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Anaesthesia for premature infants and newborns – what's important?

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Summary

Perioperative care of premature infants and newborns is a rare event. The frequency of newborn-specific previous illness and accompanying primary disease increases with the extent of prematurity. Thus the level of difficulty of patient care increases. Therefore, caregivers should be familiar with anatomical, physiological and pharmacological characteristics such as the neonatal transition. Perioperatively, pulmonary pre-existing conditions such as bronchopulmonary dysplasia or respiratory distress syndrome of the newborn as well as the unstable circulation are specific challenges for the anaesthetist in charge. Given the knowledge of intervention-specific peculiarities, it must be decided in each single case whether the institutional and individual prerequisites for safe care are given.

Introduction

Children up to an age of 4 weeks count as **newborns.** Roughly 10 % of all newborns are born before the **37th week of pregnancy** (WOP), in other words, prematurely. A disproportionately high number of these (1.25 % vs. 0.5 % in term infants) display cardiovascular malformations [1]. The **gestational age,** the age between the first day of the last menstrual bleeding and birth, is more significant than the birth weight for the survival of these children. Nevertheless, the incidence of complicating diseases such as a **pulmonary arterial hypertension** increases with very underweight premature infants (< 1,500 g), and even further when extremely underweight (< 1,000 g) [2–4].

An **anaesthesia for premature infants and newborns** carries a significant risk of perioperative mortality on account of these diseases and the resulting degree of complexity of the surgery. This is particularly true if surgery takes place between 24 – 72 hours after birth, the most critical phase in the life of a newborn. Consequently, the **risk of a perioperative cardiac arrest** is more than fifteen times higher than in children over the age of 10 during non-cardiac surgery in newborns [3–5]. This is also due to the fact that only around one in every hundred anaesthesias is carried out on premature infants or newborns [6], and even in a maximum care centre, only 3.7 % of all paediatric anaesthesias (patients under the age of 14) are performed on premature infants and newborns, as figures from our own hospital prove. This makes it difficult for anaesthetists to gain experience in this field. However, this is a relevant factor for the **quality of care** [7,8]. It could also be shown that the **treatment outcome** in hospitals with large numbers of cases is better than in those with a lower number of cases [9,10]. This is due mainly to the handling of serious complications. It can be assumed that these results for adults also apply for premature infants and newborns.

The basis for safe medical care and a good treatment outcome are knowledge of the anatomical, physiological and pharmacological characteristics, of newborn-specific pre-existing diseases, accompanying underlying diseases as well as specifics of the surgical procedure.

These will be described in the following.

Anatomical and physiological characteristics

Central nervous system (CNS)

The **brain quadruples in size** in the third pregnancy trimester alone [11]. **Neuronal growth and synapse formation** of the CNS, however, extend beyond the time of birth. The dopaminergic system and N-methyl-D-aspartate (NMDA) receptors play an important role here. The source region for growth is the so-called **germinal matrix,** a highly vascularised, cellular germ layer that is located periventricular, subependymal in the thalamostriatal region. It develops at an early stage of embryogenesis and is the site of glial and neuronal differentiation. After the 32nd WOP, the germinal matrix is present almost exclusively in the caudothalamic groove and has largely disappeared after the 35th–36th WOP. The risk of bleeding from the thin-walled, fragile vessels of the germinal matrix that are lined with single-layer endothelium decreases [12]. The vascular density is much lower in the white matter. This would appear to explain the increased incidence of periventricular leukomalacia (PVL) in premature infants [12].

The still low concentration of **serotonin receptors** could be the reason for the rarer post-operative vomiting (POV) at this age. Since **γ-aminobutyric acid (GABA) receptors** can have excitatory functions during the embryonic stage, paradoxical reactions and seizures after administering benzodiazepine to premature infants and newborns are probably due to this [13,14].

Skin receptors and perioral sensory nerves can already be found in foetuses from the 7th WOP. As of the 22nd WOP, afferent (pain) pathways have developed anatomically and functionally in the spinal cord and brain. Premature infants already react to pain stimuli almost as quickly as older children as of then (despite the incomplete myelination) [15].

Since the descending inhibitory signal pathways only mature completely as of the 32nd WOP, premature infants even feel pain stronger than older patients [16].

Lungs

The terminal bronchioles start to form and surfactant production begins around the 24th WOP. The first alveoli then form in the 28th WOP. At the time of birth, their number is 20–50 % that of adults. Type-II-pneumocytes, the main producers of surfactant, develop around the 24th WOP, but are not fully functional until the 34th–36th WOP. As a result, the **surfactant concentration often remains insufficient until the 36th WOP.**

In premature infants from the 30th WOP, the gas exchange surface is thus only 0.3 m², distributed over a few million alveoli, compared to 4 m² in term newborns with approx. 50 million alveoli, and 50–100 m² in adults, distributed over approx. 300 million alveoli.

In addition, newborns and premature infants become tired faster than adults because their diaphragm contains a lower share of fatigue-resistant, type I muscle fibres. An effective function of the diaphragm is also hindered by the elastic chest wall. The **respiratory drive** is triggered by central pCO_2 receptors in the medulla oblongata. Oxygen receptors in the carotid body are functionally immature so that **hypoxia in premature infants does not lead to an intensified respiratory activity.** Hypoxia in the first 2–4 weeks of life of term infants still leads to a temporary tachypnoea, which may then be followed by a reduction of the respiratory rate (hypoxic respiratory depression) [17,18].

Heart

The **myocardium of newborns** displays

- a lower density of contractile elements,
- is more sensitive to cardiac depression drugs (incl. anaesthetics), and
- reacts less to inotropic drugs.

The **diastolic function** is still restricted and the left ventricle less compliant than in older children. This means that the cardiac output (CO) can only be increased by approx. 30 % compared to 300 % in adults. The CO thus crucially depends on the heart rate. Due to the still immature autoregulation in premature infants, it does not increase with hypovolaemia as it usually does. The immature sympathetic nervous system also tends to react to **painful stimuli**, e.g. those resulting from intubation, oropharyngeal suctioning or the positioning of stomach tubes, more with **bradycardia** than the expected tachycardia.

Cardiovascular malformations such as pulmonary atresia with ventricular septal defect (VSD), complete atrioventricular septal defect (AVSD), coarctation of the aorta, tetralogy of Fallot and pulmonary valve stenosis are around two-and-a-half times more common in premature infants than in term infants (1.25 % v. 0.5 %). This is why pre-operative clarification is recommended.

Glucose homeostasis

Since the supply of glucose via the placenta ceases after birth, the newborn has to draw on its own sugar and glycogen reserves in the first hours of life, while hepatic gluconeogenesis begins at the same time. **Hypoglycaemia** up to 30 mg/dl are frequently asymptomatic in this case – probably because the brain can still metabolise ketones and lactate without adaptation at this time.

On account of a very limited accumulation of glycogen in the liver and the restricted possibilities for ketogenesis and lipolysis, glucose homeostasis is on the whole very fragile.

Children of diabetic mothers as well as children with a weight below the 10th percentile, relative to the gestational age, are particularly vulnerable to hypoglycaemia.

With a minor **hyperglycaemia** (145–200 mg/dl), the supply of glucose should initially be reduced intraoperatively and a close check be kept on the blood-sugar level because treatment with insulin can quickly lead to the risk of hypoglycaemia. Stronger hyperglycaemia can lead to intraventricular haemorrhages (IVH), osmotic diuresis and dehydration on account of the hyperosmolarity [19,20].

Haematopoietic system

Premature infants between the 26th–28th WOP have a **haemoglobin level** (Hb) of 13–15 g/dl, 70–80 % of which is foetal haemoglobin. The blood volume is 100–110 ml/kg bw. In mature newborns the Hb rises to 16–20 g/dl, the blood volume drops to roughly 80–85 ml/kg bw.

Both vitamin K and vitamin K-dependent **coagulation factors** are still very low in premature infants. The Quick value in the 30th–36th WOP is around 35–115 %. The platelet count may also be lower. A specific coagulation anamnesis including a parental anamnesis may be helpful here to assess the coagulation function.

