A Practical Handbook on Pediatric Cardiac Intensive Care Therapy

Dietrich Klauwer
Christoph Neuhaeuser
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Editors
Dietrich Klauwer
Center for Paediatrics and Youth
Health Singen
Singen
Germany

Josef Thul
Universitätsklinikum Gießen und Marburg
Paediatric Cardiac ICU and Heart
Transplantation Program
Gießen
Germany

Christoph Neuhaeuser
Universitätsklinikum Gießen und Marburg
Paediatric Cardiac ICU and Heart
Transplantation Program
Gießen
Germany

Rainer Zimmermann
Global Medical Leader in Medical Affairs
Actelion Pharmaceuticals
Allschwil
Switzerland

Translation from the German language edition: Pädiatrische Intensivmedizin – Kinderkardiologische Praxis, 2. erw. Auflage by D. Klauwer / C. Neuhaeuser / J. Thul / R. Zimmermann, © Deutscher Ärzteverlag 2017
ISBN 978-3-319-92440-3 ISBN 978-3-319-92441-0 (eBook)
https://doi.org/10.1007/978-3-319-92441-0

Library of Congress Control Number: 2018957468

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This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Foreword

The most sophisticated way of teaching medicine is to transfer knowledge, experience, and skills directly into newly built medical centers equipped with modern devices. A new generation of doctors is coming to the fore in neonatal cardiovascular intensive care, and it is necessary for them to start by successfully applying theoretical knowledge. This book provides patient-oriented approaches to the interdisciplinary specialists involved in decision-making at the point of care and to those who need to be able to understand and manage the concrete situations in neonates and small children with congenital heart defects.

The core value of this book for beginners is its handover of clinically relevant information while promoting the fundamentalist's style of thinking about physiology and organ function in different congenital heart defects. Such an approach drives an understanding of the forthcoming problems and how to manage them. Besides understandable and detailed descriptions of specific pitfalls and special situations relating to the diagnosis, intervention, and medical treatment of each distinctive defect, this practical handbook focuses on general daily practice and bedside medicine for doctors and nurses: easy to understand, straightforward to implement, and result-oriented. Its chapters fill the informational gaps in cardiopulmonary interactions to manage the multiple hemodynamic situations that can arise.

Doctors in Russia, Eastern European, and Asia are confronted with difficult-to-manage neonates and complex technologies in the absence of advanced knowledge in both the operating theater and the ICU. For these reasons, newly built centers suffer from high mortality and complication rates even in simple cases and are therefore only able to treat a limited spectrum of patients in urgent need of cardiac surgery. This book enables its readers to recognize in advance the signs of approaching emergency situations and adapt to the situation in a timely manner or obtain the appropriate help. For each patient on the ICU, it provides a broad knowledge base to understand what is happening, foresee complications, and react quickly to arising problems.

During their medical missions to the Neonatal Center of St. Petersburg State Pediatric Medical University where a new pediatric heart program is being developed, Dietrich Klauwer and Christian Jux provided one-on-one teaching to the local specialists. Thanks to the first German version of this book, it was possible to introduce training systems for beginners on pediatric cardiac ICU in St. Petersburg, Russia. This book details ways to manage complex problems in a pragmatic,

concrete, and experience-based way. The authors achieved the goal of creating a work with proven effectiveness that has become the cornerstone in the practical education of next interdisciplinary generation of cardiovascular critical care specialists.

January 2018

Sergey Marchenko, MD
Professor of Cardiac Surgery
Division of Cardiac Surgery
Neonatal Center of St. Petersburg State
Pediatric Medical University
St. Petersburg, Russia

Foreword

Over the past decades, the care for children with congenital heart disease has seen significant change. The number of operations and the complexity of surgery have increased. This included a move from initial palliation to early repair of several structural lesions. More challenging surgical approaches warranted more specialized pediatric cardiac critical care units which were established at larger centers in Europe and North America, leading to better outcomes but also to a need for more trained and knowledgeable nurses and physicians in this area of patient care. A new pediatric subspecialty was emerging – but sometimes without the usual established training programs. Gaining appropriate knowledge may become a challenge. For the beginner in the field of pediatric cardiac critical care, everything is new. Being exposed to (different) terminologies of congenital heart disease, making the correct diagnosis and treatment plan is sometimes challenging. In the interests of the children who need advanced care on the critical care unit, the entire team – physicians and nurses – need to understand both normal and relevant physiology of the underlying defect along with preoperative and post-intervention hemodynamics.

The great advantage of this book is that it serves the learners, while taking command as reference for advanced practitioners in that it bridges many areas, and also provides detailed problem-solving.

Without repeating the table of contents, a couple of important chapters should be highlighted, emphasizing well-explained ventilation strategies for different situations and frequently used medications (antibiotics, inotropes, vasopressors, etc.). Analgesia and sedation pathways for early extubation or prolonged ventilation are described, and a pro/con chapter for fast track is included. In addition, the authors cover important other areas like structured handover, nutrition, pulmonary hypertension, and mechanical support. Well-designed illustrations and tables provide an instant overview.

With a consistent approach that was long practiced and nurtured, the authors of this book achieved the goal of aligning all the aforementioned topics into a German version which was published several years ago and highly appreciated. It was no wonder that the first edition was rapidly sold.

I congratulate the team and the Springer-Verlag on this tremendously important project. Given that a second German edition has already been published, minor problems have been ironed out and newer treatment algorithms are included. The English edition is targeted to an international audience, including countries that are

in the process of developing cardiac surgical centers and, therewithin, nursing, pediatric intensivists, cardiologists, anesthesiologists, and surgeons who are bothin training and early practice. Rather than rigid instruction, this book truly serves as a guideline or curriculum whereupon programs can build – and I believe it will enable the next generation of caregivers in our field to reach the next level.

January 2018

Tilman Humpl, MD
Associate Professor of Pediatrics
Department of Critical Care Medicine
Division of Cardiac Critical Care Medicine
Hospital for Sick Children
Toronto, Canada

Preface

The motivation to have the second German edition of our well-received practical handbook on pediatric cardiac intensive care translated into English was to impart to the global medical community our mostly pathophysiologically and experience-oriented methods of managing children with cardiac pathologies. This intention emerged from three directions.

Need

During many travels to foreign countries in Eastern Europe, Asia and Africa on missions to help departments initiate or develop state-of-the-art pediatric heart surgery programs, it became evident that the greatest deficits in the postoperative therapy of children lie in the lack of clear, comprehensible and actionable strategies. Established protocols and workflows for clinical assessment, preoperative diagnostics through therapeutic management to planning and performing surgeries in the hands of a well-coordinated team are not in place in many developing centres.

Here, the most obvious need was how to reproduce for and share with others the combined experience gained over decades. This need for knowledge transfer applied to the clinical assessment of patients, their organ functions in critical situations, how to anticipate disease courses, teach others how to deploy modern equipment and administer pharmacological treatments in the best available way.

With the present handbook, the authors hope to create a pathophysiological understanding for the processes, problems and complications routinely encountered on a pediatric cardiac ICU so that options for action can be found and ways to find solutions made transparent.

Insofar as we wanted to do justice to the academic dispute about “evidence”, we felt a handbook structure seemed more purposeful for explaining how to achieve successful therapeutic outcomes on an individualized basis. That is only one of the reasons why this handbook does not claim to present the reader with elaborate literature searches on theoretically best practices. Rather, it combines the many authors’ multiple years of experience in establishing self-verified, innovative and advanced clinical methods that fit our own effective concepts, while also taking the currently relevant literature into account in the true sense of evidence-based medicine.

Ambition

The idea to reshape the mould of an introductory guidance intended for the Giessen pediatric ICU into a handbook of critical care on a pediatric ICU was born in the year 2011. After publication of the first German edition and its unexpectedly high acceptance, the authors decided to write a second, revised and extended version. For this second issue, the authors were able to inspire other renowned authoritative contributors and with these co-authors broaden the book's scope. To this new version, we added important related topics that are pivotal to enriching the readers' knowledge about the hemodynamics of different heart defects and the postoperative circulatory changes occurring with and without the use of respirators.

Our desire was to satisfy the unmet need described above and to compete with other English works on the subject. Convinced about its concept and committed to an implementation that goes against the grain of the conventionally practiced way of sharing medical knowledge, we aim to open up the contents of this handbook to a worldwide public working in the field of pediatric cardiology.

Opportunity

The real opportunity to be able to turn this ambitious goal of a first English edition into reality was enabled by Getinge thanks to their sponsorship of a professional medical translation. The authors also feel highly fortunate to have this work published by the distinguished Springer Verlag with their affiliated sales channels of a global distribution network.

Above and beyond that appreciation, my thanks go to all of those who participated with heart, hand and mind in realization of this project: to the Eurasia Heart Foundation for their exemplarily contribution to the original idea, to Ms. Deborah A. Landry for her infinite patience during the translation process, to Ms. Katja Kassem for the figures, to the German publisher Deutscher Ärzteverlag GmbH for transferring the rights as well as to all the authors and their families for their support in getting this book out alongside their routine clinical work.

For the authors Dietrich Klauwer, Feb. 2018

Singen, Germany — Dietrich Klauwer
Gießen, Germany — Christoph Neuhaeuser
Gießen, Germany — Josef Thul
Allschwil, Switzerland — Rainer Zimmermann

My conflict of interest is as follows: R. Zimmermann is an employee of Actelion Pharmaceuticals, Switzerland.

Contents

Part II Management of Specific Pediatric Cardiac Problems

Contributors

Maria B. Gonzalez y Gonzalez Pediatric Heart Center of Giessen, Children's Heart Transplantation Center, UKGM GmbH, Giessen, Germany

Christian Jux Pediatric Heart Center of Giessen, Children's Heart Transplantation Center, UKGM GmbH, Giessen, Germany

Dietrich Klauwer Department of Pediatrics, Singen Medical Center, Gesundheitsverbund Landkreis Konstanz, Krankenhausbetriebsgesellschaft Hegau-Bodensee-Klinikum, Singen, Germany

Edward Malec Division of Pediatric Cardiac Surgery, Münster University Medical Center, Münster, Germany

Christoph Neuhaeuser Pediatric Heart Center of Giessen, Children's Heart Transplantation Center, UKGM GmbH, Giessen, Germany

Christoph Schmidt Department of Anesthesiology, Surgical Intensive Care Medicine and Pain Therapy, Münster University Medical Center, Münster, Germany

Josef Thul Pediatric Heart Center of Giessen, Children's Heart Transplantation Center, UKGM GmbH, Giessen, Germany

Rainer Zimmermann Global Medical Affairs, Actelion Pharmaceuticals Ltd., Allschwil, Switzerland

List of Abbreviations

AA	Amino acid(s)
AB	Antibiotics
Ab	Antibodies
ABB	Acid-base balance
ABP	Arterial blood pressure
ACC	Acetylcysteine
ACE	Angiotensin-converting enzyme
Acetyl-CoA	Acetyl coenzyme A
ACT	Activated clotting time
ACTH	Adrenocorticotropic hormone
AdC	Adenylate cyclase
ADH	Antidiuretic hormone
ADP	Adenosine diphosphate
ADR	Adverse drug reaction
aEEG	Amplitude-integrated electroencephalography
AG	Anion gap
AKI	Acute kidney injury
ALI	Acute lung injury
ALS	Advanced Life Support
ALT	Alanine aminotransferase
ANP	Atrial natriuretic peptide
AP	Aortopulmonary
AP shunt	Aortopulmonary shunt
APC	Activated protein C
APh	Alkaline phosphatase
ARDS	Acute respiratory distress syndrome
AS	Aortic stenosis
ASD	Atrial septal defect
ASO	Arterial switch operation
ASS	Acetylsalicylic acid
AST	Aspartate aminotransferase
AT III	Antithrombin III
ATG	Antithymocyte globulin
ATP	Adenosine triphosphate

AVB, AV block	Atrioventricular block
$avDO_2$	Arteriovenous oxygen difference
AVNRT	Atrioventricular nodal reentry tachycardia
AVRT	Atrioventricular reentrant tachycardia
AVSD	Atrioventricular septal defect
AWMF	Association of the Scientific Medical Societies in Germany
AZA	Azathioprine
bid	Twice a day (“bis in die”)
BAL	Bronchoalveolar lavage
BAP	Balloon angioplasty
BB	Buffer base
BC	Blood culture
BE	Base excess
BEecf	Base excess of extracellular fluid
BG	Blood gas
BG	Blood group
BGA	Blood gas analysis
Bili	Bilirubin
BIPAP	Biphasic positive airway pressure
BIS	Bispectral index
BLD	Blood leak detector
BLS	Basic life support
BNP	Brain natriuretic peptide
BP	Blood pressure
BPD	Bronchopulmonary dysplasia
BS	Blood sugar
BSA	Body surface area
BT Shunt	Blalock-Taussig Shunt
BW	Body weight
Ca	Calcium
cAMP	Cyclic 3’,5’-adenosine monophosphate
CaO_2	O_2 content of arterial blood
CAPD	Continuous ambulatory peritoneal dialysis
CBF	Cerebral blood flow
CPB	Cardiopulmonary bypass
CC	Creatinine clearance
CCB	Calcium channel blocker
CCT	Cranial computed tomography
CCT	Aortic cross-clamp time
CDH	Congenital diaphragmatic hernia
Cdyn	Dynamic compliance
CF	Cystic fibrosis
cGMP	Cyclic guanosine monophosphate
CH	Charrière
CI	Cardiac Index

CID	Continuous intravenous drip infusion
CK	Creatine kinase
CK-MB	Creatine kinase-muscle/brain
CM	Contrast medium
CMV	Cytomegalovirus
CN	Cyanide
CNS	Central nervous system
CO (Q)	Cardiac output
CO_2	Carbon dioxide
CoA	Coarctation of the aorta
COX	Cyclooxygenase
CPAP	Continuous positive airway pressure
CPB	Cardiopulmonary bypass (heart-lung machine)
CPP	Cerebral perfusion pressure
CPR	Cardiopulmonary resuscitation
CPVT	Catecholaminergic polymorphic ventricular tachycardia
CRC	Concentrated red cells
CrCl	Creatinine clearance
CrP	C-reactive protein
CRRT	Continuous renal replacement therapy
CsA	Cyclosporine A
CSD	Coronary sinus defect
CT	Clotting time
CTEPH	Chronic thromboembolic pulmonary hypertension
CVC	Central venous catheter
$CvCO_2$	Venous concentration of carbon dioxide
CVP	Central venous pressure
CVVHDF	Continuous venovenous hemodiafiltration
D	Dislocation
Da	Dalton
DA	Duration of action
DAP	Diastolic arterial pressure
DCM	Dilative cardiomyopathy
DHCA	Deep hypothermic circulatory arrest
DIC	Disseminated intravascular coagulation
DILV	Double inlet left ventricle
DKS	Damus-Kaye-Stansel procedure
dl	Deciliter (100 ml)
DNA (S)	Deoxyribonucleic acid
DO_2	Oxygen delivery
DORV	Double outlet right ventricle
dP, ΔP	Pressure change (delta P)
DPG	Diphosphoglycerate
DSO	German Organ Transplantation Foundation
d-TGA	Dextro-transposition of the great arteries

dV	Volume change (delta V)
dyn	dyne, unit of force equal to 10^{-5} newton
E-lyte	Electrolyte
EBV	Epstein-Barr virus
ECC	Extracorporeal circulation
ECLS	Extracorporeal life support
ECMO	Extracorporeal membrane oxygenation
ECS	Extracellular space
EDTA	Ethylenediaminetetraacetic acid
EDV	End-diastolic volume
EF	Ejection fraction
ELSO	Extracorporeal Life Support Organization
EMA	European Medicines Agency
ERA	Endothelin receptor antagonist
ERC	European Resuscitation Council
ERO_2	O_2 extraction ratio
ESBL	Extended-spectrum beta-lactamase
ESC/ERS	European Society of Cardiology/European Respiratory Society
ET	Eurotransplant
ET-1	Endothelin-1
ET-A, ET-B	Endothelin-A, Endothelin-B
$etCO_2$	End-tidal CO_2
F	French (scale for denoting the size of catheters)
FAT	Focal atrial tachycardia
FDA	United States Food and Drug Administration
FDP	Fibrin degradation products
$FECO_2$	Fraction of end tidal CO_2
FeNa	Fractional excretion of sodium
FFA	Free fatty acids
FFP	Fresh frozen plasma
FIB	Fibrinogen
FiO_2	Fraction of inspired oxygen
FPE	First-pass effect
FRC	Functional residual capacity
FS	Fraction shortening (shortening fraction)
FS	Fractional shortening
FV	Factor V
FVIII	Factor VIII
G	Gauge
GABA	Gamma-aminobutyric acid
GABAergic	Gamma-aminobutyric acid-ergic
GCS	Glasgow Coma Scale
G-CSF	Granulocyte colony-stimulating factor
GFR	Glomerular filtration rate
GH	Growth hormone

GHB	Gamma-hydroxybutyric acid
GI	Gastrointestinal
h	Hour(s)
HA	Human albumin
Hb	Hemoglobin
HbO_2	Oxyhemoglobin
HBsAG	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCO_3^-	Hydrogen carbonate
Hct	Hematocrit
HCV	Hepatitis C virus
HD	Hemodialysis
HDF	Hemodiafiltration
HES	Hydroxyethyl starch
HF	Hemofiltration
HFOV	High-frequency oscillation ventilation
HIF	Hypoxia-induced factor
HIT	Heparin-induced thrombocytopenia
HIT-II	Heparin-induced thrombocytopenia type II
Hct	Hematocrit
HLA	Human leukocyte antigen
HLH	Hypoplastic left heart
HLHS	Hypoplastic left heart syndrome
HLM	Heart-lung machine
HOCM	Hypertrophic obstructive cardiomyopathy
HPT	Hyperparathyroidism
HPV	Hypoxic pulmonary vasoconstriction
HR	Heart rate
HTx	Heart transplantation
i.m.	Intramuscular
i.o.	Intraosseous
i.v.	Intravenous
IAA	Insulin autoantibodies
IABP	Intra-aortic balloon pump
IAP	Intraabdominal pressure
IART	Intra-atrial reentrant tachycardia
ICB	Intracranial bleeding
ICD	Implantable cardioverter-defibrillator
ICP	Intracranial pressure
ICU	Intensive care unit
ID	Internal diameter
IGF	Insulin-like growth factor
IgG	Immunoglobulin G
INR	International normalized ratio
IP receptor	Prostacyclin receptor (I-Prostanoid)

iPAH	Idiopathic pulmonary arterial hypertension
ISA	Intrinsic sympathomimetic activity
ISHLT	International Society for Heart and Lung Transplantation
ISTA	Aortic isthmus stenosis
I-time	Inspiratory time
IU	International unit
IVC	Inferior vena cava
IVH	Intraventricular hemorrhage
IVIG	Intravenous immunoglobulin
IVS	Intact ventricular septum
J	Joule
JET	Junctional ectopic tachycardia
K	Potassium
KCl	Potassium chloride
Kg	Kilogram
KUSS	Childhood Discomfort and Pain Scale (German: Kindliche Unbehagen- und Schmerz-Skala)
L/R shunt	Left/right shunt
LA	Left atrium
LAD	Left anterior descending
LAP	Left atrial pressure
LCO	Low cardiac output
LDH	Lactate dehydrogenase
LI	Liver insufficiency
LIP	Lower inflection point
LMA	Laryngeal mask airway
LMWH	Low molecular weight heparin
Lp	Lipoprotein
LP	Lumbar puncture
LPA	Left pulmonary artery
LPOHV	Left-persisting upper vena cava
LPR	Lactate-pyruvate ratio
LPS	Lipopolysaccharide
LT	Long-term
l-TGA	Levo-transposition of great arteries
LTx	Liver transplantation
LuFu	Lung function
LV	Left ventricle
LVEDD	Left ventricular end-diastolic diameter
LVEDP	Left ventricular end-diastolic pressure
LVOT	Left ventricular outflow tract
LVOTO	Left ventricular outflow tract obstruction
MA	Maximum amplitude
MA	Maximum amplitude in thromelastography

MABP	Mean arterial blood pressure
MAC	Minimum alveolar concentration
MAPCA	Major aortopulmonary collateral artery
MAPSE	Mitral annular plane systolic excursion
mbar	Millibar
MC	Microcirculation
MCF	Maximum clot firmness
mcg	Microgram
mEq	Milliequivalent
Met-Hb	Methemoglobin
Mg	Magnesium
mg%	Milligrams percent
MI	Mitral insufficiency
MIBI	Microbiology
MIC	Minimum inhibitory concentration
min	Minute(s)
ML	Maximum lysis
µm	Micrometer
MMF	Mycophenolate mofetil
mmHg	Millimeters of mercury
mmol	Millimol
MNF	Multiresistant nonfermenters
mo	Month(s)
MOF	Multi-organ failure
Mol	Mol
mosmol	Milliosmol
MRGN	Multi-resistant gram-negative
MRSA	Methicillin-resistant *Staphylococcus aureus*
MRSE	Methicillin-resistant *Staphylococcus epidermidis*
MRT	Magnetic resonance tomography
MST	Mitral stenosis
MTHFR	Methylenetetrahydrofolate reductase
MTX	Methotrexate
mU	Milliunits
MUF	Modified ultrafiltration
MV	Minute volume
mV	Millivolt
Na	Sodium
NaBi	Sodium bicarbonate
NAC	N-acetylcysteine
NAD	Nicotinamide adenine dinucleotide
NADH	Nicotinamide adenine dinucleotide (reduced)
NAPQI	N-acetyl-P-benzoquinone imine
NBP	Non-bicarbonate buffer

NEC	Necrotizing enterocolitis
NH_3	Ammonia
NIRS	Near-infrared spectroscopy
NMDA	N-methyl-D-aspartate
NO	Nitrogen oxide
NOAD	New oral anticoagulant drugs
NSAID	Nonsteroidal anti-inflammatory drug
NSE	Neuron-specific enolase
NYHA	New York Heart Association
O	Obstruction
O_2	Oxygen
OLT	Open Lung Tool
OP	Operation
ORT	Orthodromic reentry tachycardia
P	Phosphorus
p.o.	Per os
PA	Pulmonary artery
PAC	Pulmonary artery catheter
PaCO2	Arterial partial pressure of carbon dioxide
PAH	Pulmonary arterial hypertension
PAH-CHD	Pulmonary arterial hypertension associated with congenital heart disease
PAI	Plasminogen activator inhibitor
PALS	Pediatric advanced life support
PAM	Postaggression metabolism
PaO_2	Reduced oxygen tension
PAP	Pulmonary artery pressure
PAPm	Mean pulmonary artery pressure
PAPVR	Partial anomalous pulmonary venous return
PAS	Postaggression syndrome
PAT	Pulmonary atresia
PAWP	Pulmonary arterial wedge pressure
PBF	Pulmonary blood flow
PBP	Pre-blood pump
PC	Platelet concentrate
PC	Pressure control
PCA	Patient-controlled analgesia
PCH	Pulmonary capillary hypertension
PCM	Paracetamol
PCO_2	Partial pressure of carbon dioxide
PCR	Polymerase chain reaction
PCT	Procalcitonin
PCWP	Pulmonary capillary wedge pressure
PD	Peritoneal dialysis
PDA	Patent ductus arteriosus

PDE	Phosphodiesterase
PDE5i	Phosphodiesterase-5 inhibitor
PdGF	Platelet-derived growth factor
PDR	Pulmonary vascular resistance
PE	Pulmonary embolisms
PEA	Pulseless electrical activity
PEEP	Positive end-expiratory pressure
PEG	Percutaneous endoscopic gastrostomy
PET	Positron emission tomography
$PetCO_2$	Partial end-tidal carbon dioxide tension
PF	Platelet factor
PF4	Platelet factor 4
PFC	Persistent fetal circulation
PFK	Phosphofructokinase
PFO	Patent foramen ovale
PG	Prostaglandin
PGH_2S	Prostaglandin H_2 synthase
PGI_2	Prostaglandin I_2 (prostacyclin)
pH	hydrogen ion (H+) concentration (acidity) of a solution, ranging from 0 to 14
PH_2O	Hydrostatic pressure
PHT	Pulmonary hypertension
PIP	Peak pressure or positive inspiratory pressure
PJRT	Persistent junctional reciprocating tachycardia
pKa	Acid dissociation constant
PLS	Pediatric Life Support
PM	Pacemaker
PMN	Polymorphonuclear neutrophils
PN	Premature neonate
PaO_2	Partial pressure of oxygen
POCT	Point-of-care testing
POD	Postoperative day
PPHN	Persistent pulmonary hypertension of the newborn
ppm	Parts per million
PPN	Partial parenteral nutrition
PPSB	Prothrombin, proconvertin, Stuart-Prower factor, antihemophilic factor B
PPV	Positive pressure ventilation
PRA	Panel reactive antigen
PRIS	Propofol infusion syndrome
PRVC	Pressure-regulated volume control
PS	Pressure support
PST	Pulmonary stenosis
PSV	Pressure support ventilation
PSVT	Paroxysmal supraventricular tachycardia
PTA	Persistent truncus arteriosus

PTFE	Polytetrafluorethylene
PTH	Parathyroid hormone
PtO_2	Tissue oxygen partial pressure
PTT	Partial thromboplastin time
PV	Pulmonary vein
PvCO2	Venous partial pressure of carbon dioxide
PVL	Periventricular leukomalacia
PVO	Pulmonary venous obstruction
PvO_2	Low oxygen partial pressure
PVR	Pulmonary vascular resistance
PVRI	Pulmonary vascular resistance index
Qp	Ratio of pulmonary
Qp/Qs	Ratio of pulmonary-to-systemic blood flow
Qs	Systemic perfusion
RA	Right atrium
RAAS	Renin-angiotensin-aldosterone system
RACE	Repetitive alveolar collapse and expansion
RAP	Right atrial pressure
RBF	Renal blood flow
RDS	Respiratory distress syndrome
Rea	Reanimation
RI	Renal impairment
RMV	Respiratory minute volume
RNA	Ribonucleic acid
ROSC	Return of spontaneous circulation
ROTEM	Rotational thromboelastometry
Rp	Pulmonary vascular resistance
RPA/LPA	Right/left pulmonary artery
rpm	Revolutions per minute
RPP	Renal perfusion pressure
RQ	Respiratory quotient
RR	Respiratory rate
RRT	Renal replacement therapy
$rSCO_2$	Regional cerebral oxygen saturation
r-tPA	Recombinant tissue plasminogen activator
RV	Right ventricle
RVEDP	Right ventricular end-diastolic pressure
RVOT	Right ventricular outflow tract
RVOTO	Right ventricular outflow tract obstruction
RVP	Right ventricular pressure
S	Sieving coefficient
SA block	Sinoatrial block
SaO_2	Arterial oxygen saturation
SAP	Systolic arterial pressure, supra-arterial pressure

SBE	Standard base excess
SCD	Sudden cardiac death
$ScvO_2$	Central venous saturation
sec	Second(s)
SF	Surfactant
sGC	Soluble guanylate cyclase
SIADH	Syndrome of inappropriate antidiuretic hormone secretion
SID	Strong ion difference
SIDS	Sudden infant death syndrome
SIMV	Synchronized intermittent mandatory ventilation
SIPPV	Synchronized intermittent positive pressure ventilation
SIRS	Systemic inflammatory response syndrome
SO_2	Oxygen saturation in general
SpO_2	Saturation of peripheral oxygen
$SpvO_2$	Pulmonary venous saturation
SR	Sinus rhythm
STB	Standard bicarbonate
SV	Stroke volume
SVC	Superior vena cava
SVD	Sinus venosus defect
SVES	Supraventricular extra systole(s)
SvO_2	Venous saturation
SVR	Systemic vascular resistance
SVT	Supraventricular tachycardia
T3	Triiodothyronine
T4	Thyroxin
TAC	Tacrolimus
TAC	Truncus arteriosus communis
TAPSE	Tricuspid annular plane systolic excursion
TAPVR	Total anomalous pulmonary venous return
TAT	Tricuspid atresia
Tc	Transcutaneous (saturation)
TC	Time constant
TCO_2	Total carbon dioxide
TCPC	Total cavopulmonary connection
TEE	Transesophageal echocardiography
TEG	Thrombelastography
TEI	Myocardial performance index
Temp	Temperature
TFA	Total fluid amount
TFPI	Tissue factor pathway inhibitor
TGA	Transposition of great arteries
TGF	Transforming growth factor
TI	Tricuspid insufficiency

Ti/Te	Inspiratory time/expiratory time
TIVA	Total intravenous anesthesia
TMP	Transmembrane pressure
TNI	Troponin I
TOF	Tetralogy of Fallot
TOR	Target of Rapamycin
tPA	Tissue plasminogen activator
TPG	Transpulmonary pressure gradient
TPN	Total parenteral nutrition
TPG	Transpulmonary gradient
TPR	Tubular phosphate reabsorption
TRALI	Transfusion-associated acute lung injury
TRIS	Tris(hydroxymethyl)aminomethane buffer ($C_4H_{11}NO_3$)
TT	Thrombin time
TU	Tumor
TÜV	German Technical Inspection Association
TV	Tricuspid valve
U	Units
UDP-GT	Uridine diphosphate glucuronosyltransferase
UFH	Unfractionated heparin
UIP	Upper inflection point
UTI	Urinary tract infection
UTS	Ullrich-Turner syndrome
UVC	Umbilical venous catheter
V/Q	Ventilation-perfusion ratio
VA	Alveolar ventilation
VAD	Ventricular assist device
$vaDCO_2$	Venoarterial carbon dioxide difference
VAP	Ventilator-associated pneumonia
VCO2	Carbon dioxide output
VD	Volume dead space
VEGF	Vascular endothelial growth factor
VES	Ventricular extra systole(s)
VF	Ventricular fibrillation
VILI	Ventilator-induced lung injury
Vmax	Maximum velocity
VO_2	Oxygen consumption
VP shunt	Ventriculoperitoneal shunt
VRE	Vancomycin-resistant enterococci
VSD	Ventricular septal defect
Vt	Tidal volume
VT	Ventricular tachycardia
VV	Venovenous
vWF	von Willebrand factor
WBS	Williams-Beuren syndrome

WL	Week of life
WPW	Wolff-Parkinson-White syndrome
WU	Wood units
YC	Young children
yr	Year(s)

Important General Preliminary Remarks

Dietrich Klauwer

Organization

This book is addressed to the beginner in pediatric intensive care and pediatric cardiac intensive care and in its general section is intended to communicate the principles of practical management of the patient in a pediatric intensive care unit. In the authors' view, as well as a basic knowledge of the functioning and monitoring of the different organ systems, this also includes knowledge of the individual patient's problems.

This knowledge should provide the newcomer with a clear framework within which he or she can rapidly gain confidence in his or her management of frequently extremely severely ill patients, despite the complexity of the setting.

In order to be able to provide rapid help in an emergency and to obtain assistance, it is vital to know the logistics of the site and to have key data on all patients at hand. In addition to an *understanding of the monitoring unit,* this also includes knowledge about the handling of suction systems and the ventilation bags adapted to different patient sizes and the operation of ventilation devices, defibrillators, ECG equipment, and pacemakers. Moreover, when in sole charge of a patient at night and on the weekend, details on ECMO (extracorporeal membrane oxygenation), dialysis, and Berlin heart are paramount. Knowledge about resuscitation and the handling of drugs that this involves, as well as about the equipment on the emergency trolley, is equally essential.

Therefore, as well as a firm grasp of diagnostic and therapeutic concepts on which this book intends to make a start, the practical on-site introduction of the new employee to all equipment and logistical processes is particularly vital. Recommendations here include the issue of an equipment operator's license, the restocking of emergency kits or emergency trolleys after deployment alongside the regularly practiced, independent use of equipment present at the patient's bedside—jointly with the nursing staff.

More important, however, is to also identify general prodromal signs of an impending emergency and thereby to prevent the situation from arising in the first place or to seek assistance. This entails that a minimum amount of information should be available on each patient in the intensive care unit (ICU), not only for a personal understanding but also for rapid responses to questions by any colleagues who are consulted. This textbook systematically describes the most important

details needed for the reliable understanding and communication of urgent and emergency situations arising in individual patients, but also those which are essential to understand in order to be able to anticipate the most common problems encountered in patients on a pediatric ICU.

What Should Be Actively Known About Each Patient?

- Age and weight
- Disease and day of surgery, including clinical course of previous disease, where applicable
- Hemodynamics in terms of:
  - Normal serial circulation
  - PDA-dependent systemic/pulmonary perfusion, systemic-to-pulmonary arterial circulation (PDA = patent ductus arteriosus)
  - Glenn or TCPC circulation (total cavopulmonary connection)
  - Left or right ventricular obstruction
- Data on hemodynamics: Blood pressure (BP), central venous pressure (CVP), microcirculation (MC), lactate, SvO_2 (central venous saturation) etc. (see individual chapters), drains, respiratory and ventilatory status, renal function, laboratory data
- Major diseases other than cardiac:
  - Respiration
  - Kidney
  - Gastrointestinal tract
  - Neurology
- Particular aspects of the previous history (endocrinology, syndromal diseases, particular social aspects, etc.)

After reading the book, any member new to the pediatric cardiology team should have a sound grasp of the individual details that encompass the intensive care patient's overall situation. This conceptual understanding should equally allow a structured handover to the next shift and other staff involved in the patient's care. Furthermore, the defined structure ensures that key points are not lost or overlooked, for example, even for a novice on the ICU.

Structured Handover

To be able to identify a patient's problems as quickly as possible and without the loss of relevant reporting, a chart for the structured handover of information to the next shift is essential.

The details required for this are best kept in one's head or noted down at close proximity – the (electronic) record serves as a reference. The reporting regimen

described should enable information to be passed on in the form of a common thread within a short space of time:

- Disease(s)/preexisting condition(s)/prior medication
- Change in general health (GH): Better – worse – the same (during shifts)
- Circulatory parameters: Blood pressure, CVP, MC, SvO_2, urine output, cardiovascular drugs
- Rhythm and pacemaker (PM) with antiarrhythmic therapy
- Lung function with ventilation parameters: Pressures, FiO_2 (fraction of inspired oxygen), MV (minute volume), Vti (tidal volume), and type of ventilation
- Kidney with urine output, specific urine characteristics, and diuretic therapy
- Drains and specific bleeding characteristics
- Neurological status with vigilance, analgesia, sedatives, specific aspects
- Gastrointestinal tract/metabolism with nutrition/medication to act on intestinal motility/glucose metabolism
- Laboratory values, particularly troponin I (TNI), coagulation, infection markers, liver function tests, microbial data
- Important social aspects for the patient's care/further procedure

In addition:

- Type of surgery and exact procedure should be documented by the admitting staff (whenever possible: Surgeon's drawing(s)).
- Ultrasound and X-ray findings should be entered in the chart by the surgeon and should be known.

To allow an efficient and well-structured handover, including to those who are less well versed, the following ground rules must be observed:

- Listeners listen acutely and are allowed to ask questions about individual points.
- Discussion of problems and establishment of the procedure, if possible, should be held jointly and comprehensibly for everyone at the end of the handover.

Part I

General Considerations on Pediatric Cardiac Intensive Care Medicine

O_2 Supply, CO_2, and Acid-Base Balance

1

Christoph Neuhaeuser and Dietrich Klauwer

1.1 O_2 Supply and CO_2 Balance

1.1.1 O_2 Partial Pressure and Oxygen Cascade

In ambient air (and under standard conditions), an O_2 partial pressure (PO_2) of about 160 mmHg prevails.

Formula 1

$PO_2 = P_{atm} \times FiO_2$

At P_{atm} = 760 mmHg: 760 mmHg × 0.21 = *160 mmHg*

In the respiratory tract, inspired air is moistened (PH_2O = 47 mmHg) and then mixed in the ventilated alveoli with the CO_2 released. As a result, alveolar O_2 partial pressure (PAO_2) drops to about 100 mmHg.

PH_2O = hydrostatic pressure

Formula 2 = alveolar gas equation

$PAO_2 = (P_{atm} - PH_2O) \times FiO_2 - PaCO_2/RQ$

With an RQ (respiratory quotient) = 0.8 (mixed diet): (760 mmHg – 47 mmHg) × 0.21–40 mmHg / 0.8 = *100 mmHg*

Even in healthy subjects, however, arterial O_2 partial pressure (PaO_2) does not match alveolar partial pressure but is only about 95 mmHg (SaO_2 = 98–100%; see

C. Neuhaeuser (✉)
Pediatric Intensive Care Unit, Pediatric Heart Center of Giessen, Children's Heart Transplantation Center, UKGM GmbH, Giessen, Germany
e-mail: christoph.neuhaeuser@paediat.med.uni-giessen.de

D. Klauwer
Department of Pediatrics, Singen Medical Center, Gesundheitsverbund Landkreis Konstanz, Krankenhausbetriebsgesellschaft Hegau-Bodensee-Klinikum, Singen, Germany

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D. Klauwer et al. (eds.), *A Practical Handbook on Pediatric Cardiac Intensive Care Therapy*, https://doi.org/10.1007/978-3-319-92441-0_1

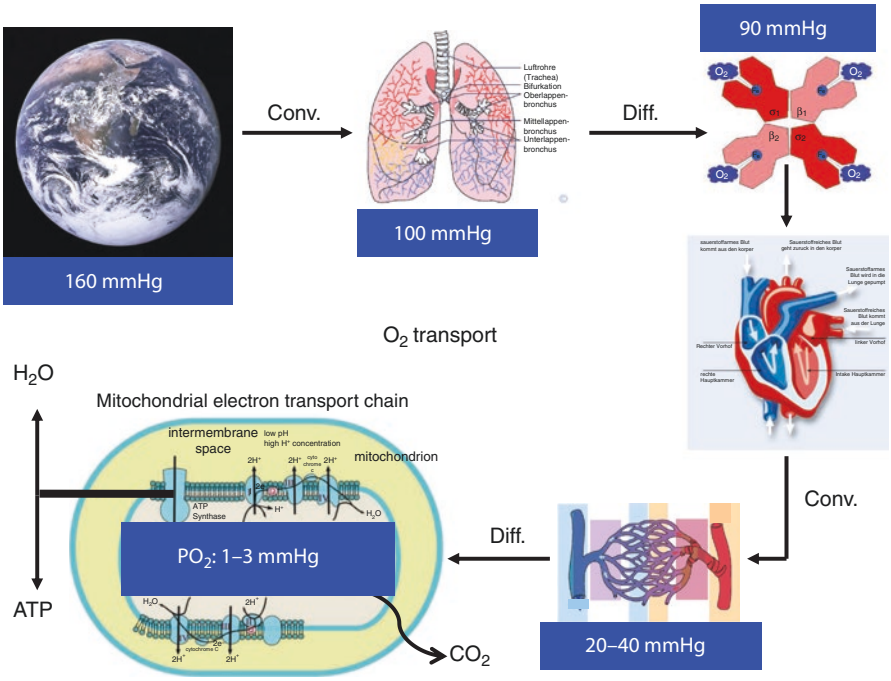


Fig. 1.1 O_2 transport from the atmosphere into the mitochondria. Conv. = convection, Diff. = diffusion

oxygen-binding curve, Sect. 1.1.3). This can be explained by diffusion losses (normally very small) and admixing of the "physiological shunt" (e.g., bronchial circulation, Thebesian = intracardiac veins) of about 1–3%.

As the diffusion distances from the capillaries to the cells are relatively large in tissue, the tissue O_2 partial pressure (PtO_2) falls to values of about 20–40 mmHg. Because of the difference in partial pressure between PaO_2 and PtO_2, the loaded oxygen is released by hemoglobin (Hb). During passage through the capillaries, the venous O_2 partial pressure (PvO_2) therefore approximates to the corresponding PtO_2 (i.e., PtO_2 and PvO_2 respond proportionately). Under normal circumstances, a PvO_2 of about 40 mmHg and venous saturation (SvO_2) of about 75% (normal arteriovenous SO_2 difference = about 25%) prevail in the veins. In the muscle, O_2 binds, for example, to myoglobin. Compared to Hb, it exhibits a left-shifted binding curve. In the mitochondria, ultimately there is only an O_2 partial pressure of 1–3 mmHg. The fact that oxygen is consumed in the mitochondria acts like a "gully" on the oxygen partial pressure gradients (Fig. 1.1)

Below What Value Does a Fall in PaO_2 Result in O_2 Deficiency (Dysoxia) of the Cells?

If PtO_2 falls below 20 mmHg, the diffusion distances in the tissue can no longer be sufficiently overcome, and oxidative energy production in the mitochondria ceases at a PtO_2 < 10 mmHg. The dysoxic threshold differs locally (i.e., from tissue to

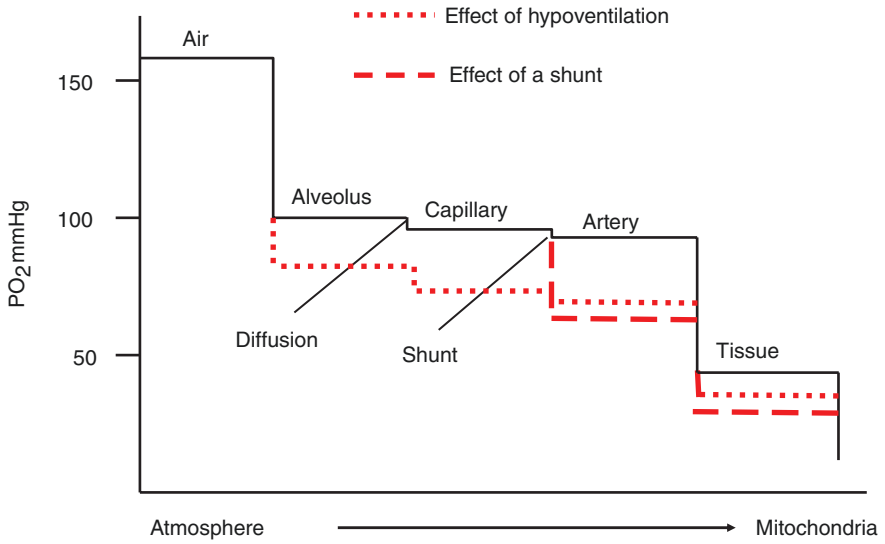


Fig. 1.2 Oxygen cascade

Table 1.1 Target values for preventing oxygen deficiency

	Noncyanotic	Cyanotic
PaO_2	> 60 mmHg (SaO_2 > 88%)	> 40 mmHg (SaO_2 > 75%)
PvO_2	> 30 mmHg (SvO_2 > 60%)	> 25 mmHg (SvO_2 > 40%)

tissue and from cell to cell) but is reported as a PaO_2 of <40 mmHg (SaO_2 < 75%) or a PvO_2 of 20–25 mmHg (SvO_2 = 35–40%) (Fig. 1.2).

If the drop in PaO_2 is too dramatic, the peripheral diffusion distances can no longer be overcome and the dysoxic threshold is reached.

The above remarks set important target values for intensive care medicine that need to be observed if oxygen deficiency is to be avoided (see Table 1.1).

Caution The stated target values for O_2 partial pressure must always be checked individually to ensure they are sufficient. Where necessary, higher ones can be targeted or lower ones tolerated. It should always be remembered that there is no room for maneuver at the lower limit and that therefore an alternative strategy for oxygenation (e.g., ECMO) must be available in the event of deterioration.

1.1.2 Causes of Reduced Oxygen Tension/Saturation in the Blood (PaO_2 or SaO_2)

Right/Left Shunt (= R/L Shunt)

When blood passes through a capillary bed (e.g., lung or peripheral tissue) without engaging in gas exchange, this is referred to as a shunt. In the case of an R/L shunt, part of the venous return flows past the lung and mixes with the arterial systemic

blood accompanied by a low O_2 partial pressure (= PvO_2). As a result, PaO_2 and SaO_2 are lower in the aorta (see saturation curve, Sect. 1.1.3). In the following, the saturations are discussed as surrogates for O_2 partial pressures.

The reduction in arterial saturation by a shunt depends directly on the extent of the shunt fraction (as a percentage of CO = cardiac output) and the level of SvO_2.

Extrapulmonary R/L Shunt

Example of Glenn anastomosis (= connection of the superior vena cava to the pulmonary arterial vascular bed as the first step to palliation in univentricular circulation):

In this case, ideally about 50% of the venous return flows via the superior vena cava into the lung and, thus oxygenated, reaches the ventricle via the pulmonary veins (pulmonary venous saturation [$SpvO_2$] ideally = 99%). The resultant pulmonary perfusion is solely responsible for oxygenating the patient. The remaining 50% of the venous return (= blood from the lower half of the body) is transported in a nonoxygenated form to the ventricle (SvO_2 = 50%) via the inferior vena cava. The ventricle serves as a mixing chamber, and the resultant SaO_2 in the aorta is approx. 75% (0.5 × 50% + 0.5 × 99% = 75%).

The ratio of pulmonary (Qp) and systemic perfusion (Qs) can be estimated from the saturation levels.

For parallel circulation (for further explanation please see Sect.15.11):

Formula 3

$CO = Qp + Qs$

Formula 4

$Qp/Qs = (SaO_2 - SvO_2)/(99 - SaO_2)$

Qp = pulmonary blood flow
Qs = systemic blood flow
99 = ideal pulmonary venous saturation ($SpvO_2$)

(This corresponds to the ratio of the arteriovenous saturation difference of the systemic circulation to the venoarterial saturation difference of the pulmonary circulation.)

In parallel circulation, a Qp/Qs ratio of 1.5:1 is the most suitable, since as a result, the volume load of the available ventricle is sustainably reduced, while at the same time, an adequate oxygen supply can still be delivered to the peripheral tissue. Such a Qp/Qs ratio is normally indicated by an SaO_2 of 75–85% (assuming there is no oxygen disorder of the lung and SvO_2 is >40%).

The calculation is of relevance, for example, in the following situations:

- HLHS (hypoplastic left heart syndrome)
- Following Norwood surgery or systemic-to-pulmonary artery shunt
- In ductal-dependent pulmonary perfusion

Caution An ideal pulmonary venous saturation ($SpvO_2$) of 99% is used in the calculation and not the actually existing $SpvO_2$ (measurement usually not possible). False low results may be obtained in oxygenation disorders of the lung (e.g., atelectasis, pneumonia) with reduced $SpvO_2$ (e.g., = 90%) (e.g., estimated, 75–50 / *99*–75 = 1.0; actual, 75–50 / *90*–75 = 1.6. Further examples in the specific part of the book).

Intrapulmonary R/L Shunt

An intrapulmonary shunt can be the cause of severe hypoxia, as, for example, in acute respiratory distress syndrome (ARDS). It occurs if alveoli are no longer ventilated as a result of compression or filling (edema fluid, secretions, cell debris). The ratio of ventilation (V) and perfusion (Q) is then equal to zero (V/Q = 0). As distinct from low V/Q areas, which are described as a "functional shunt" (see below), this is referred to as a "true shunt" (i.e., the blood flowing here is not oxygenated at all). Theoretically, a "true" and a "functional" shunt can be distinguished by an increase in inspired O_2 to 100%. With a "true" shunt, SaO_2 increases little if at all (see iso-shunt diagram according to Nunn, Fig. 1.3). By contrast, an increase in SaO_2 is to be expected when the proportion of low V/Q areas is high, as their PAO_2 increases despite low ventilation at an inspired O_2 of 100%. In practice, however, there is usually no clear separation, with the two forms of venous mixing usually present to differing degrees.

In addition, factors such as hypoxic pulmonary vasoconstriction (HPV, see below) affect the outcome. The pulmonary blood flow is redistributed by HPV. Poorly ventilated alveoli (= low PAO_2) are less perfused (vasoconstriction), and alveoli with a

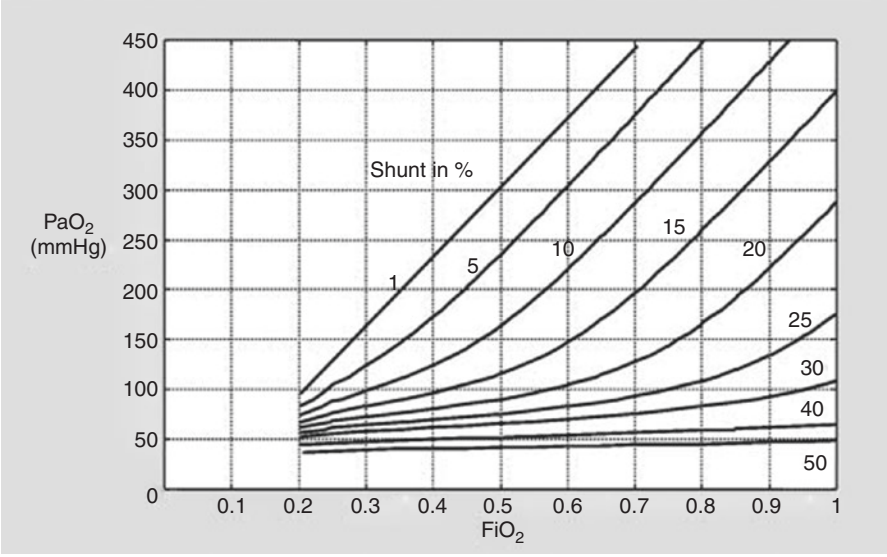


Fig. 1.3 Iso-Shunt-diagram (according to Nunn)

higher PAO_2 are more perfused (vasodilation). HPV is the most important physiological mechanism for minimizing the intrapulmonary shunt. If, for example, pulmonary vasodilators are systemically administered (e.g., b2-mimetics, nitroglycerin, sildenafil, Ilomedin) or pulmonary vasodilation results from inflammation mediators, this will lead to an increase in the intrapulmonary shunt and hence a fall in SaO_2. The shunt fraction will also rise in proportion of an increase in CO (and SvO_2).

Methods have been developed for calculating the extent to which an intrapulmonary shunt affects the oxygenation of the body. The intrapulmonary shunt (%) can be estimated on the basis of the following formula (after Berggren) from systemic arterial saturation (SaO_2) and pulmonary arterial = true mixed venous saturation (SvO_2 – see below) (measurement at $FiO_2 = 1.0$).

For serial circulation: Qp = CO = Qs

Formula 5

Qp = Qpc + Qshunt

Qpc stands for the pulmonary capillary blood flow participating in gas exchange (with $SpvO_2$ of 99%). Qshunt stands for the intrapulmonary shunt.

Formula 6

$Qshunt/Qp = (99 - SaO_2/99 - SvO_2) \times 100$

With a shunt >35%, FiO_2 has practically no effect on PaO_2 or SaO_2.

Low V/Q Areas

Regions of the lung that are underventilated relative to perfusion are described as low V/Q areas ($0 < V/Q < 1.0$). More O_2 is removed from these alveoli per unit of time by perfusion than can be supplied by ventilation, as a result of which, their PAO_2 falls (cf. Fig. 1.4). Due to the very low ventilation of these areas, their O_2 partial pressure is only marginally higher than PvO_2. Blood cannot be properly saturated during its passage through the capillaries of these alveoli and thus contributes to venous admixture. The proportion of the pulmonary blood flow that flows through low V/Q areas is also known as a "functional shunt." In many lung diseases (ARDS, asthmatic crisis), low V/Q areas are a significant cause of hypoxia.

1.1.3 Significance of the Oxygen–Binding Curve of Hemoglobin

Hemoglobin's oxygen-binding curve follows a sigmoid course (Fig. 1.5). This has the following benefits:

- In the upper, flatter part, which is relevant for oxygen uptake in in the lung (Fig. 1.5, light red area), SaO_2 barely changes at all despite possible variations in PAO_2, i.e., with fluctuations in PAO_2 of between 60 and 100 mmHg, SaO_2 changes by only about 12%.
- An increase in PaO_2 above 100 mmHg does not result in any further increase in SaO_2. An increase in FiO_2 resulting in $PaO_2 > 100$ mmHg is thus unnecessary

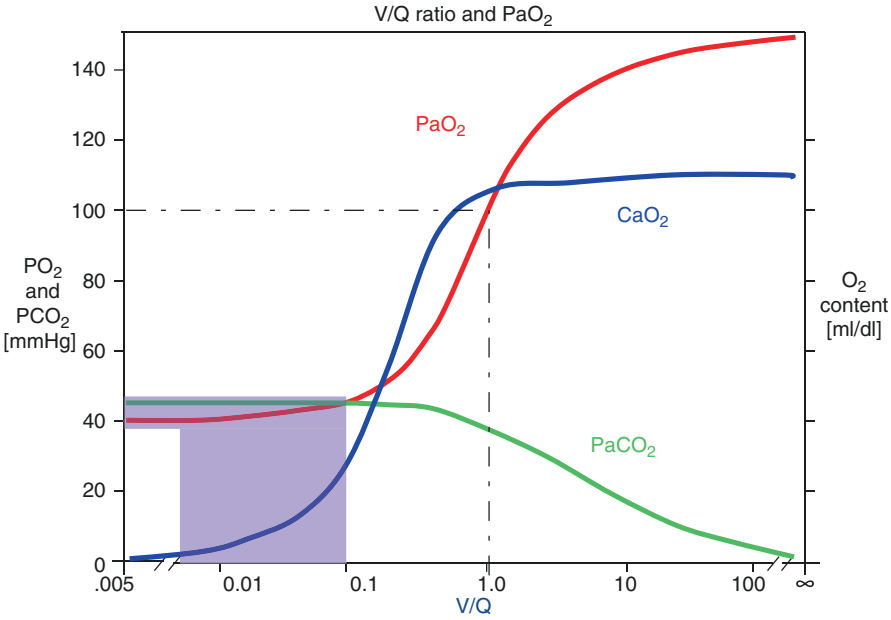


Fig. 1.4 Relationship between PaO_2 and the corresponding ventilation-perfusion ratio of an alveolus. Alveoli with a V/Q < 0.1 contribute to venous admixture with a very low PaO_2 (blue area); dotted line for V/Q = 1.0 ($PaO_2$2 = 100 mmHg)

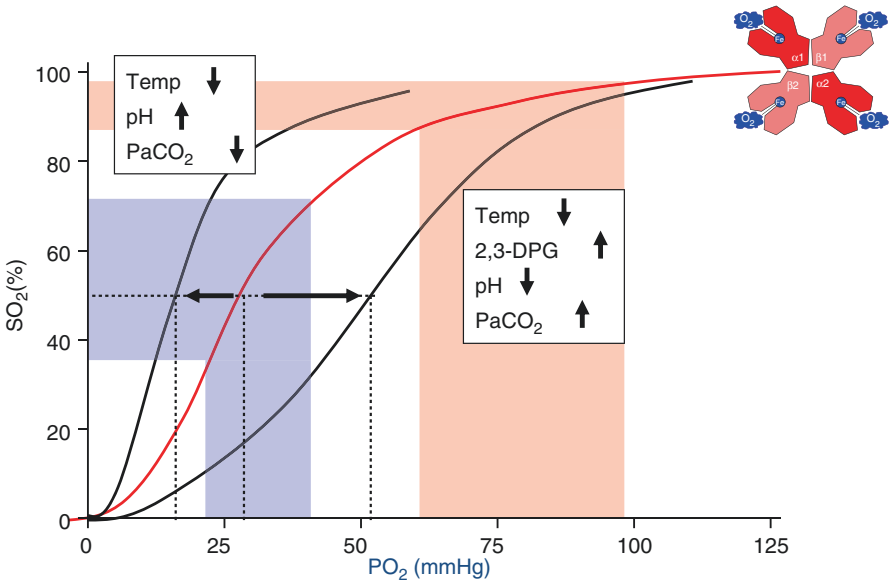


Fig. 1.5 Saturation curve (relationship of PO_2 and SO_2). (Adapted from Vincent et al.)

Table 1.2 Important key data for the normal O_2 saturation curve

PaO_2 (mmHg)	SaO_2 (%)
80	94
60	88
40	75
27	50

and with $FiO_2 > 0.6$ is potentially toxic for the pulmonary tissue in the long term.

- In the steep middle part of the saturation curve, which is relevant for oxygen release (Fig. 1.5, dark blue area), even small differences in oxygen partial pressure result in major changes in SaO_2, i.e., oxygen is released to a relevant extent by hemoglobin (about 20–30%) even with small partial pressure differences of just 10 mmHg.
- The Bohr effect plays an essential role: As a result of CO_2 release in the lung, the blood becomes "more alkaline," the saturation curve is shifted to the left, and O_2 is more easily bound, while tissue CO_2 production makes the peripheral blood "more acidic," which shifts the saturation curve to the right and promotes O_2 release.

At a PaO_2 of 27 mmHg, SaO_2 is normally 50% (= half-saturation pressure: This indicates whether the curve is shifted to the left or right; see Table 1.2 and Figure 1.5).

In intensive care medical practice, slight acidosis is beneficial compared with alkalosis in terms of its effect on the oxygen-binding curve. Sufficient saturation in the lung is usually obtained by adaptation of respiration and FiO_2. Peripheral O_2 release, however, is improved in mild acidosis. By way of example, with an O_2 partial pressure of 30 mmHg (as exists in tissue), saturation in the case of a right shift is about 40% and in that of a left shift about 70%, i.e., about 30% more O_2 is released in the case of a right shift.

Measurement of O_2 Saturation

In clinical practice, SpO_2 (measured by pulse oximetry) is used as a surrogate for SaO_2 (measured by CO oximetry).

Formula 7

$SaO_2 = O_2 - Hb/(O_2\text{-}Hb + deoxy\text{-}Hb + Met\text{-}Hb + CO\text{-}Hb)$

Formula 8

$SpO_2 = O_2\text{-}Hb/(O_2\text{-}Hb + deoxy\text{-}Hb)$

O_2-Hb = oxygenated hemoglobin
deoxy-Hb = deoxygenated hemoglobin
Met-Hb = methemoglobin
CO-Hb = carboxyhemoglobin
SpO_2 = O_2 saturation by pulse oximetry

Table 1.3 Target SpO_2

	Noncyanotic	Cyanotic	Protective ventilation	Preemies	PHT
SpO_2	≥ 92%	75–85%	≥ 88%	87–95%	≥ 95%

PHT pulmonary hypertension, *Preemies* premature neonates

The correlation or agreement in the saturation range of 70–100% is sufficient to work with SpO_2 (see Table 1.3). In case of doubt, SpO_2 must be checked arterially by CO oximetry (gold standard).

Caution As the saturations of cyanotic children are in the steep part of the oxygen-binding curve (SaO_2 = 70–80%), it should be borne in mind that even minor pulmonary disorders can cause a significant fall in SaO_2.

Oxygen Delivery (DO_2)

Oxygen is transported in the blood bound to hemoglobin (Hb). Per mol Hb, 4 mol O_2 can be bound at an O_2 saturation of 100% (Hüfner constant = about 1.39 ml O_2/g Hb). The physically dissolved quantity of O_2 in blood is negligible because of its poor solubility (at normal body temperature) and plays no role clinically (except if Hb < 3 g/dL and FiO_2 = 1.0, or in the event of hyperbaric oxygenation). The O_2 saturation of hemoglobin is dependent on the O_2 partial pressure and on the following factors: pH, temperature, PCO_2, and erythrocyte 2,3-DPG content. The O_2 content of arterial blood (CaO_2) can be calculated from the following formula:

Formula 9

$$CaO_2(mL/dL) = [Hb\,(g/dL) \times 1.39 \times SaO_2(fraction) + 0.003\,(mL/dL) \times PaO_2(mmHg)]$$

The most important parameter of oxygen delivery (DO_2), however, is CO.

Formula 10

$$DO_2(mL/min) = CaO_2(mL/dL) \times CO\ (L/min) \times 10$$

Or simplified:

Formula 11

$$DO_2 = CO \times Hb \times SaO_2$$

As Hb and SaO_2 are normally relatively fixed constants, a dynamic adaptation of the oxygen supply to the body's requirements can only be achieved by changes in CO (CO can increase about fivefold in healthy adults). The importance of CO also becomes apparent if one considers what happens when Hb or saturation falls acutely by a half: To maintain a constant O_2 supply, CO must double. If, on the other hand, CO halves acutely, this cannot be compensated by an increase in Hb if SaO_2 = 100%. However, compensation in this situation is possible by higher O_2 extraction peripherally.

Caution A child with heart disease whose CO is fixed and reduced or can be increased only slightly (e.g., due to heart failure, heart defect, outflow obstruction, shunt, etc.) can respond to only a limited extent to an increased O_2 requirement and compensate this via CO.

1.1.4 Interpretation of Venous Saturation (SvO_2) and Arteriovenous O_2 Difference ($avDO_2$)

A reduced oxygen supply results in a fall in tissue oxygen tension (PtO_2), as a result of which, the O_2 partial pressure difference between PaO_2 and PtO_2 increases and O_2 release from Hb increases. In the case of reduced CO, the contact time of blood in the capillaries is also prolonged. Overall, therefore, more mol O_2 is released to the tissue per mol Hb (higher O_2 extraction = compensation). The lower PtO_2 and the associated higher O_2 extraction result in a fall in venous oxygen tension (PvO_2) or SvO_2.

This is described by the O_2 extraction ratio (ERO_2):

Formula 12

$ERO_2 = SaO_2 - SvO_2/SaO_2$

In practice, the arteriovenous oxygen difference ($avDO_2$) can be used instead:

Formula 13

$avDO_2 = SaO_2 - SvO_2$

If Hb, SaO_2, and O_2 consumption (VO_2) are relatively constant, CO and ERO_2 respond reciprocally, i.e., if CO falls, ERO_2 increases and vice versa (Fig. 1.6).

In practice, venous saturation (SvO_2) is used as a marker of increased ERO_2 with reduced DO_2. SvO_2 depends directly on the level of SaO_2 and the ratio of oxygen consumption and delivery (VO_2/DO_2).

Formula 14

$SvO_2 = SaO_2 \times (1 - VO{-}_2/DO_2)$

Derivation: $VO_2 = CO \times (CaO_2 - CvO_2) \times 10 \rightarrow VO_2 = CO \times (SaO_2 - SvO_2) \times Hb \times 13.9 \rightarrow SvO_2 = SaO_2 - VO_2 / CO \times Hb \times 13.9$

In the postoperative situation with analgosedation (relatively constant O_2 consumption), controlled ventilation (relatively constant SaO_2), and little blood loss (relatively constant Hb), SvO_2 provides an indication of the level of CO. However, there is no linear relationship here between CO and SvO_2 (Fig. 1.7).

The case of reduced SvO_2 will be examined here specifically, as it is fairly relevant to the postoperative situation. Increased SvO_2 is found, for example, in sepsis, cyanide poisoning, hyperdynamic circulation, and hypothermia (Fig. 1.8).

Depending on its severity, anemia without hypovolemia results in an increase in CO and $avDO_2$. By contrast, in acute blood loss, reduced CO occurs as a result of volume deficiency.

Explanation of Terms

SvO_2 is understood by definition to mean mixed venous saturation. That is, the saturation of the blood in the pulmonary artery after the venous return from the lower and upper half of the body has mixed in the right ventricle. It can be

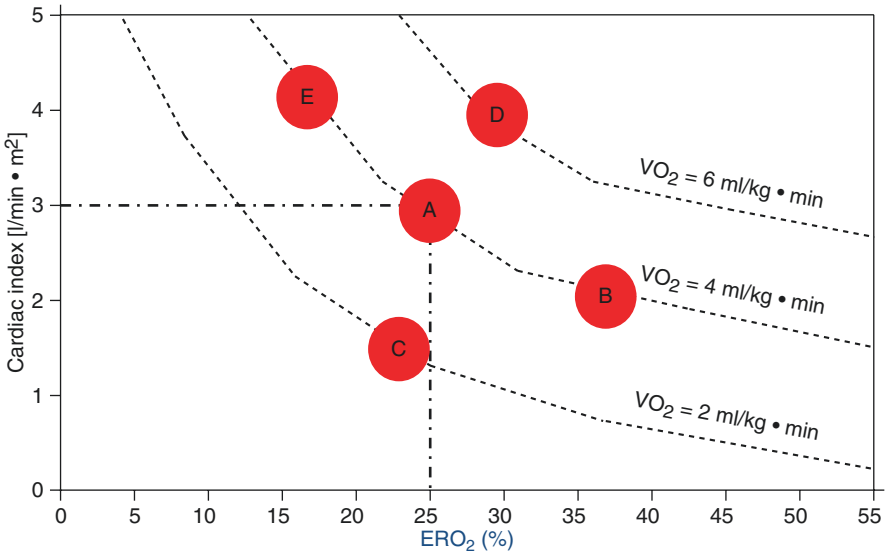


Fig. 1.6 Relationship between CO and ERO_2: A = normal VO_2/DO_2 (dotted line), B = heart failure, C = anesthesia, hypothermia, D = physical exercise, E = hyperdynamic circulation (e.g., sepsis, hyperthyroidism), lines = isoplots for VO_2, dotted line = normal ERO_2 and CI. (Adapted from Vincent et al.)

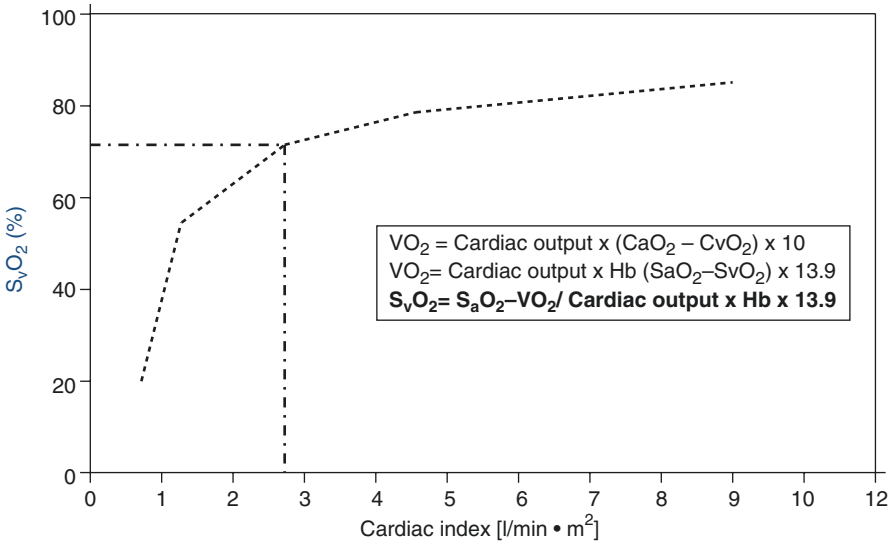


Fig. 1.7 Dependency of SvO_2 on CO

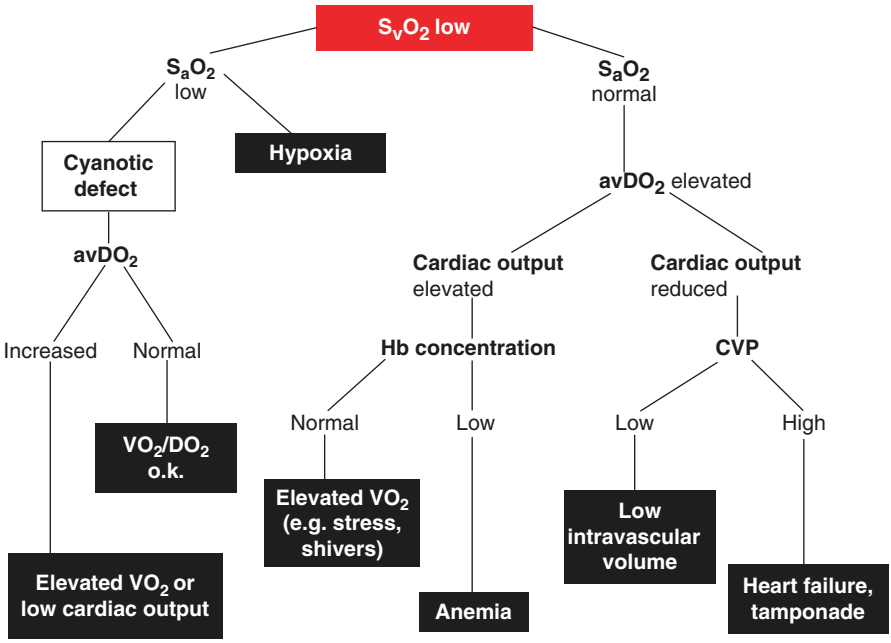


Fig. 1.8 Possible interpretations of lowered SvO_2

determined solely by means of a pulmonary artery catheter (PA catheter, Swan-Ganz catheter, flow-directed catheter). Depending on the O_2 extraction of the perfusion area concerned, the saturations of the lower and upper half of the body (normally lower 80%, upper 70%) and the heart differ. Venous saturation, which is measured from the CVC (central venous catheter), is known by definition as $ScvO_2$ (the positioning of the tip of the CVC needs to be noted). SvO_2 and $ScvO_2$ have been shown to be closely correlated with one another (albeit with a difference of about 5–10%). As only a few children have a PAC (pulmonary artery catheter) postoperatively (e.g., when there is a risk of postoperative pulmonary hypertension), for the sake of simplicity, $ScvO_2$ is determined in practice, but generally "venous saturation" is referred to.

Ratio of Oxygen Consumption (VO_2) and Delivery (DO_2)

In order to cover its metabolism, each organ requires a certain amount of oxygen, which is directly dependent on its activity. This amount of oxygen is known as VO_2 (see Table 1.4). As the amount of O_2 that the cells remove from the blood at a time is equally to the amount of O_2 that is absorbed in the lung at a time, consumption VO_2 can be calculated as follows:

Formula 15

$$CO \times (CaO_2 - CvO_2) = VO_2 = RMV \times (FiO_2 - FeO_2)$$

RMV = respiratory minute volume

Table 1.4 Normal values for VO_2

	mL/min	mL/kg/min	mL/min/m^2
Newborn (3.5 kg, 0.22 m^2)	35	10	160
Child (14.5 kg, 0.6 m^2)	100	7	165
Adult (75 kg, 1.8 m^2)	250	3	140

In the literature, the units mL/kg/min (mL/min per kilogram) and mL/min/m^2 (mL/min per square meter) are commonly used. However, mathematically, the units mL/min•kg and mL/min•m^2 are more correct

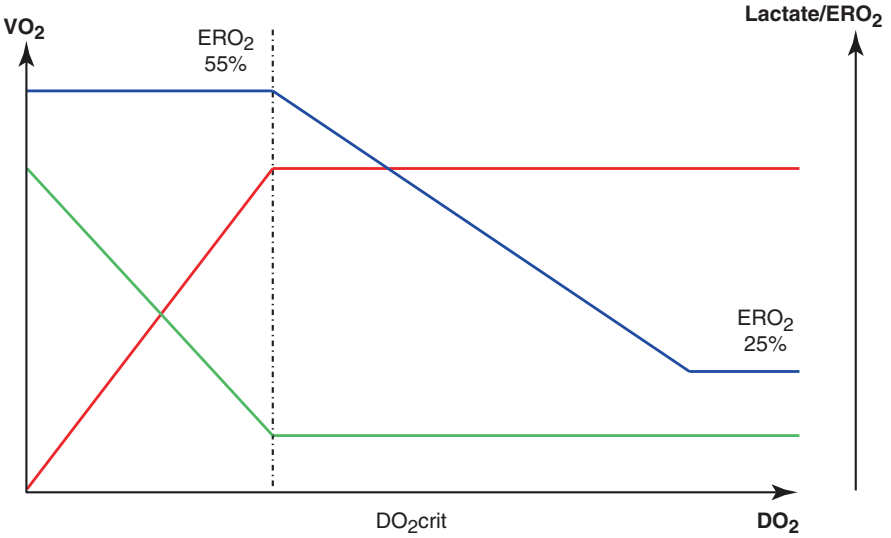


Fig. 1.9 Dependency of VO_2 on DO_2. Despite a decrease in O_2 delivery (DO_2), initially O_2 consumption (VO_2; red line) does not fall (direction of reading from right to left), as the decrease in DO_2 is compensated by increased O_2 extraction (ERO_2; blue line). If DO_2 reaches a value at which no further compensation can occur (DO_2crit; dotted black line), VO_2 then also falls (i.e., it becomes dependent on DO_2); there is an O_2 debt and hence an increase in lactate concentration (green line)

Oxygen consumption (VO_2) must be satisfied at all times by oxygen delivery (DO_2) (normal ratio $VO_2/DO_2 = 1{:}4$). If VO_2 increases, for example, during exercise, the greater O_2 requirement is covered physiologically by an adaptation of DO_2 (increase in CO). Conversely, a reduction in DO_2 barely affects VO_2 over a wide range (i.e., VO_2 is independent of DO), as adaptations occur through a higher O_2 extraction rate (see Sect. 1.1.4). Not all Hb-bound O_2 is available for tissue, for which reason, ERO_2 reaches a peak value at about 50–60% (Fig. 1.9). If DO_2 suffers a further critical fall (e.g., due to shock, anemia, hypoxia), beyond a certain (critical) value, VO_2 becomes directly dependent on DO_2 (usually with a ratio $VO_2/DO_2 \geq 1{:}2$). If DO_2 is not sufficient to cover the corresponding minimum VO_2, there

is a deficient oxygen supply and hence dysfunction of the organ (dysoxic threshold). This is manifested by the development of lactic acidosis. In dying adult intensive care patients, a mean critical DO_2 of 4 mL/kg/min has been determined (Normal resting DO_2 in adults = 10–20 mL/kg/ min).

What must be established clinically is whether the VO_2/DO_2 ratio is correct. As DO_2 and VO_2 are usually not calculated in practice, an estimate of the oxygen balance must be made on the basis of $avDO_2$, SvO_2, and lactate levels. It needs to be remembered here that the analysis of this fairly "global" surrogate marker provides an incomplete picture of the body's oxygen supply, as the situation of individual perfusion regions is insufficiently reflected, if at all (e.g., in the event of heterogeneous local VO_2/DO_2 ratios).

A mismatch of the VO_2/DO_2 ratio can have two causes:

- O_2 consumption is increased (e.g., fever, muscle tremor, exercise, etc.) without an adequate increase in O_2 delivery.
- O_2 delivery is critically reduced (low cardiac output, anemia, etc.).

In a sedated, intubated patient (with relatively constant O_2 consumption), a mismatch is usually the consequence of reduced O_2 delivery.

Example: Ratio of VO_2 and DO_2 in the brain Normal cerebral blood flow in an adult is 50 mL/100 g cerebral tissue/min (for a brain of 1500 g, this equates to 750 mL/min or about 15–20% of CO). In the brain (as also in other organs), VO_2 and DO_2 are physiologically linked to one another, i.e., if cerebral activity increases (VO_2), the blood supply, and hence DO_2, increases (metabolic coupling = proportionately more blood flow through the brain because of functionally related vasodilation). If, conversely, cerebral blood flow decreases (e.g., as a result of a fall in perfusion pressure), O_2 consumption (= metabolism) cannot be sustained beyond a critical value. If cerebral blood flow drops below 20 mL/100 g cerebral tissue/min, there is initially a reversible loss of brain function (impairment of consciousness, slowing of electrical activity), and venous jugular bulb saturation ($SvjO_2$) falls to <55%. Below 10 mL/100 g cerebral tissue/min, irreversible damage usually occurs (brain death, flatline EEG).

An "equilibrated" O_2 balance can be assumed clinically if:

- *$avDO_2$ = 25–30%*
- *SvO_2 > 65% (in noncyanotic patients)*
- *No lactic acidosis (Lactate < 2 mmol/l)*
- *Normal organ functions*

Table 1.5 illustrates how the ratio of oxygen consumption (VO_2) to oxygen delivery (DO_2) can be improved.

Table 1.5 Options for influencing or improving the oxygen balance

Increasing O_2 delivery (DO_2	Reducing O_2 consumption (VO_2)
Increasing CO (e.g., increasing preload, reducing afterload, inotropics rhythm control, mechanical support, etc.)	Analgosedation[a], relaxation
Increasing Hb concentration (e.g., transfusion)	Fever lowering, cooling[a]
Increasing SaO_2 (e.g., O_2 administration, ventilation, etc.)	Reduction of respiratory work (e.g., CPAP/BIPAP, ventilation)
	Infection control

CPAP continuous positive airway pressure, *BIPAP* biphasic positive airway pressure
[a]In terms of the brain, deep sedation (e.g., barbiturate anesthesia) simply reduces the metabolic rate of the brain cells; an additional reduction of metabolic rate is only possible by means of hypothermia (the oxygen consumption of the brain, e.g., falls by about 5–7% for each 1 °C)

1.1.5 O_2 Deficiency (Dysoxia)

Dysoxia can be caused by a reduction in blood flow (e.g., heart failure, hypotension, ischemia), a loss of hemoglobin (e.g., hemorrhage, anemia), a fall in SaO_2 (hypoxia, methemoglobinemia, CO intoxication), and/or a disorder of mitochondrial function (e.g., cyanide intoxication, septic mitochondriopathy). The four forms of dysoxia are:

- Ischemic dysoxia
- Anemic dysoxia
- Hypoxic dysoxia
- Mitochondrial dysoxia

If the O_2 content of the mitochondria falls critically, no further aerobic energy production occurs, and the cell attempts to cover its energy requirement by anaerobic glycolysis. Dysfunction of an organ may occur, as soon as the energy requirements of the cells are no longer met.

Example: Consequences of dysoxia on myocardial function In the heart, O_2 extraction is already relatively high under resting conditions, so that an increase in local O_2 consumption must be satisfied predominantly via an increase in coronary perfusion (increase in local O_2 supply). In ischemic dysoxia of the myocardium, stunning (reversible functional deficiency) occurs initially, and subsequently cell death (necrosis). As both contraction and relaxation are ATP-dependent in the myocardial cell, a disorder of both functions occurs, for example, in ischemia (chronologically: relaxation disorder before contraction disorder). Reference is made to hibernation as opposed to stunning and necrosis if adaptation of the cell has occurred in the context of an oxygen deficiency situation, e.g., by downregulation of oxygen consumption (functional deficiency without cell death). It is difficult to distinguish clinically between stunning and hibernation (although stunning can usually be stimulated by inotropics as long as perfusion is restored).

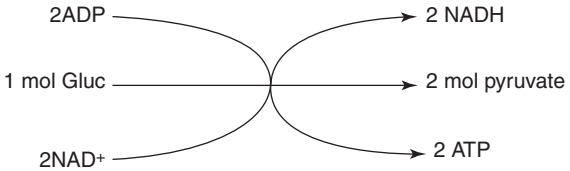
Cellular Energy Production in O_2 Deficiency, Lactate, and Lactic Acidosis

An increase in lactate always occurs when more pyruvate is produced than can actually "flow off" into the citrate cycle (via the formation of acetyl-CoA). This can be caused either "upstream" by massive pyruvate production (e.g., increased glycolysis) or "downstream" by "inhibition" of the citrate cycle or oxidative phosphorylation (e.g., O_2 deficiency). The "excess" pyruvate is converted into lactate via lactate dehydrogenase (LDH), with equilibrium of the reaction being found on the lactate side (normal lactate/pyruvate ratio, LPR = 10:1).

The primary interest in the postoperative setting is whether an increase in lactate is caused by O_2 deficiency of the cells (dysoxia). Increased lactate levels or the absence of rapid normalization following therapeutic measures are associated with a poorer prognosis in association with circulatory shock.

If oxidative phosphorylation is blocked because of the O_2 deficiency, all that remains to the cell is the considerably less effective anaerobic glycolysis for obtaining ATP (adenosine triphosphate): 36 mol ATP is produced aerobically per mol glucose, but only 2 mol anaerobically (= about 5% of normal energy production). Other nutrients such as fats and amino acids can no longer be used for ATP synthesis. As a result of the consumption of ATP, the ratio ATP/ADP (ADP = adenosine diphosphate) decreases, which results in increased glycolysis via stimulation of phosphofructokinase (PFK) and thus in accumulation of pyruvate in the cell. As mitochondrial reoxidation of NADH (nicotinamide adenine dinucleotide, reduced) to NAD (nicotinamide adenine dinucleotide) is blocked in O_2 deficiency, pyruvate must be converted to lactate to "regenerate" NAD^+ in cytosol. Without the availability of NAD^+, glycolysis can no longer proceed.

Formula 16



Formula 17

$$\text{Pyruvate} + \text{NADH} + H^+ \leftrightarrow \text{lactate} + NAD^+$$

Formula 18

$$\text{Lactate/pyruvate} = K \times \text{NADH}/NAD^+ \times H^+$$

K = dissociation constant

Equation 18 illustrates how the lactate-pyruvate ratio (LPR) rises when the NADH/NAD ratio increases or the intracellular pH falls. In the case of O_2 deficiency, therefore, there is a massively increased LPR of >20/1. However, LPR is only rarely established clinically because the determination is time-consuming and associated with technical sources of error.

For each molecule of pyruvate converted to lactate, an H^+ proton is consumed (see Eq. 17). The reaction serves as a "buffer" for intracellular pH. In addition, lactate is channeled out of the cell in the H^+ symporter. However, the anaerobic production of lactate results in metabolic acidosis (in anaerobic glycolysis a net 2 mol H^+ develops per mol glucose). There are two explanations for this:

- Under anaerobic conditions, the H^+ proton generated on the hydrolysis of ATP to ADP cannot engage in oxidative phosphorylation as usual and accumulates.
- The lactate formed is a strong anion which, to ensure electrochemical equilibrium, causes the dissociation of H_2O ($H_2O \leftrightarrow H^+ + OH^-$), as a result of which, the H^+ concentration increases (> 40 nmol/L) and pH falls (<7.35).

If the O_2 deficiency persists, the accumulation of H^+ protons ultimately results, via intracellular acidosis, in reduced energy production by anaerobic glycolysis (inhibition of phosphofructokinase), all energy-rich phosphates are consumed, and the adenosine diffusing out of the cells is converted to uric acid (refractory shock). The failure of ATP-dependent ion transporters (e.g., Ca^{2+} and Na^+/ K^+-ATPase), the inflow of Ca^{2+} and Na^+ ions, and the development of intracellular edema lead to cell death.

Among the many "nondysoxic" possibilities of lactate production (see Table 1.6), one cause is of particular interest postoperatively: Through the stimulation of sarcolemmal [Na^+/K^+]-ATPases, adrenaline can result in increased glycolysis in muscle cells and hence in increased lactate.

Table 1.6 Causes of hyperlactatemia (examples)

Increased muscle activity	Muscle work, shivering, seizure, malignant hyperthermia
Anaerobic glycolysis	In conjunction with absolute or relative dysoxia (LPR > 10/1)
Increased glycolysis	Stimulation of [Na^+/K^+]-ATPases by adrenaline
Disorders of the respiratory chain	Toxins such as cyanide, metabolic disorders (LPR > 10/1)
Inflammation/sepsis/PAS	Increased production by leukocytes, catabolic metabolic situation, etc.
Reduced clearance	Acute or chronic hepatic impairment (disorder of the Cori cycle)
Reperfusion	Flow of lactate into the macrocirculation
Iatrogenic lactate intake	Administration of Ringer's lactate (plays no role other than in liver failure)
Drugs	Metformin, valpoic acid, propofol
Thiamin and biotin deficiency	Seldom seen postoperatively

Rule of thumb: Hyperlactatemia *without* acidosis (compensation at work) is not as worrisome as hyperlactatemia *with* acidosis (e.g., shock, dysoxia)
PAS postaggression syndrome

Table 1.7 Normal values for lactate (mmol/L = mg/dL × 0.11)

	mmol/L	mg/dL
$Blood_{arterial}$	<2.1	<19
Cerebrospinal fluid	<1.8	<16

Physiological lactate formation Under normal circumstances the body's lactate production is about 1500 mmol/day (about 15–30 mmol/kg/day).

Of which:

- Muscles 25%
- Brain 20%
- Bowel 10%
- Skin 20%
- Erythrocytes 25%

Metabolism occurs predominantly in the liver (about 50–60%, max. 3.5 mol/day) and kidney (about 20–30%). Glucose is in turn synthesized from lactate with the consumption of energy (Cori cycle). Other organs such as the brain and muscles also use lactate for energy production. At lactate levels <2 mmol/L, the system is in equilibrium (see Table 1.7). The renal threshold for lactate is 5–6 mmol/L, so that normally no lactate is excreted via the kidney.

Alkalosis can also increase lactate levels:

- Increased production via activation of PFK and LDH
- Reduced clearance (respiratory alkalosis reduces hepatic clearance by 40%, i.e., the half-life of lactate increases from 15 to 45 min)

Adaptation Mechanisms in Chronic Cyanosis

Chronic low SaO_2 (or low PaO_2) is compensated in cyanotic children by a higher cardiac output (higher stroke volume (SV)), a higher Hb value (Hb > 14 g/dL, in some cases polycythemia), more pronounced peripheral capillarization (shorter diffusion distances), adaptation of the saturation curve (higher erythrocyte 2,3-DPG), and probably cellular mechanisms, e.g., higher myoglobin concentration, hypoxia-induced factor (HIF). In this case, this is not referred to as dysoxia, but as hypoxemia (low O_2 content without O_2 deficiency). The situation is similar to that of people who have adapted to living at high altitudes (at 6000 m altitude: PaO_2 = 40 mmHg, SaO_2 = 75%). The physiologic reserve, however, is limited so that oxygenation disorders of the lung (e.g., due to atelectasis, pneumonia, obstruction), restrictions of pulmonary blood flow (e.g., high pulmonary vascular resistance, pulmonary embolism, R/L shunt) or low cardiac output (e.g., in heart failure, arrhythmias, hypovolemia), and/or anemic states can more rapidly result in decompensation.

