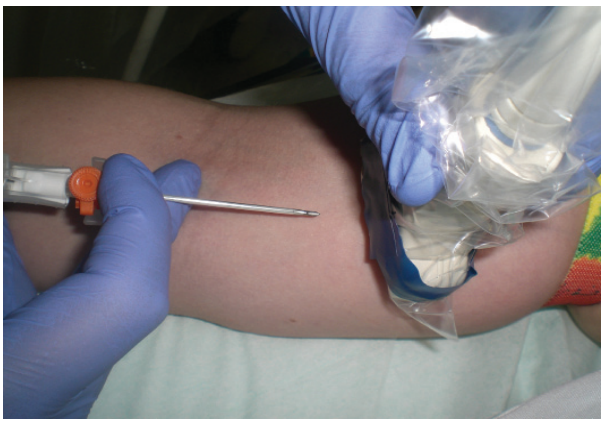
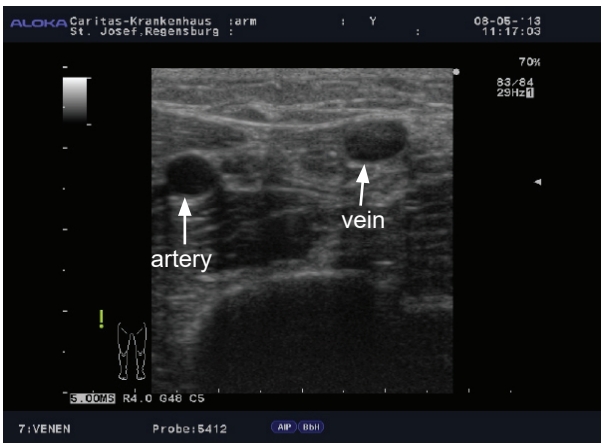
Tip for extremely poor vein status in an emergency: sonographically aided positioning of the Braunula in antecubital fossa or proximal medial upper arm





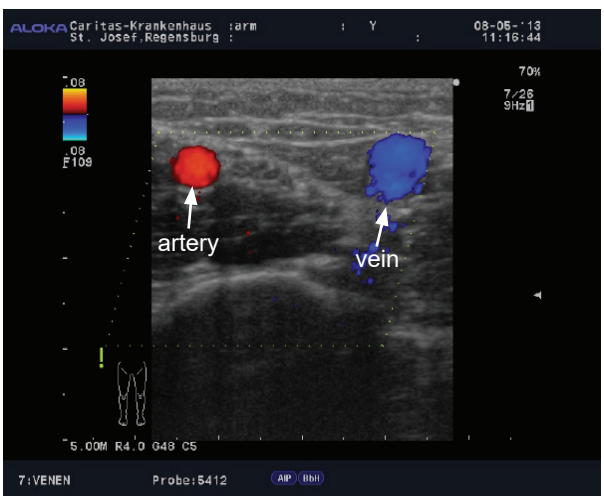


Fig. 003 sonographically aided positioning of a Braunula with the linear array probe in the proximal medial upper arm: good emergency option in case of poor vein status in the emergency room or in the intensive care unit (there should always be an ultrasound device!)

Central venous access

Definition

- central venous catheter (CVC)
- catheter in the vena cava (superior or inferior)
- made of polyurethane, coating with hydromer
- flow rate: approx. 100-150 ml/min (note: Shaldon-catheter: 300-400 ml/min)
- lumina:
  - A single catheter incorporates separate, noncommunicating access lumens within its body.
  - CVCs may have a single or multiple lumens (one to five lumens; meanwhile even CVCs with seven lumens on the market).
  - In the intensive care medicine you should at least use triple-lumen catheters. Especially in the internal intensive care medicine one should rather use multi-lumen CVCs (preferrably five-lumen catheters) in case of doubt. It is not unusual that, after a triple-lumen CVC has been positioned, the patient's condition aggravates within the next few days and additional lumens are needed for the administration of catecholamines, for parenteral nutrition or for the PiCCO techology. Then one must change to a five-lumen CVC or in case of a lay time of > 48h the CVC has to be positioned once again, which is extremely annoying. A five-lumen CVC is not more expensive than a triple-lumen CVC! However, it should be noted, that the risk of infection increases with the number of lumina.

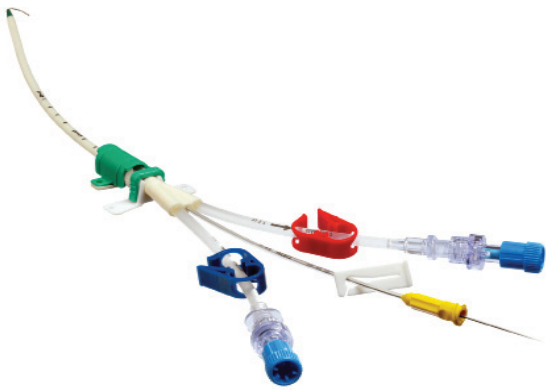


Fig. 004 central venous catheters (CVC): triple-lumen [8]

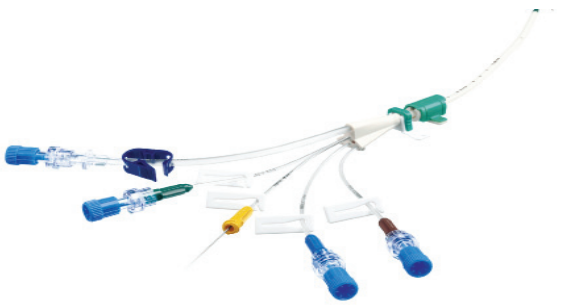


Fig. 005 central venous catheters (CVC): five-lumen [8]

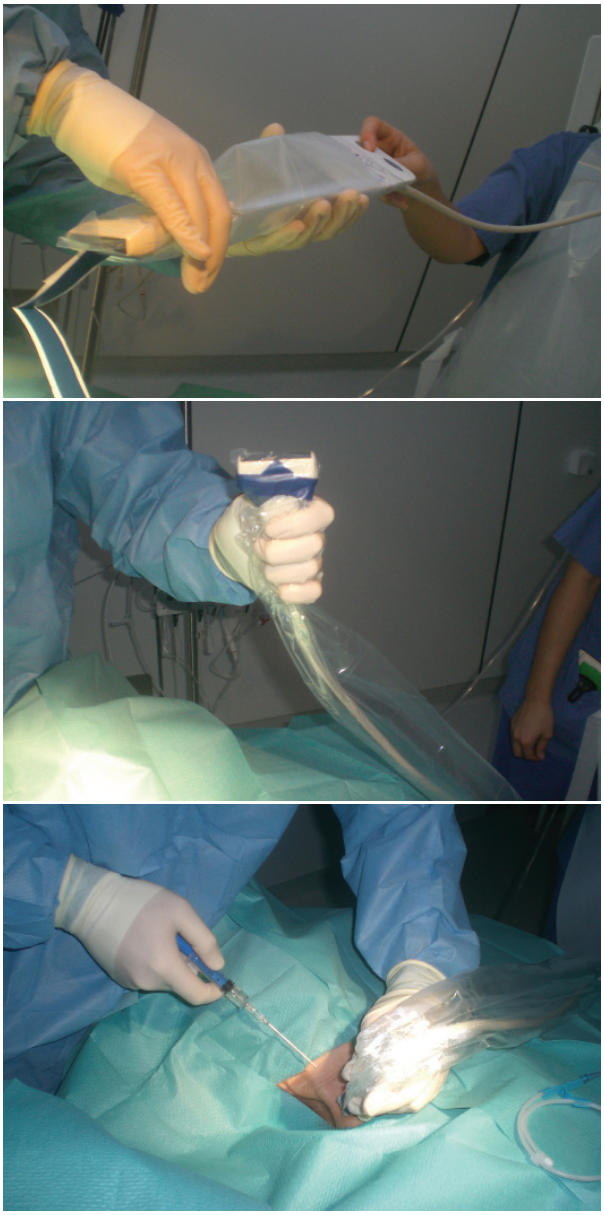


Fig. 015 CVC-insertion internal jugular vein using ultrasound: The probe is provided with a sterile cover. The puncture is done under visual control.

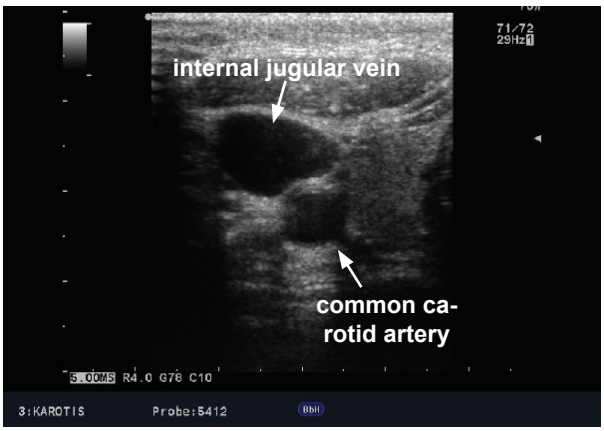


Fig. 016 Ultrasound of right cervical vessels: lateral the internal jugular vein, medial the common carotid artery (The vein can be compressed easily, but not the artery.)

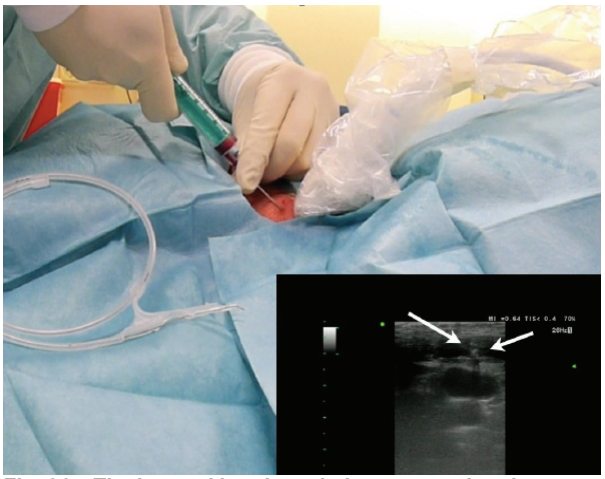


Fig. 017 The internal jugular vein is punctured under sonographic view.

CVC-insertion into internal jugular vein always under sonographic control (time saving + increased patient safety!)

There´s not only the internal jugular vein and popcorn in the neck (cave: risk of injury in blind punctures)!

Puncture of subclavian vein

- 3 cm below the clavicle
- exactly in MCL (midclavicular line) in the direction of the Clavicula
- also under sonographic control, if necessary (imaging of the vein in longitudinal view; certainly more difficult than in the case of the internal jugular vein
- contact with periosteum, then insertion towards jugulum (never deeper than jugulum due to increased risk of pneumothorax!)
- assessment:
  - advantages:
    - The ligamentous apparatus keeps open the vessel (also open during hypovolaemic shock).
    - lowest risk of infection
    - no hindrance of cerebral venous drainage: Therefore, primarily in neurosurgical intensive care units, CVCs are more often inserted into the subclavian vein and less often into the jugular vein, because the venous drainage from the brain may be impeded with an already inserted CVC in the jugular vein which leads to increased brain pressure.
  - sisadvantages:
    - increased pneumothorax rate (Therefore be careful with patients suffering from severe respiratory insufficiency: In this case a pneumothorax may have serious consequences! If you nevertheless decide to insert a CVC into the subclavian vein, you should always choose the side which looks

Placement

- extend neck
- deflate cuffs
- lubricate tube
- blind introduction of the tube (i.e. without laryngoscope) into the pharynx, until the middle depth marking lies on a level with the front teeth
- inject 70-100 ml of air (marking on the syringe); both cuffs are inflated at the same time
- If the tongue gets blue after blocking (while the lips are rosy), the cuff is overblocked and must be released. The too strong blocking (hyperinflation) leads to an obstruction of the venous vessels of the tongue and therefore to a swelling of the tongue. This can cause a difficult airway (e.g. after a successful resuscitation during which a laryngeal tube was inserted preclinically by the first responder emergency medical team), when you want to exchange the laryngeal tube through an endotracheal tube inner-clinically in the emergency room. Therefore even when using a laryngeal tube the cuff pressure should be measured, which should not exceed 60 cmH_2O. Preclinically, however, this is mostly impossible, because usually a manometer to measure the cuff pressure is not available on the vehicles.
- The laryngeal tube often moves up a little during inflation (do not hold).

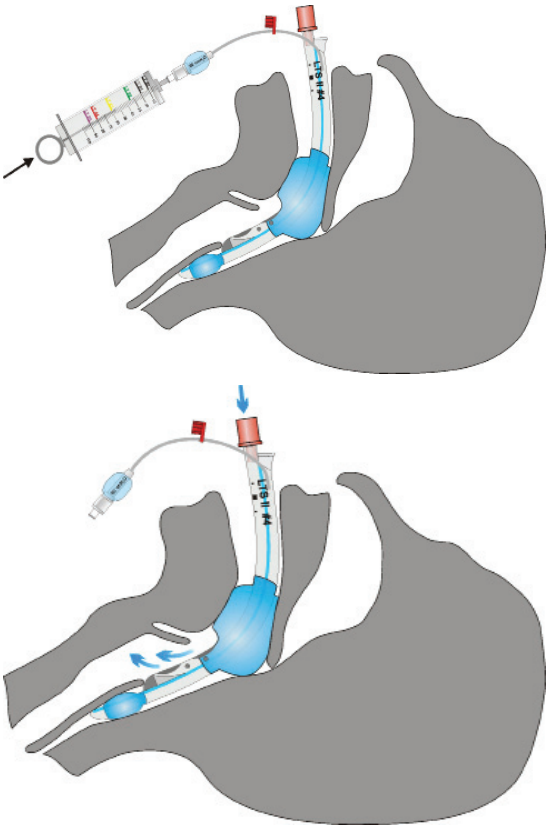


Fig. 109 laryngeal tube - placement [33]

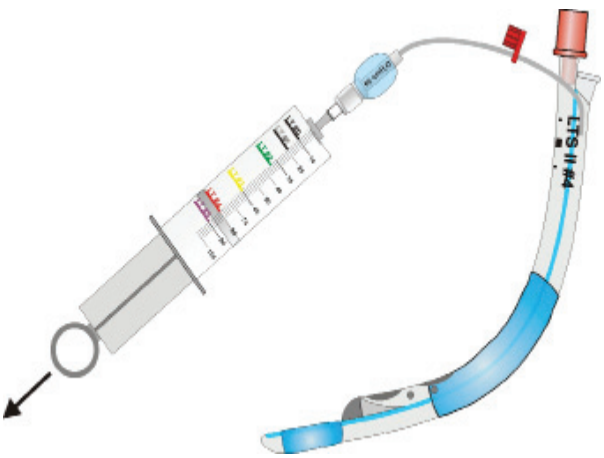
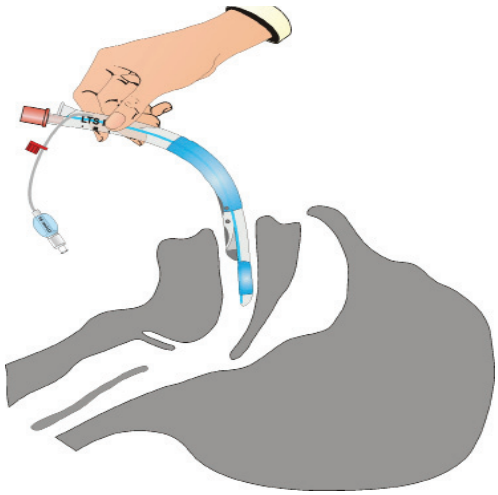
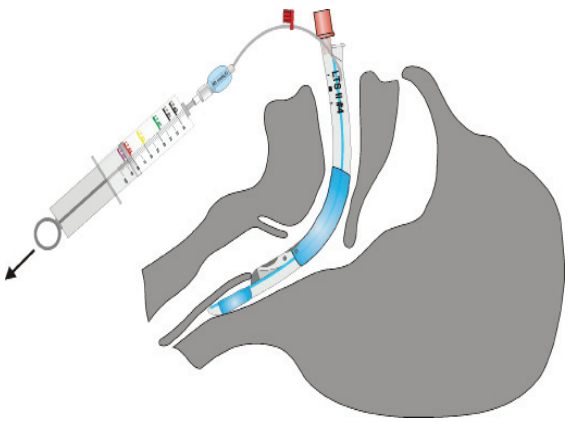
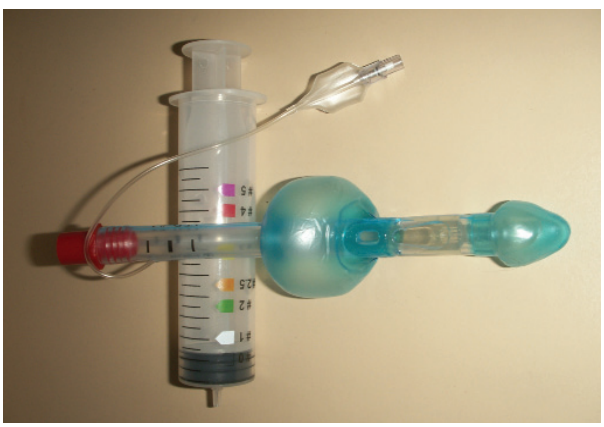


Fig. 110 cuff inflation: simultaneous inflation of both cuffs [33]







- delivery (oxygen) and release (carbon dioxide) of breathing gases
- Ventilation is determined by the respiratory minute volume (RMV).
- The respiratory minute volume is calculated from the tidal volume (TV) and the respiratory rate (RR):
  RMV = tidal volume TV x respiratory rate RR
- The respiratory minute volume is the amount of gas, which gets in- respectively outside the patient in one respiratory cycle. The inspiratory and expiratory respiratory minute volume are equal normally.
- standard values:
  - respiratory rate RR: 12/min
  - tidal volume TV: 0.5 l (exactly: 6 ml/kg ideal body weight)
  - respiratory minute volume RMV: 5-6l (70 ml/kg)
- disturbances:
  - obstruction/ restriction
  - hyper-/ hypoventilation (central / peripheral)
- types:
  - alveolar ventilation (effective gas exchange)
  - dead space ventilation
- The decisive factor for ventilation is the pCO_2 (not the pO_2): In the event of a ventilation disturbance, the pCO_2 usually increases (hypercapnic respiratory failure).
- Ventilation is determined by the respiratory minute volume, i.e. the respiratory rate and the tidal volume. Accordingly, ventilation can be increased by:
  - increasing the respiratory rate (mostly best!)
  - increasing the tidal volume: This is achieved by increasing the pressure amplitude Δp ("driving pressure"), i.e. the difference between inspiratory positive airway pressure (IPAP) and positive end-expiratory pressure (PEEP): Δp = IPAP - PEEP. The pressure difference and thus the tidal volume can be increased by:
    - increasing the inspiratory pressure (IPAP)
    - decreasing the PEEP
- The tidal volume depends on the pressure difference as well as on the compliance and the resistance of the lung.
- In case of ARDS, ventilation should only be provided with low tidal volume (6 ml/kg) to avoid damage to the lung: It is therefore necessary to work (in case of a pressure-controlled ventilation) with a small pressure amplitude, i.e. a low inspiratory pressure and a high PEEP! But in order to achieve a sufficient respiratory minute volume (RMV = RR x TV) the respiratory rate must be increased (16-30/min).
- The inspiratory pressure should be limited to a maximum of 30 cmH_2O. The higher the inspiratory pressure, the greater the mortality (meta-analysis Brower et al, AJRCCM 2002).

The physiological tidal volume is 6 ml/kg ideal body weight!

Ventilation is essential for the release of CO_2 (decarboxylation)!

The higher the pressure difference Δp between inspiratory pressure (IPAP) and PEEP, the higher the tidal volume

An increase of the respiratory minute volume and hence also the ventilation should be achieved by increasing the respiratory rate and not the tidal volume, since this may cause damage to the lung!

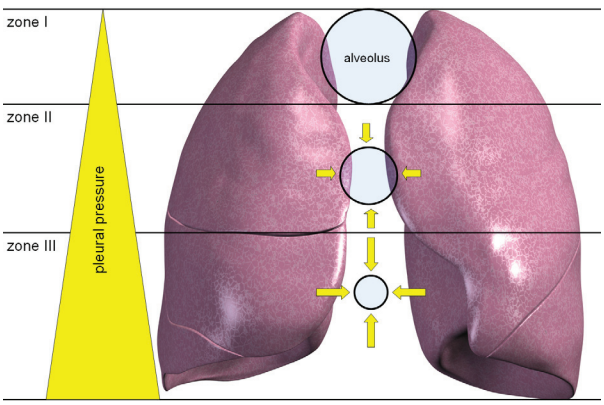


Fig. 141 3-zones-model of the ventilation: Ventilation is not homogeneous overall the complete lung. It decreases from apical to basal. Due to the own weight of the lung the pleural pressure increases depending on gravity from apical to basal. With an increasing pleural pressure (= pressure around the alveoli) the alveolus gets more and more compressed and smaller, so that the ventilation decreases. This applies to the upright position. To supine position the same changes are applied from ventral to dorsal instead of from apical to basal.

Mechanics of breathing

- parameters:
  - pressures
  - compliance, resistance
- phases:
  - inspiration
  - expiration

Pressures

- transpulmonary pressure (P_{tp}):
  - difference between intrapulmonary (alveolar pressure; pressure in alveolus ["internal pressure"]) and intrapleural (pleural pressure; pressure around the alveolus ["ambient pressure") pressure
  - The level of the transpulmonary pressure determines the filling volume and hence the expansion of the alveoli.
  - The transpulmonary pressure is the key determinant

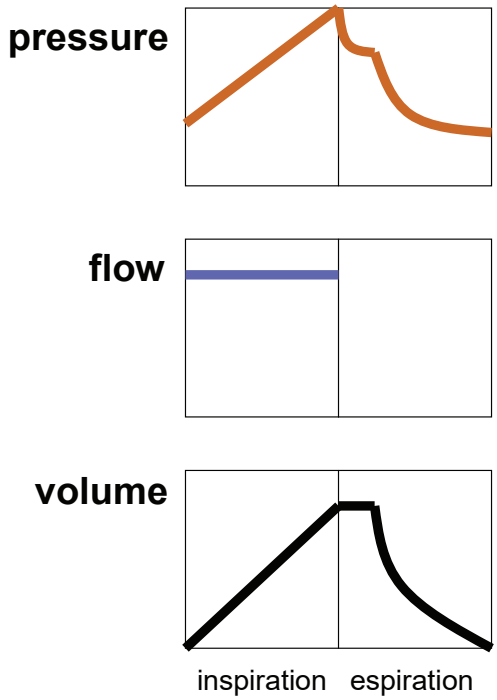
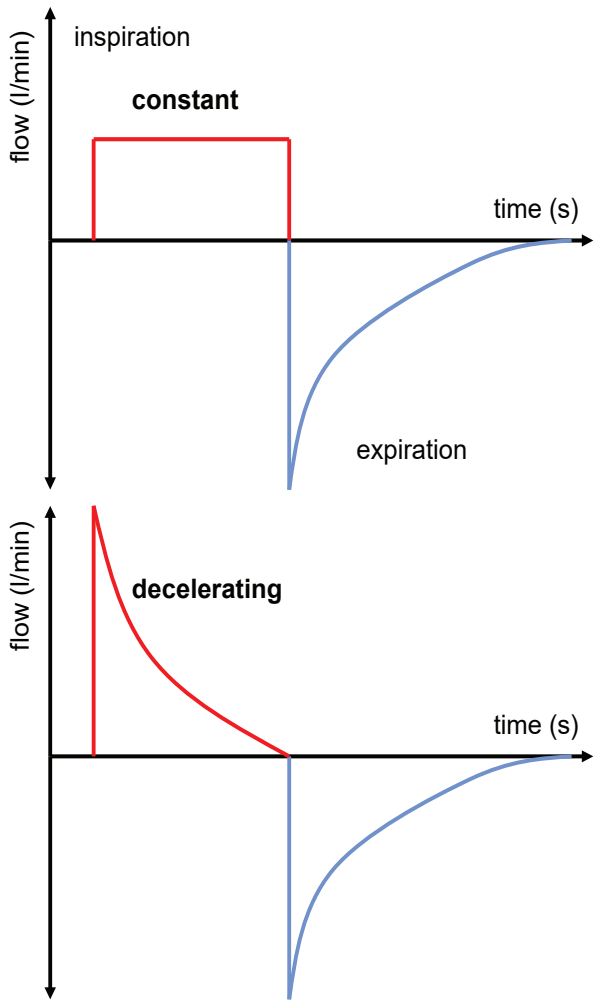


Fig. 177 volume-controlled ventilation (VCV)



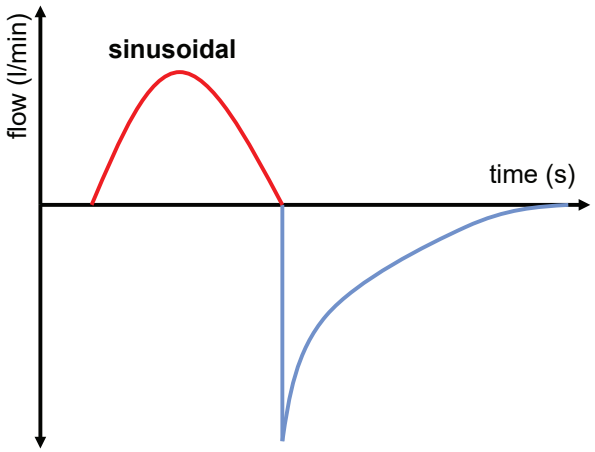


Fig. 178 the three different flow profiles (patterns of the inspiratory flow) in volume-controlled ventilation: The constant flow ("rectangle" flow) is standard today. The decelerating flow is mainly used in conscious patients, the sinusoidal flow is no longer used today.

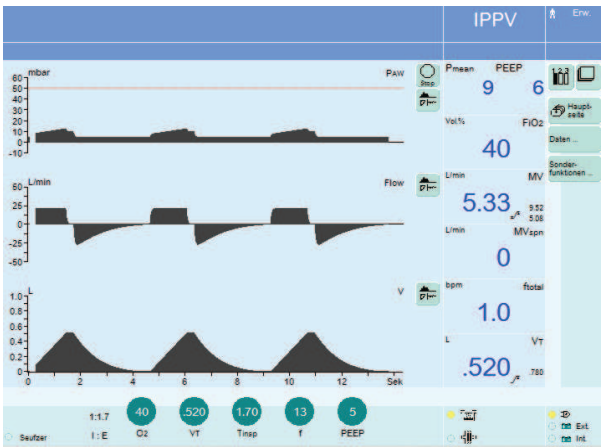


Fig. 179 IPPV (intermittend positive pressure ventilation): a typical volume-controlled ventilation (annot.: The correct term is continuous positive pressure ventilation [CPPV], because there is continuously a positive perssure in the airway and not only in the inspiration. Strictly speaking in IPPV 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:

options are preload-reducing medication (e.g., diuretics, nitroglycerin) and inotropic support (e.g. with dobutamine). Indications of weaning-induced cardiac insufficiency:
    - increase of the CVP
    - decrease of the central or mixed venous saturation
    - increase of the proBNP
    - increase of the E/E' ratio (an echocardiographic parameter for estimating the LVEDP; see page 220)
    - increase of total protein (as a result of the hemoconcentration due to oedemata) > 9% at the end of a failed spontaneous breathing trial in comparison to the initial value (highly specific; increase of < 3%: weaning-induced pulmonary oedema can most probably be ruled out [Anguel et al, Intensive Care Med 2008])
  - diagnostics:
    - echocardiography: not only the systolic, but also the diastolic function should be considered. The best parameter for the detection of a diastolic dysfunction is the E/E' ratio (for measurement see page 220). An increased E/E' ratio is strongly associated with a weaning failure (Moschietto et al, Crit Care 2012).
    - pleural sonography
    - proBNP
- CAD (coronary artery disease): A pre-existing, haemodynamically not yet relevant CAD can evolve into a cardiac ischemia in weaning due to the increased myocardial oxygen consumption during spontaneous breathing (so-called weaning-induced acute coronary syndrome). For data acquisition, a 12-channel ECG should be recorded and a cardiac enzyme test should be conducted. Sometimes patients can only be weaned after a completed cardiac catheterization with revascularization.
- malnutrition: especially
  - hypophosphatemia
    - Phosphate is essential for the formation of ATP and thus an important energy supplier
    - often in intensive care units (30% of intensive care patients, even 80% of all patients with sepsis!), especially in renal replacement therapy
    - remember and substitute!
  - vitamin D deficiency
- nosocomial pneumonia (especially VAP), aspiration
- trigger set too high on the ventilator (in spontaneous betrathing forms such as CPAP-ASB) → breathing effort ↑

If you stand at the patient's bedside wondering why weaning simply does not work, it is very helpful to go through the ABCDE of weaning (see infobox), which points out the leading causes for difficult weaning. Then make a diagnosis and start the appropriate therapy.

ABCDE

A **Airway**
increased airway resistance (if necessary anti-obstructive therapy, possibly unblock tracheal cannula), decreased compliance, poor gas ex change

B **Brain**
delirum (→ CAM-ICU), sleep disorder, cerebral lesion (→ CCT), possibly nonconvulsive status epilepticus (NCSE) → EEG

C **Cardiac**
heart failure (→ echocardiography, pro-BNP), pleural effusion (→ pleural sonography)

D **Diaphragm**
CIP, CIM (→ $p_{i\,max}$)

E **Endocrine**
adrenocortical insufficiency (→ ACTH test), hypothyroidism, electrolyte imbalance (i.a. hypophosphatemia)

according to Heunks et al, The ABC of weaning failure, Crit Care 2010

FAIL TO WEAN

F Fluid overload
A Airway resistance
I Infection
L Lying down

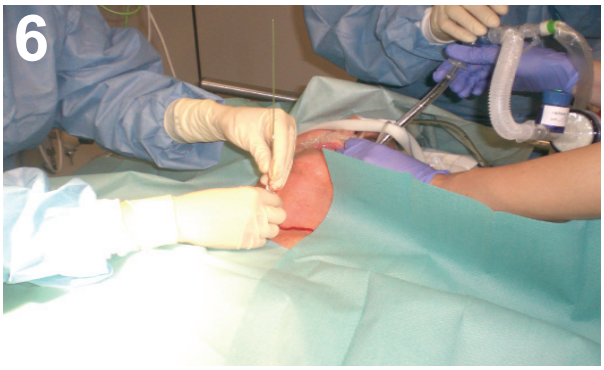
T Thyrotoxicosis (pronounced muscle weakness)
O Oxygenation insufficient

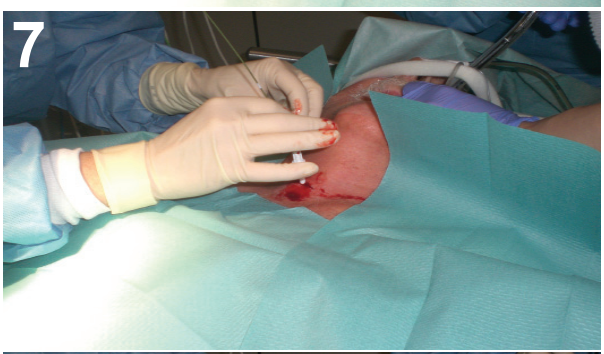
W Wheezing
E Electrolyte abnormality, Eating
A Anti-inflammatory Therapy
N Neuromuscular disease (e.g. CIP/CIM)

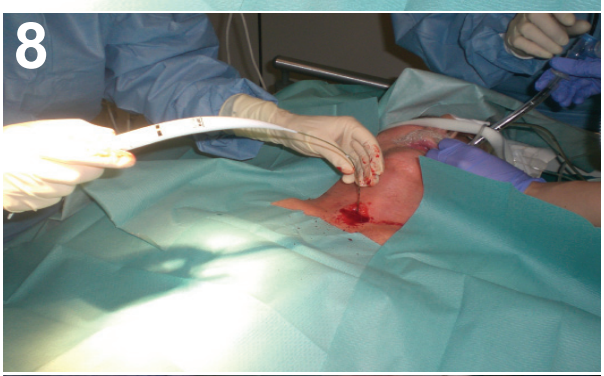
according to Ambrosino et al, The Difficult-to-wean Patient, Expert Rev Resp Med 2010

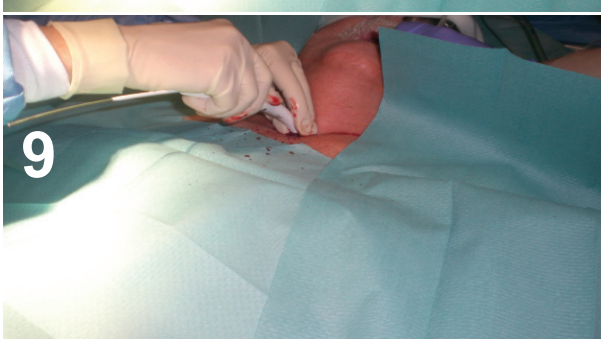
The main reason for difficult weaning is the weakness of respiratory musculature!

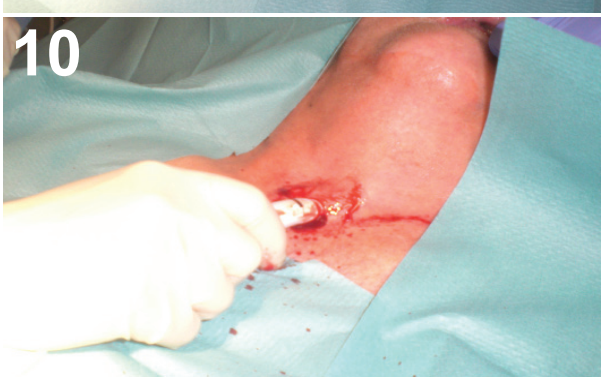
Difficult weaning: always perform pleural ultrasound on both sides (to see if there are pleural effusions) and echocardiography!

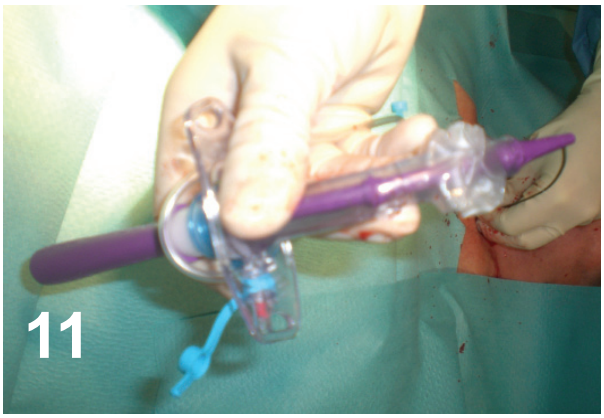


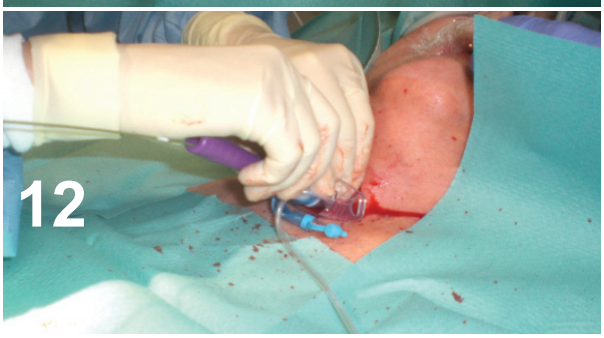


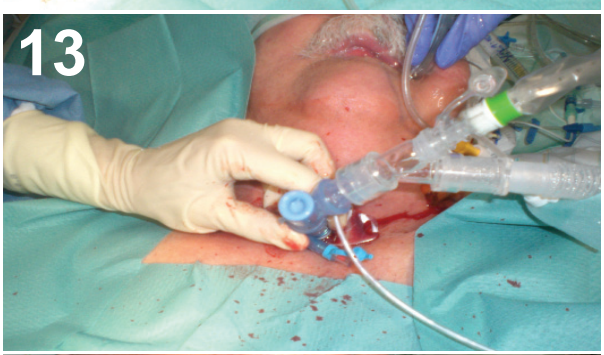












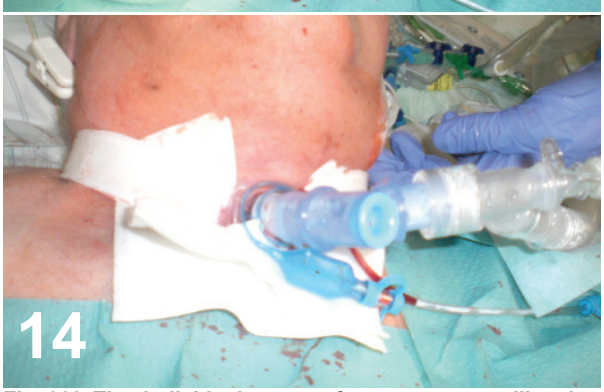


Fig. 268 The individual steps of percutaneous dilatation tracheotomy: First, a trial puncture (1) is performed strictly median between the 2nd and 3rd cartilage (between the jugulum and the larynx) with a thin needle under bronchoscopic control (bronchoscopy via the indwelling tube). Then the puncture with the Seldinger needle is performed (2). The wire is now advanced over the Seldinger needle (3, 4). All this is always done under strict bronchoscopic control (5). This is followed by pre-stretching with the small dilator (6, 7), then insertion of the conically shaped large dilator (up to the black mark) and stretching (8. 9, 10). Finally, the tracheal cannula can be inserted over the indwelling wire (11, 12, 13) and is then attached to the side with the retaining bands (14).

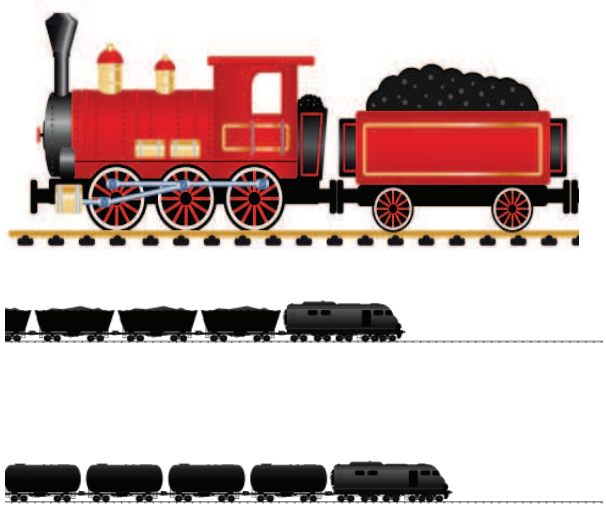


Fig. 311 The relationship should illustrated by a comparison with a train: The oxygen delivery for the cell can be compared with the amount of coal supplied by a train (e.g. for heating). In this comparison, CO corresponds to the engine (power) of the locomotive (traction engine), the Hb to the number 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

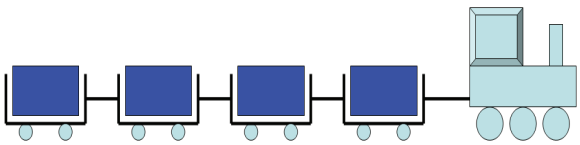


Fig. 312 normal oxygen delivery DO_2: strong traction engine (CO), enough (iin the example here 4) number of wagons (Hb), all of which are fully loaded (SaO_2 = 100%).

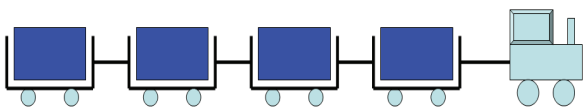


Fig. 313 reduced oxygen delivery DO_2: indeed a sufficient number (Hb) of fully loaded (SaO_2) wagons, but a to small (too weak) traction engine (CO)

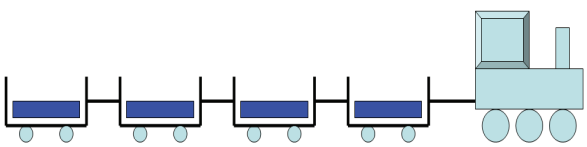


Fig. 314 reduced oxygen delivery DO_2: indeed a strong traction engine (CO) and a sufficient number (Hb) of wagons (Hb), but which are underloaded (too little saturation SaO_2)

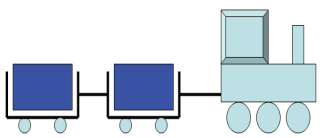


Fig. 315 reduced oxygen delivery DO_2: indeed a strong traction engine (CO) and fully loaded (SaO_2) wagons, but which are too few (only 2 instead of 4; Hb)

In shock, by definition the oxygen delivery is smaller than the oxygen consumption.

shock: oxygen delivery DO_2 < oxygen consumption VO_2

So in order to optimize the oxygen supply to the cell, the following can be done:

- increase the oxygen delivery (DO_2):
  - cardiac output (CO; the main determinant of DO_2 [90%]):
    - CO = stroke volume (SV) x heart rate (HR)
    - stroke volume: optimization of preload, ejection fraction (EF) and afterload (e.g. volume administration, catecholamines)
  - hemoglobin (Hb): administration of red cell concentrates (RCC; the simplest and most effective); note: In the case of anemia, the body automatically increases CO (usually by increasing of the heart rate) as a compensation mechanism to ensure a sufficient oxygen delivery.
  - arterial oxygen saturation: oxygen delivery (the most importat emergency drug [is the fastest]!), beginnung respectively optimization of ventilation
- reduction of oxygen consumption (e.g. by deep analgosedation, hypothermia; usually therapeutically only little accessible)

oxygen: the most important emergency drug!

An increase in arterial oxygen saturation from 85% to 99% by optimizing ventilation (this must first be achieved) increases the oxygen delivery by (only) 14%. An increase in the cardiac output from 3.0 to 3.5 l/min increases the oxygen delivery by 16% and an increase in haemoglobin by administration of RCC from 7 to 10 g/dl (SI units: from 4.3 to 6.2 mmol/l) even by 43% (most effective and simplest [i.a. Langgartner et al, Intensiv- und Notfallbehandlung 2008]). The higher the hemoglobin level, the lower saturation values can be tolerated. In case of anemia (low hemoglobin level) there is often a tachycardia: This is a physiological compensation mechanism. By increasing the heart rate the cardiac output CO (CO = SV x HR) is increased in order to supply a sufficient oxygen delivery.

Venous oxygen saturation

Oxygen is mainly chemically bound (98.5%) to haemoglobin in the blood and only a small part (1.5%) is physically dissolved in the blood. The oxygen-loaded haemoglobin is pumped by the heart (cardiac output) to the periphery and there it is released again from oxygen. However, the release (desaturation) is not complete, so that even in venous blood the largest proportion of haemoglobin is still loaded with oxygen. Under physiological conditions, only about a quarter (25%) of the oxygen is released during passage through the tissue capillaries (oxygen ext-

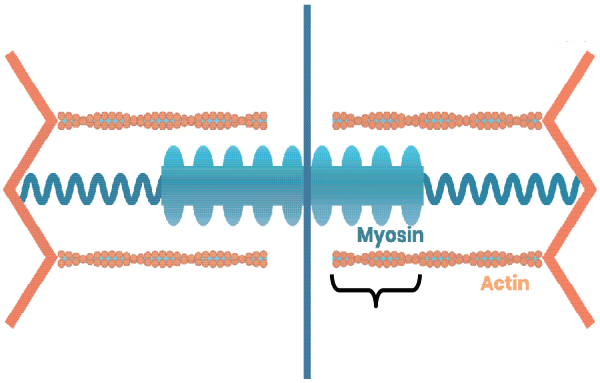


Fig. 323 sarcomere with the contractile proteins (filaments) myosin and actin: The larger the superposition, the higher is the force. Optimal is a superposition of 2.2 µm.

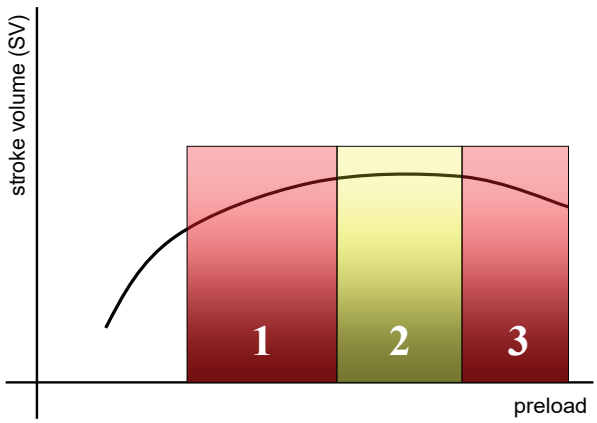


Fig. 324 relationship between preload and stroke volume: Frank-Starling curve (= cardiac function curve = force-length relationship). In section 1 of the curve, the stroke volume SV and thus the cardiac output CO (CO = SV x HR) can be increased by volume administration (preload of myocytes → increased 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.

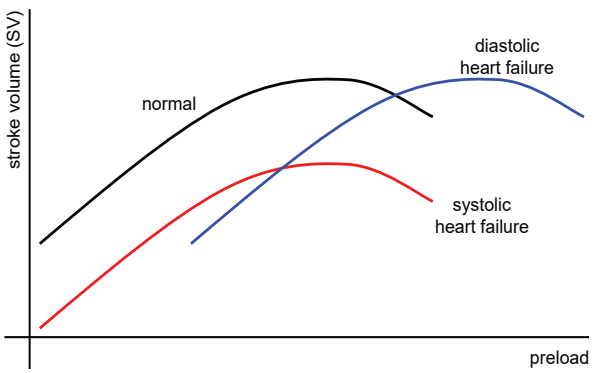


Fig. 325 Heart failure causes a shift of the Frank-Starling curve (normal [black]): in systolic heart failure (red; syn.: HFREF [heart failure with reduced ejection fraction]) downwards, in diastolic heart failure (blue; syn.: HFPEF [heart failure with preserved ejection fraction) rightwards.

Afterload

- end-systolic wall tension of the ventricle (during the systolic ejection period)
- resistance that the left ventricle must overcome during ejection into the aorta
- measure of the workload (stroke work, heart work) of the ventricle
- Laplace's law: T = P x r / 2d (named after the French physicist Pierre-Simon Laplace [1749-1827])
  - T: well tension
  - P: transmural pressure
    - difference between the pressure inside and outside (= intrathoracic pressure) of the left ventricle
    - The higher the transmural pressure, the higher is the wall tension and therefore the afterload.
    - Due to ventilation positive pressure is applied. That leads zu an increase of intrathoracic pressure, so that the pressure outside of the left ventricle increases and therefore the transmural pressure (difference of the pressure in- and outside) decreases. Thus the afterload decreases.
    - In case of a pressure load of the left ventricle (e.g. arterial hypertension, aortic valve stenosis) the pressure inside of the left ventricle and therefore the transmural pressure (difference of the pressure in- and outside) increases. In order to prevent an increase of the wall tension and therefore an increase of the afterload, physiologically the wall thickness d increases. Left ventricular hypertrophy occurs.
  - r: radius (The larger the diameter of the left ventricle [dilatation of the left ventricle], the higher is the wall tension.)
  - d: wall thickness (The thicker the wall [left ventricular hypertrophy], the lower is the wall tension.)
- The higher the wall tension, the higher is the afterload and thus the oxygen consumption and the lower the stroke volume! The higher the wall tension, the lower the contractility. This can be seen, for example, in a pheochromocytoma crisis: As a result of the massively increased blood pressure values, there is often a pronounced decrease of the ejection fraction (EF < 20%).
- The wall tension cannot be measured in clinical practice. The surrogate parameters for the afterload are the systolic blood pressure (SBP; simplified) and (better) the systemic vascular resistance (SVR: systemic vascular resistance) for the left ventricle. The same applies to the right ventricle: pulmonary arterial pressure (PAP) and pulmonary vascular resistance (PVR).
- The afterload is i.a. also increased in aortic valve stenosis.
- vascular resistance:
  - produced by the tone (contraction) of the arterioles (resistance vessels)
  - Ohm's law (from electrical engineering): R = U / I
    - R: resistance (here: SVR)
    - U: tension (here: MAP - CVP [The driving force is the pressure difference between the aorta and the right atrium.])
    - I: current flow (here: CO)

Lumina

- distal lumen ("PA distal"):
  - measurement of pressures (RA pressure, RV pressure, PA perssure [PAP], PCWP
  - measurement of the mixed venous oxygen saturation ($SmvO_2$)
- balloon lumen (balloon cap scc max), with locking → Blocking the balloon
- thermistor electrode (thermodilution 110cm; with plug): away from the catheter tip; for CO measurement
- proximal lumen ("RA proximal"):
  - 30cm away from the catheter tip
  - injection of NaCl 0.9% here for CO measurement
  - measurement of CVP
  - measurement of central venous saturation ($ScvO_2$)
- possibly RV lumen (not always available)
  - 20cm away from the catheter tip
  - This can be used to insert a pacemaker probe (e.g. in the case of a posterior myocardial infarction with bradycardia.)
- infusions possible via "RA proximal" and "PA distal"; in 5-lumen PAC, additional white lumen for infusions

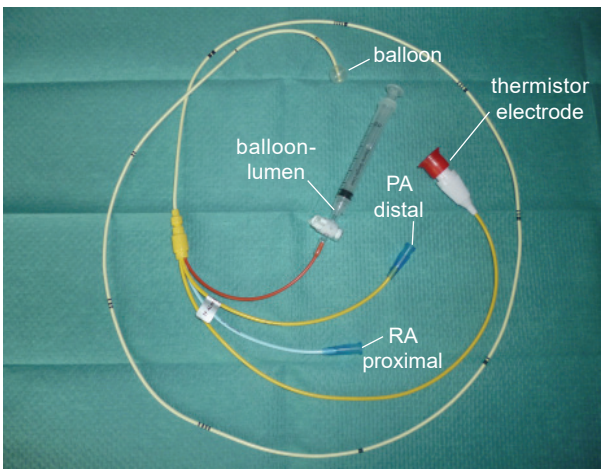


Fig. 344 pulmonary catheter: lumina

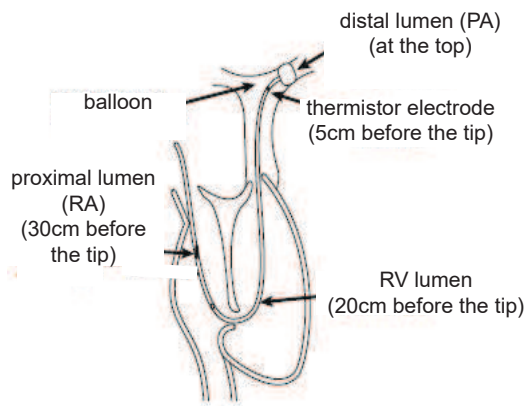


Fig. 345 pulmonary catheter in wedge position with the lumina [14]

Placement

- first of all, insertion of a sheath (7F sufficient) as in the CVC using the Seldinger technique (preferably sonographically), fixation with sutures
- preparation of drugs for emergency use (epinephrine, atropine, orciprenaline); stand-by for defibrillation
- continuous ECG monitoring (switch on the systolic tone)
- control of the balloon (1-2 ml air)
- flushing of all lumina with NaCl 0.9%
- sterile protective sleeve for repositioning the catheter without increasing the risk of contamination / infection
- insertion of the PAC via the check valve of the airlock of the sheath blindly up to 30cm, so that the tip of the PAC protrudes from the distal end of the sheath
- connection of the distal lumen with the pressure dome (pressure at "PA distal"), flushing, zeroing
- inflation (blocking) of the balloon with 1-2ml air; advance only in blocked state, retraction only in unblocked state
- advance without fluoroscopy a total of 40-60cm while observing the pressure curves (RA, RV, PA) on the monitor until the wedge curve ("curve flattens off") appears
- The current catheter position is therefore not determined by means of fluoroscopy, but by means of the typical pressure curves
- deflation (unblocking) of the balloon (After unblocking, the wedge curve should change to the PA curve!)
- fixation of the PAC by means of screw caps on the sterile sleeve
- X-ray control
  - correct position
  - exclusion of
    - pneumothorax
    - knotting of the catheter
- CO measurement → 3 x 10 ml ice-cold NaCl 0.9% (thermodilution)
- dwelling time: max. 5 days (in exceptional cases: 7 days) due to the risk of infection
- It is also possible to carry out pulmonary angiography (e.g. question of pulmonary embolism) via the lying pulmonary catheter. The catheter is placed in RV-position (right ventricle) and then the contrast medium (40ml) is injected via PA-distal. In this way, a non-selective pulmonary angiography is obtained.

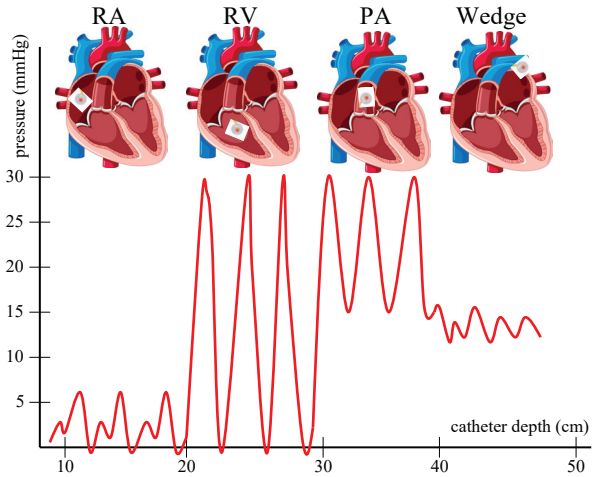


Fig. 354 the different pressure curves when the pulmonary artery catheter is inserted (RA: right atrium; RV: right ventricle; PA: pulmonary artery)

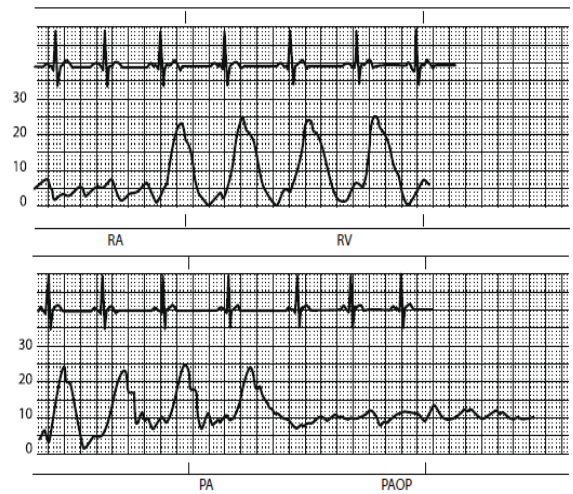


Fig. 355 pulmonary catheter: pressure curves (top RA, then RV; bottom PA, then wedge position [PAOP]) [14]

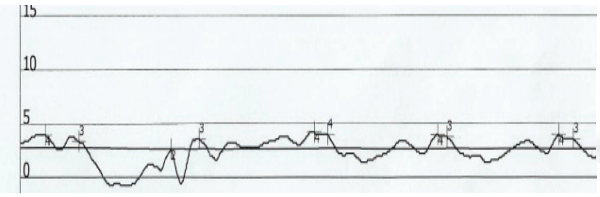


Fig. 356 pressure curve of the right atrium (RA): typical triple peak, low pressures (2-6 mmHg)

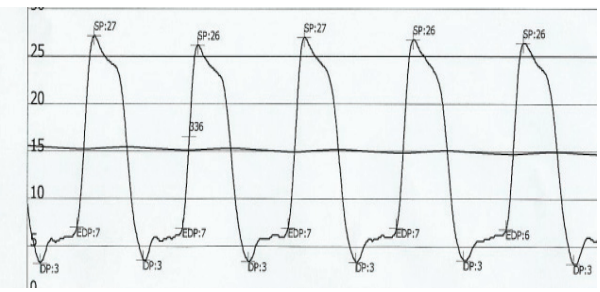


Fig. 357 pressure curve of the right ventricle (RV): systolic pressures 15-30 mmHg, diastolic towards 0 mmHg (typical for a ventricular pressure curve)

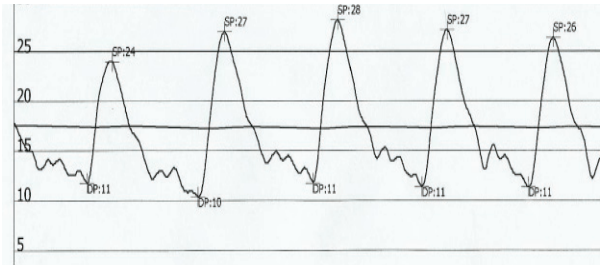


Fig. 358 pressure curve of the pulmonary artery (PA): compared to RV, same systolic but higher diastolic pressure

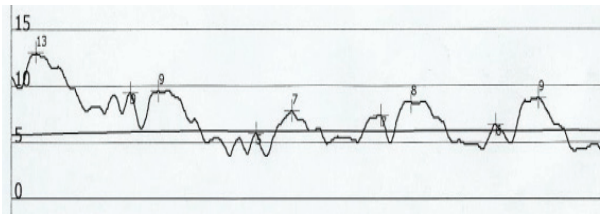


Fig. 359 pressure curve in wedge position: The curve is flattened.

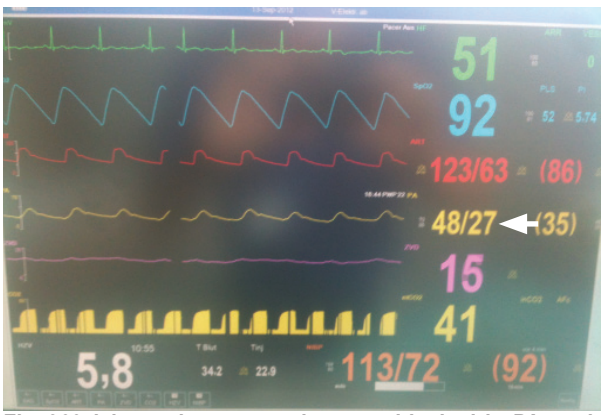


Fig. 360 lying pulmonary catheter: unblocked in PA position (arrow)

Standard values

- measurable values
- calculable values

Measurable values

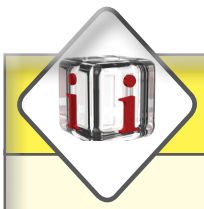
	mean value [mmHg]	standard value [mmHg]
CVC		5-10
RA	5	2-10
RV_{sys}	25	15-30
RV_{dias}		2-8
PAP_{sys}	23	5-30
PAP_{dias}	9	4-12
PCWP	9	< 15 (if ventilated: < 20)
LA	9	5-12
LV_{sys}	120	90-140
LV_{dias}	9	5-12
$SvO_{2\ central}$		70-85%
$SvO_{2\ mixed}$		65-80%

Plausibility criteria

The measured values are only plausible and therefore usable if the following criteria ("The water cannot flow uphill!") are met:

- $PCWP_{mean} \leq PA_{diast}$
- $PA_{sys} \leq RV_{sys}$
- $RA_{mean} \geq RVDEP$

Calculable values



PAC
calculable values

- **stroke volume: SV = EDV-ESV; norm: 60-90 ml**
- **cardiac output: CO = SV x HR; norm: 4-8 l/min**
- **cardiac index: CI = CO/BSA; norm: 2.5-4.5 l/min/m^2**
  body surface area: BSA = kg bw x 0.425 x heigth [cm] x 0.725 x 0.007184
- **stroke volume index: SVI = SV/BSA; norm: 2.5-4 l/min/m^2**
- **stroke work index: SWI (measure of contractility; preload-independent index of cardiac work)**
  - **left ventricular stroke work index: LVSWI = HI x (MAP - PCWP) x 13.6 / HR = SVI x (MAP - PCWP) x 13.6; norm: 50-60 g x m/m^2 (factor 13.6 for conversion mmHg x cm^{-3} in g)**
  - **right ventricular stroke work index: RVSWI = HI x (PA_{mean} - CVP) x 13.6 / HR; norm: 8-12g x m/m^2**
- **right ventricular ejection fraction: RVEF = SV/EDV; pathological < 35% (e.g. important in right ventricular myocardial infarction)**
- **arteriovenous oxygen difference: $avDO_2$ = CaO_2-$CmvO_2$**
  - **CaO_2 (arterial content of oxygen) = SaO_2 x Hb x 1.34 + paO_2 x 0.003**
  - **$CmvO_2$ (mixed venous content of oxygen) = SaO_2 x Hb x 1.34 + $pmvO_2$ x 0.003**
- **cardiac power output: CPO = MAP x CO/45; norm: 0.6-0.8 watts**
- **vascular resistance**
  - **pulmonary vascular resistance: PVR = (mPAP - PCWP) x 80 / CO; norm: < 240 dyn x sec x cm^{-5} (< 3 Wood)**
  - **systemic vascular resistance: SVR = (MAP - CVP) x 80 / CO; Norm: 900-1400 dyn x sec x cm^{-5}**

Complications

- complications due to the puncture (e.g. pneumothorax, arterial puncture, air embolism)
- pulmonary infarction, infarct pneumonia
  - causes
    - permanent wedge (You should never leave a PAC with inflated balloon in wedge position for a longer period of time, otherwise this can lead to a pulmonary infarction!)
    - spontaneous wedge (unnoticed deep sliding of the actually defalted balloom with occlusion of a small pulmonary artery branch)
  - chest X-ray: Westermark sign (wedge-shaped shadowing of the lung beginning in the area of the catheter tip)
- dardiac arrhythmias (in 3% hemodynamically relevant):
  - atrial fibrillation (especially due to the cold bolus injection)
  - sinus bradycardia (especially due to the cold bolus injection)
  - PAC (premature atrial contractions), PVC (premature ventricular contractions), salves, ventricular tachycardia (VT) up to ventricular fibrillation (VF; therefore always insert PAC under standby-defibrillation)
  - AV block (when the AV valve is passed)
  - RBBB (right bundle branch block; in 4%; cave in case of already existing LBBB [left bundle branch block] → total AV block!)
- knotting of the catheter
- thrombosis, pulmonary embolism
- venous spasms
- accidental intraarterial injection (The pulmonary artery is also an artery!)
- balloon rupture (risk of air embolism; no further "inflation attempts" in the event of a balloon rupture!)
- injuries of the tricuspid or pulmonary valve (petechial bleeding, perforations)
- infections
  - catheter-associated sepsis, endocarditis
  - significant increase from the 4th day
- rupture of the pulmonary artery

Rupture of the pulmonary artery

Definition

- iatrogenic injury of the pulmonary artery in course of the insertion of the PAC
- mechanisms:
  - over-wedging (excessive inflation of the balloon)
  - puncture of the vessel wall with the catheter tip
- imaging:
  - chest X-ray
  - chest CT
- ⚠ mortality: 50%

Symptoms

- dyspnea
- blood-tinged sputum, haemoptysis or if intubated, suddenly bloody suction
- danger of asphyxia

Risk factors

- age > 60 years
- female gender
- chronic pulmonary hypertension
  - rigid and fragile vessels
  - But especially here the pulmonary catheter is the central and most important diagnostic tool!

Hypervolemia - consequences ("polycompartment" syndrome)

- **pulmonary: pulmonary edema**
- **cardiovascular:**
  - **hypertension**
  - **decrease of contractility (due to overstretching of cardiomyocytes)**
- **gastrointestinal:**
  - **decreased gastrointestinal motility (up to ileus)**
  - **intestinal ischemia (due to increased venous mesenteric pressure)**
  - **malabsorption**
  - **anastomotic insufficiency**
  - **bacterial translocation**
  - **intra-abdominal compartment syndrome**
- **renal: ⚠ renal failure (despite volume administration! Hypervolemia leads to a reduced venous return [venous congestion] and thus to an increased interstitial pressure, so that the GFR decreases. The higher the ZVD, the lower the renal perfusion pressure [RPP = MAP - CVP].)**
- **hepatic: synthetic function disorders, cholestasis**
- **dermatologic: wound healing disorders, wound infections, decubitus**
- **hematological: hemorrhage (due to dilutional coagulopathy: Hyperhydration leads to a decreased concentration of coagulation factors. Hypervolemia is a cofactor for hemorrhage!)**
- **infectious: reduced concentration of antibiotics (especially in sepsis, where the volume of distribution is already increased due to the capillary leak)**
- **increased mortality**

Fig. 380 Be ware of hyperhydration (hypervolemia): It can have deleterious consequences (polycompartment syndrome)!

