the vein is often directly anterior to the artery and therefore ventral instead of lateral to the artery.
    - lead structure: medial edge of the sternocleidomastoid muscle
- based on sonography (at best!)
    - application of a sterile cover over probe and cable (a sterile glove as cover is hygienically not sufficient!), use of sterile ultrasound gel or skin disinfectant
    - 7.5 MHz transducer (linear array transducer)
    - compression ultrasonography (B-mode image): The vein can be compressed, but not the artery.
    - i.a. exclusion of thrombus
    - In our intensive care unit we almost exclusively perform insertions of CVC or Shaldon catheter into the internal jugular vein only under sonographic control: The puncture takes places under visual control and typically requires rarely more than one attempt (even in obese patients). Also, it is not uncommon to incidentally discover a thrombus in the internal jugular vein, which would not be seen otherwise without ultrasonography and which would then be pushed further along by the guide wire or the dilator (risk of pulmonary embolism). One can certainly also drive at night without light: If you know the way, you probably also get to the intended destination. However, if your car has headlights, you can also simply switch them on: So you can see exactly where you are going! The use of ultrasound for the insertion of a CVC is also highly recommended in the European Guideline for Interventional Ultrasound 2016 (EFSUMB: European Federation of Societies for Ultrasound in Medicine and Biology).

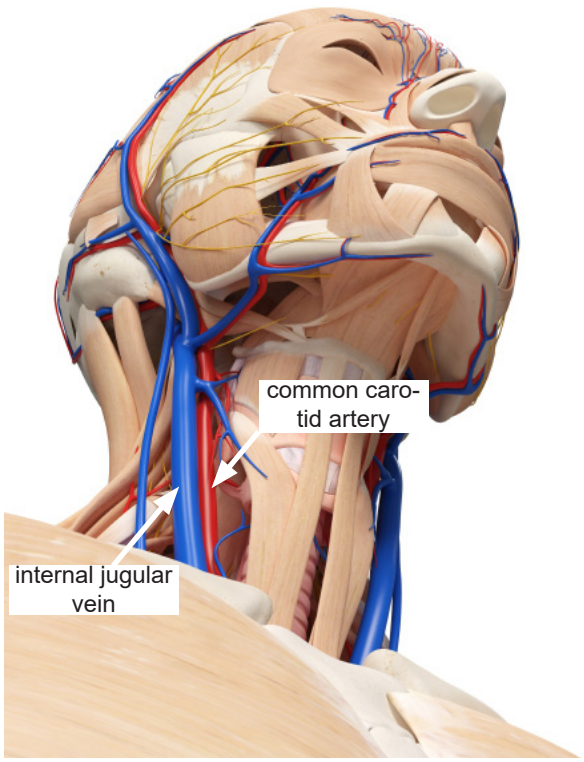


Fig. 015 schematic representation of the anatomy

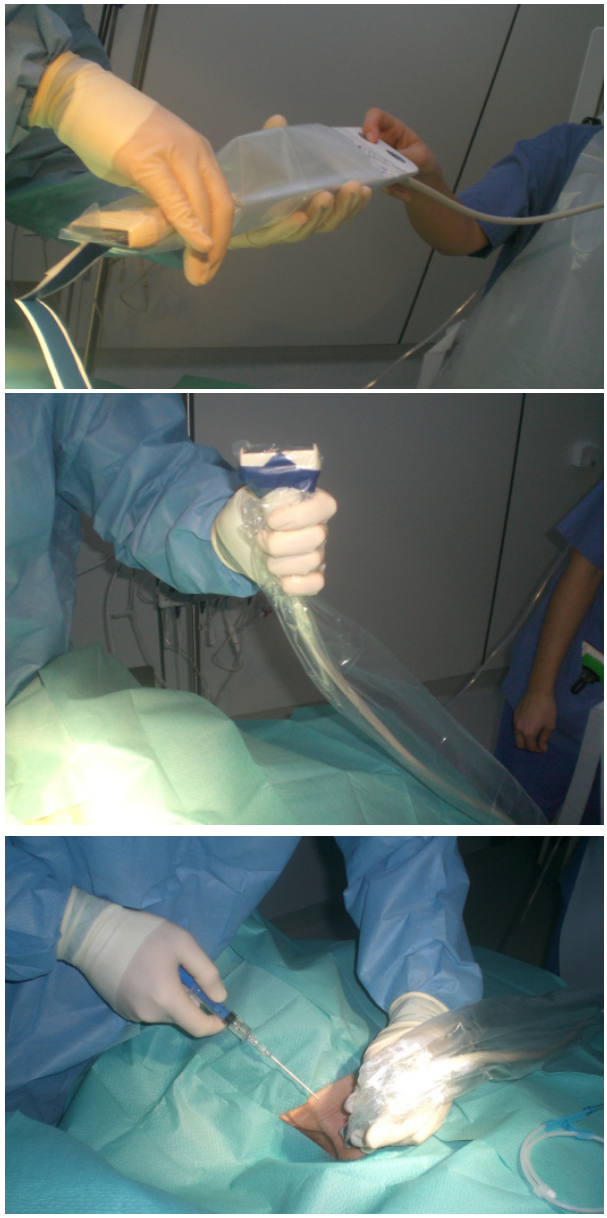


Fig. 016 CVC-insertion internal jugular vein using ultrasound: The probe is provided with a sterile cover. The puncture is done under visual control.

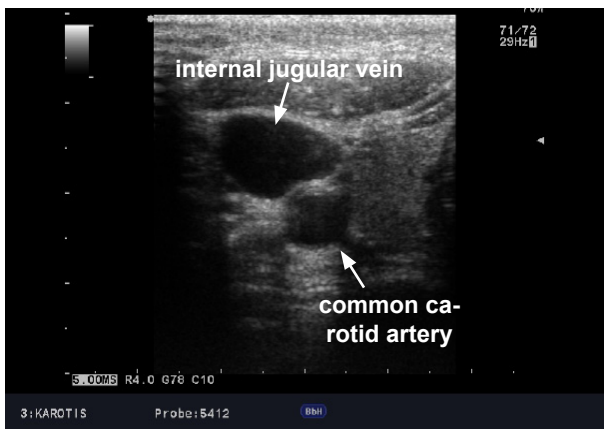


Fig. 017 Ultrasound of right cervical vessels: lateral the internal jugular vein, medial the common carotid artery (The vein can be compressed easily, but not the artery.)

- Three substances are required for anesthesia induction:
  - muscle relaxant (often necessary because the intubated emergency patients usually never have an empty stomach; ⚠ obligatory for RSI; caution: cannot intubate & cannot ventilate [CICV])
  - analgesic
  - hypnotic (sedative)

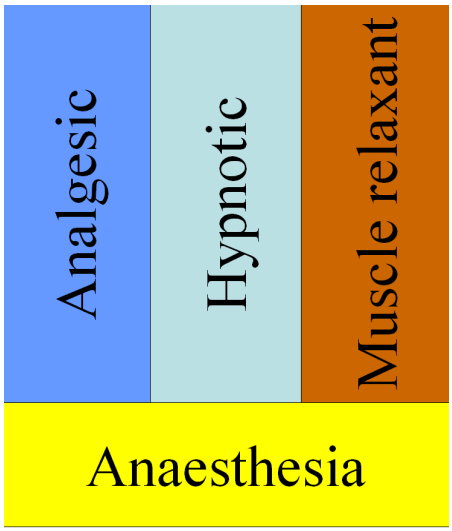


Fig. 066 components of anesthesia

An anaesthesia is obligatory for an intubation (except in cardiovascular arrest)!

Muscle relaxants

Definition

- blocking of acetylcholine receptors (postsynaptic, nicotinic) at the neuromuscular junction
- indications: Muscle relaxants are mainly used for anesthesia induction (intubation) as well as perioperatively in the operating room. Muscle relaxants are rarely used in the intensive care unit (except for anesthesia induction before intubation):
  - to facilitate ventilation: You can use them when the patient cannot be sufficiently ventilated even though the ventilation has been adapted and the ventilation mode has already been changed. Sufficient analgesia and sedation is always a prerequisite. Muscle relaxants are never an alternative to analgesic sedation!
  - during invasive procedures (e.g. tracheotomy, tube exchange)
  - early stage (< 48h) of severe ARDS (Carrico Index [paO_2/FiO_2] < 150mmHg)
- relaxometry: Whenever there is a long term medication with muscle relaxants, the effects should be monitored by relaxometry. Two transcutaneous electrodes are attached of to the distal forearm above the ulnar nerve. Then, the muscle contractions of the hand are measured: There are various stimulation patterns. The most commonly used stimulation pattern is TOF ("train of four"), in which a series of 4 stimuli are given at a frequency of 2Hz.

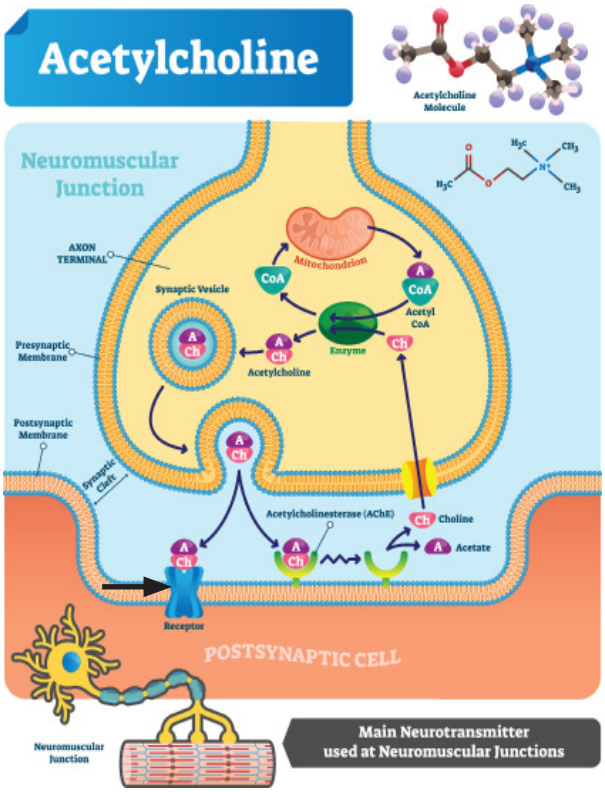


Fig. 067 Muscle relaxants block the acetylcholine receptors (see arrow) of the postsynaptic cell at the neuromuscular junction.

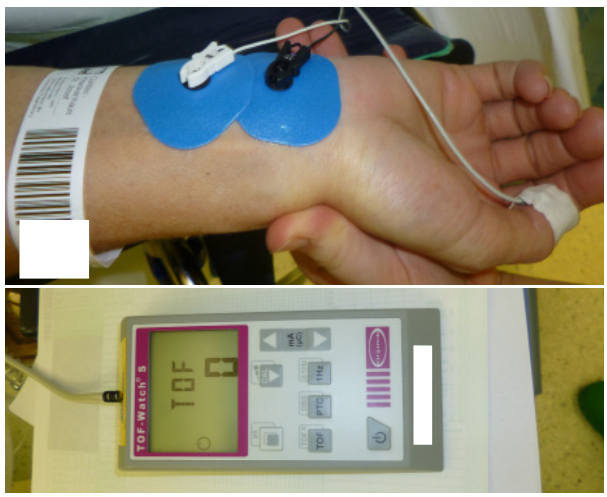


Fig. 068 TOF-relaxometry

Oxygen

Definition

- syn.: Oxygenium (molecular formula: O_2)
- discovered in 1771 by the German-Swedish chemist Carl Wilhelm Scheele (1742-1786); first described as "fire air")
- extremely poorly water-soluble (hydrophobic; carbon dioxide is 20 times more water-soluble)

Uptake

- partial pressure: the pressure that one component of a mixture of gases would exert if it were alone in a container (unit: mmHg respectively kPa (kilopascal; conversion: 1 mmHg = 0.133 kPa).
- composition of the gas mixture air (inspired air):
  - nitrogen: 78%
  - oxygen: 21%
  - rest (0.96% argon, 0.04% carbon dioxide): 1%
- The total pressure of air (syn .: air /atmosphere /barometer pressure) is 760 mmHg at sea level. Therefore the partial pressure of oxygen pO_2 in the gas mixture inspired air is p_iO_2 = 760 mmHg x 0.21 = 160 mmHg. The air pressure and thus the partial pressure of oxygen in the arterial blood p_aO_2 decreases with increasing altitude: At a height of 2000m the p_aO_2 already drops by a quarter (p_aO_2 only approx. 60 mmHg), at a height of 4000m already by half (p_aO_2 only approx. 40 mmHg). For ventilation, a FiO_2 (fraction of inspired oxygen) above 21% is usually used, so that the partial pressure of oxygen is higher (example: FiO_2 = 0.50 [i.e. 50%] → p_iO_2 = 760 mmHg x 0.50 = 380 mmHg).
- In inspiration, moistening of the airways leads to saturation (dilution) with water vapor. The partial pressure of water vapor (proportion 6.7%) is 21 mmHg at room temperature and 47 mmHg at a body temperature of 37°C. The partial pressure of oxygen in the alveolar gas p_AO_2 is therefore arithmetically: p_AO_2 = (760 mmHg - 47 mmHg) x 0.21 = 713 mmHg x 0.21 = 150 mmHg. Factually however, the partial pressure of oxygen in the alveolar gas p_AO_2 is lower with 106 mmHg: Diffusion of O_2 into the capillaries ("migration") occurs in the alveolar space, so that the proportion of oxygen in the alveolar gas is no longer 21%, but only 15%. Therefore the partial pressure of oxygen in the alveolar gas is: p_AO_2 = 713 mmHg x 0.15 = 106 mmHg. Furthermore, carbon dioxide diffuses from the capillaries into the alveoli: The proportion of carbon dioxide in the alveolar gas is 5.6%, so that a partial pressure of carbon dioxide in the alveolar gas of p_ACO_2 = 713 mmHg x 0.056 = 40 mmHg can be calculated (see also alveolar gas equation [page 101]).
- The oxygen then diffuses from the alveoli through the alveolo-capillary membrane into the capillaries. The driving force is the partial pressure difference (partial pressure gradient) between the partial pressure of oxygen in the alveolar gas p_AO_2 and the partial pressure of oxygen in the venous blood p_vO_2. The oxygen then diffuses from the arterial blood into the cells, and specifically here into the mitochondria. The driving force for the diffusion is again the partial pressure difference, in this case between the partial pressure of oxygen in the arterial blood (90 mmHg) and the partial pressure of oxygen in the mitochondria (only 1-2 mmHg). The movement of the oxygen therefore always takes place along a partial pressure gradient, whilethe partial pressure continuously decreasea on its way ("cascade").
- oxygen content:
  - inspired air: 21%
  - expired air: 16% (i.a. the rationale for mouth-to-mouth ventilation as part of a lay resuscitation)
- composition of the expired air:
  - nitrogen: 78% (the same proportion as in the inspired air, since nitrogen is neither absorbed nor consumed in the body)
  - oxygen: 16%
  - carbon dioxide: 4% (100 x more than in inspired air)
  - argon: 0.93%

	fractions		partial pressures	
	O_2	CO_2	O_2	CO_2
inspired air	21%	0.04%	160 mmHg	0.2 mmHg
alveolar gas	15%	5.6%	105 mmHg	40 mmHg
blood arterial			90 mmHg	40 mmHg
blood venous			40 mmHg	46 mmHg
expired air	16%	4%	115 mmHg	30 mmHg

Transport

- Oxygen is a gas that is extremely poorly soluble in water and therefore also in blood. For this reason, oxygen transport in the blood is predominantly chemically bound (98.5%) to hemoglobin. Only a very small part of the oxygen (1.5%) is physically (dissolved) transported in the blood. The physically dissolved amount depends on the partial pressure (Henry's law; for the gas laws see page 1396): The higher the partial pressure, the more oxygen is dissolved in the blood. For example, under hyperbaric conditions (3bar) the proportion can be increased from 1.5% (normobar [1bar]) to 8%, which is used in pressure chamber therapy (hyperbaric oxygenation [HBO]).
- hemoglobin:
  - transporter protein for oxygen
  - structure:
    - globin: 2 α-chains, 2 β-chains
    - 4 heme molecules: each one with a bivalent iron (Fe^{2+}) in the center, which reversibly binds oxygen; 1 molecule of hemoglobin can therefore bind a maximum of 4 molecules of oxygen (O_2).

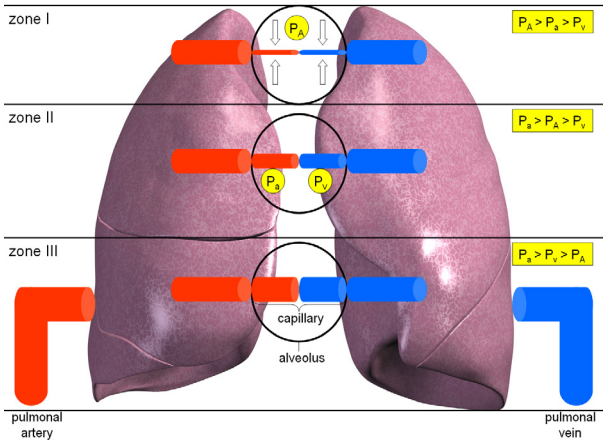


Fig. 157 3-zones-model of perfusion (lung perfusion; according to West [named after the Australian-US physiologist John B. West; born: 1928]): Perfusion is not homogeneous overall the complete lung. Due to gravity it increases from apical to basal. In the zone I (apical zone) the pulmonary arterial pressure (P_a) and the pulmonary venous pressure (P_v) a very low. Due to the alveolar pressure (P_A) the lung capillary gets compressed, so that there is only a very low perfusion. In the zone II (middel zone) the pulmonary arterial pressure(P_a) and the pulmonary venous pressure (P_v) now are significantly higher, so that her signifikant more perfusion occurs. In the zone III (basal zone; the largest zone) due to gravity as well the pulmonary arterial pressure (P_a) as the pulmonary venous pressure (P_v) are higher than the alveolar pressure (P_A), so that the lung capillary is no more compressed and stays open. The perfusion therefore is highest in this zone. This applies to the upright position. To supine position the same changes are applied from ventral to dorsal instead of from apical to basal.

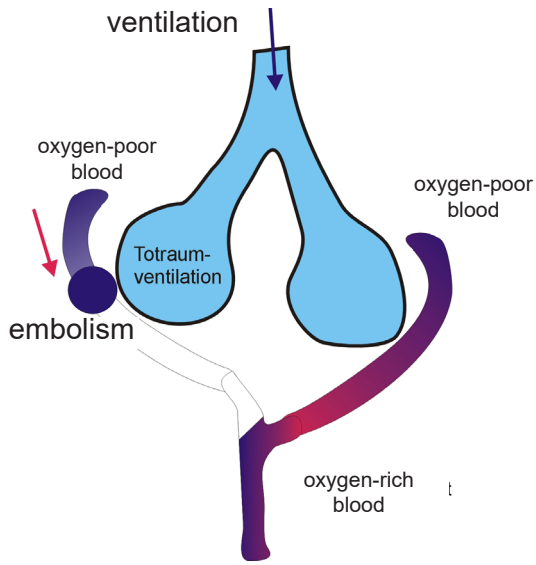


Fig. 158 disturbance of the perfusion in case of pulmonary embolism

Diffusion

- syn.: alveolar gas exchange
- transport of gases through the alveolar-capillary membrane (movement of gases between alveolar air space and the surrounding capillary blood vessels)
- amount of gas that is exchanged between alveolar air and blood through the alveolar-capillary membrane (essential role in gas exchange)
- The driving force is the partial pressure gradient between the partial pressure of oxygen in the alveolar gas p_AO_2 and the the partial pressure of oxygen in the venous (exactly: mixed venous) blood p_vO_2.
- The time it takes for an erythrocyte to deliver its CO_2 and to take up its O_2 (so-called contact time) is extremely short (only 0.15 sec).
- Bohr effect (drilling effect; for the graphical illustration see 781): The affinity of hemoglobin for oxygen decreases with an increasing pCO_2 and a decreasing pH, i.e. the oxygen release to the tissue increases. Therefore a metabolic acidosis should only be bufferd at a pH < 7,2, because a moderate acidosis improves the oxygen release to the tissue.
- Diffusion is described by Fick's law of diffusion.

Fick's law of diffusion

Diffusion According to Fick's law of diffusion (named after the German physiologist Adolf Fick [1829-1901]) the diffusion is determined by four factors:

$$\text{diffusion} \sim \frac{\text{diffusion surface} \times \text{diffusion coefficient} \times \text{diffusion gradient}}{\text{diffusion length}}$$

- diffusion surface (surface area for gas exchange):
  - 300 million alveoli: 160 m^2 (approximately corresponds to the size of a tennis court; the skin only has a gas exchange surface of about 1.5 m^2 which is approx. 1% of the human gas exchange [i.e. even if the entire skin would be covered with gold like in the James Bond movie "Goldfinger", one would not choke])
  - Diffusion is directly proportional to the diffusion surface. If the diffusion surface is reduced (e.g. lung resection, atelectasis, pneumonia, pulmonary contusion from trauma), diffusion decreases.
  - The functional residual capacity (FRC) can be seen as a measure of the gas exchange area: This is the volume of gas that remains in the lungs when the breathing is at rest, i.e. after a normal (not forced) exspiration.
- diffusion coefficient (syn.: Krogh's diffusion coefficient): Oxygen and carbon dioxide have different blood-gas partition coefficients.
  - ⚠ Carbon dioxide is 20 times more soluble than oxygen (just think of carbonated beverages such as Coke: It contains far more carbon dioxide than oxygen, because carbon dioxide simply dissolves much better in water).
  - Zherefore, the pO_2 is the parameter for diffusion impairments! Diffusion disorders (e.g. pulmonary edema, pneumonia) therefore typically lead to hypoxemia (so-called hypoxic respiratory failure) and not (or much later) to hypercapnia.
  - The treatment of first choice in case of a diffusion impairment is therefore the administration of oxygen.

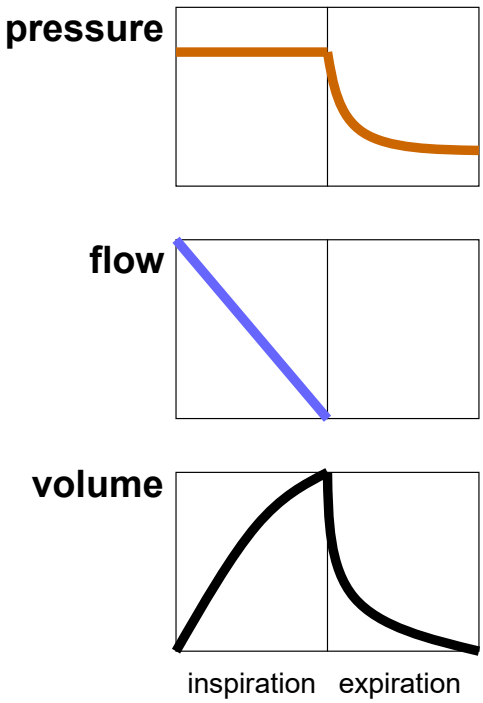


Fig. 184 pressure-controlled ventilation (PCV)

Volume-controlled ventilation (VCV)

- standard mode of ventilation in America (USA)
- The ventilator delivers a preset tidal volume (TV) within the set inspiratory time (constant flow).
- syn.: IPPV (intermittend positive pressure ventilation)
- volume constant ventilation (constant volume level):
- The resulting pressure (ventilation pressure) is determined by:
  - tidal volume
  - resistance and compliance of the respiratory system (lung, thorax)
  - inspiratory time
- The tidal volume determines the ventilation pressure.
- ventilation parameters:
  - primary (independent): volume (tidal volume [TV])
  - secondary (dependent): pressure (ventilation pressure)
- settings:
  - tidal volume (TV)
  - respiratory rate
  - I:E ratio
  - inspiratory flow
    - flow rate (common approx. 30 l/min)
      - speed of the ventilator emitting the breathing gas during inspiration (syn.: peak flow; unit: l/min)
      - The higher the inspiratory flow, the higher is the ventilation pressure (peak pressure). High flow rates induce turbulences, which heighten the airway resistance.
    - flow profiles (patterns)
      - constant ("rectangle" flow; standard today)
      - decelerating (especially for conscious patients): Initially the flow is higher and then decreases. This corresponds better to the pressure increase in the lung.
      - sinusoidal (obsolete today)
  - pressure limit (If the set pressure limits are exceeded, the not delivered volume is released [very similar to the principle of the steam cooker].)
- In the first part of the inspiration (flow phase; inflation phase) the preset volume is applicated into the lung, that leads to relativ high peak perssure. In the second part of the inspiration (no-flow phase; plateau phase) the breathing gas distributes in the lung uniformly. The pressure decreases. The pressure at the end of the inspiration is called plateau pressure.
- changes of the ventilation pressure
  - An increase of the ventilation pressure can be caused by:
    - airway obstruction, kinking of tube
    - increased airway resistance
    - reduced elasticity (compliance) of the lungs or thorax
    - coughing / "pressing" of the patient
  - A decrease of the ventilation pressure is mostly caused by a leakage.
- assessment:
  - advantage: Compared to pressure-controlled ventilation, volume-controlled ventilation leads to less desynchronisations and derecruitments. Therefore, some clinics perform a volume-controlled ventilation in the early phase of a severe ARDS.
  - disadvantages:
    - often high ventilation pressures, so that the volume controlled ventilation was almost completely abandoned in Europe
    - higher risk of barotrauma (e.g. pneumothorax) than in pressure-controlled ventilation
    - no automatic leakage compensation
- Emergency ventilators (e.g. Medumat, Oxylog) provide a volume-controlled ventilation. However, the latest generations also allow pressure-controlled ventilation. Anaesthesia ventilators (circuits) in the operation room provide both pressure- and volumed-controlled ventilation. Especially in case of abdominal surgery procedures often volumed-controlled ventilation is used.
- special mode: noisy ventilation
  - ventilation with different tidal volumes (generated randomly)
  - both for volume-controlled (noisy-VCV: randomly different tidal volumes) and pressure-controlled (noisy-PSV: randomly different inspiratory pressures) ventilation
  - extremely lung-protective (Gama de Abreu, Crit Care Med 2008; Spieth et al, AJRCCM 2009 [improvement of oxygenation in animal models])
  - no clinical use yet

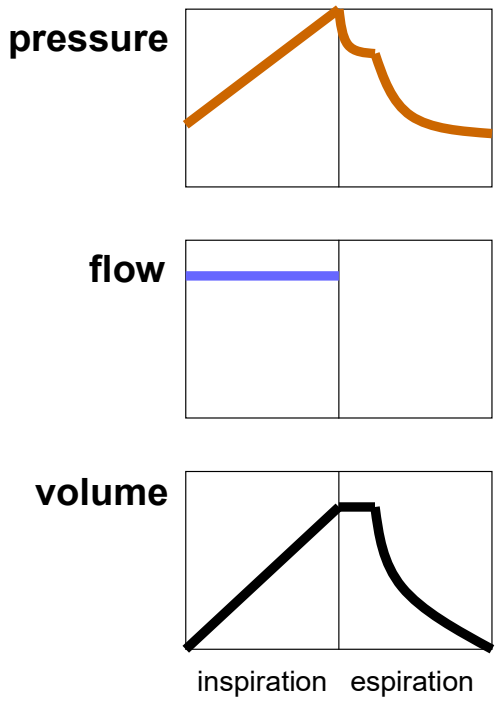
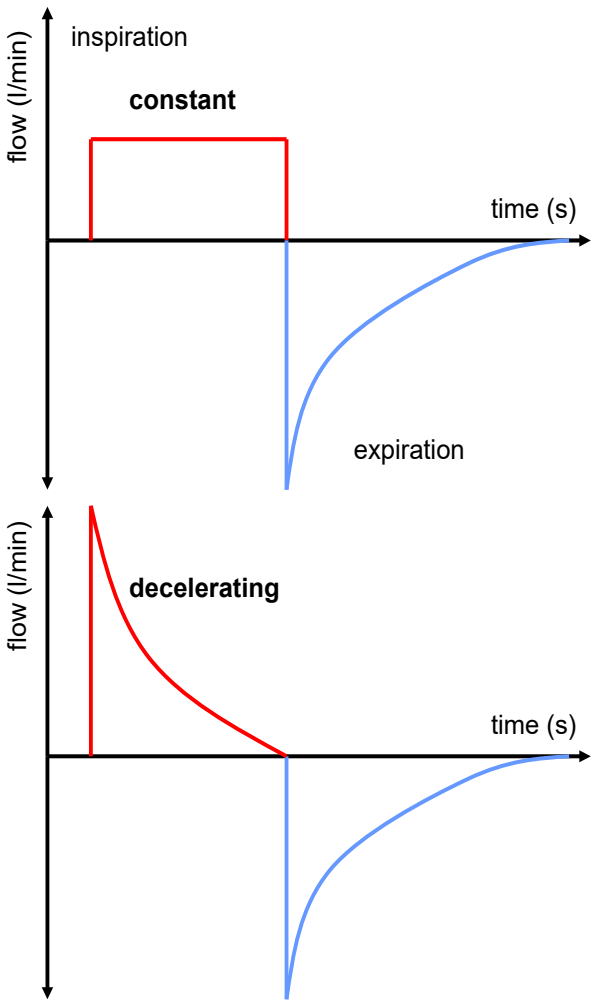


Fig. 185 volume-controlled ventilation (VCV)



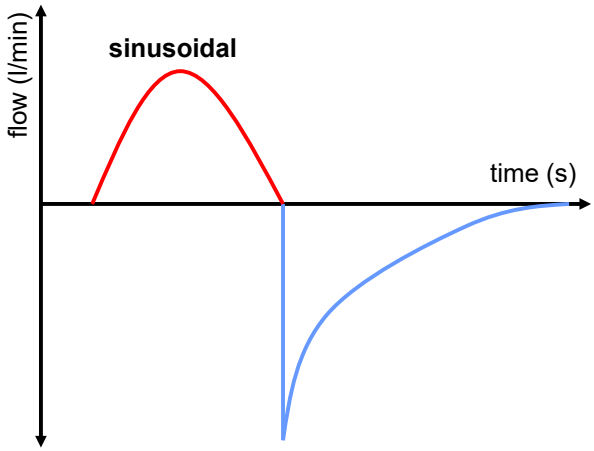


Fig. 186 the three different flow profiles (patterns of the inspiratory flow) in volume-controlled ventilation: The constant flow ("rectangle" flow) is standard today. The decelerating flow is mainly used in conscious patients, the sinusoidal flow is no longer used today.

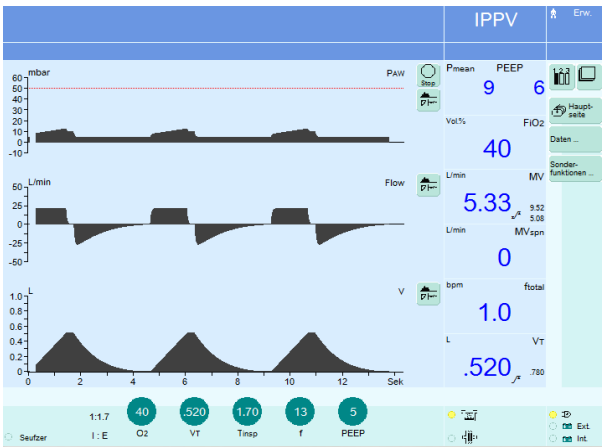


Fig. 187 IPPV (intermittend positive pressure ventilation): a typical volume-controlled ventilation (annot.: The correct term is continuous positive pressure ventilation [CPPV], because there is continuously a positive perssure in the airway and not only in the inspiration. Strictly speaking in IPPV there is no positive perssure in the expiration (no PEEP).

Flow:
- pressure-controlled ventilation: decelerating
- volume-controlled ventilation: constant

Ventilation pressures

- inspiratory pressures:
  - peak pressure
  - plateau perssure
- expiratory pressure: The pressure at the end of the expiration os called PEEP.
- mean airway pressure (MAP): the average pressure generated during the respiratory cycle
- units:

WEANING

Definition

- discontinuing of dependency on assisted ventilation
- reduction of the invasiveness of ventilation with the objective of spontaneous breathing
- gradual transfer of the work of breathing from the respirator to the patient
  - decrease of
    - FiO_2
    - IPAP, PEEP
  - normalisation of I:E ratio (e.g. from before 1:1 now to 1:2)
- Mortality increases by 2% with each day of ventilation
- average duration: 47% of the time of mandatory ventilation (Esteban et al, Chest 1994) is used for weaning.
- guidelines (German):
  - S2k-guideline 2014 "Prolonged Weaning" (German Respiratory Society [DGP]); revised 2019
  - S3-Guideline 2017 "Mechanical Ventilation and Extracorporeal Membrane Oxygenation in Acute Respiratory Insufficiency" (German Society for Anaesthesiology and Intensive Medicine [DGAI; chapter No. 7: weaning from invasive ventilation)
- Especially in the prolonged weaning the ventilation has to be continued although the initial (original) indication, that lead to ventilation (e.g. severe pneumonia), has been repaired long ago.
- successful weaning: extubation and then no ventilatory support necessary for 48 h
- weaning failure:
  - failed spontaneous breathing trial
  - need for reintubation / recannulation or for ventilatory support within 48 h after the extubation
  - death within 48 h after extubation

Approximately 50% of the total ventilation time is used for weaning!

Long-term ventilation

A lot of different definitions of long-term ventilation are circulating:

- ventilation > 48h
- multiple unsuccessful weaning trials
- mechanical ventilation for more than 6 h/day necessary for about 2-3 weeks

In 2007, a TASK-FORCE (the Budapest Consensus Conference) determined that ventilation for more than 7 days is referred to as long-term ventilation.