Hypoxia vs. Ischemia
Hypoxic states (i.e., perfusion normal, $PaO_2 < 60$ mmHg) are usually "better" tolerated than ischemic states (i.e., no perfusion), as the internal environment of the cells (PCO_2, pH, Na^-, K^-, glucose concentration, etc.) can be kept to some extent in equilibrium as long as perfusion is preserved.

Example: Hypoxia vs. ischemia in the heart In ischemia, a critical fall in or cessation of coronary perfusion (e.g., a critically low coronary perfusion pressure) has consequences for myocardial function within seconds. Hypoxia, on the other hand, is tolerated for a "relatively long" time, as in d-TGA (D-transposition of the great arteries): the coronaries predominantly receive low-saturated blood (from the aorta via the RV), particularly in the presence of a restricted intra-atrial communication.

In practice, however, the following applies: There are no "safe" time windows for either the hypoxic or the ischemic scenario; therefore a correction must be attempted as soon as possible in each case to avoid harm from dysoxia.

1.1.6 CO_2 Balance

While oxygen intake would in principle also be possible via apneic oxygenation ("flooding" of the lung with high-flow O_2), sufficient CO_2 release can only happen if the lung is adequately ventilated. The quantity of CO_2 expired per minute (VCO_2) at steady state via the RMV is equal to the quantity absorbed per minute by the blood at the periphery (formula 19).

Formula 19
$RMV \times FECO_2 = VCO_2 = CO \times (CvCO_2 - CaCO_2)$
$FECO_2$ = fraction of CO_2 in expired air
The determining factor in CO_2 release is alveolar ventilation (VA). No gas exchange occurs in the dead space (VD) (the gas composition here to a large extent matches that of the outside air, i.e., $PAO_2 = PO_2 = 160$ mmHg and $PACO_2 = 0$ mmHg). A distinction is drawn between:

- Functional dead space (alveoli are ventilated, but not perfused)
- Anatomical dead space (respiratory tract)
- Instrumental dead space (tubes)

As the anatomical and instrumental fractions of the dead space are constant, ventilation is more effective in terms of CO_2 expiration, the greater the tidal volume (Vti) is. With a greater Vti, the percentage of the anatomical and instrumental dead space decreases, and the proportion of alveolar ventilation therefore increases.

Formula 20

Vti = VA + VD

In practice, the greater the RMV, the more CO_2 is expired.

Formula 21

RMV = Respiratory rate (RR) × Tidal volume (Vti)

The venoarterial CO_2 difference ($vaDCO_2$) is normally only 5 mmHg. As a result of the 20-fold higher diffusion capacity of CO_2 in the alveoli compared with O_2, this small partial pressure difference is sufficient to eliminate the CO_2 produced. The slight venoarterial CO_2 difference also explains why, in contrast to PaO_2 (high $avDO_2$), an intrapulmonary shunt exerts only a slight effect on $PaCO_2$ (Fig. 1.10).

By contrast, $PaCO_2$ reacts sensitively to an increase in dead space, as the proportion of alveolar respiration decreases as a result. The dead space can be estimated from the following formula (after Bohr).

Formula 22

$VD = VT \times (PaCO_2 - PECO_2/PaCO_2)$

where $PECO_2$ stands for the mean expired CO_2 partial pressure (although this is not given by most capnograms). Therefore, in clinical practice, the following formula can be used as an alternative:

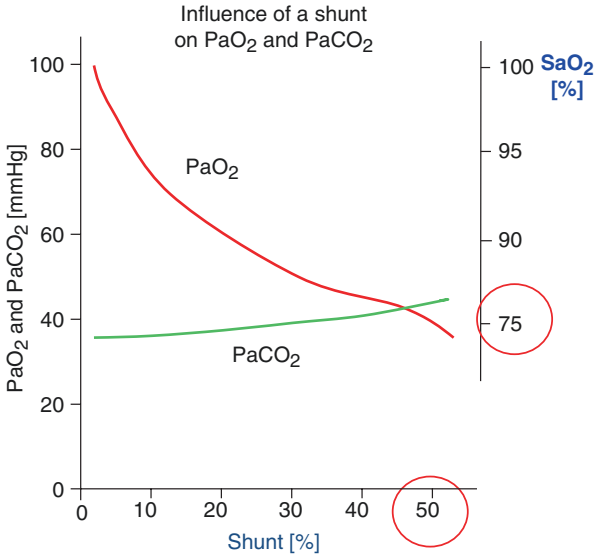


Fig. 1.10 Ratio of shunt (%), PaO_2 (mmHg), and $PaCO_2$ (mmHg)

Formula 22a

$VD = VT \times (PaCO_2 - PetCO_2/PaCO_2)$.

Ventilation inhomogeneity, i.e., a combination of hyperventilated, normoventilated, and hypoventilated alveoli, as happens in obstructive lung diseases (bronchiolitis, asthma), results in an enhanced difference between end-tidal CO_2 ($etCO_2$ or $PetCO_2$) and $PaCO_2$, as well as a change in the capnogram recording (capnogram curve). This is normally "crenellated" (rectangular), i.e., all alveoli empty homogeneously, simultaneously, and with a similar CO_2 content. With inhomogeneous ventilation, the capnogram becomes "shark-finned" (triangular), as rapid compartments (hyperventilated alveoli) empty before slower ones (hypoventilated alveoli). For very slow compartments, the set expiration time may no longer suffice at all for complete emptying (air trapping; see Sect. 2.2.8 Ventilation). If the patient is attached to the ventilator without removing the capnometer, it is possible to observe how trapped air escapes and the capnogram signal increases constantly (thereby revealing the "true" $etCO_2$). The curve continues to increase if expiration is prolonged (see Fig. 1.11, light blue area).

In addition to ventilation, however, CO_2 release also depends on the circulation (i.e., on CO or pulmonary perfusion). With constant ventilation (e.g., volume-controlled ventilation), CO_2 release is directly proportional to pulmonary perfusion.

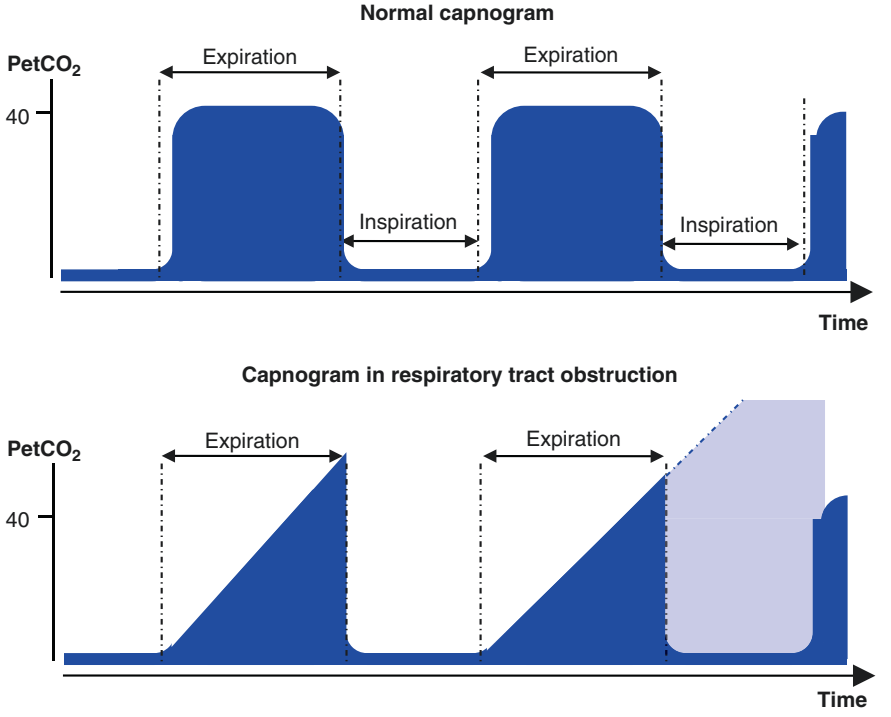


Fig. 1.11 Capnogram

During resuscitation, the appearance or increase of $etCO_2$ is a sure sign of restoration of the circulation. Conversely, a sudden fall in $etCO_2$ can indicate an acute decrease in pulmonary blood flow (e.g., in pulmonary embolism). With a low cardiac output, the difference between $PaCO_2$ and $etCO_2$ increases because of the growing proportion of alveoli with a high ventilation-perfusion ratio V/Q.

CO_2 develops in the mitochondria (aerobic CO_2 production), from where it diffuses into the blood. The majority is transported in the blood in the form of bicarbonate, a process in which carbonic anhydrase activity and erythrocytes (Hamburger shift) play a fundamental role. If aerobic energy production ceases, no further aerobic CO_2 develops, as no CO_2 is released in anaerobic glycolysis. However, even in dysoxia, CO_2 can be released from bicarbonate by H^+ proton buffering (anaerobic CO_2 production). In the event of hypoperfusion, the CO_2 formed in tissue cannot be sufficiently carried away. As a result, tissue CO_2 partial pressure and $PvCO_2$ increase, and pH decreases. Clinically, increased $vaDCO_2$ (> 10–15 mmHg) and a negative base excess (BE < −5 mmol/L) can indicate a situation of hypoperfusion.

In addition to cell activity (e.g., muscle tremor, fever), CO_2 production also depends on the type of energy carrier combusted. If carbohydrates (CH) are combusted, the respiratory quotient is 1.0 ($RQ = VCO_2 / VO_2$). If fat is combusted, it is 0.7, i.e., less CO_2 is produced relative to O_2 consumption in fat combustion (per gram).

By way of example, about 100 g of fat is required to generate 1000 kcal with a pure fat diet (1 g fat ≈ 9–10 kcal), during which about 200 L O_2 is consumed and about 140 L CO_2 is produced (140 L / 200 L = 0.7). To generate the same amount of energy (1000 kcal) with a pure CH diet, about 200 g glucose must be metabolized (1 g glucose ≈ 4–5 kcal), during which about 165 L O_2 is consumed and about 165 L CO_2 is produced (165 L / 165 L = 1.0). In comparison with fat metabolism, therefore, about 17% less O_2 is consumed, and about 17% more CO_2 is formed in pure CH combustion. Theoretically, therefore, a carbohydrate-rich diet is beneficial in oxygenation disorders (e.g., severe ARDS), and a fat-rich diet when the respiratory pump is restricted (e.g., in muscle diseases, obstructions). Clinically, however, the composition of the diet has much less effect on the CO_2 balance than, for example, the prevention of muscle tremors or the optimization of ventilation and circulation.

The significance of the CO_2 bicarbonate system ($CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^-$) in regulating the acid-base balance (ABB) is discussed in the following section.

A further important aspect of PCO_2 is its effect on vascular reactivity (see Table 1.8). In this case, arterioles in the pulmonary vascular bed react in a fundamentally different way to those in the systemic vascular bed. Hypercapnia, for example, causes pulmonary vasoconstriction (increase in PVR) and systemic vasodilation

Table 1.8 Response of vessels to an acute change in CO_2

CO_2	Pulmonary	Systemic
↑	Constriction	Dilation
↓	Dilation	Constriction

(decrease in systemic vascular resistance, SVR). The reverse is the case with hypocapnia. However, the deciding factor here is not CO_2 partial pressure, but intracellular pH. If intracellular pH is compensated over time (within 6–24 h), the CO_2 effect gradually decreases and steady state is restored. A rebound phenomenon can occur on sudden normalization of PCO_2 (e.g., hypocapnia → normocapnia).

Hyperventilation is used clinically to treat pulmonary hypertensive crises (with the aim of pulmonary vasodilation) and acute cerebral compression syndromes (with the aim of cerebral vasoconstriction). Conversely, in "lung-protective" ventilation (see Sect. 2.14 Ventilation), permissive hypercapnia is accepted as long as no major adverse effects such as right heart failure or increased intracranial pressure occur. If $PaCO_2$ increases in conjunction with permissive hypercapnia, CO_2 elimination becomes even more effective relative to the respiratory minute volume ("more" CO_2 is transported per breath).

Postoperative causes of hyper- or hypoventilation are listed in Table 1.9.

Caveat Hyperventilation in the spontaneously breathing patient with severe hypocapnia ($PaCO_2 < 30$ mmHg), as occurs in ketoacidosis (respiratory compensation of ketoacidosis), status post resuscitation, or neonatal asphyxia (as the manifestation of possible brain damage) is usually not treated or corrected.

Table 1.10 shows effects of an acute change in $PaCO_2$.

Caution An acute increase in PCO_2 should also be corrected "rapidly." A chronic increase in PCO_2 (particularly when well compensated and with a pH > 7.2) is not corrected or, if so, then only slowly (see Table 1.11).

Table 1.9 Postoperative causes of hyperventilation and hypoventilation

Hyperventilation	Hypoventilation
Stress, anxiety, pain	Pain (particularly chest pain)
Hypercapnia, hypoxia	Pharmacological (e.g., benzodiazepines, opioids, etc.)
Heart failure	Other impairment of consciousness
Central (e.g., in cerebral processes)	Respiratory tract obstructions
Compensatory (e.g., in metabolic acidosis)	Diaphragmatic paralysis, muscle weakness
	Effusions, ascites
Pharmacological	Increased intraabdominal pressure

Table 1.10 Effects of an acute change in $PaCO_2$

Hypoventilation → hypercapnia	Hyperventilation → hypocapnia
Afterload reduction for LV	Afterload increase for LV
Afterload increase for RV	Afterload reduction for RV
Increased ICP	Reduced cerebrovascular perfusion
Respiratory acidosis	Respiratory alkalosis
Activation of sympathetic tone	Decrease in free calcium (tetany)

Table 1.11 $PaCO_2$ – treatment and aims

	Normal	Permissive hypercapnia	Acute cerebral herniation	ICP > 20 mmHg	Pulmonary hypertension
$PaCO_2$	35–45 mmHg	45–65 mmHg (pH > 7.15)	25–30 mmHg[a]	30–40 mmHg	30–40 mmHg (pH 7.45–7.55)

[a]In acute cerebral herniation, strong hyperventilation can be helpful but should be used only as short-term emergency management until definitive treatment is initiated (e.g., decompression). The risk of cerebral ischemia must always be considered in the case of strong hyperventilation

1.2 Acid-Base Balance

1.2.1 General Information

Changes in blood pH indicate disorders in the body (e.g., hypercapnia, lactic acidosis or ketoacidosis, renal failure, etc.), while themselves potentially contributing to disturbances in bodily functions (e.g., negative inotropism, catecholamine resistance, shift in the Hb saturation curve, hyperkalemia, etc.). In this respect, metabolic acidosis plays an important role in postoperative intensive care medicine and will therefore be discussed here in further detail.

As long as the patient is on controlled ventilation and the lung is not severely diseased, acute postoperative respiratory acidosis or alkalosis is usually iatrogenic and can accordingly be corrected by adjusting ventilation. In the spontaneously breathing patient, these conditions naturally provide important indications of a pulmonary, metabolic, or central disorder. Chronic respiratory acidosis is fairly rare in childhood, e.g., in BPD (bronchopulmonary dysplasia), severe asthma, advanced cystic fibrosis, etc.

Metabolic alkalosis occurs postoperatively in particular as a result of the use of furosemide (chloride loss), metabolism of citrate supplied via transfusions (in the liver: citrate → $[HCO_3^-]$), and in severe hypokalemia. Chloride losses via the gastric tube (chloride-sensitive alkalosis), $[HCO_3^-]$ losses via the bowel and kidney, and hyperaldosteronism (chloride-resistant alkalosis) play a subordinate role.

Main reasons for changes in the postoperative acid-base balance:

- Ventilation (hypocapnia, hypercapnia)
- Dysoxia
- Hyperchloremia
- Metabolic changes (e.g., ketosis, catabolism, increased glycolysis)
- Medication (e.g., furosemide)
- Renal impairment (RI)
- Reperfusion
- Transfusions (initially, acidosis; later, alkalosis)
- Hypoalbuminemia

1.2.2 Pathophysiology as Exemplified by Acidosis

Respiratory Acidosis

An acute increase in $PaCO_2$ results via the formation of carbonic acid ($CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^-$) in an increase in $[H^+]$ and $[HCO_3^-]$ concentration. H^+ protons are bound by non-bicarbonate buffers (particularly protein buffers). As the consumption of non-bicarbonate buffer (NBP) and the increase in $[HCO_3^-]$ concentration balance out, the total amount of buffer (buffer base = bb) initially remains unchanged (BE = normal). Over the course of several days, as a result of renal reabsorption of bicarbonate, there is then a further increase in $[HCO_3^-]$ concentration, so that the pH is corrected (renal compensation: BE = positive) (Fig. 1.12).

Metabolic Acidosis

As a result of the newly formed H^+ protons during metabolism (e.g., in anaerobic glycolysis), bicarbonate and non-bicarbonate buffers are consumed equally for buffering. As a result, both the $[HCO_3^-]$ concentration and that of NBP fall (BE = negative). The CO_2 released on buffering by HCO_3^- ($H^+ + HCO_3^- \rightarrow CO_2 + H_2O$) is expired ($PaCO_2$ = normal initially). Within a short period (minutes), increased ventilation causes a fall in $PaCO_2$ and thus a correction of pH (respiratory

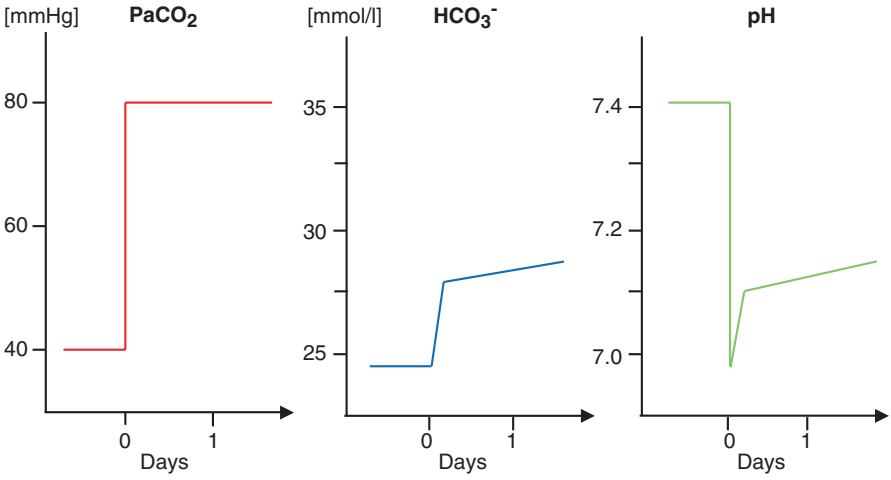


Fig. 1.12 Time course of acute respiratory acidosis (with incipient renal compensation)

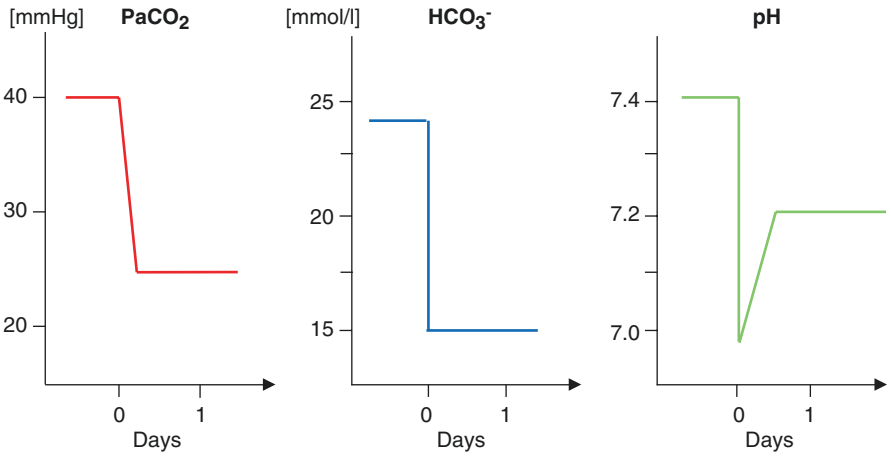


Fig. 1.13 Time course of acute metabolic acidosis (with respiratory compensation)

compensation). In the spontaneously breathing patient, therefore, metabolic acidosis with normal $PaCO_2$ will only rarely be encountered. In the intensive care patient, however, controlled ventilation and deep sedation frequently prevent spontaneous respiratory compensation (Fig. 1.13).

1.2.3 Interpretation of Blood Gas Analysis (BGA)

The determining factor in successful treatment is often the rapid establishment and correct interpretation of the acid-base disorder concerned.

Normally arterial BGA is used to analyze acid-base status, as it provides indications of pulmonary function (or alternatively capillary BGA). The situation at the periphery, however, is often better reflected by venous BGA (e.g., CVC). As BGA determinations are prone to error (blood sampling errors, calibration errors, etc.), each measurement must be checked to ensure that it:

- Is correct and credible
- Is compatible with the clinical situation

See Table 1.12 for the rule of thumb relating to pH changes as a function of $[H^+]$. Tables 1.13 and 1.14 provide a rapid indication of acid-base status.

Many commercial blood gas analyzers only measure pH and PCO_2 (mmHg) directly, while base excess (BE, mmol/L) and HCO_3^- (mmol/L) are calculated from these. Different values (up to 2 mmol/L) may therefore be provided for BE and HCO_3^-, due to differences in the implemented algorithm.

Table 1.12 pH values and equivalent $[H^+]$ concentration in H_2O (pH = − log $[H^+]$ in mol/L)

pH	$[H^+]$ concentration (nmol/L)	
7.6	~ 25	
7.5	~ 32	↑ Alkalosis
7.4	~ 40	
7.3	~ 50	↓ Acidosis
7.2	~ 63	
7.1	~ 80	
7.0	~ 100	
6.9	~ 125	

Rule of thumb: In the physiological range, the pH changes by about 0.01 for every 1 nmol/L change in $[H^+]$

Table 1.13 Change in blood gas analysis (BGA) in primary disorders

	Met. acidosis	Resp. acidosis	Met. alkalosis	Resp. alkalosis
pH	↓	↓	↑	↑
$PaCO_2$	Normal	↑	Normal	↓
HCO_3^-	↓	(↑)	↑	(↓)
BE	↓	Normal	↑	Normal
STB	↓	0	↑	0

STB standard bicarbonate

Table 1.14 Change in BGA in compensated disorders

	Met. acidosis	Resp. acidosis	Met. alkalosis	Resp. alkalosis
pH	(↓)	(↓)	(↑)	(↑)
$PaCO_2$	↓	↑	↑	↓
HCO_3^-	↓	↑	↑	↓
BE	Negative	Positive	Positive	Negative
STB	↓	↑	↑	↓

Standard Bicarbonate and Base Excess

Standard bicarbonate. STB describes the value that the currently measured $[HCO_3^-]$ concentration would assume under standard conditions (SpO_2 = 100%, T = 37 °C, and PCO_2 = 40 mmHg). The value is calculated (like the current $[HCO_3^-]$ concentration also) by BGA meter by means of the Henderson-Hasselbalch equation using pH and $PaCO_2$:

Formula 23

$pH = 6.1 + \log([HCO_3^-]/(PaCO_2 \times 0.03) \rightarrow [HCO_3^-] = 10^{pH - 6.1} \times (PaCO_2 \times 0.03) = [STB]$; Normal value for STB: 24 ± 2 mmol/L

Base excess (BE): Base excess (BE). BE describes the difference between the actual state and the normal sum of the negatively charged buffer bases (bb, measured at PCO_2 of 40 mmHg, pH of 7.4, and proteins of 7 g/dL):

Formula 24
$BE = \sum [bb]_{actual} - \sum [bb]_{normal}$

Formula 25
$\sum [bb]_{normal} = [HCO_3^-] + [A_{tot}^-] + [Phos^-] = 42 \pm 2\,mmol/L$

A_{tot}^- = dissociated proteins: predominantly albumin and hemoglobin

If the buffer base concentration falls to 32 mmol/L, e.g., by buffering of H^+ protons, BE is −10 mmol/L (32–42 = *−10 mmol/L*). As we see in Formula 25, the substances considered in the buffer base are in fact the three main weak acids in the blood. Since weak acids [A^-] are not fully dissociated at physiological pH, they act as buffers. This means that they are able to accept or donate H^+ accordingly ($A^- + H^+ \leftrightarrow AH$). If, for example, the buffering of H^+ protons "consumes" [A^-], the buffer base concentration falls to 32 mmol/L, and BE becomes −10 mmol/L (32–42 = *−10 mmol/L*).

BE can be estimated from the [HCO_3^-] concentration as follows:

Formula 26
$BE = 1.2 \times ([HCO_3^-] - 24)$.

Strictly speaking, BE applies only to the blood compartment and not to the whole of the extracellular space (ECS). Calculation of BE may therefore give erroneous results, since actual changes in [HCO_3^-] in vivo are "attenuated" by distribution of [HCO_3^-] in the ECS. To make the concept of BE applicable to the whole ECS, standard base excess (e.g., SBE, BE_{ecf}) was developed. Most blood gas analyzers nowadays report SBE rather than BE.

Formula 27
$SBE = 0.9287 \times \{[HCO_3^-] - 24.4 + 14.83 \times (pH - 7.4)\}$; Normal value for SBE: 0 ± 2.5 mmol/L

Note: BE and SBE are used to compute the effect of $PaCO_2$ on the [HCO_3^-] concentration and thus to quantify the metabolic component of the acid-base disorder. In other words, the BE and SBE are a way to quantify the presence of strong acids (metabolic acidosis) or strong bases (metabolic alkalosis) in the whole blood or in the ECF.

There is good correlation between BE of venous and arterial blood, with BE always being slightly higher in venous blood (due to higher PCO_2 leading to higher HCO_3^-).

If [HCO_3^-] and BE are not available, the following procedure using the actually measured parameters (pH and $PaCO_2$) is available to analyze the acid-base status:

- Assess pH:
  - *Acidosis if < 7.35*
  - Normal if 7.35–7.45
  - *Alkalosis if > 7.45*

- Assess $PaCO_2$:
  - *Hypercapnia if > 45 mmHg*
  - Normal if 35–45 mmHg
  - *Hypocapnia if < 35 mmHg*
- If pH and $PaCO_2$ point in *different* directions:
  - *pH ↓ and $PaCO_2$ ↑ = respiratory acidosis*
    (e.g., pH = 7.08 and $PaCO_2$ = 80 mmHg)
  - *pH ↑ and $PaCO_2$ ↓ = respiratory alkalosis*
    (e.g., pH = 7.56 and $PaCO_2$ = 20 mmHg)
- If pH and $PaCO_2$ point in the *same* direction:
  - *pH ↓ and $PaCO_2$ ↓ = metabolic acidosis with respiratory compensation*
    (e.g., pH = 7.33 and $PaCO_2$ = 33 mmHg)
  - *pH ↑ and $PaCO_2$ ↑ = metabolic alkalosis with respiratory compensation*
    (e.g., pH = 7.47 and $PaCO_2$ = 47 mmHg)
  - *In this case, $PaCO_2$ ≈ first two figures after the decimal point of the pH* (see above)
- In the event of respiratory acidosis/alkalosis, it is possible to check whether an additional metabolic disorder is present. The following rule of thumb is used to assess whether the change in pH is compatible with the change in $PaCO_2$:
- *The pH changes by about 0.08 per 10 mmHg change in $PaCO_2$***:**

Formula 28

$$pH_{expected} = 7.4 - [(PaCO_{2actual} - 40) \times 0.008]$$

- For example, for a $PaCO_2$ = 60 mmHg, a $pH_{expected} = 7.4 - (20 \times 0.008) = 7.24$ is calculated.
  - If $pH_{actual} < pH_{expected}$ = additional metabolic acidosis
  - If $pH_{actual} > pH_{expected}$ = additional metabolic alkalosis
- Remark: Strictly speaking, the pH falls by 0.1 per 10 mmHg increase in $PaCO_2$ and increases by 0.05 per 10 mmHg fall in $PaCO_2$. The value of 0.08 is an average for purposes of simplification.

Assessment of compensation mechanisms. Assessment of the compensatory mechanisms is rarely necessary postoperatively but can be helpful in metabolic or combined disorders.

- The following formula can serve to estimate respiratory compensation in metabolic disorders:

Formula 29

$$[HCO_3^-]_{actual} + 15 \approx PaCO_{2expected} \pm 2mmHg$$

– If $PaCO_{2actual} > PaCO_{2expected}$ = additional respiratory acidosis

– If $PaCO_{2aktuell} < PaCO_{2expected}$ = additional respiratory alkalosis

Identifying the primary acid-base disorder in the state of compensation:

- *The actual pH normally helps to identify the primary disorder even in a state of compensation***.**
- The body usually does not "overcompensate," *i.e., no pH values ≥ 7.4 are reached by physiological compensation of acidosis and no pH values ≤ 7.4 by physiological compensation of alkalosis***.** An acid-base disorder with high PCO_2 and increased [HCO_3^-], but with a pH <7.35, has to be interpreted as primary respiratory acidosis with renal compensation, rather than metabolic alkalosis with respiratory compensation, in which the pH was >7.4.
- Exception: Chronic respiratory alkalosis can be compensated to within the normal pH range.
- Note: Respiratory compensation (hypoventilation) is possible in metabolic alkalosis to only a limited extent.

Adequate respiratory compensation may not be possible in patients with pulmonary disorders, while in patients with renal disorders, adequate metabolic compensation may not be possible.

1.2.4 Metabolic Acidosis

The optimal treatment of metabolic acidosis assumes the identification and elimination of the underlying disorder (see Fig. 1.14)!

The two fundamental questions are:

1. What is the cause of the metabolic acidosis?
2. Is there a risk to the patient?

Response to question 1:

- If metabolic acidosis is present postoperatively, until proven otherwise, it is either the result of a disorder of O_2 supply or perfusion or the result of excessive chloride intake (see below).

Response to question 2:

Metabolic acidosis with an increased anion gap is particularly dangerous as the underlying cause is either a disorder of cell energy homeostasis (e.g., lactic acidosis), metabolism (e.g., ketoacidosis), renal failure (and complications), or intoxication (e.g., methanol, salicylates).

Possible interpretations in metabolic acidosis of unknown origin:

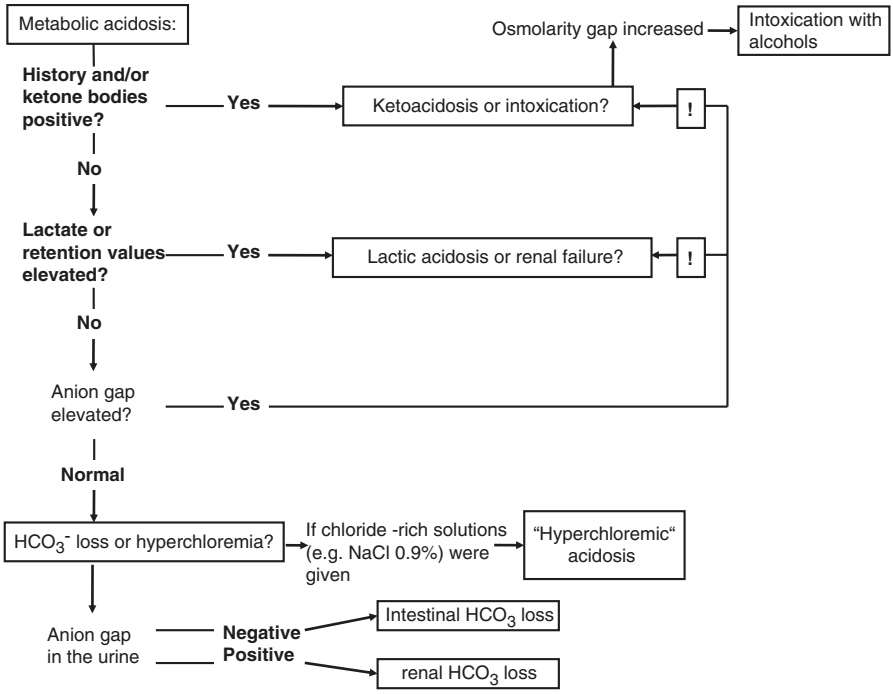


Fig. 1.14 Differential diagnosis of metabolic acidosis. (Modified after Vincent (2009))

Steward Model

- Explains changes in pH on the basis of three physiologic buffer systems:
  1. Carbonic acid ($PaCO_2$, HCO_3^-)
  2. Strong ion differential (the sum of strong cations minus the sum of strong anions in the blood): SID = ([Na^+] + [K^+]) – ([Cl–] + [lactate–]) = SID = 42 ± 2 mmol/L
  3. Weak acids (albumin, phosphates)
- In line with the electrochemical equilibrium, the sum of all negatively charged particles (anions) in the blood is equal to the sum of all positively charged particles (cations). Figuratively speaking, the sum of the cations (Na^+, K^+, Ca^{2+}, Mg^{2+}, H^+) thus "determines" the space that the anions (Cl^-, HCO_3^-, albumin$^-$, $PO4^{3-}$, $SO4^{2-}$, acids$^-$, and OH^-) can occupy. HCO_3^- is not "independent" of the anions mentioned as it can be converted into CO_2 (open system). In Steward model, HCO_3^- competes with the other anions for the available space. If the concentration of an "independent" anion increases (e.g., Cl^-, lactate), while the cation concentration remains unchanged, HCO_3^- is converted to $CO_2 + H_2O$, and the [HCO_3^-] concentration falls (and vice versa). This leads to a decrease in [bb] and therefore a negative BE. See Figs. 1.15 and 1.16.
- In Fig. 1.15:
  – Normal distribution.
  – If [Cl^-] increases disproportionately to [Na^+], [HCO_3^-] decreases (hyperchloremic acidosis).

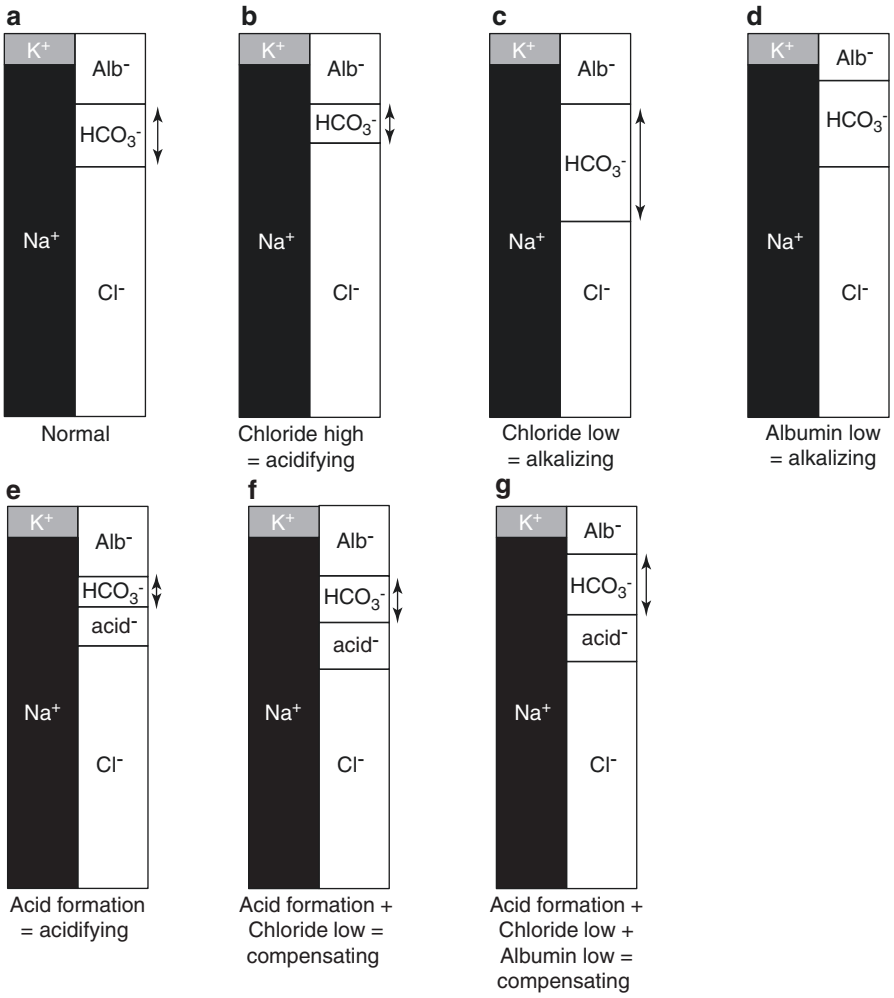


Fig. 1.15 Distribution of cations and anions. Different options (see columns) with their effect on [HCO_3^-]. (Modified after Duward (2009)). Please see text for further explanation

- If [Cl^-] increases disproportionately to [Na^+], [HCO_3^-] increases (hypochloremic alkalosis).
- If [albumin$^-$] decreases, [HCO_3^-] increases (hypoalbuminemic alkalosis).
- If an additional acid occurs (e.g., lactate), [HCO_3^-] decreases (e.g., acute lactic acidosis).
- If an additional acid occurs (e.g., ketones), [HCO_3^-] increases, as do [Cl^-] and/or albumin by way of compensation. This scenario is not uncommon in long-term metabolic acidosis (e.g., ketoacidosis).

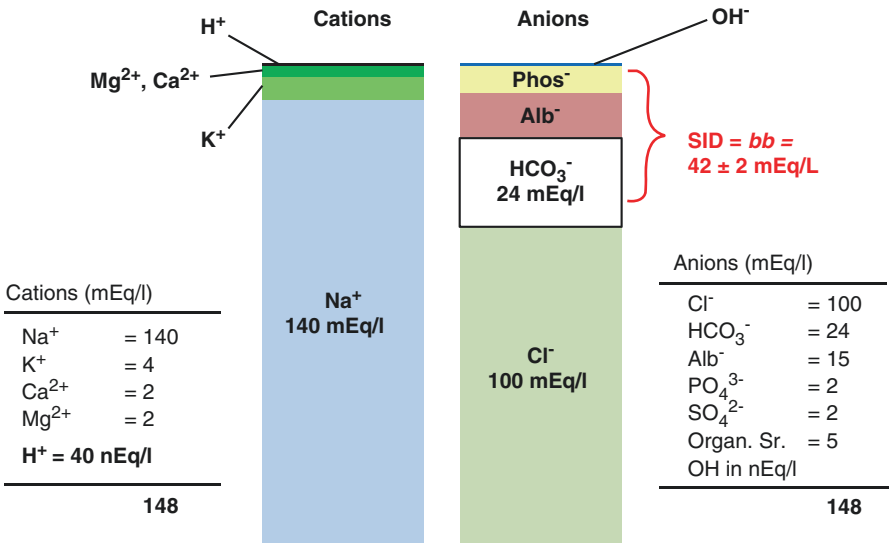


Fig. 1.16 SID (1 mmol = 1 mEq × number of charges or 1 mEq = 1 mmol/number of charges)

Note: The SID and the sum of the buffer bases [bb] have the same value (SID = [bb] = 42 ± 2 mmol/L). Therefore, $SID_{actual} - SID_{normal} = BE = [bb]_{actual} - [bb]_{normal}$.

- A comprehensive explanation can be found in Kellum and Elbers [12], and a simplified description can be obtained from the author.
- Benefits of the Steward model:
  - Understanding of specific acid-base disorders (e.g., hyperchloremic acidosis).
  - Acid-base disorders are considered in conjunction with electrolyte changes.
  - The three most important organs that contribute to the regulation of the acid-base balance (1. lung → $PaCO_2$, 2. kidney → SID, 3. liver → albumin) are involved.
- Drawback of the Steward model:
  - Calculation of SID in clinical practice somewhat unwieldy (the BE can be usually used instead).
  - The model is fairly complex and difficult to understand.

Durward Model or $[Cl^-]/[Na^+]$ Ratio

- The use of the $[Cl^-]/[Na^+]$ ratio is a simplified procedure based on the Steward model for interpreting acid-base disorders.
- As Cl^- and Na^+ are the main protagonists in quantitative terms of the anions and cations in plasma, the calculation of SID can be reduced to these. The $[Cl^-]/[Na^+]$ ratio can also be used to estimate the presence of tissue acids (e.g., lactate and unmeasured acids/anions).
- The plasma $[Cl^-]$ concentration must always be assessed in relation to the $[Na^+]$ concentration (normal values: $[Cl^-]$ = 95–105 mmol/l, $[Na^+]$ = 135–145 mmol/l):

Formula 30
$[Cl^-] : [Na^+]$ ratio = 105/140 = 0.75

- (*Normal value, 0.72–0.8*)
  - If <0.72 = alkalinizing effect
  - If >0.8 = acidifying effect
  - pH < 7.35 and $[Cl^-]/[Na^+]$ ratio < 0.72 = presence of tissue acids[1]
  - pH < 7.35 and $[Cl^-]/[Na^+]$ ratio > 0.8 = hyperchloremic acidosis
  - pH > 7.45 and $[Cl^-]/[Na^+]$ ratio < 0.72 = hyperchloremic alkalosis
- The $[Na^+]$ and $[Cl^-]$ concentrations therefore also have a calculable effect on base excess (BE):

Formula 31

$$\left[Na^+\right] - \left[Cl^-\right] - 32 = BE_{\text{due to changes in the } [Na^+]/[Cl^-] - \text{ratio}} = BE_{Cl}$$

- Example: BE = −15 mmol/L, Na^+ = 140 mmol/L, and Cl^- = 115 mmol/L; in this case, 140 – 115 – 32 = −7 mmol/L, i.e., of BE = −15 mmol/L, −7 mmol/L is due to chloride, while the remaining −8 mmol/L must be explained otherwise (e.g., lactate).
- To allow for the effect of albumin and unmeasured acids/cations, BE can be divided as follows:

Formula 32
$BE = BE_{Cl} + BE_{alb} + BE_{\text{unmeasured acids}}$ or $BE_{\text{unmeasuredacids}} = BE - (BE_{Cl} + BE_{alb})$

- BE_{Cl} = see above
- BE_{Alb}, = (42 – albumin in g/L) × 0.25

Anion Gap (AG)
- The calculation of the anion gap (AG) can be helpful in the differential diagnosis of metabolic acidosis of unknown origin.
- A distinction is drawn between acidosis with increased AG and that with normal AG (hyperchloremic acidosis).
- The anion gap is calculated from the following formula:

[1] Of the tissue acids, usually only lactate is routinely determined quantitatively in clinical practice (ketones usually only qualitatively). Others remain unrecognized: unmeasured acids/anions. In the presence of tissue acids, a reduction in the (HCO_3^-) concentration occurs initially (Fig. 1.15, column e). If the acidosis persists for longer (hours to days), there is also a compensatory decrease in the [Cl–] concentration (Fig. 1.15, column f) – even before iatrogenic Cl^- is supplied in the form of infusion solutions. Thus, acidosis with a decrease in the [Cl–]/$[Na^+]$ ratio highly probably indicates the presence of large quantities of tissue acids. By contrast, a $[Cl^-]/[Na^+]$ ratio > 0.85 excludes the presence of tissue acids as a cause of acidosis. If hyperchloremia and lactate are found, the situation is not so clear-cut. The $[Cl^-]/[Na^+]$ ratio is then between 0.72 and 0.8.

Formula 33

$AG = ([Na^+] + [K^+]) - ([Cl^-] + [HCO_3^-]) = 15 \pm 5$ mmol/L

- As already mentioned, the sum of $[Cl^-] + [HCO_3^-]$ remains unchanged if the $[Cl^-]$ concentration increases. This results in a normal AG (Fig. 1.17, middle column). By contrast, the presence of acids that are produced in the body (tissue acids) or that are supplied to it causes an acute reduction in the $[HCO_3^-]$ concentration (without a change in $[Cl^-]$). There is thus a decrease in the sum of $[Cl^-] + [HCO_3^-]$ and hence an increase in AG (Fig. 1.17, right-hand column).
- *Note about AG*: There is also the problem when calculating AG of having to determine the concentrations of the components correctly, since otherwise errors in the individual components cumulate. The 95% confidence interval for AG is ±5 mmol/L, i.e., only AG ≥ 20 mmol/L is significantly increased. In a study by Gabow et al. [9], up to 1/3 of patients exhibited no lactic acidosis or ketoacidosis at values of 20–29 mmol/l, whereas at values ≥30 mmol/L, one or the other was always present.
- *The following may be noted:*
  - AG values between 15 and 20 mmol/L are suspicious.
  - Values ≥20 mmol/L usually indicate a problem.
  - Values ≥30 mmol/L practically always indicate a severe disorder (in this case, however, the analysis should be checked).

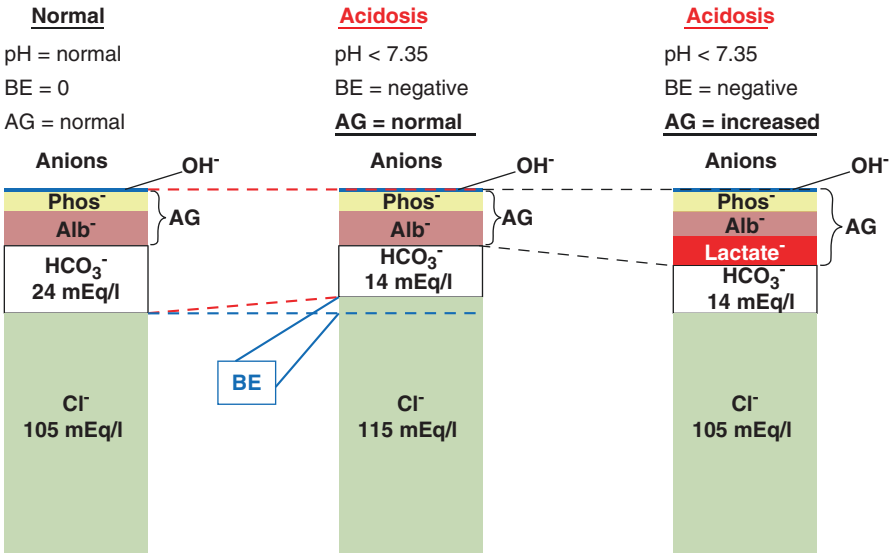


Fig. 1.17 Various anion gaps. The column for total anions is depicted. Left: normal state, SID = 42 mmol/l, AG = 15 mmol/L, and BE = 0 mmol/L. Center: acidosis with normal AG, SID = 32 mmol/l, AG = 15 mmol/L, BE = −10 mmol/L. Right: acidosis with increased AG due to lactate, SID = 32 mmol/L, AG = 25 mmol/L, BE = −10 mmol/L

- Figure 1.17 shows that the so-called anion gap is not a real gap but is only termed such because it encompasses *unmeasured* anions (albumin, phosphate, sulfate, organic acids, lactate, etc.). Changes in the concentration of these anions affect the anion gap. As albumin is a quantitatively major factor, AG must be corrected for the actual albumin value (= AG_{corr}). This applies in particular to the hypoalbuminemia <30 g/L that occurs frequently in intensive care patients (*normal value, 40 g/L*).

Formula 34
$AG_{korr} = AG + [(42 - [albumin])/4]$

- Rule of thumb: *For each decrease in albumin of 10 g/L, BE increases by about 2.5 mmol/L* (see also BE_{alb}).
- The definitive diagnosis of metabolic acidosis with increased AG (e.g., lactic acidosis, ketoacidosis, renal failure) must include previous history, clinical features, and other laboratory tests (detection of lactate, ketone bodies, increased retention values) (Fig. 1.14).

Lactic Acidosis and Hyperchloremic Acidosis

Lactic Acidosis
- For the pathophysiology of lactic acidosis, please see Sect. 1.1.5.

Hyperchloremic Acidosis

- As a result of the infusion of fairly large quantities of chloride-rich solutions (e.g., NaCl 0.9%), not infrequently iatrogenic hyperchloremic acidosis occurs.
- NaCl 0.9%: Na^+ = 154 mmol/L, Cl^- = 154 mmol/L, pH = 4.5–7.0, osmolarity = 308 mosm/L
- Cause: The difference between the physiological concentration in the blood and that in the 0.9% NaCl solution is about five times greater for chloride than for sodium. Following the infusion of saline solution, therefore, the plasma [Cl^-] concentration increases more strongly than the [Na^+] concentration ([Cl^-]/[Na^+] ratio see above). The change in [HCO_3^-] concentration relative to [Cl^-] concentration is depicted in Fig. 1.15 (column b).
- The clinical significance of the ensuing hyperchloremic acidosis in children has yet to be fully elucidated. There is however evidence in adults that hyperchloremic acidosis can result in a reduction in renal perfusion and hence a deterioration in renal function. Immunological changes are also described. However, usually no specific treatment is required, other than the avoidance of further chloride loading. Only in exceptional cases is buffering with sodium bicarbonate necessary (whereby the increase in Na^+ concentration is the correcting factor, not the bicarbonate).

Effects of Metabolic Acidosis
See Table 1.15.

Table 1.15 Effect of metabolic acidosis

Pulmonary	Hyperventilation (in association with respiratory compensation, Kussmaul breathing)
Cardiac	Negative inotropism
	Arrhythmia (e.g., with hyperkalemia)
Cerebral	Increased intracranial pressure through cerebral vasodilation (increase in intracranial blood volume)
Vascular:	
Systemic arterioles	Vasodilation, decrease in SVR
Systemic venules	Vasoconstriction, decrease in "venous pooling"
Pulmonary arterioles	Vasoconstriction, increase in PVR
Catecholamine receptors	Increased resistance to catecholamines
Sympathetic system	Increased activity
Electrolytes	Increase in serum potassium levels
O_2 binding curve	Direct effect: Right shift
	Indirect effect: Left shift via an increase in erythrocyte 2,3-DPG
Hypoxia tolerance of the cell	Increase in hypoxia tolerance by decrease in cellular O_2 consumption and protective mechanisms (e.g., hypoxia-inducible factor (HIF))

Effects that are abolished:

- Up to pH > 7.0, the directly negative inotropic effect (competition between H^+ protons and Ca^{2+} ions at channels and contractile elements, reduction in activity of contractile elements) can be compensated by the increased release of catecholamines and the decrease in afterload (decrease in SVR due to systemic vasodilation). At pH < 7.0, contractility is increasingly reduced.
- Due to the increase in sympathetic tone, there is increased catecholamine release, but at pH values <7.0, catecholamine resistance increases perceptibly, as a result of which, systemic vasodilation can predominate (decrease in SVR and blood pressure).
- The increase in pulmonary arterial resistance (pulmonary vasoconstriction) can be attenuated in the spontaneously breathing subject by compensatory hyperventilation (fall in PCO_2, increase in pH).
- Acidosis results directly in a right shift of the O_2 binding curve, but indirectly this effect is attenuated by the decreased erythrocyte 2,3-DPG concentration.

Effects that are potentiated:

- Right heart failure can be induced or potentiated by increased pulmonary arterial resistance (pulmonary vasoconstriction), increased venous return (venous vasoconstriction), and decreased inotropism.
- Arterial hypotension frequently results at pH values <7.0, as negative inotropism, peripheral vasodilation, and catecholamine resistance interact.

Ventilation in Metabolic Acidosis
If an acidotic patient who hyperventilates for compensation has to be intubated and undergo controlled ventilation, there is the risk that the acidosis, and hence the patient's status, will deteriorate in normoventilation (potentiation of intracellular acidosis, negative inotropism, PHT crisis, ICP crisis, arrhythmias, etc.). In this situation, therefore, the initial aim should be to obtain similar $PaCO_2$ values to those prior to intubation. This is then followed by gradual adaptation involving monitoring of BGA (or correction), taking due account of clinical features.

1.2.5 Buffering

Buffering is not causal therapy!
A good justification is therefore always required for the use of buffers (e.g., cardiovascular instability, hyperkalemia)!

Low pH values (up to a pH of 7.0) are usually surprisingly well tolerated. Nowadays, very few recommendations exist on buffer pH values <7.2 (without justification). In shock, buffering with bicarbonate can even exacerbate the situation peripherally. If the CO_2 released on buffering with bicarbonate diffuses into the cell, this can potentiate intracellular acidosis (see also Sect. 1.1.6). It must therefore be ensured that the resultant CO_2 can be eliminated by perfusion and ventilation.

For Practice
- If a patient is hemodynamically stable postoperatively with normal peripheral perfusion, the pH is of minor importance.
- If the circulation is unstable (which includes patients who require catecholamines to classify as stable) and/or if peripheral perfusion is impaired, the use of sodium bicarbonate (NaBi) can be considered to "correct" the pH with the aim of improving inotropism, increasing the response to catecholamines, or reducing PVR. However, this should only be done in combination with other perfusion-enhancing measures.
- *Comment*: That said, our clinical experience nevertheless has shown that the administration of sodium bicarbonate will often produce a sudden breakthrough during prolonged resuscitation, may lead to an unexpected reduction in pulmonary artery pressures in pulmonary hypertension otherwise deemed refractory, or can contribute to stabilization of "unstable circulation."

Indications for Buffers
- Symptomatic hyperkalemia (e.g., arrhythmias, asystole, etc.)
- Intoxications (e.g., tricyclic antidepressants)
- PHT episode

- Prolonged resuscitation (e.g., catecholamine resistance)
- Alkalinization of the urine in rhabdomyolysis (see Sect. 4.6.1)

Buffers

Buffering with 8.4% sodium bicarbonate
- Per mL: 1 mmol HCO_3^- and 1 mmol Na^+
- Rule of thumb in an emergency: 0.5–1–(3) mmol (mL)/kg BW
- Otherwise: mmol (mL) = BE × 0.3 × kg
- In premature infants and neonates: Administer diluted 1:1 with water or G5%

Buffering with TRIS buffer (THAM, trometamol)
- E.g., THAM-Köhler 3 M (1 mL = 3 mmol THAM)
- Rule of thumb in an emergency: 0.5–1 mmol/kg = 0.15–0.3 mL (3 M)/kg
- Otherwise: mL (3 M) = 0.1 × kg × BE
- Not in premature infants and neonates (risk of apnea)

1.2.6 Approach to Acid-Base Disorders

What Is Needed
Blood (arterial or capillary):

- Blood gas analysis: pH, PCO_2, HCO_3^-, BE
- Electrolyte concentration: Na^+, K^+, Cl^-
- Lactate
- Laboratory tests: creatinine, urea, albumin

Primary Orientation
- Step 1: Define the changes in pH and PCO_2.
- Step 2: Define the changes in [HCO_3^-], BE or STB.
- Step 3: Assess the compensation mechanisms.
- Step 4: Determine lactate.
- Step 5:Put everything in a clinical context.

Two Examples

1. Capillary BGA measurement immediately after a seizure:
   - BGA: pH = 7.08, $PaCO_2$ = 87 mmHg, BE = −2 mmol/L, [HCO_3^-] = 27.8 mmol/L
   - pH and $PaCO_2$ point in opposite directions = *respiratory acidosis*
   - $pH_{calculated}$ = 7.4 – [(87–40) × 0.008] = *7.024*
     Here: $pH_{actual} \approx pH_{expected}$
   - *Diagnosis*: acute respiratory acidosis (Table 1.16)

2. Capillary BGA measurement in newly diagnosed diabetes mellitus:
   - BGA: pH = 7.25, $PaCO_2$ = 17.6 mmHg, BE = −19 mmol/L, $[HCO_3^-]$ = 7.8 mmol/L, lactate = 1.5 mmol/L
   - Urine dipstick: ketone bodies
   - pH and $PaCO_2$ point in the same direction = metabolic acidosis with respiratory compensation
   - Assessment of respiratory compensation
   - $PaCO_{2expected} \approx [HCO_3^-]_{actual} + 15 = 7.8 + 15 = 22.8 \pm 2$ *mmHg*
     Here: $PaCO_{2actual} < PaCO_{2expected}$ = additional respiratory alkalosis!
   - Diagnosis: metabolic acidosis with respiratory compensation and hyperventilation (Table 1.17)

Monitoring and Extended Diagnosis According to Durward

If the situation is not controlled and/or the diagnosis continues to be uncertain, the following procedure can then help further:

- Step 1: Define the pH (acidosis or alkalosis).
- Step 2: Define the various factors that influence pH (acidifying and alkalinizing forces) and their balance (see Table 1.18).
- Step 3: Determination of the anion gap (AG).

For calculations, see Formulae 30, 31, 32, and 33.

Two Examples

Table 1.16 Example table of respiratory acidosis

	Resp. acidosis	Met. alkalosis
pH	↓	
$PaCO_2$	↑	
HCO_3^-	↑	
BE	Normal	

Table 1.17 Example table of metabolic acidosis with respiratory compensation

	Comp. met. acidosis	Hyperventilation
pH	↓	
$PaCO_2$	↓	↓
HCO_3^-	↓	
BE	↓	

Table 1.18 Factors influencing pH

	Acidifying force	Alkalinizing force
Respiratory component	$PaCO_2$ ↑	$PaCO_2$ ↓
Chloride	Cl^- ↑	Cl^- ↓
Albumin	Alb^- ↑	Alb^- ↓
Unmeasured acids (AA)	AA ↑	AA ↓
Phosphate[a]	$PO4^{3-}$ ↓	$PO4^{3-}$ ↑

[a]The phosphate concentration is normally too small to have any marked influence

1. Capillary BGA measurement in newly diagnosed diabetes mellitus (same BGA as above):
   - BGA: pH = 7.25, $PaCO_2$ = 17.6 mmHg, BE_{ecf} = −19 mmol/L, $[HCO_3^-]$ = 7.8 mmol/L, lactate = 1.5 mmol/L
   - Laboratory tests: Na^+ = 131 mmol/L, K^+ = 5 mmol/L, Cl^- = 90 mmol/L, albumin = 35 g/L
   - Urine dipstick: ketone bodies
   - pH = 7.25 = *acidosis*
   - $PaCO_2$ = 17.6 mmHg = *alkalinizing*
   - $[Cl^-]/[Na^+]$ ratio = 90:131 = *0.68* = Hypochloremia = *alkalinizing*
   - BE_{Cl} = Na – Cl – 32 = *9 mmol/L* = *alkalinizing*
   - $BE_{albumin}$ = (42–35) × 0.25 = *1.75* = *alkalinizing*
   - $BE_{unmeasured\ anions}$ = −19 – (9 + 1.75) = *–29.75 mmol/L* = *acidifying* (ketone bodies!)
   - AG = (131 + 5) – (90 + 7.8) = *38.2 mmol/L*
   - *Diagnosis*: ketoacidosis with respiratory and metabolic compensation (Table 1.19)
2. Postoperative BGA measurement in ventilated patient:
   - BGA: pH 7.2, $PaCO_2$ = 38.5 mmHg, BE_{ecf} = −15 mmol/L, $[HCO_3^-]$ = 14 mmol/L, lactate = 3 mmol/L
   - Laboratory tests: Na^+ = 145 mmol/L, K^+ = 4 mmol/L, Cl^- = 125 mmol/L, albumin = 25 g/L
   - pH = 7.2 = *acidosis*
   - $PaCO_2$ = 38.5 mmHg = *normal*
   - $[Cl^-]/[Na^+]$ ratio = 125:145 = 0.86 = hyperchloremia = *acidifying*
   - BE_{Cl} = Na – Cl – 32 = *−12 mmol/L* = *acidifying*
   - $BE_{albumin}$ = (42–25) × 0.25 = *4.25* = *alkalinizing*
   - $BE_{unmeasured\ anions}$ = −15 – (−12 + 4.25) = *−7.25 mmol/l* = *acidifying* (lactate)
   - AG = (145 + 4) – (125 + 14) = 10 mmol/L = normal
   - AG_{corr} = 10 + [(42–25) × 0.25] = *14.25 mmol/l*
   - *Diagnosis:* mixed metabolic acidosis (predominantly hyperchloremic) without substantial compensation (Table 1.20)

It is the net combination of acidifying and alkalinizing forces that determine pH! (Durward)

Table 1.19 Anion gap | compensation by respiration and hypochloremia

	Acidifying force	Alkalinizing force
Respiratory component		Hyperventilation
Chloride		Hypochloremia
Albumin		(hypoalbuminemia)
Unmeasured acids (AA)	Ketone bodies[a]	

AA amino acids

[a]In this case ketone bodies could be determined qualitatively in the urine

Table 1.20 Mixed metabolic acidosis with normal anion gap in hyperchloremia

	Acidifying force	Alkalinizing force
Respiratory component		
Chloride	Hyperchloremia	
Albumin		Hypoalbuminemia
Unmeasured acids (amino acids)	Lactate	

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Ventilation

2

Dietrich Klauwer

After Chap. 1 focused on an explanation of the fundamentals for understanding oxygen transport and the effect of breathing on acid-base balance, now the facts relating to positive pressure ventilation (PPV) will be elucidated.

2.1 Advantages and Disadvantages of Ventilation

See Table 2.1.

As well as exerting an influence on gas exchange and acid-base balance, all positive pressure ventilation also has particular effects on blood circulation. These effects must be addressed first before any introduction to ventilation physiology: "Positive" ventilation-induced circulatory changes are frequently utilized, whereas "negative" changes are usually only terminable by extubation.

In brief, the following changes in the circulatory situation occur as a result of ventilation:

- PEEP (positive end-expiratory pressure): Decrease in right ventricular and left ventricular preload and decrease in LV afterload
- Positive intrapulmonary pressure: Increase in RV afterload but decrease in LV afterload

D. Klauwer
Department of Pediatrics, Singen Medical Center, Gesundheitsverbund Landkreis Konstanz, Krankenhausbetriebsgesellschaft Hegau-Bodensee-Klinikum, Singen, Germany

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D. Klauwer et al. (eds.), *A Practical Handbook on Pediatric Cardiac Intensive Care Therapy*, https://doi.org/10.1007/978-3-319-92441-0_2

Table 2.1 Advantages and disadvantages of ventilation

Advantages	Disadvantages
Anesthesia possible with analgesics	Patient incapable of communication
Relaxation possible	Need for sedation
Reopening of atelectatic areas	Impaired mucociliary clearance
Targeted bronchial hygiene possible	Infection tracking
Treatment of severe gas exchange disorders	Injury due to volutrauma/barotrauma
Cardiovascular therapy under controlled conditions	Injury from tube
	Deterioration of pulmonary circulation due to positive pressure (particularly TCPC/Glenn)
Reduction in work of breathing, O_2 consumption, controlled CO_2 exhalation for postoperative stabilization	Poorer blood outflow from the brain (effect on CPP and ICP; see text[a])
	Visceral circulation falls

CPP cerebral perfusion pressure

[a]In passive pulmonary circulation, e.g., in Glenn anastomosis and TCPC, venous return and hence CO may be reduced due to the ventilation-related increase in intrathoracic pressure. If mean arterial pressure (MAP) decreases due to a reduced stroke volume with concurrently raised venous pressures (before the lung), CPP is reduced: CPP = MAP – CVP (for ICP > CVP: CPP = MAP – ICP). The critical cerebral perfusion pressure (CPP) is age-dependent and is given, e.g., in neonates as <35 mmHg

What that means overall for hemodynamics

- Ventilation can compromise the RV; the higher the ventilation values, the more difficult it is for RV (ventilation-associated cor pulmonale)
- Ventilation is frequently beneficial for systolic left ventricular function. Positive pressure ventilation can relieve the LV, since the positive intrapleural pressure under ventilation conditions in positive pressure ventilation reduces the transmural pressure of the left ventricle. This is beneficial in systolic LV failure – for example, weaning failure is possible after extubation with the recurrence of pulmonary edema in LV failure, i.e., the patient needs PEEP. However, in severe LV diastolic function disorder, a high PEEP can also stand in the way of ventricular filling

Increased ICP and PEEP: A rise in PEEP results in an increase in intrathoracic pressure and hence a decrease in cerebral venous return, as a result of which ICP can be increased. With normal intracranial compliance, however, ICP is only slightly affected by a ventilation-related increase in intrathoracic pressure. Even where intracranial compliance is impaired (e.g., cerebral edema), a PEEP of up to 10 cmH_2O with elevation of the upper body has little impact on ICP. In this situation in particular, attention must also be paid to ensuring that the cerebral perfusion pressure (CPP = MAP – ICP) is kept constant (CPP 50–60 mmHg).

2.2 Basic Concepts of Ventilation

Essentially, many different ventilators are employed for the ventilation of children and neonates. The preferred form of ventilation, particularly in neonates, is *pressure-controlled* or *pressure-limited ventilation*. These forms of ventilation use a decrease in inspiratory gas flow in line (or in parallel) with the filling of the lung (decelerating inspiratory flow): This ensures a gradually slower gas flow to the patient (decelerating inspiratory flow) following an increase in lung filling. In very simplified terms, a distinction can be drawn between *three* operating principles of ventilators:

The *first* group consists of devices in which a continuous gas flow is present over the whole breathing cycle. By opening and closing the various valves in the expiration part of the device, this continuous gas flow is "dammed back" into the patient's lung in a time-controlled manner. In the process, the defined gas flow determines the period of time required to achieve the inspiratory pressure-limited by the controller (PIP = positive inspiratory pressure). This is referred to as the principle of flow-controlled, time-controlled, and pressure-limited ventilation. If the gas flow is set too low, the upper pressure limit is not reached; if the gas flow is set too high, PIP is reached too rapidly, and ventilation injury can be exacerbated. These devices operate on the retaining wall or "dam" principle. This operational principle means that the set inspiratory pressure is reached more rapidly, the higher the continuous gas flow is set. The concept of decelerating gas flow, therefore, relates here only to the part channeled to the patient's lung. In order to empty the lung, the retaining wall is removed again (PEEP level), and the patient achieves expiratory respiration passively through the mechanical restorative forces of their lungs. In very simplified terms, this is how the Babylog (Dräger) and many other "neonatal ventilators" frequently used in neonate function.

2.2.1 Pressure-Controlled Versus Volume-Controlled

This first group is contrasted with ventilators in which a continuous basic gas flow generated at each point of the breathing cycle is coupled with a demand flow that is generated to produce either physician-specified pressures (second group) or volumes (third group). Fitted with appropriate valve and measurement technology, many ventilators reach the set pressure and volume objectives in the specified times while enabling very good synchronization of the breathing cycle with the individual's needs across a wide range of patients (2 to >100 kg BW). An added benefit is the high degree of precision of these ventilators.

To achieve the sometimes differentiated objectives of ventilation and circulatory adjustment by varying targeted ventilation, some basic concepts and an understanding of ventilators are essential.

2.2.2 PEEP: Positive End-Expiratory Pressure

Ideally, this pressure prevents the lung from collapsing between breaths and thereby prevents ventilation disorders, particularly dorsally/basally. In turn, the maintenance of the ventilatable parts of the lung (functional residual capacity, FRC) is ensured and hence a "physiological" ventilation/perfusion ratio. PEEP should be set at a level that prevents the lung from collapsing between breaths while not unnecessarily increasing the pulmonary arterial resistance altered by the constant positive intrathoracic pressure. PEEP reduces RV preload and, at very high values, can increase RV afterload as well.

In contrast to airway pressure-induced afterload augmentation, the reopening of markedly dys- or atelectatic lung areas by the use of positive airway pressure can effectively reduce RV afterload through improved ventilation (Euler-Liljestrand mechanism).

PEEP 3–7 cmH_2O – considerably higher in restrictive lung diseases.

2.2.3 Peak Pressure or Positive Inspiratory Pressure (PIP)

PIP is the maximum pressure present in the respiratory tract on inspiration. This pressure is reached after the inspiratory rise time/gradient set on the ventilators or after a time determined by the patient's respiratory conditions (compliance and resistance) as a function of gas flow in the flow-controlled ventilator. In short, the more flow, the earlier PIP is reached.

PIP determines the desired tidal volume (ventilation amplitude = PIP – PEEP generates Vti). PIP should be set in such a way that, depending on lung function and ventilation objectives, about 4–6–8–(10) ml/kg BW is inhaled and exhaled per breath.

If tidal volumes are not measured, exclusively indirect procedures must be relied upon for estimating the correct PIP (chest excursion, BGA, $etCO_2$).

In this case, PIP alone must not be held responsible for ventilation-induced lung injury. Indeed, pressure amplitudes (PIP-PEEP) and tidal volume play vital roles alongside, importantly, the cyclical reopening of collapsing lung sections between breaths (RACE trauma; see below).

PIP settings usually range between 16 and 25 cmH_2O.

2.2.4 Inspiratory Time (I-Time)

Inspiratory time refers to the time from the start of the buildup/effect of PIP to the onset of expiration.

Table 2.2 I-time

I-time (s)	Premature infants	Neonates	Infants	Young children	Adults
Ventilation	0.2–0.35	0.3–0.5	0.5–0.8	0.6–0.9	0.9–1.6

In purely flow-controlled devices, the I-time includes the inspiratory rise time. Gas flow should in this case be set so that PIP is reached after about $^1/_4$ to $^1/_3$ of the whole I-time.

In most pressure- and volume-controlled ventilators, the I-time also includes the inspiratory rise time – but this will be explicitly specified. The data given in Table 2.2 simply represent a starting point, since the times required for filling and emptying of the lung can vary markedly in the different lung diseases (see section on time constants and flow curves).

The I-time and the set RR (respiratory rate) for completely controlled breaths yield the ratio *Ti/Te* (inspiratory time/expiratory time). This should not fall below 1:2, unless severe compliance disorders are present.

2.2.5 Compliance: Lung Extensibility (dV/dP)

Only dynamic compliance can be measured by the respirator.

When measuring Vti on the respirator, this parameter can be determined by *Vti* / (*PIP – PEEP*).

Compliance is a crucial aspect for the basic understanding of the ventilation options in compliance disorders. With low compliance, only a limited amount of inspiratory gas enters the lung even at high-pressure amplitude because of the marked mechanical restorative forces. Here, gas flow occurs to a relevant extent in the direction of the lung only at the beginning of the I-time and very rapidly returns to the zero level again. If the I-time is set too long, this results in a phase without gas flow directed to the patient (= zero flow). This time is then lost to the production of respiratory minute volume in CO_2 retention associated with compliance disorders.

In this situation, it would be better to improve compliance by:

- Administration of surfactant (SF)
- Mechanical recruitment of non-ventilated lung areas
- Drainage of effusions/edema fluid

The above involves all strategies to avoid lung injury in a compliance disorder (low tidal volume strategy, best PEEP finding, recruitment maneuver, SF administration).

Given these pulmonary mechanics (compliance and resistance), how can the ventilation parameters with the *safest and gentlest setting for the lung* be obtained?

First, some basic knowledge pertaining to the question: *Which respirator settings affect gas exchange and how?*

2.2.6 Oxygenation

The most effective way of achieving the highest oxygenation is to convey as much oxygen as possible to as many ventilated *and* blood-supplied alveoli as possible. It therefore follows that:

- FiO_2 (fraction of O_2 in the breathing air) must be increased
- Mean airway pressure (MAP = as the most predictive parameter of the degree of lung recruitment) must be optimized

Lung recruitment can be improved by:

- Increasing PEEP (MAP rises)
- Increasing I-time
- Increasing PIP

The increase in these parameters, however, does not result in an unlimited improvement in oxygenation, since suitable tidal volumes with *meaningful* ventilation pressures are not reached *in overdistended states* of the lung. In addition, high ventilation pressures stand in the way of RV filling and hence cardiac output, so that the O_2 delivery (DO_2) again falls due to the decrease in cardiac output.

The pressure-volume curve on the ventilator display illustrates how the greatest compliance is reached in the steepest part of the curve. Here, the lung does not collapse on expiration as in breaths below the lower inflection point (LIP) with a not unnecessarily large PIP being required on inspiration to generate a suitable Vti. This is the case in breaths that come up against the upper inflection point (UIP) (see Fig. 2.1).

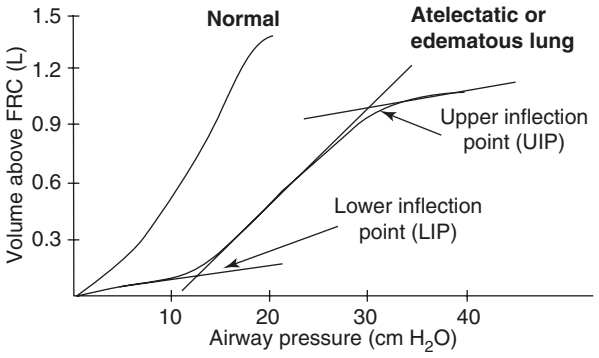

Fig. 2.1 Pressure-volume curve

2.2.7 Ventilation

The amount of CO_2 expiration results essentially from the respiratory minute volume, i.e., from the amount of inspiratory tidal volume (Vti) – if this is not in the range of the dead space volume (~ 2 ml/kg BW).

In this way, CO_2 expiration can increase through *an increase in Vti* (distance between PIP and PEEP in the non-collapsed lung) and the *increase in respiratory rate*.

A few further considerations in this respect on the limits of CO_2 expiration:

In the area of pulmonary overdistension (P/V diagram), a larger Vti can barely be generated at all as a result of the increase in PIP above the upper inflection point – and the main outcome is barotrauma.

In the area of the lower inflection point, the lung can collapse between breaths on further reduction in PEEP to increase Vti, resulting in a loss of lung recruitment and causing a deterioration in ventilation. In addition to this, the collapse-opening-collapse cycle is held responsible for some of the lung injury during ventilation (*RACE* = repetitive alveolar collapse and expansion).

2.2.8 Limits of Respiratory Rate

The deciding factor for the maximum respiratory rate on the respirator is the consideration that the drive force for the gas flow from the lung is the mechanical restorative forces, in other words, the rate of return of the lung to intermediate breathing (under ventilation = PEEP level).

This, therefore, means that *the poorer the compliance of the lung, the more rapidly expiration occurs*, since here the mechanical restorative forces are particularly high (compliance part of the time constants; see below) (see also Fig. 2.2).

In a non-obstructed airway, airway resistance is generally not a barrier for respiratory rate. However, with increased resistance, as in obstructive lung diseases (or too small a tube), expiration may not have ended before the respirator starts the new inspiration. This results in an unintended increase in intermediate breathing (*inadvertent PEEP*) and may be associated with lung injury due to overdistension, leaks and barotrauma (see Fig. 2.3).

The time constant $TC = Compliance \times Resistance$ expresses this relationship mathematically.

It indicates the length of time from the beginning of (passive) expiration to expiration of 63% of Vti.

The lower the time constant, the stiffer the lung (low compliance), and the more CO_2 can be expired by an increase in rate – as long as the patient is not obstructed.

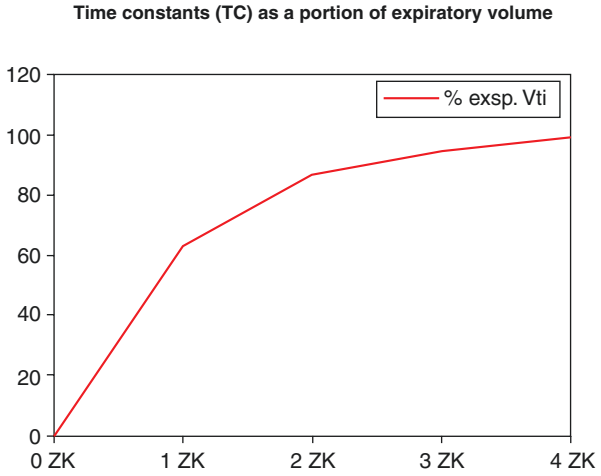

Fig. 2.2 Time constants [Text in graphic, ZK = TC]. Time constants as a portion of expiratory volume

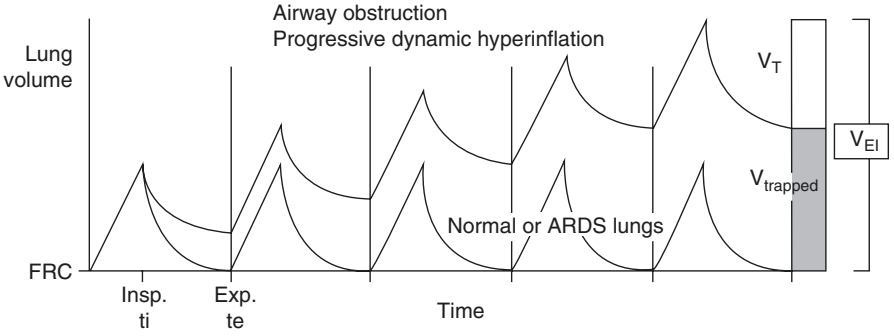

Fig. 2.3 Undesirable increase in PEEP level due to incomplete exhalation (inadvertent PEEP). (Modified after Tuxen and Lane (1987))

The patient should be allowed an expiration time of at least 3–4 time constants to avoid overdistension caused by incomplete expiration.

Problems can also occur when there is a sudden improvement in lung compliance: If the patient then no longer produces short enough expiratory breaths because of the lower mechanical restorative forces, overdistension without a reduction in respiratory rate could result in inadvertent PEEP.

The time constant provides information about the mechanical restorative forces and is thus a measure of the maximum respiratory rate that can be selected as long as the patient is not obstructed. *Caution*: Some ventilators pose possible pitfalls with what is known as SIMV ventilation (synchronized intermittent mandatory ventilation). As soon as the patient becomes conscious and the "trigger criterion" (see below) is fulfilled, the respiratory rate can be driven so high by air hunger or agitation that complete expiration is prevented. It is recommended to pay particular attention to the manufacturers' different definitions of SIMV ventilation.

If expiration is too short, particularly in the case of respiratory obstruction, undesirable overdistension can occur due to air trapping as a result of insufficient expiration between breaths (prolongation of the time constants by airway obstruction [TC ↑ if compliance × resistance ↑]).

This means in practice that a zero expiratory flow is also to be expected in expiration until the new inspiration begins (note the flow curve on the respirator).

2.3 Distinction Between Pressure-Controlled and Volume-Controlled Ventilation

In principle, an adequate amount of gas should be forced into the patient per breath administered and then passively leave the lung in accordance with the mechanical restorative forces and airway resistances.

To this end, the patient can be administered a breath that is preconfigured by the ventilator (= *volume breath*). This is pushed into the patient in the set I-time. Depending on the volume distensibility of the ventilated lung (dV/dP = compliance) and the chosen inspiratory time, the respirator generates the required pressure.

This means that if compliance is too low (ARDS, hemothorax, pulmonary edema, etc.) or if the I-time is too short, very high pressures may be applied, which can then result in ventilation complications.

With purely volume-controlled ventilation, a phase without relevant gas flow directed to the lung develops in the phase from achieving the set volume to the end of the set inspiratory time (at best to compensate for leaks). Within this phase, the lung pressure reverts to a plateau level since the additive pressure required initially to overcome the airway resistances drops out.

(This is important for identifying compliance and resistance in the pressure-time diagram with purely volume-controlled ventilation and is discussed in detail at the end of this chapter [see also Fig. 2.5].)

In *volume-controlled ventilation*, the setting of a *pressure limit* on the ventilator is *essential* to prevent traumatic peak pressures.

Alternatively *ventilation* can also be set in a *pressure-controlled* manner.

In this case, the pressure set on the ventilator is administered to the patient over the duration of the inspiratory time – after an increase in pressure in the individually set inspiratory rise time.

If low opening pressures (correctly selected PEEP) and high compliance (as in a healthy lung) are present, appropriate tidal volumes (e.g., 4/7 mL/kg BW) can already be pushed into the patient with the selection of low peak pressures.

However, depending on the changes in compliance of the patient's lung, a considerable change in tidal volumes and hence respiratory minute volume (RMV) and the overall gas exchange situation can occur as a result. It is therefore mandatory to set *limits for the respiratory minute volume*.

(Differentiation of the curves in pure volume control vs. pressure control including explanation at the end of the chapter, where information can also be found on the PRVC (pressure-regulated volume-controlled) mode)

In conclusion, it is now understandable why ventilation is divided into inspiration and expiration, with gas flow occurring passively from the lung on expiration.

A positive pressure – relative to the atmosphere – prevails at *all* times in the respiratory tract (see advantages of PEEP), and pressure is exerted on the lung or a particular volume applied depending on the choice of mode. It has been shown at the same time the peak pressure in the lung is achieved device dependently at varying rates according to the level of gas flow or the inspiratory rise time.

In addition, the illustration of the time constants shows that there must also be sufficient time for pressure-passive expiration. This applies much more in obstructive lung disease than in parenchyma-related compliance disorders. Otherwise, overdistension of the lung can occur. Observation of the flow curve on the respirator serves this purpose.

The parameters for influencing gas exchange have been discussed so that the ventilation of the muscle-relaxed patient should *theoretically not provide a problem*.

Because of the considerable disadvantages associated with this form of management, most patients, however, should not be relaxed and therefore require synchronization. Among others, the reason for this is to reduce the need for sedation (see Sect. 2.4).

2.4 Synchronization

The aims of synchronizing ventilation, i.e., initiation of ventilation breaths very shortly after the start of the patient's breathing effort, are:

- To avoid higher pressures – which also reduces the risk of pneumothorax
- To improve work of breathing and to improve gas exchange
- To reduce the need for sedation
- To pave the way for extubation

The technological prerequisite here is that the respirator detects the onset of patient respiration and then triggers the start of inspiration.

The breathing effort can be detected by changes in muscle activity (chest or abdomen and esophagus), impedance changes of the chest, or by electrical signals on diaphragm activation.

However, current ventilators (still as yet) predominantly detect changes in gas flow or changes in gas pressure. When the changes are in gas flow, the patient draws gas over the sensor into the lung, and the sensor records this. In the case of changes in gas pressure, the patient breathes in gas that was intended to maintain the PEEP, and the ventilator records this.

However, the ventilator does not allow patient-triggered inspiration in each phase, since otherwise inspiration might occur again very shortly after the start of expiration. This means: The so-called *trigger window* is – depending on respiratory rate – not opened until sometime after the beginning of expiration (the trigger window cannot be varied by the doctor on many devices).

In addition, the breathing effort/amount of gas flow/pressure variation/impulse level at which this should be detected as the start of inspiration needs to be defined individually. Thus, if the trigger is too finely tuned, any thread of secretion can simulate inspiration through pressure or flow variations, whereas triggering cannot occur at all with too heavy a trigger and the patient ceases their spontaneous efforts.

It should be mentioned that the response time of the trigger on many devices is device-dependent and ranges from 10 to 40 ms, i.e., complete synchronization is therefore technically not possible.

One particular "quick" method of synchronization is provided by the derivation of the diaphragm electrical impulses by esophageal probe (NAVA probe, Maquet Solna, Sweden). In contrast to traditional "all-or-nothing" triggers, the electrical signal is also utilized quantitatively to influence the size of the support breath applied. Consequently, there is a potential for long-term savings on sedatives. Additionally and importantly, incorrect measurements that sometimes result from considerable leaks can also be avoided in noninvasive ventilation situations by the use of NAVA probes. Particularly in the case of long-term ventilation, lack of intubation, and severely impaired pulmonary compliance, the additional financial outlay for NAVA probes can be justified, as sedatives can be spared, progression of dyspnea quantified, and asynchronicity-induced pressure peaks avoided. (Detailed information in this respect can be obtained from the manufacturer.)

2.4.1 What Does Synchronized Ventilation Mean?

With modern ventilators, the mandatory administered breaths set on the user's side, i.e., the breaths administered at least per minute, are applied in a synchronized manner. If, over and above this, the patient should attempt further inhalations (trigger criterion fulfilled), these are not supported but occur at the given gas flow at PEEP level as in CPAP with continuous gas flow (actual *SIMV mode*).

Alternatively, *the SIPPV* (synchronized intermittent positive pressure ventilation) *mode* can also be chosen. In this case, each attempted breath that meets the trigger criterion is supported by a controlled breath as long as it is in the trigger window – the patients "determine" the number of defined breaths themselves.

Methodologically, there are modes between these two forms of ventilation that work with mandatory and additive pressure- or volume-supported breaths. In this case, the respirator generates a specific number of mandatory breaths, and any breaths triggered over and above this (trigger criterion fulfilled) are then supplemented according to the setting by the application of a predefined volume or pressure. In order to adapt the duration of such supported breaths to the patient's needs, the breaths end when the gas flow directed to the patient falls below a certain proportion of the maximum gas flow of the breath (expiration trigger). In this case as well, devices that utilize nerve or muscle impulses to detect inspiration and expiration offer more accurate synchronization.

Some devices specify a fixed inspiratory time in SIMV/SIPPV mode which, in the weaning of young patients in particular, is frequently considerably longer than the patient's spontaneous I-time and can thus oppose the genuine respiratory drive.