With a given indication for a blood transfusion, the erythrocyte and thrombocyte concentrates have to be irradiated with gamma rays at 30G for premature infants up to the end of the 37th WOP as well as for newborns with a suspected immunodeficiency or in the event of an exchange transfusion.

Further indications could be a high-dose chemotherapy for leukaemia and solid tumours. Blood products should not be older than 7 days and should only be administered slowly so as to reduce transfusion reactions, hypocalcaemia and hyperkalaemia [21,22].

Pharmacokinetics and characteristics of typical drugs

Pharmacological characteristics

Newborns and premature infants have a greatly different pharmacokinetics to drugs on account of their underdeveloped liver and kidneys. Since the **drug distribution** from the blood into the subsequent compartments depends on the bloods circulation, fat and water content, there are already some big differences here to older children. An extremely premature infant consists of 90 % water, premature infants of 80 %, but only 15 % muscle fibres and 5 % fat (Fig. 1). The ratio of extracellular to intracellular fluid in premature infants is 60:20 and in newborns approx. 50:30, and thus the opposite of adults (20:60).

The **albumin and total protein concentration** of newborns is only 86 % of that of adults. The concentration of the **α-1 acid glycoprotein,** which is necessary in particular to transport the drug, is still very low. However, as an acute-phase protein, the concentration rises in the event of an infection, stress, inflammations or neoplasms [23,24].

The limited capacity of the renal tubules to absorb bicarbonate explains the "physiological" acidosis in newborns. Since the ability to effectively reabsorb sodium only develops after the 32nd WOP, the distal tubular response to aldosterone remains low up to the 34th WOP and the ADH level is high, premature infants have a **predisposition to hyponatremia** (Fig. 1, Tab. 1).

On account of **more permeable barriers between organs,** the drug is on the whole distributed faster between individual organs. As a result of the relative size of the CNS and a more permeable blood-brain barrier, there is more of a risk of an accumulation in the CNS with side effects in the central nervous system for lipophile drugs (e.g. local anaesthetics, propranolol, propofol, thiopental) [25,26].

The distribution of the administered drugs also **depends on the CO** (in newborns and premature infants approx. 250 ml/kg bw/min). The blood volume (80 ml/kg bw) of neonates circulates roughly three times a minute, but only once in adults. This accelerates the distribution of a drug in newborns and premature infants and leads to lower maximum concentrations at the site of action. A large part of the CO also enters tissue with a good blood supply, so that a saturation kinetics of the administered drug is quickly achieved here (in this tissue) [27–31].

According to a study by the Food and Drug Administration (FDA), <5 % of the drugs used for hospitalised newborns were approved for this age group. None of the drugs used as an anaesthetic were approved for premature infants between 23 and 29 weeks [32,33].

Intravenous administration should be undiluted whenever possible to avoid any dosing errors and then rinsed [34].

Inhalational anaesthetics

General remarks

Compared to the functional residual capacity (FRC), **alveolar ventilation** is very high and helps volatile anaesthetics to a rapid increase of the alveolar concentration. This occurs despite the large CO: a large part of the CO flows into the organs with a good blood supply, that quickly becomes saturated. This is why venous blood with a high concentration of anaesthetics quickly returns from the periphery, which in turn means that only a minimal additional amount of the inhalational anaesthetic from the alveolar area can be absorbed. Thus, it is not only modern inhalational anaesthetics such as sevoflurane that diffuse quickly; the inhalational induction of volatile anaesthetics with high blood-gas distribution coefficients such as halothane or isoflurane also is faster in newborns and premature infants than in adults.

Sevoflurane

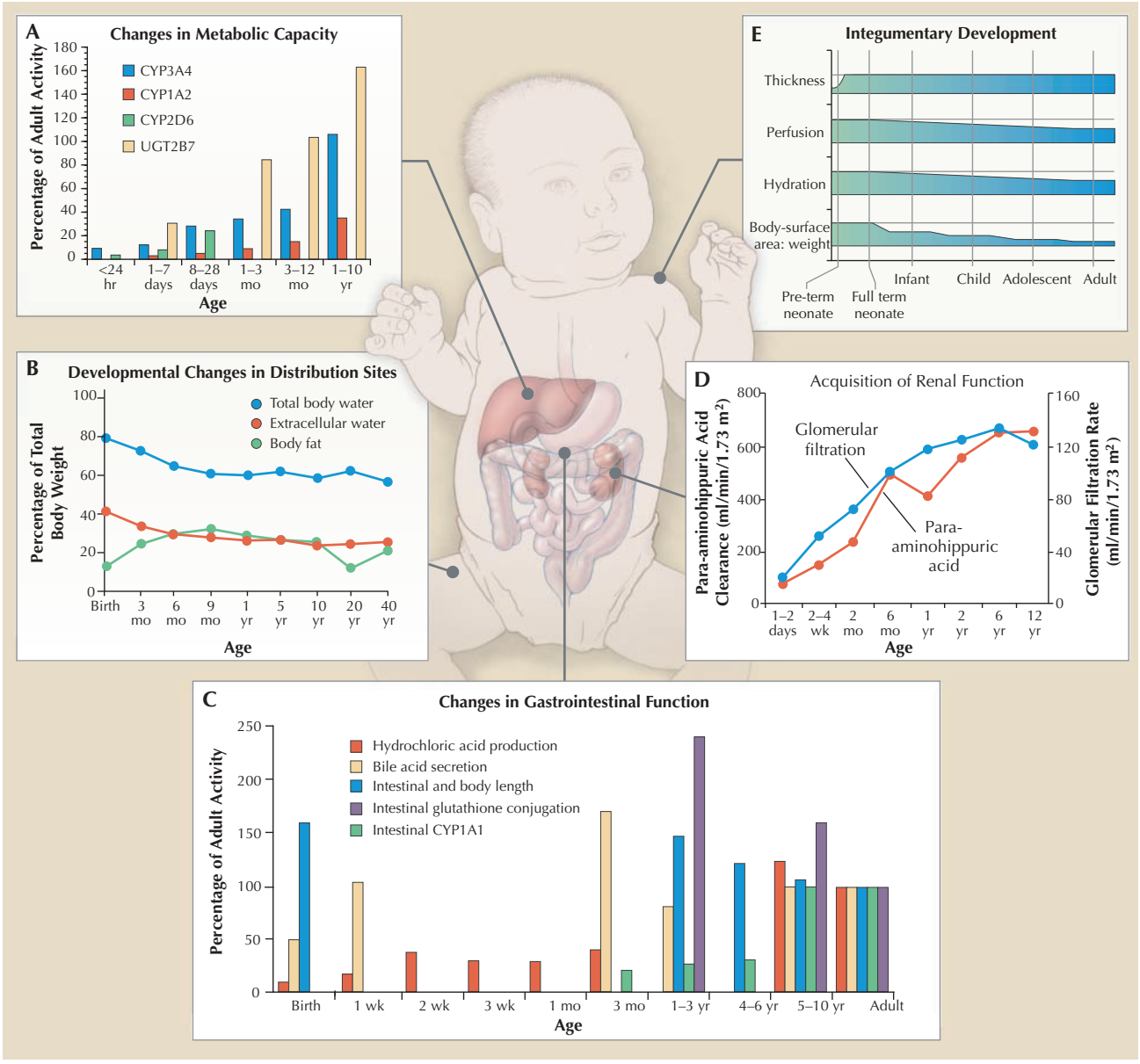
Of all the available volatile anaesthetics, sevoflurane is most suited for **inhalational induction,** especially because it rarely irritates the respiratory tract. However, relevant **drops in blood pressure** may occur, so that a close check and moni-

Table 1

Anaesthesiological characteristics of newborns and premature infants due to anatomical and physiological differences.

Lungs / (artificial) respiration	Heart / circulation	CNS	Metabolism
• Increased risk of apnoea • Low oxygen reserves • Respiratory drive mainly through CO_2 partial pressure • Reduced gas exchange surface	• Restricted cardiac contractility • Increased pulmonary vascular reactivity • Open ductus arteriosus • Reflexive bradycardia	• Increased sensitivity to anaesthetics • Periventricular leukomalacia • Intracranial bleeding • Retinopathy of prematurity • Negative consequences of untreated pains	• Reduced metabolism through liver and kidneys • Tendency to hyponatremia • Risk of hypoglycaemia

Figure 1



Changes in physiological factors that affect the pharmacodynamics and and pharmaco-kinetics of newborns and premature infants (after Kearns [31]).

toring of the blood pressure is always necessary for a prompt identification of drops in blood pressure.