The fluid responsiveness (= increase in CO due to volume addition; preload dependency) can be estimated as follows:

- clinical
  - reduced skin turgor (skin fold test), dry mucous membranes, dry axilla, soft or sunken eye bulbs, oedema (caution: Septic patients almost always have oedema due to capillary leakage and still have a pronounced fluid requirement!)
  - fluid challenge (volume challenge; volume test):
    - test for fluid responsiveness (i.e. if the preload is decreased and if the CO can be increased by fluid administration)
    - crystalloid 150-350ml (4 ml/kg) within 15min
  - Trendelenburg maneuver
- laborchemical (i.a. hematocrit [in case of lack of volume increased due to hemoconcentration], lactate [especially lactate clearance, i.e. drop > 10% within 2 hours: very good parameter], base excess, central venous oxygen saturation)
- pulse-oxymetric: With the special pulse oximeter MASIMO the PVI (pleth variability index) is determined non-invasively via a sensor using plethysmography. The higher the PVI, the greater the fluid responsiveness.
- radiological (i.a. signs of congestion, pleural effusions; note: A normal chest X-ray does not rule out hypervolemia! X-ray has only a sensitivity therefore of 50%, i.e. 50% are fluid overloaded, even the x-ray is normal! Especially in patients with COPD, pulmonary venous congestion in the chest X-ray is often not visible.)
- sonographic
  - abdominal sonography: inferior vena cava
    - measurement of the diameter directly (1-2cm) below the diaphragmatic passage
    - standard values:
      - diameter < 21mm (often increased in adolescents / athletes: up to 27mm, but with regular respiratory modulation)
      - regular respiratory modulation, i.e. inspiratory collapse > 50%
    - Ventilation with PEEP always leads to a dilated inferior vena cava → exspiration hold, if necessary short-term disconnection
    - variation of diameter > 12% (in the ventilated patient): regarding fluid responsiveness (Feissel et al, Intensive Care Med 2004)
      - positive predictive value: 93%
      - negative predictive value: 92%
  - pleural sonography
    - pleural effusions
    - B-lines ("comet tail" artifacts, reverberations; see page 380)
  - echocardiography (TTE [transthoracic echocardiography] sufficient, no TEE [transesophageal echocardiography] usually necessary; for echocardiographic estimation of the filling pressure see schematic drawing); indications for an increased filling pressure are:
    - excessive E-wave (i.e. E-wave : A-wave > 2:1) in the transmittal inflow (An E-wave < 50 cm/s or E < A [in case of a reduced ejection fraction] excludes an increased filling pressure)!
    - filling index E/E´ > 15 (tissue doppler; see page

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)
    - vasopressin
  - 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% 10ml/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 haemodynamic 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.

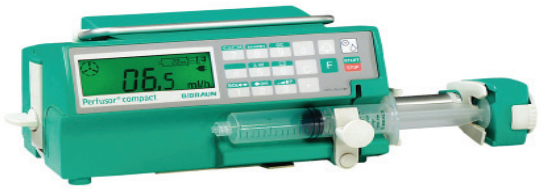


Fig. 411 Perfusor [8]

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 392]!)
- endocrinological:
  - hyperglycaemia (The stimulation of β_2-receptors in the liver leads to an increase in glycogenolysis.)
  - hypocalcaemia, hypomagnesaemia
  - 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)

Fig. 427 the different access routes for nutrition: First choice is the enteral access. If the patient can eat (e.g. monitoring in the ICU after PTCA after a myocardial infarction), the nutrition is oral. It should be startet within 24 hours of admission to the ICU. If an oral nutrition is not possible within three days, a gastral nutrition is performed (via a gastric tube). Jejunal nutrition is only indicated in exceptional cases, if the gastric residual volume (GRV) is > 500ml/d despite administration of prokinetics (metoclopramide, erythromycin). The parenteral access is the second choice. Parenteral nutrition is usually performed via a central venous access (CVC) and mostly supplementary to enteral nutrition in order to achieve the required number of calories. The amount of calories of the enteral nutrition is increased and the amount of calories of the parenteral nutrition is reduced every day.

Parenteral nutrition

Definition

- supply of the necessary nutrients via a venous access
- less physiological than enteral nutrition
- approx. 8 times more expensive than enteral nutrition

Types

- supplemental parenteral nutrition (SPE): parenteral nutrition is in addition to enteral nutrition (usually the case).
- total parenteral nutrition (TPE): parenteral nutrition alone without any ohne enteral nutrition (rarely the case [There are actually no contraindications anymore against additional minimal enteral feeding, i.e. 250ml tube food per day, so that this should always be performed!]).

Accesses

- central-venous (CVC; mostly)
- peripheral-venous; allowed (almost everything!):
  - fats
  - amino acids
  - glucose (only up to glucose 10% [At a concentration of glucose 20% and 40% effect like a "sclerosing agent"])

Indications

- necessity of nutrition and impossibility / contraindication for enteral nutrition
- overlapping until sufficient enteral nutrition is possible

Indications for a long-term parenteral nutrition

- short bowel syndrome
  - anatomical
  - functional
- chronic inflammatory bowel diseases (CIBD)
- oncological diseases
- intestinal transit disorders
- HIV
- cystic fibrosis

Components

- macronutrients:
  - carbohydrates (50-60%)
  - fats (30-35%)
  - amino acdis (15-20%)
- micronutrients:
  - electrolytes
  - vitamins
  - trace elements (minerals)

Carbohydrates

- main energy supplier (main substrate for energy production)
- Only glucose and no sugar substitutes such as e.g. xylitol, sorbitol or fructose should be used as carbohydrates.
- daily requirement: 4 g/kg bw (max. 5 g/kg bw), minimum intake 150 g/d
- calorific value: 4 kcal/g
- concentrations:
  - glucose 5%: 0.2 kcal/ml (osmolarity: 277 mosm/l)
  - glucose 10%: 0.4 kcal/ml (osmolarity: 555 mosm/l)
  - glucose 20%: 0.8 kcal/ml (500ml G20%: 400 kcal; osmolarity: 1110 mosm/l)
  - glucose 40%: 1.6 kcal/ml (500ml G40%: 800 kcal; osmolarity: 2200 mosm/l)
  - glucose 70%: 2.8 kcal/ml (osmolarity: 3885 mosm/l)
- RQ (respiratory quotient): 1.0
- monitoring: blood sugar concentration (BSC)
  - target BSC < 180 mg/dl (BSC > 180 mg/dl in intensive care patients → increased mortality; but no more intensive insulin therapy recommended, only glucose control!)
  - if necessary insulin perfusor
    - max. initially up to 6 IU/h (S2k-Leitlinie DGEM 2018: only up to 4 IE/h; note: In patients with known diabetes mellitus, higher doses may be necessary.), then first reduction of glucose and increase of fats, if necessary reduction / discontinuation of steroid therapy; only then further increase of insulin perfusor

- only very poorly accepted and used (only used in 1.7% of all [out-of-hospital] cardiac arrests [Deakin et al, Heart 2014])
- Under no circumstances, however, chest compression should be interrupted to get an AED. It must be continued and the AED brought by a second person. If this second person is not available, chest compression is continued without AED.
- only recommended for laymen, not for professionals (because it just takes too long; i.a. in-hospital: AED → even worse prognosis)

Fig. 511 examples of different AED

Pacemakers

- external pacemaker (transthoracic)
- indication: ventricular asystole (i.e. still existing P-waves in the absence of QRS complexes; in case of a complete [i.e. atrial + ventricular] asystole without recognizable P-waves: no indication)
- set to synchronization mode (SYNC)
- electrode positioning: as in defibrillation
  - sternal-apical or
  - anterior-posterior („sandwich“ technique)
- - select stimulation frequency (approx. 60-90/min)
- select energy (120-200 mA)
- pulse control
- see also page 488

study

Out-of hospital advanced life support with or without a physician: effects on quality of CPR and outcome
Olasveengen et al, Resuscitation 2009

- prospective observational study (Oslo [Norway])
- resuscitation in 977 patients with cardiac arrest
  - without physician
  - with physician (anesthesiologist)
- results (with physician):
  - significantly better CPR quality (less hands-off times)
  - no difference in mortality

Extracorporeal life support (ECLS)

Extracorporeal procedures (syn.: eCPR [extracorporeal cardiopulmonary resuscitation], mini-ECC (extracorporeal circulation), pCPS [percutaneous cardiopulmonary support], ECPB [extracorporeal cardio-pulmonary bypass]) can be used to restore circulation and save time: For example, coronary angiography with PCI in the case of acute myocardial infarction or lysis or embolectomy in the case of pulmonary embolism can be performed. The cannulation is veno-arterial (va-ECMO). There are various options for this:

- Lifebridge (Lifebridge medical technology)
  - mobile heart-lung machine (including centrifugal pump and oxygenator)
  - 2 sheaths (installation possible without a cardiac technician)
    - femoral artery (17F)
    - femoral vein (19F)
  - weight: 18kg
- MECC (minimized extracorporeal circulation; Maquet)
  - was the first mini ECLS system
  - centrifugal pump (Rotaflow; blood flow 4.0-4.5 l/min) + oxygenator (Quadrox; surface 2.4m^2)
- Cardiohelp (Maquet)
- Life-Box (Sorin)
- Resting-Heart-System (Medtronic)

Within the scope of in-hospital resuscitation it has already been shown that the survival rate through ECMO is significantly higher than through a purely conventional resuscitation (i.a. Chen et al, Lancet 2008). Also in a meta-analysis (Ouweneel et al, Intensive Care Med 2016), ECMO showed an improvement in survival and the neurological outcome. However, there are no randomized controlled studies for ECMO in resuscitation, so that the method can currently only be regarded as experimental. Large studies on this topic are ongoing currently (especially EROCA, INCEPTION, Prague-OACA, ACPAR-2). The practical feasibility with excellent results (in selected patients) could be shown in the CHEER study (see box). In a French register study (Bougouin et al, EHJ 2019), no benefit in survival could be shown.

Fig. 512 preclinical implantation (in the emergency vehicle) of a va-ECMO (Cardiohelp [Maquet]; cannulation of the femoral artery and vein on the right) during resuscitation of a 42-year-old man. With ECMO a sufficient circulation could be established despite patient's cardiac arrest. Coronary angiography showed proximal LAD occlusion. ROSC occurred a few minutes after recanalization. The patient survived without any neurological damage.

COACT study

Coronary Angiography after Cardiac Arrest without ST-Segment Elevation
Lemkes et al, N Engl J 2019

- COACT: Coronary Angiography after Cardiac Arrest
- multicenter (19 centers in the Netherlands) open prospective randomized trial
- 538 patients after successful (OHCA [out-of-hospital cardiac arrest]) resuscitation in patients without ST elevations with an initially shockable rhythm; coronary angiography:
  - immediately (within 2h [on average after 50min])
  - postponed (only after neurological recovery; on average after 5 days; usually before discharging from ICU to general ward)
- results: 😕
  - primary endpoint (mortality after 90 days): no difference
  - secondary endpoints (survival after 90 days with good neurological outcome, myocardial damage, duration of catecholamine therapy, time to reach target temperature of cooling, renewed VT / ventricular fibrillation, acute kidney injury, duration of ventilation, neurological status at discharge to general ward): no difference
- annotations:
  - PCI
    - immediate coronary angiography: in every 3rd patient performed
    - postponed coronary angiography: in every 4th patient performed
  - Coronary angiography was no longer performed in 35% of the patients randomized to the postponed group.
  - exclusion criteria:
    - ST elevation
    - shock (e.g. cardiogenic shock)
    - other apparently non-coronary causes of cardiac arrest

If there is no STEMI (no ST elevation in ECG after ROSC), an immediate cardiac catheter examination is not always necessary!

Hypothermia

Definition

- syn.: TTM (targeted temperature management [According to the ERC 2015 guidelines, this term should preferably be used.])
- Baron Dominique Jean Larrey (1766-1842; field surgeon of Napoleon) observed that wounded soldiers who were closer to fire had an increased mortality rate.
- mild hypothermia (32-34°C); annotationsto the target temperature: In the FROST-I study (Lopez-de-Sa et al, Intensive Care Med 2018; multi-center pilot study in 101 patients with OHCA), there was no difference in outcome (survival with good neurological outcome, i.e. mRS ≤ 3) between different target temperatures 32, 33 or 34°C.
- originally developed to reduce the metabolism of malignant tumours
- clear recommendation of ILCOR and ERC guideline since 2003
- previously only practiced in 25% of intensive care units in Germany (Wolfrum et al, Resuscitation 2007), now much more common
- ⚠ With an NNT (number needed to treat) of only 6, hypothermia after resuscitation is one of the most effective measures in the whole of medicine!
- Also after hypothermia the prognosis factors are reliable! Only for NSE after hypothermia a different standard value applies (< 90 µg/l instead of < 33 µg/l).

Effects

- reduction of oxygen consumption (per degree by 10%)
- reduction of the formation of oxygen radicals
- neuroprotective (neurons of the CNS have an extremely low tolerance for ischemia!)
- reduction of metabolic activity (only slight effect)
- anti-apoptotic
- anti-inflammatory
- anti-coagulant

Studies

- European: Hypothermia after cardiac arrest (HACA) study group, N Engl J 2002 (see box)
- Australian: Bernard et al, N Engl J 2002 (see box)

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).

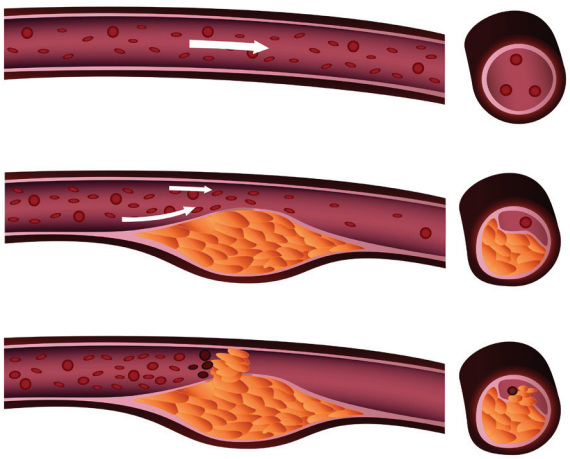
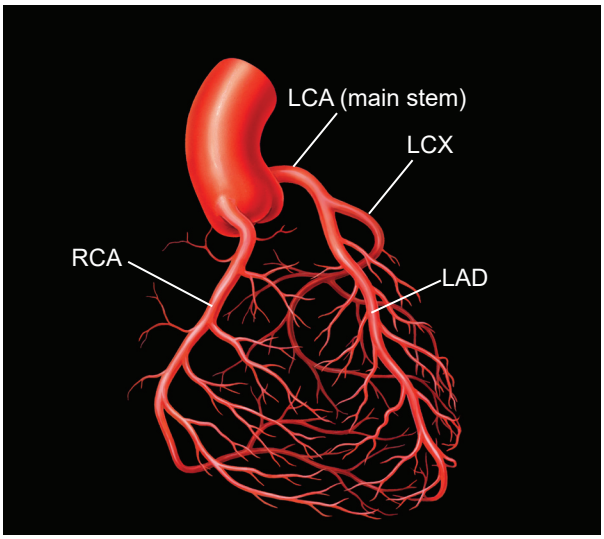


Fig. 526 Pathophysiology of acute myocardial infarction: Plaque rupture and consecutive thrombotic occlusion of the coronary vessel occur.

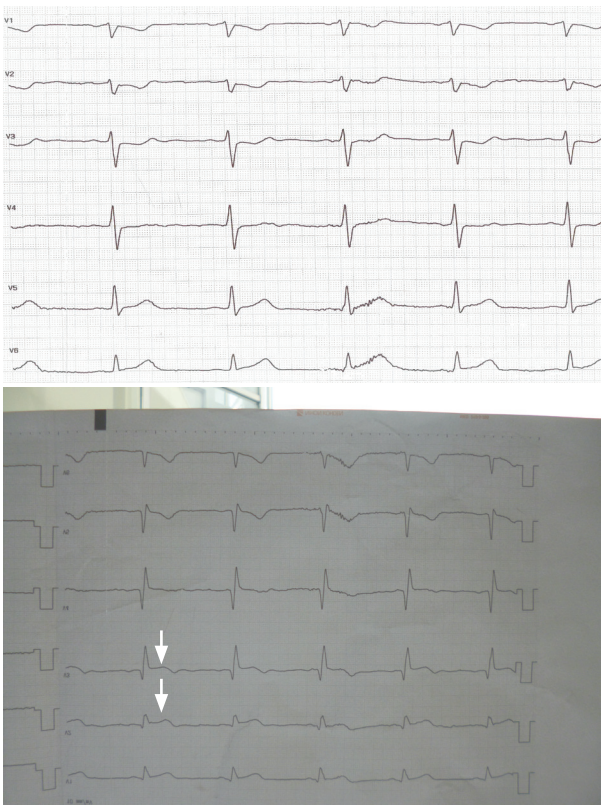
Epidemiology

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 5th-6th 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) ↑



The LCX occlusion is sometimes not visible in the ECG. But you can recognize it in the echocardiography by postero-lateral akinesia. A strictly posterior infarction ("true posterior infarct"; LCX occlusion), which occurs frequently in the inferior infarct, is only visible in V7-V9. Typical are inverse ST depressions in V2 and V3 (simply turn around ECG!), which should be reminiscent of a posterior infarction.



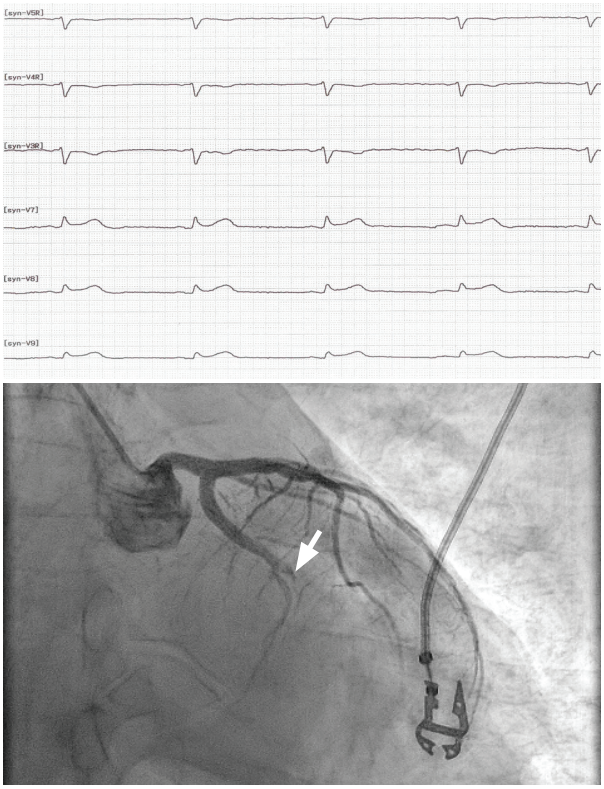


Fig. 544 In the chest wall leads one can see inverse ST depressions in V1-V3. If you turn the EKG around and look at it from behind (e.g. through a bright window), you can see ST elevations (arrows). Now the chest leads V7-V9 are additionallyderived, in which ST elevations can be seen in the sense of a STEMI. This was caused bay an LCX occlusion, in which the ST elevations are typically not seen in the (conventionally derived) 12-lead ECG.

Infarction: stages

myocardial infarction
stages

- early stage: high, tent-shaped T wave ("church tower"-T; rare)
- acute stage (st. I): monophasic deformation of QRS complex (ST-segment elevation)
- intermediate stage: beginning T-negativation, R-reduction
- subacute stage (st. II): ST-normalization, T-negativation
- chronic stage (st. III): T-normalization, pathological Q wave (Pardee-Q [named after the American cardiologist Harold Ensign Bennet Pardee, 1886-1973]; note: In obese patients, a wide and deep Q wave is often found in III. Here the morphology typically changes in the ECG. This is completely normal and constitutional.

- cardiac catheterization:
  - coronary angiography: mostly proximal RCA occlusion
  - hemodynamics:
    - RV pressure curve:
      - RVEDP > LVEDP
      - possibly dip-plateau phenomenon
    - RA pressure curve:
      - high a-wave, deep y-descent (due to compliance disorder of the right ventricle)
      - configuration: with atrial infarction M-shaped (poor prognosis), without atrial infarction W-shaped (favourable prognosis)

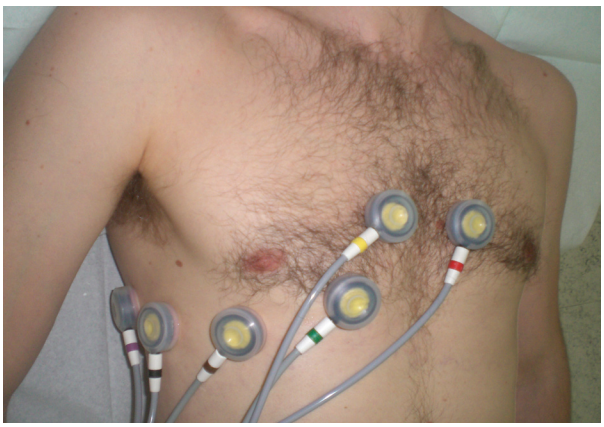


Fig. 553 ECG: right ventricular leads (simply mirror-inverted to left ventricular chest leads)

Therapy

- fluid administration (to increase preload)
  - Patients with RVMI profitieren (especially in cardiogenic shock) benefit enormously from fluid administration. The right ventricle itself is almost completely independent of the preload (volume), there is no Frank Starling mechanism like on the left ventricle. The right ventricle is largely dependent on the afterload (pressure). In RVMI the right ventricle only insufficiently pumps the blood towards the left heart, i.e. the left ventricular preload is too low. This can be increased by fluid administration with a consecutively increase of the cardiac output.
  - target CVP > 20 mmHg (orientation at the CVP only optional; for the estimation of the preload see page 225)
- recanalization:
  - Lysis is much more effective in RV infarction than in LV infarction (Zehender et al, 1993).
  - PCI nevertheless better than lysis
- ⚠ no preload-lowering drugs
  - nitrates (decrease in preload due to dilatation of venous capacity vessels)
  - diuretics
  - morphine (also lowers preload) [by dilatation of venous capacity vessels])
- ⚠ cautious use of β-blockers (since typically on day 2/3 [infarct edema] higher grade AV-blocks)
- cardiogenic shock → fluid administration + dobutamine
- ⚠ if ventilation is required: set as low a PEEP as possible (A too high PEEP lowers both the left and right ventricular preload and increases the right ventricular afterload!)

Infarct complications

If a patient is suddenly worse after a recent myocardial infarction with interventional revascularisation, acute stent thrombosis and infarct complications should be considered.

If a MI patient suddenly deteriorates, do not immediately perform a "suspeced re-infarction" and cardiac catheterization, but rather think of possible MI complications and auscultate!

Ventricular fibrillation

- most frequent cause of death in myocardial infarction
- note: The most frequent cardiac arrhythmia, however, in the context of an acute coronary syndrome is not ventricular, but atrial fibrillation.
- types:
  - primary ventricular fibrillation: < 24h (i.e. before revascularization)
  - secondary ventricular fibrillation: >24h (i.e. after revascularization; worse prognosis)
- therapy: defibrillation
- If ventricular fibrillation occurs after PCI with stent implantation, acute stent thrombosis (mortality 50%) must be considered and the patient generously catheterized again.
- procedure if it occurs after 48 hours (and acute stent thrombosis excluded):
  - amiodarone saturation (SCD-Heft study: not more effective than placebo, in NYHA III even excess mortality)
  - ICD implantation (at the earliest after 4 weeks; possibly bridging with wearable defibrillator vest [e.g. LifeVest])

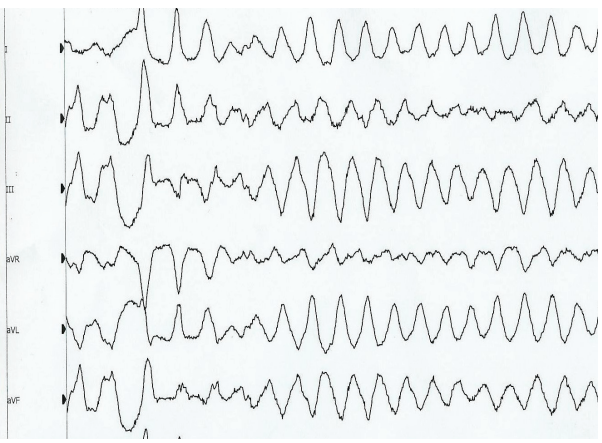


Fig. 554 ventricular fibrillation

- WATCH study (Massier et al, Circulation 2009)
- WARCEF study (Homma et al, N Engl J 2012)
- COMMANDER-HF study (Zannad et al, N Engl J 2018 [rivaroxaban for ischemic cardiomyopathy and sinus rhythm: no benefit])

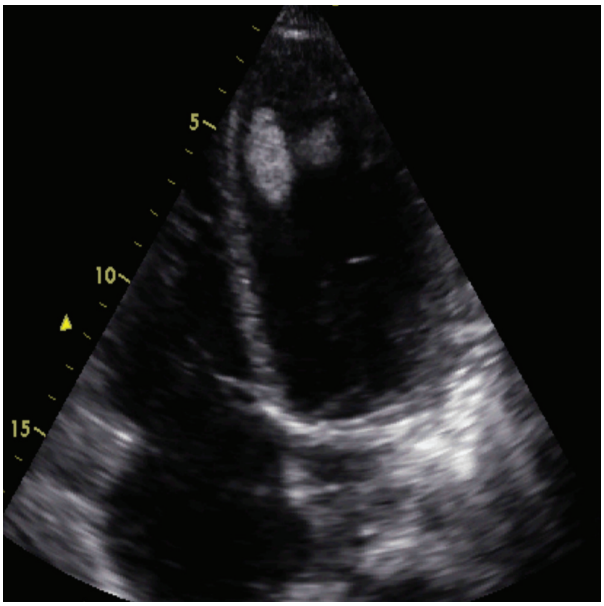


Fig. 563 Echocardiography: apical four-chamber view with thrombus in the left ventricle

DD Pseudoaneurysm

A very important differential diagnosis to a true aneurysm with enormous therapeutic consequences is the pseudoaneurysm: This is a myocardial rupture of the free wall into the pericardial space covered only by a pericardial adhesion. Echocardiographically, a narrow neck (< 40% of the maximum aneurysm diameter), a sharper angle and a more abrupt change in contour are typically seen in contrast to the real aneurysm. This differential diagnosis is important because a pseudoaneurysm is not an indication for anticoagulation (like the real aneurysm [with thrombus]), but an indication for (urgent) surgery. The differential diagnosis must be performed echocardiographically. A left heart contrast medium (e.g. SonoVue) can also be used for better visualization

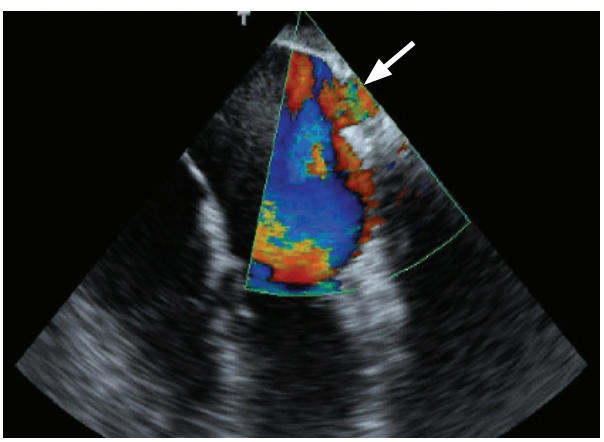


Fig. 564 pseudoaneurysma With a real aneurysm (left), both the myocardium (red) and the pericardium (black) are bulging

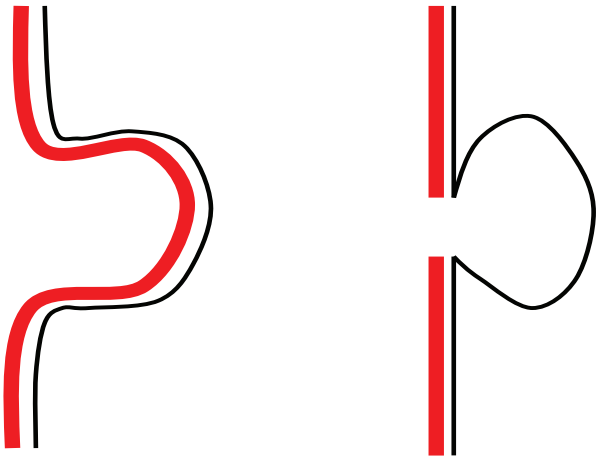


Fig. 565 With a real aneurysm (left), both the myocardium (red) and the pericardium (black; exactly: visceral part of the pericardium [syn.: epicardium]) are bulging, with a pseudoaneurysm (right) only the pericardium. Here there is a rupture of the myocardium which is only covered by the pericardium (exactly: parietal part). In the pseudoaneurysm the neck is much narrower and the angle much more pointed.

Bradycardias

- frequent and almost only inferior wall myocardial infarction
- often AV blocks
- usually harmless
- if necessary atropine or dobutamine
- spontaneous remission frequently in the first 3 days
- if necessary temporary pacemaker, but very rarely a permanent pacemaker is necessary (One should wait at least 10 days with the implantation of a permanent pacemaker! Most patients recover and then do not need a permanent pacemaker. But especially in an interdisciplinary intensive care unit, where one often feels a certain pressure from the surgical departments to provide free beds, this is unfortunately often not done and often too early unnecessary a permanent pacemaker is implanted.)

Wait at least 10 days with the implantation of a permanent pacemaker in AV block III after a inferior wall MI! Most patients recover and do not need one!

	inferior wall MI	anterior wall MI
occurence	often	rare
necessity of implantation of a permanent pacemaker	rare	often

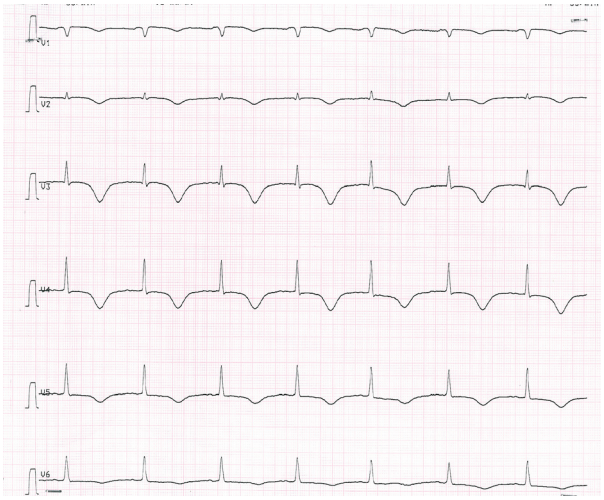


Fig. 568 ECG in Tako-Tsubo cardiomyopathy (various examples): The typical deep isosceles T-negativations above the anterior wall are visible. Furthermore, the QT interval is prolonged.

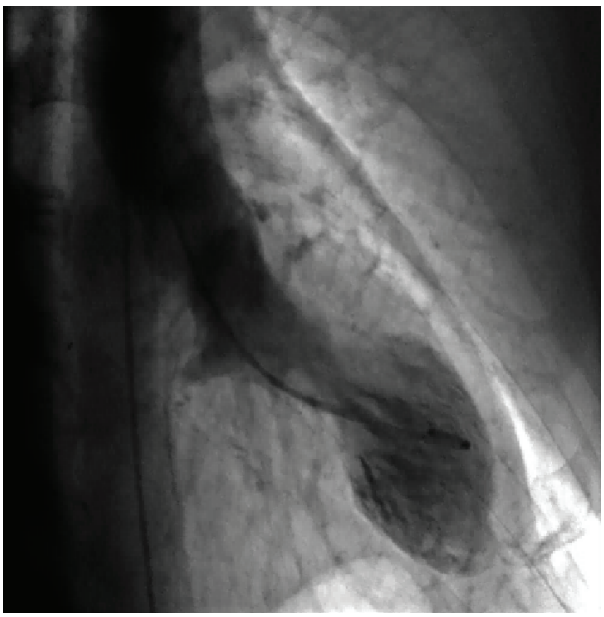


Fig. 569 Levocardiography (pigtail in the left ventricle): The balloon-like bulge of the left ventricle can be seen.

Tako-Tsubo cardiomyopathy: always exclusion diagnosis (especially exclusion of proximal LAD occlusion with anterior wall MI)!!

Therapy

- therapy option: β-blockers (protection against the further cardiotoxic effect of catecholamines)
- cardiogenic shock: catecholamines contraindicated (because they trigger the disease!); options:
  - pharmacological: phosphodiesterase-3 inhibitors, levosimendan
  - non-pharmacological: IABP, Impella, va-ECMO, VAD (ventricular assist device)

cardiogenic shock in Tako-Tsubo cardiomyopathy: catecholamines contraindicated!

Prognosis

- after 4-5 weeks typically complete restitutio ad integrum again (almost always reversible)
- mortality: 3%
- risk factors for complications (Santoro et al, JAMA Cardiology 2019; from these the GEIST score [see infobox] was also developed for estimation of prognosis) with poorer prognosis:
  - male gender
  - reduced ejection fraction
  - involvement of the right ventricle
  - neurological disorders
- poorer prognosis for physical (especially men) instead of psychical (especially women) triggers (Konstatinos et al, Front Psychol 2017)
- long-term outcome as in patients with acute coronary syndrome (Ghadri et al, J Am Coll Cardiol 2018)
- risk of recurrence: 10% (in 4 years)
- ⚠ increased risk of cancer
  - cancer incidence twice as high as in the normal population
  - cancer in every 6th patient with Tako-Tsubo cardiomyopathy (J Am Heart Assoc 2019)

GEIST score

Definition

- **score for prognostic assessment in Tako-Tsubo cardiomyopathy**
- **GEIST: German and Italian Stress Cardiomyopathy**

Parameters

- **reduced ejection fraction: EF in % x -1**
- **male gender: + 20P.**
- **neurological disorder: + 20P.**
- **involvement of the right ventricle: 30P.**

Interpretation: risk

- **< 20P.: low (complication rate: 12.7%; maybe early discharge from hospital)**
- **20-40P.: intermediate (complication rate: 23.4%)**
- **> 40P.: high (complication rate: 58.8%; generous transfer to intensive care unit)**

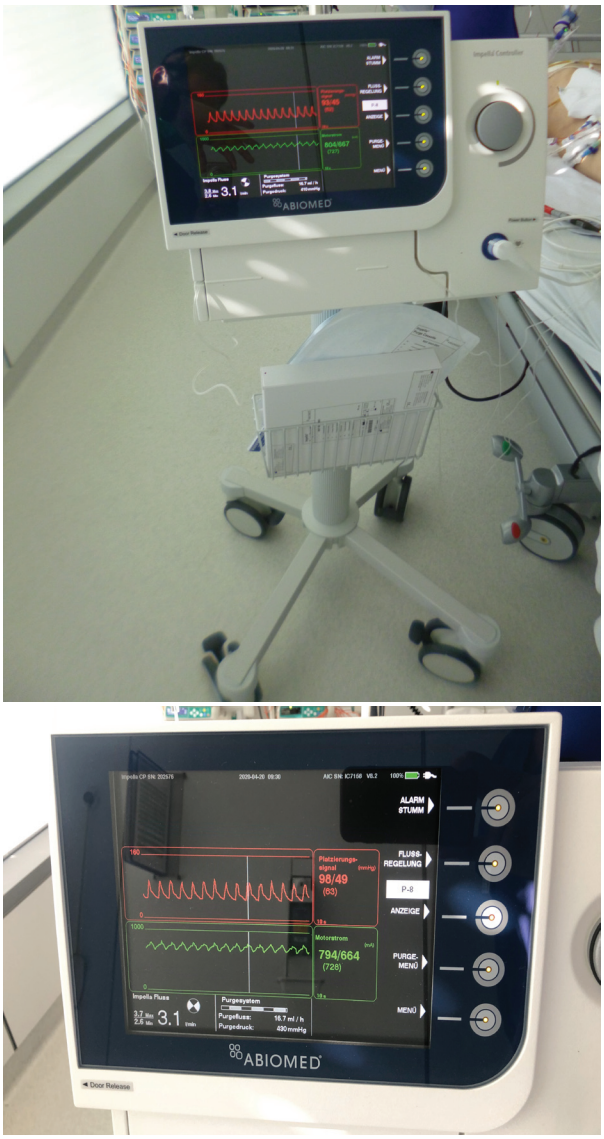


Fig. 588 Impella 5.0

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.
    - colour 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])

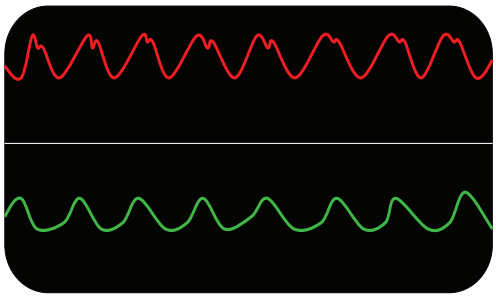


Fig. 589 curves on the display of the control console monitor: above (red) the placement signal, below (green) the motor current curve. The placement signal is configured correctly to be pulsatile and aortic, i.e. the diastolic pressure is significantly greater than zero. The position of the pump is correct. The motor current curve is also normally pulsatile.

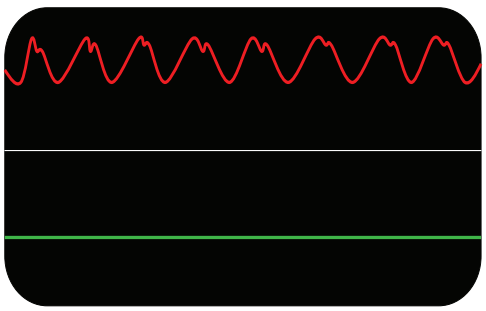


Fig. 590 The motor current curve (green) is flat, i.e. both openings (inlet and outlet) are in the same area. The placement signal (red) is configured aortally, i.e. both openings are in the aorta. The pump has slipped out of the left ventricle (most common cause: Valve was not screwed shut.) and must be pushed forward. Procedure: reduction of performance to p2, increase in catecholamines, then repositioning under echocardiographic control

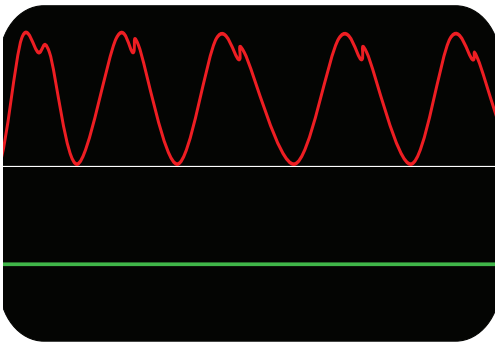


Fig. 591 The motor current curve (green) is flat, i.e. both openings (inlet and outlet) are in the same area. The placement signal (red) is configured ventricularly (diastolic blood pressure to zero), i.e. both openings are in the left ventricle. The pump has slipped too far into the left ventricle and must be withdrawn. Procedure: reduction of performance to p2, increase in catecholamines, then repositioning under echocardiographic control

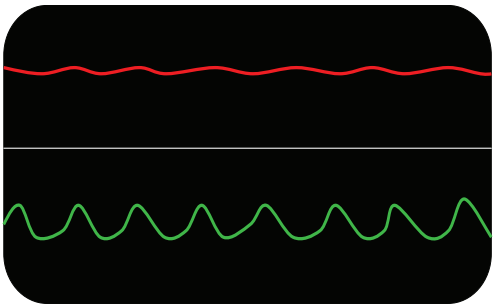
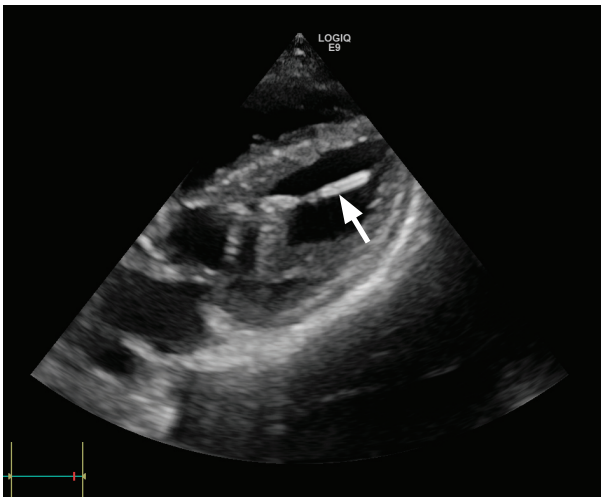


Fig. 592 The motor current curve (green) is normally pulsatile, but the placement signal (red) is flat. This is because the ejection fraction of the left ventricle is severely reduced. The lower the ejection fraction, the lower the pulsatility Most of the work here is done by the pump, which is also correct because the left ventricle should be relieved .



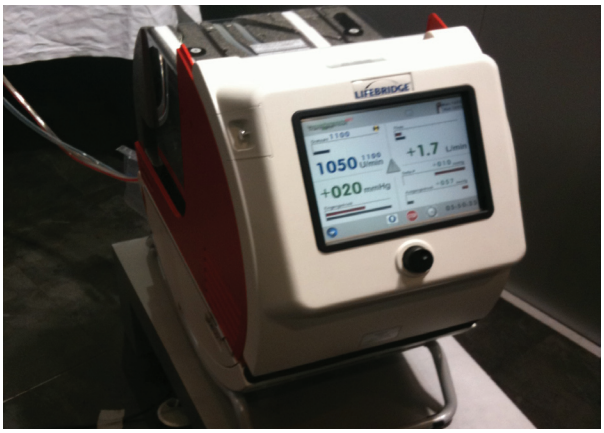
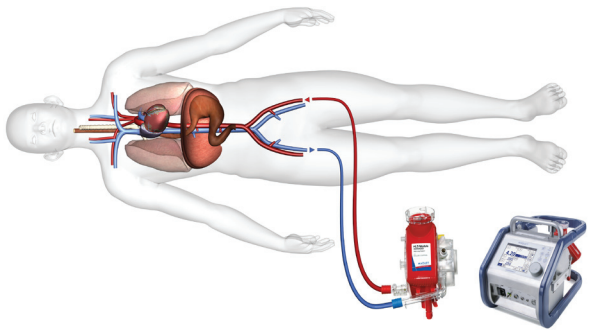


Fig. 596 Lifebridge

Cardiohelp

- company: Maquet
- mobile heart lung machine (i.a. centrifugal pump, oxygenator)
- maximum flow rate: 4-6 l/min (almost complete CO replacement!)
- 2 sheaths (implantation without cardio technician)
  - femoral artery (15-17F)
  - femoral vein (18-23F)
- transportable (weight 10kg)
- maximum dwell time: 30 days
- target-ACT: 150-200s
- operation of the system optionally also possible with heparin-free components (e.g. with HIT II)



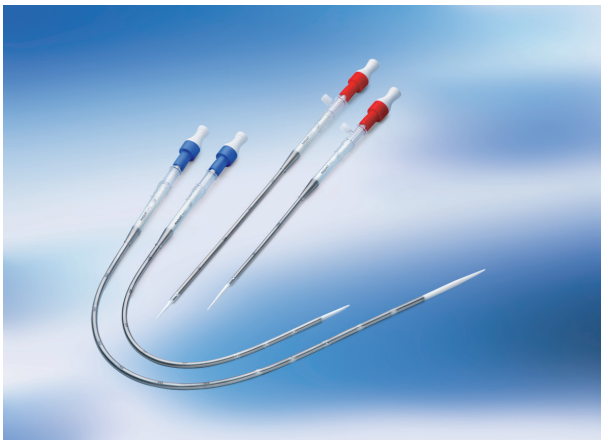


Fig. 597 Cardiohelp [23]

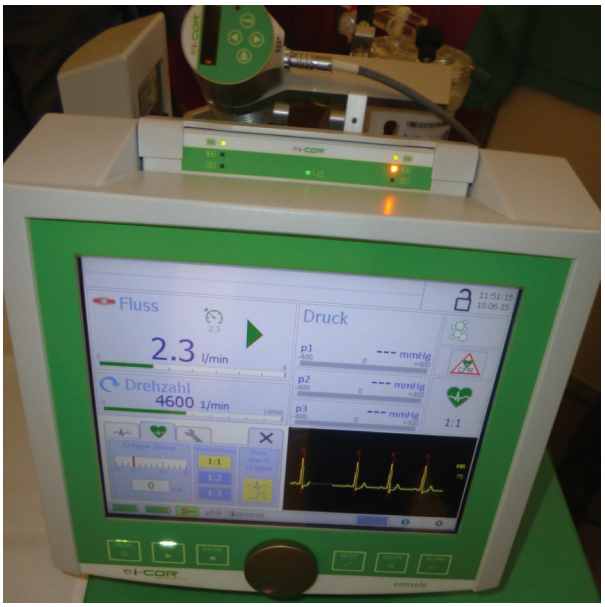


Fig. 598 i-cor (company Xenios): transportable va-ECMO system. The support is pulsatile here. Triggering is performed by ECG (also possible with atrial fibrillation). The maximum flow (analogous to IABP) is generated in the diastole, so that the coronary perfusion is improved. The i-cor system is a combination of IABP and ECMO.

Support devices
according to ejection fraction

- moderately reduced EF → IABP (nowadays only optionally)
- severely reduced EF → minimally invasive heart pump (e.g. Impella)
- cardiac arrest → extracorporeal life support (e.g. va-ECMO, Cardiohelp, Lifebridge)

Fig. 601 left ventricular assist device (LVAD): HeartMate II of company Abbott [44]

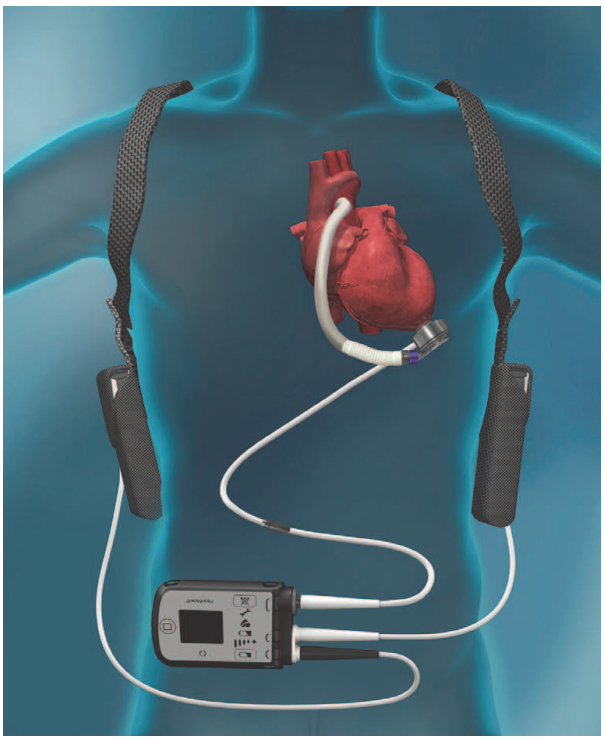


Fig. 602 left ventricular assist device (LVAD): HeartMate III of company Abbott [44] - The controller (control unit) is connected on the one hand to the Driveline (power cable to the pump) and on the other hand to the power supply (here two batteries).

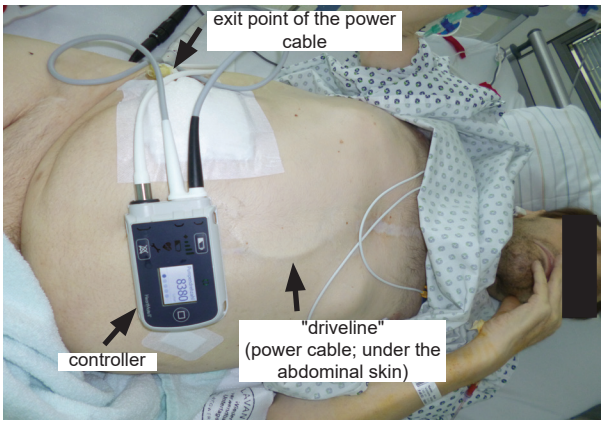


Fig. 603 patient with an LVAD system (here HeartMate II)

Goals

- "bridge"
  - "bridge to recovery" (BTR): The system is left until the pump function has recovered (e.g. after a myocardial infarction or a myocarditis). Then it will be explanted again. Overall, however, this is rarely the case (10%).
  - "bridge to transplantation" (BTT; most common indication): The system is left until the patient is transplanted (note: The number of heart transplants in Germany reached a historic low in 2013.).
  - "bridge to decision" (BTD): The system is left until a decision has been made on the further procedure (e.g. therapy limitation after prolonged resuscitation).
- "destination therapy" (DT): Due to a lack of prospects for or contraindications to transplantation, the system is the only treatment option (2-year survival rate of patients with LVAD: 80% [Kormos et al, J Heart Lung Transplant 2019])

Indications for VAD
"I NEED HELP"

I:	**inotropics necessary continuously**
N:	**NYHA class III / IV, natriuretic peptides ↑ (pro-BNP > 1000 pg/ml)**
E:	**ejektion fraction < 20%**
E:	**end organ damage (e.g. kidney failure)**
D:	**Defibrillator (implanted AICD) shocked alrea dy several times**
H:	**Hospitalizations Recurrent**
E:	**Escalation (e.g. increase in diuretics)**
L:	**Low blood pressure**
P:	**Prognosis relevant drugs (especially ACE in hibitors or β-blockers) had to be discontinu ed due to the low blood pressure.**

Therapy

- verapamil (Isoptin)
  - ⚠ means of choice (good response); alternatively, however, are β-blockers possible
  - dosage: 3-4 x 120mg
- flecainid (Tambocor)
  - 1 amp. = 50mg
  - 1 Amp. slowly over 10min i.v.; then wait 2 hours, then repeat if necessary (up to 3 amp.)
- amiodarone
- ⚠ electrical cardioversion (mostly successful!)
- ablation (success rate: 85%)
- anticoagulation: recommended if atrial frequency > 160/min as for atrial fibrillation

AV node reentry tachycardia (AVNRT)

Definition

- syn.: Bouveret's tachycardia (named after the French internist Leon Bouveret [1850-1929])
- presence of two functionally separated conduction pathways in the AV node (functional longitudinal dissociation of the AV node)
  - α-pathway: slow (antegrade) conductive
  - β-pathway: fast (retrograde) conductive
- reentry mechanism (mostly slow → fast-type-tachycardia [α → β])
- simultaneous excitation of atrium and ventricle
- mostly heart-healthy
- mostly younger women
- frequent!

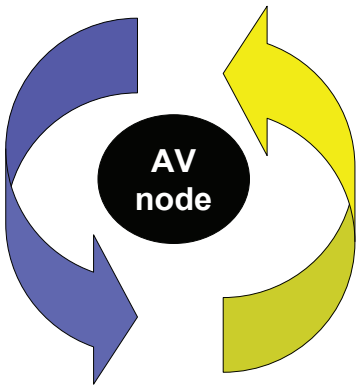


Fig. 630 AV node reentry tachycardia: Presence of two separate pathways around the AV node; reentry mostly from the slow (α) to the fast (β) pathway

Symptoms

- dizziness
- racing heart, palpitations
- typically sudden onset and end ("like turning the light switch on and off")
- urge to urinate (ANP release due to atrial overstretching due to atrial contraction against the closed AV valve)
- frog sign (simultaneous contraction of atrium and ventricle → grafting, "pulsating" jugular veins)

ECG

- regular narrow complex tachycardia with a heart rate of 180-220/min
- no P waves detectable
- sudden onset („jump“)
- possibly electrical alternans
- no signs of preexcitation in tachycardia-free ECG
- aVL-notch (for AVNRT in 51%, for AVRT [in WPW syndrome] only in 7% [Toro et al, Europace 2009])
- types (electrophysiological):
  - typical AVNRT: HA (His-atrial) ≤ 70ms, VA (ventriculo-atrial) ≤ 60ms
  - atypical AVNRT: HA (His-atrial) > 70ms, VA (ventriculo-atrial) > 60ms

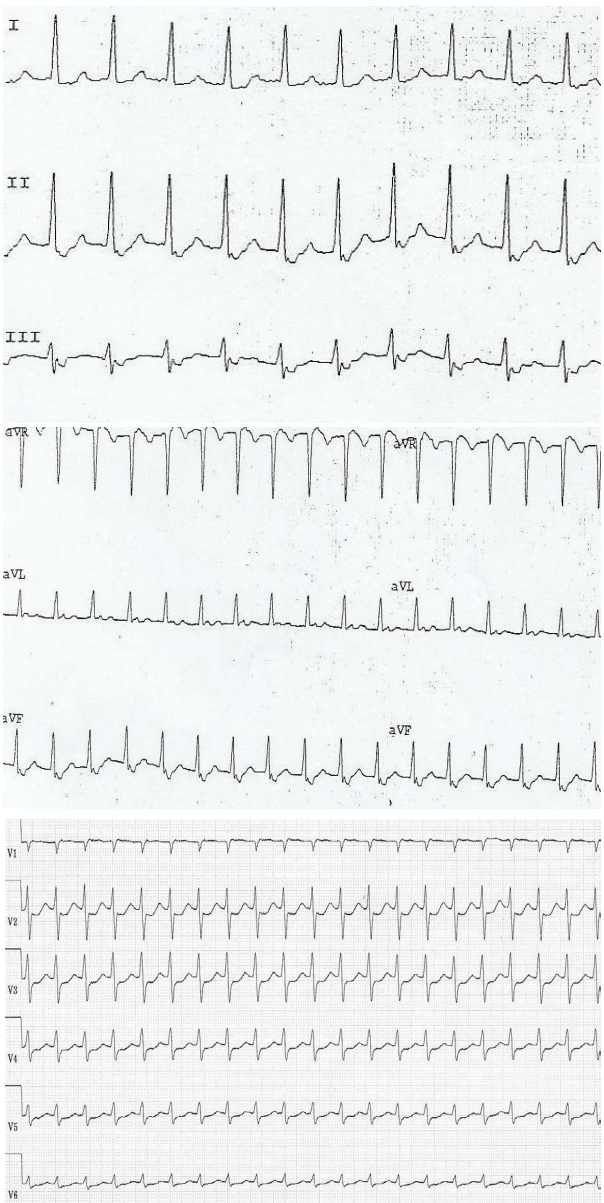


Fig. 631 AV node reentry tachycardia

DD regular narrow complex tachycardia based on the P-wave

- P wave before the QRS complex → sinus tachycardia
- no P wave → AV node reentry tachycardia
- P wave after the QRS complex → orthodromic AV reentry tachycardi , PJRT

The best way to assess atrial actions is in the Lewis lead!

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?)

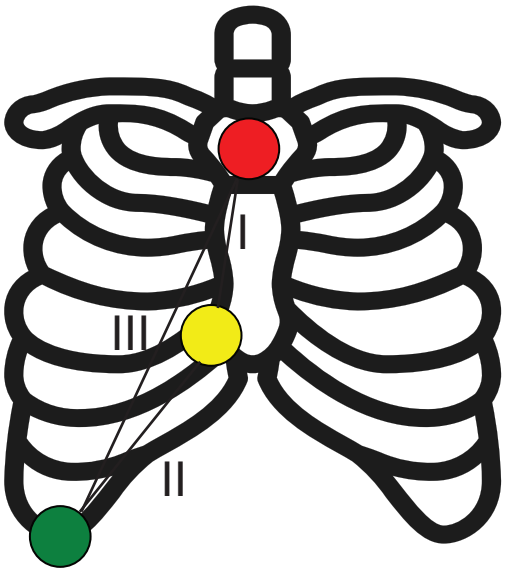


Fig. 640 modified ECG derivation according to Lewis, to better assess atrial actions (a special atrial lead): 3 of the 4 limb leads are glued to a different location: on the sternum manubrium, on the lower right edge of the sternum and on the lower right costal arch. The Lewis lead is the lead I: It 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

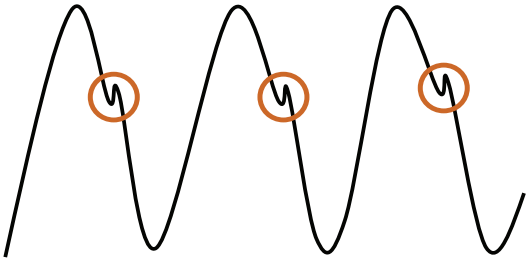
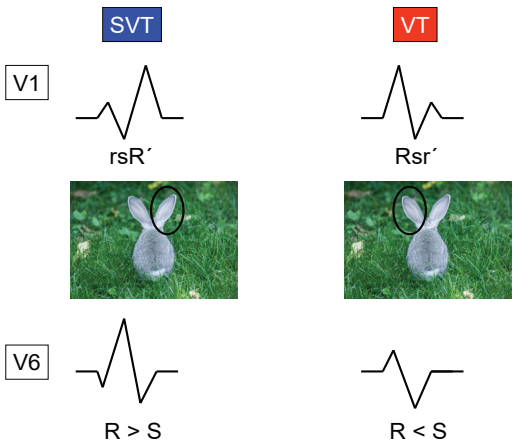
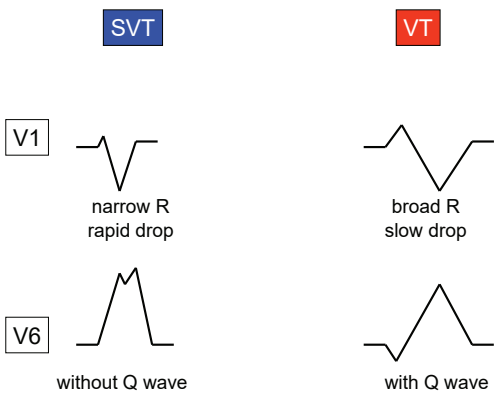


Fig. 652 The Josephson's sign is defined as a notch in the descending part of the S wave of the QRS complex. It indicates a ventricular tachycardia in the presence of a wide QRS complex tachycardia.



right bundle branch block

Fig. 653 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. 654 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.

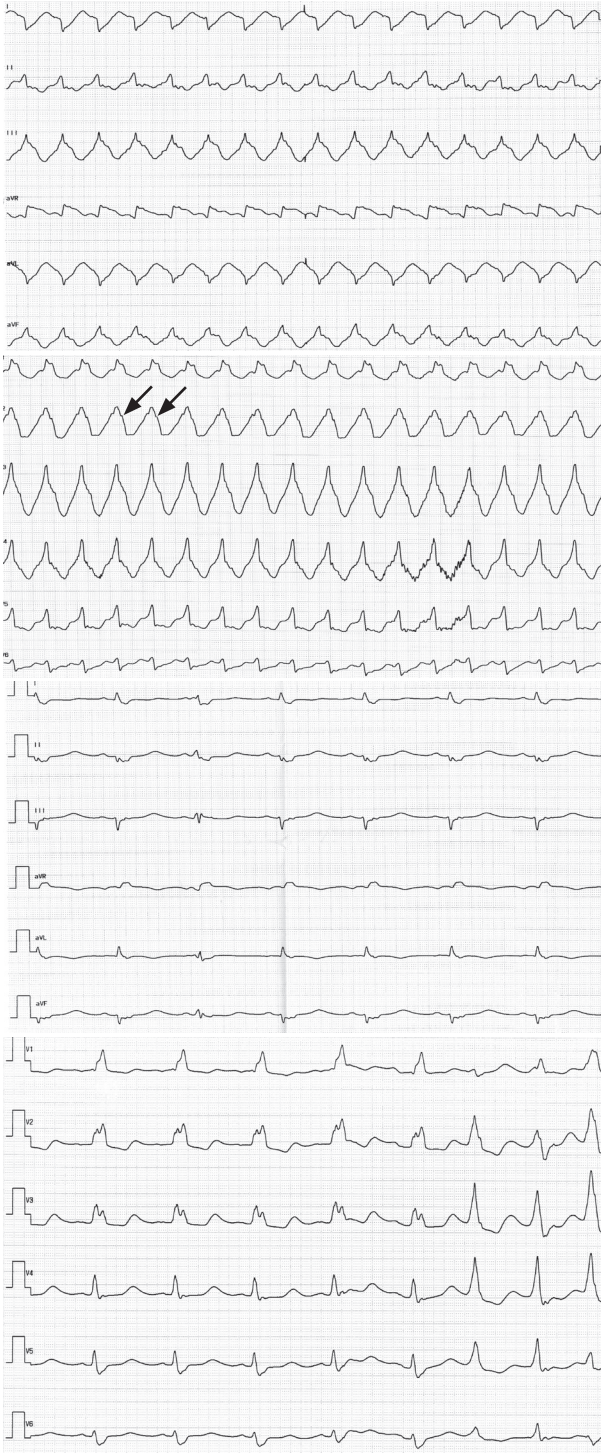
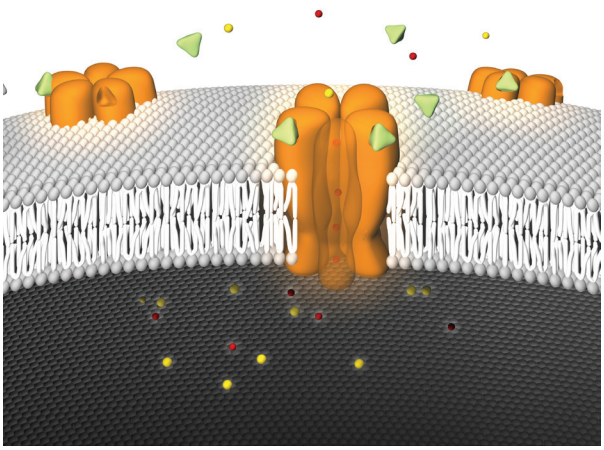


Fig. 655 right bundle branch block with left rabbit ear (Rsr´-configuration; 2 spikes in V1, of which the first spike is larger than the second spike [atypical RBBB]) and R < S in V6, Josephson´s sign (see arrows), positive concordance (consistently positive QRS complexes in all chest wall leads) and 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).

Ventricular tachycardias

- ajmaline
- ⚠ amiodarone: strictly contraindicated (only in case of absolute danger to life [e.g. therapy refractory ventricular fibrillation])
- R-wave triggered cardioversion
- after resuscitation in case of ventricular arrhythmia/ ventricular fibrillation (after exclusion of an recoverable or temporary cause [e.g. myocardial infarction]) → ICD implantation (shocks → no damage to the unborn child [Natale et al, Cirulation 1997]); alternative: WCD vest (e.g. LifeVest) during pregnancy and AICD implantation only after delivery

Ion channel diseases



- syn.:
  - channelopathies
  - primarily electrical diseases of the heart
- types:
  - Brugada syndrome (sodium channel)
  - QT syndromes (potassium channel):
    - long-QT syndrome
    - short-QT syndrome
  - catecholaminergic polymorphic ventricular tachycardia (CPVT; calcium channel)
- overwiew: ventricular tachycardia / ventricular fibrillation
  - 95% with structural heart disease
  - 5% without structural heart disease ("idiopathic" ventricular fibrillation; typically ion channel diseases)

Brugada syndrome

Definition

- first described in 1992 by the brothers Pedro and Josep Brugada in a small number (11) of patients who suddenly suffered from cardiac arrest, were successfully resuscitated, had no structural heart disease and all showed a typical ECG picture
- syncope in the own anamnesis
- sudden cardiac death in the family anamnesis
- in 30% sudden cardiac death as first manifestation
- absence of a structural heart disease

Epidemiology

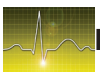
- ⚠ prevalence: 0.1-0.4% of the population (just as frequent as WPW syndrome!)
- m:w = 8:1
- first manifestation mostly in the 4th decade of life
- 30% of all SCD in structurally heart-healthy people
- high prevalence especially in Asia, there partly synonymous with SCD in men < 50 years:
  - "Lai Tai" (Thailand)
  - "Bangungut" (Philippines)
  - "Pokkuri" (Japan)

Etiology

- partially autosomal dominant inheritance, in 30% positive family anamnesis
- mutation in SCN5A gene (coded for cardiac sodium channel) on chromosome 3 (possibly genetic testing)

Symptoms

- syncope
- palpitations
- SCD or after successful resuscitation in ventricular fibrillation
- often at rest / at night during sleep
- nocturnal agonal breathing
- frequent triggers:
  - fever
  - excessive alcohol consumption
  - large (opulent) meals
  - medication (see below), drugs (i.a. cannabis, cocaine)



ECG

- right bundle branch block (complete / incomplete)
- descending (saddleback / coved-type) ST elevation in the right precordial leads (V1-V3)
- shoulder-shaped elevation of ST segment (J-point)
- The ECG changes exclusively affect the leads V1-V3.
- The corresponding ECG changes are often easier to detect if the right ventricular leads (V1 and V2) are applicated one ICS higher (2nd / 3rd ICS).
- The ECG morphology typically changes..
- concealed Brugada syndrome → provocation test with ajmaline
  - As a sodium channel blocker, Ajmalin can unmask the typical ECG findings.
  - ajmalin test: gilurytmal 1 mg/kg over 5min i.v.
  - possible complications: ventricular tachycardia, possibly ventricular fibrillation (therefore defibrillator readiness; cave: monitoring for at least 2hours!)
- possibly PQ interval↑
- malignant arrhythmias:
  - ventricular tachycardia
    - frequently polymorphic

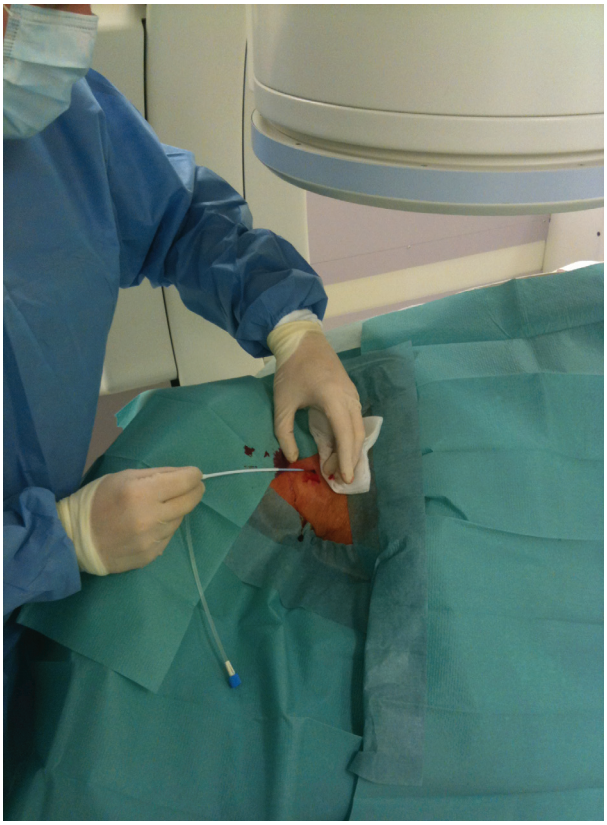


Fig. 704 A 7F sheath is inserted via a guide wire (Seldinger technique).