Definitions
TASK-FORCE 2007

- **Weaning**
  - **simple (60%): successfully completed 1st SBT (spontaneous breathing trial) (mortality: 10%)**
  - **difficult (25%): only the 2nd or 3rd SBT is completed successfully (mortality: 10%)**
  - **prolonged (15%): > 3 unsuccessful SBT erfolglos or mechanical ventilation for > 7 days after the 1st (unsuccessfull) SBT (mortality: 30%)**
- **long-term ventilation: mechanical ventilation > 7 days**
- **successful weaning: Weaning is considered successful if within 48 hours after extubation no further ventilatory assist (according to the revised S2k-guideline 2019 no invasive ventilation) was necessary.**
- **weaning failure:**
  - **failed spontaneous breathing trial**
  - **need for reintubation / recannulation or for ventilatory support within 48 h after the extubation**
  - **death within 48 h after extubation**

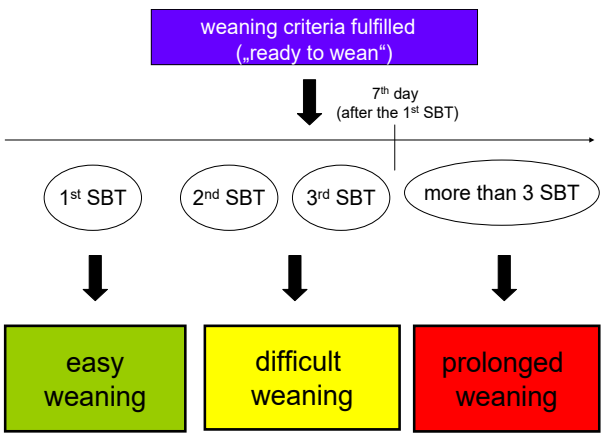


Fig. 263 overview of weaning categories

control [linear transducer; i.a. Alansari et al, Crit Care 2015; Gobatto et al, J Crit Care 2015] possible; in the TRACHUS study [Gobatto et al, Intensive Care Med 2016] it was shown that with exclusively sonographic control there were not more complications than under exclusively bronchoscopic control.)

- insertion of the tracheal cannula

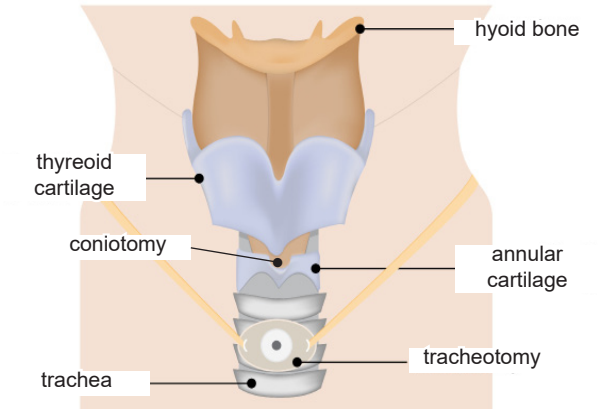


Fig. 278 Schematic representation of the anatomy: Tracheotomy is performed between the 2_{nd} and 3_{rd} tracheal ring. Coniotomy, on the other hand, is performed further cranially: between the thyroid and cricoid cartilage (cricothyreoid membrane).

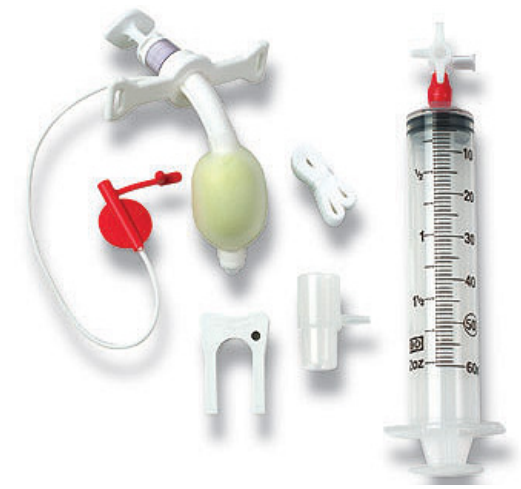
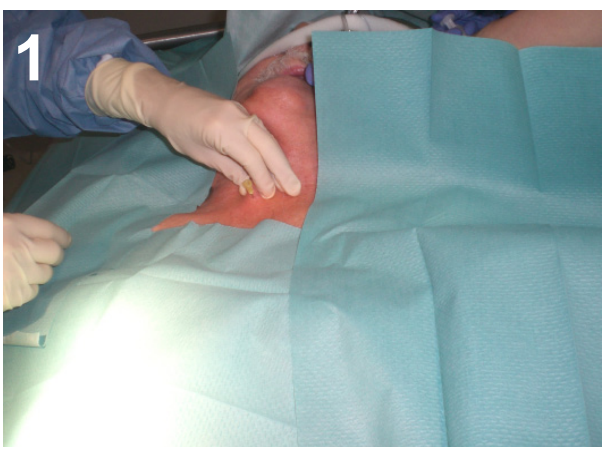
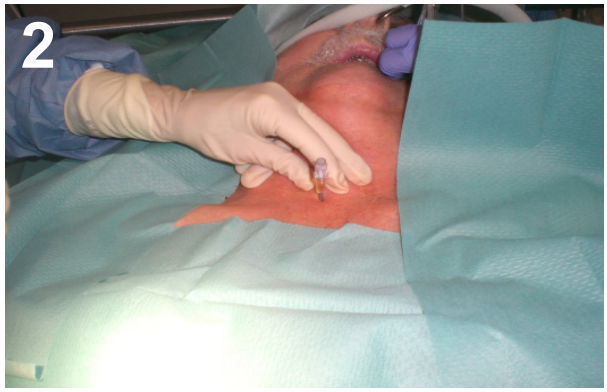
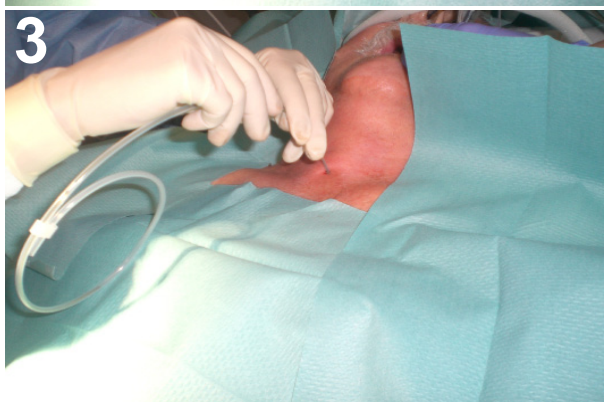
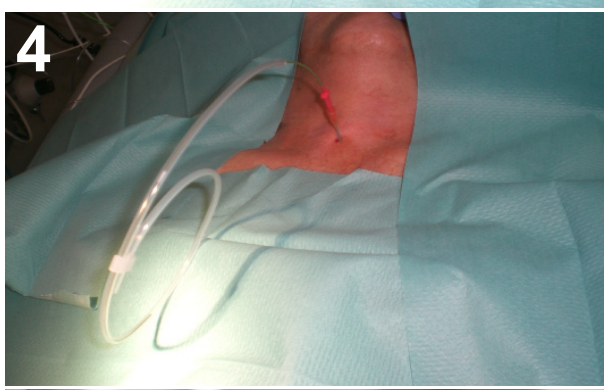


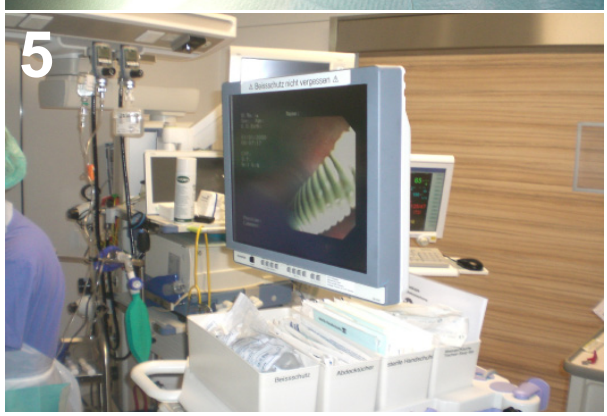
Fig. 279 tracheal cannula with accessories [32]











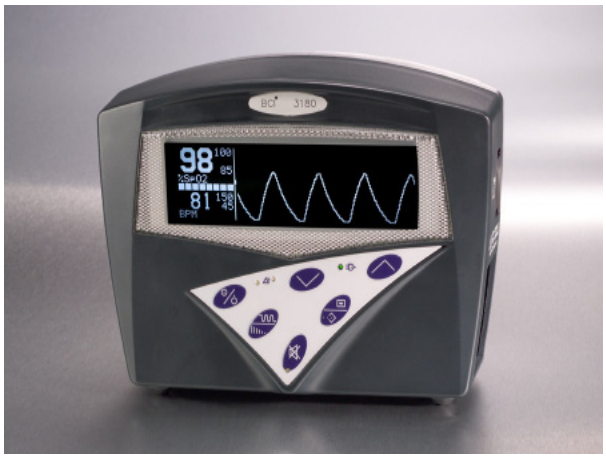


Fig. 323 pulse oximetry [32]

Oxygen supply

The oxygen enters the alveoli via the respiratory tract. By diffusion through the alveolo-capillary membrane it gets into the blood. Because oxygen is (in contrast to carbon dioxide) extremely poorly water soluble, the transport in the blood is predominantly (98.5%) chemically bound to hemoglobin. Only a small part of oxygen (1.5%) is physically dissolved in the blood. Via the blood (oxygen transport) the oxygen is deliverd to the the tissue / cells. The delivered amount of oxygen per time (oxygen delivery) is the decisive determinant of the cell. The oxygen supply for the cell therefore depends on:

- oxygen delivery (DO_2: delivery of oxygen; norm: 1000 ml/min [for survival at least 300 ml/min are necessary]): This in turn depends on
  - cardiac output (CO; the most important factor: ⚠ Oxygen delivery DO_2 depends on CO by 90%!)
  - hemoglobin (Hb)
  - arterial oxygen saturation (SaO_2)
- oxygen consumption (VO_2: volume per time of oxygen; norm: 200-250 ml/min); calculation:
  - from the blood gases (BGA): VO_2 = Hb x 1.39 x (SaO_2 - $SmvO_2$) x 10 x CO (ml/min)
  - from the breathing gases: VO_2 = RMV x (F_iO_2 - F_EO_2)
    - RMV: respiratory minute volume
    - F_iO_2: oxygen fraction inspiratory air
    - F_EO_2: oxygen fraction expiratory air

Oxygen delivery DO_2 depends on:
- CO
- Hb
- SaO_2

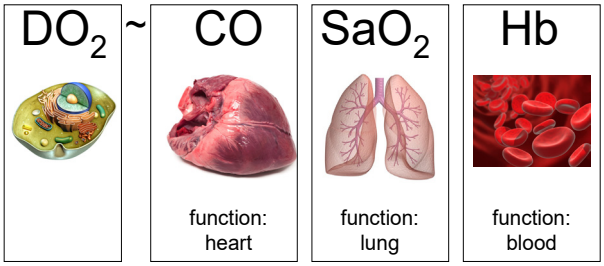


Fig. 324 The three determinants of oxygen delivery (DO_2) to the cell: the function of the heart (CO), the lung (arterial oxygen saturation [SaO_2]) and the blood (Hb).

The German physiologist Eduard Pflüger (1829-1910) stated already in 1872: "The cardio-respiratory system fulfills its physiological task in ensuring the cellular oxygen supply."

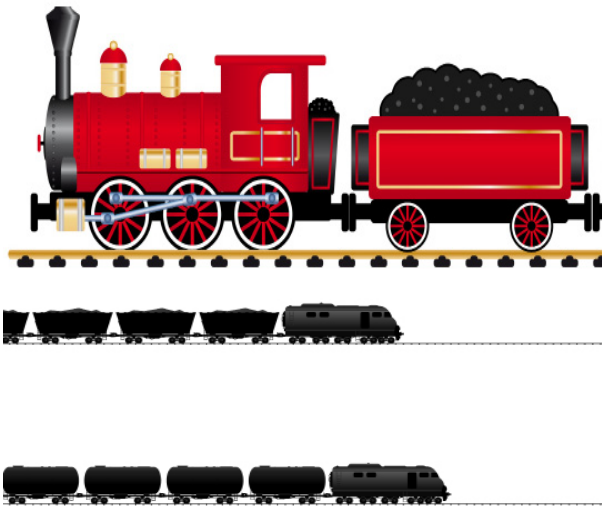


Fig. 325 The relationship should illustrated by a comparison with a train: The oxygen delivery for the cell can be compared with the amount of coal supplied by a train (e.g. for heating). In this comparison, CO corresponds to the engine (power) of the locomotive (traction engine), the Hb to the number of wagons and the SaO2 to the proportion of the load volume of each wagon loaded with coal. The larger the individual parameters (i.e. stronger traction engine, more wagons, wagons loaded with coal up to the ceiling if possible), the more coal is ultimately delivered by the train and can then be burned for energy generation

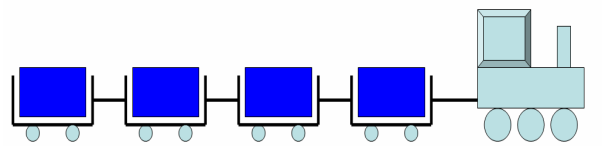


Fig. 326 normal oxygen delivery DO_2: strong traction engine (CO), enough (iin the example here 4) number of wagons (Hb), all of which are fully loaded (SaO_2 = 100%).

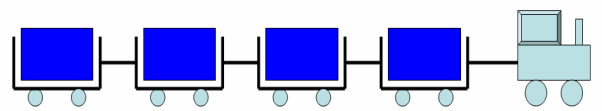


Fig. 327 reduced oxygen delivery DO_2: indeed a sufficient number (Hb) of fully loaded (SaO_2) wagons, but a to small (too weak) traction engine (CO)

load = wall tension of the ventricle
- end-diastolic: preload
- end-systolic: afterload

Preload

- end-diastolic wall tension of the ventricle
- simplified: ventricular end diastolic pressure
- end-diastolic fiber length (sarcomere)
- Frank-Starling mechanism (named after the German physiologist Otto Frank [1865-1944] an the English physiologist Ernest Starling [1866-1927]; syn.: force-length relationship): The force of the individual heart muscle fiber is proportional to the initial sarcomere length (superposition [overlapping] of actin and myosin filaments). The pre-stretching (longitudinal) of the myocytes leads to an increased calcium influx and consequently to an increase in inotropy. The contraction force of the heart muscle cells increases with their pre-stretching. The optimal sarcomere length (length of superposition) with the maximum force is 2.2 µm. Beyond 2.6 µm there is overextension with a consecutive reduction of the force. You can compare this to a balloon: The further you inflate it, the greater its pre-stretch and the faster the air will finally whistle out when you release the opening.
- The pre-stretching cannot be measured in clinical practice. As a surrogate parameter therefore the pressure in the ventricle at the end of the diastole (end-diastolic pressure; syn .: filling pressure) can be used: The higher the pressure inside the ventricle at the end of the filling phase (end-diastolic), the stronger the pre-streching of the ventricle and thus the higher the preload. The parameter for the left ventricular preload is the left ventricular end-diastolic pressure (LVEDP), parameter for the right ventricular preload the right ventricular end-diastolic pressure (RVEDP). However, as is known today, the pressures do not correlate sufficiently with the preload, so that today even other parameters are used to estimate the preload (see page 220). The estimation of the preload (volume dependency) is one of the most common and at the same time one of the most difficult questions in daily practice.
  - LVEDP; measurement:
    - directly (arterial puncture): The LVEDP can be measured directly only invasively in the cath lab (cardiac catheterization laboratory): Therefore, the pigtail catheter is retrogradly inserted from the ascending aorta via the aortic valve into the left ventricle, where the pressure at the end of the diastole then is measured.
    - indirectly (venous puncture): In the intensive care unit the LVEDP is only measured indirectly by the measurement of the wedge pressure (= PCWP [pulmonary capillary wedge pressure] with the pulmonary artery catheter [PAC].)
  - RVEDP (The ZVD is often used here indirectly very simplified. The RVEDP could certainly be measured directly with the pulmonary artery catheter [right heart catheter]. However, this is very rarely done in daily clinical practice, since the perload of the right ventricle is not so important: The right ventricle is relatively insensitive to volume, so that the Frank-Starling mechanism does not play a pronounced role an the right heart. The right ventricle, however, is extremely sensitive to pressure (afterload): If the reight ventricular afterload increases [e.g. pulmonary embolism], the right ventricular stroke volume decreases quickly.)
- options:
  - to increase the preload: volume administration
  - to decrease the preload: volume withdrawal (e.g. loop diuretics, CVVH), nitrates (especially in low dosage venous vasodilation occurs)

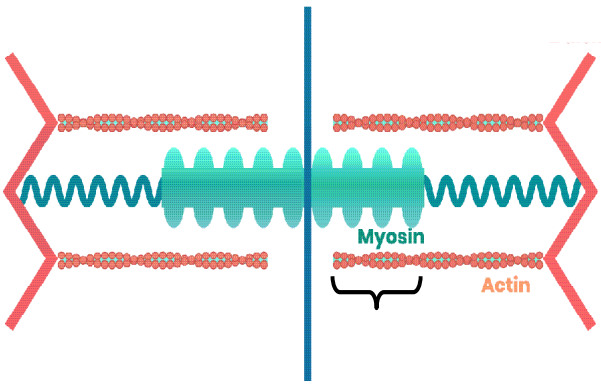


Fig. 337 sarcomere with the contractile proteins (filaments) myosin and actin: The larger the superposition, the higher is the force. Optimal is a superposition of 2.2 µm.

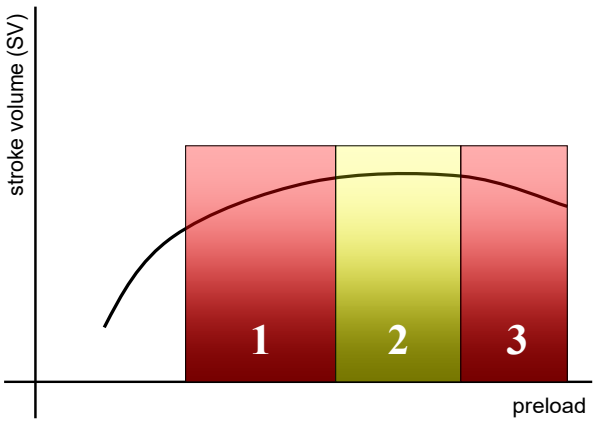


Fig. 338 relationship between preload and stroke volume: Frank-Starling curve (= cardiac function curve = force-length relationship). In section 1 of the curve, the stroke volume SV and thus the cardiac output CO (CO = SV x HR) can be increased by volume administration (preload of myocytes → increased calcium influx → increase in inotropy). In section 2 of the curve (target corridor of therapy!), the volume status and thus the preload is optimal. In section 3, the preload is too high (volume overload): Here, the preload must be lowered and thus volume withdrawn in order to increase cardiac output.

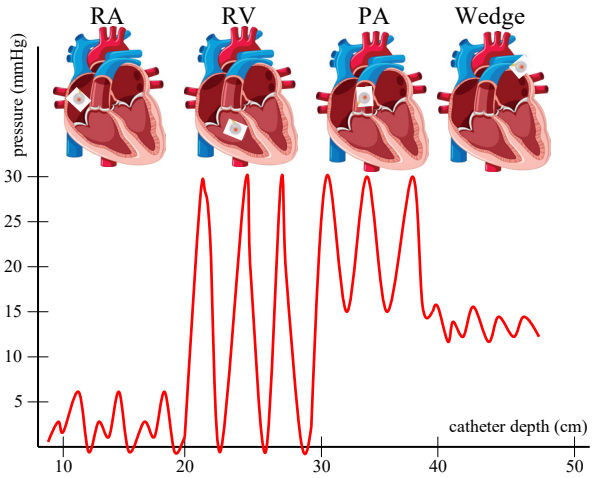


Fig. 368 the different pressure curves when the pulmonary artery catheter is inserted (RA: right atrium; RV: right ventricle; PA: pulmonary artery)

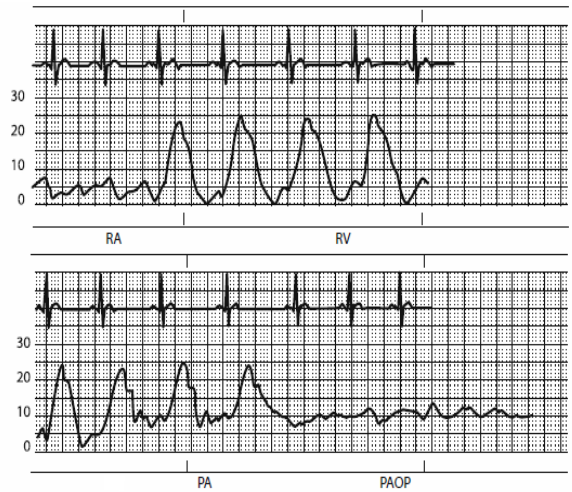


Fig. 369 pulmonary catheter: pressure curves (top RA, then RV; bottom PA, then wedge position [PAOP]) [14]

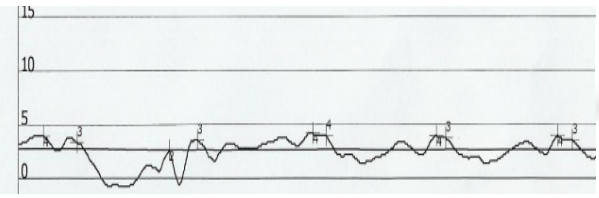


Fig. 370 pressure curve of the right atrium (RA): typical triple peak, low pressures (2-6 mmHg)

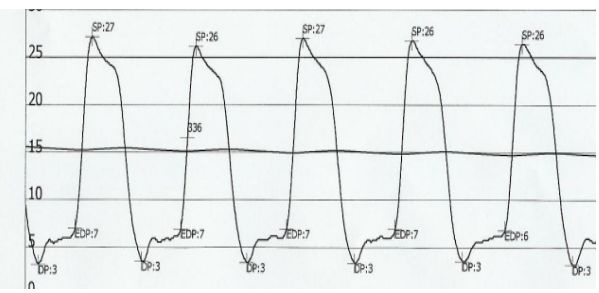


Fig. 371 pressure curve of the right ventricle (RV): systolic pressures 15-30 mmHg, diastolic towards 0 mmHg (typical for a ventricular pressure curve)

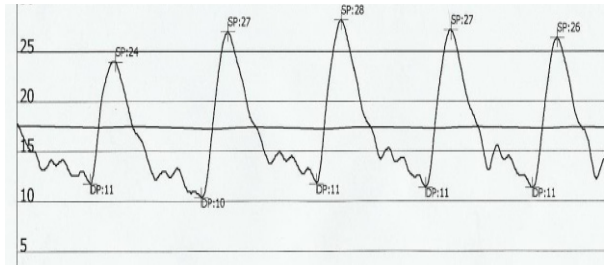


Fig. 372 pressure curve of the pulmonary artery (PA): compared to RV, same systolic but higher diastolic pressure

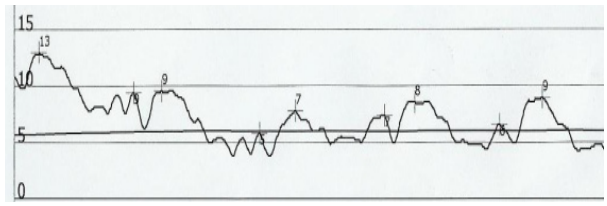


Fig. 373 pressure curve in wedge position: The curve is flattened.

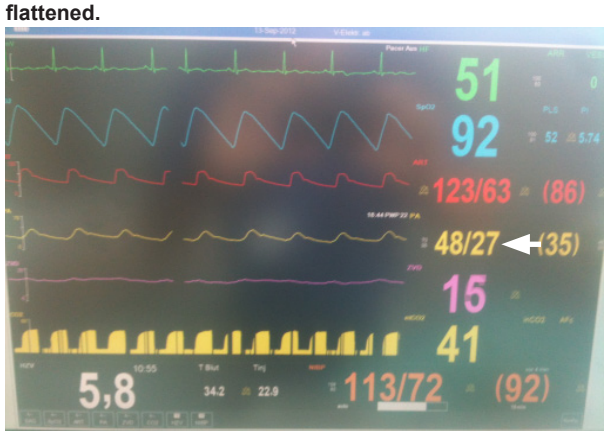


Fig. 374 lying pulmonary catheter: unblocked in PA position (arrow)

Standard values

- measurable values
- calculable values

Measurable values

	mean value [mmHg]	standard value [mmHg]
CVC		5-10
RA	5	2-10
RV_{sys}	25	15-30
RV_{dias}		2-8
PAP_{sys}	23	5-30
PAP_{dias}	9	4-12
PCWP	9	< 15 (if ventilated: < 20)
LA	9	5-12
LV_{sys}	120	90-140
LV_{dias}	9	5-12
$SvO_{2\ central}$		70-85%
$SvO_{2\ mixed}$		65-80%

Catecholamines
Classification

- according to synthesis:
  - natural catecholamines
    - as hormone: adrenaline, noradrenaline
    - as neurotransmitter: noradrenaline, dopamine
  - synthetic catecholamines (dobutamine)
- according to effect:
  - vasopressors
    - noradrenaline
    - dopamine (high-dose)
  - inotropes
    - dobutamine
    - adrenaline
    - dopamine (mid-dose)

Effects

	α_1	α_2	β_1	β_2
Adrenaline				
Noradrenaline				
Dobutamine				

Application

- via perfusor
- Perfusor syringes should always be clearly labelled (preferably with standardised syringe labels).
- If a perfusor syringe becomes empty, the change (especially with high catecholamine doses) should always be made with an overlap, i.e. with two syringes.
- always with flow (NaCl 0.9% 10 ml/h)
- catecholamine line:
  - It is always recommended to choose the distal CVC lumen as the catecholamine line, because in this way fluid doses via the proximal lumen cannot lead to unwanted catecholamine boluses. Probably it does not matter whether the distal or proximal lumen is chosen, because the distance between the exit openings is only minimal.
  - Catecholamines should always be connected directly to the hub. Infusion extension lines (e.g. Heidelberg extension line) should be avoided (dangerous dead spaces!).
  - no additional medication via the catecholamine line
- always invasive BP measurement, preferably always advanced hemodynamic monitoring ("no blind flight")
- The dosage (e.g. for transfers) should always be given in mg/h and not in ml/h, as the perfusors are often drawn up differently (e.g. noradrenaline 0.1mg/ml or 0.5mg/ml).
- attenuation of effect in an acidic environment (The lower the pH, the lower the catecholamine effect.)
- There are generally no formal dose limits for catecholamines ("upper limits", "maximum doses"): As long as they work, they can be increased.

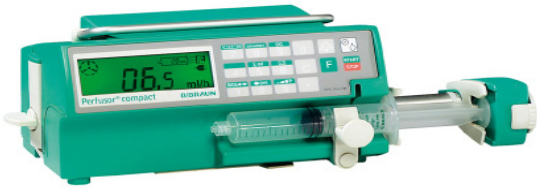


Fig. 427 Perfusor [8]

Side effects

- cardiac:
  - arrhythmia (atrial fibrillation)
  - tachycardia
  - increase in myocardial oxygen consumption (MVO_2), angina pectoris, myocardial ischemia
  - Tako-Tsubo cardiomyopathy (In 7% of cases of Tako-Tsubo cardiomyopathy a cardiogenic shock develops: Catecholamines are contraindicated in this case [see page 417]!)
- endocrinological:
  - hyperglycaemia (The stimulation of β_2-receptors in the liver leads to an increase in glycogenolysis.)
  - hypocalcaemia, hypomagnesaemia, hypophosphatemia
  - hypothyroidism
  - lactate ↑ (endogenously increased lactate production through the increased glycogenolysis mediated via the β_2-receptors)
- renal: acute kidney injury (by vasoconstriction)
- intestinal:
  - inhibition of peristalsis (gastrointestinal atony)
  - intestinal ischemia (by vasoconstriction; possibly lactate ↑)
    - small intestine: NEC (necrotizing enterocolitis)
    - large intestine: ischemic colitis
- immunological:
  - immunosuppressive (inhibition of phagocytosis)
  - pro-inflammatory
  - development of tolerance (tachyphylaxis; through down regulation of receptors)

No uncritical use of catecholamines! They have considerable side effects!

No "drug executions" (classic: norepinephrine in cardiogenic shock with high SVR and low BP)

NUTRIC score

- age
  - < 50 years: 0 P.
  - 50-75 years: 1 P.
  - > 75 years: 2 P.
- APACHE-II score
  - < 15 P.: 0 P.
  - 15-19 P.: 1 P.
  - 20-28 P.: 2 P.
  - > 28 P.: 3 P.
- SOFA score
  - < 6 P.: 0 P.
  - 6-10 P.: 1 P.
  - > 10 P.: 2 P.
- number of comorbidities
  - 0-1: 0 P.
  - > 1: 1 P.
- days from hospital admission to ICU admission
  - 0-1: 0 P.
  - > 1: 1 P.

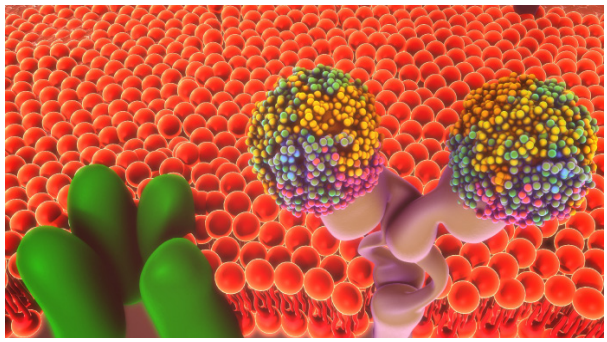
early (especially enteral) start of nutrition („early goal directed nutrition"): within 24 hours after admission / stabilization

The principle of "early goal directed nutrition" (EGDN) in nutritional medicine has come into criticism in the same way as the principle of "early goal directed therapy" (EGDT) in sepsis therapy. However, both (EGDN and EGDT) still apply, only the targets ("goals") have changed. In my opinion this term should be maintained, hence it finally succeeded in bringing nutrition from its shadowy existence into the focus of everyday activity in the intensive care unit. The goal to start start nutrition early, namely enteral nutrition, still remains, however with the goal of trophic nutrition (i.e. 250 ml/d; "villi food"; "minimal enteral feeding") with the goal to preserve the intestinal mucosa, i.e. to avoid villi atrophy in the intestine with consecutive translocation of the bacteria. The goal is certainly no longer to reach the full number of calories (normocaloric) right from the first day. This can even be dangerous (especially refeeding syndrome)! In the initial phase of a severe illness (aggression phase), externally added calories cannot be utilized at all anyway. It is completely sufficient to increase the number of calories slowly. In principle, in the first week, as long as there is no malnutrition, you should only nourish hypocalorically (i.e. 10-15 kcal/kg). Only after about a week a fullcaloric nutrition (i.e. 25 kcal/kg) should be offered. Hyperalimentation is harmful and should definitely be avoided. Another goal is to make sure you have a sufficient protein intake to avoid catabolism.

Nutrition in the intensive care unit is best done using a standardized protocol (nutritional protocol). In the ACCEPT study (Clifford et al, Crit Care Resusc 2010) the duration of intensive care was shortened and the mortality also tended to be lower.

Nutritional therapy: use of a protocol (nutritional protocol) in the intensive care unit!

Stress metabolism



Definition

- syn.: post aggression syndrome
- physiological reaction of the body to a sudden onset of a serious disease or surgery to provide the substrates and energy necessary for reconvalescence
- increase in metabolism
  - gluconeogenesia ↑ → glucose ↑
  - reduction of storage depots
    - lipolysis
    - proteolysis
    - glycogenolysis
- insulin resistance
- activation of sympathetic nervous system → stress hormones (catecholamines [adrenaline, noradrenaline], cortisol, glucagon) ↑
- release of cytokines (e.g. TNFα, Il-1)

Phases (according to Cuthbertson and Moore)

- acute phase
- flow phase
- reparation phase

Acute phase

- syn.:
  - aggression phase
  - ebb phase
- duration: hours (12-24h; 1st day)
- The acute phase is usually rarely found in internal intensive care patients: The disease process (e.g. pneumonia) often goes on for several days, so that this phase is often already over when the intensive care dependency arises. However, the acute phase is often found in postoperative intensive care patients (e.g.

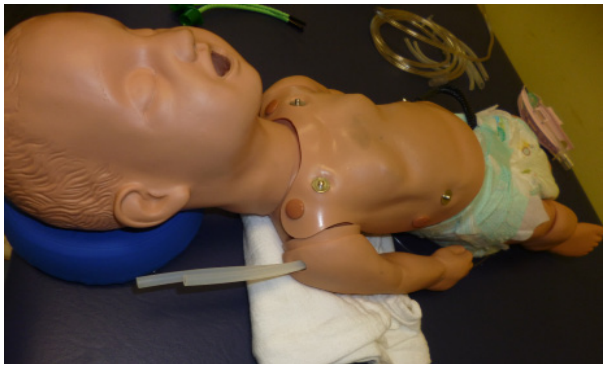


Fig. 489 example of the optimum position

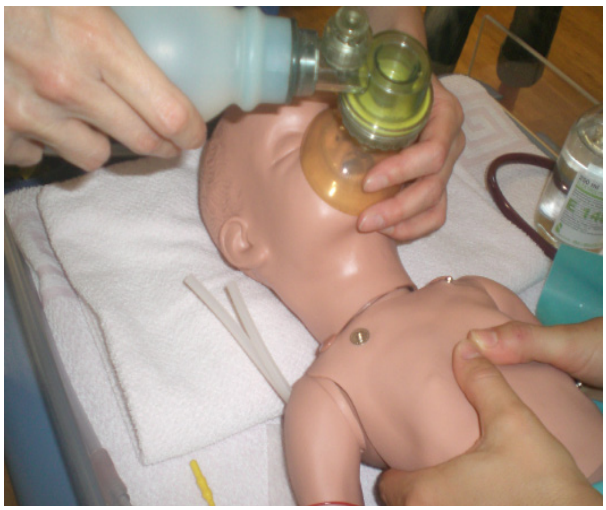


Fig. 490 BMV (bag mask ventilation)

The first choice for ventilation in children is bag mask ventilation and not intubation! In newborns and infants always insert gastric tube additionally!