Equipped with suitable options, this problem can be resolved for example by means of pressure support ventilation (*PSV*). In this mode, inspiration is detected on the patient's side by means of flow triggers, not by a fixed I-time, but is also ended by means of patient triggering.

As described above, the respirator's algorithm uses the parabolic flow curve in the case of decelerating gas flow to end inspiration: for example, the expiration valve opens when the actual gas flow falls below 15% of peak flow. It is important that a maximum I-time is defined so that leaks with long-term peak flow do not simulate too long an I-time.

In the combination of PSV with a defined breath size – pulmonary mechanics permitting – the patient then expires at PEEP level of the continuous gas flow and is supported on inspiration only until the predefined Vti is reached (mandatory indication of upper pressure limit).

This can be used for pressure reduction on the device side as compliance improves (administration of SF) or in neuromuscular diseases for atraumatic long-term ventilation.

From what has been said, it is clear that it is important to know the mode of operation and nomenclature of the devices used, since on the one hand ventilation modes of various devices are not necessarily transposable and on the other hand studies for ventilation assessment can only be understood if it is known how the devices used work.

This can be described in summary as follows:

A distinction is made between flow-controlled, pressure-controlled, and volume-controlled ventilation. Either pulmonary mechanical function parameters (pressure or flow or thoracic impedance changes) or muscle or nerve signals are used to synchronize patient and device.

Through synchronization, the patients themselves determine the inspiration (with a latency defined by the device) – for which the trigger criterion must be defined.

The breath triggered on the patient's side is then administered and ended in different ways.

Completely mandatory breaths are applied with a predefined volume/PIP and predefined inspiratory time, in contrast to which "only" supported breaths are ended by a criterion for expiration. To this end, some manufacturers make use of the flow curve (discontinuation at a certain percentage of the maximum flow) or use muscle or nerve signals.

When the patient breathes completely spontaneously, pressure- or volume-supported ventilation remains at PEEP level – in this case, limit values for the respiratory minute volume must again be urgently defined. The aim of spontanization with sufficient lung function and sufficient respiratory drive as well as desired circulatory conditions is extubation or, in the event of prolonged ventilation, the sparing of sedatives by improved comfort through synchronization.

The technical options support staff and patients in estimating whether respiratory drive and alertness (and associated with this also the cough stimulus) are sufficient to extubate the patient.

All of this means that it is now possible to set the ventilation parameters meaningfully and to read off the ventilation situation and baseline lung function parameters from the ventilator.

How does that work in practice, however?

Broadly three situation scenarios can be distinguished:

- The patient is transferred postoperatively to the ward – which is described here
- The patient is electively intubated
- The patient is intubated as an emergency (on resuscitation)

2.5 Ventilation After Postoperative Transfer

The primary source for obtaining a picture of the patient's ventilation situation is an examination focused on the following aspects:

- Auscultation of the (hopefully bilaterally equal) breathing sounds
- Extent of chest excursion
- Read-off of ventilation parameters from the anesthesiologist's device
- Comparison with the preset device on the ward
- Also ask whether there were any specific ventilation features intraoperatively (intubation, ventilation disorders, difficulty breathing). Since in many places extubation is now attempted intraoperatively, it should always be asked whether there were any barriers to this process.

It should be noted postoperatively that all heart surgery can be associated with considerable lung changes:

- Surgically related intraoperative partial compression of the lung. This causes atelectasis, surfactant inactivation, inflammation, and hence possibly smaller intrapulmonary shunts
- Increased capillary leak on cardiopulmonary bypass (FRC ↓)
- Inhibition of breathing by pain
- Medicinal change in respiratory drive and pulmonary perfusion

In addition, preexisting lung diseases prior to surgery can obviously affect the postoperative ventilation situation.

Since increased capillary leak, a particular susceptibility to hypoxia, and possibly preexisting hyperhydration of the lung are to be expected in patients following cardiopulmonary bypass (CPB) surgery, the default settings for this case (depicted here for corrective cardiac surgery) are listed in Table 2.3.

Table 2.3 Basic setting for postoperative ventilation

	Mode	Volume (ml/kg)	PEEP (cmH_2O)	PIP (cmH_2O)	I-time (s)	RR (x/min)	Limits
Neonates	Pressure controlled (PC)	6–8	4–5	20–25	0.4–0.6	20–25	Pressure/RR/MV
Neonates e.g. Babylog[a]	Pressure-limited	On measurement 6–8	4–5	20–25	0.4–0.6	20–25	MV high and low – Flowmeter
Infants	PC, as needed PRVC	6–8	4–5	20–25	0.6–0.75	18–25	Pressure/RR/MV
Young children	PC, as needed PRVC	6–8	4–5	20–25	0.7–0.8	15–25	Pressure/RR/MV
Children	PC, as needed PRVC	6–8	4–5	20–25	0.9–1.0	13–22	Pressure/RR/MV
Adults	PC, as needed PRVC	6–8	4–5	20–25	1.0–1.5	10–15	Pressure/RR/MV

PC pressure control, *PRVC* pressure-regulated volume-controlled, *MV* minute volume, *RR* respiratory rate

[a]With flow-controlled, time-controlled ventilation ensures that the flow is set so that PIP is obtained in about the first third of the I-time – as described, observation of the flow curve also serves to set an inspiratory time adjusted to the patient's lung function

Lower peak pressures can usually be chosen for the postoperative admission of children *who have not undergone cardiac surgery*; otherwise the settings do not differ substantially.

As well as the clinical examination and the immediate previous history from the surgical procedure, the *X-ray* and the *initial blood gas analysis* are the guiding features postoperatively.

On the *X-ray*, particular attention should be paid to ensuring that all foreign bodies (tube, CVP, drains, gastric tube) are in the correct position and also that the lung is equally ventilated on both sides and the diaphragmatic domes are between the 8th and 9th ribs.

In the *first arterial BGA*, PaO_2 – here in the case of a corrected heart defect and recording from the artery – should be regarded as a measure of the oxygenation capacity of the lung.

Thus, for example, a PaO_2 of 200 mmHg postoperatively with FiO_2 of 100% despite 100% O_2 saturation of the blood can already indicate an impending lung function disorder. Under these conditions and with good ventilation, a healthy lung can generate a (pulmonary venous) PO_2 of over 600 mmHg beyond the neonatal age.

Where a blood gas analysis is performed postoperatively via the central venous line, it must be ensured that:

- The CO_2 values – and accordingly also pH – have changed relative to the arterial BGA. CO_2 about 5–10 mmHg higher, pH about 0.3–0.5 lower
- O_2 saturation should be regarded as a measure of peripheral O_2 supply. In this case, saturation measured by pulse oximetry (SpO_2) is regarded as a measure of the quality of the patient's oxygenation

Ventilation of the individual groups of heart defects and the associated weaning objectives will be discussed specifically below.

The essential preconditions for extubation on the patient's side *and* on the staff side are:

- Circulation functions well and without much support – *caution*: LV function might need PEEP!
- The lung functions well without any marked compliance disorder (not much pressure is required for good Vti) – an O_2 requirement of about 35% can readily be achieved in an extubated patient with a nasal cannula
- BGA is acceptable (criteria: PaO_2 >60 mmHg with FiO_2 <0.4 – serial circulation)
- No relevant bleeding/effusions and no marked CO_2 retention
- Patient is sufficiently conscious, not edematous; there is no evidence of diaphragmatic paralysis or relevant pleural effusions and no fever
- Extubation not at times of staff shortage, in the event of foreseeable difficulties only with experienced staff, only following discussion with the experienced member of staff

It is also useful to have alternatives ready for treatment of problems after extubation over and above the aids usually available at the bedside.

- Inhalational material and medications for swelling-induced stridor
- Guedel and Wendel tubes for airway stabilization
- Antidote (naloxone/flumazenil) for anesthetic hangover
- Tray for airway management if reintubation is required
- Resuscitation cart

2.6 Transpositions of Great Arteries

Corrective surgery of d-TGA in neonates also exhibits specific aspects in respect of the ventilation regimen (see Table 2.4):

- The aortic cross-clamp time (CCT) is usually very long (ca. 80–120 min) because extensive dissection is required, sometimes in deep hypothermia
- Neonatally there is a greater tendency to capillary leak – both in the lung and peripherally
- There is therefore frequently a substantial volume requirement and hence peripheral and pulmonary edema
- Neonates also have a higher resting O_2 consumption relative to their body weight and therefore require more alveolar ventilation (comparative Table 2.13 neonates vs. adults for pulmonary parameters at end of chapter)
- Because of the long CCT, severe myocardial dysfunction frequently occurs after about 6 h on the ward

Table 2.4 Example of neonatal ventilation (flow- and time-controlled and pressure-limited) post-ASO

TGA	Mode	PEEP (cmH_2O)	PIP (cmH_2O)	I-time (s)	RR (x/min)	Vti (ml/kg)	Flow (l/min)	FiO_2
Initially	(S) IMV	5	22	0.6	22	8	11–14	80–100
Oxygenation disorder		6–7 (X-ray!)	Increase	Increase		Note		100
Ventilation disorder		Increase, as FRC usually ↓	Increase (usually markedly)	0.6	Increase moderately	Note		

To select appropriate I-time, always note flow curve
ASO arterial switch operation (see Chap. 15)

- LV function can be overburdened postoperatively by systemic vascular resistance in the case of later surgery and already low preoperative pulmonary arterial resistances and thus predispose to backward heart failure

For the above reasons, it must be ensured in the direct postoperative phase that there is good oxygenation (SpO_2/SaO_2 over 95%, PaO_2 over 75 mmHg), balanced ventilation (CO_2 about 40–45 mmHg arterially), and a balanced pH (≥7.30). Since, in the event of a substantial capillary leak and a developing negative BE with intravascular volume deficiency, intravascular filling can only be compensated by considerable amounts of fluid, which then frequently disappear in the lung and interstitial tissue, many TGA patients develop a marked tendency to edema externally and an edema-related diffusion disorder in the lung.

Weaning generally cannot be performed until urine output ensures a negative balance, edema has been eliminated, and the often necessarily increased PIP has been reduced again (e.g., 20–22 mmHg with sufficient Vti or chest excursion). Additionally, patients with myocardial dysfunction and a need for ventilation are treated with analgesics/sedatives for tolerance of ventilation, reduction of the O_2 requirement, and for pain relief. It is therefore particularly important in this case to ensure the patient is sufficiently conscious. If lung function is good, the unphysiologically long I-time (e.g., 0.4 s) should be reduced before extubation in order to promote the patient's respiratory drive.

Supportive CPAP therapy is not infrequently required following extubation of TGA patients in the event of a persistent compliance disorder of the lung (edema) and respiratory drive disorder (opiates). Furthermore, as described, PEEP relieves the left ventricle.

2.7 Ventricular Septal Defect

During surgery for ventricular septal defect (VSD; see Table 2.5), ventilation difficulties generally only occur when surgery has been performed on large ventricular septal defects with large shunt volumes. In this case, the increase in pulmonary arterial resistance caused by the shunt-induced increase in pulmonary arterial flow is

Table 2.5 Postoperative ventilation after surgical closure of VSD

VSD	Mode	PEEP (cmH_2O)	PIP (cmH_2O)	I-time (s)	RR (x/min)	Vti (ml/kg)	Flow (l/min)	FiO_2
Initially	PC, as needed PRVC	5	22	0.8	16–20	6–8	Servo-i or other "adult" respirators	60–80
Oxygenation disorder		6–7 (X-ray!)	Increase	Increase		Note		100
Ventilation disorder		Increase	Increase (usually markedly)	0.8	Increase moderately	Note		

also found to an increased extent postoperatively. This results in a tendency to postoperative pulmonary arterial resistance crises (*PA crises*), which can result in RV failure and must be treated by a prolonged ventilation phase or systemic pulmonary arterial resistance-lowering agents (prolonged adaptation phase).

On the other hand, if surgery has been delayed, pulmonary infections may have occurred via the lung, affecting the postoperative ventilation regimen.

In both cases it should be borne in mind that Down's syndrome patients both tend to be more susceptible to infection and also exhibit an earlier increase in PA resistance.

In uncomplicated cases, the patient should be rapidly switched to synchronized/pressure-supported ventilation following ultrasound monitoring and the fulfillment of general postoperative assessment criteria and – where this has not already occurred during surgery – extubated with sufficient analgesia after a short time on the day of surgery itself.

If, however, there are contraindications to rapid extubation (trisomy 21, confirmed PA crises, problems with aspiration, pulmonary infection), the patient should be placed on controlled ventilation under analgosedation, when it is essential to avoid falls in pH, increases in CO_2 and desaturation, as well as uncontrolled aspiration and irritation maneuvers as triggers for PA crises.

The pulmonary vascular bed generally adapts within 1–2 days postoperatively so that the patient can then be extubated more safely.

Supportive sedation or also, as indicated, the use of a systemic pulmonary arterial vasodilator can be helpful in this respect. (This is examined in greater detail in Chap. 9 Pulmonary Hypertension.)

2.8 Atrioventricular Septal Defect and AV Canal

As in VSD, preoperative conditions (large shunt volume, previous infections, trisomy 21, patient's age) determine the postoperative ventilation situation.

Added to this, however, is the fact that in the case of prolonged valvular reconstruction, LV function may be impaired, while left atrial filling pressures may be increased if the ventricular size is not entirely balanced or postoperatively as a result of mitral valve stenosis or insufficiency.

The related considerable volume requirement and the weakness of the LV/valvular dysfunction can result in a considerable increase in pressure in the left atrium, which can culminate in pulmonary edema via pulmonary congestion.

If, therefore, in the postoperative adaptation phase (i.e., *extubation in the event of a marked increase in LAP in conjunction with a borderline surgical outcome preferably not on the day of surgery*), a deterioration occurs in the ventilation situation (PaO_2, CO_2), an X-ray is indicated at an early stage to exclude pulmonary edema.

A patient who sleeps for the first night after AV canal surgery (drip infusion with, e.g., fentanyl/midazolam) requires an increased urine output for drainage in the event of pulmonary congestion.

Patients with AV canal frequently have trisomy 21.

These patients not infrequently have pulmonary problems and specific physiological features that affect postoperative ventilation and weaning management:

- Tendency to pulmonary arterial resistance crises (PA crises)
- Sedation often with on/off phenomenon: Hypopnea alternates with massive agitation
- Increased mucus secretion, previous pulmonary infections (consider safeguarding tracheal secretion – early extension of antibiotics), and tendency to postextubation stridor

For these reasons a patient with status post AV canal surgery should, depending on the surgical outcome, be extubated only if LV function and heart rate are optimized (where necessary with a pacemaker) and following any reduction of afterload required to reduce pulmonary congestion, as well as X-ray monitoring of lung ventilation. In addition, physiotherapy after extubation can increase the chances of permanent success – that also is usually better during the day. If, however, all hemodynamic, pulmonary, and staffing requirements are met, early extubation can also be attempted after AV canal surgery (see Table 2.6).

Table 2.6 Postoperative ventilation after corrective surgery for atrioventricular septal defect (AVSD)

AV canal	Mode	PEEP (cmH_2O)	PIP (cmH_2O)	I-time (s)	RR (x/min)	Vti (ml/kg)	Flow (l/min)	FiO_2
Initially	PC, as needed PRVC	5	22	0.6–0.9 depending on age	16–20	8	Servo-i or other "adult" ventilators	100
Oxygenation disorder		6–7 (X-ray!), higher also if required	Increase	Increase		Note		100
Ventilation disorder		Increase, X-ray!	Increase (usually markedly)	0.8	Increase moderately	Note		

2.9 Ventilation in Glenn Anastomosis

In Glenn anastomosis (see Table 2.7), the venous blood of the upper half of the body is conveyed to the (usually right-sided) pulmonary artery. The drive force for the blood of the upper half of the body for perfusion of the lung is therefore the venous preload (hereinafter known as PAP) upstream from the pulmonary arterial vascular bed. Collateral vessels (azygos vein), if known, are closed. The arterialized blood mixes with the venous blood of the lower half of the body in the now common atrium under the systemic ventricle. The inferior vena cava pressure (CVP) prevails upstream from this atrium. The transpulmonary gradient (PAP – CVP) can be taken as a measure of resistance in the pulmonary circulation. It can be imagined that the lower the transpulmonary gradient is with good arterial saturation, the more easily the blood flows through the lung via the Glenn anastomosis and is oxygenated in the process.

For an understanding of the complex relationships between ventilation of the lung, intrapulmonary positive pressure under ventilation, and intrapulmonary shunt in ventilation disorders and effusions, some relationships need to be explained first of all:

- Low ventilation pressures stand least in the way of passive pulmonary perfusion via the Glenn anastomosis in ventilation
- Good alveolar ventilation without ventilation disorders reduces pulmonary arterial resistance (and reduces bronchial resistances)
- Oxygen, low CO_2 values, and NO (nitrogen oxide) reduce PA resistance
- Good systemic ventricular function with a leaktight AV valve reduces the need for CVP and thus indirectly reduces the transpulmonary gradient
- Good urine output prevents the development of interstitial pulmonary edema with an extended diffusion pathway

Table 2.7 Glenn anastomosis in SIMV + PS mode

Glenn	Mode	PEEP (cmH_2O)	PIP (cmH_2O)	I-time (s)	RR (x/min)	Vti (ml/kg)	Support	FiO_2
Initially	SIMV, PC + PS	4–5	24	0.8–0.9	12–15	10 (MV limits!)	Note MAP (7–8)	100
Oxygenation disorder		X-ray! If possible no higher	Increase	Increase		Note	Volume, NO, extubation	100
Ventilation disorder		(see above)	Increase (usually markedly)	0.8	Preferably do not increase	Note		

Please strictly note: Adapt end-inspiratory cycle in SIMV mode to patient's I-time, and set pressure support (PS) so that, e.g., 5 ml/kg, BW Vti is generated even in the supported breaths and at the same time the SIMV rate can be reduced – otherwise MAP also increases
RR respiratory rate

Unfortunately, however, a vicious circle often develops, in which, for example, respiratory acidosis requires increased ventilation, in turn resulting in poorer Glenn flow, while the acidosis itself increases PA resistance and promotes intrapulmonary shunts. In the event of reduced flow via the Glenn anastomosis (SpO_2 <70%), hypoxia can also result and only be corrected by volume replacement (increase in pulmonary blood flow). In the process, "excess" volume must be avoided in order not to overhydrate the lung (longer diffusion distances) and to prevent the formation of effusions, i.e., a vicious circle with increased ventilation requirement, increased intrathoracic pressures, lower pulmonary flow, increased effusion formation, etc.

The main focus should therefore be on the attempt to extubate the patient immediately postoperatively and do so with as little volume replacement as possible, a well-ventilated lung and a good saturation, since positive pressure ventilation then ceases to be an obstruction to pulmonary perfusion and the onset of the respiratory pump (= negative intrathoracic inspiratory pressure) can replace the right heart. With the onset of spontaneous ventilation, the patient must be rapidly transferred to a synchronized ventilation mode (e.g., pressure-controlled SIMV with pressure support or CPAP with pressure support) (or admitted already in this mode).

With some ventilators, it must be ensured that the onset of the patient's spontaneous respiration does not increase the mandatory ventilation breaths so much that the intrathoracic positive pressure of ventilation prevents passive pulmonary blood flow.

On no account should Glenn patients, in particular, suffer from longer air hunger on the respirator (or even after extubation). Otherwise, this could trigger pulmonary edema due to the severely negative intrapulmonary pressures induced on the patient's side. The choice of a sufficiently large ventilation tube also plays a role here.

Before weaning the patient from ventilation, their breathing and cough capacity should be assessed. In addition to the previously mentioned extubation criteria, it should also be ensured that the patient's analgesia is sufficient but not respiratory depressant, their circulatory status is stable, and an experienced physician is present at their bedside.

If extubation is not possible under these circumstances, ventilation in pressure-supported mode at CPAP level should be maintained under light analgosedation (clonidine/dexmedetomidine, ketamine, paracetamol and where necessary NSAIDs, to a lesser extent benzodiazepines).

Extubation may be successfully approached by instituting systemic PA vasodilation with, e.g., sildenafil, improved heart rate – *caution*: beta-mimetics! – after effusion drainage or improved anticongestive therapy (afterload reduction). (See postoperative therapy of individual heart defects.)

2.10 PA Banding in the Univentricular Heart

PA banding is used surgically in situations of univentricular hemodynamics to stem the blood flow to the lung. After neonatal adaptation, pulmonary vascular resistance here is about 25% of systemic vascular resistance. This way, the blood flow which otherwise would have chosen the route of least resistance is made available to the

systemic circulation. An arterial saturation of the patient of about 75–80% – corresponding to PaO_2 of about 40–50 mmHg – makes it possible to achieve a pulmonary to systemic blood flow ratio of about 1:1 (if not severe atelectasis formation results in intrapulmonary shunts).

Even at a saturation of 85%, about twice as much systemic flow recirculates through the lung, while at 90–95% the amount is quadrupled.

Thus, (transcutaneous) saturation can also be regarded postoperatively as a measure of the ratio of systemic blood flow to pulmonary blood flow (on condition that the lung is healthy).

By means of ventilation-induced changes in PA resistance, it is now possible to channel more blood to the lung – hyperventilation, O_2 administration – or to provide more to the systemic flow. To this end the patient is then kept permissively hypercapnic, FiO_2 at room air.

Extubation should then be attempted if at:

- (More or less) room air
- Tolerable pH values (from about 7.3 venous)
- Low ventilation rates
- Safe circulatory conditions are obtained

Besides BP and urine output, these also include primarily central venous saturation and ultrasound findings.

It is possible to exert a temporary effect on pulmonary flow by means of ventilation, during which time an attempt can be made to optimize systemic flow, for example, medicinally.

Nevertheless, success essentially depends on the intraoperative assessment of the banding effect. This must then be checked postoperatively by echocardiography.

At our center in Giessen, *systemic-to-pulmonary arterial shunt or BT shunt procedures* are hardly performed at all. Therefore, it will simply be emphasized here that only the simultaneous evaluation of lung function parameters (tidal volume, pressure requirement, O_2 requirement, and X-ray) and circulatory function parameters (clinical features, BP, urine output, central venous O_2 saturation (SvO_2), and ultrasound) will produce a correct interpretation of BGA, of transcutaneous saturation (SpO_2), and of the patient themselves for this conceptually very similar case and in all cases of *parallel* pulmonary and systemic circulation. In principle, the ventilation of patients with systemic-to-pulmonary arterial/BT shunt does not differ from those with PA banding (see Table. 2.8).

2.11 Ventilation of Larger Patients with a Serial Circulatory Situation

Examples of such situations include Ross procedure, homograft replacement, valve replacement, and noncardiac surgical patients.

As long as there are no abnormalities intraoperatively, these patients should be rapidly weaned from the respirator while bearing in mind the general criteria for

Table 2.8 Ventilation after pulmonary artery (PA) banding

PA banding	Babylog or similar mode	PEEP (cmH_2O)	PIP (cmH_2O)	I-time (s)	RR (x/min)	Vti (ml/kg)	Flow (l/min)	FiO_2
Initially	(S)IMV	4	20–22	0.4	22	6	11–14	21–25
Oxygenation disorder		SpO_2 <70% (X-ray!), banding too tight?	Excursion	Leave as is		Note		Increase moderately
Ventilation disorder		Aim for CO_2 60 mmHg	Note Vti	0.4	Increase moderately	Note		

Table 2.9 Ventilation after cardiac surgery with serial circulation

Large patient[a]	Mode	PEEP (cmH_2O)	PIP (cmH_2O)	I-time (s)	RR (x/min)	Vti (ml/kg)	FiO_2
Initially	PC, as needed PRVC	4–5	Limit	0.9–1.3	12–15	Approx. 8	70
Rapid switch	SIMV, PC + PS	4					Reduce rapidly
Oxygenation disorder		X-ray! Increase if necessary	(Increase)	Increase		Note and note MV	Increase, urine output↑
Ventilation disorder			Vti ↑, if OK, leave as is	Leave as is	Increase	Note and note MV	

[a]Serial circulation

extubation (see Table 2.9). A patient may be assumed to be capable of extubation if he or she;

- Is sufficiently communicative
- Has a strong hand grip on command
- Needs less than 35% oxygen for a SpO_2 of 95% (PaO_2 about 70 mmHg)
- Adequately expires CO_2 under a tolerable ventilation amplitude
- Needs not more than 22 cmH_2O of ventilation pressure for a Vti of about 6–8 ml/kg BW (with a suitable I-time)

Here, as well, it should be ensured that the patient has a Vti of about 5 mL/kg BW with pressure-supported mandatory breaths with a pressure support of, e.g., 10 cmH_2O.

If this is achieved, the number of mandatory breaths can be rapidly reduced, and, where this has not yet happened during surgery, the patient can be extubated.

2.12 Ventilation in Total Cavopulmonary Connection

As in Glenn anastomosis, positive pressure ventilation in total cavopulmonary connection (TCPC) surgery gets in the way of hemodynamics with passive lung perfusion. Given that most post-Glenn patients' respiratory pump is well trained, the venous blood should be aspirated by the inspiratory negative pressure in the lung, which is transferred to the pulmonary arterial vascular bed. Passive lung perfusion should replace the right heart (Table 2.10).

The more ventilation (MAP) the patient now receives, the more preload is required upstream from the pulmonary circulation for the blood to flow through the lung. As pulmonary resistance is frequently high and so extreme a preload is required to bring the total CO through the lung, many patients on TCPC obtain a so-called window between venous and atrial blood under the now single ventricle. This particularly applies to the case of a known increase in pulmonary resistance, leaky AV valve, impaired ventricular function or ventricular outflow tract stenosis.

However, as a result of the high preload required, abdominal and pleural effusions rapidly develop in these patients. Such effusions will hamper early extubation attempts and must be drained as soon as possible, i.e., bilateral pleural drains will be urgently required.

Rapid extubation should also be attempted in TCPC patients, preferably intraoperatively, in order to counteract the vicious circle previously described for Glenn anastomosis: The ventilation requirement is increased and results in an increasing volume requirement, effusion formation, and poorer cardiac output with reduced pulmonary perfusion.

If immediate extubation is not possible, the rapid introduction of synchronized ventilation, use of oxygen as a pulmonary vasodilator, where necessary NO ventilation or iloprost (Ilomedin) inhalation; the early systemic administration of a PA vasodilator (sildenafil) is recommended when there are no signs of an intrapulmonary mismatch. Under sufficient analgesia, early extubation can be undertaken with the doctor at the bedside.

Table 2.10 Ventilation after TCPC

TCPC	Mode	PEEP (cmH_2O)	PIP (cmH_2O)	I-time (s)	RR (x/min)	Vti (ml/kg)	Support	FiO_2
Initially	SIMV, PC + PS	4–5	22–24	0.9–1.2	12–15	8–10 (MV limits!)	Note MAP (7–8)	100
Before extubation					6–8			40

Oxygenation disorders in passive lung perfusion are more likely caused by defective pulmonary perfusion, a large window, low CVP, or mismatch (effusion). They are usually unresponsive to ventilation.

If extubation does not work, careful sedation with synchronized, preferably pressure-supported, CPAP ventilation should be attempted (here too it should be ensured that the patient obtains a Vti of about 5 mL/kg BW in the pressure-supported breaths with a pressure support of, e.g., 10 cmH_2O).

If this is achieved, mean airway pressure can be optimized, which improves pulmonary perfusion.

2.13 Ventilation on ECMO Therapy

In ECMO therapy, lung function can be completely or partially replaced. This is possible because, in ECMO, alongside circulation support, the blood is pumped through an oxygenator in which – depending on gas flow, FiO_2, and the proportion of CO maintained by the ECMO – the blood is oxygenated allowing CO_2 to be exhaled (see Table 2.11).

Insofar as the ECMO takes over the heart/lung function, this should allow the lung to be ventilated sparingly, as well as relieving the heart.

There is certainly general agreement about this, although the best means of sparing the lung continues to be disputed.

Essentially, however, some basic principles should be noted:

- Avoidance of FiO_2 above 50% – this can possibly reduce oxidative stress but definitely any tendency to atelectasis induced by marked O_2 absorption
- Avoidance of excessive tidal volumes to reduce volutrauma
- Avoidance of shear forces from excessively steep inspiratory rise times
- Avoidance of excessive peak pressures to reduce barotrauma
- Maintaining the lung open by selecting a higher PEEP
- Regular – not too early – evaluation of lung function:
  - On the respirator (which Vti with which pressure = compliance)
  - Clinically by auscultation
  - By X-ray
  - Preferably not by very traumatic manual bag ventilation

One fact plays a decisive role here: Even with only partially preserved RV function but markedly worse or absent LV function, the RV still actively pumps blood into the lungs. Because this blood is not carried away by the LV, it collects in the lung. As a result, deterioration of lung function with the development of pulmonary edema occurs within a very short time. If this situation persists, massive pulmonary bleeding can occur. Such bleeds in turn promote the development of ARDS and intravascular coagulation – particularly undesirable under ECMO therapy. Moreover, an increase in the patient's inherently triggered inflammation reaction is also induced.

Table 2.11 Example of ECMO ventilation

ECMO	Mode	PEEP (cmH_2O)	PIP (cmH_2O)	I-time (s)	RR (x/min)	Vti (ml/kg)	Support	FiO_2
Initially	PC or PRVC	6–8-12	22–24–28 set limits	Age-dependent fairly long	Age-dependent fairly few	2–4–6 set MV limits	Note PIP	30–40

Therefore, immediately on the patient's transfer, the question should be asked as to whether an overflow valve should be created at the atrial level (= desired L-R shunt or vent). If this has not been created surgically, lung function should be monitored very closely for the development of pulmonary edema (watery flesh-colored aspiration secretion).

As an example, Table 2.11 shows an initial respirator setting in ECMO therapy.

2.14 Ventilation in ARDS

See Table 2.12.

Fortunately, ARDS in childhood is generally amenable to therapy as long as it is not due to any untreatable underlying diseases. These mostly include oncological or preexisting massive lung disease such as BPD or CDH, congenital diaphragmatic hernia.

Nevertheless, there is a need to be sensitively aware of when a patient on ventilation has an increasing O_2 requirement and increasing mean airway pressure (MAP) with decreasing compliance. It is precisely at this point that the vicious circle of hypoxia, multiorgan failure (MOF), and increasing pulmonary arterial resistance needs to be broken, not only by ventilation but also by appropriate flanking therapy.

As well as suitable antibiotics (AB), this includes sedation, antipyresis, urine output (fluid restriction), CO optimization, high-calorie diet, regular bronchial hygiene, positioning, and physiotherapy.

In addition, ventilation strategies are aimed at ventilating and keeping as many lung areas open as possible with the least possible mean airway pressure. Moreover, a form of ventilation with decelerating flow should be selected since there is less of tendency with this to overdistend well-ventilated areas and not to reach obstructive ones (see Sect. 2.15).

The aims here are:

- Vti about 4–6 ml/kg BW
- PEEP above the opening pressure, if possible not above 12 cmH_2O for a sustained period (from about this level, the intrathoracic effect of the ventilation pressure starts to get markedly in the way of RV filling)
- I-time not (much) longer, when gas flows into the lung (note flow curves)
- Permissive hypercapnia with good pH (renal HCO_3^- absorption lasts 1–2 days)
- Ventilation based on rate and not on PIP
- (Early use of NO)

Table 2.12 Acute respiratory distress syndrome (ARDS)

Definition	Cause	Pathophysiology	Treatment approaches	Support
Patient over 4 weeks old	Pneumonia, aspiration	Alveolar injury, SF inactivation, alveolar collapse	O_2 administration, antibiotics (steroids)	Sedation, antipyresis
Noxae-induced acute pneumonia, secondarily due to shock, DIC, transfusion, pancreatitis	Lung trauma (mechanical/inhalational)	PMN invasion, mediator release, hyaline membranes	PEEP, ventilation, NO, SF administration	High-calorie diet, fluid restriction
X-ray with bilateral shadowing	Mediators, SIRS, sepsis, pancreatitis, mass transfusion, burns, collagenosis	Microvascular thrombosis, pulmonary and systemic hypoxia, ARDS → MOF, MOF → ARDS	Reduction in O_2 consumption, supportive agents, CO optimization	Bronchial hygiene, positioning and physiotherapy
Predominant oxygenation disorder (PCWP not measured)	Renal failure	Vicious circle	Shortened diffusion distance, CVVHDF, ECMO	

ALI (acute lung injury): $PaO_2/FiO_2 < 300$; ARDS, $PaO_2/FiO_2 \leq 200$. *CVVHDF* continuous venovenous hemodiafiltration, *DIC* disseminated intravascular coagulation, *MOF* multiorgan failure, *PCWP* pulmonary capillary wedge pressure, *PMN* polymorphonuclear neutrophils, *SIRS* systemic inflammatory response syndrome

A further increase (e.g., above 35–40) in oxygenation index under optimized ventilation (MAP / PaO_2) × FiO_2 is associated with a threat of pulmonary ECMO.

In patients with lung failure, the possibility of high-frequency oscillation ventilation (HFO) may be mentioned in passing, although its handling varies even more greatly across centers than conventional ventilation.

One particular option for standardized lung recruitment and for finding the best PEEP, as well as for lung-sparing ventilation, is the *Open Lung Tool* module from Servo-i, which will be explained separately further below.

2.15 Volume Curves/Explanation of Pressure-Regulated Volume Control

2.15.1 Volume Curves

The 2nd curve in the left diagram of Fig. 2.4 is intended to illustrate how, in the case of purely *volume-controlled* ventilation, gas flow is constantly high on inspiration until the set volume is pumped into the lung.

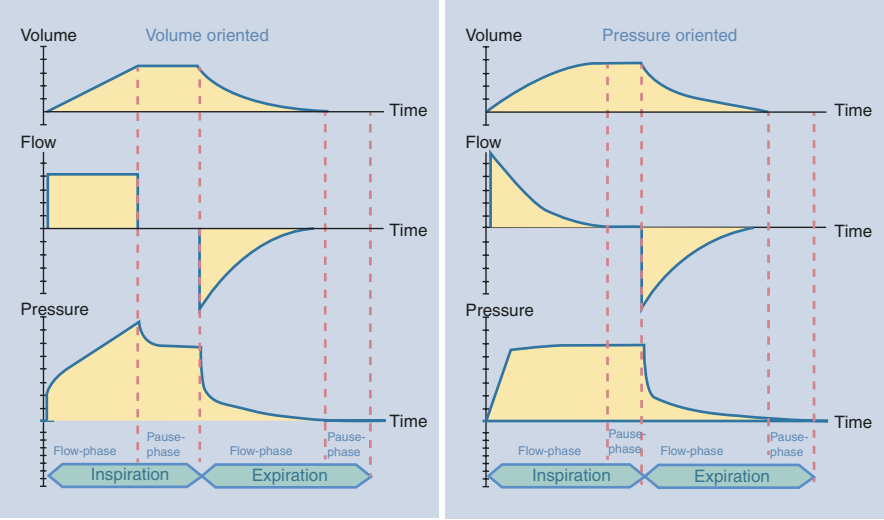

Fig. 2.4 Time course of volume, flow and pressure over the ventilation cycle in volume-controlled and pressure-controlled ventilation illustrating decelerating gas flow in the pressure-controlled mode. (Reprinted by kind permission of Drägerwerk AG & KGaA, Lübeck – all rights reserved)

In the rest of the I-time, there is no gas flow into the lung (with an airtight system) and the gas volume in the lung remains the same. In volume-controlled ventilation, the pressure initially increases steeply (resistance pressure) to overcome the airway resistance. In the subsequent phase of inspiration, a slower increase is then apparent until the complete administration of the set gas volume. Since no further gas then flows to the lung, no airway resistance (naturally total resistance of the thoracic/pulmonary system) needs to be bridged either, and the pressure falls to the plateau level. Expiration occurs pressure passively as a function of the time constants of the whole system.

By contrast, the pressure increases moderately steeply in *pressure-controlled ventilation* (as a function of the set inspiratory rise time), and the lung initially fills rapidly with a large gas flow. As the lung increasingly fills with air, the pressure gradient conveys less air into the lung. The flow *decelerates* to zero, the thoracic gas volume is maintained, and following the end of the I-time, the gas can dissipate pressure passively (see Table 2.13).

In the initial phase of lung filling, pressure in the system increases steeply with purely volume-controlled ventilation to overcome the given airway resistances. The pressure falls again by the same amount after the end of lung filling in the system to stay at the plateau level (resistance pressure).

Thus, in purely volume-controlled ventilation, the fall in pressure peaks occurring after the peak pressure is reached is an indicator of respiratory obstruction – resistance pressure.

Accordingly, only the set tidal volume is found in the plateau phase in addition to lung filling at the time of the effect of PEEP (FRC) in the lung (compliance pressure).

Table 2.13 Characteristic values of lung function parameters

Parameter		Neonates/infants	Adults
Alveolar number	mill./kg BW	8	4
Alveolar diameter	µm	60	250
I-time spontaneously	s	0.3–0.6	1.2
TV	mL/kg BW	6	6
FRC	mL/kg BW	30	30
Vital capacity	mL/kg BW	35	55
Resting O_2 consumption	ml/kg BW/min	6	3
VD	ml/kg	2	2
RMV	ml/kg BW/min	250	100
Respiratory resistance	mbar/l/s	60	6

FRC functional residual capacity, *TV* tidal volume

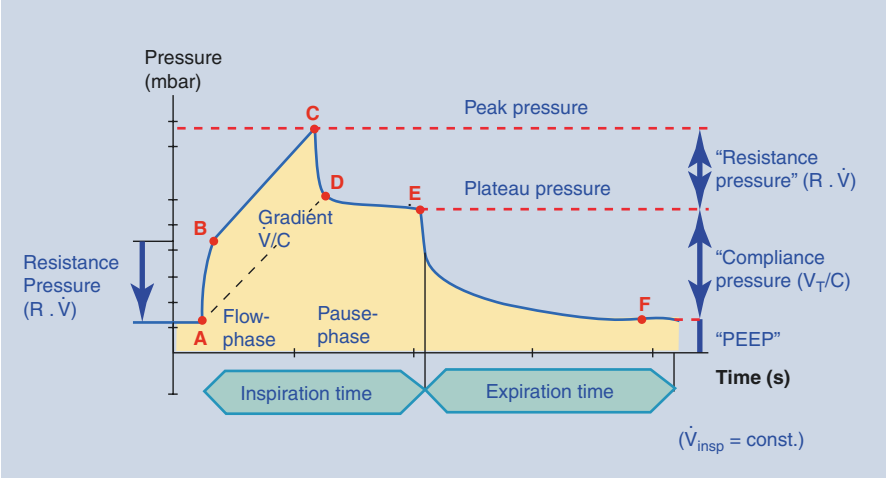

Fig. 2.5 Pressure-time diagram in volume-controlled ventilation. (By kind permission of Drägerwerk AG & KGaA, Lübeck – all rights reserved)

Therefore, the difference of plateau pressure and PEEP describes the pressure difference that must be applied to introduce the tidal volume. The closer point E is to point F, the better the pulmonary compliance.

What Is Meant by Pendelluft?

In diseases with increased airway resistances, these airway obstructions usually do not occur to the same extent in all areas of the lung. In volume-controlled ventilation, in other words, areas behind obstructions will be less filled, while areas with a good, i.e., relatively open, supply tend to be overdistended. This is due to the fact that volume is administered and gas flow conveyed constantly and not in decelerated fashion into the lung. This "swinging air" or pendelluft is one reason why it is preferable to undertake pressure-controlled ventilation in diseases with airway obstructions (Fig. 2.5).

In the pressure-controlled mode, the gas flow decelerates, the obstructed areas are slowly filled, and there is a more homogeneous filling of the lung with gas.

The Servo-i attempts to overcome the problem of "only volume-controlled" ventilation in the PRVC mode (pressure-regulated versus volume-controlled mode).

Here, the compliance of the lung is measured from inspiration to inspiration and the given tidal volume administered with the lowest possible pressure. Since, in so doing, the device administers the gas with decelerated flow, lung filling is more homogeneous. PRVC reduces the volutrauma to the areas with low airway resistances, while at the same time reducing barotrauma. The whole concept does not function well enough in severe obstructive diseases.

2.16 Recruitment Procedure Using the Example of the Servo-I Open Lung Tool

The Servo-i enables a standardized recruitment procedure which, after electronic processing by the device's processor, presents all relevant data on changing lung function parameters during recruitment. In principle, the maneuver can be performed with any ventilator in pressure-controlled mode, although it must then be documented by hand.

2.16.1 Application in Acute Lung Injury in Conjunction with Ventilation Disorders

The aims of the procedure are to open the lungs and thus to open underventilated areas and to determine the best PEEP at which the lung does not collapse between breaths. The result is that there is no cyclical opening and closing of the alveoli and shear trauma to the alveoli is minimized.

In addition, ventilation of the patient in the steepest part of the V/P diagram ensures that shear trauma and volutrauma are minimized. This frequently results in higher PEEP levels with relatively low PIP settings, but which still generate a suitable tidal volume.

With a standardized ventilation algorithm, the OLT (Open Lung Tool) thus allows *visualization* of pulmonary mechanics and primarily dynamic compliance – the parameter that best represents successful recruitment (see Table 2.14).

The course of the maneuver is standardized and undertaken with pressure-controlled ventilation and a *long I-time* (adults I/E 1:1, children I/E 1:2).

Documentation of PIP, PEEP, dynamic compliance (C_{dyn} = Vti / ΔP), and Vti

The maneuver proceeds in phases:

1. Recruitment
2. Establishment of the closing pressure
3. Reopening
4. Maintenance of the lung open
5. Parallel monitoring of arterial (invasive) BP, CVP, and where necessary PAP

Table 2.14 First phase – recruitment (all pressures in cmH_2O)

	Parameters before OLT (example)	Start	2nd step (2 min)	3rd step (2 min)	4th step
PIP	35	40	45	50	↓
PEEP[a]	15	20	20	20	20
ΔP	20	20	25	30	Gradual reduction until Vti returns to 10 ml/kg BW
Vti (ml/kg BW)	10	Increases slightly	Increases slightly	Increases slightly	10
Compliance	↑↓	↓	↓	↓	↑
RR	20	20	20	20	20
I/E	1.0/1.0	1.0/1.0	1.0/1.0	1.0/1.0	1.0/1.0

BW body weight, *OLT* Open Lung Tool, *Vti* = tidal volume
[a]To reduce shear trauma, initial PEEP should be about 5 cmH_2O above the expected closing pressure during the maneuver

A recruitment maneuver is described here by way of example – and in accordance with the video guide from Maquet:

1st Phase: Lung Recruitment.
The first or "recruitment" step starts with a PEEP of, e.g., 12–15 cmH_2O and a pressure amplitude of 20 cmH_2O (or the pressure amplitude with which a tidal volume of 8–10 ml/kg BW can be generated). With short-term incremental steps of PEEP up to 20 cmH_2O, an increase in Vti is identified initially and hence, with unchanged pressure amplitude, improved compliance. Following a further increase in pressure amplitude above 25 cmH_2O and 30 cmH_2O, Vti then no longer increases relevantly, and compliance therefore falls – the lung is recruited, and ventilation occurs in the area of pulmonary overdistension (stay here only a short time). Conversely, this ensures that all openable areas are recruited. However, increased lung injury is induced in the area above the UIP (see Fig. 2.1). Therefore, it is recommended to not ventilate for more than 1–2 min in this area.

In the next step of the recruitment phase (gradual reduction of ΔP until the preexisting Vti of 10 ml/kg BW is reached), the reduction in pressure amplitude occurs in 2 cmH_2O steps over several breaths with a constant PEEP of 20 cmH_2O.

In ARDS, a Vti of 4–6–8 ml/kg BW is to be preferred if ventilation is acceptable. Moreover, a PEEP of 20 cmH_2O can adversely affect hemodynamics so that recruitment can also be performed at a PEEP level of, e.g., 15 cmH_2O. The latter two statements particularly apply to children.

2nd Phase: Establishment of Closing Pressure
At the end of the 1st phase, PEEP is still, for example, 15–20 cmH_2O and ΔP about 20 cmH_2O (a value required to achieve the Vti of 10 ml/kg BW).

A slow reduction in PEEP follows, while ΔP is maintained.

This produces a rise in Vti and hence an increase in dynamic compliance.

Compliance reaches a peak, i.e., a plateau of compliance becomes established over several PEEP levels, and if this is exceeded, a *cyclical collapse of the alveoli* then again results in a reduction of compliance (Vti at constant ΔP). The maximum value can now be read off from the compliance curve generated in this way (after opening of the lung = in deflation), which if not reached results in a reduction in compliance (= closing pressure).

The closing pressure + a safety margin of 2 cmH_2O represents the PEEP set in the definitive ventilation.

3rd Phase: Short-Term Recruitment

In the *3rd phase* short-term recruitment is again undertaken as described above.

PEEP 20 cmH_2O and ΔP for 2 min over 20–25–30 cmH_2O until pulmonary overdistension corresponding to the maximum achievable ventilation (This phase constitutes the *reventilation phase*.)

4th Phase: Keeping the Lung Open.

The *4th phase* now uses the closing pressure +2 cmH_2O as PEEP to keep the lung open.

ΔP (which results in PIP) is now again reduced in steps of a few breaths to the value required to generate a Vti of 10 (in children 6–8) ml/kg BW.

The aim here is to ventilate the range of maximum pulmonary compliance (steepest area of the P/V curve, which happily often shifts to the left after successful recruitment = deflation curve), to avoid the cyclical collapse of the alveoli as an expression of shear trauma, and also to ventilate at a safe distance from the pressure of pulmonary overdistension.

OLT simply makes the necessary pressure levels and ΔP values visible, the recruitment step transparent, and thus the "best" ventilation parameters at this time of the disease phase quantifiable.

It is essential here to ensure that:

- Recruitment does not last too long
- Hemodynamics are closely monitored
- Monitoring is undertaken in parallel by means of BGA
- Frequent PEEP loss due to disconnection is avoided

Why is it desirable to ventilate at a relatively high PEEP level with low PIP settings?

What causes ventilator-induced lung injury (VILI)?

Influencing factors are:

- Volutrauma/barotrauma/shear stress
- Capillary leak from the terminal pulmonary vessels
- SF inactivation
- Cytokine and mediator release
- Repeated alveolar collapse and expansion

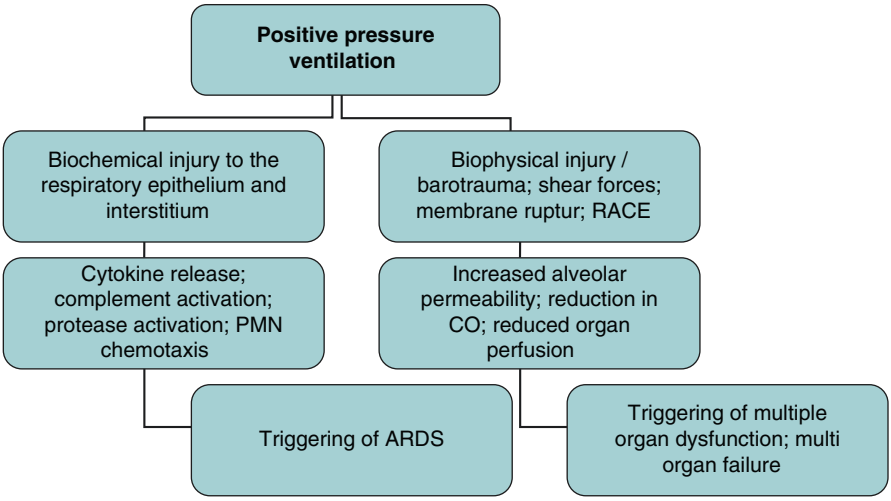

Fig. 2.6 Negative effects of positive pressure ventilation

- (RACE)
- Increase of intrathoracic pressure differences
- Overdistension (local and generalized)

This can have consequences on the lung itself (VILI exacerbates ARDS), on organ perfusion by reduction of CO and – mediator-mediated – in the exacerbation of SIRS (see Fig. 2.6).

2.16.2 Conclusion

Sufficient hemodynamic monitoring (BP, CVP, saturation, BGA, where necessary $etCO_2$ and PA catheter) is essential for the use of OLT.

The patient should exhibit a compliance disorder, ventilation at a high-pressure level, poor oxygenation, and noncardiac-related V/Q mismatch and therefore also need this time-consuming and labor-intensive maneuver.

The preconditions for performing this maneuver are an understanding of pulmonary mechanics (C_{dyn} = Vti / PIP – PEEP), pressure/volume curve, and the meaningfulness of using decelerating flow in late inspiratory alveolar opening.

Lung recruitment is fun but can also take place against the backdrop of complete interdisciplinary management of the patient and their organ situation, as depicted in Table 2.14 (ventilation in ARDS).

Sedation, antipyresis, urine output, CO optimization, high-calorie diet, regular bronchial hygiene, positioning, and physiotherapy as well as an open lung are all basic prerequisites for ARDS therapy.

The following are particularly suitable for an introduction to lung recruitment:

- Servo-i training record from Maquet (http://www.maquet.com/content/Documents/Brochures/FEATURE_maq_olt_pvm_050615.pdf) [12.09.12]).
- Servo-i demonstration video on OLT recruitment. This can be requested from Maquet.

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Cardiovascular Monitoring and Cardiovascular Drug Therapy

3

Dietrich Klauwer and Christoph Neuhaeuser

3.1 Parameters for Cardiovascular Monitoring

In the immediate postoperative phase following CPB surgery, there are:

- Instability of intravascular volume, e.g., due to blood loss or fluid shift from the intravascular to the interstitial compartment (capillary leakage).
- Peripheral vasoconstriction (in some cases also inadequate vasodilation or vasoplegia).
- Myocardial depression (myocardial edema, stunning [status post ischemia/reperfusion], altered working conditions of the heart [e.g., increased afterload]).
- In some cases incomplete rewarming with an additional fluid volume requirement.
- Altered hemodynamics without adaptation as yet to the new "flow conditions".

The initial assessment of postoperative cardiovascular conditions and ventilation status therefore plays a vital role.

Initial instruments for assessment (in this order):

1. Detailed handover by the anesthesiologist – what happened in the operating room?
2. Physical examination.

D. Klauwer (✉)
Department of Pediatrics, Singen Medical Center, Gesundheitsverbund Landkreis Konstanz, Krankenhausbetriebsgesellschaft Hegau-Bodensee-Klinikum, Singen, Germany

C. Neuhaeuser
Pediatric Intensive Care Unit, Pediatric Heart Center of Giessen, Children's Heart Transplantation Center, UKGM GmbH, Giessen, Germany
e-mail: christoph.neuhaeuser@paediat.med.uni-giessen.de

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D. Klauwer et al. (eds.), *A Practical Handbook on Pediatric Cardiac Intensive Care Therapy*, https://doi.org/10.1007/978-3-319-92441-0_3

3. Assessment of vital signs on the monitor (BP, heart rate, cardiac rhythm, CVP, response to changes in preload, afterload, and ventilation pressures).
4. Which vasoactive agents, sedatives, and analgesics were last given and when or are still ongoing?
5. Echocardiography.
6. Chest X-ray.

3.1.1 Admission History or Handover Report

In the history-taking during handover, it is particularly important to ask about the surgery carried out and its hemodynamic consequences; administration of catecholamines, milrinone, heart rhythm, and antiarrhythmics; bleeding and coagulation abnormalities; fluid volume administration; diuretics (e.g., after the end of surgery); ischemic time of the heart (aortic cross-clamping time); and duration of CPB (because of the possibility of SIRS).

Data on preexisting long-term medication (e.g., beta-blocker therapy) should be included in the calculation when preparing the patient's curve and writing postoperative orders.

3.1.2 Physical Examination

The physical examination is brief and objective-oriented:

- Chest excursion (relative to the ventilation setting)
- MC and peripheral circulation (recapillarization time, warm hands, and feet?)
- Heart sounds, shunt noise, pulmonary ventilation, rhythm
- Height of liver edge, abdominal palpation
- Bleeding from drains (amount and dynamics)
- All pulses
- Degree of vigilance and pupillomotor activity

3.1.3 Assessment of Pressures Displayed on the Monitor (Preferably in Comparison with the Anesthesia Monitor)

Blood pressure (for reference values see Table 3.2). Is the invasive blood pressure curve correct and readily interpretable? Is the blood pressure sufficient for perfusion of the coronaries, as well as of the brain and kidneys?

For coronary perfusion, diastolic arterial pressure should not fall below 30 mmHg where possible. Exceptions to this must be monitored very closely. For renal perfusion a *mean arterial pressure* (MAP) of at least <40–50 mmHg should be maintained as a function of urinary output (see also Chap. 4).

Systolic arterial pressure (= SAP) gives an idea of the ejection performance of the heart (or the interaction of SV and SVR). Rule of thumb for SAP (lower limit) in children >1 year: 70 mmHg +2 × (patient's age).

Detection of any arterial swing is important (i.e., ventilation-realted fluctuations of the whole arterial curve, which may occur, e.g., in association with fluid volume deficiency or pericardial tamponade).

CVP (Normal, 6–12 mmHg)

- Is the quality of the measurement good? (correct height?, good curve?, zeroing?)
- CVP as a marker of changes in fluid volume status and cardiac performance (assess the trend individually in each patient).

High values (CVP >14 mmHg) may be indicative of, e.g., poor cardiac performance in backward failure or tamponade, a diastolic compliance disorder of the (right) ventricle, or PHT.

Low values (CVP <6 mmHg) in association with arterial hypotension can suggest fluid volume deficiency.

PAP (Normal, <1/3 systemic)

In patients with a preexisting large L/R shunt and markedly increased pulmonary perfusion, e.g., a marked tendency postoperatively to pulmonary artery resistance crises (particularly in trisomy patients or in shunt defects with an L/R shunt that have not been operated on early enough; see also Chap. 9). The use of a transthoracic PA catheter is useful here as well as in the pulmonary hypertension that frequently occurs after heart transplantation (HTx) (see also Chap. 16). Ideally, the need for a PA catheter should already have been discussed preoperatively.

A PA catheter can be used for the invasive measurement of pressure in the PA (pulmonary artery) and also to determine the saturation of the PA blood (= true mixed venous saturation).

After a Glenn anastomosis, the filling pressure is measured from the indwelling CVC in the SVC (see also Chapter 15.12.1). This is usually also known as *PAP*. Although this pressure corresponds to the pressure in the pulmonary artery, it is a venous pressure. It is possible to estimate the preload before the pulmonary circulation by means of this pressure. By subtracting the CVP (in this case pressure in the IVC or atrium), the transpulmonary pressure (TPP) can be calculated as a measure of pulmonary artery resistance (TPP = PAP – CVP). In addition, SvO_2 (of the upper half of the body) can be determined via the CVC.

3.1.4 ECG

Heart rate normal? Pacer? Tachycardia, bradycardia (rare)? Rhythm? ST changes?

Including in particular: SR (sinus rhythm), AV dissociation with persistent slower rhythm (JET = junctional ectopic tachycardia), AV blocks (see also Chap. 11). For better diagnosis of a rapid rhythm (e.g., JET), an "atrial ECG" can be recorded via the pacemaker wires following cardiac surgery (see also Chap. 11).

3.1.5 Delta T (Normal, <3 °C)

Using an indwelling rectal/transurethral temperature probe, the temperature difference between the body core and the body shell can be determined by means of an additional skin probe (e.g., on the distal calf). It serves as a measure of peripheral perfusion (or microcirculation). A Delta T >3 °C may be the manifestation of a perfusion disorder or of centralization of the circulation.

3.1.6 Transcutaneous O_2 Saturation (Aim for SpO_2: Depending on Defect) as Well as Further Parameters of Adequate Oxygen Supply (and Organ Perfusion)

Target saturations must be defined for each individual patient.

On the one hand, SpO_2 can provide evidence of pulmonary function or oxygenation (depending on the defect and relative to FiO_2) while additionally being a measure of the blood's O_2 loading (see also Chap. 1). The signal quality must be checked, since in some cases like centralization or cold skin, it is not possible to evaluate SpO_2.

Mixed Venous Saturation (Normal: About 25–35% Lower than SaO_2)
As an estimate of the body's O_2 balance (for explanations see Chap. 1).

Urine Excretion (Normal: See Sect. 3.4)
Since vigilance as an indication of the quality of cerebral perfusion is not always evaluable postoperatively because of the effect of medication, the determination of the quantity and concentration of the urine is of particular importance in assessing cardiovascular function.

However, as diuretics may, if necessary, have been given at the end of surgery in conjunction with anesthesia (not standardized), the quantity of urine in the first 2 h postoperatively may be deceptive. Otherwise inexplicable postoperative acute oliguria/anuria, as well as an increase in lactate (normal: <2 mmol/L), should be interpreted as an indication of possible circulatory dysfunction (low output). Oliguria may occur before the increase in lactate.

NIRS (Near-Infrared Spectroscopy; Normal: 60–80%)
A continuous, noninvasive, light adsorption-based method for estimating oxygen supply in tissue (e.g., of the brain or kidneys) (penetration depth about 2–3 cm). Changes can be due to both local (e.g., vasoconstriction in hyperventilation) and systemic factors (e.g., anemia or low output). As NIRS predominantly records venous saturation (arterial/venous = about 1:3), in the case of normocapnia and

stable Hb, there is usually a good correlation between NIRS saturation (e.g., measured at the forehead) and SvO_2 (NIRS = SvO_2 ± 5–10%). For cyanotic defects, the normal value for NIRS saturation is about 20–30% lower than SpO_2. If the difference between NIRS and SpO_2 increases (>30–40%), this usually indicates low output postoperatively (in the absence of hypocapnia).

3.1.7 Which Vasoactive Agents, Sedatives, and Analgesics Were Last Given and When or Are Still Ongoing?

As each handover of a patient represents a considerable potential source of error, it is vital to check immediately whether the medications are all being administered as reported verbally.

3.1.8 Echocardiography

In addition to the information from the anesthesiologist, a rapid postoperative ultrasound scan has a vital role to play in assessing the cardiovascular situation. Nevertheless, the conditions can be substantially affected by bandages, drains, and the ventilation situation.

The following should be assessed first of all:

- RV and LV *function* (contractility *and* relaxation, where necessary VTI as a measure of SV)
- Valve functions (all four heart valves)
- Obstructions of the outflow tracts (LVOT and RVOT)
- Residual defects (e.g., after VSD closure)
- Artificially created connections (status post AP shunt, TCPC window, PFO)
- Artificially created stenoses (status post banding)
- Assessment of right ventricular pressure (or PAPs)
- Perfusion in end arteries (e.g., celiac trunk).
- Pericardial and pleural effusions, as well as any hematomas. (In neonates, a cranial ultrasound can be performed at this opportunity.)

In assessing right ventricular pressure, each measurable (= dopplerable) gradient should be determined and the resulting pressure difference put in relation to the invasive pressures.

Together with the vital parameters and all measured data, the values mentioned should be integrated to obtain an overall picture which is then immediately evaluated by a team highly experienced in managing complex cases of this nature. Essential questions about the postoperative hemodynamics can best be answered in this way. The clinical course is of particular importance in this respect, since sudden hemodynamic changes can be common and need to be viewed in the context of the patient's previous status. The aims of treatment can also be defined here within the team.

3.1.9 Chest X-ray

The following features must be described on the postoperative chest X-ray:

- Position of all foreign bodies introduced (e.g., tube tip at the level of the clavicle? CVC tip at the level of the carina? Intrapleural drains? Extrapleural drains?); correct any positioning as needed.
- Cardiac silhouette and mediastinum (enlarged? hematoma? effusion?).
- Diaphragm (visible? height?).
- Pulmonary parenchyma (infiltrates? pulmonary edema? atelectasis?).
- Pleural space (pneumothorax? effusion?).

3.1.10 Summary

In order to maintain the peripheral and central O_2 supply, it is necessary to ensure both sufficient cardiac output and a minimum (adequate) perfusion pressure for the organs. The abovementioned values (see also Tables 3.1 and 3.2) also provide a basis to guide postoperative cardiovascular therapy.

Compensation is frequently possible if the vital values should fall below the limits only briefly, whereas profound or persistent changes can have severe consequences (reduced cerebral and coronary perfusion).

Table 3.1 Circulatory goal

Parameter	Therapeutic goals
Blood pressure (BP)	Usually, to achieve the lowest BP with good "values" while ensuring coronary and organ perfusion with the lowest possible afterload
Heart rate (HR)	Avoid tachycardia (>150/min) to achieve better myocardial O_2 balance. Treatable causes for tachycardia (fever, pain, fluid volume deficiency, tamponade) must be excluded. HR may be raised by using the external pacemaker to increase cardiac output (where necessary)
Cardiac rhythm	Sinus rhythm is preferred. In JET or AVB, AV synchrony should be established (where possible) by using the external pacemaker. Arrhythmias with circulatory compromise must be treated aggressively (e.g., medication, cardioversion)
Central venous pressure (CVP)	To optimize preload! If CVP >14 mmHg with hepatic congestion, rule out RV failure, RV obstruction, PHT, and/or tamponade? In TCPC/Glenn, is CVP (or PAP) sufficient for passive perfusion?
SvO_2	Preferably 20–30 points below SaO_2
Temperature	Avoid fever, since it raises O_2 consumption and HR. active cooling may therefore be necessary (beware of coagulopathy <34 °C). Use cooling for brain protection (and JET therapy)
Extubation	Early extubation is preferred, since it usually improves hemodynamics and renal function. Caution must be applied in patients with PHT and marginal left ventricular function.
Sedation	May be advantageous in patients with marginal ventricular function (to balance VO2/DO2). A disadvantage is often the need for more circulatory support (e.g., catecholamines)

Table 3.2 Lower limits of blood pressure – reference values by age/weight

	Mean arterial pressure (mmHg)	Systolic arterial pressure (mmHg)
Neonates	40	50–60
4–8 kg	45–50	60–70
10–20 kg	50–60–65	70–80
Older children/adults	70–80	90–100

3.2 Basis of Postoperative Cardiovascular Therapy

3.2.1 Milrinone, Ventilation, and Normal Ionized Calcium

Milrinone (Corotrop®), an "inodilator," appears ideal for postoperative therapy in pediatric intensive care medicine (see Table 3.3). It improves contractility and probably also diastolic relaxation of both ventricles without any relevant increase in myocardial O_2 consumption. At the same time, it causes a reduction in afterload by direct vasodilation. If preload is sufficient (or optimized), the increase in stroke volume compensates for the fall in blood pressure induced by vasodilation. However, in the presence of fluid volume deficiency and/or marked vascular responsiveness, this can result in arterial hypotension (particularly in adults). Its effect on pulmonary vascular resistance is discussed in Chap. 9 (pulmonary hypertension). In some cases, (high-dose) milrinone therapy can result in unwanted tachycardia (with a subsequent increase in myocardial O_2 consumption).

The beneficial effects of ventilation on the circulation are discussed in Chap. 2, including the fact that controlled ventilation usually tends to be counterproductive (particularly in Glenn, TCPC). The benefits of early extubation are presented in Chap. 18. It is generally the case that ventilation must be adjusted to obtain the "best cardiac output" (e.g., optimal PEEP).

Neonates and infants in particular are very "dependent" on normal ionized calcium. A fall in extracellular Ca^{2+} levels can result in a reduction in contractility (negative inotropic effect) and hypotension (vasodilation) (Table 3.3).

3.3 Volume Replacement Therapy

3.3.1 Theoretical Fundamentals

The blood volume is distributed between the vessels and the heart. It is also referred to as intravascular volume. The constancy of the intravascular volume is normally hormonally governed (e.g. RAAS, ADH). Intensive care patients usually cannot respond sufficiently themselves to changes in their volume status; this must be monitored and controlled "externally."

While the arteries essentially act as a "conduit" (e.g., aorta) and "distributor" (e.g., arterioles, resistance vessels) of the bloodstream, one of the tasks of the venous system is to serve as a "reservoir." The volume of blood, on the one hand, and

Table 3.3 Basic cardiovascular therapy

	Effect	Dose	Therapy	Draw-up	PVC	Adverse reactions
Milrinone	Inhibits breakdown of cAMP, O_2 ↑, consumption constant	0.25–0.75–(1) µg/kg body weight/min	Acute and long-term	Dilution with: NaCl 0.9%, G5%, G10%; 3–20 kg: 10 ml Milrinone to 50 ml total >20 kg: 20 ml Milrinone to 50 ml total	OK	Hypotension, cardiac arrhythmias, thrombocytopenia, liver enzymes ↑, renal excretion, bronchospasm
PPV	Reduces O_2 consumption, reduces left ventricular afterload, increases right ventricular afterload		Acute			See ventilation (Chap. 2) for further explanation
Calcium-Gluconate 10% (1 ml = 100 mg Ca^{2+})	Increases contractility and causes vasoconstriction	1 ml/kg/d as continuous infusion; 0.1–1 ml/kg as iv-bolus; aim for ionized Ca^{2+} >1.2 mmol/l	Continuous Ca^{2+} -infusion in the first 48 h postoperative; iv-bolus, if Ca^{2+} -value is <1.0 mmol/l	NaCl 0.9%, G5%, G10%	Less preferable	None at correct dose. Caution: Electromechanical decoupling on rapid administration possible!

PPV positive pressure ventilation, *cAMP* cyclo-3′,5′-adenosine monophosphate

venous vessel tone, on the other, result in a positive pressure prevailing in the venous system. This pressure increases with an increase in blood volume and/or vessel tone. The heart receives the returning venous blood and pumps it on (the direction is determined by the valves). To this extent, the heart is in direct contact with the pressure conditions pertaining in the venous system. The two "components" have a reciprocal effect on one another. As a result of the fact that the heart empties in systole before refilling in diastole, a "suction effect" is produced that contributes to the reduction in central venous pressure. The pressure difference between the venous pressure in the venules and the central venous pressure provides the driving force for the venous return (= cardiac output). If cardiac function deteriorates, CVP then increases and cardiac output decreases ("backward failure").

On the other hand, an increase in venous return (e.g., by increased tone of the venous system, change of position from standing to lying, or increase in blood volume) results in an increase in diastolic ventricular filling. The contractile myocardial filaments are stretched and the end-diastolic volume (EDV) is increased. This is also known as preload. With the increase in EDV, in line with the *Frank-Starling curve,* stroke volume and, hence, cardiac output increase. The steeper the Frank-Starling curve, the more pronounced the effect (see Fig. 3.1). End-diastolic pressure and end-diastolic volume are related to one another through the corresponding ventricular compliance ($C = \Delta V/\Delta P$). In clinical practice, therefore, RAP or CVP (for the right heart) or, respectively, LAP (for the left heart) is frequently used as a surrogate for preload. While studies show that the absolute values of these pressures are not suitable for estimating either blood volume or preload, nevertheless they can provide important information in the individual patient as trend parameters.

CVP thus represents the product of two "forces": (1) pressure in the venous system (determined by blood volume and vessel tone) and (2) heart function (although further influences from ambient pressures, e.g., intrathoracic pressure, etc., may also contribute).

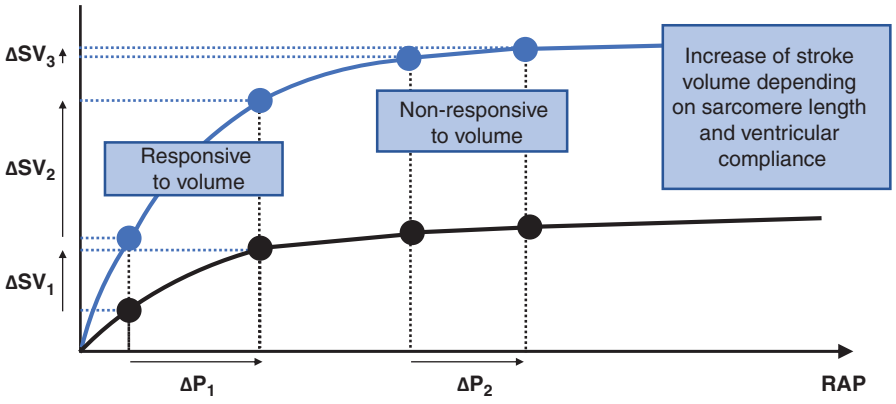

Fig. 3.1 Frank Starling curve

The aim of volume replacement therapy is essentially to restore intravascular volume and to optimize cardiac output via ventricular filling. The determining factor in this respect is whether the ventricle can respond to volume loading with an increase in stroke volume. Since ventricles in the steep slope of the Frank-Starling curve increase their SV very significantly, they are termed preload-responsive or preload-sensitive. With increasing end-diastolic ventricular volume, however, the curve becomes flatter, and an increase in SV is then less and less likely to be achieved by further filling of the ventricle. Hearts working in the flat part of the curve can therefore be described as "preload-insensitive." The same applies also to failing, dilated hearts as their Frank-Starling curves usually tend to follow a flat course (see Fig. 3.1, black line and circles).

Causes of Postoperative Fluid Loss

Following general surgery, there are a series of changes that occur that can contribute to a reduction in intravascular volume, e.g.:

- Blood loss.
- Fluid shifts from the intravascular to the interstitial compartment (e.g., capillary leakage).
- Fluid losses into the "third space" (e.g., ascites, effusion).
- Blood volume redistribution by peripheral vasodilation (e.g., vascular regulation disorders) and temperature variations (e.g., rewarming).

These processes require a constant reassessment of fluid volume status in the postoperative phase. *Fluid must be administered after almost all CPB surgery.*

Symptoms of Fluid Volume Deficiency

In most cases, *arterial hypotension* is a reason for considering a fluid bolus. Further evidence of a fluid volume deficiency can be obtained from the assessment of CVP; the response to pressure on the liver, but also from heart rate; the arterial curve; and echocardiography.

The *classic constellation* is characterized by:

- Low blood pressure and low CVP.
- Sinus tachycardia.
- Breathing-related fluctuation of the arterial curve.
- Where applicable, restricted peripheral perfusion as a consequence of any reduction in cardiac output (e.g., prolonged recapillarization, marbling, cold extremities).
- Concentrated urine (where applicable oliguria).

In practice, however, not all the symptoms mentioned need be present concurrently. Ultrasound shows:

- Reduced end-diastolic LV volume with good systolic function (e.g., kissing walls).

- Collapse of the inferior vena cava (normal diameter at the level of the liver: IVC = DAo).

Other disorders that compromise the circulation (tamponade, residual shunts, outlet stenoses, valve insufficiency, PHT, etc.) will obviously also be identified on echocardiography, and these will require measures other than volume replacement therapy.

Indication for Fluid Administration

Whether a patient requires or benefits from volume replacement will not only be determined by the position of ventricular filling on the Frank-Starling curve (see above), but above all by their clinical status. Fluid administration is only beneficial in patients when it results in *a clinically necessary* increase in cardiac output, blood pressure, and organ perfusion.

The question therefore is not only "Is the heart preload-responsive?" but specifically "Does the patient need better cardiac output or higher blood pressure?"

Examination of the patient for volume responsiveness. Whether or how the ventricle responds to fluid volume administration (fluid challenge) must be established individually in each patient. It is possible to ascertain this even without administering an intravenous fluid bolus. While observing the monitor, (gentle) pressure is exerted on the liver in neonates, infants, and small children. This causes the heart to fill by mobilizing a certain amount of blood. The same effect is obtained in schoolchildren, adolescents, and adults by raising their legs. Otherwise, a bolus of, for example, 5–10 mL/kg Ringer's solution can be administered as a trial dose.

Finding the *"optimal" ventricular preload* is vital for cardiovascular therapy. The absolute CVP value is less important here than the corresponding changes in blood pressure and CVP on fluid volume administration. The determining factor is that the increase obtained in blood pressure is relatively greater than the increase in CVP (e.g., increase in SAP from 50 to 65 mmHg, while CVP increases from 8 to 10 mmHg). In hypertrophic or relatively stiff ventricles (low ventricular compliance), further fluid volume administrations, for example, may be useful in increasing SV despite an already increased CVP. The ultrasound can also provide valuable information here for "optimizing" ventricular filling (see above). In addition, a clinical improvement in peripheral perfusion should be identifiable (e.g., increase in urine output).

Procedure for Fluid Volume Administration

The patient's status determines the *amount and rate* of volume replacement. If there is an acute or critical fluid volume deficiency, volume replacement must be undertaken rapidly. In the event of heavy bleeding or deep hypotension with signs of shock, this should be done, for example, "by hand." In this case, the fluid volume bolus is administered rapidly by syringe via a venous access (e.g., PVC, CVC) while observing the monitor. The following syringe sizes are possible, depending on the child's weight: 10 or 20 mL in neonates, 20 or 50 mL in infants, and 50 mL in children.

Slower replacement is usual in patients whose losses cause only mild fluid volume deficiency symptoms, or in whom there is a concern that overly rapid administration might place excessive demands on the ventricle. The latter include, for

example, patients who either have high-grade impairment of ventricular function (EF <20%) or very stiff, small ventricles (e.g., restrictive cardiomyopathy). In this case slow fluid volume administration over 30–120 min appears appropriate.

The fluid volume administered must be made dependent on the ventricular response and any clinical changes. A fluid volume bolus of 10 mL/kg is usually given initially. This can be repeated several times as required (at doses >40 mL/kg and in the absence of success: reassess the situation).

Type of Fluid Volume Replacement

The *type of fluid volume replacement* depends on the circumstances. If bleeding persists after surgery, primarily blood products (fresh frozen plasma [FFP], concentrated red cells [CRC] (see Table 3.4.), platelet concentrates [PC]) should be used to replace losses (see also Chap. 8). Otherwise, crystalloid volume expanders such as Ringer's solution and 0.9% NaCl are the solutions chiefly used. However, it is important to realize that the "crystalloids" are distributed throughout the entire ECS. After the infusion of 400 mL Ringer's solution, only 100 mL remain in the vascular system, whereas the remaining 300 mL disappear in the interstitium. In other words, to replace a blood loss of 100 mL, about 400 mL Ringer's solution is required to replenish the intravascular volume. Alongside the abovementioned blood products, colloidal volume expanders like hydroxyethyl starch (HES), gelatin, and human albumin (HA) produce a better "volume effect." Of these, we use only HA in children (HA 5% has a volume effect of about 100%, i.e., of 100 mL HA 5%, 100 mL also remains in the intravascular compartment). After CPB with capillary leakage, however, HA can also disappear into the interstitium, where it may then "bind" water in the tissue.

Detrimental Effects of Volume Replacement Therapy

After optimization of preload and ventricular filling, any further fluid volume administration must be critically assessed. Otherwise, a volume overload of the patient can cause edema to form (e.g., pulmonary edema, effusions, etc.), which in turn is detrimental to organ function. When large quantities of Ringer's solution and/or 0.9% NaCl are used, this can also result in hyperchloremic acidosis (see Chap. 1), in addition to which coagulation factors and plasma proteins can be critically diluted. Caution should also be exercised in the case of hearts with very poor systolic ventricular function and already increased EDV. Unnecessary fluid volume administration increases wall tension without the patient benefiting from a marked increase in SV (preload-insensitive).

In the event of impending or existing fluid overload, this therefore must be corrected promptly with diuretics (or by renal replacement therapy, RRT). To prevent excessive edema formation where there is a continuing need for volume replacement, noradrenaline can be used cautiously to stabilize blood pressure while monitoring peripheral circulation and SvO_2 (and given acceptable ventricular function). This intervention frequently "saves" on fluids, the children do not "swell up" so

Table 3.4 Hb reference values

	Good postoperative general status	Poor hemodynamics, SvO_2
Ø Cyanotic	>8 g/dL	>10 g/dL
Cyanotic	>10–12 g/dL	>12–14 g/dL

much and can be weaned more easily from ventilation, for example, after overcoming the postoperative phase.

During optimization of fluid volume status, an ultrasound examination is performed at the outset to ascertain whether any other hemodynamic problems are present that compromise the circulation:

- Is there an increase in right ventricular afterload (e.g., PHT) resulting in RV dysfunction? Does this need to be treated – e.g., by sedation, optimization of ventilation, or use of NO?
- Are diastolic filling and contractility affected by tachycardia or a rhythm disorder?
- Is diastolic compliance reduced by postoperative (CPB-induced) swelling? Could chest opening help ("dry tamponade", see Sect. 14.4.1)?
- Are any unexpected surgically induced anatomical changes present?
- Does LV function need to be supported pharmacologically (*Caution*: catecholamines increase myocardial O_2 consumption!), or can left ventricular function be improved by a reduction in afterload?

3.4 Improvement in Cardiac Output by Afterload Reduction

In hearts with impaired systolic function and high end-diastolic volume, a reduction in afterload can contribute to a marked increase in stroke volume. These hearts can also be described as afterload-sensitive. The aim is to economize heart work, i.e., increase cardiac output without causing an increase in myocardial O_2 consumption.

A classic example is found in DCM or ALCAPA, i.e., in patients with extremely severe systolic LV failure (EF <20%). Despite a massively reduced SV, the diastolic blood pressure may still be very high because of the increased sympathetic tone. It is therefore the manifestation of increased systemic vascular resistance (SVR). The blood pressure amplitude in this case tends to be small, the patient centralizes (cold periphery), and SvO_2 is reduced because of the low cardiac output. In this situation, a reduction in afterload (i.e., in SVR) can contribute to both an increase in cardiac output and an improvement in peripheral and central O_2 supply. The decrease in blood pressure associated with the reduction in afterload can be tolerated as long as organ perfusion is ensured (the motto here is: flow is better than pressure).

Also in the case of heart defects (e.g., HLHS) or of palliation (PA banding, systemic-to-pulmonary artery shunt) with parallel pulmonary/systemic circulation, a reduction in SVR (by arterial vasodilation in the systemic circulation) can increase blood flow to the benefit of the systemic circulation. The reduction in pulmonary perfusion here also provides concurrent treatment for any existing heart failure.

In principle, the sparing of heart work by reducing afterload is a central component of treatment for any patient with impaired left ventricular function and is therefore a pillar of postoperative circulatory management, for example, after prolonged CPB surgery.

A reduction in afterload can initially be achieved by adaptation of analgesia/sedation, use of physical measures for temperature control, and positive pressure

ventilation (temperature control, e.g., central cooling and peripheral warming with warm packs). If that is insufficient or if ventilation needs to be avoided for the reasons described, a systemic vasodilator can be introduced via a drip (drip infusion) under close blood pressure monitoring (any vasoconstrictors should where possible have been discontinued beforehand). To stabilize blood pressure, it may be necessary to add fluid carefully (the motto is: "Open up and fill up"). As previously mentioned, the aim is to achieve an improvement in cardiac output by increasing stroke volume. If the increase in SV offsets the reduction in SVR, the blood pressure remains relatively constant (with increased blood pressure amplitude as a result). Apart from inodilators such as milrinone (see above), the first-line drugs of choice are clonidine/dexmedetomidine, sodium nitroprusside, but also phentolamine and urapidil (see Sect. 3.5 and Table 3.5). Preoperatively initiated levosimendan therapy is also an option.

For the longer-term reduction of afterload, the use of an ACE (angiotensin-converting enzyme) inhibitor is indicated. At the Giessen Pediatric Heart Center in Germany, the authors prefer lisinopril. A precondition is usually that the patient is tolerating enteral nutrition (oral administration), and the circulation is to some extent stabilized (i.e., discontinuation of administration of noradrenaline). In shock or in borderline compensated renal failure, ACE inhibitors can result in anuria. Intravenous ACE inhibitors have not become established because of their long half-lives and the lack of predictability of their effect in direct postoperative therapy.

3.5 Intravenous Vasodilators

Intravenous vasodilators (see Table 3.5) must be administered via secure accesses and in some cases are suitable only for short-term treatment because of their adverse effects.

Sodium nitroprusside is a potent, short-acting, and reliable drug for reducing SVR and arterial blood pressure. The formation of cyanide is harmful, so that both dose and duration of administration should be limited. It should not be used without invasive blood pressure measurement. Administration also requires a separate access. Nitroprusside is still available from international pharmaceutical suppliers.

Phentolamine is also a very potent SVR-reducing agent. It is hardly used at all now (in Giessen) in postoperative medicine.

Urapidil acts by blocking α1 receptors with a vasodilator effect. From clinical experience, the effect is age-dependent: it is less pronounced in infants and children (compared to adults). The duration of action tends to be short and, when administered by drip, the effect often diminishes over time (tachyphylaxis). Adverse effects tend to be rare.

Clonidine is probably the drug most frequently used postoperatively in this group (see also Chap. 6, Sedation). Similar to dexmedetomidine, the combination of sedation, analgesia, and reduction in sympathetic tone (reduction in HR and afterload) makes it ideal for this indication.

Table 3.5 Afterload reducers

	Mechanism	Site of action	Starting dose	Usual dose	Special features
Nipruss® (sodium nitroprusside)	NO donor	Arterial primarily	0.3–0.5 µg/kg body weight/min	2–3 up to max. 5 µg/kg body weight/min	Acts immediately – disappears within a few minutes. Reflex tachycardia is present. Cyanide intoxication possible (sodium thiosulfate/dialysis), max. 3–5 days, dark syringe
Phentolamine (Regitine®)	α-Blocker	Arterial primarily (also central = pharmacological sympathicolysis), PAP somewhat ↓	0.2 µg/kg body weight/min	0.5–1–2 µg/kg body weight/min	Reflex tachycardia. Caution: Adrenaline reversal!
Urapidil	α-Blocker	Predominantly peripheral, also central acting α-receptor blocker	0.2–0.5 mg/kg/h	1 mg/kg body weight/h	Relatively short half-life
Clonidine	α2 Agonist	Reduction of sympathetic tone, morphine agonist	0.5 µg/kg/min	1–2–3 µg/kg/min	Reduces opiate consumption, heart rate ↓, blood pressure ↓

3.6 ACE Inhibitors

ACE inhibitors (see Table 3.6) are suitable (as previously mentioned) primarily for the long-term treatment of heart failure. In this case, a combination of ACE inhibitors and diuretics (e.g., spironolactone +/− hydrochlorothiazide) is standard. Treatment should be initiated during the postoperative stay, i.e., as soon as possible (for criteria see above).

For long-term treatment of pediatric heart failure, see the AWMF's (Association of the Scientific Medical Societies in Germany) guideline for the treatment of chronic heart failure (http://www.uni-duesseldorf.de/AWMF/ll/023-006.htm).

A common feature of all ACE inhibitors is that they must be "titrated" at low doses, as their effect on blood pressure is difficult to predict. In addition, inhibition of RAAS (particularly when co-administered with spironolactone) can produce an increase in serum potassium. Bilateral renal artery stenoses (or renal artery stenosis in a single kidney) represent a contraindication.

One essential benefit of ACE inhibitors is also that they exert a positive effect on myocardial adaptation processes (remodeling). At the same time they reduce, for

Table 3.6 ACE inhibitors – always titrate dose to lowest effective dose

	Test dose	Target dose (max.)	Dose interval	Onset of action
Captopril	Neonates 0.05–0.1 mg/kg Small children 0.15–0.5 mg/kg Adults 12.5–25 mg per single dose	Neonates 0.5 mg/kg/SD Small children 2 mg/kg/SD Adults 2 × 25–150 mg Relatively rapid increase possible	2–3–4 ×/d 2–3 ×/d 2 ×/d	15–60 min
Enalapril (iv possible, but difficult to titrate – acts hours afterwards)	Neonates 0.1 mg/kg Small children 0.05 mg/kg Adults 2.5 mg/kg	Neonates 0.5 mg/kg per single dose Small children 0.5 mg/kg per single dose Adults 5–20 mg per single dose	1–2 ×/d	60 min
Lisinopril	Neonates (less preferable – given the long half-life) Small children 0.05–0.1 mg/kg Adults 5–10 mg per single dose	Increase slowly	1–2 ×/d	60 min

instance, hypertension-induced fiber proliferation in high blood pressure or end-diastolic ventricular diameter in CM (cardiomyopathy), as markers of ventricular dilation (ACE inhibitors reverse remodeling).

Possible adverse effects are cough, cholestatic jaundice, proteinuria, as well as liver failure (rare) and allergy.

All the abovementioned therapeutic measures (basic therapy, volume replacement, and afterload reduction) serve to optimize O_2 delivery by increasing cardiac output without any substantial increase in myocardial O_2 consumption. The use of levosimendan should actually also be included here. However, as levosimendan is used as a "reserve inodilator," it is not mentioned until the next section.

The myocardial pump performance of the heart can be reduced to such an extent that an increase in contractility can only be achieved by additional pharmacological stimulation of the myocytes. Arterial pressure can also be so low as to jeopardize organ perfusion ("no flow, no pressure – no pressure, no flow"). In these situations, catecholamine therapy is then required. However, with the use of catecholamines, this is achieved only at the expense of an increase in myocardial O_2 consumption.

3.7 Catecholamine Therapy

All catecholamines commonly used in intensive care medicine exert their effects simultaneously via several receptor types (see Table 3.7). The clinical effect is dependent on the affinity of the catecholamine used to the various receptors (e.g., beta receptor, alpha receptor) and their distribution in the respective target organ.

