supported breath. Therefore, the Edi signal can be used as a tool for interpreting different types of ventilator-induced asynchronies and apneas. (Apneas are of special interest for the infant patient category).

6.1 PATIENT-VENTILATOR INTERACTION

6.1.1 PATIENT-VENTILATOR INTERACTION

The term patient-ventilator interaction refers to the ability of a mechanical ventilator to deliver respiratory assist in tandem with patient effort.

Patient-ventilator interaction can be monitored by comparing the patient's breathings signal (the Edi waveform), and the ventilator pressure signal. Overlay of the Edi and pressure curves permits immediate visualization of how well (or poor) the ventilator is synchronized with the patient.

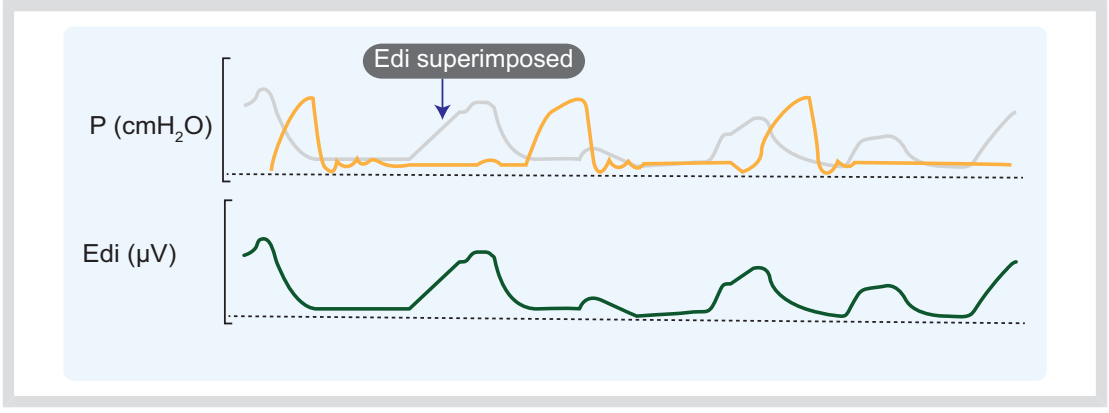


Fig. 64 – Visualization of patient-ventilator interaction. Example of the pressure waveform (orange) and the Edi waveform superimposed (grey) in a patient breathing with partial ventilator assist. The Edi waveform is superimposed on the pressure waveform to observe the patient-ventilator interaction. Note in this example, that the ventilator is not in synchrony with the patient's breathing activity, known as poor patient-ventilator interaction, or patient-ventilator asynchrony

6.1.2 TYPES OF PATIENT-VENTILATOR ASYNCHRONIES

There are several types of poor patient-ventilator interaction.

WASTED EFFORTS:

Also known as ineffective triggering, this is the type of poor interaction where the patient makes a neural inspiratory effort (upward increase in Edi waveform) and the ventilator fails to trigger.

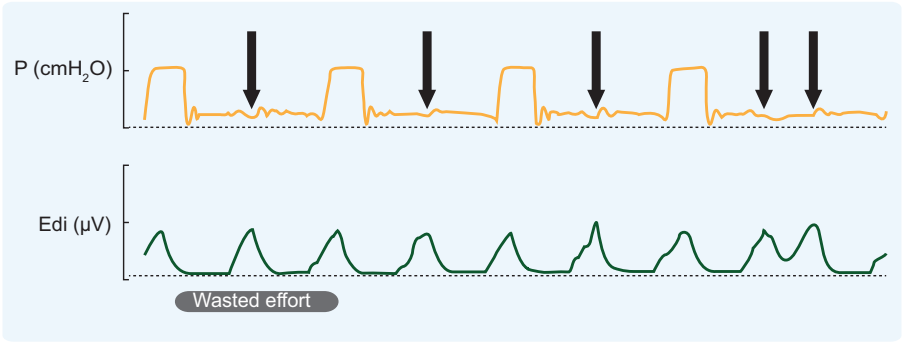


Fig.65 - Example of wasted efforts, where the patient makes an inspiratory effort and the ventilator does not trigger (indicated by arrows). Note several wasted efforts in this example.

DELAYED TRIGGERING:

Delayed triggering represents a situation where the ventilator starts delivering a breath later than the onset of neural inspiratory effort.

Fig. 66 – The Edi waveform begins (green vertical line) earlier than the time that the pressure waveform begins to increase (red vertical line).