Tips
to optimize bag mask ventilation

- **shoulder and neck roll (e.g. towel, diaper)**
- **double C-grip (EO-technique; bimanual sealing; by helper)**
- **insert a nasogastric tube (especially in infants)**
- **insert the Guedel tube (OPA [oropharyngeal airway]; e.g. in case of tonsil hyperplasia)**
- **deepen anesthesia**

Intubation

- only rarely necessary (only in 1% of newborn resuscitation!)
- As an emergency physician it happens on average every 6 years that a child > 1 year needs to be intubated and only every 13 years that an infant (i.e. child < 1 year) needs to be intubated (Eich et al, Resuscitation 2009). Therefore, it is definitely not possible to learn these skills only through the emergency medical service! On principle, intubation of children (especially under preclinical conditions; out-of-hospital) should only be performed with caution and only if expertise is available. Otherwise this is too dangerous (high complication rate)!
- most common indication for preclinical intubation in childhood: polytrauma
- However, intubation is not absolutely necessary: Sufficient mask ventilation is just as good. Regarding mortality, intubation does not show any advantage. The risk of aspiration under mask ventilation is only very low. Another good option is the use of intubation alternatives (especially the laryngeal mask or nasopharyngeal CPAP).
- Do not overstretch the head ("sniffing position"; neutral position), because the trachea is short and soft and would otherwise be bent!
- straight laryngoscope blade (Foregger)
- The epiglottis is lifted on the blade (in contrast to the adult).
- orotracheal (for non-pediatricians)
- tube
  - unblocked (blocked tubes are also possible, but usually not necessary in children under 8 years of age [exception e.g. status asthmaticus, where higher ventilation pressures are necessary]); S1-guideline "Prehospital airway management" 2019 of the the German Society of Anaesthesiology and Intensive Care Medicine and ERC guidelines 2021: Prehospital only blockable tubes should be used in children, since this can reduce the risk of dislocation of the tube, which is higher out-of-hospital than in-hospital.)
  - size in newborns: 3.5
- tube marking at 9-10 cm from the alveolar ridge (cave: only short trachea [3-4cm]), fixation with plaster strips
- formulas:
  - tube size ~ thickness of the little finger (of the child)
  - inner diameter in mm = week of pregnancy (WOP) / 10 (for newborns)
  - inner diameter in mm = 4 + age/4 (with blocked tubes 0.5 smaller)
  - tube depth (cm) = 3 x inner diameter
- after ROSC connection to the ventilator (e.g. Dräger Babylog 2000; ventilation mode IPPV, max. pressure 25 mbar)
- ventilation frequency (if invasively ventilated via a ventilator during resuscitation; according to the results of the prospective multicenter observational study by Sutton et al, Crit Care Med 2019 now also recommended in the ERC guidelines 2021):
  - 1st year of life: 25/min
  - 1st-8th year of life: 20/min
  - 8th-12th year of life: 15/min
  - > 12th year of life: 10/min
- Mask ventilation often causes a pronounced hyperinflation of the stomach, so that after intubation ventilation may be difficult (extrathoracic restriction). Therefore, a

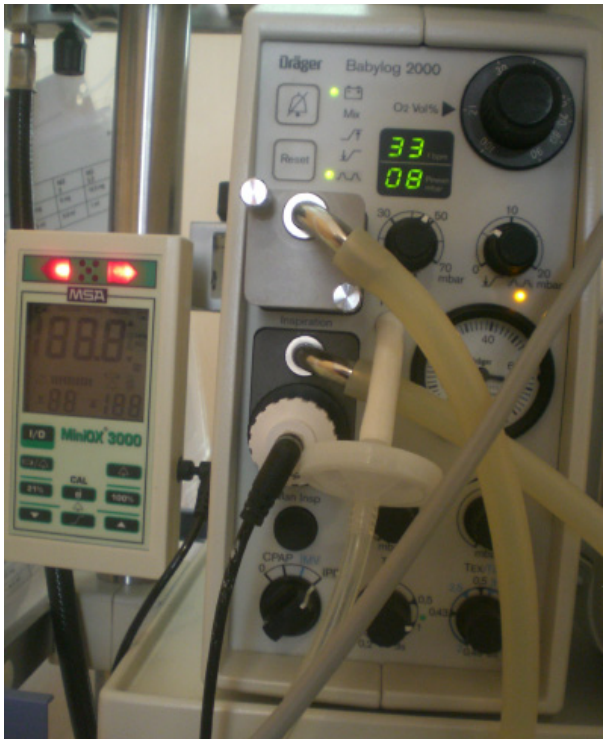


Fig. 495 ventilator for children (here as an example Babylog 2000, Dräger)

Intubation alternatives

- non-invasive:
  - laryngeal mask (very simple and effective option) - sizes:
    - < 5kg (e.g. newborns; possible from a birth weight of 1500g or 34th WOP): size 1 (filling volume: 4ml)
    - 5-10kg: size 1.5 (filling volume: 6ml)
    - 10-20kg: size 2 (filling volume: 10ml)
    - 20-30kg: size 2.5 (filling volume: 14ml)
    - 30-50kg: size 3 (filling volume: 20ml)
  - laryngeal tube: ☹ not suitable for infants, as the larynx is too high (not recommended for children < 2 yeras)
  - nasopharyngeal CPAP (good especially for infants): A normal tube (e.g. size 3.5) is inserted blindly (i.e. without laryngoscope) through a nostril (lubricated with silicone beforehand) 5cm wide. The end of the tube is then approximately at the level of the soft palate (supraglottic). Then the other nostril and the mouth is covered and the patient is ventilated via the tube adapter. If the stomach gets hyperinflated during ventilation, the tube is too deep in the esophagus, so that it should be pulled back a few centimeters. The insertion depth corresponds to the distance from the earlobe to the tip of the nose.
- invasive:
  - transtracheal puncture
  - coniotomy: In the newborn there is almost no space between the cricoid and the thyroid cartilage, so that a coniotomy in newborns is usually not possible. If necessary, a tracheotomy must then be performed.

very simple and effective alternatives to intubation (besides bag mask ventilation) in the newborn: laryngeal mask or nasopharyngeal CPAP!!

Fig. 496 laryngeal mask size 1 (is blocked with 4ml of air): a very good alternative to intubation in the newborn

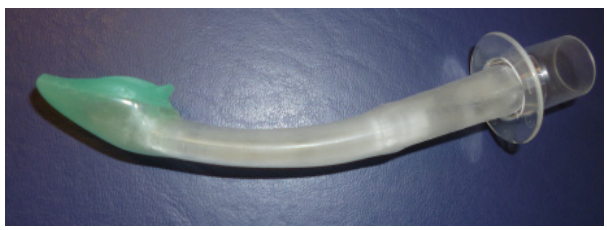


Fig. 497 I-Gel-mask

Fig. 498 nasopharyngeal CPAP: a very elegant and effective alternative to intubation

Ranking of the importance of ventilation in children:
1. BMV (bag mask ventilation)
2. laryngeal mask, nasophyryngeal CPAP
3. intubation (only in the last place!)

TTM-2 study

Hypothermia versus Normothermia after Out-of-Hospital Cardiac Arrest
Dankiewicz et al, N Engl J 2021

- international multicenter randomized controlled study
- 1850 (the largest study on hypothermia [twice the size of the TTM-1 study]) unconscious patients after out-of-hospital cardiac arrest (OHCA):
  - hypothermia (target temperature: 33°C for 24 hours; 925 patients)
  - normothermia (only goal of avoiding fever ≥ 37.8°C [Only then was the temperature actively lowered.]; 925 patients)
- 🙁 results: hypothermia
  - primary endpoint (mortality after 6 months): no difference (hypothermia: 50%, normothermia: 48%)
  - secondary endpoints:
    - ◦ neurological outcome (mRS [modified Rankin Scale] ≥ 4 P.): no difference
    - ◦ significantly more hemodynamically relevant cardiac arrhythmias (especially bradycardia)
- annotations:
  - Bystander CPR was performed in 78%.
  - Although the target temperature should have been reached after 90 minutes, it was only reached after an average of 5 hours in every second patient. The randomization took place only after 3 hours. In the end, the patients were only in the target area for 18 hours (and not for 24 hours).
  - 46% of the patients in the normothermia group (goal of avoiding fever ≥ 37.8°C) required active temperature management.
  - Withdrawal of life supporting therapies (WLST) already took place if 2 prognostic factors were present (pupils on both sides without a light reaction, NSE > 90 µg/l, lack of median SSEP on both sides, EEG: burst suppression, possibly zero line, CCT: GWR < 1), while according to the S1 guideline "Hypoxic-ischemic encephalopathy" of the German Society for Neurology (DGN) 2018 at least 3 prognostic factors are required for this.
  - In contrast to the TTM-1 study, patients with shock were also included.

HYPERION study

Targeted Temperature Management for Cardiac Arrest with Nonshockable Rhythm
Lascarrou et al, N Engl J 2019

- multicenter (25 centers in France) randomized-controlled study (intervention study; open-label)
- 584 comatose patients after resuscitation after cardiovascular arrest (in 75% OHCA, in 25% IHCA) at a non-shockable rhythms (asystole, pulseless electrical activity [PEA]): for 24h
  - hypothermia (moderate; target temperature: 33°C)
  - normothermia (target temperature: 37°C)
- results: hypothermia
  - 🙂 survival with godd (p.d. Cerebral Performance Category [CPC] 1-2 P.) neurological outcome (after 90d; primary endpoint) → significantly increased (10.2% versus 5.7%; absolutely by 4.5%, relatively by 80%)
  - mortality: no difference (survival rate after 3 months: 18%)

"Be hot - cool down" ((always cool after successful resuscitation!) - as soon as possible!

Indications

- In the ERC guidelines of 2005, hypothermia was only recommended after resuscitation for ventricular fibrillation. In the ERC guidelines since 2010 it is recommended after every successful resuscitation regardless of the initial rhythm (both in ventricular fibrillation and asystole; i.a. Testori et al, BJM 2010: resuscitation in asystole / EMD → significantly lower mortality and better neurological outcome due to hypothermia; i.a. HYPERION study 2019 [see box]).
- ERC guidelines 2010 + 2015 + 2021: Unconscious adult patients with spontaneous circulation after prehospital (accoring to guidelines; applies also to in-hospital) cardiac arrest should be cooled for 24 hours regardless of whether the initial rhythm was shockable or not (i.e. hypothermia after both ventricular fibrillation and asystole! After all, the brain does not really care what kind of rhythm disturbance caused its hypoxia!).
- also recommended in cardiogenic shock (These patients were excluded in the two large hypothermia studies.) after successful resuscitation (i.a. Skulec, Acta Anaesthesiol Scand 2008; Zobel et al, Crit Care Med 2012; COOL-Shock study [Schmidt-Schweda et al, Resusc 2013]: even improved hemodynamics [cardiac output ↑, CPO [cardiac power output] ↑])
- also recommended (ERC since 2010) for children and asphyxial (mature) newborns (peripartum ischemic encephalopathy)
- not mandatory if the resuscitation time is short (< 5min)

ACUTE CORONARY SYNDROME

Classification

According to a proposal by the European Society of Cardiology (ESC) and the American College of Cardiology (ACC), acute coronary syndrome has been divided into the following 3 groups since 2000:

- STEMI (ST-elevation myocardial infarction): with ST-elevations (exact: persistent, i.e. > 20min)
- NSTEMI (Non-ST-elevation myocardial infarction): without (persistent) ST-elevation, but positive troponin
- unstable angina pectoris: by definition troponin negative (twice); definition unstable angina pectoris: first event (de novo angina), symptoms at rest, increase in duration, intensity or frequency

To simplify matters, the division can also be made into:

- STE-ACS (acute coronary syndrome with ST elevation myocardial infarction)
- NSTE-ACS (acute coronary syndrome without ST elevation myocardial infarction)

The earlier division into Q-wave and non-Q-wave infarcts is obsolete, since Q-waves only develop after about 12h and can occur in both STEMI and NSTEMI.

As a counterpart to acute coronary syndrome, there is now also the term chronic coronary syndrome (i.a. ESC Guidelines for the diagnosis and management of chronic coronary syndromes 2019) instead of the term stable coronary heart disease (CHD).

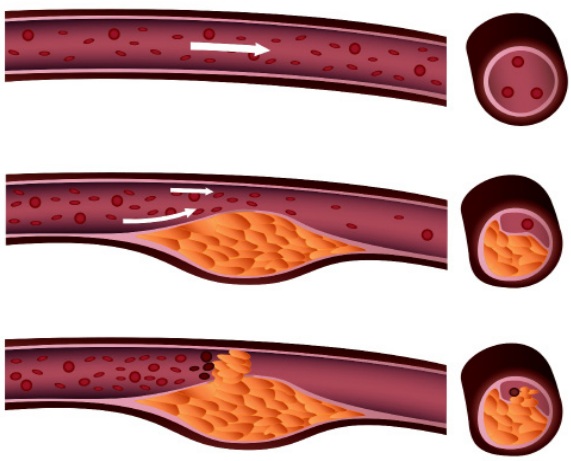


Fig. 550 Pathophysiology of acute myocardial infarction: Plaque rupture and consecutive thrombotic occlusion of the coronary vessel occur.

Epidemiology

CHD (coronary heart disease) is the most frequent fatal disease in industrialized nations like Germany before malignancies (No.2) and stroke (No.3) and is responsible for 13% of all deaths. Approximately 300 infarcts / 100,000 inhabitants occur per year with about 140000 deaths annually. Myocardial infarctions occur more frequently in the 5^{th}-6^{th} decade of life. Myocardial infarction is the most frequent cause of cardiovascular arrest and thus the most frequent reason for resuscitation. The probability of suffering a myocardial infarction in the course of life (lifetime prevalence) is 30% for men and 15% for women. At an age below 75 years, men predominate, at an age above 75 years, women are at higher risk (each in a ratio of 2:1). The mortality rate of myocardial infarction is still 16% despite all the progress made. If the evaluation of death certificates with a suspected myocardial infarction is included in the statistics, the mortality rate is even 50%. The main mortality is pre-hospital. More women (52%) die of heart attacks than men (48%). The mortality rate in women is almost twice as high as in men ("Eva infarction"), partly due to the frequently atypical clinic and the associated delayed diagnosis. Early mortality in NSTEMI is ten times lower than in STEMI, but the cumulative mortality after one and two years is just as high as in STEMI. After four years, the mortality in NSTEMI is even twice as high as in STEMI (mainly due to the higher age and comorbidities). In an observation study (Yeh et al, N Engl J 2010) on 46086 North American patients, both the myocardial infarction rate and myocardial infarction mortality decreased by 24% during the observation period 1999-2008. The incidences were 70/100,000 for STEMI and 132/100,000 for NSTEMI. ACS is the second most frequent emergency medical intervention with a fraction of approximately 20% (after the seizure). 30% of all patients presenting with thoracic pain in the emergency room have acute coronary syndrome.
The average pre-hospital time in Germany is 225 min (GOAL register) and has even increased over the last 10 years (1995: 160 min) despite all efforts to educate patients. The main loss of time lies in the extended time between the onset of symptoms and the patient's emergency call. 40% of all infarctions occur in the early morning hours (12 PM-6 o'clock AM; due to the sympathicoadrenergic activation). In 30% an acute myocardial infarction occurs in previously asymptomatic patients (in the sense of a first manifestation of CHD). Unfortunately in Germany it is still the case that despite all the discussion about thrombolysis and PTCA, 40% of STEMI patients do not receive any reperfusion therapy at all. According to data from the German Heart Attack Register 2013, however, the proportion has decreased to 10%

Epidemiology:
STEMI (1/3) ↓
NSTEMI (2/3) ↑

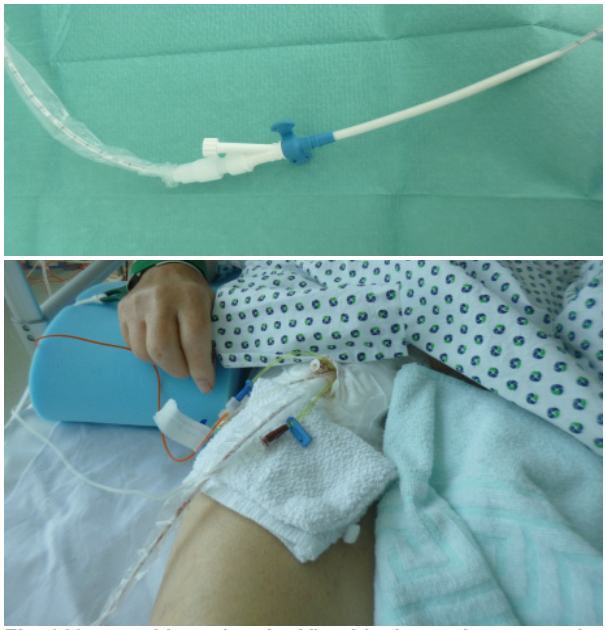


Fig. 616 reposition sheath: Via this he catheter can be pulled back and forth over a sterile protective cover after opening the Tuohy valve, thus correcting the position of the Impella.

Fig. 617 Impella 2.5

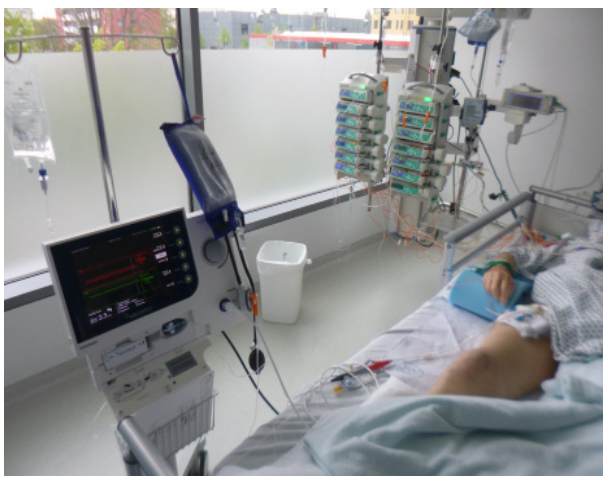


Fig. 618 Impella 5.0

Contraindications

- aortic valve vitium:
  - aortic valve stenosis with valve opening area < 1.5cm^2 (moderate)
  - aortic valve regurgitation (from moderate; the catheter in the aortic valve itself induces a mild aortic valve regurgitation)
- hypertrophic obstructive cardiomyopathy
- mechanische Aortenklappenprothesemechanical aortic valve prosthesis
- ascending aorta aneurysm
- ventricular septal defect (e.g. after infarction)
- thrombus in left ventricle
- PAD (severe)

Control

- performance levels (p):
  - p1-p8 (maximum)
  - The goal is the maximum setting to relieve the ventricle as much as possible.

- p2: neutral run rate (effectively no more support here [only compensates the mechanically induced aortic valve regurgitation by the catheter; therefore never set lower than p2])

- position control
  - by curves on the monitor:
    - placement signal (above; red; unit: mmHg): It indicates the position of the outlet. This should be in the aorta. The signal should be configured pulsatile and aortic (i.e. diastolic pressure present). If it is configured ventricularly (i.e. no diastolic pressure present), the pump has slipped too far into the left ventricle and must be withdrawn.
    - motor current curve (below; green; unit: mA): This should be pulsatile. The pulsatility comes from the fact that the current consumption in the systole is higher than in the diastole. If it is flat, the pump does not work and there is no support because it has no pressure gradient to overcome. This is because both the inlet and outlet are in the same area: either both in the ventricle (ventricular placement signal → The pump must be withdrawn.) or both in the aorta (aortic placement signal → The pump must be pushed forward.). Since a flat curve means that the pump is not working and therefore there is no mechanical circulation support, the pharmacological circulation support (catecholamines) must always be increased.
  - by echocardiography
    - B-mode:
      - The inlet should be in the left ventricle 3.5 cm in front of the aortic valve (exactly: aortic valve annulus).
      - The tip of the pump should be in the area of the apex of the heart. It should lie free here, d.h. without contact to the wall. The mitral leaflets (especially the anterior mitral leaflet) should not be disturbed in their movement.
    - color Doppler: Aliasing (mosaic pattern; due to the blood being ejected through the outlet) should only be recognized after the aortic valve, not in or in front of the aortic valve.
  - by chest X-ray
- purge: flushing of the motor
  - To prevent blood from entering the motor and cooling it, it is purge with an infusion solution containing glucose (to increase viscosity; mostly G5%) and heparin (usually 10 IU UFH per ml).
  - purge flow: 3-30 ml/h (standard: 15 ml/h)
  - purge pressure: 300-1100 mmHg
    - purge pressure too high:
      - leak
      - too high glucose concentration in the purge solution
    - purge pressure to low:
      - kink
      - too low glucose concentration in the purge solution
- suction alarm (possibly oscillations in the motor current curve) → always first (until the cause is clarified and corrected) reduce the performance level by 1-2 levels)
  - causes:
    - ventricular filling too low (preload too low; Impella depends on preload) → fluid administration
    - incorrect position → repositioning (under echocardiographic control)
    - right ventricle failure
  - consequences:
    - The Impella flow is less than expected.There is an average expected flow rate for the respective Impella version for each performance level, which can be found in the corresponding tables of the company.
    - only insufficient circulatory support
    - hemolysis
- heparin perfusor (UFH) according to target-ACT 160-180s or target-PTT 50-70s (if HIT II: argatroban systemically [but not locally in the purge solution; here then only glucose without heparin])

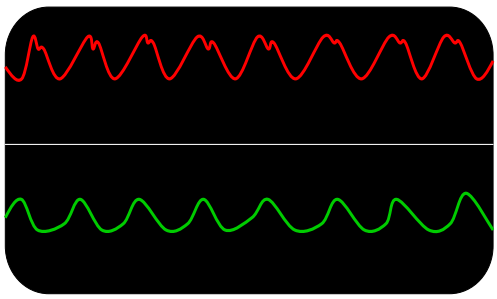


Fig. 619 curves on the display of the control console monitor: above (red) the placement signal, below (green) the motor current curve. The placement signal is configured correctly to be pulsatile and aortic, i.e. the diastolic pressure is significantly greater than zero. The position of the pump is correct. The motor current curve is also normally pulsatile.

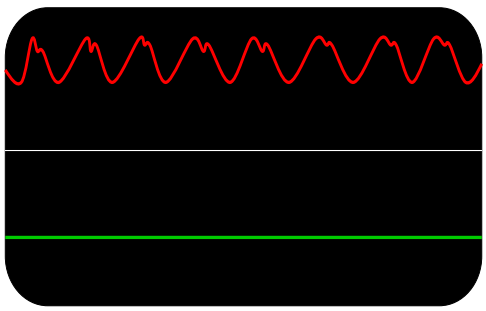


Fig. 620 The motor current curve (green) is flat, i.e. both openings (inlet and outlet) are in the same area. The placement signal (red) is configured aortally, i.e. both openings are in the aorta. The pump has slipped out of the left ventricle (most common cause: Valve was not screwed shut.) and must be pushed forward. Procedure: reduction of performance to p2, increase in catecholamines, then repositioning under echocardiographic control

Lewis lead

- definition:
  - a modified 12-lead ECG derivation, with which one can better assess the atrial excitation (atrial actions; P wave discrimination)
  - named after the British cardiologist Sir Thomas Lewis (1881-1945; originally developed to better detect atrial fibrillation waves)
- procedure (goes very quickly!): You apply a normal 12-lead ECG (note: also possible on the monitor ECG). The chest leads remain unchanged. The limb leads are changed at 3 of the 4 positions:
  - electrode right arm (red) → to the manubrium sterni
  - electrode left arm (yellow) → to the right of the lower egde of the sternum (5th ICR parasternal right)
  - electrode right leg (green) → lower right costal arch
  - electrode left leg (black; "mass") → remains
- interpretation: The lead I is called a Lewis lead. It runs exactly through the atrium. This is the best lead to identify and assess atrial actions, because this lead is parallel to the atrial vector. However, it is perpendicular to the ventricular vector, so that the atrial actions can be assessed better, the ventricular actions, however, can be assessed more poorly.
- indication:
  - unclear basic rhythm (possibly P waves recognizable in the Lewis lead?)
  - unclear regular tachycardia
    - unclear regular narrow complex (possibly flutter waves recognizable in the Lewis lead?)
    - unclear regular wide complex (differential diagnosis VT / SVT: possibly AV dissociation as evidence of VT recognizable in the Lewis lead?)

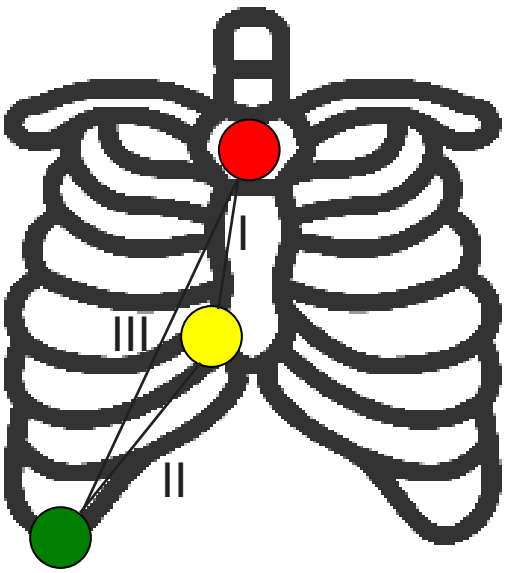


Fig. 673 modified ECG derivation according to Lewis to better assess atrial actions (a special atrial lead): 3 of the 4 limb leads are glued to a different location: on the sternum manubrium, on the lower right edge of the sternum and on the lower right costal arch. The Lewis lead is the lead I: It runs directly through the atrium and is best suited for analysis of atrial actions.

Therapy (regular narrow complex tachycardia)

- vagal maneuver (e.g. carotid sinus massage)
  - terminates AV node reentry tachycardia and orthodromic AV reentry tachycardia
  - demasks atrial flutter
- adenosine (Adrekar)
- digitalis
  - e.g. digoxin (Lanicor) 0.5mg, 0.25mg, 0.25mg (30min interval)
  - effect more after clinic (less after drug level)
  - cave:
    - ectopic atrial tachycardia (digitalis intoxication as a frequent cause!)
    - contraindication in atrial fibrillation in WPW syndrome
  - not listed at all in the ESC Guidelines 2019 for the management of supraventricular tachycardia
- verapamil (Isoptin) 2.5-5mg (max. 20mg) slowly i.v. (not in combination with β-blocker or in patients pretreated with β-blocker and also not in systolic heart failure [HFREF])
- β-Blocker
  - long-acting: metoprolol (Beloc) i.v. (slowly 1-3mg repetitively up to max. 15mg)
  - short-acting: esmolol (Brevibloc, Esmocard) 40-50mg (exactly: 0.5 mg/kg; over 1min) i.v.
  - ultrashort-acting: landiolol (Rapibloc)
- amiodaron (Cordarex) 150-300mg i.v. or as short infusion (in 250ml G5%)
- R-wave triggered cardioversion in short anesthesia
- with atrial flutter possibly atrial overdrive pacing

Adenosine (Adrekar)

- an endogenous purine nucleoside (a body's own substance)
- 1 amp. = 6mg; new: 1 amp. = 10mg
- agonist at the A_1 and A_2 receptor
  - A_1 receptor: sinus and AV node; activation leads to negative chrono- and dromotropy
  - A_2 rezeptor: smooth musculature; activation leads to vasodilation
- dosage: 5, 10, then 15mg (children: 0.2 mg/kg)
- ⚠ One must see an AV block in the monitor ECG, otherwise the applied dose was insufficient!
- application as close to the heart as possible (e.g. in the cubital fossa or CVC [if available]) quickly i.v. (10ml NaCl 0.9% immediately afterwards; $T_{½}$ only 8 sec) [Adenosine is rapidly deaminated to inosine, which is no longer active.])
- side effects:

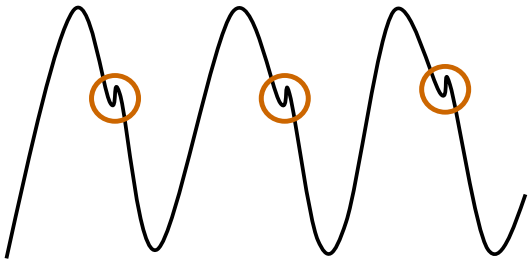
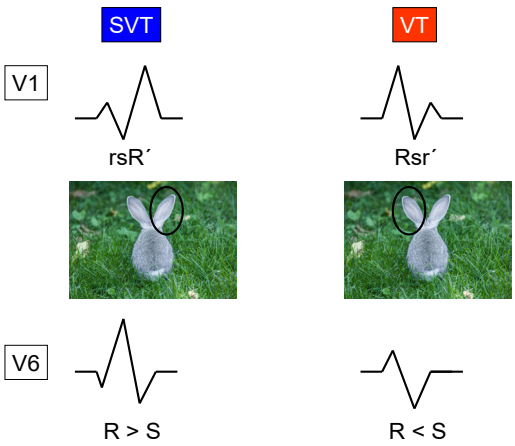
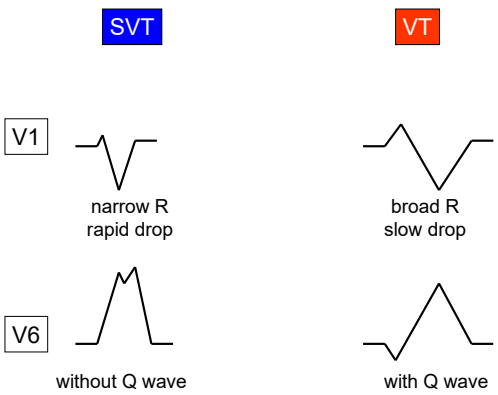


Fig. 685 The Josephson's sign is defined as a notch in the descending part of the S wave of the QRS complex. It indicates a ventricular tachycardia in the presence of a wide QRS complex tachycardia.



right bundle branch block

Fig. 686 Wide QRS complex tachycardia with right bundle branch block: The chest wall leads V1 and V6 are considered. A rsR´-configuration in V1 (right rabbit ear, i.e. the second spike is higher than the first spike [typical RBBB]) indicates a SVT, a Rsr´-configuration (left rabbit ear, i.e. the first spike is hiherer than the second spike [atypical RBBB]) indicates VT. If the R wave in V6 is larger than the S wave, it speaks for an SVT. If the R wave is smaller than the S wave, this speaks for a VT.



left bundle branch block

Fig. 687 Wide QRS complex tachycardia with left bundle branch block: The chest wall leads V1 and V6 are considered. A narrow R wave with a rapid drop from RS in V1 speaks for an SVT, a wide R wave with a slow drop in RS speaks for a VT. If there is a Q wave in V6, this speaks for a VT. If this is not the case, this speaks for an SVT.

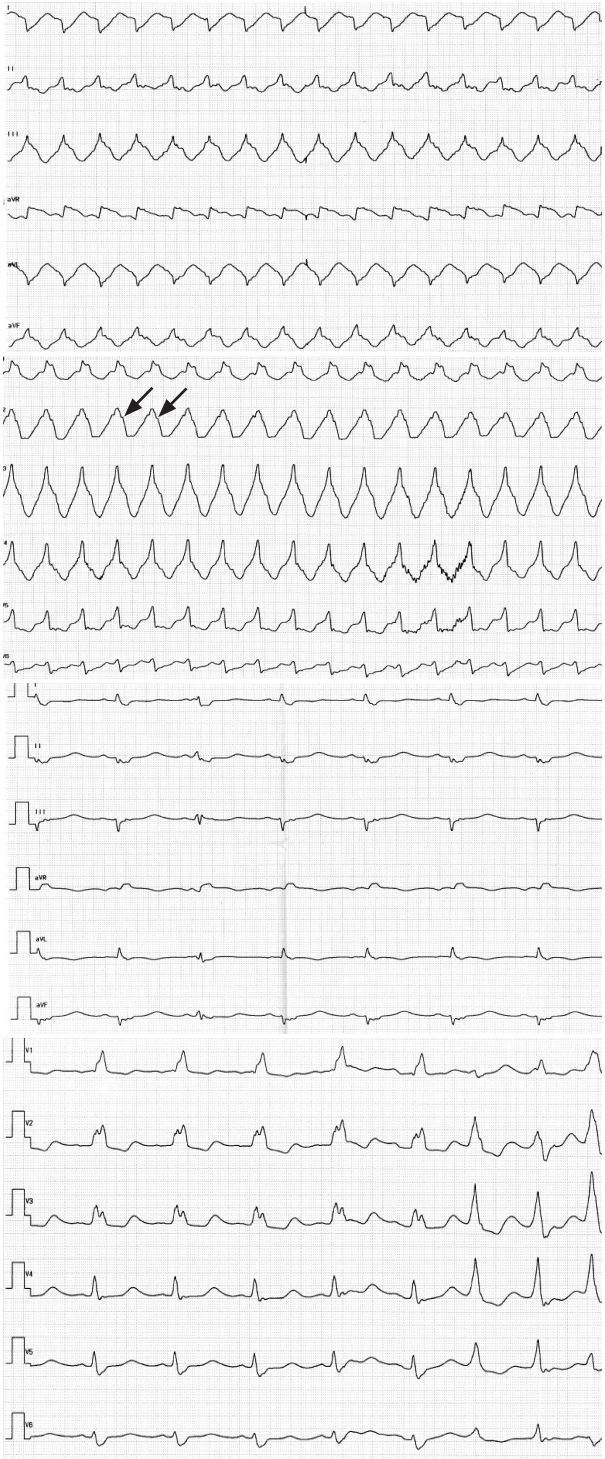


Fig. 688 right bundle branch block with left rabbit ear (Rsr´-configuration; 2 spikes in V1, of which the first spike is larger than the second spike [atypical RBBB]) and R < S in V6, Josephson´s sign (see arrows), positive concordance (consistently positive QRS complexes in all chest wall leads) and positive aVR: All of the criteria mentioned speak for ventricular tachycardia. The tachycardia-free ECG (after electrical cardioversion) also shows a right bundle branch block, but here with a right rabbit ear (rsR´-configuration [typical RBBB]). You can also see the significant change in the axis: Whereas the tachycardia-free ECG shows a LAD (left axis deviation), the tachycardia ECG shows a RAD (right axis deviation).