Table 3.7 Catecholamine receptors

	Mechanism	Effect	Reference substances
α1	IP3 system	Vasoconstriction, mydriasis, uterine contraction, mucous saliva	Dopamine, noradrenaline (adrenaline)
α2: Ubiquitous in sympathetic nervous system, reduction in noradrenaline by retrograde inhibition	cAMP reduction	General sympathicolysis, less insulin secretion, platelet aggregation ↑	Clonidine
β1	Increased Ca influx	Sinus node stimulation, increased contractility, conduction acceleration, increased renin	Orciprenaline, dobutamine (adrenaline)
β2	Increased Ca outflow	Bronchodilation, muscle vessel dilation, uterus + bladder wall relaxation, anti-insulin	Formoterol, reproterol

Alpha-receptor specificity (in descending order):

Noradrenaline (predominantly) → *dopamine* → *adrenaline* → *dobutamine* → *orciprenaline* (hardly used any more)

Beta-receptor specificity (in descending order):

*Orciprenalin*e (almost exclusively) → *dobutamine* → *adrenaline* → *noradrenaline* → *dopamine* (hardly used any more)

The effect of adrenaline can best be observed by the "fight or flight" reflex:

- Stimulation of the adrenal gland (adrenaline secretion)
- Increase in sympathetic tone (noradrenaline secretion)
- Dilation of pupils and bronchi
- Inhibition of salivation and digestion
- Provision of energy (e.g., sugar)

Furthermore, arterial resistance increases as a result of contraction of the arterioles (particularly in the so-called shock organs: kidney, skin, and bowel), the blood volume is redistributed (away from the venous capacitance vessels to the central blood compartment), and cardiac output increases (increase in heart rate and stroke volume).

The (short-term) beneficial effects of increased sympathetic tone for the healthy heart can be detrimental to a damaged, failing heart (both in the short term and particularly in the long term) and can exacerbate the heart failure still further (by an increase in afterload, a tendency to tachycardia with cardiac arrhythmias, the risk of

ischemia, and downregulation of beta receptors). For this reason, beta-blocker therapy is useful in chronic heart failure (e.g., bisoprolol in Giessen).

In intensive care medicine, the adrenergic receptors particularly in the heart muscle, stimulus conduction system, and vessels are important for catecholamine therapy.

However, it should be borne in mind that all catecholamines increase myocardial O_2 consumption to differing degrees and have a pro-arrhythmogenic effect (the pro-arrhythmogenic effect appears to be more pronounced with synthetic catecholamines, e.g., dobutamine, than with endogenous catecholamines). In addition, catecholamines trigger postaggression metabolism (PAM, see Chap. 5), with hyperglycemia and a negative nitrogen balance (protein degradation), etc.

3.7.1 Clinical Use of Catecholamines

Catecholamines are highly efficacious circulatory drugs that can maintain the perfusion pressure of the coronary arteries, brain, GI tract, and kidneys in the event of severe hypotension with optimized preload and contractility (see Table 3.8). In addition, the contractility of heart muscle fibers can be increased by the beta component.

The general rule for the use of catecholamines is: "as little as possible, as much as necessary. What needs to be checked is that cardiac output and blood pressure are increased and that the body's O_2 balance is improved (lactate/urine/SvO_2/NIRS). The negative effects of catecholamine therapy can markedly outweigh the positive ones, particularly in the case of severe tachycardia, impaired diastolic function, and high-grade valve insufficiency. It should also be ensured that catecholamines are administered via a secure vascular access at a sufficient infusion rate to prevent fluctuations in HR and blood pressure. For example, the "stop and go" phenomenon produced by an irregular infusion rate, inadvertent bolus administrations of catecholamine residues in the catheter, and delayed onset of action due to insufficient priming of the catheter is detrimental. The catecholamine effect can be potentiated by the compensation of acidosis and the administration of steroids, which may entail a subsequent dose reduction.

A special situation is present if a ventricle is obstructed by hypertrophy, valvular stenosis, or dynamic stenoses (muscle bundles, local hypertrophy) at the outlet. These situations require urgent heart rate monitoring (prolongation of the myocardial perfusion phase in diastole) and, where necessary, a concomitant increase in afterload to ensure sufficient coronary perfusion. The combination of iv beta-blockers (e.g., esmolol) with noradrenaline with concurrent volume replacement has become established for this purpose. As well as the bradycardiac effect of the beta-blocker, its positive effect on the reduction of any contraction-induced dynamic stenosis is utilized simultaneously (avoid hypercontractility!).

At the Pediatric Heart Center in Giessen, the "standard" catecholamine in postoperative therapy is noradrenaline (usually in combination with milrinone). The use of noradrenaline appears helpful in many situations, given the coexistence of beta stimulation, which exerts a positive effect on cardiac output and an only moderate increase in HR. In addition, the increase in blood pressure and the contraction of the veins result in volume saving (see above). In our experience, the

Table 3.8 Catecholamines

	Noradrenaline	Adrenaline	Dobutamine	Dopamine	Orciprenaline
Use	Maintains perfusion pressure, saves fluid volume	Poor heart function + capillary leakage	In poor heart function; right heart failure	Maintains perfusion pressure, saves fluid volume	AV blocks
Receptor	Little β action, α >> β	α + β	β >>> α	α >>> β (less β than noradrenaline), low doses: Dopamine receptor	β
Dose	0.05–0.1–1 µg/kg/min	0.05–0.1–0.5 µg/kg/min	2.5–5 µg/kg/min	2.5–5–20–X µg/kg/min High doses act like noradrenaline	0.1 µg/kg/min
Problem	Afterload + O_2 consumption ↑. Caution: Poor heart function!	Afterload + O_2 consumption ↑, tachycardia, cardiac arrhythmia	O_2 consumption ↑, tachycardia, cardiac arrhythmia	Afterload + O_2 consumption ↑. Caution: Poor heart function!	O_2 consumption ↑, tachycardia, cardiac arrhythmia
When	When preload is optimized (PA crisis/ Fallot)	When milrinone is insufficient, resuscitation	When milrinone does not suffice and blood pressure is still OK	Improves urine balance in premature infants and neonates; caution: rhythm problem!!	Extremely rare
When not		(Muscular) outflow tract obstruction	(Muscular) outflow tract obstruction		

Resus. resuscitation (in neonates)

theoretic disadvantage arising from an increase in afterload is of secondary importance in most patients. In Giessen, adrenaline (Suprarenin®) is used only at inotropic doses (<0.05 µg/kg/min) in patients with severely impaired LV function. We use dobutamine almost exclusively in "bradycardiac situations" (e.g., AV block) to increase heart rate. The same applies with orciprenaline. Dopamine is hardly used at all now.

3.8 Other Inotropic Agents

3.8.1 Levosimendan (Simdax®)

Levosimendan is a calcium sensitizer that causes an increase in myocardial contractility without increasing O_2 consumption. Levosimendan also induces vasodilation,

which is associated with a reduction in ventricular filling pressures through a decrease in afterload. Levosimendan is ascribed a positive effect on diastolic function. It has little pro-arrhythmogenic effect and is also otherwise fairly devoid of adverse effects (although in adult patients, arterial hypotension can occur as a result of vasodilation).

Levosimendan represents an almost ideal medication for the treatment of severe heart failure. In addition, it can be given for "preconditioning" even before the start of CPB. Fortunately, levosimendan also reduces pulmonary artery resistance and hence RV afterload. From clinical observation, the effect of the medication persists for up to 7–10 (−21) days (for dosage see Table 3.9).

Because of the (still) high price, it makes sense to calculate the dose for the total infusion of a patient and where necessary to allocate the rest to other children with severe heart failure (the reconstituted solution is stable for 24 h). Aliquoting by the hospital pharmacist is also possible.

The initial administration of a bolus is increasingly less indicated.

Indications for levosimendan:

- Severe myocardial dysfunction.
- Weaning from ECMO or assist device.
- Other, individual patient-specific.
- Alternative if milrinone is not available.

3.8.2 Thyroid Hormones

Like in other severe diseases, CPB surgery and myocardial dysfunction can result in an imbalance of thyroid hormones. In this case, administration of thyroxine (T4), and even better triiodothyronine (T3), has been shown to exert a positive effect on cardiac function after the use of CPB, particularly in infants.

At the Giessen Pediatric Heart Center, the following therefore applies to infants after CPB surgery (<1 year): 5 µg/kg T4 iv or 1–2 µg/kg T3 iv for 3 days post-CPB. Administration of T3 as a drip infusion at a rate of 0.05 µg/kg/h has actually been studied more extensively. Nevertheless, a single dose of T4 or T3 over 3 days has become established at many institutions for practical reasons.

A decision on whether to continue treatment (orally) must then be taken on an individual basis. At the Giessen Pediatric Heart Center, all children with Down syndrome are routinely prescribed with L-thyroxine.

Table 3.9 Levosimendan (Simdax®)

	Bolus	Drip	Draw-up
Inodilator (calcium sensitizer and potassium channel opener)	Over 10 min 1–2 µg/kg/min	Thereafter, 0.1–0.2 µg/kg/min	5 ml Simdax +495 mL 5% glucose

3.9 Beta-blockers

Beta-blockers (see Table 3.10) also have a firm place in postoperative medicine. Like other measures or medications described in this chapter, they serve to economize on heart work. A reduction in heart rate increases coronary perfusion, reduces myocardial O_2 consumption, and improves diastolic filling. Severely hypertrophic ventricles (e.g., TOF, HCM) in particular generally benefit from administration of a beta-blocker with a reduction in HR and myocardial contractility.

Only very conditionally do we share the view that children (including neonates) are dependent on a high heart rate (HR) to maintain their cardiac output ("concept" of compensatory tachycardia). In our experience, HR >150/min are usually not beneficial. With respect to cardiac output, the ratio of SV and HR is vital. At a lower HR, cardiac output can be compensated by an increase in SV (longer diastolic filling time), with an improved myocardial O_2 balance. Other beneficial effects of beta-blockers include:

- Antiarrhythmic effect (esp. ventricular ectopic activity).
- Protection against catecholamine-induced myocardial toxicity.
- Prevention of downregulation of beta-1 receptors.
- Synergy with ACE inhibitors (for RAAS inhibition).

The latter effects are also of particular importance in the treatment of chronic heart failure. In this case also we would advocate beta-blocker therapy despite a lack of study findings (by analogy with adult data).

We prefer beta-blockers with a high affinity for the beta-1 receptor. We use esmolol, metoprolol, and bisoprolol in the postoperative phase for heart rate control.

Beta-1 selectivity (in descending order): bisoprolol > esmolol > metoprolol.

Esmolol has the major advantage of a very short half-life of only a few minutes, and therefore its action can be terminated rapidly (e.g., if the patient does not tolerate the treatment). In addition, degradation of esmolol is independent of hepatic or renal function (hydrolysis by esterases in the erythrocyte). Administration is by drip. The dose is titrated according to effect.

Table 3.10 (Relative) indications for beta-blockers

Postoperative heart rate monitoring	Esmolol or metoprolol
Ventricular ectopic activity (e.g., VES, runs)	Metoprolol
Heart rate monitoring (medium to long term)	Bisoprolol
Treatment of heart failure and pulmonary hypercirculation	Bisoprolol
Hypercontractility (e.g., in TOF, HCM)	Bisoprolol, propranolol
Supraventricular arrhythmia	Propranolol (see Sect. 11)
Myocardial ischemia	Metoprolol

Metoprolol can be administered immediately postoperatively as a drip; otherwise it is administered intermittently by the oral or iv route. The half-life is 3–4 h but can be twice as long in neonates. Metoprolol is metabolized in the liver.

Bisoprolol is available in tablet form only, so that it cannot be given unless the patient has adequate gastrointestinal transit. Because of the long half-life, it need only be administered once or twice daily and is therefore very well suited to long-term therapy. It has very high beta-1 selectivity (beta1:beta2 = 75:1). In Giessen, almost all patients with heart failure are treated with bisoprolol (conventional combination of drugs in heart failure: bisoprolol, lisinopril, and spironolactone). Treatment is usually initiated at a low dose (e.g., 0.05 mg/kg) and increased to the desired effect (max. 0.2–0.3 mg/kg/d). It can also be readily used in neonates and infants.

Propranolol is a nonselective beta-blocker but has a long "tradition" in pediatric cardiology. It is used for the treatment of both hypertrophic hearts and cardiac arrhythmias (see Chap. 11).

Conclusion

In the monitoring and management of cardiovascular therapy, it is frequently necessary to deal with the aftereffects of surgery and the preceding period of intensive care. It may therefore happen that sometimes contradictory or even conflicting treatments are initiated in a patient, which can potentiate or mutually abolish one another. In the worst case, these treatments have no benefit or entail a disadvantage to the patient.

Therefore, it is incumbent upon the person(s) responsible to review the patient's situation as a whole and to ensure the optimal and rational therapeutic composition at all times. This implies certain principles, as well as some exceptions:

The aim, wherever possible, should be (early) extubation. Sedation and ventilation can often be the reasons for "unnecessary" circulatory therapy. Even patients with increased pulmonary resistance can respond positively to extubation. Careful sedation and administration of O_2 as well as specific measures (e.g., sildenafil) are then simpler than treatment with catecholamines (which may even exacerbate the problem in some cases).

Cardiovascular therapy should be undertaken with a complete awareness of the previous medical history, monitoring data, and ultrasound findings – which may entail the need for several follow-ups per shift.

The possibility of decreasing O_2 consumption by reducing body temperature (physical measures, paracetamol, slight sedation, etc.) should always be considered before intensifying cardiovascular therapy.

The key frequently lies in the assessment of heart rate (incorporating ultrasound findings, medication, and temperature). Cardiac output can frequently be (paradoxically) increased by carefully reducing the heart rate (also by using beta blockade or central α_2 agonists such as clonidine or dexmedetomidine). The use of the term "compensatory tachycardia" as justification in a tachycardiac patient should be avoided, since it often reflects an insufficient (fairly unequal) manage-

ment of the myocardial O_2 balance. It is vitally important to economize the heart's work by reducing heart rate (improved diastolic filling and improved coronary perfusion) as well as by adapting preload and afterload.

Making sure that the aftereffects of the surgery performed are taken into account is likewise imperative. Ideally, surgically relevant problems can be excluded by intraoperative transesophageal echocardiography (TEE) before the end of CPB. However, new echocardiographic findings can be obtained postoperatively. Examination by cardiac MRI, CM-CT, or cardiac catheter (CC) should also be considered in individual cases. Some problems can only be resolved by a CC intervention or revision surgery.

If stabilization is not achieved by the usual means, consideration should also be given to the possibility of (temporary) mechanical circulatory support (e.g., ECMO or VAD; see Chap. 10).

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Renal Aspects of Cardiac Intensive Care

4

Christoph Neuhaeuser and Dietrich Klauwer

4.1 Assessment of Renal Function

4.1.1 Importance of Urine Output

Apart from the clinical assessment of the patient, monitoring of postoperative renal function is primarily focused on the determination of hourly urine output (diuresis). An (age-commensurate) normal urine output in the absence of diuretic substances indicates adequate organ perfusion.

Urine output should not fall *unnoticed* below a value of 2 mL/kg BW/h postoperatively, as this may indicate a deteriorating cardiovascular situation. Blood pressure, heart rate, CVP, SvO_2, BE, lactate, and urine output thus represent objective parameters that allow the clinician to gain a picture of the patient's systemic circulation. By definition, oliguria is referred to if urine output is reduced to the following cutoff levels:

- Premature neonates/neonates: < 2.0 mL/kg BW/h.
- Children <1 year of age: < 1.0 mL/kg BW/h.
- Adolescents: < 0.5 mL/kg BW/h.

C. Neuhaeuser (✉)
Pediatric Intensive Care Unit, Pediatric Heart Center of Giessen, Children's Heart Transplantation Center, UKGM GmbH, Giessen, Germany
e-mail: christoph.neuhaeuser@paediat.med.uni-giessen.de

D. Klauwer
Department of Pediatrics, Singen Medical Center, Gesundheitsverbund Landkreis Konstanz, Krankenhausbetriebsgesellschaft Hegau-Bodensee-Klinikum, Singen, Germany

© Springer International Publishing AG, part of Springer Nature 2019
D. Klauwer et al. (eds.), *A Practical Handbook on Pediatric Cardiac Intensive Care Therapy*, https://doi.org/10.1007/978-3-319-92441-0_4

4.1.1.1 Definition of Oliguria

With a daily production of substances excreted in the urine of about 10 mosmol/kg/day = 0.42 mosmol/kg/h and a renal concentrating capacity of about 1200 mosmol/kg = 1.2 mosmol/mL, at least 0.35 mL/kg/h urine is required to keep the system in balance. However, if more urinary excreted substances are produced (e.g., with increased metabolism, catabolism, tissue necrosis) or if the renal concentrating capacity is restricted (e.g., due to immaturity of the kidney, kidney diseases, and drugs), a correspondingly larger quantity of urine must be excreted.

Urine output plays a vital role in the patient's fluid balance. In the absence of an adequate output, the i.v. fluid supply usually required in the postoperative setting can quickly lead to an increasingly positive fluid balance. This may contribute to the formation of edema and effusion, as well as respiratory problems and electrolyte fluctuations. For example, for a 10 kg child, the calculated input via drips and infusors on the first postoperative day (intake) adds up to 1000 mL/m^2/day ≈ 2 mL/kg/h (or more). An hourly urine output of at least 2 mL/kg/h (≈ 50 mL/kg/day) is therefore necessary to maintain fluids in balance. A patient is mathematically in negative balance if his or her output is greater than his or her input.

On the *input* side, (mL/day) can be reckoned, e.g.:

- Fluid volume administrations (mL/24 h).
- Infusors (mL/h × 24 h).
- Parenteral nutrition (mL/h × 24 h).
- Volume of all antibiotics and drugs (mL/24 h).
- Transfusions (mL/24 h).
- Enteral nutrition (proportion of fluid in the nutritional solution/quantity: mL/24 h × approx. 0.7).

On the output side, (mL/day) can be reckoned, e.g.:

- Amount of urine (mL/24 h).
- Blood losses (mL/24 h).
- Gastric juice losses (mL/24 h).
- Drain losses (mL/24 h).

The balance also includes losses via insensitive perspiration (approximately 20–40 mL/kg BW/day, depending on the moistening of inhaled air, fever, room temperature, etc.) and the oxidation water produced in metabolism, but these are not directly measurable and therefore are not included in the mathematical balance.

The daily body weight provides the clinician with the most accurate idea of the actual fluid balance (gain or loss). However, taking the body weight is often hardly possible in critical ill patients.

4.1.2 Laboratory Tests

In plasma

- Creatinine ($Crea_P$):
  - Dependent on muscle mass.
  - Increase if glomerular filtration rate (GFR) < 50% of normal.
- Urea:
  - Dependent on metabolism (e.g., increased in catabolism).
  - Dependent on urine output (e.g., increased in oliguria).
  - Dependent on nutrition (e.g., intake of amino acids).
  - Increase if GFR < 25% of normal.
- Blood gas analysis.
- Electrolytes (including calcium and phosphate).
- Creatine kinase (CK) (see Sect. 4.5.2).
- Plasma osmolarity ($Osmo_P$):
  - Normal: 280–310 mosmol/L.

$$\text{Osmo-estimated}\left(\text{mosmol/L}\right) = 2 \times \text{Na}\left(\text{mmol/L}\right) + \text{urea}\left(\text{mg/dL}\right)/6 + \text{glucose}\left(\text{mg/dL}\right)/18.$$

In urine

- Urine sodium (NaU):
  - Normal: 20–250 mmol/L.
  - Dehydration/fluid volume deficiency with antidiuresis: < 20 mmol/L (concentrated urine).
  - Increased in diuretic administration, salt-losing nephritis, adrenal insufficiency, etc.
- Urine creatinine ($Crea_U$):
  - Normal: 20–130 mg/dL.
- Urine osmolarity (Osm_U):
  - Normal (spot urine): 200–1200 mosmol/L.
  - Dehydration/fluid volume deficiency with antidiuresis: > 800 mosmol/L (concentrated urine).

Calculated Values

Fractionated sodium excretion (FeNa):

- Estimation of tubular function or concentrating capacity:

$$\text{FeNa}\left(\%\right) = \left(\text{Na}_\text{U} \times \text{Crea}_\text{P}\right) / \left(\text{Na}_\text{P} \times \text{Crea}_\text{U}\right) \times 100$$

Na_U and Na_P in mmol/L; $Crea_U$ and $Crea_P$ in mg/dL

- Dehydration/fluid volume deficiency with antidiuresis: FeNa <1%.
- Tubulopathy (e.g., acute tubular necrosis): FeNa >3%.
- With the use of diuretics: FeNa not evaluable.
- Similarly, FeK as well as tubular phosphate reabsorption (TPR) and calcium/creatinine can also be used to estimate tubular function.

Creatinine clearance (CC):
- Amount of blood plasma cleared of creatinine per minute.
- Estimation by the Schwarz formula:

Formula 35
(Patient's height (cm) × factor) / Serum creatinine (mg/dL)

– Factor for adolescents 0.7 (see also sect. 17.6.2).
– Factor for children 0.55.
– Factor for infants 0.45.

- Measurement by urine collection (duration of collection of 6–8 h usually suffices).
  – Creatinine: 1 mg/dL × 88.5 = µmol/L.

4.2 Physiologic Bases of Renal Function

The following relationships between renal blood flow (RBF), renal perfusion pressure (RPP), GFR, and urine output should be known.

The amount of urine excreted (urine output) depends on:

- GFR.
- Hormonal effects:
  – Antidiuretic: aldosterone, ADH (vasopressin).
  – Diuretic: ANP (atrial natriuretic peptide), BNP (brain natriuretic peptide).

Also on:

- Osmotic factors (e.g., glucose, mannitol).
- Drugs (e.g., diuretics, dopamine, caffeine, alcohol, etc.)
- Tubule disorders.
- Impaired concentrating capacity.

GFR in turn depends on:

- RBF – the most important influencing factor: the greater the renal blood flow, the greater the GFR.
- Hydrostatic pressure in the glomerular capillaries:
  - The higher the hydrostatic pressure, the greater the GFR.
  - The hydrostatic pressure is normally relatively constant and is regulated by the interaction of afferent and efferent vascular resistance, i.e., vascular tone of the afferent and efferent arterioles, respectively.
- Oncotic pressure in the blood: increasingly counteracts the hydrostatic pressure at the end of the filtration distance.
- Filtration area (Kf): for example, catecholamines and angiotensin result in a reduction of Kf through mesangial contraction, so that GFR decreases.

Also on:

- Changes of the glomerular membrane (charge, pore size, thickness of the basement membrane, etc.)
- Number of functioning nephrons (decreases physiologically >40 years; reduced in renal failure).
- Hydrostatic and oncotic pressures in Bowman's capsule.

RBF depends on:

- Cardiac output: normally the kidney receives about 20% of CO (in adults about 1.2 L/min).
- Renal perfusion pressure (RPP).
- Intrarenal vascular resistance (R_{Kidney}): RBF = RPP/R_{kidney}.

RPP depends on:

- MAP = renal inflow pressure.
- CVP = renal outflow pressure:
  - Thus, $RPP = MAP - CVP$.
  - As CVP is normally small in relation to MAP, $RPP \approx MAP$.
  - With an MAP <60 mmHg, there is an impending threat of oliguria in adults (correspondingly lower perfusion pressures in neonates and infants).
  - A CVP >18 mmHg is critical in terms of RBF.
- If intra-abdominal pressure (IAP) exceeds CVP, then $RPP = MAP - IAP$:
  - An IAP > 15–20 mmHg is critical.
  - At IAP values >20 mmHg, there is the impending threat of abdominal compartment syndrome.

Intrarenal vascular resistance depends on:

- Tone of the afferent arterioles in the glomerulus (main component).
- Tone of the efferent arterioles.
- Various factors are involved here in the effect on arteriolar tone:
  - Intrinsic (myogenic): myogenic stretch.
  - Passive extension of the arteriolar wall is followed by a reactive vascular muscle contraction.
  - Extrinsic (paracrine, endocrine, neurogenic).
    Vasodilation: PGE, NO, and ANP (afferent arterioles > efferent arterioles), dopamine (low dose via D1 receptors: afferent = efferent arterioles), adenosine (systemic effect).
    Vasoconstriction: Noradrenaline/adrenaline (alpha-1 receptors: afferent = efferent arterioles), angiotensin II and endothelin (afferent < efferent arterioles), vasopressin (ADH), adenosine (local effect)
- Pathological factors such as:
  - Microthrombosis.
  - Endothelial swelling.
  - Interstitial edema (the kidney possesses a capsule, so that intracapsular pressure increases in interstitial edema).
  - Tubular obstruction.

A deeper insight into the regulatory principles of the kidney (with good pictures) can be found at http://legacy.owensboro.kctcs.edu/gcaplan/anat2/notes/APIINotes3%20urinary%20system.htm.

Relationship of Flow, Pressure, and Resistance in Relation to Renal Hemodynamics

- *RBF and vascular autoregulation*: The determining parameter for the kidney is RBF. Regulation of RBF is physiologically important as the main task of the kidney is filtration. To maintain GFR relatively constant over the course of the day (rest vs. activity), RBF must not vary excessively. If arterial pressure increases (expressed here as MAP), autoregulation prompts a rise in intrarenal vascular resistance due to vasoconstriction of the afferent arterioles, and RBF therefore increases only slightly (e.g., in an adult kidney with an increase in MAP from 100 to 150 mmHg, RBF increases by only 10%). The reverse is the case if MAP falls.
- *Critical RBF and RPP:* If MAP falls below a certain physiologic minimum (critical limit in adults, 60–80 mmHg), this can no longer be counteracted by autoregulation (maximum vasodilation is reached), and RBF subsequently falls pressure-passively. If RBF decreases by a half, GFR ceases. A further decline in RBF (to less than a 1/4 of normal) results in ischemic damage to the renal parenchyma (particularly the tubular cells). In the isolated adult kidney, RBF ceases at an RPP of 30 mmHg (closing pressure).

- *Dehydration* or *mild hypovolemia*: In moderate hypovolemia, GFR remains unchanged as a result of counterregulatory mechanisms (due in particular to angiotensin II; AT II). As AT II constricts the efferent arterioles more than the afferent ones, the filtration pressure in the glomerulus can initially be maintained despite the overall reduction in RBF. Concentrated urine is excreted.
- *Shock*: If MAP falls significantly as a result of a decrease in intravascular volume (e.g., hypovolemic shock) or low CO (hypovolemic or cardiogenic shock), activation of the sympathetic nervous system and other blood pressure-stabilizing hormonal feedback cycles (RAAS, ADH) occur. Autoregulation is suspended, and vasoconstriction of the afferent and efferent arterioles prevails under the effect of noradrenaline, angiotensin, and vasopressin. Because of the increase in renal vascular resistance in association with low renal perfusion pressure, RBF consequently decreases markedly (until the point when the kidney is literally "switched off" in the context of shock). The primary aim of the body in this situation is to preserve blood flow to the heart and brain (centralization of circulation) and prevent volume losses by diuresis. If the shock is not reversed in time, acute kidney injury occurs with tubular necrosis and renal cortical edema.
- Special situations:
  - Some patients have normal renal function or normal urine output despite very low blood pressure values (habitual hypotension). CO in these patients is usually normal. There is probably very low renal vascular resistance in these cases; as a result of which, RBF and hence GFR remain normal despite low RPP. If urine output is normal, pharmacologic "blood pressure cosmetics" should be avoided. However, intensive monitoring may be justified as physiologic reserves are sometimes small.
  - In long-term hypertension, the autoregulation range is shifted to higher values, i.e., higher MAPs are required for normal RBF.
  - Vasoplegic states (e.g., sepsis, post-CPB syndrome, liver failure, etc.) often result in a pathologically reduced peripheral vascular resistance with hypotension via systemic vasodilation (CO may be reduced, normal, or increased). At the same time, severe vasoconstriction can be present intrarenally (sympathetic activity, hormones, cytokines, mediators, etc.). In this case, autoregulation is usually impaired or abolished. Taken altogether, this results in a markedly reduced RBF and a fall in GFR, even with higher MAP values.
  - Drugs such as NSAIDs (inhibition of PGE2 synthesis), ACE inhibitors (AT II inhibition), dopamine (D1 receptor agonist), and theophylline (adenosine receptor-1 antagonist) have an effect on the vascular tone of the afferent or efferent arterioles. They may exert positive or negative effects, depending on the situation. In a situation of fluid volume deficiency, NSAIDs (abolition of afferent vasodilation) and ACE inhibitors (abolition of efferent vasoconstriction) in particular can cause a reduction in GFR and hence acute anuria.

Conclusion for Clinical Practice

- Normalization of CO and intravascular volume is the most important measure in terms of the treatment of oliguria.
- If MAP does not increase as a result, the restoration of adequate blood pressure is the second most important measure. This may require catecholamines.
- The concentration of urine (e.g., in connection with dehydration and fluid volume deficiency) means work for the kidney (O_2- and ATP-consuming processes in the tubules). The administration of isotonic volume replacement solutions (e.g., 0.9% NaCl, Ringer) reduces the concentrating work and therefore relieves the burden on the kidney (*Caution*: in patients with stiff LV, reduced pump function, or outflow obstruction, fluid replacement must be given under close monitoring). On the other hand, the developement of hyperchloremic acidosis should be avoided, for example, by using "balanced" electrolyte solutions, since renal function may be affected due to inappropriate intrarenal vasoconstriction.
- With reduced CO (e.g., cardiogenic or hypovolemic shock), the use of vasopressors to restore normal blood pressure can be counterproductive in respect of renal perfusion.
- By contrast, administration of noradrenaline in a situation of septic shock usually results in an increase in RBF and GFR.
- In manifest hypotension but with normal urine output, adequate organ perfusion may be assumed (no blood pressure therapy required).
- In the context of catecholamine therapy, evidence of adequate urine output can contribute to titration of blood pressure (although unfortunately there is generally a time lag between measure and effect, which means that the outcome frequently cannot be verified immediately).
- In chronic hypertension or diseases with intrarenal vasoconstriction, a higher than normal MAP should be targeted.

4.3 Pathophysiology in the Cardiac Patient

In cardiac patients, CO is often relatively fixed, i.e., it can be increased to only a limited extent. The development of oliguria is common following cardiac surgery (particularly within the first 24–72 h postoperatively).

The following points should be considered:

- Intravascular volume deficiency (e.g., hemorrhage, capillary leakage, effusion).
- Reduced CO: e.g., post-CBP stunning, myocardial edema, ischemia, downregulation of beta receptors, anatomic causes (residual defects), slow circulatory adaptation following corrective surgery.
- O_2 deficiency (R-L shunt with cyanosis, hypoxia, anemia), acidosis.
- Arterial hypotension (reduced RPP due to low MAP).
- Increased antidiuretic hormone levels (e.g., RAAS, catecholamines, ADH, etc.)
- Impaired autoregulation (e.g., pressure-passive behavior, intrarenal vasoconstriction).

- Drugs (e.g., NSAIDs, paracetamol, ACE inhibitors, catecholamines).
- Noxae (e.g., myoglobin, nephrotoxins, contrast agents, nephrotoxic drugs, cytokines, etc.)
- Reduced RPP as a result of a rise in back pressure due to increased intra-abdominal (IAP), intrathoracic, or right atrial pressure (CVP). Causes: ascites, pleural effusion or pulmonary edema, high ventilation pressures (or mean airway pressure), tamponade, PHT, RV failure, stiff RV.
- Post-CPB: ischemia-reperfusion injury, SIRS, vasoplegia, etc.

In a situation of low CO, GFR is reduced due to a reduction in RBF. In the presence of additional arterial hypotension, which is frequent after cardiac surgery, RBF and hence GFR decrease till further. Increased intrarenal vascular resistance from afferent and/or efferent vasoconstriction due to, e.g., high sympathetic tone or catecholamines may also complicate the situation. In addition, RAAS activation and increased ADH secretion occur postoperatively.

However, acute deterioration of renal function (AKI, acute kidney injury) may not just be hemodynamically induced but is often multifactorial in origin (see list above).

The therapeutic intention to stabilize renal function via normalization of CO, intravascular blood volume, and arterial blood pressure may be straightforward but cannot always be achieved immediately in the postoperative period (despite inotropic support, fluid volume administration, and vasopressors). It should be borne in mind that overly aggressive blood pressure therapy with vasopressors can be detrimental to organ perfusion in low cardiac output states.

If urine output remains insufficient despite optimization of all possible parameters or factors, furosemide should be administered in an attempt to increase it (see Sect. 4.4). This measure serves in the first place to maintain fluid balance, as the development of effusion and edema can contribute to a deterioration of the situation. However, acute kidney injury usually cannot be prevented by the use of furosemide.

Against the background of the relationships described above, the following questions therefore arise in the individual case:

- Can CO be increased?
- What does echocardiography reveal about cardiac function?
- Can catecholamines, fluid administration, rhythm control (e.g., cardiac pacing), etc. help?

Is intravascular filling sufficient?

- Are there any signs of centralization present (poor microcirculation, prolonged recapillarization time, or increased ΔT)?
- Is CVP decreased (< 6 mmHg) or increased (> 12 mmHg)?
- Is compensatory tachycardia present?
- Does the arterial curve undulate (increased pulse pressure variation)?

Is the perfusion pressure sufficient to generate adequate urine output?

- Target MAP:
  - Neonates: 40 mmHg.
  - Infants: 45–50 mmHg.
  - Young/school children: 55–60 mmHg.
  - Adolescents: 60–70 mmHg.
- What dose of catecholamines and how much fluid are needed to achieve the target MAP?

Are there any signs of dysoxia (or reduced perfusion) present?

- Assessed on the basis of SvO_2, $avDO_2$, lactate, BE, microcirculation, and ΔT.

Very important What other risk factors are present?

- For example, duration of CPB, nephrotoxins, previously known kidney diseases, and renal impairment.

Is rhabdomyolysis or hemolysis present (e.g., after CPB surgery)?

If urine output cannot be sufficiently stimulated despite optimization of CO and blood pressure, diuretics should be used in our opinion to try to increase urine production in an effort to avoid complications from a positive fluid balance (for explanation see below).

4.4 Furosemide Therapy

Furosemide is very suitable for increasing urine output postoperatively, as it can be given intravenously as an SD or drip (which usually requires a separate access) (see Table 4.1).

The aim of treatment is to maintain the patient's fluid balance and thus to prevent (prophylactically) or treat (therapeutically) effusion and edema formation.

If oliguria is present postoperatively with otherwise good circulatory conditions, urine output can frequently be "push-started" by a single dose of furosemide. However, the subsequent development of an intravascular volume deficiency must be avoided. The cause of the diminished urine output in this context is then usually residual intrarenal vasoconstriction or stress-related hormonal antidiuresis, and not a true "kidney problem."

If postoperative low cardiac output syndrome is the reason for oliguria to occur, which usually occurs 6–48 h after surgery, urine output should be maintained by means of repeated or, preferably, continuous furosemide administration *after optimization of all hemodynamic parameters or factors*. In our experience, this can

Table 4.1 Information on furosemide

Possible benefits	Increase in RBF Tubular rinsing Reduced tubular O_2 consumption
Possible disadvantages	Hypovolemia Hence: decrease in CO Electrolyte imbalance Metabolic alkalosis
Mechanism of action	Is actively secreted in the proximal tubule Acts from the luminal side Inhibition of the Na-K-2Cl transporter Inhibition of reabsorption of about 25–30% of filtered Na Excretion of semi-isotonic to isotonic urine Increase in fractional excretion of Na, K, Cl, Ca, and Mg
Pharmacokinetics	Oral availability very variable (10–90%) Onset of action within minutes Short duration of action (half-life 1–2 h) High albumin binding (> 95%) Elimination: 50% unchanged in urine In renal impairment: higher dose In neonates: higher dose (immature tubular function)
Benefits of a drip	Better efficacy (more effective urine excretion) Less toxicity Fewer electrolyte problems
Adverse effects	Hypokalemia, hypomagnesemia, hypocalcemia Hyper- or hyponatremia Metabolic alkalosis Ototoxicity (rare) Loss of water-soluble vitamins Allergic reactions Interstitial nephritis

control the usually temporary impairment of excretory function until the low cardiac output is corrected or overcome (improvement usually within the first 3 days postoperatively). Patients whose urine production ceases completely without furosemide usually recover considerably more slowly, even if peritoneal dialysis (PD) is ultimately initiated. In our view, the general rule should therefore be *urine output should never be allowed to drop off*. Postoperative PD, a treatment which in our view seems considerably more invasive, is only very rarely necessary with this approach.

We start with multiple doses of furosemide (e.g., 4–6 × 0.2–1.0 mg/kg). If the total dose of 4–6 mg/kg/day is reached, a furosemide drip is used (max. 0.3–0.5 mg/kg/h). As shown in Table 4.1, a drip has various advantages (see Table 4.1), so that it should be considered at an early stage.

Theophylline (0.2 mg/kg/h) can be added to the furosemide drip. Theophylline acts as an adenosine-1 receptor antagonist and can increase RBF. However, in the prevention of AKI (acute kidney injury), the scientific evidence to support the use of theophylline is lacking. The same applies to the use of "renal dose dopamine."

Table 4.2 Furosemide dosage

	"Push starting" of urine excretion	Inadequate urine output (after or during optimization of circulation)	Inadequate urine output despite single furosemide doses	Prophylactic or therapeutic furosemide administration in special situations with risk of volume overload, e.g., Glenn, TCPC, ECMO (without hemofiltration)
	Dose absolute	Dose absolute	Drip (mg/kg BW/day)	Drip (mg/kg BW/day)
Neonates	1–2 mg	6 × 1–4 mg	3–6 mg/kg BW/day	3–6 mg/kg BW/day
Infants	2–3 mg	4–6 × 1–6 mg	3–6 mg/kg BW/day	3–6 mg/kg BW/day
Young children	3–5 mg	4–6 × 2–10 mg	3–6 mg/kg BW/day	3–6 mg/kg BW/day
Older child	5–10 mg	4–6 × 5–20 mg	2–6 mg/kg BW/day	2–6 mg/kg BW/day

A further option for stimulating urine output with loop diuretics involves the administration of ethacrynic acid (Reomax®, Hydromedin®). This usually enables an additive diuretic effect to be achieved despite maximum furosemide therapy (dose, 1–2 mg/kg BW/day in 1–3 SD). The additional use of thiazide diuretics and spironolactone appears useful theoretically for selective nephron blockade (inhibition of the compensatory increase in Na absorption in distal tubular segments) but is generally not used in the acute treatment of oliguria. Stimulation of urine output with mannitol (0.25–1.0 g/kg BW) or dopamine (renal dose, 1–3 mcg/kg/min) is also not a routine measure. For the dosage of furosemide, see Table 4.2.

If, despite pharmacological support, urine output cannot be stimulated sufficiently to achieve an equilibrated fluid balance, i.v. fluid intake (particularly of "free water", i.e., low-percentage glucose solutions) must be reduced no later than the first postoperative day. Infusions, drugs, and enteral intake should be reviewed for their nature, composition, and the need for them. In this context we recommend using individually customized parenteral solutions rather than industrially pre-prepared solutions, including drugs in the balance calculations (draw up drugs, e.g., antibiotics, in the smallest possible volume), and discussing with nursing staff how to spare fluids.

A maxim of chronic diuretic therapy is that Na restriction increases the effectiveness of treatment. However, this usually cannot be achieved in an acute situation since losses of ECS (extracellular space), for example, should be offset by isotonic electrolyte solutions. Furthermore, additional noxious substances that can further impair renal function must be avoided in the phase of oliguria (or renal impairment).

4.5 Nephrotoxins

Many potentially nephrotoxic drugs are used in postoperative intensive care therapy. Table 4.3 provides an overview of possible nephrotoxic factors associated with cardiac surgery.

Table 4.3 The main nephrotoxins in the intensive care unit

Nephrotoxic drugs	Current risks	Preexisting risks
Antibiotics/antifungals: aminoglycosides, vancomycin/teicoplanin, beta-lactam AB, amphotericin B Acyclovir, ganciclovir	CPB with fluid volume deficiency CPB with DHCA Prolonged CPB ECMO Hemolysis Rhabdomyolysis Abdominal compartment	Morphological kidney injury Cyanotic heart defect Syndromal diseases Urine transport disorders Recurrent pyelonephritis Neonatal asphyxia UVC Status post-cardiac surgery with renal injury
Cyto-/immunostatics CsA, tacrolimus Cyclophosphamide Cisplatin		
Other: Contrast media, NSAID, ACE inhibitors, ATR blockers, HES?		

DHCA deep hypothermic circulatory arrest, *UVC* umbilical venous catheter

4.5.1 Dosage of Drugs in Renal Impairment (Critical Reduced GFR)

If there are signs of renal impairment (decrease in GFR and/or increasing creatinine levels), the doses of drugs that are primarily eliminated by the kidneys may need adjustment. The repeated determination of plasma levels (trough levels) can be helpful in this respect, e.g., with aminoglycosides. Even in renal failure, the initial dose should normally be chosen to obtain effective levels. However, dose and/or interval must be adapted accordingly for all following administrations to prevent toxic levels from occurring. GFR-related dosage recommendations can be found at https://kdpnet.kdp.louisville.edu/drugbook/pediatric/ (for estimating GFR, see above).

4.5.2 Rhabdomyolysis

Following the death of muscle cells, larger quantities of myoglobin are released. This can happen if the muscle is damaged:

- By trauma (e.g., accident, electrical current, excessive muscle activity, pressure lesions in the case of immobility).
- By ischemia (e.g., thromboembolic, compartment syndrome, shock).
- By inflammation (e.g., myositis, necrotizing fasciitis).
- By hyperthermia (e.g., malignant hyperthermia).
- By drugs (e.g., statins, cocaine).
- Disturbance of the internal environment (e.g., hypokalemia, hypophosphatemia).

Rhabdomyolysis can follow an asymptomatic course but can also result in life-threatening acute kidney injury. The most sensitive indicator of muscle damage in the blood is creatine kinase (CK, normal, < 250 IU/L). In the

absence of cardiac or cerebral infarction, CK levels >5000 IU/L indicate severe muscle damage (increase within about 12 h after muscle damage, maximum after 1–3 days, fall about 2–3 days after muscle damage; half-life of CK about 1.5 days).

The myoglobin released in rhabdomyolysis (molecular weight, 17 Da(ltons); half-life, 2–3 h) is converted in the liver to bilirubin and is excreted as such or directly as myoglobin via the kidney; at urinary concentrations of > 100 mg/dL (normal, < 0.3 mg/dL), the urine is colored brown. However, three factors must be combined for acute kidney injury to occur: hypovolemia, acidosis, and formation of myoglobin conglomerates in the renal tubules. The combination of intrarenal vasoconstriction, tubular obstruction, and directly cytotoxic effects ultimately culminates in oliguria/anuria. This explains why there is no clear serum myoglobin cutoff value above which AKI occurs. Serum values as low as >500 ng/mL can be critical (or urinary myoglobin >10 mg/dL). There is also no 100% correlation between CK levels and serum myoglobin.

At serum myoglobin levels >500–1000 ng/mL (or serum CK >5000–10,000 IU/L), forced dialysis with urinary alkalinization is recommended for prophylaxis of AKI (if urine output is maintained). The main effect is adequate hydration. It is disputed whether diuretics or alkalinization contributes additionally to the prevention of AKI. Hemofiltration (HF) should be considered at values >5000 ng/mL, particularly in the presence of oliguria (myoglobin is eliminated better by hemofiltration than by hemodialysis).

Procedure of Forced Diuresis

Hyperhydration:

- 1.5–2 × Intake (= about 2–3 L/m^2/day)
- With 0.9% NaCl or half electrolyte solution.
- Target urine output: > 4 mL/kg/h.

Diuretics:

- Mannitol:
  - Benefit: no acidic urine.
  - 0.25–1 g/kg i.v. over 20 min every 4–6 h
- Furosemide:
  - Disadvantage: acidic urine.
  - 0.5–3–6 mg/kg/day in 4–6 SD
  - Drip: 0.1–0.3 mg/kg/h.

Urinary alkalinization:

- Sodium bicarbonate 8.4%: 0.25 mmol/kg/h.

Duration of forced diuresis: 24 to max. 72 h (depending on fall in serum myoglobin)

4.5.3 Possible nephroprotective substances

The following substances had positive or protective effects on renal function in experimental situations:

- L-thyroxine (5 µg/kg BW/day).
- Theophylline (5 mg/kg BW/day).
- N-acetylcysteine (NAC/ACC; 30–45 mg/ kg BW/day).

However, a general recommendation about the use of these substances cannot be given, since the clinical evidence for their effectiveness is lacking.

4.6 Definition of Renal Failure (see Table 4.4) and Indication for Renal Replacement Therapy (RRT)

The cause of acute postoperative renal failure is usually multifactorial (hemodynamic factors, ischemia-reperfusion, nephrotoxins, etc.). A clear distinction between prerenal and renal disorders is frequently difficult in postoperative intensive care medicine (postrenal disorders other than catheter obstruction or preexisting urinary tract disease can generally be ruled out). If there is a further decrease in urine output (anuria) despite optimization of hemodynamics, avoidance of nephrotoxic substances, and pharmacological diuretic therapy, renal function can be temporarily replaced by a renal replacement therapy (e.g., PD or hemodialysis). The argument for starting RRT in the postoperative period is often the increasingly positive fluid balance rather than a precise laboratory parameter (e.g., creatinine or BUN values). However, the clinical dynamics of the renal failure must also be taken into account.

The indication for a renal replacement procedure is usually established in:

- *Hyperhydration with effusions* (*pleural effusion*, *ascites*) and *edema* (*lung*, *brain*).
- Hyperkalemia (K > 6.5 mmol/L or symptoms).
- Cardiac volume overload (CVP > 18 mmHg).
- Anuria and AKI > 2 days.
- Increasing metabolic acidosis (pH < 7.0).
- Urea >200 mg/dL (> 35 mmol/L).
- Rhabdomyolysis (myoglobin >5000–10,000 ng/mL) *and* oliguria.

Table 4.4 Network definition and staging of AKI – acute deterioration of renal function

Stage	Serum creatinine criteria	Urine output criteria
1	Increase ≥0.3 mg/dL or increase to more than 150–200% from baseline	< 0.5 mL/kg/h for more than 6 h
2	Increase to more than 200–300% from baseline	< 0.5 mL/kg/h for more than 12 h
3	Increase to more than 300% from baseline or increase ≥4.0 mg/dL with an acute increase of at least 0.5 mg/dL	< 0.3 mL/kg/h for 24 h or anuria for 12 h

4.7 Treatment of Transient Renal Failure by PD

4.7.1 Principles

In peritoneal dialysis, the peritoneum serves as a large, well-perfused (semipermeable) membrane through which both fluid and substance exchange occurs. By introducing an osmotically active fluid into the peritoneal cavity, water can thereby be removed from the blood. In addition, urinary excreted substances diffuse concentration- and time-dependently into the peritoneal dialysis fluid, resulting in these substances being cleared from the body.

By analogy with hemodiafiltration, it can be said that:

- The peritoneum is the dialysis filter (surface, permeability).
- The perfusion of the peritoneum corresponds to the blood flow in hemodialysis.
- The composition of the dialysis fluid, the quantity of dialysate, and the contact time determine the exchange factors.

4.7.2 Contraindications

There are only a few contraindications to PD:

- Abdominal surgery <5–7 days or abdominal drains.
- Abdominal wall defects.
- Communication between abdomen and thorax (e.g., congenital diaphragmatic hernia).
- Extensive abdominal adhesions.
- VP shunt (ventriculoperitoneal shunt) = relative contraindication.

Gastrostomy (PEG, percutaneous endoscopic gastrostomy), ileostomy, vesicostomy, and prune-belly syndrome are not contraindications for PD.

4.7.3 Benefits and Disadvantages of PD

See Table 4.5.

4.7.4 Procedure

4.7.4.1 Insertion of a PD Catheter

- By the Seldinger technique:
  - PD catheter without cuff, straight (e.g., 8.5 F Cook® PD catheter).
  - Tenckhoff catheter with one cuff, straight or curled (e.g., 9.5 F Cook®-Tenckhoff catheter).

Table 4.5 Benefits and disadvantages of PD

Benefits	Disadvantages
No vascular access No systemic heparinization No blood contact with foreign surfaces Ease of handling Gentle substance and fluid exchange Also possible in circulatory instability	Less effective in: Intoxication Hyperkalemia Metabolic diseases (e.g., hyperammonemia) Massive volume overload (e.g., acute pulmonary edema) Bowel damage possible on catheter insertion (rare) Inflammation with peritonitis possible Increased intra-abdominal pressures with impairment of respiratory situation possible (IAP during PD normally <10 mmHg)

  - Pigtail catheter (e.g., 8 F Cook® pleural/pneumopericardial drainage set); one or (if necessary) two catheters can be used.
  - Puncture site: e.g., left or right lower abdomen, on a line between the umbilicus and the superior iliac crest, half way along, puncture more or less vertical to the table beneath – ultrasound-guided.
  - Complications: injury to the bowel or other abdominal organs, bleeding, infection, mechanical obstruction of the catheter, leakage.

- By pediatric surgery in OR:
  - Usually Tenckhoff catheter with two cuffs, straight or curled (e.g., 9.5 F Cook®-Tenckhoff catheter).
- PD catheter size:
  - ≤ 3 kg: e.g., 8.5 F, 8 cm
  - 3–20 kg: e.g., 9–11 F, 15 cm
  - ≥ 20 kg: e.g., 11–15 F, 20 cm.

4.7.4.2 Choice of PD Fluid

- Frequently used PD solutions (Fresenius):
  - High glucose solution (4.25% glucose): for maximum water removal (CAPD = continuous ambulatory peritoneal dialysis).
  - Intermediate glucose solution (2.5% glucose): at steady state, gentle to the peritoneum.
  - Low glucose solution (1.5% glucose): Standard solution, more rarely used for acute dialysis.
  - All three solutions contain lactate (35 mmol/L).
- Additives:
  - Heparin 200 IU/L (200 to max. 1000 IU/L).
  - In hypokalemia: 7.45% KCl max. 4 mmol/L *(never more).*
  - In infection: antibiotics (cefuroxime, cefazoline, ceftazidime 125 mg/L; vancomycin, 30 mg/L; teicoplanin, 20 mg/L; tobramycin, 8 mg/L; gentamicin, 8–10 mg/L).

- Use of a closed catheter system (change of system every 48 h).
- Bicarbonate-buffered solutions are probably more beneficial in circulatory shock than lactate-buffered solutions as they may support lactate clearance.

4.7.4.3 Prescribing PD

Examples of prescribed dialysate amounts and PD cycles (duration and number) are given in Table 4.6.

Smaller dialysate volumes are used to begin with to prevent leaks from the catheter entry site (avoidance of increased intra-abdominal pressures while peritoneal compliance still remains low). Usually this can be increased to the target volume over the course of a few days (depending on tolerability and dialysis requirement).

The best water elimination can be obtained with frequent short cycles (30–60 min.) (A negative water balance is usually the main aim initially.) This requires the choice of a more highly concentrated glucose solution. Conversely, urea and creatinine clearance are better with longer cycles (>60 min.). Therefore, lower-concentrated glucose solutions are used at steady state (also because they cause less osmotic irritation of the peritoneum). The cycles can be extended over several hours as required.

Rule of thumb:

Frequent, short cycles, high glucose concentration→ increased elimination of water.
Longer cycles→ better elimination of substances normally excreted in the urine.

4.7.4.4 Monitoring

- Vital parameters: EKG, BP, SpO_2, temperature.
- Daily laboratory tests:
  - In blood: differential blood count, CrP, creatinine, urea, protein, electrolytes, BGA.
  - In the dialysate: protein and cells and prophylactic microbial examination (if stable, only every 48–72 h, where necessary).
- Repeated blood glucose: can vary considerably with high glucose solutions.

Table 4.6 Prescribing PD – recommendations

	Amount of dialysate (mL/kg BW)		Cycle
	Start	Aim	
Neonates	10–20	20–30	Inflow: about 5–10 min (depending on flow resistance) Dwell time, 30 + X min; initially, 30–45 min; later, 45–60 min; in hyperkalemia or hypervolemia, if necessary 20–30 min Outflow: 10–30 min (depending on flow resistance) Number of cycles/day; initially, usually without interruption (e.g., 24–36 cycles/day); then, 6–12–24 cycles/day, according to need; after target dialysate volume achieved, 2–4 cycles/day
Infants/ young children	15–20	40–50	
> 25 kg BW	15–20	30–40	

4.7.4.5 Complications

Losses via the dialysate:

- Protein loss: about 0.3–0.5 g/kg BW/day.
- Phosphate and electrolyte loss.
- Losses should accordingly be replaced through the diet.

Leakage from the catheter outlet port:

- Discontinuation for 24–48 h.
- Smaller volumes, more frequent cycles.
- Where applicable, try to seal the leak (fibrin glue, cerclage), otherwise surgical reinsertion.

Peritonitis:

- Usually: staphylococci (60%), enterococci, and gram-negative intestinal bacteria (20%), fungi (< 5%).
- Symptoms (not always present): cloudy peritoneal fluid (>100 leukocytes/μL, >50% neutrophils), fever, abdominal pain.
- Antibiotics (systemic and intraperitoneal):
  - Vancomycin and ceftazidime.
  - Systemic dosage according to estimated GFR (and levels).
  - Intraperitoneal dosage (see above).
  - Duration: about 2–3 weeks.
- Antifungals (systemically only):
  - Amphotericin B not intraperitoneally (damages the peritoneum).
  - Liposomal Amphotericin B (AmBisome®) i.v.
- It is not absolutely necessary to interrupt PD in the presence of peritonitis. (PD is associated with rinsing of the abdominal cavity; where necessary, prolonged cycles, which increase exposure time to antibiotics, can be chosen.)
- PD should be interrupted in the case of uncontrollable (life-threatening) abdominal infections and *always* in fungal peritonitis.

Problems with inflow or outflow:

- Never “pump” in or “aspirate” out dialysate by syringe.
- Positional check of the catheter (X-ray), rinsing of catheter.
- Treatment of constipation and intestinal paralysis.
- Where applicable, increase dialysate volume.
- Change patient’s position.
- Where applicable, increase quantity of heparin in the dialysate; where applicable, catheter lysis.
- Where applicable, reinsertion elsewhere.
- Where applicable, surgical resection of the omentum.

If the PD is inefficient (insufficient control of fluid balance and retention values), a severe abdominal infection occurs, or the patient otherwise does not tolerate PD, switch to a hemodialysis procedure.

4.8 Hemodialysis

4.8.1 Practical Procedure in Continuous Venovenous Hemodialysis

Essentially four physical principles underlie hemodiafiltration (see also the Prismart lecture by Gambro-Hospal, which is available as a tutorial at http://www.Gambro.com). See Table 4.7 for the operating principle.

To be able to begin blood cleansing, the catheter access site and type of catheter must be chosen (see Table 4.8 and 4.9).

4.8.1.1 Choice of Filter

The choice of filter (e.g., the Prismaflex filter from Gambro; see Table 4.10) can be made on the basis of the following rule of thumb: filter surface area (m^2) ≤ patient's body surface area (m^2). The filter consists of 6000–9000 hollow fibers, and the internal diameter of a hollow fiber is a few hundred µm with a wall strength of about 10–40 µm. Filter life-span (with heparin): about 72 h (in practice, as long as the filter is good).

Table 4.7 Operating principles in substance elimination

Diffusion	Osmosis	Ultrafiltration	Convection (solvent drag)
Equalization of the particle concentration across a semipermeable membrane along a concentration gradient Effective diffusion only occurs for substances <1000 Da	Equalization of the particle concentration by liquid movement through the semipermeable membrane when particle balance is prevented	Compression of fluid (e.g., primary urine) through a semipermeable membrane due to a pressure gradient that exists across the membrane	Transfer of dissolved particles through a semipermeable membrane with the compressed ultrafiltrate (for molecules with an S = 1, the concentration in the ultrafiltrate corresponds to that of plasma) Substances >1000 Da can also be eliminated according to their S.
Particularly in dialysis		Particularly in filtration	Particularly in filtration

Adsorption is utilized in hemoperfusion if noxious substances, e.g., in the charcoal filter, are adsorbed during circulation. Adsorption (e.g., proteins, cytokines) is also present to some extent with the filters used today

S sieving coefficient

Table 4.8 Venous access

Access site	Internal jugular vein (1st choice)	Subclavian vein	Femoral vein	Umbilical vein
	In children <5 kg, place catheter tip in RA	To be spared if there is a high risk of long-term dialysis due to danger of thrombosis or stenosis	Disadvantageous in "restless" patients due to risk of kinking; recirculation possible if high blood flows	In preemies and neonates in 1st WL

WL week of life

Table 4.9 Catheter for CVVHDF

Weight	Catheter	Catheter flow rates[a]	Blood flows in CVVHDF[a]
< 3 kg	2 × 4 F or 5 F (e.g., Cook®, single-lumen, 12 cm), also suitable for arteriovenous procedures	Up to 50 mL/min	10–30 mL/min
3–10 kg	6.5 F (e.g., Joline®, double-lumen, 10 cm), 7 F (e.g., MedComp®) double-lumen, 10 cm)	Up to 75 mL/min	3.0–5.0 kg: 10–50 mL/min 5.0–10 kg: 25–75 mL/min
10–30 kg	8 F or 9 F (e.g., Arrow®, double-lumen, 15 cm)	Up to 150 mL/min	10–15 kg: 50–75 mL/min 15–20 kg: 75–100 mL/min 20–30 kg: 100–150 ml/min
> 30 kg	12 F (e.g., Arrow®, double-lumen, 15 cm)	Up to 200 mL/min	150–200 mL/min
> 50 kg	14 F (e.g., Arrow®, double-lumen, 15 cm)	Up to 400 mL/min	200–400 mL/min

[a]All data are merely guide values

The occurrence of a bradykinin release syndrome (flush and arterial hypotension) with the use of AN69 filters is reported in the literature. However, we have not observed any such problems in the last approximately 15 years.

Examples of some sieving coefficients are given in Table 4.11.

4.8.1.2 System Preparation and Filling (Priming)

The system (set and filter) is filled with 0.5–1.0 L 0.9% NaCl with 5 IU/mL heparin strictly as instructed by the dialysis machine (e.g., Prismaflex menu). The pressure sensor should be carefully vented (an air bubble at the top of the filter shows the existence of the shield and is therefore normal).

Table 4.10 Prismaflex filters from Gambro

Name	Membrane	Patients	Filter surface area	Volume	Min. blood flow
HF 20	PAES hollow fiber	> 3 kg (see ref. [5]) 8–30 kg (according to Gambro)	0.2 m^2	Set: 60 mL; filter: 17 mL	20 mL/min
M 60	AN69 hollow fiber	> 10 kg	0.6 m^2	Set: 93 mL; filter: 42 mL	50 mL/min
M 100	AN69 hollow fiber	> 30 kg	0.9 m^2	Set: 152 mL; filter: 66 mL	75 mL/min
M 150	AN69 hollow fiber	> 50 kg	1.5 m^2	Set: 189 mL; filter: 105 mL	100 mL/min

Table 4.11 Some sieving coefficients with M 60–150 filters (Sustance-filtrate/substance-plasma)

Substance	Urea (60 Da) Creatinine (113 Da) Vitamin B12 (1355 Da)	Insulin (5200 Da)	Myoglobin (17,000 Da)	Albumin (68,000 Da)
Sieving coefficient	1	0.95	0.55	0.01

Priming with red blood cell concentrate should be considered in children aged <1 year (or BW <10 kg) and low Hct (<30%), since in these cases purely crystalloid priming is associated with marked hemodilution (particularly at a priming volume >7–8 mL/kg, i.e., about >5–10% of the blood volume). We prime the Prismaflex system after a rinsing process by attaching a red blood cell concentrate in place of the rinsing solution and filling the filter system with blood via the manual rinse function.

4.8.1.3 Dialysis/Replacement Solution

As *dialysis or replacement solution*, respectively, we use PhoXilium® (two-chamber system with NaHCO3), which has the following composition:

- Ca: 1.25 mmol/L.
- Mg: 0.6 mmol/L.
- Na: 140 mmol/L.
- K: 4.0 mmol/L.
- Cl: 115.6 mmol/L.
- HPO4: 1.2 mmol/L.
- HCO3: 30 mmol/L.
- Osmo: 293 mmol/L.

Bicarbonate-buffered solutions are generally to be preferred, particularly in the case of hepatic impairment after LTx (liver transplantation) in young infants or shock.

4.8.1.4 Connection to the Patient

The red catheter limb (red clamp) is connected to the red dialysis line. Red means that the blood is conveyed from the patient to the filter (red = aspiration). The blue catheter limb (blue clamp) is connected to the blue dialysis line. Blue means that the blood is returned from the filter to the patient (blue = pressure). In practice, any limb (red or blue) can be tried for the best conditions of blood withdrawal from and return to the patient, respectively (trial and error!).

In children >10 kg with Hct >25–30% and without severe coagulation disorders, CVVHDF can be started after the dialysis lines have been connected and the three-way valves have been opened. Hemodilution due to the filling volume (usually <10 mL/kg) and an associated heparin dose (< 5 IU/kg) is usually tolerated without any problems. For children < 10 kg, see under "Priming" (above).

4.8.2 Anticoagulation

Anticoagulation is necessary to guarantee the life-span of the filter. If, however, the patient has a severe coagulation disorder with a high risk of bleeding, anticoagulation may be omitted initially (although the filter may then need to be changed more frequently).

Anticoagulation can be given systemically with heparin (i.e., patient and dialysis unit) or locally with citrate (i.e., dialysis unit only).

Alternatives to heparin in HIT include prostacyclin (Flolan), danaparoid (Orgaran), and hirudin.

Anticoagulation with unfractionated heparin as standard procedure:

- Initial heparin bolus: 50 IU/kg (10–100 IU/kg) i.v. depending on initial PTT (thromboplastin time).
- Maintenance dose by continuous infusion: Administration in dialysis machine before the filter or via CVC directly into the patient: Dose: 10–40 IU/kg/h, depending on PTT.
- Target PTT: 45–65 s (1.5–2.0 × normal); no test on lines through which heparin is given; where necessary, AT III determination and replacement.
- Target ACT: 140–180 s (see Table 4.12).

ACT (activated clotting time) is a relatively simple rapid general coagulation test suitable for point-of-care monitoring or in emergencies (trend measurement). This involves measuring the time in which native blood coagulates at 37 °C in the presence of an activator, such as kaolin (Hemo-Tec® ACT-II from Medtronic). Normal ACT is 120 ± 15 s – each patient usually has his or her own baseline (Medtronic values are on average 20–50 s lower than Hemochron values).

Table 4.12 Target anticoagulation values in normal CVVHDF with heparin

	ACT (s)	Platelets (10^9/μL)	PTT (s)	AT III (%)
Normal operation	140–180	80–200	45–65	> 80

Table 4.13 Heparin management after ACT

Current ACT	Heparin bolus (IU/kg BW)	Increased heparin infusion
ACT <100 s	100	Test first, then increase
ACT <130 s	50	Test first, then increase
ACT >130 s	No bolus	About 10–15%
ACT >150 s	No bolus	About 5–10%
ACT 170–200 s	No bolus	Monitor in 2–4 h
ACT >220 s		Reduction by 10–15%
ACT >230 s		Reduction by 20%
ACT >250 s		Discontinue heparin for 1 h

Interfering factors: prolonged in hypothermia and hemodilution, heparin (no linear dose-effect relationship), disseminated intravascular coagulation (DIC); relatively resistant in respect of platelet disorders, prolonged in (severe) thrombocytopenia.

4.8.2.1 Management of Heparin Dosage

Unfortunately, we cannot give a general rule for the heparin dosage, since both the patient's conditions (bleeding, platelet count, fibrinogen, hemolysis, etc.) and dialysis-related factors (pressures, filter problems, etc.) must be taken into consideration.

From experience, following the initial bolus, treatment can be continued with a heparin dose of about 12.5 IU/kg/h (= 300 IU/kg BW/day).

ACT is then tested before the bolus heparin dose and 30 min after the bolus. Anticoagulation is then guided by ACT (monitoring, e.g., every (1–4 h). See Table 4.13.

These are guide values, which may need to be modified in each individual case. In particular, active bleeding, hemolysis, thrombocytopenia, or thrombocytosis, as well as signs of DIC or hyperfibrinolysis have to be taken into consideration. Further laboratory tests as well as the determination of ACT will therefore also need to be undertaken regularly:

- Every 6–8 h: blood count, coagulation tests (PTT, prothrombin time (INR), fibrinogen).
- Every 12–24 h: additionally liver and kidney function tests, hemolysis parameters, AT III, D-dimers.

4.8.2.2 Anticoagulation with Citrate (Prismaflex in CVVHF Mode) (See Table 4.14)

In citrate renal replacement therapy (RRT) with the Prismaflex, sodium citrate is administered via the "pre-blood pump" (PBP, for explanation see below) for extracorporeal anticoagulation. As soon as the blood has left the patient, it is mixed with the citrate solution (see Fig. 4.1). We use Prismocitrate®, which contains sodium, chloride, and also 18 mmol/L trisodium citrate. Citrate binds the Ca2+ in the blood,

Table 4.14 Citrate dialysis with Prismaflex®

Prismaflex®	
Parameters to be set:	
Mode	Preferably CVVHF (alternatively also CVVHDF)
Target citrate concentration (mmol/L)	3.0–3.5 mmol/L
Blood flow rate (mL/min)	Age-dependent: 20–200 mL/min (see Table 4.15)
Dialysate rate (mL/h)	Not applicable in CVVHF mode (for CVVHDF see Table 4.15)
Replacement rate; post (mL/h)	Min. rate to be set: 5 mL/kg/h (according to manufacturer, min. 100 mL/h)
Removal (mL/h)	Depending on balance target
Nonadjustable parameters:	
PBP rate (ml/h)	Obtained from chosen citrate concentration and blood flow
"Bags" used:	
Prismocitrate®	On the PBP scale (white)
PhoXilium®	On the replacement scale (purple); in CVVHDF also on the dialysate scale (green)
Haemosol B0® or Prismosol 2.0®	In hyperkalemia instead of PhoXilium®
Rinsing process/priming:	
Rinsing	First pass always with 1000 mL 0.9% NaCl +5000 IU heparin (= 5 IU heparin/mL), and then if desired second pass with 1000 ml 0.9% NaCl only
Priming	Where necessary in children <10 kg; using the menu field "Manual rinse," fill the set with RBCC (by eye)
Target parameters:	
Ca2+ concentration (extracorporeal)	0.3–0.4 mmol/L (if Ca2+ < 0.25 mmol/L, reduce citrate concentration; if Ca2+ > 0.45 mmol/L, increase citrate concentration)
Ca2+ concentration (in the patient)	1.0–1.2 mmol/L
Effluent rate (= "dialysis dose")	35–45–(60) mL/kg/h (can be adjusted to only a limited extent because of the relatively "fixed" PBP rate); in CVVHDF mode the dialysis rate must be reduced accordingly, where necessary
Filtration fraction (FF)	< 30–(40)%
Controls:	
Ca2+ concentration (extracorporeal)	Record from blue port (after the filter)
	Initially, every 1–2 h (for the first 4–6 h); if stable (for 2 h), every 4–6 h
Ca2+ concentration (in the patient)	Arterial (or also central venous)
	Initially, every 1–2 h (for the first 4–6 h); if stable (for 2 h), every 4–6 h
	If total Ca2+ > 3 mmol/l (> 12 mg/dL or Ca2+tot/Ca2+ion >2.5 risk of citrate intoxication (then if necessary reduce blood flow and/or citrate conc. (< 3.0 mmol/l); where necessary, replace Prismocitrate® temporarily by PhoXilium®)

(continued)

Table 4.14 (continued)

Replacements:	
10% Ca2+ gluconate IV	Into the patient via CVC (distant from dialysis catheter)
	Starting dose: 0.2–0.4 mL/kg/h (or 0.045–0.09 mmol/kg/h)
	Then, depending on value, increase/reduce by 10–20%
	Caution! When 10% Ca2+ chloride is used, twice as much ionized Ca2+ is released (for comparison: 10% Ca2+ gluconate: 1 mL = 0.225 mmol; Ca2+ chloride: 1 mL = 0.5 mmol)
Magnesium i.v.	0.15–0.3 mmol/kg/day (or 0.01 mmol/kg/h)
8.4% Na bicarbonate	0.25–1.0 mmol/kg/h (in metabolic acidosis)
AA, trace elements, water-sol. vitamins	Increase intake (if necessary, double daily dose)

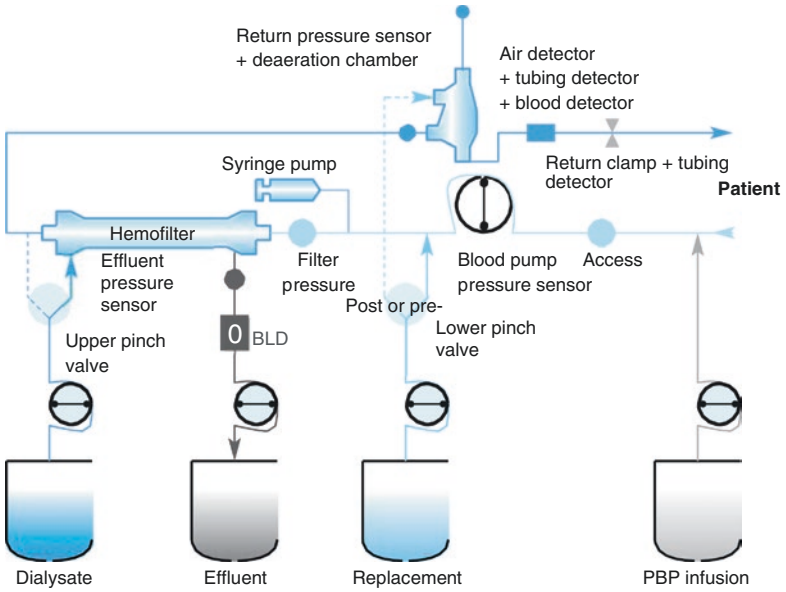

Fig. 4.1 Prismaflex (Gambro) diagram

thereby inhibiting coagulation. In the machine, the ionized Ca2+ must be 0.3–0.4 mmol/L, which is usually achieved with a citrate concentration of 3–3.5 mmol/L. The target citrate concentration and the selected blood flow determine the PBP rate (which cannot be freely set). The coagulation efficiency of citrate administration is checked postfilter (blue port) by tests of calcium (BGA), and the citrate concentration is adjusted as necessary. To prevent citrate-induced hypocalcemia in the patient (and the associated adverse effects), continuous Ca2+ replacement or Ca2+ restitution is required (target serum Ca2+, 1.0–1.2 mmol/l). At the Giessen Pediatric Heart Center, we use 10% calcium gluconate for this, infused directly into the patient via a CVC (initial dose, about 0.2–0.4 mL/kg /h or 0.045–0.09 mmol/kg/h). In addition, patients receive Mg2+ replacement (e.g., 0.15–0.3 mmol/kg/day).

We use the Pho*X*ilium® solution as a dialysis and post-replacement solution in citrate RRT, even though it contains 1.25 mmol/L calcium ("Collin protocol"). This simplifies the performance of citrate RRT without the slight transmembrane transfer of calcium causing major problems (the citrate concentration must be increased slightly, where necessary).

Adverse effects with citrate RRT: Citrate is normally metabolized in the patient's liver to bicarbonate, which can cause metabolic alkalosis. By contrast, citrate-induced metabolic acidosis can occur in the event of citrate intoxication or reduced hepatic metabolism (e.g., in small patients due to still inadequate hepatic performance, hepatic impairment). Additive sodium bicarbonate replacement has proved helpful in this respect (targets in BGA: pH 7.3–7.4, HCO3– = 20–25 mmol/L).

Increased citrate values may also induce hypocalcemia (and hypomagnesemia) as well as a consequent coagulation disorder. An increased total plasma Ca2+ concentration of > 3 mmol/L usually indicates citrate intoxication (discrepancy between increasing total Ca2+ and decreasing ionized Ca2+). Low serum calcium values can also have a circulatory-depressant effect, particularly in neonates and infants (vasodilation, negative inotropism).

Because of the usually high "turnover" in citrate RRT (high PBP rate), small patients also tend to cool off more. This can be avoided (if not therapeutically required) by additional warming (e.g., Bair Hugger®)

4.8.3 Prescription or Setting of CVVHDF (See Table 4.15)

The CVVHDF mode is beneficial for combining the benefits of HF (hemofiltration) with those of HD (hemodialysis).

- In the first step, an appropriate blood flow is chosen:
  - < 10 kg: 3–10 mL/kg BW/min
  - > 10 kg: 2–5 mL/kg BW/min
- In the next step, the target clearance rate is defined:
  - Clearance rate = dialysis rate + replacement rate + removal rate.
  - Is shown by the Prismaflex on the display in mL/kg/h and is called "effluent rate"
  - For a simpler description: *Clearance rate = dialysis rate + replacement rate* (for removal see below)

Table 4.15 Guideline values for basic setting, e.g., CVVHDF

	Blood flow[a] (ml/min)	Fluid removal[a] (mL/kg BW/h)	Dialysate flow[a] (mL/h)	Replacement rate[a] (mL/h)
Neonates	10–50	1–2 (max. 5)	250	150
Infants/young children	30–75	Ditto	400	300
Small children	75–100	Ditto	500	450
Adolescents/adults	100–200	Ditto	1000	1000

[a]All data are merely guide values

Replacement rate in Table 4.15 = sum of PBP rate and the replacement rate in the Prismaflex

  - aim for:
    < 10 kg: 35–55 mL/kg BW/h
    > 10 kg: 25–45 mL/kg BW/h
  - Using the Prismaflex it has to be considered that the total replacement rate is the sum of the "PBP rate" plus the "replacement rate".

- Ratio of HF to HD:
  - Usually 50:50.
  - For elimination of substances >1000 Da, HF is superior to HD.
  - For elimination of substances <1000 Da, HD is superior to HF.

- Ratio pre- to postdilution:
  - Usually 50:50 (where applicable, 33:66).
  - With high Hct > 0.4, where applicable 100% predilution.
- With HF: max. replacement rate = blood flow × 0.2.
- Lastly, a balance aim is defined and removal is set:
  - Removal rate (mL/h) = *A* + *B*.
    A (ml/h) = input (e.g., oral nutrition × 0.7 + i.v. administrations).
    B (mL/h) = target negative fluid balance.

- Example for prescriptions on the display of the Prismaflex:
  - Modus CVVHDF, anticoagulation with heparin.
  - Weight of the child = **20 kg.**
  - Prismaflex filter = **M60** (min. blood flow = 50 ml/min).
  - Catheter = 9F Sheldon catheter.
  - **Blood flow = 80 ml/min** (range 50–100 ml/min).
  - Desired clearance dose, for example, = 40 ml/kg/h × 20 kg = **800 ml/h.**
  - If HD and HF are wished to be 50:50:
  - **Dialysate rate = 400 ml/h.**
  - Replacement rate = 400 ml/h.
  - In the Prismaflex, the "total" replacement rate of 400 ml/h must be further partitioned in:
  - **PBP rate**, for example, = **300 ml/h** (then predilution).
  - **Replacement rate** (at the display), then = **100 ml/h** (pre- or postdilution as desired).
  - The filtration fraction should not be larger than 30%.
  - Last, the **removal rate** is set at the rate to achieve the desired fluid balance (e.g., **40–60 ml/h**).

4.8.4 Start of CVVHDF

Hypotension can occur on starting CVVHDF (due to hemodilution, volume shifts, mediator release, etc.). The resultant volume deficit should be corrected in the case of low CVP (< 6–8 cmH_2O) and hypotension by fluid volume administration (e.g.,

10 mL/kg 0.9% NaCl) or adaptation of the catecholamine dose. For monitoring during hemodiafiltration, see Table 4.16.

4.8.5 Pressure and Pumps

See Figs. 4.1 and 4.2. The Prismaflex has 5 roller pumps:

The blood pump aspirates the blood from the vein (negative pressure before the pump), pumps it through the filter, and then back into the patient (positive pressure after the pump). Blood flow rates are between 6 and 450 mL/min (adjustable in steps of 2–10 mL/min).

The replacement pump is responsible for replacement of the ultrafiltrate and pumps replacement solution (e.g., Pho*X*ilium® solution). It can administer the replacement solution pre- or post-hemofilter (settings 0–8000 mL/h).

The dialysate pump pumps the dialysis fluid (e.g., Pho*X*ilium® solution) through the dialysis phase of the hollow filter on the countercurrent principle. Its setting corresponds to the dialysis rate (setting 0–8000 mL/h).

The removal pump conveys the ultrafiltrate and the dialysate to the effluent bag. The hydrostatic pressure across the membrane, and hence the amount of ultrafiltration, is regulated via the removal pump (see below under TMP): Amount of ultrafiltration = replacement + removal.

Fluid removal can be adjusted between 0 and 2000 mL/h (in steps of 5–10 mL/h).

Table 4.16 Monitoring during hemodiafiltration

Patient	Balance	Filter[a]	Flows[a]	Pressures[a] (mmHg)	Coagulation	Laboratory
Temperature	Input	Operating time, when change, if applicable	Blood flow rate (mL/min)	Access pressure	ACT every 1–4–8 h	Urea, creatinine every 12–24 h
Circulation (BP, HR, CVP, ultrasound)	Output	ΔP, TMP	Dialysate rate (mL/h)	Effluent pressure	PTT every 6–12 h	BGA, electrolytes every 4–8 h
Weight			Replacement rate (mL/h)	Filter pressure	Platelets every 12–24 h	Protein every 24–48 h
			Predilution, postdilution	Return pressure		Phosphate, magnesium, total calcium every 24 h
			Removal rate (ml/h)	TMP		Drug levels
				ΔP		

[a]All these informations are shown by the Prismaflex

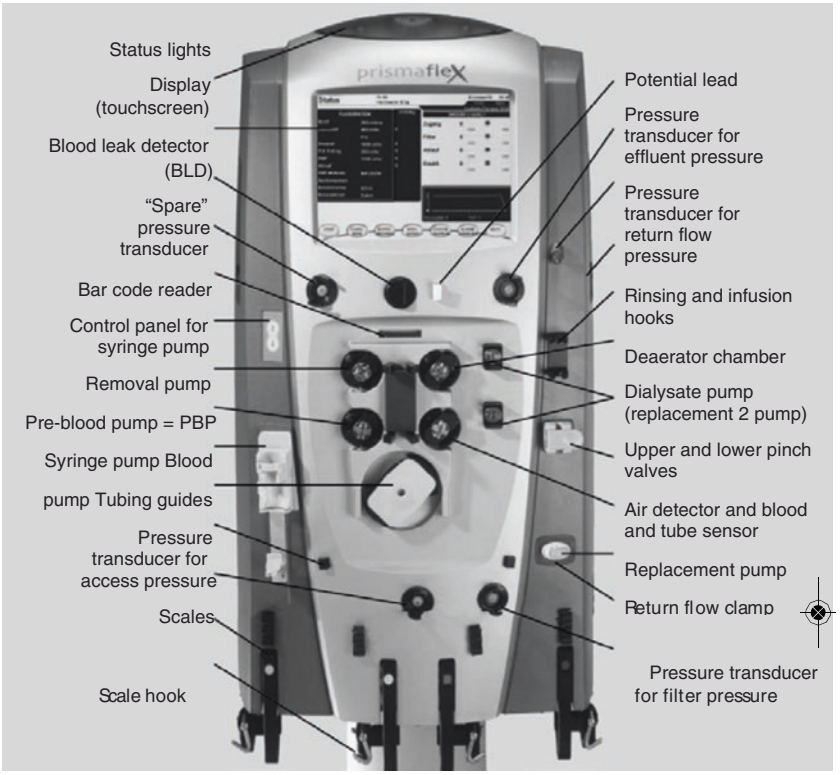

Fig. 4.2 Prismaflex device (Gambro). Explanation of the individual components

The removal pump has an output of between 0 and 10,000 mL/h (dialysate and ultrafiltration are conveyed to the effluent bag via this pump).

The *pre-blood pump* (adjustable between 0 and 4000 mL/h) is responsible for the rate of predilution replacement (at 100% predilution it corresponds to the replacement rate, at 50% predilution to half the replacement rate). In citrate RRT, the PBP pumps Prismocitrate®, for example, as anticoagulant before the blood pump (before the filter). The rate of Prismocitrate® pumped is considered a "replacement rate" (= filtration) and therefore adds to the effluent rate (= clearance rate; see Sect. 4.8.3).

The Prismaflex displays six pressures:

The *access pressure* (mmHg) is taken before the blood pump and – with a venous access – is usually negative. In adults, the access pressure values are between −150 and −50 mmHg. In children with a relatively large Shaldon catheter, the pressures are less negative. If the Prismaflex sounds an alarm (disconnection alarm) because an adequate access pressure is not detected, there are options for canceling the alarm, increasing the blood flow or Hct or incorporating artificial resistance by means of a clamp. By contrast, with very negative pressures (in which case the catheter usually suctions), the catheter should be rinsed, the catheter lumen replaced, or

the catheter changed. If the lower pressure limit is exceeded, the machine switches off to prevent possible damage from suction (if necessary, fluid volume administration in the event of intravascular fluid volume deficiency).

The *filter pressure* (mmHg) is recorded after the blood pump and before the filter. It is always positive (highest pressure in the whole system). Normal values for filter pressure are +100 to +250 mmHg.

The *effluent pressure* (mmHg) is recorded at the effluent sensor, i.e., between filter and filtrate collection bag. It is positive to negative. The removal pump regulates the effluent pressure according to the requirements from blood, replacement, and dialysate flow, as well as filter function, so that the specified removal rate is obtained (normal values −150 to +50 mmHg).

The *return pressure* (mmHg) is recorded behind the filter in the blood flow and is always positive (drive force for the return of blood to the patient; normal, +50 to +150 mmHg). With the Prismaflex, it is at least 10 mmHg and increases in the event of an obstructed catheter lumen, increased blood flow, or small catheter lumen, for example.

Calculated pressures:

- TMP = transmembrane pressure = mean pressure difference between blood phase and dialysate phase of the filter.
  - TMP = effective filtration pressure.
  - Prismaflex: TMP = $(P_{filter} + P_{return} / 2) - P_{effluent}$.
  - $(P_{filter} + P_{return} / 2)$ = hydrostatic pressure of blood (always positive).
  - $P_{effluent}$ = hydrostatic pressure of ultrafiltrate (negative to positive).
  - Determines the amount of ultrafiltrate (i.e., the higher the TMP, the higher the ultrafiltration quantity – for a constant filter quality).
  - Normal: +100 to max. +350 mmHg.
  - Increased blood flow and/or replacement rate in predilution (higher hydrostatic pressure of blood) and an increase in removal rate (more negative pressure of ultrafiltrate) result in an increase in TMP.
  - TMP also increases with deterioration of filter quality (microthrombosis of the hollow fibers or clogging of the membrane pores), because increasingly higher pressures are needed to achieve the set aims (e.g., if filter pressure is very positive and effluent pressure very negative).
  - If TMP increases critically (> 250–300 mmHg), exchange the filter.

- *Filter pressure drop (ΔP)* – in the blood phase of the filter:
  - ΔP = (Pfilter−Preturn).
  - Corresponds to the pressure drop across the filter (on passage of the blood through the filter's hollow fibers).
  - Indication of the quality of the filter (i.e., ΔP rises with increased microclotting in the hollow fibers).
  - The ΔP profile during operation is the determining factor (e.g., at the beginning 10 mmHg, after 24 h 80 mmHg).

4.8.6 Management of Catheter Problems During Operation (e.g., Rinsing)

If suction by the machine or constantly increased return pressures recur frequently because of a catheter, it is better to allow the machine to circulate on its own for a short time. A short circuit between the inflow and outflow end of the catheter can be created for this purpose. Removal from the patient must then be turned back to 0 mL/h. The catheter can then be checked while the dialysis is running (i.e., lower risk of clotting). If this is freely aspirable (always begin with aspiration) and if the same problems occur after a further attempt at connection, each limb of the catheter must be rinsed with an arterial rinse (24 IU heparin/48 mL 0.9% NaCl) and if necessary changed.

4.8.7 Ending of CVVHDF Therapy

This is generally a clinical decision. Possible criteria are:

- Spontaneous urine output >0.5–1.0 mL/kg/h.
- GFR (kidney) > 20 mL/min.
- Clinical improvement of disease process.
- Stable urea and creatinine values despite interruption of RRT for 24–48 h.

Where applicable, pharmacological support is given (kidney initiation trial) with, e.g., furosemide and theophylline as a drip. After RRT is stopped, where possible the blood in the system is returned to the patient.