DELAYED CYCLING-OFF:

When a patient has finished his/her neural inspiratory effort, and switches to neural exhalation, if the ventilator does not cycle into expiration, it will continue to deliver air.

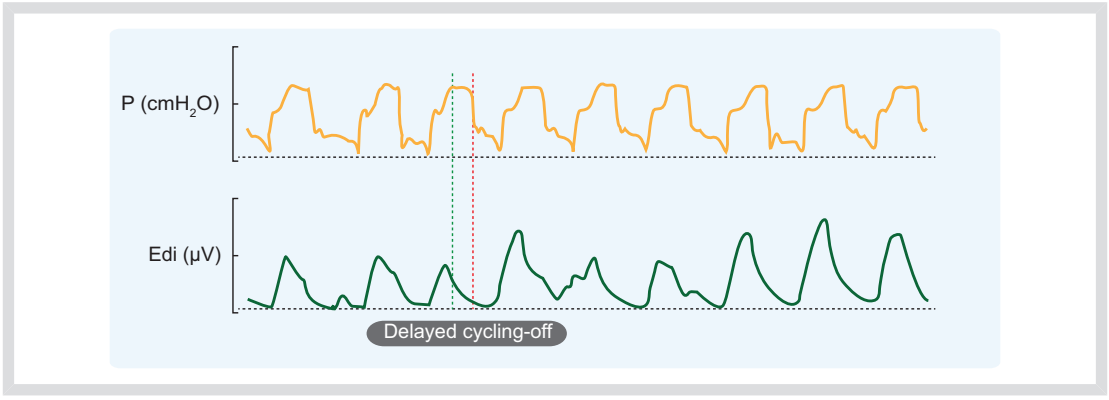


Fig. 67 - The airway pressure waveform stops (red dotted vertical line) after the neural inspiration switches to neural exhalation (green dotted vertical line).

PREMATURE CYCLING-OFF:

This type of asynchrony is characterized by the ventilator terminating the breath before the end of neural inspiration.

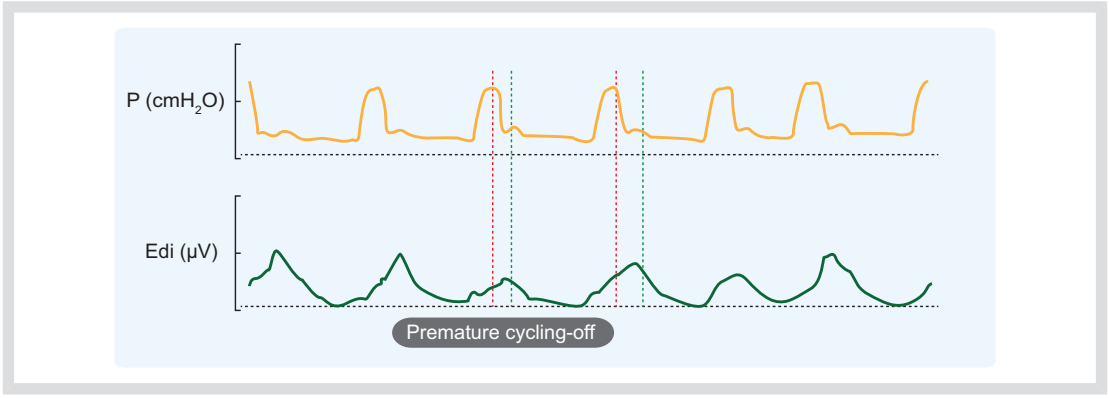


Fig 68 - The airway pressure waveform stops (red dotted vertical line) before the neural inspiration switches to neural exhalation (green dotted vertical line).

DOUBLE TRIGGERING:

Double triggering is characterized as two ventilator-delivered breaths for one neural inspiratory effort.