The MAC value (minimum alveolar concentration) and the induction time rise in premature infants with an increasing post-menstrual age [35].

Intravenous anaesthetics and relaxants

General remarks

The pharmacokinetics of newborns differs greatly from that of adults: following administration, intravenous anaesthetics are distributed very quickly by the large CO and the plasma levels fall rapidly. In order to achieve equally high concentrations at the site of action as in adults, newborns and premature infants need **higher doses of the induction hypnotic agent,** but lower doses than infants and toddlers. However, the maximum clinical effect through a sufficient concentration at the site of action is often achieved later than expected.

Midazolam

On account of the as yet immature hydroxylation by certain enzymes in the cytochrome P_{450} superfamily (CYP3A4 and CYP3A5), the elimination half-life (EHL) of midazolam in newborns is 4–6 hours and in premature infants even up to 22 h, later only 1.9 h. Due to the appearance of **chorea-like movements** following long-term administration, midazolam is frequently no longer used to sedate premature infants.

Thiopental

Newborns only require up to a maximum of 3 mg/kg bw on account of the lower protein binding. It quickly takes effect. The termination of the effect depends on the **redistribution,** which may be faster than in adults on account of the higher CO. However, since the redistribution in fatty tissue is not possible to the same extent as in adults, and the decomposition in the liver is delayed by the still immature metabolic pathways, the effect can nevertheless last longer than at a later age. The **accidental intra-arterial administration** may lead to vasospasms and a necrosis of the arm (pH-value 10.6).

Ketamine

One has to consider **pharyngeal hypersecretion** and hyperreflexia in association with the risk of laryngospasm. A cardiac left-to-right shunt can be further intensified by ketamine.

Propofol

According to a survey in the german Scientific Study Group for Paediatric Anaesthesia (WAKKA) in June 2019, 65 % of the respondents now use propofol regularly with newborns as a sedative, 20 % occasionally. However, it is still not approved for use with children under the age of one month, so that parents of newborns have to be informed separately to this indication. One has to consider that a **propofol infusion syndrome** (PRIS) in newborns has also been reported after only a single dose [36]. Propofol must not be administered continuously on account of this risk. In addition, there is a risk of dangerous **drops in blood pressure** in premature infants, even after the administration of low doses of propofol [37]. A cardiac right-to-left shunt may occur or be intensified in this connection.

Succinylcholine

Its use entails considerable uncertainties as regards hyperkalaemic complications, whose lethality has been reported as being up to 50 %, on account of muscular disorders that often have not yet been diagnosed. An initial treatment option is adrenalin (5–10 µg/kg bw) because it stimulates the Na^+-K^+ pump.

Non-steroid anti-inflammatory drugs (NSAIDs)

These lead to the **closure of a patent ductus arteriosus.** They are therefore contraindicated with duct-dependent heart diseases.

Bicarbonate

Sudden changes in the blood osmolarity can lead to intracranial bleeding. An 8.4 % sodium bicarbonate solution should thus always be diluted 1:1 with distilled water and should not be administered faster than 1 ml/kg bw/min.

Heat regulation

Premature infants and newborns run a particular risk of becoming hypothermic in the operating theatre. This is due amongst other things to the relatively large body surface area, an underdeveloped skin with a low skin thickness and greater perfusion, less subcutaneous fatty tissue, a higher percentage of body water and as yet poorly developed metabolic compensation mechanisms.

The heat loss occurs through convection, conduction, evaporation and radiation (Tab. 2). Counter-regulatory mechanisms set in much later under anaesthetics such as propofol and sevoflurane. The **thermoregulation zone,** the temperature range around 37°C as of which the counter-regulatory reactions set in, is extended from 0.4°C to 3–4°C. Volatile anaesthetics also inhibit the thermogenesis from brown fatty tissue.

The initial **compensatory mechanism** is primarily the metabolically complicated generation of heat through **lipolysis of the brown fatty tissue** (non-shivering thermogenesis) that is possible shortly

Table 2
Possible pathways for heat loss.

Convection	Conduction	Evaporation	Radiation
• Large body surface area in relation to weight	• Low skin thickness before 32nd WOP • Little subcutaneous fat	• Very hydrated immature skin (up to 15-times higher loss of water through evaporation) • Open abdomen • Respiratory passages	• Cool walls and other surfaces

WOP: week of pregnancy.

Table 3
Consequences of hypothermia.

Extended effect of drugs Increased apnoea and ventilatory support Hypoglycaemia Acidosis	Intraventricular haemorrhage Coagulation disorders, post-operative bleeding Bradycardia

Table 4
Active (cascade) versus passive (artificial nose) warming and humidification of the airways.

Cascade	Artificial noses
+ Sufficiently high humidity in the lines (44 mg H_2O/l air) + Possibility to adjust any air humidity and gas temperature + No additional dead space - Risk of infections and overheating	+ No overheating + Easy handling and operation ± Supplies sufficient air humidity - Blockage through deposited secretion (high flow resistance) - Increase in dead space

after birth. Thermogenesis through muscle tremors is only possible in children over the age of 6. The risks for patients due to hypothermia are shown in Table 3.

In order to **minimise the loss of heat** through conduction and convection, the child should at best be placed on padding and covered with a blanket. A **warm operating theatre** with warm walls reduces the loss through radiation. An active supply of heat perioperatively can be carried out very effectively either by convection (e. g. Bair Hugger®) or conduction (warming mat). The loss through evaporation via artificial respiration can be reduced by an HME (heat and moisture exchanger) filter or active warming (Tab. 2 and 4). The fresh gas flow of the anaesthetic equipment should also be adjusted appropriately for this reason (see below). **Infusions and blood products** should be warmed before administration to prevent hypothermia. The **temperature of the medical care room** should be 23–25°C, and even over 25°C for children born before the 28th WOP [38].

Stress reactions caused by cold trigger the release of norepinephrine and lead to an increased oxygen consumption with hypoxia and (lactate) acidosis. This promotes a relapse into the foetal circulation.

Transition of the newborn

The transition from the foetal to the post-natal phase is associated with a unique change-over of the blood circulation. There is a parallel circulation pre-natal. In this case, the **most oxygen-rich blood** of the foetus ($p_{nv}O_2$ 30 mmHg, $S_{nv}O_2$ 60–65 %) flows out of the placenta, through the umbilical vein, the ductus venosus Arantii and the inferior vena cava to the right atrium. From here, it is guided to the left atrium through the crista dividens, primarily via the foramen ovale, from where it flows to the left ventricle and supplies the heart and brain (via sinistra). The **less oxygen-rich blood** from the superior vena cava flows through the right ventricle and 90 % through the ductus arteriosus and with an S_aO_2 of 45 %, it supplies the remaining body (via dextra) through the descending aorta [39]. Only around 10 % of the blood flows through the lungs.

The change-over to a **serial circulation** (Tab. 5) begins during birth. The foetal lung fluid has to be reabsorbed through the pulmonary epithelium during birth to ensure an unproblematic post-natal adaptation. High concentrations of foetal stress hormones (above all epinephrine, cortisol and triiodothyronine) that are released during birth are crucial for this. This marks the start of a three to four-day-long gradual **normalisation of the lung resistance.** With an increasing pulmonary bloodflow, the venous reflux from the lungs to the left atrium also increases. Together with a rapid **increase in the systemic resistance,** this leads to a **functional closure of the foramen ovale** a few minutes after birth. The anatomical closure of the foramen ovale usually takes place during the

Table 5
Change-over in circulation through birth.