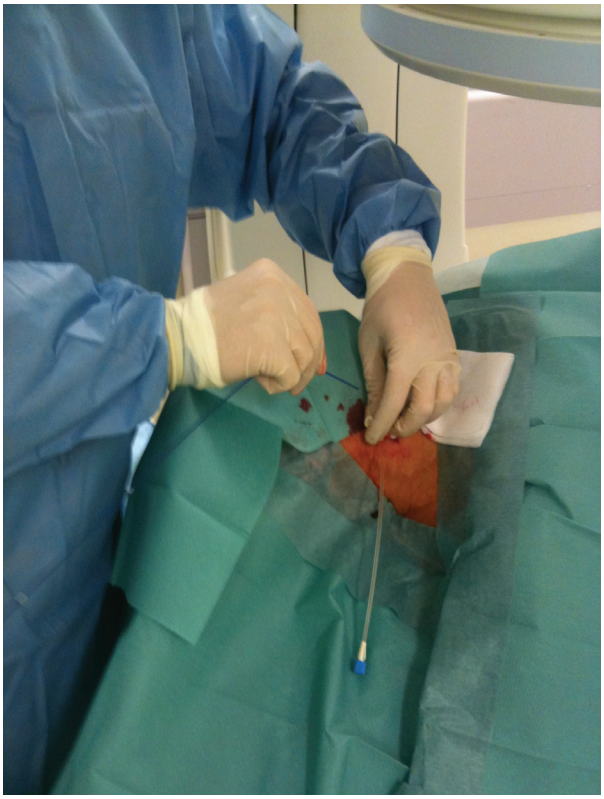


Fig. 705 The pacemaker lead (electrode) is now inserted via the 7F sheath and advanced into the right ventricle (apex of the heart) under X-ray fluoroscopy.

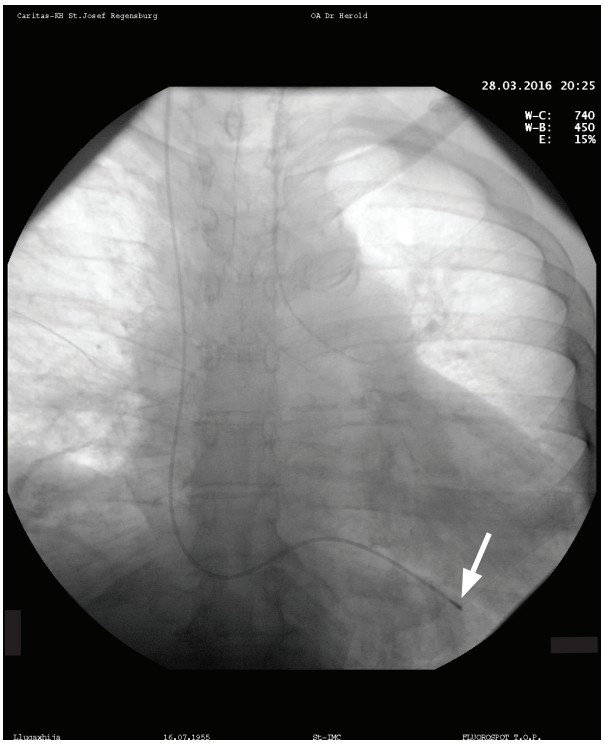


Fig. 706 Under fluoroscopy, the lead is correctly positioned at the apex of the right ventricle with a slightly S-shaped course.

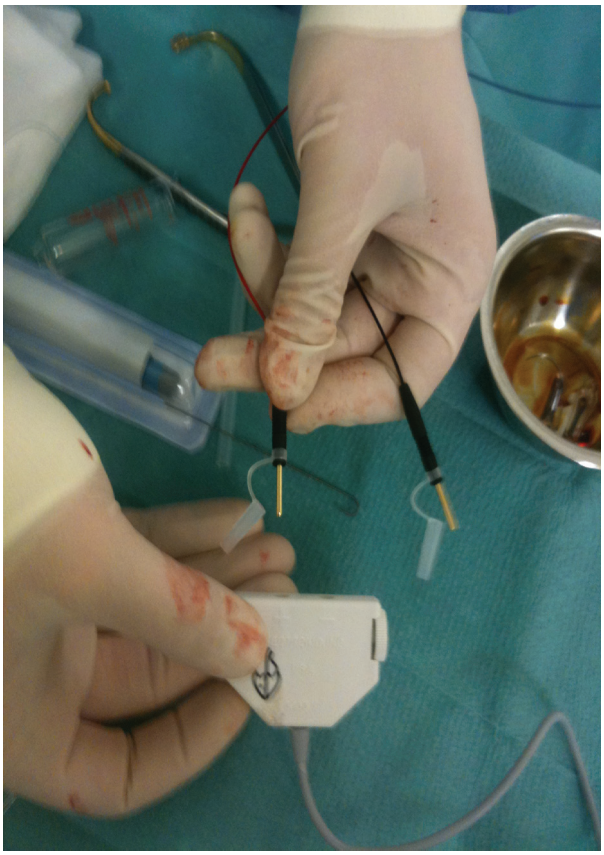


Fig. 707 After the electrode has been correctly placed, its two plugs are connected to the pacemaker aggregate (red in plus, black in minus).

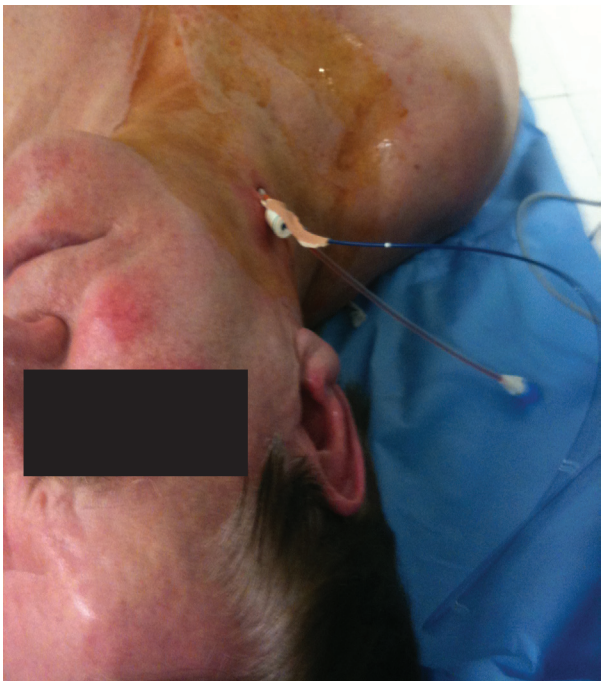


Fig. 708 The electrode is fixed lengthwise in the sheath with a plaster strip.

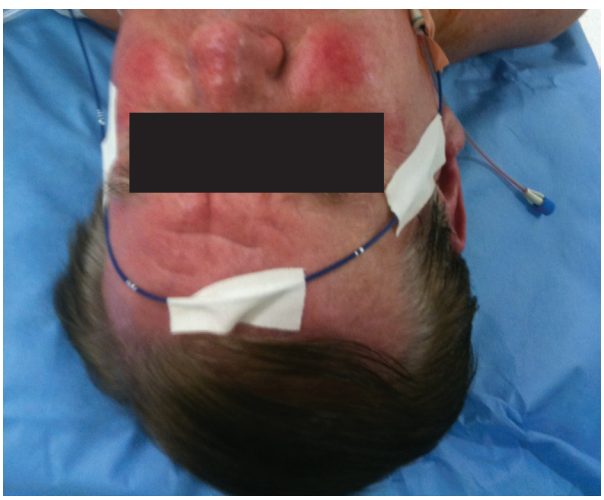
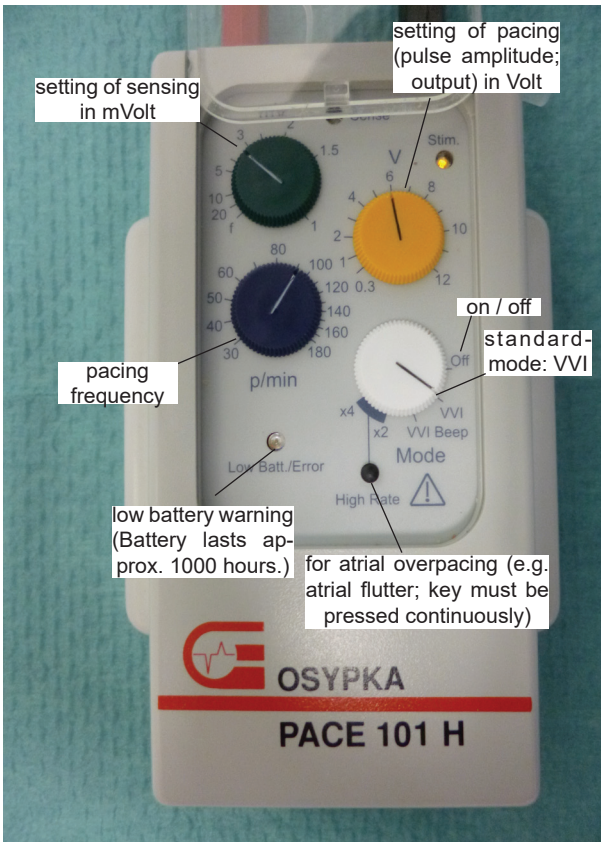
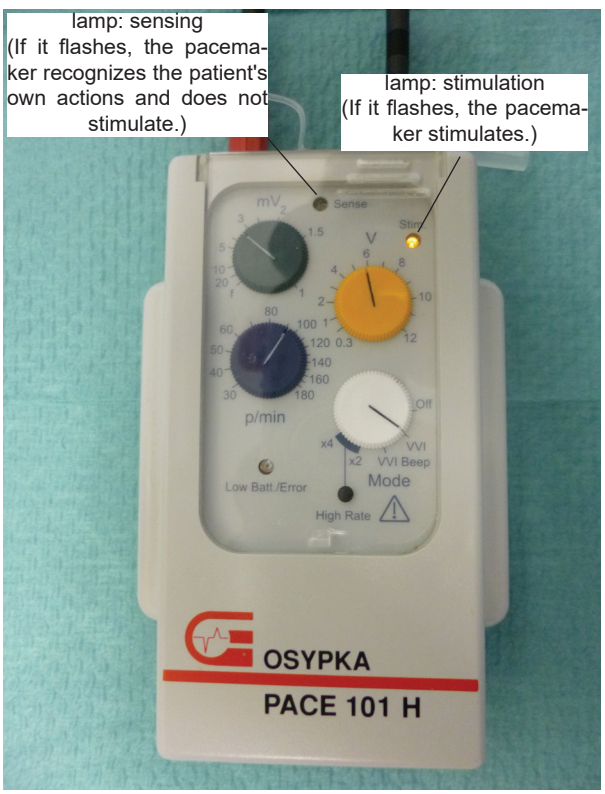


Fig. 709 The electrode is fixed circularly to the forehead with plaster strips.





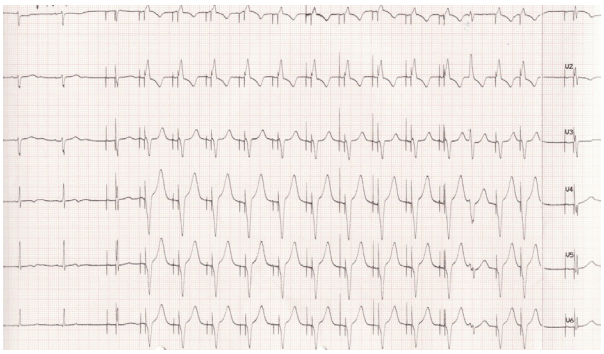


Fig. 712 Here, after magnet application, a regular fixed-rate stimulation (here D00 for two-chamber pacemaker) with the manufacturer-specific heart rate (here Biotronik: 90/min) can be seen. So there is no evidence of battery depletion here.

cave magnet application to pacemaker: always only in readiness for defibrillation (Ventricular fibrillation can be triggered!)

Failure to capture (exit block)

- definition: spikes still visible, but no more stimulated QRS complex (ineffective spike ["naked spike"]: no depolarization and thus no more myocardial contraction)
- causes
  - electrode (lead):
    - lead dislocation
      - types: macrodislocation (also visible in X-ray) / microdislocation
      - causes: e.g. Twiddler's syndrome (The pacemaker aggregate rotates in the pacemaker pocket with the result that the electrode rolls up spirally and thus dislocates from the myocardium.), e.g. pneumothorax (Especially in tension pneumothorax, the mediastinal shift can cause a lead dislocation), e.g. lead dislocation by insertion of a CVC (central venous catheter) or PAC (pulmonary artery catheter)
    - lead fracture
      - strikingly high electrode impedance (> 2000Ω)
      - e.g. subclavian crush syndrome (SCS): Here the electrode is crushed like by a pliers between the clavicle and the first rib. This occurs above all if the subclavian vein is punctured too far medially Therefore the subclavian vein should be punctured as far as possible laterally.
  - increase of stimulation treshold:
    - fibrosation at the electrode tip (This is also the rational reason why some lead heads contain steroids to prevent fibrosation.).
    - drugs (e.g. amiodarone, sotalol, propafenone, flecainide
    - hyperkalemia
    - right ventricular myocardial infarction (Myocardium can no longer be excited there due to the infarction.)
    - after cardioversion / defibrillation (mostly short-term massive increase in stimulation threshold!)
- therapy
  - magnet application: ineffective (does not increase the output)
  - pharmacological increase in heart rate (e.g. atropine, orciprenaline)
  - increase in pulse amplitude or extension of pulse duration (Here you should immediately fetch the pacemaker control device from the respective company of the implanted pacemaker and increase the output!)
  - possibly temporary pacemaker
  - in case of a lead problem surgical lead revision

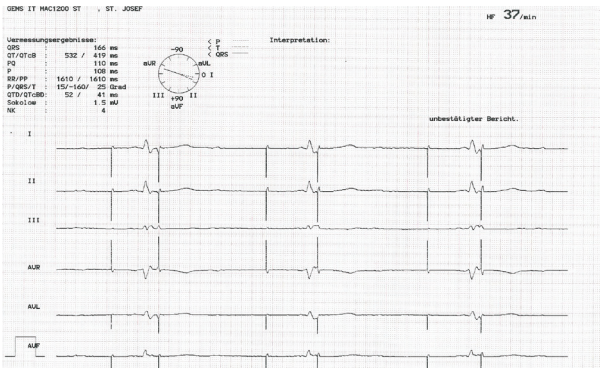


Fig. 713 Exit block: spikes still recognizable, but no stimulated QRS complex recognizable (ineffective spike ["naked" spike])

common causes for an exit block in ICU: cardioversion / defibrillation, amiodarone, hyperkalemia, right ventricular MI!

Pacemaker syndrome

- definition: Occasionally it happens that a VVI pacemaker is implanted in supposedly permanent atrial fibrillation and then sinus rhythm shows up again. Then the retrograde pathway causes atrial excitation and atrial contraction against the closed AV valve. The result is a reflectory drop in blood pressure with dizziness and possibly even syncope.
- occurrence: in 20% of all patients with a VVI pacemaker
- symptoms:
  - palpitations
  - reduced resilience
  - dizziness, possibly syncope (despite pacemaker implantation!)
  - dyspnoea (up to pulmonary edema)
- therapy:
  - reduction of the stimulation frequency (e.g. from 60/min [mostly set like this] to 50/min), in order to guarantee patient´s own (intrinsic) rhythm, so that no stimulation takes place; alternatively, you can also program the hysteresis function (Greek "hysteros": later, afterwards) to e.g. 50/min, i.e. the stimulation frequency of the pacemaker is officially still 60/min,

Definition

- second most common pathogen (formerly No.1)
- physiological colonization of the oropharynx (therefore syn.: oral streptococci)
- types:
  - S. mutans, S. mitis
  - S. sanguinis, S. anginonsus, S. salivarius
- lethality: < 10%
- penicillin resistance: only 1%

Therapy

Viridans streptococci

Monotherapy for 4 weeks:**

- **penicillin* G 20 Mio E/Tag i.v. (in 4 doses) or**
- **amoxicillin 100-200 mg/kg (in 4 doses) or**
- **ceftriaxon 2g/Tag (in 1 dose)**
- **annot.: 😕 A combination with gentamycin is no longer recommended for therapy over 4 weeks according to the 2015 ESC guidelines.**

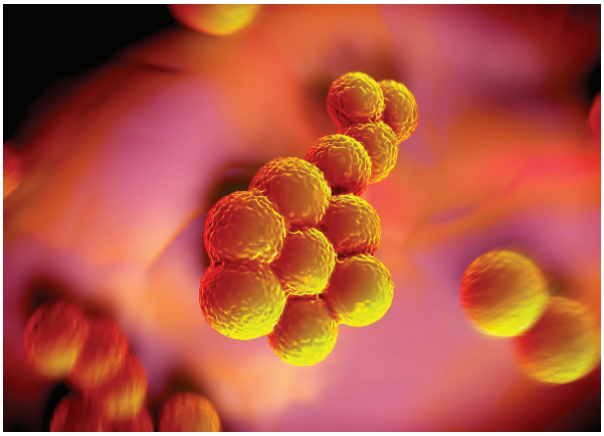
*penicillin allergy: vancomycin 30 mg/kg/day (in 2 doses)

**uncomplicated course, low age (< 65 years), duration of illness < 3 months, normal kidney function → 2 weeks (but then in combination with gentamycin 3 mg/kg/day (in 3 doses [administration of aminoglycoside after penicillin; ESC 2015: only in 1 dose])

Other streptococci

- S. gallolyticus (former name: S. bovis)
  - physiological colonization of the gastrointestinal tract (tooth extractions!)
  - especially in gastrointestinal malignancies (therefore, if detected, prompt gastroscopy and colonoscopy to search for tumors), colonic polyps (after polypectomy)
  - good penicillin sensitivity
  - therapy as with viridans streoptococci
- S. pneumoniae (pneumococci)
  - only rarely pathogens of endocarditis (2%)
  - more frequent in
    - alcoholics, accompanying pneumonia or meningitis
    - aortic valve (rapid destruction)
    - intramyocardial abscesses
  - lethality: 40%

Staphylococcus aureus



Definition

- ⚠ meanwhile the most common pathogen
- types:
  - MSSA: 75%
  - MRSA: 25%
- course: mostly acute
- in 40% cerebral embolisms
- often large vegetations
- risk factors:
  - i.v. drug abuse
  - haemodialysis
  - diabetes mellitus
- lethality: 40%

Therapy

MSSA

- **native valve**
  - **flucloxacillin 6 x 2g/day i.v. for 4-6 weeks or 2nd generation cephalosporin (cefazolin) or (in case of penicillin allergy [note: for non-anaphylactic penicillin allergy also cefazolin possible!]) 30mg/kg/day (in 2 doses) and**
  - **gentamycin 3 mg/kg/day (in 3 doses) for 5 days (faster decline of bacteremia); ESC 2009: only optional, ESC 2015: 😕 no longer recommended (in case of MSSA and native valve)!**
- **artificial valve**
  - **flucloxacillin 6 x 2g/day i.v. for 6 weeks and**
  - **gentamycin 3 mg/kg/day (in 1 dose; ESC 2015: bei MSSA and artificial valve still recommended) for 2 weeks and**
  - **rifampicin 900 mg/day (in 3 doses) p.o. / i.v. for 6 weeks**

Calculated antibiosis native valve

- ampicillin 12 g/day i.v. (in 4 doses) for 4-6 weeks and
- flucloxacillin 2g 4-6x daily for 4-6 weeks and
- gentamycin 3 mg/kg/day (in 3 doses; ESC 2015: in 1 dose) i.v. for 4-6 weeks (in case of good response: only 2 weeks)

in case of penicillin allergy:

- vancomycin 30 mg/kg/day i.v. (in 2 doses) for 4-6 weeks and
- gentamycin 3 mg/kg/day (in 3 doses; ESC 2015: in 1 dose) i.v. for 4-6 weeks and
- ciprofloxacin 800 mg i.v. (in 2 doses) or 1000mg p.o. (in 2 doses) daily; note: was the recommendation in the ESC guidelines 2009; no longer recommended in the ESC 2015 guidelines

Calculated antibiosis artificial valve

- early infective endocarditis (< 12 months)
  - vancomycin 30 mg/kg/day in 2 doses > 6 weeks and
  - gentamycin 3 mg/kg/day (in 3 doses; ESC 2015: in 1 dose) for 2 weeks and
  - rifampicin 1200 mg/day (in 2 doses) p.o. / i.v. for > 6 weeks
- late infective endocarditis (> 12 months): calculated antibiotic therapy as with native valve infective endocarditis

Gentamycin

- Normally, aminoglycosides are only given once a day due to the "first dose phenomenon". They have a pronounced post-antibiotic effect, i.e. they are still bactericidal, even though the peak level has already fallen In cases of endocarditis, the daily dose (gentamycin 3 mg/kg based on the ideal weight) is divided into three single doses as an exception! In endocarditis, aminoglycosides are only given as a comedication in addition to aminopenicillin (e.g. ampicillin), as this leads to an increased effect. Since ampicillin is also given several times a day, gentamycin, which only acts as an enhancer, is also given several times a day. The aminoglycoside should always been administered after the penicillin. In the European guidelines (ESC-Guidelines 2015), however, only once daily administration (gentamycin 3 mg / kg) is now recommended, while the American guidelines continue to recommend three times daily administration. In MSSA, aminoglycosides are now no longer recommended for the therapy of native valve endocarditis, as an advantage could not be proven and the risk of kidney failure is increased by nephrotoxicity. In the case of artificial valve endocarditis due to MSSA or endocarditis due to MRSA (regardless of whether native or artificial valve) aminoglycosides are still recommended
- dose reduction in renal insufficiency (see table; half of all patients with acute endocarditis have an impaired renal function! The nephrotoxicity is lower with the administration in one dose than with the division into three doses per day.)
- therapeutic drug monitoring; target level:
  - trough level (immediately before administration; predose)
    - when administered one time a day (currently recommended [ESC]): < 1 mg/l (< 1 µg/ml)
    - when administered three times a day (currently no longer recommended [ESC]): < 2 mg/l
  - peak level (1h after administration; post-dose)
    - when administered one time a day (currently recommended [ESC]): 10-12 mg/l
    - when administered three times a day (currently no longer recommended [ESC]): 3-4 mg/l

Creatinine clearance (ml/min)	Percent of normal dose (3 mg/kg bw)
> 70	100
60	98
50	97
40	94
30	88
20	75
< 10	50

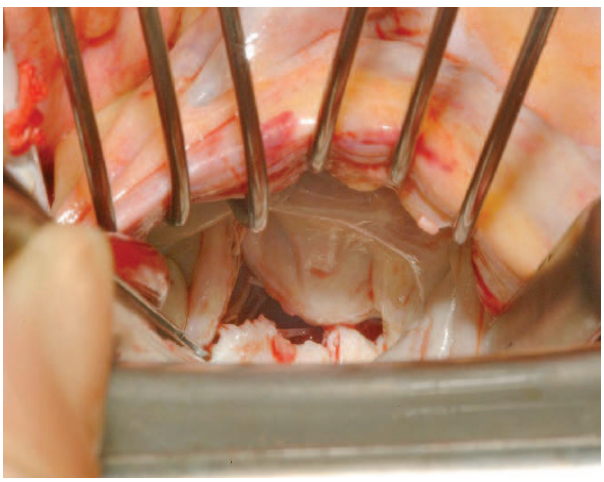
Principles ("rules of the game")

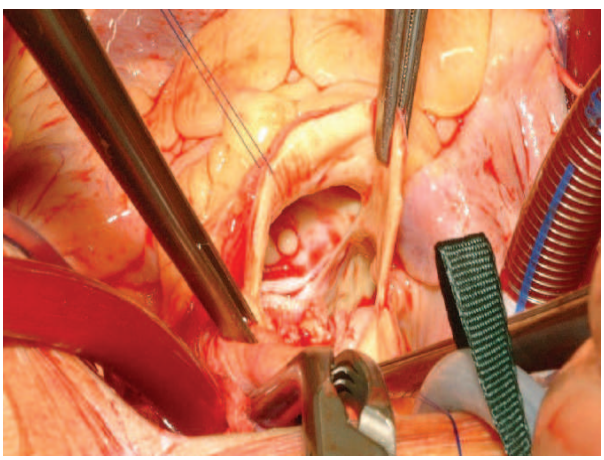
- The treatment of endocarditis (especially when complications have occurred) should be carried out on an interdisciplinary basis by or in consultation with an endocarditis team (cardiologist, heart surgeon, infectiologist) at a reference centre (ESC Guidelines 2015 IIa recommendation). In a French study (Botelho-Nevers et al, Arch Intern Med 2009), this dramatically reduced mortality (after 1 year 8.2% versus 18.5%).
- Antibiosis should always be administered parenterally (via peripheral cannulae; no central venous catheter in infectious endocarditis [if possible, but often unavoidable in septic patients with intensive care). The POET study (see box) showed, however, that in the second half the antibiosis can also be given orally without endangering the patient, so that a more rapid discharge from hospital is possible.
- always abdominal sonography (especially splenic infarction)
- positive blood culture with S.aureus → always TEE (in 15% endocarditis; note: The VIRSTA score is helpful in deciding which patient with S. aureus bacteremia actually needs a TEE (see infobox on page 669).
- Defervescence should occur after 7 days at the latest.
- initial bed rest
- duration of antibiosis

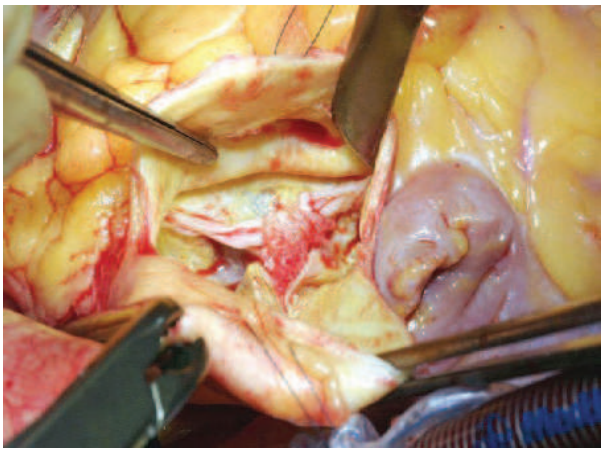
EASE study

Early Surgery Versus Conventional Treatment in Infective Endocarditis
Kang et al, N Engl J 2012

- prospective randomized study (Korea)
- EASE: endovascular atherectomy safety and effectiveness
- 76 patients with infective endocarditis and vegetations > 10mm (aortic or mitral valve)
  - conservative (in 77% but then still in the course [i.e. after 48h] surgery; [note: a very unusual "conservative" group])
  - surgical (surgery within 48h)
- results: surgical
  - significantly reduced combined endpoint of hospital mortality and embolism (especially less embolism!)
  - no difference in mortality







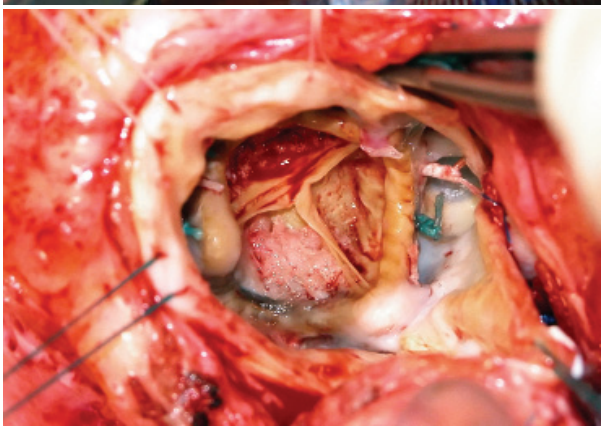
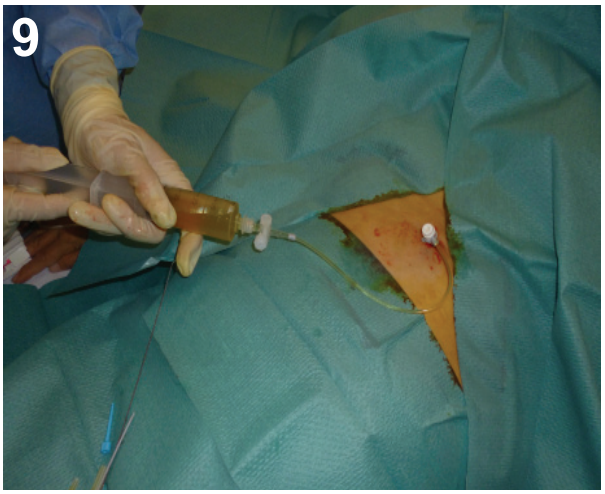


Fig. 738 different surgical images in endocarditis: in the first image vegetation on the mitral valve, then on the aortic valve (bicuspid, below tricuspid), finally on an aortic valve prosthesis (courtesy of PD Dr. med. Florian Wagner, deputy director of the Clinic for Cardiovascular Surgery, University Heart Center Hamburg)

Coronary angiography

- Preoperative coronary angiography is recommended in the ESC guidelines before urgent (1-3 days) and elective surgery, but not before emergency surgery (< 24h) in the following:
  - men > 40 years of age
  - postmenopausal women
  - at least one cardiovascular risk factor
  - known CHD
- rationale: If a cardic surgery with a sternotomy takes place anyway, then it would make sense to provide the patient with appropriate bypass grafts (CABG [coronary artery bypass graft]) at the same time if necessary.
- cave: triggering of a septic embolism by coronary angiography (especially in aortic valve endocarditis: Here, instead of conventional coronary angiography,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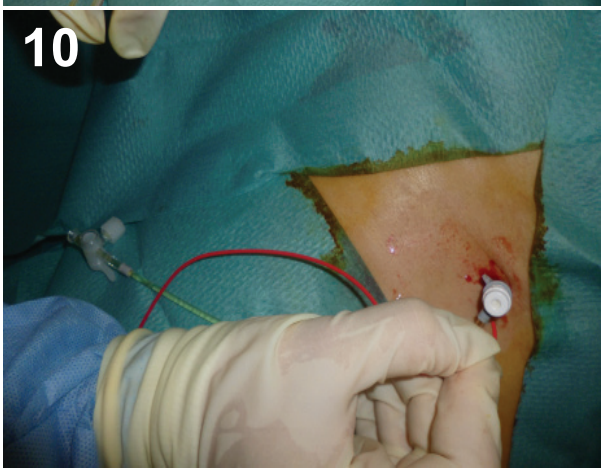
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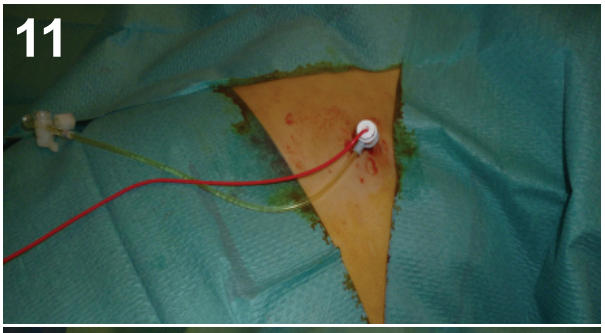
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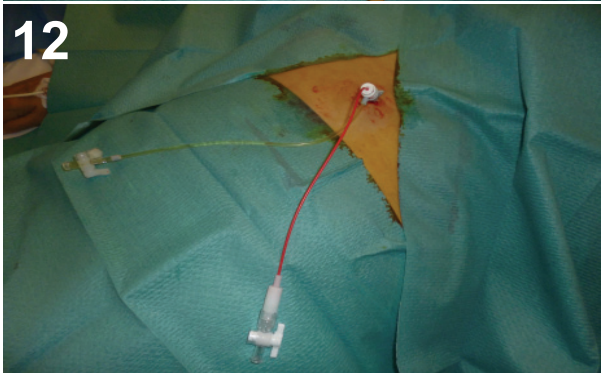
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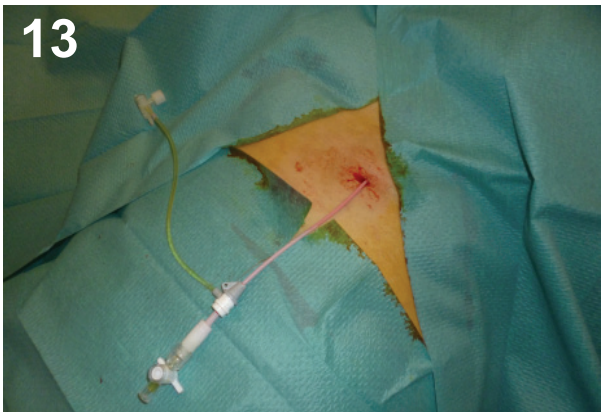
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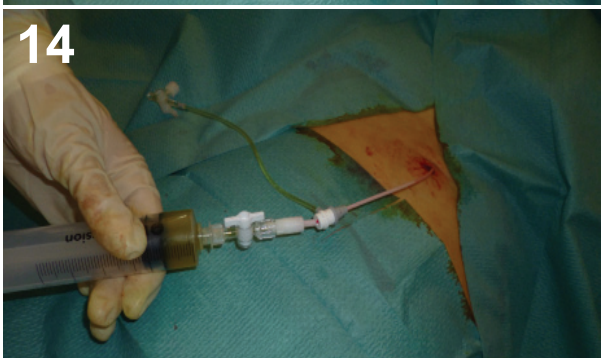
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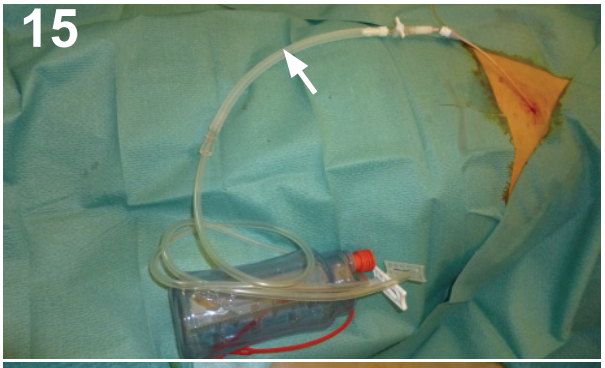
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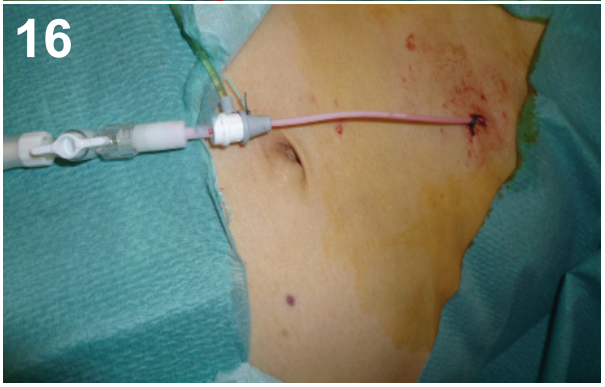
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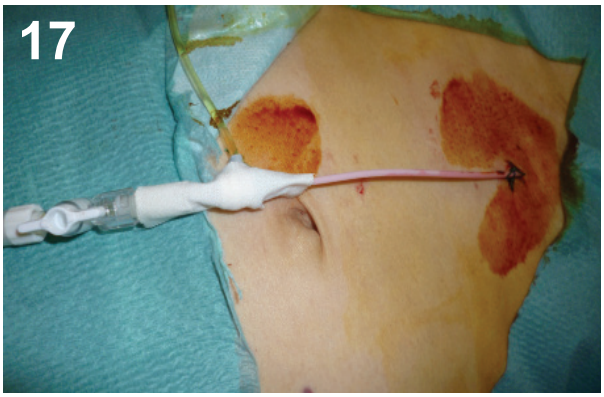


Fig. 765 The individual steps of pericardiocentesis (pericardial puncture): After sterile wiping and masking with adhesive tissues (1), local anesthesia with xylocaine (2) is performed. Then a conventional Seldinger needle is used to puncture (3) from subxiphoidal position in the direction of the left 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 haemorrhagic 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 been advanced, it must not be removed under any circumstances, as otherwise the bleeding into the pericardial space may cause the tamponade to increase. In this case, a drainage must first be correctly inserted into the pericardial space. Once this has been done, the drainage misplaced in the right ventricle can be removed.
- vascular injury (internal thoracic artery, coronary arteries [especially right coronary artery; therefore, remember this in case of a inferior wall infarction after pericardiocentesis!)
- injury to the left lobe of the liver (possibly abdominal sonography)
- pulmonary oedema with pre-existing reduced left ventricular ejection fraction (Pericardiocentesis increases the right ventricular ejection fraction again. Now suddenly increased blood comes to the left ventricle again. If the left ventricle is previously insufficient, pulmonary oedema may occur.)
- pneumothorax)complication especially in apical puncture)
- pericardial pleural fistula (complication especially in apical puncture)

Examination (pericardial effusion)

- laboratory:
  - LDH, protein, cell count (differentiation of transudate / exudate [Light criteria])
  - BGA (incl. hemoglobin, pH value)
  - possibly tumour markers (ESC-Guidelines 2015 IIa-recommendation; CEA < 5 ng/ml, CYFRA 21-1 < 100 ng/ml; furthermore NSE, CA 19-9, CA 72-7)
  - possibly adenosine deaminase (ADA; norm < 40 U/l; if increased: indicative for tuberculosis), possibly unstimulated INFγ (if increased: indicative for tuberculosis)
  - triglycerides > 500 mg/dl (note: in the pleural effusion limit value already at 110 mg/dl) → chylopericardium (usually due to an injury of the thoracic duct; therapy trial with octerotide 100µg s.c. three times a day for 2 weeks to reduce production of chyle, but often surgery is necessary)
- microbiological (it is best to inoculate additionally blood culture bottles; examination for pus, including mycobacterium tuberculosis)
- cytological (Here you should not only send in one sin-

alveolar dead space fraction < 0.1 in connection with an inconspicuous finding in leg vein duplex sonography makes a pulmonary embolism (very) unlikely.

- studies:
  - Roy et al, BMJ 2005
  - Verschuren et al, J Thromb Haemostas 2009
  - Ozlem et al, Am J Emerg Med 2010

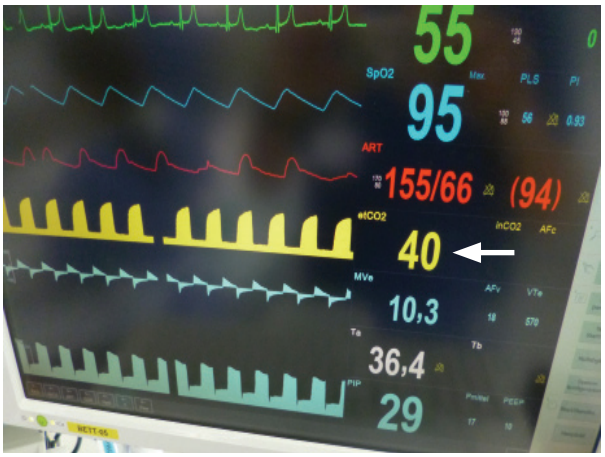


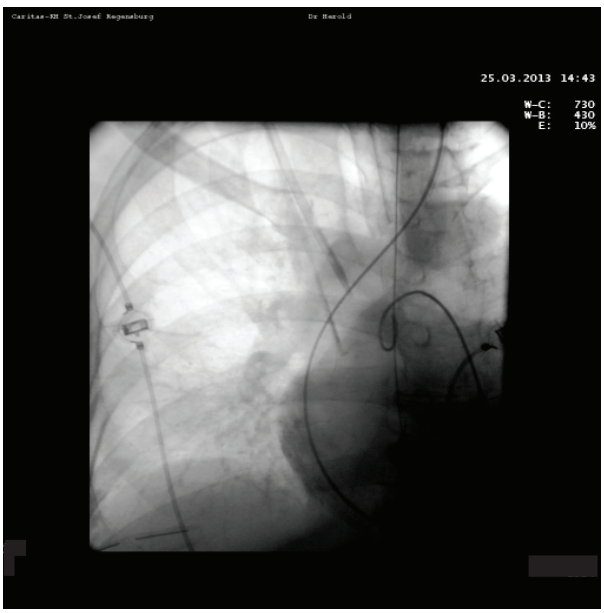
Fig. 777 Measurement of end-tidal CO_2 concentration in spontaneously breathing patients: A conventional respiratory mask is placed as tightly as possible (e.g. patient can hold it by himself). Then he spontaneously breathes through the mask (room air) for approx. 1-2 minutes. The $ETCO_2$ is then measured either on the monitor or alternatively on the ventilator.

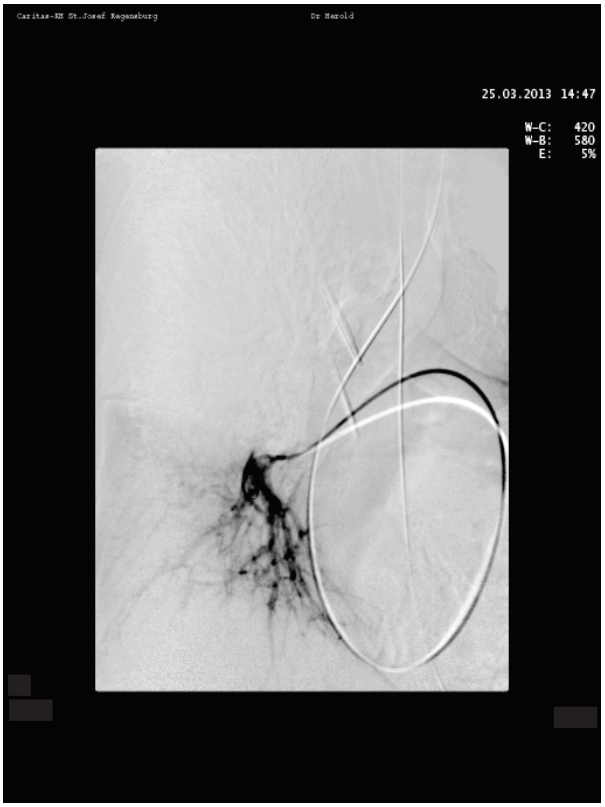
ECG

- sinus tachycardia
  - ⚠ the most sensitive sign
  - ⚠ Sinus tachycardia must be left unchanged and not treated with a β-blocker: It is an important compensation mechanism to still achieve a sufficient cardiac output with a reduced stroke volume (cardiac ouptut = stroke volume x heart rate). A pre-existing β-blocker therapy should be paused (especially in case of right ventricular dysfunction).
- SI-QIII type (Mc Ginn-White syndrome; note: Strictly speaking, the SI-QIII type is defined by the indeterminable heart axis and the delayed R-progression over the chest wall. A deep and wide S-wave in I is physiologically always found in right bundle branch block.), $S_IS_{II}S_{III}$ type
- change of the electrical axis (location type) to right axis deviation (RAD)
- right bundle branch block (RBBB; new)
- ST elevation with terminal negative T in III (DD inferior myocardial infarction [possibly even with right ventricular myocardial infarction!] in intermediate stage
- negative T waves in V1-V3, I, III
- P-pulmonale (P-wave > 0,25 mV)
- possibly extrasystoles
- atrial fibrillation
  - pulmonary embolism as a cause of new tachyarrhythmia absoluta (Especially in the case of newly occured tachyarrhythmia absoluta postoperatively, one should always think of pulmonary embolism!)
  - PERGO register (Pulmonary Embolism Registry Göttingen; Ebner et al, J Intern Med 2019):
    - atrial fibrillation at diagnosis of pulmonary embolism in 11% (new occurrence in 60%)
    - however, not prognostically relevant
- shift of the R/S transition point to the right
- resuscitation

- example: EcoSonic-Device (catheter with transducer at the tip and local lysis, fragmentation of the embolus by means of ultrasound waves)
- studies:
  - improvement of hemodynamic parameters (Engelhardt et al, Thromb Res 2011)
  - significant improvement of RV dysfunction (in echocardiography) without increase in bleeding rate in patients with intermediate risk compared to patients who were only anticoagulated (Kucher et al, Circulation 2014)

- studies:
  - ULTIMA (Kucher et al, Circulation 2014)
  - PERFECT (Kuo et al, Chest 2015)
  - SEATTLE II (Piazza et al, JACC 2015)
- meta-analysis (Catheter-directed therapy for the treatment of massive pulmonary embolism: systematic review and meta-analysis of modern techniques; Kou et al, J Vasc Interv Radiol 2009):
  - success rate: 87%
  - complication rate: 7.9%
- possibly with local lysis
  - alteplase (Actilyse) 15mg into the pulmonary artery
  - Jaff et al, Circ 2011: no advantages for local lysis, only increased bleeding at the puncture site
- ⚠ very good also under fluoroscopy with the C-arm, as possible at the intensive care bed and no transport is necessary!
- our procedure: installation of a 7F sheath, then insertion of 7F guiding catheter with wire (Terumo 0, 018"), then pigtail catheter (e.g. 5F)





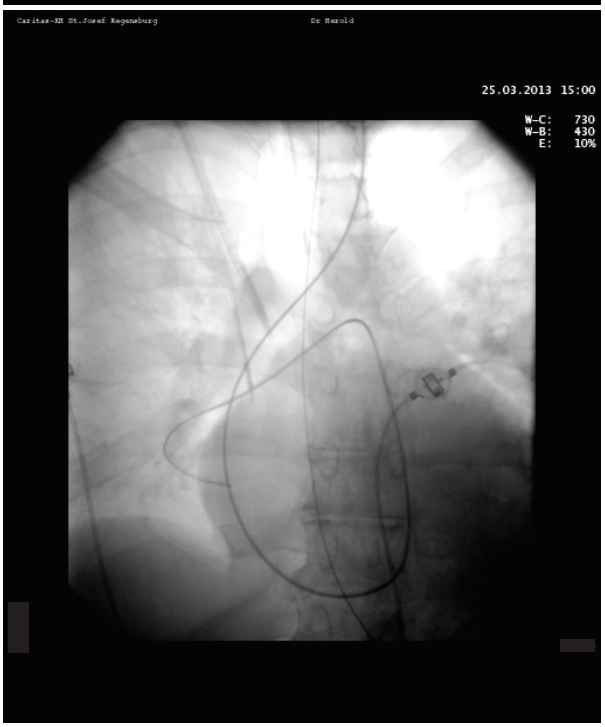
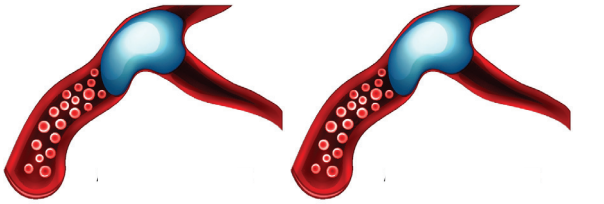


Fig. 815 Interventional embolectomy: After a sheath (7F) has been established in the internal jugular vein, the right ventricle and then the right pulmonary artery, which is almost subtotally obstructed by an embolus (DSA pulmonary angiography), are probed with a pigtail catheter (7F) via a guidewire (e.g. Terumo 0,018"). Then the guidewire passage takes place. The lying wire is now used for splinting and the catheter is moved back and forth several times, which usually leads to recanalization. In addition, we usually also perform local lysis via the catheter (e.g. 20mg Actilyse).

Air embolism



Definition

- syn.: vascular gas embolism
- penetration of air into the vascular system (mostly venous) with consecutive obstruction of the pulmonary arteries or the right ventricular outflow tract ("airlock") in venous or obstruction of coronary or cerebral arteries in arterial form
- also right-left shunt via a patent foramen ovale possible
- lethal dose:
  - venous: 50-100ml
  - arterial: already from 1ml potentially fatal (e.g. in the coronary arteries)

Types

- arterial (arterial gas embolism [AGE]; less often; more dangerous; e.g. air in the coronary arteries in case of improper coronary angiography [conduit system not free of air], diving accident with pulmonary barotrauma)
- venous (venous gas embolism [VGE]; more often)

Etiology

- mostly iatrogenic
- occurrence:
  - CVC placement (⚠ most common cause; especially if patient is exsiccated and the insertion is not performded in head-down position) or CVC removal (e.g. while sitting instead of lying down)
  - improper manipulations of the dialysis or Port catheter
  - endoscopy with air insufflation (especially in case of punctures; therefore better under CO_2 atmosphere),
  - lung biopsy (bronchoscopic transbronchial or CT-guided)
  - rupture of the balloon of the pulmonary artery catheter (especially if further "attempts to inflate" were made)
  - surgery: thoracic surgery, cardiac surgery (especially valve surgery), neurosurgery (especially when surgery while sitting)
  - diving accident (arterial gas embolism)
  - helium intoxication (arterial gas embolism; e.g. inhalation of helium gas ["balloon" gas] for amusement ["Mickey Mouse" voice])

Diagnosis

- anamnesis, clinical examination (e.g. auscultation of the heart: "mill wheel" murmur)
- ECG
- BGA
- ⚠ echocardiography: detection of air bubbles in the right system
- chest X-ray
- CT
  - chest-CT: ventrally located round or mirror-like opacities
  - CCT (cranial; detection of air bubbles in the brain)

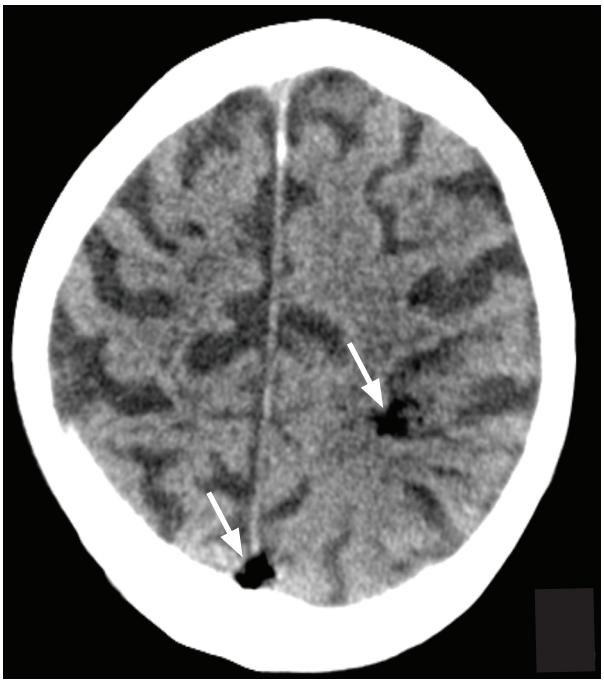
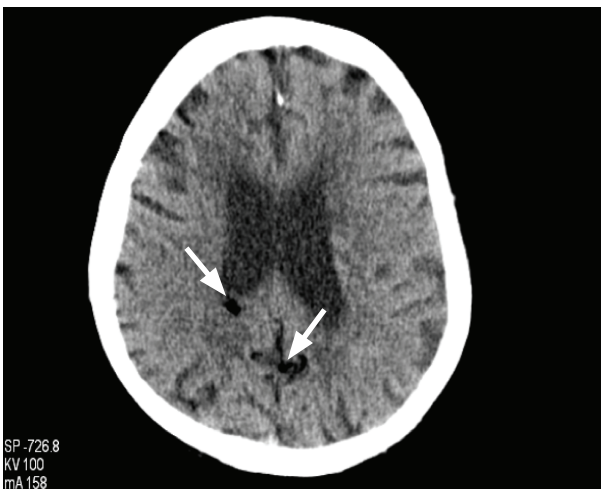
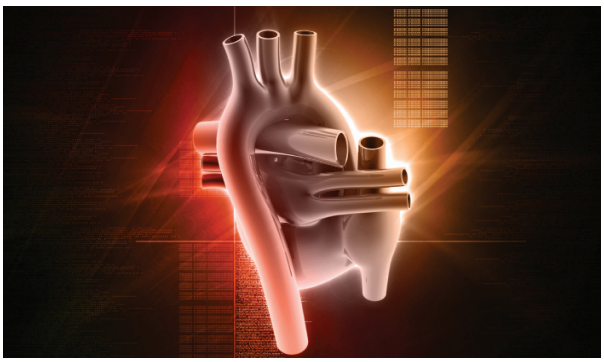


Fig. 822 CCT: detection of air in the brain (see arrows; here in the sinus veins)



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.

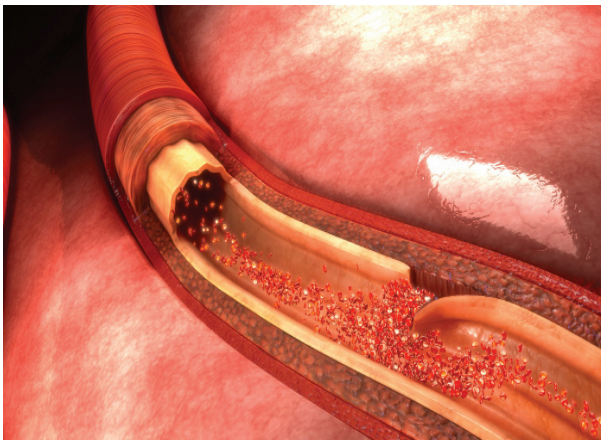


Fig. 827 aortic dissection: schematic illustration of the intimal tear

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)

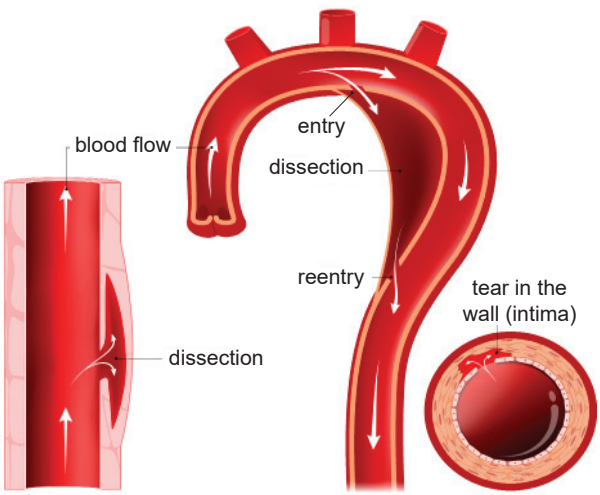
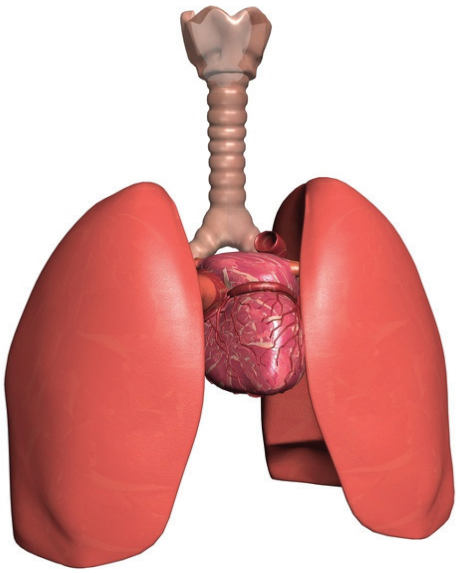


Fig. 828 aortic dissection: schematic illustration of the pathophysiology

Causes

- cardiovascular: arterial hypertension (no.1)
- genetic: connective tissue diseases (genetic aortic

ARDS



Introduction

- "The fetal lung in the unborn child - pathology, therapy and forensic medication" (Eduard Jörg, 1835)
- first described by David Ashbaugh and Thomas Petty in a case series of 12 patients (Lancet: "acute respiratory distress in adults")
- acute lung failure
- designations:
  - IRDS: infant respiratory distress syndrome
  - ARDS: adult (today better: acute) respiratory distress syndrome
- ARDS is the pulmonary manifestation of multiorgan failure (MOF).
- ARDS is a syndrome and not a disease!

Definition

(according to AECC [American European Consensus Conference] 1992; "old" definition)

- acute occurrence
- Horovitz quotient (paO_2/FiO_2; syn.: P/F ratio, oxygenation index):
  - 200-300 mmHg: ALI (acute lung injury)
  - < 200 mmHg: ARDS
- bilateral infiltrates in the chest X-ray (a.p.); Note: According to more recent radiological recommendations one no longer speaks of infiltrates but of consolidations.
- pulmonary capillary wedge pressure (PCWP; Wedge-Druck) < 18 mmHg or missing signs of left heart failure, i.e. no cardiac pulmonary edema (p.d. a non-cardiac pulmonary edema). Pulmonary capillary wedge pressure is measured using a pulmonary catheter, which is rarely used nowadays. Today one uses above all:
  - Echocardiography (Especially pulmonary edema due to a severe acute mitral valve regurgitation often is often very similar to ARDS!)
  - PiCCO: pulmonary vascular permeability index (PVPI):
    - PVPI < 3: cardiac (hydrostatic pulmonary edema)
    - PVPI > 3: ARDS (permeability pulmonary edema)
  - pro-BNP (The cut-off value of 100 pg/ml has a relatively high sensitivity of 95%, but only a relatively low specificity of 27% [i.a Levitt et al, Crit Care 2008].)
    - > 100 pg/ml: cardiac
    - < 100 pg/ml: ARDS

Criticism of the old definition

- no consideration of PEEP and ventilation ("blood gas" ARDS)
- increased PCWP also possible in septic cardiomyopathy; ARDS may also be present in sepsis

Due to these criticisms, an ARDS Task Force developed a new definition which was presented at the 2011 ESICM (European Society of Intensive Care Medicine) congress in Berlin as the ARDS "Berlin Definition" (published by Ranieri et al, JAMA 2012).

Berlin-Definition (ARDS)

	mild	moderate	severe
time	acute onset (< 1 week)		
Horovitz quotient (mmHg)	200-300	100-200	< 100
PEEP (cmH_2O)	5-10	5-10	> 10
origin of edema	respiratory insufficiency (not fully explained by heart failure or volume overload)		
radiological changes (chest X-ray, CT)	bilateral	bilateral	3-4 quadrants
additional physiological disorder	-	-	$V_{E\ corr}$ > 10 l/min compliance < 40 ml/cmH_2O

$V_{E\ korr}$: corrected RMV (V_E x pCO_2 / 40); Criticism: Patients with a Horovitz quotient < 100 mmHg and a PEEP between 5-10 cmH_2O are not considered.

Innovations (Berlin-Definition)

- The term "acute" was determined at less than 1 week.
- no more ALI (p.d. mild ARDS)
- consideration of PEEP (Therefore the diagnosis of

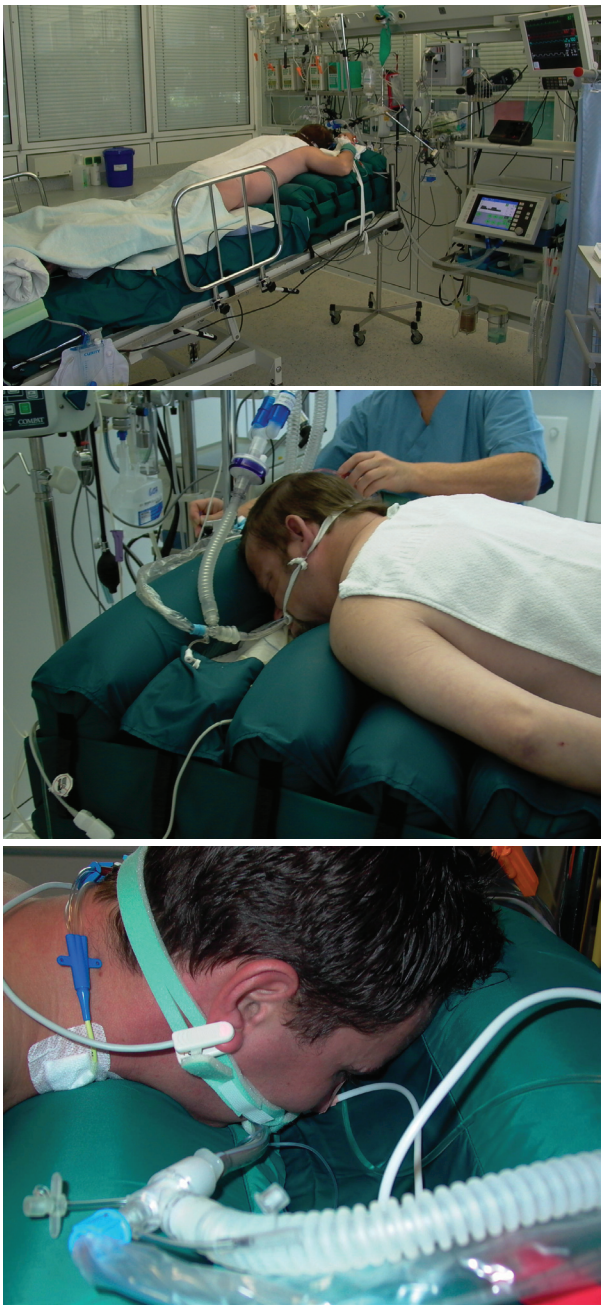


Fig. 617 prone positioning

Effects

- homogenization of respiratory gas distribution
- improvement of pulmonary perfusion and increase of ventilation-perfusion ratio
- decrease of pulmonary edema in the gravity-dependent lung sections → recruitment of dorsal lung sections by prone position
- reduction of pleural pressure gradient
  - ⚠ main effect
  - transpulmonary pressure = alveolar pressure - pleural pressure
  - In a patient in supine position the pleural pressure increases from ventral to dorsal..
- increase of the functional residual capacity (FRC)
- reduction of the frequency of ventilator-associated lung injury (VALI; prone positioning shows physiological protection!)
- improvement of the respiratory mechanics (change of the position of the diaphragm
- reduction of the intrapulmonary shunt: The atelectatic dorsobasal parts of the lung are ventilated again by the abdominal positioning, which leads to a reduction of the shunt (already perfused alveoli are now ventilated again).
- secretion mobilization (After turning back from the prone to the supine position, it is often necessary to suck of the patient endobronchially [if necessary by bronchoscopy].)

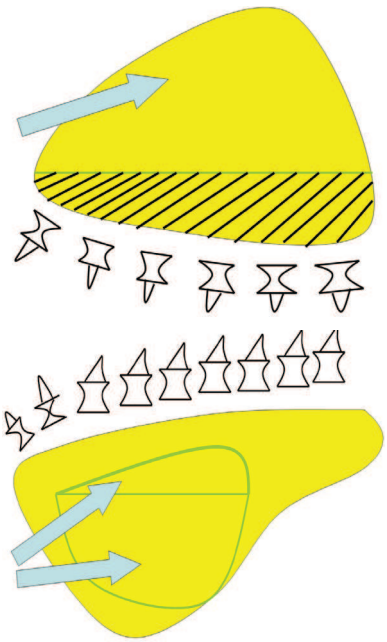


Fig. 618 Compared to the supine position on the left, the dynamics of the diaphragm in the prone position on the right are increased (increase in muscular dynamics in the area of the spine). The respiratory gas distribution (arrows) is homogenized and atelectasis (hatched) reduced.

Studies

- The studies on prone positioning (until 2013) showed an improvement in oxygenation (in 75%), but no mortality advantage (two earlier outcome studies on prone positioning: Gattinoni et al, N Engl J Med 2001; Guerin et al, JAMA 2004); points of criticism of the two outcome studies:
  - no lung-protective ventilation performed there (V_T 12 ml/kg instead of 6 ml/kg)
  - far too low PEEP
  - prone position far too short (only 7 hours)
- post-hoc analysis in subgroup with Horovitz quotient < 88 mmHg even significant survival advantage (Gattionini et al, N Eng J 2001)
- The milestone study for the prone position finally was the PROSEVA study (see box).

for Anaesthesiology and Intensive Care Medicine)!

- computer tomography (disadvantage: elaborate transport)
  - local (e.g. dorsal): lower PEEP
  - diffuse (homogeneous): higher PEEP
- pleural pressure s
- tress index
- determination of FRC (functional residual capacity)
- EIT (electrical impedance tomography)

Fig. 630 The search for the "best PEEP" sometimes resembles the search for the Holy Grail!