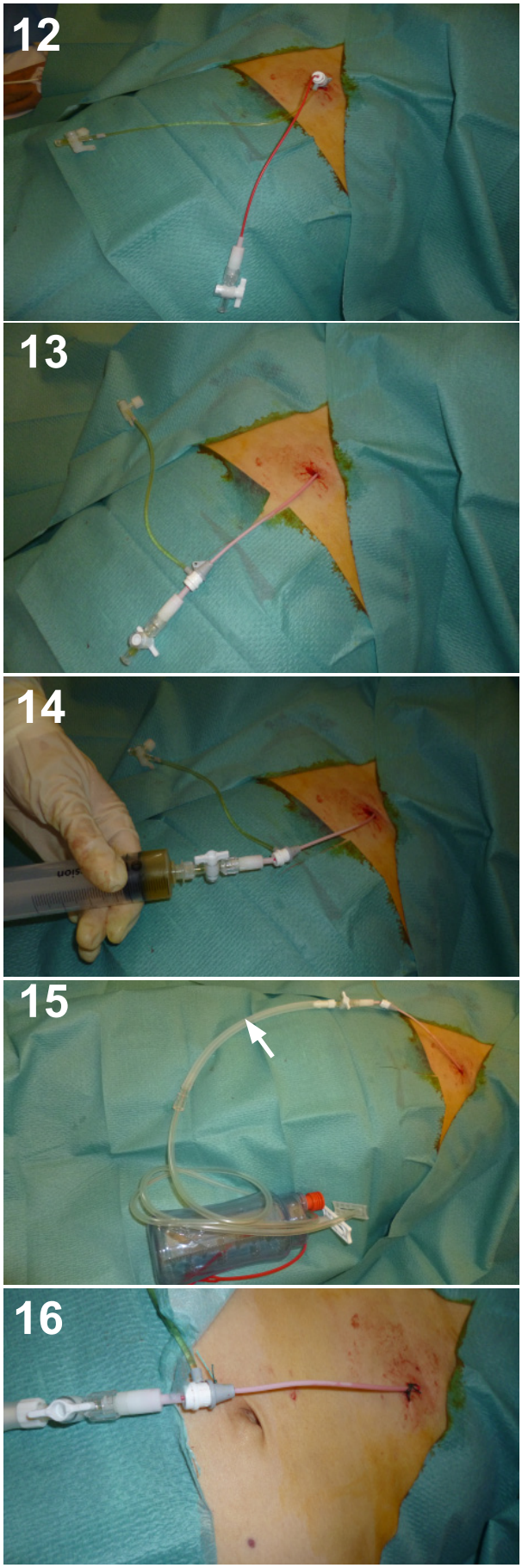
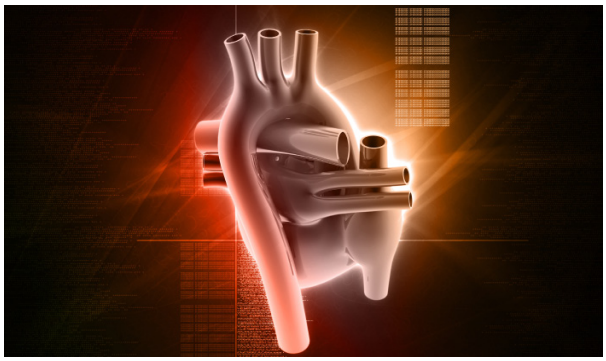


Fig. 801 The individual steps of pericardiocentesis (pericardial puncture): After sterile wiping and masking with adhesive tissues (1), local anesthesia with xylocaine (2) is performed. Then a conventional Seldinger needle is used to puncture (3) from subxiphoidal position in the direction of the left shoulder almost parallel to the sternum, until finally fluid can be aspirated (4). A Seldinger wire is now advanced over the lying Seldinger needle (5) and the needle is finally pulled out. A small stab incision is made with the scalpel at the point of the entry of the wire. Then a 5F sheath is inserted over the wire (7, 8). Before this, the dilator is inserted into the sheath. After the sheath is inserted, the wire and dilator are removed. Pericardial effusion can already be removed on a trial basis using the side instruments of the sheath (9). A pigtail catheter is advanced through the check valve of the sheath (10-12). Then the sheath is retracted to skin level (13) while the pigtail catheter is completely advanced. Pericardial effusion can now be punctured via the pigtail catheter (14). The pigtail catheter is connected to a Redon bottle. A connection adapter is necessary for this. We use the Urotech catheter (15 [see arrow]; alternatively also possible: e.g. Can adapter, Renodrain). The sheath is sutured proximally and distally (16) and the connection point between pigtail catheter and sheath is secured with a patch strip (17). Finally, the suction of the Redon drain is opened and the pericardial effusion drains off (18).

Complications

- puncture of the ventricles (mostky right ventricle):
  - in case of uncertainty (especially in hemorrhagic pericardial effusions), whether one is actually in the pericardium or the heart (e.g. in the ventricular cavity) or in a vein
    - 2ml syringe (BGA): hemoglobin, oxagen saturation; comparison with previously taken values
    - injection of X-ray / echo contrast medium (e.g. 5-10ml shaken NaCl 0.9%)
  - If it is confirmed that the right ventricle has been punctured, this is usually harmless, but one should not advance the sheath. If the sheath has already

ACUTE AORTIC SYNDROME



Definition

- acute chest pain (the 3 most important differential diagnoses):
  - acute coronary syndrome
  - acute pulmonary embolism
  - ⚠ acute aortic syndrome
- classification according to Svennson
- guidelines: ESC guidelines on the diagnosis and treatment of aortic diseases 2014

Svennson classification
acute aortic syndrome

- **Svennson type I: classic dissection**
- **Svennson type II: intramural hematoma (IMH)**
- **Svennson type III: local dissection**
- **Svennson type IV: penetrating aortic ulcer (PAU)**
- **Svennson type V: traumatic or iatrogenic dissection**

Acute aortic dissection (Svennson type I)

Definition

- rear of the intima layer of the aortic wall with dissection
- structure of the aortic wall:
  - intima (endothelium, basal membrane, connective tissue)
  - media (elastic fibres, musculature)
  - adventitia: connective tissue, vessels, nerves
- mostly hypertensive blood pressure situation
- Contrary to frequent opinion, the aorta in aortic dissection is not dilated previously (in 80%), i.e. there is no pre-existing aortic aneurysm.

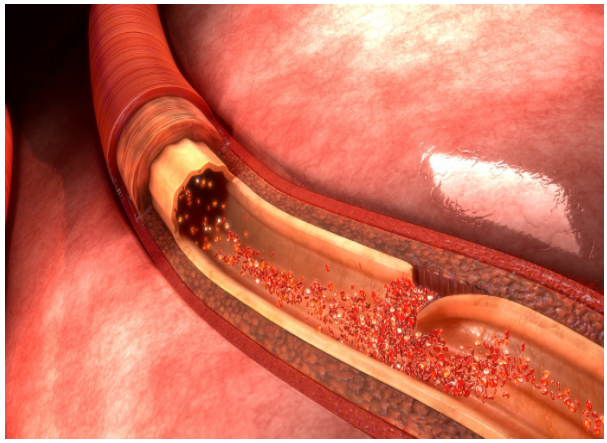


Fig. 867 aortic dissection: schematic illustration of the intimal tear

Pathophysiology

- first tear (entry) into the intima layer of the aortic wall (in 90% ventral)
- Most dissections (65%) have their origin in the proximal ascending aorta immediately after the aortic valve (mostly in the area of the ostium of the RCA), because this is where the load on the aortic wall is greatest due to the flow properties.
- intramural bleeding into the aortic wall (bleeding inside the media)
- splitting into an inner and outer layer of the vascular wall (dissection)
- The blood flow opens up a new path, a false lumen develops.
- spread of the dissection:
  - antegrade (towards distal; mostly)
  - retrograde (towards proximal; rarely)
- mostly second tear (reentry)

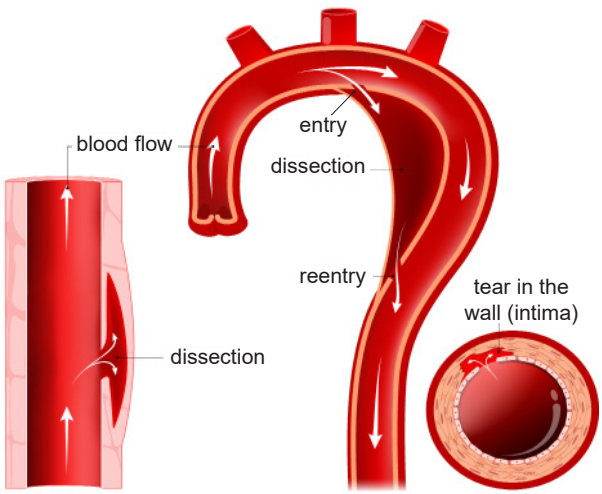


Fig. 868 aortic dissection: schematic illustration of the pathophysiology

mation that the oxygen device with tank will be delivered in three weeks. If a patient in intensive care in the BGA has a paO_2 of 49 mmHg, it is not uncommon for panic to break out (not that code blue alarm is almost triggered) and ventilation is forced to such an extent that VALI is unfortunately often generated. The Italian anesthetist Antonio Pesenti described ventilation as "a life saving procedure that can kill the lung". Actually one should prohibit BGAs in the ARDS (exaggeratedly formulated)! The most important thing about ventilation in ARDS is the motto: "Keep cool man!"

Fig. 931 To ventilate a damaged lung is similar to running a 400m run with a broken leg: You only have to go around the stadium round once here, so you have to do it slowly and don't want to set a world record with a super time, otherwise everything will break completely and you won't get 5 feet!

SpO_2 > 90%, paO_2 > 60 mmHg and $paCO_2$ < 70 mmHg completely sufficient! Most important: no damage to the lungs due to forced ventilation!

no BGA cosmetics at the ARDS! no atmo-centric therapy (not the BGA values are in the foreground, paO_2 is not the target parameter)! Improvement of oxygenation ≠ Improvement of survival!

Patients in ARDS rarely die of hypoxemia, but unfortunately often of the consequences of VALI!

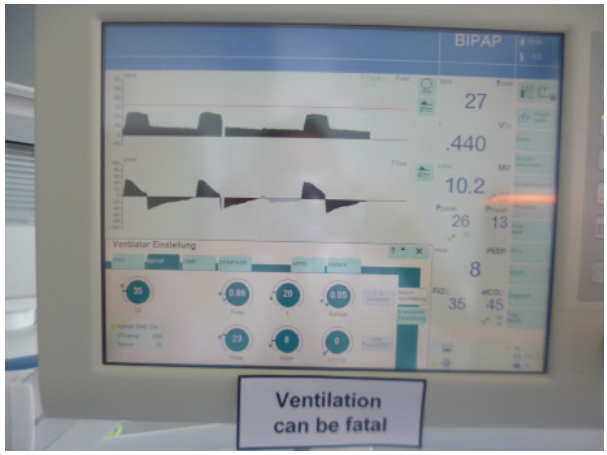
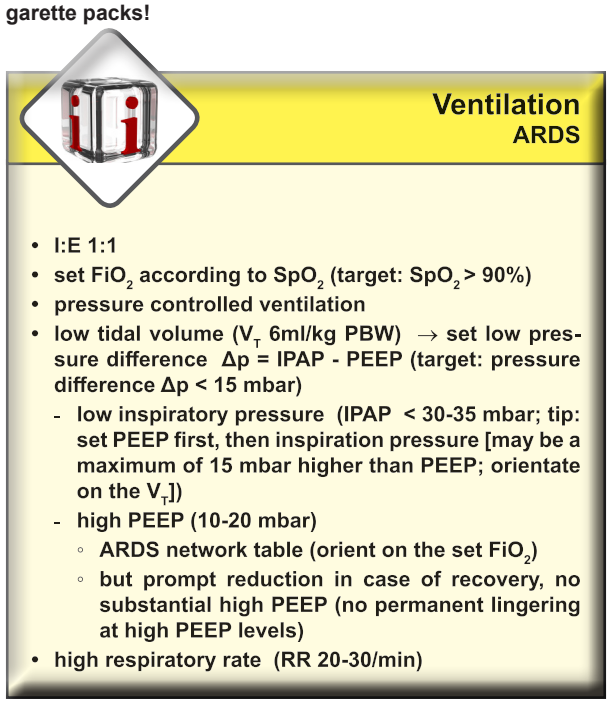


Fig. 932 The warning "Ventilation can be fatal" should be affixed to the ventilators in the intensive care unit (especially with ARDS) analogously to the inscription on the cigarette packs!



Recruitment maneuver

Definition

- maneuver to reopen closed (atelectatic) lung areas that are no longer participating in the gas exchange
- The clinically most common recruitment manoeuvre is (better: was) the Lachmann maneuver.
- effective especially in the early phase of an extrapulmonary ARDS

Types

- intermittent sighs (respiratory form in which several intermittent breaths with high inspiratory pressure and PEEP are applied at a set frequency per hour, resulting in hyperinflation of the lung and recruitment of atelectatic areas)
- airway-pressure-release-Ventilation (APRV):

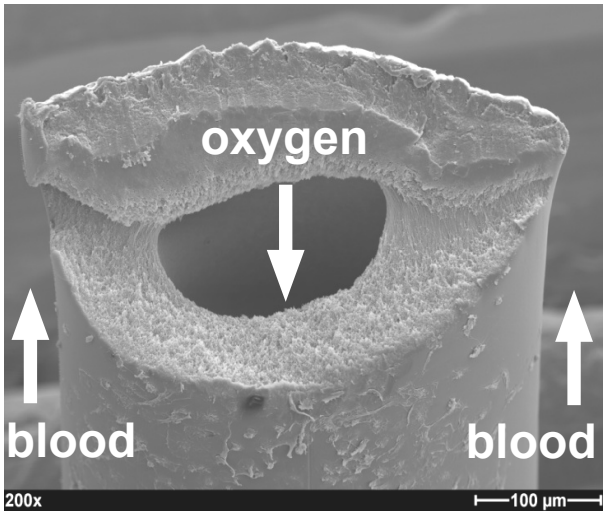


Fig. 938 scanning electron microscopy of a membrane (oxygenator): It consists of numerous capillaries in which oxygen flows. The blood flows between the capillaries in tcountercurrent principle (courtesy of Mr. Alois Philipp, cardiotechnician at the Clinic for Cardiac, Thoracic and Cardiac Vascular Surgery of the University Hospital Regensburg [Germany]).

Pumps

- roller pump
  - mostly double bow roller pump
  - occlusive
  - disadvantage: increased hemolysis (very cell traumatic)
  - today obsolete
- centrifugal pump
  - impeller-driven pump (Impella)
  - today most frequently used
  - significantly less cell traumatic than roller pumps and thus significantly less hemolysis
  - non-occlusive (If the rotor is stops, the blood can flow in both directions. Therefore, the arterial line must be disconnected when the rotor is stopped!)
  - blood flow rate: 3.0-4.5 l/min (in weaning reduction to 1.0-1.5 l/min; note: The pump in a renal replacement procedure [e.g. Prismaflex] achieves a maximum of 500 ml/min, i.e. 0.5 l/min.)
  - measurement of the pump flow (electromagnetic or sonographic [Doppler])
  - rotational speed: up to 10000 rpm (rpm: revolutions per minute)
  - filling volume: 35-80ml
  - examples:
    - Centrimag (Levitronix)
    - Rotaflow (Maquet)
    - Capiox (Terumo)
    - Delphin (Sarns)
- axial pump
  - advantage: very small
  - disadvantage: increased hemolysis (very cell traumatic due to the high rotational speed)
- diagonal pump (e.g. Deltastream pump)

Cannulation

Definition

- Cannulation of the femoral vessels (vein and artery) is performed percutaneously according to the Seldinger technique and preferably under sonographic control. Cannulation of the subclavian artery is performed by open surgery using a vascular prosthesis.
- It should always be done in pairs: One punctures, the other takes care of the wire so that it always runs freely.
- A skin incision (e.g. stab incision with a scalpel before advancing the dilator) should be avoided as it can bleed during the course of the procedure. Under ECMO there is frequent bleeding anyway (e.g. frequent thrombocytopenia and thrombocytopathy, heparin perfusor).
- Two red blood cell concentrates should be available before cannulation.
- For cannulation (after successful placement of the guide wires) 5000 IU of heparin (UFH) are administered as i.v. bolus.
- Finally, the cannulas must be secured to avoid dislocation.
- As a rule, mobilization during ECMO therapy does not occur. However, kinetic therapy such as prone positioning (e.g. Kipping et al, Int J Artif Organs 2013) or CLRT (e.g. Knedel et al, Perfusion 2014) is possible with ECMO.
- Depending on the indication, cannulation (connection technique) is carried out veno-venously or veno-arterially. The blood is always withdrawn from a vein and then returned depending on the indication either to a artery (va-ECMO) or a vein (vv-ECMO) The machine is always the same.

Types

- according to location (exactly: according to the type of vessel into which the blood is returned)
  - veno-venous (vv-ECMO)
  - veno-arterial (va-ECMO)
- according to invasiveness (technique)
  - interventional (percutaneous)
  - surgical (open)

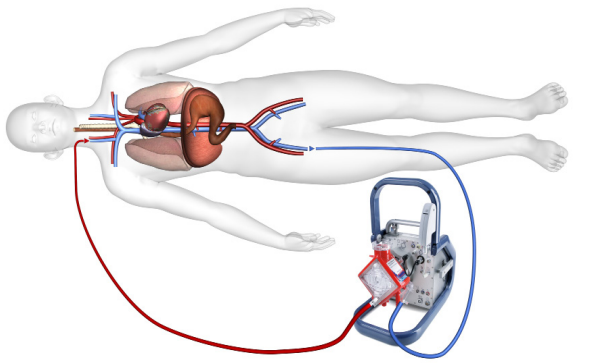


Fig. 939 ECMO veno-venous (vv-ECMO [23])

Pitfalls
Persistent hypoxemia

In case of persistent hypoxemia despite ECMO the following reasons should be considered:

- **recirculation: It may be that recirculation takes place. Indicative is an increase in saturation before the membrane oxygenator ($S_{pre}O_2$) on the one hand and a decrease in saturation after the membrane oxygenator, i.e. arterial saturation (S_aO_2), on the other hand. This is mainly the case if the tips of the cannulas are too close to each other. A distance of at least 20 cm is obligatory. For this purpose an X-ray or even better a CT should be performed. In case of recirculation the cannulas must be repositioned.**
- **oxygenator malfunction (e.g. too small, clotted → replace the oxygenator)**
- **pulmonary hypertension: As a result of the high PA pressure, the pressure in the right ventricle and thus in the right atrium is also increased. The blood oxygenated by the ECMO is returned to the body via the superior caval vein. However, if the pressure in the right atrium is high, the blood can flow out of the superior caval vein into the right atrium and therefore drains into the inferior caval vein (short circuit; shunt]). The ECMO is ineffective. Therapeutically, attempts can be made here to lower the PA pressure with right ventricular afterload-lowering (PAH-specific) drugs.**
- **pulmonary shunts → optimization of ventilation, possibly inhalation of selective pulmonary vasodilators (e.g. iloprost, NO)**
- **decreased oxygen transport (e.g. anemia → administration of RCC**
- **too high cardiac output (e.g. hyperdynamic circulation in the initial stage of sepsis; the higher the cardiac output, the higher the blood admixture of venous backflow blood after ECMO in the right heart, so that the oxygenation effect decreases! For sufficient oxygenation, the blood flow of the ECMO must be at least 60% of the cardiac output) → increase of ECMO blood flow, possibly hypothermia (35°C), possibly β-blockers (to reduce the cardiac output)**

Monitoring

- monitoring of the patient
- monitoring of the system

Monitoring (patient)

- ECG
- invasive blood pressure measurement
- urine production (diuresis)
- pulse oximetry (in va-ECMO always on the right arm)
- arterial BGA (in va-ECMO always on the right arm)
- laboratory: i.a. blood count, hemolysis parameters, D-dimers, fibrinogen, ACT or PTT (anticoagulation), CRP
- central venous oxygen saturation (target: > 70%)
- arterial cannulation:
  - femoral artery: NIRS (near infrared spectroscopy) with adhesive electrodes on the lower leg
  - subclavian artery: measurement of the extent of the ipsilateral arm (An increase indicates hyperperfusion. The blood flow can be reduced by pulling on a loop distal to the prosthesis anastomosis that was put on during the surgical cannulation.)
- temperature (cave: the heat exchanger automatically regulates the temperature and keeps it constant so that fever is masked under ECMO!)
- chest X-ray
- neuro-monitoring (cerebral) with NIRS (with adhesive electrodes on the forehead; for va-ECMO)

Monitoring (system)

- Pressure measurements: In the system 3 pressures are measured by default. The pressures must be zeroed once per shift (by opening the three-way valve to the atmosphere.
  - p_1: pressure before the pump (suction pressure; is always negative; standard: - 50mmHg)
    - If the negative pressure exceeds 80mmHg, the risk of hemolysis increases.
    - procedure if the suction pressure is exceeded:
      - reduction of the rotational speed (The cannula often sucks itself into the vessel wall when the blood flow is too high.)
      - retraction of the cannula (Possibly it lies against the vessel wall.)
      - intravascular fluid administration
  - p_2: pressure between pump and membrane (membrane pressure; the highest value in the entire system; usually < 250mmHg; membranes are approved up to approx. 450mmHg; an increasing membrane pressure is an indication of a clotting of the membrane)
  - p_3: pressure after the membrane (reperfusion pressure)
    - The difference between p_2 and p_3 is referred to as transmembrane pressure gradient. An increase of the transmembrane pressure gradient is an indication for a clotting of the membrane.
    - The pressure p_3 should always be lower than the pressure p_2.
- blood flow, pump rotational speed
- gas flow
- temperature
- inspection pump head, oxygenator

Weaning

Weaning from vv-ECMO

- If the gas exchange has improved (i.a. FiO_2 < 0.4; pO_2 > 80mmHg, pCO_2 < 45mmHg), the blood flow at the ECMO is reduced to 1.5 l/min and the gas flow to 1.0 l/min.
- If the patient is then stable (circulatory, respiratory [blood gases]), the gas flow is switched off for one hour Then the device is no longer effective. However, this may only be done with vv-ECMO and never with va-

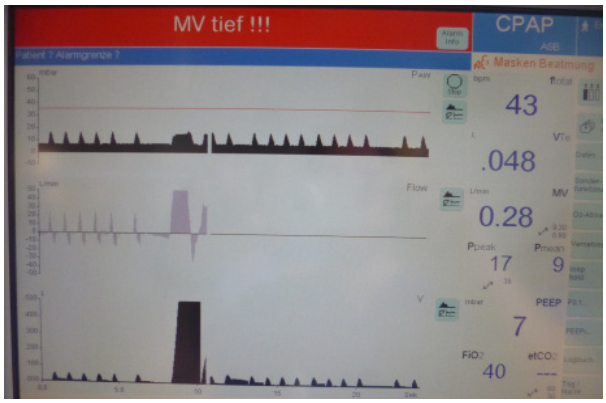


Fig. 1019 "missed efforts" during NIV with CPAP-ASB

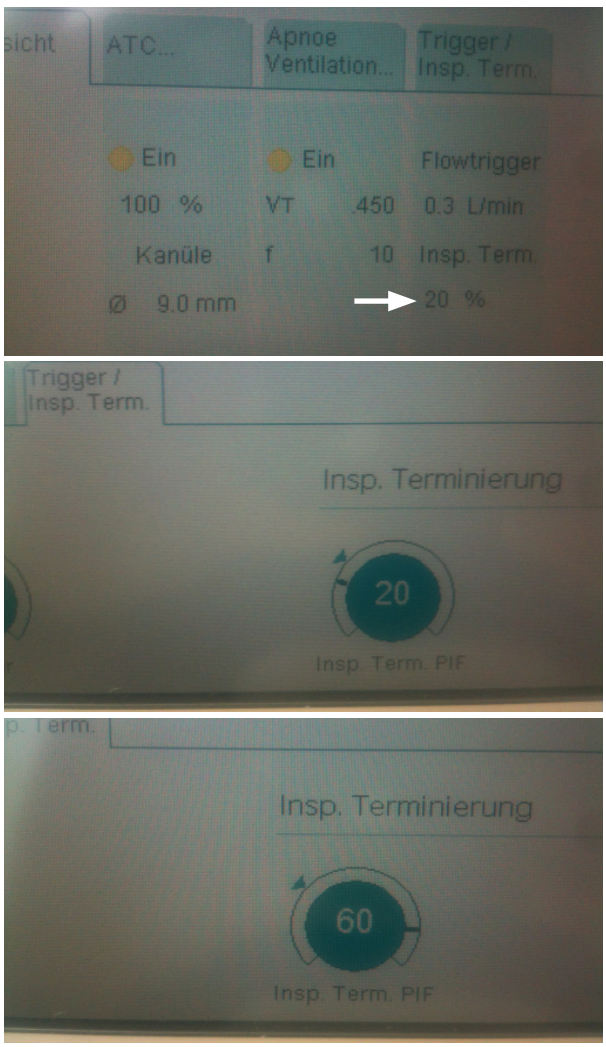


Fig. 1020 Changing the "cycling off" (expiratory trigger, inspiratory termination) from 20% to 60%: This allows the expiration time to be extended even further.

Mechanical ventilation
Obstructive pulmonary diseases

- **pressure controlled ventilation (inspiratory peak pressure < 35 cmH_2O)**
- **PEEP: measure intrinsic PEEP and therefrom set 80%**
- **low respiratory rate (10-12/min; high RR → overinflation!), for this permit higher tidal volumes (8-10ml/kg PBW)**
- **I:E 1:3 (set long expiratory time)**
- **trigger**
  - **inspiratory trigger (for spontaneous forms of breathing such as CPAP-ASB [e.g. under NIV], flow trigger): set low (0.25-0.5 l/min)**
  - **expiratory trigger ("cycling off"): change from 25% to 60% (to extend the expiratory time)**
- **short pressure rise time (0.1s; i.e. steep ramp; to reduce the work of breathing; especially in weaning and under NIV)**
- **ATC (automatic tube compensation; set to 100%; however only the inspiratory ATC [switch off expiratory ATC])**
- **perform decompression maneuver if necessary**

Extracorporeal decarboxylation ($ECCO_2$-R)

Types

- without pump (pumpless; av-$ECCO_2$-R [arterio-venous extracorporeal carbon dioxide removal]): pECLA (iLA; i.a. Kluge et al, Intensive Care Med 2013: iLA in NIV failure → 90% intubation avoided, but no effect on mortality [see infobox])
- with pump (pump driven; vv-$ECCO_2$-R [veno-venous extracorporeal carbon dioxide removal])
  - PALP (pump assisted lung protection; Maquet)
  - Hemolung (Alung)
  - Decap (Hemodec): a hemofiltration device in whose circuit a membrane for gas exchange is built in (only a Shaldon catheter needs to be installed; very low flow ECMO; i.a. Forster et al, Crit Care 2013; meanwhile no longer on the market)
  - ila activve (Novalung)

GASTROINTESTINAL BLEEDING

Classification

- upper gastrointestinal gastrointestinal bleeding (80%): proximal to the ligament of Treitz (duodenojejunal flexure)
- lower gastrointestinal gastrointestinal bleeding (20%): distal to the ligament of Treitz

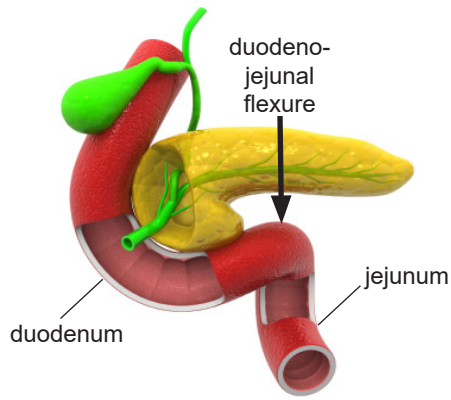


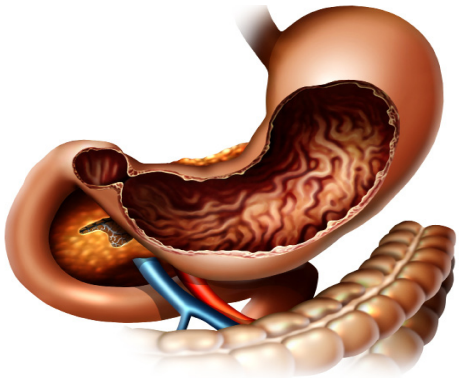
Fig. 1043 The duodenojejunal flexur (syn.: flexure of Treitz; starting point of the ligament of Treitz [named after the Czech pathologist Václav Treitz, 1819-1872; syn.: suspensory ligament of duodenum]) represents the boundary between the duodenum and jejunum and thus between the upper and lower GI tract.

The term mid gastrointestinal bleeding ("small intestinal" bleeding) is also becoming increasingly common: It is defined as bleeding from the ligament of Treitz to the Bauhin valve (= ileocecal valve). The most common cause of mid gastrointestinal bleeding are angiodysplasia followed by erosions / ulcers (especially with NSAIDs, Crohn's disease). Mid gastrointestinal bleeding is the least common and has the lowest mortality.

Guidelines

- national (Germany): S2k guideline gastrointestinal bleeding 2017 (German Society for Gastroenterology, Digestive and Metabolic diseases [DGVS])
- international (Europe): European Society of Gastrointestinal Endoscopy (ESGE) Guidelines
  - upper gastrointestinal bleeding:
    - non-variceal: Endoscopic diagnosis and management of nonvariceal upper gastrointestinal hemorrhage (2021)
    - variceal: Endoscopic treatment of variceal upper gastrointestinal bleeding (2020)
  - lower gastrointestinal bleeding: Diagnosis and management of acute lower gastrointestinal bleeding (2021)

UPPER GI BLEEDING



Causes

- ulcer (50%)
  - duodenal ulcer (No.1)
    - upper abdominal pain that gets better after eating
    - duodenal ulcer twice as frequent as gastric ulcer cause of bleeding
    - Also the probability of a recurrent bleeding is higher in duodenal than in gastric ulcer.
    - In the case of recurrent and therapy-refractory duodenal ulcers, you should also think of Zollinger-Ellison syndrome (gastrinoma) and determine gastrin in the serum (cave: false negative under proton pump inhibitors)!
  - gastric ulcer (No.2)
    - upper abdominal pain that gets worse after eating
    - in 4% upper GI bleeding due to a malignant ulcer (tumor bleeding, e.g. in gastric cancer, GIST)
  - esophageal ulcer (very rare)
  - anastomotic ulcer
  - Exulceratio simplex (= Dieulafoy´s ulcer [named closely to the French surgeon and pathologist Paul Georges Dieulafoy, 1839-1911]):
    - gastric ulcer, which arrodes a submucosal artery (vascular stump on normal mucous membrane)
    - can easily be overlooked (is frequently only discovered after several gastroscopies)
  - Cameron´s lesion
    - lomgitudinal ulcer (tear in the mucous membrane) in an (usually large) axial hernia
    - mechanically caused by sliding back and forth of the mucosa
    - rarely a cause of acute bleeding (more likely a cause of chronic blood loss [iron deficiency anemia])
- erosions (35%)
  - in the stomach → erosive gastritis (23%)
  - in the duodenum (mostly in the bulb) → erosive duodenitis (bulbitis; 6%)
- hemorrhagic necrosis (Among others after resuscitation, hemorrhagic necroses are found in almost all pati-

- esophageal varices → in 30% esophageal variceal bleeding
- spontaneous arrest of bleeding: only in 30% (usually only stops when the varices are empty and exsanguinated)
- ⚠ mortality: 30%
- ⚠ recurrent bleeding in 70% (mortality of recurrent bleeding: 70%)

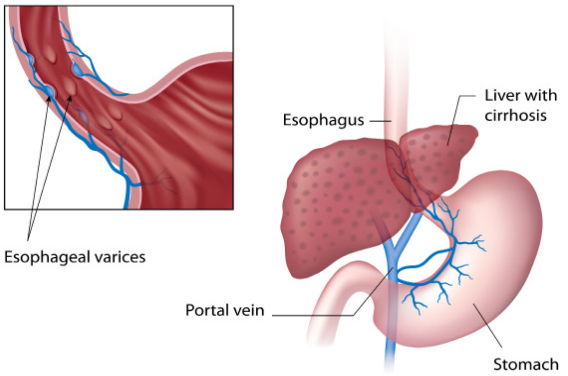


Fig. 1086 As a result of liver v, the blood from the portal vein can no longer flow into the liver. The congestion leads to portal hypertension. Bypassing circuits (porto-caval anastomoses) are formed (to the superior vena cava: especially via the gastric veins → esophageal veins; to the superior and inferior vena cava: i.a. via the umbilical veins; to the inferior vena cava: via the inferior mesenteric vein → rectal veins).