	Before transition	After transition
Respiratory passages	• Fluid accumulation through chloride secretion from pulmonary epithelial cells • Stiff, immature alveoli with little elastin	• Fluid clearance • Rise in NO, PGI_2 from endothelium • O_2 consumption rises
Pulmonary circulation	• PAP_{mean} 40–60 mmHg • Little blood flow	• PAP_{mean} initially still up to >30 mmHg • Drop in resistance through rise in pO_2
S_pO_2	• max. 65 %, during birth up to 30 % w/o acidosis	• 1st minute: 60–70 % • 10th minute: >90 %
Circulation	• Parallel circulation • RV: 60 % of the comb. output	• Serial • Rise in SVR through catecholamines
Foramen ovale	• Open	• Functional closure through increased LA pressure
Ductus arteriosus	• Right-to-left shunt	• Transitory left-to-right shunt • Functional closure after 48–72 h

PAP_{mean}: mean pulmonary arterial pressure; **RV:** right ventricle; **NO:** nitrogen monoxide; **PGI_2:** prostaglandin I_2; **SVR:** systemic vascular resistance; **LA:** left atrium.

Table 6
Risk factors for the persistence or recurrence of a foetal circulation (after Wu [42]).

pre-existing	Affected by anaesthesia
Meconium aspiration Sepsis Pneumonia Respiratory distress syndrome (RDS) Congenital diaphragmatic hernia (CDH)	Hypothermia Hypercapnia Acidosis Hypoxia

first year of life. However, it can still be detected by echocardiography in up to 20 % of adults [40,41]. The **ductus arteriosus** closes functionally within the first 24 to 72 hours of life in healthy newborns on account of the increase in the partial pressure of oxygen and the disappearance of prostaglandin E_2. 6 hours after birth, the right-to-left shunt has dropped from 90 % to 20 %. The incidence of a patent ductus arteriosus (PDA) rises with a decreasing gestational age and is over 30 % after the third day of life with a birth weight < 1,500 g. The majority of these children experience a permanent spontaneous closure during their first year of life.

A very rapid birth, particularly in the event of a primary caesarean section with no prior contractions, is very often accompanied by the development of a **wet lung** and thus a **higher pulmonary arterial pressure** in newborns. A pressure load on the right ventricle can lead to a right-to-left shunt via the forarmen ovale and thus to a foetal blood circulation situation if suprasystemic pressures are reached. A right-to-left shunt may also occur via ductus arteriosus, and thus lead to a venous admixture volume in the area of the descending aorta (Tab. 6) [42].

With anaesthesia of a newborn or premature infant, there is always the risk of a relapse to the foetal circulation in case of an increased pressure in the pulmonary circulation or a sharp drop in the afterload.

A right-to-left shunt via the ductus arteriosus can be identified at an early stage by means of **pre- and post-ductal pulse oximetry** on the basis of the drop in post-ductal saturation. Pre-ductal saturation can only be detected at the right ear in the event that there is an arteria lusoria (atypical dextral subclavian artery that does not originate from the brachiocephalic trunk but directly from the aortic arch).

Preoperative Evaluation

General remarks

A comprehensive **anamnesis** and a **physical examination** of all organ systems, including the clarification of genetic syndromes and thus associated anomalies, is essential to assess the risk before any anaesthetic.

Those parameters listed in Table 7 should also be queried anamnestically. During the physical examination, particular attention must be paid to

- skin turgor,
- mucous membranes,
- fontanelle level,
- urine production, and
- anaesthesia-relevant accompanying illnesses (e. g. craniofacial anomalies, congenital heart diseases, chronic pulmonary diseases).

The attending anaesthetist should familiarise with the specifics of the patient before the start of anaesthesia and check whether there are any individual or institutional requirements for adequate medical care and whether according personnel and structural backup levels are available.

Apnoea risk

An **apnoea-bradycardia syndrome** is defined as a pause in regular breathing of longer than 20 seconds or a shorter pause in breathing in connection with bradycardia and/or cyanosis. This is only rarely found in premature infants after the 36th+ 0 WOP. The risk is higher in babies born earlier with the same post menstrual age (PMA).

Table 7
Relevant anamnesis parameters for newborns and premature infants.

	Characteristics to be queried
Maternal case history during pregnancy	Rh-/ABO compatibility Diabetes mellitus Infections Drug/alcohol abuse
Gestational age/weight	Extremely premature and/or extremely underweight
Perinatal events	APGAR score (problems with neonatal transition?) Neonatal asphyxia Meconium aspiration Additional oxygen requirement/ventilatory support
Drugs	Drugs taken, possibly allergies
Accompanying illnesses	Respiratory distress syndrome or bronchopulmonary dysplasia Intraventricular haemorrhage Periventricular leukomalacia Retinopathy of prematurity Patent ductus arteriosus

Table 8
Factors increasing the risk of apnoea in premature infants.

Pre-existing	
Gestational age	Airways obstruction
Bronchopulmonary dysplasia	Retarded growth and development
Cardiac insufficiency	Endocrine or metabolic illness
Intracranial bleeding	Drugs
Subglottic stenosis	Sepsis
Perioperative	
Anaemia (HCT < 30 %)	Hypothermia
Hypocalcaemia	Hypoglycaemia
Hypoxia	

Former premature infants should thus have reached a post-menstrual age of at least 44, but ideally 60 weeks for any elective surgery.

When scheduling surgery, the risks of postponing the operation should always be balanced against the risk of apnoea, taking into account the institutional resources (Tab. 8). In the event of urgent operations before 60 weeks PMA, **apnoea and bradycardia monitoring** including pulse oximetry and ECG overnight is advisable. If apnoea phases occur during the first 12 hours of monitoring, further observation on an intensive-care ward is necessary.

Fasting times

If fasting times are too long, this can lead to feelings of ill health, keto-acidosis, dehydration and a drop in blood pressure during anaesthetic induction [43]. Drops in blood pressure after anaesthetic induction as well as post-operative pain and restlessness can be reduced through milk feeds up to four hours and clear fluids up to one hour before the anaesthetic, and the ketone body concentrations remain normal [44,45].

Accesses and bacteria filters

In order to detect peripheral veins, **cold light sources** can be used. With **sonographic monitoring,** even newborns and premature infants can be punctured with good success in the median vein of the forearm, or alternatively the long saphenous vein. A so-called "walk down" in a short axis view of the vessel is recommended (out-of-plane technique). This method is also suitable for inserting a central venous catheter (internal jugular vein, femoral vein) or arterial catheters (radial artery, dorsal digital artery of the foot, femoral artery).

Microscopic, insoluble particles as well as germs can enter the bloodstream through a venous access and can lead to thrombocyte and leucocyte activation, microcirculatory disorders, vascular traumatisation, inflammation or embolisation. This is why the Robert-Koch-Institute (RKI) recommends using particle-filter systems (0.2 µm filter membrane for aqueous solutions; 1.2 µm filter membrane for solutions containing lipids) in the infusion system for newborns and premature infants. However, the recommendations are only based on studies in which the patients spent at least 6 hours on an intensive-care ward. The use of bacterial filters is nevertheless recommended for newborns and premature infants being treated on intensive care unit, even though there is no clear evidence of this [46].

If using an umbilical arterial catheter, pay attention to its correct position. Most meta-analyses support the high position (Th 6–10) of the catheter tip over the low position (L3–L5) because thromboses, renal artery stenoses, intestinal ischaemias, vesical wall necroses, aneurysms and infections are less likely to occur.

Airway and ventilation of the newborn and premature infant

Airway

Newborns are **obligate nasal breathers,** so a **choanal atresia** can be life-threatening. The neonatal glottis lies at the level of the 4th cervical vertebra (unlike the 5th cervical vertebra in adults), so that the angle between the oropharynx and laryngopharynx is smaller. Together with a narrower, longer epiglottis, this hampers the **direct visualisation of the vocal chords.** Unblocked tubes are usually used for airway management until a suitable **High Volume – Low Pressure Cuff** of the right size is available [47]. A close, and if possible constant monitoring of the cuff pressure (for example, via Cuffwatch®) is important. A tube without a cuff should display a leakage as of a peakpressure of 20–25 cmH_2O (Tab. 9) [48].

Rule of thumb for the depth of the tube:

tube depth from the gingival margin = 6 cm + 1 cm/kg bw [49]

Table 9
Size of unblocked tube and insertion depth.

	Size of tube	Oral insertion depth	Spatula size
Premature infants	(2,0)–2,5 ID	6–8 cm	< 32nd WOP: 00
Term infants	3.0–3.5 ID	9–10 cm	0 (< 3 kg)

ID: inner diameter; **WOP:** week of pregnancy.