LIP measurement

- determination of the LIP (lower inflection point) in the individual static PV curve
- A pressure e.g. 2 cmH_2O above the LIP is then selected as PEEP.
- measurement
  - static (Supersyringe method: The lung is filled step by step with a large syringe and emptied. To do this, the patient must be disconnected from the ventilator.)
  - dynamic; settings:
    - volume-controlled ventilation (The measurement is only possible with volume-controlled ventilation and not with pressure-controlled ventilation!)
    - flow 60l/min (constant flow), Plateau 1-2s
    - low respiratory rate (e.g. 5/min)
    - long expiratory time (e.g. set I:E to 1:8)
    - PEEP 0 mbar (ZEEP [zero PEEP])
    - Deep analgosedation (if necessary relaxation; patient must not breathe spontaneously)
- Almost all ventilators meanwhile have automatic measuring maneuvers (e.g. LowFlow PVLoop at EVITA XL from Dräger as part of the Lung Protection Package) to derive the points.
- The LIP measurement has numerous weaknesses with considerable limitations and is therefore of minor importance in clinical everyday life:
  - The measurement is relatively complex and risky (including increased pneumothorax risk, circulatory instability [measurement only possible if the patient is circulatory stable]).
  - In ARDS, often no inflection points can be deduced.
  - The PEEP is usually set above the LIP anyway. The question in everyday clinical life is rather, how high one can go with the PEEP, so that there is no overinflation.
  - Furthermore the static PV curve considers inspiration, but PEEP is a parameter of expiration!

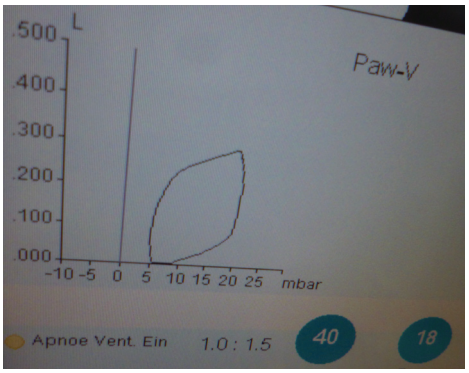


Fig. 631 derivation of the PV curve (pressure-volume curve) on the ventilator - here using the LowFlow PV loop measurement maneuver on the Evita XL: The lung is filled here with a very low flow (usually only 4-10 l/min) constantly slowly (volume-controlled ventilation).). This makes the breathing cycle extremely long (20-30s). Complications include circulatory depression and pneumothorax. The lower (LIP) and the upper (UIP) inflection points can be determined by a cursor line that can be adjusted with the rotary knob-

ARDS-network table (NIH protocol)

⚠ Coupling ("Tandem" setting) of PEEP to the set FiO_2 (set FiO_2 so, that SpO_2 > 90% or p_aO_2 > 60 mmHg); two tables proposed by the ARDS network: low-PEEP (most common) and high-PEEP table

Low-PEEP table

FiO_2	PEEP (cmH_2O)
0.3	5
0.4	5-8
0.5	8-10
0.6	10
0.7	10-14
0.8	14
0.9	14-18
1.0	20-24

High-PEEP table

FiO_2	PEEP (cmH_2O)
0.3	5-14
0.4	14-16
0.5	16-18
0.6	20
0.7	20
0.8	22
0.9	22
1.0	24

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. 642 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!

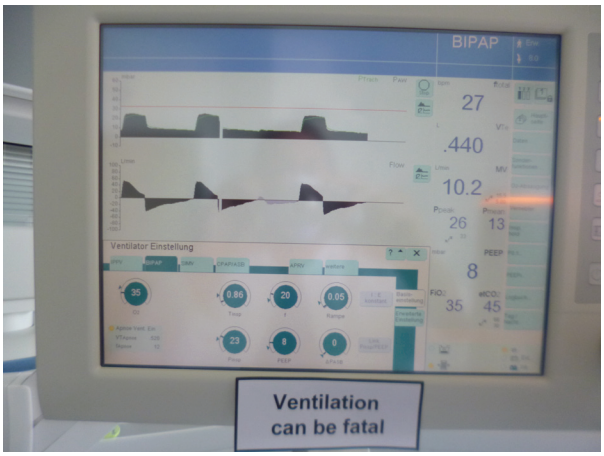
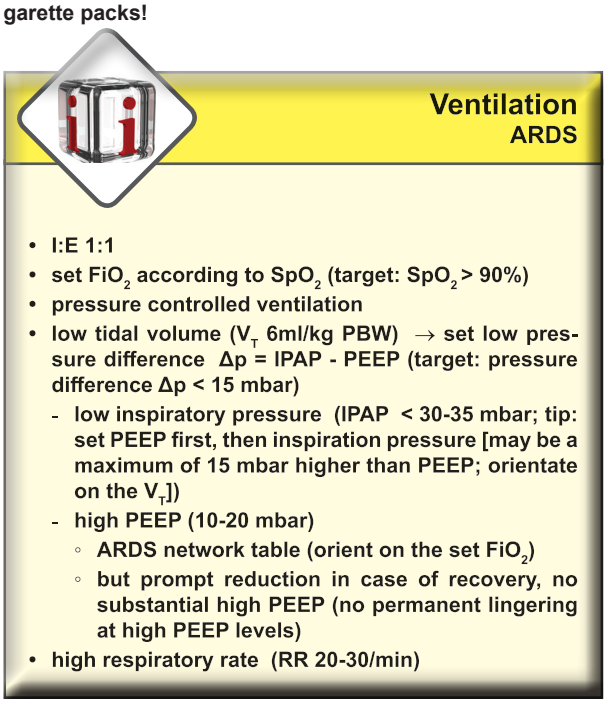


Fig. 643 The warning "Ventilation can be fatal" should be affixed to the ventilators in the intensive care unit (especially with ARDS) analogously to the inscription on the cigarette packs!



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. 649 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).

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)

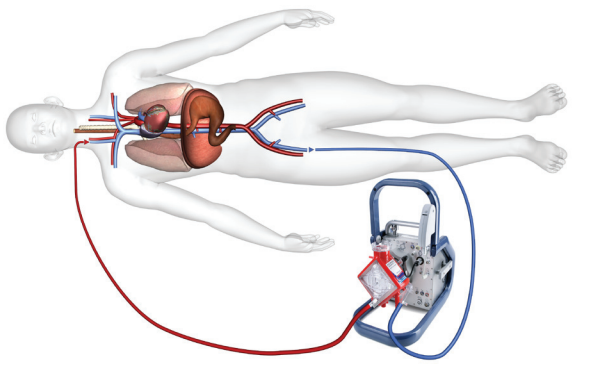


Fig. 650 ECMO veno-venous (vv-ECMO [23])

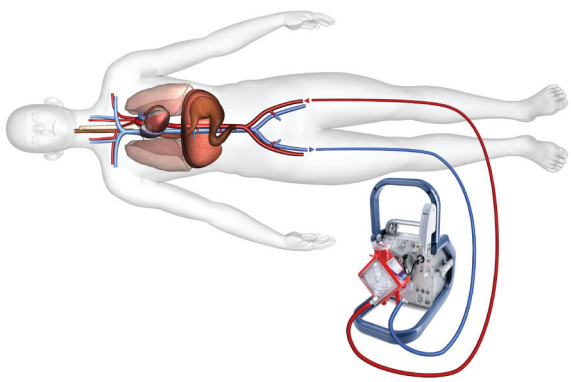


Fig. 651 ECMO veno-arterial (va-ECMO [23])

vv-ECMO

- more often than va-ECMO
- Orte: The blood is usually withdrawn from the femoral

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 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-ECMO, as deoxygenated blood would then be pumped into the arterial system! The ECMO continues to run, cannot thrombose and is no longer effective.
- If the patient then remains stable, the heparin is switched off after two hours and the cannulas are removed after one hour. The PTT should be normal before the cannula is pulled out.
- An extubation under still running ECMO is the exception. First decanulation, then extubation!
- After withdrawing the cannulas, compression is carried

Nice Classification 2018

- group 1: pulmonary arterial hypertension (PAH)
  - IPAH: idiopathic PAH
  - HPAH: heriditary PAH
  - APAH: associated PAH
  - PAH in venous or capillary lung diseases (worst prognosis):
    - pulmonal-venoocclusive disease (PVOD)
    - pulmonary capillary hemangiomatosis (PCH)
  - PPHN: persistent pulmonary hypertension of the newborn
- group 2: PH due to left heart disease (most common type; note: Specific PH drugs are not indicated here [ESC 2015: IIIC].)
  - dysfunction
    - systolic (HFREF [heart failure with reduced ejection fraction])
    - diastolic (HFPEF [heart failure with preserved ejection fraction])
  - valvular diseases
  - congenital / acquired left heart inflow / outflow tract obstruction and congenital cardiomyopathies
- group 3: PH due to lung diseases or hypoxia (second most common)
  - COPD
  - interstitial lung disease
  - CPFE (combined pulmonary fibrosis and emphysema)
  - sleep-disordered breathing
  - alveolar hypoventilation
  - ARDS
  - chronic exposure to high altitude
  - developmental lung diseases
- group 4:
  - CTEPH (chronic thromboembolic pulmonary hypertension [see page 572])
  - other causes of vascular obstruction (e.g. angiosarcoma, arteriitis, congenital pulmonary artery stenosis, parasites [especially schistosomiasis, hydatidosis])
- group 5: others
  - hematologic (chronic hemolytic anemia [i.a. sickle cell anemia, thalassemia, spherocytosis], myeloproliferative syndromes, splenectomy); ; explanation: In case of hemolysis hemoglobin is released. Free hemoglobin binds NO which then no longer acts as a vasodilator. Furthermore the enzyme arginase is released from the erythrocytes during hemolysis which degrades L-arginine (= source substance for NO).
  - systemic (i.a. sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis)
  - metabolic (i.a. glycogen storage disease, Gaucher disease)
  - mechanical (compression of the pulmonary vessels [tumor, fibrosing mediastinitis])

The most common cause of pulmonary hypertension is disease of the left heart!

Pulmonary hypertension group 1 (pulmonary arterial hypertension [PAH])

- idiopathic pulmonary arterial hypertension (IPAH; No.1; formerly: primary pulmonary hypertension)
- familial pulmonary arterial hypertension (FPAH)
  - syn.: hereditary (HPAP)
  - numerous genetic mutations: BMPR2 (bone morphogenetic protein receptor 2; most common mutation), ALK-1, ENG, Smad9, CAV1, KCNK3 (i.a. channelopathy [reduced potassium channel current]: defect in the KCNK3 gene [Ma et al, N Engl J 2013])
- PAH associated (APAH; No.2) with:
  - drugs (DPAH: drug-induced PAH; i.a. appetite suppressants [e.g. aminorex, fenfluramine, dexfenfluramine], SSRI, interferon, chemotherapeutics [especially cyclophosphamide], dasatinib, pergolide, St. John's wort), drug abuse (i.a. amphetamines, cocaine), toxins (e.g. canola oil, rapeseed oil)
  - HIV (1000 times increased risk of pulmonary hypertension; frequency of pulmonary hypertension in HIV infected persons: 0.5%)
  - collagenosis (especially scleroderma [new term: systemic sclerosis])
  - portal hypertension (porto-pulmonary hypertension [POPH])
  - congenital heart diseases (CHD-PAH):
    - left-right shunt (ASD [atrial septal defect; mostly only mild pulmonary hypertension], VSD (ventricular defect), PDA [persistent ductus arteriosus])
    - Eisenmenger syndrome (shunt reversal; named after the Austrian physician Viktor Eisenmenger [1864-1932])
  - schistosomiasis
- PAH in venous or capillary lung diseases
  - pulmonal-venoocclusive disease (PVOD)
    - diagnosis: HR-CT
    - therapy: Lungentransplantation (lung transplantation; cave: Specific PAH drugs would worsen the situation here!)
  - pulmonary capillary hemangiomatosis (PCH)
- persistent pulmonary hypertension of the newborn (PPHN)

ACUTE RIGHT HEART FAILURE

Definitions

- right heart insufficiency (right ventricular insufficiency)
  - right ventricular filling pressure > 9 mmHg
  - cardiac index < 2.5 l/min/m^2
- right heart failure
  - low-output syndrome (cardiac index < 1.5 l/min/m^2 despite sufficient fluid administration) with cardiogenic shock
  - right atrial pressure > 18 mmHg

Guidelines

ESC guidelines 2016 Contemporary management of acute rightventricular failure: a statement from the Heart-Failure Association and the Working Group on Pulmonary Circulation and Right Ventricular Function (Harjola et al, Eur Heart J)

Etiology

- acute pulmonary embolism (No.1; PAP rarely > 50 mmHg)
- acute right ventricular myocardial infarction (in every third inferior myocardial infarction)
- decompensated pulmonary hypertension; frequent (especially in ICU) reasons for acute decompensation of a pre-existing pulmonary hypertension:
  - hypoxia of different genesis (e.g. pneumonia) via the Euler-Liljestrand reflex (hypoxia → vasoconstriction of the pulmonary arteries → pulmonary arterial pressure ↑)
  - ventilation with high PEEP (too high PEEP → overinflation → compression of the pulmonary capillaries → right ventricular afterload ↑)
  - hypercapnia (e.g. in the context of an exacerbated COPD or permissive hypercapnia): Hypercapnia increases the pulmonary arterial pressure! Hyperpapnia (high pCO_2) leads to vasodilation systemically (including cerebral), but to a pulmonary vasoconstriction.
  - ⚠ noradrenaline (e.g. in the context of sepsis; noradrenaline massively increases the pulmonary arterial pressure!)
  - cardiac arrhythmia (e.g. tachyarrhythmia absoluta [no more active atrial filling → CO ↓])
  - anemia
  - infections (strongest mortality factor [Sztrymf et al, Eur Resp J 2010]!)
  - incompliance
- septic cardiomyopathy
- mechanical ventilation
  - with high pressures (increased right ventricular afterload)
  - permissive hypercapnia (pCO_2↑ → PVR↑)
- acute tricuspid valve endocarditis (i.v.-drug abuse)
- perforated sinus-valsalva aneurysm (e.g. in endocarditis)
- ventricular septal rupture (VSR)
- congenital heart diseases in adulthood (e.g. ASD, pulmonary stenosis, Ebstein anomaly)
- decompensated arrhythmogenic right ventricular dysplasia (ARVD)
- amniotic fluid embolism (peripartal only)
- after thoracic surgery (e.g. lobectomy, pneumectomy)
- after implantation of a left ventricular assist device (LVAD; in 20%; caused on the one hand by septal displacement in the context of volume relief [venting] of the left ventricle, on the other hand by increased right ventricular preload)

Symptoms

- dyspnea
- cyanosis
- congested jugular veins, prominent jugular vein pulse
- possibly pulmonary edema (also possible in right heart failure due to a disturbed lymphatic drainage from the lung and thus a congestion in the thoracic duct)
- centralization (cold acres, mottled skin)
- pronounced 2nd heart tone
- angina pectoris
- leg edema, ascites
- pain in the right upper abdomen (tension of the liver capsule due to congestion of the liver); cave pitfall: Usually the LFT are also increased and the gall bladder wall is sonographically triple-layered (consequence of right heart failure, has nothing to do with cholecystitis!), no wrong indication for a cholecystectomy!
- bowel congestion → translocation → sepsis

Monitoring

- basic monitoring (i.a. central venous oxygen saturation)
- extended (advanced) hemodynamic monitoring with pulmonary artery catheter (PAC)
  - The pulmonary artery catheter is clearly superior to the PiCCO system in acute right heart failure!
  - ⚠ Acute right heart failure is the domain of the pulmonary artery catheter!
  - cave: If the cardiac output is determined here by thermodilution (PAC / PiCCO [especially here this applies to all higher-grade valve insufficiencies, i.e. for also for mitral or aortic valve insufficiency]), it is measured incorrectly too low. Due to pulmonary hypertension, there is almost always a relevant tricuspid valve insufficiency (secondary). Due to tricuspid valve insufficiency, the applied cold injection solution is repeatedly thrown back into the right atrium so that it ultimately has more time to warm up: The result is a larger temperature increase, so that a

Function (right ventricular function)

Right ventricular function
Parameter

Systolic right ventricular function
- ellipsoidal shell model
- FAC (fractional area change)
- right ventricular pressure increase rate (dp/dt_{max})
- TAPSE
- TASV
- Tei index
- IVA (myocardial acceleration during isovolumic contraction)
- strain, strain rate

Diastolic right ventricular function
- transtricuspid inflow profile
- deceleration time (normal value: 120-230 ms)
- isovolumetrische Relaxationszeit (Norm: 23-73 ms)
- isovolumic relaxation time (normal value: 23-73 ms)
- E/E´
- RA area

Ellipsoidal shell model
- determination of right ventricular ejection fraction: EF = (EDV - ESV) / EDV
- volume V = 2/3 x RV area x d
  - RV area: planimetry of the end systolic and end diastolic area of the right ventricle in apical 4-chamber view
  - d: RV-diameter anterior-posterior (parasternal short axis at the level of the aortic valve
- inaccurate (no general recommendation)

Fractional area change (FAC)
- FAC = (area end-diastolic - area end-systolic) / area end-diastolic
- pathological: < 35%

Right ventricular pressure increase rate
- dp/dt_{max}
- spectrum of the cw-Doppler of the transtricuspid regurgitation flow in tricuspid valve insufficiency: increase of pressure per time
- Spectrum represents the pressure difference between right ventricle and right atrium (does not depend on the severity of tricuspid insufficiency).
- The steeper the pressure increase, the better the global pump function.
- calculation:
  - time t to increase of velocity from 1 to 2 m/s → dp/dt_{max} = 12 mmHg/t or
  - time t to increase of velocity from 0.5 to 2 m/ → dp/dt_{max} = 15 mmHg/t
- norm: > 400 mmHg/s

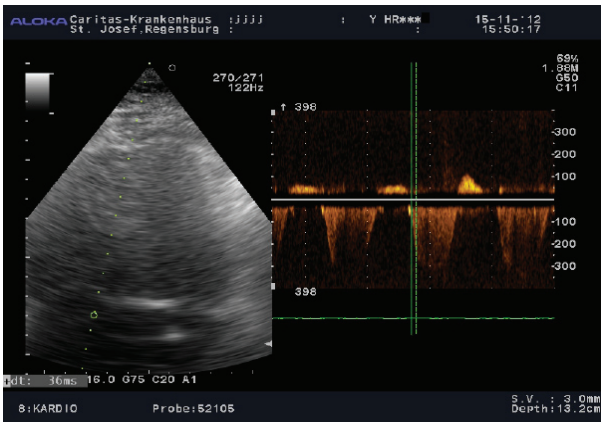


Fig. 946 Determination of the right ventricular pressure increase rate dp/dt_{max}: derivation of the cw-Doppler spectrum of tricuspid valve insufficiency in the apical 4-chamber view: The time is measured until the velocity has increased from 100 to 200 cm/s (here 36ms). From this a pressure increase rate is calculated: dp/dt_{max} = 12mmHg/0,036s = 333 mmHg/s (reduced)

TAPSE
- tricuspid annular plane systolic excursion
- syn.: TAM (tricuspid annular motion)
- baso-apical excursion of the tricuspid valve annulus (systolic
- distance between tricuspid valve annulus in diastole and systole
- The main contraction of the free wall occurs mainly longitudinally, i.e. in longitudinal direction.
- M-Mode measurement (lateral tricuspid valve annulus)
- norm: > 20 mm (pathological < 15 mm; new guidelines: < 16 mm)
- The right ventricular ejection fraction (RV-EF) can easily be calculated from the TAPSE: ⚠ RV-EF = TAPSE x 3.2
- limitations:
  - incorrectly high TAPSE despite poor RV function with volume overload of the right ventricle (e.g. higher degree tricuspid insufficiency, ASD)
  - considers only the longitudinal, not the circumferential RV function, i.e. TAPSE may still be normal even though RV function is already reduced

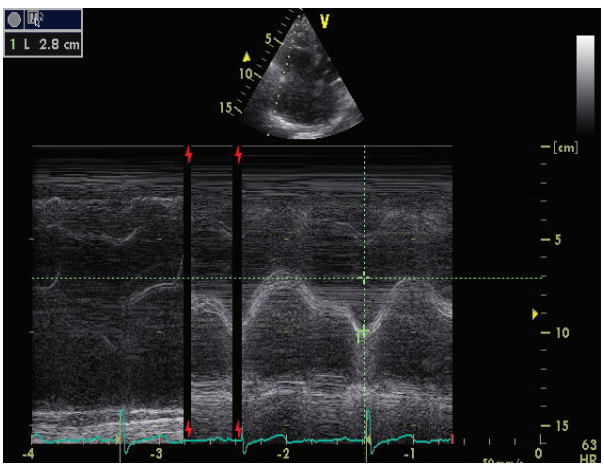


Fig. 947 normal TAPSE

expiration trigger (as well as the inspiration trigger) only makes sense for procedures of pressure-supported spontaneous breathing (e.g. CPAP-ASB).

- optional:
  - NAVA (see page 113)
  - extracorporeal decarboxylation
- In the weaning of COPD patients, one should generously use energy-rich tube feeding preparations (1.5 kcal/ml) for enteral nutrition. Here the carbohydrate content is reduced and the fat content increased. The reduced carbohydrate content reduces the work of breathing.

Intrinsic-PEEP (iPEEP)

- syn.: auto-PEEP
- cause: dynamic overinflation (syn.: hyperinflation, "air trapping", volumen pulmonum auctum)
- The resting breathing position becomes higher and the inspiratory load increases.
- Overinflation causes compression of the adjacent capillaries: This increases the dead space (areas that are still ventilated but no longer perfused) and the reduced alveolar ventilation leads to an increase in pCO_2 (hypercapnia). Intrinsic PEEP is harmful and should therefore be reduced.
- reduction of the iPEEP by extending the expiration time
  - I:E 1:3
  - reduction of the respiration rate to 10-12/min (no "down-ventilating" of an increased pCO_2 by increasing the respiration rate!)
  - possible decompression manoeuvers: An extremely long expiration time is set (under sufficient sedation) for some cycles. If the tidal volume increases, it was successful.
- measurement of the intrinsic PEEP
  - end-expiratory closure maneuver: By closing the expiration cycle for 10-30s at the end of the expiration (e.g. Evita: expiration hold) there is pressure equalization between the alveolar space and the expiration hose. Then the intrinsic PEEP is measured automatically. After opening the expiration valve, the trapped air is released in an extended expiration and measured.
  - One should then set 80% or 2/3 of the measured intrinsic PEEP as PEEP on the ventilator. This applies to both controlled (mandatory) ventilation and supported spontaneous breathing (CPAP-ASB). The PEEP that is set on the ventilator is also called extrinsic PEEP.
  - For a reliable measurement the patient should be deeply analgosedated or sometimes even relaxed, so that he does not change independently again to the inspiration!
  - only measurable with invasive, not with non-invasive ventilation (NIV)
- The flow curve should always be observed on the ventilator: The flow should be zero at the end of the expiratory cycle in order to avoid overinflation.
- With assisted spontaneous breathing (CPAP-ASB), the patient must first reduce the intrinsic PEEP before there is a pressure drop in the alveoli and thus triggering by the ventilator. The instrinsic-PEEP increases the inspiratory trigger work. This leads to a massively increased work of breathing due to the non-flow-effective attempts (to be recognized as "missed efforts" [= untriggered inspiration efforts] at the flow curve). Dem kann ein entsprechend hoch am Beatmungsgerät applizierter extrinsischer PEEP entgegenwirken.

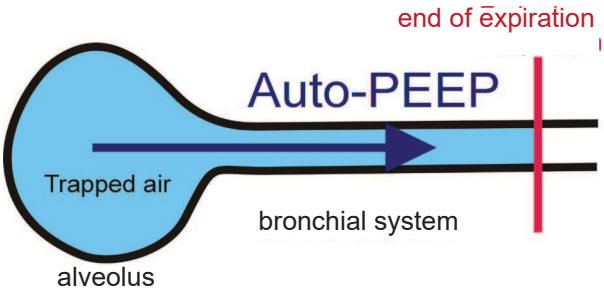


Fig. 968 Intrinsic PEEP: Not all the air can be exhaled, air remains trapped in the alveoli ("trapped air"), resulting in dynamic overinflation. The pressure that is created thereby in the alveoli is called intrinsic PEEP (syn.: auto-PEEP).

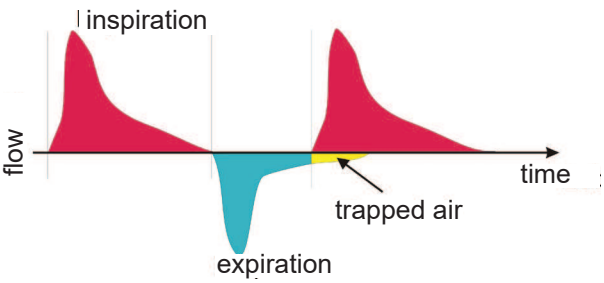


Fig. 969 Intrinsic PEEP: This shows that the air cannot be fully exhaled (air-trapping). If now in the BGA the pCO_2 value is increased, very often the mistake is made that one increases the respiratory rate at the ventilator in order to "down-ventilate" the pCO_2: However, this is exactly contraindicated in this case. Here you have to increase the expiration time and decrease the respiration rate!

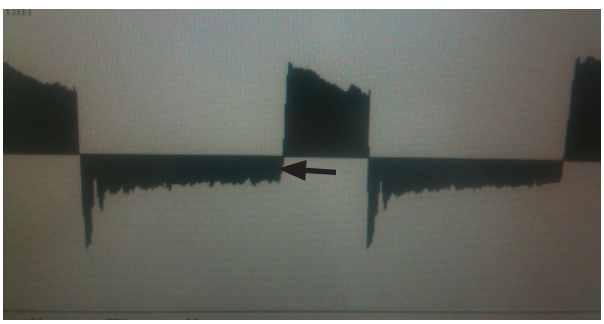


Fig. 970 Air-trapping: typical remaining stage at the end of expiration (The expiratory flow does not return to baseline.)

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)
  - Prismalung (Gambro)
    - membrane, which is built into the circuit of a conventional CVVH machine (Prismaflex; only a Shaldon catheter needs to be installed)
    - also possible without additional hemofilter
    - mode: CVVHF
    - anticoagulation with heparin (citrate anticoagulation not possible
    - maximum flow: 500 ml/min (note: Blood flow rates in renal replacement procedures are usually indicated in ml/h and not in ml/min.)
    - CO_2 elimination possible by 17%
  - vv-ECMO (low-flow, i.e. only with a blood flow from 0.8-2.0 l/min instead of the otherwise usual blood flow from 3.0-4.5 l/min)

Fig. 979 Prismalung: The membrane is built into the circuit of a conventional CVVH and enables (moderate) CO_2 elimination.

Fig. 980 extracorporeal CO_2 elimination with a pump-driven procedure (vv-$ECCO_2$-R [veno-venous extracorporeal carbon dioxide removal) in a patient with spontaneous breathing. Intubation could be avoided in this way (according to the motto "cannula instead of tube").

Assessment

- No prospective randomized trials on this subject have been conducted to date, so this is still considered experimental.
- currently ongoing studies: VENT-AVOID, CORAIL, ORION, Cologne-X-COPD
- meta-analyses (Fitzgerald et al, Crit Care 2014; Sklar et al, Intensive Care Med 2015): significant reduction in $paCO_2$, but no reduction in mortality

Differential diagnoses

- pneumonia
- tuberculosis
- chronic pulmonary congestion (cardiac induced)
- diffuse alveolar hemorrhage (e.g. Goodpasture syndrome, ANCA-associated vasculitis)
- lymphangiosis carcinomatosa
- bronchioalveolar carcinoma
- alveolar proteinosis
  - definition: accumulation of surfactant in the alveoli (overloaded phagocytic capacity of the alveolar macrophages)
  - types
    - primary (congenital; genetic [especially mutation in the gene for surfactant proteins or GM-CSF])
    - secondary (e.g. autoimmune [most common; antibodies against GM-CSF], inhalative [dusts], infectious, neoplastic)
  - epidemiology
    - mostly men
    - mean age: 40 years
  - diagnosis: i.a.
    - bronchoscopy: PAS-positive macrophages in BAL
    - HR-CT: crazy-paving pattern (mosaic pavement / tile-like network pattern [through thickened lobular septa] with ground glas opacities [mostly subfield]; also typical for COVID pneumonia [SARS-CoV-20; for CT pictures see page Seite 817])
  - therapy: therapeutic bronchoalveolar lavage (30-40 liters of NaCl 0.9% per side; under general anesthesia)

Respiratory decompensation

Epidemiology

- per year in 14% acute respiratory decompensation in patients with IPF
- especially in winter and spring
- median survival after an acute exacerbation: 6 months

Causes

- infections (40%; most common reason)
- acute exacerbation (AE-IPF), i.e. progression of the underlying disease (30%; i.a. Song et al, Eur Resp J 2011): Therefore one should consider early whether to initiate or escalate immunosuppressive therapy (especially steroids, possibly in combination with cyclophosphamide). The S2k guideline recommends steroid therapy for acute exacerbation. Acute exacerbation is defined as clinical worsening with no indication of infection, pulmonary embolism, pneumothorax or heart failure. Therefore, a bronchoscopy with sampling of bronchial secretion (if necessary BAL) for germs, a chest CT and an echocardiography should always be performed. The prognosis for AE-IPF is very poor with a hospital mortality rate of 57% and a 6-month mortality rate of 70% (i.a. Collard et al, AJRCM 2007). Even with AE-IPF an antifibrotic therapy should be initiated early (i.a. Matsumoto et al, ERS 2017: significant survival benefit).
- pneumothorax
- pulmonary embolism
- decomposed cor pulmonale (pulmonary hypertension [11% of all patients with IPF])
- iatrogenic (after extensive BAL, after lung biopsy [VATS])

Acute respiratory insufficiency in IPF: always exclude reversible (treatable) causes (e.g. chest CT, echocardiography, bronchial secretion / BAL on germs

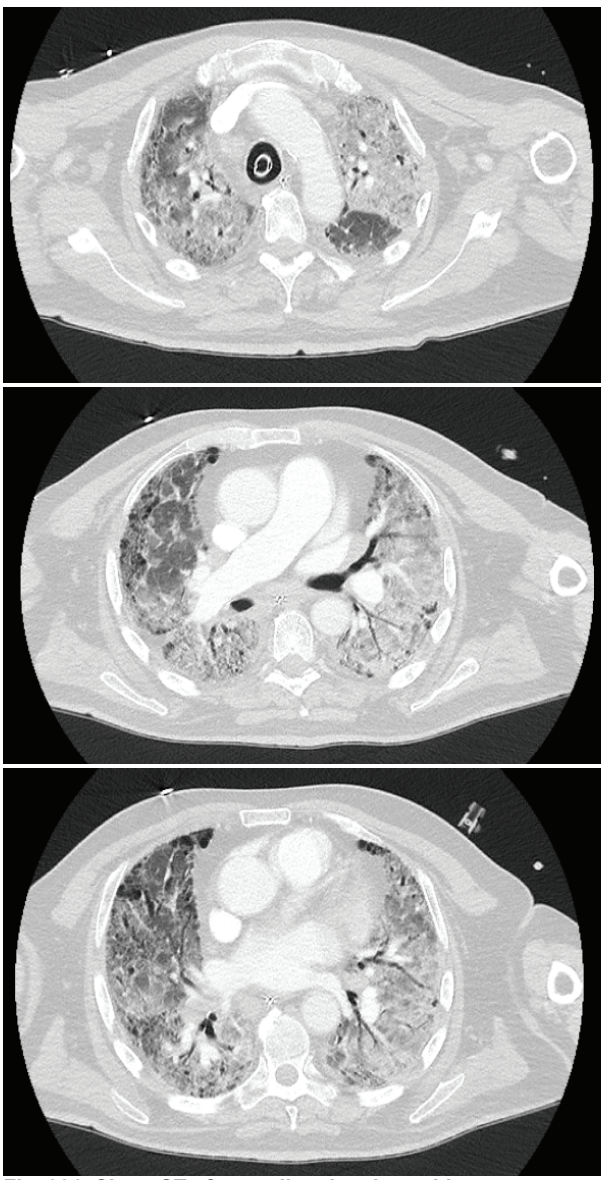


Fig. 991 Chest CT of a ventilated patient with acute exacerbation of the previously known IPF

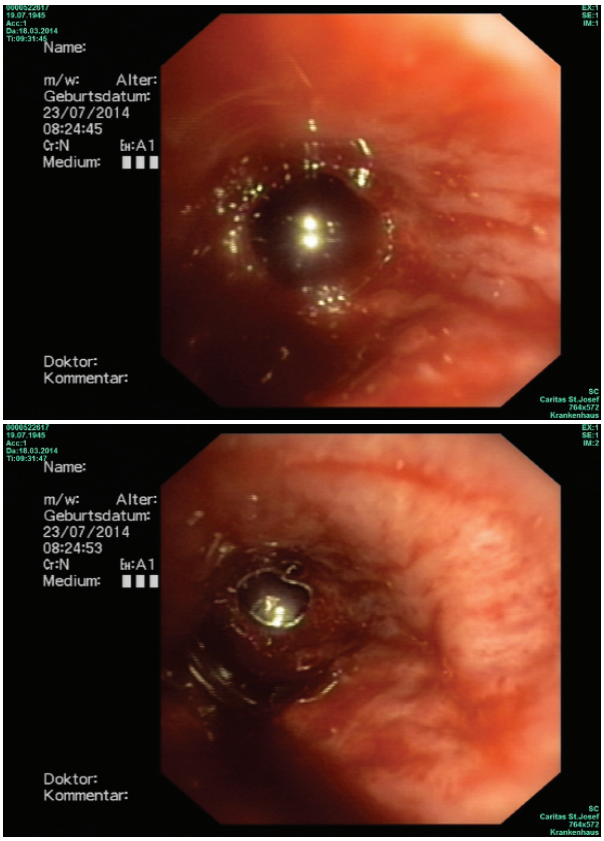


Fig. 995 Bronchoscopy: The endobronchial bleeding is recognizable.

Therapy

- general measures:
  - oxygen administration
  - positioning on the bleeding side (So the blood flows less into the healthy side.)
  - generous antibiotic prophylaxis (e.g. amoxicillin / clavulanic acid)
  - coagulation therapy (e.g. administration of FFP)
  - in case of pronounced bleeding, immediate intubation (danger of asphyxia), use of a large-lumen tube (e.g. size 8-9; thus better bronchoscopy possibility afterwards), ventilation with high PEEP
  - if necessary one-sided intubation (ventilation of only one of the two lungs):
    - ⚠ with a conventional tube (bronchoscopically placed in the main bronchus of the healthy side); note: If the tube is inserted into the right main bronchus during a left-sided bleeding, the outgoing upper lobe bronchus, which goes off relatively far up on the right, is frequently obstructed by the cuff, which can lead to atelectasis and further deterioration of the gas exchange. It is therefore better to use a bronchial blocker in case of bleeding from the left side.
    - with a special tube:
      - double-lumen tube (disadvantage: no more bronchoscopy possible then)
      - Bronchosafe tube (bronchoscopically placed; tube in the healthy side)
      - Univent tube (tube with integrated bronchus blocker)
- hemostasis:
  - bronchoscopical
    - flexible bronchoscopy
    - rigid bronchoscopy (mostly, however, only available at centres)
  - interventional (embolization by angiography)
    - bronchial artery embolization (BAE; high success rate): bronchial artery occlusion with coils or polyvinyl alcohol particles (cave: paraplegia due to accidental embolization of a spinal artery in the case of atypical ramification), possibly stent implantation in aorto-bronchial fistula
    - pulmonary artery embolization (PAE)
  - surgical (thoracic surgery; e.g. lobectomy)

The main therapeutic goal in bronchial hemorrhage is to protect against asphyxia!

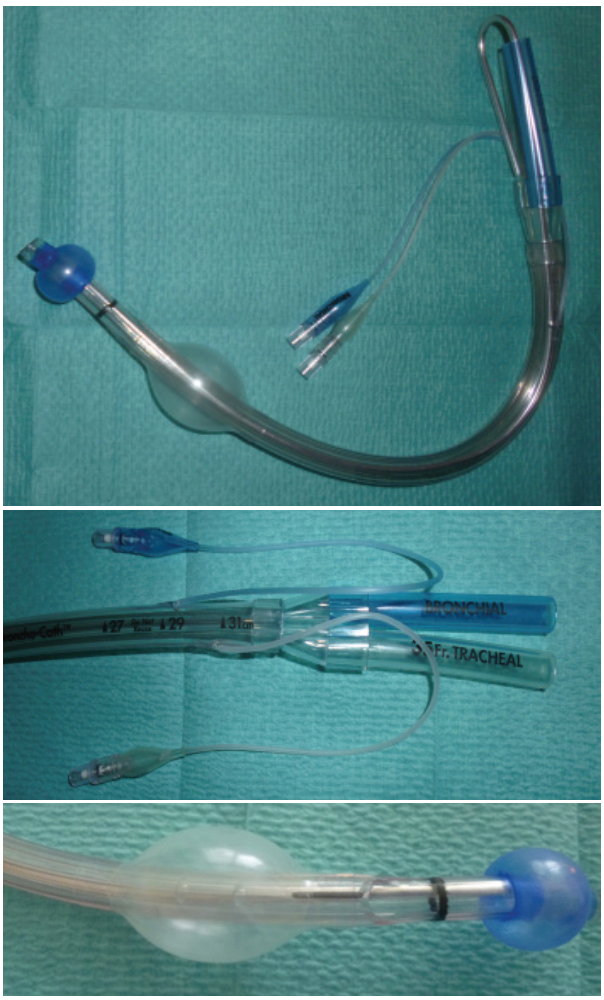


Fig. 996 Double lumen tube

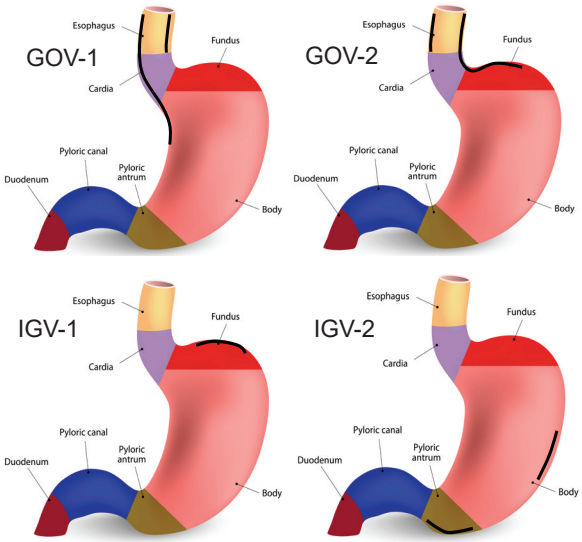


Fig. 1052 Sarin classification of gastric varices

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)!

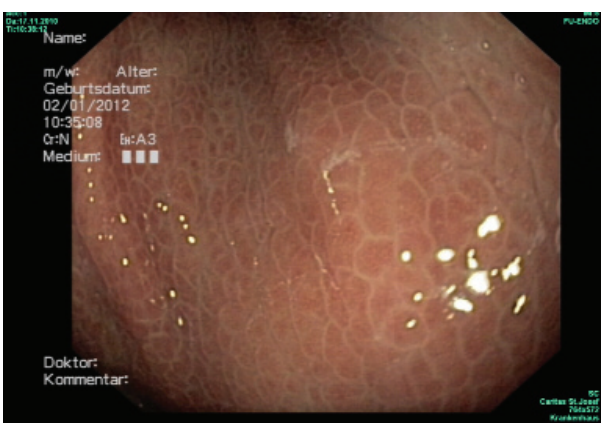
Upper GI bleeding in liver cirrhosis

- 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"
    - ectasias of the vessels, especially in the antrum
    - frequent occurrence in:
      - liver cirrhosis
      - scleroderma (systemic sclerosis)
    - frequent cause of chronic blood loss (iron deficiency anemia)
    - therapy: APC (argon plasma coagulation; settings: mode pulsed-APC, power 20 Watt)

50% of all patients with liver cirrhosis and hematemesis have no esophageal variceal bleeding!

If a liver cirrhotic shows a pronounced decline in hemoglobin with shock and there is no tarry stool / hematochezia or if the upper GI bleeding has been excluded endoscopically, it is absolutely necessary to consider intraabdominal bleeding and if there is sonographic evidence of free fluid ("ascites") and a diagnostic test puncture should be performed immediately (bloody? BGA with hemoglobin). If blood shows up during the test puncture, laparotomy must be performed immediately. Not infrequently, liver cirrhosis patients suffer from intraabdominal bleeding, e.g. due to a splenic rupture (portal hypertension with splenomegaly) or a ruptured internal caput medusae. Falling in the cotex of of alcohol abuse often triggers intraabdominal bleeding. It can also bleed as a result of portal hypertension from mesenterial veins (pressure often up to 20mmHg): Here, in addition to surgical hemostasis, an emergency lowering of the portal pressure (e.g. with terlipressin, possibly emergency TIPS) is necessary..

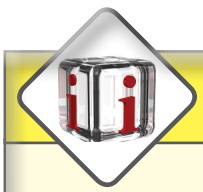
Cirrhotic patients with shock and hemoglobine decline without evidence of GI bleeding: always with evidence of free fluid sample puncture to exclude intraabdominal bleeding!



tube is, besides enteral nutrition, the fact that recurrent bleeding can be detected at an early stage due to bloody discharge via the gastric tube. It is best to perform the procedure endoscopically!

- Nutrition (parenteral) must start within 12 hours: Cirrhotic patients have no reserves at all and become catabolic immediately.
- ⚠ no proton pump inhibitors: In contrast to non-variceal upper GI bleeding, PPI have no overall benefit in variceal upper GI bleeding (i.a. meta-analysis Lo et al, Ann Pharmacother 2015). On the one hand there is a lower rate of ligation ulcers (after rubber band ligation), but on the other hand a higher rate of spontaneous bacterial peritonitis and hepatic encephalopathy in patients with liver cirrhosis. They also do not lower the rate of rebleeding.

Esophageal variceal bleeding: generous intubation before endoscopy!



Therapy plan
Esophageal variceal bleeding

- **immediate EGD (preferably in the intensive care unit) with band ligation (generous protective intubation)**
- **two large-lumen peripheral venous accesses**
- **crystalloids (e.g. Ringer solution), possibly colloid (e.g. Gelafundin)**
- **terlipressin (in case of contrainications [especially CHD] octreotid [Sandostatin] as a perfusor) for 2-3 days**
- **ceftriaxone 2g 1 x daily i.v. for 5 days**
- **hemostaseology:**
  - **RCC (especially if hemoglobin < 7 g/dl)**
  - **FFP (especially if Quick < 50% or PTT > 45s; e.g. 4 FFP)**
  - **PC (with platelets < 20000/µl; rarely necessary)**
  - **tranexamic acid (1g over 10min, then 1g within 8h)**
  - **fibrinogen (determine it subsequently in the laboratory; if < 1 g/dl: substitution [e.g. 2g Haemocomplettan])**
  - **compensation for hypocalcemia**
- **parenteral nutrition incl. Amino hepar 10% 500ml and thiamine (300mg i.v. [especially for ethyltoxic liver cirrhosis, but also for malnutrition])**
- **lactulose 1 measuring cup 3 times a day p.o. (if not mechanically ventilated [otherwise also via enema])**
- **NIL (nil per os) on the first day, then mashed food**
- **no PPI, no gastric tube**

Vasopressors

- effect: They lead to a vasoconstriction especially of the arteries in the splanchnic area, so that the pressure in the portal vein and thus also in the bypass circuits such as the varices decreases.
- assessment:
  - equivalent to endoscopy (D´Amico et al, Cochrane Database Syst Rev 2010)
  - signifikante Reduktion der Mortalität (meta-analysis Wells et al, Aliment Pharmacol Ther 2012)
- representatives (all three equally effective [Seo et al, Hepatol 2015]):
  - terlipressin (Glycylpressin, Hämopressin): means of first choive
  - octreotide (Sandostatin; in case of contraindications against terlipressin)
  - somatostatin (bolus 250 µg, then 500 µg/h; in case of contraindications against terlipressin)

Terlipressin

- a vasopressin analogue
- 2mg every 4h as bolus
- side effects:
  - ischemia
    - cardiac
    - intestinal (therefore no combination with noradrenaline)
    - peripheral (i.a. digital ischemia, toe necrosis, skin necrosis)
  - intracranial pressure (ICP) ↑ (i.a. Shawcross et al, Hepatology 2004; careful use therefore in acute liver failure [Here the increased intracranial pressure is the most common cause of death!])
  - hyponatremia
  - diarrhea
- contraindications:
  - arterial hypertension
  - symptomatic CHD
  - symptomatic PAD
  - cerebral edema, increased ICP
- means of choice (in case of contraindication: somatostatin or octreotide [Sandostatin])

study

Early administartion of terlipressin plus glyceryl trinitrate to control active upper GI-bleeding in cirrhotic patients Levacher et al, Lancet 1995 (relatively old, but important study!)

- prospective double-blind randomized controlled study
- 76 cirrhotic patients with upper GI bleeding; already preclinical (out-of-hospital) administration by the emergency physician (without previous endoscopic confirmation of the diagnosis!):
  - terlipressin
  - placebo
- results: terlipressin
  - significantly better bleeding control
  - significantly less RCC administration
  - ⚠ significant survival benefit (only applies to Child C)

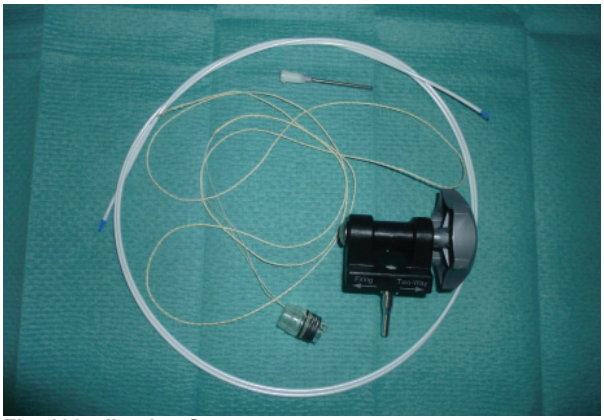
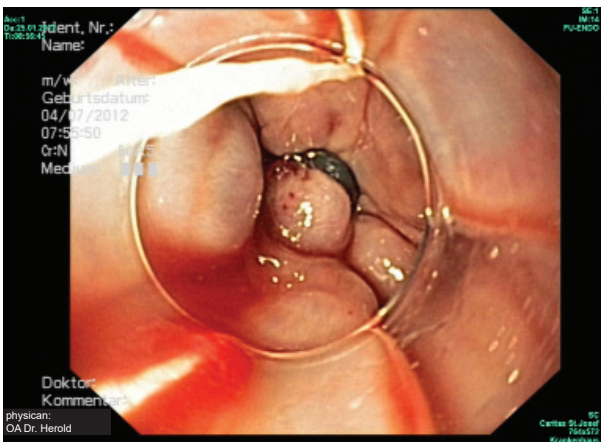
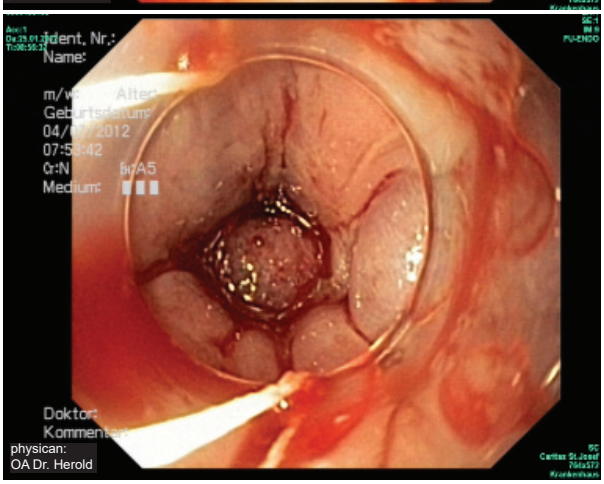


Fig. 1064 ligation Set

Fig. 1065 The cap with the rubber bands is attached to the tip of the endoscope.





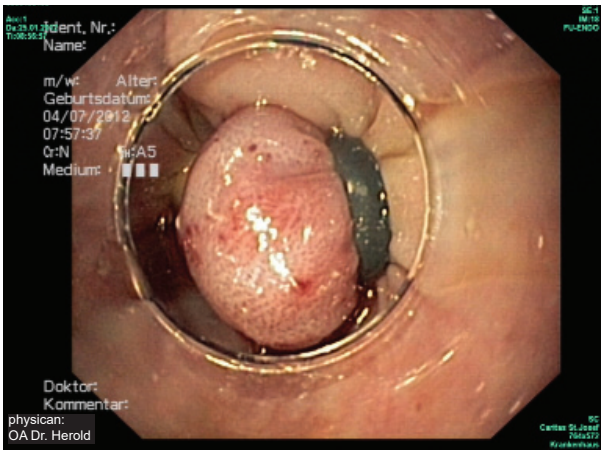


Fig. 1066 ligated varices

Injection of cyanoacrylate (Histoacryl)

- sclerotherapy
- a rapidly hardening plastic (tissue glue)
- Compared to band ligation, it is very complex and prone to complications (preferably with two physicians).
- indications:
  - gastric varices (especially in the non-muscular part of the cardia; ligation is contraindicated there)
  - esophageal varices and poor overview / massive bleeding (very rarely necessary)
  - duodenal varices
- application strictly intravascular and if possible always under X-ray fluoroscopy to monitor the correct injection into the variceal vein (note: In the context of acute bleeding, this is usually not possible. The patient is prepared normally for emergency EGD without the option of fluoroscopy. As a rule, the fundal variceal bleeding is only detected during the emergency EGD, so that the intervention will take place immediately.)
- complications: i.a.
  - gastric wall necrosis
  - pulmonary embolism (cave: fibrinolysis here ineffective!)
- flush working channel of the endoscope with 2ml of silicone oil
- safety glasses (cave eye injuries; for physician, care staff and patient)
- mixture of 1ml Lipiodol (serves as contrast agent) + 0.5ml Histoacryl (serves as glue; butyl cyanoacrylate) in 2ml syringe
- first inject 5ml NaCl 0.9% into the variceal vein, then inject the mixture of Histoacryl and Lipiodol, then again inject 5ml of NaCl 0.9%
- flush working channel of the endoscope with 5ml NaCl 0.9%
- sclerosing needle: check tip for adhesion

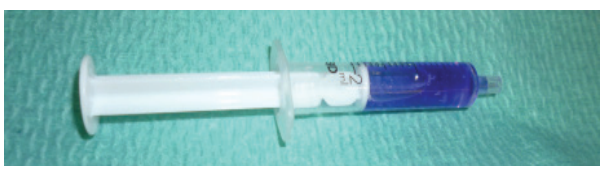


Fig. 1067 Lipiodol-Histoacryl mixture

Symptoms

- abdominal pain
  - band-like pattern
  - epigastric
  - periumbilical
- elastic abdomen ("rubber belly")
  - retroperitoneal location → mostly only moderate muscular defense (no board-like abdomen)
  - ⚠ high negative predictive value for a necrotizing pancreatitis (no "rubber belly" → with a high probability no necrotizing pancreatitis)
- nausea, vomiting
- meteorism
- paralytic subileus to ileus (frequent!)
- ascites
- fever
- hypotension, shock signs
- jaundice
- facial flushing
- bluish spots (ecchymosis, in 1%; necroses continuing from the inside of abdominal cavity from the pancreas to the outside of the skin; poor prognosis [mortality 30%])
  - in the navel area (periumbilical): Cullen sign
  - in the flank area: Grey-Turner sign
  - in the groin region (inguinal): Fox sign
- pleural effusion (often left-sided)
- signs of endocrine pancreatic insufficiency (blood sugar derailment; typically in necrotizing pancreatitis; in order for the endocrine function of the pancreas to be impaired, at least 80% of the pancreatic tissue must have already be destroyed!)
- disturbance of consciousness („encephalopathia pancreatica“)

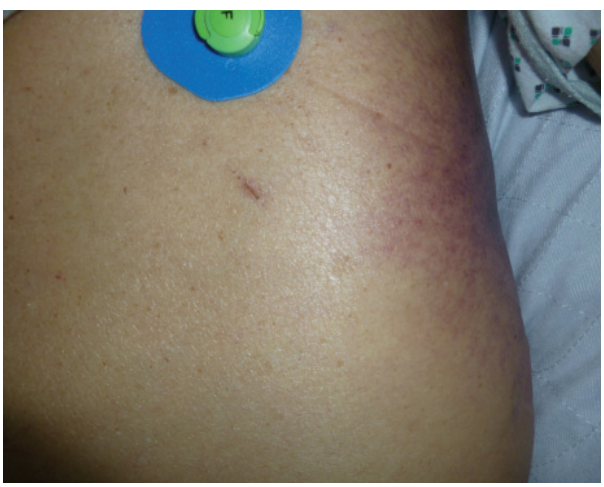


Fig. 1109 Grey-Turner sign (ecchymosis in the area of the left flank)

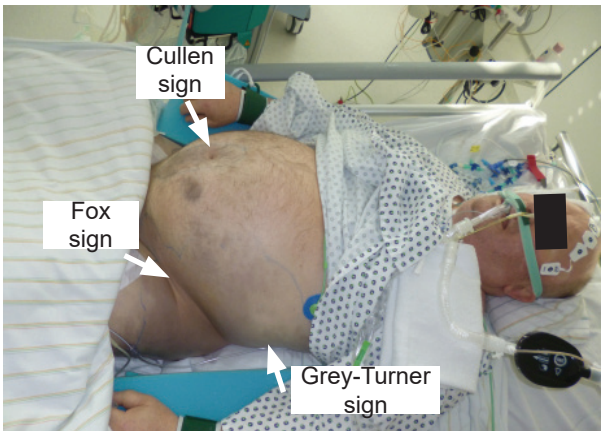


Fig. 1110 all 3 skin signs (ecchymoses) of pancreatitis: Cullen sign at the navel, Grey-Turner sign in the flank and Fox sign in the groin

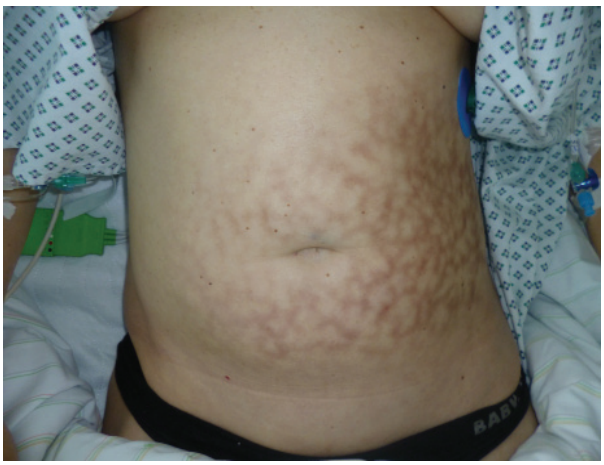


Fig. 1111 Not to be confused with ecchymosis is erythema ab igne ("reddening from the fire"): This is a burn of the skin caused by too frequent application of hot water bottles. The net-like pattern of the hot water bottle can be seen here. Erythema ab igne is typical in chronic pancreatitis, in which patients often try to apply heat to relieve pain.

Complications

- infection of necroses
- intraabdominal abscesses (e.g. pancreas, subphrenic)
- sepsis, septic shock, multiple organ failure
- hypovolemic shock (20% in severe pancreatitis)
- coagulation disorders:
  - disseminated intravascular coagulation (DIC)
  - hyperfibrinolysis
- ⚠ ARDS (in severe pancreatitis in 45% [Therefore we do not place patients with severe pancreatitis in the IMC (intermediate care), where we do not have the possibility of mechanical ventilation, but in the ICU [intensive care unit].)
- ⚠ acute kidney failure (in 36% in severe pancreatitis)
- arrosion of vessels (e.g. splenic artery; therapy of choice: interventional radiology [e.g. coiling]) or spleen with massive bleeding (cave sudden hemoglobine decline! especially in case of involvement of the pancreatic tail)

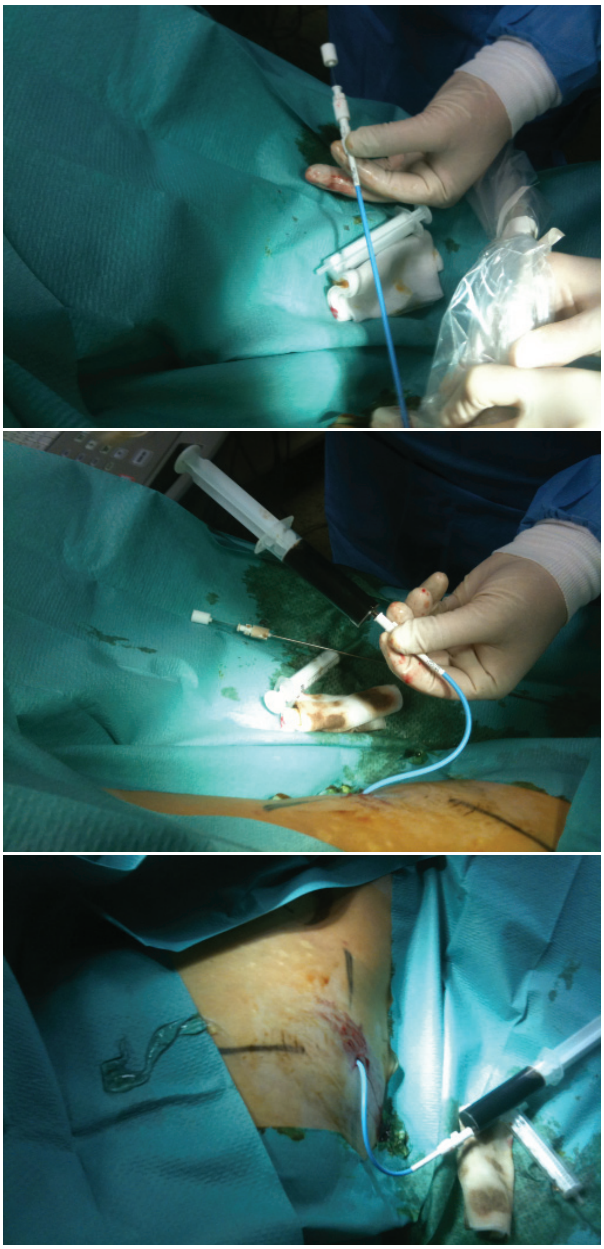
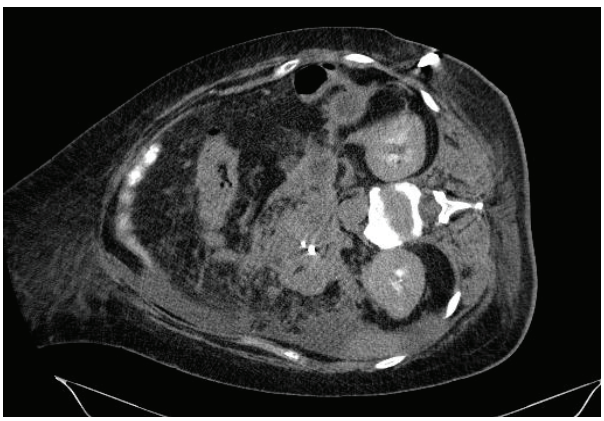


Fig. 1153 sonographically (with puncture transducer) guided percutaneous insertion of a drainage (here Hydroplus drainage catheter: size 10F, length 29cm), access from left-lateral retroperitoneal



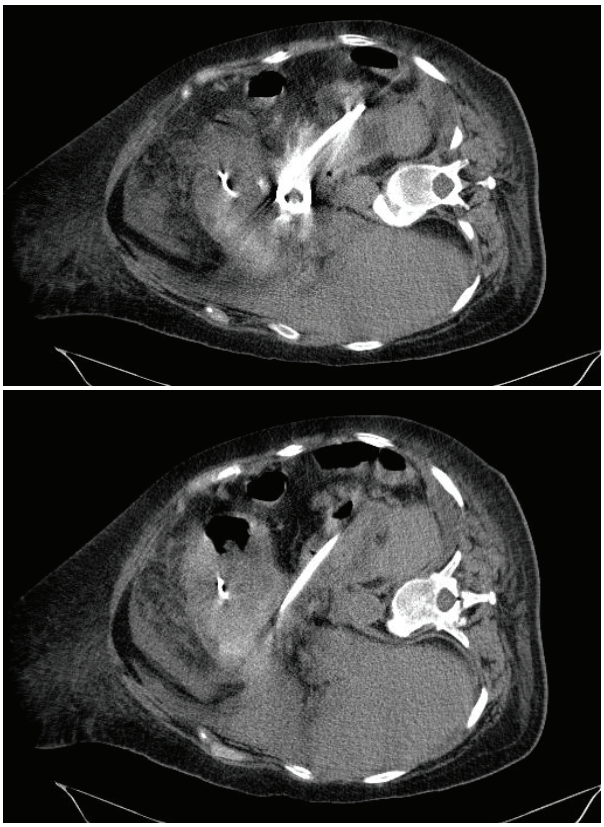


Fig. 1154 CT-guided percutaneous insertion of a drainage

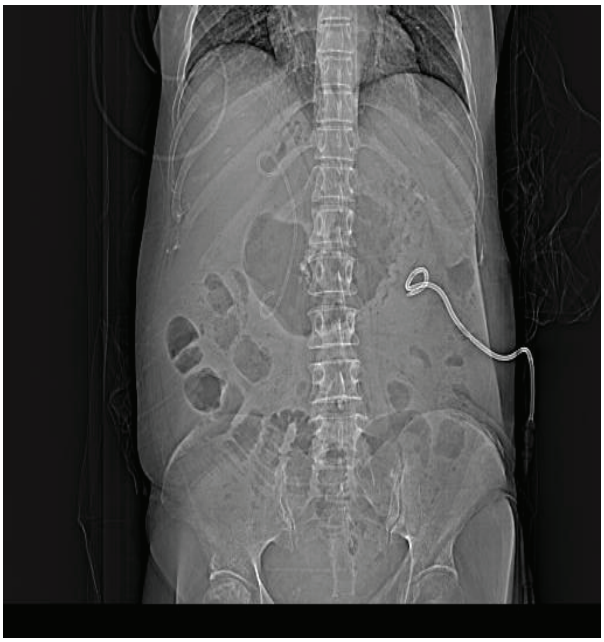
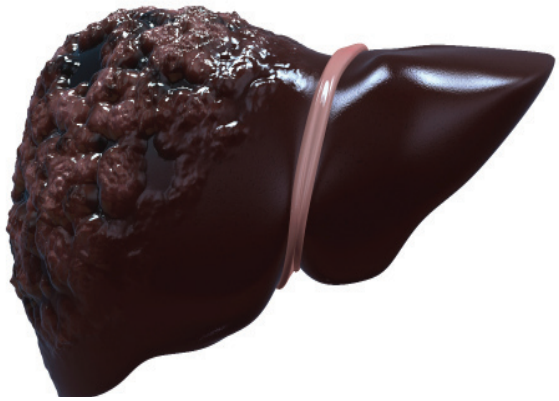


Fig. 1155 CT abdomen (topogram): inlying drainage

Endoscopic necrosectomy

- access:
  - transgastric (often; posterior wall of proximal corpus
  - transduodenal (rare; especially for necroses in the pancreatic head)
- NOTES (natural orifice transluminal endoscopic surgery)
- always under control by endosonography and X-ray

COMPLICATIONS OF LIVER CIRRHOSIS



Epidemiology (liver cirrhosis)

- incidence
  - 250/100000
  - increasing
- prevalence: 0.7%
- approx. 1 million people in Germany
- approx. 20000 deaths / year in Germany
- 9th most frequent cause of death
- proportion of total mortality: 2.2%
- The number of liver cirrhosis-related deaths has doubled in the last 25 years.
- m:w = 2:1

Fig. 1176 left normal liver, right with cirrhosis

Liver cirrhosis
causes

- **toxic: especially alcohol abuse (50%)**
- **infectious: especially chronic hepatitis (40%; hepatitis B and C)**
- **autoimmune: autoimmune hepatitis (AIH)**
- **biliary: PBC (primary biliary cholangitis), PSC (primary sclerosing cirrhosis)**
- **metabolic: hemochromatosis, Wilson´s disease, α_1-antitrypsin deficiency (syn.: Laurell-Eriksson syndrome), NASH, cystic fibrosis, glycogenosis**
- **vascular: Budd-Chiari syndrome**
- **cardiac (cirrhosis cardiaque): especially constrictive pericarditis**

Tip for clarifying the etiology of liver cirrhosis:
- IgA ↑ → alcohole
- IgG ↑ → AIH
- IgM ↑ → PBC

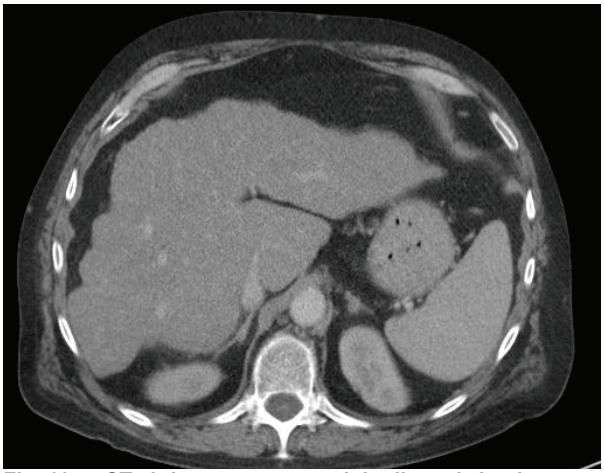


Fig. 1177 CT abdomen: macronodular liver cirrhosis

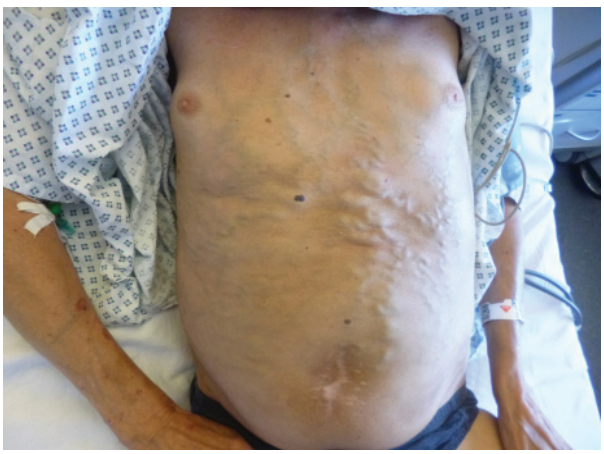


Fig. 1178 pronounced caput medusae

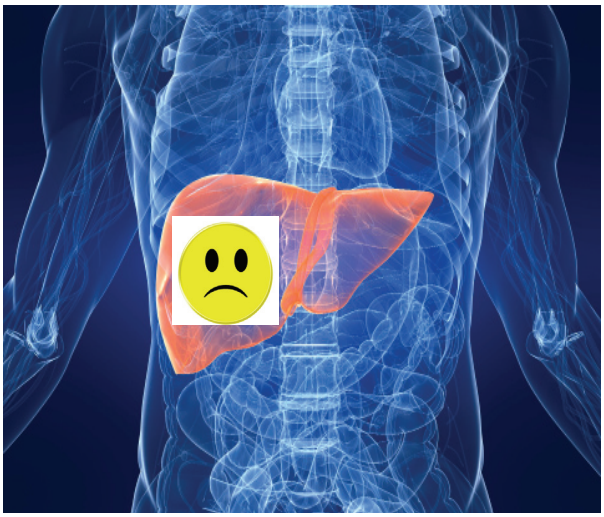
Classification

- Child-Pugh classification (exactly actually Child-Turcotte-Pugh score)
- MELD score (see infobox)

Child-Pugh classification

	1 point	2 points	3 points
albumin (g/dl)	> 3.5	2.8-3.,5	< 2.8
ascites	none	few	pronounced
bilirubin (mg/dl)	< 2	2-3	> 3
Quick INR	> 70% < 1.7	40-70% 1.7-2.3	< 40% > 2.3
hepatic encephalopathy	none	mild (grade I-II)	severe (grade III-IV)

ACUTE LIVER FAILURE (ALF)



Definition

- a syndrome (not a disease)
- sudden loss of liver function in previously liver-healthy individuals (no pre-existing chronic liver damage)
- potentially reversible
- syn .: hepatic disintegration coma
- duration of illness < 6 months (exceptions: Wilson´s disease, Budd-Chiari syndrome, autoimmune hepatitis, vertically [i.e. acquired during childbirth] hepatitis B); > 6 months: chronic liver failure
- to be distinguished from terminal liver failure in patients with chronic liver disease ("acute on chronic"; ACLF: acute on chronic liver failure [see infobox])
- clinical triad:
  - jaundice
  - coagulation disorder (coagulopathy; INR > 1.5)
  - disturbance of consciousness (hepatic encephalopathy [type A]):
    - most important diagnostic criterion (especially with regard to a HU [high urgent] transplant listing): Without hepatic encephalopathy, it is p.d. only acute liver insufficiency, not acute liver failure.
    - most important sign: flapping tremor (highly specific!)
- period between failure of liver function (jaundice) and onset of hepatic encephalopathy (O´Grady classification)
  - < 7 days: fulminant (peracute [most common cause: paracetamol])
  - 8-28 days: acute
  - > 28 days: subacute

Without hepatic encephalopathy there is no acute liver failure!