4.8.8 Appendix

4.8.8.1 Ultrafiltration via the Filter (See Fig. 4.3)

The blood pump removes the blood from the patient and pumps it over the filter back to the patient. Pressure in the blood compartment is highest before the filter (P_{filter}) and decreases across the filter (P_{return}). This fall in pressure is described as ΔP.

TMP exists across the filter membrane. It describes the mean pressure difference between the hydrostatic pressure of the blood compartment and that of the filtrate compartment. While the hydrostatic pressure in the blood compartment is defined by the pressures P_{filter} and P_{return} (i.e., by the set blood flow and the resistances in the system), the hydrostatic pressure in the filtrate can be regulated by the removal pump (which conveys the filtrate to the effluent bag). This provides control of the TMP and thus the quantity of fluid filtered (ultrafiltrate). Substance exchange occurs with the ultrafiltrate (convection) according to molecular

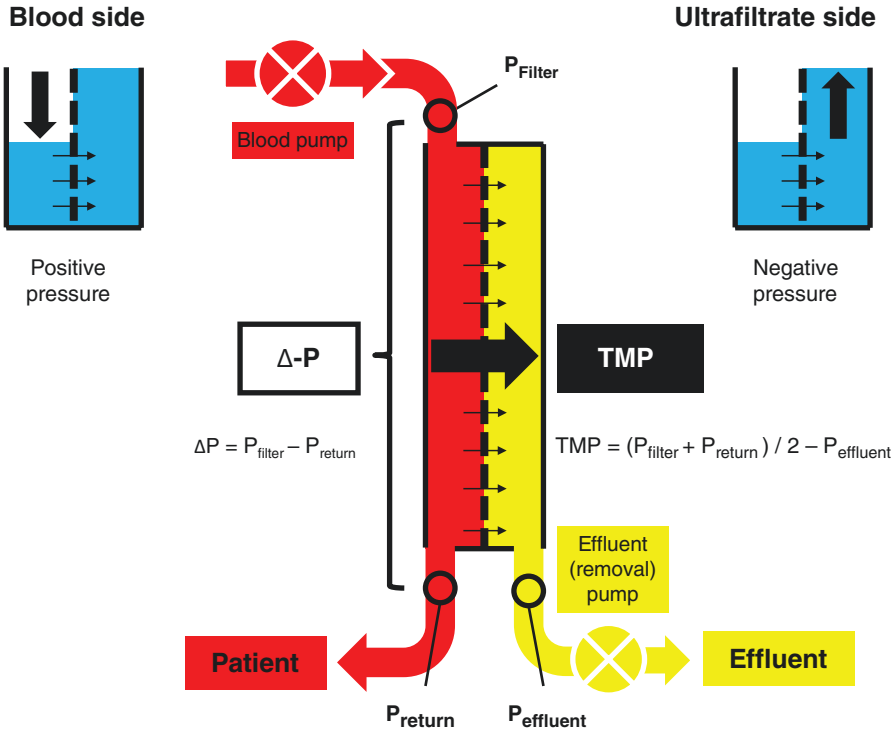

Fig. 4.3 Ultrafiltration via the filter (diagram)

weight, sieving coefficient, and membrane properties. In hemofiltration, the proportion of the volume of the ultrafiltrate that should not be lost to the patient is replaced by a replacement solution (not depicted here). Therefore, replacement rate + removal rate = ultrafiltration rate. The replacement solution can be administered before the filter (predilution) or after the filter (postdilution) (not depicted here; see Fig. 4.1).

4.8.8.2 Dialysis via the Filter (See Fig. 4.4)

The blood pump removes the blood from the patient and pumps it through the filter. The dialysate pump pumps the dialysate in the opposite direction through the filter (countercurrent principle). In pure dialysis, the exchange of substances occurs across the membrane as a result of the concentration gradient between the blood compartment and the dialysate compartment. Molecular weight, sieving coefficient, and membrane properties play a significant role in this process. The removal pump conveys the dialysate enriched with the eliminated substances to the effluent bag.

If additional fluid is removed from the blood in HD, the removal pump increases its rate relative to the dialysate pump; as a result of which, there is additional fluid filtration.

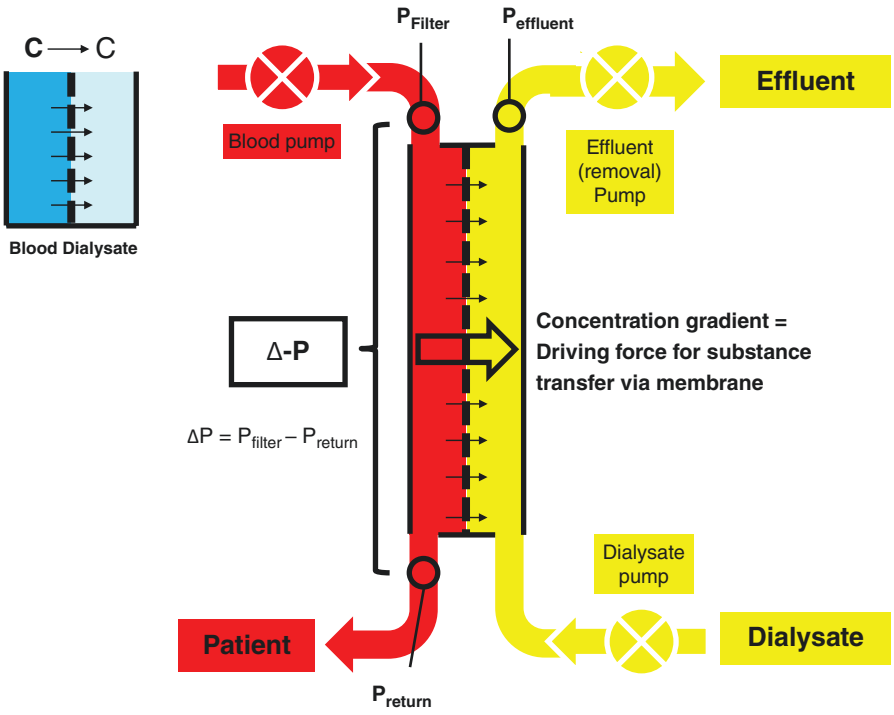

Fig. 4.4 Dialysis via the filter (diagram)

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Important Websites

1. http://www.dosing.de
2. http://legacy.owensboro.kctcs.edu/ gcaplan/anat2/notes/APIINotes3%20 urinary%20system.htm
3. http://lane.stanford.edu/portals/picu_ ppslides/Stanford_Prismaflex_ trainingPW.pdf (20.11.2012).
4. Further information on renal replacement therapy and prismafelx is available by contacting baxter international Deerfield IL, USA via: http://www.baxter.com/contact-and-support/contact.page

5 Fluid, Electrolyte, and Nutritional Management

Dietrich Klauwer

5.1 Basic Requirements

The basic fluid requirements in healthy humans vary considerably according to body weight and age. The baseline parameters are listed in Table 5.1.

Notwithstanding the above, these parameters play a subordinate role in intensive care medicine.

In this context, it is more on the following aspects that are contrasted with one another:

- Weight profile – fluid intake
- Clinical impression of hydration status – diuretic therapy
- Urine output, urine concentration – calorie requirement

Table 5.1 Basic fluid requirements

	mL/kg BW/d	In heart failure
Neonates	140	100
Infants <5 kg BW	120	90
Infants 5–10 kg BW	100	80–90
Young children 10–20	1000 + 50 × (BW – 10 kg)	1750 mL/m² BSA
20–30 kg	1000 + 50 × (BW – 10 kg) + 25 × (BW – 20 kg)	1750 mL/m² BSA
>30 kg	2000–2500 mL/m² BSA	1750 mL/m² BSA

In neonates start on 1st day of life with 60 mL/kg BW/d, increase to final amount by day 7
BSA body surface area

D. Klauwer
Department of Pediatrics, Singen Medical Center, Gesundheitsverbund Landkreis Konstanz, Krankenhausbetriebsgesellschaft Hegau-Bodensee-Klinikum, Singen, Germany

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D. Klauwer et al. (eds.), *A Practical Handbook on Pediatric Cardiac Intensive Care Therapy*, https://doi.org/10.1007/978-3-319-92441-0_5

- CVP, BP, SvO_2 – perspiration
- Heart rate – drainage losses
- Lung function – overall balance

5.2 Basic Requirements Post-cardiopulmonary Bypass (CPB)

It can normally be said that *after CPB* the total fluid amount, excluding volume replacement, should be calculated according to the postoperative time interval.

These figures should be regarded as a guide and represent an upper limit for the supply of free water in infusions. They are a consequence of the capillary leak induced by the extracorporeal circulation (ECC) phase. At the same time, the intracellular space, which remains constant in its composition during ECC, must be prevented from being further distended by free water from the extracellular space.

This very limited amount of fluid, particularly for critically ill patients, is in competition with enteral and parenteral nutrition and also with the frequently large quantities of drugs (drip and short-term infusion), so that the amount of free fluid, particularly in the configuration of long-term drips and the solution volumes of short-term infusions, must be strictly included in the calculation and reconciled (Table 5.2).

The fluid management of the intensive care patient must be subordinated to the primary aim, i.e., improving the O_2 supply to the body. This produces to a hierarchy of aims.

5.2.1 Treatment Aims of Circulatory Therapy

Specifically in patients with impaired cardiac function and *post-CPB leak*, a good CO can frequently only be ensured by increased preload and sufficient CVP. In addition, high CVP (= PAP) values are frequently required to improve pulmonary blood flow and increase saturation, particularly in passive lung perfusion (Glenn, total cavopulmonary connection [TCPC]).

In this case, following optimization of hemoglobin levels by pack red blood cells or of coagulation by fresh frozen plasma (FFP) or coagulation products, volume replacement therapy is then provided predominantly by Ringer's solution or normal saline solution. This volume must also be excreted again, as at least 70% reaches the extravascular space after a number of hours.

Table 5.2 Total post-CPB fluid volume

Surgery	POD 1	POD 2	POD 3	POD 4	POD 5	POD 10
750 ml/m²	1000 ml/m²	1250 ml/m²	1500 ml/m²	1750 ml/m²	And so on	And so on

POD postoperative day

Table 5.3 Total fluid amount and clinical particulars

Aspects	Laboratory results and findings
Edema	Hb
Fever	Electrolytes (esp. Na)
Urine color	Balance starts becoming negative?
Edema, but "dry" intravascularly	Ultrasound: cardiac findings and effusions
Microcirculation, warm hands	Weight?
Respiration/pulmonary auscultation	

This can be achieved only by sufficient CO, sufficient (renal) perfusion pressure, and diuretic therapy. Even so, urine output in the capillary leak phase lags behind intake, so that the patient must be balanced daily in this phase but more importantly still: urine production must not cease, and the intake of free water must be minimized, as the target parameters CO, HR, CVP, SvO_2, and urine output are of primary importance.

5.2.2 Treatment Aim of Lung Function

Since oxygenation in particular depends on the diffusion distance, i.e., to a large extent also on the interstitial pulmonary fluid, while on the other hand, the pulmonary capillary bed is particularly affected by leakage, fluid restriction represents a foundation stone in the treatment of lung function. In addition, fluid losses in the pleural space and abdominal cavity must be included in the calculation and also drained if necessary in order not to impair lung function as a result of compression from outside (Table 5.3).

5.2.3 Patient's Aspect

As a physical examination is the first procedure at the beginning of any patient visit, the clinical hydration status plays a primary role in the assessment of total fluid amount and diuretic therapy.

5.3 Practical Procedure in Fluid Management

After the clinical examination, go through blood gas analyses, laboratory tests, SvO_2, ultrasound findings, urine output, and any specific individual aspects conscientiously, and discuss the patient's status and the amount/type of fluid that is possible enterally with nursing staff:

- Establish *whether the patient is doing well* – certainly the case in more than half of pediatric (cardiac) surgical patients. In these patients follow the above rules on total fluid amount, and adjust carefully with diuretics in the event of a markedly increased need to drink.

- Establish *whether the patient is "poorly."* In this case, after reviewing all the circulatory and pulmonary parameters, renal function, and clinical parameters (see relevant individual chapters), it is necessary to work through the patient's data strictly and subsequently to adapt, i.e., usually minimize, the total fluid amount by suitable infusion and drug therapy.

As with fluid management, a basic plan for partial and total parenteral nutrition should be known. The patient clientele is then divided into those with an uncomplicated postoperative course and early institution of enteral nutritional on the one hand and critically ill patients with severe postaggression metabolism and prolonged parenteral nutrition on the other.

(See also Sect. 5.8).

Although each surgical intervention, and in particular each intervention with CPB, is a considerable stressor for the body as a whole, the severity of postaggression metabolism is not the same in each patient. As well as individual features, the following factors predispose to postaggression metabolism:

- Preoperative nutritional status
- Degree of surgical trauma, duration of surgery, and extent of circulatory changeover
- Shock
- Intra- and postoperative pain prevention
- Duration of ventilation
- Perioperative infections

To summarize *If the patient is critically ill, postaggression metabolism develops.*

Ideally a relevant disorder of glucose utilization will not occur in the patient postoperatively as a manifestation of *postaggression metabolism*. Although it is not known exactly what constitutes optimal metabolic control – how much glucose and at what point insulin – in the postaggression phase, the procedure outlined in Table 5.4 can be followed as a guideline for uncomplicated patients.

(Rule of thumb: total fluid amount equates more or less to the calorie requirement)

In order now to be able to generate the infusions in the postoperative phase, the following starting points are required:

- Amount of sugar in grams should be at least four times the amount of AA.
- Peripheral infusions not more than 12.5% sugar, 600–700 mosmol/L.
- The older (and larger) the patient, the longer it is possible to wait to introduce fat and AA.

Table 5.4 Memo water and nutrition (figures in g/kg BW/d)

	NN	YC 5–15 kg	Children 15–25 kg	Older children
Day of surgery	Minimum 3–4 g Sugar (G40%), BS 100–160 mg/dL, no AA	Minimum 3 g Sugar (G40%), BS 100–160 mg/dL, no AA	Minimum 2–3 g Sugar (G40%), BS 100–160 mg/dL, no AA	Minimum 1–2 g Sugar (G40%), BS 100–160 mg/dL, no AA
1st POD	>5 g sugar, 0.5 g AA, BS as described, initiation of enteral nutrition, first meal tea	4–5 g sugar, 0.5 g AA, BS as described, initiation of enteral nutrition (on previous day even)	3–4 g sugar, AA not mandatory, initiation of enteral nutrition (20–40% usually possible)	2–3 g sugar minimum, no AA, initiation of enteral nutrition
2nd POD	30–50% enterally, 0.5–1 g AA, 2–3 g sugar	50–70% enterally, AA not mandatory, 1–2 g sugar	50–70% enterally, AA not mandatory, 1–2 g sugar	As left column
3rd POD	60–80% enterally, residual infusion, 1–2 g sugar, no AA	60–80% enterally, residual infusion, 1–2 g sugar, no AA, or infusion for electrolytes only	Residual infusion for electrolytes or none	As left column
4th POD	No residual infusion	No residual infusion		
Final requirement	Sugar 12–14 g, AA 3 g, fat 3–4, TFA 100–140 ml/kg BW/d	Sugar 10 g, AA 2–3 g, fat 3 g, TFA approx. 100 ml/kg BW/d	8 g sugar, 2 g AA, fat 2 g, TFA 70–80 ml/kg BW/d	5–7 g sugar 1–1–2 g AA, 1–2 g fat, TFA 50 ml/kg BW/d

AA amino acid(s), *BS* blood sugar

(*Postaggression metabolism* is more severe in neonates but conversely lasts longer in older patients.)

5.4 Infusion Therapy in the Critically Ill Patient

If a patient has a severe disorder of glucose utilization and possibly also lactatemia as a manifestation of defective intracellular glucose utilization, there are two main approaches:

On the one hand, as described in Chap. 3 (Cardiovascular Monitoring and Cardiovascular Drug Therapy), the peripheral circulation must be optimized, and on the patient's part, the O_2 requirement must be reduced by analgosedation, optimized ventilation, and physical measures (cooling, peripheral warming).

On the other hand, the patient's "metabolic management" must be adapted. Since hyperglycemia accompanied by relative insulin resistance is the primary pathophysiologic manifestation, in addition to which the optimal patient management has yet to be precisely elucidated, it is only possible to proceed empirically:

Table 5.5 Energy in dietary components

	Calories
Glucose 1 g	4 kcal
Amino acids 1 g	4 kcal
Fat 1 g	9 kcal

Table 5.6 Blood sugar upper limits

	Insulin (insuman rapid)	Monitoring after start of insulin
Blood sugar >200–250 mg%	0.05 IU/kg BW/h	30 min
Blood sugar >400 mg%	0.1 IU/kg BW/h	30 min

- Reduction of glucose intake to the weight-adjusted minimum (given in Tables 5.4 and 5.5).
- If hyperglycemia >200–250 mg/dL persists on this treatment, initiate an insulin drip (see Table 5.6)

The target range for BS values is 100–180 mg/dL. As a rule, *postaggression metabolism* should not entail an external insulin requirement for more than 24–48 h. It is possible in these patients to start with 0.5 g AA/kg BW on the 1st postoperative day and to increase this subsequently to 1 g/kg BW on the 2nd–3rd postoperative day. In this case, administration of fat does not begin until after triglyceride levels have been determined (target <200 mg/dL).

Although enteral nutrition is frequently difficult because of the parallel development of a gastrointestinal transport disorder and the intense analgosedation (relaxation) in the critically ill patient, this should be initiated cautiously. In the continuing absence of intestinal activity, prokinetics should be tried (e.g., erythromycin i.v. 3–5 mg/kg BW/single dose t.i.d.).

5.5 Electrolytes

As well as supplementation with nutrients, the provision of electrolytes is essential.

Sodium, calcium, and potassium in particular play the primary role here, while the chloride concentration parallels the sodium concentration except in the case of severe intestinal losses. Since, however, magnesium also exerts a considerable membrane-stabilizing effect, magnesium levels should be monitored and treated in heart surgery patients with a tendency to arrhythmias. Normal phosphate levels are important for energy metabolism.

5.5.1 Potassium

In the postoperative phase and in patients with a tendency to cardiac arrhythmias, potassium levels must be kept constant in the range of 4.0–4.9 mmol/L. There are few exceptions to this rule. The most important factors here are essentially:

- *Regular potassium monitoring* (*in some cases hourly*)
- *Monitoring of urine output*
- *Monitoring of pH*: *Every*↑↓ *of 0.1 in pH entails a parallel* ↑↓ *in potassium of 0.3*

In any "energy deficiency situation," a potassium deficiency occurs simply as a result of increased accumulation of potassium from the body's cells (= potassium transport into the cell is energy-dependent) and the lack of reabsorption by the kidney.

However, increased accumulation in the presence of deficient renal perfusion can also result in the congestion of the accumulated potassium with a subsequent risk of hyperkalemia. In practical terms, this means that a high potassium requirement is also an indicator of sufficient renal perfusion, but at the same time, this must be closely monitored to prevent the complications of potassium deficiency.

By contrast, in the presence of slight heart failure and concomitant loop diuretic therapy, hypokalemia occurs almost as a matter of course in the postoperative phase. Apart from furosemide therapy, the predominant factor here is the renin-angiotensin-aldosterone system (RAAS) triggered in heart failure in the form of hyperaldosteronism. For this reason, as well as adequate administration of potassium (if possible orally), treatment with spironolactone is also beneficial.

In practical terms:

- *On the day of surgery*, calculate out 2–4 mmol/kg BW/d G10% drip infusion; in patients of less than 15 kg BW, with 1 mL/kg BW 10% magnesium (equivalent to 0.3 mmol/kg BW/d magnesium).
- *On postoperative day 1*, potassium drip infusion (with G10%) only, and add magnesium to the nutrition infusion depending on measured levels.
- *On postoperative day 2*, start oral potassium; if tolerated and if there is a low potassium requirement (always ask whether the patient still needs as much furosemide and whether spironolactone is to be added if necessary), potassium also in the main infusion (beneficial with a potassium requirement of ≤3 mmol/kg BW/d).

Hypermagnesemia can develop in parallel with hyperkalemia. In this case, simply reduce intake, use loop diuretics if necessary, and treat any coexisting hypocalcemia. EKG changes can appear at magnesium concentrations of about 2.5 mmol/L and above, and neuromuscular blockade and contraction failure of the heart (extremely rare) can occur from 5 mmol/L.

Hypomagnesemia due to inadequate postoperative intake or (drug-induced) increased renal excretion is more common. As there is both a risk of cardiac arrhythmias, contraction failure, and seizures, i.v. replacement therapy should be initiated (at values <0.8 mmol/L), and if they persist, treatment should then also be continued orally.

In practical terms: Daily requirement is approx. 0.3 mmol/kg BW/d Magnesium first with potassium (see above) and then in main infusion and then if necessary orally (particularly with large amounts of diuretics). If low values in the immediate postoperative phase, continue i.v. in patients with cardiac arrhythmia; high normal levels up to 2 mmol/L should be aimed for – replace up to 0.9 mmol/kg BW/d (Tables 5.7 and 5.8).

Table 5.7 Hyperkalemia

Hyperkalemia	Causes	Treatment	How exactly
Paresthesia	Urine output ↓, renal failure, and adrenal insufficiency	Stimulate urine output (Lasix)	10–15 ml/kg BW 0.9% NaCl and then 1–2 mg/KG KG Lasix
Bradycardia	Hemolysis	Increase renal perfusion	Resonium rectally (uncommon)
QRS prolongation (QT shortening) High T	Tumor lysis, rhabdomyolysis	Stop intake (no ringer as volume replacement)	Check all meds
Paralysis	Iatrogenic intake	Beta-mimetics (inhalational)	Inhalation of salbutamol, where necessary reproterol drip 0.1–0.5 µg/kg BW/min
Intestinal hypomotility (more common in hypokalemia)	Concealed potassium	(glucose) insulin drip acutely in 15 min: 0.1 IU/BW insulin +1 g/kg BW glucose	Thereafter 0.05–01 IU/kg BW/h Equalize Approx. 3 g sugar/kg BW/d
Confusion	Acidosis	Alkalosis induction, dialysis	Sodiumbicarbonate (to pH 7.5) if adequate ventilation, otherwise TRIS
	ACE inhibitors, Aldactone, sartans	Keep calcium high (membrane stabilization)	1 mL/kg BW 10% ca

Table 5.8 Hypokalemia

Causes	Symptoms	Treatment
Inadequate intake	Muscular weakness	Oral potassium
Loop diuretics	Intestinal atony	Always potassium drip 2 mL/h postoperatively = 2–4 mmol/kg BW/d
RAAS ↑		Start with Aldactone
Alkalosis	Tendency to cardiac arrhythmias	Always with magnesium replacement 0.3 mmol/kg BW/d
GI losses		Always treat hypomagnesemia concurrently
Renal losses (Bartter syndrome and pseudo-Bartter in cystic fibrosis)		Reduce ventilation in respiratory alkalosis

RAAS renin-angiotensin-aldosterone system

5.5.2 Calcium Metabolism

Calcium stores:

- Free Ca in serum (approx. 50% constitutes the physiologically active part)
- Protein-bound Ca in serum (particularly albumin)
- Complex-bound Ca in serum

Table 5.9 Hypocalcemia

Symptoms	Causes	Diagnostic features	Treatment
Hypotension	Hyperventilation	Ca (ion. + tot.), phosphate, mg, total protein	Ca gluconate 10% drip 1 ml/kg BW in G5%, start with 1 mL/kg BW/h
Contraction failure	Protein administration	PTH	First ca follow-up after $^1/_2$ h
Cardiac arrhythmias	Hypoparathyroidism (catch 22)	Catch diagnostics	Thereafter according to measured levels
Tetany	Vitamin D deficiency	Vitamin D, 25-OH-D (prerenal), 1–25-OH-D (renal hydroxylation)	Alkalosis therapy
Seizures			Ca administration, diazepam
Apnea in preemies			In event of metabolic problem, treatment according to disease

Rule of thumb: the younger the patient, the higher the Ca requirement and the more likely symptoms of hypocalcemia
PTH parathyroid hormone

Table 5.10 Calcium requirement

Requirement	mL/kg BW (calcium 10%)	mmol/kg BW in the postop phase and for TPN
Preemies <1500 g	10–12	(2.5–3)
Preemies >1500 g	8–10	(2.2–5)
Neonates	4–6	(1.1–5)
Infants <10 kg	2–4	(0.5–1)

TPN total parenteral nutrition

Acidosis releases Ca from protein binding; (hyperventilation) alkalosis binds Ca to proteins and results in hypocalcemic tetany (Tables 5.9 and 5.10).

In (postoperative) pediatric cardiologic therapy, hypocalcemia is of vital importance. It occurs to an increased extent after administration of FFP and albumin, since in this case previously ionized serum calcium is protein bound. In the event of hypocalcemia (<0.9 mmol/L serum Ca_{ion}), specifically postoperative symptoms can occur with major consequences, for which reason it is necessary to ensure Ca levels of more than 1 (total calcium more than 2) mmol/Lg.

Important As the body tries to keep the solubility product of Ca and phosphate constant, hyperphosphatemia (excessive intake, cell death, hypoparathyroidism or vitamin D intoxication, acidosis, and sepsis, as well as renal failure) can be accompanied by hypocalcemia, and this should be treated by reducing phosphate nutrition and, where applicable, oral chelating agents.

Hypercalcemia Since hypercalcemia (>2.8 mmol/L Ca in serum) in pediatric cardiologic intensive care occurs only in the event of infusion errors and extremely rarely in neonates with primary hyperparathyroidism (HPT), only a tabulated overview is given here (Table 5.11).

Table 5.11 Hypercalcemia

Causes	Clinical features	Diagnostic features	Treatment
Hyperparathyroidism	Intestinal atony, vomiting	Ca, P, PTH, APh	Stop Ca intake
Vitamin D intoxication	Arrhythmias	Steroid diagnostics, vitamin D diagnostics	Steroid bolus
Malignancy	Polyuria, alkalosis	Imaging search for tumor	Loop diuretic
Thyrotoxicosis	Encephalitis symptoms, lethargy		Calcitonin as needed
Thiazides			Specific therapy of underlying disease

APh alkaline phosphatase, *Ca* Calcium, *P* Phosphorus, *PTH* parathyroid hormone

5.6 Tips for Parenteral Nutrition

In the initial postoperative phase, the aims of infusion therapy are BS monitoring and, where necessary, adjustment and insulin therapy (as described), together with fluid management and monitoring and treatment of the serum electrolytes potassium, calcium, magnesium, and sodium. Enteral nutrition can be initiated on postoperative day 1 and 2, assuming a normal course, and is usually fully established by postoperative day 3.

This is done on the basis of careful consideration of the clinical findings (bowel sounds, state of distension, stool transit) and in consultation with the nursing staff, who are usually better informed about the "patient's abdominal status."

If the buildup of enteral nutrition does not work, the reason must be investigated and prokinetic therapy also initiated, if necessary.

If in response to this, there is still no progression in enteral nutrition, the energy, fluid, and electrolyte requirement, together with the requirement for vitamins and trace elements, must be covered by partial parenteral nutrition (PPN).

PPN should provide the following:

- Approx. 70% CH energy
- 20–30% fat energy
- Approx. 6 g AA/250 kcal

Subsequently, monitoring of body weight, serum electrolytes/acid-base status, and liver values is fundamental, as well as urea and triglycerides.

Bone metabolism should be monitored via Ca-/P excretion in the urine and alkaline phosphatase and protein metabolism via total protein, albumin, and an aminogram when establishing long-term total parenteral nutrition (TPN).

A fundamental problem with TPN in the long term is the development of liver disease, prompted by an excess of fat, intercurrent infections, or prolonged hyperglycemia. Therefore, in addition to the determination of triglycerides, a 4-weekly hepatic ultrasound scan and investigation for gallstone is also required (Table 5.12).

Table 5.12 Guide for TPN values (do not apply to preemies)

	Minimum	Mean	Maximum
Amino acids (g/kg BW/d)	1	2	3
Glucose (g/kg BW/d)	8	12	20
Fat (g/kg BW/d)	0.5	1.5	3
Na (mmol/kg BW/d)	0	3.5	7
K (mmol/kg BW/d)	0	3	7
P (mmol/kg BW/d)	0.4	1	1.5
Ca (mmol/kg BW/d)	0.2	0.6	1–2 (preemies even more)
Mg (mmol/kg BW/d)	0.1	0.3	0.5

Since there are undoubtedly marked individual differences also in the utilization of parenterally supplied dietary components, a tabulated listing of the composition of infusions can provide only pointers.

5.7 Thought of Everything for the Postoperative Infusion Following CPB

Table 5.13 lists everything to be considered when preparing the postoperative infusion following CPB.

For further information in the event that long-term parenteral nutrition is required, http://www.awmf.org/uploads/tx_szleitlinien/073-023l_S3_Parenterale_Ernährung_Pädiatrie_Kinder_Jugendmedizin_2014–08.pdf can provide useful assistance.

5.8 Postaggression Metabolism

The chart in Fig. 5.1 provides an overview of postaggression metabolism in conjunction with hypermetabolism as a stress response. The treatment options for postaggression metabolism are limited. However, they can exert a positive effect on the mechanisms of development:

- Early extubation, whenever possible
- Good analgosedation
- Synchronized ventilation (= no counterbreathing means reduced respiratory work)
- Improvement of circulatory situation and peripheral circulation
- Treatment of infection
- Good urine output to reduce diffusion distances

If capillary leak predominates, steroid therapy can be attempted in order to support the circulation, reduce the sympathetic trigger, and thus positively influence postaggression metabolism (paradoxically, as steroids have an anti-insulin effect) (Table 5.14).

Table 5.13 Memo for infusion therapy

Surgery	POD 1	POD 2	POD 3	TPN
BS 100–180	BS 100–180	BS 100–180		Age-dependent energy requirement
Glucose to age-dependent minimum and then insulin	Start enteral nutrition	>50% enterally	90–100% enterally	Sugar, amino acids, fat age-dependently (for amounts see Table 5.12)
Ø amino acids	Amino acids 0.5 g/kg	Amino acids 0.5–1 g/kg	Enterally	1 ml/kg BW Peditrace in LT TPN (max. 15 mL), Unizink after 1 wk. 5 µmol < / kg = 0.2 mL/kg
Ø fat	No fat	0.5–1 g/kg, if not enterally		From initiation of fat with Soluvit/ Vitalipid 0.5–1 mL/kg BW/d, 1:2 (preemies + neonates), 1:1 in older children max. 10 mL
K/mg drip	Potassium drip	In main infusion initiation of enteral nutrition	Electrolyte infusion, if necessary	
Ca_{ion} > 0.9	Age-dependently in main infusion	Age-dependently in main infusion (only in neonates/ small infants)	Electrolyte infusion	
Mg > 0.8	Mg in main infusion	Main infusion, if possible p.o.	Electrolyte infusion	Approx. 0.3 mmol/ kg BW/d in all
Ø phosphate	Target 0.8–1.5 mmol/L, replacement acc. To value	Ditto	Ditto	0.5–1 mmol/kg BW/d
TFA 750 mL/ m^2	TFA 1000 mL/ m^2	TFA 1250 mL/m^2	TFA 1500 mL/m^2 to 1750 mL/ m^2	

No trace elements (other than zinc in TPN and renal failure – half dose in dialysis)
BS blood sugar, *LT* long-term, *POD* postoperative day, *TFA* total fluid amount, *TPN* total parenteral nutrition

Table 5.14 Steroids in postaggression metabolism

Capillary leak	Hydrocortisone initially	Thereafter	Alternatively dexamethasone
High catecholamine requirement	5 mg/kg BW	3 × 2 mg/kg BW	1–2 × 0.25 mg/kg BW (1–2–4–8 mg in absolute terms)

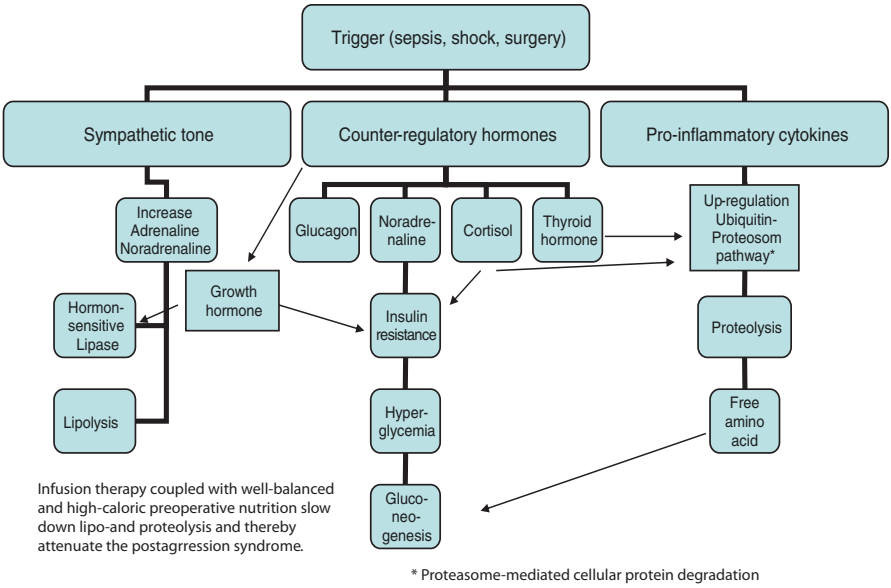

Fig. 5.1 Diagram of postaggression metabolism. *Hypermetabolism is a stress response*: The body's attempt to supply maximum amounts of energy leads to neuronal, endocrine and mediator-driven pathways to lipolysis (increase in triglycerides), protein catabolism and increase in glycogenolysis and gluconeogenesis. Heart rate and stroke volume increase (at onset), induction of capillary leak, renal salt and water absorption, the liver converts its production from structural protein to acute-phase proteins. In some patients, the counter regulatory mechanism is overwhelmed, with a transient insufficiency of the adrenal cortex and T4 deficiency resulting. Copyright © 2018 with authors

Suggested Reading

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Analgosedation

6

Christoph Neuhaeuser and Dietrich Klauwer

6.1 Objectives of Pain Therapy

Postoperative pain therapy in children serves the following objectives:

- To reduce pain-related postoperative stress response (e.g., accompanied by hyperglycemia, tachycardia, tachypnea, hypertension, etc.)
- To protect the patient psychologically and promote their tolerance
- To allow painful measures to be tolerated (tube, drain "milking," aspiration, positioning, etc.), invasive procedures (insertion of catheters and drains) and cooling
- To prevent awakening reactions with adverse consequences (e.g., pulmonary hypertensive crisis; detachment of tubes, catheters, and drains)
- To reduce O_2 consumption in the postoperative adaptation process (possibly to a new circulatory situation), or in the event of limited O_2 supply (e.g., low cardiac output, low pulmonary oxygenation)
- To prevent traumatization or chronification

The objective of all pain therapy is to reduce the pain sufficiently for the patient to be able to tolerate it without problems. Total elimination of the perception of pain (anesthesia, narcosis) is *rarely* necessary during the postoperative period. In

C. Neuhaeuser (✉)
Pediatric Intensive Care Unit, Pediatric Heart Center of Giessen, Children's Heart Transplantation Center, UKGM GmbH, Giessen, Germany
e-mail: christoph.neuhaeuser@paediat.med.uni-giessen.de

D. Klauwer
Department of Pediatrics, Singen Medical Center, Gesundheitsverbund Landkreis Konstanz, Krankenhausbetriebsgesellschaft Hegau-Bodensee-Klinikum, Singen, Germany

© Springer International Publishing AG, part of Springer Nature 2019

D. Klauwer et al. (eds.), *A Practical Handbook on Pediatric Cardiac Intensive Care Therapy*, https://doi.org/10.1007/978-3-319-92441-0_6

principle, pain alleviation measures comprise nonmedical (oral sugar solutions, massage, music*, rest, etc.*) and medical (drug) treatments. Only the medical options will be discussed here.

The effectiveness of any pain therapy should be checked against standardized scales (see below) or verified by clinical means (a "give and go" prescription is entirely unacceptable). The sensation of pain is a very individual experience that is dictated by multiple factors. Predicting the efficacy of a pain-reducing intervention is therefore only possible to a limited extent. In addition, the following accompanying circumstances on the intensive care unit (ICU) need to be borne in mind:

- Is the patient intubated and being ventilated?
- Has the patient been extubated and is breathing spontaneously?
- Is extubation possible or planned?
- Is cardiovascular stability given?
- What do the organ functions look like (clearance)?
- What is the plasma protein content like (binding capacity)?
- Have any adverse reactions or contraindications been noted? And the list goes on.

Essentially, a combination of different principles of action is recommended for postoperative pain therapy, i.e., the use of nonopioid analgesics, opioids, and opioids in combination with regional anesthetic techniques. However, not all of these options can always be used after cardiac surgery, thus constituting a clear limitation.

It has proved beneficial to limit the use of drugs to a few, well-known representatives. As a rule for routine patients, only one product from each drug class should be used, i.e., only one opioid, one nonacidic nonopioid analgesic, one NSAID (nonsteroidal anti-inflammatory drug), etc., to avoid confusion. However, we prefer to use paracetamol in combination with metamizole for pain therapy in the postoperative phase.

In principle, we divide analgosedation into the following types of postoperative strategy:

6.1.1 First Strategy: Continue Deep Analgosedation Over the Next 24 h and Longer

Possible indications:

- Open-chest patients
- Patients with pulmonary hypertension or at risk of pulmonary hypertensive crises
- Hemodynamically unstable patients (with severely reduced pump function, bleeding, etc.)

- Poor lung function, extubation not possible in the short term (PEEP > 6 cmH_2O, FiO_2 > 50%)
- Long machine time (e.g., major or complicated surgery)

Examples of complex surgery in which early extubation is usually not achievable: Commonly Norwood procedure or TGA correction; rarely tetralogy of Fallot correction, pulmonary atresia with or without VSD, tricuspid atresia, Ebstein, total anomalous pulmonary venous return (TAPVR), truncus arteriosus, interrupted aortic arch, critical aortic stenosis, hemodynamically relevant cardiac arrhythmia (e.g., junctional ectopic tachycardia (JET)).

Procedure:

- Deep sedation by continuous administration of a potent opioid (e.g., morphine, fentanyl, remifentanil) and a hypnotic (e.g., midazolam) by infusion, dose adaptation via the infusion rate.
- Where necessary, additional bolus doses can be given (e.g., before endotracheal aspiration, drain milking, positioning).
- Where necessary, consider clonidine or dexmedetomidine drip at an early stage.

Nonopioid analgesics should be administered additionally to spare the use of opioids (particularly before planned extubation), but in deep analgosedation, they probably play a subordinate role.

6.1.2 Second Strategy: Pain Therapy Aimed at Extubation Within 6–24 h Postoperative

Process- or patient-related factors may prevent immediate extubation.

Possible indications:

- Straightforward valve replacement
- Straightforward allograft exchange
- Systemic-to-pulmonary artery shunt
- PA banding
- Ross procedure
- Stable AVSD (without pulmonary hypertensive crises)
- Problem-free tetralogy of Fallot correction

Procedure:

- Moderate (to deep) sedation by continuous administration of a potent opioid (e.g., morphine, fentanyl, remifentanil) and a hypnotic (e.g., midazolam, propofol) by infusion for weaning from ventilation; dose adaptation via the infusion rate.

- Where necessary, additional bolus doses can be given (e.g., before endotracheal aspiration, drain milking, positioning).
- Early initiation of nonopioid analgesics (paracetamol and Novalgin) in order to be able to discontinue analgosedation rapidly.
- Opioid boluses as required (continuation of a low-dose opioid infusion, if necessary).
- Where necessary, clonidine or dexmedetomidine drip should be considered at an early stage.

6.1.3 Third Strategy: Pain Management Leading to the Earliest Postoperative Extubation (If the Patient Was Not Extubated in the OR)

Possible indications:

- Glenn anastomosis
- TCPC
- Uneventful CPB surgery for complex heart defects (ASD, VSD without PHT, partial anomalous pulmonary venous return (PAPVR), uncomplicated tetralogy of Fallot correction, myocardial or inguinal resection in LVOTO)
- Uneventful surgery without CPB: Aortic isthmus stenosis (ISTA), ductus arteriosus closure
- "Stage 1" (bilateral banding in HLHS/HLHC)
- Added to these are all the indications described under 2. that take uneventful courses

Procedure:

- No continuous administration of opioids (where necessary, low-dose continuous administration if tolerated).
- No hypnotics.
- Where necessary, clonidine or dexmedetomidine drip should be considered at an early stage.
- Morphine boluses as required.
- Initiation of nonopioid analgesics intraoperatively even.
- Paracetamol and metamizole i.v. alternately every 3 h.

6.1.4 Fourth Strategy: Aimed at Extubation

- Timely administration of nonopioid analgesics (at least 30–60 min before discontinuation of analgosedation).
- Discontinuation of analgosedation.
- Where necessary, low-dose opioid and benzodiazepine boluses (situationally adapted).

- Extubation under low-dose propofol also possible (with sufficient spontaneous respiration and protective reflexes).
- Where necessary, clonidine or dexmedetomidine drip should be considered at an early stage.

6.2 Nonopioid Analgesics

Nonopioid analgesics can be divided into nonacidic nonopioid analgesics (e.g., paracetamol, metamizole) with a pKa value >5 and acidic nonopioid analgesics (NSAIDs, such as ibuprofen, diclofenac) with a pKa < 5. Because of their low pKa value, acidic nonopioid analgesics accumulate in tissues with a low pH (e.g., inflamed tissue, stomach, kidney). While the analgesic effect of paracetamol and metamizole is probably exerted via central mechanisms, NSAIDs work by inhibiting cyclooxygenases (COX-1 and COX-2) in peripheral tissue. This also explains their good effect on pain in the musculoskeletal system and in inflammation (epicritical pain, mediated by A-delta fibers). In C-fiber-mediated, protopathic pain (e.g., visceral pain), however, their effect is limited (in this case, opioids and metamizole are better) (see Table 6.1).

6.2.1 Paracetamol (Perfalgan®, Ben-u-ron®)

Supplied as: syrup (e.g., 40 mg/mL), suppositories (e.g., 80, 125, 250, 500, or 1000 mg), i.v. solution (e.g., 10 mg/mL), tablets (rarely used in pediatrics).

Analgesic mode of action Not definitively elucidated. Analgesic action presumed to be purely centrally mediated via descending serotoninergic activation. Inhibition

Table 6.1 Summary of nonopioid analgesics

	Standard postop.	<1 month of life possible	Dosage	Maximum dose	Contraindication
Paracetamol	Yes	Yes	7.5–15 mg/kg i.v. as short-term infusion every 6–8 h	30–60 mg/kg/day	Hepatic insufficiency and renal insufficiency, PDA
Metamizole	No	No	10 mg/kg i.v. as short-term infusion every 6–8 h	40–80 mg/kg/day	Allergy, bone marrow depression
Ibuprofen	No	No	10 mg/kg p.o. every 8 h	40 mg/kg/day	RI, coagulation disorders, PDA
Diclofenac	No	No	1 mg/kg p.o. every 8 h	3 mg/kg/day	RI, coagulation disorders, PDA

PDA patent ductus arteriosus

of prostaglandin synthesis by inhibition of prostaglandin H_2 synthase (PGH_2S) and the effect of an active metabolite on cannabinoid receptors are mooted.

Co-administration of 5-HT_3 antagonists (e.g., ondansetron) can reduce the analgesic effect of paracetamol

Conventional postoperative dosage (according to marketing authorization):

Intravenously:

- 1–10 kg: 7.5 mg/kg over 15 min every 6–8 h (max. 30 mg/kg BW/day)
- >10 kg: 15 mg/kg over 15 min every 6–8 h (max. 60 mg/kg BW/day)

Rectally:

- <3 months:
  - Postoperative loading dose 20 mg/kg
  - After 8 h continue with 15–20 mg/kg every 8 h (max. 60 mg/kg BW/day)
- 3 months:
  - Postoperative loading dose 40 mg/kg BW
  - After 8 h continue with 15–20 mg/kg every 8 h (max. 100 mg/kg BW/day)

Some pharmacokinetic data

- Rectal absorption: 150–200 min
- Gastric absorption: 60–120 min (AD 30–45 min)
- Elimination half-life: Premature neonates 5–11 h, infants 1.5–2.0 h, children 2.5–3.0 h
- Effect after i.v. administration: after about 20–30 min

Paracetamol (i.v.) Nowadays, the i.v. preparation of paracetamol is more frequently used for postoperative pain therapy (controlled pharmacokinetics). It should be administered as a short-term infusion to prevent venous irritation (not relevant with CVC administration) and hemodynamic effects (e.g., rarely hypertension). On the other hand, the effectiveness of paracetamol is dependent on the rate at which sufficient CSF levels are reached. Consequently, too long an infusion time is detrimental. In adults, 1 g paracetamol i.v. is approximately equipotent with 75 mg diclofenac i.m., 1 g metamizole i.v., and 10 mg morphine i.m.

As i.v. paracetamol has a concentration of 10 mg/mL, there is not infrequently a tenfold overdose in children as a result of confusion of mg and mL (e.g., 15 ml/kg is prescribed, but 15 ml/kg = 150 mg/kg is administered). With an SD of >60 mg/kg BW, N-acetylcysteine (NAC/ACC) should be given prophylactically. In case of doubt, paracetamol levels are determined 4 h after administration, and the procedure determined by the Rumack-Matthew nomogram is followed. If paracetamol intoxication occurs, an initial ACC dose of 150 mg/kg BW is recommended over 60 min,

followed by 50 mg/kg BW over 3 h, and 100 mg/kg BW over a further 16 h (in total 300 mg/kg BW within 20 h).

Toxicity Paracetamol itself does not cause liver damage, but its toxic metabolite N-acetyl-p-benzoquinine imine (NAPQI) does.

About 90% of absorbed paracetamol is conjugated by uridine diphosphate-glucuronosyltransferase (UDP-GT) and sulfonated via sulfotransferases. The end products (and 5% unchanged paracetamol) are eliminated via the kidney. The remaining 5% is oxidized by cytochrome P450 (CYP2E1), resulting in the formation of the toxic metabolite NAPQI. In the liver, NAPQI is rapidly bound to glutathione and excreted as a nontoxic conjugate in the urine. If the glutathione system is exhausted, NAPQI accumulates in hepatocytes and causes centrilobular hepatic necrosis. The glutathione pool can be restored by administration of ACC. Paracetamol toxicity is increased in the event of increased P450 activity (e.g., induction by anticonvulsants, isoniazid) or reduced glutathione supply (e.g., cachexia, consumption) and in chronic liver damage (e.g., ethanol). The toxic dose is given in children as >(75–)100–150 mg/kg BW/day, but the critical dose following long-term intake can be lower.

Generally, paracetamol is very well tolerated in children, and adverse effects or intoxication are rare. The liver of preterm and mature neonates is even regarded as less susceptible to injury because of the still immature oxidative clearance. On the other hand, the half-life of paracetamol is prolonged in these neonates, which increases the risk of accumulation.

Slight to moderate increases in transaminases can occur postoperatively but are usually of minor clinical significance.

The following children should *not* receive paracetamol:

- Children with duct-dependent defects (particularly those receiving PGE1 therapy). Although paracetamol is not a COX-1 or COX-2 inhibitor, ductus closure can occur
- Children already with severe renal impairment preoperatively (creatinine >1.5 mg/dL) or postoperative oliguria/anuria
- Children with hepatic failure (INR >1.5, raised transaminases, raised bilirubin)
- Children with myopathies

6.2.2 Metamizole (Novalgin®)

Supplied as Drops (e.g., 500 mg/mL; 20 drops = 1 mL), i.v. solution (e.g., 500 mg/mL).

Analgesic mode of action Not definitively elucidated – probably exclusively central (CNS, spinal cord) via nonselective COX inhibition (COX-3?). Metamizole is particularly effective in colic-like pain in the gastrointestinal and urogenital tract.

Authorization The manufacturer approves oral administration >5 kg BW and i.v. administration from the age of 1 year (the Physician's Desk Reference 2017). Intravenous administration from the 1st month of life is acceptable from a medical perspective (off-label use).

Usual postoperative dosage
Intravenously:

- Short-term infusion: 10–(20) mg/kg BW over 20 min every 6–8 h (max. 80 mg/kg BW/day)
- Drip: 40–60 mg/kg BW/day = 1.5–3.0 mg/kg BW/h
- Orally: 10 mg/kg BW every 6–8 h

Adverse reactions

- A fall in blood pressure can occur on rapid infusion due to vasodilation (less frequent in children).
- Allergic reactions with flushing symptoms.
- Agranulocytosis.

Agranulocytosis Metamizole is used extensively in German hospitals. By contrast, in England, Sweden, Australia, and the USA, it has been taken off the market because of the risk of agranulocytosis. Metamizole-induced agranulocytosis is due to a hapten-mediated autoimmunological reaction that usually occurs after ≥5–7 days of treatment. In cases of prior sensitization, immediate reactions are also possible. The risk of this is fairly small (about 30 reported cases annually in Germany) and is given as between 1:1000 and 1:100,000 uses (depending on the reference). Nowadays, life-threatening situations have become less common given that regular blood counts can be measured, timely discontinuation is possible, but also thanks to the availability of granulocyte-colony stimulating factor (G-CSF). Metamizole is actually contraindicated in disorders of BM function or diseases of the hematopoietic system but is nevertheless frequently used by many pediatric oncologists.

6.2.3 Ibuprofen (Nurofen®), Diclofenac (Voltaren®)

Supplied as Ibuprofen oral solution (e.g., 20 mg/mL), tablets (less common in pediatrics), and suppositories. Diclofenac suppositories (e.g., 25, 50, 100 mg), tab. (e.g. Voltaren Resinat® 75 mg), and i.v. (e.g., 25 mg/mL – not available in Germany).

Analgesic mode of action The analgesic action is due to reversible inhibition of the constitutive (physiological) COX-1 and the, for example, inflammation-inducible, COX-2 in peripheral tissue. NSAIDs thus have not only an analgesic but also an anti-inflammatory effect (in contrast to paracetamol and metamizole).

Usual postoperative dosage
Ibuprofen

- Children >7 kg BW:
  - Orally: 10 mg/kg BW every 8 h (max. 40 mg/kg BW/day)

Diclofenac:

- Children >6 years:
  - Orally/rectally: 1 mg/kg BW every 8 h (max. 3 mg/kg BW/day)

Adverse reactions

- Postoperative oliguria/anuria (particularly in hypovolemia; *do not* administer in the event of renal impairment)
- Reversible platelet aggregation inhibition (*do not* administer in the event of bleeding)
- Risk of gastroduodenal ulcer, particularly with impaired perfusion and other risk factors (*do not* administer in ISTA, risk of necrotizing enterocolitis, history of ulcers, or gastroesophageal reflux)
- Risk of exacerbation of asthmatic disorders (*do not* administer in asthmatic patients who require treatment for their asthma)
- Closure of the ductus arteriosus (*do not* administer in duct-dependent defects)

Remark Because of their side effect profile, NSAIDs are rarely used in pediatric cardiac intensive care, particularly in the immediate postoperative period. However, they can be very helpful in stable, convalescent children with musculoskeletal or inflammatory pain. Diclofenac can be used effectively for pain therapy in adult patients following cardiac surgery. Diclofenac can also be administered for postcardiotomy syndrome (alternatively aspirin), together with steroids.

6.3 Opioids

Among opioids, morphine, pethidine, piritramide, fentanyl, and remifentanil are frequently used for postoperative pain therapy (Tables 6.2 and 6.3).

Supplied as

- Morphine: 10 mg/mL (1 or 2 mL ampoules)
- Pethidine (Dolantin®): 50 mg/mL (1 mL ampoule)

Table 6.2 Frequently used opioids

	Morphine	Pethidine	Piritramide	Remifentanil	Fentanyl
Potency	1	0.1	0.5–1	55–75	80–100
Duration of action	2–4 h	2–4 h	2–6 h	5 min	30–45 min
Max. effect after	20–30 min	15 min	15–20 min	3–5 min	5–10 min
Histamine release	Yes	No	No	No	No
Special indication		Shivering		Glenn, TCPC fast track extubation	
Contraindication	RI, (PHT), asthma	Epilepsy			
Dose	Bolus: 50–100 µg/kg Drip: 5–40 µg/kg/h	Bolus: 50–100 µg/kg	Bolus: 50–100 µg/kg	Drip: 0.05–0.5 µg/kg/min	Bolus: 1–10 µg/kg Drip: 2–20 µg/kg/h

- Piritramide (Dipidolor®): 7.5 mg/mL (2 mL ampoule)
- Fentanyl: 50 µg/mL (2 or 10 mL ampoules)
- Remifentanil (Ultiva®): Vials of 1, 2, or 5 mg

Opioids constitute the basis of postoperative pain therapy after cardiac surgery. Their analgesic action is mediated by binding to central opioid receptors (particularly µ1 receptors). They differ, for example, in terms of potency, pharmacokinetics, side effect profile, hemodynamic effects, and sedative or hypnotic components.

General opioid adverse reactions

- Respiratory depression
- Hypotension, bradycardia
- Inhibition of intestinal peristalsis
- Urinary retention
- Pruritus
- Nausea
- Sedation
- Chest rigidity
- Habituation

Table 6.3 Specific opioids

Morphine	Hydrophilic Volume of distribution: greater in neonates, from 3 mo = adults Elimination half-life: Premature neonates: 10–20 h Young children: 1–2 h Schoolchildren: 2–4 h Hepatic metabolites, renal elimination of sometimes active metabolites such as morphine-6β-glucuronide, can accumulate in renal insufficiency Has a good hypnotic and/or sedative effect (particularly in neonates and infants) Histamine release (rare)
Pethidine	Hepatic metabolites The metabolite norpethidine can accumulate in renal insufficiency (proconvulsant) Less spasmogenic than other opioids Slow injection because of possible hypotension
Piritramide	More lipophilic than morphine (more rapid action) Elimination half-life: Infants/young children < adults < neonates Pruritus, nausea, and respiratory depression less common than with morphine
Fentanyl	Lipophilic High protein binding High volume of distribution: neonates > adults Clearance: infants > neonates > children/adults (depending on hepatic blood flow) Hepatic metabolites No active metabolites Context-sensitive half-life: neonates/children < adults Neonates and children require comparatively higher doses than adults Hemodynamic stability: fentanyl > morphine Respiratory depression: fentanyl > morphine (particularly in premature neonates and neonates) Rapid injection of fentanyl (>2 μg/kg) not infrequently results in chest rigidity and can also lead to upper airway obstructions (e.g., laryngospasm) Transcutaneous fentanyl patch (dose: 2.5 μg/kg/h) Anesthesia with high doses (>10 μg/kg) possible (no amnesia, awareness possible)
Remifentanil	Weakly lipophilic Volume of distribution: neonates > children > adults Metabolism by unspecific plasma and tissue esterases (independently of pseudocholinesterases) Decrease in plasma concentration by 80% within 10 min (independently of infusion duration) Clearance: neonates > children > adults Neonates and infants may require higher doses Practically always administered as a drip (but slow single dose possible for intubation, e.g., 2 μg/kg) Well suited to rapid extubation (Glenn, TCPC) Essential to start 30–60 min before stopping the paracetamol and Dipidolor drip (high doses may be necessary); otherwise, extremely severe pain can occur as effect of remifentanil fades More frequent bradycardia, hypotension, and chest rigidity than with fentanyl

mo months, *TCPC* Total cavopulmonary connection

6.3.1 Opioid Therapy: Titrate to Effect

Opioids should generally be administered in such a way that the patient's pain is adequately treated and that as few opioid-related adverse reactions occur as possible. As the pain level is sometimes difficult to assess and responses to opioids are not always predictable in individual cases, opioids should be titrated to effect. Thus, in the conscious, extubated, and spontaneously breathing patient, risks such as respiratory depression and apnea are reduced. The principle of titrate to effect is based on repeated administration of fairly small doses (e.g., morphine 15–100 mcg/kg). This entails a good knowledge of the pharmacokinetics of the drugs (Table 6.2). Following a bolus administration of morphine, it is necessary to wait for, e.g., 15–20 min to see whether the desired effect occurs before administering further doses. Otherwise, an overdose can occur.

Titration of a drip is somewhat more difficult. Treatment usually starts with a "fixed" rate, for which it is assumed that the administered dose is "sufficient" (e.g., morphine 10–20 µg/kg/h). If the effect is too "strong," the rate can be reduced gradually (waiting for the effect between steps, which makes the procedure a lengthy one). If the effect of the initially set rate is too "weak," a bolus should be administered first of all (to rapidly achieve higher plasma levels), and the infusion rate then increased (here too it can take time to find the "right" dose). Increasing the drip rate without a bolus takes hours for the required plasma level to be achieved.

In the postoperative handover of an initially still well pain-controlled, cardiovascularly stable patient who is due to undergo extubation shortly (Strategy 3 and 4), morphine boluses can be given (in combination with paracetamol) on the first signs of pain, for example. To make the patient more "controllable" in the targeted awakening phase (beyond extubation) and to suppress the psychomotor agitation (or stress), the additional administration of a small benzodiazepine bolus (e.g., midazolam) can be helpful. For extubation, the patient should be breathing spontaneously, adequately, and calmly on the ventilator with low pressure support (PEEP <5 cmH_2O, PS < 12 cmH_2O), FiO_2 < 35%, and good blood gases, be cardiovascularly stable, and exhibit sufficient protective reflexes (swallowing, coughing), as well as awakening reactions (eye opening, hand pressing, spontaneous movements).

If the patient is not extubated immediately postoperatively (Strategy 1 and 2), analgosedation is initiated by drip (e.g., fentanyl/midazolam, ketamine/midazolam, morphine, and/or clonidine or dexmedetomidine). Additional bolus doses are possible at any time as described above.

In this case, also the specific pharmacokinetic properties of the individual substances must be noted to ensure that they are used according to their strengths and weaknesses (see Tables 6.2 and 6.3).

It should be borne in mind as a matter of principle that the elimination half-life of all drip-infused opioids and sedatives/hypnotics can increase with the duration of infusion ("context-sensitive" half-life = the longer the duration of infusion, the longer the elimination half-life and hence the duration of action after switching off the drip). This applies in particular to lipophilic drugs such as fentanyl, midazolam, and clonidine (keywords: high volume of distribution, storage, accumulation). With

propofol, the context-sensitive half-life is less marked, and with remifentanil it is practically nonexistent (elimination via nonspecific plasma and tissue esterases).

The duration of action of opioids can also be prolonged if clearance is limited (e.g., morphine in renal impairment). A (temporary) reduction in hepatic perfusion, e.g., in association with a low output syndrome or congestion, can also be responsible (e.g., fentanyl).

As mentioned previously, premature infants and neonates are more sensitive to opioids in relation to the occurrence of apnea. However, a fear of such should not result in "undertreating." Consequently, this group of patients must be constantly monitored when opioids are used, and equipment for possible resuscitation measures must be kept to hand (e.g., bag and O_2, if necessary naloxone).

As a partial opioid antagonist (antagonist at the μ1 receptor and agonist at the κ receptor), *nalbuphine* can offer an alternative here. With comparable analgesic potency to morphine, the respiratory depressant component is almost nonexistent, and nalbuphine can even be used postoperatively to antagonize an opiate hangover (0.1–0.2 mg/kg BW). As a single dose for severe pain (0.05–0.2 mg/kg BW) or as a drip at 0.1 mg/kg BW/h), nalbuphine is also particularly suitable for patients in whom intubation is to be avoided. The effect after i.v. administration sets in after about 2–3 min and persists for several hours (up to 6 h). Because of the "ceiling effect," an increase in the nalbuphine dose >0.4 mg/kg does not produce any additional benefit.

6.4 Ketamine (e.g., Ketanest Inresa®)

Supplied as i.v. solution (50 mg/mL; 2 mL or 10 mL ampoules)

Action The S-(+) enantiomer of ketamine is four times as potent clinically as its S-(−) enantiomer and about twice as potent as the racemate (= stereochemical mixture of both). S-(+)-ketamine is a noncompetitive NMDA receptor inhibitor in the CNS. At other receptors (opioid, muscarinergic, dopaminergic), it binds only at supraclinical dosages.

The S-(+) enantiomer of ketamine is available as a preparation (Ketanest S®), whereas "ketamine" otherwise generally refers to the racemate (e.g., Ketanest inresa®).

General remarks Ketamine is highly lipid-soluble and is therefore rapidly distributed in the CNS after bolus administration (onset of action after 30–60 s). Administration of Ketamine creates a "dissociative state", including analgesia, hypnosis, amnesia, tolerance to interventions, and also psychomimetic side effects (in older children this may cause nightmares). Patients frequently have their eyes open, stare blankly, do not respond when addressed, and sometimes exhibit spontaneous movements and nystagmus. As a result of redistribution to other tissue, the effect starts to decline within 10–20 min after bolus administration of 2 mg/kg BW. The

analgesic effect can persist for up to 4 h, as lower plasma levels are required. In visceral pain, ketamine is inferior to opioids. The extent to which ketamine can be used for pain modulation (i.e., to prevent or treat chronic pain states) has as yet not been well established in pediatric patients.

In neonates, hepatic clearance is still reduced, but in children, it matches that of adults.

Usual postoperative dosage
Intravenously:

- Bolus 1–2 mg/kg BW (every 10–30 min)
- Analgosedation: 2–4 mg/kg/h (possible also: additive diazepam boluses of 0.1–0.2 mg/kg every 4 h) or low-dose midazolam drip
- Analgesia (with spontaneous respiration): from 25–100 μg/kg/h

Special properties of ketamine relative to other anesthetics (see also Chap. 18)
The great benefit of ketamine is that it has a sympathomimetic effect on the circulation and therefore helps offset, for instance, the cardiodepressant effects of other hypnotic/analgesics (although caution should be exercised in beta-blocked patients, severe heart failure, and/or hypovolemia). It is particularly suitable in circulatory unstable patients for anesthesia induction or intubation (e.g., in combination with etomidate or propofol). It should also be used in an asthma attack because of its bronchodilator action.

A further major benefit of ketamine is that it is highly suitable for analgosedation in short procedures (in combination with midazolam or propofol). Respiration and protective reflexes in the spontaneously breathing patient usually remain sufficiently preserved. Admittedly, psychomimetic adverse drug reactions can be detrimental in this case, as they cannot always be definitively suppressed by combination with midazolam or propofol. However, these effects rarely occur in younger children (e.g., under 3 years).

Actions

- Cardiovascular stimulation or stability (MAP, heart rate, cardiac output, systemic vascular resistance (SVR))
- Little effect on pulmonary vascular resistance (PVR) if the pulmonary vascular bed is normal. Use in preexisting PHT is a matter of dispute (in our view, ketamine can be used in PHT without any problem)
- Little or no respiratory depression (with a bolus of 2 mg/kg BW or drip <2 mg/kg BW/h)
- Protective reflexes largely preserved (albeit not 100%)
- Bronchodilation

- Cerebral blood flow, intracranial pressure (ICP), and cerebral autoregulation are unaffected if the patient is analgosedated and the $PaCO_2$ is kept constant (e.g., under controlled ventilation). However, according to the manufacturer, Ketamine is still not authorized in the presence of intracranial hypertension (off-label use).
- Intraocular pressure unaffected
- Both proconvulsant and anticonvulsant effects are described (ketamine is probably best avoided in epilepsy). On the other hand, it may be helpful in "benzodiazepine-refractory" status epilepticus (downregulation of GABA receptors, upregulation of NMDA receptors).
- Can be used in malignant hypothermia and muscle diseases.
- Directly negatively inotropic when co-administered with beta-blockers.

Adverse reactions

- Salivation and bronchial secretion (if necessary give low dose atropine or glycopyrrolate).
- Psychomimetic effects (can usually be avoided in combination with midazolam).
- Vomiting (fairly rare in our experience).
- Spontaneous muscle movements, pupil differences.
- Possibly QT interval prolongation (give with caution during amiodarone therapy; better to avoid in long QT syndrome).
- Following repeated use (long-term therapy) of higher doses, induction of nervous cell apoptosis was described in models of premature and neonatal animals. Therefore larger doses of ketamine are better avoided in premies and neonates.

6.5 Pain Scales

Scores can help quantify pain reactions such as increased blood pressure, tachycardia, facial grimacing, limb movements, increased muscle tone, sweating, crying, etc. However, as heart surgery patients either are unable to make any distinct utterances (e.g., tube, sedation, etc.) or sometimes can exhibit unusual autonomic reactions, these scores do not replace the clinical assessment of experienced nursing staff and physicians. It should also be borne in mind that the use of drugs, cooling, mechanical circulatory support, etc. can make it difficult to assess pain based on autonomic parameters.

There are many common pain scores (e.g., Bernese Pain Scale for Neonates; Childhood Discomfort and Pain Scale (KUSS, Kindliche Unbehagen- und Schmerz-Skala) for nonventilated neonates, infants, and young children <5 years; Smiley Analogue Scale for children >5 years; visual and numerical analog scales for school children and adolescents).

The comfort score is illustrated here by way of example (Table 6.4). In contrast to the abovementioned scales, it is not dependent on the patient's cooperation and therefore can also be used in intubated patients. Scores of between 1 and 5 points are assigned in eight categories (minimum 8, maximum 40 points).

Table 6.4 Comfort score

Alertness	Deeply asleep	Lightly asleep	Drowsy	Fully awake and alert	Hyper alert
Calmness, agitation	Calm	Slightly anxious	Anxious	Very anxious	Panicky
Respirator response	No coughing and no spontaneous respiration	Spontaneous respiration with little or no response to ventilation	Occasional cough or resistance to ventilator	Actively breathes against respirator or coughs regularly	Fights ventilator, coughing, or choking
Physical movement	No movement	Occasional, slight movement	Frequent, slight movement	Vigorous movement limited to extremities	Vigorous movement, including torso and head
Blood pressure (MAP)	Below baseline	Consistently at baseline	Infrequent elevations of 15% or more (1–3/observer)	Frequent elevations of 15% or more (>3/observer)	Sustained elevation ≥15%
Heart rate	Below baseline	Consistently at baseline	Infrequent elevations of 15% or more (1–3)	Frequent elevations of 15% or more (>3)	Sustained elevation ≥15%
Muscle tone	Totally relaxed; no tone	Reduced	Normal	Increase tone and flexion of fingers and toes	Extreme muscle rigidity and flexion of fingers and toes
Facial expression	Totally relaxed	Normal; no facial tension evident	Tension evident in some facial muscles	Tension evidence throughout facial muscles	Facial muscles contorting and grimacing
Points	1	2	3	4	5

6.6 Analgosedation Continuous Drip Infusion

As mentioned previously, continuous analgosedation of varying depth is sometimes required following anesthesia during postoperative intensive care medicine. For straightforward postoperative courses, however, basic analgesia with paracetamol and single doses of morphine (30–50–100 µg/kg BW/SD) is sufficient.

Various combinations of an opioid (analgesia/sedation) and a hypnotic (sedation) are possible. The following combination is widely used:

Fentanyl + midazolam drip. In special cases, the combination of remifentanil + propofol (early extubation in Glenn and TCPC) and ketamine + diazepam single

doses (sedation with the preservation of spontaneous respiration by tube) is also used. In the neonatal period (premature neonates/neonates), a morphine drip alone may also suffice (e.g., 20 µg/kg BW/h).

In adults, it has been shown that a brief interruption of long-term sedation daily (for a few hours) can result in more rapid weaning from and less habituation to analgosedation. However, this is (unfortunately) not as yet routine procedure in postoperative pediatric cardiac intensive care medicine. In this context, "early extubation" shortly postoperatively or even intraoperatively is of particular significance. With the interplay of basic analgesia, spontaneous respiration without a tube, clonidine or dexmedetomidine, early nutrition, support from caregivers, and low-dose morphine boluses, it is possible to achieve good patient satisfaction, guaranteed spontaneous respiration, and easier circulatory management.

6.6.1 Proposals for Initiating a Drip

Fentanyl (usually used 2 or 10 mL ampoules: 50 µg/mL)

- <20 kg: 125 µg × kg in 50 mL G5% or 0.9% NaCl; 1 mL/h = 2.5 µg/kg BW/h
- >20 kg: pure

Midazolam (usually used 3 mL ampoules: 5 mg/mL)

- <50 kg: 5 mg × kg in 50 mL G5% or 0.9% NaCl; 1 mL/h = 100 µg/kg BW/h
- >50 kg: pure

Morphine (usually used 2 mL ampoules: 10 mg/mL)

- 0.5 mg × kg in 50 mL G5% or 0.9% NaCl: 1 mL/h = 10 µg/kg BW/h

Clonidine (used 5 mL ampoules: 150 µg/mL)

- <30 kg: 50 µg × kg in 50 mL G5% or 0.9% NaCl: 1 mL/h = 1 µg/kg/BW/h
- >30 kg: 10 ampoules in 50 mL G5% or 0.9% NaCl: 1 mL/h = 30 µg/h

Ketamine (used 2 mL or 10 mL ampoules: 50 mg/mL)

- <25 kg: 50 mg × kg in 50 mL G5% or 0.9% NaCl: 1 mL/h = 1 mg/kg BW/h
- >25 kg: pure

Remifentanil (5 mg ampoule: 5 mg in 50 mL = 100 µg/mL)

- <16.6 kg: 300 µg × kg in 50 mL G5% or 0.9% NaCl: 1 mL/h = 0.1 µg/kg BW/min
- >16.6 kg: pure

6.7 Sedatives and Hypnotics

Since anxiety, agitation, defensive behavior, and stress are detrimental in the postoperative phase for the reasons already adduced, additional sedation is frequently necessary despite sufficient pain therapy. Young children in particular frequently lack the insight into the medical measures, so that the necessary tolerance must be provided medicinally. The aim is not only a pain- and stress-free patient but also a "cooperative" one.

6.7.1 Benzodiazepines (Table 6.5)

Supplied as

- Midazolam (Dormicum®): i.v. solution (e.g., 1 mg/mL in 5 mL ampoules, 5 mg/mL in 3 mL ampoules), oral solution (e.g., 2 mg/mL), and tab. (7.5 mg)
- Lorazepam (Tavor®): i.v. solution (e.g., 2 mg/mL), tab. (1 mg)
- Diazepam (Valium®): i.v. solution (e.g., 5 mg/mL), rectal tubes (5 mg, 10 mg), drops (10 mg/mL), and tab. (5 mg)

Action Benzodiazepines bind to specific receptor sites of the postsynaptic GABA-A receptor complex and potentiate its inhibitory effect on the downstream neuron. The sedative, anxiolytic, amnesiac, anticonvulsant, and central muscle relaxant effects of benzodiazepines can be explained by the widespread presence of GABA receptors in very different regions of the CNS (cortex, hypothalamus, hippocampus, limbic system, reticular formation, striatum, medulla oblongata, and spinal marrow).

General remarks Benzodiazepines are lipophilic but differ in terms of their duration of action and potency. While diazepam and lorazepam belong to the longer-acting benzodiazepines, midazolam belongs to the short-acting group.

Benzodiazepines do not possess a directly negative inotropic effect and generally exhibit "high" cardiovascular stability. However, they can result in a

Table 6.5 Benzodiazepines

Benzodiazepine	Dose	Onset of action	DA	Intervals
Diazepam	Bolus: 0.1–0.2 mg/kg	2–4 min	6–8 h	Every 4–8 h
Midazolam	Bolus: 0.05–0.1 mg/kg BW/SD	2–4 min	30–60 min	Every 30–45 min or drip
Lorazepam	Bolus: 0.02–0.05 mg/kg BW/SD	2–4 min	6–8 h	Mainly at night

reduction in systemic (and pulmonary arterial) vascular resistance and hence a reduction in blood pressure. Conversely, heart rate increases slightly. Fluid volume deficiency and comedications (e.g., opioids, etc.) can potentiate a fall in blood pressure. The therapeutic breadth of benzodiazepines is generally relatively large, but respiratory depression can also sometimes occur even at therapeutic doses.

Anxiolysis and anterograde amnesia occur even at low doses (useful for premedication), while increasing doses ultimately induce a state of sleep progressing to narcosis. Lorazepam has the highest anticonvulsant efficacy.

There is a considerable risk of accumulation, particularly with the longer-acting benzodiazepines, which can result in a delayed awakening reaction after discontinuation. On the other hand, habituation develops in the patient over time, necessitating the use of increasing doses. To prevent problems, it can sometimes be helpful in this case to add other medicines with a sedative effect (e.g., clonidine or dexmedetomidine, promethazine, phenobarbital, gamma-hydroxybutyric acid, etc. – see below). Increased secretion production can cause problems in the ventilated patient, but this can generally be controlled by bronchial hygiene.

6.7.2 Barbiturates

Supplied as

- Thiopental (Trapanal®): i.v. solution (500 mg in 20 mL: 25 mg/mL)
- Phenobarbital (Luminal®): i.v. solution (200 mg/mL), tab. (15 mg, 100 mg)

Action Barbiturates also act by binding to a specific receptor site of the postsynaptic GABA-A receptor complex. At lower concentrations, the physiological effect of GABA at the receptor is prolonged and enhanced (sedative hypnotic effect), while at higher concentrations, barbiturates themselfs stimulate the GABA-receptor ("barbiturate narcosis").

The energy consumption (work metabolic rate) of neurons decreases with increasing barbiturate concentration. The maximum effect (reduction in cerebral metabolism by about 55%) is achieved with the occurrence of burst suppression or a flat line EEG.

General remarks Thiopental in particular is not the drug of first choice in pediatric cardiac intensive care therapy because of the directly negative inotropic action. Severe hypotension with reflex tachycardia is also relatively typical in anesthesia induction with thiopental.

Phenobarbital is therefore used in many places as a barbiturate for sedation in the postoperative phase. It can help increase the "cooperation" of, for instance, restless,

extubated patients who cannot yet be moved. As a barbiturate with a very long half-life (1–4 days), it also is associated with the risk of accumulation (blood level monitoring!). In addition, enzyme induction (cytochrome-P450 system) occurs in the liver, which can affect the pharmacokinetics of other drugs.

Phenobarbital dose For example, on day 1 give twice daily 5–10 mg/kg BW p.o. or as short-term infusion; thereafter, daily 5 mg/kg BW p.o. or as a short-term infusion. Blood level monitoring after a few days (target level: 20–40 mg/L) is only necessary if phenobarbital is not discontinued again after 3–5 days—the usual aim. In our opinion, relevant neurotoxic adverse reactions are also only to be expected after this time.

6.7.3 Propofol (e.g., Propofol®-Lipuro)

Supplied as i.v. solution 1% (10 mg/mL) or 2% (20 mg/mL); dilutable with 0.9% NaCl

Action The hypnotic effect of propofol can also be explained by the interaction with the postsynaptic GABA-A receptor complex. The downstream neuron becomes hyperpolarized (increased chloride influx) and, as a result, unexcitable.

Propofol results in vasodilation with a fall in arterial blood pressure (reduction in systemic vascular resistance and venous pooling). By contrast, pulmonary vascular resistance barely decreases at all, which can have an effect on a shunt defect. Bradycardia not infrequently occurs initially after a propofol bolus administration, and arrhythmias (junctional rhythms, AV blocks) are also described. Experimental and clinical studies suggest a directly negative inotropic effect of propofol, but the exact mechanism at the myocardial cell level is still a matter of dispute (reduction in Ca^{2+} sensitivity of the microfilaments, reduction in intracellular cAMP, and Ca^{2+} concentration).

In critically ill patients with, for instance, a preexisting fluid volume deficiency (e.g., diuretic therapy) or high compensatory sympathetic tone (e.g., heart failure), propofol should be used only with great caution since the fall in blood pressure in this case can be very marked.

Authorization according to the manufacturer

- Sedation (by which is meant long-term sedation in the intensive care unit): >16 years
- Narcosis, total intravenous anesthesia (TIVA): >1 month of life

Propofol is a very potent hypnotic that is very suitable for anesthesia induction, TIVA, and for sedation for short procedures and imaging (e.g., CT, MRI). Because of the risk of propofol infusion syndrome (PRIS; see below), it is not used for

long-term sedation in the intensive care unit in children <16 years. Patients who leave the operating theater on propofol and are to be extubated on the same day are an exception (duration <6–12 h; dose <5 mg/kg BW/h).

Dosage i.v.

- Short-term sedation:
  - Bolus: 1–2 mg/kg BW (titrate to effect)
- Intubation of stable patients without cardiovascular risk
  - Bolus: 2–4 mg/kg BW
- Drip:
  - Anesthesia: 5–10 mg/kg BW/h
  - Sedation: 2–5 mg/kg BW/h

Some data

- Lipophilic substance, dissolved in soybean fat (1% propofol contains 0.1 g/mL fat; max. rate, 2 mL/kg BW/h).
- Onset of action within 30 s after i.v. bolus.
- Duration of action of about 5–10 min after i.v. bolus.
- Easily controllable, pleasant sleep induction, and awakening.
- Hepatic and extrahepatic metabolism.
- Rapid redistribution.
- Antiemetic.
- Frequently apnea after bolus administration, loss of protective reflexes.
- Reduction in cerebral metabolism, cerebral blood flow, and ICP.
- *Not* with food allergies: egg, soya, peanuts, etc.
- *Severe injection pain* on administration via a peripheral vein. Solution: Either dilute 0.9% NaCl to 0.5 mg/mL, mix 1 mL 1% lidocaine with 20 mL propofol, and/or "mini-Bier" (anesthesia of the vein with 0.5–1 mL 1% lidocaine).
- Use infusion syringes at room temperature for not more than 6 h.
- In young children, higher drip rates may contribute to lipid loading.

Propofol infusion syndrome (PRIS) PRIS is defined as refractory bradycardia to asystole (sometimes onset of right bundle branch block), metabolic acidosis (lactate), rhabdomyolysis with crush kidney, hyperlipidemia, and hepatic steatosis progressing to acute liver failure, as well as circulatory failure, occurring during the use of propofol and not otherwise explicable. This phenomenon has occurred in particular on use for >48 h, at a dose >5 mg/kg BW/h, and in severely ill children. A propofol-induced mitochondrial disorder (e.g., inhibition of oxidative phosphorylation) is mooted. In addition to high-dose, long-term use of propofol, risk factors include the use of catecholamines, steroids, infections, and a low sugar intake.

6.7.4 Etomidate (Etomidate Lipuro®)

Supplied as i.v. solution (2 mg/mL)

Etomidate is a short-acting hypnotic used in particular for i.v. anesthesia induction (intubation) of circulatory stable or unstable patients. While less potent than thiopental or propofol in its hypnotic effect, in return, it also exhibits the fewest cardiodepressant effects. The combination of etomidate and ketamine S can therefore be beneficial in the induction of patients in shock. As the activity of 11β hydroxylase is inhibited for 6–24 h by an etomidate bolus (less cortisol synthesis in the adrenal cortex), it has become a subject of criticism in recent years. It should also not be used for drips. Nevertheless, from our perspective, the benefits of etomidate outweigh the risks in the induction of patients with unstable circulation and/or heart failure. Hydrocortisone (e.g., 1 mg/kg BW i.v. every 6 h) can be substituted temporarily (for 24 h) (alternatively 11β hydroxylase activity can be restored by administration of vitamin C; see also drugs table at the end of the book).

Myoclonus can occur on induction and is sometimes misinterpreted as a seizure.

Induction dose 0.15–0.3 mg/kg BW i.v. (*Caution*: possibility of injection pain!)

6.7.5 Gamma-Hydroxybutyric Acid (Somsanit®)

Supplied as i.v. solution (10 mL ampoule; 200 mg/mL; sodium content, 18 mmol/g gamma-hydroxybutyric acid = 3.6 mmol/ mL, pH = 8.0)

Gamma-hydroxybutyric acid (GHB) is a sedative that has practically no adverse cardiac or respiratory effects (see Table 6.6).

As Somsanit has a high sodium concentration (see above), it can cause hyperaldosteronism, or hypernatremia in the presence of renal impairment, particularly in younger patients. Its disadvantages also include a marked emetic action (particularly with bolus doses) and a very variable awakening time after the end of the infusion.

Table 6.6 Somsanit – summary

	Induction dose	Drip dose	ADR	Advantages	Disadvantages
Somsanit	50 mg/kg BW over 20 min	10–20 mg/kg BW/h	Hypernatremia, nausea	Cardiorespiratory stability, spares other sedatives and analgesics, good for weaning	No analgesia

Somsanit is ideally suited, for example, as on-top medication in habituation associated with benzodiazepine sedation. Respirator weaning is frequently successful using a Somsanit drip since the respiratory drive is hardly affected at all and it is possible to cut down on opiates, while the patient still exhibits good tube tolerance and "cooperation." According to the manufacturer, Somsanit-induced sleep is even particularly similar to natural sleep.

In the event of hypernatremia (>150 mmol/L), the Somsanit drip should be discontinued, and treatment with spironolactone can be tried if necessary.

The sedative effect can be partially antagonized by central acetylcholinesterase inhibitors such as physostigmine and naloxone (Narcanti).

6.7.6 Chloral Hydrate (Chloraldurat®)

Supplied as Rectal tubes (200 mg/mL) and capsules (250, 500 mg).

Chloral hydrate was first manufactured in 1832 and is thus the first synthetically produced hypnotic. In stable patients without cardiac arrhythmias and without postoperative nausea (the most common ADR), chloral hydrate can be used for induction of a prolonged night's sleep. Chloral hydrate is also indicated, for example, in the case of known paradoxical benzodiazepine reaction. It has also proved to be beneficial in the sedation of children with Down's syndrome. Relevant respiratory depression is fairly rare, whereas nausea and vomiting are common. One disadvantage is that the nature and duration of the effects are often not predictable (see Table 6.7).

Some data

- Rapid enteral and rectal absorption
- Pronounced first-pass effect (FPE)
- Hepatic metabolism
- Pharmacologically active metabolite: 2,2,2-trichlorethanol (half-life, 30 min)
- Renal elimination of metabolites (urocholic acid)
- Onset of action on oral administration after about 15–30 min

Table 6.7 Chloral hydrate – summary

Chloral hydrate	Oral dose	30–60 mg/kg BW, every 24 h, higher if needed
	Rectal dose	Infants 300 mg, young children 600 mg, every 24 h, higher if needed
	Indication	Sedation, paradoxical reaction, Down's syndrome
	Adverse drug reactions	Nausea, sensitized to catecholamines, uncertain duration of action and strength
	Contraindication	Tachycardiac arrhythmia, catecholamine therapy, severe hepatic insufficiency, renal insufficiency and/or heart failure, increase in intracranial pressure

Table 6.8 Promethazine – summary

Promethazine	Dose	0.5–1.0 mg/kg BW p.o. or slow i.v.
	Effect	Sedation, antiemetic, anticholinergic, antihistaminergic
	Adverse drug reactions	Tachycardia, hypotension, dry mouth, dyskinesia
	Interval	Max. every 6–8 h
	Caveat:	Not in the presence of tachycardiac arrhythmias!

- Duration of action about 4–8 h
- Risk of sensitization of the heart muscle to catecholamines (as also with other organic halogen compounds, e.g., halothane)
- No analgesic effects

6.7.7 Promethazine (Atosil®)

Supplied as i.v. solution (25 mg/mL), syrup (1 mg/mL), drops (20 mg/mL), sugar-coated tabs (10, 25, 100 mg).

Promethazine is a low-potency neuroleptic belonging to the group of phenothiazines, used primarily nowadays as a sedative (as an antihistamine only if a sleep-inducing action is required). As a ligand, it acts via central and peripheral histamine-1 receptors. Psychological stress (restlessness, agitation, anxiety) can be effectively treated, particularly in Down's syndrome patients as well (see Table 6.8).

Predominantly vagolytic (atropine-like) adverse reactions occur. At 4–8 h, the duration of action is fairly long. Paradoxical reactions (confusion) are possible.

6.7.8 Clonidine (Catapresan®) and Dexmedetomidine (Dexdor®)

Supplied as Clonidine i.v. solution (150 µg/mL), Clondine tablet of 300 µg. Dexmedetomidine i.v. solution (100 µg/mL) (see Table 6.9).

Action Stimulation of central postsynaptic α-2 receptors reduces central noradrenergic activity (central sympathicolysis). Clonidine and dexmedetomidine also have sedative, analgesic, antiemetic, and even amnesiac effects. Respiratory depression usually does not occur (*Caution*: when co-administered with, e.g., opioids or benzodiazepines and in premature neonates/neonates!). In addition to the stimulation of central postsynaptic α-2 receptors, stimulation of endorphin release (particularly in the brainstem) also probably plays a role. These properties are utilized in sympathicolysis, in pain therapy, as well as for opiate withdrawal.