Types

- esophageal varices (90%)
- gastric varices (9%; especially fundal varices; classification according to Sarin → see infobox)
- duodenal varices (1%)

Classification according to Sarin

- **gastroesophageal varices (GOV)**
  - **GOV-1 (74%): esophageal varices that extend over the cardia into the corpus of the stomach (on the minor side, i.e. small curvature) → lower risk of bleeding**
  - **GOV-2 (16%): esophageal varices that extend over the cardia into the fundus of the stomach (possibly also into the corpus [on the major side, i.e. large curvature]) → higher risk of bleeding**
- **isolated gastric varices (IGV)**
  - **IGV-1 (8%): varices in the fundus (highest risk of bleeding among all gastric varices)**
  - **IGV-2 (2%): varices in all other parts of the stomach**

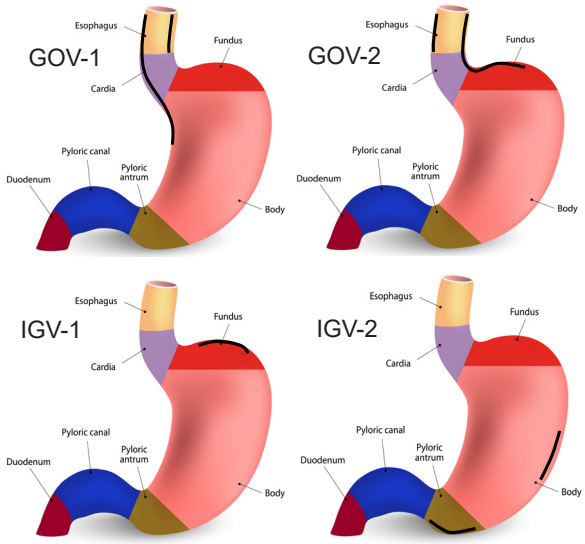


Fig. 1087 Sarin classification of gastric varices

Symptoms

- hematemesis
- tarry stool
- dizziness
- hypovolemic shock
- disturbance of consciousness; reasons:
  - reduced cerebral perfusion as a result of hypovolemic shock
  - hepatic encephalopathy (1000ml blood = 200g protein → $NH_3\uparrow$)

Predictors (variceal GI bleeding)

- liver disease (previously known)
- thrombocytopenia (platelets < 88000/µl)
- splenomegaly
- The lower the platelet count and the larger the spleen, the higher the probability of variceal bleeding: ⚠ ratio of platelet counts per µl / size of the spleen (longitudinal diameter) in mm < 909 → varicose bleeding (Colli et al, Cochrane Database Syst Rev 2017)!

Upper GI bleeding in liver cirrhosis

- variceal (50%)
- non-variceal (50%)
  - erosive gastritis
  - ulcer
  - reflux esophagitis
  - Mallory-Weiss syndrome
  - PHG (portal hypertensive gastropathy)
    - PHG can also bleed (mostly chronic blood loss, less acute bleeding)! Detection of portal hypertensive gastropathy is an indication for a non-selective β-blocker!
    - frequent cause for inappetence and thus cachexia in the cirrhotic patients
  - GAVE (gastric antral vasal ectasia)
    - "watermelon stomach"

Often, however, instead of the β-blocker therapy, ligation is already performed in the clinical routine for primary prophylaxis, because the compliance of the patients to take the β-blocker permanently is not infrequently low.

- liver cirrhosis without varices: no prophylaxis necessary
- portal hypertensive gastropathy → β-blocker

NEIC (north italian endoscopic club)

- **Child stage**
  - **A: 6.5 P.**
  - **B: 13 P.**
  - **C: 19.5 P.**
- **size of varices**
  - **small: 8.7 P.**
  - **medium: 13.0 P.**
  - **large: 17.4 P.**
- **red color sign**
  - **absent: 3.2 P.**
  - **persent**
    - **mild: 6.4 P.**
    - **moderate: 9.6 P.**
    - **severe: 12.8 P.**

bleeding risk per year

- **< 20 P.: 1.6%**
- **20-25 P.: 11%**
- **25-30 P.: 15%**
- **30-35 P.: 23%**
- **35-40 P.: 38%**
- **> 40 P.: 69%**

Pharmacological primary prophylaxis

- means of the choice: non-selective β-blockers (Only non-selective β-blockers lower the pressure in the portal vein circulation!)
- representatives:
  - propranolol (Dociton; 2 x 40mg up to 2 x 160mg; mean dose: 80 mg/day)
  - ⚠ carvedilol (Dilatrend; probably even better; 2 x 12.5-25mg)
- reduction of progression of size of the varices and incidence of bleeding (mortality ↓ by 30%)
- target:
  - decrease in heart rate by 25% (to max. 50/min) and reduction of SBP to 100 mmHg or
  - maximum tolerable dose
- response rate: 70%
- in case of contraindications against β-blocker (e.g. PAD [according to current guidelines no longer a contraindication!], bronchial asthma): :
  - ISMN (not a good alternative [Garcia-Pagan et al, Hepatology 2003])
  - ligation (especially in large varices)

Secondary prophylaxis

- Without secondary prophylaxis re-bleeding occurs in 60% within 2 years.
- ligation and β-blocker (for secondary prevention both, for primary prevention only one of the two)
- The combination of ligation and β-blocker reduces of the risk of recurrent bleeding from 70% to 15%.
- variceal eradication at the earliest 2 weeks after primary ligation therapy
- if necessary TIPS
- possibly statins (reduction of risk of variceal bleeding [Orman et al, AASLD 2013: Statins are associated with a decreased risk of variceal bleeding in compensated cirrhosis.])
- If necessary evaluation of liver transplantation (the only curative option!)

Primary prophylaxis: no combination therapy (β-blocker OR ligation)
Secondary prophylaxis: combination therapy (β-blocker AND ligation)

TIPS

Definition

- transjugular intrahepatic portosystemic shunt
- bypass connection between portal vein and hepatic veins (usually between right portal branch and right hepatic vein)
- goal: portal decompression (reduction of pressure in the portal vein circulation)
- first TIPS implantation 1988 by Roessle (University Hospital Freiburg [Germany])
- performance: approx. 2 liters/min

Types

- uncoated (high complication rate, occlusion rate by thrombosis after 1 year: 80%)
- coated: stents covered with PTFE (polytetrafluoroethylene [Teflon]; significantly higher rate of patency after 2 years [76% versus 36%; Bureau et al, Gastroenterology 2004])

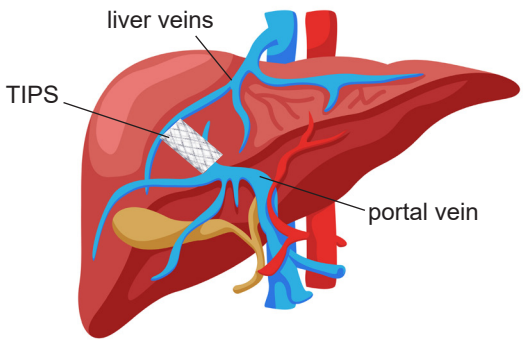


Fig. 1114 TIPS: bypass connection between the portal vein and hepatic veins

- Along with urea, glucose is the substance with the strongest osmotic effect, i.e. it binds water very strongly. If glucose is removed (lowered) too quickly from the blood vessels, the water is no longer retained intravascularly and passes into the tissue (especially brain tissue), causing cerebral edema.
- Decisive for the genesis is the osmotic gradient between the intra- and extracellular space and the blood brain barrier. Under hyperosmolar conditions, brain cells protect themselves from swelling by producing intracellular osmotically active molecules (so-called idiogenic osmolecules). These molecules dissolve only slowly. If the serum osmolarity is reduced too quickly (e.g. by the administration of free water), a gradient is formed which draws water into the brain cells.

- risk factors:
  - too rapid reduction of blood glucose (> 50 mg/dl per hour [SI unit > 2.8 mmol/l])
  - therapy with sodium bicarbonate
  - pCO_2 ↓ on admission (hyperventilation as a sign of increased intracranial pressure)
  - urea ↑
- signs:
  - headaches
  - blood pressure ↑, heart rate ↓ (Cushing reflex [In the case of additional irregular breathing, one speaks of the Cushing triad.])
  - disturbed pupil response

Types

- ketoacidotic coma (DKA: diabetic ketoacidosis; 75%)
- hyperosmolar coma (HHS: hyperglycemic hyperosmolar syndrome; 25%)

	ketoacidotic coma	hyperosmolar coma
frequency	75%	25%
type of diabetes	type 1	type 2
age	younger	older
insulin deficiency	absolute	relative
blood sugar	mostly < 800 mg/dl	mostly > 800mg/dl
osmolarity	normal	increased
onset	rapid	slow
lethality	2-5%	20-25%

Ketoacidotic coma

Definition

- diabetic ketoacidosis (DKA)
- more frequent (75%)
- mostly younger patients with diabetes mellitus type 1 (especially children < 5 years), but also possible in type 2
- absolute insulin deficiency
- no inhibition of lipolysis (Insulin is the strongest antilipolytic!) → fatty acids ↑ , formation of ketone bodies → acidosis
- hyperglycemia and exsiccosis (osmotic diuresis: From a serum concentration of 180 mg/dl the sugar can no longer be reabsorbed via the kidneys and is lost via the urine. It draws plenty of water with it.)
- in 25% initial manifestation of diabetes mellitus
- most feared complication: cerebral edema
- lower lethality (2-5%)
- note: Ketoacidosis can occur not only in diabetics (diabetic ketoacidosis), but also in alcoholics (alcoholic ketoacidosis). This occurs primarily after excessive alcohol intake and prolonged periods of sobriety (e.g. malnutrition, prolonged sleep) or vomiting (e.g. alcohol-induced gastritis or pancreatitis).

Symptoms

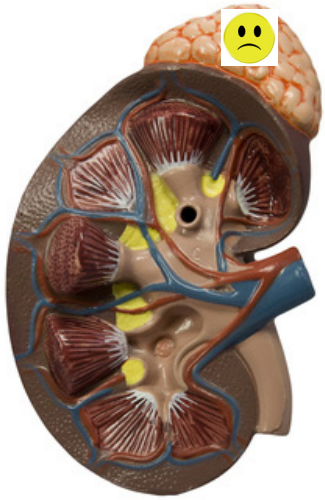
- polyuria, polydipsia, exsiccosis
- weight loss, performance dip
- coma
- hypotension, tachycardia
- Kußmaul breathing (see page 777)
- acetone odor (nail polish remover, rotten apples)
- visual disturbance (due to loss of fluid with consecutively reduced turgor of the lens)
- nausea, vomiting (note: Due to vomiting, the patient himself often reduces the insulin dose for fear of hypoglycemia, which of course intensifies the hyperglycemia.)
- abdominal pain (diabetic pseudoperitonitis [very frequent!])
- possibly cerebral edema (most feared complication)

Diagnostics

Laboratory

- glucose ↑ (p.d. blood sugar > 250 mg/dl); note: Even with a blood sugar < 250 mg/dl, a ketoacidotic coma can still be present (euglycemic ketoacidosis ["sour but not sweet"]), especially in:
  - pregnant women
  - patients who consume only few carbohydrates
  - sGLT2 inhibitors
- metabolic acidosis (pH ↓, bicarbonate ↓) with increased anion gap (only with ketoacidotic, not with hyperosmolar coma); degrees of severity of DKA:
  - mild:
    - pH 7.3-7.2
    - bicarbonate 15-18 mmol/l
  - moderate:
    - pH 7.2-7.1
    - bicarbonate 10-15 mmol/l
  - severe:
    - pH < 7.1
    - bicarbonate < 10 mmol/l
- note: In hyperglycemia (ketoacidotic or hyperosmolar coma), pseudohyponatremia is often found as a result of a measurement error, i.e. hyponatremia with no reduced serum osmolarity (> 275 mosm/l). The true

Addison crisis



Definition

- acute primary adrenocortical insufficiency
- adrenocortical insufficiency:
  - 80% primary (defect of both adrenal cortex; syn.: Addison disease)
  - 20% secondary (defect of the pituitary gland with consecutively reduced ACTH release)
- named after the English physician Thomas Addison (1793-1860), who first described it in 1855 ("bronze disease")
- mostly pre-existing adrenocortical insufficiency (mostly autoimmune) and insufficient or missing dose adjustment in stress situations etiology
- with known Addison disease in 40% Addison crisis

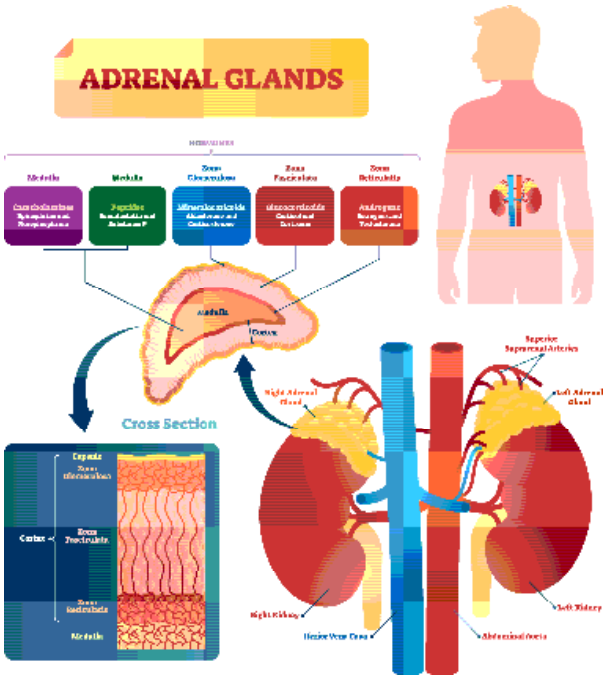


Fig. 1298 adrenal gland: structure and function

Adrenal gland
Hormones

- **adrenal medulla: adrenaline (epinephrine)**
- **adrenal cortex:**
  - **Zona glomerulosa (outer layer): mineralocorticoids (aldosterone); no central control of the synthesis (only peripheral: via RAAS [renin-angiotensin-aldosterone system; especially via angiotensin II])**
  - **Zona fasciculata (middle layer): glucocorticoids: cortisol (syn .: hydrocortisone), cortisone (inactive); central control of the synthesis (hypothalamus: CRH [corticotropin-releasing hormone]; pituitary: ACTH [adrenocorticotropic hormone, adrenocorticotropin; ⚠ only the synthesis of glucocorticoids in the adrenal cortex is ACTH-dependent!])**
  - **Zona reticularis (inner layer): sex hormones (especially androgens [testosterone], but also estrogens); Precursor for the sex hormones: DHEA (dehydroepiandrosterone); central control of synthesis (hypothalamus: GNRH [gonadotropin-releasing hormone]; pituitary: gonadotropins [LH, FSH])**

Etiology

- decompensation (by certain triggers) of a pre-existing chronic adrenocortical insufficiency; causes for chronic adrenocortical insufficiency:
  - inflammatory (adrenalitis)
    - autoimmune (most frequent cause [80%]); in 40% isolated, in 60% associated with other autoimmune diseases in the context of polyglandular autoimmune syndrome (PAS) II (syn. Schmidt-Carpenter syndrome): diabetes mellitus type I, autoimmune thyropathy (Hashimoto thyroiditis, Graves disease); i.a. also possible with immune checkpoint inhibitors (e.g. ipilimumab, nivolumab)
    - infectious (tuberculosis, AIDS, CMV, mycoses)
  - neoplastic (metastases in the adrenal gland, e.g. small cell lung cancer)
- adrenocortical atrophy under prolonged steroid therapy (cause of a secondary adrenocortical insufficiency)
  - too rapid weaning
  - missing increase in stress situations: Long-term steroid therapy (e.g. polymyalgia rheumatica, Crohn's disease) leads to adrenocortical atrophy. If these patients, who have been on steroid therapy for a long time, suddenly experience an acute stress situation (e.g. surgery for perforated appendicitis with septic shock, traffic accident with polytrauma), 100 mg hydrocortisone must always be administered!
- Waterhouse-Friderichsen syndrome
- bleeding
  - meningococcal sepsis
  - oral anticoagulants (warfarin, NOAC)
- bilateral adrenal vein thrombosis (e.g. in HIT II, anti-

Hyponatremia only occurs when the water intake is greater than the water excretion!

Fig. 1306 Hyponatremia: In most cases the patient is senselessly salted only!

Etiology

- sodium loss via the gastrointestinal tract (vomiting, diarrhea, gastroenteritis), skin (heavy sweating), third space (ascites, pleural effusion, ileus); blood loss
- adrenocortical insufficiency
  - hyocortisolism
  - hypoaldosteronism (aldosterone deficiency [e.g. due to spironolactone; also here, as with hyocortisolism, hyponatremia, hyperkalaemia and metabolic acidosis]; see infobox)
- renal insufficiency (loss of sodium; "salt loss kidney")
- SIADH (see page 964)
- non-osmotic stimulation of ADH secretion in intravascular volume deficiency via baroreceptors (although edema, but the effective blood volume is reduced! [hypovolemia!]):
  - decompensated heart failure (in 27% hyponatremia)
  - decompensated liver cirrhosis (in 50% hyponatremia)
  - nephrotic syndrome
- drugs (pharmacological):
  - diuretics [most frequent cause: thiazides [hydrochlorothiazide, xipamide, indapamide, chlortalidone]! note: Loop-diuretics such as furosemide do not cause hyponatremia and therefore do not have to be discontinued compulsorily. They are more likely to lead to hypernatremia through increased water diuresis! Loop diuretics mainly cause hypokalemia.)
  - neuroleptics (e.g. haloperidol), tricyclic antidepressants, SSRI (e.g. citalopram [frequent!])
  - anti-epileptic drugs (especially carbamazepine [classical], lamotrigine)
  - cyclophosphamide, vincristine
  - tranexamic acid
  - terlipressin
  - colonoscopy preparation solutions (cave not rarely severe hyponatremia!)
  - morphine, ⚠ NSAID
  - infusions with G5%,
- drugs (toxical): especially amphetamines, ecstasy
- hypothyroidism - pregnancy
- ventilation: venous return flow to the right heart ↓ → left atrial filling ↓ → ADH release (diuresis ↓, water and sodium retention [hyponatremia], edema)
- strong beer drinkers ("beer potomania"; potomania: "drinking madness" [Latin "potus": drinking); like SIADH euvolemic hyponatremia, but urinosmolarity < 100 mosm/l; therapy: fluid restriction),
- water intoxication (mostly in psychosis, but also as part of an extreme diet; e.g. excessive consumption of green tea)
- psychogenic polydipsia
- malnutrition
- exercise associated hyponatremia (EAH)
  - due to endurance sports (e.g. after marathon running)
  - mostly due to wrong (too much!) drinking (too much supply of free water ["overdrinking"])
  - EAH is the most frequent non-cardiac cause of death in endurance sports!
- TUR syndrome: hypotonic hyperhydration by infusing salt-free rinsing solution in the course of a TUR of the prostate (transurethral resection; frequency: 2%) via injured veins in the surgical area
- renal tubular acidosis type I (see infobox page <?>)
- cerebral salt losing syndrome (CSW: cerebral-salt-wasting)
  - occurring after damage to the CNS (e.g. subarachnoid hemorrhage)
  - hyponatremia with increased sodium excretion via the urine (urine sodium > 40 mmol/l, urine osmolarity > 100 mosmol/l)
  - reduced intravascular volume
    - In contrast to SIADH an exsiccosis is present, therapy therefore consists of fluid administration (isotonic NaCl 0.9%).

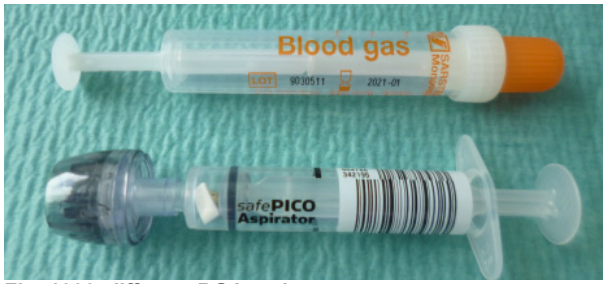
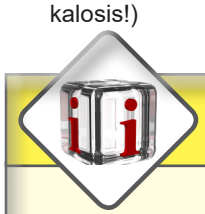


Fig. 1330 different BGA syringes

Basic rules

- Disorders of the acid-base balance are always accompanied by disorders of the electrolytes
- First and foremost the clinic (symptoms) should be treated and not values.
- The decisive factor is the dynamic: While fast changes are dangerous, slow changes are usually rather harmless.
- Often several disorders of the acid-base balance are present at the same time, which unfortunately are often overlooked.
- A normal pH does not rule out a disorder of the acid-base balance at all. According to the Henderson-Hasselbalch equation, the pH is always only determined by the ratio between HCO_3^- and pCO_2. Both an HCO_3^- of 24 mmol/l and a pCO_2 of 40mmHg as well as an HCO_3^- of 12 mmol/l and a pCO_2 of 20mmHg have a normal pH, since the ratio HCO_3^- / pCO_2 is the same in both cases; example:
  - pH = log (HCO_3^- 24 mmol/l / pCO_2 40mmHg) = 7.4 (This is a normal finding.)
  - pH = log (HCO_3^- 12 mmol/l / pCO_2 20mmHg) = 7.4 (This is not a normal finding. There are even two disorders: a metabolic acidosis and a respiratory alkalosis!)



Normal values

- **pH: 7.36-7.44**
- **HCO_3^- (standard bicarbonate): 22-26 mmol/l**
- **BE (base excess): -2 to +2 mmol/l**
- **pCO_2: 36-44 mmHg**
- **gaps:**
  - **anion gap: 8-16 mmol/l**
  - **delta gap: 1**
  - **osmotic gap: < 10 mosm/kg**

A normal pH value does not exclude a disorder of the acid-base balance at all!

Compensation

- definition: There is often a respiratory compensation of a metabolic disorder and vice versa a metabolic compensation of a respiratory disorder.
- types:
  - pH not yet normal: partial compensation
  - pH normal again: complete compensation
- mechanisms (secondary changes):
  - metabolic: pCO_2 (lung; lung; reacts quickly; limited capacity)
    - acidosis: pCO_2 ↓ (hyperventilation)
    - alkalosis: pCO_2 ↑ (hypoventilation)
  - respiratory: HCO_3^- (kidney [It can excrete acid valences in the form of ammonium NH_4^+ [= ammonia NH_3 + proton H^+] in the urine.]; reacts slowly; [nearly] unlimited capacity [Arthur Clifton Guyton (American physiologist, 1919-2003): "The buffer capacity of the kidneys is inexhaustible!"])
    - acidosis: HCO_3^- ↑
    - alkalosis: HCO_3^- ↓
- limitations:
  - In patients with lung diseases (e.g. COPD) the respiratory compensation mechanisms are considerably reduced, so that metabolic disorders have a considerably stronger effect here than in patients without lung diseases.
  - In patients with kidney diseases (e.g. hemodialysis patients) the metabolic compensation mechanisms are considerably reduced, so that respiratory disorders have a considerably stronger effect here than in patients without kideny diseases.
- extent: It is always important to check whether the BGA findings can be explained by the compensation alone or whether there is an additional disorder of the acid-base balance, which is often the case! The following compensations are normal (normal value for pCO_2 40mmHg, for HCO_3^- 24mmol/l) and can be expected:
  - metabolic
    - metabolic acidosis: decrease of pCO_2 $\Delta pCO_2 = 1.2 \times \Delta HCO_3^-$
    - metabolic alkalosis: increase of pCO_2 $\Delta pCO_2 = 0.7 \times \Delta HCO_3^-$
  - respiratory
    - respiratory acidosis:
      - acute (pH not yet balanced): increase of bicarbonate $\Delta HCO_3^- = 0.1 \times \Delta pCO_2$
      - chronic (pH already balanced): increase of bicarbonate $\Delta HCO_3^- = 0.3 \times \Delta pCO_2$
    - respiratory alkalosis:
      - acute (pH not yet balanced): decrease of bicarbonate $\Delta HCO_3^- = 0.2 \times \Delta pCO_2$
      - chronic (pH already balanced): decrease of bicarbonate $\Delta HCO_3^- = 0.4 \times \Delta pCO_2$

Example 1:
- pH 7.31, pCO_2 20mmHg, HCO_3^- 12 mmol/l
- There is a metabolic acidosis with partial respiratory compensation
- extent of respiratory compensation (expected): ΔpCO_2

calcaemia can also develop. Furthermore, glycolysis is stimulated (cave hyperglycemia) and the stimulation of 6-phosphofructokinase with consecutive release of organic acids can even lead to an increase in metabolic acidosis! In addition, excessive alkalization may occur, resulting in cerebral (seizures, neurological deficits) and coronary (coronary spasms, arrhythmias) vasoconstriction and central respiratory depression (cave in spontaneously breathing patients) due to inhibition of the respiratory drive. Sodium bicarbonate can also cause hypocalcaemia.

Fig. 1334 sodium bicarbonate 8.4% (syn.: sodium hydrogen carbonate) [8]

BICAR-ICU study

Sodium bicarbonate therapy for patients with severe metabolic acidaemia in the intensive care unit
Jaber et al, Lancet 2018

- multicenter prospective randomized controlled study
- 389 critically ill patients with severe metabolic acidosis (pH < 7.20, bicarbonate < 20 mmol/l); within 48 hours of admission to the intensive care unit:
  - sodium bicarbonate (target-pH > 7.30)
  - placebo
- results: sodium bicarbonate
  - 😕 primary endpoint (combined from death by day 28 and at least one organ failure by day 7): no difference (significant reduction only in the subgroup of patients with pre-existing renal failure stage AKIN 2 or 3)
  - secondary endpoints: i.a. significant reduction in the need for renal replacement therapy (RRT)

TRIS buffer

- active ingredient: trometamol (THAM [trishydroxymethylaminomethane])
- strongly alkaline (pH = 10), cave tissue necrosis in extravasation (therefore best via CVC), dilution with G5% (1:10; only if applied peripherally; if applied via CVC, the perfusor is filled with pure TRIS)
- indications:
  - ⚠ metabolic acidosis and hypernatremia: TRIS buffer is a good option for buffering with simultaneous hypernatremia because it does not contain sodium in contrast to sodium bicarbonate.
  - increased intracranial pressure (ICP; TRIS buffer crosses the blood-brain barrier much better than sodium bicarbonat and lowers ICP by lowering the intracerebral acidosis; target-pH 7.50-7.55, only as ultima ratio)
- side effects:
  - TRIS buffer leads (especially if administered too quickly) via a decrease in pCO_2 to a reduction in respiratory drive or even to respiratory depression and must therefore not be used in cases of respiratory insufficiency without mechanical ventilation.
  - Hyperkaliämie
  - hyperkalemia
  - hypoglycemia (due to increased insulin release
- contraindications:
  - renal insufficiency with anuria (risk of accumulation; excretion of H^+-THAM via the kidneys)
  - Hyperkaliämie
  - respiratory insufficiency without mechanical ventilation
- dosage:
  - TRIS 36.34%: 1 amp. = 20ml = 60mmol (1ml = 3 mmol [3-molar solution; note: available as 0.3-molar solution])
  - TRIS 36.34% in ml = BE x kgBW x 0.1
  - maximum dose: 1.7ml/kg, maximum infusion rate: 0.3 ml/kg/h

no buffering of hypoperfusion-induced metabolic acidosis at pH > 7.15

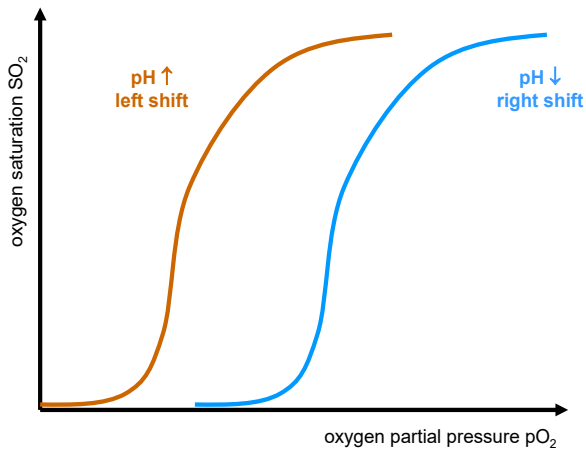


Fig. 1335 Bohr effect (named after the Danish physiologist Christian Bohr [1855-1911]: Shown here is the oxygen binding curve of the hemoglobin, which shows the relationship between oxygen partial pressure (pO_2) and oxygen saturation (SO_2). In acidosis (regardless of whether it is respiratory or metabolic) the oxygen binding curve is shifted to the right (Bohr effect) due to the decrease of the pH: This effect is beneficial because it increases the oxygen release to the tissue. If you buffer here uncritically (e.g. with sodium bicarbonate), the increase of pH leads to a left shift in the oxygen binding curve, with the result that oxygen can only less be released to the tissue and thus tissue hypoxia occurs. Therefore, buffering should only pe performded from a pH below 7.15.

- standard at ICU in Europe
- responsibility: staff of the intensive care unit
- maximum pump flow (CVVH): 500 ml/min
- advantage especially in
  - hemodynamic instability
  - cerebral edema (lower sodium shifts; lower risk of dysequilibrium syndrome in continuous procedures)
  - acute liver failure (also mainly due to cerebral edema

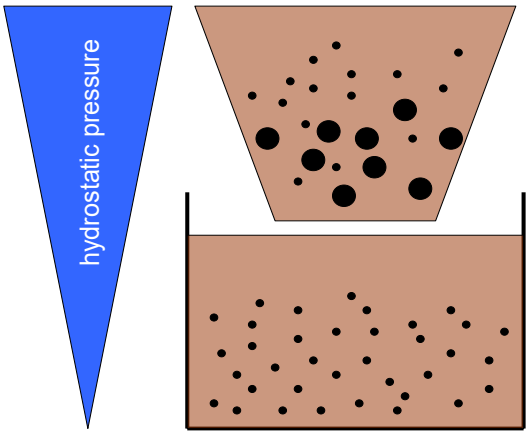
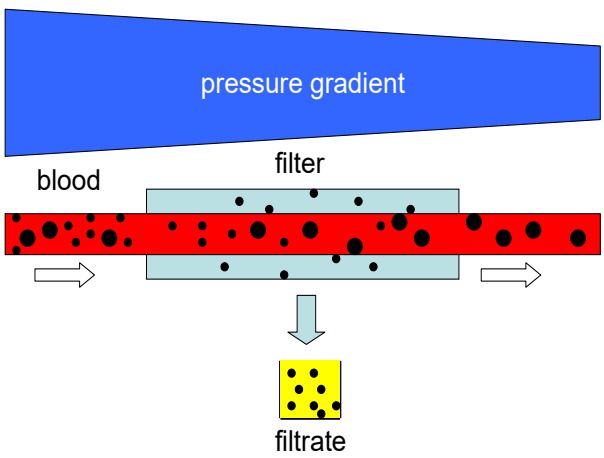


Fig. 1351 Hemofiltration is illustrated by a simple example from everyday life, the coffee filter. The driving force here is the hydrostatic pressure difference between the top and bottom of the coffee machine caused by gravity. The coffee powder ("grounds"; analogous to blood: blood cells, larger proteins) is retained by the filter, which is only permeable for smaller particles. The liquid that now arrives in the coffee pot, i.e. the coffee, corresponds in analogy to the ultrafiltrate.

dialysis: diffusion ("tea bag")
filtration: convection ("coffee filter")



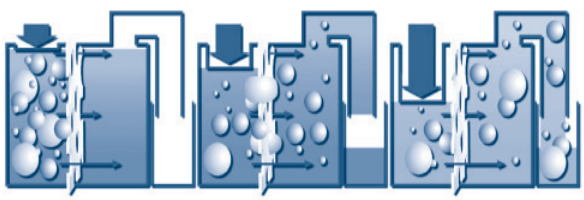


Fig. 1352 principle of convection [17]

Types

- CAVH(F): continuous arterio-venous hemofiltration (blood pressure generates pressure gradient; abandoned today)
- CVVH(F): continuous veno-venous hemofiltration (pump generates pressure gradient; standard today

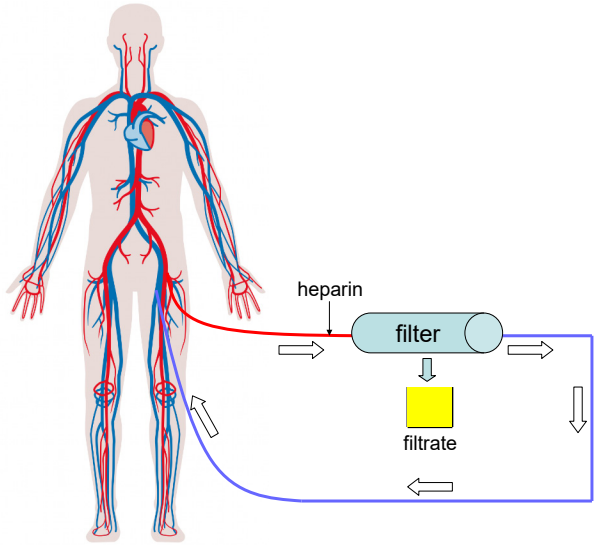


Fig. 1353 scheme CAVH: The pressure gradient is generated by the blood pressure (arterio-venous pressure difference; heart as pump). Arterial cannulation is necessary here. This procedure is abandoned today.

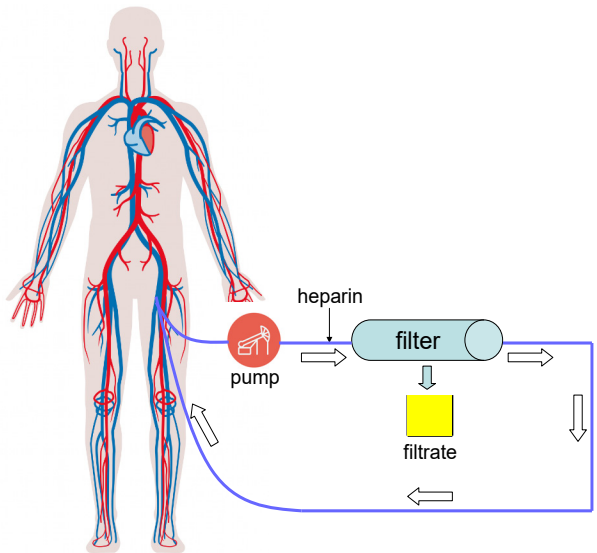


Fig. 1354 scheme CVVH: The pressure gradient is generated by a pump. Arterial cannulation is not necessary. This procedure is standard today.