ACLF
acute on chronic liver failure

- **definition:**
  - **acute decompensated liver cirrhosis with organ failure (kidney [most common organ failure], liver, lung, blood coagulation, circulation, brain)**
  - **frequent (in 30% of all non-elective hospitalised patients with liver cirrhosis [in 20% already on admission, in 10% during the hospital stay])**
  - **very high short-term mortality (mean after 28d 33%, after 90d 51% [CANONIC study 2013])**
- **syn.: hepatic failure coma**
- **in contrast to acute liver failure (ALF), much more frequent, completely different patient population, other complications and no HU listing (high urgent) possible**
- **trigger: especially**
  - **bacterial infection (No.1; e.g. spontaneous bacterial peritonitis, urinary tract infection, pneumonia)**
  - **gastrointestinal bleeding (e.g. variceal bleeding)**
  - **excessive alcohol consumption**
  - **surgery**
- **CLIF-SOFA score (CLIF: chronic liver failure)**
  - **parameters: bilirubin, creatinine, INR, severity of hepatic encephalopathy, Horovitz quotient, MAP**
  - **> 64P.: poor prognosis (consider discontinuing therapy)**
- **degrees of severity:**
  - **grade 0: 1 organ failure (not kidney failure); mortality (after 3 months): 10%**
  - **grade I: kidney failure (creatinine > 1.5 mg/dl) or 1 other organ failure + HE; mortality: 40%; note: mortality in ACLF with kidney failure requiring renal replacement therapy: ⚠ 83% after 28 days, 92% after 1 year (Staufer et al, Liver Int 2017); therefore renal replacement therapy on principle only in candidates for liver transplantation**
  - **grade II: 2 organ failure; mortality: 50%**
  - **grade III: 3 organ failure; mortality: ⚠ 80%**

Guidelines

EASL (European Association for the Study of the Liver) Clinical Practical Guidelines on the management of acute (fulminant) liver failure 2017

Epidemiology

- rare (in Germany approx. 400-500 cases per year, in the United States approx. 2000 cases per year)
- prevalence: 5/1000000
- average age: 38 years
- w:m = 4:1

        - mostly only slightly increased (GOT [ASAT] on average 122 U/l, GPT [ALAT] on average 23 U/l (Berman et al, Gastroenterology 1990])
        - ⚠ significantly increased de-Ritis quotient (GOT/GPT) > 2.2 (sensitivity 94% and specificity 86% for Wilson's disease [Korman et al, Hepatology 2008])
- chelating agent (successive increase up to normalization of free copper in serum; however, usually no longer effective in acute liver failure)
  - penicillamine (Metalkaptase)
    - dosage: 0.9-1.5 g/d p.o. in 2 single doses
    - additional vitamin B6 (pyridoxin)
    - side effects: initial worsening of neurological symptoms, skin reactions, blood count changes, kidney damage
  - trien (Trientine)
    - dosage: 1.2-2.4 g/d p.o. in 3 single doses
    - side effects: i.a. allergy, iron deficiency
    - not available in Germany
- possibly plasmapheresis for copper elimination
- rapid liver transplantation (almost always necessary in acute liver failure due to Wilson's disease)
- prognosis:
  - without liver transplantation: very poor (Survival is only possible with liver transplantation!)
  - with liver transplantation: very good (5-year survival rate: 90%)

Acute liver failure: AP / bilirubin < 4, GOT / GPT (de-Ritis quotient) > 2.2 → Wilson´s disease

Acute fatty liver of pregnancy (AFLP)

Definition

- mostly in the last trimester of pregnancy (3rd trimester; usually after the 30th week of pregnancy)
- frequency: 1:10,000 pregnancies
- cause: congenital defect of LCHAD (long-chain 3-OH-CoA dehydrogenase) → accumulation of long-chain fatty acids, which have a hepatotoxic effect
- more frequent to tetracyclines (therefore contraindicated in pregnancy)
- a life-threatening disease

female patients with unclear acute liver failure → pregnancy test!

Symptoms

- nausea, vomiting
- general feeling of illness (malaise)
- abdominal pain
- headache
- ⚠ hypoglycemia (severe and persistent)
- polyuria, polydipsia (central diabetes insipidus [due to increased ADH release in the hypothalamus])
- jaundice
- hepatic encephalopathy
- ascites

Key symptom of AFLP: severe and persistent hypoglycemia!

Diagnosis

- laboratory:
  - transaminases
    - ⚠ often not significantly increased (mostly <500 U/l; cave often seductively low!)
    - de-Ritis quotient (GOT/GPT) < 1 (as in acute viral hepatitis)
  - bilirubin ↑, ammonia ↑
  - hypoglycemia
  - PTT ↑, INR ↑
  - creatinine, urea ↑
  - proteinuria
  - fibrinogen ↓, AT III ↓
  - hyperuricemia
  - blood count: leukocytosis, thrombocytopenia (DD HELLP), possibly fragmentocytes (DD HELLP)
- sonography:
  - noticeably hyperechogenic liver (due to the fat deposits)
  - ascites
  - exclusion of Budd-Chiari syndrome
  - exclusion of portal vein thrombosis
- histology (liver biopsy; but mostly not necessary): microvesical fatty infiltration

cially available, also not yet approved)

- hepatocyte cultures
- HepatAssist (Alliqua Inc.)
  - with porcine hepatocytes
  - Demetriou et al, Ann Surg 2004: no survival benefit
- ELAD (extracorporeal liver assist device; Thompson et al, Hepatology 2016: no survival benefit)
- AMC-BAL (academisch medisch centrum bioartificial liver)
- BELS (biological extracorporeal liver support)
- MELS (modular extracorporeal liver support; with human hepatocytes)

MARS

Definition

- MARS: molecular adsorbent recycling system
- filtration procedure for detoxification ("liver dialysis")
- extracorporeal detoxification
- developed at the University of Rostock in 1993 by Stange
- Gambro Hospal company

Principle

- removal of water-soluble toxins (especially ammonia) via conventional dialysis membrane
- removal of albumin-bound toxins via special MARS membrane (dialysis against albumin [acts as "attractant protein"]; principle of albumin dialysis)
- subsequent recycling of albumin via carbon adsorbers and ion exchangers

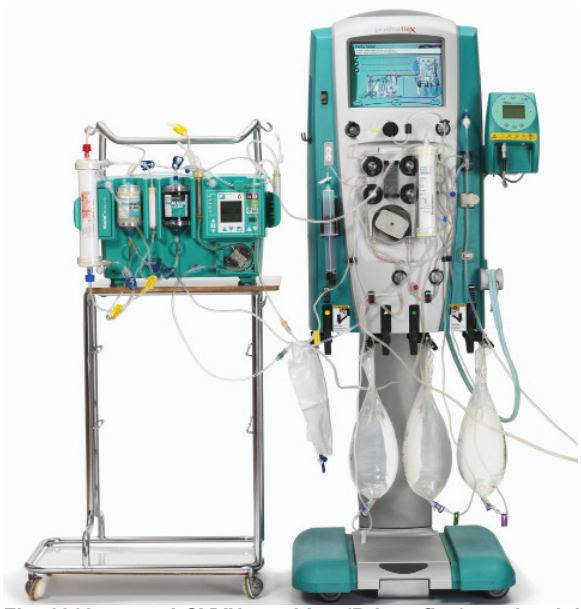


Fig. 1218 normal CVVH machine (Prismaflex) on the right, MARS as additional module on the left [18]

Fig. 1219 MARS

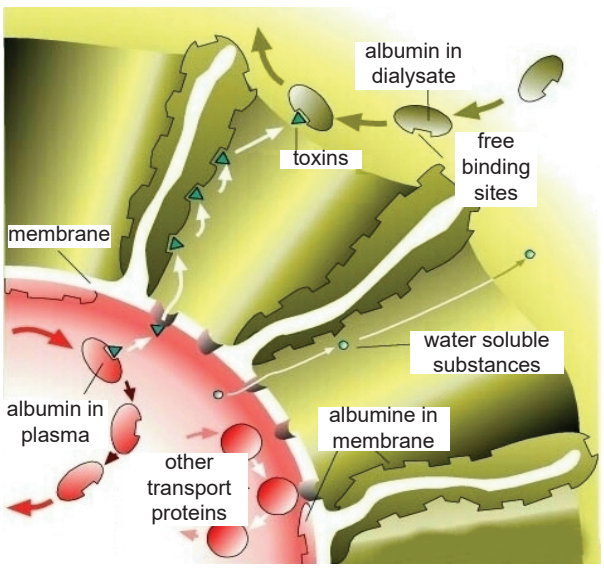


Fig. 1220 MARS membrane: Albumin is embedded in the membrane and acts as an attractant protein [18].

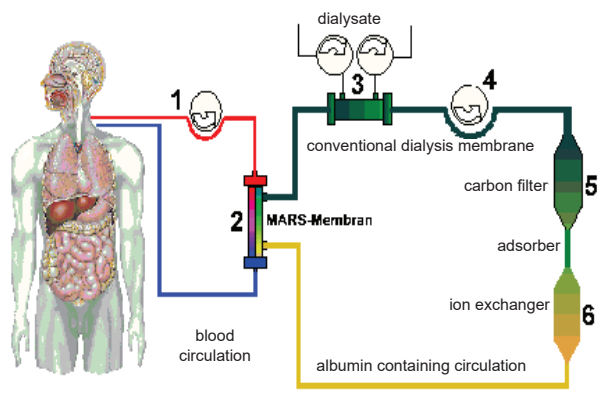


Fig. 1221 MARS flow circuit: Venous blood from the patient's Shaldon catheter is transported via a roller pump (1) to the MARS membrane (2): There detoxification of the albumin-bound toxins takes place. Then the blood flows to a conventional dialysis membrane (3): There detoxification of the water-soluble toxins takes place. Finally the "contaminated" albumin is recycled via carbon filters (5) and ion exchangers (6). [18]

Assessment

- significant improvement in liver function and hepatic encephalopathy, but no mortality benefit (i.a. Schmidt et al, Liver Transpl 2005; Hassanein et al, Hepatol 2007; Saliba et al, AASLD 2008)
- indication: „bridging to transplantation“ (optional)
- alternative to MARS: conventional CVVHD, only addition of albumin to the substituate solution
  - 4.5 liter bag with substituate solution, replace 1 liter of it with human albumin 20% (1 bottle 100ml → 10 bottles necessary [costs: approx. 1200 €])
  - substitution over 7h, i.e. exchange of 650ml in the first 7h
  - afterwards normal CVVH with albumin-free substituate

FULMAR study

A randomized controlled multicenter trial evaluating the efficiaty and safety of albumin dialysis with MARS in patients with fulminant and subfulminant hepatic failure
Saliba et al, Ann Intern Med 2013

- multicenter randomized controlled study
- 102 patients with acute liver failure
  - with MARS
  - without MARS
- 🙁 result: no significant mortality benefit (6-month survival)

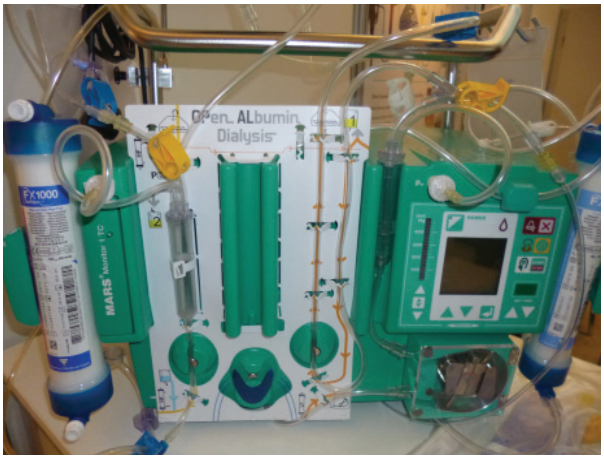
MARS-RELIEF study

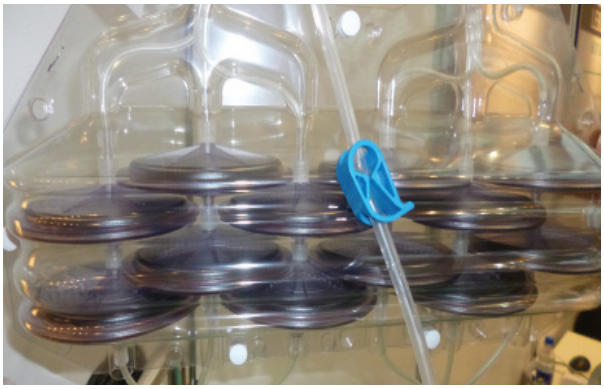
Extracorporeal albumin dialysis with the molecular adsorbent recirculating system in acute-on-chronic liver failure
Banares et al, Hepatology 2013

- multicenter randomized controlled study
- largest study of MARS
- 189 patients with acute-on-chronic liver failure (ACLF)
  - with MARS
  - without MARS
- results: MARS
  - 🙁 primary endpoint (28-day mortality): no difference
  - secondary endpoints
    - bilirubin, creatinine: significant reduction
    - hepatic encephalopathy: significant improvement

Further developments (albumin dialysis)

- OPAL system (OPAL: open albumin dialysis; Albutec company; is the successor system to MARS): A special adsorber (made from Hepalbin) is installed here, which purifies the albumin binding sites in the dialysate even more, so that the effectiveness is increased .
- ADVOS system (ADVOS: ADVanced Organ Support; Hepa Wash company [now ADVITOS]): Here, the albumin is recycled by changing the pH of the dialysate, which changes the binding sites: By decreasing of the pH, positively charged toxins are removed from albumin, by increasing of the pH, negatively charged toxins are removed from albumin.





- 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
- 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)
  - 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 diabetes	type 2 diabetes
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 sodium value is obtained with the correction formula: $sodium_{corrected}$ (mmol/l) = $sodium_{measured}$ (mmol/l) + 0.16 x (glucose [mg/dl] - 100). The sodium value from the BGA is not subject to this measurement error.

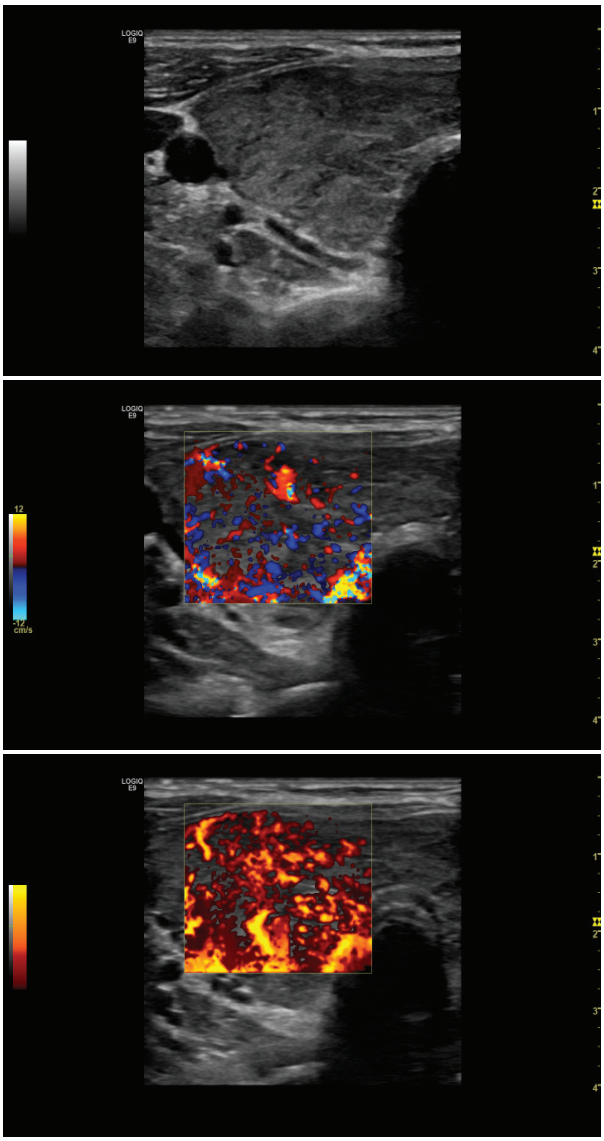


Fig. 1007 sonography of the thyroid gland in Graves disease: It is enlarged (goiter [p.d. > 18ml in women and > 25ml in men], here diffuse goiter, i.e. without knots), hypoechoic (i.e. it has the same echogenicity as the neighboring neck muscles) and the pathognomonic hypervascularization can be seen in color duplex and in power mode ("vascular inferno").

Trigger

- ⚠ iodine-containing contrast agent (e.g. contrast CT, coronary angiography)
- iodine-containing drugs, e.g..
  - amiodarone (note: Amiodarone often leads to a drop in TSH and an increase in fT4 [possibly also an increase in fT3], which is completely normal. It is only necessary to discontinue amiodarone and also to administer a thyreostatic if TSH < 0.01 U/l + fT3 ↑ and clinical symptoms of hyperthyroidism are present. In amiodarone-induced hypothyroidism, amiodarone does not have to be discontinued at all, only hormone replacement [e.g. L-thyroxine 50µg] should be performed.)
  - indocyanine green
  - external products
  - excessive intake of thyroid hormone tablets
    - e.g. in the context of paranoid schizophrenia, e.g. for weight reduction
    - Most of them are T4 preparations, so that correspondingly increased fT4 values can also be measured in the laboratory.
    - The administration of thyreostatic drugs, which only inhibit the synthesis and secretion of new thyroid hormones and have no influence on externally supplied thyroid hormones, is pointless.
- discontinuation of thyrostatic drugs
- definitive therapy, although there is still hyperthyroidism and not yet euthyroidism:
  - radioiodine therapy for hyperthyroidism
  - surgery

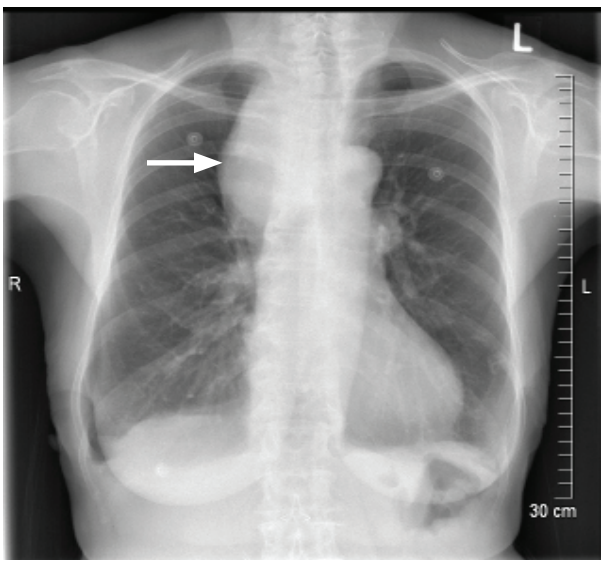


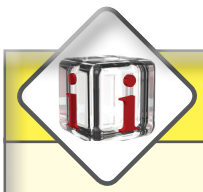
Fig. 1008 pronounced goiter extending to the retrosternally with mediastinal widening (see arrow), which was manifestly hyperthyroid in the laboratory (The patient was admitted with a STEMI. Therefore, without waiting for any laboratory tests, cardiac catheter examination with PCI and stent implantation was carried out immediately. In the further course the patient showed symptoms of an unclear "sepsis". Ultimately it was a thyrotoxic crisis triggered by the applied contrast medium.)

Symptoms

- sinus tachycardia (often > 140/min), tachyarrhythmia absoluta
- fever; warm, wet skin ("sepsis")
- massive sweating
- vomiting, diarrhea ("gastroenteritis")
- dehydration, exsiccosis
- possibly thromboembolism (including increased risk of sinus vein thrombosis)
- ⚠ tremor (pronounced!)
- restlessness, anxiety
- muscular weakness (pronounced!), adynamia
- blood pressure
  - initial hypertensive (high BP amplitude [DD aortic valve insufficiency])

- hypothermia → warming up; cave at body temperature < 30ºC no active-external (e.g. electric blankets, warm air blower [Bair Hugger]), but only active-internal (e.g. CoolGard) warming up (reason: danger of peripheral vasodilation with consecutive circulatory insufficiency)

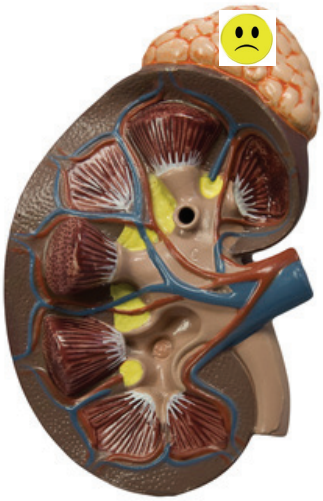
high dosage of thyroid hormones (e.g. L-thyroxine 500µg i.v.): always combine with hydrocortisone 100mg i.v. (otherwise risk of Addison crisis!)



low-T3 syndrome

- syn.:
  - NTIS (non-thyreoidal illness syndrome)
  - ESS (euthyreot sick syndrome)
  - TACITUS syndrome (thyroid allostasis in critical illness, tumors, uremia and starvation)
- frequent in intensive care patients (correlates with increased mortality)
- fT3 ↓, fT4 mostly normal, mostly also TSH ↓
- cytokines
  - decrease of selenium-dependent deiodinase activity → decreased conversion from T4 to T3
  - direct inhibition of pituitary TSH secretion
- The decrease in active hormone (fT3) is a physiological response to stop catabolism.
- sufficient supply of the organs with thyroid hormones (clinically no hypothyroidism [only laboratory]; ⚠ no substitution necessary [even increases mortality! increased risk of iatrogenic thyroid storm!])
- cave: Even in patients who previously have a primary thyroid dysfunction (possibly still unknown) the laboratory changes in the low-T3 syndrome take place, if they are critically ill, so that a thyroid dysfunction can be concealed and overlooked:
  - primary hypothyroidism: As a result of the low-T3 syndrome, TSH is no longer elevated, but false normal, so that primary hypothyroidism (up to myxedema coma) can be overlooked!
  - primary hyperthyroidism: As a result of the low-T3 syndrome, fT3 (and possibly also fT4; TSH is already suppressed) is no longer elevated, but false normal, so that primary hyperthyroidism (up to thyrotoxic crisis) can be overlooked! If you are unsure, you can perform a TRH test (stimulation test; note: the only indication for a TRH test at all): TSH is determined before and 30 minutes after administration of TRH (thyrotropin-releasing hormone) 200 µg. In the case of the low-T3 syndrome, TSH can be stimulated (i.e. it rises > 2 mU/l), in primary hyperthyroidism this is not the case (TSH remains < 2 mU/l).

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

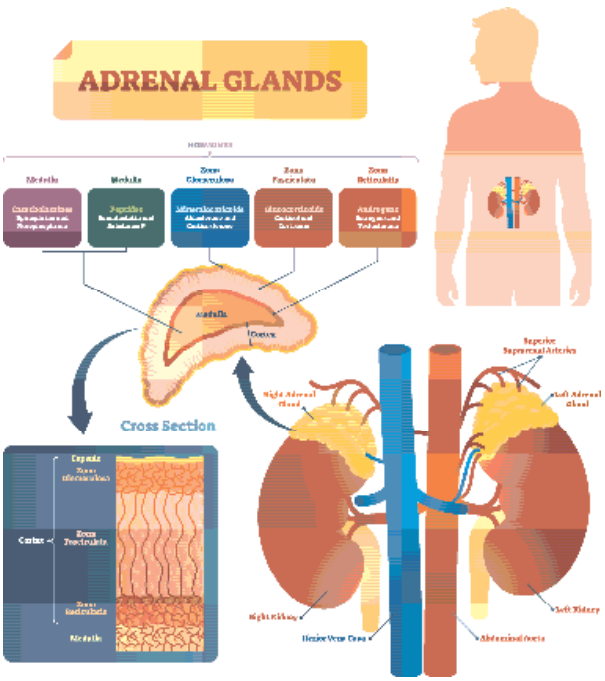


Fig. 1011 adrenal gland: structure and function

Fig. 1019 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 757)
- 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%).
    - The diagnosis may be made only with clear signs of volume deficiency (e.g. skin folds, increased haematocrit)!

DD Hyponatremia

- **serum osmolarity not decreased: pseudohyponatremia (hyperglycemia, hyperproteinemia, hyperlipidemia)**
- **serum osmolarity decreased: true hyponatremia**
  - **hypervolemic (i.e. with edema):**
    - **urine sodium < 20 mmol/l: extrarenal (decompensated heart failure [note: Most patients receive diuretics, so that the urine sodium can therefore also be > 20 mmol/l.], Liver cirrhosis, nephrotic syndrome)**
    - **urine sodium > 20 mmol/l: renal (renal insufficiency)**
  - **euvolemic:**
    - **urine osmolarity > 100 mosm/l or urine osmolarity > serum osmolarity**
      - **SIADH (most frequent; urine sodium > 30 mmol/l)**
      - **cortisol deficiency (hypocortisolism)**
      - **drugs**
      - **hypothyroidism**
    - **urine osmolarity < 100 mosm/l or urine osmolarity < serum osmolarity: water intoxication (psychogenic polydipsia, potomania, exercise associated hyponatremia [EAH])**
  - **hypovolemic (i.e., desiccated):**
    - **urine sodium < 20 mmol/l: extrarenal (e.g. vomiting, diarrhea, bleeding, peritonitis, burn)**
    - **urine sodium > 20 mmol/l: renal**
      - **diuretics (note: Especially with a thiazide diuretic, the urine sodium can also be < 20 mmol/l, if the intake took place well before the urine sample was taken. This can lead to an increased sodium reabsorption via a postdiuretic effect.)**
      - **aldosterone deficiency (hypoaldosteronism)**
      - **osmotic diuresis (e.g. ketonuria)**
      - **cerebral salt loss syndrome (cerebral wasting sysndrome)**
      - **renal tubular acidosis type I**

Therapy

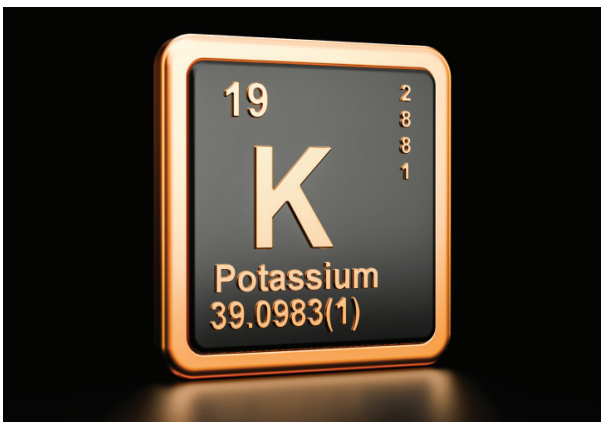
- hypovolemic
  - volume administration only (NaCl 0.9%; 1000ml NaCl 0.9% contain 9g NaCl and 154 mmol sodium [1ml NaCl 0.9% corresponding to 0.154 mmol sodium])
  - possibly discontinuation of diuretics
  - possibly food rich in sodium chloride (bouillon, NaCl wafers; not a general recommendation)
  - tablets / pills containing sodium chloride (salt tablets, "Swedish tablets"; not a general recommendation); p.o. substitution only up to 130 mmol/l; if sodium < 130 mmol/l: i.v.; note: Salt tablets should be used very cautiously. They increase the patient's thirst so that they drink more, which further aggravates hyponatremia!
  - raising of sodium (e.g. 1-2 vials of NaCl 20% in 500ml NaCl 0.9%)
  - possibly hypertonic NaCl (3%)
    - preparation:
      - 1000 ml NaCl 0.9% + 7 amp. NaCl 20% a 20ml (9g [1000ml NaCl 0.9%] + 7 x 4g [7 x NaCl 20% a 20ml] = 37g to 1140ml → 3g to 100ml [3%]) or
      - 500 ml NaCl 0.9% + 3 ½ amp. NaCl 20% a 20ml
    - infusion rate: 0.5 ml/kg/h
    - electrolyte controls every 6h are obligatory
    - 1-2 ml/kg/h according to sodium deficit
    - 1ml of NaCl 3% = 0,5 mmol sodium; 513 mmol/l sodium
    - 1 liter NaCl 3% → sodium increase by 10 mmol/l
- eu-/ hypervolemic:
  - water restriction (sufficient in asymptomatic patients
  - ⚠ no additional supply of sodium (This even aggravated hypervolemia!)
  - if necessary with hypervolemia additional loop diuretics (e.g. 80mg furosemide/day, e.g. add 2 x 40mg to the hypertonic NaCl infusion), thiazides should be discontinued!
  - possibly with edemas: hypertonic NaCl 3% + furosemide 40mg
  - hyponatremia with heart failure → ACE inhibitor
  - hyponatremia with liver cirrhosis → aldosterone antagonists (e.g. spironolactone)
  - In severe cases of overhydration combined with reduced diuresis renal replacement therapy can be used.

Fig. 1020 NaCl 20% ampoules: 1 amp. = 10ml = 2g sodium chloride; 1ml contains 3.4 mmol sodium [8]

Do not salt hypervolemic patients (very frequent error)! This aggrevates the hypervolemia!

- hepatotoxicity (Red-Hand-Letter 2013)
- daily therapy costs: 88€
- guidelines (recommendations):
  - European guideline (Clinical Practice Guidelines 2014 [Spasovski et al, Eur J Endocrinology]): ☹ not recommended (in the case of severe hyponatremia even clearly rejected) as, on the one hand, the studies did not show any mortality advantage and, on the other hand, the risk of an excessive increase of sodium and thus central pontine myelinolysis is too high; note: It is noteworthy that in this guideline the administration of urea is recommended as the second choice for SIADH after fluid restriction. Urea causes increased water excretion via osmotic diuresis. A dose of 30-120g per day is recommended. On the one hand, this therapy principle is almost not validated, and on the other hand, due to the extremely bitter taste of urea (like urine; even if dissolved in orange juice), it is often impossible to implement.
  - American guideline (Verbalis et al, Am J Med 2013; Expertenkonsensus): ☺ recommended (second choice at SIADH after the fluid restriction)

Disorders of potassium



- hyperkalemia (potassium > 5.5 mmol/l)
- hypokalemia (potassium < 3.5 mmol/l)

98% of potassium is intracellular and only 2% extracellular. The intracellular potassium concentration (K_i) is 120-140 mmol/l, the extracellular potassium concentration (K^e) only 3.5-5.5 mmol/l. The measured concentration in the serum can therefore only be used with restrictions. ECG is therefore very valuable diagnostically, especially in the case of acute changes in potassium! Potassium is the most important intracellular ion. The ratio of intra- and extracellular potassium (K_i/K_e) determines the membrane potential and thus the neuromuscular excitability of the cell. The sodium-potassium-ATP-ase (syn .: sodium-potassium pump) maintains this ratio by actively transporting potassium into the cell and sodium out of the cell. The enzyme is magnesium dependent. Insulin and a stimulation of β-receptors stimulate the sodium-potassium-ATP-ase and thus lead to a decrease in the extracellular potassium in the serum via an increased potassium uptake in the cells. Hyperkalemia lowers the membrane potential and increases excitability, hypokalaemia increases the membrane potential and reduces excitability.The daily potassium intake with food is approx. 50-150 mmol/l. 90% of the potassium is excreted renally and 10% enterally. In case of renal insufficiency, enteral excretion is increased as compensation (up to 25%), but the mechanism is limited. Potassium is filtered glomerularly in the kidney and almost completely reabsorbed in the proximal tubule. A small part is secreted in the distal tubule and collecting tube. The excretion of potassium is stimulated by mineralocorticoids (especially aldosterone) via mineralocorticoid receptors in the distal tubule and collecting tube. The higher the distal urine flow rate (diuresis; e.g. polyuria in derailed diabetes mellitus), the more potassium is excreted in the urine.
Via the H^+/K^+ exchanger (Hamburger Shift), potassium also has an influence on the acid-base balance: Hyperkalaemia leads to acidosis and hypokalaemia to alkalosis. Similarly, acidosis leads to hyperkalaemia and alkalosis to hypokalaemia.

Hyperkalemia

Etiology

- acute kidney failure, renal insufficiency (⚠ most frequent cause)
- drugs
  - potassium-sparing diuretics (mineral corticoid receptor antagonist [MRA], syn .: aldosterone antagonists: spironolactone, eplerenone)
  - ⚠ RAAS inhibitors (ACE inhibitors, ATII antagonists, ARNI [angiotensin receptor neprilysin inhibitor]): from potassium > 5.0 mmol/l dose reduction by 50%, from potassium > 5.5 mmol/l contraindicated!
  - NSAID
  - ⚠ digitalis (inhibition of the sodium-potassium-ATP-ase)
  - β-blockers (inhibition of the sodium-potassium-ATP-ase)
  - ⚠ heparin (inhibition of aldosterone synthesis → hypoaldosteronism; usually only in case of long-term therapy)
  - cotrimoxazole (inhibition of potassium secretion in the distal tubule and collecting tube)
  - succhinylcholine
  - ciclosporin
- Addison disease
- acidosis (H^+/K^+ exchanger [Hamburger shift]):
  - A decrease of the pH value by 0.1 leads on average to increase of potassium of 0.6 mmol/l.
  - not the case with lactic acidosis and ketoacidosis
- cytolysis with consecutive release of potassium:
  - myolysis (e.g. rhabdomyolysis)
  - hemolysis
  - tumorlysis
- transfusion of erythrocyte concentrates (especially older preparations, massive transfusion)
- pronounced constipation
- crush syndrome
- diabetes mellitus (hyporeninemic hypoaldosteronism =

DISORDERS OF THE ACID-BASE BALANCE

Basics

- pH-value:
  - pH: "potentia hydrogenii"
  - negative decadic logarithm of H^+ ion-concentration: pH = - log [H^+]
- acids:
  - volatile (especially carbonic acid): are eliminated pulmonary
  - fixed: are eliminated renally
- buffer systems:
  - open buffer system: bicarbonate system (most important; largest capacity): The pH-value (H^+ ions; protons) depends on the bicarbonate (HCO_3^-) and pCO_2. This relationship is described by the Henderson-Hasselbalch equation (syn.: buffer equation):

$$pH \sim \log (HCO_3^- / pCO_2)$$

  - closed buffer systems (low capacity only):
    - phosphate
    - proteins (i.a. albumin, hemoglobin)
    - ammonia
- disorders:
  - acidoses (pH < 7.36)
  - alkaloses (pH > 7.44)
- changes:
  - respiratory disorders: primary change of pCO_2 (lung)
    - respiratory acidosis: $pCO_2 \uparrow$
    - respiratory alkalosis: $pCO_2 \downarrow$
  - metabolic disorders: primary change of HCO_3^- (kidney)
    - metabolic acidosis: $HCO_3^- \downarrow$
    - metabolic alkalosis: $HCO_3^- \uparrow$
- most important diagnostic: blood gas analysis (the most frequent laboratory examination in the intensive care unit!)
- differences between arterial and venous BGA:
  - pO_2: in the arterial BGA higher than in the venous BGA
  - pCO_2: normally approximately equal (in the venous BGA only 3-4mmHg higher than in the arterial BGA; so called veno-arterial pCO_2 difference [dCO_2], usually the central veno-arterial pCO_2 difference is used, i.e. BGA from CVC and BGA from artery; a dCO_2 > 8mmHg is typical for shock [cardiac output ↓, anaerobic metabolism ↑])
  - pH: normally approximately equyl (in venous BGA only 0.02 higher than in arterial BGA; a veno-arterial pH difference > 0.1 is typical for shock)
  - blood sugar (glucose): in the venous BGA about 10 mg/dl (0.6 mmol/l) lower than in the arterial BGA
- hemodynamics:
  - acidosis → vasodilatation (tip: just think of the COPD patients who almost always have quite good and thick veins.), hypotension (on the one hand due to vasodilatation, on the other hand due to the fact that in acidosis the endogenous catecholamines no longer act sufficiently [weakening of the effect of the catecholamines in an acid environment]), reduction of contractility
  - alkalosis → vasoconstriction (i.a. cerebral [seizures, neurological deficits], coronary [coronary spasm, cardiac arrhythmia])
- oxygen binding curve (hemoglobin):
  - alkalosis → left shift → deterioration of oxygen delivery to tissue
  - acidosis → right shift → improvement of oxygen delivery to tissue (Bohr effect)

Fig. 1041 BGA meter (blood gas analysis; syn.: Astrup [named after the Danish physiologist Poul Bjørndahl Astrup, 1915-2000])

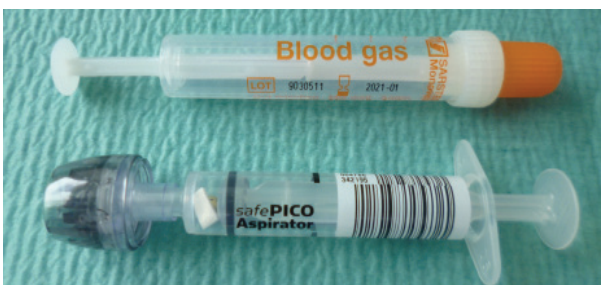


Fig. 1042 different BGA syringes

MUDPILERS
causes of metabolic acidosis <u>with</u> increased anion gap

M	Methanol (intoxication)
U	Uremia
D	Diabetic ketoacidosis
P	Paraldehyd / Phosphor (intoxication)
I	Isoniazid (intoxication)
L	Lactic acidosis
E	Ethylene glycol (intoxication)
R	Rhabdomyolysis
S	Salicylate (intoxication)

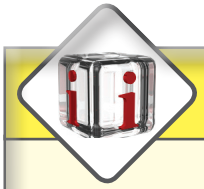
In metabolic acidoses with an increased anion gap (increased accumulation of acids [exogenous / endogenous]) sodium bicarbonate does not help at all (only the conscience)! only reasonable option: renal replacement therapy (RRT)!

HARD UP
causes of metabolic acidosis <u>without</u> increased anion gap

H	Hyperalimentation, Hyperchloremia
A	Acetazolamide, Addison´s disease
R	Renal tubular acidosis
D	Diarrhea
U	Ureteroenterostomy
P	Pancreatic fistula

USED CARPS
causes of metabolic acidosis <u>without</u> increased anion gap

U	Ureteroenterostomy
S	small bowel fistula
E	Excess chloride
D	Diarrhea
C	Carbonic anhydrase inhibitors (acetazolamide)
A	Adrenocortical insufficiency
R	Renal tubular acidosis
P	Pancreatic fistula
S	Spironolactone



Delta gap
Δgap

- **delta gap = (anion gap [mmol/l] - 16) / (24-HCO_3^- [mmol/l])**
- **interpretation:**
  - **< 1: additional hyperchloremic metabolic acidosis or chronic respiratory alkalosis**
  - **> 1: additional metabolic alkalosis or chronic respiratory acidosis**

Osmotic gap

- **syn.: osmolal gap**
- **The osmotic gap represents the difference between the calculated and (in the laboratory) measured plasma osmolarity**
- **osmotic gap = measured osmolarity - calculated osmolarity**
- **normal value: < 10 mosm/kg**
- **formula for the calculated osmolarity (mosm/kg):**
  - **with units mmol/l: 1.86 x sodium (mmol/l) + glucose (mmol/l) + urea (mmol/l)**
  - **with units mg/dl: 1.86 x Natrium (mmol/l) + glucose (mg/dl) / 18 + urea (mg/dl) / 6 + 9**
- **An increased osmotic gap indicates an osmotically active substance not taken into account in the formula.**
- **causes for an increased osmotic gap:**
  - **lactic acidosis, ketoacidosis**
  - **uremia**
  - **intoxications: especially**
    - **salicylate**
    - **alcoholes**
      - **ethanol (1 per mille increases the osmotic gap by 22 mosm/kg.)**
      - **⚠ methanol, ethylen eglycol (classic)**

Types

- addition acidosis (accumulation of too many acids): i.a. lactic acidosis, ketoacidosis, intoxications; see esp. KUSMALE; ⚠ here administration of sodium bicarbonate pointless; classification:
  - endogenous
    - ketoacidosis
      - diabetic
      - alcoholic
      - starving
    - lactic acidosis (see chapter endocrinological emergencies [page 727])
  - exogenous
    - intoxications (poisoning)

dividual components of the metabolic part of the acid-base balance
- aslo assessment of several simultaneous metabolic disorders possible
- in its original form too complex for everyday clinical practice, therefore mostly used in a simplified form (simplified Stewart approach [according to Story et al, Br J Anaesth 2004])
- standard base excess (SBE)
  - norm: -2 to +2 mmol/l
    - < -2 mmol/l: net metabolic acidosis
    - > 2 mmol/l: net metabolic alkalosis
  - SBE: sum of 4 effects

SBE = electrolyte effect + albumin effect + lactate effect + UMA effect

Fig. 1047 Simplified Stewart approach (ionogram: Due to the principle of electroneutrality, the sum of the anions is equal to the sum of the cations.)

Stewart approach: a good option for differentiated assessment of metabolic acidosis

Electrolyte effect

- The relevant ions (strong ions) that affect the acid-base balance are sodium (cation) and chloride (anion). All other ions (potassium, calcium, magnesium, phosphate) can be neglected. The difference between sodium and chloride is usually 38 mmol/l.
- calculation: sodium - chloride - 38
- assessment:
  - < - 2 mmol: hyperchloremic acidosis
    - supply of too much chloride (infusion NaCl 0.9%)
    - diarrhea
    - renal tubular acidosis (RTA)
    - renal failure with tubular damage
    - compensation (counter-regulation) of a respiratory alkalosis (hypocapnia)
    - supply of free water
  - > 2 mmol: hypochloremic alkalosis
    - recurrent vomiting with loss of gastric acid
    - diuretics
    - dehydration
    - compensation (counter-regulation) of a respiratory acidosis (hypercapnia)
    - Compensation (counter-regulation) of ketoacidosis
- A deviation of 1 mmol/l explains a deviation in the BE of 1 mmol/l.

Albumin effect

- calculation: (42 - albumin [g/l]) / 4
- assessment: > 2 mmol/l → ⚠ hypoalbuminemic alkalosis (Albumin is a weak acid!)
  - liver synthesis disorder (e.g. liver cirrhosis)
  - malnutrition
  - catabolism
  - loss of albumin
    - capillary leak (typical in sepsis)
    - abdominal surgery, larger wounds, burns
    - nephrotic syndrome
    - protein losing enteropathy (PLE; Gordon syndrome)
- A decrease of albumin by 10 g/l increases the BE by 2.5 mmol/l.

Lactate effect

- calculation: 1 - lactate [mmol/l]
- assessment: < 2 mmol/l → lactic acidosis (see page 727)
- The lactate value in mmol/l explains the decrease of BE in mmol/l, i.e. a lactate of 10 mmol/l explains a BE of -10 mmol/l.

UMA effect

- UMA: unmessured anions
- "KUSME": ketoacidosis, uremia, salicylates, methanol, ethylene glycol
- calculation: SBE - electrolyte effect - albumin effect - lactate effect
- assessment < 2 mmol/l → metabolic acidosis due to UMA
  - uremia
  - ketoacidosis
  - intoxications (including salicylates, methanol, ethylene glycol)

in this case, with the result that the venous pressure in the shunt arm increases and complications can occur frequently in the Cimino shunt (e.g. formation of aneurysms, bleeding). However, if the atrial catheter has two lumina, the CVVH can also be performed over it and and no additional Shaldon catheter has to be installed.

Fig. 1008 Shaldon catheter [18]

Place of first choice for the shaldon catheter: right internal jugular vein!

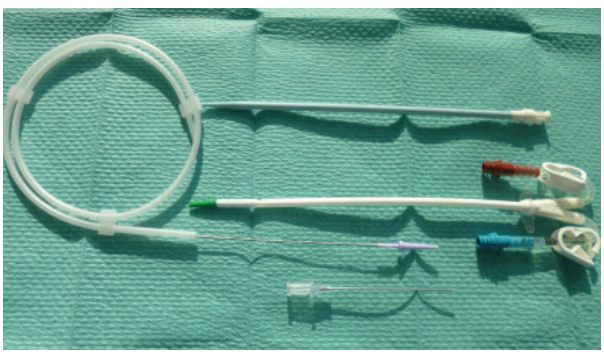


Fig. 1009 Shaldon catheter set: catheter, Seldinger needle and Seldinger wire, dilator

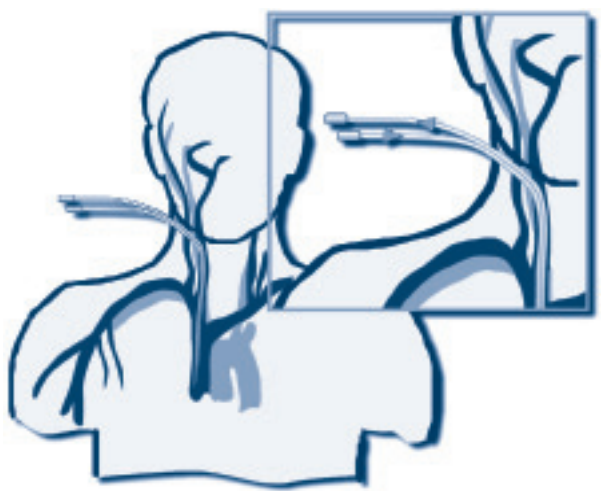


Fig. 1010 Shaldon catheter in the internal jugular vein [17]

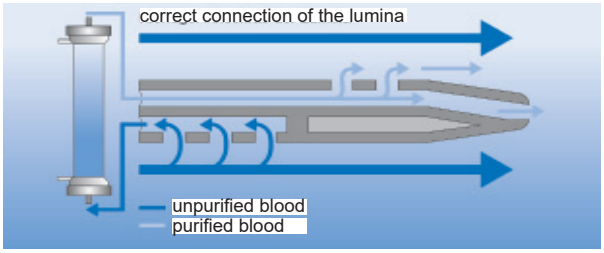


Fig. 1011 Shaldon catheter: connection of the lumina [17]

Types

- according to the principle of substance separation
  - hemodialysis (HD)
  - hemodialysis (HD)
  - hemodiafiltration (HDF; mixture of both methods; most frequently in intensive care)
- according to duration of use
  - kontinuierliche procedures
    - CAVH (continuous aterio-venous hemofiltration; driving force: blood pressure; abandoned today)
    - CVVH (continuous veno-venous-hemofiltration; driving force: pressure generated by a pump)
  - intermittent procedures (e.g. intermittent hemodialysis [IHD])

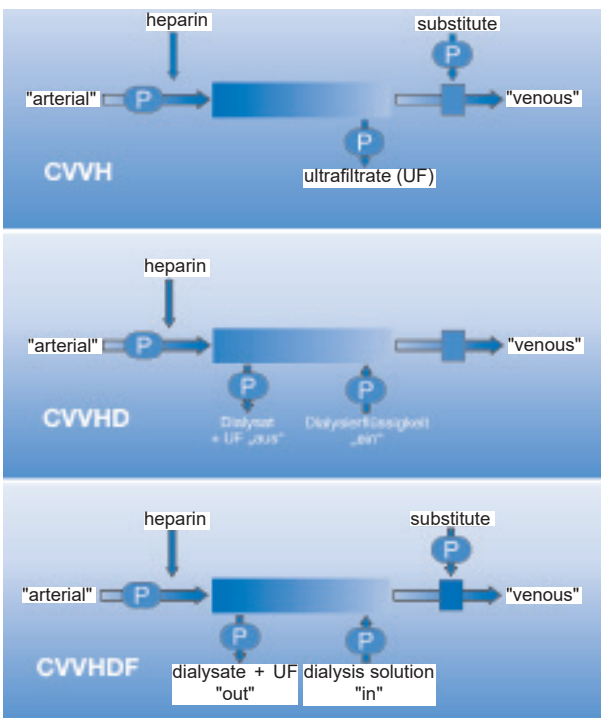


Fig. 1012 Overview of the various renal replacement methods [17]

Hemodialysis

Definition

- principle: diffusion (diffusive method)
- The driving force for substance transfer is the difference in concentration between two liquids separated by a semi-permeable membrane. The basis for diffu-

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

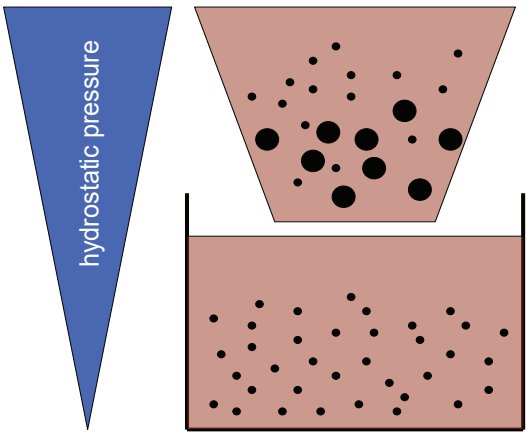
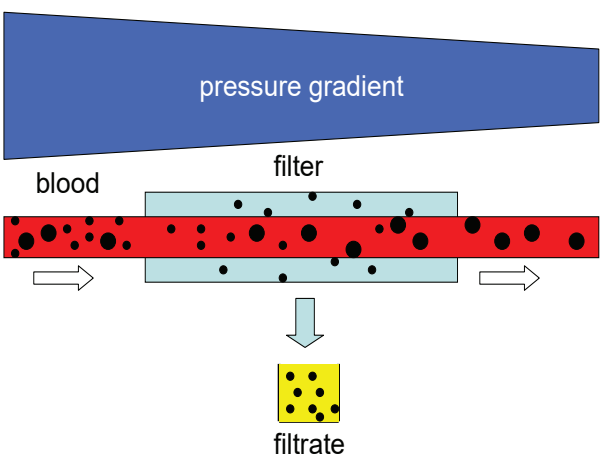


Fig. 1015 Hemofiltration is illustrated by a simple example from everyday life, the coffee filter. The driving force here is the hydrostatic pressure difference between the top and bottom of the coffee machine caused by gravity. The coffee powder ("grounds"; analogous to blood: blood cells, larger proteins) 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")



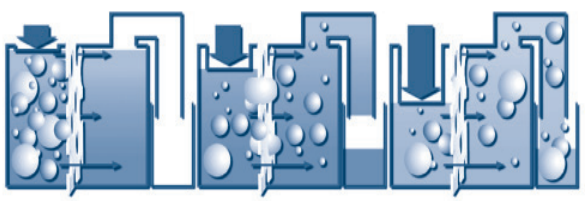


Fig. 1016 principle of convection [17]

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

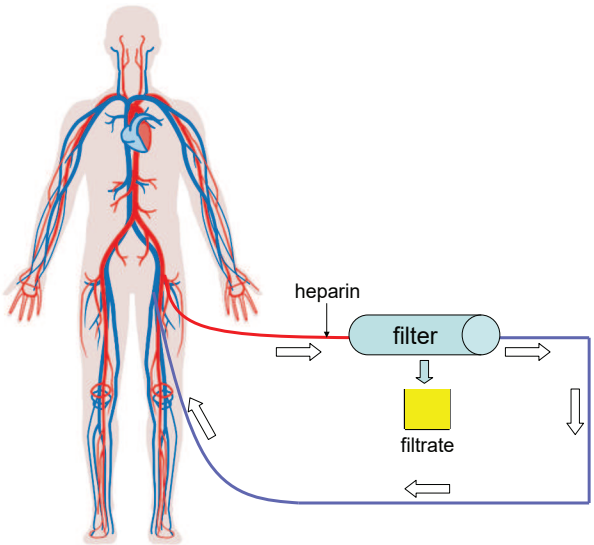


Fig. 1017 scheme CAVH: The pressure gradient is generated by the blood pressure (arterio-venous pressure difference; heart as pump). Arterial cannulation is necessary here. This procedure is abandoned today.

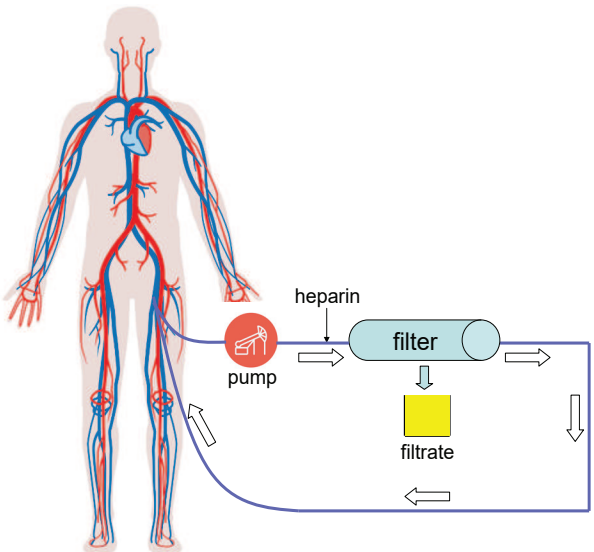


Fig. 1018 scheme CVVH: The pressure gradient is generated by a pump. Arterial cannulation is not necessary. This procedure is standard today.

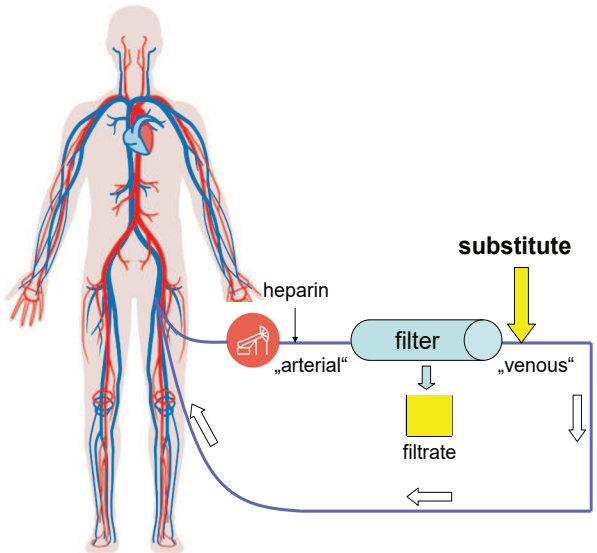


Fig. 1023 Postdilution: The substitute solution is only added past the filter (in the "venous" branch). This has the advantage that the clearance function is better. However, this has the disadvantage that a haemoconcentration occurs in the filter due to the pressing of the filtrate, so that filter thromboses more frequently (more clotting).

Pressure measurements (monitoring) in the system

- arterial pressure:
  - before the filter (pre-filter)
  - target: -50 to -100mmHg (Suction is generated by the pump.)
  - Most frequent cause for arterial pressure < -100mmHg is a contact of the catheter with the vessel wall, which can usually be corrected manually.
- venous pressure:
  - after the filter (post-filter)
  - target: +50 to +150mmHg
- transmembrane pressure (TMP):
  - pressure gradient in the filter at the membrane, i.e. between the blood and fluid compartment
  - TMP = (filter pressure + inlet pressure) / 2 - outlet pressure
  - An increase in TMP (> 200mmHg) is the typical sign of clotting (decrease in membrane permeability due to clotting) of the filter. With a TMP > 300mmHg the filter must be changed.

Termination

- If the renal function recovers (usually the case), hemofiltration can be stopped. In the case of a spontaneous (i.e. without diuretics) diuresis > 500 ml/d, an omission attempt is justified (i.a. Uchino et al, Crit Care Med 2009). Be careful not to stop the hemofiltration too early. The elimination function (drainage [tubule function]) of the kidney recovers earlier than the detoxification function (glomerulum function])! Hemofiltration can only be stopped when this function has also recovered. It is not uncommon for the patient to experience muscle atrophy during a prolonged intensive care stay with the result that only little creatinine (Phosphorylation of the creatine formed in the liver takes place in the muscles.) can be produced, which can simulate a normal kidney function. Evaluation of the kidney function with cystatin C would make make sense here.
- If the renal function does not recover (this is rarely the case), but the patient is now circulatory stable, it can be switched to intermittent hemodialysis.

Special form: SCUF (slow continuous ultrafiltration)

- only ultrafiltration (= filtration of water due to a difference in pressure) of plasma water (only drainage), no detoxification
- only indicated in individual cases (e.g. in cardiac decompensation and simultaneous anuria [cardiorenal syndrome in the context of a cardiogenic shock]: Here, only the water should be removed.)

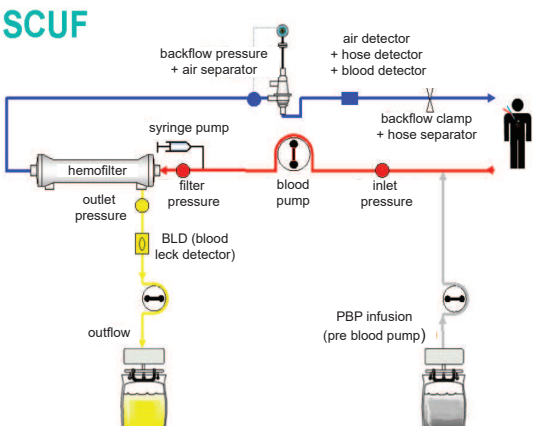


Fig. 1024 SCUF: slow continuous ultrafiltration [18]

The combination of hemodialysis and hemofiltration (CVVHDF) is most frequently used in the intensive care unit!

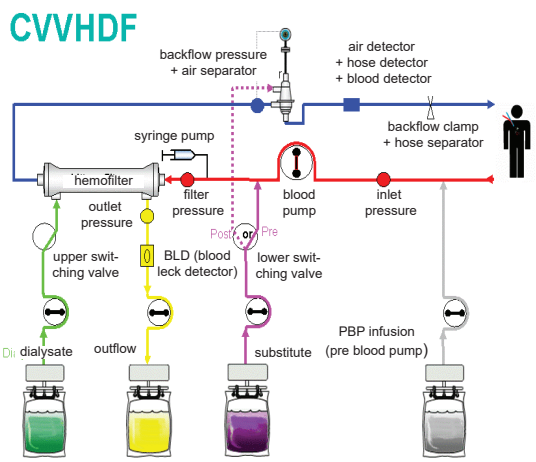


Fig. 1025 CVVHDF (hemodiafiltration) [18]

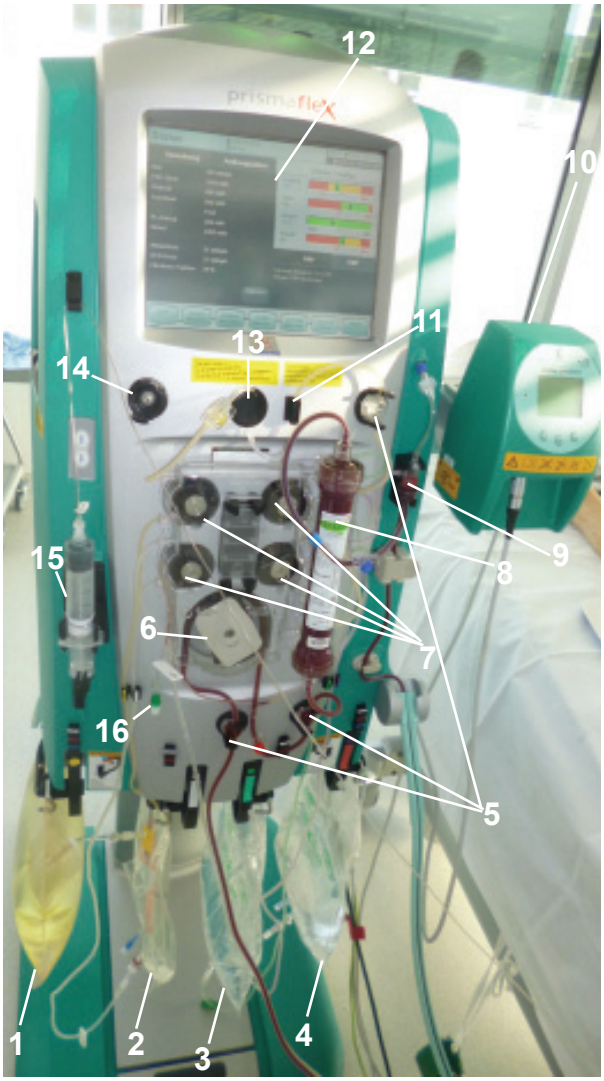


Fig. 1026 Construction: 1: drain bag, 2: citrate bag, 3 and 4: substitute bag, 5: pressure sensor, 6: pump for the blood, 7: pumps for the substitute and citrate, 8: hemofilter, 9: air bubble detector ("air trap"), 10: heating, 11: equipotential bonding, 12: operating window (touchscreen), display (prescription, anticoagulation, pressures), 13: blood leak detector (BLD; indicates leakage of erythrocytes; can be caused by a filter rupture [e.g. due to too high TMP]), 14: connection for MARS system (as additional module in acute liver failure), 15: syringe with calcium, 16: connection for heparin (if anticoagulation is performed with it [in our clinic it is performed with citrate])

Settings

(example for Prismaflex Gambro Hospal)

- substitute: Kalilactasol (electrolyte solution with lactate and potassium
- filter: Prismaflex M 100 (Pre)
- dilution method: predilution
- blood flow rate: start with 80ml/h and increase to at least 150 ml/h
- anticoagulation:
  - unfractionated heparin
  - 10000 IU of heparin-Na in 20ml NaCl 0.9% syringe → 500 E/ml
  - control according to ACT (activated clotting time): target 150-200s
  - Since 2011 we have introduced citrate anticoagulation in our clinic.
- mode: CVVHDF
- pump settings:
  - pre-blood pump: 200 ml/h
  - substitute pump: 800 ml/h
  - dialysate pump: 1000 ml/

SLED

- slow extended dialysis (sustainded low-efficiency dialysis)
- syn.:
  - PIRRT (prolonged intermittent renal replacement therapy)
  - Kolff dialysis (according to the Dutch internist Willem Johan Kolff [1911-2009]))
  - tank dialysis
- hybrid procedure of CVVH and IHD (intermittent hemodialysis)
- extended (8-12h) daily dialysis
- single-pass batch GENIUS system ("tank kidney"; Fresenius Medical Care)
- 90 litre tank for the dialysis fluid
- without industrially produced substitute solution (less expensive)
- low flow rates:
  - blood flow: 100-200 ml/min
  - dialysate flow: 100-200 ml/min
- evaluation (i.a. Kielstein et al, Am J Kidney Dis 2004) SLED versus CVVH:
  - equally effective (with regard to urea reduction)
  - equal hemodynamic stability
  - lower consumption of anticoagulants
  - In contrast to the CVVH, which runs 24 hours a day, here the patients are "free" for a few hours a day, so that for example CT transport trips or interventions can be carried out.
- citrate anticoagulation also possible here
- SLED is not a therapy mode which can be easily set on the device. If one decides in a hospital to accomplish a SLED, first the appropriate infrastructure, which is relatively complex (among other things storage of the tanks), must be created.