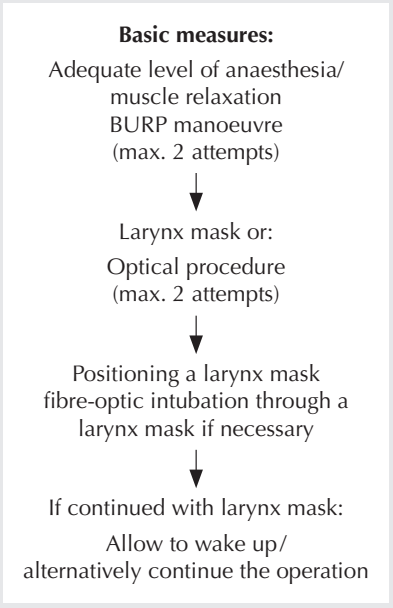
Difficult airway

Difficult airways are usually due to **obvious respiratory tract anomalies** such as a Pierre-Robin sequence or a Goldenhar syndrome. An unexpectedly difficult endotracheal intubation is very rare in newborns and premature infants. A difficult airway can normally be overcome by using a **laryngeal mask** or a **nasopharyngeal tube** by holding the other nostril and mouth closed. The procedure shown in Figure 2 is recommended for any remaining unexpected problems.

The goal is a sufficient oxygenation with no traumatisation of the respiratory passages. Bleeding and swelling caused by unsuccessfull intubation attempts might make further measures impossible.

In cases of difficult ventilation or insufficient oxygenation despite an inserted endotracheal tube, a step-by-step elimination of problems is recommended based on the acronym **DOPES:**

Figure 2



Algorithm for unexpectedly difficult intubation (after Weiss et al. [111]).

BURP: Backward Upward Right Pressure.

- **D**isplacement of the tube
- **O**bstruction of the tube
- **P**neumothorax
- **E**quipment failure (e. g. leakage from hoses, technical problems with the equipment etc.)
- **S**tomach and specific problems (mask ventilation often leads to a highly distended stomach)

Modified or controlled Rapid Sequence Induction (mRSI)

Preventing any life-threatening hypoxia takes priority compared to the infrequent aspiration events. The latter rarely have a serious morbidity [50]. Modified RSI includes a sufficient pre-oxygenation, anaesthetic induction and relaxation (non-depolarising muscle relaxants, possibly in a slightly higher dose) to avoid regurgitation during manipulation of the airway. Following induction, mask ventilation is carried out without cricoid pressure and a maximum of 10–12 cmH_2O.

In the event of a gastrointestinal obstruction, a gastric tube should be inserted before the start of induction to ensure an effective closure of the lower oesophageal sphincters by reducing the volume. The tube can be left in place for the continuous extraction of secretions and/or air during the induction [51].

In critical situations during airway management, and during mRSI, the technically simpler oral intubation should be performed. It is then possible to switch to a nasotracheal intubation, if necessary.

Ventilation

Although the FRC of 25–30 ml/kg bw and the dead space of 1.5 ml/kg bw are the same at all ages, the **ratio of alveolar ventilation to FRC** differs at the time of birth (5:1) significantly from that in adulthood (1.5:1). The advantage is the **faster inhalational anaesthetic induction,** the disadvantage a lower oxygen reserve during apnoea. This "reservoir" is used up so quickly as a result of the high oxygen consumption of 6–9 ml/kg/min (or even up to 20 ml/kg/min by sick newborns), that saturation without pre-oxygenation drops to 90 % after only 7 seconds. This will also be the case after approx. 1 minute even with 3 minutes of pre-oxygenation. The **closing capacity,** which remains larger than the FRC up to the age of 6 and thus ensures a partial closure of the alveoli at the end of each expiration, also increases the risk of a desaturation [52]. In order to prevent this collapse of the alveoli (and therefore an increase of a pulmonary right-to-left shunt), ventilation should always be carried out with a **positive end-expiratory pressure (PEEP).** This is also particularly true for **mask ventilation** during the anaesthetic induction. Values of 4–6 cmH_2O are adequate for children with healthy lungs in most situations. Beyond this, the PEEP has to be adjusted individually [17,53].

The filling volume of the lungs during inspiration, like the exhaled volume during expiration, follows exponential functions. The **time constant τ,** the product of resistance and compliance, plays an important role for an age-appropriate adjusting of the inspiratory and expiratory times for newborns and premature infants. It describes the time after which a 63 % change in volume has occurred.

At least 3–5 time constants are necessary for a complete inspiration and expiration.

Since the expiratory resistance, and thus its time constant τ, is practically always higher than the inspiratory resistance, the **expiratory time should usually be longer than the inspiratory time.** If expiration is too short, this can lead to **air trapping** with successive emphysematous expansion and volutrauma of the lungs. Nevertheless, in order to manage with the smallest possible tidal volume, the **expiratory time** should not be longer than necessary. Incomplete inspiration leads to a reduced tidal volume with a relatively high dead space share of the respiratory air, thus causing a reduced oxygen absorption via the alveoli. Although a long inspiratory time can im-

prove oxygenation, it does impose a mechanical load on the lungs.

Rule of thumb for the inspiratory time Ti:

Premature infant <1,500 g: 0.3s

Premature infant <1,000 g: 0.25s

(Ti (s) = gestational age in weeks/100)

The time constant τ can be shortened greatly with very stiff lungs so that much shorter inspiratory times should be selected (Tab. 10).

In order to minimise shearing forces, the goal should be **tidal volumes** of 4–6 ml/kg bw. Relatively **high respiratory rates** are therefore necessary for an adequate respiratory minute volume (RMV).

Rule of thumb for respiratory rate:

AF = respiratory minute volume (200 ml/kg bw) ∗ Body weight (kg)/ Tidal volume (VT)

The respiratory rate has biological-physical limits depending on the mechanical properties of the lungs (Tab. 10) and the tube diameter. Every part that enlarges the dead space will diminish the CO_2 washout, which has to be "paid for" by a larger tidal volume and greater damage to the lung due to artificial respiration.

The optimum situation is a high respiratory rate with an adequate expiratory time, combined with the lowest possible peak inspiratory pressure (PIP) to achieve the blood gas goals.

Depending on the **respiration/anaesthetic equipment** that is used, the following conditions should apply for newborns and premature infants [53,57]:

- The ability to change the pressure in the respiratory tube system quickly
- Minimisation of the compressible volume (use of a smaller tube diameter, in particular with volume-controlled ventilation, and small humidifiers to minimise the dead space), so as to enable a rapid response of the ventilation equipment to changes in pressure
- Freely adjustable flow of fresh gas. The fresh gas flow should be three times the RMV in order to avoid rebreathing. Increasing this leads to higher shearing forces inside the respiratory passages, with the risk of interstitial pulmonary emphysema or a pneumothorax
- Fast-working pneumatic technology
- F_iO_2 should be freely adjustable
- Tidal volumes of ≤2 ml must be guaranteed
- Possibility of using active humidifiers during longer periods of ventilation.

The **infant respiratory distress syndrome (IRDS)**, also called the hyaline membrane disease (HMD), is due to a reduced production of surfactant in type II pneumocytes. It affects 90 % of babies born in the 26th WOP. The reduced production of surfactant is due to the physiologically low production of cortisol in premature infants. As a result of the exogenous supply of cortisol during the development of the lungs with the threat of a premature birth, the effect of endogenic cortisols on the surfactant production is greatly enhanced [54].

Bronchopulmonary dysplasia (BPD) is characterised by an increased oxygen requirement and/or ventilatory support. The diagnosis is made in retrospect. The incidence depends on the birth weight.

Table 10

Pulmonary diseases with which attention has to be paid to the altered time constant for the respirator setting.

Illnesses with reduced time constant	Illnesses with extended time constant
Respiratory distress syndrome (RDS), Pulmonary hypoplasia, Restrictive ventilation disorder	Pneumonia, BPD, Bronchial spasms, Tracheobronchomalacia

RDS: respiratory distress syndrome; **BPD:** bronchopulmonary dysplasia.

Unlike an untreated IRDS, the inspiratory and expiratory time selected after the administration of surfactants has to be comparatively higher for several hours on account of the increasing compliance and at the same time higher resistance (Tab. 10).