Antibiotic therapy

Basics

Antibiotics
Types I

- according to classes (see red infobox; e.g. β-lactams [penicillins, cephalosporins, carbapenems], macrolides, fluoroquinolones, aminoglycosides, glycopeptides, tetracyclines)
- according to effect
  - bactericidal (e.g. β-lactams [penicillins, cephalosporins, carbapenems], fluoroquinolones, aminoglycosides, glycopeptides [e.g. vancomycin], daptomycin, colistin, metronidazole, rifampicin, fosfomycin)
  - bacteriostatic (e.g. macrolides, tetracyclines, clindamycin, linezolid, tigecycline)
- according to pharmacology
  - according to pharmacodynamics ("what the drug does with the body")
    - time-dependent (e.g. β-lactams [penicillins, cephalosporins, carbapenems], macrolides, clindamycin, oxazolidiones, fosfomycin, cancomycin [exactly: dependent on AUC/MIC; AUC: area under the curve, i.e. area under the concentration-time curve; MIC: minimum inhibitory concentration], fluorchinolones [exactly: dependent on AUC/MIC]):
      - The time T in which the concentration is above the MIC is decisive here. A prolonged infusion is therefore important (target: T > MIC [in at least 50%]). note: However, the initial dose should be given as a bolus in order to quickly achieve a therapeutically effective level.
      - in case of adaptation to renal function: dose reduction (not interval prolongation)
    - concentration-dependent (e.g. aminoglycosids, metronidazole, daptomycin):
      - The level of concentration (peak concentration C_{max}; peak level) is decisive here. It should be 10-fold the MIC (target: C_{max} > 10 x MIC).
      - in case of adaptation to renal function: interval prolongation (not dose reduction); ⚠ note: If for example the level of aminoglycosides is too high, the dose should not be reduced, but the interval should be prolonged!
  - according to pharmacokinetics ("what the body does with the drug")
    - hydrophilic (e.g. β-lactams [penicillins, cephalosporins, carbapenems], aminoglycosides, glycopeptides [e.g. vancomycin], linezolid, daptomycin, colistin): mostly eliminated renally; small volume of distribution; orientation on the ideal body weight
    - lipophilic (e.g. macrolides, fluoroquinolones, tetracyclines, clindamycin, metronidazole, tigecycline, rifampicin): mostly eliminated hepatically; large volume of distribution; orientation on the real body weight

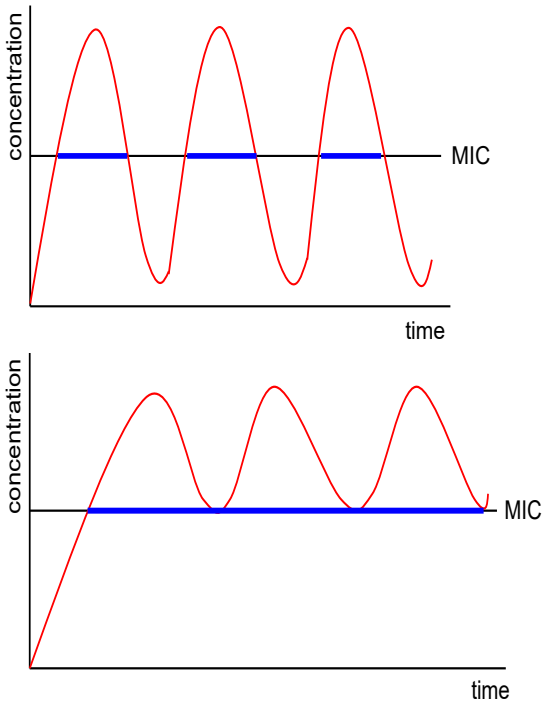


Fig. 1390 The pharmacodynamics of time-dependent antibiotics are shown here. The time in which the concentration is above the MIC (minimum inhibitory concentration) is decisive for their effectiveness. This time (shown in blue in the graphic) is significantly shorter with only three bolus doses (top) than with prolonged infusions (bottom) or continuous administration.

Antibiotics
Types II

- according to plasma protein binding
  - antibiotics with high protein binding (e.i. > 90%; e.g. sulfonamides, tetracyclines, isoazylpenicillins, ertapenem, teicoplanin): If the protein level in the plasma is low (albumin < 25 g/dl), these antibiotics are increasingly excreted. Here the dose has to be increased.
  - antibiotics with low protein binding
- according to elimination
  - renal (60%): In critically ill patients, they should not be underdosed because of false regard to the kidneys. You should also be careful if the GFR is increased (> 130 ml/min; frequently hyperdynamic circulation in the initial phase of sepsis): Here the renal clearance is increased (augmented renal clearance [ARC]), so that the dose has to be increased here! This applies especially to the β-lactams. If the GFR > 130 ml/min, e.g. piperacillin / tazobactam has to be administered 4-5 times a day.
  - hepatic (40%)

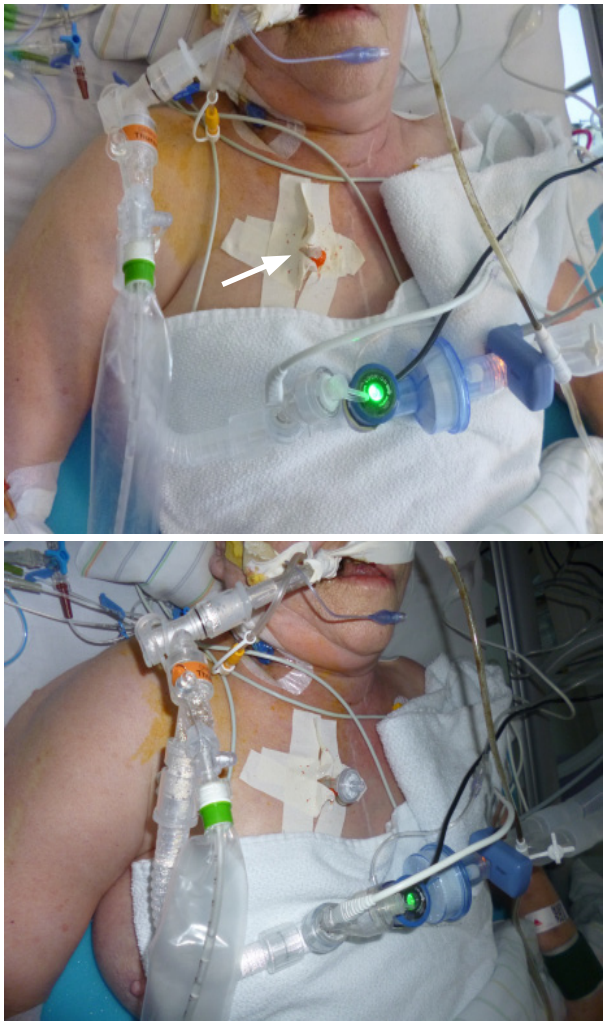


Fig. 1450 The patient suddenly had a ventilation problem: The respirator couldn't get any more air into the patient, she had to be ventilated manually by the hand (Ambu bag). The saturation kept falling. Furthermore there was a breakdown of the circulation, the catecholamine perfusors were turned up massively. During auscultation, the right side showed a weaker breathing sound compared to the opposite side. Pleural sliding was absent in pleural ultrasound. Immediately the relief puncture was performed with an orange peripheral venous cannula (14G) in Monaldi position on the right. As a result, the air hissed out, so that both the ventilation situation and the circulation immediately improved dramatically. In the further course, a chest X-ray and the installation of a thoracic drainage wa performed. The cause of the entire symptomatology was a tension pneumothorax induced by excessive ventilation pressures (RAP: respirator-associated pneumothorax).

If a ventilated patient suddenly experiences problems in ventilation ("I can't get any more air in") AND in circulation (hemodynamically unstable), the most common cause is a tension pneumothorax! immediate auscultation + pleural sonography (do not wait until X-ray), then generous relief puncture (takes 1 second! no false restraint!)

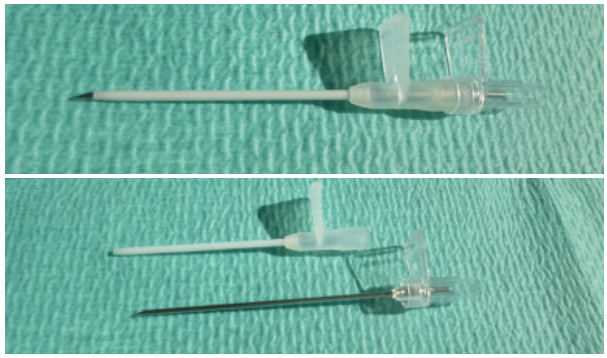


Fig. 1451 Meanwhile the are now special needles for relief puncture in a tension pneumothorax on the market. They have the advantage over peripheral venous cannulas that they are longer.

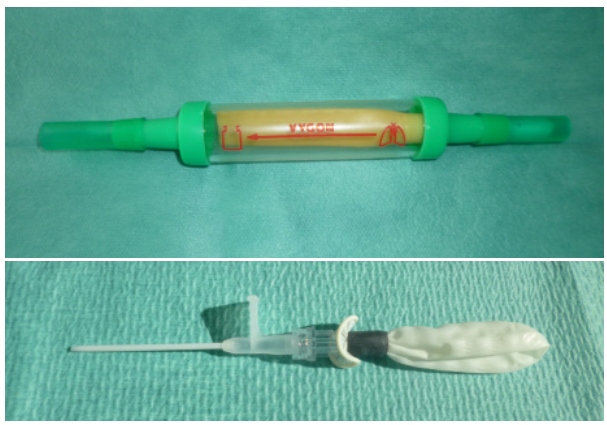


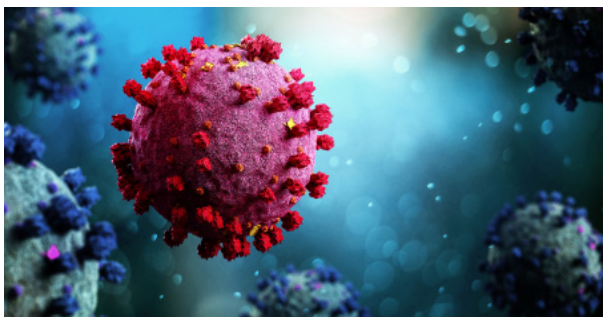
Fig. 1452 Heimlich valve (first picture; drainage valve according to Heimlich for chest tubes; named after the American physician Henry Heimlich [1920-2016]): This is necessary for spontaneously breathing patients, as otherwise air is drawn into the thorax during inspiration. This is not necessary for mechanically ventilated patients. The second picture shows a self-made (provisional) Heimlich valve with an incised rubber fingerling ("glove" valve; also known as Tiegel valve [named after the German surgeon Max Tiegel; 1877-1952]).

Localization

- according to landsmarks:
  - Bülau drainage (named after the German internist Gotthard Bülau [1835-1900]): 4th/5th ICS, anterior axillary line (⚠ to be preferred; never below or medial the mamille!)
  - Monaldi drainage (named after the Italian physician Vincenzo Monaldi [1899-1969]: 2nd ICS, mediolavicular line (only recommended cautiously due to immediate proximity to large vessels [cave especially injury of the pulmonary artery]]; relatively narrow intercostal space; only suitable for pneumothorax)
- according to imaging:
  - guided by sonography
  - guided by CT (good option e.g. for chambered parapneumonic effusion or pleural empyema)

- average age of deceased patients:
  - worldwide: 79 years
  - in Germany: 81 years
- A autopsy series of 65 deceased COVID patients in Hamburg (Germany) showed that all patients had co-morbidities (Püschel et al, Dtsch Arztebl Int 2020)
- main cause of death: ARDS (Mostly it is a mono-organ failure of the lung!)
- infectiousness (contagious risk): ⚠ 2 days before to 10 days after the onset of symptoms (maximum on the day of symptom onset)

SARS-CoV-2



- taxonomy
  - order: nidovirals
  - suborder: coronaviridae
  - family: coronaviruses (Latin "corona": wreath [visible in the electron microscope)
  - genus: β-coronaviruses
- classification of human corona viruses (HCoV [H: human]; in total 6): see infobox
- designation: Both the SARS pandemic 2002/2003 (SARS: severe acute respiratory distress syndrome; number of infections: approx. 8000; mortality: 10%; reservoir: Sneak cats; since 2004 no more proven cases) in China (especially Guangdong Province; was almost not in Europe [only a few cases]) and the MERS epidemic 2012 (MERS: middle east respiratory syndrome; number of infections: approx. 2500; mortality: 35%; reservoir: camels) in the Near East (Arabian Peninsula; especially Saudi Arabia [90%]) were caudes by coronaviruses (SARS-CoV respectively MERS-CoV). The current COVID pandemic since 2020 is caused by a different and previously unknown coronavirus (new variant), which is why the term "novel" corona virus (nCoV) was introduced. The coronavirus that caused the SARS epidemic in 2002/2003 is now referred to retrospectively as SARS-CoV-1, the corona virus that caused the COVID pandemic since 2020 as SARS-CoV-2. SARS-CoV-2 is definitely not a mutation of SARS-CoV-1. In addition, there are four harmless ("endemic") coronaviruses (OC43, HKU1, 229E, NL63) with which we become infected every two years on average and which cause a harmless respiratory infection (15% of all colds; especially in autumn and winter [seasonal]; especially in childhood).
- a zoonosis:
  - SARS-CoV-1: passed from sneak cats to humans
  - SARS-CoV-2: passed from bats to humans
- nucleic acid: a RNA virus, single-stranded genome, high genetic variability
- size: relatively large (120nm; for comparison influenza virus: 100nm, rhinovirus: 3nm)
- envelope: present (lipid envelope; viruses with an envelope such as SARS-CoV are much easier to inactivate [e.g. by alcoholic hand disinfection] as non-enveloped viruses [e.g. norovirus])
- thermolabile (Coronaviruses are killed at temperatures above 70°C.)
- groups: 4 main groups, 10 sub-groups (viral diversity; Chen et al, MedRxiv 2020)
- mutations (sequencing required for proof; compulsory in Germany for all positive PCRs since 02/19/2021 [vPCR]): i.a.
  - D614G
    - At position 614 the amino acid aspartic acid (N) has been exchanged for glycine (G).
    - with increased infectivity
    - even the dominant form worldwide since November 2020! The original wild-type form from Wuhan from 12/2019 is very rare.
  - VOC mutations (VOC: variant of concern; see infobox):
    - designation:
      - according to the country in which the mutation was first detected
      - according to Greek letters: To avoid discrimination, the WHO introduced Greek letters as a new designation in May 2021.
      - according to Phylogenetic: PANGO (Phylogenetic Assignment of Named Global Outbreak Lineages): The letters (A, B) and numbers denote the descent from different genome lines.
    - The most important gene change here is N501Y: In the RNA of the S1 subunit (receptor binding domain) of the spike protein, the amino acid Asparagine (N) at position 501 has been exchanged for tyrosine (Y). The E484K mutation is also significant: This is an escape mutation with which the virus can escape recognition by the immune system.
- pathophysiology (both SARS viruses):
  - docking via the virus spike protein (S protein) to the ACE-2 receptors (ACE: angiotensin converting enzym; an aminopeptidase) of the epithelial cells of the respiratory system (highest concentration of ACE-2 receptors: nasal) and then invasion into the cell
  - S protein: subunits
    - S1 (for attachment): It contains the receptor binding domain (RBD; also the target structure of the neutralizing antibodies).
    - S2 (for fusion): It mediates the fusion of the virus envelope with the cell membrane.
  - The cell entry is supported by proteases (especially by the serine protease TMPRSS2 [transmembrane protease serine subtype 2]). TMPRSS2 leads to a proteolytic cleavage of the S2 subunit. TMPRSS2 can be inhibited for example by camostat.
  - SARS-CoV-2 has a much higher affinity to the ACE-2 receptors than SARS-CoV-1 and also causes an

ACCT-1 study

Remdesivir for Treatment of COVID-19
Beigel et al, N Engl J 2020

- multicenter randomized controlled study
- ACTT: Adaptive COVID-19 Treatment Trial
- 1063 patients with proven SARS-CoV-2 infection and evidence of lower respiratory tract involvement
  - Remdesevir (d1 200mg i.v., d2-d10 100mg i.v.)
  - Placebo
- results:
  - 🙂 time to clinical improvement (primary endpoint): significantly reduced (11 versus 15 days); rate ratio of recovery: all in all 1.32; subgroups:
    - without additional oxygen (low-flow): 1.38
    - with additional oxygen 1.47 (⚠ benefited the most)
    - with HFNOT / non-invasive ventilation: 1.20
    - with invasive ventilation / ECMO: 0.95 (benefited the least [no benefit at all here])
  - mortality: no difference

ACCT-2 study

Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19
Kalil et al, N Engl J 2021

- multicenter randomized controlled trial
- 1033 hospitalized with COVID-19 and remdesivir
  - with baricitinib (a Janus kinase inhibitor; 4mg p.o. for 14 days)
  - without baricitinib
- results: with baricitinib
  - 🙂 primary endpoint (time to recovery to day 29): significant reduction (from 8 to 7 days [by one day); rate ratio of recovery: total 1.16; subgroups:
    - without additional oxygen: 0.88
    - with additional oxygen (low-flow): 1.17
    - with HFNOT / NIV: 1.56 (⚠ benefited most; time to recovery shortened from 18 to 10 days)
    - with invasive ventilation: 1.08
  - secondary endpoints:
    - clinical status on day 15: significantly better
    - mortality: no difference

Remdesivir: no longer recommended (WHO)

all in all no evidence for a causal antiviral or therapy!

Immunotherapy

- active (with own antibodies): vaccination (see prophylaxis)
- passive (with foreign antibodies):
  - with naturally occurring (produced by the body) antibodies: convalescent plasma
  - with artificially (biotechnologically) produced antibodies: neutralizing monoclonal antibodies (nMAB)

Convalescent plasma

- a passive immunotherapy with antibodies from already recovered COVID patients via a plasma donation
- a relatively old method
- typical side effect: hypersensitivity reaction
- studies:
  - no clinical benefit in the studies (e.g. Li et al, JAMA 2020; Shen et al, JAMA 2020; Valk et al, Cochrane Database Syst Rev 2020)
  - In a propensity score analysis (Salazar et al, American Journal of Pathology 2020) from Houston / USA, it could be shown that plasma therapy is successful and also leads to a reduction in mortality if it is carried out early (< 72h) and if there is sufficient antibody titer (≥ 1: 1350) in the donor plasma.
  - In a retrospective single-center case-control study (Liu et al, Nat Med 2020), plasma therapy showed a reduction in mortality in patients with severe COVID-19.
  - randomized controlled trials (RCT):
    - PlasmAr study (Simonovich et al, N Engl J 2020): In a total of 333 patients with severe COVID pneumonia, there was no reduction in mortality compared to placebo.
    - PLACID study (Agarwal et al, BMJ 2020): In a total of 464 patients with moderate COVID pneumonia, there was neither a reduction in progression to severe COVID pneumonia nor in mortality compared to placebo.
    - INFANT-COVID-19 study (Libster et al, N Engl J 2021): significantly less severe course in older patients
    - CAPSID study (Körper et al, J Clin Invest 2021; RCT from Germany): no reduction in mortality
    - RECOVERY study (see page 1157): no reduction in mortality
    - SIREN-C3PO study (Korley et al, N Engl J 2021): no prevention of progression (i.e. need for emergency care, hospital admission or death) in patients > 50 years of age or at least one risk factor for a severe course
    - REMAP-CAP study 2021: no benefit
  - currently ongoing study in Germany: RECOVER
- approved by the FDA
- antibody titre recommended by the WHO: > 1:160
- S2k guideline (23.11.2020) and S3 guideline

retrospective study (Franco et al, ERJ 2020) the infection rate among medical staff here was 11.4%. The risk of infection with NIV with a ventilation helmet may be lower. However, the COVID guideline of the SSC 2020 does not make an explicit recommendation for the helmet. The HENIVOT study (Grieco et al, JAMA 2021) showed no advantage for NIV with a helmet compared to HFNOT with regard to the primary endpoint (number of days without respiratory support). A mouth-nose mask or a full face mask is also possible. You should definitely use closed systems (non-vented masks). Leakages should be kept to a minimum. Furthermore, a filter with virus protection should be used at NIV. It is best to use systems with a double-barrel hose system (i.e. in addition to an inspiratory hose there is also an expiratory hose): This is the case with almost all intensive care respirators, only turbine devices have only one hose (for inspiration). A filter with virus protection should then be attached in front of the exhalation valve here. The staff has to wear the appropriate personal protective equipment (especially FFP-2 masks) during NIV or HFNOT. Patients with HFNOT should wear a mouth and nose mask over the nasal cannula: This reduces the expiratory cloud (simulation study Leonard et al, Chest 2020).This study also showed a significantly lower expiratory cloud in patients with HFNOT who wore mouth and nose mask than in patients with spontaneous breathing without mouth and nose mask. This even leads to an improvement in oxygenation without worsening decarboxylation (Montiel et al, Ann Intensive Care 2020).

- HFNOT is very effective on the one hand in patients with hypoxemic respiratory failure such as COVID, but on the other hand it is also associated with a high risk of infection due to the high flow (up to 60 l/min) in the nose and pharynx. Up to a flow of 30 l/min, the risk of infection under HFNOT seems to be justifiable. However, there was no evidence of a significantly increased delivery of infectious aerosols in vitro or in vivo under HFNOT compared to spontaneously breathing patients without HFNOT (simulation studies Hui et al, Chest 2009; Hui et al, Eur Resp J 2019). Here it could even be shown that the expiratory cloud under HFNOT is smaller than under conventional oxygen therapy (i.e. low-flow), which was explained by the closer fit of the high-flow cannula.
- According to the position paper on the practical implementation of the differential therapy of acute respiratory failure in COVID-19 by the German Society for Pneumology (DPG), both HFNOT and NIV can be carried out without an increased risk of infection, if the personal protective equipment is worn. The fear of a possible infection must not be a reason to withhold HFNOT or NIV from the patient and therefore to perform a hasty and premature intubation: The risk of infection is significantly higher here! In the COVID guideline of the SSC 2020, both NIV and HFNOT are primarily recommended (but only weakly), HFNOT, however, is favored, since on the one hand the failure rate is significantly increased (70%) under NIV in hypoxemic respiratory failure in pneumonia and on the other hand the aerosol formation is more pronounced under NIV than under HFNOT. NIV would only be an option in hypercapnic respiratory failure (e.g. infect exacerbated COPD as a result of SARS-CoV-2 infection). Furthermore, the use of HFNOT leads to a conservation of the resource of ventilators.
- HFNOT is clearly recommended in the national guideline of the DGIIN (S1 guideline, S2k guideline [23.11.2020], S3 guideline [23.02.2021 + 17.05.2021]) as well as in the international guideline of the SSC (first update from 28.01.2021)! In the S3 guideline of 05.10.2021, a preference for NIV over HFNOT was expressed!

COVID + acute respiratory failure (ARI):
hypoxemic ARF (common) → HFNOT
hypercapnic ARI (rare) → NIV

RECOVERY-RS study

An adaptive randomized controlled trial of non-invasive respiratory strategies in acute respiratory failure patients with COVID-19
Perkins et al, medRxiV 2021

- RS: Respiratory Support
- multicenter randomized controlled study
- study funded by the National Institute for Health Research (NIHR) in the UK
- the largest RCT to date on non-invasive ventilation for COVID
- 1272 patients with acute respiratory failure in COVID pneumonia:
  - low-flow oxygen therapy (conventional oxygen therapy)
  - high-flow oxygen therapy (HFNOT)
  - NIV (CPAP)
- result: significant reduction in the primary combined endpoint (mortality and need for intubation after 30 days) by NIV (but not by HFNOT) compared to conventional oxygen therapy

Invasive ventilation

- intubation and ventilation if Horovitz quotient paO_2/FiO_2 < 200 mmHg (according to the 1st version of the S1 guideline of DGIIN 2020; since the 2nd version: only if paO_2/FiO_2 < 150 mmHg [optional, but obligatory from < 100 mmHg at the latest]); note: conversion with spontaneous breathing: FiO_2 = 0.21 + 0.03 x liter O_2 per minute
- cave high risk of infection (therefore always RSI [rapid sequence induction; i.e. always with muscle relaxation and without bag mask ventilation] and always only by a very experienced physician)
- use of a introducer guide for intubation
- Intubation is best performed with a video laryngoscope (introducer guide obligatory here), since the distance

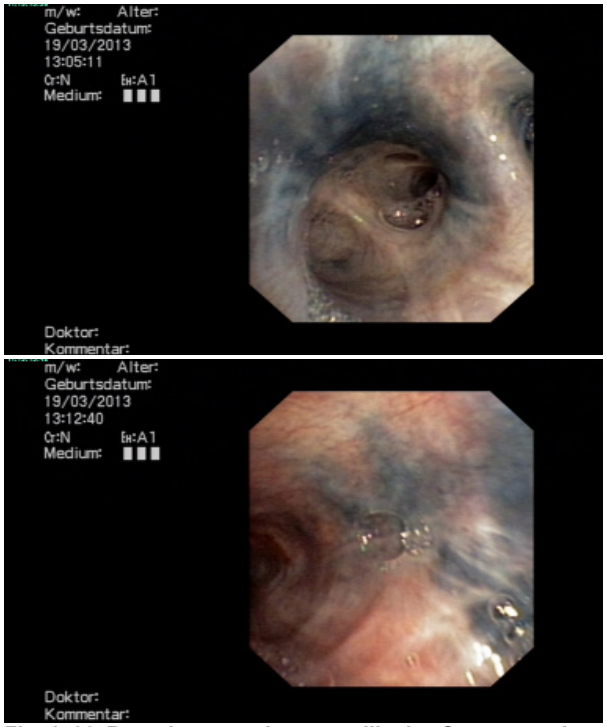


Fig. 1530 Bronchoscopy in aspergillosis: One recognizes the typical grey membranes.

Aspergillus: if there is positive evidence of aspergillus in the endotracheal secretion, always start therapy (never ignore it)!

Therapy

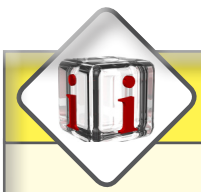
- principles
- antifungals

Principles

- eliminate risk factors (e.g. antibiosis [discontinue if possible!], steroids, discontinue hydrocortisone if possible)
- candidemia → always "plastic change", i.e. change of all accesses (e.g. CVC [if still needed; no over-the-wire exchange, but new installation!], shaldon catheter, arterial line, urinary catheter)
- candidemia → search for organ participation, i.a.
  - TEE (generously on the question of endocarditis [if confirmed, always indication for surgery!])
  - fundoscopy (ophthalmologic consultation [if available in the hopsital])
    - on the question chorioretinitis (most common; every 6th patient with candidemia) or endophthalmitis
    - in previously neutropenic patients again after the leukocytes have increased, as the pus can often only then be produced in the eye
    - recommended, but often not practicable
    - Azole or liposomal amphotericin B are better than echinocandins for the treatment of candida chorioretinitis / endophthalmitis. Therefore, one of the two substances is added to the echinocandin. Surgery (vitrectomy) is useless.
- regular blood culture controls (initially daily, then every two days until the blood culture is negative)
- duration of therapy: up to 14 days after the first negative blood culture (i.e. again draw blood culture after start of therapy daily until it is negative; applies to Candida [at least 4 weeks for aspergillus])

With the detection of candidemia one now has a sufficient reason for sepsis, i.e. now the antibiotics have to be discontinued, which unfortunately one often doesn't dare to do!

Antifungals



Antifungals

- **azoles (inhibition of ergosterol synthesis)**
  - **1st generation:**
    - **fluconazole (Diflucan)**
    - **itraconazole (Sempera)**
  - **2nd generation:**
    - **voriconazole (Vfend)**
    - **posaconazole (Noxafil)**
    - **isavuconazole (Cresemba)**
- **polyenea (pore formation [perforation] of the fungal cell membrane)**
  - **amphotericin B**
  - **nystatin (no relevance for ICU)**
- **echinocandines**
  - **inhibition of glucan synthesis (osmotic lysis → fungicidal)**
  - **only i.v. application (almost no oral bioavailability), single dose sufficient**
  - **All of the 3 echinocandins are equally effective.**
  - **effect: fungicidal**
  - **gap in effectiveness: candida parapsilosis (azoles here means of choice)**
  - **representatives:**
    - **1st generation: caspofungin (Cancidas)**
    - **2nd generation:**
      - **anidulafungin (Ecalta)**
      - **micafungin (Mycamine)**
    - **3rd generation: rezafungin (only necessary once a week; in the STRIVE study [Thompson et al, Clin Infect Dis 2020] not inferior to caspofungin in candidemia; not yet approved)**

keys) in Singapore; transferable to humans
  - named after the malaria researcher Robert Knowles (1883-1936)
  - especially in Southeast Asia (especially in Malaysia: Plasmodium knowlesi is already the most common malaria pathogen there!)
  - ⚠ frequently severe courses (fulminant!)
  - difficult to differentiate microscopically from other plasmodia species (mostly only molecular biologically, i.e. by PCR
  - therapy like tropical malaria (artesunate also the first choice for the complicated form)

Types

- benign forms (1/3):
  - quartan malaria (plasmodium malariae)
  - Tertian malaria (plasmodium vivax / ovale)
- malignant form (2/3): tropical malaria (plasmodium falciparum)

Incubation periods

- tropical malaria: 12 days
- tertian malaria: 12-18 days
- quartan malaria: 3-6 weeks (longest incubation period)
- notes:
  - ⚠ A feverish disease < 7 days after return is usually not malaria (minimum incubation period of malaria 1 week, mean incubation period 1 month).
  - but also incubation period over several months → stays abroad in malaria areas up to 2 years back still relevant!

Pathogenesis

- Humans and anopheles mosquitoes are the only reservoir of pathogens.
  - mosquito: end host (here sexual phase [= gamogony])
  - human: intermediate host (here asexual phase [= schizogony])
- Anopheles mosquitoes (female form) use their saliva to transmit the sickle germs (sporozoites) into the blood of humans during bites.
- first infestation of the liver (short liver phase [5-8 days]; liver schizont), then infestation of the erythrocytes (erythrocytic phase)
- in erythrocytes multiplication and maturation (schizogony; blood schizont) → bursting of erythrocytes (hemolysis) and release (merozoites) → infestation of further erythrocytes and multiplication
- synchronization of intraerythrocytic parasitic growth → fever attacks every two (tertian malaria) or three days (quartan malaria)
- After some cycles, the sexual forms develop (sex form = gametocyte) → infection of the anopheles mosquito
- in synchronization (not the case with plasmodium falciparum) of parasite development: fever
- In tertian malaria (plasmodium vivax and plasmodium ovale), resting forms in the liver (hypnozoites) can remain asymptomatic for years and then lead to relapses. Therefore a final therapy with primaquine is necessary!
- In tropical malaria there are no liver forms, therefore relapses are not possible in this type of malaria!
- special property of plasmodium falciparum: alteration of the erythrocyte surface (e.g. production of PfEMP1: plasmodium falciparum infected erythrocyte membrane protein 1) → "bonding" of erythrocytes (sequestration)

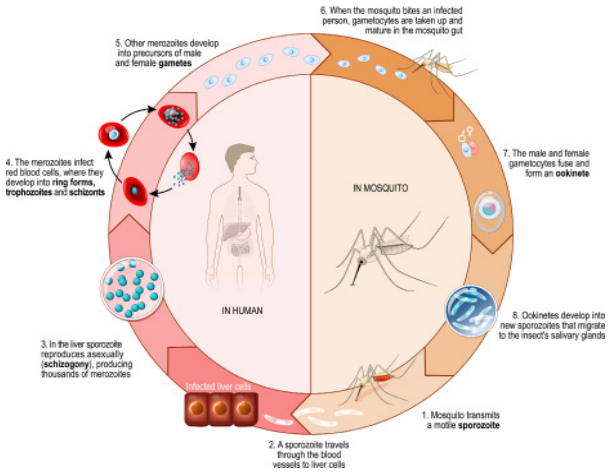


Fig. 1531 Life cycle of plasmodia (malaria cycle): Asexual reproduction (schizogony) takes place in human: First the hepatocytes (exoerythrocytic phase) and then the erythrocytes (erythrocytic phase) are infected. Sexual reproduction (gamogony) takes place in the anopheles mosquito. After the mosquito bite, the sporocytes (infectious form of the pathogen) get from the saliva of the mosquito into the human blood. There they multiply in the liver (liver schizonts) and in the erythrocytes (blood schizonts). The liver schizonts disintegrate into numerous merozoites, which then infect the erythrocytes. Finally, gametocytes (immature germ cells) develop, which are ingested by the anopheles mosquito when it bites (blood meal). In the gut of the mosquito, these then mature into gametes (mature germ cells). The female (macrogamete) and male (microgamete) gametes fuse to form the ookinet, from which the sporocytes then develop (sporogony).