Table 6.9 Clonidine/dexmedetomidine – summary

Drip with clonidine 1–2–(3) µg/kg BW/h	Start dexmedetomidine slightly lower
Fall in HR, fall in BP	Dexmedetomidine slightly less marked
Better diastolic filling with lower HR	
Cardioprotective and antiarrythmogenic	
Reduced opioid requirement	
Stops shivering	
Good in weaning phase (alleviates withdrawal symptoms)	
Stronger fall in blood pressure possible in volume deficiency	Less marked with dexmedetomidine
Oral administration possible	More experience with clonidine (about the same dose oral/i.v.)

Following rapid bolus administration, there is initially an increase in blood pressure (via stimulation of peripheral α-1 receptors), which is then followed after a few minutes by a decrease in blood pressure and heart rate (via the central α-2 effects). The hemodynamic effects are less pronounced with continuous administration.

Clonidine is playing an increasingly greater role in postoperative therapy. It has additive effects in combination with opioids and sedatives. Central sympathicolysis with clonidine is very helpful, particularly in patients who have to undergo extubation rapidly and suffer from agitation and increased sympathetic tone (e.g., after Glenn anastomosis or TCPC). It can also be used in weaning from analgosedation.

The effect of clonidine/dexmedetomidine on cardiac output is variable (cardiac output = heart rate × stroke volume). By reducing heart rate, there can even be improved ventricular filling due to a longer duration of diastole (higher stroke volume). This is of particular benefit with stiff ventricles (diastolic dysfunction, e.g., in TCPC patients with HLHS, Fallot patients). Depending on the product of heart rate and stroke volume, cardiac output can increase, remain constant, or decrease slightly. Treatment should therefore also be monitored by means of echocardiography (blood pressure and SvO_2 response can obviously already provide an indication here). However, the increased endogenous sympathetic tone can frequently be a major disadvantage, especially in the postoperative phase. Here, it can be particularly helpful to administer a sympatholytic to reduce the oxygen requirement of the whole body. This will induced a heart rate reduction, not only by direct inhibition, but mainly to economize the O_2 requirement (afterload reduction, temperature decrease, pain therapy, antiemesis, reduction of muscle tremor etc.) and hence directly also in heart work.

In contrast to beta-blockers, the effect of central α-2 stimulants is less negatively inotropic. Clonidine is also used in postoperative hypertension, but the antihypertensive effect is usually relatively limited. If there is a postoperative fall in blood pressure with clonidine /dexmedetomidine but at the same time the required

sedative effect is obtained, this can be countered by a low dose of noradrenaline if sufficient preload is present (i.e., after fluid volume administration).

Some data for clonidine

- Slow i.v. bolus administration possible (e.g., 1–2 μg/kg BW with postoperative shivering)
- Onset of action after 5–10 min
- Duration of action about 4–8 h (half-life, 8–12 h)
- Elimination: 30% hepatic, 70% renal
- In the event of severe hypotension after clonidine, naloxone or noradrenaline if necessary; adrenaline in the event of bradycardia
- ADR: hypotension, bradycardia (caution with beta-blockers and in presence of AV-block), dry mouth, rebound hypertension on discontinuation, reduction in intestinal peristalsis, urinary retention

Taken together, central postsynaptic α-2 stimulants have several positive characteristics during emergence from anesthesia as well as during weaning from analgosedation (on the ICU). They have relatively good sedative and analgesic effects, do not suppress spontaneous breathing (in a significant manner), and help to avoid sympathetic activation during arousal and extubation. Other respiratory depressant medications (e.g., opioids) can therefore be safely withdrawn in their presence, without risking tachycardia, arterial hypertension, and O_2 mismatch (due to sudden agitation). In this regard they also help to economize cardiac performance during these critical moments of the therapeutic process. Myocardial O_2 consumption is reduced (by control of heart rate), coronary perfusion is optimized (by the resultant prolongation of diastole), while the reduction in afterload improves the working conditions for the heart.

- There are certain advantages of dexmedetomidine over clonidine. Dexmedetomidine is more "sedative" (higher potency at the α-2 receptor) but at the same time less "hypotensive" compared to clonidine. The dosages of dexmedetomidine are therefore somewhat lower (0.5–1–(3) μg/kg BW/h). Due to the shorter half-life (2 h for dexmedetomidine vs. 6–8 h for clonidine), the desired depth of sedation can be better titrated, which also makes it very suitable for intraoperative use, particularly in "fast track" extubation (please see chapter 18 for more details on dexmedetomidine and "fast track" extubation).

Conclusion

Analgosedation is often necessary postoperatively but does not replace an empathetic approach by parents, relatives, nursing staff, and other therapists. All those involved in the care of the patient should constantly endeavor to reduce the need

for sedation and analgesia (e.g., by attention, physical comfort, oral feeding, avoidance of noise and light, improving sleep-waking rhythm, etc). In concert with these measures, an early (or preferably immediate postoperative) extubation of the patient is the best option to avoid harm from (unnecessary) prolonged analgosedation.

With rare exceptions, pain relief by strong analgesics (e.g. opioids) should not be any more necessary after the 2nd to 4th postoperative day. Usually form hereon, paracetamol and/or metamizole will suffice. However, some "soft" sedation may still be needed, especially in infants and smaller children as well as in patients with down syndrome, who tend to agitation. This can often be achieved by chloral hydrate, phenobarbial, and/or oral clonidine, administered on demand.

Delirium (caused by sedatives) and symptoms of withdrawal (from sedatives and opioids) must not be mistaken. In case of a delirium, sedatives like benzodiazepines are better avoided. In contrast, after long-term analgosedation (>3–5 days) gradual tapering of benzodiazepines and opiods as well as the early use of central postsynaptic α-2 stimulants are usually beneficial to avoid symptoms of withdrawal. A switch to oral "withdrawal"-medication (e.g., methadone, diazepam, and clonidine) may also be considered. If long-term ventilation is required for pulmonary or hemodynamic reasons, an appropriate form of assisted ventilation with proper synchronization, along with low-dose opioids and central postsynaptic α-2 stimulants to induce and maintain tube tolerance, is advantageous. The motto for sedatives here is: "as less as possible, as much as necessary" (goal: patient awake, calm and comfortable).

Finally, a few further considerations about analgosedation (see Tables 6.10 and 6.11).

Table 6.10 Analgosedation – memo

Consideration	
Does the intervention hurt?	Type of intervention or procedure
What signs of pain or agitation are present?	Parameters on monitor; patient; pain scales
Does it involve pain or other forms of discomfort?	What drugs have already been given? When? How much?
What do nursing staff at the bedside think?	Profit from their experience; they may be "closer" at the patient and may have a different perspective, too
Could detrimental adverse drug reactions occur? If so, what can I do about them?	Fall in blood pressure (volume, catecholamines), respiratory depression (bag)
Is the monitoring adequate?	For example, in apnea risk
How long should the patient sleep?	Is extubation indicated?
Is the caregiver absent?	Provide pain relief through emotional support and distraction

Table 6.11 Cardiovascular effects – summary

	BP	HR	Inotropism
Opioids	↓	↓	No effect
Ketamine	↑	↑	Positive[a]
Benzodiazepines	↓	↑	No effect
Barbiturates	↓	↑	Negative
Propofol	↓↓	↓	Negative[b]
Etomidate	(↓)	(↓)	No effect
Clonidine	↑[c], ↓	↓	(Negative)[d]
γ-Hydroxybutyric acid	Ø	Ø	No effect

[a]Via sympathomimetic effect, positive inotropic; direct effect, negative inotropic (e.g., in beta-blockade)
[b]See text
[c]Initially on bolus administration, increase in blood pressure
[d]Via central sympatholytic effect, negative inotropic (usually no clinical relevance – mostly even positive effects on stroke volume by improved ventricular filling)

Suggested Reading

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Antibiotic Therapy

7

Christoph Neuhaeuser and Dietrich Klauwer

Alongside rational considerations and scientific evidence, local factors and personal experience frequently dictate the choice of antibiotic therapy. This explains why there is not always an internationally uniform standard for a specific infectious disease. In principle, the chosen antibiotic or combination of antibiotics must be effective against the suspected or demonstrated bacteria. However, it is often unclear whether one or other theoretically effective antibiotic therapies are comparatively more effective and what the minimum treatment duration should be.

A distinction must be made as to whether the treatment concerned involves prophylactic antibiotics administration, untargeted (also called empirical or calculated) antibiotic therapy for a suspected infection, or targeted antibiotic therapy of a proven infection with a known pathogen. The patient's clinical condition also plays a decisive role, particularly in untargeted antibiotic therapy. If they have a severe disease, it is preferable to start with the most potent and broadest antibiotic therapy possible (and later de-escalate or adapt specifically, as needed). If the disease is a milder, the opposite strategy can be adopted initially.

Not only is the choice of the correct drug essential for the success of antibiotic therapy, but the dose and method of administration also play important roles. When combining antibiotics, synergistic effects can be utilized, e.g., combination of a beta-lactam antibiotic and aminoglycoside. On the other hand, mechanisms that increase the selective pressure for resistance need to be borne in mind, e.g., the

C. Neuhaeuser (✉)
Pediatric Intensive Care Unit, Pediatric Heart Center of Giessen, Children's Heart Transplantation Center, UKGM GmbH, Giessen, Germany
e-mail: christoph.neuhaeuser@paediat.med.uni-giessen.de

D. Klauwer
Department of Pediatrics, Singen Medical Center, Gesundheitsverbund Landkreis Konstanz, Krankenhausbetriebsgesellschaft Hegau-Bodensee-Klinikum, Singen, Germany

© Springer International Publishing AG, part of Springer Nature 2019

D. Klauwer et al. (eds.), *A Practical Handbook on Pediatric Cardiac Intensive Care Therapy*, https://doi.org/10.1007/978-3-319-92441-0_7

combination of carbapenems with a beta-lactam increases the probability of extended-spectrum beta-lactamase (ESBL)-producing strains.

In the method of administration, a distinction is drawn, for example, between whether the effect of a product is more time-dependent or concentration-dependent. When time-dependent drugs are administered, the maintenance of a minimum inhibitory concentration (MIC) over a long period is a determining factor. The dose and administration must therefore be selected accordingly (e.g., multiple doses over the day or continuous drip infusion). This group includes beta-lactam antibiotics among others (e.g., vancomycin). In practice, determination of the blood concentration of the administered antibiotic is impractical but should be considered. In exceptional cases, the dose has to be adjusted to stay above the MIC. By contrast, the highest possible dose or tissue concentration is important for the mode of action of when administering concentration-dependent drugs. This group includes aminoglycosides, where administration of the whole daily dose at one time has become established practice.

The molecular properties of the antibiotic also affect how well it can penetrate a specific tissue and thus reach a possible focus of infection. Since glycopeptides, for instance, are rather large molecules, the dose must be increased in the treatment of meningitis in order to ensure a sufficient tissue concentration. Aminoglycosides, by comparison, are ineffective in an acidic medium, as in an abscess. Only lipophilic substances can exert an intracellular effect (e.g., macrolides, quinolones).

As all antibiotics can have considerable adverse drug reactions (ADR), toxicity must naturally be taken into account, and the dosages or intervals between doses must be adapted to the metabolic and excretory functions of the body. The glomerular filtration rate (GFR) of the kidney or the effluent rate (= clearance rate) in renal replacement therapy (RRT) is of particular importance here (see also Chap. 4).

Irrespective thereof, all antibiotic therapies run the risk of promoting bacterial resistance by selective pressure. Unfortunately, the burden of multiresistant microorganisms has increased considerably in recent years in pediatric intensive care units.

7.1 Perioperative Prophylaxis in Open-Heart Surgery

Perioperative administration of antibiotics primarily serves to prevent surgically related infectious complications. However, in addition, the exacerbation of previously undiscovered (or latent) infections can occur in the course of elective surgery (e.g., respiratory tract infection). Lastly, infections due to inserted foreign material (e.g., cannulas, allograft, artificial tissue) or even open wound surfaces (e.g., “open chest”) are possible.

In principle, antibiotics that are effective against gram-positive skin microorganisms are candidates for perioperative antibiotic prophylaxis in elective heart surgery (e.g., cefazoline and cefuroxime). Current recommendations advocate the shortest possible use (<72 h) to prevent resistance formation. By contrast, prolonged prophylactic antibiotic administration has become established practice at our center in Giessen (duration,

5–14 days). Our own experiences with fairly low postoperative infection rates following open-heart surgery play a role here. In addition, the authors consider extended antibiotic therapy of open-chest patients (mostly neonates and small infants who have undergone complex and usually lengthy surgery under hypothermia) and patients with ECMO or at the beginning of Berlin Heart therapy to be advisable.

7.1.1 Standard Prophylaxis with Cefuroxime

For routine *standard perioperative prophylaxis*, *cefuroxime* is used as a 2nd-generation cephalosporin effective against staphylococci in all patients at our center in Giessen (see below).

Exceptions:

- Neonates with a history of infections and neonatal infection: ampicillin/gentamicin
- Preexisting antibiotic therapy on other wards/in other hospitals
- Preexisting antibiotic therapy on the present ward

Cefuroxime treatment is usually sufficient and is discontinued after removal of the CVC in cases of uncomplicated surgery, unremarkable wounds, and following a reduction of existing inflammatory markers.

7.1.2 Extension of Standard Prophylaxis

Extension of the standard prophylaxis must be considered if an infection is suspected (see Table 7.1) or there are additional specific risk factors.

This sort of situation is present, for example, in the following circumstances:

- Raised CrP on the 2nd/3rd postoperative day >150–200 mg/L
- Clinical signs of infection (e.g., infiltrates on chest X-ray, abnormal tracheal aspirate, fever, etc.)
- Open wound surfaces (e.g., open chest)
- Implanted foreign material with contact to the outside (e.g., ECMO, Berlin Heart)
- Patients at particular risk (Table 7.2).

This requires a targeted search for further indicators of infection (see Sect. 7.2) and initially an untargeted extension of perioperative antibiotic therapy.

On *suspicion of a respiratory infection, combination therapy with cefuroxime and tobramycin* has become established practice at our center in Giessen.

On *suspicion of sepsis, with an open chest, or with implanted foreign material with contact to the outside,* we prefer a combination of *teicoplanin and ceftazidime*, or alternatively meropenem (for teicoplanin, see Sect. 7.9.13; for ceftazidime, see Sect. 7.9.6; for meropenem, see Sect. 7.9.7).

Table 7.1 Signs of infection

Appearance	CrP, etc.	Leukocytosis	Fever	Ventilation	Wound	Ultrasound
Dirty grayish	Increases after more than 36 h	Over 20,000/μL	With good hydration	O_2 requirement ↑	Red/protruding	Poorer function
MC impaired	Increases above 150 mg/L	Increases secondarily	Over 39 °C	Auscultation findings	Painful	Vegetations
Hypercirculation (rare in children)	Increases secondarily		Increases secondarily	Radiographic findings	Fluctuating	Intrathoracic hematoma
Cool periphery	Liver function parameters, lactate		May be seen after homograft implantation (without infection)	Tracheal secretion abnormal	CVC puncture site infected	
Liver enlarged						

Table 7.2 Patients at risk of infection

Neonates	Patient-related	Surgery-related	Wart-related
Long CVC	Catch 22, etc.	Emergency surgery	Preoperatively in ICU, long-stay patient
Asphyxia	Trisomy 21	Open chest	Previous antibiotic therapy (too many, too long)
Compromised GI perfusion, HLHS, aortic isthmus stenosis, PDA closes	Mental retardation with risk of aspiration	Long machine time, deep hypothermia	Many foreign bodies (e.g., central venous line, Foley catheter, drains, etc.)
	Previously sick lung, status post recurrent pneumonia	Critically ill patient	Insufficient hygiene measures under stress (e.g., forgot to disinfect hands)
	Status post resuscitation	Dialysis, ECMO, VAD	
	Status post endocarditis, status post-CPB surgery	Synthetic material (valves), homografts, etc.	

CPB cardiopulmonary bypass, *GI* gastrointestinal, *VAD* ventricular assist device

7.2 Investigations on Suspicion of Infection

In the workup following a clinical suspicion of infection, there are three principal approaches:

1. Laboratory changes (or laboratory profile):
   - Blood count (leukocytosis or leukopenia; ratio of immature to total neutrophiles)
   - CrP, procalcitonin (more effective than CrP in differentiating from SIRS), IL6

- Coagulation parameters, platelets, and D-dimers (particularly on consumption).
- Acute phase proteins (e.g., increase in fibrinogen)
- Organ functions (e.g., creatinine, urea, gas exchange, etc.)

2. Microbiological detection:
   - Blood culture (from CVC and peripherally, repeated where applicable)
   - Endotracheal secretion collection (bronchoscopic sample collection, where applicable)
   - Urine culture
   - Culture of pleural effusions and ascites, where applicable
   - Wound smears (where applicable pus, where applicable surgical revision)
   - Samples of surgically inserted foreign materials (e.g., allografts, vascular prostheses, artificial valves, etc.)
   - Rare: CSF, stool samples (e.g., clostridial toxins), biopsies
3. Imaging:
   - Chest X-ray (e.g., pneumonia, aspiration, etc.)
   - CT (e.g., sinusitis, abscesses, pneumonia, septic emboli, etc.)
   - Echocardiogram (e.g., endocarditis, pericarditis, effusions, vegetations, valve incompetence, thrombi, etc.)
   - Abdominal ultrasound (e.g., ascites, liver size, biliary tract changes, urinary tract changes, etc.)
   - Rare: leukocyte scintigraphy or PET/CT scan (PET = positron emission tomography)

7.3 Postoperative Infections

Postoperative infections are usually pulmonary (e.g., lobar pneumonia, bronchopneumonia, aspiration pneumonia, septic emboli, pulmonary sequester, etc.), some of which were preexistent and are exacerbated following cardiopulmonary bypass (CPB) surgery. The second most common forms of infection are catheter infections, while wound infection, mediastinitis, endocarditis, urinary tract infection, or infections from inserted foreign material occur more rarely. In many cases, a focus cannot be identified (e.g., failure of microbiological detection during ongoing antibiotic therapy, difficult diagnosis, systemic inflammatory response syndrome (SIRS), occult infection). In the case of negative blood cultures (e.g., after prior antibiotic treatment), prokaryotic PCR (polymerase chain reaction from blood or secreta) can sometimes still provide evidence of bacterial infection.

Depending on the clinical suspicion, the following microbiological examinations should be performed to identify the focus of infection.

Nosocomial infections after cardiac surgery in children:

- Catheter sepsis → blood cultures (central and peripheral), dispatch of catheter tip (after removal)
- With drains → drainage fluid, drainage material
- Respiratory tract infection → tracheal secretion, bronchial secretion, where applicable bronchial secretion by bronchoscopy, chest X-ray, in exceptional

cases: chest CT, serology, or PCR on suspicion of *Mycoplasma*, *Chlamydia*, *Legionella*, or viruses, etc.
- Wound infections→ smears, revision by surgeons
- Urinary tract infection, particularly with indwelling bladder catheter→ urinstix, urine culture, ultrasound where applicable
- Endocarditis → blood cultures (at least 5–6), transthoracic ultrasound, or TEE (transesophageal echocardiography)
- In rare cases: LP (lumbar puncture) where applicable; stool culture where applicable (particularly *Clostridium* difficile toxin); on suspicion of osseous spread: X-ray, PET-scan; on suspicion of cerebral spread (brain abscesses): cCT (cranial computed tomography)/MRI, etc.

A distinction must be drawn between:

- Increase of inflammatory markers without clinical change/deterioration (nonspecific reaction)
- Increase of inflammatory markers with clinical change/deterioration (suspicion of infection)
- Systemic inflammatory response syndrome (general change without demonstration of infection)
- Manifest infection or sepsis

7.4 Systemic Inflammatory Reaction (SIRS) vs. Sepsis

Following open-heart surgery, a clinical picture can develop associated with laboratory signs of inflammation, hypotension, capillary leakage, increased volume and catecholamine requirement, deterioration of organ functions, temperature instability, and metabolic disorders (e.g., hyperglycemia). By definition, the distinction between a systemic inflammatory response syndrome (SIRS) and sepsis depends purely on the detection of an infectious focus or bacteremia. Since this detection is frequently unsuccessful in everyday practice and it therefore remains unclear whether the changes are due to the CPB surgery (please see Chap. 10 on ECMO and CPB also) or are in fact caused by bacteria, we will advocate a fairly practical approach here.

Once microbiological studies have been performed (see Sects. 7.2 and 7.3), broad-spectrum antibiotic therapy must be initiated immediately under all circumstances (e.g., teicoplanin or vancomycin, combined with ceftazidime or meropenem). In addition, symptomatic treatment must be given to maintain organ function as adequately as possible (see also Sect. 7.8).

Fulminant septic conditions are fairly rare in postoperative intensive care medicine. This is because most surgery is elective and is usually undertaken on infection-free children and all procedures are performed under strictly sterile conditions and the patients receive antibiotic treatment perioperatively. As mentioned earlier, differentiation from CPB-mediated SIRS is difficult, particularly in the first 48 h after

surgery. Immunosuppressed patients (e.g., congenital or acquired immunodeficiency, administration of immunosuppressive agents), premature infants/neonates, and children with chronic or occult infections (e.g., ciliary dysfunction, cystic fibrosis, etc.) represent a particular risk group. Patients with trisomy 21 are also frequently prone to infection.

Postoperative SIRS frequently lasts no more than 72–96 h at most, i.e., it resolves without any further specific measures. If, however, a focus of infection can be identified, confining this is the main priority. Antibiotic therapy (dose, combination, intervals, etc.) must be adapted in such a way that limitations due to defective penetration into bradytrophic tissue or areas with poor blood supply are compensated. Examples of this include infected (chest) hematomas, infected catheters and foreign surfaces, infected sternum wounds, poorly ventilated infected areas of the lung, necrotizing enterocolitis (e.g., in bowel ischemia), and postoperative endocarditis. Infected dead tissue must be surgically debrided, as otherwise it is insufficiently accessible to antibiotic therapy. Infected foreign materials (e.g., CVCs, cannulas, artificial valves, prostheses, allografts, etc.) must be exchanged, if this is possible.

7.5 Pneumonia or Ventilation-Associated Pneumonia (VAP)

Infections of the respiratory tract, including the lung, are fairly common in children and may be "brought into surgery" undetected. In terms of the microbial spectrum, "community-acquired pneumonia" (e.g., due to pneumococci, streptococci, *Haemophilus influenzae*, etc.) is the usual culprit. Treatment with cefuroxime is usually sufficient.

If a pulmonary infection occurs after a ventilation duration of >48 h, this is then referred to as ventilator-associated pneumonia (VAP) (Table 7.3).

The diagnosis is made on the basis of microbiological findings: endotracheal or bronchial secretion (where necessary, bronchoalveolar lavage [= BAL]), infiltrations on the X-ray film, and clinical signs (deterioration of lung function). In this scenario, gram-negative microorganisms are more likely to be the causative agents of infection. Therefore, antibiotic therapy should be extended to include an aminoglycoside. Antibiotic therapy should only be adapted on the basis of microbiological resistance testing if special problem microorganisms are detected (e.g., *Pseudomonas*, extended-spectrum beta-lactamase (ESBL) producers, etc.).

Further therapeutic measures include the avoidance or reopening of atelectatic areas and good bronchial hygiene. The possibilities for (prone)-positioning the patient (intended to drain and open up lung segments) are frequently limited in postoperative therapy. In the case of sonographically or radiologically demonstrated atelectasis, recruitment maneuvers and ventilation strategies with higher PEEP can be used (see Chap. 2). Improvement of mucociliary clearance can be obtained with mucolytics (NAC at an appropriate dose), inhalation (e.g., 3% NaCl), and intensive physiotherapy.

Table 7.3 Memory card on antibiotic therapy

Cardiac surgery	Signs of infection without SIRS	Signs of infection with SIRS	Open chest	Extracorporeal circulation
Cefuroxime	Cefuroxime + tobramycin	Vancomycin, ceftazidime	Initially: Vancomycin, ceftazidime	Initially: Vancomycin, ceftazidime
		Escalation pneumonia	Escalation gr^+	Escalation gr^- (see SIRS)
		Vancomycin, ceftazidime, + tobramycin, or ciprofloxacin	Consider linezolid, rifampicin, or clindamycin. Close chest as soon as possible	Extracorporeal circulation, escalation gr^+ (see open chest, escalation gr^+)
		Alternative: Vancomycin, carbapenem, and tobramycin	In difficult cases with suspected mediastinitis, tigecycline may be considered	In all cases of suspected or proven infection during extracorporeal circulation (e.g., ECMO) or assist (e.g., berlin heart), consider explantation as soon as possible
		In special cases: Switch tobramycin to amikacin		In difficult cases with suspected mediastinitis, tigecycline may be considered
			Teicoplanin may be used instead of vancomycin	

SIRS systemic inflammatory response syndrome

If more extensive antibiotic therapy is required, the following antibiotics may be proposed:

- Ceftazidime (see also Sect. 7.9.6): gram-negative problem microorganisms, including *Pseudomonas*, *Serratia*, and *Acinetobacter*.
- Quinolones (see also Sect. 7.9.10): effective against *Enterobacteriaceae*, *H. influenzae*, and *Legionella* and weaker against staphylococci, streptococci, enterococci, *Chlamydia*, and *Mycoplasma*. Ciprofloxacin is very effective against *Pseudomonas* but ineffective in pneumococci. In our view, there is no longer a general reticence about the use of quinolones in children (administration usually <14–21 days).
- Carbapenems (see also Sect. 7.9.7): broad spectrum of action in the gram-negative and gram-positive range, beta-lactamase-stable. However, multiresistant nonfermenters (MNF) such as *Stenotrophomonas maltophilia* can be selected.
- Erythromycin or clarithromycin (see also Sect. 7.9.12): in suspected "atypical pneumonia" due to *Mycoplasma*, *Chlamydia*, or *Legionella* (a quinolone could also be used instead).
- Combination therapies may offer certain advantages (synergies, extended spectrum of action, etc.). Thus, beta-lactam antibiotics combine well with aminogly-

cosides or quinolones. In unclear situations of pneumonia and sepsis in which it is decided to use a carbapenem (e.g., meropenem) and in which previous combination therapy has been given (e.g., glycopeptide plus ceftazidime plus aminoglycoside), ceftazidime should be replaced by the carbapenem. Where applicable, administration of the aminoglycoside can also be discontinued during meropenem therapy.

7.6 Treatment of Infections with Resistant Staphylococci (Coagulase-Negative Staphylococci, MRSA)

Patients with barrier disorders, open chest, indwelling foreign bodies (e.g., central venous catheter), and extracorporeal circulatory support (e.g., ECMO, Berlin Heart) are particularly prone to staphylococcal infections.

Coagulase-negative staphylococci are not uncommon on microbiological testing. They occur physiologically on human skin and are usually resistant to beta-lactam antibiotics. The question as to whether the sample is contaminated or there is an infection can frequently only be answered clinically. Infections with coagulase-negative staphylococci can be sufficiently treated, for example, by means of glycopeptides. However, the characteristic feature of these bacteria is that they form a biofilm on foreign surfaces that protects them from the action of antibiotics. For this reason, effective debridement is usually only possible by removing or exchanging the foreign materials, after having weighed the risks and benefits.

Colonizations or infections with methicillin-resistant *Staphylococcus aureus* (MRSA) constitute an increasing problem in hospitals. Compared with the intensive care treatment of adults, however, infections due to MRSA are still the exception in most pediatric intensive care units. MRSA are resistant to all beta-lactam antibiotics but can be treated with glycopeptides (vancomycin, teicoplanin; see also Sect. 7.9.13) or linezolid (see also Sect. 7.9.11) (depending on antibiotic susceptibility testing, rifampicin, fosfomycin, clindamycin, or gentamicin is also possible).

In selected cases, switching from a glycopeptide to linezolid, which inhibits protein biosynthesis, can be considered. The determinants here are the good efficacy of linezolid against gram-positive microorganisms and its excellent tissue penetration – even after oral administration, it shows an almost 100% bioavailability. Nevertheless, experience with this drug in pediatrics is still limited.

7.7 Treatment for Suspected Necrotizing Enterocolitis

Unlike in premature infants, necrotizing enterocolitis usually does not occur in neonates without an identifiable cause. Compromised bowel perfusion associated with a heart defect and following resuscitation, circulatory shock, and severe asphyxia are the primary features. The leading cause is usually ductal closure in PDA-dependent systemic perfusion (hypoplastic left heart syndrome (HLHS), critical aortic stenosis, and critical aortic isthmus stenosis (synonym: coarctation of the aorta).

About 1–3 days after the initially successful circulatory stabilization, deterioration occurs in the "abdominal compartment" with a subsequent septic reaction. For this reason, with the previous history mentioned above, only a very careful nutritional buildup is possible, if at all, in addition to which increased attention must be paid to any clinical changes in the abdomen.

The combination of vancomycin and meropenem (with or without metronidazole) has become established practice as antibiotic therapy for necrotizing enterocolitis (alternatively: ampicillin, gentamicin, and metronidazole).

As with all severe bacterial infections, impairment of all organ functions can occur in the course of necrotizing enterocolitis, including disseminated intravascular coagulation (DIC). A daily surgical consultation with an assessment of the situation is essential. Indications for laparotomy and/or laparoscopy in our view include:

- Signs of perforation on the plain abdominal X-ray (free air)
- Indications of migratory peritonitis with laboratory and clinical deterioration
- A "fixed" loop with clinical signs of ileus
- Demonstrated or suspected intra-abdominal abscess or an intra-abdominal compartment syndrome (IAP > 15–20 mmHg).

Otherwise, a "conservative" strategy (without surgery) can also be promising (Table 7.4).

Table 7.4 Necrotizing enterocolitis in mature neonates

History	Caution	Clinical features abdomen	Clinical features body	Diagnostic features	Treatment
Resuscitation?	Examine the abdomen several times daily	Transport disorder? Paralytic ileus?	Apnea?	Clinical appearance	Gastric decompression (e.g., open gastric tube)
Asphyxia?	Cautious (slow) dietary buildup	Abdomen distended, painful? Fixed loop? Masses present? Resistances?	Circulation worse?	X-rays: Pneumatosis, football sign, perforation, persistent loop, intestinal gas distribution?	Fasting
Heart defect with impaired circulation in lower half of body?		Resistance, shiny abdominal skin, persistent loops?	Impaired lung function?	Ultrasound: Free fluid, gas bubbles in portal vessels, ascites?	Antibiotics

Table 7.4 (continued)

History	Caution	Clinical features abdomen	Clinical features body	Diagnostic features	Treatment
		Bloody diarrhea?	Impaired kidney function?	Laboratory parameters: Blood count, coagulation, CrP, liver, lactate by Astrup method (metabolic acidosis), blood corpuscles, stool culture?	Surgical intervention
			Disseminated intravascular coagulation (DIC)?		Supportive, circulation, ventilation, kidney
			Metabolism, disorder of carbohydrate metabolism, lactate formation, impaired hepatic function?		Blood glucose balancing, total parenteral nutrition, coagulation therapy

CrP C-reactive protein

7.8 Septic Shock

The term "septic shock" usually covers a complex of symptoms in intensive medicine that involves an underlying dysregulation of the immune response and that by definition is caused by a demonstrable infection. The hallmark clinical features are the changes already described in Sect. 7.4, which may be potentially life-threatening (see Table 7.5).

While only few septic clinical pictures exhibit a relatively standard phenotype, such as meningococcal sepsis with purpura fulminans, the cause is initially unclear in most of the cases. The causative pathogen must be identified as rapidly as possible (for workup, see Sect. 7.2), and broad-spectrum, untargeted antibiotic therapy must be initiated immediately even before the microbiological results are received. In other words, "hit hard and early."

The treatment of sepsis involves relatively unspecific, fairly symptomatic measures, such as stabilization of the circulation, as well as pathogen-specific approaches. The latter would include targeted antibiotic therapy and debridement of the focus of infection (e.g., abscess drainage, removal of infected foreign bodies, etc.), as well as administration of immunoglobulins in toxic shock syndrome

Table 7.5 Sepsis-induced multi-organ failure

Lung	Circulation	Kidney	Coagulation	Heart	Liver	Brain
Development of ARDS	Hypotension	Diversion of intrarenal blood flow away from the renal cortex	Disseminated intravascular coagulation (DIC)	Initially compensation by hypercirculation	Glycogen consumption Gluconeogenesis inhibited Mitochondrial disorder	Agitation, apathy
Development of effusions	Endothelial damage	Glomerular necrosis	Platelet consumption	Contractility disorder	Lactic acidosis	Energy deficiency, vasoplegia in acidosis
Intrapulmonary shunt	Microthrombosis, terminal capillary vessels	Excretion disorder	Factor consumption	Ventricular dilation	Protein catabolism	Cell swelling, microhemorrhage
PHT	Generalized edema	Swelling	Microthrombosis, terminal capillary vessels	RV failure	NH_3 and bilirubin increase	Increasing loss of consciousness
Lung failure	Catecholamine-refractory shock	Renal failure	Generalized bleeding tendency	Circulatory arrest	Liver failure	Coma

NH_3 ammonia, Bili = bilirubin

(streptococcal or staphylococcal toxic shock syndrome). In our opinion, the replacement of protein C can be useful in the case of purpura fulminans (target: protein C levels >80%). However, care has to be taken, since official guidelines recommend against the use of protein C in pediatric sepsis (due to the risk of bleeding complications). Although initial results may point in this direction, it remains to be proven whether cytokine- or endotoxin-reducing measures (e.g., by specific dialysis filters or hemadsorption) exert a demonstrably positive effect on the disease course.

The pathophysiology of septic shock is extremely complicated and complex. The bacteria and/or bacterial toxins activate granulocytes (polymorphonuclear neutrophils, PMN) and macrophages, which in turn produce cytokines and activate a series of endogenous mediator or effector systems (e.g., complement system, coagulation system, etc.). In simplified terms, the path may be depicted as follows: noxae → activation of the body's defenses → microcirculatory disorder → cell dysfunction → organ failure (including PMN/macrophage activation, mediator release↑, complement [etc.], mediator release ↑, coagulation activation, and hyperfibrinolysis). The focal point is therefore the massive disorder of the terminal capillary vessels ("microcirculatory disorders"), including permeability of the capillary membrane (capillary leakage), endothelial dysfunction, and peripheral "vascular failure" (refractory hypotension). In addition, a "mediator-induced mitochondrial cell function disorder" results in a generalized metabolic crisis with lactate formation (not just from impaired perfusion) and a glucose utilization resistance.

In the treatment of septic shock, the principal options for safeguarding the circulation and O_2 supply are fluid volume administration and catecholamine therapy (α-adrenergic in vascular failure, β-adrenergic in myocardial contraction weakness) (early goal-directed therapy). In respiratory failure, this also includes invasive ventilation (or preferably noninvasive ventilation, if feasible).

Close monitoring by echocardiography should always be undertaken in all patients (from neonates to adolescents) in addition to the usual monitoring (including invasive blood pressure and CVP) in order to be able to obtain an impression of the patient's filling status and myocardial function and to enable the treatment to be adapted accordingly.

Primary goals are a sufficient arterial blood pressure (in line with the age-commensurate lower limit of normal) to maintain organ perfusion (e.g., urine output >1 mL/kg/h, GCS 13–15) and an appropriate O_2 supply to the body (appropriate cardiac output, $SvO_2 > 70\%$, CVP = 8–12 mmHg, Hb > 8 g/dL, $SpO_2 > 90\%$, lactate <5 mmol/L, BE > −8 mmol/L).

If cardiac output is massively reduced as a result of septic cardiomyopathy (cold shock), milrinone (where necessary levosimendan) can be tried additionally, or ECMO treatment may even be necessary. In the event of massive vasodilation with severe hypotension and organ failure (warm shock or vasoplegic shock), at noradrenaline doses >1.0 µg/kg/min, additional treatment with vasopressin (e.g., 0.0002–0.0008 IU/kg/min) or terlipressin (e.g., 10 µg/kg every 4–6 h i.v.) can be helpful.

Since impairment of lung function often occurs in association with volume therapy and a general barrier disorder, controlled ventilation must be considered at an

early stage (to ensure gas exchange and reduce work of breathing). On intubation, induction agents (e.g., ketamine, etomidate, rocuronium) must be dosed very carefully and syringes kept available for additional catecholamine administration, since there is the risk of an acute circulatory collapse. If etomidate is chosen, hydrocortisone replacement should be considered for at least 24 h.

In right heart overload due to increased pulmonary resistance, consideration must be given to a protective form of ventilation (PEEP 5-(10) cmH_2O, driving pressure < 14-(18) cmH2O, Vt 4–6 ml/kg) and the administration of NO (20(−40) ppm).

At a volume replacement of more than 40–60 mL/kg, the transfusion of red blood cell concentrates is often necessary to maintain Hb >8 g/dL.

In oliguria, after optimization of cardiac output and perfusion pressure, a long-term furosemide drip (at our center in Giessen, combined with low-dosed theophylline) can be tried in order to increase urine output and to achieve fluid balance in the patient. If acute renal failure occurs (urine output <0.5–1.0 mL/kg/h for >24 h with an increase in retention parameters), renal replacement therapy (RRT) should be initiated early in the context of sepsis (effluent rate = clearance dose >35 mL/kg/h seems beneficial, a "cytokine-eliminating" filter may also be considered).

Other measures:

- Treatment of coagulation disorder and thrombocytopenia.
- Cutoff values for platelets:
  - Without bleeding >10,000–30,000/μL
  - Before surgery or catheter placement at a noncompressible site >50,000/μL
- Platelet transfusion: In the event of bleeding, high risk, or platelets <10,000/μL.
- No routine AT-III administration.
- No routine administration of fresh frozen plasma (except with active bleeding).
- Heparin (UFH: 50–300 IU/kg BW/d or LMWH, low-molecular-weight heparin):
  - In DIC with signs of peripheral circulatory disorders (e.g., purpura fulminans)
  - If no active bleeding, PTT < 50 s and/or INR < 2.0
- Stress ulcer prophylaxis (in children, only with steroid therapy).
- Whenever possible, enteral nutrition (otherwise parenteral nutrition with sufficient calories (hyperglycemia with BG > 200 mg/dL and triglyceridemia with triglycerides >300 mg/dL must be avoided).
- NaBic only if pH < 7.1, or BE < −10 mmol/L, or massive PHT (CO_2 must be able to be expired).
- Monitoring of organ perfusion by regular SvO_2, lactate determination, and NIRS (where applicable).
- Hydrocortisone administration: In the absence of an adequate response to catecholamines (catecholamine-refractory shock), steroids can both reduce the catecholamine requirement and in some cases improve lung function. An examination for corticoadrenal insufficiency (relative or absolute) is recommended before the beginning of therapy, but in our view is usually too time-consuming.

  - Hydrocortisone dose: Initially up to 10–(50) mg/kg BW i.v. and then 1–(10) mg/kg BW every 6 h (depending on the severity of the circulatory instability – standard dosage, see Chap. 19). Treatment should be stopped again after 3–4 days (or depending on the clinical picture). It is not absolutely necessary to taper off treatment after a treatment duration of <7 days.
- Immunoglobulins: In severe sepsis, administration of immunoglobulins (usually IgG) can be considered as a supportive measure: Dose 0.5 g/kg BW/day, e.g., on 2 successive days. It is not definitively established whether administration of IgM has benefits over that of IgG.

Detailed recommendations on the treatment of sepsis in children can be found in the recommendations of the "Surviving Sepsis Campaign," most recently published in 2016.

7.9 Frequently Used Antibiotics in the Intensive Care Unit

7.9.1 Penicillin

Sensitive: *Pneumococci, beta-hemolytic and viridans streptococci*, beta-lactamase-negative staphylococci, *Corynebacterium diphtheriae*, *Bacillus anthracis*, beta-lactamase-negative gonococci, *meningococci*, *Pasteurella multocida*, anaerobes (e.g., *Fusobacteria*, peptostreptococci, clostridia [except difficile]), *Bacteroides* (except fragilis), actinomycetes, *Treponema*, *Borrelia*, *Leptospira*.

Resistant: *Enterobacteriaceae*, nonfermenters (*Pseudomonas aeruginosa*, *Stenotrophomonas*, and *Acinetobacter*), beta-lactamase-forming gram-negative pathogens (gonococci (>20%), *Haemophilus*, *Moraxella*), enterococci, beta-lactamase-producing staphylococci (>90%), MRSA, *Clostridium difficile* and *Bacteroides fragilis*, *Mycoplasma*, *Chlamydia*, *Legionella*.

Indications: Streptococcal, pneumococcal, meningococcal infections, syphilis, borreliosis, scarlet fever, tonsillitis, erysipelas, rheumatic fever, subacute bacterial endocarditis.

Dosage: 0.25–0.5 million IU/kg BW/day i.v. in 4–6 single doses or 30–50 mg/kg BW i.v. every 4–6 h.

Penicillin G (benzylpenicillin): 1 µg = 1.67 IU; 1 IU = 0.6 µg.

Adjustment in RI (depending on GFR in mL/min):

- GFR > 50: normal dosage
- GFR 10–50: 50,000–100,000 IU/kg every 8 h
- GFR < 10: 50,000–100,000 IU/kg every 12 h
- PD: 50000–100,000 IU/kg every 12 h
- HF: 50000–100,000 IU/kg every 8 h

Adverse drug reactions: Allergic reactions can occur with all beta-lactam antibiotics (e.g., skin reactions, eosinophilia, bronchospasm, anaphylactic shock); hemolytic

anemia, leukopenia, thrombocytopenia, drug fever; neurotoxic reactions in patients on high-dose therapy with a predisposition to seizures or renal impairment.

Caveat Cross-allergy with other beta-lactam antibiotics!

7.9.2 Ampicillin

Sensitive: as penicillin.

Additionally: *Proteus mirabilis*, *Salmonella*, *Shigella*, *E. coli* (40%), *Haemophilus*, *Moraxella catarrhalis*, *enterococci* (except *E. faecium*), *Listeria*.

Resistant: As penicillin.

Indication: Neonatal infection without microorganism detection, enterococcal endocarditis, listeriosis.

Dosage: 100–200 mg/kg BW/day i.v. in 3–4 single doses.

Adjustment in RI (depending on GFR in mL/min):

- GFR > 50: normal dosage
- GFR 10–50: 50 mg/kg every 8 h
- GFR < 10: 50 mg/kg every 12 h
- PD: 50 mg/kg every 12 h
- HF: 50 mg/kg every 8 h

ADR: allergic and anaphylactic reactions (drug fever, bronchospasm, fall in blood pressure, etc.), gastrointestinal disorders, such as pseudomembranous enterocolitis, blood count changes (granulocytopenia, thrombocytopenia, anemia)

Caveat Contraindicated on suspicion of infectious mononucleosis (rash)

7.9.3 Piperacillin/Tazobactam (Ratio 80:10)

Sensitive: like ampicillin.

Additionally: *Pseudomonas aeruginosa*, beta-lactamase-forming *Haemophilus*, gonococci and *Moraxella*, beta-lactamase-forming staphylococci, anaerobes extended to include *Bacteroides fragilis*, *Enterobacteriaceae* (incl. *Serratia*, *Citrobacter*, *Proteus vulgaris*, *Morganella morganii*, *Providencia*) – depending on susceptibility testing.

Resistant: *Stenotrophomonas*, *Burkholderia cepacia*, *Enterococcus faecium*, MRSA, *Mycoplasma*, *Chlamydia*, *Legionella*.

Indication: Severe intra-abdominal infections (here authorized also in children), urinary tract, genital tract, and biliary tract infections; infections due to susceptible gram-negative rods, *Pseudomonas* infections, severe general infections, mixed infections – can readily be combined with an aminoglycoside.

Dosage: 300–400 mg/kg BW/day i.v. in 3–4 single doses.
Adjustment in RI (depending on GFR in mL/min):

- GFR > 50: normal dosage
- GFR 10–50: 50–75 mg/kg every 8 h
- GFR < 10: 50 mg/kg every 12 h
- PD: 50 mg/kg every 12 h
- HF: 50 mg/kg every 8 h

7.9.4 Cefuroxime

Sensitive: *Streptococci, pneumococci*, beta-lactamase-forming *staphylococci*, *E. coli*, *Klebsiella*, *Salmonella*, *Shigella*, *Proteus mirabilis*, other *Enterobacteriaceae* (after susceptibility testing), gonococci, meningococci, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Fusobacteria*, *Prevotella*, *Porphyromonas*, anaerobes.

Resistant: Nonfermenters (*Pseudomonas aeruginosa*, *Acinetobacter*, *Stenotrophomonas*), Enterobacter, *Proteus vulgaris*, *Providencia*, *Morganella morganii*, *Serratia*, *Citrobacter*, *enterococci*, MRSA, MRSE, *Listeria*, *Bacteroides fragilis*, *Mycoplasma*, *Chlamydia*, *Legionella*. Cefuroxime is extensively beta-lactamase-resistant but can be hydrolyzed by extended-spectrum beta-lactamases (ESBL).

Indications: community-acquired pneumonia, urinary tract infection (UTI), perioperative prophylaxis.

Dosage: 100–150 mg/kg BW/day in 3 single doses i.v.
Adjustment in RI (depending on GFR in mL/min):

- GFR > 50: normal dosage
- GFR 10–50: normal dosage
- GFR < 10: 30–50 mg/kg every 12 h
- PD, HF: 30–50 mg/kg every 12 h

ADR: allergic reactions, rarely circulatory reactions, allergic neutropenia (reversible on discontinuation), bleeding tendency with impaired renal function, increase in transaminases, immune hemolysis.

7.9.5 Cefotaxime

Sensitive: as cefuroxime.

Additionally: many *Enterobacteriaceae* (after susceptibility testing – e.g., *Acinetobacter*), beta-lactamase-forming staphylococci (less good than cefazoline or cefuroxime), particularly good against *E. coli* and *Klebsiella pneumoniae.*

Resistant: as cefuroxime.

Indications: Empirical first-line treatment in intensive care patients for sepsis, pneumonia (particularly postoperative pneumonia with suspected involvement of problem microorganisms), peritonitis, phlegmon, abscesses, meningitis and ventriculitis, and hospital-acquired infections with severe underlying conditions; for neuroborreliosis, however, in contrast to ceftriaxone, three daily doses required.

Dosage: 25 mg/kg BW i.v. every 6–8 h (max. 1 g/dose); in meningitis: 50 mg/kg BW i.v. every 6 h (max. 2–3 g/dose) – good CSF penetration.

Adjustment in RI (depending on GFR in mL/min):

- GFR > 50: normal dosage
- GFR 10–50: normal dosage
- GFR < 10: 25 mg/kg every 8 h
- PD: 25 mg/kg every 12 h
- HF: 25 mg/kg every 8 h

7.9.6 Ceftazidime

Sensitive: as cefotaxime.

Additionally: *Pseudomonas aeruginosa*, *Acinetobacter*, *Enterobacter cloacae*, *weaker* against staphylococci.

Resistant: as cefuroxime.

Dosage: 100–150 mg/kg BW/day i.v. in three single doses.

Adjustment in RI (depending on GFR in mL/min):

- GFR > 50: normal dosage
- GFR 10–50: 30–50 mg/kg every 12 h
- GFR < 10: 30–50 mg/kg every 12 h
- PD: 30 mg/kg every 24 h
- HF: 30–50 mg/kg every 12 h

7.9.7 Meropenem

Sensitive: *Almost all gram-positive, gram-negative, and anaerobic microbes* (compared with imipenem/cilastatin somewhat better in the gram-negative and somewhat weaker in the gram-positive range).

Resistant: *Stenotrophomonas maltophilia*, carbapenemase-formers (enterobacteria, *Klebsiella pneumoniae*, *E. coli*, *Serratia marcescens*, *Citrobacter freundii*, *Enterobacter cloacae*, *Morganella morganii*, and nonfermenters, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*), *Burkholderia cepacia*, *Enterococcus faecium* and *faecalis* (susceptibility testing), *MRSA*, MRSE, *Corynebacterium jeikeium*, *Clostridium difficile*, *Mycoplasma*, *Chlamydia*, *Legionella*.

Indications: nosocomial and severe infections (e.g., peritonitis), particularly in immunodeficiency, in sepsis, and in infections due to microorganisms resistant to other antibiotics.

Dosage: 60–120 mg/kg/d i.v. in 3–4 single doses.

Adjustment in RI (depending on GFR in mL/min):

- GFR > 50: normal dosage
- GFR 10–50: 20–40 mg/kg every 12 h
- GFR < 10: 10–20 mg/kg every 24 h
- PD: 10–20 mg/kg every 24 h
- HF: 20–40 mg/kg every 12 h

ADR: gastrointestinal reactions; in 1–2% CNS (dose-dependent) ADR (tremor, myoclonus, seizures, confusional states, somnolence, dizziness), particularly in the case of renal impairment or previous CNS injury; increase in transaminases (usually insignificant), allergic reactions, eosinophilia, leukopenia, thrombocytopenia, fall in Hb, immune hemolysis, temporary prolongation of PTT, rarely renal impairment/urine discoloration (red), seizures in combination with ganciclovir

Caveat Carbapenems exhibit relatively poor penetration into CSF! No combination therapy with beta-lactam antibiotics: carbapenems induce the production in gram-negative bacteria of chromosomally coded beta-lactamases, which inactivate other beta-lactam antibiotics (other than carbapenems). Beta-lactam antibiotics can be reinstated 12 h after discontinuation of carbapenems.

7.9.8 Clindamycin

Sensitive: *Staphylococci, streptococci, pneumococci, Corynebacterium diphtheriae*, *Bacillus anthracis*, almost all *anaerobes* (incl. *Bacteroides fragilis*), *Mycoplasma hominis*, *Pneumocystis jiroveci*, *Toxoplasma gondii.*

Resistant: *Enterobacteriaceae*, nonfermenters, *Haemophilus influenzae*, gonococci, meningococci, enterococci, some clostridia, *Mycoplasma pneumoniae*, *Ureaplasma urealyticum.*

Indications: alternative in staphylococcal infections and infections due to gram-positive cocci in the event of an allergy to beta-lactam antibiotics, bone and soft tissue infections, MRSA infections.

As a combination antibiotic to inhibit toxin formation in severe staphylococcal and streptococcal infections (toxic shock).

Anaerobe infections, particularly due to *Bacteroidaceae* or *Fusobacteria.*

Dosage: 10–20 mg/kg BW/day i.v. in 3–4 single doses.

Adjustment in RI:

- None (according to dosing.de)
- GFR <10 ml/min: where necessary 10 mg/kg every 12 h

- PD: where necessary 10 mg/kg every 24 h
- HF: where necessary 10 mg/kg every 12 h (clindamycin is not dialyzable)

Adverse drug reactions: *allergic*: skin reactions, rash, anaphylaxis; *toxic*: 10–30%, predominantly gastrointestinal disorders, not dose- and time-dependent, rare in children, diarrhea; pseudomembranous colitis.

Clindamycin is particularly suitable in bone and soft tissue infections because of its good tissue and bone penetration and is also well suited for use in severe staphylococcal/streptococcal and anaerobe infections.

7.9.9 Tobramycin

Sensitive: *Pseudomonas aeruginosa*, *enterobacteria*, *Yersinia*, *Campylobacter fetus*, *Pasteurella*, *Brucella*, *staphylococci*.

Compared with gentamicin, better against: *Pseudomonas aeruginosa.*

Resistant: *Enterococci, streptococci, pneumococci*, *Stenotrophomonas maltophilia*, *Burkholderia cepacia*, *all anaerobes*, *Providencia.*

Synergism exists with:

- Piperacillin/Tazobactam: *Pseudomonas*
- Ampicillin: *Listeriae*, enterococci
- Penicillin G: streptococcus viridans
- Cephalosporins: *Klebsiella*

Indications: *Pseudomonas infections* (combination with piperacillin, cephalosporin, carbapenem, or gyrase inhibitors). As part of the described escalation regimens but also as first line in peritonitis and (uro-)sepsis. Endocarditis treatment in combination with a beta-lactam antibiotic and/or a glycopeptide. *No monotherapy*. Poor penetration of abscesses and weak tissue penetration

Dosage: 3–5 mg/kg BW/day i.v. as a single dose.

Adjustment in RI:

Initial administration with normal dose and then extension of the interval depending on levels (target trough level, < 2 mg/L)

Adverse drug reactions: inner ear damage, nephrotoxicity

7.9.10 Ciprofloxacin

Sensitive: *Pseudomonas aeruginosa*, *Acinetobacter*, *Enterobacteriaceae*, *Campylobacter*, *Pasteurella*, *Haemophilus influenzae*, *Moraxella catarrhalis*, gonococci, meningococci, *staphylococci*, *Legionella*, mycobacteria.

Moderately to poorly effective in: Pneumococci, streptococci, enterococci, *Mycoplasma*, *Chlamydia*, *Rickettsia*, *Stenotrophomonas maltophilia*.

Resistant: *Enterococcus faecium*, anaerobes, *Listeria*.

Indication: hospital-acquired pneumonia (e.g., VAP), suspected *Pseudomonas* infection, in severe infections in combination with beta-lactam antibiotics instead of aminoglycosides, urinary tract infections. Prophylaxis for meningococci (adults).

Dosage: 20–30 mg/kg/d i.v. in 2 single dose.

Adjustment in RI (depending on GFR in mL/min):

- GFR > 50: normal dosage
- GFR 10–50: 10 mg/kg every 12 h
- GFR < 10: 5 mg/kg every 12 h
- PD: 5 mg/kg every 12 h
- HF: 10 mg/kg every 12 h

ADR: gastrointestinal reactions, central nervous systems disorders (seizures, psychotic states, vigilance disorders, taste disorders), rash, circulatory disorders, phototoxicity, Achilles tendon rupture, arthropathies.

Interactions: Increased theophylline levels, cyclosporine; increased tendency to seizures in combination with NSAIDs (not with aspirin); reduced absorption following administration of mineral antacids.

7.9.11 Linezolid

Sensitive: *Staphylococci* (*S. aureus*, *S. epidermidis, MRSA, MRSE, coagulase-negative staphylococci), streptococci, enterococci (faecalis, faecium, VRE)*, corynebacteria, *Listeria*, *Bacillus*, *Pasteurella*, gram-positive anaerobes (*Clostridium perfringens*, *Peptostreptococcus*), *Mycobacterium tuberculosis* complex, *Mycobacterium avium* complex.

Resistant: aerobic gram-negative rod bacteria, gram-negative anaerobes.

Indication: Reserve antibiotics following detection of abovementioned gram-positive microorganisms (especially VRE), soft tissue infections due to gram-positive microorganisms.

Dosage: 20–30 mg/kg/d i.v. in 2–3 single doses.

Adjustment in RI:

– *None* (according to Zyvoxid® product information)
– Adverse drug reactions: raised blood pressure, hyperthermia, CNS disorders (headache, dizziness), *thrombocytopenia*, sometimes pancytopenia, gastrointestinal disorders

7.9.12 Erythromycin and Clarithromycin

Erythromycin

Sensitive: *Mycoplasma* (other than hominis), *Chlamydia* (other than psittaci), *Legionella*, *Ureaplasma*, streptococci, staphylococci, pneumococci, *Bordetella pertussis*, *Corynebacterium diphtheriae*, *Listeria*, gonococci, meningococci, *Haemophilus*

influenzae, *Moraxella catarrhalis*, *Campylobacter*, *Helicobacter pylori*, clostridia, peptostreptococci, propionibacteria, actinomycetes, *Borrelia*, *Treponema*, some atypical mycobacteria.

Resistant: *Enterobacteriaceae*, *Pseudomonas*, *Acinetobacter*, many enterococci (> 50%), MRSA, MRSE, gram-negative anaerobes, *Mycoplasma hominis*, *Nocardia*, *Mycobacterium tuberculosis.*

Indications: atypical and community-acquired pneumonia, whooping cough, meningitis due to mycoplasmas, to increase bowel motility.

Dosage: 40 mg/kg/d i.v. in four single doses; to increase bowel motility, 10–15 mg/kg/d in three single doses p.o. or i.v.

Adjustment in RI (depending on GFR in mL/min):

- GFR > 50: normal dosage
- GFR 10–50: 5–10 mg/kg every 8 h
- GFR < 10: 5–10 mg/kg every 12 h
- PD: 5–10 mg/kg every 12 h
- HF: 5–10 mg/kg every 8 h

Adverse drug reactions: Because of the *triggering of arrhythmias* and *hepatotoxicity*, erythromycin is used reticently in intensive care therapy as a prokinetic in gastroparesis.

Caveat May increase theophylline and cyclosporine A blood levels and enhanced effect of anticoagulants; do not use in long QT syndrome!

Clarithromycin

Sensitive/resistant: as erythromycin.

Indications: atypical and community-acquired pneumonia, whooping cough, meningitis due to mycoplasmas.

Dosage: 15–20 mg/kg/d p.o. in two single doses (good oral availability).

Adjustment in RI (depending on GFR in mL/min):

- GFR > 50: normal dosage
- GFR 10–50: normal dosage
- GFR < 10: 7.5 mg/kg every 12 h
- PD: 7.5 mg/kg every 24 h
- HF: 7.5 mg/kg every 12 h

7.9.13 Vancomycin and Teicoplanin

Vancomycin

Sensitive: all gram-positive pathogens (incl. MRSA) and gram-positive anaerobes (incl. *Clostridium difficile*); compared with teicoplanin, better against

staphylococci and worse against streptococci, pneumococci, enterococci, *Clostridium difficile.*

Resistant: all gram-negative pathogens, glycopeptide-resistant staphylococci and enterococci (e.g., VRE), intracellular pathogens.

Indications: severe infections with beta-lactam-resistant gram-positive pathogens (MRSA, coagulase-negative staphylococci, *Enterococcus faecium*), primarily catheter sepsis, infections due to MRSA, infection due to clostridia (then oral use).

Dosage: 40–60 mg/kg BW/day i.v. in four single doses.

Intraperitoneal administration on peritoneal dialysis (see Chap. 4) and intrathecal therapy for shunt infections are also possible (e.g., 10–20 mg intrathecally every 24–48 h and then clamp off external ventricular drain for 4 h). In *Clostridium*-induced pseudomembranous colitis, oral administration (no enteral absorption) is used (e.g., 4 x 20–40 mg/kg p.o.).

Adjustment in RI (depending on GFR in mL/min):

- GFR > 50: 10 mg/kg every 6–8 h
- GFR 10–50: 10 mg/kg every 12–24 h
- GFR < 10: 10 mg/kg every 24–96 h
- PD: 10 mg/kg every 24–96 h
- HF: 10 mg/kg every 12–24 h (vancomycin is hemofiltered but not dialyzed)

Dose reduction in RI according to levels (target trough level < 15 mg/L); drug level monitoring where necessary before next administration.

Adverse drug reactions: allergies, red-man syndrome (flushing symptoms), sometimes nephrotoxicity in combination therapies, ototoxicity.

"Change of doctrine with vancomycin?" The (putative) nephrotoxicity was traditionally the focus of attention in treatment with vancomycin. Therefore, consideration was always given when dosing to ensuring that trough levels did not exceed 15 mg/L. On the basis of new findings in the last 10–15 years, the recommendations for the treatment of invasive staphylococcal infections in adults (incl. MRSA) have changed. To guarantee effective treatment and prevent resistance formation, target levels of 15–20 mg/L (before the next dose) are now recommended (i.e., the dose would be increased at trough levels of 10 mg/L).

As this procedure has not yet become established practice in German pediatrics (to our knowledge) and also good results can be achieved with the traditional regimen (in our experience), the recommendations of the "Infectious Diseases Society of America" have (as yet) not been implemented in our practice.

Teicoplanin

Sensitive/resistant: see under vancomycin.

Indications: see vancomycin (benefits over vancomycin: single daily dose, no levels strictly required); almost no CSF penetration.

Dosage: 8–10 mg/kg/d i.v. in one single dose (initially: as necessary 16–20 mg/kg/d i.v. in two single doses).

Adjustment in RI (depending on GFR in mL/min):

- GFR > 50: 8 mg/kg every 24 h
- GFR 10–50: 8 mg/kg every 48 h
- GFR < 10: 8 mg/kg every 72 h
- PD: 8 mg/kg every 72–96 h
- HF: 8 mg/kg every 24–48 h

Dose reduction in RI where necessary, based on drug levels (target trough level < 10–15 mg/L).

Adverse drug reactions: Teicoplanin is usually well tolerated. Ototoxicity and nephrotoxicity can sometimes be potentiated in combination with other ototoxic and nephrotoxic substances.

7.9.14 Metronidazole

Sensitive: *all anaerobes* (except *Propionibacterium*, actinomycetes), *Campylobacter fetus*, *Helicobacter pylori*, *Gardnerella vaginalis*, lamblia, *Trichomonas*, *Entamoeba histolytica.*

Resistant: all aerobic and facultative aerobic bacteria, propionibacteria, actinomycetes.

Indications: infections due to anaerobes in combination with a beta-lactam antibiotic, infections due to gas-formers, infections due to *Clostridium difficile* (if vancomycin cannot be given p.o.), amebic dysentery.

Dosage: 30 mg/kg/d iv in three single doses.

Adjustment in RI: *none* (according to manufacturer).

Adverse drug reactions: primarily gastrointestinal ADR, at higher doses possibly neuropathies and central nervous system disorders.

7.9.15 Tigecycline

Sensitive (practically all): gram-positive, including MRSA and VRE, gram-negative (incl. ESBL, *Klebsiella*), anaerobes, and atypical microorganisms.

Resistant: *Pseudomonas aeruginosa*, *Burkholderia cepacia*, *Proteus*, *Providencia*, *Morganella.*

Indications: severe skin and soft tissue infections (e.g., necrotizing fasciitis, mediastinitis), severe mixed infections, severe intraabdominal infections. Preferably not in pulmonary and urinary tract infections.

Dose: Initially 2 mg/kg i.v. (Ad. 100 mg/dose) and then 1 mg/kg (Ad. 50 mg/dose) i.v. every 12 h.

According to our microbiology, the manufacturer's stated dose should be doubled.

Halving of the dose in severe hepatic impairment (Child-Pugh C).

Adjustment in RI: *none* (see dosing.de or manufacturer's information).

Adverse drug reactions: Tigecycline is usually well tolerated; occasionally abdominal symptoms, slight increase in transaminases, allergic reactions, blood count changes.

Remark on the information in this chapter about dose adjustments in renal impairment (RI) The authors assume no liability for the information on dose adjustments in RI. It is intended to serve as a guide and should be checked in each individual case (please also see for example: https://kdnet.kdp.luoisville.edu/drugbook/pediatric/).

Remark on liver conditions emergent on antibiotic therapy (in particular, increases in transaminases, cholestasis) Many antibiotic therapies can cause an elevation in transaminases without necessarily being a sign of liver damage (a classic example of this is meropenem). Some antibiotics, however, are directly hepatotoxic (e.g., rifampicin). By contrast, cholestasis of varying degrees of severity can occur infrequently on antibiotic therapy; classic examples of this are penicillins, cephalosporins, and macrolides. The website "LiverTox" (https://livertox.nih.gov/) of the National Library of Medicine can provide guidance.

In case of doubt, the suspect medications must be discontinued or exchanged.

7.10 Management of Multiresistant Microorganisms

The "problem" microorganisms in hospitals can be divided into three main groups: (1) methicillin-resistant *Staphylococcus aureus* (MRSA), (2) vancomycin-resistant enterococci (VRE), and (3) multiresistant gram-negative (MRGN) pathogens.

While MRSA isolates have decreased slightly in recent times, those from MRGN pathogens have been on the constant rise. Although the patients themselves usually bring microorganisms into the hospital, they can obviously also become contaminated or infected in the hospital or "develop" a resistant microorganism on antibiotic therapy.

7.10.1 Methicillin-Resistant *Staphylococcus aureus*

Methicillin-resistant *Staphylococcus aureus* (MRSA) predominantly colonize the nasopharyngeal cavity but can also be found in chronic wounds and the perianal region. Transmission of MRSA occurs primarily by hands and also as a droplet infection. However, MRSA can also remain contagious for months on contaminated surfaces and objects (e.g., stethoscope). Most MRSA carriers can be identified by systematic screening procedures on admission to the ward (smears from both nasal vestibules and where necessary from the throat or from wounds).

Basic hygiene measures (see Table 7.6) and personally assigned materials (e.g., patient-specific stethoscope) are effective in preventing transmission. In the event of proven or known MRSA colonization of the patient, *single room isolation* and *MRSA-reducing treatment* are also recommended. The "decolonization plan" includes the use of mupirocin nasal ointment, washing the skin and hair with an

Table 7.6 Hospital hygiene measures

Pathogens	Single room	Cohorting	Protective gown and disposable gloves	Face mask
MRSA	Yes	Yes	Yes	Yes
2MRGN2 NeoPed	No	Yes	Yes	No[a]
3MRGN and 4MRGN[b]	Yes	Yes	Yes	Yes
VRE	Yes	Yes	Yes	No
P. aeruginosa *S. Marcescens* (without MRGN properties)	No	Yes	Yes	No[a]

After http://dgpi.de/go/wp-content/uploads/2014/08/MRGN_DGPI_PaedIC-Empfehlung_HygMed.20141.pdf

[a]Only in activities with an increased risk, e.g., when aspirating the nasopharynx, in ventilated children requiring open aspiration

[b]In patients colonized or infected with 4MRGN bacteria, a sufficient number of nursing staff should be assigned to ensure other patients not colonized with those pathogens are not treated at the same time

antimicrobial washing lotion, and mouth rinses (see www.gosh.nhs.uk/health-professionals/clinical-guideline/meticillin-resistant-staphylococcus-mrsa-control-and-mangement).

7.10.2 Vancomycin-Resistant Enterococci

Vancomycin-resistant enterococci (VRE) constitute a particular problem as they can transfer the glycopeptide resistance gene to staphylococci, for example. *Enterococcus faecium* in particular already possesses a broad spectrum of intrinsic resistance. VRE usually occur perianally or around colostomies. Contamination occurs by direct contact with secreta (droplet or smear infection). Dried isolates can remain viable for many months. The recommendations for infection prophylaxis in VRE (see Table 7.6) are to a large extent identical to those for MRSA (with the exception of a decolonization plan). Restrictive use of glycopeptides can help prevent the development of VRE.

7.10.3 Multiresistant Gram-Negative Pathogens (MRGN)

Pathogens collectively referred as multiresistant gram-negative (MRGN) differ in the group of antibiotics they are resistant to. Of mention here are *E. coli*, *Klebsiella*, *Serratia*, *Pseudomonas*, *Acinetobacter*, and other gram-negative rod bacteria. These microorganisms are usually found in the gastrointestinal or urogenital tract. Colonization with MRGN bacteria therefore mainly occurs perianally but can also be present in pharyngeal or tracheal secretions. As with vancomycin-resistant enterococci (VRE), transmission usually involves a droplet or smear infection. The pathogens of the MRGN group are divided according to the presence of resistance

to 2–4 of the relevant antibiotic drug classes, acyl-ureidopenicillins (piperacillin), 3rd−/4th-generation cephalosporins (e.g., cefotaxime, ceftazidime), carbapenems (e.g., meropenem), and fluoroquinolones (ciprofloxacin), into either 2MRGN, 3MRGN, or 4MRGN. While 2MRGN do not play any role in terms of hygiene measures on adult wards, they must be given due consideration in the risk area of a pediatric intensive care where neonates and sometimes premature infants are also cared for. If 2MRGN are present, glove and gown nursing is usually sufficient. From 3MRGN, the patient should receive barrier nursing as well (preferably an isolation room), in addition to which a face mask should be worn. A patient with a 4MRGN must always be isolated in a single room (see Table 7.6). Decolonization measures are also of no relevance here.

Generally, all measures to protect the patient against iatrogenic infections must be implemented. Above all, the following should be mentioned:

- Disinfect hands as well as instruments, stethoscope, etc.
- Comply with the specified hygiene measures (in accordance with institutional hygiene plan)
- Comply with special hygiene measures in immunosuppressed patients (e.g., reverse isolation of patients)

Suggested Reading

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Website

1. https://redbook.solutions.aap.org/redbook.aspx.

Coagulation System

8

Dietrich Klauwer

8.1 Coagulation Products on the ICU

This chapter recapitulates the coagulation process and describes common agents that exert an effect on coagulation followed by a discussion of routine anticoagulation post-cardiopulmonary bypass (CPB) surgery. The causes and treatment of bleeding and hypercoagulability will be discussed alongside the most common coagulation problems associated with postoperative pediatric heart surgery are concisely outlined.

The basics for an understanding of coagulation problems after pediatric heart surgery are illustrated in Fig. 8.1 in a greatly simplified form but provide a clinically representative illustration of the coagulation cascade. Basically, the vascular lesion triggers constriction of the vascular smooth muscle and platelet adhesion. The platelets aggregate, and a clot forms on their surface or in their vicinity. Next, factor XIII stabilizes the clot.

Table 8.1 lists the coagulation products commonly administered on the ICU. Some additional therapeutic applications for coagulation products with individual factors in children are still currently undergoing testing in clinical trials.

8.2 Effect of Cardiopulmonary Bypass on Coagulation

CPB induces the consumption of coagulation factors by adhesion to foreign surfaces, whereas deep hypothermia and acidosis result in dysfunction of coagulation factors and their increased degradation. Coagulation properties can also be seriously adversely affected by fluctuating calcium levels, e.g., following the administration

D. Klauwer
Department of Pediatrics, Singen Medical Center, Gesundheitsverbund Landkreis Konstanz, Krankenhausbetriebsgesellschaft Hegau-Bodensee-Klinikum, Singen, Germany

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D. Klauwer et al. (eds.), *A Practical Handbook on Pediatric Cardiac Intensive Care Therapy*, https://doi.org/10.1007/978-3-319-92441-0_8

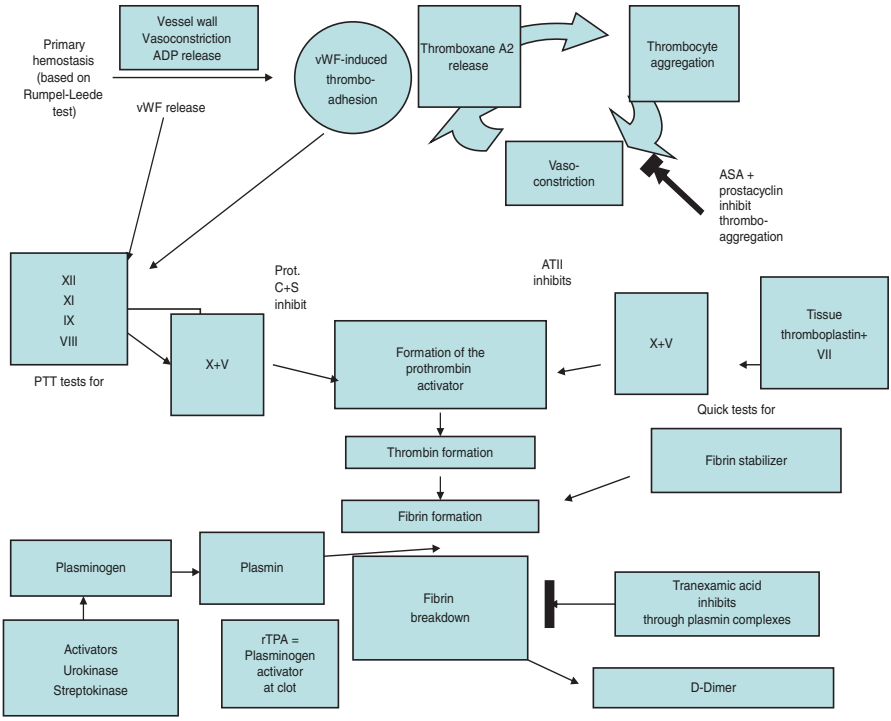

Fig. 8.1 Coagulation flow chart

of proteins and by reduced hemoglobin content in the blood (<7–8 g/dL). The intraoperative activation of blood platelets in contact with foreign surfaces results in platelet loss and dysfunction with considerable implications for the postoperative phase as well.

CPB induces hyperfibrinolysis. The reductions in fibrinogen, factor V (FV), factor VIII (FVIII), and plasminogen can only be reliably diagnosed by thrombelastography (TEG, see below) or multichannel measurements in rotational thromboelastometry (ROTEM).

As the coagulation process involves platelet factors and factors on the platelet surface, both platelet count and platelet functions affect the bleeding tendency and coagulation. In general, *hypothermia, particularly of less than 34 °C*, represents a considerable bleeding risk. In addition, (pre)operatively administered drugs such as coumarins, heparin, or platelet aggregation inhibitors exert a considerable effect on the patient's bleeding tendency both intraoperatively and postoperatively.

Thus, a careful drug history and knowledge of both the duration of CPB as well as of any problems with surgical hemostasis constitute an essential basis for successful coagulation diagnostics following any heart surgery. Blood temperatures >34.5 °C, prevention of acidosis (pH < 7.2), normocalcemia, and Hb > 7–8 g/dL are the indispensable basal parameters of postoperative coagulation management.

Table 8.1 Coagulation products in the ICU

Heparin	
UFH	Increases the effect of AT III, inhibits thrombin formation, thus substantially reduces prothrombin activator activity and thrombin formation (control of effect via PTT – But also prolongs TT) Note urine output for dosing because of renal elimination
LMWH	Increases only AT III effect, longer half-life (8 vs. 2 h) Monitoring via anti-Xa activity (0.4–0.6 IU/mL = prophylactically) 0.8–1.0 IU/mL = therapeutic, less risk of HIT Thrombolytic effect?
Protamine	Antagonizes heparin (1:1), less with LMWH
Coumarins	Inhibit synthesis of II, VII, IX, X (as well as proteins S and C) (effect controlled via prothrombin time/INR) Start of treatment overlapping with heparin
PPSB	Combination of factors in bleeding due to hepatic coagulopathy (II, VII, IX, X) – Indication in extremely severe bleeding or after CPB (see Chap. 18)
Clopidogrel	Inhibits ADP-dependent platelet aggregation
Dipyridamole	Inhibits ADP reuptake (increase in local concentration)
Novoseven	Factor VIIa – directly activates prothrombin activator
Fibrinogen	Factor I Administration in event of bleeding and possibly with low values (<1.5 mg/L) and after CPB (see Chap. 18)
Factor XIII	Fibrin stabilizer Administration in event of Confirmed deficiency (< 40% of normal value for age) Wound healing disorder Bleeding with "normal" coagulation
Tranexamic acid	Antiplasmin Stabilizes the thrombus by inhibiting fibrinolysis Administration postoperatively, with bleeding or confirmed hyperfibrinolysis

PPSB prothrombin, proconvertin, Stuart-Prower factor, antihemophilic factor B, *HIT* heparin-induced thrombocytopenia, *TT* thrombin time, *UFH* unfractionated heparin

Obviously, the frequency and type of intraoperatively administered coagulation products must be reported and documented.

Skin color, heart rate, CVP, and blood pressure alongside the indirect signs of circulation described, together with drain flow (quantity over time, consistency, and color) and body temperature, are the determining clinical factors for optimal immediate postoperative monitoring. In this context, the initial blood gas analysis (BGA) can provide indications as to the causes of bleeding (acidosis/hypocalcemia) and progression of blood loss (Hb).

After the case history, clinical parameters, and the initial BGA have been evaluated, it is possible to establish whether further coagulation tests are necessary above and beyond the routine determinations of blood count, PTT, TT, fibrinogen, prothrombin time, INR, and ACT (see Table 8.2).

In the presence of an uncomplicated bleeding situation, the initial question to be asked is whether prophylactic anticoagulation is needed or not.

Table 8.2 Basic coagulation tests

PTT ↓	PTT ↑	Prothrombin time ↓ (INR)	FIB ↓	ACT ↑ (normal: 100 s)	TT ↑ (tests heparin, FIB, and AT III)
Hyperco-agulability	Postop. coagulation disorder	Postop. coagulation disorder	Postop. coagulation disorder	Postop. coagulation disorder	Heparin[a]
	DIC	DIC	DIC	DIC	DIC
	Hemophilia	Liver disease	Liver disease	Liver disease	Hyperfibri-nolysis
	Heparin therapy	Coumarins	Hyperfibri-nolysis	Heparin	Fibrinogen deficiency
	Way too much coumarin Lupus anticoagulant	Way too much heparin			

[a]An isolated increase in PTT with normal TT can be interpreted as evidence of DIC; PTT and TT are likewise increased following a heparin overdose

Table 8.3 Basic coagulation clinical data

Previous history	Preop. laboratory tests	Intraop. case history	Postop. clinical features	Postop. laboratory tests
Bleeding tendency	Blood count	Bleeding tendency	Bleeding in drains	Blood count
Thromboses	PTT, prothrombin time (INR), FIB, AT III	Adhesions	Bleeding from wound, stitches	PTT, prothrombin time (INR), FIB, D-dimer, AT III
	Infection markers	Last ACT, administration of coagulation factor concentrates, administration of Minirin?		ACT, possibly ROTEM/TEG

TEG thrombelastography, *ROTEM* rotational thromboelastometry

8.3 Basic Coagulation Data

See Table 8.3.

Where the case history reveals no abnormalities and postoperative bleeding is not excessive, prophylactic postoperative anticoagulation can be stratified relatively simply according to the following categories:

- CPB surgery not involving the coronary arteries
- CPB surgery without prosthetic valves
- Surgery without artificial systemic-to-pulmonary artery shunt
- Surgery without passive pulmonary perfusion
- Surgery without R/L shunt (particularly with an inguinal CVC)

In other words, patients undergoing surgery for atrial septal defect (ASD), ventricular septal defect (VSD), atrial ventricular septal defect (AVSD), total anomalous pulmonary venous return (TAPVR) and AV canal, as well as after a homograft change, tetralogy of Fallot (TOF) correction, PA banding, myocardial resection for subaortic stenosis, CoA surgery, PDA closure, commissurotomy, etc., *are given 100 IU UFH/kg BW/day by drip infusion*. Heparinization can be initiated after the evening blood draw, unless there is severe bleeding or the coagulation parameters are completely out of control. Following removal of the CVC, administration of heparin is usually no longer necessary.

8.4 Category 300 IU/kg BW/day Heparinization

In this case, patients who have undergone coronary artery surgery (d-TGA, Ross, Ross-Konno) *without* the aim of prolonging PTT are given 300 IU heparin/kg BW/day. This dose should be reached as quickly as possible, with due allowance for bleeding tendency and laboratory values.

Tip: 150 IU/kg BW after the evening blood draw if values are within the target range, then increase to 300 IU/kg BW/day heparin after 3–4 h if there is no increase in bleeding, otherwise repeat workup as above.

In these patients, AT III levels should be within the age-commensurate normal range (30–40% in neonates, increase to 70–120% of normal from about 6–12 months).

8.5 Which Patients Require PTT-Effective Coagulation?

PTT-effective coagulation is indicated in patients who have undergone a Glenn procedure, total cavopulmonary connection (TCPC), prosthetic valve surgery, or systemic-to-pulmonary artery shunt placements (and some special indications).

Glenn and TCPC After these procedures, there is a higher risk due to delayed and slow passive pulmonary perfusion, particularly at the beginning and on ventilation. Thromboses can occur in the Glenn anastomosis or in stenosed areas of the pulmonary arteries. Thrombosis is also associated with the risk of embolism, for example, in a Glenn anastomosis because of R/L shunt "from below" or in TCPC possibly via the window. Preoperative diagnostics (see below) for thrombophilia are recommended in patients who are dependent on passive pulmonary perfusion after surgical treatment.

Systemic-to-pulmonary artery shunt A small tube made from foreign material with very variable, turbulent flow, vital for oxygenation.

Prosthetic valve Turbulent flow, artificial, thrombogenic material, risk of arterial embolism.

Since the bleeding risk is naturally the predominant factor in the immediate postoperative phase in these patients as well, heparinization is performed with due regard to:

- CVP (indicator of tamponade)
- Bleeding in drainage vessels (flow plus color and color change)
- Coagulation tests (blood count, PTT, prothrombin time, AT III, and ACT)

Tip: Similar to patients undergoing coronary artery surgery, the heparin dose – e.g., 150 IU/kg BW/day – should be initiated where possible after the second evening blood draw and increased at night up to 300 IU with due regard to the clinical picture.

Particularly after placement of a systemic-to-pulmonary artery shunt, it should be auscultated regularly. Otherwise inexplicable drops in saturation should mandate the ordering of emergency tests and, where necessary, a heparin bolus intervention.

Important The determination of PTT in particular should be repeated if the values seem implausible. This might entail an emergency test, since incorrect values are not infrequently measured (e.g., wrong amount of citrate in the test tube). ACT can also be determined in parallel.

It can happen that the heparin dose needs to be constantly increased to reach the desired prolongation of PTT to 55–65 s. At the same time, it must be ensured that AT III is within the normal range (from 80%).

Caution: Heparin resistance may be present (or may develop). However, a diagnosis of heparin resistance cannot be made *until an AT III deficiency has been ruled out.* In this case, it must be assumed that an imbalance of coagulation factors prevents heparin from achieving its effect. Fibrinogen and FVIII, for example, are acute phase proteins.

In this case, anti-Xa factor must be determined and must lie within the therapeutic range (about 0.7–0.9 IU/mL). Heparin must then not be increased further. Otherwise, treatment should be switched to LMWH, or anticoagulation should be instituted with hirudin or a similar product. Alternatively, treatment with vitamin K antagonists can be initiated (as long as there are no contraindications – in particular the time to surgery [at least 7 days]).

A possible procedure for long-term anticoagulation following heart surgery is described in Table 8.4.

8.6 Managing Severe Postoperative Bleeding

Because of the abovementioned change in the coagulation system (dysfunction and consumption of platelets and factors due to contact with foreign surfaces, hypothermia, and a very large wound area relative to the body with the possibility of coexisting hyperfibrinolysis), there is a considerable bleeding risk immediately postoperatively – *every patient bleeds* (see Table 8.5).

Table 8.4 Anticoagulation recommendations of the Pediatric Cardiology in Giessen, Germany

Regimen			
(permanent)	Procedures	Exceptions	Thrombophilia investigations
No anticoagulation	ASD, VSD, AV canal, AVSD, TAPVR, homograft change, TOF correction, PA banding, myocardial resection for subaortic stenosis, CoA, PDA closure, commissurotomy	Known thrombophilia Status post thrombosis	Only on justified suspicion
Aspirin, alternatively CPG (exceptionally combination aspirin + CPG)	PDA stent[a]	Known thrombophilia	Always before Glenn (level I) and TCPC (if not already done)
	BT shunt		
	Glenn[b]		
	TCPC without window[b]	Status post thrombosis or embolism	
	On- or in-house instruction		
Aspirin for 3 months	Biovalves Homograft	Status post thrombosis or embolism – assessment versus Marcumar	
Marcumar	Mechanical valves Status post thrombosis After Glenn/TCPC in thrombophilia[c] TCPC with window After thromboses in confirmed thrombophilia		

[a]With PDA stent with only one stent, no aspirin; no CPG/with PDA stent with 2 stents, CPG only; in isolated cases, combination of aspirin + CPG
[b]If there is no increased risk of thrombosis
[c]In the event of doubt: Pro Marcumar

Fortunately, however, severe postoperative bleeding is rare. Monitoring of the basic measurement data (case history, clinical signs of bleeding intraoperatively, prevention of acidosis, normothermia, prevention of anemia [Hb > 8 g/dL] and normocalcemia – Ca^{2+} is here the F IV of coagulation-preventive avoidance of fibrinolysis by tranexamic acid) and in special cases preventive factor replacement play a major role here, while meticulous surgical hemostasis is obviously indispensable.

Thus, in addition to the complete antagonism (1:1) of heparin doses intraoperatively and in the HLM priming solution to the machine outlet, preventive tranexamic acid therapy has become an established practice, e.g., with a bolus dose (10 mg/kg BW) at the beginning of anesthesia and a drip infusion at 3 mg/kg/h until the end of surgery. Furthermore, preventive administration of fibrinogen (50 mg/kg BW) and 30 IU PPSP/kg BW following protamine antagonism can be helpful (particularly in deep hypothermia/revision surgery/large wound areas).

Lastly, the blood count is also monitored during surgery and the platelet count measured and where necessary replaced. If, despite the measures mentioned, severe

Table 8.5 Postoperative bleeding

	Surgery	Surgery	Surgery	Surgery
Bleeding	<2–3 mL/kg BW/h, regressing, becoming more serous	<2–3 mL/kg BW/h, not regressing	3–6 mL/kg BW/h	>5 mL/kg BW/h
Platelets	>100,000/µL, otherwise consider replacement 20 mL/kg in 1 h	>100,000/µl, otherwise replacement 20 mL/kg BW in 1 h	Give	Give
ACT	Not necessary	Do	Do	Do
FIB	>1 g/L, otherwise FFP 20 mL/kg	Keep above 1.5 (FFP)	Keep above 1.5 (FFP) Administration of fibrinogen	Keep above 1.5 (FFP) Administration of fibrinogen
PTT	<60 s, otherwise FFP 20 mL/kg	Aim for <60, otherwise FFP, FFP as volume replacement	FFP as volume replacement Hb > 8 g/dL	FFP as volume replacement, risk of mass transfusion
D-dimers	<2, observe	Note	*Caution*: hyperfibrinolysis! If necessary, thrombelastography	Mainly surgical
Start 100 IU/kg BW/day UFH	After 6 h	Not	None	None
Other		Consider administering platelets, note CVP and drain levels	Administer PC depending on number, inform consultant and surgeons, possibly Novoseven	Administer PC depending on number, inform consultant and surgeons, possibly Novoseven

ACT activated clotting time, *FFP* fresh frozen plasma; *PC* platelet concentrate

intra−/postoperative bleeding occurs, the coagulation regimen must be reassessed. Nevertheless, not infrequently immediate postoperative bleeding can be resolved surgically, at least partially.