Respiratory gas humidification and warming

Since dry, cold respiratory air can deprive the child of a great amount of **heat** through evaporative cooling in the respiratory passages, and secretion drying in the small endotracheal tubes leads to the risk of obstructions in the tubes, **adequate heating and humidification of the respiratory air** is extremely important. It would appear that the administration of respiratory gas with an absolute humidity of 30 mgH_2O/l and a relative humidity of 80–90 % at at least 30°C is sufficient [55]. A temperature of 32–34°C and more than 30 mgH_2O/l is recommended in the USA.

Excess humidification of the respiratory air can adversely affect the ventilation through the formation of condensation and its recurrent aspiration.

The systems that are available are divided up between **heated active humidifiers (HH) and passive heat and moisture exchangers (HME)**. The latter involve a slight enlargement of the dead space and a slight increase in the airways resistance (Tab. 4) [56].

Oxygen

Numerous publications have shown that the too liberal use of oxygen for premature infants and newborns can be disadvantageous. The cerebral blood flow drops, oxidative stress and free oxygen radicals increase (Tab. 11) [58,59]. Oxygen should therefore always be administered **as required** and **purposefully** with a view to the intended peripheral saturation.

The pre- and postductal oxygen saturation should both be measured in newborns and premature infants. The target value for premature infants is an S_pO_2 of 88–94 % [60–63).

Table 11
Consequences of increased F_iO_2 verified in experiments.

Clinical consequences of repeatedly high F_iO_2-values
• Indications for an increased neuroapoptosis rate in animal experiment studies
• Direct pulmonary damage with metaplasia, oedema, growth inhibition
• Direct and indirect astringent effect on vessels
• Retinopathy of prematurity (especially <34th week of gestation)

CO_2 monitoring

Measurement of the **end-tidal carbon dioxide partial pressure** is more difficult in newborn and premature infants than in older children. Measurements of both the side stream and mainstream tend to return **false low values** and thus underestimate the arterial pCO_2. A mainstream measurement also enlarges the dead space volume by around 0.5–1.5 ml depending on the manufacturer [64,65]. It has repeatedly been shown that a **transcutaneous measurement** ($tcpCO_2$), usually in combination with a measurement of the oxygen partial pressure, is more precise than an end-tidal measurement [66,67]. But since $tcpO_2$ and $tcpCO_2$ are measured electrochemically in the sensor, there are some relevant perioperative limitations. Thus, calibration takes 10–15 min., a change is required every 2–4 hours and arterialised values can only be achieved with a good perfusion and a hyperaemia by warming to 44°C. This is why (possibly capillary) blood gas analyses are often needed intraoperatively to determine the actual $paCO_2$.

No capnography waveform is reliable in case of BPD on account of the ventilation/perfusion mismatch [68].

The p_aCO_2 should remain constant at 45–55 mmHg. This helps to avoid shearing forces on the germinal matrix and guarantee a sufficient cerebral perfusion [69,70]. Hyperventilation (p_aCO_2 <35 mmHg) leads to a higher mechanical load on the pulmonary tissue and increases the incidence of a BPD. The risk of periventricular leukomalacia also rises on account of the resulting cerebral vasoconstriction [71,75].

Blood pressure and perfusion

General remarks

Cardiac baroreflexes are weaker in premature infants. The ability to **compensate hypovolaemia** is consequently still limited and is further affected by anaesthetics. Reductions of the intravascular volume of up to 40 % in conscious newborns thus hardly leads to a drop in blood pressure.

A drop in the systolic blood pressure by more than 20 % of a reliable initial value or a drop below the 5th–10th percentile of the normal value perioperatively can be regarded as requiring treatment [73,74]. The **mean arterial pressure** (MAP) should probably **never fall below 30 mmHg** under an anaesthetic, even with the smallest of premature infants [75,76]. The **maintenance of the heart rate** (120–160/min before the 30th WOP and 90–130/min for mature newborns) is also relevant here.

The **preload** can be maintained perioperatively by administering a balanced electrolyte solution with 1–2 % glucose at an initial rate of 10 ml/kg bw/h [44]. A further increase of the preload, however, quickly leads to a transgression of the Frank-Starling curve, which probably is already intact in neonates [77].

The tissue perfusion can be evaluated by means of the capillary refill time. A time >2 s indicates a reduced peripheral perfusion.

The **combination of hypotension and hypocapnia** led to noticeable changes in cerebral perfusion, signs of neuronal dysfunction and earlier neuronal ischaemia in animal experiments and should therefore be carefully avoided [78]. Furthermore, it should be remembered that the cerebral blood flow (CBF) depends more on the pCO_2 than on the MAP in the first hours of life. In unanaesthetised premature infants, it is 20 ml/min/100 g brain weight, in infants 100 ml/min/100 g and in adults 50 ml/min/100 g [79,80].

The **width of the blood pressure cuff** should be at least 40 % of the mid upper arm circumference for a correct measurement in accordance with the AHA recommendations. A closed system helps avoid air injections with potentially deleterious consequences with an **invasive blood pressure measurement.** The rinsing pressure must be adjusted depending on the blood pressure so that no retrograde flow of rinsing liquid to intracranial can occur (risk of cerebral ischaemias).

The perioperative **micturition** as an indication of a sufficient renal perfusion is of very limited use. 1–2 ml/kg bw/h is normal, but can hardly be measured in the lines. In the first hours of life, or during a laparoscopy, even anuria can be sporadically physiological [81].

Near-infrared spectroscopy (NIRS)

A Cochrane review was unable to either prove or disprove any impact of the use of NIRS on the clinical outcome in children born more than 8 weeks too early [82]. Nevertheless, it can provide valuable additional information if used with high-risk patients. Its use appears particularly expedient during intrathoracic surgery for pathophysiological reasons.

Anaesthesiologically-relevant syndromes for newborns and premature infants

Periventricular leukomalacia (PVL)

This is caused by a **hypoxia** with ischaemia of the periventricular region. This leads to a necrosis of the oligodendrocyte precursor cells, axon damages and an apoptosis of the white matter. The oxygen deficiency is usually due to a **drop in the cerebral blood flow** caused by

- hypocapnia,
- hypotension or
- hypoxia.

A combination of these factors is therefore particularly dangerous. Children with an open duct and retrograde diastolic flow, hypoplastic left heart syndrome or ECMO therapy are also at risk [69,83,84]. This leads to varying degrees of **failures of motor functions** right through to spastic cerebral palsies [85].

Intraventricular hemorrhage (IVH)

Bleeding initially occurs alongside the ventricles as **periventricular hemorrhage** (PVH). IVH then occurs through a further increase and spread of the volume of blood in the neighbouring lateral ventricles. The cause of this is the **fragility of the vessels in the germinal matrix**. Incidence and severity correlate with the gestational age (25 % of all premature infants with a birth weight <1,500 g).

The risk increases through disturbances in the cerebral autoregulation or serum osmolarity, hypercapnia, variations in the blood pressure, hypoxia, hypoglycaemia and anaemia. The result is an increase in the cerebral perfusion, leading to a rupture of the fragile vessels.

It is therefore important to avoid
- hypocapnia (p_aCO_2 <39 mmHg),
- hypercapnia (p_aCO_2 >60 mmHg), though also
- larger fluctuations in p_aCO_2

during the first 4 days of life in particular [69]. The consequences could be **lifelong neurological deficits** such as cerebral palsy, developmental disturbances and convulsions [86].

Retinopathy of prematurity (ROP)

ROP is a rare **vasoproliferative retinopathy** in premature infants that do not yet have fully developed retinal vessels. It would appear to occur in connection with various genetic mutations. An aberrant angiogenesis can lead to an intravitreal neovascularisation with fibrotic scarring and a partial or complete retinal detachment, right through to vision loss. The morbidity correlates closely with the degree of prematurity. Risk factors in the perioperative environment include
- a high oxygen partial pressure,
- undulating post-natal oxygenation,
- a low birth weight,
- a low gestational age,
- variations in the blood pressure,
- blood transfusions,
- artificial respiration for longer than one week or, respecitvely,
- surfactant therapy.