Sepsis-3 definition

- 3rd International Consensus Conference (Singer et al, JAMA 2016)
- 3rd sepsis definition
- definitions:
  - SIRS: abandoned (out; because too unspecific)
  - sepsis:
    - life-threatening organ dysfunction (p.d. SOFA score ≥ 2P. [or increase ≥ 2P.]; for SOFA score see page 592; for screening Quick-SOFA score recommended [qSOFA; see page 592]) caused by an inadequate response of the body to an infection
    - simplified: sepsis = infection (clinical / microbiological) + organ failure
  - severe sepsis: abandoned
  - septic shock: sepsis +
    - vasopressor necessary to maintain a MAP > 65 mmHg in persistent hypotension and
    - lactate > 2 mmol/l (or > 18 mg/dl)
    - despite sufficient fluid administration

new sepsis definition (Sepsis-3): Especially the organ dysfunction is in the foreground!

The disadvantage of the old definition with the SIRS criteria was certainly the low specificity. The advantage, however, was the high sensitivity, i.e. almost no patient with sepsis has been overlooked ("early warning system"). At most it only happened that one patient was admitted to the intensive care unit for one night for nothing. The disadvantage of the new sepsis definition, however, is that sepsis can only be recognized very late, i.e. only when organ failure has occurred, i.e. when "the horse has left the barn". The SIRS criteria are out as definition criteria for sepsis, but they are certainly still important criteria for an infection!

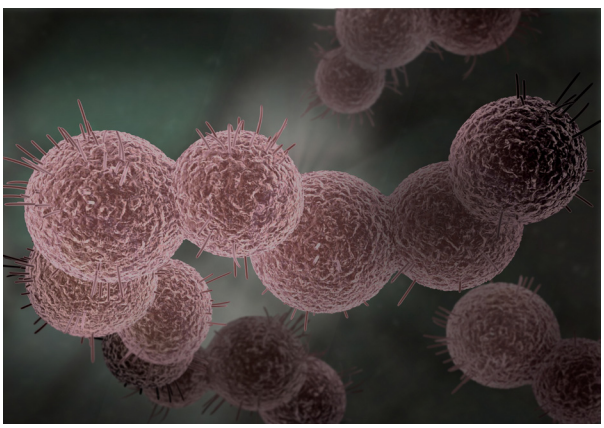
Epidemiology

- ⚠ sepsis: main cause of death on intensive care units
- incidence sepsis:
  - 300/100000
  - increasing
- incidences (according to ICD-10-GM; Heublein et al, Intensiv-News 4/13)
  - sepsis: 106/100000 (hospital mortality: 10.5%)
  - severe sepsis: 84/100000 (hospital mortality: 43%)
  - septic shock: 23/100000 (hospital mortality: 60.5%)
- severe sepsis / septic shock: 75,000 cases per year in Germany
- approx. 70,000 deaths per year in Germany (third most common cause in Germany; approx. 15,000 would be avoidable)
- the 5th leading cause of death worldwide (in 40% children < 5 years.; f > m [Rudd et al, Lancet 2020])
- ⚠ 30% of all intensive care patients (sepsis in every 3rd patient in intensive care units!)
- median age: 67 years
- acquisition:
  - in 50% community acquired
  - in 50% hospital acquired (nosocomial; mostly VAP)
- SIRS → in 6% septic shock
- 😕 47 percent of the community never heard the term „sepsis“ although incidence and mortality is comparable to myocardial infarction (also 300/100000; Rubulotta et al, Crit Care Med 2009).
- costs: 5.8 billion euros annually (Germany)
- sepsis resolution of the WHA (World Health Assembly; the decision-making body of the WHO [World Health Organization]) at 26/05/2017: classification of sepsis as a health problem to combat with priority

Sepsis: main cause of death in intensive care units!

Every 6-7 minutes a person dies of sepsis (in Germany)!

Etiology



- ⚠ pneumonia (most common cause at all of sepsis, escpecially ventilator associated pneumonia [VAP])
- surgical infection (perioperative), intraabdominal focus; peritonitis (classification see infobox; most common germs: E. coli [No.1], Bacteroides fragilis [No.2], anaerobic germs; mostly mixed infections; note: Pseudomonas does not play a pathogenic role in this case!)
- cholangitis, cholezystitis, Mirizzi syndrome (→ cholangiosepsis)
- pancreatitis
- meningitis, encephalitis
- urogenital (→ urosepsis)
- endocarditis

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

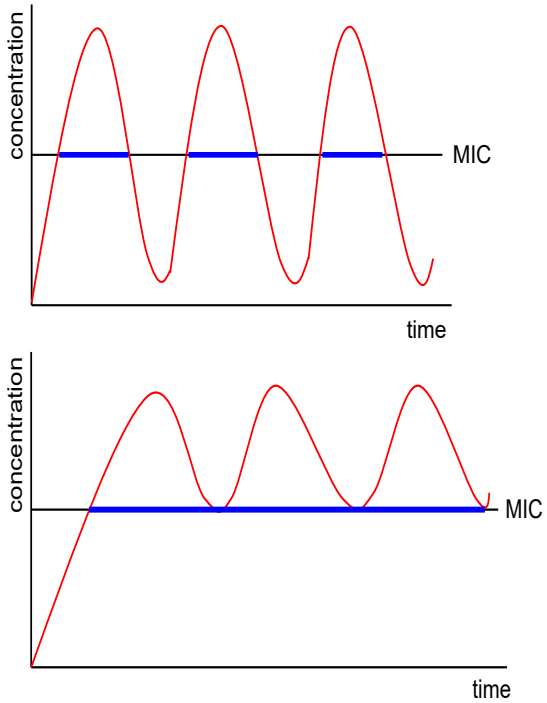


Fig. 798 The pharmacodynamics of time-dependent antibiotics are shown here. The time in which the concentration is above the MIC (minimum inhibitory concentration) is decisive for their effectiveness. This time (shown in blue in the graphic) is significantly shorter with only three bolus doses (top) 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%)

Antibiotics
classes

- β-lactams
  - penicillins
  - cephalosporins
    - oral (note:
    - almost no oral bioavailability and therefore almost no importance)
    - parenteral
  - carbapenemes
  - monobactames: aztreonam (Azactam)
- fluorchinolones (gyrase inhibitors)
- macrolides
- aminoglycoside
- oxazolidinones
  - linezolid (Zyvoxid)
  - tedizolid (Sivextro)
  - radezolid
- glycopeptides
  - vancomycin
  - teicoplanin (Targocid)
- lipoglycopeptides
  - telavancin (Vibativ)
  - dalbavancin (Xydalba)
  - oritavancin (Orbactiv)
- tetracyclines
  - tetracyclin
  - minocyclin (Minocin)
  - doxycyclin (Vibravenös)
- glycylcyclines: tigecycline (Tygacil)
- polymyxines
  - polymyxin B
  - polymyxin E (= colistin)
- other:
  - sulfonamides (folic acid antagonists): cotrimoxazole (trimethoprim sulfonamide [Bactrim, Cotrim])
  - lipopeptides: daptomycin (Cubicin)
  - lincosamides: clindamycin (Sobelin)
  - nitroimidazoles: metronidazole (Clont)
  - nitrofuranes: nitrofurantoin
  - epoxides: fosfomycin (Infectofos)
  - ansamycines: rifampicin (Eremfat)
  - streptogramines: quinupristin-dalsopristin (Synercid)

Penicillins

- benzyl penicillin: penicillin G
- phenoxymethyl penicillin: penicillin V (Oralpenicillin; Propicillin)
- amino penicillins
  - ampicillin (Glycylcyclin)
  - amoxicillin (Amoxypen)
  - pivmecillinam (X-Systo)
- isoxazolyl penicillins (syn.: carboxy penicillins, staphylococcal penicillins)
  - oxacillin (Stapenor, InfectoStaph)
  - flucloxacillin (Staphylex)
- acylamino penicillins (syn.: acylureido penicillins)
  - mezlocillin (Baypen)
  - piperacillin (Pipril)
- methoxy penicillin: temocillin (Temopen; only effective in the gram-negative range [not against pseudomonas, anaerobes, acinetobacter])

β-lactamase inhibitors

- clavulanic acid (Augmentan = amoxicillin + clavulanic acid)
- sulbactam
  - Unacid = ampicillin + sulbactam
  - Pipril / Combactam = piperacillin + sulbactam
- tazobactam (more effective than sulbactam [in vitro])
  - Tazobac = piperacillin + tazobactam
  - Zerbaxa = ceftolozane + tazobactam
- avibactam (Zavicefta = ceftazidime + avibactam)
- vaborbactam (Vabomere = meropenem + vaborbactam)
- relebactam (Recarbio = imipenem + cilastatin + relebactam)

LeoPARDS study

Levosimendan for Prevention of Acute Organ Dysfunction in Sepsis
Gordon et al, N Engl J 2016

- multicenter randomized controlled study
- 516 patients with septic shock who had been treated with vasopressors for > 4h:
  - levosimendan
  - placebo
- 🙁 results: levosimendan
  - primary endpoint (SOFA score): no difference
  - sekundary endpoints: i.a.
    - mortality: no difference
    - less fequent successful weaning (longer duration of ventilation)
    - more frequent arrhythmia (supraventricular tachycardia)
- note: The majority of patients had no septic cardiomyopathy, and exactly for those levosimendan would have made sense to increase inotropy. Therefore in my opinion levosimendan is still an alternative to dobutamine in patients with septic shock and septic cardiomyopathy.

Vasopressin (Pitressin)

- a hormone (syn.: ADH [antidiuretic hormone])
- as an alternative vasopressor to noradrenaline (e.g. in case of massively reduced SVR and severe acidosis where noradrenaline is less effective)
- maybe as rescue medication (ultima ratio)
- reduced vasopressin levels in sepsis
- vasopressin analogue: argipressin (Empressin)
  - approved since 2015 in Germany for the therapy of catecholamine refractory septic shock
  - dosage:
    - 1 Amp. = 2ml = 40 IE
    - perfusor: 1 ampoule a 2ml + 48ml NaCl 0.9% → 0.8 IE/ml
    - initially 0.6 IE/h (0.75 ml/h), then every 15min increase if necessary to 1.2 IE/h (1.50 ml/h) up to a maximum of 1.8 IE/h (2.25 ml/h)
  - pulmonary artery pressure (PAP) ↓, pulmonary vascular resistance (PVR) ↓
- studies:
  - VASST (see box)
  - VANISH (see box)
  - VANCS (in postoperative cardioplegic syndrome in cardiac thoracic surgery [see page 402])
  - meta-analysis (Polito et al, Intensiv Care Med 2012): no reduction in mortality
- recommendations:
  - international (SSC guideline2016): recommended (but only weakly) in therapy-refractory cases in addition to noradrenaline (note: from noradrenaline > 0.3 µg/kg/min [corresponds to 1.3 mg/h with a body weight of 72kg], early [within 6 hours after initiation of noradrenaline])
  - national:
    - S2k guideline 2010: not recommended
    - S3 guideline 2018: weak recommendation in therapy-refractory cases in addition to noradrenaline
- We administer argipressin (empressin) in the rare cases of a severe therapy-refractory vasodilatory (mostly septic) shock, in which despite high-dose (p.d.> 1.3 mg/h) noradrenaline and hydrocortisone, there is still a massively reduced systemic vascular resistance (SVR).
- other vasopressin analogues
  - terlipressin (glycylpressin): not recommended because it mainly causes selective vasoconstriction only in the splanchnic area and not systemically (furthermore no benefit proven [Liu et al, Intensive Care Med 2018; see box])
  - selepressin (a selective vasopressin V1a-receptor agonist): no effect in septic shock (SEPSIS-ACT study [Laterre et al, JAMA 2019])

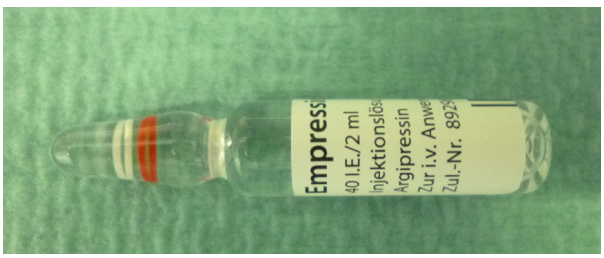


Fig. 799 empressin (1 amp. = 2ml = 40 IE)

VASST study

Vasopressin versus Norepinephrine Infusion in Patients with Septic Shock
Russell et al, N Engl J 2008

- multicenter randomized controlled study
- 778 patients with septic shock; vasopressor:
  - noradrenaline
  - vasopressin
- 😐 result: vasopressin → no difference in mortality (neither after 28 nor after 90 days); note: In a posthoc analysis of the subgroup of patients with only mild septic shock (i.e. noradrenaline 5-15 µg/kg/min), however, vasopressin showed a reduction in mortality.

CITRIS-ALI study

Effect of Vitamin C Infusion on Organ Failure and Biomarkers of Inflammation and Vascular Injury in Patients With Sepsis and Severe Acute Respiratory Failure
Fowler et al, JAMA 2019

- multicenter randomized placebo-controlled study (phase II)
- 167 patients with sepsis and ARDS (requiring ventilation)
  - high-dose vitamin C infusion 50 mg/kg 4 x daily over 4 days
  - placebo
- results: vitamin C
  - primary endpoints (organ failure, decline in biomarkers for inflammation [CRP] and vascular injury [thrombomodulin]): no difference
  - secondary endpoints:
    - mortality after 28d: significantly reduced
    - length of ICU stay: significantly reduced
    - length of hospital stay: significantly reduced
    - all other secondary endpoints (i.a. oxygenation index, creatinine, vasopressor therapy): no difference
- note: The study had 49 endpoints, 46 of which were negative.

ACTS study

Effect of Ascorbic Acid, Corticosteroids, and Thiamine on Organ Injury in Septic Shock
Moskowitz et al, JAMA 2020

- ACTS: Ascorbic Acid, Corticosteroids and Thiamine in Sepsis
- multicenter randomized placebo-controlled study
- 200 patients with septic shock
  - over 4 days 4 x daily i.v. each vitamin C (ascorbic acid) 1500mg, thiamin 100mg and hydrocortisone 50mg
  - placebo
- results:
  - primary endpoint (decrease in SOFA score, i.e. improvement of organ dysfunction): no difference
  - secondary endpoints: especially
    - mortality after 30d: no difference
    - kidney failure after 30d: no difference

Fig. 802 The cemetery of adjunctive sepsis therapy: All of this meanwhile is buried here!

study

The Surviving Sepsis Campaign: results of an international guideline-based performance improvement program targeting severe sepsis
Levy et al, Crit Care Med 2010

- therapeutic bundles (SSC 2004)
  - resuscitation bundles (< 6h)
  - management-Bundles (6-24h)
- 15002 patients, 165 intensive care units, 30 countries
- implementation in only 31%

study

Improvement in Process of Care and Outcome After a Multicenter Severe Sepsis Educational Program in Spain
Ferrer et al, JAMA 2008

- training of 59 intensive care units in Spain in sepsis therapy according to the SSC guidelines (average 10.5 hours)
- result: significant reduction in mortality

Scores

SOFA score (Sepsis-related Organ Failure Assessment)

organ	parameters	1	2	3	4
lung	paO_2/FiO_2 mmHg	400-300	300-200	200-100 with ventilation	< 100 with ventilation
kidney	creatinine (mg/dl) diuresis (l/d)	1.2 -2.0 normal	2.0 - 3.5 normal	3.5 - 5.0 < 500	> 5.0 < 200
liver	bilirubin (mg/dl)	1.2 - 2.0	2.0 - 6.0	6.0 - 12.0	>12.0
heart/ circulation	BB (mmHg) catecholamines	MAP < 70	catecholamines low	catecholamines moderate	catecholamines high
blood	platelets per nl	< 150	< 100	< 50	< 20
CNS	GCS	14-13	12-10	9-6	< 6

SOFA score: 0P. → mortality 1%, 1P. → mortality 3%, 2P. → mortality 8-10%, 3P. → mortality > 20%

new sepsis definition (Sepsis-3): i.a. SOFA score ≥ 2P. (or increase ≥ 2P.)

The SOFA score is meanwhile a central component in the new sepsis definition (sepsis-3 definition). However, since no one can remember the score, it makes sense to implement it in the PDMS (patient data management system) in the intensive care unit.
A quick SOFA score (qSOFA; see infobox) was also introduced as part of the sepsis-3 definition (Seymour et al, JAMA 2016): This is especially recommended as a screening tool for the preclinical, emergency department and normal ward, since here the use of the classic SOFA score is not as widespread and common as in the intensive care unit.

Quick-SOFA score
qSOFA

- **only 3 parameters:**
  - **respiratory rate ≥ 22/min**
  - **changed consciousness (GCS < 15)**
  - **SBP < 100mmHg**
- **positive if 2 of the 3 criteria are met**
- **If 2 of the 3 criteria are met, the classic SOFA score should be determined.**
- **for screening only (no diagnostic criterion for sepsis)**
- **high specificity, but only low sensitivity (only 60%, i.e. 40% not covered; note: in contrast to the SIRS criteria [low specificity, but high sensitivity])**
- **recommended for preclinical, emergency department, normal ward (not for intensive care)**
- **prognosis:**
  - **2 criteria met → 4-fold increased mortality**
  - **3 criteria met → 14-fold increased mortality**
- **calculator: www.qsofa.org (risk in % for poor outcome)**

SIRS criteriea: high sensitivity, low specificity
qSOFA: low sensitivity, high specificity

MOF-score according to Goris

	0	1	2
lung failure	no ventilation	ventilation with FiO_2 < 0.40	ventilation with FiO_2 > 0.40
heart / circulation failure	BB normoton without support	BB normoton with fluid administration	requiring catecholamines
kidney failure	creatinin < 2 mg/dl	creatinin > 2 mg/dl	RRT (CVVH, HD)
liver failure	bilirubin < 2 mg/dl, GOT < 25 U/l	bilirubin 2-6 mg/dl, GOT 25-50 U/l	bilirubin > 6 mg/dl, GOT > 50 U/l
coagulation failure	platelets normal	platelets < 50/nl	hemorrhagic diathesis
CNS failure	none	slightly limited responsiveness	severely limited responsiveness
gastrointestinal failure	normal	cholecystitis, stress ulcer	Stress ulcer bleeding, NEC, pancreatitis, perforation of gall bladder

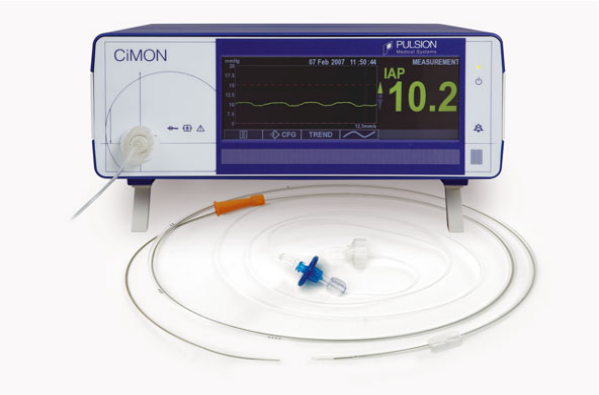


Fig. 809 CiMON system: continuous measurement of intra-abdominal pressure indirectly by measuring the intra-gastric pressure [30]

generous measurement of IAP in ICU (especially in case of unclear organ failure)!

Degrees of severity

degrees of severity	IAP (intra-abdominal pressure)
I	12-15 mmHg
II	16-20 mmHg
III	21-25 mmHg
IV	> 25 mmHg

Therapy

- conservative: i.a.
  - prokinetic agents, rectal enema, if necessary decompression probe
  - reduction or abandonment of enteral nutrition
  - flat positioning
    - This improves the compliance of the abdominal wal.
    - Elevation of the upper body is contraindicated here because the flexion in the hip joint can increase the intra-abdominal pressure.
    - Alternatively, anti-Trendelenburg positioning can be used for these patients.
  - removal of tight abdominal bandage (after abdominal surgery)
  - sufficient analgosedation (A pain-related increased tone of abdominal muscles increases the intra-abdominal pressure.)
  - possibly ascites puncture (if present)
  - The higher the IAP the higher the PEEP level during mechanical ventilation should be set (extrathoracic restriction!).
- surgical (in refractory cases): surgical decompression (decompressive laparotomy) followed by temporary abdominal closure (TAC; standard today in VAWCM technique ([vacuum assisted wound closure and mesh mediated fascial traction])

Septic cardiomyopathy

Definition

- term inaugurated by Schuster in 1989
- a secondary cardiomyopathy
- insufficiently increased or even decreased cardiac output relative to the distinctly reduced systemic vascular resistance SVR ("vasoplegia")
- Often, septic cardiomyopathy is not diagnosed because the cardiac output, which is often still normal, is considered in isolation without the SVR. However, in relation to the massively decreased systemic vascular resistance (SVR; afterload) it is far too low. Therefore cardiac output has always to be set in relation to the reduced afterload (SVR; afterload-related cardiac output).
  - ACP (afterload-related cardiac performance):
    - In the study of Werdan et al (Septic cardiomyopathy: hemodynamic quantification, occurrence, and prognostic implications; Clin Res Cardiol 2011) the measured cardiac output was set in relation to normal cardiac output (for a distinct SVR in each case). This quotient was designated ACP (afterload-related cardiac performance; unit: percentage of the normal value).
    - $ACP = CO_{measured} / CO_{normal}$
    - $CO_{normal} = 560.68 \times SVR^{-0.64}$
    - With ACP < 80% there is septic cardiomyopathy.
    - The lower the ACP, the higher the mortality (i.a. ACP 60-80% → mortality 36%, ACP 40-60% → mortality 67%).
  - In the clinical routine we like to use the product of CO and SVR respectively (related to the body surface) CI x SVRI. The product of cardiac index (unit: $l/min/m^2$) and systemic vascular resistance index SVRI (unit: dyn x sec x cm^{-5} x m^{-2}) CI x SVRI / 60 should be > 100 l x dyn x cm^{-5} x m^{-4}. If the product of CI x SVRI / 60 undershoots this threshold, septic cardiomyopathy is present (annotation: own experience value useful in daily practice, no scientific evidence for this).
- commonest cause of death in sepsis: cardiogenic shock caused by septic cardiomyopathy
- anyway the commonest cause of death in ICU!
- maybe daily ECG (unspecific signs of ischemia) and troponin (note: not very helpful)

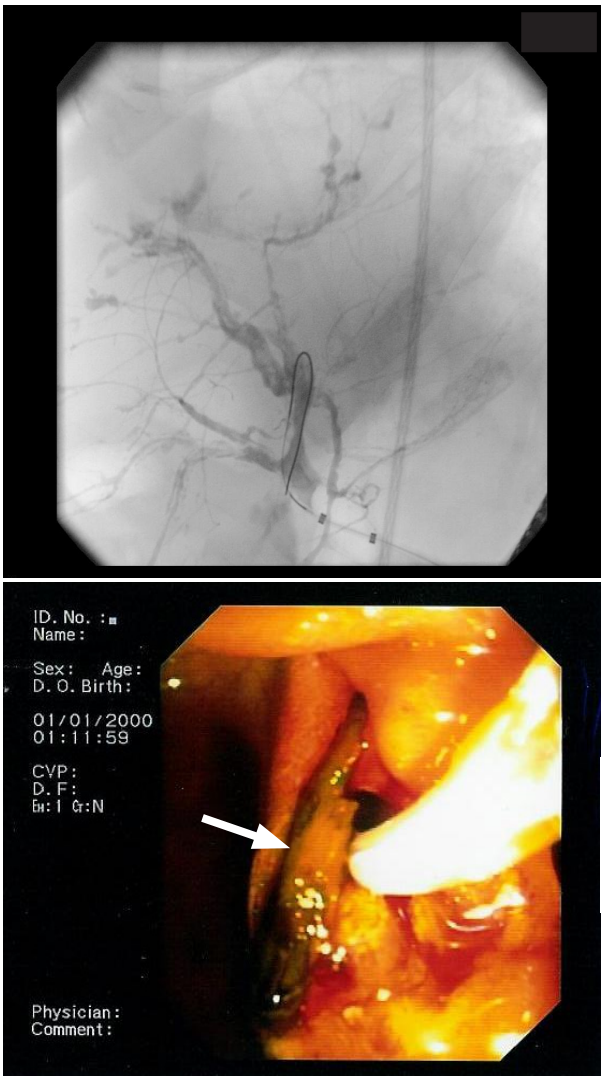


Fig. 812 ERCP: The typical picture of a biliary-cast syndrome with poured out lumps in the bile ducts can be seen. Some of these casts could at least be removed from the common bile duct (DHC; see arrow). However, they still remain in the small bile ducts, so that the endoscopic removal of these lumps is usually only a purely cosmetic measure.

Differential diagnoses

- primary sclerosing cholangitis (PSC)
  - most common in patients with ulcerative colitis
  - laboratory: pANCA ↑
- IgG4 associated sclerosing cholangitis (can immitae exactly the same picture and ican be treated with steroids very effeticely; therefore always determine IgG4 levels in the serum)

Therapy

- ursodesoxycholic acid (10-15 mg/kg p.o.)
- antibiosis in case of infection
- liver transplantation if necessary

Prognosis

- ⚠ mortalitity: 50% (Voigtländer et al, Endoscopy 2012)
- median survival time: 13 months (Ruemmele; Nat Rev Gastroenterol Hepatol 2009)

Diagnostics

- sonography: i.a. resistance index (RI; syn.: Pourcelot index) in the hepatic artery $(v_{sys} - v_{dias}) / v_{sys}$ > 0.8 indicates reduced liver perfusion
- laboratory

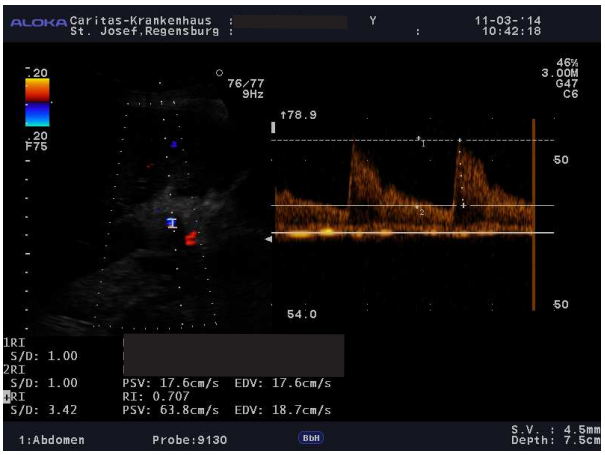


Fig. 813 determination of the resistance index RI (syn.: Pourcelot index) in the hepatic artery by determination of the maximum systolic velocity and the end-diastolic velocity; RI = $(v_{sys} - v_{dias}) / v_{sys}$; RI > 0.8 indicates a reduced liver perfusion

Laboratory

- static tests:
  - bilirubin
    - ⚠ pragmatic p.d. liver dysfunction from bilirubin > 4 mg/dl (septic cholestasis; note: An increase in liver function tests [transaminases, µGT] can be found relatively frequently in ICU. This is usually due to drug-toxicity [mainly due to antibiotics]. As rule of thumb for the clinical everyday life with an increase of liver function tests one can remember: If bilirubin is not elevated, it is usually harmless [Hy's law]).
    - ⚠ Typically the direct (conjugated) bilirubin is increased. The conjugation still works, but energy-dependent excretion and transport processes no longer work (typically intrahepatic cholestasis!).
  - GOT (= AST), GPT (= ALT)
  - parameters of liver synthesis
    - Quick < 50% resp. INR > 1.5
    - albumin ↓ (half-life 19 days → reacts only very slowly → subordinated significance in acute liver failure)
    - cholinesterase ↓ (half-life 14 days → reacts only very slowly → subordinated significance in acute liver failure)
    - factor V (activity) ↓
- dynamic tests:
  - ICG clearance
  - LiMAx test
  - MEGX test

Fig. 1103 skin emphysema: Air accumulates in the subcutaneous fatty tissue. The patients seem massively bloated In addition to the neck, thorax, trunk and extremities, the face (especially the eyelids [it may not be possible to open the eyes]; the nose is usually left out) and the scrotum are particularly affected. Classically, you can palpate a crackling on the thorax. Although it looks frightening, it is usually harmless and, if the triggering cause has been eliminated, usually disappears again quickly. If skin emphysema occurs with an already inlying thoracic drainage, you should check that the drain is not dislocated: If this slips out a little, it may be that the side holes of the drainage are no longer in the pleural space, but in the subcutaneous fatty tissue and thus cause the skin emphysema. Then you just have to push the drainage back into the pleural space.

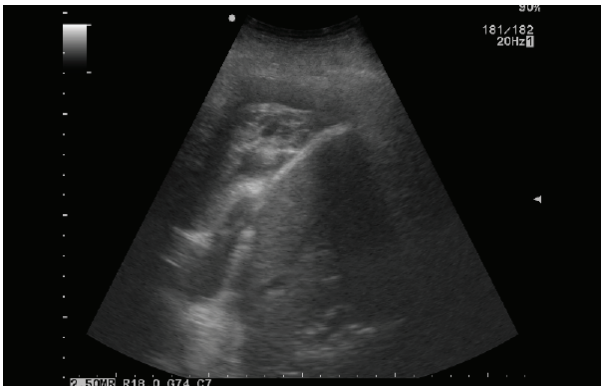


Fig. 1104 pleural sonography for a hemothorax: An organized hematoma can already be seen.

Pneumothorax
pitfalls in X-ray

There are several important differential diagnoses of pneumothorax in the chest X-ray (pitfalls). You must not fall for this, otherwise you will unnecessarily place a thoracic drainage and thus endanger the patient. In case of any doubt one should generously perform a chest CT (without contrast medium, completely sufficient).

- skin fold (In contrast to the pneumothorax, the pulmonary vessels are still visible up to the periphery here.)
- ccapula (medial edge)
- large emphysema bulla (example for a chest x-ray see page 692)
- cavern (e.g. in case of tuberculosis)
- pleural effusion in the interlobar gap (e.g. after pleural puncture and subsequent x-ray control)
- pneumothorax e vacuo: This occurs as a complication of a segmental occlusion, e.g. due to mucus, foreign bodies or too deep a position of the tube. In this segment, the intrapleural pressure increases with the result that air accumulates in the pleural space. Bronchoscopy is the therapy of choice here, thoracic drainage is not indicated.

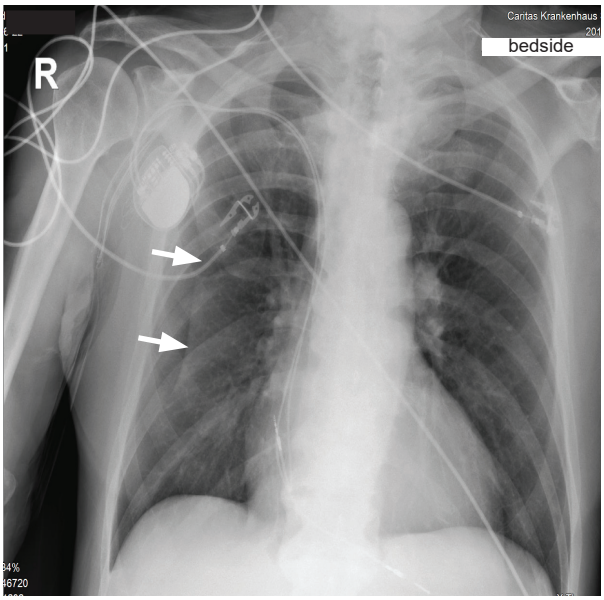


Fig. 1105 pitfall skin fold (here routine chest x-ray after the implantation of a permanent pacemaker): On the right, there is no pneumothorax, just a skin fold (see arrows). The line runs over the lung border, furthermore the vessels can be seen up to the periphery.

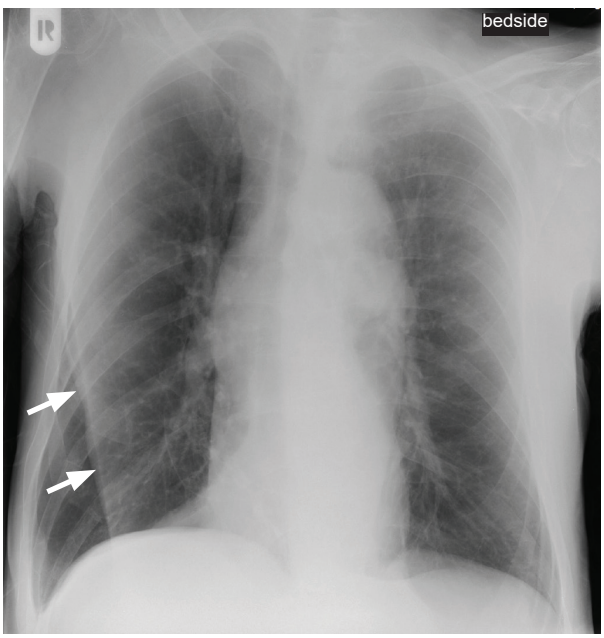
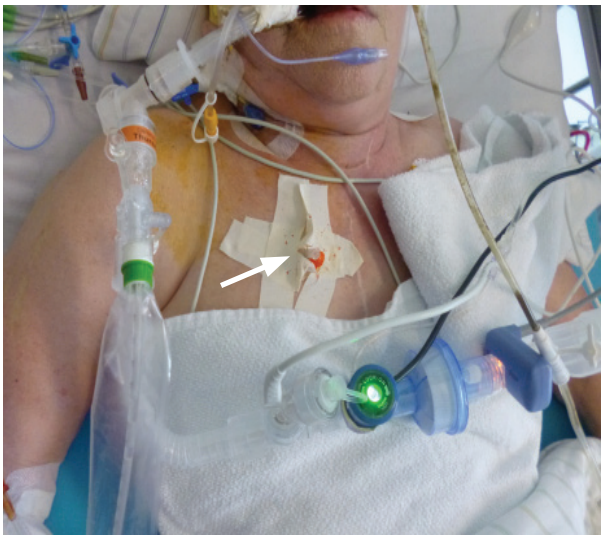


Fig. 1106 pitfall skin fold: On the right, there is no pneumothorax, but just a skin fold (see arrows). The vessels can be seen up to the periphery.



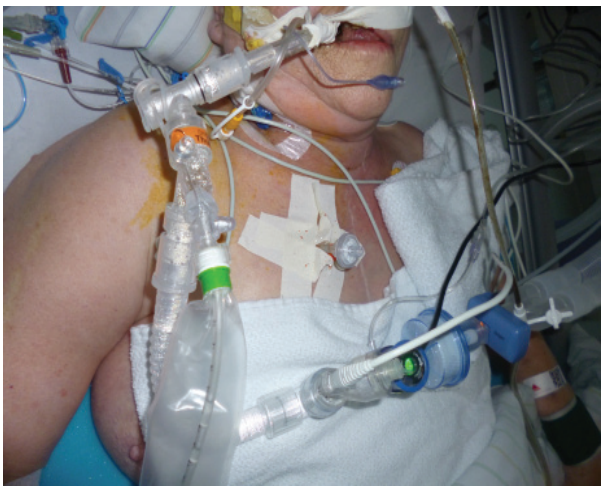


Fig. 1110 The patient suddenly had a ventilation problem: The respirator couldn't get any more air into the patient, she had to be ventilated manually by the hand (Ambu bag). The saturation kept falling. Furthermore there was a breakdown of the circulation, the catecholamine perfusors were turned up 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!)

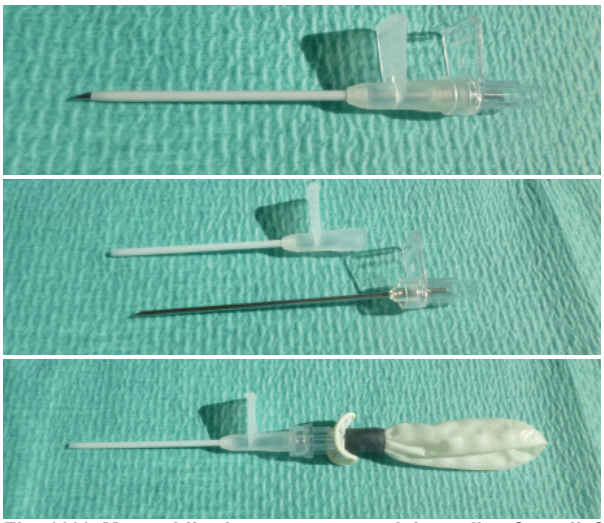


Fig. 1111 Meanwhile the are now special needles for relief puncture in a tension pneumothorax on the market. They have the advantage over peripheral venous cannulas that they are longer. In the last picture a Heimlich valve is attached, but this is not absolutely necessary in practice.

Localization

- according to landsmarks:
  - Bülau drainage (named after the German internist Gotthard Bülau [1835-1900]): 4th ICS, anterior axillary line (⚠ to be preferred; never below 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; 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)

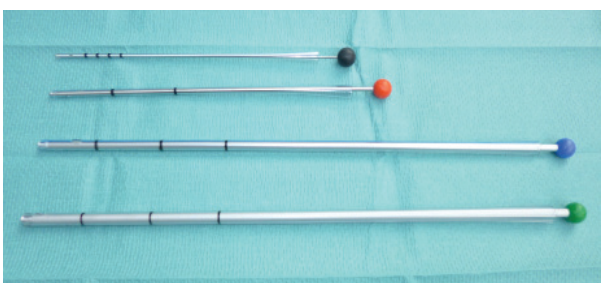
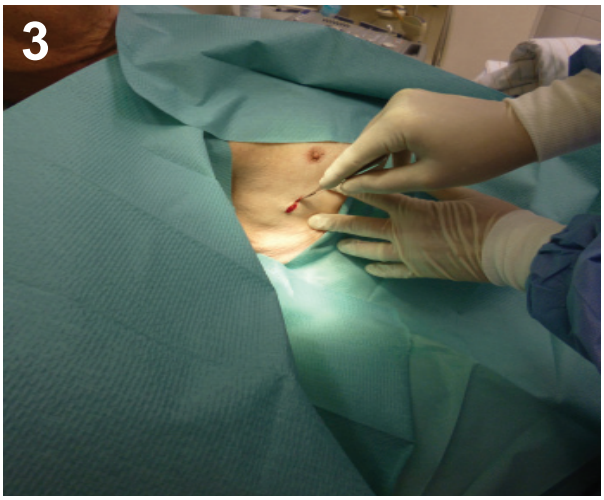


Fig. 1112 Thoracic drainage catheters (chest tubes) with trocar in different sizes: black (10Ch), orange (16Ch; mostly sufficient for pneumothoraces), blue (24Ch; mostly sufficient for pleural effusions), green (28Ch)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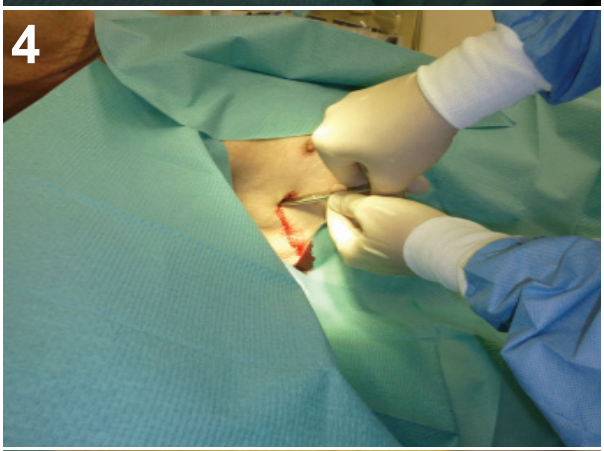
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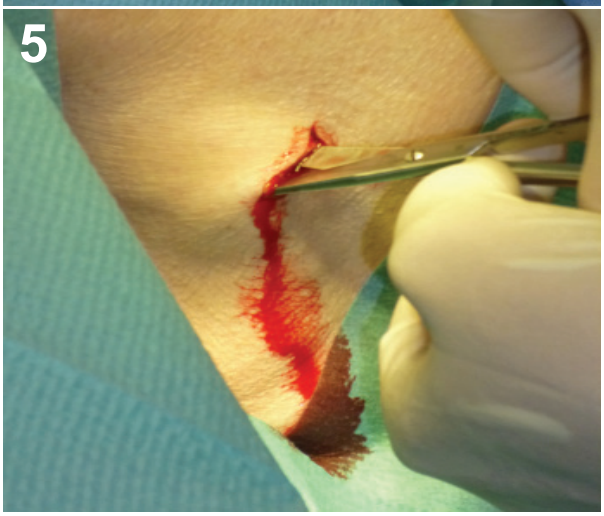
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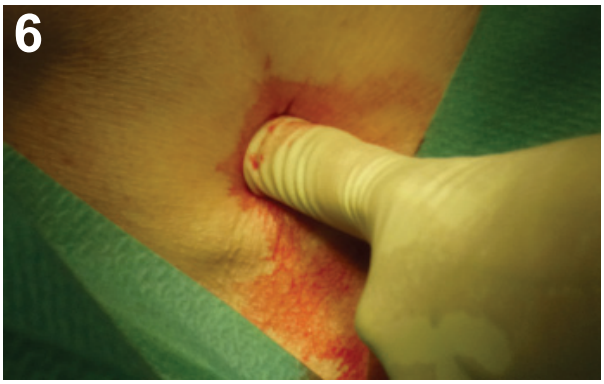
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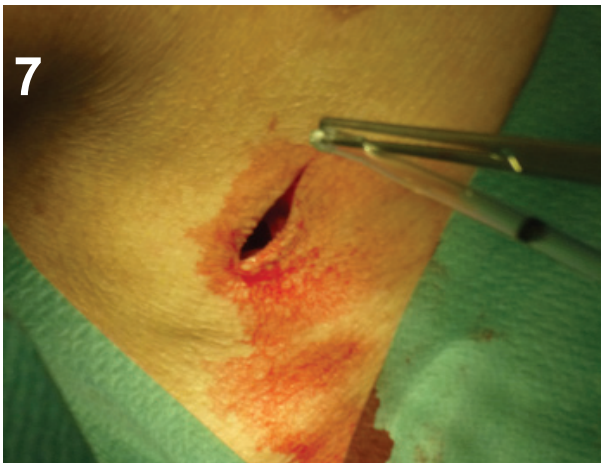
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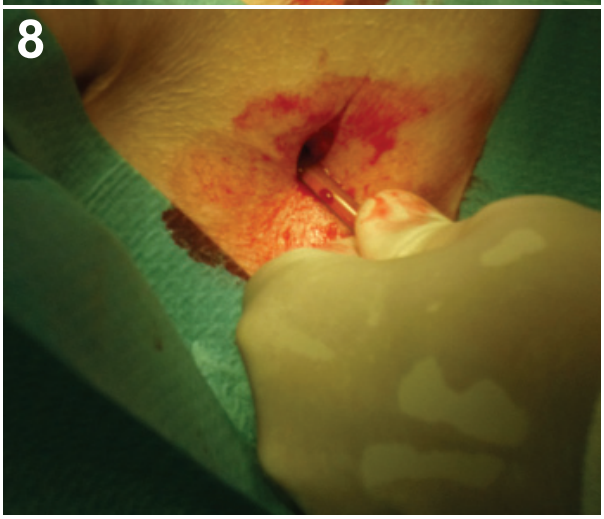
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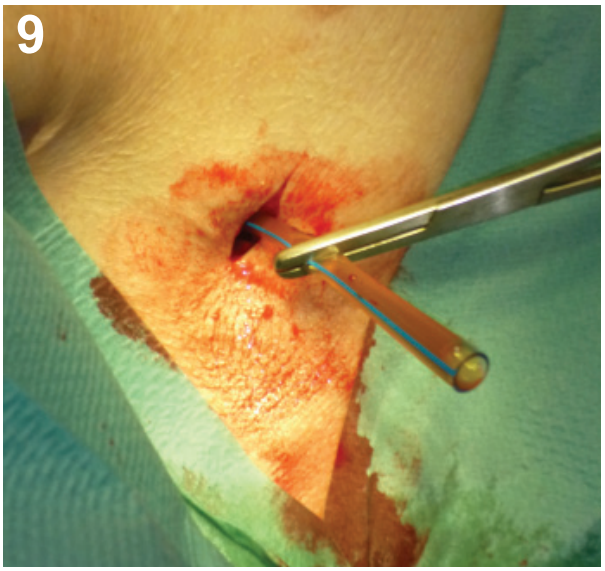
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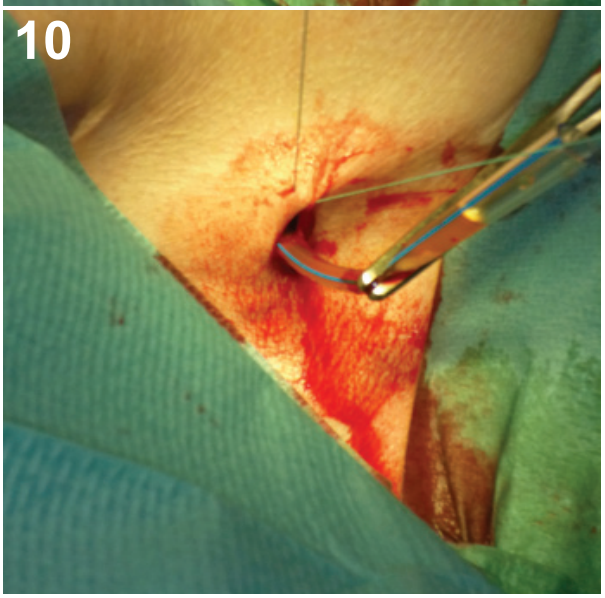
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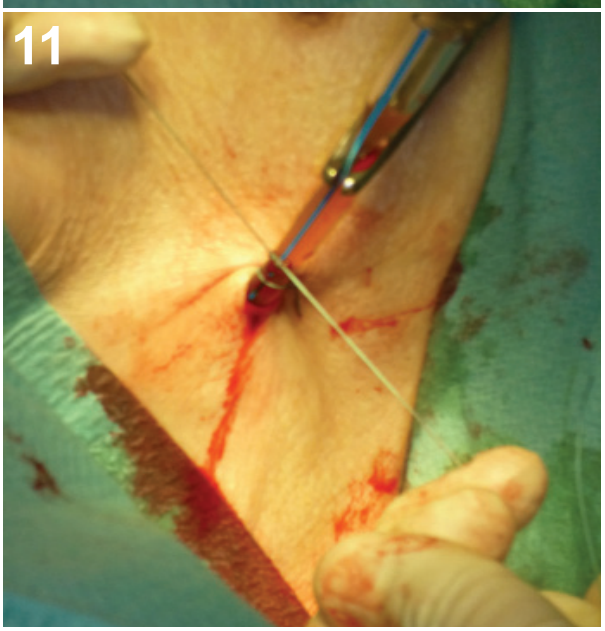
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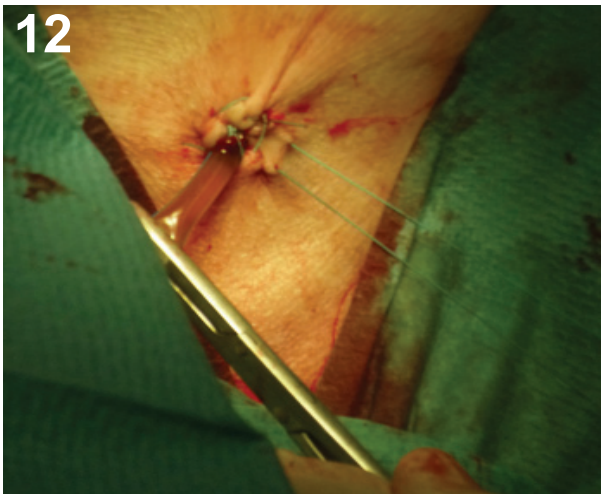
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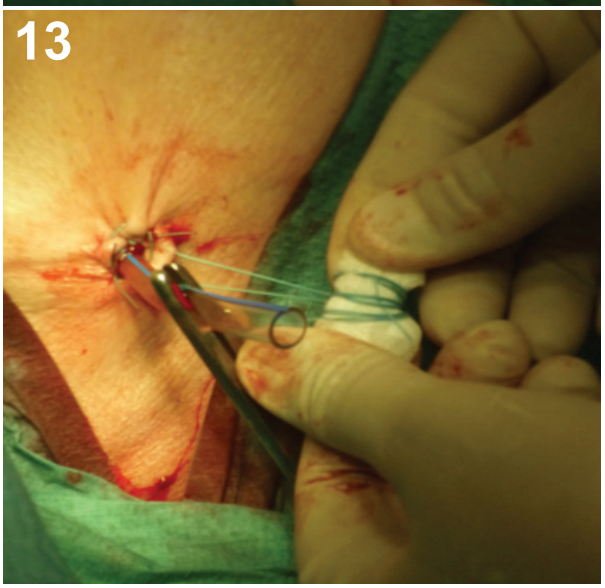
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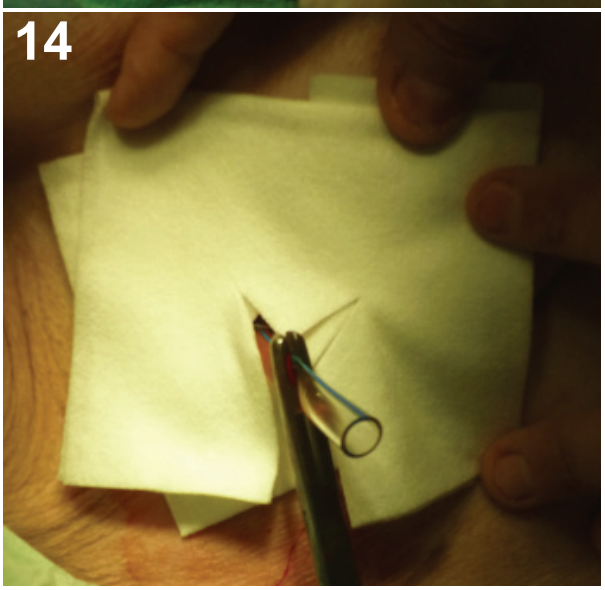
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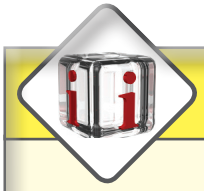
Excursus: Thoracic sonography pneumothorax

The domain of pneumothorax diagnostics is usually X-ray. In the case of a lying patient (the classic intensive care patient), however, the chest X-ray image has only a low sensitivity, so that usually only a very pronounced pneumothorax can be excluded by X-ray. Otherwise an inconspicuous chest X-ray in a lying patient does not exclude a pneumothorax at all! A chest X-ray is only suitable for excluding a pneumothorax in a standing patient. Especially in a lying patient thoracic sonography is clearly superior to X-ray: In a meta-analysis (Wilkerson et al, Academic Emergency Medicine 2010) there could be shown that sonography (with the same specificity) has a significantly higher sensitivity in the diagnosis of a pneumothorax than X-ray. In another meta-analysis (Alrajhi et al, Chest 2012), sonography showed a sensitivity of 91%, X-ray only of 50%. Thoracic sonography in the intensive care unit is also explicitly recommended especially on the question of pneumothorax and infiltrates (International evidence-based recommendations for point-of-care lung ultrasound; Volpicelli et al, Intensive Care Med 2012).

Chest X-ray in a lying patient excludes only a (very) large pneumothorax

In lying patients (typically intensive care patients), sonography is superior to X-ray in the diagnosis of pneumothorax!

A linear transducer (7.5 MHz) is best used for thoracic sonography. In thoracic sonography, one works with artifacts: These are desired here, so that all improvement modes (e.g. THE [tissue harmonic imaging]) that suppress artifacts should be switched off on the ultrasound device. The classical sonographic signs of a pneumothorax are the missing pleural sliding (breath dependent movement of the pleura [echo rich band]; "like running ants") and the missing B-ligns ("comet tail", "flashlight" phenomen). If B-lines are shown, a pneumothorax is excluded. Furthermore, in pneumothorax the pulse-synchronous movement of the pleura (lung pulse) is missing. The point where the pleural sliding and the B-ligns reappear, i.e. where the lung is again closed to the thoracic wall and no pneumothorax is present, is called the lung point. Air always collects at the highest point in the thorax, which is the sternum in lying patients. If the pleural sliding and B-ligns can be detected sonographically there, a pneumothorax is excluded! The easiest and fastest of all is to put the M-mode through the pleura: If the seasore sign (normal finding) appears, no pneumothorax is present. If the stratosphere sign appears, a pneumothorax is present.



Pneumothorax
sonographic signs

- **absent pleural sliding (= breath synchronous movement of the pleura)**
- **absent lung pulse (= pulse synchronous movement of the pleura)**
- **absent B-lines ("comet tail", "flashlight" phenomenon)**
- **M-mode: absent "seashore-sign" (granular pattern below the pleural line; normal finding), but present stratosphere sign (repetitive echoes in the form of hyperechoic parallel bands dorsal to the pleural line)**

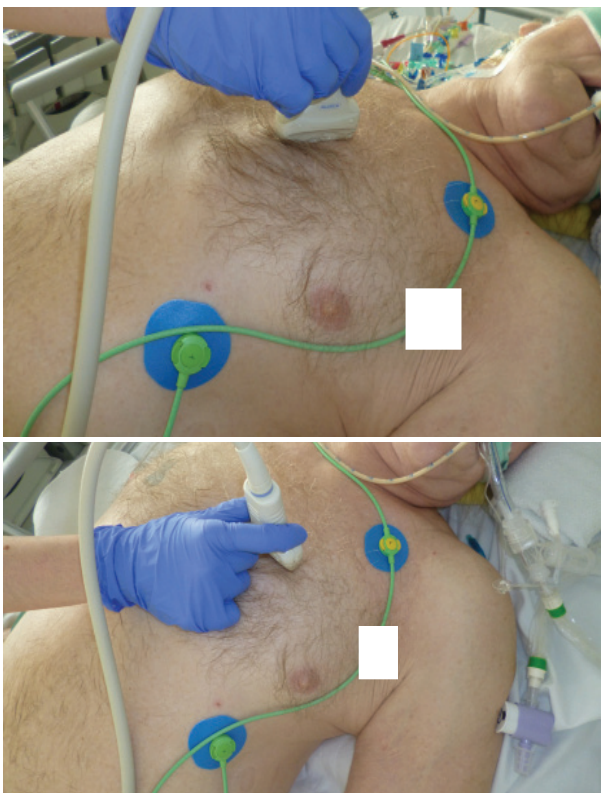


Fig. 1130 Thoracic sonography (first image: cross section to rib, second image: longitudinal section to rib): The linear transducer is placed at the highest point of the thorax. This is the sternum in case of a lying patient. For the question of a left-sided pneumothorax, the transducer is placed parasternally left, for the question of a right-sided pneumothorax, the transducer is placed parasternally right.

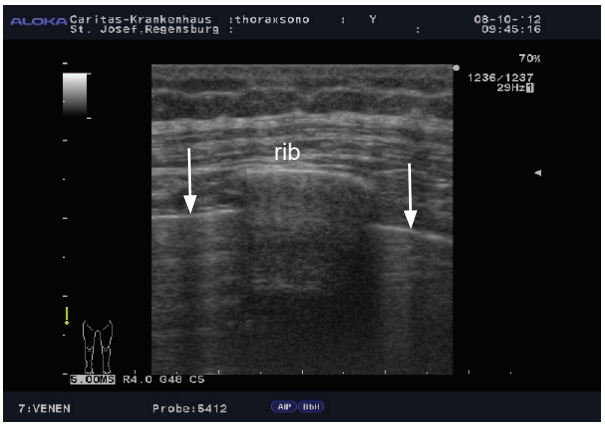


Fig. 1131 Thoracic sonography (cross section): Pleura (echo-rich band; see arrows), rib with posterior acoustic shadowing

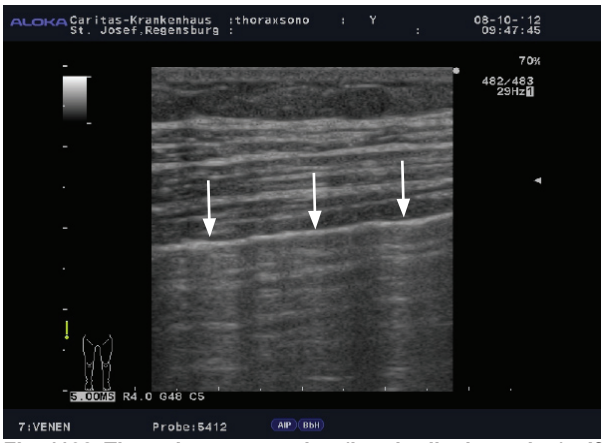
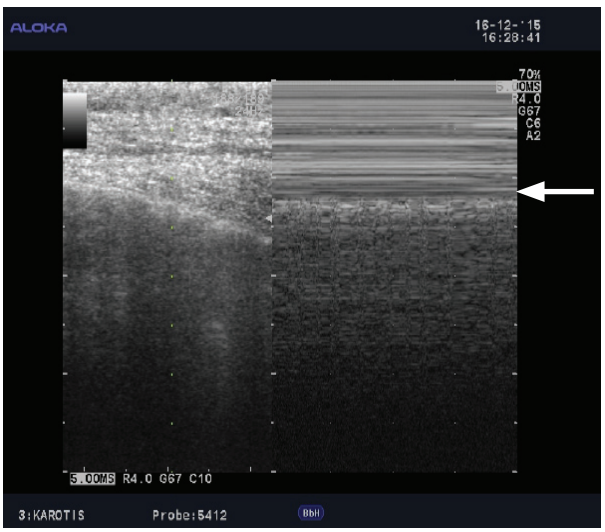


Fig. 1132 Thoracic sonography (longitudinal section): If the sliding of the pleura (see arrows) at the highest point of the thorax (in the case of a lying patient: the sternum) can be detected, a pneumothorax is excluded (simply place the linear transducer to the right or left of the sternum in the longitudinal section).



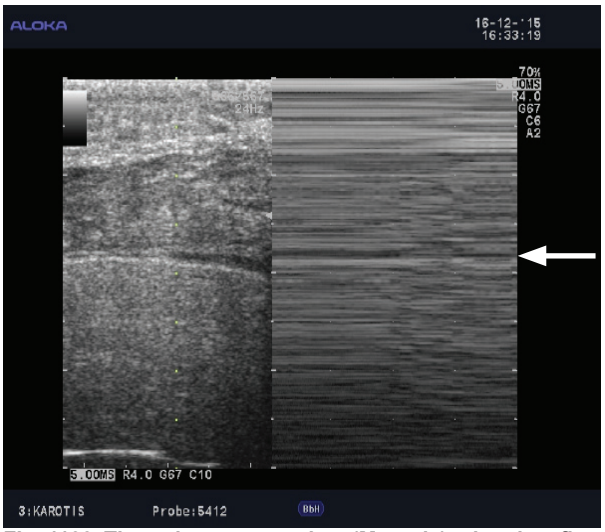
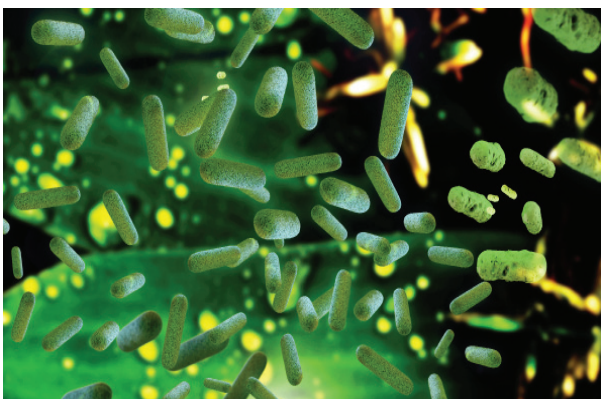


Fig. 1133 Thoracic sonography (M-mode): in the first image Seashore sign (no pneumothorax; normal finding): Above the pleura (arrow points to the pleura) air-induced reveberation artifacts are visible, below the pleura a finely granulated tissue (above waves ["sea"], below granulated ["beach"]; "seashore"; memo: "When you see the sea and the beach, you are relaxed"); in the second image stratospheric sign (pneumothorax): Here the reverberation artifacts caused by air can not only be seen above, but also below the pleura. This is caused by a complete mirror artifact at the pleura which is no longer adjacent to the wall, i.e. above the pleura one sees exactly the same as below the pleura.