For formation of the primary thrombus:

- Sufficient heparin antagonism, sufficient replacement of platelets (platelet concentrate) and fibrinogen (e.g., fresh frozen plasma (FFP), fibrinogen concentrate, cryoprecipitate)
- Formation of secondary thrombus: Replacement of sufficient coagulation factors (FFP, PPSB)
- Fibrinolysis: Inhibition by, e.g., tranexamic acid

Naturally, the basic parameters (Hb content, temperature, acid-base status, and Ca levels) also need to be reviewed again here. If there is then still a marked bleeding tendency, specific coagulation measurements should be taken.

Fortunately, bedside determination methods have become an established practice in many places, and these have resulted in the previously empirical (and also usually helpful) treatment being switched to a structured, and in some cases preventive, therapy of coagulation disorders and bleeding.

In most cases, multichannel measurement devices are used to record general in vitro coagulation, enabling the coagulation system to be optimized while still in the operating room and with the chest still open after disconnection from the heart-lung machine and attainment of surgical hemostasis. The procedure involving rotational thromboelastometry (ROTEM) will be described here by way of example with detailed information provided in the literature (see Fig. 8.2).

Essentially, the procedure goes back to a simple thrombelastogram and uses rotating cylinders in cups that measure the time from coagulation activation (tissue factor in EXTEM, FIBTEM, and APTEM and ellagic acid activation of the intrinsic system in INTEM and HEPTEM) until the first clot formation in the cup (CT), the firmness of the clot 10 min later (A10), the maximum clot firmness (MCF), and its potential redissolution by fibrinolysis (LI30 and ML) by means of an index (see Suggested Reading). Table 8.6 presents these five principal assays and their targets.

On the onset of coagulation, the deflection of the torsion pendulum suspended in the cup filled with citrated blood is impaired by the developing clot. The amplitude of the coagulation curve (*y*-axis in mm) reflects the degree of impairment, while the time is plotted on the *x*-axis. Relevant reference parameters are:

- *CT* (clotting time), i.e., the time until a clot results in a deflection of the amplitude of 2 mm
- *A10* (the amplitude 10 min after measurement of CT), which gives an initial indication of the formation of a solid clot

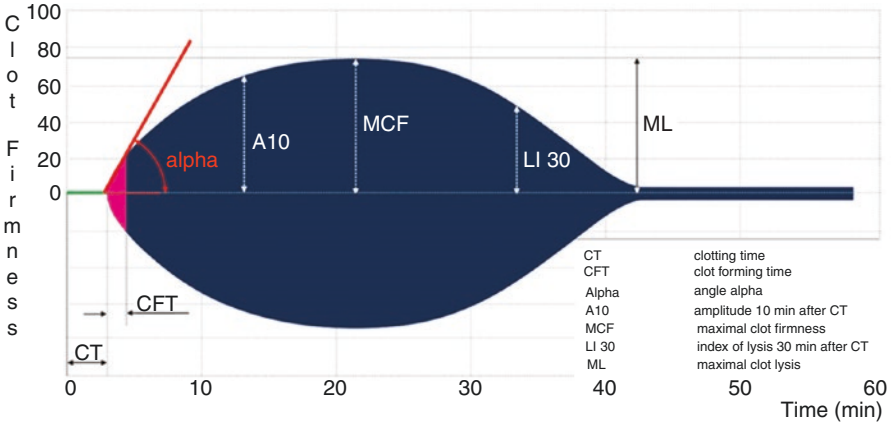

Fig. 8.2 TEMogram with explanation (By courtesy of TEM international GmbH, Munich, Germany)

Table 8.6 Tests with ROTEM

	Activator	Additional reagent	Measurement targets
EXTEM	Tissue factor (TF)		Extrinsic pathway of activation (e.g., coumarins, etc., inhibit this) Global coagulation test
INTEM	Ellagic acid (EA)		Intrinsic pathway of activation (e.g., heparins) Global coagulation test
FIBTEM	TF	Cytochalasin D → inactivates platelets, reveals only fibrin formation and possibly lysis	Global coagulation test without platelets → fibrin formation and fibrinolysis
HEPTEM	EA	Heparinase → distinguishes between heparin effect and factor deficiency if CT is prolonged in INTEM	Discriminates heparin effect from factor deficiency (intrinsic system)
APTEM	TF	Aprotinin (tranexamic acid) → On detection of thrombus reduction in EXTEM	Reveals treatable fibrinolysis as cause

Table 8.7 ROTEM measurement parameters

	CT	A10	MCF (MA in thrombelastography)	LI30 in %	ML
Definition	Time from activation to 2 mm amplitude deflection	Clot amplitude (firmness) 10 min after CT	Maximum amplitude achieved (firmness)	Amplitude 30 min after CT relative to MCF	Minimum relative to maximum amplitude
Influences	Coagulation factors heparin and other anticoagulants	Platelets, fibrinogen (F XIII)	Platelets, fibrinogen (F XIII)	Fibrinolysis index	Fibrinolysis index

CT clotting time, *MA* maximum amplitude in thromelastography, *MCF* clot firmness, *ML* maximum lysis

- Maximum amplitude (MA)/maximum clot firmness (*MCF*) in ROTEM terms, which represents the maximum deflection of the curve from the zero line
- *Li 30* (lysis index), which expresses the ratio of the clot amplitude 30 min after the start of clot formation to the MCF in percent

Maximum lysis (*ML*) is the ratio of the minimum deflection induced by fibrinolysis after MCF to the MCF itself (see Fig. 8.2 and Table 8.7).

In addition to the "simple" curves that are obtained following whole blood activation by tissue factor with a shorter CT and activation of the intrinsic system by ellagic acid in INTEM with a longer CT, distinctions can be drawn between individual coagulation disorders by the addition of specific reagents to other measurement channels.

The addition of cytochalasin D inactivates the platelets in the cup. After this step, tissue factor induces coagulation so that the plasmatic clot formation and lysis can be visualized and measured by FIBTEM.

APTEM measures the coagulation process on administration of aprotinin (or tranexamic acid), so that hyperfibrinolysis that is amenable to treatment with antifibrinolytics can be detected and assessed.

If the clotting time (CT) is prolonged in ellagic acid-activated INTEM, it is possible to ascertain comparatively in HEPTEM – measured with the addition of heparinase – whether the prolongation of CT is due to an effect of heparin (CT is massively reduced) or a factor deficiency where heparinase does not shorten the prolonged CT in HEPTEM.

It is of particular importance that, in addition to the pathophysiologic understanding of the underlying coagulation disorder by means of the shape of the curve and by figures, a targeted therapeutic intervention is possible on the basis of the absolute level of the amplitudes/quotients and coagulation times. This is helped by the development of algorithms that are now becoming more and more established and standardized in pediatric heart surgery, so that administration of blood products is less frequent as a result of targeted coagulation therapy, allowing postoperative bleeding to be treated preventively at the intraoperative stage.

FIBTEM: Maximum amplitude <8 mm → Fibrinogen requirement.

EXTEM: MCF reduction >15% (with normal APTEM) → Tranexamic acid requirement.

Thus, a MCF <8 mm in FIBTEM indicates a requirement for fibrinogen (administration 50–100 mg/kg BW), while a reduction in MCF by >15% in EXTEM (with normal APTEM) indicates an additional administration of tranexamic acid (e.g., 10 mg/kg BW repetitively). However, as described above, this is almost never necessary in preventive administration.

In addition, a normal FIBTEM amplitude (fibrinogen in order) with a reduced maximum amplitude in EXTEM (and INTEM) indicates a platelet problem. If the MCF here is less than 45 mm, platelets should be administered, and, where there is a corresponding case history, diagnostic investigations should be initiated to identify the thrombopathy, e.g., by Multiplate, or thrombelastography with platelet mapping.

A marked prolongation of the clotting time (CT) in EXTEM and INTEM (without a relevant effect of heparinase in HEPTEM) can also be regarded as an indication of factor deficiency of the extrinsic system (CT in EXTEM >100 s), so that administration of PPSB (e.g., 30–50 IU/kg BW) can be triggered.

On the other hand, administration of coagulation-active substances should never become an automatic response. Particularly in the case of shunt-dependent systemic or pulmonary circulation, with assist devices or in coronary surgery and with passive pulmonary circulation, hypercoagulability can be deleterious, and bleeding (even if severe) can be the lesser evil.

As the bleeding that develops after heart surgery regularly occurs in the chest, in addition to the somewhat chronic volume deficiency with a lack of drainage, there is the threat of acute tamponade with (in most cases) a filling disorder of the heart.

Indications of tamponade

- Blood pressure low, markedly fluctuating, CVP high/increasing, BP responding strongly to volume replacement, tachycardia
- Saturation curve and BP curve show a swing (due to a strongly fluctuating stroke volume)
- Drains convey little or very bloody liquid – or all of a sudden nothing more at all ("from 100 to 0")
- The diagnosis can be elicited by ultrasound – the area around the right atrium in particular should be investigated
- Volume replacement: platelet concentrate and FFP, packed red blood cells if necessary
- Coagulation analysis as an emergency test (always on the first postoperative blood draw) plus ACT; possibly ROTEM (see above)
- If platelets >100,000/µL and ACT prolonged: Administration of protamine (caution: this can exacerbate hypotension). Protamine dose: 50–100 IU/kg BW; prepare FFP if heparin rebound is not a causal factor
- *With low BP, presence of effusion on ultrasound, and high CVP:*
  - Further volume replacement, initiation of noradrenaline infusion to maintain perfusion pressure, forced drain stripping
  - Emergency intervention in the unit or, if sufficient time and the patient is still stable, intervention in the operating room by emergency surgical thoracotomy
  - The emergency thoracotomy set can also be used during resuscitation (almost never necessary)
  - Ensure that sufficient blood products are present
- With low BP and normal/low CVP, typically *in the presence of profuse bleeding which can be readily mobilized by forced stripping of the drains, resulting* in volume deficiency, anemia, tachycardia and arterial swing:
  - Volume replacement with FFP, platelet concentrate, packed red blood cells; if high ACT, protamine where necessary
  - Where there is time, a ROTEM analysis should be performed, as this allows a prompt investigation of whether the bleeding is being perpetuated by a platelet deficiency/hypofibrogenemia, a heparin effect or fibrinolysis
  - If hyperfibrinolysis (hypofibrogenemia), thrombocytopenia, a heparin effect, and a factor deficiency (trial administration of PPSP) are ruled out, administration of activated factor VII (Novoseven) can constitute an option in cases of life-threatening bleeding; dosage of Novoseven: 4.5–6 kIU/kg BW/SD = 90–120 µg/kg BW/single dose
  - Novoseven assumes the presence of functioning platelets as prothrombin activator and sufficient fibrinogen
  - *Caveat*: *No* Novoseven in a *non*-life-threatening situation with systemic-to-pulmonary artery shunt or extracorporeal circulation (e.g., extracorporeal membrane oxygenation [ECMO])!
  - Optimization of coagulation under constant observation (ultrasound) and information to the surgeon
  - Continuous drain stripping

How should blood products be optimally administered?

- Platelet concentrates (storage at room temperature, keep in constant movement) – over a maximum 1(−2) h
- Order FFP thawed only in order to obtain maximum benefit. FFP should also be administered as a bolus over half an hour to an hour, as there is a time-dependent loss of activity. FFP older than 6 h has practically no further effect on blood coagulation but can be administered as volume replacement
- Red blood cell concentrates, platelet concentrates, and FFP contain citrate and proteins. Therefore, ionized calcium levels require attention when large quantities are transfused, as hypocalcemia is associated with poorer postoperative heart function, coagulation disorders, and cardiac arrhythmias (BGA every 1–2 h), where necessary calcium replacement
- Always administer coagulation factors (other than Novoseven) as a short infusion over 5 min
- Never give factor VIIa at the same time as platelet concentrate/FFP – clotting occurs already in the line. Parallel administration with PPSB should also be strictly avoided because of the risk of thromboembolism (interval 4–6 h)

8.7 Bleeding Due to Hyperfibrinolysis

Following any marked mediator release, there can be an excessive activation of coagulation and also hyperfibrinolysis in conjunction with this (see Fig. 8.2).

Risk factors: major surgery, large blood loss, hypothermia, acidosis, sepsis.

In this case, primary thrombus formation still functions, but the thrombus is rapidly broken down again so that bleeding persists but coagulation factor/platelets are consumed, and an initially local and possibly subsequently disseminated intravascular coagulation is perpetuated.

The consumption of fibrinogen (which is therefore low) and the associated prolonged PTT, a low prothrombin time (both of these also test for thrombin activator and fibrin formation), and the production of fibrin degradation products (D-dimers) caused by the marked plasmin activation point to the cause.

Since the introduction of thrombelastography and thromboelastometry, which detect fibrinolysis at its very onset and even perioperatively, this coagulation disorder is only rarely still found as a cause of significant postoperative bleeding. A long-term infusion of tranexamic acid (as described above by way of example) can be initiated during surgery itself.

However, treatment with tranexamic acid (blocks plasmin by complex formation) assumes a sufficient quantity of fibrinogen, so that *fibrinogen* must be replaced (at levels <1.5 g/dL) at the same time as tranexamic acid (see above) (Table 8.8).

Table 8.8 Suspected hyperfibrinolysis

Bleeding	PTT	Prothrombin time	FIB	Thrombosis	D-dimer	TEG/ ROTEM
Hyperfibrinolysis	↑	↓	↓	↓	(↑)	(See above)

Formula 36
Fibrinogen dose (g) = desired increase (g/L) × 0.05 × kg BW

(Example: To increase fibrinogen levels from 0.5 g/l to 1.5 g/L in a 10-kg patient, 0.5 g fibrinogen must be administered).

With persistent bleeding despite normal plasma coagulation and a normal platelet count, the possibility of *local hyperfibrinolysis* due to a hematoma in the wound area should also be considered. In this case, a chest revision can resolve the problem, even though a circumscribed source of bleeding is not found and the coagulation tests also remain largely normal.

An aid to interpretation of ROTEM can be found at the URL https://learning.rotem.de/en/.

Lastly, thrombopathies can obviously also trigger (severe) bleeding. These can occur (rarely) congenitally (usually vWF deficiency) or can (more frequently) be acquired due to platelet aggregation inhibitors. In addition to the case history and the clinical and visual improvement of the bleeding symptoms or maximum amplitude in ROTEM, platelet aggregation can also be assessed by means of specific tests if required. In this case, various manufacturers provide automated procedures using impedance aggregometry for testing the extent of platelet aggregation inhibition and its causes. The essential platelet receptors (ATP, GPIIb/IIIa, vWF, and PGE1, as well as thromboxane A2) can be tested directly in terms of their activity inhibition, while metabolite-mediated platelet activation inhibitors such as cyclooxygenase inhibitors, etc. can also be tested indirectly, and the extent of inhibition can be determined quantitatively.

This plays a subordinate role in the diagnosis and treatment of acute postoperative bleeding in pediatric heart surgery (with a known previous history). If the bleeding persists without any effect of the abovementioned measures, and particularly also the administration of platelets, then Minirin is administered instead empirically for the treatment of a suspected vWF deficiency, e.g., 0.3 µg/kg Minirin i.v. If that has no effect, vWF can also be administered directly (in combination with F VIII) at a dosage of 50–100 IU vWF of the product Haemate.

An alternative to impedance aggregometry is the assessment of whole blood coagulation curves in thrombelastography versus samples tested after adding arachidonic acid, ADP, or other reagents. These analysis methods tend to play more of a role in long-term anticoagulation of extracorporeal support systems than in the treatment of postoperative bleeding. The device manufacturer usually specifies the method for monitoring the titration of the platelet aggregation inhibitors used (e.g., see the Berlin Heart protocol).

8.8 Development of Heparin-Induced Thrombocytopenia Type II (HIT-II)

Platelet factor 4 (PF4) binds to the heparin molecule, as a result of which its surface alters. The immune system then forms antibodies (AB) to these altered “foreign” PF4. The complex of heparin, PF4, and antibodies attaches to and activates the

blood platelet. Ultimately, this results in a fall in the platelet count in the blood and in the obstruction of blood vessel.

The decrease in platelets to about 20,000–80,000/μL occurs in about 70% of cases from day 5 after the start of heparinization but can start as early as the 1st day of treatment.

The following can then occur:

- Thromboses in venous and arterial flow territories
- Skin lesions that can progress to necrosis at the insertion sites
- General symptoms (fever, chills, drop in blood pressure, dyspnea)

On the slightest suspicion:

- *Detection of anti-heparin AB* (antigen test or rapid test)
- *Detection of platelet activation* (patient serum + foreign platelets) – if platelet activation is detected, HIT II is also very probably present

(The difference in principle between the tests is important: The antigen test can be used to demonstrate the presence of HIT antibodies, while the platelet activation test is used to demonstrate what this antibody "switches on.")

On the clinical suspicion of HIT II (unexplained thrombocytopenia, possibly associated with thrombosis or embolism), stop heparin and initiate anticoagulation with hirudin/argatroban (see Chap. 19), no Marcumar, no LMWH, and no platelet concentrate, unless there is a life-threatening risk of bleeding. It is also very important to check all blood replacement products for heparin content (e.g., PPSB), arterial flush without heparin, etc.

Hirudin therapy (*Refludan = lepirudin*).

Thrombin inactivator with immediate onset of action, non-antagonizable.

Refludan therapy is controlled via *PTT* (ACT). Because of *an uncontrollable bleeding tendency* following overdose, this should be *not more than 60 s*.

Gradually increasing dosage: 0.05 mg/kg BW/h in a long-term drip infusion.

Increase, e.g., 0.025 mg/kg BW/h every 2–4 h with PTT monitoring until PTT about 50–60 s.

Do not combine with other coagulation inhibitors (aspirin, lysis therapy).

Adverse drug reactions include bleeding and, in rare cases, allergic reactions.

Indication to date HIT II only.

Alternatively: *Argatroban* (Agatra).

Other possible causes of thrombocytopenia:

- Other drugs (other than heparin, e.g., quinine, quinidine, co-trimoxazole, rifampicin, paracetamol, diclofenac, carbamazepine)
- EDTA-induced pseudothrombocytopenia, posttransfusion purpura, systemic hematologic disease
- Sepsis, immune thrombocytopenia, thrombotic-thrombocytopenic purpura

8.9 Anticoagulation in ECMO and Prismaflex Therapy

Similar to the heart-lung machine (HLM), ECMO or dialysis induce a platelet/coagulation factor dysfunction with coexisting latent consumption due to the now constant contact of the blood with foreign surfaces. Blood pumps also induce hemolysis which is not only self-perpetuating but also perpetuates intravascular coagulation through mediator release and activation.

This is one of the reasons why extracorporeal procedures are time-limited. In order to extend this period potentially for as long as possible, an individualized balance must be found between anticoagulation and bleeding protection. In this context, the prevention of infection and SIRS is of vital importance, as the complex interplay of coagulation, hemolysis, and bleeding can be easily disrupted by infections.

As ECMO support is usually not planned but initiated as emergency therapy or as a last resort after a prolonged CPB surgery, initial anticoagulation is particularly difficult. Bleeding is therefore frequently the main feature in the initial phase (Table 8.9).

The main questions here are:

- Is the predominantly thoracic bleeding completely drained externally/protrusion of the patch?
- Is there a risk of the complications of mass transfusion from the bleeding (>1.5–2 times the patient's blood volume)?
- Is coagulation inhibited to such an extent that countermeasures need to be taken?

Table 8.9 ECMO steady-state target values

	Target range	Frequency of monitoring	Bleeding	Check
Hb, Hct	10 g/dL | 30–40%	With each blood gas analysis	Drains	Twice per shift
ACT	180–200 s	With each blood gas analysis	Brain	Once a day
Platelets	Over 80,000–100,000/µL	Every 6 h	Mainly chest	X-ray/ultrasound – Depending on ventilation
PTT, FIB, AT III	>70–80 s | >1.5 | >70%	Every 6 h	Abdomen	Ultrasound
D-dimer	<1 mg/mL	Every 12 h	GI hemorrhage	Stool?
Free Hb only if haptoglobin saturated	0.1 g/L	Every 12 h	Urine color clinical hemolysis	Nursing

Table 8.10 illustrates how ACT as a global coagulation assay primarily tests the effect of heparin, in vivo platelet function, and coagulation factors, particularly fibrinogen.

Where bleeding is the predominant feature in ECMO, the essential factor is that the blood is well drained externally.

The following are the primary potential causes of bleeding (with overlaps):

- Surgical hemorrhage
- Coagulation due to thrombocytopenia/thrombasthenia
- Bleeding due to (plasma) coagulation disorder or hyperfibrinolysis

Clarification is not always possible because of the overlap between DIC and hyperfibrinolysis. In addition, treatment can only be given with caution, as iatrogenically induced hypercoagulability (Novoseven therapy) induces clotting in the machine and thus jeopardizes its functioning.

Table 8.10 No significant bleeding

Simplest case (A)	Coagulation inhibited (B)	Coagulation inhibited (C)	Coagulation relatively uninhibited (D)	Coagulation inhibited
ACT 140-190	ACT > 220	ACT 180-220	ACT 160-180	ACT 160-180
No significant bleeding	No significant bleeding	No significant bleeding	No significant bleeding	No significant bleeding
Platelets > 100,000/μL	Platelets > 100,000/μL	Platelets > 100,000/μL	Platelets > 100,000/μL	Platelets < 80,000/μl
PTT not/ marginally prolonged	PTT markedly prolonged/>120	PTT markedly prolonged/> 120	PTT not/ marginally prolonged	PTT prolonged
FIB > 1.5, ATIII > 70%	FIB 1.5–2	FIB < 1	FIB 1.5–2	FIB > 1.5
Hb approx. 10 g/dL	Hb 10 g/dL	Hb approx. 10 g/ dL	Hb < 8 g/dL	Hb approx. 10 g/ dL
Start heparin 100 IU/kg BW/day	No heparinization	Minimal to no heparinization	Start heparin 100 IU/kg BW/ day	Start heparinization, give platelet concentrate (over 1 h)
Monitor ACT 1–2 h, keep values in target range	Monitor after 1 h, then if necessary as (A)	Administration of FFP 20 mL/kg BW in 1 h, then monitor with coagulation and ACT	Administration of EC, monitor ACT 1 h	Monitor while running platelet concentrate and immediately afterward

Table 8.11 Diagnostic investigations for bleeding in ECMO

	Thrombocytopenia	DIC	Hyperfibrinolysis	Heparin overdose
PTT	OK	↑	↑	↑
Prothrombin time	OK	↓	↓	OK
ACT	↑	↑	↑	↑
Platelets	↓	↓	(↓)	OK
FIB	OK	↓	(↓)	OK
D-dimers	OK	(↑)	↑	OK
Thrombelastogram MA	MA slightly to severely reduced	MA severely reduced	MA OK, secondary MA reduction	MA OK to slightly reduced
R time	OK	(↑)	OK	↑↑

MA maximum amplitude, R, time (in thrombelastography, corresponds to MCF and CT in ROTEM)

Although thrombelastography (in this case, e.g., whole blood testing and testing with heparinase in two channels) represents a useful and meaningful test, ROTEM (possibly supplemented by platelet analysis) can also provide a rapid decision-making tool here (Table 8.11).

Where it is not possible to reduce bleeding by replacement of fibrinogen/FFP, platelets and red blood cells and possibly by careful antifibrinolytic treatment, only surgical revision of the chest, with a change of system if there is clotting in the system, is left in order to control the bleeding.

In the case of bleeding in an extracorporeal circulation (e.g., ECMO, ventricular assist device, CVVHD), consideration should also be given to the possibility of an "acquired vW syndrome" (test for: VIII + vWF; treatment: Haemate = combination product of FVIII and vWF).

(See Chap. 10 for clotting in the system.)

8.10 Prismaflex

Coagulation management on the Prismaflex is easier, as the blood flow can be maintained via a Sheldon catheter without having to open a body cavity.

The following are recommended:

- Platelet count over 80–100,000/µL, blood count twice daily
- PTT over 60 s, ACT 180 s, coagulation/hemolysis twice daily
- Fibrinogen over 1.5 g/L
- ACT every 4–6 h
- Sufficiently high blood flow rates

The thicker the Sheldon, the more likely is clotting; the thinner, the more likely is hemolysis. ACT every 4–6 h, twice daily base excess with blood count,

coagulation, and signs of hemolysis are usually sufficient but particularly monitoring of the device (pressures) and the patient (signs of bleeding).

A more detailed description, including weight-dependent catheter sizes, can be found in Chap. 4. The anticoagulation with citrate that occurs in the device is also described there.

8.11 Anticoagulation on the Berlin Heart

As distinct from ECMO, which can only temporarily replace heart function, and hence also additively lung function, the objective with the ventricular assist device (in this case Berlin Heart EXCOR) has a longer-term perspective.

Since a pulsatile flow is generated and a microcapillary network is not incorporated ECMO's oxygenator, coagulation therapy as a rule can be designed for the longer term following the more time-consuming initial phase.

Oral anticoagulants therefore also have their merits in treatment.

Although there are differences between the instructions by Berlin Heart and the "reality" at our center in Giessen in terms of experiences with how to handle coagulation management, the guidelines should be followed when initiating an EXCOR program. (Reference is made to the Berlin Heart Anticoagulation company's current recommendations which can be found on the Berlin Heart's website for medical professionals.)

After the patient's handover from the operating room, repeated echocardiographic monitoring must be performed to show that there are no intrathoracic hematomas (pericardial effusion) present.

A ROTEM analysis (with a platelet function test) or a simple TEG analysis can be performed (in about 10 min) with fresh blood – preferably taken by puncture – in parallel with the coagulation analysis and ACT, as well as BGA. Self-performed platelet mapping via the TEG requires at least an hour of work and is not really suitable for inclusion in the unit's procedures, with results that are often no readily evaluable. ROTEM impedance aggregometry, which can be performed by the laboratory, has clearly proved to be superior in such instances.

However, in isolated cases, it is necessary to clarify with the laboratory and Berlin Heart whether the locally available platelet function tests can be used for running the extracorporeal procedure (see Tables 8.12 and 8.13).

In the introductory phase of oral anticoagulants, it has become an established practice to maintain anti-Xa levels at about 1 IU/mL and to use low doses of platelet aggregation inhibitors.

Particular attention must also be paid to visual inspection of the chambers and tubes in order to be able to detect even minor changes in deposits at an early stage. Furthermore, monitoring intervals must be reduced on any clinical or laboratory signs of infection, since there is a particular risk of hypercoagulability.

Caution Gastroenteritis symptoms are commonly associated with altered absorption of anticoagulants.

Table 8.12 Berlin Heart anticoagulation

Immediately postoperatively	In the first few days	From weeks 2–3	When completely stable
No heparin for 12–24 h	Heparin at 10–20 IU/kg/h	As soon as drains are out	Marcumar (instead of heparin)
No heparin until bleeding stops	Target PTT 50–60 s target ACT 180–200 s or anti-Xa 0.8–1.0 IU/ml	Additionally aspirin 1 mg/kg/day	Target INR 2.0–3.0

Table 8.13 Bleeding diagnostics on the Berlin Heart

Postoperative	6–8 h	Day 1 postop.	Days 2–4 postop	Thereafter
Coagulation	Coagulation	Coagulation	Coagulation	Start dipyridamole/ where necessary also aspirin 4 times daily 1–2 mg/kg
Blood count	Blood count	Blood count	Blood count	TEG monitoring
ACT	ACT	ACT	ACT	R-time reflects heparin (20–30 min OK)
Ultrasound	Ultrasound	Ultrasound	Ultrasound	TEG with platelet mapping, target ADP < 50%, target arachidonic acid < 30%
	Start UFH 100–200 IU/kg BW/day	UFH 300 + X IU/kg BW/day, target PTT 50–60 s	Switch LMWH, target 0.8–1 IU/mL, anti-Xa, or Marcumar	Platelet mapping is laborious, liable to many errors, and often not reproducible

8.12 Thrombophilia

Thromboses occur in children with neonatal and pubertal peaks.

As well as *vessel wall changes* (surgery, inflammation, i.v. access, external compression) and *changes in blood flow* (stasis in surgery, immobilization, flow obstruction due to external compression), coagulopathies play a major role. These, in turn, can be caused by an exogenous disease or noxae (trauma/asphyxia, etc.) or by congenital changes in the coagulation system. Various mechanisms of the change in coagulation come into play here (see Table 8.14).

Obviously, genetic tests can be undertaken at any time without interfering with surgery/thrombotic events. Conversely, all coagulation proteins should be determined at an interval of about 3 months between events (thrombosis/surgery) and analyzed on a blood sample taken by puncture (see Table 8.15).

The results of the analysis have immediate consequences in the postoperative phase, particularly in patients with complex defects with an R/L shunt and defects that culminate in univentricular palliation.

Thus, marcumarization should be initiated at the end of the immediate postoperative phase in the abovementioned patients following a positive diagnosis of thrombophilia. For these patients, a preoperative level I analysis should therefore be performed routinely (see Table 8.16).

Table 8.14 Causes of thrombosis

Vessel wall	Blood flow	Exogenous coagulopathy	Endogenous coagulation disorder	Detail (investigate primarily)	Very rare (investigate after hematologic consultation)
Surgery/ trauma	Surgery	Asphyxia	Change of antithrombotic proteins	AT III, protein S, protein C	Dysfibrinogenemia, heparin cofactor deficiency, dys- and hypoplasminogenemia, rare genetic polymorphisms
Inflammation	Immobilization	Sepsis, infection	Mutation of coagulation factors	Factor V Leiden (G1691A) = APC resistance, prothrombin (G20210A)	
Compression	Compression	Dehydration	Metabolic disorder	MTHFR polymorphism, homocystinuria (homocysteine levels < 13 µmol/L)	
Access (i.v.), tumor process	Change of hemodynamics	Rheumatism, tumor + leukemia	Increased plasma proteins	Lipoprotein(a)	
Inflammation	Heart failure	Medication			
Valve defect		Nephrotic syndrome			

APC activated protein C, *MTHFR* methylenetetrahydrofolate reductase

Table 8.15 Age-related normal values (median, range)

Parameter	Neonates	3 mo	6 mo	1–5 yr	6–9 yr	10–18 yr
Activated protein C %	35 (14–55)	55 (25–82)	60 (38–95)	75 (45–102)	84 (64–125)	88 (62–128)
Protein C antigen %	30 (12–50)	50 (22–75)	55 (40–100)	70 (45–98)	80 (55–120)	82 (55–120)
Free protein S antigen %	38 (15–55)	55 (35–92)	77 (45–115)	78 (62–120)	80 (62–130)	85 (60–140)
Total protein S antigen %	35 (14–55)	58 (35–90)	75 (50–110)	85 (60–120)	82 (59–118)	80 (60–115)
Antithrombin %	52 (30–85)	90 (55–120)	98 (65–126)	101 (85–140)	100 (85–136)	98 (84–139)
Plasminogen %	50 (35–70)	68 (45–95)	87 (65–100)	98 (63–123)	95 (68–120)	90 (70–115)
Lipoprotein(a) mg/dL	4.4 (0–125)					

Modified after [4]
mo month(s), *yr* year(s)

Table 8.16 Differentiated coagulation tests in thrombophilia

Level I	Level II	Level III
Blood count, coagulation, CrP	Dysfibrinogenemia	
(FDP, FIB, TT, reptilase time)	Factors VIII, XI, XII, vWF (activity and multimers)	
AT III (%)	Heparin cofactor	Platelet aggregation
Protein S	Plasminogen activity	Plasminogen activity
Protein C	Hb electrophoresis	TFPI
Antiphospholipid antibody	Functional activated protein C (APC) resistance	
Factor V Leiden (= APC resistance)		
Homocysteine (<13 µmol/l)		
Lupus anticoagulant		
Lipoprotein (a)		

FDP fibrin degradation products, *vWF* von Willebrand factor, *TFPI* tissue factor pathway inhibitor

In the case of other patients, the procedure is a follows: if thrombosis has occurred without other risk factors at an unusual site – mesenteric, cerebral, arterial – a level I diagnostic procedure must be performed. If this yields no result, further diagnostic investigations for thrombophilia are indicated following consultation with the hematologists.

8.13 Thrombolysis

Thrombolysis is activated by plasminogen activation and hence ultimately by fibrinolysis.

As r-tPA (recombinant tissue plasminogen activator) acts only on bound fibrin, i.e., at the thrombus, this active substance is clearly superior to streptokinase (frequent allergic reactions in children) and urokinase.

Urokinase is occasionally still used in catheter thromboses.

Indication for r-tPA (Actilyse) – preferably following signed parental consent.

In pediatric cardiac intensive care, the indication for administration of Actilyse therapy must be established scrupulously given that the patient usually has a recent history of cardiac surgery, jugular vessel puncture, and arterial catheter insertion.

This involves the consideration of embolic events with major consequences:

- Severe embolic cerebral infarction (after ruling out intracerebral or intracranial bleeding) within 6 h
- Embolic extremity infarction with impending loss of the extremity
- Acute pulmonary embolism or vena cava obstructions, bilateral renal vein thrombosis
- Complete vena cava obstruction

One dose recommendation is 0.5 mg/kg BW /h for 6 h. Longer-term treatment with lower doses is also possible – short half-life of Actilyse, e.g., 0.1–0.2 mg/kg bolus in 2 min and then 0.05–0.1 mg/kg BW/h over 24 h.

Life-threatening thrombosis: 0.1 mg/kg BW – 0.2 mg/kg BW as bolus, thereafter 0.8 mg/kg BW over 2 h.

Any external bleeding that occurs during Actilyse treatment can be well controlled, whereas cerebral bleeding after Actilyse frequently has a deleterious outcome.

In addition to lysis therapy with Actilyse, PTT-effective anticoagulation with UFH is indicated (start with 300 IU/kg BW/day) – PTT target about 50–60 s.

To ensure a sufficient plasminogen concentration, administration of, e.g., 10 mL/kg of FFP should be given in parallel, where necessary every 6 hours.

8.14 Urokinase for Catheter Thrombolysis

There are many different suggestions in this respect. Common to all of them is that:

- Kinking is excluded as a cause
- Precipitates of incompatible drugs are excluded as a cause (these cannot be lysed)
- The patient is encouraged to change position and increase intrathoracic pressure (Valsalva maneuver/cough)
- After which a further flush is attempted

If the catheter aspiration problems still persist, urokinase can be given, for example, according to the following algorithm: 5000 IU/mL (in 0.9% NaCl) as a bolus (bolus size depends on the catheter filling volume) every 10 min with trial aspiration in between. See the dosage regimen depicted in Table 8.16.

It is important to note here that extremely high pressures can develop with small syringes, which can result in rupture of or leakage from the catheter. Therefore 5 mL or larger syringes should be used.

Alternatively, an attempt can be made to render the CVC lumen flushable again by means of r-tPA (Actilyse) – children over 10 kg BW. This involves injecting 1–2 mL (dilution 1 mg/mL) Actilyse into the blocked lumen and leaving it there for about 1 h.

After aspiration of the catheter, flushing with saline solution should then be repeated and aspiration attempted. This can also be repeated several times (e.g., every 2 h). In between times, a heparin block should be established where possible in the obstructed catheter.

If the vessel conditions are extremely poor, an attempt can be made to advance a wire through the temporary CVC and to pass a dilator over the wire using the Seldinger technique (risk of infection).

Common to all lysis procedures is the fact that there is an increased risk of bleeding on injection of large quantities of the lytic drug into the patient, so that a risk/benefit assessment is always indicated, particularly in the case of premature infants and neonates and patients with status post cerebral hemorrhage or CPB (Table 8.17).

(The topic of marcumarization is touched upon cursorily in the list of drugs in Table 19.4.)

Table 8.17 Catheter thromboses

	Urokinase	Every 10 min
Neonates	0.5 mL 2500 IU	Not after surgery, not in status post intracranial bleeding, not in premature infants
<10 kg 1 lumen	1 mL 5000 IU	Applies to all
<10 kg 2 lumen	1 mL 5000 IU/limb	
>10 kg 1 lumen	1.5 mL 7500 IU	
>10 kg 2 lumen	1.5 mL each 7500 IU/limb	

Suggested Reading

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Pulmonary Hypertension

9

Rainer Zimmermann and Dietrich Klauwer

9.1 Definition of Pulmonary Hypertension

Pulmonary hypertension (PHT) is generally defined as a mean pulmonary arterial pressure exceeding 25 mmHg. This "symptom" can be due to both pre- and postcapillary causes.

The precapillary pulmonary hypertension is referred to as pulmonary arterial hypertension (PAH) and is defined as an elevation of the mean pulmonary arterial pressure (PAPm) $\geq$ 25 mmHg with a pulmonary arterial wedge pressure (PAWP) $\leq$ 15 mmHg and a pulmonary vascular resistance (PVR) > 3 Wood units. PAPm values $\leq$ 20 mmHg are considered normal; the clinical significance of PAPm 21–24 mmHg is unclear. The classic example of a pure PAH is idiopathic pulmonary arterial hypertension (IPAH), whereas a combination of pre- and postcapillary hypertension is often found in left heart disease.

Notably, the Fontan circulation/TCPC is a meaningful exception to the general definition: due to the lack of a subpulmonary pump, the now passive flow through the lung depends on the pressure gradient between central venous pressure and ventricular end-diastolic pressure, as well as the pulmonary vascular resistance. In this constellation, it is nearly impossible to encounter values that are consistent with the actual definition of PAH. Consequently, even a minor increase in PVR is problematic for these patients since a compensatory elevation in pressure is not possible.

In this chapter and in the entire book, the general term PHT is used to subsume all forms of pulmonary hypertension and particularly reflects those situations where

R. Zimmermann (✉)
Global Medical Affairs, Actelion Pharmaceuticals Ltd., Allschwil, Switzerland
e-mail: rzimme15@its.jnj.com

D. Klauwer
Department of Pediatrics, Singen Medical Center, Gesundheitsverbund Landkreis Konstanz, Krankenhausbetriebsgesellschaft Hegau-Bodensee-Klinikum, Singen, Germany

© Springer International Publishing AG, part of Springer Nature 2019

D. Klauwer et al. (eds.), *A Practical Handbook on Pediatric Cardiac Intensive Care Therapy*, https://doi.org/10.1007/978-3-319-92441-0_9

pre- and postcapillary components are present. For the international, globally valid classification, see Sect. 9.2.2.

9.2 Classification of Pulmonary Hypertension

The different clinical pictures that lead to or are associated with PHT can be classified according to different criteria. Therefore, different PHT classifications exist.

9.2.1 Classification by Anatomic Origin of Pulmonary Hypertension

The diseases can be classified according to the anatomic circumstances and the mechanism of the development of PHT as follows:

- Those with elevated precapillary pulmonary vascular resistance due to pathological changes in the pulmonary arterial vascular bed with vasoconstriction, vaso-obliteration, and vaso-obstruction are also referred to as pulmonary arterial hypertension (PAH). The most important etiologies in pediatrics are:
  - Idiopathic or hereditary (familial) PAH, rare.
  - Increased blood flow in the normal pulmonary vascular bed with normal PVR (initially), i.e., with elevated cardiac output due to L/R shunt (congenital heart defects).
- Those with elevated postcapillary resistance:
  - Pulmonary venous obstruction.
  - Obstruction in the left atrium or of the mitral valve.
  - Obstruction in the LV, e.g., LVOTO, e.g., due to aortic stenosis.
  - LV dysfunction: Restriction/compliance disturbance/congestion (high LVEDP → high LAP → high pulmonary venous pressure → elevated pulmonary capillary pressure → immediate and direct [reactive] elevation in PAP).

This classification serves as the basis for tailored approaches to the therapeutic strategy. In most cases the desired reduction in PVR is only possible and/or sensible in diseases with primary elevated precapillary resistance. Specific measures for lowering PVR in postcapillary resistance elevation are problematic and often even contraindicated. The focus here must be directed at the effective therapy of the underlying problem, e.g., left ventricular dysfunction. It is essential to be aware that in the presence of a postcapillary obstruction a reduction in the often reactively elevated precapillary resistance, e.g., pharmacologically induced, can lead to clinically relevant pulmonary edema within a few hours and in the presence of a L/R shunt to an adverse increase in shunt volume.

9.2.2 Clinical Classification by Etiology

In the clinical classification according to the 2015 ESC/ERS Guidelines, the different forms of pulmonary hypertension are divided into five groups according to etiological criteria:

1. Pulmonary arterial hypertension, which also includes PAH associated with congenital heart defects, pulmonary capillary hemangiomatosis (PCH, 1′), and persistent pulmonary hypertension of the newborn (PPHN, 1″).
2. PH due to left heart disease.
3. PH due to lung disease and/or hypoxia.
4. Chronic thromboembolic PHT or due to other pulmonary arterial obstructions, e.g., congenital pulmonary artery stenosis.
5. Mixed clinical picture (e.g., lymphangiomatosis).

PAH-CHD, pulmonary arterial hypertension associated with congenital heart disease, is additionally subdivided into four groups:

- Eisenmenger's syndrome.
- PAH associated with a systemic-to-pulmonary shunt.
  - Operable.
  - Inoperable.
- PAH associated with a small/coincidental shunt.
- PAH after correction of a defect.

9.3 Checklist of Possible Symptoms and Corresponding Findings

Most symptoms and findings listed in Table 9.1 can occur in more or less pronounced forms at any time over the course of the disease.

9.4 Pathophysiology of Pulmonary Hypertension

Similar to the systemic circulation, the cardiac output (Q) in the pulmonary circulation must be pumped through the pulmonary vasculature with the pressure generated by the right ventricle. The level of this pressure is primarily dependent on the pulmonary vascular resistance that needs to be overcome. From the right ventricle and/or pulmonary artery trunk to the left atrium, the pressure drops, expressed as the transpulmonary pressure gradient (TPG). This drop is expressed as:

Formula 37

$$TPG = PAP_m - LAP$$

Table 9.1 Checklist of potential symptoms in PHT

Clinical features	Caveat	ECG	X-ray	Ultrasound
Dyspnea, fatigue, decrease in general performance, loss of energy	Dyspnea without detectable cardiac and pulmonary disease	SI-QIII type	Can be normal, particularly at the onset	Estimation of the systolic PAP via TI[a]
Angina pectoris, syncope, epigastric pain (congestive gastritis)	Increase in unexplained dyspnea	Signs of right ventricular hypertrophy	Pulmonary arteries are centrally sharply delineable and dilated (dilated lumen of the right PA in the pars intermedia)	Absent expiratory collapse of the IVC as a sign of a RV failure with elevated RAP
Increased waist circumference in the presence of ascites, edema, congestion, cough, hepatomegaly, cyanosis	Split or pounding 2nd heart sound, 3rd or 4th heart sound	Right bundle branch block	Sudden change in vessel caliber with poorly vascularized periphery, increased recruitment of apical lung regions	RV dilatation
Symptoms at rest = advanced disease, NYHA class III–IV	Tricuspid insufficiency (systolic murmur), pulmonary insufficiency (diastolic murmur)	Supraventricular tachycardia due to hypoxemia and RA dilatation	Right heart enlargement	Flattening and left deviation of the septum toward LV; LV diseases (valvular, atrial, ventricular), obstruction of pulmonary veins

NYHA New York Heart Association, *IVC* inferior vena cava, *RA* right atrium, *RAP* right atrial pressure

[a]Caveat: Even in advanced PHT with markedly elevated PAP, there is not necessarily a measurable tricuspid insufficiency (TI), i.e., it may not be satisfactorily detectable and measurable with the Doppler!

Among other parameters, the pulmonary vascular resistance is dependent on the overall cross section (r^4) and the length (l) of the vascular system. The flow properties of blood (viscosity $\acute{\eta}$) also have an impact.

These relationships are expressed by the Hagen-Poiseuille equation as follows:

Formula 38

$Q = \Delta P \times \pi \times r^4/8 \times \acute{\eta} \times l$ corresponding to $Q = \Delta P/\mathrm{PVR}$

According to Ohm's law, the PVR can consequently be expressed as the ratio of the pressure drop ΔP and the cardiac output. In practical terms, this means that the blood flow is dependent on the "available" pressure "against" the prevailing resistance.

It should be emphasized that PVR cannot be measured directly but must be calculated. The required values for the equation can most accurately be measured invasively, i.e., through a right heart catheterization:

Formula 39
PVR = TPG/cardiac output

As described above, TPG = PAP_m – LAP. To avoid having to probe the left atrium, the pulmonary arterial wedge pressure (PAWP) can be used as a directly measurable variable to estimate LAP.

Formula 40
PVR = (PAP_m − PAWP)/cardiac output

Important: Factoring the calculated cardiac output into the equation results in the value for PVR, while using the cardiac output index (CI, cardiac index) results in PVRI (I = index)! Caution should be exercised when working with VO_2 tables to estimate the oxygen uptake, because VO_2 may be provided "indexed," i.e., as m^2 BSA.

In general, PAP reflects the pressure in the pulmonary artery; the differential PAP_m – PAWP reflects the pressure drop in the arterial, capillary, and venous portion of the pulmonary vasculature.

In pediatrics, PVR is usually stated in Wood units (WU); the PVRI (I = index) refers to the PVR value in relation to the patient's body surface area (m^2).

Formula 41
WU = mmHg × min × L^{-1}

The corresponding metric unit for the resistance is dyn × sec × cm^{-5} and can be calculated by multiplying the WU by 80 (dyn = WU × 80).

The normal value for PVRI related to the BSA is <3 WU/m^2; by comparison, the normal systemic arterial resistance is >10 WU/m^2 (cf. Fig. 9.1).

9.4.1 Pulmonary Arterial Wedge Pressure (PAWP)

The measurement of the PAWP (previously called: pulmonary capillary wedge pressure [PCWP]) is based on the principle of communicating tubes. PAWP is

	Wood units (WU)		CGS-units (dyn)		SI-units
Unit	mmHg * min * L^{-1}	x 80	dyn * s * cm^{-5}	x 0.1	Pa * s * m^{-3}
Unit index (per m^2 BSA)	mmHg * min * L^{-1}/m^2	x 80	dyn * s * cm^{-5}/m^2	x 0.1	Pa * s * m^{-3}/m^2

Wood-Units are so called HRU (hybrid reference units), which are illustrative as the calculation is based on mmHg for pressure and L/min for CO
CGS stands for centimetre, gram, second; the system with CGS units was used before the SI-System was introduced
SI stands for international unit system (système international d'unités)
1 Pascal = 1 N/m^2

Fig. 9.1 Wood units, CGS units and SI units

measured by means of a pulmonary artery catheter that is advanced into the pulmonary arteries (via vena cava, RA, and RV). The wedge pressure is measured by inflating a small balloon at the catheter tip in order to occlude a distal pulmonary artery. Therefore, the term wedge pressure is also referred to as occlusion pressure. It is imperative that the right position of the catheter be identified by means of the characteristic pressure curve (*Caveat:* Erroneous measurements are common!). The downstream pressure (behind the balloon) can now be measured. From a purely physics perspective, the pressure in the pulmonary venous vasculature cannot be lower than the end-diastolic left ventricular pressure (LVEDP). Based on the pressure equalization in the communicating vessels, the following applies: LVEDP = LAP = pressure in the pulmonary veins = pulmonary capillary pressure = PAWP (provided there are no relevant stenoses anywhere).

The transpulmonary pressure gradient (TPG), i.e., the pressure differential between the mean PA pressure (PAP_m) and the LAP (and/or LVEDP), is the driving blood pressure across the pulmonary vasculature. If the cardiac output is known, e.g., determined by the Fick or thermodilution method, PVR can be calculated.

9.4.2 Pulmonary Hypertension Due to Volume and Pressure Stress in Shunt Defects

Starting from birth, congenital shunt defects lead to volume and sometimes pressure overload in the pulmonary vascular bed, dependent on defect position and size. Acute episodes with sudden increases in PVR can occur postoperatively, depending on the duration and intensity of this overload. A situation like this is also referred to as pulmonary hypertensive crisis, which is generally reversible. The susceptibility to pulmonary hypertensive crises is usually only temporary in nature, i.e., lasting hours to days, and rarely longer than 1 week. Experience has shown that the risk of a pulmonary hypertensive crisis increases with the prior duration of volume and pressure overload of the vascular bed. In defects with (additional) pressure stress, e.g., a nonrestrictive (pressure-equalizing) VSD, the postoperative course after a correction at the age of around 6 months should pose no problems (*Caveat:* Children with trisomy 21 are prone to and/or suffer earlier from pulmonary hypertensive crises!). The later the correction of such a defect is performed, the more important is the preoperative determination of PVR, not only for estimating the immediate postoperative risk. If the preoperative PVR exceeds around 6 WU/m^2 and depending on the results of vasoreactivity testing, there is a higher likelihood of postoperatively persisting pulmonary hypertension which may further increase over the long term. In addition, if the PVR is exceeding 8–10 WU/m^2, a substantial risk for acute and long-term right heart failure must be anticipated. Under these circumstances a correction is generally seen as contra-indicated.

Another parameter affecting the postoperative risk is the transpulmonary gradient (PAP_m – PAWP): the risk is elevated >15 mmHg (see Table 9.2).

Caveat Applying the physical consideration of a rigid tube system (Hagen-Poiseuille equation) to the pulmonary vascular system has limitations, particularly

Table 9.2 Examples of hemodynamic findings, operability

	PAPm	PAWP/LAPm	Qp	PVRi WE	Operability
VSD restrictive	25	5	5	4.0	Yes
VSD nonrestrictive	55	8	12	3.9	Yes
VSD nonrestrictive	50	8	4.3	9.8	No
(4a) VSD preop FiO_2 1.0[a]	60	8	21.4	2.4	Yes
(4b) VSD postop FiO_2 1.0, PaO_2 500 mmHg	60	8	6.8	7.6	–
(5a) Cardiomyopathy	55	30	1.7	15	HTx: potentially
(5b) Cardiomyopathy after afterload reduction	50	25	4.2	6	HTx: Yes

[a]When O_2 is administered before the VSD is closed, the L/R shunt is increased, leading to equalization of the pulmonary venous and pulmonary arterial saturation, high Qp with mathematical (false) low PVRi

due to the passively extendible pulmonary venous segment. In theory, by adding substantial volume, the PAWP could approach the PAP_m (i.e., PAP_m – PAWP becomes smaller), which would result in a lower value for PVR. In practical terms, the danger of (acute) pulmonary edema is given when pulmonary arterial flow improves without improvement in cardiac function, thereby leading to congestion. Despite the fact that heart rate, pulsatile flow, alveolar pressure (ventilation), body position, and viscosity—along with many other factors—are not considered in the model, the physical relationships provide hints for the choice of therapeutic approaches and help in clinical decision-making.

Right ventricle

Under moderately elevated afterload pressure (PHT), the physiologically less muscular and more elastic right ventricle (higher compliance) becomes primarily hypertrophic. With longer duration and an increasing elevation in pulmonary vascular resistance, dilatation of the right ventricle develops. In advanced stages and with markedly elevated (particularly suprasystemic) PVR, a clinically increasingly relevant reduction in filling of the left ventricular occurs. Due to the low cardiac output and the elevated transmural pressure in the RV, the situation becomes critical because of the increased oxygen demand of the RV (caused by hypertrophy and dilatation), resulting in insufficient coronary perfusion. Possible symptoms include dyspnea, reduced exercise capacity, and chest pain. Right heart failure is the leading cause of death in PHT (cf. Table 9.3).

Pulmonary vascular bed

The pulmonary vascular bed is a low-pressure system. Since PVR declines postnatally and physiologically remains markedly lower, i.e. approx. $^1/_6$ of SVR, about 20% of the blood pressure in the systemic circulation is sufficient to pump the complete cardiac output from the RV into the pulmonary artery. As a consequence of the high compliance of the pulmonary vascular bed, in shunt defects, up to 250% of the cardiac output can flow through the pulmonary circulation without any noticeable elevation in resistance.

Table 9.3 Mediators, modulators, and pathomechanisms of PHT

PVR ↑ and PAP ↑	Mediators – elevated in PHT[a]	Mediators – lowered in PHT[b]
Hypoxia	Endothelin 1	Prostacyclin
Acidosis	Growth factors (PdGF1, IGF-I, TGF-B)	NO
Hypercapnia	Adrenaline	Thrombomodulin
Intrathoracic pressure ↑[c]	Thromboxane	Matrix metalloproteinases
Agitation, cough, counterbreathing, suction	vWF, PAI	VEGF
Alpha-agonists	Serotonin	ANP
High Hct, high viscosity	Others	Others
Thrombosis		
Medicines		
Hypoglycemia/hypocalcemia		

PdGF platelet-derived growth factor, *IGF* insulin-like growth factor, *TGF* transforming growth factor, *PAI* plasminogen activator inhibitor, *VEGF* vascular endothelial growth factor, *ANP* atrial natriuretic peptide

[a]Lead to PVR ↑ or PAP ↑

[b]Lead to PVR ↓ or PAP ↓

[c]Caveat: Do not hyperventilate too long or too intensively; extreme hyperventilation maneuvers lower the venous inflow to the RV – dangerous in patients with strongly preload-dependent RV like in PHT!

Over the clinical course, the persisting volume and pressure overload in the pulmonary vascular bed causes pathological changes involving endothelial proliferation, medial hypertrophy, and muscularization of vessel segments that were formerly elastic with normal lumens. Before and concurrent with these vascular changes, there is an increasing susceptibility to (reversible) vasoconstriction, mainly due to the increasing imbalance of vasoconstrictors and vasodilators. Additionally, an increased risk of thrombosis arises from the increased production of procoagulant mediators and the changed flow conditions for the blood.

9.5 Measuring and Estimating PAP

Ideally, patients at high risk for postoperative pulmonary hypertension and/or pulmonary hypertensive crises receive a percutaneous PA catheter with a wedge balloon intraoperatively, enabling direct and continuous monitoring of the relevant pressures. Since it is not always possible to place such a catheter, it is often possible to use echocardiographic measurements as an alternative to calculate the pressure gradient between the relevant heart sections (LV and RV and/or RV and RA) via a VSD and/or PDA jet or via a tricuspid valve insufficiency, allowing estimation of the right ventricular pressure and thereby of the systolic PAP as well. In the Doppler echocardiographic recordings of each jet, attention must be paid that the transducer is as held as orthogonally as possible to the respective jet. It is a precondition for calculating the pressure gradient via a VSD or PDA that the left ventricular and/or aortic pressure is known; the systolic arterial blood pressure can be applied alternatively. The RV pressure and/or PAP are calculated by subtracting the pressure gradient from the systolic blood pressure.

To calculate the pressure gradient via an regurgitant tricuspid valve, knowledge of the central venous pressure (CVP) is helpful. Under intensive care circumstances, the CVP is usually measurable via the CVC. However, when calculating the pressure gradient and thereby the PAP, it is generally of minor relevance whether the central venous pressure is 5 or 10 mmHg, since the values are overall low and their variability is negligible (see Table 9.4).

The diastolic and mean pulmonary arterial pressure can frequently be estimated via an existing pulmonary valve insufficiency. It is a precondition that the Doppler echocardiography depicts a double-peaked curve. Here, V_{max} of the regurgitation jet at the start of the diastole (first spike) can be used to calculate PAP_m and the (lower) V_{max} at the end of the diastole (second spike) to calculate the diastolic PAP.

Each pressure differential can now be estimated using the simplified Bernoulli equation:

Formula 42

ΔP mmHg = V_{max}^2(m/s) × 4

Table 9.4 Estimation of the pressure gradient, examples

(TI jet m/s)² × 4	+ CVP	PAP (mmHg)
(3 m/s)² × 4 = 36	+ 6	= 42
(4 m/s)² × 4 = 64	+ 10	= 74

Example: ΔP in a tricuspid valve insufficiency with a jet of 3 m/s: $3^2 \times 4 = 36$ mmHg or 4 m/s: $4^2 \times 4 = 64$ mmHg.

Postoperatively, such a single measurement usually reflects the currently prevailing state, i.e., mainly at rest or under sedation. If elevated values are already evident under these circumstances, a further (critical) increase in resistance in the pulmonary vascular system has to be expected when the patient awakens or may be triggered by other stimuli.

Further parameters that can be helpful in the echocardiographic assessment of the right heart's function and burden include the eccentricity index, tricuspid annular plane systolic excursion (TAPSE), and (right ventricular) TEI index. The eccentricity index can be determined without greater effort. This is done by measuring the anteroposterior ("longitudinal"; D2) and septolateral ("transverse", D1) diameter of the left ventricle in the parasternal short axis at the level of the papillary muscle; a D2/D1 ratio > 1 is pathological. In severe PHT accompanied by markedly elevated RV pressure, a flattening of the IVS is even visible with the naked eye; when suprasystemic pressures are present, a left shift can even be observed. When using TAPSE and the TEI index, at least in younger children, the age-matched normal values must be considered.

9.6 Which Patients Have Pulmonary Hypertension?

In pediatric cardiac intensive care, there are five main scenarios, in which PAP and/or PVR elevation play a role.

1. *After (late) correction of a large L/R shun*t

In general, any potential increase in PVR will not be problematical when the defect is corrected by the 6th–12th month of life. This is because the PVR increase is primarily caused by reversible vasoconstriction. With increasing duration of pressure and/or volume overload up until the time of surgery, exceeding the mentioned time frame, postoperative problems will be more likely, and PVR will become increasingly irreversible. This particularly applies to nonrestrictive L/R shunts with post-tricuspid localization, i.e., with additional shear stress due to substantial pressure overload.

2. *Post heart transplantation in patients with preoperative left heart failure and post-capillary PHT*

In these patients, reflexive vasoconstriction can be observed in the precapillary pulmonary circulation, i.e., on the side of the arterioles, as a protective mechanism. This means that pulmonary edema usually does not occur despite a decreased post-capillary outflow. Depending on how long this situation persists, the reversibly constricted pulmonary arteries may also undergo irreversible morphological changes (intimal proliferation, medial hypertrophy, etc.). On the one hand, this can have a major impact immediately post transplantation because of the ischemic impairment of the donor heart which generally has a healthy "untrained" RV, leading to right heart failure. On the other hand, the adaptability of the donor heart coupled with today's targeted treatment options, if needed also as long-term therapy, certainly allows successful transplantation even with preexisting (acutely) "irreversible" PHT. Duration and extent of preexisting PHT in the recipient must be known to all those involved in the patient's peri- and postoperative care. One of the potential postoperative rescue measures to always be thought of following HTx or closure of a hyper-circulatory defect is to strive for a pH of >7.45 by (over-) buffering.

Caveat In pediatric cardiac intensive care, a pulmonary hypertensive crisis ranks among the most common indications for resuscitation!

3. *PPHN/PFC: Persistent fetal circulation*

In neonates, some degree of physiological pulmonary hypertension persists for around another 5–10 days during the postnatal adaptation from fetal to adult circulation. A moderate elevation in resistance and pulmonary pressure is considered normal up to 3 months. In neonates, the anatomic separation of the circulation is not yet completed, i.e. ductus and foramen ovale are only functionally closed, their pulmonary arterial resistance is still elevated, and their sensitivity to triggers like acidosis and hypothermia is higher. As a result, a R/L shunt may be observed through the interatrial septum or the PDA in this patient group. Persistent pulmonary hypertension or PFC syndrome is diagnosed when the fetal circulation persists

primarily or recurs secondarily. Like a vicious circle, lack of oxygenation as well as CO_2 expiration, leading to respiratory acidosis, can cause this syndrome to self-perpetuate and worsen.

4. *Glenn/TCPC*

After surgical interventions for an anatomically or functionally univentricular heart, i.e. after partial (Glenn) or complete separation of the pulmonary and systemic circulation resulting in passive pulmonary perfusion (total cavopulmonary connection, TCPC), a minor elevation in pulmonary arterial resistance can already cause substantial problems. This is because the heart as a pumping force is partially or entirely lacking, requiring the blood to flow through the lung passively. In spontaneous respiration, one of the main drivers is negative intrathoracic pressure. It is important to consider that mechanical ventilation stands in the way of this "breathing pump by negative pressure," and thus the earliest possible extubation is desirable for hemodynamic reasons.

5. *Chronic pulmonary disease*

In children with chronic pulmonary problems like BPD, ventilator-induced lung injury, developmental impairment due to a diaphragmatic hernia (CDH), CF, or pulmonary defects, the pulmonary arterial resistance can increase, caused or aggravated by the corresponding mechanical and/or morphological problems such as pulmonary hypoplasia, reduced total cross-sectional area of the pulmonary arteries, etc.

In these patient groups, it may be indicated to try to therapeutically influence the pulmonary arterial resistance, although the success of therapy tends to be limited.

Note In primary parenchymatous lung disease and/or in hypoxia due to ventilation disorders, a white lung is often evident radiologically; secondarily, PHT develops due to constriction of pulmonary arteries in the poorly ventilated areas (Euler-Liljestrand mechanism), e.g. in ARDS. By contrast, for example, in idiopathic PAH with a primary constriction of the pulmonary arteries and normal (unremarkable) ventilation of the lungs, radiologically the lungs appear black.

9.7 Match and Mismatch

In the presence of localized pulmonary hypoxia as in atelectasis, the blood is redirected by reflectory vasoconstriction in the affected area to ventilated, i.e. non-hypoxic, areas (match). This mechanism, also known as the Euler-Liljestrand effect, may ensure good oxygenation because the blood mainly flows through lung sections participating in gas exchange. In contrast, however, a more generalized alveolar hypoxia can lead to an acute or chronic cor pulmonale (right heart failure).

Caveat A classic example of an indiscriminate administration of drugs is when systemic vasodilatators with a "nonselective" effect on the entire vascular system are administered in the presence of a ventilation disorder. This results in an increased perfusion of the still poorly ventilated lung areas, leading to a deterioration in global oxygenation (mismatch), since the protective mechanism described above is pharmacologically neutralized! See also Chap. 1 (Sect. 1.3.2).

9.8 General Mechanisms to Reduce Pulmonary Vascular Resistance

To avoid an increase and/or to lower the PVR, it is of fundamental importance to avoid hypoxia, i.e., maintain $SpO_2 > 95\%$, e.g. by ensuring optimal ventilation, not least also to prevent vasoconstrive hypercapnia. The goal of > 95% is only valid in serial circulation. *Caveat:* In certain heart defects, e.g., HLHS, indiscriminate oxygen delivery can be dangerous! A general elevation in the O_2 supply is not only beneficial because more oxygen improves the diffusion gradient but also because of its property as a highly potent pulmonary arterial vasodilator. As a general principle in intensive care medicine, primary attention needs to be turned to the reduction in peripheral O_2 consumption through sedation, antipyresis, pain reduction, and avoidance of catabolism.

Given that acidosis, similar to hypoxia, is a strong trigger for pulmonary arterial vasoconstriction, therapy with NaBic/TRIS ($C_4H_{11}NO_3$) or similar agents along with volume management and cardiac output optimization are regarded as sensible and accepted measures in circulation-related metabolic acidosis.

In contrast, the decision to ventilate in order to keep a respiratory acidosis in check is not rarely controversial. While improved ventilation can help compensate for the acidosis, the elevation in right ventricular afterload[1] can lower, cancel, or even reverse the effect on a reduction in PVR and PAP. Therefore, any adverse effects of ventilation on RV function must be monitored (e.g., by echocardiography) and managed correspondingly.

Ventilation of patients with PAH should aim at:

- Low mean arterial pressure (MAP).
- Good synchronization.
- As much spontaneous respiration as possible.

Especially in patients with elevated pulmonary arterial resistance and/or passive pulmonary perfusion, the aim is to avoid pulmonary parenchymatous triggers that intensify the elevation in PVR even more. Every ventilation disorder (atelectasis, pneumothorax or pleural effusion, pulmonary edema or bronchial obstruction, but even ascites and meteorism) can contribute to raising pulmonary vascular resistance, promoted by a vasoconstriction-induced redirection of the blood intended

[1] Due to the positive intrathoracic pressure and a reduction in venous flow to the RV.

for ventilated areas into unventilated ones, as described above. For that reason, knowledge of the ventilation parameters as well as of the clinical and radiological picture of the lung is indispensable in these patients.

The efforts to optimally synchronize (partially) spontaneous respiration with low MAP contrast with the tendency of those less sedated patients to react to airway irritations with critical PAP elevations. This often leads to rapidly progressing RV failure accompanied by an increase in CVP and a drop in cardiac output with a drop in blood pressure and coronary hypoperfusion. These irritation-related PA crises induced by various triggers are one of the most common indications for postoperative resuscitation. Prophylactic measures, e.g., additional sedation and relaxation before suction/nursing care, can help prevent or at least markedly abrogate a PA crisis.

Otherwise, it is imperative to respond immediately with the following measures to be conducted in parallel:

- Sedation (etomidate, propofol, midazolam, fentanyl), and in case of doubt, relaxation.
- Mild hyperventilation on the respirator and 100% O_2.
- Immediately terminate any airway irritations, unless it is a tube obstruction.
- Increase the coronary perfusion pressure with noradrenalin.
- If bradycardia occurs despite these measures, rapidly initiate cardiac massage.

These measures are aimed at achieving the highest SpO_2, "good pH," optimal gas exchange, optimal sedation, effective pulmonary edema therapy, and improved cardiac output. If they do not produce a sufficient reduction in PVR and PAP, more targeted measures are available for lowering pulmonary arterial resistance (see also Table 9.3).

9.9 Pharmacological Approaches to Influencing Pulmonary Hypertension

Various pharmacological measures are available to lower elevated PA resistance by influencing PHT directly through vasodilatation of the pulmonary arteries or indirectly, e.g., through antiproliferative effects:

- Less specific pulmonary resistance-lowering drugs which also have a systemic effect and are not primarily intended for treatment of PHT.
- Intravenous drugs, including those with (adverse) systemic action (Caveat: hypotension), with main indication PAH.
- Inhaled substances, often with specific vasodilator action on the pulmonary vascular system, with no or only minimal systemic action.
- Specific oral PAH therapeutic agents that also have some systemic effects (however, systemic action mostly without clinical relevance); these therapeutic agents play a role particularly during long-term therapy.

- Anticoagulants intended to prevent any further elevation in resistance through microthromboses (their importance in children may be underestimated, e.g., in TCPC in conjunction with elevated PVR where even the slightest elevations can cause clinically significant problems given the hemodynamic situation).

9.9.1 "Specific" Pharmacological Management of Pulmonary Hypertension with Primary Dilatory and/or Antiproliferative Action

Caveat The drugs mentioned in this section are specifically approved and indicated for the precapillary form of pulmonary hypertension, i.e. for PAH. The official marketing authorization is limited, as with many drugs, mostly to adults.

Ventilation with nitric oxide
Effects on the NO signaling pathway: NO (nitric oxide) added to the ventilation gas gets into the ventilated pulmonary regions where it leads to local pulmonary arterial vasodilatation without major systemic side effects. Under ventilation with < 40 ppm NO (higher concentrations are not presumed to lead to any greater improvement in efficacy), a relevant formation of Met-Hb is usually as unlikely to be observed as are changes in the coagulation system.

In practical terms, this means: Since certain patients can be expected to experience postoperative problems attributable to an elevated and/or critical increase in PVR, the NO delivery system should be integrated into the ventilation circulation before the postoperative transfer of the patient from the OR to the ICU. The default dose can be set to 20 ppm. Examples of patients with elevated risk are:

- Children after placement of a Glenn or TCPC (even moderate increases in PVR lead to complications).
- Children after correction of an AV canal (particularly in children with trisomy 21), "late" correction of larger VSD, post-HTx, or in PPHN.

Once the circulatory parameters are within the target range, the FiO_2 is reduced to < 50–60%. Afterward, NO can be reduced in one step to 5 ppm and then to 1–2 ppm slowly over several hours. If the patient's cardiorespiratory stability can be maintained with these measures, an attempt can be made to end NO administration completely. In this context, the parallel elevation in FiO_2 by 15% has proven its merits because it might happen that complete NO termination causes a rebound effect with a (critical) renewed increase in PVR.

Prostanoids, inhaled
Effect on the prostacyclin pathway: Inhalation of iloprost (Ventavis, Ilomedin), a prostacyclin (PGI_2) analogue (prostanoid) → activation of adenylate cyclase (ADC) → elevation in cAMP → primarily vasodilatation.

The inhalation of prostacyclin/prostanoids induces selective vasodilatation in (well) ventilated areas of the lung. The major advantage of this therapy over NO is the longer half-life of iloprost (half-life 20–25 min vs. 1–2 min of NO and prostacyclin). *Caveat:* Particularly in small children, airway irritation can occur during inhalation, meaning that the positive vasodilatory effect leading to improved perfusion is diminished, cancelled, or even reversed by bronchial obstruction (worsened ventilation). Therefore, the therapeutic benefit should be monitored carefully (increase in saturation, PAP drop in the echo, improvement in SvO_2). The dosage ranges between 0.25 and 0.5 µg/kg BW/inhalation. In children whose bronchial systems are known to react sensitively, lower starting doses are advised. Inhalations may be required hourly or even more frequently; for practical reasons, the inhalation frequency is often reduced to 6–8 times daily.

PDE-5 inhibitors, oral (i.v.)
Effect on the NO signaling pathway: Inhibition of phosphodiesterase (PDE)-5, sildenafil, and tadalafil, causing reduction of the breakdown of cGMP (cyclic guanosine monophosphate) → prolongation of the cGMP action as a mediator of pulmonary vasodilatation.

If gastric motility is present, sildenafil (Revatio) can be administered orally through a gastric tube already in the early postoperative phase. As with all systemically acting pulmonary arterial vasodilators which reach pulmonary vascular bed through the systemic circulation, it is imperative to ensure that the lung is well ventilated (*Caveat:* Mismatch!). In clinical practice, PDE-5 inhibitors are not only used to improve the pulmonary flow in passive pulmonary perfusion (Glenn/TCPC), but likewise for shunt-related pulmonary arterial vasoconstriction due to pressure and/or volume overload, e.g., temporarily after AV canal (AVSD) correction or VSD closure (see Table 9.5).

In the EU, sildenafil is approved for the treatment of PAH in children.

Sildenafil is also supplied as a solution for intravenous injection (infusion); reports on experience in children have been published.

Caveat The concomitant use of (continuous drip infusions containing) nitrates should be avoided under all circumstances because of the risk of severe drug-drug interactions (potentiation of the nitrate effect!)

sGC stimulators, oral
Effect on the NO signaling pathway: Riociguat, an agent approved for the treatment of PAH in adults (further indication: CTEPH), stimulates soluble guanylate cyclase.

Table 9.5 Sildenafil dosage

Weight	Dosage
<10 kg	2.5 mg t.i.d. to q.i.d.
<20 kg	2.5–5 mg t.i.d. to q.i.d.
<40 kg	5–10 mg t.i.d. to q.i.d.

Endothelin receptor antagonists (ERA), oral

Effect on the endothelin signaling pathway: ERAs block the endothelin receptors ET-A and/or ET-A and ET-B, thereby reducing the vasoconstrictive action of ET-1, among other potential effects.

ERA are particularly used during long-term therapy. At most centers, bosentan (Tracleer) is used in children. Compared to other ERA (macitentan, ambrisentan) and other specific PAH therapeutic agents, the most data on the safety profile and efficacy in children are available for bosentan. A pediatric dosage form with soluble tablets of 32 mg each (4 × 8 mg, with 2 scores) was approved in 2010; bosentan is approved for the use in children with PAH both in the EU and in the USA. Due to possible hepatic side effects, i.e., increase in transaminases, monthly monitoring of aspartate aminotransferase/alanine aminotransferase (AST/ALT) is required during long-term therapy. However, a clinically relevant increase in transaminases occurs with a much rare frequency in children than in adults and is reversible after dose reduction or discontinuation.

Dosage recommendation: 2 mg/kg BW b.i.d.

Prostacyclin (analogues) as continuous i.v. infusion

Effect on the prostacyclin pathway: In severe postoperative pulmonary hypertension or during long-term therapy of severe pulmonary arterial hypertension, continuous infusion with Epoprostenol (Flolan®, Veletri®, prostacyclin with a short half-life, 5–10–20 ng/kg BW/min) or Ilomedin (Iloprost, prostacyclin analogue with a half-life of 20–25 min) are used.

In the immediate postoperative phase, e.g. reactive precapillary vasoconstriction postoperative post-HTx with preoperatively poor left ventricular function, or in reactive precapillary vasoconstriction after corrective surgery of a large L/R shunt, the use of an i.v. vasodilator may be indicated. Administration through a PA catheter is therefore desirable to allow infusion close to or directly into the pulmonary artery.

Nevertheless, due to the *reversible impairment of platelet function* (→ postoperative bleeding risk) and the potentially considerable (dose-dependent) systemic hypotension induced by systemic vasodilatation, caution is advised and dose titration is imperative.

Thanks to its short half-life of several minutes, epoprostenol is more controllable. Nevertheless, it has the disadvantage that any problems with the delivery system (e.g., catheter dislocation) can lead more quickly to rebound PHT. By comparison, iloprost has a longer half-life of approx. 20–25 min. However, its relatively strong inhibition of platelet aggregation may become relevant postoperatively or in other situations with an increased bleeding tendency. Treprostinil, which can also be used as a subcutaneous infusion, is used as well, primarily in adults.

Prostacyclin receptor agonists, oral

Effect on the prostacyclin pathway: Selexipag, an orally administered selective agonist of the prostacyclin receptor (IP receptor), is the most recent globally approved drug for adult patients with PAH. Some data has been published on its therapeutic use in children, but is limited. Treprostinil is a prostanoid that can also be administered oraly but is approved for the treatment of PAH in adults in the USA only.

Beraprost is an oral prostanoid that is approved for the treatment of PAH in Japan and South Korea only. Data for the use in children is limited.

9.9.2 Non-specific Management of Pulmonary Hypertension

There are also several non-specific drugs (with different main indications) that confer benefit in the (long-term) therapy of various forms of pulmonary hypertension.

Anticoagulant therapy in PHT
The morphological changes in the pulmonary vascular bed, such as endothelial damage and intimal proliferation, along with the locally elevated concentration of procoagulatory mediators can cause an elevated clotting tendency, in turn potentially producing a vicious circle and thereby a (further) increase in PVR. Therefore, PTT-active heparinization is indicated (postoperatively), particularly in patients with passive pulmonary perfusion, and, if an (permanently) increased thrombosis risk exists, long-term therapy with a vitamin K antagonist (target INR 2.5–3.5) (see also Chap. 8).

PDE-3 inhibitors
Corotrop (milrinone, a phosphodiesterase-3 inhibitor) also acts as a PA vasodilator.

Like in the arterial system, milrinone also exerts a dilatatory effect on the pulmonary arterial vascular bed as well as a positive inotropic effect on the right ventricle (inodilator). Adverse reactions can include systemic hypotension, arrhythmia, thrombocytopenia, elevation in liver enzymes, and bronchospasm. *Caveat:* Accumulation in renal failure!. Primarily due to its positive inotropic action, without increasing the O_2 consumption in the myocardium, milrinone plays an important role in the postoperative phase in patients with PHT or with a tendency to pulmonary hypertensive crises (dosage: 0.5–1 µg/kg BW/min).

Diuretics
Among others, diuretics play a role in reducing the diffusion distance.

Calcium antagonists: high-Dose (depending on blood pressure tolerance) in PHT
In responders to the acute vasodilator test (see below), Ca^+ antagonists continue to have a place in PHT therapy. Independently of vasoreactivity testing, Ca^+ antagonists are used in postoperatively hypertensive patients with a tendency to PHT, e.g. post-HTx. A higher dose should be selected in PAH than in other indications, e.g. arterial hypertension. *Caveat:* Drop in systemic blood pressure!

In the past, diltiazem (0.5 mg/kg BW t.i.d.) was common; nowadays, amlodipine (Norvasc 0.05–0.1 mg/kg BW/d initially) is increasingly used.

Caveat In PHT, great caution is advised with all negative inotropic drugs (beta-blockers, Ca^+ antagonists) since, e.g., the RV can decompensate!

9.10 Reactivity Testing

Before the initiation of long-term therapy with specific PAH drugs, every patient should undergo a cardiac catheterization, including a test for reactivity of the pulmonary vascular system. Accordingly, responders can be distinguished from nonresponders depending on the inducible acute drop in PAP (while cardiac output is stable or improved!) following e.g. NO, O_2, and inhaled iloprost administration. In the test with pure oxygen on patients with defects involving L/R shunt, the physically dissolved O_2 proportion can have a considerable impact on the calculated reduction in PVR, because a significant proportion of blood containing "maximum" O_2 flows directly into the pulmonary arteries. This deserves particular attention if vasoreactivity test is an important determinant of operability. Problems can occur when weaning from the heart-lung machine in the presence of a low FiO_2 and/or a lower partial O_2 pressure in the pulmonary arteries.

On the ICU, the effect of oral drugs can be assessed and documented over several hours or days, if a PA catheter was placed. On the ICU, it is generally recommended to review the effect of each pharmacological intervention (SvO_2, echocardiographic changes/PAP estimation).

The following factors are to be considered when evaluating vasoreactivity:

- Absolute drop in PAP.
- Relative drop in PAP.
- Improvement/normalization of CI.
- Ratio of PAP: SAP.

9.11 Thought of Everything for Your Patient with Pulmonary Hypertension?

See Table 9.6.

Table 9.6 Memory chart on pulmonary hypertension

Localization	Cause	Clinical particulars	General therapy	Medicines
Precapillary Postcapillary Increased flow/shunt	Vascular disease Left heart disease Pulmonary disease Thrombosis Mixed picture	PA crisis Echo diagnosis Poor saturation High central venous pressure "High" PAP (preload pressure) with passive lung perfusion Monitoring via PA catheter	Optimal lung ventilation O_2 as vasodilator (pulmonary) Avoid acidosis and hypercapnia Short diffusion distance Ventilate with low MAP Sufficient RV preload Sufficient sedation	Corotrop as inodilator with PA effect NO (no mismatch) Iloprost, inhaled (no mismatch) Iloprost/epoprostenol i.v., caveat: mismatch! Anticoagulation PAH-specific chronic therapy

9.12 Positive Effects of a Tolerated or Intended Elevation in Pulmonary Vascular Resistance

In the situations described thus far, treatment of the elevated pulmonary arterial resistance is required to improve hemodynamics. That said, there are also clinical situations where an elevated PVR protects the patient. These include:

- Diseases with parallel pulmonary and systemic perfusion. In shunt-dependent pulmonary perfusion, an elevated PVR can protect the patient against substantial pulmonary hyperperfusion. In these patients, a moderate respiratory acidosis and an FiO_2 of 21% can be used to limit pulmonary flow and thereby prevent or reduce pulmonary hyperperfusion. Correspondingly, an improvement in the systemic flow can be achieved in shunt-dependent systemic perfusion (AP shunt, Giessen approach, PA Banding).
- Also, in the preoperative management of d-TGA, the PHT existing postnatally to a certain (physiological) degree should only be treated in the presence of pronounced, causally related hypoxemia. It is the goal to keep the subpulmonary ventricle which postoperatively will become the systemic ventricle "in training" for its actual task, i.e. to perfuse the systemic circulation with physiologically much higher vascular resistance, and thus making the left ventricle postoperatively less dependent on support.

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ECMO Therapy and the Heart-Lung Machine

10

Dietrich Klauwer

For a limited period, usually not exceeding 20 days, ECMO can be used to treat life-threatening dysfunctions of the pulmonary and cardiovascular systems.

To support or replace cardiac function, the entire heart including the pulmonary circulation is cut off from the circulation. The blood is aspirated upstream from or in the right atrium and pumped back again into the aorta behind the left ventricle. Under ideal conditions, the total cardiac output can be channeled through the machine; in the most extreme case, the heart is thus at complete standstill.

However, the method is encumbered by multiple complications and can potentially only temporarily replace organ functions. That is why ECMO is only used when conservative measures do not appear to be able to compensate sufficiently for cardiopulmonary functions (see Sect. 2.13).

10.1 Indications

- Post-cardiac surgery: Disruption of myocardial function due to longer periods of ischemia, RV/LV pump failure in pre-damaged pump function.
- Severe pulmonary hypertension.
- As an acute bridge to longer-term circulation replacement procedures (e.g., berlin heart) when cardiac output is too low – For example, when decompensation occurs in dilated cardiomyopathy (DCM).
- Post-resuscitation when the decision situation is still unclear – Bridge to decision.
- Alongside other rare indications, pulmonary ECMO in acute respiratory distress syndrome (ARDS) is also an area of application for venovenous (VV) ECMO, albeit which is not described in this chapter.

D. Klauwer
Department of Pediatrics, Singen Medical Center, Gesundheitsverbund Landkreis Konstanz, Krankenhausbetriebsgesellschaft Hegau-Bodensee-Klinikum, Singen, Germany

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D. Klauwer et al. (eds.), *A Practical Handbook on Pediatric Cardiac Intensive Care Therapy*, https://doi.org/10.1007/978-3-319-92441-0_10

The ECMO is set up in the operating room under sterile conditions, and, in the majority of cases, the transthoracic approach is used with open chest. In an emergency, this can also take place during resuscitation on the ward. During this process, the venous cannula is positioned briefly upstream from or in the right atrium – mostly only one cannula. The arterial cannula is located either as an aortic cannula in the ascending aorta post-cardiopulmonary bypass (CPB) or, alternatively, a cannula is advanced through the right internal carotid artery and the blood stream channeled in the direction of the aortic arch.

Unless a failure to end CPB intraoperatively results in the indication for ECMO, cannulation will commonly also take place cervically on the right side.

As an emergency access, this is faster, more gentle, and associated with fewer complications in terms of bleeding and infection, particularly thanks to the smaller wound surfaces. In this context, common indications for an emergency cannulation outside of the operating room are persistent pulmonary hypertension of the newborn (PPHN) or severe sepsis with cardiovascular/pulmonary failure. Here, the venous cannula extends into the right atrium (at best at the transition to the IVC), whereas the arterial cannula points to the aortic arch via the internal carotid artery.

Repeated checks of the cannula's position clinically, radiologically, and sonographically are paramount. The venous cannula must ensure sufficient cardiac output and protect the tricuspid valve; the arterial cannula must not directly "target" the aortic valve but reliably ensure sufficient coronary and cerebral perfusion.

In most cases, the ECMO is driven by a centrifugal pump.

During this process, the negative pressure prevailing upstream from the propeller sucks the blood out of the vena cava and it is driven out by the centrifugal force created by the rotors located on the inside. The rotors are kept in motion by a magnet located outside of the pump. Afterward, the blood is carried to the oxygenator, where oxygenation and CO_2 release take place as a function of blood flow and sweep gas setting. After flowing through the heat exchanger, the actively warmed and passively cooled blood is channeled back into the patient. The bridge between arterial and venous branches serves as a bypass and can be merited in ECMO weaning. Also, it can be helpful if it becomes necessary to exchange any parts (oxygenator replacement, ECMO system exchange).

In addition to rotor speed in revolutions per minute (rpm) and the resulting flow (L/min), several other parameters and settings that can be adjusted on the device are important for its operation (Figs. 10.1 and 10.2).

10.1.1 Pressures Upstream and Downstream from Oxygenator

The pressure is measured upstream and immediately downstream from the oxygenator by means of two Statham elements and transmitted to the patient monitor. A *transoxygenator pressure gradient* is produced as a function of flow volume and oxygenator size. A rise in this gradient is a sign, albeit a late one, for clotting in the oxygenator.

Under all circumstances, a gradient >250 mmHg should be a cause for alarm because such a pressure drop could start to destroy the oxygenator.