When dealing with high-risk patients, special attention should be paid perioperatively to **avoiding an unnecessarily high supply of oxygen** and too timely **blood transfusions** [87].

Analgesia

General remarks

A sufficient analgesia in newborns and premature infants is essential to prevent acute reactions to pain such as a rise in the heart rate and blood pressure, but above all a rise in the pulmonary arterial pressure.

Numerous studies have also shown that the long-term effects of inadequately treated pain can be persistent hyperalgesia, stunted growth, a limited motor development, neuroendocrine and cognitive changes, right through to neuronal cell death [15,88-91].

Opioids

At the time of birth, the **opioid receptor density** in all of the superordinate areas of the brain stem is still much lower than in adults. Thus, the density of the opioid binding sites in the hippocampus of the mature newborn is less than 14 % of the density of adults, but on the other hand it is almost 40 % in the brain stem. As a result, opioids have a stronger effect in the brain stem of newborns and premature infants, resulting in **respiratory depression**, than in the midbrain, where the modulation of emotional pain sensation and cortical pain transmission is mediated.

Newborns and premature infants can already display a pronounced respiratory depression with opioid levels that do not cause sufficient analgesia. An opioid titration until free from pain without respiratory depression is thus not possible [91].

An altered opioid receptor distribution and density also contributes to an increased sensitivity in the dorsal root ganglion and in the spinal cord.

At the blood-brain barrier, **morphine** has a higher effect in younger years with the same CNS tissue concentration on account of changes in permeability [91]. A lot of experience has been gained with morphine in the field of neonatology. Attention has to be paid to circulatory depression and histamine release.

Sufentanil or **fentanyl** are accompanied by an increased irritation of the throat and thus a greater risk of laryngo- or bronchospasms during anaesthetic induction.

Remifentanil should only be used with caution on account of the possibility of an acute thoracic rigidity (**wooden chest**) and the generally marked drops in the heart rate with a successive reduction of the CO.

Codeine is unsuitable for newborns due to the absence of CYP2D6 and the consequential lack of any metabolism to morphine. There is no analgesic effect.

Codeine and **tramadol are** increasingly converted into their active metabolites morphine and O-desmethyltramadol (M1) in the liver by nursing mothers, who are ultra-fast metabolisers because of their CYP2D6 activity (among white Europeans 1–10 %). This can lead to dangerously high levels in the blood and breast milk. The American agency for the regulation of prescription drugs (FDA) thus published a Drug Safety Communication that does not recommend breast feeding during treatment with codeine or tramadol on account of the risk of excessive fatigue, serious respiratory depression, right through to the death of the child [92].

Regional anaesthesia

Locoregional procedures also offer an excellent quality of analgesia in premature infants and newborns. It should be noted that there are much **higher fractions of the free local anaesthetic** in the plasma on account of the lower protein concentration. Thus, identical bupivacaine doses administered continually via a caudal catheter to children under the age of six months displayed more than twice as high of a share of the free – and thus possibly toxic – bupivacaine than in children over the age of six months [93]. The increased CO also makes for a **faster vascular absorption** of the local anaesthetic from the tissue with a higher initial plasma concentration and shorter duration of action. This therefore increases the risk of a local anaesthetic intoxication [94]. Consequently, the maximum administered dose of **bupivacaine** and **ropivacaine** should be 3 mg/kg bw. However, ropivacaine has some advantages over bupivacaine as regards the risk of a systemic intoxication with a continuous supply [95]. The risk of an accumulation due to degradation by unspecific esterases is at its lowest with **chloroprocaine**. **Prilocaine** is not recommended on account of the met-Hb formation in premature infants; if used as an EMLA cream, at least pay attention to the dosage. Maximum doses should be regarded additively with respect to the toxicity.

In the case of **spinal anaesthesias**, a **relatively higher dose of the local anaesthetic** is needed on account of a relatively larger volume of liquor and the enlarged surface area of the nerve roots. The duration of action is shorter compared to older children and adults. The haemodynamics are maintained, however, through the low vasomotor tone and the reduced vagal activity.

Non-opioid analgesics (NOPA)

Non-steroid anti-inflammatory drugs (NSAID) can lead to a **closure of a ductus arteriosus** and promote a necrotising enterocolitis (NEC) or IVH. Moreover, NSAID are **not approved** for pain therapy in this age class.

What can be used is **acetaminophen (paracetamol)**, for which much experience is available in terms of postoperative analgesia for premature infants. There are great variations in the absorption with rectal administration, and in any case a high interindividual variability as regards the bioavailability. Sufficiently high plasma levels are needed to overcome the blood-brain barrier. This can vary by a factor of 3 in newborns and premature infants, the time until this value is reached can be between 60 and 240 min. (Tab. 12) [96,97].

For less painful procedures, and as a supplementary measure, **non-pharmacological procedures** such as

- breast feeding,
- non-nutritive nursing,
- direct skin-on-skin contact,
- holding in a frog position (facilitated tucking),
- swaddling or
- glucose administration

should also be employed to reduce pain. The precise mode of action in such cases is often not fully clear. Effects on opiate, glutamate and $GABA_A$ receptors, an increased dopamine release and an effect via ACh release have been discussed, as has a missing cortisol release [98].

Typical operations and their characteristics

General remarks

The **underlying cardiac diseases** mentioned at the beginning, such as ventricular or arterial septal defect, stenosis of the aortic isthmus, tetralogy of Fallot or pulmonary valve stenosis, must always be taken into account. These are often still untreated at the time of the anaesthesia and increase the perioperative risk.

Pyloric stenosis

Pay attention to a **balanced volume and acid-base status** as well as the **electrolyte balance** before the operation. The stomach should be emptied via a gastric tube, if possible before induction.

Congenital diaphragmatic hernia

On account of a gap in the diaphragm, the intestine, stomach and/or parts of the liver are within the thorax. In 80 % of cases, the defect is on the left side. The **pulmonary hypoplasia** is particularly pronounced on the operating side [99]. The content of the abdomen is normally reduced by a transverse epigastric laparotomy, in some centres also with thoracoscopy, and the diaphragm closed either directly or with a patch [100]. A pronounced **pulmonary hyperreactivity** can trigger a vasospasm at any time. Aggravated by the reduced number of pulmonary vessels, this can lead to pulmonary arterial hypertension (PAH). Some children initially experience a so-called **honeymoon phase**. This means that the newborn initially does relatively well directly after birth, until a massive pulmonary arterial hypertension with hypoxia suddenly occurs.

Table 12

Recommendation for rectal dosage to optimise the possible analgesic effect of paracetamol [109,110].

	Initial dose (mg/kg bw)	Maintenance dose (mg/kg bw)	Dosage interval (h)	Max. daily dose (mg/kg bw)	Length of max. daily dose (h)
28th–32th WOP	20	15	12	30	48
32th–36th WOP	20–30	20	8–12	45	48
37th–1ML	30	20	8	60	48

WOP: week of pregnancy; **ML:** month of life; **bw:** body weight.

The best time for an operation should be agreed between disciplines: ideally, the pulmonary arterial pressure is within the normal range and the ductus arteriosus has closed before the operation.

Avoid a forced mask ventilation during induction since an increase in the volume of air in the stomach and intestine can acutely aggravate the oxygenation.

With conventional ventilation, the target respiration pressure should be ≤ 25 cmH_20, the target respiratory rates between 40–60/min, the target PEEP ≤ 5 cm H_2O, the target preductal p_aO_2 > 60 mmHg, the target p_aCO_2 < 60 mmHg (permissive hypercapnia) and the target pH > 7.20. Other options include the inhalational administration of nitrogen monoxide (or in individual cases sildenafil, bosentan, iloprost, epoprostenol), high-frequency oscillatory ventilation (HFOV) as well as extracorporeal membrane oxygenation (ECMO) [101].

Pulmonary hypertonia and hypoxia lead to a persistent ductus arteriosus with a right-to-left shunt. This is followed by a vicious circle with increasing hypoxaemia, reduced CO and acidosis, a further increase in the pulmonary resistance and increase in the right-to-left shunt (Tab. 13).