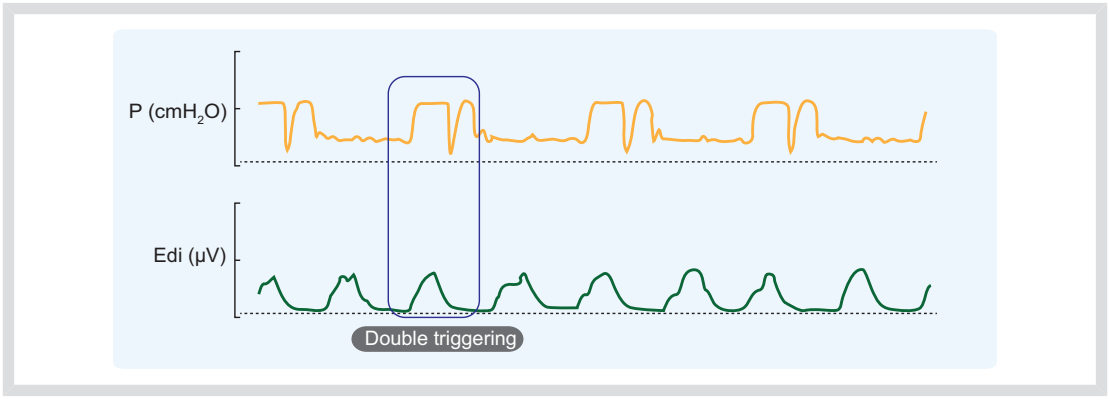


Fig 69 – The airway pressure waveform (orange curve) delivers two breaths for one neural inspiration (green curve).

AUTO-TRIGGERING:

Auto-triggering represents a situation where assist is initiated in the absence of inspiratory effort, indicating that the ventilator delivered a breath that was not triggered by the patient.

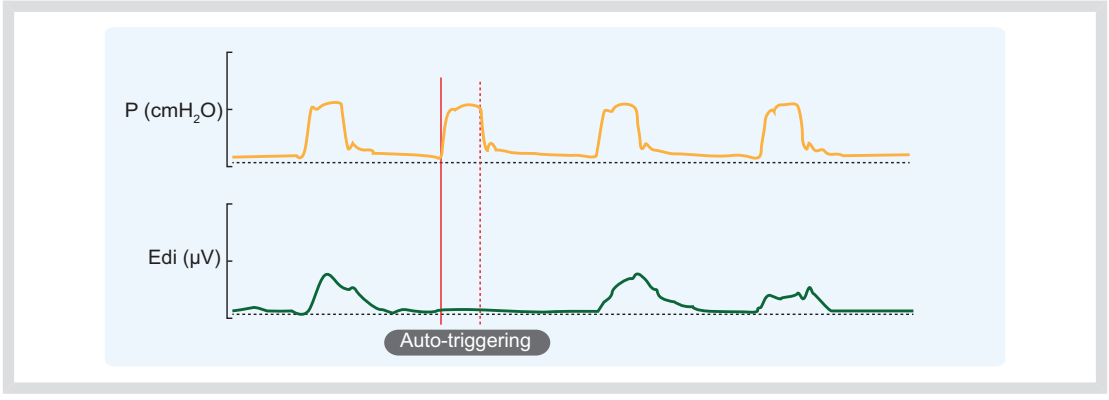


Fig. 70 - Auto-triggering is presented. The airway pressure is delivered when no diaphragm activity is present (highlighted by the red vertical lines).

6.2 APNEA

Apnea is defined as a period where there is a cessation of inspiratory flow.

Central apneas are characterized by no respiratory drive (a flat Edi waveform).

Obstructive apneas occur when respiratory drive is present (Edi curve shows its characteristic phasic inspiration and expiration) but due to an airway obstruction, no flow can occur. A tonic apnea can occur when the Edi curve is continuously elevated (at a high Edi min value), without any phasic deflection in the curve, and no flow is generated.