Symptoms

- fever (remember this even up to 2 years after your stay in the tropics)
  - quartan malaria: 1 day fever, 2 days no fever
  - tertian malaria: 1 day fever, 1 day no fever
  - tropical malaria: fever irregular
- chills
- headache (typically severe!)
- back pain
- limb pain
- myalgia
- hepatosplenomegaly, pain in the right upper abdomen (liver capsule tension)
- jaundice (due to hemolysis)
- nausea, vomiting
- diarrhea (frequent misdiagnosis: travel diarrhea)
- cough

Immunological transfusion reactions (ITR)

ITR
overview

- **antibodies against blood cells:**
  - **antibodies against erythrocytes: hemolytic transfusion reaction (HTR)**
  - **antibodies against leukocytes:**
    - **general: febrile non-hemolytic transfusion reaction (FNHTR)**
    - **special (against neutrophil granulocytes): TRALI (transfusion-related ALI)**
  - **antibodies against thrombocytes (platelets): post-transfusion purpura (PTP)**
- **antibodies against blood plasma (proteins): allergic transfusion reaction (ATR)**

- allergic transfusion reaction (ATR)
  - definition: allergic reaction by antibodies against soluble plasma components (mainly proteins, drugs, IgA [frequent in patients with IgA deficiency!])
  - ⚠ most frequent relevant transfusion reaction (frequency: 28 cases per 1 million transfused units)
  - symptoms:
    - as for allergy or anaphylaxis
    - ⚠ but no fever!
  - therapy:
    - stop the transfusion (note: If only cutaneous symptoms appear, the transfusion can be continued under monitoring).
    - prednisolone 500mg i.v.
    - antihistamines i.v.
      - H_1 blocker, e.g. dimetindene (Fenistil) 4mg
      - H_2 blocker, e.g. ranitidine (Zantic) 100mg, famotidine (Pepcid, Pepdul) 20mg, cimetidine (Tagamet) 200mg
      - possibly adrenaline i.v.
    - in case of proven IgA deficiency only transfusion of washed blood components
- hemolytic transfusion reaction (HTR)
  - definition:
    - destruction of the erythrocytes by antibodies (mostly IgM; complement activation) due to an ABO-incompatible transfusion (false transfusion)
    - ⚠ most frequent lethal transfusion reaction (the most important complication with regard to emergency medicine; frequency: 11 cases per 1 million transfused units; incidence: 1:25000 transfusions)
    - Cell damage is mainly caused by the free hemoglobin released during hemolysis: This leads to oxidative stress in the cells of the kidney tubules with consecutive necrosis and obstruction of the tubules (hence also flank pain and renal failure).
  - causes:
    - mix-up of blood sample and patient (80%, more frequent; therefore ABO identity test ([bedside test] obligatory!)
    - incorrect determination of blood group by the laboratory (20%; less frequent)
  - types:
    - early reaction: < 24h (usually begins immediately and often after just a few milliliters; usually intravascular; less frequent; more dangerous)
    - late reaction: > 24h (mostly extravascular; more frequent; less dangerous [mostly harmles]; boosting of primary allo-antibodies, not safely avoidable; in the course of transfusion unclear drop of hemoglobin, hemolysis, jaundice)
  - symptoms:
    - fever, chills
    - ⚠ pain (especially at injection site, flank, abdomen, back [especially in the lumbar spine region; pathognomonic!])
    - dyspnea, tachypnoea
    - cave: oligosymptomatic in analgosedated patients (e.g. mechanically ventilated patients in ICU!)
    - jaundice
    - dark urine
    - arterial hypotension (blood pressure decline), tachycardia
    - diffuse bleeding
    - oliguria, anuria
  - complications:
    - shock
    - DIC
    - acute kidney failure
  - diagnosis:
    - hemolysis parameters (hemoglobin ↓, LDH ↑, indirect bilirubin ↑, haptoglobin ↓, hemoglobinuria)
    - direct Coombs test (positive)
    - DIC: platelets ↓, AT III ↓, fibrinogen ↓, D-dimer ↑
    - determination of blood group (ABO, rhesus) from recipient and erythrocyte concentrate
  - therapy:
    - stop the transfusion (but leave the i.v.-access in situ and keep it free; reserve the rest of the RCC and transfusion set)
    - immediate reporting to the blood bank (If confused by the laboratory, another patient may be at risk!); send to the blood bank: 20ml native blood, 10ml EDTA blood, rest of the RCC and transfusion set, transfusion feedback and transfusion report
    - prednisolone 500mg i.v.
    - antihistamines i.v.
      - H_1 blocker, e.g. dimetindene (Fenistil) 4mg
      - H_2 blocker, e.g. ranitidine (Zantic) 100mg, famotidine (Pepcid, Pepdul) 20mg, cimetidine (Tagamet) 200mg
    - therapy of shock
    - therapy of acute kidney failure (if necessary renal replacement therapy)
    - therapy of DIC
    - in particularly severe cases: exchange transfusion
- febrile non-hemolytic transfusion reaction (FNHTR)
  - definition: antibody-mediated activation of leukocy-

Types

- rapid-onset (< 5d)
- typical onset (5-10d)
- late onset (> 10d)

from d5 regular control of the platelets under therapy with unfractionated heparin (not only PTT controls)!

If possible use LMWH instead of UFH!
UFH: 10 times more HIT than LMWH!

Pathophysiology

- auto-antibodies against complex (neo antigen) of heparin (strongly negatively charged) and platelet factor IV (strongly positively charged)
  - antibody-mediated destruction and degradation of thrombocytes → thrombocytopenia
  - antibody-mediated activation (via the Fc part) of thrombocytes → release of procoagulatory mediators → thrombocyte aggregation → thromboses
- HIT-antibodies destroy and activate the platelets.
- white clot syndrome

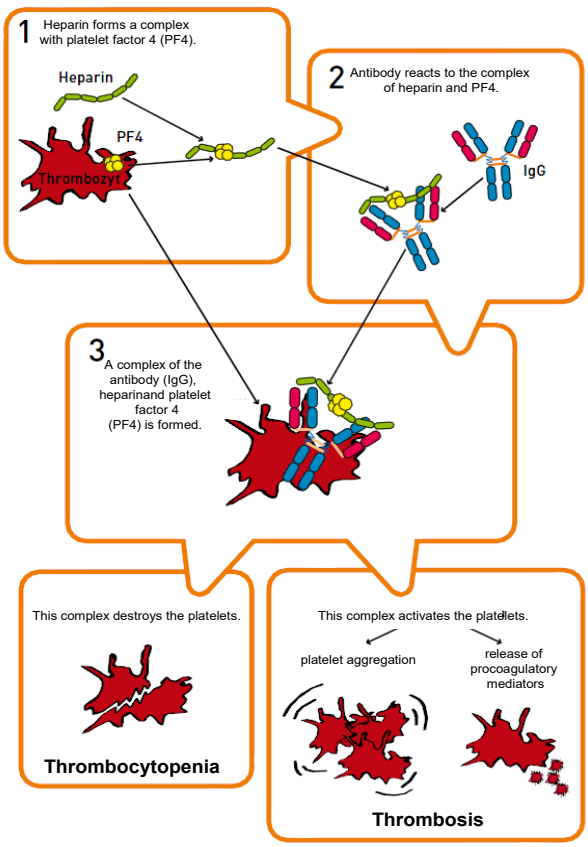


Fig. 1574 Pathophysiology of HIT II [18]

Complications

during ongoing (adequate) heparin therapy!

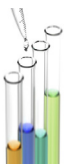
- venous (80%)
  - deep vein thrombosis (possibly with phlegmasia coerulea dolens [most frequent cause of amputation in HIT!]), acute pulmonary embolism (50%!)
  - sinus vein thrombosis
  - adrenal vein thrombosis (frequent on both sides) → acute adrenocortical insufficiency (Addison crisis)
  - mesenteric vein thrombosis
  - CVC thrombosis
  - strikingly frequent clotting of the filter in CVVH (often first sign!)
- arterial (20%)
  - acute myocardial infarction
  - stroke
  - acute vascular occlusion (especially lower extremity)
  - skin necrosis (microthrombosis)
- acute systemic reaction after heparin i.v. (anaphylactoid; shock)

thrombosis / pulmonary embolism despite adequate heparinization → do not increase heparin, but think of HIT II!

Diagnosis

- thrombocytopenia
  - platelets < 100000/µl or decrease > 50% of the initial value
  - but mostly only moderate: platelets almost never < 20000/µl (atypical for HIT → possibly additional DIC [In the combination of HIT and DIC e.g. in the context of severe sepsis, however, severe thrombocytopenia may occur!] or other cause [e.g. ITP, leukemia])
  - in 10-15% HIT without thrombocytopenia
- ⚠ PTT ↓ (despite actually relatively high dose heparin perfusor)
- tests
  - immunological (ELISA)
  - functional (HIPA)
- scores

thrombosis & thrombocytopenia
Think of:
HIT II (PTT ↓)
Antiphospholipid syndrome (PTT ↑)



Tests

- antibody test (ELISA)
- HIPA test
- serotonin release test (radioactive; clinically insignificant)

system, creating a vicious circle. C5 activates i.a. MAC (membrane attacking complex), which leads to cell lysis via pore formation in the cell membrane.

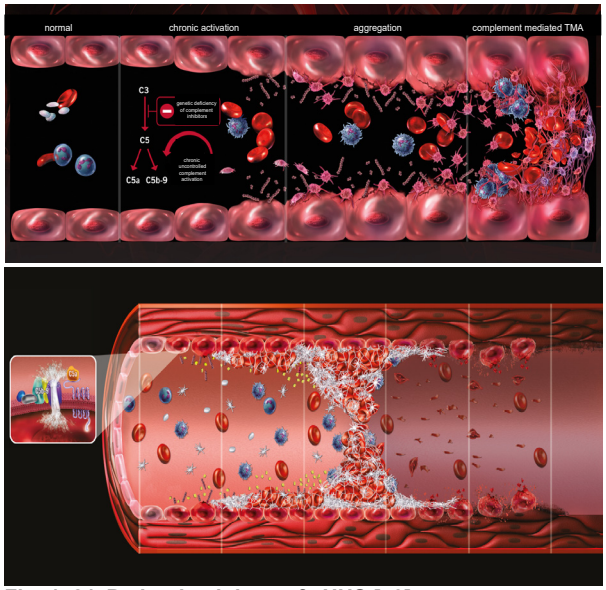


Fig. 1581 Pathophysiology of aHUS [43]

Etiology

- congenital (mostly): mutation in genes for complement inhibitors (often positive family history)
- acquired (rarely; auto-antibodies against complement inhibitors [especially against the complement factor H])

Epidemiology

- incidence: 2/1,000,000 (rarer than TTP)
- prevalence: 10/1,000,000
- especially children and young adults
- w > m

Classification

- The previous division into a primary (85%; without causes ["idiopathic"]) and secondary (15%; with causes) form has been abandoned today. The entities previously listed under the secondary forms are now understood as triggers (see page 1293) which can then trigger thrombotic microangiopathy (TMA), if there is a corresponding disposition (in case of TTP congenital deficiency of or auto-antibodies against ADAMTS-13 or in csae of aHUS congenital deficiency of or auto-antibodies against complement inhibitors).
- triggers: These further intensify the activity of the already chronically over-activated complement system (sote: The triggers of aHUS are the same as the triggers of a TTP.)

Symptoms and complications

- similar to TTP
- mostly asymptomatic (only symptomatic by a trigger [see infobox])
- mainly affects the kidneys (as is typical for a HUS; frequently acute kidney failure, possibly permanent hemodialysis); note: 2/3 of all patients will develop end stage renal disease (requiring permanent hemodialysis) or die (Noris et al, Clin J Am Soc Nephrol 2010).

Diagnosis

- microangiopathic hemolytic anemia (MAHA):
  - hemoglobin ↓
  - hemolysis parameters: LDH ↑, bilirubin ↑ (indirect), haptoglobin ↓ (note: Haptoglobin is an acute phase protein and can therefore be false normal in inflammation.), reticulocytes ↑, hemoglobinuria
  - Coombs test: negative
  - fragmentocytes (syn.: schistocytes; in the blood smear; microscopic blood count)
- thrombocytopenia < 150000/µl and/or decrease > 25% of the initial value
- exclusion:
  - TTP
    - ADAMTS-13 activity > 5%
    - auto-AB against ADAMTS-13: negative
  - typical HUS (STEC-HUS)
    - Shiga toxin (serum): negative
    - EHEC (stool): negative
- not recommended:
  - genetic tests: not useful (since numerous mutations; gene mutation also only detectable in 50% of patients; very expensive), but also not necessary
  - complement diagnostics (mostly normal complement values)

Therapy

- causal therapy (therapy of the underlying disease) in the presence of triggers
- plasmapheresis
  - initially mostly urgently required as an emergency measure in thrombotic microangiopathy in general, where as a rule there is no time to wait for the laboratory results for further differentiation into a special thrombotic microangiopathy
  - in the longer term, however, not efficient in the case of confirmed atypical HUS (in contrast to TTP)
- eculizumab (Soliris)

Eculizumab (Soliris)

- complement antibody (monoclonal humanized antibody against C5 [thus blocks the alternative complement cascade that is classically activated in atypical HUS]; terminal [distal] complement inhibitor; note: The immune response of the proximal complement remains intact.)
- previously only approved for paroxysmal nocturnal hemoglobinuria (PNH; also here uncontrolled complement activation), since 2011 now also officially approved for the therapy of HUS in childhood and adulthood (note: but only for atypical HUS)
- also possible optionally (but off-label-use) for TTP or HELLP syndrome (permitted in pregnancy), since here too, pathophysiologically an uncontrolled complement activation takes place

        - laboratory: troponin ↑ (in 94%; from > 1.5 ng/ml 4 times increased MACE risk [MACE: major adverse cardiac event]), pro-BNP ↑ (in 66%)
        - echocardiography: mostly localized (similar to cardiac sarcoidosis), in 50% reduced ejection fraction
        - cardiac catheter examination to exclude CHD (should be performed generously, provided it is not a very young patient; especially with increased troponin and limited ejection fraction)
        - cardiac MRI (LEG [late gadolinium enhancement]; generous!)
        - endomyocardial biopsy (not absolutely necessary [only rarely performed]): lymphocytic infiltration, giant cells
    - often fulminant course with high mortality (17%); i.a. Mahmood et al, JACC 2018: in 46% a MACE (major adverse cardiac event): AV block III (in 9%), cardiogenic shock (in 9%), cardiovascular arrest (in 11%), death (in 17%); also acute left heart failure (in 42%) and atrial arrhythmias (in 26%)
    - therapy:
        - discontinuation of the immune checkpoint inhibitor
        - methylprednisolone (first choice; preferably in a high dose, i.e. 2 mg/kg), possibly immunoglobulins (0.4 g/kg body weight daily for 5 days), mycophenolate mofetil, ATG (anti-thymocyte globulin), infliximab (ave: deterioration possible)
  - pericarditis (therapy: methylprednisolone)
- pulmonary (in 5%):
  - pneumonitis (hypersensitivity pneumonia, possibly ARDS; therapy: methylprednisolone [after excluding an infectious cause], if refractory to therapy: infliximab, mycophenolate mofetil, cyclophosphamide)
  - pleuritis
- renal (in 3%; possibly acute kidney failure):
  - interstitial nephritis
  - glomerulonephritis
- neurological (in 2%):
  - tremor
  - ataxia
  - seizures
  - PNP (peripheral polyneuropathy)
  - Guillain-Barré syndrome (GBS)
  - myasthenia gravis
  - meningitis, encephalitis
  - myelitis
- musculoskeletal:
  - myositis (possibly rhabdomyolysis)
  - fasciitis
  - arthritis (therapy: possibly MTX, TNFα blockers)
- ophthalmological: especially uveitis (most common), conjunctivitis, episcleritis, keratitis, retinitis (up to blindness), optic neuritis, inflammation of the orbit, endocrine orbitopathy
- hematological:
  - hemolysis
  - anemia, leukopenia, thrombopenia (pancytopenia)
  - thrombotic microangiopathy (TMA)
  - hemophilia
  - arteritis
- psychical: fatigue (very often [in 25%]!)

CAR-T-cell therapy

Definition

- new form (ATMP [Advanced Therapy Medicinal Products]) of cancer therapy (immunological, gene therapy; only offered by the corresponding specialized centers)
- CAR: chimeric antigen receptor (synthetic hybrids of receptor and signal units to target T cells against target proteins of tumor cells [especially malignant B cells])
- discovery and development by the Israeli immunologist Zelig Eshhar at the Weizmann Institute in Rechovot (Israel) in the late 1980s ("T-body", "immune receptor")
- The patient's own T cells are modified ex vivo in such a way that they express chimeric antigen receptors on their surface that are directed against a cancer-specific antigen (most commonly CD 19) of malignant cells (mostly B cells) and then destroy them.
- Detection independent of the MHC (major histocompatibility complex; HLA [human leukocyte antigen system])
- The CAR-T cells are produced individually for each patient. The production takes about 4 weeks.
- This therapy was first carried out at a 6 year old girl (Emily Whitehead from Pennsylvania, USA). At the age of 5, she developed acute lymphoblastic leukemia (ALL) and received intensive chemotherapy. The second relapse occurred at the age of 6, so that all conventional therapy options were exhausted. The parents agreed to an experimental CAR-T-cell therapy, which was carried out for the first time in 2012. The girl is now (2021) 13 years old and completely tumor-free.
- indications (if refractory or relapsed):
  - lymphomas (B-cell non-Hodgkin lymphomas; adults)

than atrial fibrillation)
    - ▪ anterior wall aneurysm (e.g. after a large anterior wall infarction
    - ▪ paradoxical embolism in patent foramen ovale (PFO)
    - ▪ endocarditis
  - ◦ aorto-arterial (plaques / atheromas of the ascending aorta or aortic arch; especially from > 4mm)
  - ◦ vasculitis (very rare; CNS vasculitis; remember this especially in younger patients without cerebrovascular risk factors)
    - ▪ primary CNS vasculitis (PACNS: primary angiitis of the CNS) ▪ secondary CNS vasculitis (infect-associated or non-infect-associated, e.g. Horton´s disease, Takayasu´s disease)
  - ◦ antiphospholipid syndrome (20% of all patients < 45 years [Every 5th stroke patient who is younger than 45 years has an antiphospholipid syndrome!])
  - ◦ Moyamoya disease (progressive, genetically determined fibrosis with severe stenosis or occlusion of the distal internal carotid artery and middle cerebral artery with formation of pronounced collaterals that look like "fog" or "smoke" [Japanese: moyamoya] in the angiogram; especially children and young people; especially in Asia)
  - ◦ unknown (40%)
- thrombotic; especially microangiopathic:
  - ◦ ⚠ frequent (about 1/3 of all ischemic strokes!)
  - ◦ typical in elderly patients with arterial hypertension and diabetes mellitus
  - ◦ lacunar infarctions (p.d. subcortical infarction in the territory of the small cerebral arteries with a maximum extension of 1.5 cm in the CT or 2.0 cm in the MRI)
  - ◦ in CCT mostly not visible, in MRT tiny, mostly subcortical located lesions
- hemorrhagic (intracranial bleeding; 20%)

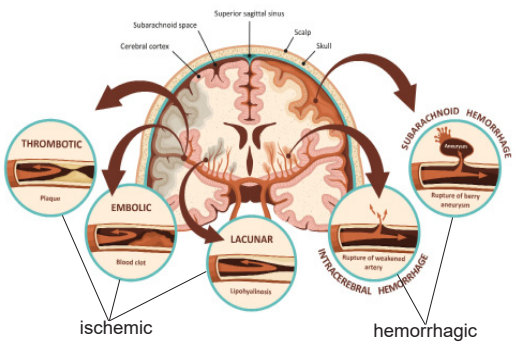


Fig. 1607 the different types of stroke

Symptoms

- hemiparesis (predominantly arm weakness; facial palsy [central])
- hemihyp-/ paresthesia
- visual disturbances
  - amaurosis fugax (ipsilateral)
  - homonymous hemianopsia (contralateral visual field)
- conjugate eye deviation (CED) to the ipsilesional side (non-paretic side)
- dysarthria (speech disorder)
- aphasia (language disorder)
  - motor aphasia (syn.: Broca aphasia): disorder of language production
  - sensory aphasia (syn.: Wernicke aphasia): disorder of speech language
- somnolence, coma
  - ⚠ absolutely untypical for ischemic stroke on the anterior circulation (only in malignant media infarction)
  - Think of other differential diagnoses (hemorrhagic stroke [intracranial bleeding], basilar thrombosis, status post epileptic seizure)!

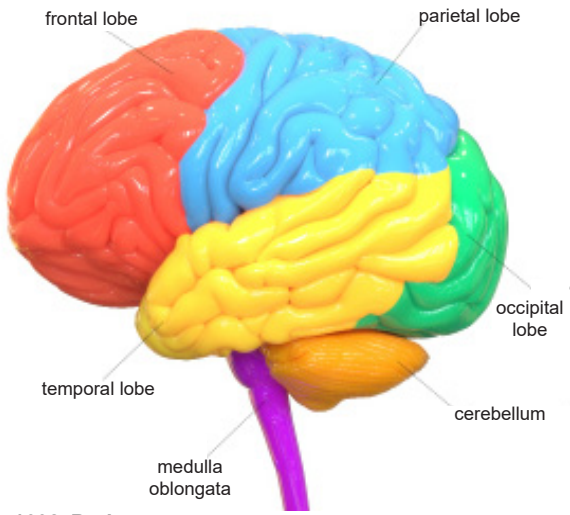


Fig. 1608 Brain: anatomy

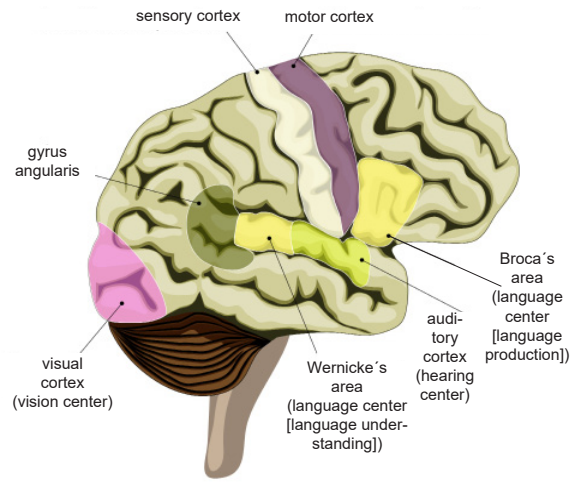


Fig. 1609 Brain: function

Territories (supply areas)

- anterior cerebral artery (ACA)
- middle cerebral artery (MCA; (the most common infarct vessel))
- posterior cerebral artery (PCA)

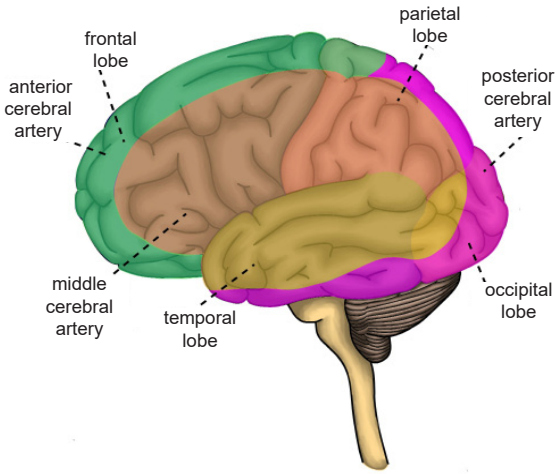


Fig. 1610 Brain: territories (sagittal plane)

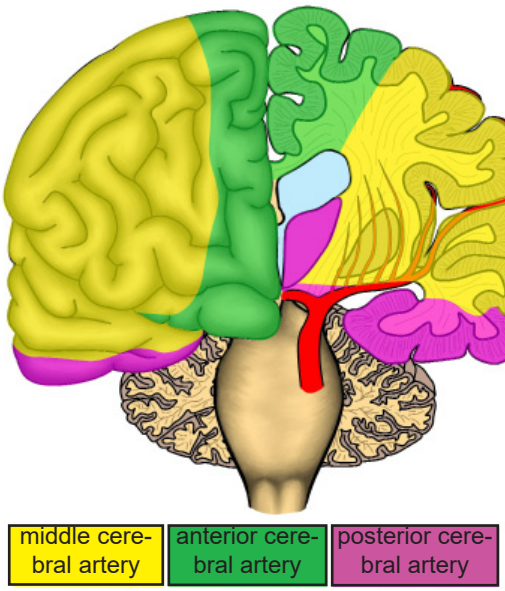


Fig. 1611 Brain: territories (frontal plane [syn.: coronal plane])

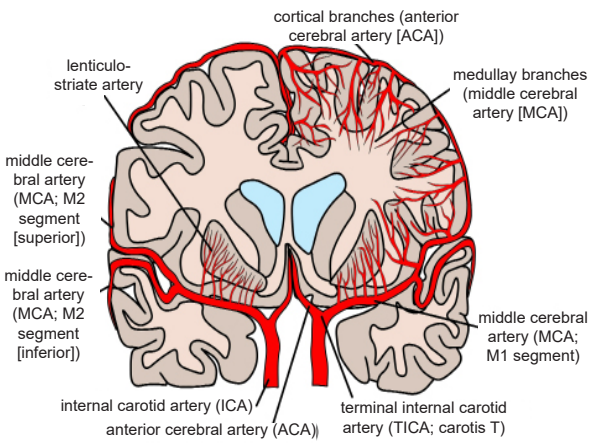


Fig. 1612 Brain - arteries: anterior circulation (carotid territory): The internal carotid artery (ICA) divides at the carotid T (syn.: TICA [terminal internal carotid artery]) into the anterior cerebral artery (ACA) and the middle cerebral artery (MCA), which is the larger branch. The middle cerebral artery is divided into 4 segments from proximal to distal: M1 (sphenoidal segment; syn.: main trunk), M2 (insular segment), M3 (opercular segment) and M4 (terminal [syn.: cortical] segment).

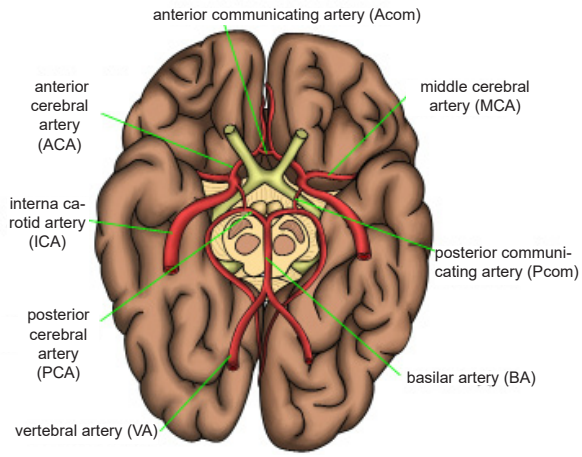


Fig. 1613 Brain - arteries: posterior circulation (vertebrobasilar territory): The anterior and posterior circulation are connected to one another via the circle of Willis at the bottom (inferior) side (base) of the brain (named after the English physician Thomas Willis [1621-1675]).

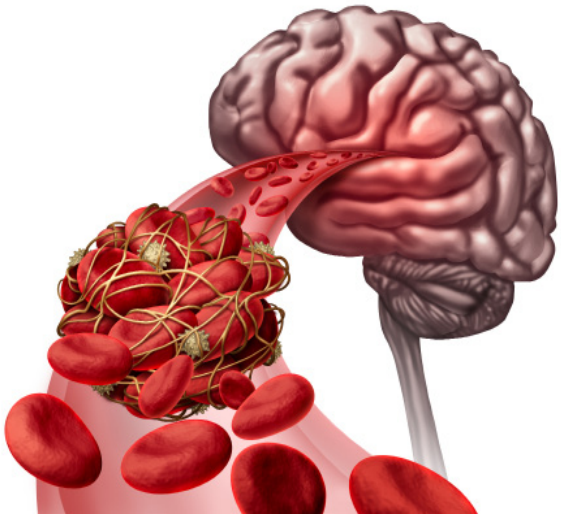
Anterior cerebral artery (ACA)

- amaurosis fugax
- anopsia
- motor aphasia
- personality change
- hemiparesis with predominantly leg weakness (in contrast to middle cerebral artery: predominantly arm weakness!)
- urinary incontinence
- akinetic mutism (if the anterior cerebral arteries on both sides are affected [bilateral ACA infarction]; typical defect syndrome)

Middle cerebral artery (MCA)

- contralateral hemisymptomatics (predominantly brachiofacial pareses)
  - hemiparesis (predominantly arm weakness; i.a. facial palsy [central, i.e. frowning is still possible])
  - hemihyp-/ paresthesia
  - hemineglect (The affected side of the body is not perceived.)
- aphasia (language dominant side [right-handed: left])
- dysarthria
- apraxia
- conjugate eye deviation (CED) to the ipsilesional side (non-paretic side)
- dysphagia (in 30%; cave: aspiration!)
- consciousness: almost always preserved

INTRACRANIAL HEMORRHAGE



Types

- epidural hemorrhage (EDH)
- subdural hemorrhage (SDH)
- subarachnoid hemorrhage (SAH)
- intracerebral hemorrhage (ICH)

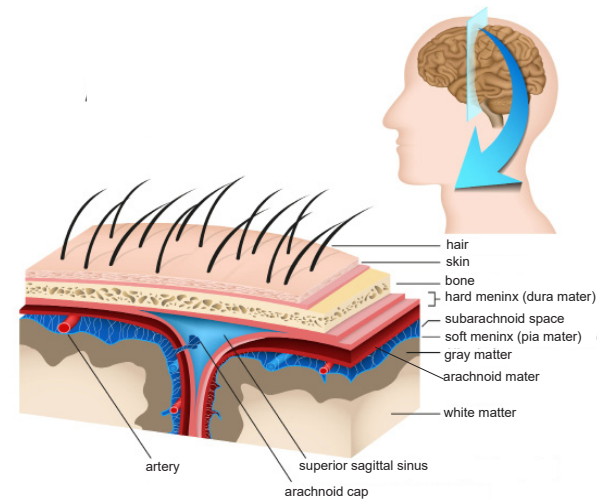


Fig. 1665 representation of the anatomy of the meninges

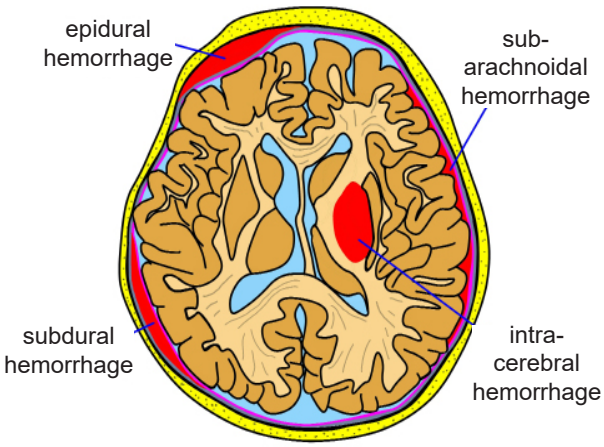
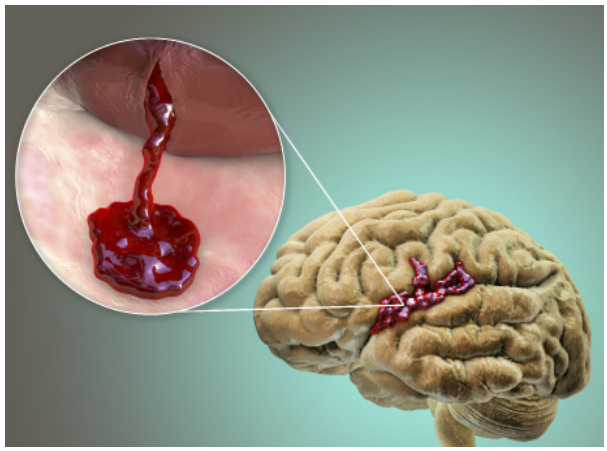


Fig. 1666 the four different types of intracranial hemorrhages at a glance

Epidural hemorrhage (EDH)



Definition

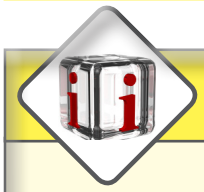
- bleeding in the epidural space (= between hard meninx [dura mater] and bone)
- almost always traumatic (traumatic brain injury [TBI])
- an arterial bleeding (rapidly expanding; tear of the middle meningeal artery or fracture hematoma)
- mostly temporal

CCT

- hyperdense
- ⚠ lenticular (biconcave)
- possibly midline shift, compression of the ventricles

diazepine i.v. in the first 5 minutes only driven by sheer actionism, hence you only buy disadvantages such as respiratory depression, muscle relaxation and possibly even the need for intubation!)
- clearing and keeping the airways clear
- no bite block (risk of injury)
- oxygen administration
- hypoglycemia → glucose 40% (cave: in alcoholics previously thiamine i.v.!)
- with pre-existing antiepileptic therapy: determine plasma levels of antiepileptic drugs
- hypothermia: no benefit (HYBERNATUS study [Legriel et al, N Engl J 2016])

Drugs (Status epilepticus)



Step-by-step therapy
Status epilepticus

Step 1 (initial status epilepticus): benzodiazepines (termination rate: 50%)

Step 2 (established status epilepticus): antiepileptic drugs (AED; anticonvulsants)
- phenytoin (Phenhydan)
- valproic acid (Orfiril, Ergenyl)
- ⚠ levetiracetam (Keppra, Desitin; means of choice!)
- lacosamide (Vimpat)
- brivaracetam (Briviact; new anti-epileptic drug; 1 amp. = 5ml = 50mg; 2 mg/kg i.v. over 15 minutes; extremely rapid influx in the brain)

Step 3 (refractory status epilepticus): narcotics

(induction of anesthesia and intubation)
- barbiturates
  - thiopental (Trapanal)
  - phenobarbital (Luminal)
- propofol (Disoprivan; just as effective as barbiturates [Prabhakar et al, Cochrane Database System Rev 2012: even higher termination rate than thiopental with fewer hemodynamic side effects and shorter mechanical ventilation]; recommended here in a very high dose [10 mg/kg/h] → cave PRIS [propofol infusion syndrome])
- inhalation anesthetic (e.g. isoflurane, sevoflurane; e.g. via AnaConDa system; only possible in mechanically ventilated patients)

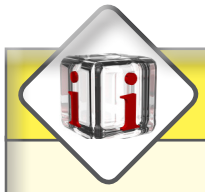
rule of thumb: "2 ampoules on each step"; after 1 ampoule wait for 5 min each

Out-of-hospital, the step 2 is almost always skipped, because usually no antiepileptic drugs are kept in stock on the ambulance vehicle. That must not be actually, since thereby many patients could be saved from intubation!