Since the abdominal cavity is underdeveloped for the space needed, the abdominal pressure rises postoperatively, even up to an abdominal compartment syndrome. The elevated diaphragm and distended abdomen also hinder the gas exchange in the contralateral lung.

Oesophageal atresia and tracheo-esophageal fistula (TEF)

On account of the **risk of aspiration**, this should be treated within the first 24 hours of the diagnosis. The surgical procedure is a dextral thoracotomy or thoracoscopy. Anaesthetic induction takes place immediately before the start of surgery to keep the time during which air can enter the stomach through ventilation as short as possible.

During initial mask ventilation, the stomach can quickly fill with air through the tracheal fistula (type III b and c after Vogt), and cannot be relieved. In extreme cases, this may require an emergency needlestick incision of the stomach to release the air and to re-enable mechanical respiration and a venous reflux [102].

Before intubation, a **bronchoscopy to locate the fistula** should be carried out. In the case of large fistula (> 3 mm) on the carina or directly above this, a Fogarty embolectomy catheter may be positioned in the stomach through the fistula and this is then closed by inflating and retracting the balloon in the stomach area. The tip of the tube should then be positioned distal to the fistula, but proximal to the carina, during subsequent intubation. If the tube hereby slips fully into the fistula, respiration will be impossible despite a safe endotracheal position! A renewed fibre-optic check of the position is therefore recommended after intubation [102,103].

Abdominal wall defects (omphalocele, gastroschisis)

An early operative treatment through a closure of the abdominal wall or the application of a patch, a so-called Schuster prosthesis or a Silo-Bag®, eliminates the reduced perfusion of the intestine and prevents any further loss of fluids and hypothermia. With a gastroschisis or ruptured omphalocele, the exposed parts of the intestine have to be covered with a sterile dressing and kept moist before surgery to prevent the loss of fluids and hypothermia. A lateral position of the patient can reduce the risk of an intestinal ischaemia through bent vessels. Before anaesthetic induction, **gastrointestinal decompression** via a gastric tube is advisable.

When moving the intestine back inside the abdomen, the intra-abdominal pressure may rise up to a compartment syndrome and the ventilation pressures may also increase.

The estimation of the increase in intra-abdominal pressure with consecutive perfusion problems through the closure of the abdominal wall is facilitated by measuring the central venous pressure (CVP). A rise in the CVP by 4 mmHg is associated with a significant reduction of the CO [104]. The blood pressure also has to guarantee a sufficient perfusion of the intestinal loops above the level of the abdominal wall. The perioperative fluid requirement can be very high [105,106].

Cardiac diseases may be anticipated in 20 % of all children who have omphalocele. Pulmonary arterial hyper-

Table 13

Treatment of an increased pulmonary arterial resistance in ventilated newborns and measures to prevent a drop in saturation and rise in pCO_2 with the risk of a relapse into foetal circulation.

General measures	

• Sedation optimisation and relaxation
• Avoid increases in blood pressure during invasive procedures
• Optimisation of the oxygen saturation
• Lowering of the pCO_2 if necessary
	• Treatment of a metabolic acidosis according to its cause:
	  • CO increase (e.g. dobutamine)
	  • Inotropic support for the right ventricle (e.g. milrinone)
	  • Buffer solutions

Vasoactive drugs	
• Nitrogen monoxide (NO) in the inhalation air • Nitroglycerine (usually with little effect) • Magnesium	

tension is found in up to 57 % of these children [107]. Syndromes like the Beckwith-Wiedemann overgrowth syndrome, which is accompanied by malformations and tumours and is based on a genetic mutation, are also not uncommon.

Necrotising enterocolitis (NEC)

A NEC mostly occurs in premature infants (incidence approx. 7 %, lethality 15–30 %). Hypoxia and exchange transfusion, a patent ductus arteriosus with left-to-right shunt, premature feeding with formula milk and colonisation with pathogenic germs, indomethacin and corticosteroid therapy also play a role aetiologically.

Intubation and ventilation can be aggravated on account of the abdominal distension with a consecutive reduction of the FRC. Decisive for the further course are an adequate **prompt anti-infective therapy** and **preoperative circulatory support** with the help of a massive volume substitution and positive inotropic and vasopressor drugs. **Electrolyte shifts, hypovolaemia** and **protein losses** also have to be offset as well as possible in an emergency before the start of anaesthesia. Massive spontaneous hepatic haemorrhaging is possible with NEC.

Perioperative anaesthesiological management is hampered by the common simultaneous occurrence of extreme prematurity as well as haemodynamic instability, acidosis, respiratory failure, sepsis, coagulopathy (DIC), electrolyte imbalances and a patent ductus arteriosus.

Patent ductus arteriosus (PDA)

The operative ligation usually takes place in **a dextral lateral position** by means of a thoracotomy in the 3rd ICR on the left. The diameter of the exposed ductus arteriosus may be similar to that of the aorta. A pulse oximeter on the foot can help to identify an accidental ligation of the aorta in good time.

Hypovolaemia is often present during anaesthetic induction, which can lead to a drop in blood pressure. A restrictive supply of fluids is still necessary wherever possible during surgery since the operative closure of the ductus arteriosus entails an acute increase in volume in the systemic circulation with a rise in the blood pressure and risk of consecutive intracranial haemorrhaging. A **deepening of the anaesthesia** is recommended before ligation of the duct. The heart rate usually drops slightly. In addition, operative irritation of the vagus nerve can trigger a **bradycardia**. Oxygen saturation and p_aCO_2 affect the pulmonary resistance and should be kept within the optimum range during surgery in order to reduce any haemodynamic complications [108].

Neural tube defects

A **meningomyelocele** with an exposed neural plate or a **meningocele** with a membrane-like thinning of the skin requires emergency treatment.

A latex-free procedure is necessary on account of the high rates of allergisation.

Intubation takes place either in the dorsal position, placed on a large foam rubber cushion with a suitable opening ('donut' ring), or if necessary in the lateral position, so as not to damage a large cele. If a neurostimulator is used during surgery to locate nerve roots, no muscle relaxants can be used during surgery.

A **hydrocephalus internus** may require the application of a **ventricle shunt to drain the liquor** directly after birth on account of the risk of increased cerebral pressure. If there is a suspected increased intracranial pressure (ICP), ICP-enhancing factors such as volatile inhalational anaesthetics, hypoventilation, higher PEEP or a Trendelenburg position must be avoided. A modified RSI has to be considered.

Irrespective of the presence of an Arnold-Chiari malformation, it would appear that some of these patients have a **developmental disturbance in the area of the brain stem** that is manifested through heaped **drops in saturation** and a reduced response to a rise in p_aCO_2. This has to be taken into account during postoperative monitoring.

Postoperative phase

The primary postoperative concern is to detect apnoea promptly and treat this if necessary. **Apnoea and bradycardia monitoring** including pulse oximetry and ECG overnight is thus highly advisable. If apnoea phases occur during the first 12 hours of monitoring, **further monitoring on the intensive-care ward** is necessary.

In order to **prevent postoperative apnoea** after a general anaesthetic, **caffeine** can be used. The therapeutic range is much broader and the rate of side effects is much lower than with theophylline. The occurrence of **apnoea requiring intervention** can be treated by means of tactile stimulation, ventilatory support such as CPAP or mask ventilation, right through to invasive respiration and treatment of the factors named in Table 8.

Up to now, and regardless of any intervention, no scientific data has been available on from which age a former premature infant can be **treated on an outpatient basis**. With a postconceptional age below 56–60 weeks, the patient should be monitored until an apnoea-free interval of 12 hours is guaranteed. After reaching the 60th week after conception, children who no longer have apnoea can be cared for as outpatients, unless further accompanying illnesses indicate otherwise. The monitoring period before discharge into the domestic environment must be prolonged until the children are fully alert and recovered and can drink independently.

Conclusion

The anaesthesiological care of newborns and premature infants not only differs significantly from the care of adult patients, but also greatly from the care of older children. An in-depth understanding of typical underlying and

accompanying illnesses as well as knowledge of the anatomical, physiological and pharmacological characteristics of this special group of patients, such as the change-over in circulation after birth, are needed to take on the perioperative medical care. The safe anaesthesiological care of newborns and premature infants can only succeed together with institutional and individual requirements that also allow an adequate postoperative care.

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