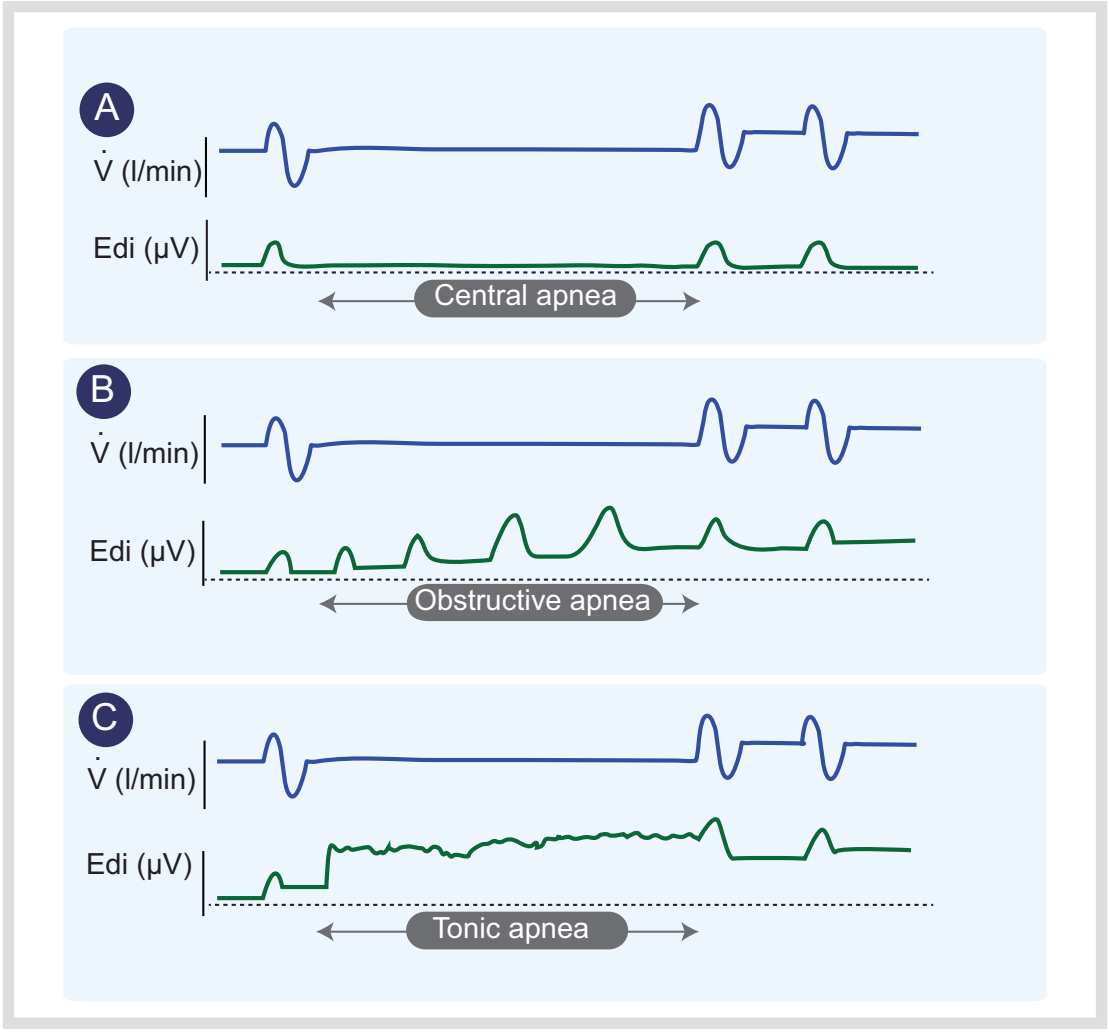


Fig. 71 - Examples of apnea: Apnea (no flow) can occur because of no respiratory center output (A, central apnea), or because of an airway obstruction even if Edi is present (B, obstructive apnea), or because the Edi waveform does not demonstrate its characteristic phasic activity and Edi min is elevated (C, tonic apnea).

7 GLOSSARY

A

- **Acidosis:** an excess of acid, low pH.
- **Action potential:** the change in electrical potential associated with the passage of an impulse along the membrane of a muscle cell.
- **Alkalosis**: an excess of alkali (base), high pH.
- **Alveolus**: terminal airspace.
- **Apnea:** temporary cessation of airflow. Can be caused by central mechanisms (no signals from respiratory centers or blockage of flow in airways).
- **Asthma**: episodic reversible attacks of airway obstruction (various causes).
- **Atelectasis**: Partial or complete collapse or imperfect expansion of the air sacs of the lung.

B

- **Barotrauma:** Injured airways and lung tissues due to applied excessive airway pressures.
- **Bronchioles**: the very smallest airways, between the bronchi and the alveoli.
- **Bronchitis**: inflammation of the bronchi.
- **Bronchospasm**: a constriction of the small airways caused by bronchial muscle spasm.

C

- **C dyn i:** dynamic compliance, breath to breath.
- **C stat**:static compliance (no flow).
- **Chemoreceptors:** receptors sensitive to changes in arterial blood values of oxygen, carbon dioxide and pH. Located centrally in the medulla of the respiratory centers or peripherally in the carotid bodies.
- **Cilia**: microscopic hair-like processes covering the cells lining the airways, capable of transporting a film of mucus.
- **CO_2**: carbon dioxide.
- **Compliance**: a measure of the stiffness of the lungs, defined by the change in volume produced by a unit change in pressure.
- **Costal:** portion of the diaphragm (respiratory muscle) inserted into the costal margin of the rib cage.
- **Crural**: the portion of the diaphragm (respiratory muscle) surrounding the esophagus.