Special forms (pneumonia)

- legionella pneumonia
- swine flu (H1N1)
- COVID-19
- pneumocystis jirovecii pneumonia

Legionella pneumonia

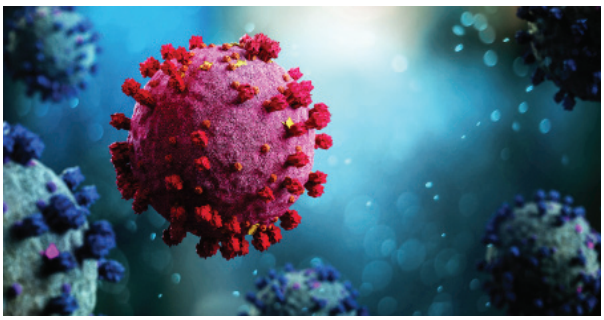


Definition

- legionella pneumophila
  - gram-negative, aerobic, non-spore-forming, intracellular rod-shaped bacteria
  - 16 serogroups (most important: serogroup 1)
  - environmental germ in fresh water (especially in

- 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: Coronaciridae
  - 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 (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 2020 is caused by a different and previously unknown coronavirus (new variant), which is why the term "novel" corona virus (2019-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 2020 as SARS-CoV-2. 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; 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])
- groups: 4 main groups, 10 sub-groups (viral diversity; Chen et al, MedRxiv 2020)
- mutations (sequencing required for proof): i.a.
  - D614G (with increased infectivity; even the dominant form worldwide since November 2020!)
  - B.1.1.7
    - first detected in England in September 2020 (meanwhile 90% of all SARS-CoV-2 infections in England caused by this mutation [as of 02/08/2021]; in Germany: 02/08/2021 6%, am 02/18/2021 22%)
    - 17 gene changes (especially N501Y and Deletion 69-70 Delta; also at the receptor binding sites of the spike protein)
    - The most important gene change (applies not only to B.1.1.7, but also to B.1.351 and P.1) 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).
    - increased infectivity (by 30%; especially for people < 20 years), no increased pathogenicity
    - mRNA vaccines from Biontech / Pfizer (Comirnaty) and Moderna probably effective (neutralization demonstrated by serum from vaccinated persons [Muik et al, bioRxiv 2021; Liu et al, N Engl J 2021])
    - variant of concern (VOC)
  - B.1.351 (South Africa)
    - especially mutation 501Y.V2
    - increased infectiousness
    - mRNA vaccines from Biontech / Pfizer (Comirnaty) and Moderna probably only less effective (only insufficient neutralization by serum from vaccinated persons [Wibmer et al, bioRxiv 2021; Liu et al, N Engl J 2021]), vector vaccine from Astra Zeneca / Oxford University not effective at all
  - P.1 (B.1.1.28; Brasilia)
- thermolabile (Coronaviruses are killed at temperatures above 70°C.)
- 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 upregulation of the receptors!
  - In contrast to SARS-CoV-1, SARS-CoV-2 not only docks on the ACE-2 receptors of the lungs, but also on those on the nose with consecutive replication,

BAS²IC-Score

- **definition:**
  - **risk score (at hospital admission) for a severe course**
  - **according to Kaeuffer et al, Open Forum Infect Dis 2020**
- **parameters:**
  - **BMI:**
    - **25-30 kg/m²: 2 P.**
    - **> 30 kg/m²: 3 P.**
  - **Age > 65 J.: 1.5 P.**
  - **Sex: male → 3 P.**
  - **Shortness of breath (dyspnea): 3.5 P.**
  - **Inflammatory parametes:**
    - **neutrophiles > 8000/µl: 3 P.**
    - **lymphocytes < 1000/µl: 1.5 P.**
  - **CRP:**
    - **10-20 mg/dl: 2 P.**
    - **> 20 mg/dl: 5.5 P.**
- **interpretation: risk**
  - **≤ 6 P.: low (outpatient treatment)**
  - **6-14 P.: moderate (hospital admission [normal ward])**
  - **≥ 14 P.: high (hospital admission [IMC / ICU; administration of dexamethasone]**

Symptoms

- fever (in 88%; i.e. in 12% but also without a fever; in Germany according to RKI (Robert Koch Institute) only fever in 40%, i.e. in 60% without fever)
- cough (usually dry; in Germany according to RKI only in 54%)
- rhinorrhea (However, a runny nose is relatively atypical for COVID and speaks more for a harmless cold).
- dyspnea
  - usually only after 7 days
  - There is often a discrepancy between condition (no or only slight dyspnea) and the finding (pronounced hypoxemia in the BGA [„silent hypoxemia“, "happy hypoxemia"; Dhont et al, Resp Research 2020]: This often only becomes clinically manifest through tachypnea, which is a surrogate parameter for increased work of breathing and thus an early indication of an impending respiratory decompensation!).
- athralgia, myalgia
- sore throat
- headache
- tiredness (fatigue)
- inappetence
- nausea, vomiting, ⚠ diarrhea (frequent), possibly abdominal pain
- ⚠ disturbance of the sense of smell and taste (anosmia; frequent; in 21% [but not surprising: The most common cause for a disturbance of the sense of smell and taste are viral infections!]; often persistent for weeks)
- dermatological: chilblains-like changes on the toes and fingers ("COVID toe"; i.a. Landa et al, International Journal of Dermatology 2020)
  - reddish-purple discoloration and swelling
  - painful
  - mostly self-limiting (harmless; no therapy necessary)
- dermatological (skin changes in 20% of all hospitalized [Hay et al, Br J Dermatol 2020]):
  - ⚠ chilblains-like changes on the toes and fingers ("COVID toe"; i.a. Landa et al, International Journal of Dermatology 2020)
    - reddish-purple discoloration and swelling
    - painful
    - especially children and adolencents
    - especially in (with regard to the classic COVID symptoms) asymptomatic patients (in 41% SARS-CoV-2 positive [Galvan et al, Br J Dermatol 2020])
    - Antibodies against SARS-CoV-2 could be detected in 30% of all patients who currently presented with chilblains (Hubiche et al, JAMA Dermatol 2020).
    - mostly self-limiting (harmless; no therapy necessary)
  - exanthema (erythematous, maculopapular)
  - urticaria (wheals)
  - vesicular eruptions (vesicles like chickenpox)
  - scaling (desquamation)
  - livedo racemosa, necrosis

Complications

- lung:
  - pneumonia (atypical, interstitial; on average 4 days after the onset of symptoms)
  - ARDS
    - on average 8 days after the onset of symptoms
    - ⚠ in 15% of all hospitalized patients (Sun et al, J Med Virol 2020)
    - main cause of death
  - pneumothorax (generally increased incidence in all viral pneumonia, especially with COVID-19 in 1% [Martinelli et al, Eur Resp J 2020]), formation of bullae, mediastinal emphysema
  - fibrosis (in the long-term; significantly stronger tendency to fibrosis than with influenza)
- heart (the second leading cause of death with 10%):
  - myocarditis (i.a. increased troponin: In a cohort [Shi et al, JAMA Cardiol 2020] of 419 hospitalized COVID patients, 20% had an increased troponin. Mortality in this group was significantly increased at 50%! In a meta-analysis [Li et al, Crit Care 2020], 37% of all intensive care COVID patients showed an increased troponin.)
  - cardiomyopathy with cardiogenic shock
  - arrhythmias (i.a. atrial fibrillation in 27.5% of all intensive care patients [Colon et al, JACC Clinical Electrophysiology 2020])

- lower respiratory tract (cave increased risk of infection):
  - sputum (for productive cough [rarely the case])
  - endotracheal secretion
  - bronchoalveolar lavage (BAL) by bronchoscopy (not absolutely necessary since there are no advantages over the endotracheal secretion)

- assessment:
  - specifity: very high (nearly 100%), i.e. almost no false positive results, no cross-reactions with other (harmless ["endemic"]) coronaviruses (A positive test proves SARS-CoV-2!)
  - sensitivity:
    - ⚠ only 75% (Therefore, if the test is negative and there is an urgent suspicion, another test should follow!); note: The tests have improved significantly, so that the sensitivity is meanwhile 98% (with correct preanalytics).
    - The test from the upper respiratory tract can be false negative in the second week because the viruses have already migrated from the upper to the lower respiratory tract. In contrast, the test from the lower respiratory tract can be false negative in the first week because the viruses have not yet migrated from the upper to the lower respiratory tract. For this reason, samples from the lower respiratory tract (endotracheal secretion sufficient) should always be taken from intubated patients (if the test is negative from the upper respiratory tract)!
- transport: in a UTM tube (universal transport medium), does not have to be cooled (only necessary in case of longer storage at 4°C)
- virus load (indirectly proportional to the cycle threshold [Ct]; quantification):
  - low: Ct S-gen > 30 (from here on it can no longer be grown in cell culture [amount of RNA < 250 copies / 5µl RNA eluate; swab is resuspended in 1ml liquid, 140µL of which is extracted with the QIAamp Viral RNA Mini Kit and the RNA is eluted in 60µl] and therefore no longer infectious [depending on the time of infection: This is especially true 10 days after the onset of symptoms. At the beginning of the infection however, the Ct value can decrease in the further course and the infectivity can increase accordingly!])
  - moderate: Ct S-gen 20-30
  - high: Ct S-gen < 20 (i.a. < 5: highly infectious ["superspreader"])
- duration of the test: 3h (In the meantime there are also rapid tests [POCT: point-of-care-testing; e.g. GeneXpert, IDNow], with which the result is finished much faster.)
- cost per test (medically validated): 100-150 € (in Germany)
- ⚠ For self protection, the samples should only ever be taken with protective clothing (especially FFP-2 mask, safety glasses, gloves)!
- According to the S2k guideline of the DGIIN of 23.11.2020 a PCR test should be carried out in the context of the pandemic situation for every patient who is admitted to the hospital (strong recommendation).

The most common cause of a false negative test is incorrect sampling (error in preanalytics)!

Fig. 1463 PCR rapid test: here as an example the GeneXpert system of the company Cepheid from our emergency department, with which you can test as POCT not only for influenza, RSV, MRSA, A streptococci, Mycobacterium tuberculosis and Clostridium difficile, but also for SARS-CoV-2: The result is available within 45 minutes. Since this is also a PCR test, the specificity and sensitivity are comparable to the conventional test.

Serology (indirect virus detection)

- detection of antibodies against the S protein (spike; the decisive antibody for virus elimination)
- unsuitable for the question of an acute infection, since seroconversion only occurs in the second week of illness (on average on day 10)
- well suited to the question of a past infection (but earliest useful after 14 days)
- Immunosuppressed patients often cannot form antibodies at all, so that no seroconversion occurs at all.
- Furthermore, cross-reactions against the harmless ("endemic") coronaviruses, against which most people have high antibody titers anyway, may be seen.
- study Li et al, J Med Virol 2020: detection of antibodies against the S protein
  - sensitivity: 89%
  - specifity: 91%
- i.a. EUROIMMUN test currently approved
- However, the currently available tests are not yet so reliable, so that, based on the current status, the detection of antibodies should not lead to the conclusion that one is supposedly protected and no longer has to wear protective clothing.
- rapid antigen tests
  - strip assays according to the "lateral flow" principle

study

A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe COVID-19
Cao et al, N Engl J 2020

- randomized controlled study (open-label)
- 199 hospitalized patients with proven SARS-CoV-2 infection with respiratory insufficiency (SpO_2 < 94% or Horovitz quotient < 300 mmHg)
  - lopinavir / ritonavir 2 x 400mg/100mg daily p.o. for 14 days
  - placebo
- 🙁 results: lopinavir / ritonavir
  - primary endpoint: time to clinical improvement → no difference (no clinical benefit)
  - secondary endpoints: i.a.
    - mortality: no difference
    - viral load: no difference
    - more frequent gastrointestinal side effects
- note: However, the patients in this study were already seriously ill and all had already alung damage, so that the drug might have been given too late. They were included on average only 13 days after the onset of symptoms.)

study

Triple combination of interferon beta-1b, lopinavir–ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19
Hung et al, Lancet 2020

- multicenter randomized controlled study (open-label)
- 127 hospitalized patients with proven SARS-CoV-2 infection; lopinavir / ritonavir 2 x 400mg/100mg daily p.o. for 14 days; in addition:
  - ribavirin 400mg 2 x daily + (if duration of disease < 7 days) interferon-β up to max. 3 x 8 millions IU s.c. every 2 days
  - placebo
- results: triple therapy
  - significantly faster virus elimination (by 5 days)
  - significant reduction in duration of the disease (was halved)

Remdesivir

- a nucleotide analog (inhibition of the RNA polymerase; exactly: RdRP [RNA-dependent RNA polymerase])
- trade name: Veklury
- was actually developed for the therapy of the Ebola and Marburg viruses, but was not effective here; in animal experimental studies, however, well effective against MERS-CoV and in vitro also against SARS-CoV (Wang et al, Cell Research 2020)
- dosage: d1 200mg i.v., then 100mg i.v. for 5-10 days (SIMPLE Severe study [Goldman et al, N Engl J 2020]: no difference between 5 or 10 days; Spinner et al, JAMA 2020: Only the administration over 5 days showed a significant clinical improvement, but not the administration over 10 days.); note: dosage for children: d1 5mg/kg, then 2.5mg/kg (but only approved for those aged > 12 years and body weight > 40kg)
- was not commercially available for a long time, but as "Compassionate Use" (use of a not yet approved drug in particularly serious cases of illnesses) via the Gilead company (prerequisites: invasive ventilation, no catecholamines, GFR > 30 ml/min, transaminases < 5-fold of the norm; special approval in the USA since 03/05/2020); "Compassionate Use" program has meanwhile ended and the substance is also commercially available (also for non-intubated patients)
- contraindications:
  - renal failure with a GFR < 30 ml/min
  - transaminases (GOT or GPT) > 5-fold of the norm
- side effects (rare [a relatively safe drug]): especially
  - vomiting
  - constipation
  - hepatopathy (transaminases ↑)
  - renal dysfunction
  - hypotension
- studies:
  - in the first randomized controlled trial (Wang et al, Lancet 2020; see box) no clinical benefit demonstrated
  - ACCT-1 study (Beigel et al, N Engl J 2020; see box): faster clinical improvement but no reduction in mortality (note: Patients with moderate disease benefited most. However, this is only a subgroup analysis.); 🙁 overall only marginal effectiveness
  - currently two ongoing phase-III studies (RCT)
  - 🙁 SOLIDARITY study (see page 1129; but only preprint and has not been peer-reviewed): no benefit at all (no reduction in mortality, in the rate of requiring ventilation or in the length of hospital stay)
  - studies on combination therapy (note: The ACCT-1 study was the study on monotherapy with remdesivir, the studies ACCT 2-3 are the studies on combination therapy.)

- resuscitation: ERC guidelines COVID-19 (April 2020)
  - basic life support (BLS)
    - Since resuscitation (especially chest compression, intubation) is an aerosol generating procedure (AGP), the personnel should put on personal protective equipment (PPE) before starting the resuscitation. That takes time. This may also be the reason why the success rate of resuscitation decreased dramatically in 2020 (with an increase in the number of resuscitations).
    - Since chest compression with PPE is much more strenuous than without PPE, a change should be made after 1 (and not after 2 minutes).
    - A mouth and nose mask should be attached to the patient (if necessary, only provisionally e.g. pulling up the T-shirt).
    - bag mask ventilation always with bimanual sealing of the mask by a second person
  - advanced life support (ALS)
    - Defibrillation is not an aerosol generating procedure, so it can take place before the PPE is put on.
    - ⚠ Since the patients have a significantly increased risk of pulmonary embolism, the option of lysis should be considered!
- antipyretic therapy:
  - acetaminophen (paracetamol; i.a. recommended [weakly] in the SSC-COVID guideline [first update from January 28, 2021])
  - metamizole (Novalgin)
  - cave NSAR (e.g. ibuprofen [initially advised against by the WHO, but the warning was then withdrawn]: detorioration of the disease has been described in individual cases; up-regulation of the ACE-2 receptors via which SARS viruses enter the cells; however, the data situation is inconsistent)
- A pre-existing immunosuppressive therapy (e.g. azathioprin, calcineurin inhibitor, mycophenolate-mofetile) should be reduced or even discontinued in the case of severe infection (especially with lymphocytopenia [especially if lymphocytes < 800/µl])!
- if hemophagocytosis syndrome is detected, immunosuppressive therapy (see page 1022)

Steroids

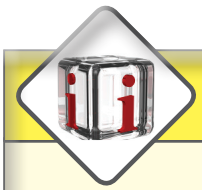
- guidelines (previous recommendations regarding steroids in ARDS):
  - national (S1 guideline DGIIN 2020 [1st and 2nd version]): not recommended (explicitly); except hydrocortison 200mg/day with therapy-refractory septic shock or with proven adrenocortical insufficiency or prednisolon 1 x 40mg p.o. over 5 days in exacerbated COPD
  - international (COVID guideline of the SSC 2020): recommended (but only weakly with very little evidence); note: However, if there is only pneumonia without ARDS, steroids are clearly not recommended here either.
- studies: There are no randomized controlled trials here for a long time. The recommendations were mainly derived from the analogy to influenza. In a retrospective analysis (Wu et al, JAMA Intern Med 2020) of 221 patients with COVID-19 pneumonia methylprednisolone (Urbason) showed a lower mortality compared to placebo. In the worldwide largest therapy study RECOVERY low-dose administration of dexamethasone (Fortecortin; 6mg once a day p.o. or i.v. for 10 days; dosage in children: 0.2 mg/kg [max. 6mg/d]; note: 6mg dexamethasone corresponds to 45mg prednisolone [conversion factor: 7.5].) showed a significant reduction in mortality, so that it is now (by the NHS and WHO) regarded as the therapy standard! Dexamethasone is also recommended in the position paper of the German Society for Pneumology (DPG) as soon as there is an indication for the administration of oxygen. It is also clearly recommended as a standard in the 3rd version of the S1 and the S2K guideline of DGIIN and by the IDSA (Infectious Diseases Society of America). Alternatively, another glucocorticoid (e.g. hydrocortisone 3 x 50mg i.v.) is also possible.
- recommendation (i.a. WHO, ISDA, DGP [German Society for Pulmonology], SSC [first update of the COVID guidelines on January 28th, 2021]): dexamethasone 1 x 6 mg daily p.o. or i.v. over 10 days as soon as the additional administration of oxygen is necessary (i.e. SpO_2 breathing room air < 94% [S2k guideline DGIIN: only < 90%])

RECOVERY study

Randomized Evaluation of COVid-19 thERapY
Hobry et al, N Engl J 2020

- RECOVERY: Randomized Evaluation of COVid-19 thERapY
- multicenter randomized controlled study
- therapy study of the NHS (National Health Service) in the UK (175 hospitals)
- largest worldwide (11500 patients) clinical trial for the treatment of COVID-19
- 6 substudies:
  - hydroxychloroquine (1542 patients) versus placebo (3132 patients) → 😕 no significant reduction in 28-day mortality (also no effect on length of hospital stay or other outcome parameters)
  - lopinavir / ritonavir (1596 patients) versus placebo (3367 patients) → 😕 no significant reduction in 28-day mortality
  - azithromycin: still ongoing
  - tocilizumab: still ongoing
  - immuntherapy with convalescent plasma: statement from RECOVERY trial chief investigators vom 15.01.2021 → 😕 no significant reduction in 28-day mortality (premature stop of this study arm)
  - dexamethasone (2104 patients; low-dose: 6mg p.o. / i.v. for 10 days) versus placebo (4321 patients) → 🙂 significant reduction in 28-day mortality (in mechanically ventilated patients by 35% [NNT only 8!], in patients with additional O_2 application by 20%; in patients with additional O_2 application no effect)

occurs. There is absolutely no scientific evidence for this. With only 4 common amino acids, there is only very little similarity.
    - vaccination possible (no increased rate of miscarriages)
    - According to the recommendations of the European Society for Reproductive Medicine, the vaccination (2nd vaccination) should take place at least 2 months before the onset of pregnancy.
    - No routine pregnancy test is necessary in women in potentially childbearing age prior to vaccination.
- children: Their disease burden is relatively low. Furthermore, the vaccines are not tested here, so that no general vaccination is recommended. Exceptions are children with chronic diseases (e.g. cystic fibrosis).
- oral anticoagulants: i.m. application of Comirnaty (only 0.3ml) in deltoid muscle possible



Vaccines
overview

- **inactivated vaccines: with killed viruses (established; dead vaccine; example: from China CoronaVac [only moderately immunogenic] and Sinovac)**
- **attenuated vaccines: with weakened but still living viruses (established [e.g. mumps, measles, rubella]; live vaccine)**
- **nucleotide-based (= gene-based) vaccines**
    - **RNA (mRNA [m: messenger]; contains the genetic blueprint (packaged in lipid nanoparticles [necessary because the RNA is extremely unstable and would be broken down immediately by RNA-ases]) for the spike protein, which is then only produced in the body's own cells and acts as an antigen against which antibodies [the actually effective vaccine] are then produced in the body; does not get into the cell nucleus, no re-transcription in DNA possible, therefore no influence on the genetic material); examples: BNT162b2 (Biontech / Pfizer), mRNA-1273 (Moderna), CVnCoV (CureVac [Tuebingen, Germany])**
    - **DNA**
- **protein-based vaccines: against protein components of the virus (e.g. CoV2373 [Novavax company]: in phase III study effectiveness of 89.3% including the mutations B.1.1.7 [England] and B.1.351 [South Africa])**
- **vector-based vaccines: Viruses harmless to humans (e.g. adenoviruses) are used as transporters: They are genetically modified in such a way that, like SARS viruses, they develop the spike protein on their surface. These modified viruses are then injected in a weakened form. Examples: Sputnik V [Gam-COVID-Vac [Gamaleya]; Russia], AZD1222 (Astra Zeneca + University of Oxford; protective effect only 70% [Voysey et al, Lancet 2021]), CanSino (emergency approval in China)**

study

Safety and immunogenicity of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine in two formulations
Logunov et al, Lancet 2020

- 2 open non-randomised phase I/II studies (Russia)
- 38 participants (healthy adults) in each study
- vaccine (Sputnik V [Gam-COVID-Vac]): recombinant adenovirus vector (containing a gene from the spike protein) in two formulations (frozen and lyophilized; [rAd26 and rAd5])
- All produced neutralizing antibodies against the spike protein.
- side effects (reactogenicity): especially
    - pain at injection site (58%)
    - fever (50%)
    - headache (42%)

study

Safety and efficacy of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine: an interim analysis of a randomised controlled phase 3 trial in Russia
Logunov et al, Lancet 2021

- multicenter (25 centers in Moscow [Russia]) randomized controlled double-blind study (phase III study [interim analysis])
- 21,977 participants (healthy adults)
    - caccine (Sputnik V [Gam-COVID-Vac]): recombinant adenovirus vector (with a gene for the spike protein) in 2 formulations (frozen and lyophilized) and 2 adenoviruses (rAd26 and rAd5; heterologous prime boost principle) i.m. at an interval of 21 days (1st vaccination: rAd26; 2nd vaccination: rAd5)
    - placebo
- results: Gam-COVID-Vac
    - ☺ significantly fewer confirmed SARS-CoV-2 infections (> 21 days after the 1st vaccination; protective effect: 91.6%)
    - side effects:
        - mild: in 94%
        - severe: in 0.4%

Fig. 1153 The cuff pressure must be checked regularly (once per shift and after each suction) and should be between 22-32 cmH_2O (= mbar; 16-25 mmHg; rule: 5 cmH_2O above the inspiration pressure). If it is too low, the risk of aspiration is increased. If it is too high, the risk of tracheal damage due to pressure necrosis is increased [33].

Special endotracheal tubes

- tubes with an additional lumen for subglottic secretion suction (CASS: continuous aspiration of subglottic secretions)
  - i.a. Evac tubes (additional lumen for suction of the subglottic space; standard in our hospital in the intensive care unit), i.a. PneuX P.Y. system
  - significant reduction in VAP rate (i.a. Smulders et al, Chest 2002; meta-analysis Dezfulian et al, Am J Med 2005; Lorente, Am J Respir Crit Care Med 2007; Lacherade et al, Am J Respir Crit Care Med 2010; meta-analysis Muscedere et al, Crit Care Med 2011; meta-analysis Mao et al, Crit Care 2016; meta-analysis Caroff et al, Crit Care 2016)
  - recommendations: for ventilation> 48h
    - S2k guideline sepsis 2010 + S3 guideline 2018: can be considered
    - S3 guideline 2017 "Invasive ventilation and use of extracorporeal procedures in acute respiratory insufficiency": weak recommendation
- silver-coated endotracheal tubes
  - silver: antimicrobial effect (inhibition of biofilm formation)
  - NASCENT study (Kollef et al, JAMA 2008): In this multicenter randomized controlled study in 1932 patients (ventilation > 24h), the use of a silver-coated tube showed a significantly lower VAP rate (4.8% versus 7.5%) compared to a conventional tube without (significant) reduction in mortality.
  - Bewertung: teuer, keine allgemeine Empfehlung
- tubes with ultra-thin polyurethane cuffs
  - The cuffs of these tubes are made of polyurethane and are only 7µm thick, so the trachea is sealed better. The cuffs of conventional tubes are made of polyvinyl and are 50-80µm thick.
  - reduction of the VAP rate (i.a. Lorente et al, Am J Crit Care Med 2007; Miller et al, J Crit Care 2011)
  - assessment: expensive, no general recommendation
- tubes with a cone-shaped ("tapered") instead of the usual cylindrical cuff (i.a. Jaillette et al, ICM 2017: no use; no general recommendation)

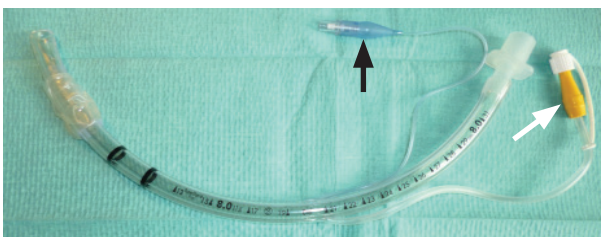


Fig. 1154 Evac tube: In addition to the lumen for blocking (black arrow), it has a lumen for suctioning off the subglottic space (white arrow).

PneuX P.Y. system

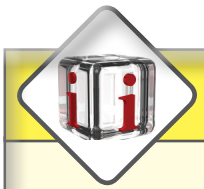
- Venner Medical Germany GmbH Company
- endotracheal tube with 3 irrigation cannulas above the cuff for suction of the subglottic space
- special coating to reduce biofilm formation
- tracheal wall pressure monitor that continuously measures the cuff pressure, automatically adjusts and maintains it constant
- goal: VAP prophylaxis

- complicated intra-abdominal infections
- complicated urinary tract infections, acute pyelonephritis

- ⚠ Cephalosporins are ineffective in ESBL (even if "sensitive" in the antibiogram).

ESBL: carbapenem or tigecyclin!

Excursus: Carbapenem-resistant organisms (CRO)



CRO

- **carbapenem-resistant organisms**
- **p.d. always 4-MRGN**
- **mechanisms (of carbapenem-resistance):**
  - **formation of carbapenemases (most common)**
  - **loss of porins (loss of specific channel proteins, especially in case of pseudomonas)**
  - **efflux pumps that actively pump the antibiotic out of the bacterium again**
- **types:**
  - **carbapenem-resistant enterobacteriaceae (CRE; 25%; most common carbapenemase: OXA-48)**
  - **carbapenem-resistant non-fermenters (75%)**
    - **pseudomonas aeruginosa (60%; most common carbapenemase: VIM-2)**
    - **acinetobacter baumanii (15%; most common carbapenemase: OXA-23)**

CRE

Definition

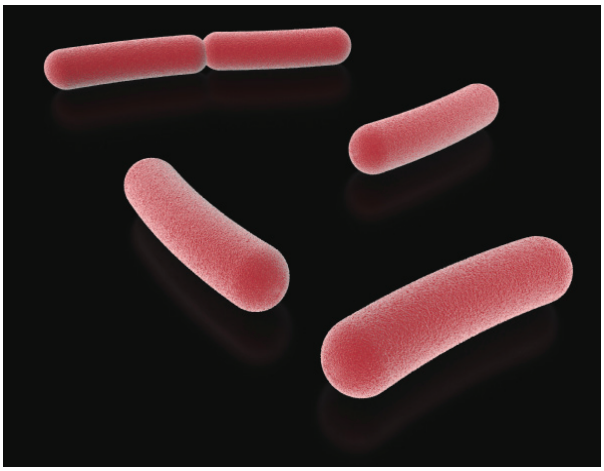
- carbapenem-resistant enterobacteriaceae (especially K. pneumoniae [most common CRE], E. coli)
- syn.: carbapenemase-producing enterobacteriaceae (CPE)
- proportion only 2-3% in Germany (more often in Greece, Italy, Turkey, Malta, Israel, USA, India, Iran, Iraq, Egypt, China, Thailand, Japan), but a significant increase in Germany
- They will be the largest problem in the future!
- ⚠ mortality: 50% (Correa et al, BMC Inf Dis 2013), 4-fold mortality
- especially klebsiella
- carbapenemases (Ambler classifikation [according to the British molecular biologist Richard Penry Ambler [1933-2013]):
  - class A: z.B. Klebsiella pneumoniae-Carbapenemase (KPC)
  - class B
    - VIM (Verona integron encoded metallo-betalactamase; most common)
    - NDM (Neu-Delhi-Carbapenemase)
    - IMP (Imipenemase)
  - class C (e.g. AmpC)
  - classD (e.g. OXA-48 [Oxacillinase])
- Carbapenemasen are β-lactamases:
  - class A, C and D: serin-β-lactamases (SBL)
  - class B: metallo-β-lactamases (MBL)
- the most common carbapenemases in Germany: OXA-48 (No.1), KPC (No.2), VIM (No.3), NDM (No.4)

Therapy

- polymyxins
  - colistin (⚠ the "backbone" [basis] of CRE therapy! renaissance! see page 904)
  - polymyxin B
- tigecycline (but not for sepsis or urinary tract infections, as insufficient levels are achieved; off-lable for pneumonia)
- fosfomycin
- ceftazidime + avibactam (Zavicefta): The β-latamase inhibitor avibactam is very effective against CRE (especially KPC [i.a. CRACKLE study van Duin et al, Clin Infect Dis 2018] and OXA-48; however, not effective against metallo-β-lactamases [Ambler class B]: As a trick, however, one can combine ceftazidime / avibactam with the monobactam aztreonam [not available in Germany] here [Marshall et al, Antibiol Agents Chemo 2017]).
- carbapenem (e.g. meropenem 3 x 2g) as a combination partner to colistin or fosfomycin (actually absurd; also recommended only for MIC <8 mg/l)
- meropenem + vaborbactam (Vabomere)
  - vaborbactam: new β-latamase inhibitor with effectiveness against carbapenemases (especially KPC)
  - already approved in the USA (not yet in Germany) as a reserve antibiotic for complicated urinary tract infections (including pyelonephritis) caused by klebsiella pneumoniae, escherichia coli or enterobacter cloacae
  - dosage: 2g/2g 3 x daily. as short infusion over 3h
  - dose reduction in renal insufficiency:
    - GFR 30-50 ml/min: 1g/1g 3 x daily
    - GFR 15-30 ml/min: 1g/1g 2 x daily
    - GFR < 15 ml/min: 0,5g/0,5g 2 x daily
  - approval study: TANGO-1
- Recarbio = imipenem + cilastatin + relebactam
  - cilastatin: an inhibitor of dehydropeptidase in the kidney that prevents the renal inactivation of imipenem
  - relebactam: new β-latamase inhibitor with activity against carbapenemases of classes A and C (not active against classes B and D)
  - approvals (FDA since 2019): infections due to aerobic gram-negative bacteria with limited treatment options
    - complicated urinary tract infections
    - complicated intra-abdominal infections
    - nosocomial pneumonia (incl. VAP; not yet approved; study: RESTORE-IMI 2)

Enterococci - therapy:
VSE:
- E. faecalis: ampicillin
- E. faecium: vancomycin
VRE: linezolid

Clostridium difficile



Definition

- new designation: Clostridioides difficile
- germ:
  - anaerobic gram-positive rod
  - spore forming bacteria (survives outside the colon in the form of spores that are very resistant to the environment)
  - toxin producing
- also detectable in 3% in the intestines of healthy people
- virulence factor: toxins
  - toxin A (enterotoxin)
  - toxin B (cytotoxin; 1000 times stronger)
- causes:
  - antibiotics (50%)
    - usually 5-10 days after beginning of antibiotic treatment
    - most common: clindamycin, cephalosporines, fluoroquinolones
    - In most cases, however, diarrhoea under antibiosis is only an antibiotic-associated diarrhoea (due to changes in the intestinal flora).
  - transmission (50%; C. difficile is highly contagious!)
- transmission from person (fecal-oral) or from contaminated objects to person
- highly infectious (excretion 10^7-10^8 pathogens per gram of stool)
- resistant to alcohol (The alcoholic hand disinfection does not help here, but washing hands with soap!)
- incubation period: 1-3 days

Epidemiology

- one of the most common nosocomial pathogens (nowadays twice as many nosocomial infections from C. difficile as from MRSA!)
- most common pathogen of nosocomial diarrhoea
- colonisation: 3% of all people (30% of hospital patients)
- incidence:
  - 10.2 / 10000 patient days (Germany)
  - ⚠ dramatic increase (The number of reported infections has tripled between 2008 and 2013). 65% of them were severe [Epi Bull 2014]).
- average age: 76 years
- strains:
  - most common strain in Germany: ribotype 001
  - new strain with high virulence: ribotype 027 (produces quantitatively more toxins)

Clostridium difficile: dramatic increase on ICUs!

Diseases

- clostridium difficile associated diarrhoea (CDAD, 50%)
- pseudomembranous colitis (20%)
- toxic megacolon (see infobox; possibly sepsis and perforation)

Risk factors

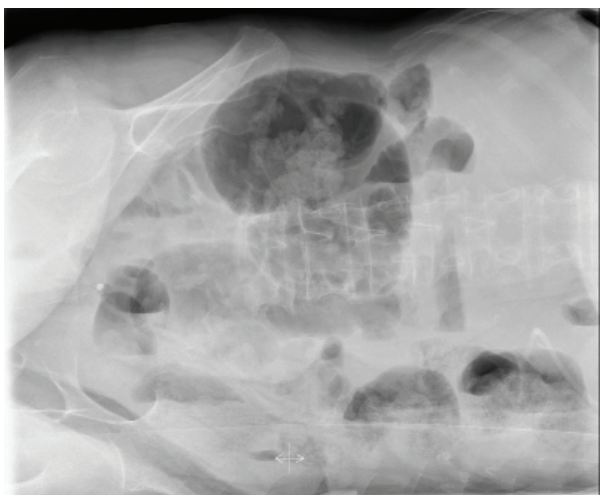
- antibiotic therapy (especially clindamycin, cephalosporines, fluoroquinolones); 4C group (colitogen): Clindamycin, Cephalosporins, Chinolons, Clavulanic acid (in Augmentan)
- ulcus prophylaxis (i.a. Tariq et al, JAMA Int Med 2017; especially proton pump inhibitors [i.a. Buendgens et al, Crit Care 2014], but also applies to H_2-blocker [i.a. Mac Laren et al, JAMA Intern Med 2014])
- chronic inflammatory bowel disease (Crohn's disease, ulcerative colitis)
- hospital stay (especially intensive care unit)
- age > 65 years
- immunosuppression
- tube feeding
- severity of the underlying disease
- chemotherapy

Symptoms

- diarrhea (watery, possibly bloody; note: The sicker the patient, the more likely it is that there is no diarrhea.)
- typical smell of cresol ("horse stable" smell; could even be smelled by the dog "Cliff" with a success rate of 86% [Bomers et al, BMJ 2012])
- dehydration
- abdominal pain (especially lower abdomen; cramp-like)
- fever

toxic megacolon
part II

- therapy
  - conservative; i.a.
    - knee-elbow position (positional relief of abdominal gases; 2 x 5-10min per hour)
    - o parenteral nutrition
    - analgetic therapy (e.g. paracetamol, metamizol; no NSAR or opioids [contraindicated])
    - antibiotics (e.g. ceftriaxone + metronidazole i.v.)
    - especially for ulcerative colitis
      - high dose steroids i.v. (e.g. prednisolone 2 x 50mg)
      - if necessary ciclosporin (Sandimmun 2 mg/kg i.v.; level determination after 3 days; in the course switching to p.o 4-5 mg/kg) or infliximab (Remicade 5 mg/kg i.v.; prerequisite: negative quantiferon test and negative hepatitis B serology)
    - endoscopic insertion of a decompression probe: ⚠ only indicated in individual cases (due to high risk of perforation! if so, then only with minimal air insufflation); good alternative: intestinal tube (no air insufflation necessary)
  - surgical
    - type of surgery: subtotal colectomy with residual rectal stump (Hartmann's procedure) and terminal ileostomy; in the further course (8-12 weeks) ileoanal pouch
    - indications for surgery:
      - no improvement with conservative therapy after 72h
      - progressive dilation
      - perforation
      - uncontrolled bleeding



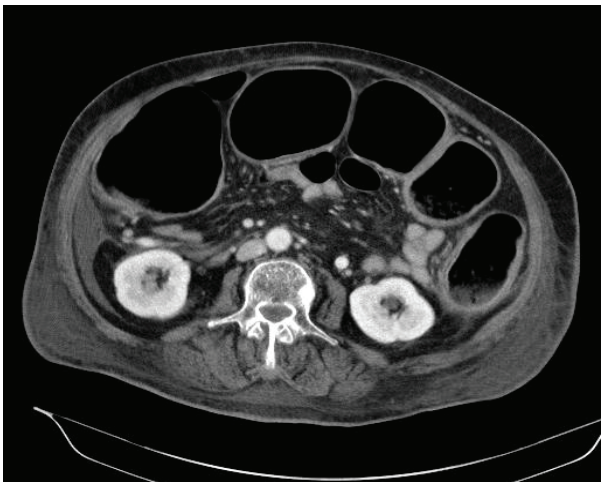
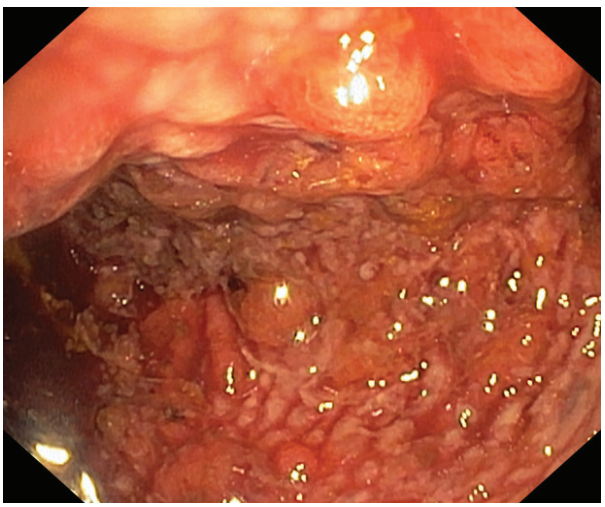
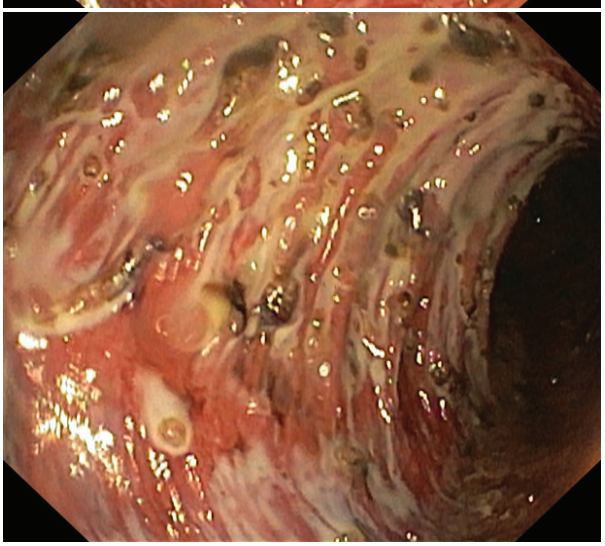


Fig. 1158 X-ray abdomen and CT abdomen (toxic megacolon): One recognizes the clearly dilated colon.





Symptoms

- sharply limited (≠ phlegmone: blurred) redness (overheated, painful
- possibly regional lymphadenitis (e.g. Cloquet's node in groin)
- fever

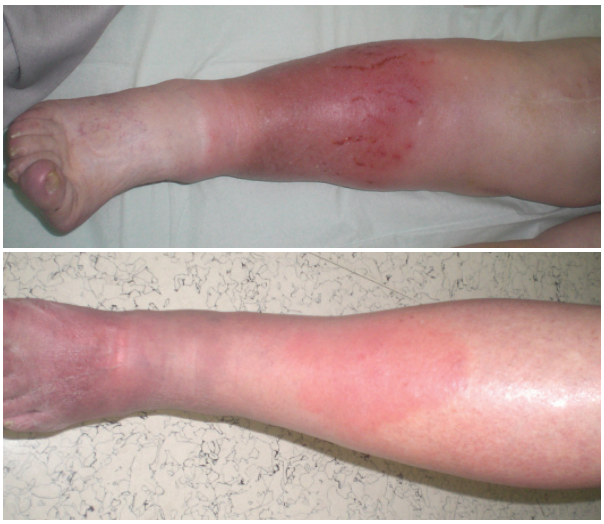


Fig. 1163 Erysipelas on the lower leg: The typically sharply defined redness can be seen.

Complications

- Erysipela bullosum, gangraenosum, migrans
- necrotizing erysipelas
- lymphedema
- poststreptococcal glomerulonephiritis

Therapy

- antibiotics
  - penicillin G (means of choice; 3 x 10 Mega i.v., in case of renal insufficiency [creatinine > 2 mg/dl] 3 x 5 Mega; possibly continuously via perfusor)
  - cefotaxime (Claforan)
  - clindamycin (Sobelin)
- immobilisation, cooling, dressing (e.g. Retterspitz)
- rehabilitation of the portal of entry (e.g. antifungal therapy for tinea pedis)
- in case of frequent relapses prophylaxis with long-term penicillin

Necrotizing fasciitis

Definition

- bacterial infection of the fascia with consecutive necrosis of the cutis and subcutis
- inzcidence: 0.4/100000
- most common pathogen: streptococci (group A)
- most common severe SSTI
- mostly lower extremity
- mostly severe sepsis
- ⚠ mortality: 33% (one of the few dermatological emergencies!)

Types (according to Giuliano)

- type I: mixed infection
- type II: streptococcus group A

Symptoms

- ⚠ extreme local pain („pain out of proportion“)
- livid discoloration (map-like)
- edema, swelling
- blisters, skin detachment
- bluish-black bleeding
- superficial (cutaneous) anaesthesia (through nerve involvement)
- crepitation (due to gas formation)
- fever

Diagnosis

- anamnesis, clinical examination
- laboratory (e.g. leukocytes, CRP, procalcitonin, CK)
- imaging
  - sonography (linear transducer)
    - hypoechoic seam over the fascia
    - feathering of the muscles
    - STAFF (mnemonic): subcutaneous thickening, air, fascial fluid
    - tip: always display in right-left comparison
  - CT
    - native sufficient (no contrast agent required)
    - ⚠ most quickly available
  - MRI (best)
- if necessary biopsy

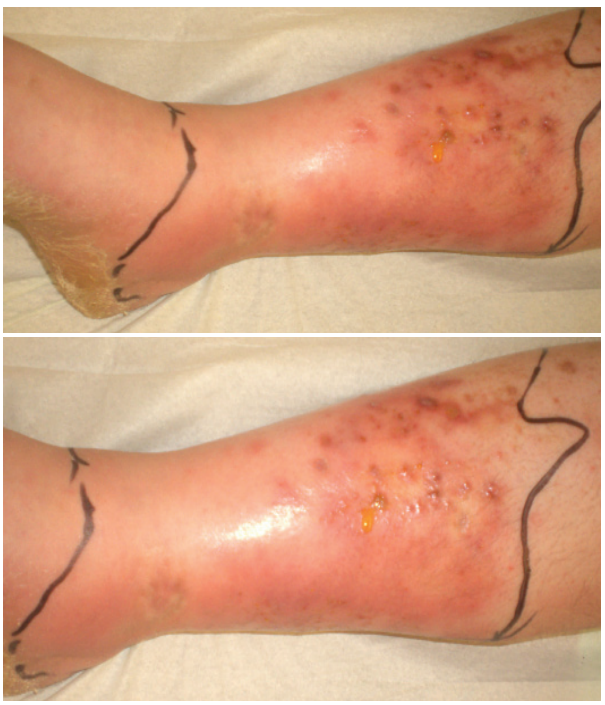
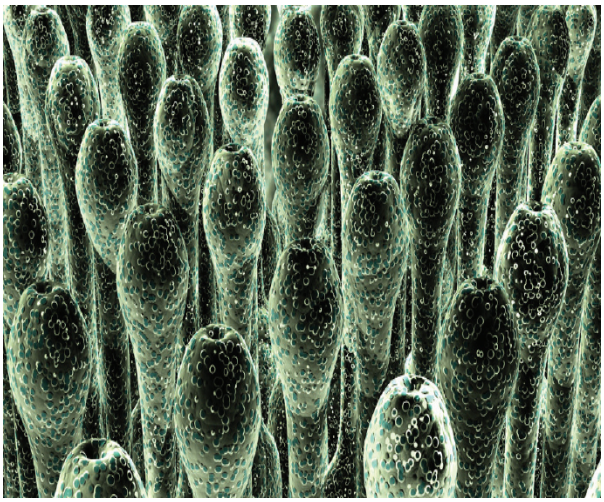


Fig. 1164 necrotizing fasciitis of the right lower leg

FUNGAL INFECTIONS (MYCOSES)



Arten

- candida (yeast / sprout fungus; No.1 [80%])
- aspergillus (mold; No.2 [15%])
- rare fungi (5%; see infobox at the end of the chapter [page 923])

Candida

- C. albicans (60%; No.1)
- non-albicans species (40%):
  - C. glabrata (19%; No.2)
    - especially in elderly patients
    - long incubation period (results usually only after 6-7 days!)
    - Infections with C. glabrata have a higher mortality than infections with C. albicans.
    - ⚠ worst prognosis among all candida infections (therefore also in stable patients no fluconazole, but echinocandin)
    - increasing resistance to fluconazole (therefore therapy only with echinocandins)
  - C. parapsilosis (9%; No.3)
    - especially in children (frequent in neonatology) and adolescents
    - best prognosis among all candida infections
    - Echinocandins are not effective here (gap in effectiveness), so that azoles here are means of choice!
  - C. tropicalis (2%; No.4)
  - C. krusei
  - C. kefyr
  - newly described: C. auris (high mortality [60%], resistant to most antifungals, several outbreaks already documented, difficult to identify with conventional laboratory methods [often misinterpreted as candida haemulonii or saccharomyces cerevisiae])

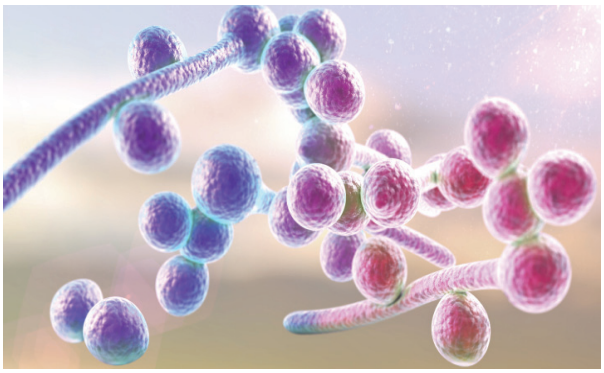


Fig. 1170 schematic representation of candida (yeast / sprout fungus)

Aspergillus

- occurrence: classically in immunosuppression (Aspergillus spores occur ubiquitously and are inhaled daily by humans. In a functional immune system, inhalation of the spores usually does not lead to disease.)
- transmission: aerogenic (inhalation of spores; no human-to-human transmission)
- sources:
  - air conditioners with inadequate filtration
  - potting soil (Therefore no potted plants should be placed in the patient´s room in the hospital or on the ward.)
  - renovation / demolition work
  - whirling up of rotten leaves
- types:
  - A. fumigatus (most common)
  - A. flavus
  - A. niger
  - A. nidulans
  - A. terreus
  - A. parasiticus
  - A. repens
- diseases:
  - allergic bronchopulmonary aspergillosis (ABPA)
  - aspergilloma (detection in a preformed cave)
  - invasive aspergillus tracheobronchitis
  - invasive pulmonary aspergillosis (mortality: 70%)
  - disseminated invasive aspergillosis (especially brain; mortality: almost 100%)

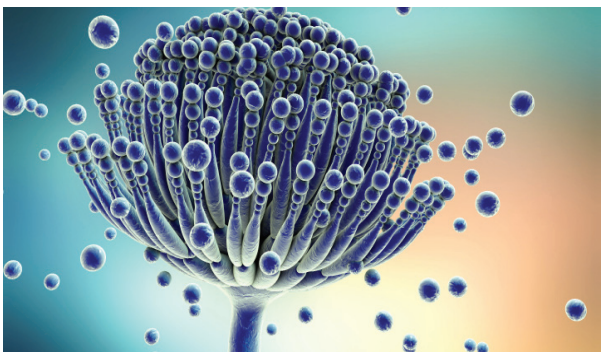


Fig. 1171 schematic representation of aspergillus (mold)

ICE study

Anidulafungin for the treatment of candidaemia/invasive candidiasis in selected critically ill patients
Ruhnke et al, Clin Microbiol Infect 2012

- Invasive Candidiasis Intensive Care study (ICE)
- prospective observational study
- 216 patients with candidaemia / invasive candidiasis
- results
  - clinical success rate of anidulafungin: 69.5%
  - survival rate (90 days): 53.8%
  - Blood cultures were median negative already on day 2!

study

Efficacy of Anidulafungin in Patients with Invasive Candidiasis: Focus on non-Albicans Candida spp.
Conte et al, ICAAC 2012

- 504 patients with invasive candidiasis
- global response to anidulafungin:
  - C. albicans: 76%
  - non-albicans species: i.a.
    - C. krusei: 73% (data on this for the first time, as C. krusei was excluded from the approval study)
    - ⚠ C. parapsilosis (78%; very good response despite higher MIC! To date the following opinion was valid: no echinocandins in C. parapsilosis)

Micafungin (Mycamine)

- echinocandin of the 2nd generation
- broad-spectrum echinocandin
- approved for prophylaxis (e.g. after stem cell transplantation with neutropenia) and therapy of candida infections (systemic candidiasis, candida esophagitis)
- the only echinocandin that is also approved for prophylaxis
- on the market since 2009
- dosage (as short infusion):
  - prophylaxis: 50 mg 1 x daily
  - therapy:
    - systemic candidiasis: 100 mg 1x daily
    - candida esophagitis: 150 mg 1x daily
- no dose reduction in renal or liver insufficiency
- restriction of approval according to official drug information and EMEA due to warnings regarding liver damage (including liver tumors) in cases where other antimycotics are not effective ("last line")
- Physician is liable.

Antifungal therapy

- **candida***
  - **stable (i.e. no mechanical ventilation, no catecholamines) → fluconazole****
  - **instable → echinocandin*****
- **aspergillus****** →
  - **first line: voriconazole (in the case of neutropenia alternatively also isavuconazole)**
  - **second line:**
    - **caspofungin**
    - **liposomale amphotericin B**

*** duration of therapy: 14 days after the last negative blood culture (renewed blood cultures 2-3 days after initiation of therapy)**

**** only applies to C.albicans (and C. parapsilosis); C.glabrata, C.krusei, C. tropicalis → immediately echinocandin**

***** possibly de-escalation to fluconazole after 5 days (only in case of C. albicans and stable patient)**

****** duration of therapy: at least 4 weeks (best: 6 weeks) [until the HR-CT is inconspicuous])**

The European guideline (ESCMID guidelines for the diagnosis and management of Candida diseases 2012: non-neutropenic adult patients; Cornelly et al, Clinical Microbiology and Infection) also recommends echinocandins as the highest grade (recommendation grade A) for candidemia or invasive candidiasis (not only for unstable but also for stable patients), while only a grade C recommendation is still available for fluconazole.

no more therapy of candidemia in critically ill patients with fluconazole (only fungistatic)! means of choice: echinocandins (fungicide)! Here one must do things in a big way (mortality 50%)!

Candida → echinocandin
Aspergillus → voriconazole

duration of therapy in invasive aspergillosis: at least 4 weeks!

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)

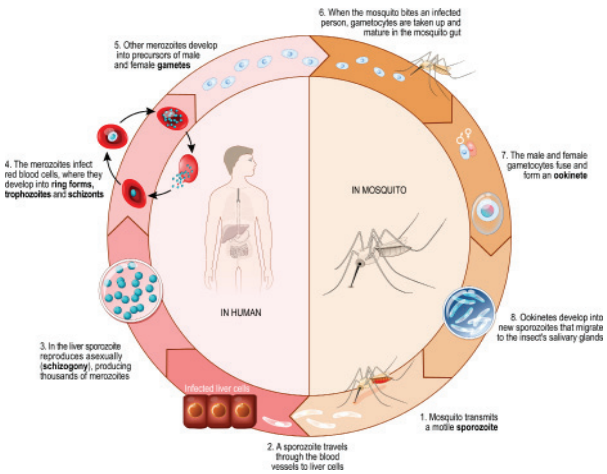


Fig. 1178 Life cycle of the plasmodia (malaria cycle): Asexual reproduction (schizogony) takes place in human: First the hepatocytes (exoerythrocytic phase) and then the erythrocytes (erythrocytic phase) are infected. Sexual reproduction (gamogony) takes place in the anopheles mosquito. After the mosquito 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

- interactions (reduction of the atovaquone level)
  - MCP (metoclopramide)
  - rifampicin
  - doxycycline
- contraindicated in creatinine clearance < 30 ml/min

Riamet

- = artemether + lumefantrine
- ⚠ indication: therapy of uncomplicated tropical malaria and tertian malaria
- 1 tablet = 20mg artemether + 120mg lumefantrine
- dosage: 4 tablets each at the beginning, then after 8h, 24h, 36h, 48h and 60h (i.e. 24 tablets in total)
- taking with a high-fat meal (e.g. with a glass of milk)
- side effects:
  - headache (often very severe; Note: Headaches are a classic side effect of Riamet. Nevertheless, we generously carry out a CCT for patients with thrombopenia to reliably rule out intracranial hemorrhage.)
  - QT interval prolongation
  - dizziness
  - insomnia
  - abdominal pain
- interactions (especially tricyclic antidepressants, neuroleptics, macrolides, fluoroquinolones, metoprolol, class IA and III antiarrhythmics): inhibition of cytochrome CYP2D6, which degrades artemether

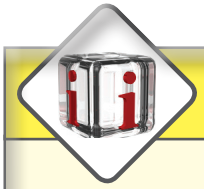
Always take Riamet tablets with a glass of milk!

Euratesim

- = dihydroartemisinin + piperaquine
- indication: therapy of uncomplicated tropical malaria
- 1 tablet = 40mg dihydroartemisinin + 320mg piperaquine
- dosage: for 3 days
  - < 75kg: 3 tablets per day
  - > 75kg: 4 tablets per day
- taking: fasted
- side effects:
  - QT interval prolongation
  - headaches
  - anemia
  - asthenia
  - fever
  - abdominal pain
  - seizure
  - transaminases ↑

Halofantrine (Halfan)

- reserve agent for the therapy of tropical malaria in WHO zone B/C
- 1 tablet = 250mg; 6 tablets (1500mg) at the beginning, then after 6h and again after 12h, repetition after one week
- cave: QT interval prolongation (ECG controls)



Malaria
therapy

- **quartan malaria: chloroquine**
- **tertian malaria: Riamet or Malarone (followed by primaquine)**
- **tropical malaria**
  - **uncomplicated:**
    - **Riamet (artemether + lumefantrine; best)**
    - **Malarone (atovaquon + proguanil)**
    - **Euratesim (dihydroartemisinin + piperaquine)**
  - **complicated: artesunate (1st choice), ansonsten quinine (quinine in combination with doxycycline or cindamycin)**

Malaria
therapy: pregnancy

- **quartan malaria: chloroquine**
- **tertian malaria: therapy like tropical malaria, but without subsequent primaquine**
- **tropical malaria**
  - **uncomplicated:**
    - **1st trimenon: quinine p.o. + clindamycin**
    - **2nd/3rd trimenon: Riamet (artemether + lumefantrine)**
  - **complicated:**
    - **1st trimenon: quinine i.v. + clindamycin**
    - **2nd/3rd trimenon: artesunate**

Symptomatic Therapy

- fever → fever reduction:
  - physical
  - pharmacological
    - e.g. paracetamol, ibuprofen
    - no ASA (inhibition of thrombocyte aggregation in anaway increased risk of bleeding)
- hypoglycemia (frequent [due to the parasitic consumption]; therefore tight glycemic control) → glucose infusions
- anemia → red cell concentrate transfusions only restrictive, since the microcirculation disorders can be intensified!
- fluid administration rather restrictive (danger of pulmonary edema; up to max. 1000ml/d or CVP < 5 cmH_20 [optional])
- acute renal failure → renal replacement therapy
- acute respiratory failure → intubation and mechanical ventilation
- seizures → benzodiazepinen (Phenytoin is contraindicated during therapy with in quinine.)
- parasitemia > 20% → exchange transfusions (very ra-

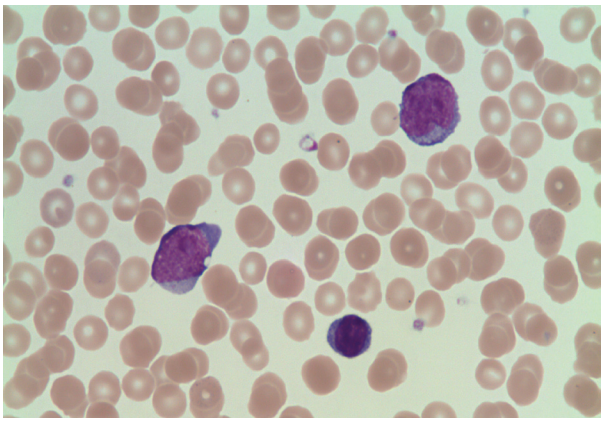


Fig. 1235 Acute leukemia as a cause of DIC: The blasts are recognizable. Especially acute promyelocytic leukemia leads to DIC (courtesy of PD Dr. Drobnik, Medical Director of the MVZ Synlab Regensburg).

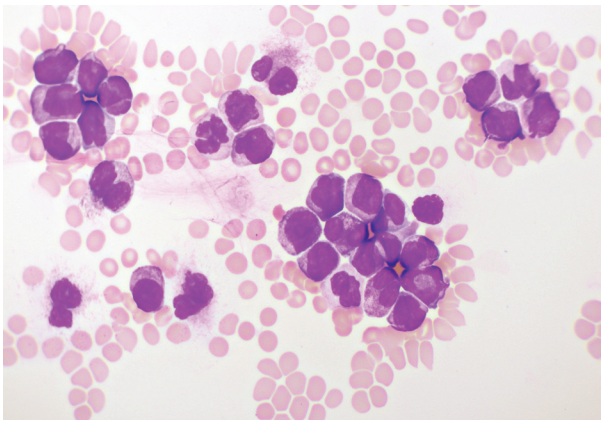


Fig. 1236 acute promyelocytic leukemia (APL)

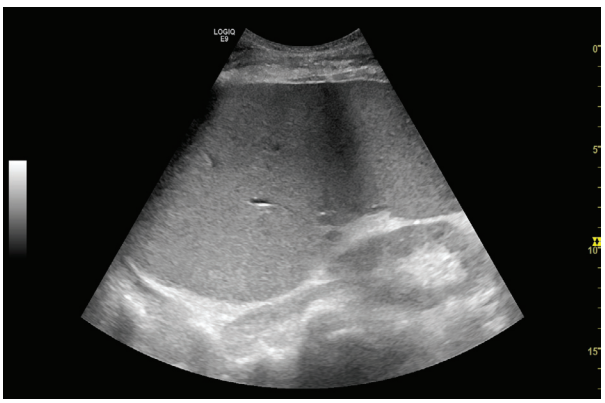


Fig. 1237 sonography of the abdomen: pronounced splenomegaly in acute myeloid leukemia (here APL)

APL
acute promyelocytic leukemia

- FAB classification: AML M3
- the rarest acute myeloid leukemia
- acute myeloid leukemia with the best prognosis (remission rate: 85%; long-term survival rate: 75%)
- mittleres Alter: 40-50J.
- cave: early mortality caused by coagulation disorders
  - in 90% bleeding (⚠ often fatal!)
  - in 10% thromboembolism
- diagnostic evidence: chromosome translocation t (15;17) or detection of the fusion gene PML/RARA (PML: promyelocytic leukemia protein; RARA: retinoic acid receptor alpha)
- Sanz score (for risk stratification):
  - low: leukocytes < 10000/µl, platelets > 40000/µl
  - intermediate: leukocytes < 10000/µl, platelets < 40000/µl
  - hoch: leukocytes > 10000/µl
- therapy (a hematological emergency [immediate transfer to an appropriate center]!):
  - low and intermediate risk: ATRA (all-trans-retinoic acid [vitamin A]) + ATO (arsenic trioxide), i.e. healing without chemotherapy (despite leukemia)
  - high risk: ATRA + anthracycline + Ara-C (cytarabine)
  - note: in the case of hyperfibrinolysis, only cautious administration of an antifibrinolytic agent (such as tranexamic acid), as this can induce thromboembolism

Types

- according to duration:
  - acute
  - chronic (e.g. liver cirrhosis)
- according to course:
  - compensated (non-overt)
  - decompensated (overt)

Epidemiology

- ⚠ 35% of all patients with severe sepsis
- 😕 one of the most frequently overlooked diagnoses in intensive care
- mortality dependent on the underlying disease

DIC: often overlooked!
Almost everyone thinks of HIT, almost nobody of DIC!

Laboratory

- platelets ↓ (most sensitive parameter)
- fibrinogen ↓ (cave acute phase protein → in inflammation ↑; also increased after HES administration)
- AT III ↓
- Quick ↓ or INR ↑
- PTT ↑

bleeding [sugillations, ecchymoses], massive hematomas ["as if beaten"])
- musculoskeletal (bleeding into the musculature, possibly compartment syndrome, bleeding into joints [but in contrast to congenital hemophilia in acquired hemophilia almost never])
- urogenital (hematuria))
- gastrointestinal
- pulmonary
- intraabdominal, retroperitoneal
- intrakranial

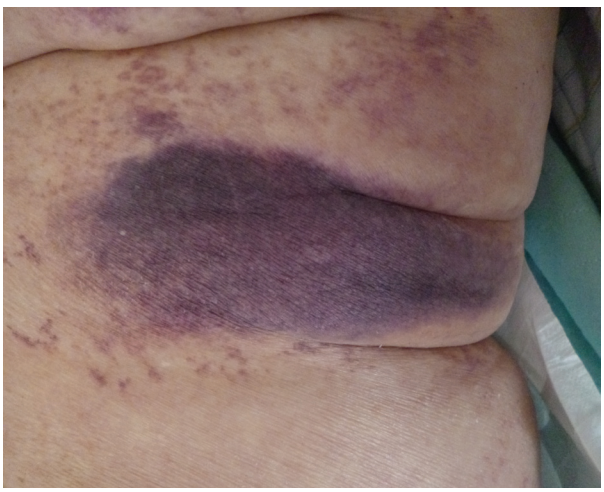


Fig. 1254 Distinct hematoma in the left flank (Large-scale bleeding is a typical consequence of a plasmatic coagulation disorder [disorder of secondary hemostasis].)

In older patients with sudden spontaneous bleeding (especially skin), always remember acquired hemophilia A (AHA)!

Diagnosis

- (often no longer measurable)
- normal values for platelets, Quick / INR, fibrinogen, thrombin time (syn.: plasma thrombin time [PTZ]; exclusion of effect of unfractionated heparin), anti-factor-Xa (exclusion of effect of low molecular weight heparins)
- exclusion of lupus anticoagulant as a cause of PTT prolongation (An antiphospholipid syndrome does not cause bleeding but thrombosis.)
- plasma exchange test (mixed test, in vitro tube test: In the laboratory, normal plasma, i.e. plasma from a healthy person, is mixed with the patient's plasma in a tube at a ratio of 1:1: In contrast to a real factor deficiency, PTT does not normalize here. The PTT remains extended.)
- reduced factor VIII level and activity (Factor VIII is an acute phase protein, so the level can be false normal especially with inflammation)
- Bethesda sest:
  - determination of antibody concentration to factor VIII (inhibitor titre)
  - specification in Bethesda units: 1 Bethesda units B.U. = amount of inhibitor necessary to halve factor VIII activity in healthy plasma
  - classification:
    - high antibody titre (high titre): > 5 B.U./ml
    - low antibody titre (low titre): < 5 B.U./ml

unclear bleeding + PTT ↑ → acquired hemophilia A (AHA)!

PTT ↑:
<u>bleeding</u> → acquired hemophilia A (AHA)
<u>thrombosis</u> → antiphospholipid syndrome (APS)

Never ignore unclear PTT increase (always clarify!)

Prolongation of PTT
causes

- **incorrect sampling (preanalytics; e.g. insufficiently filled tube, stowage for too long, hematocrit > 60%; most common cause, therefore always control it first!)**
- **drugs (especially heparin [especially UFH; less LMWH], coumarins, dabigatran [not the other NOAC], argatroban, fibrinolytics)**
- **hemophilia**
  - **congenital:**
    - **hemophilia A (85%; factor VIII deficiency)**
    - **hemophilia B (15%; factor IX deficiency)**
  - **acquired: acquired hemophilia (inhibitors)**
- **von Willebrand disease**
- **antiphospholipid syndrome**
- **DIC**
- **liver insufficiency**
- **deficiency factor I (fibrinogen), XI, XII (note: Factor XII deficiency leads to a pronounced PTT prolongation, but almost never to bleeding [irrelevant].)**

very common and completely harmless cause of a PTT prolongation: factor XII deficiency!

Therapy

- for the therapy of bleeding or prophylactically before emergency surgery: bypass preparation
  - recombinant activated factor VII (NovoSeven)
    - officially also approved for this purpose
    - means of first choice (especially for severe blee-

the clot early (including pathological lysis indices [CLI, ML]), this is not the case with APTEM (here normal finding). The EXTEM-ML is pathological (> 15%), the APTEM-ML is normal (<15%). Tranexamic acid should now administered therapeutically. If, in addition to the EXTEM-ML, the APTEM-ML is also pathological, the instability is not due to hyperfibrinolysis, but (most often) due to a factor XIII deficiency in the sense of the term of a fibrinogen polymerization disorder. Then factor XIII should be administered.