Benzodiazepines
- lorazepam (Tavor)
  - ⚠ guidelines of the German Society of Neurology: means of first choice!
  - significantly faster termination of status epilepticus than with midazolam (Silbergleit et al, N Engl J 2012)
  - 1 amp. = 2mg
  - dosage: 0,1 mg/kg i.v. (up to max. 10mg; mostly 2-4mg, i.e. 1-2 ampoules; also good option: Tavor Expidet over oral mucosa [buccal])
  - refrigerated storage: Lorazepam must be stored refrigerated. But on many ambulance vehicles there is no refrigerator. However, it is known that lorazepam is also effective at 30°C for 60 days. Therefore, it is also possible to stock lorazepam without cooling on the ambulance vehicle. One should exchange only the ampoules every two months then.
  - Lorazepam must be diluted for injection. Do not inject purely!)
- clonazepam (Rivotril)
  - 1 amp. = 2mg (up to max. 6mg)
  - dosage: 0.015 mg/kg i.v. (e.g. 2mg)
- midazolam (Dormicum)
  - ampoule sizes:
    - 1 amp. = 5ml = 5mg
    - 1 amp. = 3ml = 15mg (cave confusion!)
  - dosage: 0.2 mg/kg i.v. (e.g. 5mg)
  - also i.m. and intranasal (via MAD [mucosal atomization device; see page 40]: < 50kg: 2.5mg [0.5ml], > 50kg: 5mg [1ml]) applicable, if no access possible during status
- diazepam (Valium)
  - 1 amp. = 2ml = 10mg
  - dosage: 0,15 mg/kg i.v. (e.g. 10mg; up to max. 30mg)
  - also rectally applicable
  - only restrictive due to very long half-life (50h!)

Benzodiazepine of choice for status epilepticus: lorazepam

Tip (if no i.v. / i.o. access): midazolam 10mg i.m. or 5mg intranasally



Tips with children
Status epilepticus

In children and infants an intravenous access is frequently impossible, but on the other hand also not essential. Very good and mostly sufficient alternatives are as follows:

- **diazepam rectal**
  - **< 15kg: 5mg (small RecTube)**
  - **> 15kg: 10mg (large RecTube)**
- **midazolam**
  - **i.m.: 0.1 mg/kg (very good option!)**
  - **intranasal (e.g. via MAD [Mucosal Atomization Device; see page 40]): 0n5 mg/kg (good option!)**
  - **buccal: 0.2 mg/kg (e.g. Buccolam 5mg into the oral cavity)**

Phenytoin (Phenhydan)

- more effective than valproic acid
- the only antiepileptic drug officially approved for the treatment of status epilepticus
- dosage: 2 amp. a 250mg over 5 min i.v.
- children: 15-20 mg/kg
- rapid saturation: 750mg (3 giant vials a 250 mg) to 500ml NaCl 0.9% over 4h, then the same again over 24h; note: According to the technical information the Phenhydan injection solution of 250 mg may not be diluted with NaCl 0.9% or other solutions. As an alternative, the 750 mg infusion concentrate is available. This may be dissolved in 250-500 ml NaCl 0.9% and then applied as an infusion.)
- perfusor: 750 mg/50ml = 1.5 mg/ml → 2 ml/h
- cave extravasation → severe necrosis (purple-glove syndrome; with a pH value of 12, phenytoin is a lye, so that colliquation necrosis occurs), therefore always safe and separate access; CVC then in the course
- then phenytoin tablets p.o. 100mg 1-1-1 (very simple oralization
- TDM (therapeutic drug monitoring): target level 10-20 µg/ml
- contraindications:
  - heart failure with EF < 35% (Phenytoin is a class IB antiarrhythmic and acts negatively inotropic.)
  - AV-Block II/III (acts negatively chronotropic)
  - after myocardial infarction (proarrhythmogenic effect)
  - intoxication with theophylline (If seizures occur during intoxication with theophylline, phenytoin must never be given, as lethal interactions are known!)
  - mitochondriopathies
  - pregnancy
  - quinine therapy for malaria tropica
- side effects:
  - cardiac (i.a. cardiac arrhythmias; therefore ECG monitoring obligatory)
  - fever
  - Stevens-Johnson syndrome, Lyell syndrome (TEN: toxic epidermal necrolysis)
  - cave intoxication (double vision, tremor, nystagmus, dizziness, nausea; for phenytoin intoxication see especially page 1467)
  - gingival hyperplasia (only with long-term use)

Valproic acid (Orfiril, Ergenyl)

- preparations:
  - 1 amp. Orfiril = 300mg
  - 1 amp. Ergenyl = 400mg
- dosage: 900mg in 250ml G5% in 1h, then 1500mg in 250ml G5% over 24h
- children 20-30 mg/kg
- TDM (therapeutic drug monitoring): target trough level 100-120 µg/ml (was raised, no longer as before only 50-100 µg/ml)
- often high doses (up to 1800 mg/d) necessary
- then oralize or via nasogastric tube: Orfiril liquid 15ml (=1500mg; 1ml = 60mg; 3 x daily administration [is not a retard preparation])
- side effects: i.a.
  - pancreatitis (incidence 1: 40,000, mortality 20%)
  - encephalopathy (valproate encephalopathy)
  - disturbance of blood coagulation with an increased tendency for hemorrhage as a result
    - thrombocytopenia and thrombocytopathy (acquired von Willebrand disease)
    - fibrinogen ↓ (hypofibrinogenemia)
- interactions: via UGT (UDP-glucuronosyl transferase: This enzyme catalyzes the glucuronidation of hydrophobic substances. This makes them hydrophilic, so that they can be excreted in the urine.)
  - ⚠ no simultaneous administration of carbapenems (e.g. meropenem), as these activate the UGT and thus valproic acid is increasingly eliminated via the kidneys (Carbapenems lower the valproic acid level and are therefore contraindicated here because they lead to a weakening even to the loss of the effect of valproic acid!)
  - propofol: Valproic acid itself inhibits UGT so that propofol can be excreted less, which leads to an increase in the plasma level of propofol.
- contraindications:
  - known mitochondriopathies in own or family history
  - pancreatitis
  - liver damage
  - thrombocytopenia
  - drugs: especially carbapenems (e.g. meropenem), VKA (increased risk of bleeding because valproic acid inhibits CYP2C9 and thus the breakdown of VKA)
- for valproic acid intoxication see page 1469
- not officially approved for status epilepticus (off label-use)

- circulatory disorder of the cerebrospinal fluid, malabsorptive hydrocephalus
- brain edema, increased intracranial pressure, possibly herniation, possibly also swelling of the spinal cord (e.g. cervical spine paraplegia)
- cerebral vasculitis, vasospasm (as with SAB [therapy also with nimodipine]), cerebritis with cerebral ischemia (in 14%)
- hearing impairment (deafness)
  - caused by purulent labyrinthitis; possibly in the course of labyrinthitis ossificans
  - a frequent long-term complication
- SIADH
- rhabdomyolysis

Diagnostics

- anamnesis (wear a mask!), clinical (especially neurological) examination: i.a.:
  - Lasègue sign (pain when bending the stretched leg in the hip joint; syn.: SLR [straight leg raise] test; named after the French internist and nuerologist Ernest-Charles Lasègue [1816-1883])
  - Kernig sign (flexion of the knee when bending the stretched leg in the hip joint; named after the Russian neurologist Wladimir Kernig [1840-1917])
  - Brudzinski sign (flexion of the knee and hip joint when bending the head forward; named after the Polish pediatrician Jozef Brudzinski [1874-1917])
  - head shake test (saying "no"; jolt accentuation): amplification of the headache by rapid horizontal rotation of the head (but not very specific and sensitive [Hidetaka et al, Am J Emerg Med 2013]).
- laboratory: i.a. leukocytosis, CRP ↑ (A normal CRP excludes bacterial meningitis by 97% [Nathan et al, Curr Clin Top Infect Dis 2002].), procalcitonin ↑)
- blood culture
- CCT
  - generous before lumar puncture to exclude elevated ICP (otherwise danger of herniation!)
  - The ophthalmoscopy, which almost nobody can do any more anyway, is not sufficient for this! Usually, an ophthalmologist is only available around the clock at centres anyway: However, only a small fraction of intensive care patients are treated there.
  - Mostly, however, one is too afraid of herniation, the risk is only 1%. Much more dangerous for the patient is the time delay before the start of antibiosis. If there is no disturbance of consciousness (German guideline: GCS ≥ 13, European guideline: GCS ≥ 10), no focal neurological deficit and no seizure, CCT can and should be avoided before lumbar puncture (time delay). Nevertheless, CCT should then be carried out in the further course (within 24 hours, but only after lumbar puncture) to clarify the cause (e.g. mastoiditis) and possible complications (e.g. brain abscess, subdural empyema).
  - identification of a possible infection focus (e.g. sinusitis, mastoiditis)
- lumbar puncture (spinal tap; CSF [cerebrospinal fluid])
- if pneumococci is detected: ENT council with the question of parameningeal infection (e.g. otitis media, sinusitis, mastoiditis) and, if necessary, surgical focus control

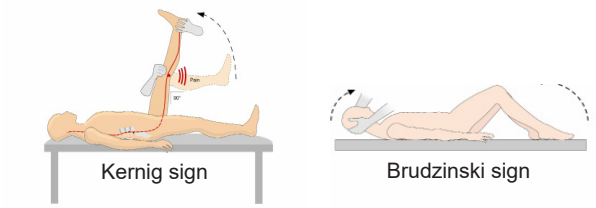
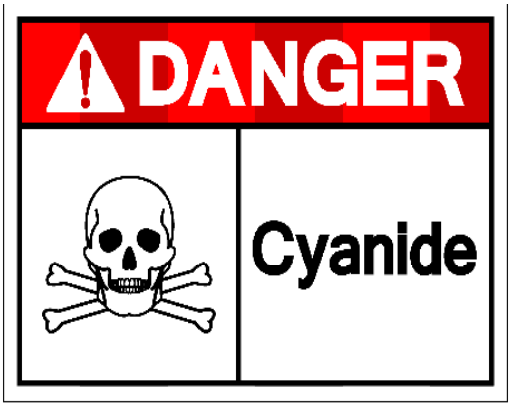


Fig. 1726 clinical signs of meningitis (as a sign of meningeal irritation): left Kernig sign (If the physician bends the extended leg in the hip joint, the patient bends in the knee joint due to the pain.), right Brudzinski sign (If the physician bends the head in the atlanto-occipital joint, pain-related flexion occurs in the patient in both the hip and knee joint, with the result that the legs are tightened.)

Lumbar puncture

- syn.: spinal tap
- to gain and examinate CSF (cerebrospinal fluid)
- before starting antibiotic treatment
- informed consent of the patient
- prerequisite: Quick > 40%, platelets > 50,000/µl (in case of emergency > 20,000/µl sufficient; if necessary, administration of coagulant therapeutics before the puncture); according to the current recommendations of the German Society for Neurology, however, the laboratory values for concerning coagulation should not be awaited if there are no petechiae (e.g. not in the case of Waterhouse-Friderichsen syndrome)
- position: seated ("cat's arched back"; mostly) or lateral (legs tightened; if e.g. ventilated in intensive care unit)
- local anesthesia (especially in awake patients; e.g. lidocaine)
- puncture site(lumbal):
  - level: connecting line between the posterior superior iliac spines on both sides (usually L3-L4)
  - between the spinous processes
- first prick cannula, then puncture needle
- examination:
  - laboratory (cerebrospinal fluid status)
  - microbiology (gram staining and cerebrospinal fluid culture)
  - virology (i.a. herpes simplex virus, enteroviruses, FSME virus)
- storage: In principle, cerebrospinal fluid (CSF) should never be stored, but processed immediately! If you store CSF, then at room temperature and never in the refrigerator: Meningococci will then no longer grow! Blood culture bottles inoculated with CSF should be stored in the incubator. A 24h readiness of the microbiological institute is actually obligatory!
- post-lumbar puncture syndrome (PLPS):
  - definition: CSF negative pressure syndrome as a result of CSF loss (leakage) through a perforation site in the dura mater with severe headache (typically depending on the position) after the lumbar puncture
  - prophylaxis:

Intoxication with cyanides



Definition

- hydrocyanic acid (hydrogen cyanide [HCN]; syn.: prussic acid)
- potassium cyanide (KCN; "cyanide"): potassium salt of hydrogen cyanide
- ⚠ most common cause of death in a fire (even more toxic than carbon monoxide; very quick effect)
- $T_{1/2}$ = 1h (only very short)

Pathophysiology

- blocking of the cytochrome oxidases (especially of the cytochrome C oxidase [binding to the heme a3 cofactor]) in the mitochondrial respiratory chain ("cell respiration") → internal asphyxiation (Cyanide ions attach to the iron [only to the trivalent, not divalent iron] of the cytochrome oxidases and thereby inhibit oxidative phosphorylation. The blockage of oxygen utilization leads to anaerobic glycolysis and consequently to lactic acidosis.)
- In the body, cyanide is physiologically broken down by the rhodanide synthetase to rhodanide (= thiocyanide), which is completely non-toxic and is excreted renally. However, if too much cyanide accumulates, this degradation path is oversaturated and no longer sufficiently possible.

Occurrence

- smoke gas (No.1; especially when burning nitrogenous material; typical domestic fire); especially
  - plastics (especially polyurethane, polyacrylamide, polyvinyl chloride [PVC])
  - textiles (especially wool, silk, nylon)
- metalworking (metal hardening) and chemical industry
- gold cleaner (e.g. goldsmith)
- pesticides: i.a.
  - methyl isocyanate (MIC; including 1984 in Bhopal, India, the largest chemical accident of all time with approximately 8,000 deaths due to the escape of methyl isocyanate from the company Union Carbide)
  - Zyklon B (originally developed by Degesch in 1922 as a pesticide, but then mainly used in 1942-1944 for mass murder in the concentration camps during the Holocaust)
- potassium cyanide
- sodium nitroprusside (in addition to NO also release of cyanide [from dosage > 0.15 mg/min therefore additional administration of sodium thiosulphate recommended])
- stone fruit kernels
  - content: cyanogenic glycosides, especially amygdalin (is degraded to hydrocyanic acid by intestinal bacteria)
  - e.g. apple kernels, apricot kernels (> 10 pieces potentially lethal; i.a. propagated as an alternative healing method ["vitamin B17"] against cancer)
- cherry laurel (see also page 1562)
  - a popular hedge plant in gardens and parks
  - content: cyanogenic glycosides (especially prunasin; only in seeds and leaves, not in the pulp; prussic acid, which is synonymous to hydrocaynic acid, is formed when chewed and swallowed)
- bitter almonds
  - content: amygdalin (is degraded to hydrocyanic acid by intestinal bacteria)
  - dangerous for adults: > 80 bitter almonds, for children: > 10 bitter almonds
- Brix (plus): cutting agent for cannabis (mixture of sugar and liquid plastic): During consumption (smoking), the liquid plastic is burned and smoke gases (e.g. cyanide, CO) are inhaled.
- laser ablation (laser hair removal): Toxic substances such as carbon monoxide and cyanide might be released with a potential risk for physicians and patients (Chuang et al, JAMA Dermatol 2016). Smoke outlet and ventilation must therefore be ensured.

Etiology

- smoke gas from burning plastic, textiles (most common cause; especially at low combustion temperature [smoldering])
- accident in electroplating plants
- suicide / murder with (postassium) cyanide

most common cause of cyanide intoxication: smoke inhalation in a fire! most common cause of death from smoke inhalation: cyanide intoxication!

Symptoms

- bitter almond odour (cannot be smelled by all people [only approx. 40%; genetically determined])
- headache
- ⚠ rosy skin color (as in case of CO intoxication; despite hypoxia; pulse oximeter shows high saturation!)
- nausea, vomiting
- colics
- dizziness
- dyspnoea (agonizing breathlessness without cyanosis!)
- angina pectoris (due to the lack of oxygen; often also

Therapy

- ⚠ highly dosed oxygen therapy
  - 15 l/min via mask untril CO-Hb < 3% (target value)
  - very good option here also: HFNOT (high-flow nasal oxygen therapy; up to 60 l/min oxygen possible)
  - usually necessary over several hours
  - Oxygen is the only antidote and means of choice in CO intoxication! It displaces the carbon monoxide from the hemoglobin. The administration of oxygen reduces the half-life of CO-Hb from 320 minutes to 74 minutes (Hampson et al, Am J Resp Crit Care Med 2012).
  - impaired consciousness or respiratory insufficiency → intubation and mechanical ventilation with FiO_2 of 1.0
- metabolic acidosis → sodium bicarbonate 8.4% (but only from a pH < 7.2: The shift to the right of the hemoglobin oxygen binding curve is a physiological mechanism to facilitate the release of oxygen to the tissue [Bohr effect]!)
- rhabdomyolysis (CK > 5000 U/l) → fluid administration and alkaline diuresis (sodium bicarbonate 8.4%)
- brain edema → (exceptionally) glucocorticoids i.v. (dexamethasone)
- An antidote (i.v. application) is currently being researched: It is neuroglobin H64Q-CCC. This is a special hemoglobin with 500 times higher affinity for carbon monoxide than hemoglobin, so it binds carbon monoxide. It has already been investigated in mice (Azarov et al, Science Translational Medicine 2016).
- hyperbaric oxygen therapy (HBO: hyperbaric oxygenation; pressure chamber)

the most important and only antidote in carbon monoxide poisoning: highly dosed oxygen!

Even if you work in a clinic with a hyperbaric center and no HBO is performed for CO intoxication (because it is not indicated), you should still not forget to administer oxygen!

Hyperbaric oxygenation (CO intoxication)

Definition

- reduction of half-life of CO-Hb from 320 min to 23 min
- according to TS 300-90 (TS: therapy scheme, 300 kPa over 90 min, syn.: Boerema scheme); total duration of one session: 155min; one session is almost always sufficient
- time: start within 6 hours if possible (no more after 24 hours)
- In the case of inpatient treatment, the costs are covered by the statutory health insurances in Germany (according to § 137c SGB V "sufficient, appropriate, economical"; however, no costs are covered for outpatient treatment).

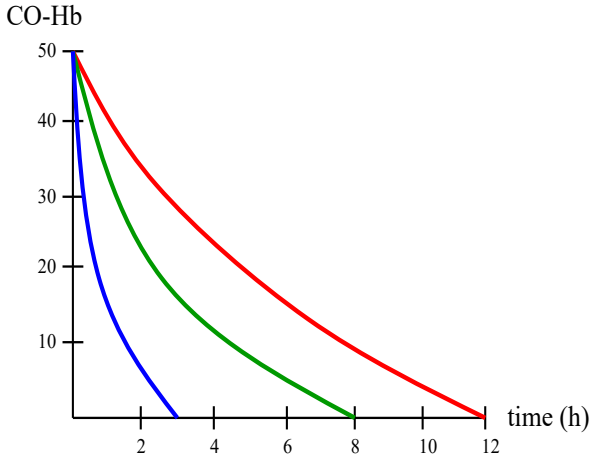


Fig. 1819 Hyperbaric oxygenation (pressure chamber therapy) can significantly shorten the half-life $T_{1/2}$ of CO-Hb. The curve is shown in red under room air (O_2 21%; $T_{1/2}$ 320min), green under 100% O_2 under normobaric (1 bar) conditions ($T_{1/2}$ 74min) and finally in blue 100% O_2 under hyperbaric (3 bar) conditions ($T_{1/2}$ 23min).

Indications

- continued impairment of consciousness, unconsciousness
- neurological deficits
- myocardial damage (e.g. signs of ischemia in the ECG, ⚠ positive troponin [note: Patients with CO intoxication and positive troponin do not need a cardiac catheter examination, but an HBO!])
- respiratory failure
- metabolic acidosis (pH < 7.20)
- pregnant women
  - ⚠ Pregnancy is not a contraindication for HBO!
  - Im Vordergrund steht die fetale Gefährdung! Diese ist extrem hoch, da Kohlenmonoxid zum fetalen Hämoglobin eine noch viel höhere Affinität hat als zum adulten Hämoglobin!
- infants (Carbon monoxide has an even higher affinity to fetal hemoglobin than to adult hemoglobin!)
- CO-Hb > 25% (Since the CO-Hb concentration only correlates modestly with the severity of CO poisoning, this parameter can only be regarded as relative [just a surrogate parameter].)

severe CO intoxication: think about hyperbaric oxygenation!

Assessment

- very little evidence
- In some studies, a significant improvement in neurological outcome was demonstrated, but no evidence of a reduction in mortality.
- Overall, the evidence for HBO in CO intoxication is inconclusive, as the available studies (i.a. Annane et

Fig. 1851 plants containing digitalis: lily of the valley

Fig. 1852 plants containing digitalis: oleander

Monkshood

Definition

- syn.: wolfsbane, Devil's helmet (aconitum napellus)
- ⚠ most dangerous plant in Europe
- occurrence:
  - ornamental plant in gardens (unfortunately frequent)
  - damp meadows, brook banks, around alpine huts (Only a few plants grow there which are not eaten by cattle!)
  - use of the plant for homeopathy and TCM (Traditional Chinese Medicine): Cooking causes hydrolysis of the aconitine. However, incorrect preparation can lead to intoxication.
- poisonous plant of the year 2005 (highly toxic!)
- poison: aconitine
  - lipophilic
  - acts especially as a neurotoxin → central respiratory paralysis
  - It causes a persistent activation of voltage-dependent sodium channels of the cell membrane (especially of the nervous system, myocardium and peripheral muscles).
- lethal dose: 5-10 mg (About 4 blossoms are enough!)
- serum level of aconitine measurable in toxicological laboratory (from > 2,6 µg/l mostly lethal)
- history: i.a. used by Pope Clement VII for executions
- The first monkshood grew on the hill akonitos (today Turkey) where Herakles dragged the hellhound Kerberos up from Hades (underworld). It was said that Kerberos had a poisonous bite and his poison dropped onto the ground and sprung up as monkshood.

Etiology

- accidental
  - ingestion of the blossoms by small children (These plants should not be planted in gardens, in which children play!)
  - confusion of the leaves of monkshood with those of parsley or lovage
- suicidal (e.g. mixing the blossoms in tea, Chinese herbal teas, ingestion of topical substances from TCM [traditional Chinese medicine])

Fig. 1853 monkshood: most toxic plant in Europe (should not be planted in gardens, in which children play)

- pathophysiology: The current mainly flows over the body surface ("flashover"). This leads to a drop in voltage.
- It is completely harmless to touch a patient struck by lightning, i.e. no false restraint here in rescue measures.
- Resuscitation after a lightning accident has a very high chance of success, which should be considered when triaging several injured persons: A lifeless patient has priority in this case.
- mortality: "only" 30 % (since usually not directly, but only indirectly struck by lightning)

Epidemiology

- approx. 800 lightning accidents / year (Germany; 2019: 329,000 lightning strikes, 110 injured, 4 deaths)
- approx. 1000 deaths from lightning accidents / year (worldwide)
- frequent in young men (m:w = 4:1; especially outdoor athletes)
- in Germany:
  - especially in southern Germany
  - especially July to August

Damage mechanisms

- direct (rare): usually complete body destruction (burning, charring), so that the outcome is usually lethal
- indirect (frequent)
  - contact effect (conduction): Lightning strikes an object (e.g. golf club), which is in contact with the victim.
  - side flash effect: Lightning strikes primarily another object (e.g. a tree). Part of the energy is then transferred secondarily to a person nearby.
  - lightning step effect (ground current): partial current flow mostly from foot to foot (potential difference) without involvement of the heart in people who are in some distance (< 200m) from the lightning strike on the ground (relatively harmless)

Symptoms

- unconsciousness
- severe burns (especially head, neck, shoulder)
- marks on the skin
  - syn.: Lichtenberg figure (named after the German physicist Georg Christoph Lichtenberg [1742-1799])
  - fern- or tree-like dendritic erythema ("electrical treeing", "lightning tree")
  - proof of a lightning accident that took place (only available here!)
- shoes often completely torn (classic finding in a high-voltage accident such as a lightning strike)
- temporary paralysis (keraunoparalysis [lightning paralysis; Greek "keraunos": lightning]; especially respiratory paralysis due to a lesion of the respiratory center in the medulla oblongata with consecutive respiratory arrest)
- hearing disorder (mainly due to eardrum rupture as a result of barotrauma caused by the shock wave)
- visual disorder (mainly due to keratoconjunctivitis ["arc eye"])
- pupils often wide and not responsive to light (caused by sympathicotonic activation; normal and no sign of brain damage!)
- ventricular fibrillation or asystolia
- possibly rupture of internal organs caused by the shock wave (e.g. splenic rupture, aortic rupture)
- possibly intracranial hemorrhage (CCT!)

unclear somnolence + torn shoes: typical for a high-voltage accident (if, in addition, located outdoors, existing Lichtenberg figure and a recent thunderstorm: typical for a lightning accident)

Therapy

- self-protection (especially of the rescue staff): circuit interruption
  - low-voltage accidents (e.g. in the household):
    - switch off the device, pull out the mains plug, if necessary switch off the fuse in the household (fuse box), if necessary isolate the location
    - If the patient is still in contact with the power source, he should never be separated directly, but only indirectly (e.g. with a dry wood slat, broomstick, leather gloves).
  - high-voltage accidents:
    - rescue only by specialized staff (aualified electrician)
      - always contact the system operator; first ensure that the system is disconnected from the power supply, then make sure that it cannot be restarted and cover adjacent voltage carriers, earth and short-circuit
      - e.g. fire brigade, e.g. technical commissioner, e.g. emergency manager at the railway company (e.g. in Germany Deutsche Bundesbahn: The emergency manager disconnects the earth rods in front of and behind the accident site [rail earthing]. Before earthing, one may approach the overhead line [e.g. contact wire] of the railway [15000 V!] up to max. 1.5 m, because of the electric arc risk. In the case of parts of the overhead line [e.g. contact wire] hanging down the safety distance must even be 10m! One must also never walk on the tracks, as they may also be live!)
      - 5 safety rules: switching off the power supply, feedback, securing before switching on again, checking the absence of voltage, visible earthing
    - always maintain safety distance (distance to current-carrying parts: at least 1 m per 1000 V), never approach the high-voltage accident victim in the dangerous area before approval of the corresponding specialized rescue team (may be difficult, but otherwise you would risk your own life [no false helper syndrome!])

- swimming pool
  - private
  - public (outdoor, indoor)
- other:
  - bath tub (especially for infants)
  - rain / water barrel
  - wells, water ditches
  - building excavation
  - canals, harbour basins
- especially in the summer months and on weekends
- m > w (2:1)
- frequent accident-related cause of permanent disability and death
- third most frequent cause of death (among toddlers, i.e. children < 5 years, even the second most frequent cause of death [after traffic accidents, i.e. polytrauma])
- annual deaths:
  - in Germany: approx. 500
  - worldwide: approx. 450000

drowning: the second most frequent cause of death among toddlers!

Etiology

- unattended toddlers (most common cause; e.g. child falls into insufficiently secured garden pond; e.g. toddler unattended in bathtub)
- non-swimmers
- exhaustion
- alcohol intoxication
- epilepsy (e.g. seizure), disability (physical / mental)
- injury when jumping into the water
- boat accident, ship accident
- swimming pool blackout: Before diving (e.g. as a "competition" with friends in the public swimming pool), hyperventilating is done consciously so that the pCO_2 drops. By venting down the pCO_2, the respiratory drive is eliminated and you can dive longer. The point in time from which the rising pCO_2 exceeds the critical value, from which the respiratory drive and thus the ascent is forced, is delayed. The hypoxemia causes almost no respiratory drive, only the hypercapnia. However, the hypoxemia can cause the diver to become unconscious.
- suction pumps in swimming pools: If these are insufficiently secured (e.g. in hotel pools on vacation, wave pool), children in particular can be sucked in under water (especially through their hair) and drown while diving.

Pathophysiology

- initial panic reaction with frantic automatic swimming movements (fight for survival)
- after submersion, deliberate cessation of breathing (apnea) for 1-2 minutes
- then forced breathing due to the no longer deliberately suppressible stimulation of the respiratory centre due to the pCO_2 increase (maximum breathing stimulus) with aspiration
- diving reflex:
  - reflexive laryngospasm
  - In this phase, large amounts of water are often swallowed.
  - increased hypoxemia and hypercapnia
  - usually only present in small children
- unconsciousness
- release of the laryngospasm (persists in 10 %, which then leads to dry drowning) → aspiration of water
- The amount of inhaled (aspirated) water is usually low (< 22 ml/kg; the average is usually only about 10 ml/kg). Most of it is swallowed!
- The aspiration of water leads to inactivation and washout of surfactant, which causes atelectasis with intrapulmonary shunts, reduced compliance of the lung and ARDS.
- seizures (caused by hypoxia; hypoxic convulsions; asphyxiation cramps)
- agonal breathing
- hypoxia-induced bradycardia and cardiovascular arrest

Cardiovascular arrest during drowning is not primarily a cardiac problem, but a respiratory problem (due to hypoxemia)!

Drowning accident: The lung is empty, but the stomach is full!

Differential diagnoses

- unconsciousness during bathing or swimming without direct exposure to water (e.g. myocardial infarction [especially in elderly people], epileptic seizures, syncope): no aspiration of liquid (dry drowning)
- Finding an unconscious patient in the bathtub one should consider:
  - electrical accident (especially in the bathtub [hair dryer]; accident or even homicide)
  - carbon monoxide intoxication (e.g. defective instan-

ETHICS & LAW

Intensive care medicine has the primary goal of treating potentially reversible damage that has led to an acute risk to the patient. It is intended to bridge life-threatening phases and create time for causal therapy of the underlying disease. But it also has its limits, which should be accepted. The death of an intensive care patient must not be understood as an accident or even as defeat. Dying should be accepted as an inevitable process. Especially at the end of life, dying with dignity and with peace must be made possible for the patient, preferably in the presence of his relatives. The natural limits of life are artificially pushed further and further by intensive medicine. It does not make sense to do everything that can be done. The maxim "to live at any price" (rule of rescue) or "to prevent death at any price" must not apply, which would only prolong an irreversible dying process. "The progress in medicine is tremendous - one is no longer sure of one's own death" (Hermann Kesten, German writer, 1900-1996). In case of hopelessness, intensive therapy is pointless ("futility"; Latin: futilis [useless, in vain]). Intensive care medicine should not be too intensive ("less is more"). It should always be questioned whether the often extremely high burden of intensive care treatment for the patient is at all justified with regard to the realistically achievable quality of life for the patient. A major problem that is common especially in the intensive care unit at the end of life, is overtherapy (oversupply), i.e. overuse of medical services. It plays a major role, especially in industrialized nations such as Germany. With 34 intensive care beds per 100,000 inhabitants (a total of approx. 28,000 intensive care beds), Germany has the highest density of intensive care beds in the world. Overtherapy is understood to mean the excessive use of medical services (diagnostics, therapy), which no longer lead to any relevant improvement in duration (prognosis) or quality of life, and ultimately do more harm than good ("senseless" therapy) or which is anyway not wanted or even rejected by the patient (after appropriate information). Overtherapy disregards all four basic medical ethical principles (see page 1572) and finally represents a burden resources of the health system. In a meta-analysis (Cardona-Morrell et al, Int J Qhal Health Care 2016) it could be shown that every third patient at the end of his life is still receiving an unjustified therapy in the sense of overtherapy. The problem of overtherapy is also taken into account in a corresponding position paper of the Ethics section of DIVI and DGIIN 2021 in Germany. In palliative situations, decisions must be made about limitation or discontinuation of therapy (so-called "controlled" intensive medicine; WLST: withdrawal of life-sustaining therapy). In this case, the therapy objective is changed. This should and must also be clearly and unambiguously documented (e.g. no resuscitation, no intubation) and not for unfounded fear of any legal consequences with acronyms (DNE: do not escalate, DNR: do not resuscitate, DNI: do not intubate, AND: allow natural death) or any drawings (e.g. "flowers") on the temperature curve. For this we use a document (see infobox for content), on which the individual therapy limits for the patient are clearly documented and signed by the doctors involved and then filed in the patient file. Proper documentation should always be ensured. The documentation sheet on therapy limitation of the Ethics section of the DIVI (available on the homepage of the German Interdisciplinary Association for Intensive Care and Emergency Medicine [www.divi.de]) is analogous and can strongly be recommended.

Therapy limitation
Checklist

- **reasons:**
  - **no more medical indication (e.g. further maximum therapy poinlless, dying process has already begun)**
  - **will of the patient (rejects intensive care therapy)**
  - **pronounced frailty (Clinical Frailty Scale [CFS] ≥ 7; see infobox)**
  - **other**
- **advance directive / health care proxy present**
- **team meeting or (if necessary) ethic council has taken place**
- **clarification talking / information discussion has taken place (with patient, relatives, caregiver)**
- **The following measures will no longer be carried out (the corresponding should be ticked):**
  - **resuscitation**
    - **mechanical**
    - **electrical (defibrillation)**
  - **ventilation:**
    - **invasive**
    - **non-invasive**
    - **increased invasiveness of ventilation**
  - **extracorporeal support procedures**
  - **catecholamine therapy (start or increase)**
  - **renal replacement procedure**
  - **therapy with blood products**
  - **antibiotic therapy**

The decision should and must be made by the treating physician himself and must not be left to the relatives alone, which unfortunately happens very often in practice (e.g. when relatives are asked: "Should we still put your mother in intensive care and artificially ventilate her with machines?"). Relatives are often not physicians. They should also not be expected to decide on the life and death of close relatives, which could lead to con-