D

- **Dead space**:The portion of tidal volume that is not involved with gas exchange. The dead space can be anatomical or physiological.
- **Diffusion**: movement of a substance through a fluid or a gas from an area of high concentration of the substance to an area of low concentration.

E

- **Edi**: Electrical activity of the diaphragm: A physiological signal representative of diaphragm activation, and hence neural respiratory drive. The Edi is displayed as a waveform, and is measured in microvolts continuously over time.
- **Edi min:** The lowest value of the Edi waveform measured during the exhalation phase (for every breath).
- **Edi peak**: The highest value of the Edi waveform measured during the neural inspiration (for every breath).
- **Electromyogram:** A graphical representation of the electrical events occurring during muscle activation.
- **Emphysema**: pathological increase in the size of the alveoli throughout the lungs, caused by a destruction of the walls of the alveoli. (Also used to describe the pathological presence of air in tissues, for example, subcutaneous air originating from the airway).
- **Endotracheal tube**: a tube placed either orally or nasally down between the vocal cords into the trachea.
- **Epiglottis:** The thin structure located at the base of the tongue that folds over the glottis to prevent food and liquid from entering the trachea during the act of swallowing.
- **Erythrocyte**: red blood cell.
- **Esophagus**: the canal for the passage of food from the throat to the stomach.
- **Extubation**: removing the endotracheal tube.

F

- **Fallot´s tetralogy**: congenital malformation of the heart, which has a hole between the left and right ventricles and a narrowing of the pulmonary artery, causing venous blood to flow from the right ventricle to the left and out into the aorta.
- **Fistula**: abnormal narrow opening either congenital or as a result of disease or operation.

G

Gastro-esophageal junction: Anatomical structure describing the transition between the esophagus and the stomach. At this point, the crural diaphragm surrounds the esophagus.

H

- **Hemoglobin**: the red substance in the red blood cells, easily combines with oxygen and carbon dioxide.
- **Hering-Breuer reflex**: A general term to describe vagally-mediated reflexes arising from the lungs. The Hering-Breuer *inflation-sensitive* reflex is a reflex modulated by stretch receptors in the lung. During inspiration, at a critical inspired volume, this vagally-mediated reflex feeds back to the respiratory centers to terminate inspiration. The Hering-Breuer *deflation-sensitive* reflex is a reflex modulated by stretch receptors in the lung. If lung volume decreases below a critical end-expiratory lung volume, this vagally-mediated reflex feeds back to the respiratory centers to stimulate inspiration.
- **Hypercapnia**: an excess of CO_2 in the blood.
- **Hypoxia**: reduced O_2 level in the blood.

I

- **Intrapleural**: within the pleural cavity.
- **Intrathoracic pressure**: the pressure within the chest.
- **Intubation**: inserting the endotracheal tube.

M

- **Mechanoreceptors**: Receptors sensitive to mechanical pressure or distortion.
- **Muscle relaxants**: agents that chemically paralyze the muscles.

N

- **Neural expiratory time:** The time taken for the neural expiration. This is measured from the peak of the Edi waveform, and decreases back to the baseline.
- **Neural inspiratory time:** The time taken for the neural inspiration. This is measured from the beginning of inspiration (start of upward deflection in Edi waveform) to the peak of the waveform.
- **Neural respiratory rate:** The rate of breathing, per minute, as defined by the Edi waveform.
- **Neuro-mechanical coupling:** The process linking activation and force production.

P

- **P_AO_2**: the partial pressure of oxygen in the alveoli.
- **P_aO_2**: the partial pressure of oxygen in arterial blood.
- **P_ACO_2**: the partial pressure of carbon dioxide in the alveoli.
- **P_aCO_2**: the partial pressure of carbon dioxide in arterial blood.
- **PEEP**: Positive End Expiratory Pressure.
- **Perfusion**: flow of a fluid through blood vessels.