- FIBTEM:
  - to differentiate the plasmatic from the thrombocyte part of the clot formation (only the part of the fibrinogen, i.e. without platelets, of the coagulation. is measured)
  - activation: like EXTEM + blockade of platelets (cytochalasin D)
  - FIBTEM-A10 < 7mm: fibrinogen deficiency → administration of fibrinogen (target FIBTEM-A10: 10-12mm)
- HEPTEM:
  - for the detection of a heparin effect: Here it is examined whether a heparin effect (i.e. too much heparin; e.g. after intraoperative retransfusion of blood from an autotransfusion system [CellSaver]) is the cause of a bleeding. If this is the case, protamine is administered to antagonize the heparin.
  - for ROTEM analysis in fully heparinized patients
  - activation: like INTEM + blockade of heparin (heparinase)
  - Heparin effect is present if the CT and CFT are prolonged in the INTEM, but normal in the HEPTEM.
- note: NATEM (without activator and inhibitor; NA: not activated; only addition of calcium chloride for recalcification)

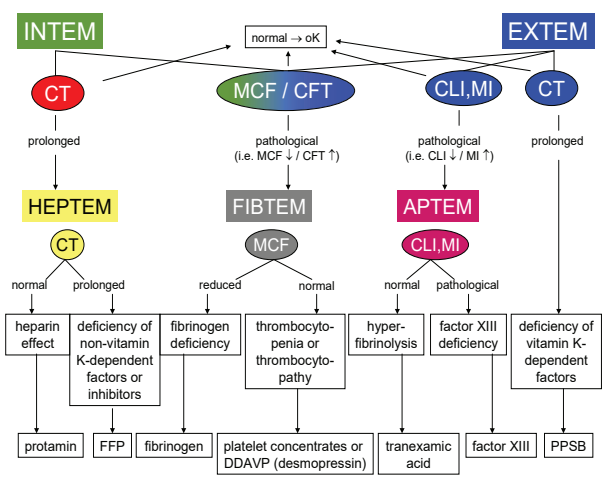


Fig. 1262 Interpretation of ROTEM (procedure for acute diffuse bleeding); as an alternative to the fibrinogen deficiency, it can also be a fibrinogen polymerisation disorder (i.e. factor XIII deficiency); note: In the case of active bleeding despite normal CT and MCF in EXTEM and INTEM, the following should be considered or checked: cofactors (general conditions such as hypothermia, metabolic acidosis, hypocalcaemia), presence of bleeding that can be surgically stopped, von Willebrand disease, thrombocytopathy due to platelet inhibitors (e.g. ASA)

Therapy algorithm
ROTEM

- **EXTEM-ML > 15%**
  - **APTEM-ML < 15% → hyperfibrinolysis → administration of tranexamic acid**
  - **APTEM-ML > 15% → factor XIII deficiency → administration of factor XIII (fibrogammin; e.g. 1250 U)**
- **FIBTEM-A10 < 7mm: fibrinogen deficiency → administration of (Haemocomplettan)**
  - **FIBTEM-A10 0-3mm: 6g**
  - **FIBTEM-A10 3-6mm: 3g**
- **EXTEM-CT > 80s (with normal FIBTEM) → deficiency of vitamin K-dependent coagulation factors → administration of PPSB:**
  - **EXTEM-CT 80-100s: 500E Beriplex or 600E Baxalta**
  - **EXTEM-CT 100-120s: 1000E Beriplex or 1200E Baxalta**
  - **EXTEM-CT > 120s: 1500E Beriplex or 1800E Baxalta**
- **INTEM-CT > 240s:**
  - **HEPTEM-CT normal → heparin effect → administration of protamin**
  - **HEPTEM-CT prolonged → deficiency of non-vitamin K-dependent coagulation factors or inhibitors → administration of FFP**
- **EXTEM-A10 < 40mm (FIBTEM-A10 > 7mm, platelets < 50000/µl) → lack of platelets → administration of platelet concentrates**

Limitations

- thrombocytopathies (e.g. thrombasthenia Glanzmann [absence of GIIb/IIIa receptors])
- platelet inhibitors (ASA, clopidogrel, prasugrel, ticagrelor)
- von Willebrand disease
- factor XIII deficiency
- GpIIb-IIIa receptor antagonists (especially abciximab)
- only relatively low sensitivity for oral anticoagulants (e.g. coumarins; NOAC, however, have no influence on the measured values), LMWH, danaparoid (Orgaran) and fondaparinux (Arixtra)
- no standard validation (yet) using round robin tests

Multiplate

Definition

- multiple platelet function analyzer (Roche company)
- measurement of platelet function (overview of possible

Fig. 1265 Idarucizumab (Praxbind): the antidote against dabigatran; 1 amp. = 50ml = 2.5g

Antagonization
in case of bleeding (part I)

- fibrinolytics (in case of fibrinolysis) → antifibrinolytics (tranexamic acid) + fibrinogen
- heparin (UFH) → protamin
  - 1 amp. = 5ml, 1ml = 1000 IU = 10 mg
  - simple dosage: 1000 IU of protamine antagonize 1000 IU of heparin (equimolar).
  - also possible with LMWH (however, only 60% of the dose is antagonizable), e.g. enoxaparin: within the first 8 hours after administration 100 IU of protamine per mg of enoxaparin, 8-12h: 50 IU of protamine per mg of enoxaparin, > 12h: protamine no longer indicated
  - side effects:
    - allergic reaction (especially with fish protein allergy, as protamine is obtained from salmon, and with status after vasectomy in men [sterilization; reason: After vasectomy, the sperm are reabsorbed into the circulation. 60% of men develop auto-antibodies, including against proteins similar to protamine.])
    - BP ↓↓ (therefore slowly as a short infusion)
    - pulmonary vasoconstriction, PAP ↑
    - hypercoagulability
- antiplatelet drugs (ASA, clopidogrel, prasugrel → desmopressin (Minirin; 1 amp. = 0.4µg; dosage: 1 amp. per 10kg BW; note: not effective with ticagrelor (only administration platelet concentrates possible here; monoclonal antibody PB2452 as antidote in phase I study [Bhatt et al, N Engl J 2019])

Fig. 1266 Protamin: 1 amp. = 5ml = 5000 IU (1ml = 1000 IU = 10mg)

Antagonization
in case of bleeding (part II)

- oral anticoagulants:
  - vitamin K antagonists (coumarins) → vitamin K (Konakion) 10mg i.v. (not as a short infusion*) + PPSB 50 IU/kg BW
  - novel oral anticoagulants (NOAC: dabigatran, rivaroxaban, apixaban, edoxaban)
    - PPSB 50 IE/kg BW (25 IU/kg are usually sufficient [but not for intracranial bleeding: here 50 IU/kg])
    - activated charcoal (if ingestion < 3h)
    - hemodialysis: only possible in case of dabigatran
    - tranexamic acid
    - antidots
      - factor II inhibitor (dabigatran): idarucizumab
      - factor X inhibitors (rivaroxaban, apixaban): andexanet alfa
    - with severe life-threatening bleeding (e.g. intracranial):
      - activated prothrombin complex concentrate (FEIBA) 50 IU/kg BW or
      - recombinant factor VII (NovoSeven; 100 µg/kg BW; more expensive but also more effective than FEIBA)
- GpIIbIIIa receptor antagonists:
  - abciximab: not dialyzable, possibly administration of platelet concentrates
  - tirofiban: dialyzable
  - eptifibatide: dialyzable

* Vitamin K is lipophilic and is present in the solution as a micellar structure. If it is diluted (e.g. as a short infusion) this structure is destroyed and the solubility is reversed. Then the vitamin K precipitates as small fat droplets and often condenses on the edge of the bag/bottle; therefore vitamin K administration only iv. or p.o.; i.v.: 1 amp = 1ml = 10mg; p.o. 1ml emulsion = 20gtt = 20mg (1gtt = 1mg)

parenteral administration of vitamin K (Konakion): never as a short infusion (since it is fat-soluble and thus precipitates and becomes ineffective), but always only i.v. (alternatively: p.o.)!

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

Pathophysiology

- auto-antibodies against complex 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

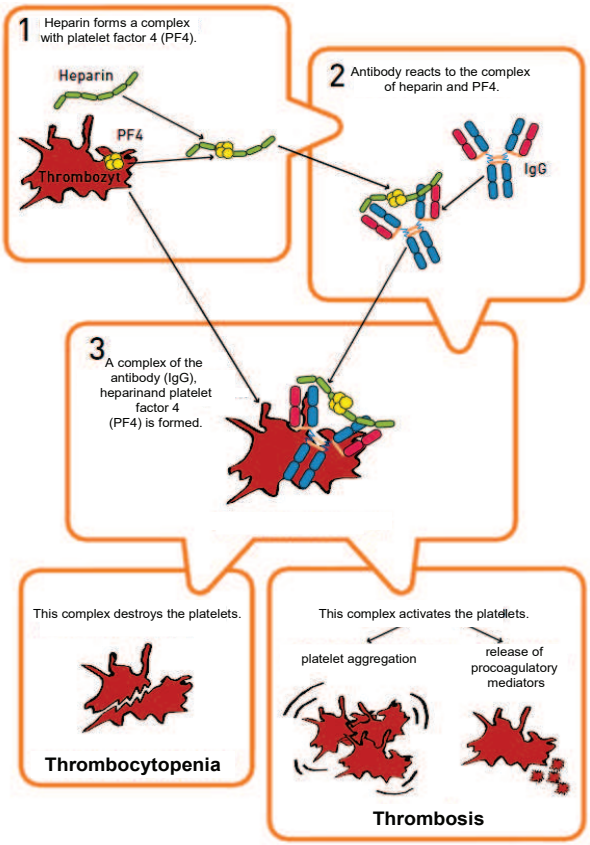


Fig. 1268 Pathophysiology of HIT II [18]

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)

ELISA

- detection of heparin-induced platelet factor IV / heparin antibody (standard)
- duration: 1-2 hours
- ⚠ high sensitivity (99.5%): negative test (almost) excludes HIT II!
- ⚠ low specificity (only 50%; 40% of all patients who received heparin develop antibodies)
- often false positive results!

HIPA test

- heparin-induced platelet activation
- not suitable for emergency diagnosis (duration: 1-2

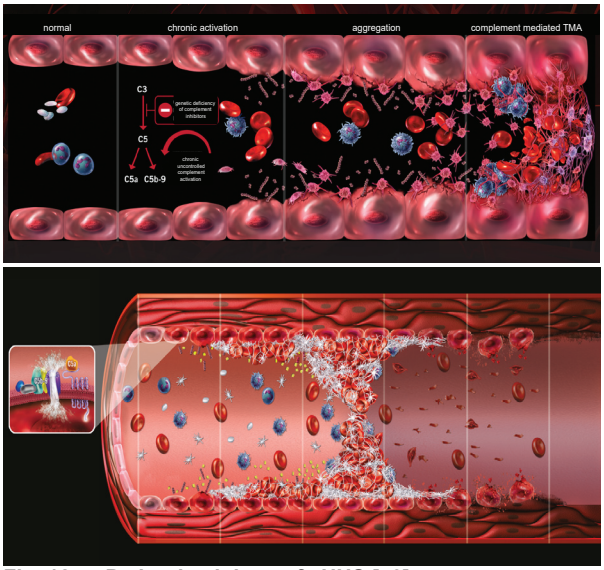


Fig. 1275 Pathophysiology of aHUS [43]

Etiologyy

- 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 1052) 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
- 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
- indication for typical HUS (STEC-HUS; off-lable; during the HUS epidemic in Northern Germany in 2011 eculizumab was necessary in 50%; the Shiga toxin also causes an uncontrolled complement activation): despite 3 plasmaphereses still (no improvement under plasmapheresis):
  - platelets < 50000/µl

ONCOLOGICAL EMERGENCIES

Introduction

The decision whether to transfer a critically ill patient with an underlying haemato-oncological disease (especially AML, autologous / allogeneic stem cell transplantation, non-Hodgkin´s lymphoma) to an intensive care unit or not is often not easy in clinical practice. In chronically bedridden patients (> 3 months), lack of a life-prolonging therapy option, uncontrolled or refractory GvHD or an overall prognosis of less than one year, the intensive care admission must certainly be considered very critically. Life and not suffering should be prolonged. 20% of all intensive care patients have cancer. The most common reason (No. 2: sepsis; especially neutropenia) for admitting a hematological-oncological patient to intensive care is acute respiratory insufficiency. Early non-invasive ventilation is particularly important here: It leads to a significant reduction in mortality (Hilbert et al, N Engl J 2001; Molina et al, Crit Care 2012) and should be used early to avoid intubation. However, another study (Lemiale et al, JAMA 2015) could not show any mortality reduction in cancer patients with acute respiratory insufficiency (mostly due to pneumonia) by using NIV compared to pure oxygen therapy. Intensive-care mortality is determined by organ dysfunction and not by malignancy. Malignancy determines long-term mortality. If the acute problem leading to admission to the intensive care unit is being survived, the prognosis is exactly the same as before admission to the intensive care unit. They practically return to their initial prognosis before the intensive care stay.

The prognosis of critically ill cancer patients has improved considerably in recent years: Mortality has been reduced by 30% (absolute risk reduction) over the last thirty years (i.a. Gristina et al, Crit Care Med 2011). Long-term survival is possible with some tumors even in the metastatic stage (e.g. in metastatic malignant melanoma, 20% still live 10 years). Therefore, a generally restrictive intensive care unit admission policy for cancer patients should be abandoned. In addition, the emergency and intensive care physician is often unable to make an adequate assessment of the prognosis due to the time pressure of the emergency situation, incomplete information and possibly also a lack of knowledge of the underlying disease. Patients with advanced solid tumors should also be treated with full code management according to the recommendations of an international team of experts (Azoulay et al, Ann Intensive Care 2011) if a life-prolonging oncological therapy option still exists. This includes, for example, patients with colorectal cancer with liver metastases, who today have a survival time of approximately 30 months with modern chemotherapy. In principle, full code management is indicated for remission, existing curative therapy approach or initial diagnosis (prognosis > 1 year). On the other hand, patients with "common diseases" are often admitted to intensive care ("without batting an eyelid"), although the prognosis, which is unfortunately often unknown to many, is sometimes considerably worse than for many cancers: e.g. heart failure (5-year-survival rate 50%), COPD (GOLD IV: 5-year survival rate 30%) or cirrhosis of the liver (Child C: 1-year survival rate 50%). Furthermore, the fact that a palliative patient is still young is in itself not a sufficient reason for admission to an intensive care unit ("Oh, he's still so young!"). Children also die of cancer!

Intensive mortality is determined by organ dysfunction and not by malignancy!

no generally restrictive intensive admission policy towards cancer patients!

In any case, mortality has decreased significantly over the last twenty years: For example, the mortality rate of a mechanically ventilated hematological-oncological intensive care patient in the early 1980s was 90%, but is currently 58% (Gristina et al, Crit Care Med 2011). No other area of intensive care medicine has been able to achieve such a successful improvement in prognosis (reduction of mortality by more than 30% in the last twenty years)! In the ICU trial (Lecuyer et al, Crit Care Med 2007) it could be shown that in the first three days not a single parameter made it possible to reliably estimate the course and the prognosis. Therefore, the guiding principle is: no therapy withdrawal before day 3! The not infrequently practiced strategy of placing the cancer patient in the intensive care unit for one or two days, observing the course and then possibly withdrawing is therefore a very bad one! Meanwhile it is also known that neither recent chemotherapy nor neutropenia have a negative influence on survival (i.a. Vandijck et al, Intensive Care Med 2008). The mortality rate of haematological-oncological patients requiring intensive care (Bird et al, Br J Anaest 2012) is:

- ICU mortality: 34%
- hospital mortality: 46%
- 6-month mortality: 59%

The 12-month mortality rate of purely hematological intensive care patients is 43% (Azoulay et al, JCO 2013). In a meta-analysis (de Vries et al, Crit Care Med 2017), long-term outcome of hemato-oncological intensive care patients with multiple organ failure was examined. The

CSF or GM-CSF are explicitly not (no longer) recommended in the AGIHO guideline "Sepsis in Neutropenic Patients" 2018 (level of evidence DI), as there was no evidence of a benefit in the studies (i.a. Darmon et al, ICM 2002)! On the other hand, especially patients with sepsis are at risk that after the growth factor-induced normalization of the neutrocytes, the respiratory function deteriorates up to ARDS due to the leukocyte aggregation described above.

- G-CSF is also not approved for therapy, but only for prophylaxis!

Prophylaxis

Primary prophylaxis

- with corresponding risk constellation (therapy protocol, age, cycle interval)
  - Especially with dose-tight protocols, G-CSF support is usually necessary.
  - example: R-CHOP 14 in patients > 60 years with B-NHL (non-Hodgkins´s lymphoma), escalated BEACOPP with Hodgkin's lymphoma, Campath for CLL (chronic lymphocytic leukemia), 2-CDA with hairy cell leukemia, high-dose therapy with subsequent HSCT
- G-CSF s.c.: usually from day 3 of therapy until neutrocyte nadir is passed (here clearly recommended for prophylaxis in the case of high risk [in contrast to therapy])
- prophylactic antibiosis (for high risk): e.g. cotrimoxazole (e.g. Cotrim forte 960mg 2 x every second day) or fluoroquinolone, if necessary prophylactic antiviral therapy (e.g. famciclovir [Famvir] 2 x 250 mg)

high risk of neutropenic fever (> 20%) → prophylaxis with G-CSF and antibiotic

Secondary prophylaxis

- to avoid fever / neutropenia if fever occurred in neutropenia without primary prophylaxis or if intervention was necessary
- measures as with primary prophylaxis

Significance for ongoing chemotherapy

- The next chemotherapy cycle should only take place again if:
  - leukocytes > 3000/µl
  - platelets > 50000/µl
  - hemoglobin:
    - variable (if possible > 10 g/dl)
    - if necessary RCC administration
    - However, anaemia hardly ever delays therapy.
- avoidance of cycle interval extensions in adjuvant, neoadjuvant and curative protocols (e.g. aeminoma)
- in palliative therapies cycle shift, dose reduction or switch to another protocol

Pneumocystis jirovecii

Definition

- former name: pneumocystis carinii (PC; carini: Latin "nut brown"; however, this pathogen occurs only in rats and differs from the humanpathogen germ)
- today named after the Czech microbiologist Otto Jírovec (1907-1972)
- a fungus (tubular fungus [ascomycota]; previously assigned to the protozoa); particularities:
  - antifungal drugs ineffective because the cell wall does not contain ergosterol (Therefore, pneumocystis jirovecii, although it is a fungus, is not treated with an antifungal, but with an antibiotic [cotrimoxazole].)
  - no cultivation possible
- opportunistic pathogen of pneumonia (PCP: pnemocystis pneumonia)
- especially in immunosuppression
- most common opportunistic infection in HIV patients (used to be the most common AIDS-defining disease), often first manifestation of HIV disease
- ⚠ mortality: 25% (in non-HIV patients; in HIV patients: only 3%), ⚠ if requiring intensive care even 60%

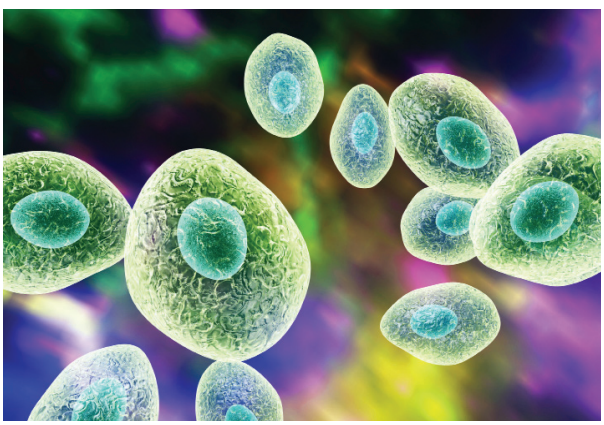


Fig. 1538 Pneumocystis jirovecii - schematic representation

Risk factors

- HIV (most common; 50% of all patients with pneumocystis pneumonia are HIV positive [Schmidt et al, Crit Care 2018]!)
- immunosuppressants (especially steroids, cyclophosphamide, methotrexate [MTX], calcineurin inhibitors [tacrolimus, cyclosporine], TNFα blockers, rituximab)
- rheumatological diseases (especially granulomatosis with polyangiitis [Wegener's disease; the highest PCP risk among all rheumatological diseases], SLE, dermato- / polymyositis, panarteriitis nodosa [Kussmaul-Maier´s disease], microscopic polyangiitis, rheumatoid arthritis)
- malignancies (especially under chemotherapy)

- tube length = distance external auditory canal - point of the chin - xiphoid process
- check position of the tube (inject 50 ml of air via bladder syringe and perform epigastric auscultation)
- fill the funnel with lukewarm water (100-200 ml, isotonic sodium chloride solution for children)
- lifting and lowering of the funnel (lift-lower principle)
- repeat until lavage fluid is clear (up to 10 liters)
- finally administration of activated charcoal and lactulose, then removal of tube
- good alternative: endoscopy (EGD with the therapeutic ["thick"] device) with targeted lavage (lavage [e.g. with Endowasher] and suction); if the stomach is empty or if the stomach was already empty beforehand, then the charcoal is given via the working channel of the gastroscope [note: This should not be forgotten either. Otherwise, due to the sedation during gastroscopy, it takes 1-2 hours until the patient can then take the charcoal without increasing the risk of aspiration.])

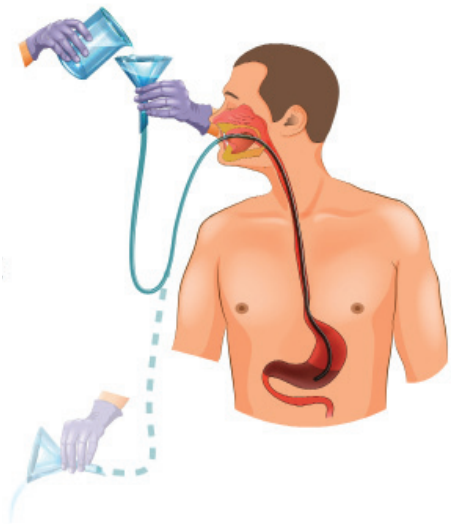
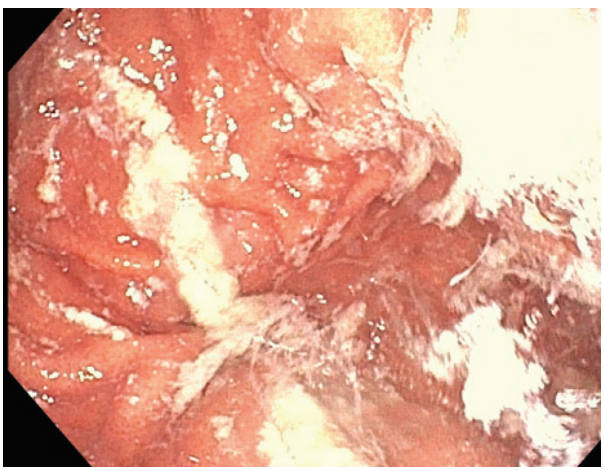


Fig. 1580 principle of gastric lavage

better than a blind gastric lavage: endoscopic gastric lavage!



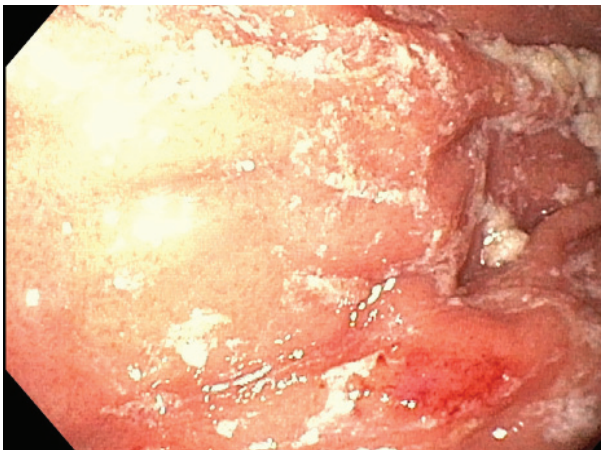
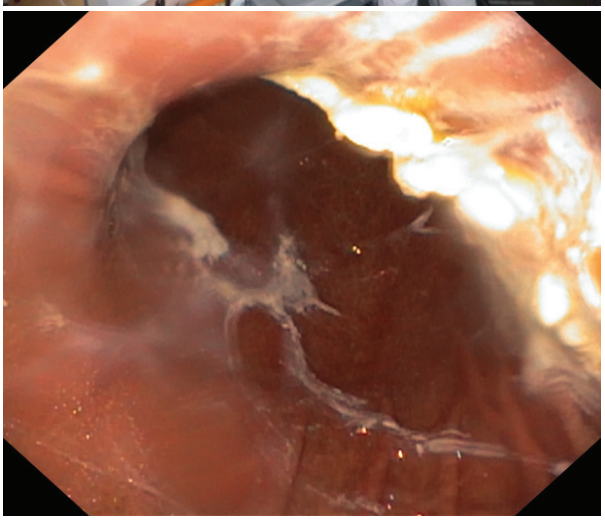


Fig. 1581 endoscopic gastric lavage in a female patient who had taken 50 tablets of paracetamol 30 minutes beforehand: You can still see clear tablet residues that are firmly attached to the stomach wall. These can be easily washed away with the Endowasher. The whole thing is then sucked off. It is best to always use the "thick" (therapeutic) gastroscope. Finally, the dissolved charcoal (Ultracarbon) is applied via a 50 ml syringe that is placed on the working channel of the gastroscope. This is best done post-bulbar (i.e. in the duodenum) to reduce the risk of aspiration.



Antidotes
Overview part II

- **metals**
  - **iron: deferoxamine (Desferal)**
  - **copper: D-penicillamine (Metalcaptase)**
  - **thallium: Berlin blue (Prussian blue)**
  - **mercury: DMSA (dimercatosuccinic acid [Chemet, Succimer])**
  - **arsenic, lead, chromium: dimercaptopropane sulfonic acid (DMPS, Unithiol, Dimaval)**
- **gases**
  - **cyanide (CN; hydrocyanic acid): hydroxycobalamin (Cyanokit; 1st choice), 4-DMAP (Dimethylaminophenol), sodium thiosulphate (S-Hydril)**
  - **carbon monoxide (CO): oxygen**
- **toxins of living organisms**
  - **death cap mushroom (amanita): silibinin (Legalon; 1st choice) or penicillin**
  - **botulism: botulism antitoxin (Behring)**
  - **adder: antiserum (Antivenin; Vipera TAB)**
- **syndromee**
  - **anticholinergic syndrome: physostigmine (Anticholium)**
  - **cholinergic syndrome: atropine**
  - **opiate syndrome: naloxone (Narcanti)**
  - **extrapyramidal syndrome: biperiden (Akineton)**
  - **serotonin syndrome: cyproheptadine (Peritol)**
  - **akinetic crisis: amantadine (PK-Merz)**
  - **"malignant" syndromes: dantrolene**
    - **malignant hyperthermia**
    - **neuroleptic malignant syndrome**
    - **malignant L-DOPA withdrawal syndrome**

Atropine

- 1 ampoule
  - small ampoule: 1 ml = 0.5 mg
  - large ampoule: 10 ml = 100 mg
- indications:
  - intoxication with organophosphates (alkyl phosphates; e.g. E605, Metasystox)
  - mushroom poisoning with muscarine syndrome: fibrecap (inocybe), common funnel (clitocybe)
  - intoxication with nicotine (e.g. ingestion of cigarettes)
- dosage (for intoxications with organophosphates):
  - 5 mg (e.g. 10 small ampoules) i.v.
  - children: 1 mg/kg
  - in case of cardiac arrest immediately 50 mg (large ampoule)

Berlin Blue (Prussian blue)

- ferric hexacyanoferrate (Antidotum Thallii-Heyl)
- ⚠ indication: intoxication with thallium
- mechanism of action: It interrupts the enterohepatic circulation of thallium, reduces the reabsorption of thallium in the intestine and thus reduces the half-life from 8 to 3 days.
- dosage: 3 g (10 capsules) p.o.
  - d1: every 3h
  - in the following days every 8 h (until thallium concentration in 24-hour urine collection < 500 µg/l)

Fig. 1584 Berlin Blue (ferric hexacyanoferrate): the antidote for thallium intoxication

Biperiden (Akineton)

- indication: extrapyramidal syndrome (e.g. intoxication with neuroleptics or metoclopramide)
- dosage: 2.5-5 mg (= 0,5-1 ml solution for injection) as a single dose i.v. or i.m., if necessary, repeat after 30 min
- maximum daily dose: 10-20 mg (= 2-4 ml of injection solution)

Calcium

- indications:
  - intoxications with calcium channel blockers
    - calcium gluconate 10%: 20-40 ml over 10 min i.v.
    - calcium chloride 10% (better): 10-20 ml over 10 min i.v.
  - intoxication with hydrofluoric acid: calcium gluconate 10%
    - local injection (infiltration of the affected tissue)
    - intravenous
    - in rare cases even intraarterial (e.g. in case of chemical burns on fingers)
  - hyperkalemia
    - fastest effect (does not lower the potassium level but protects the myocardium from cardiotoxic effect)
    - 10 ml calcium gluconate 10 % for 10 min (rule of 10; children: 0.2-0.3 ml/kg i.v.)
  - hypocalcemia
- types:
  - calcium gluconate
  - calcium chloride
- never in digitalized patients!

INTOXICATIONS WITH DRUGS

Classification

- "uppers" (stimulants: i.a. amphetamines, cocaine, ecstasy, synthetic cathinones)
- "downers" (i.a. opiates / opioids [e.g. heroin], cannabis, synthetic cannabinoids, gamma hydroxybutyric acid)

Epidemiology

- About 200,000 people in Germany take drugs (according to a report on the drug situation (2020) of the Federal Ministry of Health).
- approximately 1000-1500 drug-related deaths per year (2019: 1398; primarily due to heroin intoxication); note: deaths associated with "normal" drugs:
  - alcohol: 40,000 / year
  - nicotine: 110,000 / year
- most common drug: cannabis (mostly harmless; rarely relevant for intensive care; since March 2017 in Germany also prescribable via prescription [Controlled Substances Act])
- most common drug intoxication: heroin

Intoxication with heroin

Epidemiology

- most common drug intoxication
- m:w = 2:1
- mean age: 30-40 years
- Comorbidities of heroin addicts:
  - hepatitis C (75%), HIV (3%)
  - epilepsy (7%; never prescribe pregabalin [Lyrica] to a heroin addict, as they mostly become dependent on it and severe intoxication [see page 1330] can occur!)
  - CHD (17%)
  - bronchial asthma (8%)
  - cerebral infarction (autopsy in every 4th heroin user!)

Heroin

- diacetyl morphine
- a semi-synthetic, strongly analgesic opioid
- preparation:
  - Morphine is obtained by extraction from the dried milk juice (= opium) of the opium poppy (Paper somniferum).
  - heroin: acetylation of morphine (compound with acetic acid)
- agonist at the μ-opioid receptor
- duration of action: 6 hours
- drug scene slang: "H", "brown sugar", „schore“
- extremely high dependence potential
- lethal dose (non-dependent individual): 100 mg

History

Diacetyl morphine (heroin) was first produced from morphine and acetic acid in 1896 by the German chemist Felix Hoffmann (1868-1946) employed by Bayer. So heroin is a German invention. The substance was considered and touted as an omnipotent ("heroic") drug: It was used as a cough syrup (e.g. for infants), pain reliever, as a remedy for intestinal colic (e.g. for infants), against lung diseases (e.g. bronchial asthma), against multiple sclerosis, as an antidepressant, as an antihypertensive and as an agent for induction of childbirth or anesthesia. This is why the substance was given the artificial name "Heroin" (Greek: hero) from the Bayer company. The company also had the name and the manufacturing process patented accordingly. As a result, the substance (without major clinical testing [only animal experiments]) was sold and marketed worldwide for decades. Heroin became a "box office hit" and that is how Bayer ultimately achieved its breakthrough into a global corporation. Heroin and aspirin (first synthesis also by Felix Hoffmann) were the first chemical drugs in history to be marketed worldwide. Bayer finally stopped heroin production in 1931, and in 1971 heroin was banned by the Controlled Substances Act (BTM) in Germany. With the exception of Great Britain, the manufacture of heroin is now banned in all countries worldwide. A legal medicament ultimately became an illegal drug.

- dimethoxy-amphetamines
  - dimethoxybrom-amphetamine (DOB)
  - bromodimethyloxy-phenylethylamie (Bromo-DragonFLY, DOB-DragonFLY, 2C-B-Fly; "Bromo", "Nexus")
- methylendioxy-amphetaminee
  - methylendioxyamphetamine (MDA; "Ice", "love drug")
  - methylendioxymethylaminoindane (MDMAI)
  - methylendioxypyrovalerone (MDPV)
  - methylendioxyethyl-amphetamine (MDEA; "Eve")
  - methylendioxymethyl-amphetamine (MDMA)
- methylbenzodioxol-butanamine (MDBE; "Eden")
- paramethoxy-amphetamine (PMA; "Mitsubishi", "death"; is often wrongly offered as Ecstasy, significantly stronger effect)
- piperazine (new psychoactive drugs, mostly in pill form; SSRI inhibitors → serotonin syndrome):
  - benzyl-piperazine (BZP)
  - meta-chlorphenyl-piperazine (mCPP)
  - trifluormethylphenyl-piperazine (TFMPP)
  - dibenzyl-piperazine (DBZP)
- methylphenidate (Ritalin ["children's coke"])
  - indication: ADHD (attention deficit hyperactivity disorder) in childhood
  - not infrequently abuse in adulthood
- doping substances (e.g. athletes)
- ephedrine (a naturally occurring amphetamine from the herba ephedra plant)

Fig. 1602 Ecstasy

Fig. 1603 Crystal Meth

Synthetic cathinones

- mephedrone, methyl meth cathinone (MMC)
  - drug („seventh heaven", „Cloud 9", „MMC-Hammer", „M-Cat", "Ease", "Vanilla Sky", "White Magic")
  - was legally available as bath salt for a long time (so-called bath salt drugs) or plant food in Germany
  - forbidden in Germany since 2010
  - It is not uncommon for consumers to become extremely aggressive, so that self-protection should be observed here.
  - uptake:
    - p.o. (swallowing)
    - inhalative (smoking)
    - nasal (sniffing
- Methylon (MDMC [methylen-dioxy-methyl-cathinone]; "Mina", "Explosion")
  - a β-ketone analogue of MDMA (Ecstasy)
  - officially offered as a room air mixer in liquid form
  - uptake:
    - p.o. (swallowing)
    - nasal (sniffing
- alpha-pyrrolidinophenones
  - alpha-PVP (pyrrolidinopentiophenone)
    - white crystalline powder
    - uptake: nasally or inhalatively (vaporization)
    - legally available
  - alpha-PHP (pyrrolidinohexiophenone): similar to alpha-PVP, only slightly weaker

Fig. 1604 Mephedron

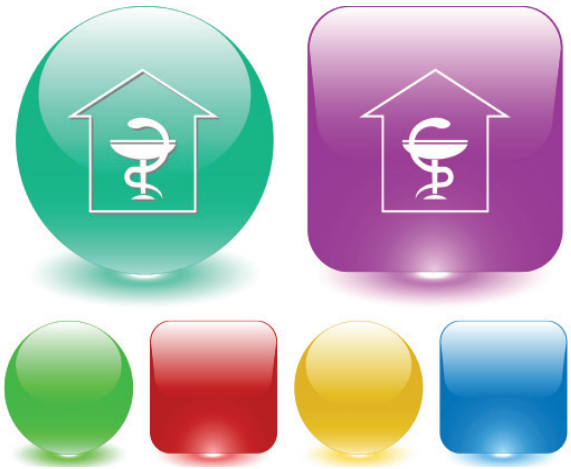
Effect

- stimulating
- euphoric, intoxicating
- concentration enhancing
- appetite suppressant

Symptoms

- psychomotor agitation, anxiety, paranoia
- bruxism (gnashing of teeth)
- hyperthermia, exsiccosis
- mydriasis
- hypertensive crisis
- tachycardia
- note: If symptoms similar to tetanus occur, one should

INTOXICATION WITH CHEMICALS



Intoxication with alkylphosphates

Definition

- syn.: organophosphates, phosphonic acid esters, acetylcholinesterase inhibitors
- occurrence
  - plant protection agents (pesticides, insecticide [The most frequently used pesticides are organophosphates!]); representatives
    - Parathion (E 605; taken from the market in Germany, but relatively easily available abroad, e.g. from the Czech Republic; furthermore, many farmers still have remainders)
    - Methydemeton (demeton S-methyl sulfoxide; Metasystox)
    - Dimethoate (Roxion, Bi 58)
    - Sulfotep (an acaricide [agent for combating mites and ticks]; no longer approved in the EU since 2007)
  - warfare agents (neurotoxins; poison gases)
    - Sarin (e.g. Tokyo subway sarin attack in 1995 committed by the Aum cult with 12 dead and 5500 injured persons; poison gas use in Syria 2013)
    - VX nerve agent (i.a. murder of the half-brother of the North Korean ruler Kim Jong Un in February 2017)
    - Nowitschok
      - Russian: "newbie" (developed in Russia)
      - a nerve warfare agent
      - i.a. assassination of the former Russian spy and defector to England Sergej Skripal and his daughter on March 8th, 2018, assassination of the Kremlin critic Alexej Navalny on August 20th, 2020
    - tabun (i.a. produced during the final phase of WWII, but no longer used; tons of it were dumped in the Baltic Sea after the end of WWII])
    - soman
- blue warning colour
- irreversible inhibition of acetylcholinesterase
- almost exclusively with suicidal intent
- typical cholinergic syndrome
- ⚠ mortality: 90%

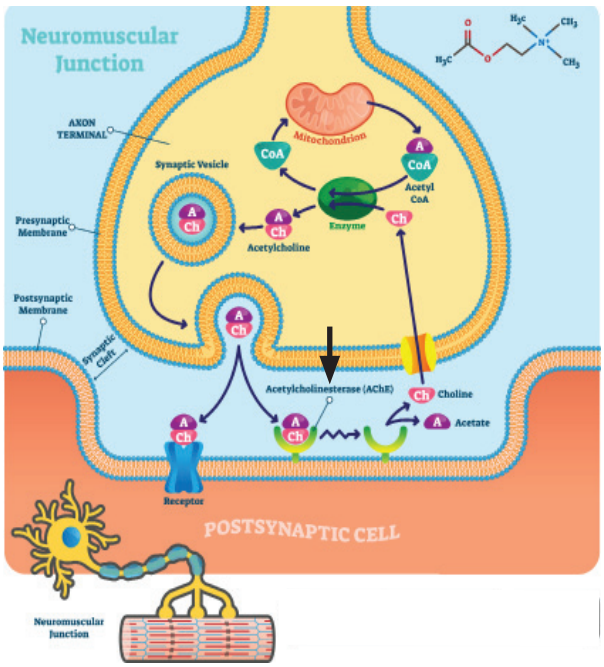


Fig. 1618 The enzyme acetylcholine esterase (AChE; see arrow) splits the neurotransmitter acetylcholine (ACh), which has bound to the acetylcholine receptor of the postsynaptic membrane, into acetic acid and inactivates it. Alkylphosphates inhibit acetylcholine esterase, so that there is permanent depolarization of the postsynaptic membrane, so that the cell is ultimately no longer excitable.

Etiology

- suicidal (almost ever)
- accidental (almost never)

Uptake

- peroral (No.1)
- percutaneous (No.2; contact poison; don't forget to protect yourself!)
- inhalative (No.3)

Symptoms

- blue-coloured oral mucosa (warning colour)
- excessive sweating
- secretion of saliva (blue foam), epiphora, rhinorrhoea, bronchorrhea (Patients “drown” in their own secretion!)
- urination, stooling
- nausea, vomiting (possibly blue coloured vomit), diarrhea, abdominal pain (spastic; "gastroenteritis")
- ⚠ foetor: smell of garlic (typical!)
- ⚠ miosis (very narrow pupils; prefinal: mydriasis)

- Benzene has formerly been used as a solvent, but was abandoned due to its carcinogenicity and replaced by less carcinogenic solvents such as toluene or xylene.

- uptake: mostly by inhalation
- intoxication:
  - accidental (e.g. work accident)
  - intentional ("sniffing")
- target organs:
  - acute intoxication: CNS
  - chronic intoxication: bone marrow (bone marrow toxicity up to complete aplasia; carcinogenic: increased risk of leukemia [especially AML] and lymphoma; especially in case of long-term exposure to benzene [i.e. at work])

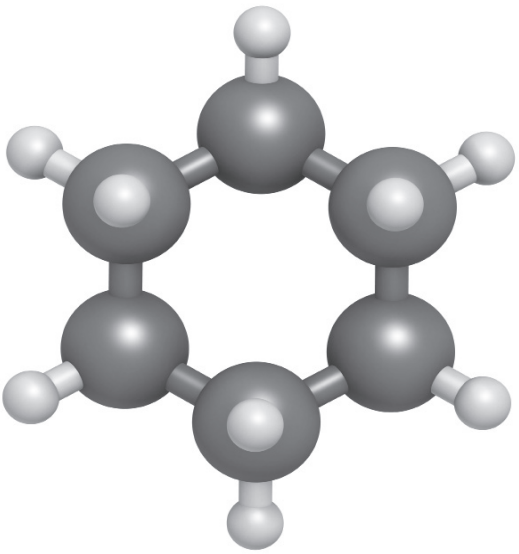


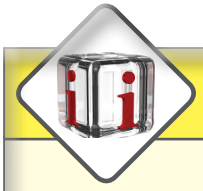
Fig. 1628 Benzene: the smallest organic aromatic hydrocarbons consisting of only one ring

Toluene

- syn.: methylbenzene
- occurrence: solvent in paints (main field of application), varnishes, adhesives, petrol (antiknock agent), diluents, degreasers (for metals, textiles), furniture care products, insecticides, pesticides
- Intoxications with toluene most often occur in adolescents who sniff it because of its intoxicating effect. Toluene is the main problem of sniffing addiction!
- significantly less toxic than benzene

Phenol

- syn.: hydroxybenzene, carbolic acid
- colorless substance with a typical unpleasant and penetrating aromatic odour
- use in the production of plastics and adhesives (formerly also used as disinfectants [for example in laundries])
- Phenol is also the degradation product of benzene.
- severe burns after drinking phenol, which are usually painless because phenol acts like a local anesthetic
- special form: dinitrophenol (DNP; see infobox)



Dinitrophenol
DNP

- **definition: yellowish crystalline powder (lipophilic, odorless, explosive)**
- **occurrence:**
  - **Dinitrophenol was already used as an explosive in World War I. DNP is highly explosive. After it was discovered that the workers in the explosives plants that made DNP lost significant weight from inhaling DNP, itwas used as a weight loss agent (slimming agent) for obesity in the 1930s.**
  - **In the meantime it is banned as a medicament due to severe side effects (i.a. agranulocytosis, hemolytic anemia, cataract, liver failure), but it is still illegally available in the internet as a slimming product ("diet pill", "fatburner"; mostly in capsule form; trade names: Chemox, Aldifen, Nitophen, Dinofan). It is especially used by bodybuilders, competitive athletes or patients with eating disorders. DNP is touted as the compound that will help you lose the most weight in the shortest possible time. It is also used industrially as a wood preservative, photo chemical and insecticide.**
  - **lethal dose: 1-3g**
- **effect: decoupling of oxidative phosphorylation in the mitochondrial respiratory chain (lactic acidosis)**
- **symptoms:**
  - **headache**
  - **nausea, vomiting**
  - **sweating (pronounced)**
  - **⚠ hyperthermia (pronounced [up to 45 °C] due to increased thermogenesis; "dieting by cooking yourself!")**
  - **flush (crimson face)**
  - **tachycardia, hypotension**
  - **disturbance of consciousness**
    - **qualitative (confusion)**
    - **quantitative (somnolence, coma)**
  - **muscle cramps, seizure**
  - **yellowing of the skin (after long-term use)**
  - **hyperglycemia**
  - **possibly multiple organ failure**
- **therapy: symptomatic (i.a. cooling, dantrolene as a therapy attempt)**

bodybuilders with unclear shock that almost "burns up" (fever up to 45 °C): think about DNP intoxication!

Styrene

- syn.: vinylbenzene
- colorless, sweet-smelling liquid
- use in the production of plastics (i.a. styrofoam, polystyrene [thermal insulation material])

INTOXICATION WITH METALS

- arsenic
- mercury
- thallium
- iron
- cadmium
- chrome
- lithium (see chapter antidepressants [page 1309])

Intoxication with arsenic

Definition

- metal; abbreviation: As
- types:
  - trivalent (arsenic trioxide [more toxic])
  - pentavalent (arsenate)
- white, odourless and tasteless powder
- lethal dose: 180 mg
- elimination: renal
- ⚠ the classic murder poison for centuries
  - Napoleon Bonaparte was killed with arsenic aged 51 on the island of St. Helena in 1821.
  - In "Inrigue and Love" by Friedrich Schiller the protagonist Ferdinand von Walter first poisoned his love Louise and then himself with arsenic.
- This intoxication is often not recognized because it usually looks like a severe gastroenteritis or food poisoning.

Fig. 1631 Arsenic has always been considered a classic murder poison. It has always been very popular: The murderers often escaped unscathed, since arsenic could not been detected until 1836. Also, it was not uncommon in times of poor hygiene, that people suddenly died after a severe gastroenteritis (the main symptom of arsenic intoxication!), so that people did not get suspicious.

Occurrence

- semiconductor industry (microchip production: Arsenic is used in gas form [so-called arsine] for doping.)
- pesticides in some countries (not in Germany)
- ore smelting, zinc electrolysis, glass manufacture
- admixture of lead alloys, to increase its solidity

Mechanism of action

- inhibition of pyruvate dehydrogenase (enzyme which brings pyruvate into the citric acid cycle → degradation to lactate → lactic acidosis)
- inhibition of α-ketoglutarate dehydrogenase (an enzyme of the citric acid cycle), so that arsenic replaces phosphate in ATP → decoupling of oxidative phosphorylation and thus of the respiratory chain
- inhibition of all enzymes containing thiol groups (disulfide bonds)
- vasodilatation of the capillaries ("capillary poison" → circulatory shock)
- chemical burn of the mucous membranes (especially gastrointestinal tract)
- encephalopathy (Arsenic passes the blood-brain barrier.)

Symptoms

- nausea, vomiting, diarrhea, abdominal pain (misdiagnosis "gastroenteritis", "food poisoning")

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).

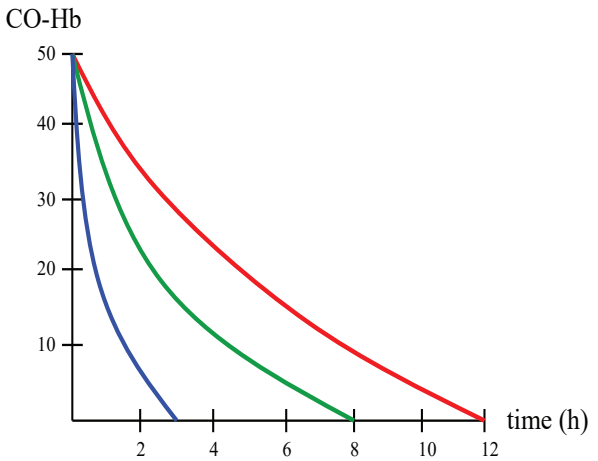


Fig. 1642 Hyperbaric oxygenation (pressure chamber therapy) can significantly shorten the half-life $T_{1/2}$ of CO-Hb. The curve is shown in red under room air (O_2 21%; $T_{1/2}$ 320min), green under 100% O_2 under normobaric (1 bar) conditions ($T_{1/2}$ 74min) and finally in blue 100% O_2 under hyperbaric (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 haemoglobin than to adult haemoglobin!)
- 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 al, Intensiv Care Med 2011) come to contradicting results or have methodological deficiencies. Two meta-analyzes (Juurlink et al, Cochrane Database Syst Rev 2011; Buckley et al, Cochrane Database Syst Rev 2011 [see box]) could not show any convincing benefit. In a randomized study (Weaver et al, N Engl J 2002), HBO was able to show a significant reduction in cognitive disorders after 6 weeks and 12 months. In two retrospective studies (Huang et al, Chest 2017; Rose et al, Crit Care Med 2018), HBO was able to show a mortality advantage in adults. This was not the case in a retrospective study in children (Chang et al, Pediatr Neonatol 2017). To date, there is not a single randomized controlled study that could have shown a mortality benefit for HBO in CO intoxication.

- In the 2015 ERC guidelines (ERC: European Research Council), the importance of HBO therapy for CO intoxication therefore was relativized and its importance downgraded ("Reduced emphasis is placed on hyperbaric oxygen therapy in carbon monoxide poisoning.")

meta-analysis

Hyperbaric oxygen for carbon monoxide poisoning
Buckley et al, Cochrane Database Syst Rev 2011

- meta-analysis from 6 RCTs
- 1361 patients (adults; not pregnant) with carbon monoxide poisoning
  - NBO (normobaric oxygenation)
  - HBO (hyperbaric oxygenation)
- results (HBO): 😟 no improvement in neurological outcome (after one month)
- note: The result should be treated with caution (according to the authors' statements). In 2 of the 6 RCTs an improvement in the neurological outcome could be demonstrated, in 4 it could not. The methods and statistics were relatively heterogeneous. In some cases, pressures that were far too low were used in the studies, and in some cases patients were included (much) too late, so that it was already clear that the HBO would no longer be effective.

Excursus: Hyperbaric Oxygenation (HBO)

Definition

- syn.: HBOT (hyperbaric oxygen therapy)
- medical treatment procedure in which patients receive pure oxygen in a pressure chamber with overpressure (p.d. > 1 bar, usually 3 bar; note: 1 bar = 100 kPa)
- HBO has two pillars:
  - overpressure
  - inhalation of pure oxygen (This is done [in spontaneously breathing patients] through a special, tightly fitting mask.)
- Our normal air pressure (normobaric, isobaric), in which we live, is 1 bar (= 100 kPa). With HBO there is a pressure of 3 bar (total pressure, i.e. an overpressure of 2 bar; note: pressure in a car tire: 2-3 bar).
- The pressure increases by 1 bar for every 10 m of water depth, i.e. 3 bar total pressure (= 2 bar overpressure) corresponds to a water depth of 20 m.
- development from diving medicine
- founded by Ite Boerema (Dutch cardiac surgeon from Amsterdam [1902-1980]; i.a. Lancet 1953: "Life without blood" [Completely desanguinated pigs were able to survive under HBO, although they only had pure plasma without erythrocytes.])
- In the blood, oxygen is predominantly (98.5%) chemically bound (to hemoglobin) and only a very small part (1.5%) is physically dissolved. The overpressure significantly increases the physical solubility of oxygen in

the plasma (8% at 3 bar).

- TS (therapy scheme): The first number relates to the pressure in kPa, the second number to the duration of the therapy (precisely: to the time of breathing pure oxygen) in minutes (e.g. TS 300-90: Therapy scheme with 300 kPa for 90min).
- pressure chambers:
  - multiplace chamber (for more persons)
  - monoplace chamber (only for one person; e.g. Haux-Oxystar)
- phases of treatment (so-called pressure trip, diving trip)
  - compression: creation of overpressure (hyperbar)
  - isopression: maintainance of overpressure
  - decompression: restoring of normal pressure (isobaric)
- HBO is based on the gas laws.

Gas laws

- Boyle-Mariotte: The product of pressure and volume is constant. In contrast to liquids, gases are compressible. If ambient pressure increases (e.g. with HBO), the volume (e.g. of gas bubbles in diving accidents, air bubbles in air embolism) decreases. The smaller the gas bubbles finally become, the smaller is their negative effect on hemodynamics (no more clogging of vessels). HBO thus causes a mechanical reduction of bubbles. The nitrogen bubbles are particularly dangerous because they are the largest. Everyone knows that from the swimming pool: When you exhale under water, gas bubbles rise: The small gas bubbles are the oxygen bubbles, the large gas bubbles are the nitrogen bubbles. If, for example, one dives under water with two plastic bottles, one of which is filled with water, the other one only with air (empty), the bottle filled only with air is completely compressed with increasing diving depth (compression; approximately at 10 m, i.e. overpressure of 1 bar), while the shape of the bottle filled with water does not change at all. The bottle filled with air expands again when it resurfaces (decompression).
- Dalton: The sum of the partial pressures results in the total pressure. An increase in the ambient pressure leads to an increase in the partial pressure for oxygen (e.g. ambient pressure 300 kPa [= 3 bar] leads to a pO_2 of 2280 mmHg with pure O_2 respiration).If an arterial BGA is performed on patients in a hyperbaric chamber, paO_2 values between 2000-2500 mmHg can be seen! Under hyperbaric (3 bar) conditions, the pO_2 is 20 times higher than under isobaric (1 bar) conditions. Example apnea divers: The deeper they dive, the higher the ambient pressure and the higher the pO_2 in the body.
- Henry: The amount of gas dissolved in a liquid is proportional to its partial pressure on the surface of the liquid. The higher the pressure, the greater the amount of gas that goes into solution (dissolvation). An increase in the ambient pressure leads to an increase in the dissolved oxygen in the blood (e.g. ambient pressure 300 kPa [= 3 bar] increases the physically dissolved proportion of oxygen in the blood from 0.3 ml O_2/dl blood to 6.8 ml O_2/dl blood). This can be explained using the example of a soda bottle: If the cap of the bottle is removed, the pressure inside the bottle decreases. The solubility of the gas (here carbon dioxide) in the liquid decreases and it spills.

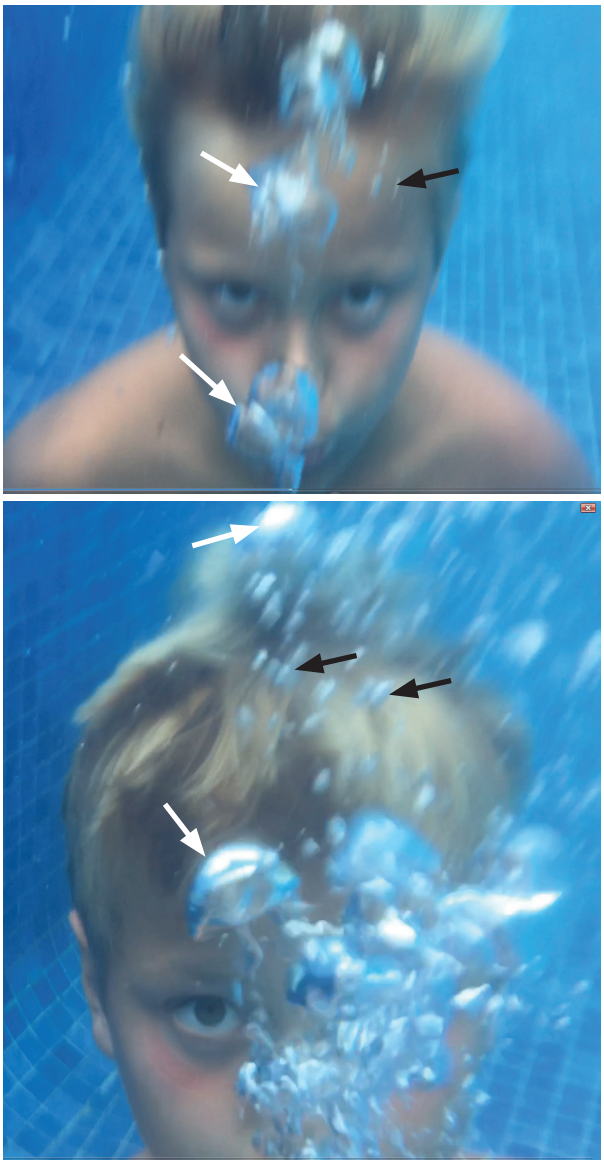
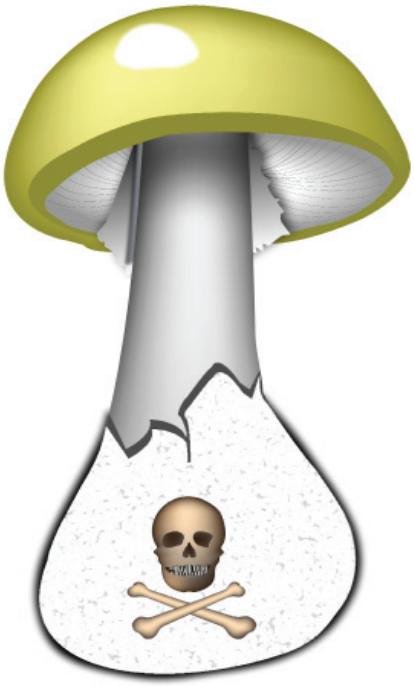


Fig. 1643 When you exhale under water, you can clearly see the gas bubbles of the exhaled air: This is composed mainly of nitrogen (78% [the same proportion as in the inspired air]) and oxygen (16%). The large bubbles are nitrogen bubbles (white arrows), the small bubbles are oxygen bubbles (black arrows). Due to their size, the nitrogen bubbles are particularly dangerous with regard to clogging of arteries (especially the brain, heart; with many thanks to my son Lukas).

INTOXICATIONS WITH MUSHROOMS



Definition

- syn.: mycetism
- Most physicians are no mushroom pickers and therefore do not know much about mushrooms. If a patient brings a mushroom, the poison information centre can contact a mushroom expert to identify the fungus species.
- if possible, collection of mushroom remains (e.g. residues of the mushroom meal, mushroom peels from the garbage, mushroom remains in vomit [Experts can sometimes even identify the mushroom by looking at the hyphae under the microscope.])
- causes:
  - accidental: The most frequent cause is confusion of poisonous mushrooms and edible mushrooms.
  - intentional (abusive): consumption of mushrooms as a drug (rarely; i.e. fly agaric, hallucinogenic mushrooms such as psilocybe)
- differential diagnoses:
  - allergy
  - mushroom intolerance
  - spoiled mushrooms (bacterial superinfection, protein degradation products because of reheating) or insufficiently cooked mushrooms
- By far the most common fatal mushroom poisoning is the death cap mushroom poisoning (phalloides / amanita syndrome).
- increase in mushroom poisoning in Germany (according to health insurance DAK in 2013 34 cases [41% more than in the previous year]; most of them in Bavaria)
- An important factor in mushroom poisoning is the latency period between the mushroom meal and the onset of symptoms. A distinction is made between mushroom toxidromes with short (< 4 h) and long (> 4 h) latency period.
- rules of thumb:
  - latency period:
    - short latency period: low toxic potential
    - long latency period: high toxic potential
  - structure:
    - sponge mushrooms (spongy surface under the cap [boletes]): low toxic potential
    - lamellar mushrooms (gills under the cap [agaricales]): high toxic potential

Mushroom toxidromes

- **mushroom intoxications with short latency period (< 4 h)**
  - **muscarinic syndrome**
  - **pantherina syndrome**
  - **coprinus syndrome**
  - **paxillus syndrome**
  - **psilocybin syndrome**
  - **resinoid syndrome**
- **mushroom intoxications with long latency period (> 4 h)**
  - **phalloides syndrome**
  - **gyromytic syndrome**
  - **oranellus syndrome**
  - **tricholoma syndrome**
  - **acromelalga syndrome**

Mushroom intoxications with short latency period

Muscarinic syndrome

Definition

- mushrooms:
  - fibrecap mushrooms (inocybe)
    - deadly fibrecap (inocybe erubescens; most common; turns red when pressed)
    - bittersweet inocybe (inocybe dulcamara)
    - conic fibrecap (inocybe fastigiata)
    - white fibrecap (inocybe geophylla)
    - spreading fibrecap (inocybe umbrina)
  - funnels (sloping head mushroom; clitocybe)
    - white funnel (clitocybe rivulosa)
    - clouded funnel (clitocybe nebularis)
    - ivory funnel (clitocybe dealbata)
    - heath funnel (clitocybe ericetorum)

Fig. 1664 death cap mushroom (amanita phalloides): A typical feature is the tuber at the bottom of the stem. The stem is elongated and slender. The hat is hemispherical. The mushroom has white lamellae.

Fig. 1665 deadly skullcap (syn.: toxic skullcap, funeral bell; galerina marginata; also contains the amatoxin and can therefore also cause phalloides syndrome)

Fig. 1666 sheathed woodtuft (kuehneromyces mutabilis; an edible mushroom: The deadly skullcap is sometimes confused with it.

Fig. 1667 Poisonous umbrella mushrooms also contain the amatoxin and can therefore also cause a phalloides syndrome.

Fig. 1668 Parosol (an edible mushroom): It is sometimes confused with poisonous umbrella mushrooms.

Gyromyta syndrome

Definition

- mushroom: false morels (gyromitra)
  - brain mushroom (gyromitra esculenta; most common)
  - giant's false morel (gyromitra gigas)
  - pouched false morel (gyromitra infula)
- toxin: gyromitrin (methylformylhydrazone)
  - The toxin is converted to monomethylhydrazine (MMH) through boiling or in the gastrointestinal tract.
  - MMH inhibits pyridoxal phosphokinase in the CNS and thus reduces the formation of pyridoxine (= vit-

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!)
- suicidal (e.g. mixing the blossoms in tea)

Fig. 1676 Monkshood: most toxic plant in Europe (should not be planted in gardens, in which children play)

Symptoms

- ⚠ relatively typical toxidrome (burning paresthesia on the acra and face)
- dry mouth
- nausea, vomiting, diarrhea, abdominal pain (convulsive; usually very strong)
- ear noises, impaired vision
- chills, strong sensation of cold, typical icy cold ("anesthesia dolorosa")
- • numbness all over the body ("I can no longer feel my body.")
- muscle weakness, respiratory paralysis
- seizures
- cardiotoxicity
  - bradycardia (i.a. third-degree AV block)
  - tachycardia (i.a. multidirectional ventricular tachycardia [several autonomous focal centres])
- dyspnoea, tachypnoea (later bradypnoea and apnoea)
- hypersalivation, hyperhidrosis
- mydriasis
- consciousness: mostly preserved for a long time

Therapy

- symptomatic
- possibly primary toxin elimination (gastric lavage in case of ingestion < 1 h, activated charcoal)
- possibly ERCP with insertion of a nasobiliary probe (Wurbs probe) to drain the bile to interrupt the enterohepatic circulation to which the toxin is subject (rinsing the probe with 500ml NaCl 0.9% / 24h)
- cardiac arrhythmia
  - bradycardic: if necessary temporary pacemaker
  - tachycardic: amiodarone (Amiodarone is a sodium channel blocker. Aconitine activates the sodium channels).
- in case of prolongation of the QT interval or torsade de pointes: magnesium (initially 2g as a bolus i.v., then continuously 120-140 mg/h until a serum concentration of 1.2-2.0 mmol/l is reached)
- sodium bicarbonate 8.4%
- 20% lipid emulsion (e.g. Intralipid, Clinoleic)
  - Aconitine is highly lipophilic.
  - dosage: 100 ml as a bolus, then administration of the remaining 400 ml over 20 min

Tobacco (nicotine intoxication)

Definition

- nicotiana tabacum
- poisonous plant of the year 2009 (highly toxic!)
- second most common (No.1: medication) intoxication in children (especially 1.-2. year of age)
- usually harmless (is mostly completely overestimated)
- main content: nicotine
  - an alkaloid
  - agonist at the acetylcholine receptor (nicotinergic) → parasympathetic nervous system ↑ (⚠ therefore frequent cholinergic syndrome)
  - named after Jean Nicot (French diplomat and envoy who introduced the plant as a medicinal plant in France; 1530-1604)
  - a highly toxic substance
  - short half-life (8 h)
  - lethal dose: 1 mg/kg bw
    - adults: 40-60 mg (4-5 orally ingested cigarettes)

that enteral nutrition via a gastric tube (initially also additional parenteral nutrition via CVC if necessary) will be necessary.
- antibiosis: not indicated (only in case of wound botulism)
- if necessary mechanical ventilation in case of respiratory insufficiency (necessary for three 3 weeks on average)
- if necessary temporary pacemaker in case of severe high-grade AV block
- magnesium: contraindicated (intensifies the effect of the toxin)
- wound botulism: wound debridement (surgical) + antibiosis (first choice: penicillin G i.v.)

Prognosis

- ⚠ mortality: 15 % (without therapy: 90 %)
- The effect of the toxin may last up to 12 weeks. It can take a long time until the neuromuscular transmission is completely restored, i.e. the symptoms (especially double vision) can persist for months! Healing only takes place when new nerves sprout!

Snakebite intoxications

Definition

- In Europe there are almost exclusively adder species (vipers) in the wild as poisonous (also called venomous) snakes. Of these, the only relevant poisonous snake in Germany is the cross adder.
- The most common snakes in Germany are the natters (colubridae), which are non-toxic. The most common natter is the ring natter. It is typically found around and in waters (especially lakes and streams), is about 1 m long and has two crescent-shaped spots in the neck as a distinguishing feature. Also common in Germany is the blindsnake (syn.: slow worm), which is actually no snake, but a lizard. It is usually 30-40 cm long and is often confused with a snake because of the missing legs. It is also completely harmless.
- Bites of tropical snakes (e.g. in the reptile zoo, domestic snakes) are very rare: It is advisable to contact the poison information center, in which the antisera of almost all of the world's relevant snakes are available. The bite of tropical snakes is clearly more dangerous, in this case the administration of an antiserum is usually always indicated!
- more frequent in men than in women
- Children and elderly people are particularly vulnerable.
- occurrence:
  - step on a snake while hiking in the woods or at the shore of a lake
  - collecting mushrooms or berries in the bushes
  - trying to catch a snake
  - trying to remove a snake from the road
  - grasping in crevices while climbing

Snakes
Europe

- **natter species (colubridae): non-toxic (non-venomous)**
  - **ring natter (natrix natrix; most common snake in Germany)**
  - **dice natter (natrix tessellata)**
  - **smooth natter (coronella austriaca)**
  - **Aesculapian natter (zamenis longissimus)**
- **adder species (vipera): toxic (venomous)**
  - ⚠ **Vipera berus (crossed adder; most common venomous snake in Germany)**
    - **hell adder (black)**
    - **copper adder (brown)**
  - **(mainly in France, Italy; only found in the Black Forest in Germany; more toxic than the crossed adder)**
  - **Vipera ammodytes (most common in Southern Europe)**
  - **Vipera ursini (most common in Eastern Europe)**
  - **Vipera latasti (especially in Spain)**

Fig. 1694 The only relevant venomous snake in Germany is the crossed adder (vipera berus); distinguishing features: 50-70 cm long, typical dorsal crossbars on the back

Fig. 1695 The most common snake in Germany is the ring natter. It is completely non-venomous. It is usually about 1 m long, occurs typically in water and has two distinctive whitish spots on the neck.