- **pH**: a measure of the hydrogen ion solution, i.e., the degree of acidity or alkalinity. Chemical substances capable of donating hydrogen ions (H^+) are acids. Chemical substances accepting hydrogen ions are alkalis, or bases. The hydrogen ion concentration of a solution is a measure of its acidity and is expressed as the pH value. pH is the negative logarithm of the hydrogen ion concentration. Acidosis means low pH. Alkalosis means high pH.
- **Plasma**: the part of the blood in which the blood cells are transported.
- **Pleura**: the membranes enveloping the lungs.
- **Pulmonary**: adjective, "of the lungs", from latin "pulmo, pl. pulmones" meaning lung.
- **Pulmonary edema**: too much fluid in the lungs.
- **Pulmonary embolus**: blockage of the arteries to the lungs, usually by blood clots, but also air, bacteria, and foreign material transported in the blood stream.

Q

- $\dot{Q}$: abbreviation for perfusion, flow of blood, volume/unit of time.

R

- **Resistance:** A measure of the hindrance of airflow through the upper and lower airways to the tracheobronchial tree and the alveoili, defined by the change in flow produced for a given change in pressure.
- **Respiratory centers:** Anatomical structures located in the medulla portion of the brainstem. Their function is to send and receive information about the neural control of breathing.

S

- **Sedation**: administration of a sedative drug in order to induce a state of calmness.
- **Shunt**: admixture of venous blood in arterial blood and/or mismatch in $\dot{V}/\dot{Q}$ distribution.
- **Silicosis**: restrictive lung disease caused by chronic exposure to silica containing stone dust.
- **Support ventilation:** refers to modes of mechanical ventilation where the patient and the ventilator share the work of breathing.

T

- **Trachea**: the main air passage from the larynx to the bronchi.

V

- $\dot{V}$: abbreviation for alveolar ventilation, flow of gas, volume/unit of time.
- **VT**: tidal volume.
- **VILI:** lung injuries due to incorrect ventilator settings.
- **Volutrauma:** Injured lung tissue due to over-distention of lung units.

8 SUGGESTED READING/REFERENCES

CONTROL OF BREATHING:

Respiratory Control: Central and Peripheral Mechanisms by Donald A. Frazier, Dexter F. Speck and W. Robert Revelette, University Press of Kentucky, 1992.

Reflexes from the lungs and the respiratory tract. Widdicombe JG. Acta Physiol Pol. 1971;22(Suppl 2):397-418Widdicombe

DIAPHRAGM ELECTRICAL ACTIVITY:

Basmajian JV, Deluca CJ. Muscles Alive: Their functions revealed by electromyography 5th ed. Williamsand Wilkins, Baltimore, 1986.

Aldrich, T., Sinderby, C., McKenzie, D, Estenne, M., and Gandevia, S. Electrophysiological Techniques for the Assessment of Respiratory Muscle Function. ATS/ERS Statement on Respiratory Muscle Testing. Am. J. Respir. Crit. Care Med. 166: 518-624, 2002.

Lourenco, R. V., N. S. Cherniack, J. R. Malm, and A. P. Fishman. 1966. Nervous output from the respiratory center during obstructed breathing. J Appl Physiol 21:527-533.

Beck J, Reilly M, Grasselli G, Qui H, Slutsky AS, Dunn MS, Sinderby CA. *Characterization of Neural Breathing Pattern in Spontaneously Breathing Preterm Infants.* Pediatr Res. Dec;70(6):607-13, 2011.

GENERAL RESPIRATORY PHYSIOLOGY

Lumb AB. Nunn´s Applied Respiratory Physiology, 7:th Edition.

Churchill, Livingstone, Elsevier, 2010.

Hedenstierna G. Respiratory Physiology, in Miller´s Anesthesia 7th edítion. Elsevier By Ronald D. Miller, MD, Lars I. Eriksson, Lee A.

Fleisher, MD, Jeanine P. Wiener-Kronish, MD and William L. Young 3312 pages ISBN: 978-1-4160-6624-8, 2010.

MAQUET
GETINGE GROUP

MAQUET Medical Systems USA
45 Barbour Pond Drive
Wayne, NJ 07470
www.maquetusa.com
ca.maquet.com

GETINGE GROUP is a leading global provider of products and systems that contribute to quality enhancement and cost efficiency within healthcare and life sciences. We operate under the three brands of ArjoHuntleigh, GETINGE and MAQUET. ArjoHuntleigh focuses on patient mobility and wound management solutions. GETINGE provides solutions for infection control within healthcare and contamination prevention within life sciences. MAQUET specializes in solutions, therapies and products for surgical interventions, interventional cardiology and intensive care.

MCV00023555 REVA

ANATOMY & PHYSIOLOGY OF RESPIRATION