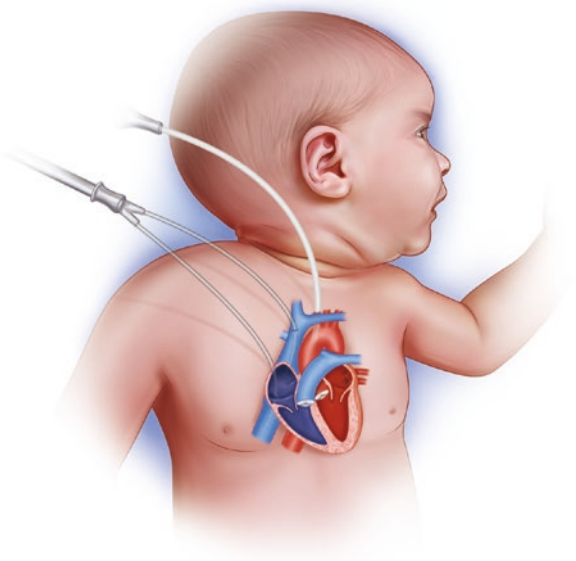

Fig. 10.1 Cannulation. It is important to document both cannula size as well as (echocardiographic and radiological) position

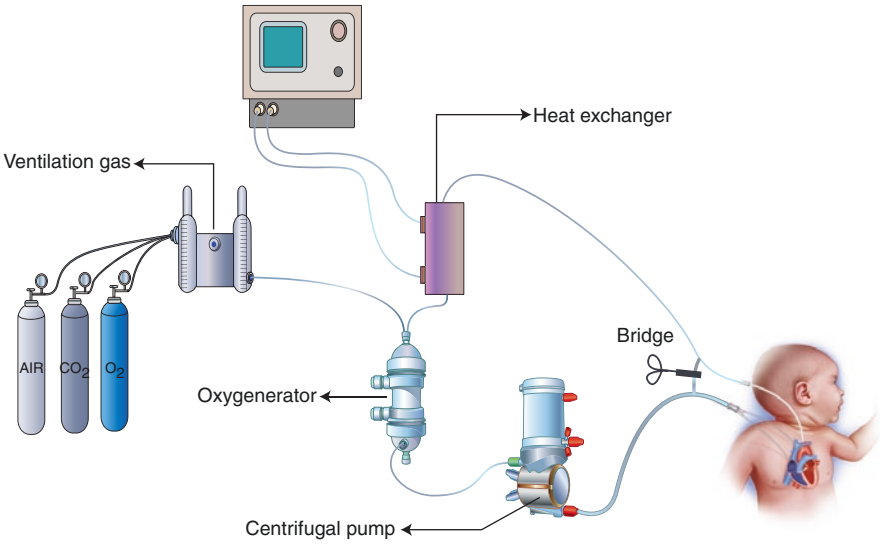

Fig. 10.2 Function and setup

10.1.2 Temperature

Given the relatively large extracorporeal blood volume and large foreign surfaces in contact with room air, the tendency of the blood and, as a result, of the patient to lose heat is of course significant; the blood returned into the patient can be heated. In general, the target core temperature of the patient, measured

by rectal probe, is approx. *35–36 °C* (reduction in oxygen consumption and possible neuroprotection).

Below 34 °C, coagulation changes like clotting inhibition can occur; above 36 °C, the patient's O_2 consumption may unnecessarily rise.

10.1.3 ECMO Flow

The speed in rpm is set on the centrifugal pump; the flow rate depends on the system options – it is not possible to primarily set the flow. At the given speed, the flow is mainly dictated by cannula size and the preload upstream from the venous cannula. Even the afterload (too narrow aortic cannula) or a too high arterial wall tension can theoretically limit the flow. However, this is rarely the case in practice.

10.1.4 SvO_2 for ECMO

Upstream from the oxygenator, this value is continuously determined through the wall of the tubing (calibration: usually carried out by the cardiovascular technician).

10.2 ECMO Operation

In order for the centrifugal pump to be able to generate sufficient flow, it requires a preload of usually not <4–8 mmHg central venous pressure, provided the cannula is positioned correctly. During this process, the pump can freely pump blood without suctioning itself onto the wall of the atrium or caval vein. Before the cannula gets suctioned onto the wall of the vessel, which ends in a massive decline in blood flow, a less dramatic drop in flow is usually already detectable at low central venous pressures. This drop can be interpreted as a sign of volume deficiency. Physically, the ECMO tubing will then start to flap in a conspicuous manner.

However, if extremely elevated central venous pressure values (>15 mmHg) should be required to achieve sufficient flow, then a technical check of all pressure measurement systems must be conducted first, then the *position of cannulas* verified, and a *thoracic hematoma* excluded.

10.2.1 Setting Flow Amount and Flow Alarm Limits

In theory, the ECMO flow rate can be defined as follows:

The cardiac output calculated for a patient at rest is replaced by the machine and stated in reference to the body surface area: *neonates 2.8 L/m², (small) children* and *adults 2.6–2.4 L/m²* (in children <10 kg BW also 130–150 mL/kg BW).

In practice, the flow rate is limited by technical or patient-related requirements:

- *Cannulas size and position of the cannulas in the vascular system*
- *Ventricular function*
- *Preload of the patient (central venous pressure)*
- *Systemic arterial afterload*
- *Oxygenator status* (free flow or incipient clotting)
- *Pressures in the extracorporeal circulation system*

It is crucial that the machine is able to cover the patient's perfusion needs (in combination with the residual ejection of the heart). It has been frequently proven that the lowest blood flow to meet the organ perfusion requirements is the best for long-lasting operation of system (for additional perfusion parameters, see Table 10.1).

After determining the flow, which has usually already been calculated by the cardiac perfusionist, the options offered by patient and system are reviewed.

Which flow is sufficient to meet the needs described above and which central venous pressure is required to achieve this?
Next, set the lower flow limit on the device that triggers the lower flow alarm when a lower excursion occurs. The upper flow limit is set such that the upper flow alarm sounds whenever an elevation in flow occurs from opening the A/V bridge (circuits of the blood in the device).

Can the O_2 carrier status be improved?
For rheological reasons (hemolysis tendency/pressures up- and downstream from the oxygenator), target hematocrit levels should be eyed at around 30–40%.

How high are the pressures in the system, i.e., up- and downstream from the oxygenator?
In this regard, the baseline documentation is decisive because trending elevation in ΔP (at the same flow rate!) can indicate oxygenator malfunction over time.

Table 10.1 Criteria for sufficient organ perfusion on ECMO

Perfusion pressure	Neonates approx. 40 mmHg MAP Small children approx. 45–50 mmHg MAP School children approx. 55–60 mmHg MAP
Diuresis	>2 ml/kg BW/h – If insufficient, include hemofiltration in the extracorporeal circulation
SvO_2	> 60–65% (caveat: False-high values in ASD with L/R shunt!)
Lactate	<2 mmol/l)
Peripheral microcirculation	Sufficient
NIRS	Sufficient
SaO_2	>95% – If possible with FiO_2 for ECMO <40%
ΔT	<4–5 °C, better 2–3 °C

ASD atrial septal defect, *BW* body weight, *ECMO* extracorporeal membrane oxygenation, *MAP* mean arterial pressure, *NIRS* near-infrared spectroscopy

What signs of bleeding are evident? What does the coagulation status look like?

- Bleeding volume and blood texture in drains.
- Rapidly determine coagulation parameters: Platelets, fibrinogen, PTT, quick (INR), AT III, as well as immediate determination of ACT
- (coagulation management on the ECMO; see chapter 8 coagulation system.)

How does gas exchange work?
Adjust FiO_2 as well as gas flow on the venoarterial ECMO:

For this purpose, an arterial BGA should be carried out. In order to reach a target PaO_2 of approx. 60–100 mmHg in the patient (this is sufficient to achieve a saturation > 93–95% as a function of the O_2 binding curve status), an FiO_2 < 40% for ECMO should be sufficient in the presence of adequate flow in the machine. The arterial CO_2 should range between approx. 40 and 50 mmHg. The gas inflow required for this is controlled (high gas flow → low PCO_2; lower gas flow → high PCO_2, corresponding to the respiratory minute volume during ventilation; the gas flow is hardly relevant for oxygenation – whereas the FiO_2 is decisive).

Tip: Since condensation water collects in the oxygenator over time, the oxygenator should be vented approx. 5 min before a later BGA in order to make the gas exchange values comparable. For this purpose, the gas flow is set to a maximum of approx. 10–20 s until water stops dripping out of the oxygenator.

How much does the patient's heart/lung contribute to cardiac output and gas exchange?
→ Section 10.3.

10.3 Estimating Intrinsic Pulmonary and Cardiac Output During ECMO

The following parameters are primarily suited for estimating cardiac output:

- Description of echocardiographic function – Primarily including opening the aortic valve against the relatively high afterload pressure built up against the centrifugal pump. Although the pressure in the aortic arch under ECMO (e.g., MAP = 40 mmHg) corresponds to a "normal" mean pressure (or normal to high-normal diastolic pressure), a correctly positioned cannula will still not blow directly onto the aortic valve. Frequently, this normally unproblematic mean pressure cannot be generated by the barely functioning systemic ventricle. This is one reason why the aortic valve only opens slightly or not at all.
- The blood pressure amplitude, the height of which correlates with the LV stroke volume.
- Change in blood pressure and blood pressure amplitudes at reduced ECMO flow.

As described in Chap. 2 (Ventilation), pulmonary function can be estimated based on

- Dynamic *compliance* (Vti/ PIP – PEEP)
- *Chest excursions* with given ventilation parameters
- *X-ray images*

Further signs indicative of the ventilation quality can be ascertained by changes in the ventilation parameters (e.g., elevation in respiratory rate by 5/min) and the resultant changes in BGA. This only works, however, if the patient is producing his own cardiac output.

Without sufficient diuresis in the patients, either spontaneously or by means of a hemofilter, any too early attempts at lung recruitment are not feasible because they simply cause more injury to the lungs. For this purpose, repetitive uncontrolled bag ventilation maneuvers also contribute to this. Although they impart a good "feel to the hands," the authors are very critical of them, especially in severely damaged lungs and small patients.

10.4 Neurology During ECMO

Even though patients on ECMO are initially under deep sedation, the neurological assessment is particularly significant given the complications that led to ECMO therapy and the potential ones resulting therefrom. Clinically, the assessment should include spontaneous movements, pupillomotor activity, and manipulation reactions. In terms of apparatus, an NIRS probe can visualize changes in cerebral O_2 delivery; a cerebral sonography should be performed daily. By measuring through the skullcap, NIRS is used to assess regional dynamic changes in the blood oxygen levels, the concentration of deoxyhemoglobin (Hb) and oxyhemoglobin (HbO_2). Based on the principle of neurovascular coupling, conclusions can be drawn about the activation of the investigated area of the cerebral cortex from these concentration changes.

Fundamentally, the lowest sedation level that enables the therapy should be the striven-for aim. During this process, pain control with an open chest and the safety of the cannulas (manipulation) on the one hand have to be weighed against an elevated infection tendency and an enhanced requirement for vasopressors/volume in a patient under deep sedation on the other. As long as the nursing staff can assure its safety, a shallow state of consciousness with low communication ability in patients able to communicate can be titrated. However, a necessary deep sedation can also be interrupted phasically so that the patient's neurology can be assessed ("wake up calls").

10.5 Memory Chart on ECMO

The memory chart in Table 10.2 presents the parameters to be considered and monitored during ECMO.

Table 10.2 Memory chart on ECMO

Patient	ECMO	Bleeding	Gas exchange	Cardiac function	Search for complications
Blood pressure/MAP amplitude	Speed (rpms)	Drains	Gas flow/FiO_2	History; why ECMO?	Hemolysis (lab work), hemolytic urine
Arrhythmia	Flow	Chest dressing	Ventilation setting	Echocardiography	Thrombus in system, bridge, air separator, oxygenator
CVP	Alarms	Puncture sites	Compliance/chest excursions	Blood pressure amplitude	Thoracic bleeding, high central venous pressure – despite cannula suctioning onto vessel wall
SpO_2	Temperature	ACT	X-ray	(vital parameters under reduced flow)	Vasoplegia, need for vasopressor agents, sepsis
SvO_2	SvO_2 for ECMO	HB, FIB, PTT, quick (INR), platelets	What is aspirated on tracheal suctioning?		Arrhythmia
Microcirculation	Check bridge	Monitoring intervals set?			Total LV failure with hemorrhagic pulmonary edema
ΔT	Check tubing	D-dimer, TEG/ROTEM for hyperfibrinolysis	BGA from CVC and artery		Oxygenator pressures too high, oxygenation poor despite venting
NIRS	Check air trap				Renal failure (hemolysis, drugs, vascular failure)
Sedation	P Preoxy				
Neurological exam	P Postoxy				

ACT activated clotting time, *BGA* blood gas analysis, *CVC* central venous catheter, *CVP* central venous pressure, *ECMO* extracorporeal membrane oxygenation, *LV* left ventricle, *MAP* mean arterial pressure, *NIRS* near-infrared spectroscopy, *TEG* thrombelastogram

What parameters can be influenced?

- Gas flow: Regulates CO_2 elemination
- FiO_2: Regulates oxygenation
- Speed (rpm): Regulates flow (cardiac output)
- Heart exchanger: blood temperature

What needs to be monitored?

- PaO_2 and $PaCO_2$
- SvO_2
- Flow
- Delta P via oxygenator
- MAP, central venous pressure
- "Neurology," pupils, NIRS
- ACT, coagulation, platelets
- Hb, hemolysis, hematuria
- Thrombus origin: Tubing and pump
- Bridge (open once or twice per shift)
- Body temperature

10.6 Complications

Since ECMO therapy can rarely be performed without complications, the following will first list the complications that disrupt functional operation (very rare).

The complications immediately threatening for the patient include:

- Device failure
- Ruptured hose or disconnection (air embolism)
- Oxygenator bursts
- Large clot in the arterial part of the tubing

In these cases, the only possibility is to disconnect patients from the device. During this process, clamps are used to shut off the inlets to both the ECMO and the patient; the A/V bridge is opened, and then the machine is powered down. Depending on the quality of the patient's own circulation, mechanical resuscitation must also be initiated along with pharmacological resuscitation as necessary.

In the event of the mechanical failure of the first pump head, a second with manual crank and speed indication is available.

Even though such failures are extremely rare, they should be checked for on the ward at the commencement of therapy:

- Can the pump head be replaced – How does the locking mechanism work?
- Can the manual crank be operated?

- Are enough clamps hanging in ready so that an emergency clamping off is possible?
- What is the actual direction of blood flow – Where is the bridge?
- Who is responsible for which handle in the event of an emergency?

Furthermore, complications can occur that do not pose an acute danger to the patient but can limit operation of the system to hours or days or that mandate an intervention such as thoracic surgical revision or replacement of device, oxygenator, or tubing. These particularly include bleeding, hemolysis, and clotting.

Even though "havoc has been wrought" on the coagulation system of patients with status post-circulatory arrest by hypothermia, HLM with foreign surfaces, and usually hemolysis as well, bleeding and coagulation tendency must hold the balance for as long as possible. In this context, the following guide values have proven their merits:

- ACT 180–200 s
- Platelets > 100,000/µl – Lower if absence of any bleeding tendency
- Fibrinogen > 1.5 g/dl
- PTT > 80–100 to > 120 s
- Quick > 50%

In practice, compliance with these guide values is essentially dictated by the patient's bleeding tendency. During this process, the unimpeded drainage of blood outward (via drains and under the thoracic patch) is very important for operation of the system because thoracic bleeds can:

- Impair venous cannula filling (central venous pressure high, less flow)
- Disrupt pulmonary function
- Represent a source of infection

Bleeding of 2–3 mL/kg BW/h that is well-drained outwardly, but persistent, usually represents the tolerance limit. Faced with larger bleeding volumes, heparinization should be reduced, albeit temporarily (e.g., ACT at 150–160 s), volumes replaced with FFP. If the bleeding persists, a surgical revision might be necessary. Moreover, hyperfibrinolysis should be excluded or detected by TEG/ROTEM if there is still persistent bleeding on the ECMO. Therapy for this could be fibrinogen >1.5 g/dl and, as appropriate, tranexamic acid; see Chap. 8.

In general, the bleeding from the patient will fade into the background after 1–3 days, and excessive coagulation activation with clotting, frequently concurrent with increased hemolysis, moves to center stage (see Table 10.3).

Clinical signs of too much clotting are evidenced by clots in around the bridge, at the connectors, as well as in the apical part of the air separator. On the other hand, an even more intensive heparinization (ACT > 220 s) or thrombocytopenia <80,000/µl (set limit individually) already raises the patient's bleeding risk – e.g.,

Table 10.3 Clotting during ECMO

	ACT	Platelets	Monitoring	Evaluation	Consequence
Clotting without bleeding	200–220 s	>80,000/μl (set limits individually)	Minimum once per shift	On-duty physician and cardiac perfusionist	If not increased → continue; if increased→ replace system
Clotting with bleeding	180 s	>100,000/μl	Frequently per shift	On-duty physician and cardiac perfusionist	Hyperfibrinolysis? DIC? System exchange, as needed with hemostasis

ACT activated clotting time, *DIC* disseminated intravascular coagulation, *ECMO* extracorporeal membrane oxygenation

including cerebral – to such a high level that it is only possible to give treatment up to the upper limits of coagulation inhibition. In that case, the clots should be documented at least once a shift but also discussed with the cardiovascular perfusionist. If clotting progresses, the only remaining alternative is elective system exchange. In this case, the patient has to be disconnected for a short period anyways, so that consideration might be given to attempting to end CPB by turning down the machine under echographic monitoring and, as appropriate, with inotropic support.

Even if, theoretically, D-dimer provides an indication for excessive intravasal clotting or hyperfibrinolysis, it is not until very high values – e.g., >5–10 mg/mL – are reached that they would influence the decision to exchange the system. Indeed, clinical aspects are paramount here.

10.7 Hemolysis During ECMO

Turbulent flow can lead to mechanically induced hemolysis, particularly along hard foreign materials (cannula tips and oxygenator capillaries). This continues to be triggered by coagulation activation and mediator secretion so that hemolysis will be observed in nearly every patient after several days.

During this process, it is of utmost urgency to prevent hemolytically induced renal failure and keep the hemolysis from triggering mediator release that the clotting and bleeding become so extreme that they can no longer be treated.

When hemolysis is immediately present at patient's transfer to the ICU, the primary imperative is to evaluate position and size of cannulas. This is because relatively too small cannulas at high flow can induce hemolysis (Table 10.4).

Additionally, sufficient renal perfusion pressure should be maintained (within the high-normal range) and diuretic therapy with adequate intravasal filling (administration of NaCl or Ringer's) initiated at an early stage. The second, perhaps even more important approach, is heparinization as this can inhibit hemolysis (mediator-triggered, above all in the presence of platelet consumption) (ACT > 180 s).

Table 10.4 Hemolysis

Hemolysis	What to do?	Options of last resort
Hb ↓, haptoglobin ↓, bilirubin ↑, LDH ↑, free Hb in the plasma	Check cannulas: Size and position	System exchange
Red urine	Can flow be reduced?	
Diuresis ↓	Can heparinization be increased? Hct reducible?	
	Bleeding? Clotting?	
	Stimulate diuresis	

Hb hemoglobin, *Hct* hematocrit, *LDH* lactate dehydrogenase

10.8 Antibiotic Therapy During ECMO

ECMO operation with an open chest and large foreign material inlets followed by the expectation of longer-term intensive care is already started with an antibiotic combination therapy consisting of vancomycin and ceftazidime (at the Giessen Center), even though the Extracorporeal Life Support Organization (ELSO) only recommends prophylactic therapy against Gram-positive bacteria. This should not be forgotten if the medical records have not been prepared in this context.

Since then an escalation of therapy is only possible to a limited extent, an aminoglycoside (tobramycin/amikacin) alone can be added in the 2nd step. In the Gram-negative range, ceftazidime can be substituted with carbapenem (zienam/imipenem). Notwithstanding the above, a system exchange still remains the option of last resort when faced with mounting signs of the inflammation and the need for vasopressors (indicating SIRS or sepsis). Given the compartments that are difficult to reach for antibiotics, a treatment-inaccessible infection during ECMO nevertheless restricts the therapeutic options of the system.

10.9 Sedation During ECMO

Since ECMO therapy usually involves an open chest and it is undesirable to perform manipulations to the cannula position on the patient's side, profound analgosedation is initiated. Analgosedation is similarly indicated given the background knowledge that critically ill ECMO patients can usually be expected to undergo pronounced postaggression syndrome. This means: Start a continuous drip infusion with, e.g., fentanyl/midazolam (5–10 µg/kg BW/h fentanyl, 0.1–0.2 mg/ kg BW/h midazolam). These doses can be elevated. Usually, it is not necessary to elevate the dose to >15 µg/kg BW/h fentanyl and 0.2–0.3 mg/kg BW/h midazolam. In patients whose sleep on this regimen is not deep enough, saturation loading with phenobarbital (day 1: 10 mg/kg BW per single dose b.i.d. and then 5 mg/kg BW per single dose once to twice daily) can be sensible. During this process, it is mandatory to keep an ongoing exchange with the nursing staff in order to ascertain the patient's state of consciousness and pain status (see scales in Chap. 6).

In painful interventions, single doses of ketamine (1–2–3 mg/kg BW per single dose) may additionally help.

In order to palliate any drug withdrawal syndrome in ECMO patients, clonidine should be initiated early as a continuous drip infusion with clonidine (i.e., when starting opiate reduction) especially in patients after longer-lasting administration of fentanyl. The question as to the depth of sedation and the possibility of neurological evaluability cannot be answered without assessing the nursing possibilities available within that context (see Chap. 5). Although extubation is becoming more and more common in ECMO, this is not an option in patients with open chest or severely impaired cardiac function. In such cases, it is recommendable to switch to a long-term device like the Berlin Heart or similar.

10.10 Postaggression Syndrome During ECMO

ECMO patients are critically ill. Therefore, they can be expected to develop postaggression metabolism (PAM) (see Fig. 5.1, Chap. 5).

The main focus should be on sufficient pain management and blood glucose control. As described in Chap. 5, the target values range between 100 and 180 mg/dl glucose. At an upper excursion of these values, the glucose supply is reduced to the age-commensurate minimum, and, if hyperglycemia persists, insulin administration is initiated (see Chap. 5).

If enteral nutrition is not possible, parenteral nutrition is introduced (Table 10.5).

In patients with adequate liver and kidney function, amino acids can be introduced on postoperative day 1–2 – according to the recommendation in Table 5.4, Chap. 5.

After stabilization of the patient on ECMO and overcoming of PAM, the fat intake can be started cautiously, but however should not exceed 1 g/kg BW/d.

In terms of fluid regimens, the inflow of free water, e.g., in the form of lower-concentration glucose solutions, should be minimized because patients on ECMO have a very pronounced tendency to capillary leaks. Moreover, the focus of fluid

Table 10.5 Memory chart on sedation

Sedation	Start	Increase	Does not sleep	Surgery
Fentanyl/ midazolam	5–10 µg/kg BW/ h0.1–0.2 mg/kg BW/h	15 µg/kg BW/ h0.2–0.3 mg/ kg BW/h		
Phenobarbital			10 mg/kg BW per single dose b.i.d. And then 5 mg/kg BW per single dose once to twice daily	
Ketamine				1–2–3 mg/kg BW per single dose
Clonidine			Start if heart rate and blood pressure are tolerable, 1–2 µg/kg BW/h	

BW body weight, *b.i.d.* twice a day (“bis in die”)

Table 10.6 Memory chart on ECMO metabolism: enteral nutrition is best

	Target	Upper excursion:	Further upper excursion	
Blood glucose	100–180 mg/dl	Minimum dose, age-dependent	Start insulin	
Amino acids max. $^1/_4$ of glucose volume		Post-op day 1–2 0.5 g/kg BW/day	Increase when glucose tolerance is good	
Fat			Start when glucose tolerance is good	Dose 1 g/kg BW/h max.
Free water	Minimize	Balance		

BW body weight, *ECMO* extracorporeal membrane oxygenation

management should be placed on the central venous pressure in order to prevent the cannula from suctioning itself onto the caval veins/atrial wall and to maintain the system's flow.

Given the patient's pronounced edema tendency, therapy with a furosemide continuous drip (possibly with theophylline) at a lower dose, e.g., 1–2 mg/kg BW/d initial dose, should be initiated right at the beginning of ECMO.

Alternatively, a hemofilter or a hemodiafiltration can be incorporated into the circulation in the case of borderline circulatory conditions (Table 10.6).

Fundamentally, the ECMO can also be run by means of a roller pump. During this process, very negative pressures may arise upstream from the roller pump; a "venous" reservoir is incorporated there similar to the HLM in order to ensure free run of the filling up to the pump.

Unlike on the HLM, this reservoir however is not openly exposed to air (see below).

10.11 Heart-Lung Machine

Basically, the functions of a heart-lung machine are similar to those of an ECMO device (see Fig. 10.3). Both feature an oxygenator and (several) pumps which drain off the blood upstream from the heart and return it under pressure back into the arterial system behind the heart (beyond the aortic clamp), thereby ensuring cardiopulmonary functions.

Since several other bodily functions must also be replaced, the HLM constitutes a much more complicated system indeed, with many significant differences to a closed ECMO circulation (Table 10.7).

The pivotal difference is that the entire amount of venous blood from the right atrium or the caval veins collects in a reservoir into which the blood flows pressure passively. This principle is additionally supported by the system's roller pumps by varying the level (or use of clamps).

This is also where the blood from the surgical suckers and any intracardiac cannulas (vents) is collected. Thus, in contrast to ECMO, the HLM circulation is *not* a closed system (Table 10.8).

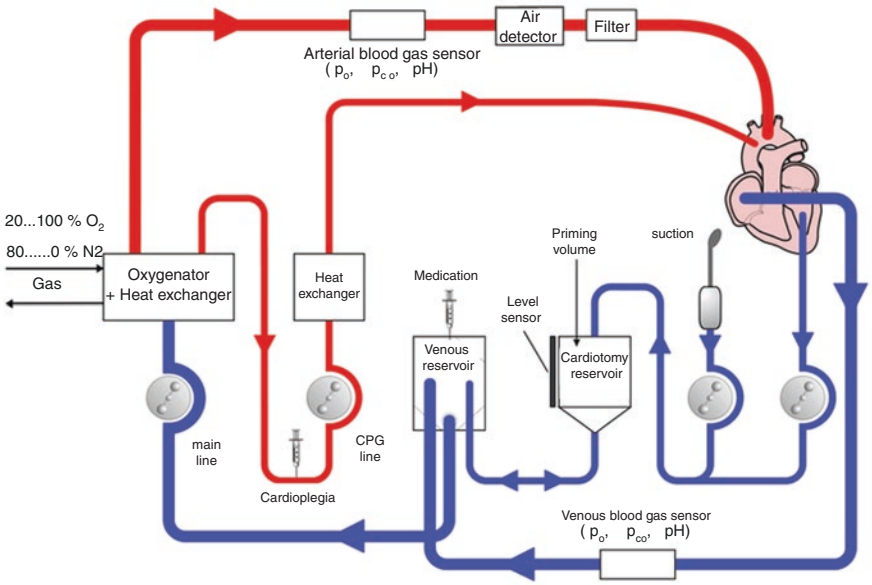

Fig. 10.3 Heart-lung machine, setup. Nowadays, HLM systems still usually work with occlusion pumps/roller pumps, the inflow of which is controlled from a reservoir. Reservoir filling is supported by the pumps (not purely pressure passive). (Reproduced with kind permission of Bochum University)

Table 10.7 Cannula sizes and flow rates (Cardiovascular Engineering Dept. at the Giessen Center)

BSA ($m^{2)}$)	Cardiac output (ml/min)	Arterial cannula (mm)	Arterial cannula (F)	Venous cannula (CH)	Venous cannula (F)
0.15	440	2	8	14	12
0.2	520	2	8	16	12
0.25	610	2.2	8	16	14
0.3	720	2.4	8	18	14
0.35	840	2.4	8	18	14
0.4	1000	2.6	10	20	16
0.5	1200	2.6	10[a]	20	16
0.6	1440	3	12	22	16
0.7	1680	3.2	12	24	16
0.8	1920	3.4	12[a]	26	16
0.9	2160	3.4	14	28	18
1	2400	3.8	14	30	18
1.1	2600	3.8	14	32	18
1.2	2800	3.8	14[a]	32	20
1.3	3080	3.8	16	34	20
1.4	3360	4.4	16	34	20
1.5	3600	4.4	16	36	20

(continued)

Table 10.7 (continued)

BSA ($m^{2)}$	Cardiac output (ml/min)	Arterial cannula (mm)	Arterial cannula (F)	Venous cannula (CH)	Venous cannula (F)
1.6	3840	4.4	18	36	20
1.7	4060	4.9	18	38	22
1.8	4320	4.9	20	38	22
1.9	4560	5.4	20	38	22
2	4800	5.4	22	40	22
2.1	5040	5.4	22	40	24
2.2	5280	5.9	22	42	24
2.3	5520	6.4	24	42	24

Numbers indicate inner diameter
BSA body surface area, *CH* Charrière
[a]Caveat: high outlet pressure!

Table 10.8 Practicable cannulas conditions

	Arterial cannula F (Stöckert/Medtronic)	Venous cannula (Edwards)
Neonates 3.5 kg	8–10 F	4–16 F
Infants 8 kg	10–12 F	18–20 F
Small children 15 kg	12–14 F	20–24 F
School children 25 kg	14–16 F	28–32 F
Adults	16–18 F	34–38 F

Besides the fact that the blood "stands" in the reservoir and comes into contact with air, vents and suction cannulas additionally traumatize the blood, likewise contributing to post-pump syndrome (see Sect. 10.12).

The blood is pumped from the reservoir – in the case of HLM by means of roller pumps – through the oxygenator and through filters and air separators back into the patient.

Additionally, there is second internal circulation through which blood – enriched with cardioplegia solution – can be pumped into the coronary vessels of the patients. These two circuit lines are separated on the patient's side by the aortic clamp.

In contrast to ECMO, the HLM also enables fast cooling of the patient to within the desired temperature range.

Whether the hemofilter is incorporated in series or parallel will depend on the type of system used.

What is important to note with regard to the filter system is that the system can also be used for arteriovenous hemofiltration, i.e., against the former direction of flow to perform modified ultrafiltration (MUF) at the end of CPB (see below).

Another difference to ECMO lies in the oxygenator's function that is not only responsible for CO_2 separation and O_2 enrichment. Besides anesthetic gases, it can also channel CO_2 for pH monitoring into the system. A CO_2 induction on ECMO only takes place in exceptional cases.

10.11.1 Practical Procedure

If the patient has venous and arterial cannulas, the heart surgeon will open the venous clamp whereby the height differential between table and patient and HLM (approx. 1 m) allows the venous backflow to be channeled into the reservoir. Concurrently, the HLM powers up and compensates for the lacking ejection fraction of the heart. After a phase of relative hypotension (dilution of Hct, attainment of a steady state, volume administration), equilibrium is reached between venous drainage and flow toward the aorta (the level in the reservoir is relatively constant and always positive). The "relieved" intrathoracic blood volume is thus maintained in the reservoir.

To end CPB, heart surgeon and/or the perfusionist reduces the venous outflow on the HLM by means of a clamp/level variation. This "pumps out" the reservoir and the intrathoracic blood volume of the patient is refilled (autologous blood transfusion). The heart fills and starts to resume performing cardiac output. Now, the machine flow can be reduced additionally.

The differences depicted show that, compared to ECMO, an even larger extracorporeal volume must be filled on the HLM in addition to its larger surface contact. Furthermore, the system is not a closed system given its contact with air (suction devices and connections to Cellsavers). This significantly increases the adverse reactions to extracorporeal circulation by means of HLM, as detailed later below.

The patients are cooled on the HLM (approx. 5–7% O_2 reduced consumption per °C cooling) in order to increase the tolerance to oxygen deficits in the event of the too low or no flow in the extracorporeal circulation that, depending on the type of the surgical intervention, can occur during certain surgical procedures.

Here, three different strategies can be followed:

- Moderate hypothermia (28–32 °C) with markedly lower flow reduction in the extracorporeal circulation compared with profound hypothermia. That has the advantage that adverse reactions related to cooling are less common and less hemodilution is required because the viscosity increase in the patient's blood is lower. This, in turn, means that less volume needs to be filtered off toward the end of CPB in order to achieve the target postoperative hematocrit.
- Profound hypothermia (18–20 °C) with significant flow reduction in marked hemodilution due to increased viscosity of the patient's blood. During this process, the HLM is not powered down completely in order to guarantee low organ flow. This method improves the view onto the surgical field during organ perfusion and therefore tends to be used more for complex heart defect repairs in neonates and small infants.
- Profound hypothermia (18–20 °C) can be coupled with complete circulatory (cardiac) arrest (max. 40 min) in order to make the heart completely bloodless and, if needed, also allow removal of the atrial and aortic cannula whenever this is surgically necessary. When complex aortic arch anomalies are operated on, this method can be combined with selective cerebral perfusion via the brachiocephalic artery and/or selective coronary perfusion.

- Despite improved organ protection thanks to reduced O_2 consumption, both deep cooling strategies can result in more severe postoperative organ damage, particularly to the brain.

Before surgery, the extracorporeal circulation is prepared based on the requirements of the surgical technique (is profound hypothermia with circulatory arrest needed?), of hemodilution, and of patient size (= priming).

The smaller the patient, the larger is the ratio of extracorporeal to intracorporeal volume. In very small neonates, this ratio can shift in favor of the extracorporeal volume, despite minimized HLM volumes. The lowest extracorporeal circulation volume is approx. 115 mL (*without modified ultrafiltration (MUF) at least 80–95 mL)*.

Commonly, for priming a mixture of *preferably fresh* packed red blood cells (contain less potassium than older ones), FFP, albumin, electrolytes, mannitol, buffer, and, where necessary, steroids is selected. To improve microcirculation, particularly in profound hypothermia, the hematocrit is down-titrated (minimum Hct 25%).

Consideration should be given to the fact that anticoagulation in the packed red blood cells is achieved with citrate which binds with the patient's calcium in the transfusion (→ risk of hypocalcemia) (Table 10.9).

Following cannulation of the caval veins or the right atrium and the ascending aorta, the HLM can start the bypass (bypass start or HLM time). During this process, obstruction-free venous drainage is equally as important as the correct position of the perfusion cannula in the aorta. The job of this perfusion cannula is to ensure adequate perfusion of the vessels of the head, neck, and lower body half. Caveat: perfusion pressures are lower in neonatal HLM!

With regard to cannulation, modifications must be made whenever a persitent left superior vena cava (l-SVC) drains into the coronary sinus and thereby into the right atrium or relevant aortopulmonary collaterals pump blood into the surgical field via the pulmonary veins. These possible anatomic particularities deserve special attention during preoperative diagnostics.

As soon as the bypass relieves the heart and delivers undisturbed perfusion to the body, the aortic clamp can be placed proximally to the origin of the brachiocephalic artery.

Table 10.9 Times in cardiac surgery

Surgery times	Start	End
Total duration	Skin incision	Skin closure
Bypass time	Start HLM mode	Weaning from HLM completed
Ischemic time, aortic clamp time	Aortic clamp placement	Aortic clamp reopening
Selective craniocerebral/coronary perfusion	Start of perfusion via extra circulation	End of perfusion via extra circulation
Deep hypothermic circulatory arrest (DHCA)	Start DHCA	End DHCA

DHCA deep hypothermic circulatory arrest, *HLM* heart-lung machine, *ICU* intensive care unit

This is when clocking of the ischemic time of the heart starts. Using a cold cardioplegia solution (mixed with blood and introduced through the cardioplegia circulation), the heart is now briefly perfused (usually) from the antegrade direction through the cardioplegia cannula into the coronary vessels. This will result in an elevated ischemia tolerance during cooling and (cardiac) arrest. Cardioplegia and cooling are repeated intraoperatively as needed.

If necessary, a left ventricular drain is ultimately placed (LV vent) which drains the blood flowing through the pulmonary veins (bronchial artery blood) and the coronary veins (thebesian veins or venae cordis minimae) into the ventricle.

During the actual cardiac surgery now taking place, the anesthesia can be run by means of gas through the oxygenator and/or by means of drugs via the venous line on the extracorporeal circulation system.

Moreover, alkalinization of the blood induced by the profound hypothermia and the better CO_2 solubility occurring can be counteracted with CO_2 induction.

Whether controlling the pH by means of this CO_2 induction (pH-stat) is superior to the free pH shift into the alkaline range under hypothermia (alpha-stat) or whether, if necessary, the methods should be combined and used in a more sophisticated manner has not yet been validated to date.

After completing the intracardiac operation, cardioplegia solution is washed out, and the heart starts to beat again with rewarming and coronary reperfusion (where necessary after electrical stimulation). After achieving a satisfactory outcome that is verified visually and by echocardiography, the heart is now weaned from the extracorporeal circulation. For this purpose, milrinone is usually given and catecholamines as needed.

Anticoagulation during HLM operation: Prior to cannulation, the patient must be fully heparinized (300–400 IU/kg BW of unfractionated heparin). The success is ACT-controlled (ACT time > 400 s) – repetition is necessary approx. every 30–60 min.

After decannulation, protamine is administered for antagonism (caveat if the infusion is given too fast: severe hypotension, in rare cases, thromboxane-mediated PHT crisis). Usually, the total heparin dose is antagonized (protamine dose = total heparin dose) – alternatively, also antagonism of the initial dose only is aimed for.

10.12 Negative Effects of Heart-Lung Machine Operation: Post-pump Syndrome

Many of the negative effects of HLM operation are dependent on:

- Duration of myocardial ischemia
- Depth of hypothermia
- Ratio of extracorporeal circulation volume to patient size
- Extent of hemodilution and re-transfusion
- Extent of cytokine and coagulation activation

Even on steroid therapy, cytokine activation is unavoidable when the patient's blood comes into contact with the surfaces of components of the extracorporeal circulation. This in turn triggers generalized inflammatory processes, which continue to be maintained by a complex, cascading interplay between coagulation activation, microthrombosis, and fibrinolysis in conjunction with endogenous and iatrogenic anticoagulation. Other triggers of these inflammatory processes are perfusion disturbances in the presence of low flow and perfusion pressure on the machine side. At relatively high filling pressures upstream from the venous cannula (and intercurrent low perfusion pressure), the organ circulation can also be negatively influenced by the pressure gradient described previously.

This results in a generalized swelling tendency of the cells with increased capillary permeability, which in turn causes generalized edema with additional negative impacts on the microcirculation around parenchymatous organs.

In this state, the postoperatively re-improved perfusion of the body, particularly after rewarming, can cause reperfusion injury with an additional tendency to swelling and lysis while diminishing microcirculation as well.

Particular attention must also be devoted to the adverse reactions extracorporeal circulation can have on the brain. Not rarely, microembolisms, ischemia, reperfusion injury, and microvasculopathy with thrombosis along with transient sequelae – like seizures and transient neurological deficits – can leave behind irreversible damage (Table 10.10):

- Periventricular leukomalacia
- Movement disorders
- Intellectual developmental deficits
- Behavioral abnormalities

Immediate deleterious complications of HLM can range from intracerebral bleeding to cerebral herniation or larger thromboembolic occlusions in terms of a stroke.

During operation of the HLM, the objective of the various surgical and anesthesiological efforts must be to prevent or mitigate any irreversible consequences at all times.

Online patient monitoring includes monitoring by means of NIRS, BIS (bispectral index), and intermittent transcranial Doppler sonography alongside core temperature measurements of the upper *and* lower body halves. Also, transesophageal echocardiography contributes to monitoring and documents the hemodynamic outcome of the operation.

In addition to factors like selective cerebral perfusion, intermittent complete circulatory arrest only, or profound hypothermia, neuroprotection can be particularly pivot on the duration of surgery whereby the ischemia phase and/or the phase of the complete circulatory arrest can be shortened.

It is certainly helpful to use foreign blood products restrictively, to shrink foreign surface areas, particularly in "open" areas of the system (venous reservoir).

Table 10.10 Adverse reactions from heart-lung machine

Causes	Reaction	All organs	Lung	Heart	Kidney
Surface contact	Activation and consumption of leukocytes and platelets	Cell swelling	Interstitial pulmonary edema	Cell swelling	Renal vascular resistance ↑
Cooling	Cytokine activation, free radical formation	Microcirculatory disorder	Collapse of the small airways	Microthrombosis	GFR ↓
Hemodilution	Coagulation activation	Interstitial edema	Loss of FRC	Reperfusion injury	Swelling
Myocardial ischemia	Hypoxemic cell swelling	Microthrombosis	Microatelectases, PVR ↑	Systolic and diastolic dysfunction	Microthrombosis
Artificial (nonpulsatile) perfusion with low pressure gradient	Stasis	Reperfusion injury	Alveolar inflammation	PVR ↑ → LV filling ↓ (ventricular interdependence)	
Cannula-related shearing trauma, microembolisms	Hemolysis	Microcirculatory disorders → stress → exacerbation of post-aggression metabolism	Further cytokine activation		

FRC functional residual capacity, *GFR* glomerular filtration rate, *LV* left ventricle, *PVR* pulmonary vascular resistance

Moreover, the MUF is used particularly in neonates and infants after ending CPB where aortic blood (via the aortic cannula) is pumped back to the heart through a hemofilter and oxygenated – if necessary – via the atrial cannula.

This can be used to elevate hematocrit (and thereby the colloid osmotic pressure), reduce PVR by means of oxygenation of the right atrial blood, as well as wash out toxins and tissue fluids. This reduces swelling-related microcirculatory disorders in parenchymatous organs.

Finally, assessments need to be made as to how much hemodilution produces the best balance between O_2 transport capacity and viscosity, which pH strategy (pH-stat vs. alpha-stat) confers the better neuroprotection, and whether drugs favorably influence inflammation (steroids) or the microembolism (tranexamic acid) cannot yet be conclusively ascertained.

However, it is important for the admitting intensive care specialist to be aware of the department-specific procedures of the local HLM perfusion and anesthesiology techniques and be informed about any peculiarities during the HLM operation and anesthesia in order to be able to anticipate any potential postoperative complications.

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Cardiac Arrhythmias

11

Maria B. Gonzalez y Gonzalez

The causes of cardiac arrhythmias in the intensive care unit can be various. Apart from electrolyte disturbances, drugs used in the intensive care unit can trigger cardiac arrhythmias (e.g., dobutamine, adrenaline). In addition, certain surgical techniques or intraoperative complications are associated with an increased incidence of postoperative cardiac arrhythmias. For this reason, a detailed description of the intraoperative course and knowledge of the hemodynamics are essential on postoperative handover of a patient. Of greatest importance for intensive medical care following the acute onset of an arrhythmia is an immediate assessment of whether this constitutes an acute, a subacute, or a minor (or no) risk for the patient.

11.1 Diagnostic Procedures

ECG

With the correct electrode positioning/cable connection (red, right arm/chest; yellow, left arm/chest; green, left leg/left lower abdomen), a lot can be established simply from the curve on the monitoring screen. As a rule, these curves correspond to leads I, II, or III of the limb leads. They already allow some conclusions to be drawn about heart rate (bradycardia, tachycardia), rhythm (sinus rhythm [positive P in I, II] or other basic rhythms), AV blocks, width of the QRS complex (bundle branch block morphology), and presence of extrasystoles. Only a limited conclusion about repolarization disorders is possible.

M. B. Gonzalez y Gonzalez
Pediatric Intensive Care Unit, Pediatric Heart Center of Giessen, Children's Heart Transplantation Center, UKGM GmbH, Giessen, Germany
e-mail: MariaBelen.GonzalezyGonzalez@uk-gm.de

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D. Klauwer et al. (eds.), *A Practical Handbook on Pediatric Cardiac Intensive Care Therapy*, https://doi.org/10.1007/978-3-319-92441-0_11

These conclusions can best be assessed at an ECG chart speed of 25 or 50 mm/s. A precise conclusion, however, is only possible with the conventional ECG leads (whenever possible complete 12-channel ECG with limb and chest wall leads).

Atrial ECG

An atrial ECG can be derived via the corresponding transcutaneous leads of the temporary pacemaker, usually inserted intraoperatively, or via an esophageal ECG probe. This makes the atrial actions more clearly visible and allows a conclusion to be drawn about atrial rate (e.g., in atrial flutter) and the relationship to ventricular rate (AV dissociation or 1:1 AV - conduction). With some monitoring screens, the atrial ECG can be projected on the monitor below the limb ECG so that changes can be depicted more rapidly.

Further diagnostic procedures using the external pacemaker

In cardiac surgical procedures, transcutaneous epicardial electrodes are implanted in the atrium and ventricle usually for temporary stimulation (in case of need). These are very helpful in the diagnostic process and for therapy as well when postoperative arrhythmias are present. Following the development of atrial flutter or supraventricular tachycardia on the basis of a reentry mechanism, an attempt can be made to terminate this by atrial overdrive pacing. This frequently requires a higher output (high amplitude and impulse width) of the atrial electrode. Similarly, the atrial probe can be helpful in checking the AV node conduction capacity in postoperative AV blocks. In the presence of hemodynamically poorly tolerated atrial tachycardia with 1:1 conduction to the ventricles, an attempt can be made to overtake this by means of very fast stimulation of the atrium beyond the Wenckebach point of the AV node. The Wenckebach point designates the atrial stimulation interval at which a second-degree AV block (proximal to the bundle of His) occurs. The induced 2:1 conduction results in a reduced ventricular rate, which might be better tolerated.

Use of adenosine in the diagnostic process

Adenosine induces short-term complete AV block and as a result can terminate supraventricular tachycardia based on a reentry mechanism in which the AV node is part of the tachycardia. In the presence of atrial flutter, this can be unmasked by adenosine since the typical sawtooth pattern becomes detectable as a result of the AV blockade. The tachycardia itself is not terminated. Similarly, focal atrial tachycardia can be revealed more clearly by the AV blockade. However, rare cases of focal atrial tachycardia can also be terminated by adenosine. What is most important is a sufficient adenosine dosage. If the tachycardia cannot be terminated by the administration of adenosine, it can be assumed when ventricular extrasystoles occur, that the dosage was sufficient but the tachycardia was not adenosine-sensitive (e.g., junctional ectopic tachycardia) (See also Sect. 11.5). Adenosine has only a very short half-life so that AV blockades persist for only a few seconds. In rare cases, adenosine results in more persistent bronchoconstriction.

Table 11.1 Recommended energy in external cardioversion/defibrillation (J/kg BW)

	1st shock	If unsuccessful
Cardioversion (synchronized)	0.5–1.0	2.0
Defibrillation	2.0–4.0	4.0

Electrical cardioversion/defibrillation
If electrical cardioversion is necessary, it should always be applied in synchronized mode when supraventricular and stable monomorphic ventricular tachycardias are manifest. This is accomplished by synchronizing the current delivery with the ECG via the paddles, via ECG electrodes on the defibrillator or via a cable connection from the defibrillator to the patient monitor (current delivery at R peak), avoiding the induction of ventricular fibrillation by impulse delivery in the vulnerable phase (increasing portion of the T wave). Conversely, in the presence of ventricular fibrillation or torsade de pointes, synchronization must not be switched on since otherwise no energy delivery occurs.

Nowadays, biphasic defibrillators are generally used; in this case, the current vector reverses once during the shock delivery, resulting in a lower energy requirement than with monophasic defibrillators.

Caveat In synchronized cardioversion, ensure that the machine correctly marks/detects the R wave.

Note "Sync." off in the case of polymorphic ventricular tachycardia (VT), ventricular fibrillation, or torsade de pointes (Table 11.1).

11.2 Cardiac Conduction System

See Fig. 11.1.

11.3 Bradycardiac Arrhythmias

11.3.1 Sinus Bradycardia

When sinus rhythm is present, bradycardia can occur in the following situations:

- Pharyngeal or endotracheal suctioning
- Increased intracranial pressure (ICP)
- Hypoglycemia
- Hypercalcemia
- Acidosis
- Drug-induced (digitalis, beta-blocker, amiodarone, etc.)

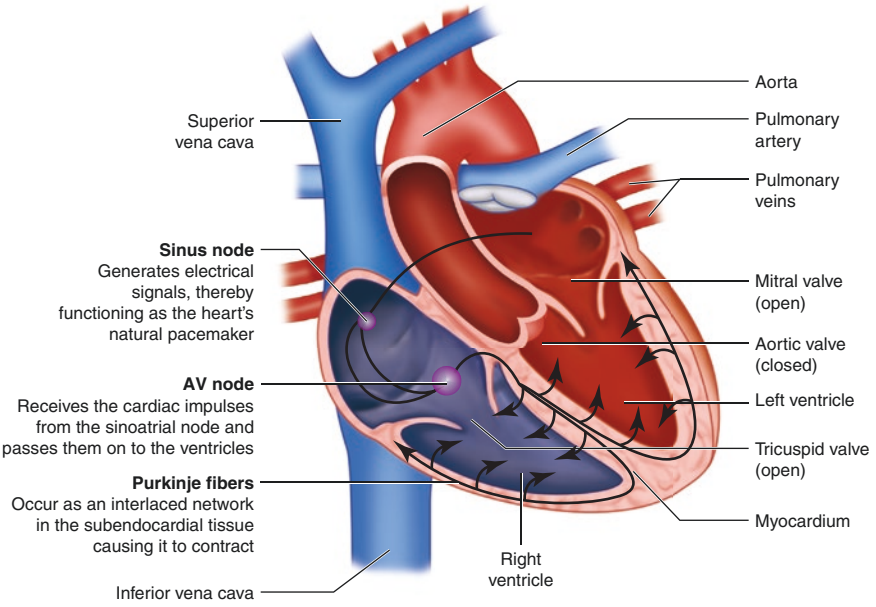


Fig. 11.1 Cardiac conduction system

Bradycardia cutoffs (heart rate by age):

- Neonates: <100/min
- 1–24 mo: <90/min
- 2–6 y: <80/min
- >6 y: <70/min
- >11 y: <60/min

Sinoatrial block

Sinoatrial block can occur after surgery in the atrial region (total cavopulmonary connection (TCPC) with extracardiac tunnel, status post-atrial switch surgery for transpositions of great arteries (TGA), sinus venosus defect, etc.) but generally is rare.

First-degree SA block – Conduction from the sinus node to the atrial tissue is continuously prolonged.

Second-degree SA block – As with second-degree AV block, distinction between:

- Wenckebach type: P-P intervals increasingly decrease in length until a P is lost (the delay in conduction is typically greatest between the 1st and 2nd beat of the periodicity and then increases only slightly. As a result, the P-P interval on

the surface ECG becomes increasingly smaller until a sinus node potential is no longer conducted. The ensuing pause is less than twice the last P-P interval).
- Mobitz type: Every 2nd, 3rd, or 4th beat (P wave) is lost without any change in the P-P interval.
- Sinus arrest (third-degree SA block): the normal P wave is lost. Occurrence of a slower automaticity center (atrial escape rhythm, junctional escape beat, ventricular escape rhythm).

Possible measures:

- Atrial stimulation: Possible if AV conduction is preserved in sinus bradyarrhythmia or in sinus arrest (AAI).
- Drugs: e.g., orciprenaline or theophylline stimulates impulse generation in the sinus node (dose according to effect).

11.3.2 AV Blocks

In addition to increased vagal tone, drugs, and electrolyte disturbances, inflammatory noxae (e.g., *Borrelia*, *Chlamydia*), heart defects with congenital AV node abnormalities (e.g., AV canal, cc-TGA), or cardiac surgery can cause an AV block. A congenital AV block as a result of intrauterine damage to the AV node by maternal antibodies (anti-SS-A, anti-SS-B, e.g., in lupus) is more rare.

The most common cause, however, is surgical irritation or injury of the AV node. Permanent AV node injury must be expected with increasing time (more than 7 days post-cardiac surgery) so that implantation of a pacemaker is indicated.

- First-degree AV block: There is simply prolongation of the PQ interval. The longer this has already existed unchanged, the less pathological it is. If it occurs for the first time, attention must be paid to the possibility of an increase in AV blockade.
- Second-degree AV block: A loss of electrical conduction to the ventricles occurs, but the P-P interval remains constant.
  - Second-degree AV block Wenckebach type: In this case, the PQ interval becomes increasingly longer until ultimately a QRS complex is lost.
  - Second-degree AV block Mobitz type: Only every 2nd, 3rd, or 4th P is conducted.
- Third-degree AV block: No conduction occurs to the ventricle. The atrium has its own rate-different from that of the ventricle (AV dissociation). There is either a junctional escape rhythm (narrow QRS complex) or a ventricular escape rhythm (wide QRS complexes – urgent indication for a pacemaker because frequently hemodynamically unstable) (Fig. 11.2).

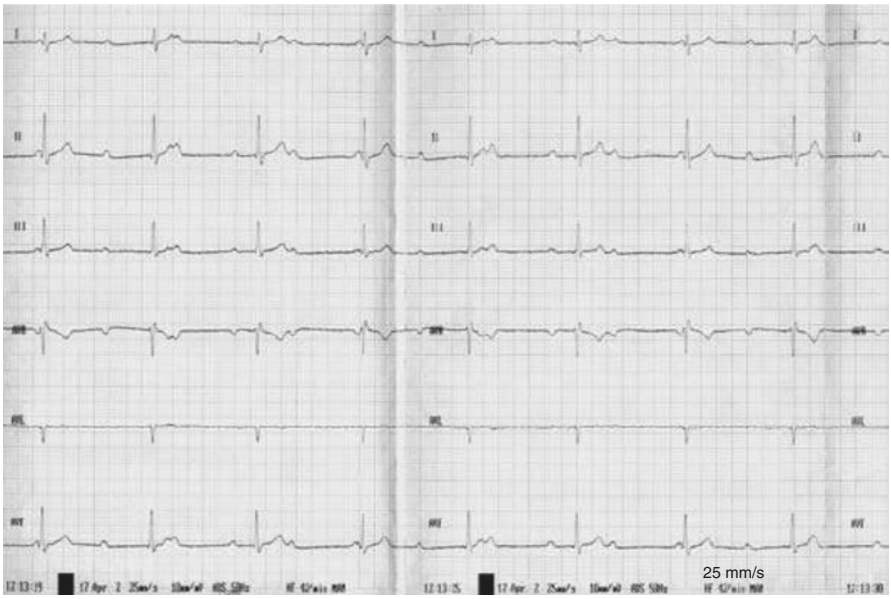


Fig. 11.2 Congenital complete AV block with junctional escape rhythm. AV dissociation, more P waves than QRS complexes

Normal PQ intervals

- <1st LT: 80–160 ms
- 1st DL-1 mo: 70–140 ms
- 1–2 mo: 70–130 ms
- 3–5 mo: 90–150 ms
- 6–12 mo: 90–160 ms
- 2–3 y: 90–150 ms
- 4–6 y: 90–160 ms
- 7–10 y: 90–170 ms
- 11–15 y: 100–180 ms

11.3.3 Treatment of Bradycardiac Arrhythmias

Treatment is indicated in all patients with symptomatic or potentially dangerous bradyarrhythmia. In the intensive care unit, the situation can be improved simply by reducing the dose or by discontinuing negative chronotropic drugs. Pharmacologic therapy, e.g., with orciprenaline, is indicated only in the short term or as a bridge until pacemaker implantation. Pacemaker therapy in children with sinus bradycardia is only indicated in documented bradycardia and asystole when there are symptoms as well. In children with high-grade AV block (second-degree AV block of the

Mobitz type, second-degree AV block of the Wenckebach type on exercise, or complete AV block following cardiac surgery), there is an indication for pacemaker implantation if the block persists for more than 7 days after the cardiac procedure. The indications for pacemaker implantation in children with congenital complete AV block are also clearly defined.

Indications for pacemaker implantation in neonates with congenital complete AV block:

- Escape rhythm with a wide QRS - complex.
- Occurrence of complex ventricular extrasystoles.
- Ventricular dysfunction with enlargement of the ventricle or signs of heart failure.
- Structurally normal heart with ventricular rate < 50–55/min or in the presence of a heart defect and ventricular rate < 70/min averaged over 7 beats.
- Persistent bradycardia – induced ventricular tachycardia (with or without QT prolongation).

Pacemaker therapy

Pacemaker stimulation in the intensive care unit after cardiac surgery is most often performed via the temporary transcutaneous epicardial leads.

The most common pacemaker settings are the VVI mode (ventricular demand pacemaker), the AAI mode (atrial demand pacemaker), and the DDD mode (AV sequential pacemaker). Permanent devices additionally offer rate-adapted settings, in which the stimulation rates increase by detection, for example, of movement on physical exercise in a predefined range (Table 11.2).

Pacemaker settings on the external pacemaker

In addition to the pacemaker mode (AAI, VVI, DDD) and the intervention rate, the AV conduction time as well as the sensing threshold and output (after stimulation threshold testing) must be programmed into the external pacemaker. At the same time, the AV conduction time must be adapted to the heart rate. In the presence of a complete AV block, it is advisable to program the AV conduction time (AV interval) between 80 and 130 ms.

Table 11.2 Pacemaker nomenclature

Letter	Stands for	Relevance		
First letter	Impulse delivery sites	A: atrial	V: ventricular	D: dual[a]
Second letter	Sensing site	A: atrial	V: ventricular	D: dual[a]
Third letter	Response to the sensed impulse	I: inhibition[b]	T: triggering[c]	

[a]Dual: Can be inhibited or triggered in both the atrium and the ventricle depending on the presence of intrinsic activity

[b]Inhibition: If impulse is sensed, no PM impulse is generated

[c]Triggering: If impulse is not sensed, a PM impulse is generated, i.e., the PM responds to intrinsic signals of the heart or of the other lead

The *sensing threshold* is defined as the threshold (in mV) at which an electrical impulse from the heart must be detected by the pacemaker. If the sensing threshold is set too low, impulses that do not belong to the electrical heart action at all are also detected. In the worst case, bradycardia, for example, can then persist. If the sensing threshold is set too high, impulses that are actually present are not sensed, and the pacemaker generates an intrinsic impulse regardless of the underlying rhythm (parasystole). With ventricular stimulation this can overlap the refractory phase and in the worst case result in ventricular fibrillation. Prior determination of the *stimulation threshold* is important for programming *the output*. To this end, the impulse amplitude (usually in mA) is constantly reduced (with an unchanged impulse duration of usually 0.5 ms) until a previously still triggerable PM impulse no longer results in depolarization on the ECG. The impulse amplitude is then programmed at least 5 mV above the established stimulus threshold for safety's sake but should be rechecked regularly in postoperative patients (at least every 8 h). Stimulation thresholds can temporarily worsen postoperatively because of edema formation or as a result of drugs (amiodarone). In the case of high stimulation threshold values and an adapted high amplitude, it should be checked whether stimulation results in diaphragmatic spasms. These are painful for the patient and need to be treated. With many of the external pacemakers in use, the impulse duration cannot be varied – if this were the case, an increase in impulse duration rather than increased amplitude would be an option specifically in the presence of diaphragmatic spasms.

Caveat Whenever a PM is used, the heart rate alarm limits must be checked on the patient's monitor.

Conventional therapeutic and diagnostic use of the external PM:

- Sinus bradycardia: If AV conduction is preserved, a coordinated sequential atrial and ventricular contraction can be achieved by AAI stimulation at the minimum pacing rate.
- AV block: Stimulation in DDD mode or VVI mode. In DDD mode, atrial-triggered ventricular stimulation is achieved. This sequential stimulation is required immediately after cardiac surgery to increase CO, particularly in patients with impaired ventricular function. In the long term, VVI stimulation with positioning of the ventricular lead on the LV apex should be preferred to DDD stimulation in infants and young children. Experience shows that pacemaker-induced cardiomyopathies occur more frequently in this age group with DDD stimulation.

Note In neonates with congenital complete AV block, VVI stimulation with a low-normal pacing rate has a better prognosis than DDD stimulation.

Caution In inotropic- or volume deficiency-induced sinus tachycardia, sequential stimulation can also worsen CO; sometimes, slower VVI stimulation is hemodynamically better. To optimize treatment, therefore, note the arterial blood pressure!

The use of a temporary pacemaker for diagnosis and treatment in tachycardiac arrhythmias will be discussed in greater detail under the corresponding forms of tachycardia.

11.4 Tachycardiac Arrhythmias

Tachycardiac arrhythmias are characterized by paroxysmal or a chronic permanent increase in atrial and/or ventricular rate. They are based on different pathological mechanisms and are divided primarily into supraventricular and ventricular tachyarrhythmias. The clinical symptoms depend on age, cardiac anatomy, ventricular function, and type of tachyarrhythmia. Healthy infants can develop signs of heart failure with paroxysmal supraventricular tachycardia (PSVT) at ventricular rates > 250/min. This is due to the shortened diastolic filling time of the ventricle. Children and adolescents with chronic persistent supraventricular tachycardia frequently do not have any acute symptoms but present with tachycardia-induced cardiomyopathy, which frequently results in the diagnosis of dilated cardiomyopathy. This "cardiomyopathy" is usually reversible after treatment of the tachyarrhythmia.

Sinus tachycardia in the true sense is not a tachycardiac arrhythmia but, over time, can also result in a reduction in CO specifically in patients with a congenital heart defect or following cardiac surgery. Possible causes include fever, volume deficiency, pain, reduction in CO, acidosis, and drugs (e.g., dobutamine, theophylline, ketamine, etc.). In the surface ECG, the P waves are positive in I, II, and aVF, and each is followed by a QRS complex after a constant PQ interval. Sinus tachycardia accelerates slowly and does not terminate abruptly but instead decelerates slowly.

By contrast, *sinus node reentry tachycardia* exhibits an abrupt onset and an abrupt end ("on-off" phenomenon). Even in the ECG, this is difficult to distinguish from sinus tachycardia, but it can result in reduced coronary perfusion and an increase in myocardial O_2 consumption despite the coordinated atrial and ventricular contraction.

11.4.1 Supraventricular Tachycardia (SVT)

In contrast to ventricular tachycardia (VT), supraventricular tachycardia (SVT) is defined by the fact that anatomical structures above the bifurcation of the bundle of His are involved in generating and maintaining the tachycardia. SVT is present if more than three successive atrial impulses occur with a tachycardia rate faster than 20% of the underlying base rhythm. This is the difference from an accelerated supraventricular rhythm.

SVT based on accessory pathways (atrioventricular reentry tachycardia, AVRT)

This is the most common cause of SVT in children. In about 50% of children with an accessory pathway, this has only retrograde conduction during the

tachycardia - also defined as “concealed” accessory pathway. During tachycardia, the electrical impulse is conducted via the AV node to the ventricles and back via the accessory pathway – this is referred to as an “orthodromic SVT” (Table 11.3) (see Fig. 11.3).

Table 11.3 Differentiating features of supraventricular tachycardia (SVT)

	Cycle length	RP interval	P axis	Special features
ORT	Regular	>70 ms, but shorter than PR interval	Neg. in II, III, aVF	
Typical AVNRT (slow-fast)	Regular	P in QRS-P not detectable		
Atypical AVNRT (fast-slow)	Regular	RP interval > PR interval	Neg. in II, III, aVF	
FAT	Irregular	RP interval > PR interval	Variable	Warm up-cool down, frequently aberrant conduction
PJRT	Regular	RP interval > PR interval	Neg. in II, III, aVF	Persistent SVT
JET	Regular	Frequent AV dissociation	Sinus P	Usually postoperative
Atrial flutter	Usually regular	(Ir)regular	Sawtooth	Frequently more P than QRS

ORT orthodromic reentry tachycardia, *AVNRT* AV nodal reentry tachycardia, *FAT* focal atrial tachycardia, *PJRT* persistent junctional reciprocating re-entry tachycardia, *JET* junctional ectopic tachycardia

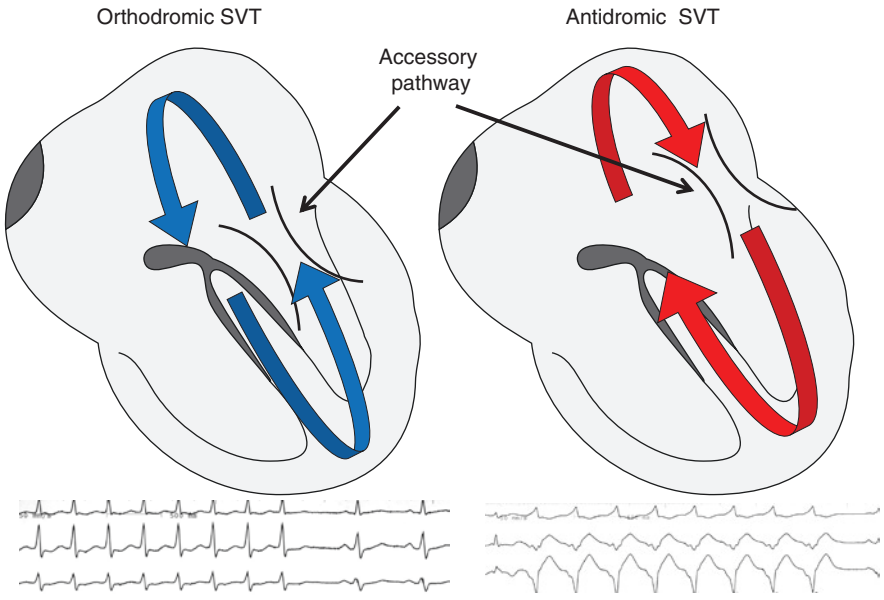


Fig. 11.3 Orthodromic and antidromic supraventricular tachycardia (SVT)

The combination of sinus rhythm with antegrade conduction via the accessory pathway and the occurrence of SVT define the Wolff-Parkinson-White (WPW) syndrome. These patients can exhibit antidromic SVT (antegrade conduction via accessory pathway and retrograde conduction via AV node), so that the result is a tachycardia with wide QRS complexes as sign of maximum preexcitation (see Fig. 11.4). Atrial flutter and atrial fibrillation can occur three times as often in children with a preexcitation syndrome as in the normal population. Degeneration of SVT into atrial flutter and fibrillation is presumed to be a cause, but spontaneous onset is equally possible. Patients with an Ebstein abnormality or hypertrophic cardiomyopathy in particular have additional (sometimes even several) accessory pathways.

Surface ECG (orthodromic AVRT):

- Mostly narrow QRS complexes (functional bundle branch block rare in children)
- Regular interval of QRS complexes
- On-off phenomenon
- P wave (neg. in II, aVF) detectable following on from the QRS complex (–80 ms)

AV nodal reentry tachycardia (AVNRT)

AVNRT occurs more rarely in children than in adults. Schoolchildren and adolescents are mainly affected. Two anatomically distinct AV nodal pathways with different conduction properties are present due to a functional longitudinal dissociation of

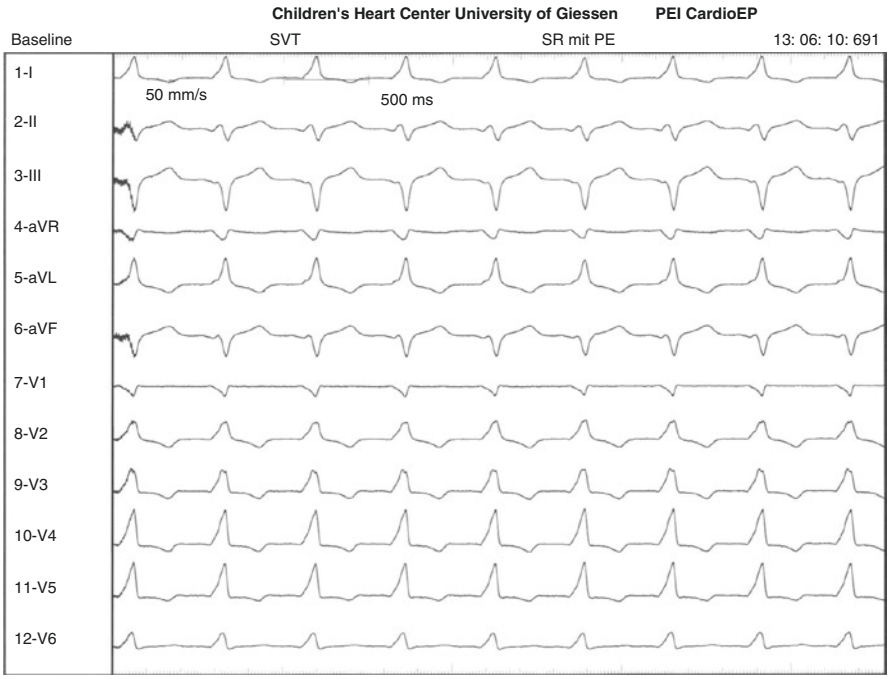


Fig. 11.4 WPW syndrome

the AV node. The most common form is the typical AV nodal reentry tachycardia (slow-fast type); here the electrical impulse is conducted antegrade via the slow pathway and retrograde via the fast pathway.

Surface ECG:

- Narrow, regular QRS complexes.
- Heart rate: 150–220/min (usually somewhat slower than AVRT), frequently triggered by sport/stress.
- Typical AVNRT: retrograde conducted P wave not detectable (hidden within the QRS complex).
- Atypical AVNRT (fast-slow type, rare): ventriculoatrial conduction prolonged, retrograde P with long RP interval. In the differential diagnosis of these ECG characteristics, focal atrial tachycardia can also be present.

In AVNRT, there is no risk of sudden heart death; patients with a normal cardiac anatomy will generally not experience any complications either (see Fig. 11.5).

Treatment of AVRT and AVNRT

As both forms of tachycardia require the AV node to perpetuate the tachycardia, this arrhythmia can be terminated by temporary blockade of the AV node. This can be achieved by vagal maneuvers (50% success rate) or administration of adenosine.

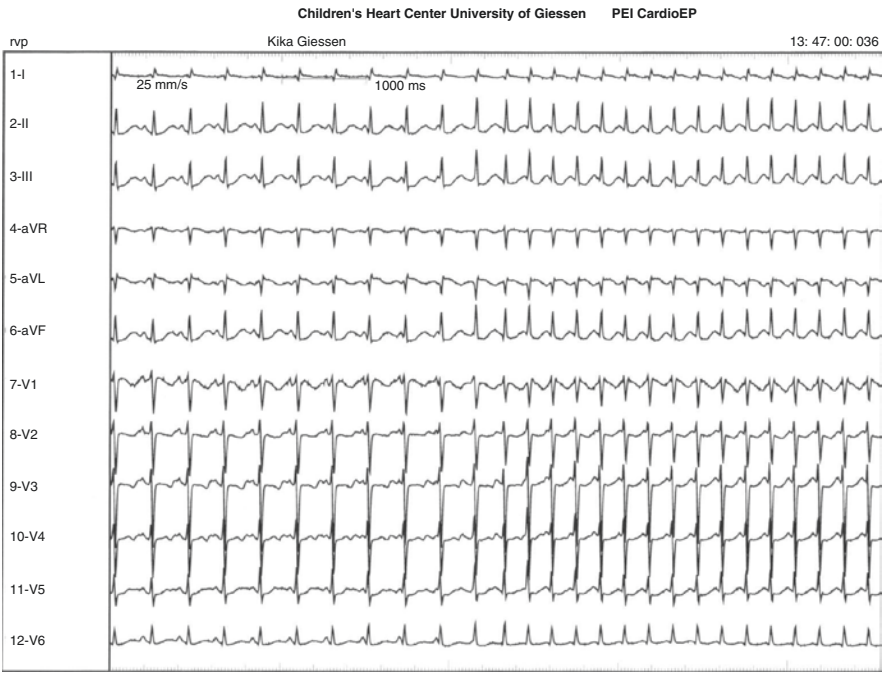


Fig. 11.5 AV nodal reentry tachycardia

Verapamil i.v. is rarely used for AV block. Verapamil is contraindicated in infants and young children because of the marked tendency to hypotension but is an additional option in older children and adolescents. Synchronized cardioversion can also be performed. In the presence of antidromic SVT (wide QRS complexes), which is difficult to differentiate from VT, cardioversion should always be performed in the event of doubt.

Atrial fibrillation can be induced by adenosine in rare cases and can be life-threatening in patients with a preexcitation syndrome. If there is fast antegrade conduction via the accessory pathway, rapid ventricular tachycardia or fibrillation can be induced.

Vagus nerve stimulation

- Rapid drinking of very cold water
- Placing an ice pack on the neck
- Pharyngeal or endotracheal suctioning
- Have the patient do an abdominal press

Note Administration of adenosine in patients with SVT without knowledge of the presence of a delta wave in the resting ECG only if defibrillator is available!

Permanent form of junctional reciprocating tachycardia (PJRT)
This form of tachycardia occurs in about 1–6% of all children with SVT. It usually involves a chronic persistent, but occasionally also paroxysmal, SVT with age-dependent ventricular rates of between 100 and 250/min. Typical of this form of SVT is an increase in the mean heart rate level, which is also detectable at night. The symptoms vary and are dependent on ventricular rate and the frequency of tachycardia. The majority of patients present as young children with clinical signs of heart failure or secondary dilated cardiomyopathy.

In the surface ECG:

- Long RP interval, the PR interval is shorter (PR/RP ratio < 1).
- P waves are negative in the II, III, aVF, and V3–V6 leads.
- No warm-up phenomenon.
- Rate between 100 and 250/min.

PJRT is often a tachyarrhythmia that responds poorly to medication (see Fig. 11.6). Usually an improvement in myocardial function can be achieved by reducing ventricular rate. Administration of adenosine or (transesophageal) cardiac overdrive pacing is generally not effective in the long term. In terms of pharmacotherapy, class Ic (propafenone, flecainide) and class III (sotalol, amiodarone) antiarrhythmics have become established, frequently in combination with beta-blockers and, if that is not sufficient, with digoxin also. However, in drug-refractory forms or once a body weight > 15 kg is reached, catheter ablation is the method of choice and to be preferred to long-term pharmacological therapy.

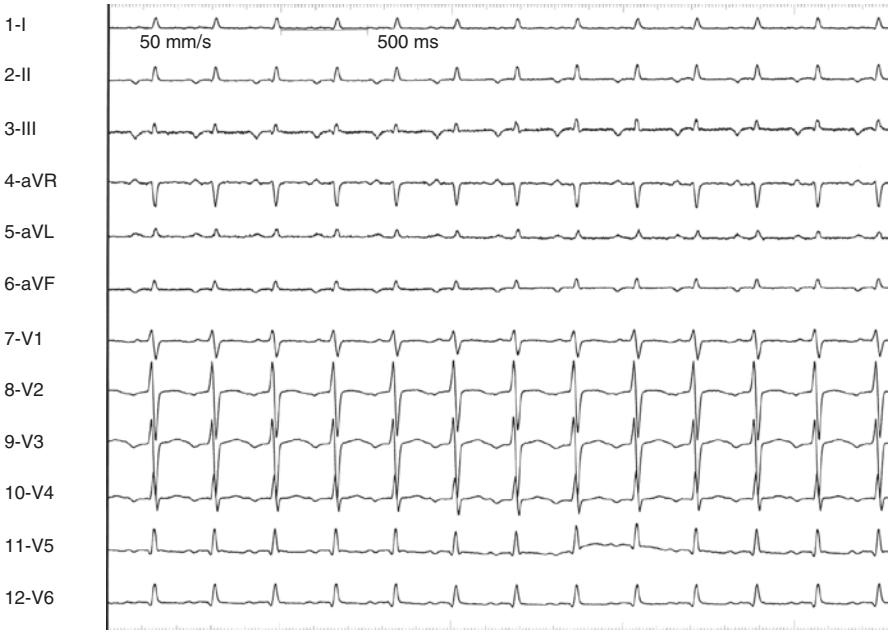


Fig. 11.6 Persistent junctional reciprocating re-entry tachycardia (PJRT)

Focal atrial tachycardia (FAT)

FAT is a form of tachycardia due to an ectopic atrial focus with pathologically increased automaticity.

In the surface ECG:

- P wave has a different axis from the sinus P wave.
- Frequently with a warm-up and a cooldown phenomenon (unstable tachycardia cycle length).
- Often aberrantly conducted (wide) QRS complexes at the start of tachycardia.
- The AV node or the ventricular muscle is not part of the tachycardia mechanism.
- AV conduction times can vary; sometimes P waves are not conducted.

Chronic persistent tachycardia is usually present because of the increased automaticity, with the possible risk of tachycardia-induced cardiomyopathy. AV conduction is blocked in the short term by administration of adenosine, which allows a diagnosis if the FAT persists; however, FAT can also be terminated in the short term by adenosine, which complicates the diagnosis. Overdrive pacing or external cardioversion is of no use because of the continued presence of automaticity. Like PJRT, FAT is difficult to control pharmacologically. In this case as well, class Ic (propafenone, flecainide) and class III (sotalol, amiodarone) antiarrhythmics have become established, frequently in combination with digoxin. Additional treatment with a beta-blocker can result in a reduction in the

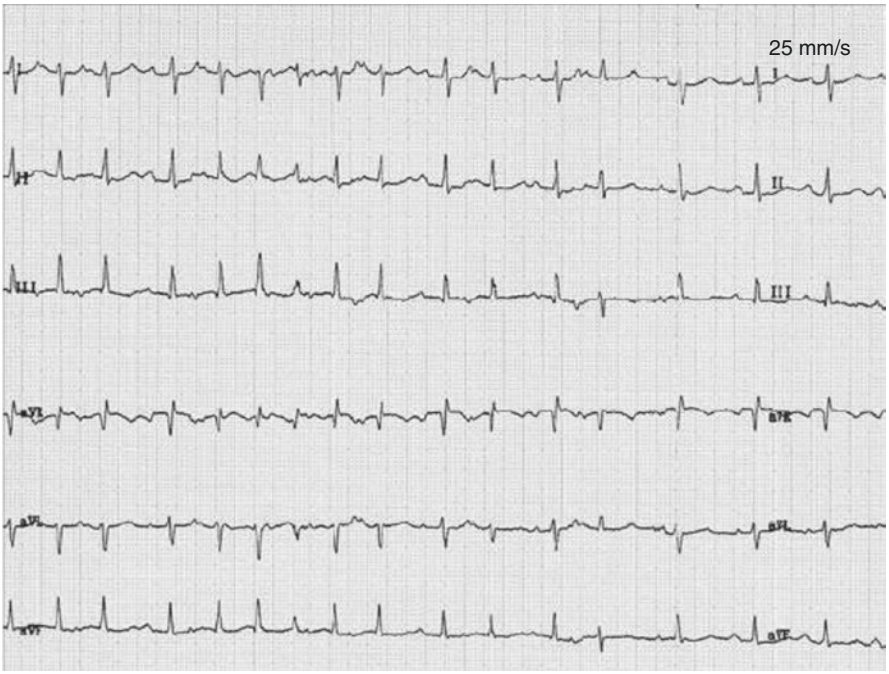


Fig. 11.7 Multifocal atrial tachycardia

ventricular rate by affecting AV conduction time. High-frequency ablation of the anatomical substrate is a curative treatment. The success rate is >80% and should be favored by a body weight >15 kg.

Multifocal atrial tachycardia represents a special form. At least three different P wave morphologies are identifiable in the surface ECG. The electrophysiological properties correspond to FAT, and, like the latter, multifocal atrial tachycardia is difficult to control pharmacologically.

Note If a slow ectopic atrial rhythm is present (slower than sinus rhythm), this has to be defined as an atrial escape rhythm. If the atrial rhythm is at more than 20% faster than the sinus rhythm, then an accelerated atrial rhythm is present, and this usually does not require treatment (Fig. 11.7).

Junctional ectopic tachycardia (JET)

JET is a relatively common complication following cardiac surgery, probably caused by intraoperative mechanical irritation of the conduction system and usually resolving spontaneously after 2–4 days. It exhibits a rate of about 160–220/min, which can result in a deterioration of CO, mainly because of the lack of atrial and ventricular coordination – particularly in diastolic myocardial dysfunction.

In JET, an ectopic impulse center is found in the area of the AV node or the proximal bundle of His. Electrical stimulation passes from this ectopic focus to the

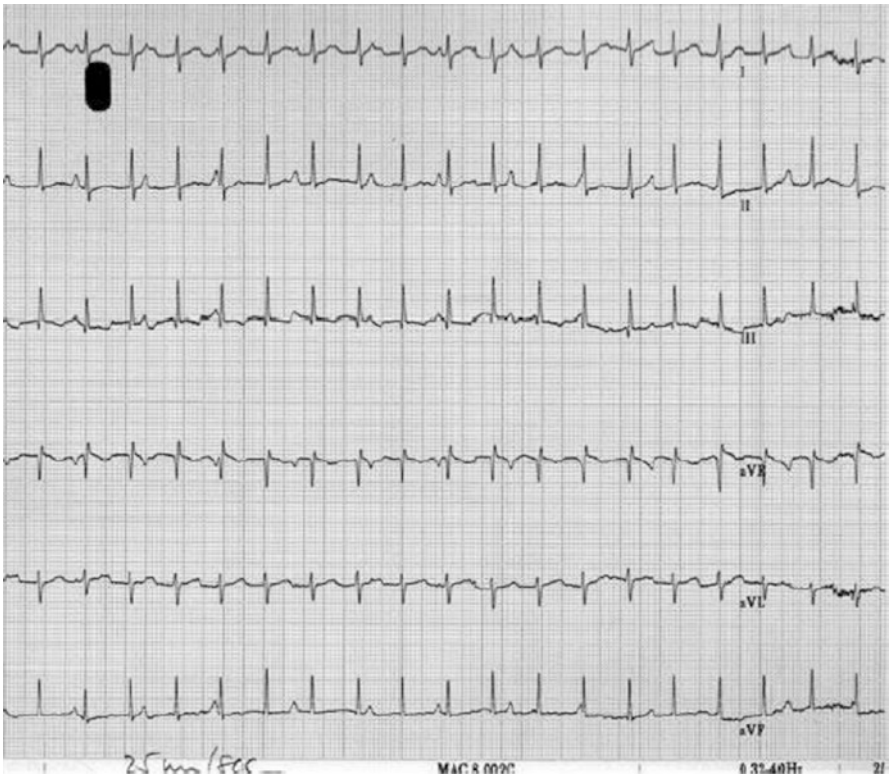


Fig. 11.8 AV dissociation in JET. Unlike third-degree AV block, more QRS complexes are detectable than P waves

ventricles, usually without retrograde electrical activation of the atrium. AV dissociation is therefore frequently present in the ECG. Thus, normally configured P waves (sinus beats) with a slower rate than the ventricular action are present. As the origin of JET lies in the bundle of His, the morphology of the QRS complex matches that in sinus rhythm (usually narrow QRS complex). If there is aberrant conduction with wide QRS complexes, it is difficult to differentiate JET from stable ventricular tachycardia, since this too can be associated with AV dissociation. Postoperative JET without AV dissociation is rarely present. Following the ventricular action, retrograde VA conduction occurs from the bundle of His, so that a retrograde P wave is detectable, although it exhibits a different axis (neg. in II, III, aVF) (Fig. 11.8).

Diagnosis on suspicion of the presence of JET

In JET with a normally wide QRS complex, AV dissociation can be detected in most cases by recording an atrial ECG (via temporarily inserted pacemaker wires). In this case, the P waves migrate through the QRS complexes.

If AV dissociation is not present, a retrograde VA block can be induced by administration of adenosine without altering the ventricular rate.

If the QRS complex is widened, as in unifocal ventricular tachycardia, normal conduction to the ventricles can be achieved by slightly faster atrial stimulation (10–20% faster than the tachycardia) without altering the morphology of the QRS complex.

Note Ventricular tachycardia would not be amenable to this stimulation maneuver.

Treatment of JET

- Cooling, depending on bleeding tendency, to 34–35 °C for rate reduction (with analgosedation to prevent muscle tremor).
- Amiodarone for rate reduction
- After rate reduction: Atrial stimulation slightly faster than JET rate; coordinated atrial and ventricular action as a result.
- Coordinated atrial and ventricular action can also be achieved by placing the ventricular wire of the temporary pacemaker in the atrial outlet of the external pacemaker and the atrial wire in the ventricular outlet. As a result, the ventricular action is recognized by the pacemaker as "atrial action," and the atrium is then stimulated after a long AV conduction time is programmed. However, this maneuver should be checked repeatedly for the programmed times, particularly following a change in JET rate. At high rates, PVARP must be substantially reduced in this setting, which is only possible with special pacemakers (PACE 300, version JJ, Osypka Medical GmbH, Berlin, Germany).

Caveat The intrinsic rate must be regularly checked when amiodarone and atrial stimulation are used. Accumulation of amiodarone can result in sinus bradycardia, AV blocks, and QRS widening. The stimulation threshold is increased with amiodarone treatment.

Note An accelerated junctional rhythm is present if the rate of the junctional rhythm is up to 20% faster than sinus rhythm. Usually this does not require treatment.

Atrial flutter and intraatrial reentry tachycardia (IART)

Typical atrial flutter involves a primary atrial tachycardia on the basis of a macroreentry mechanism in the right atrium, where the critical zone is the isthmus (region between the tricuspid valve and the junction of the inferior vena cava). The typical "sawtooth pattern" in the surface ECG can be unmasked following bolus administration of adenosine (see Fig. 11.9). Without congenital heart defects, this tachycardia may already occur in utero and also postnatally. Particularly in neonates with normal cardiac anatomy and unexplained tachycardia with HR between 200 and 300/min without detectable P waves, the possibility of atrial flutter should be considered.

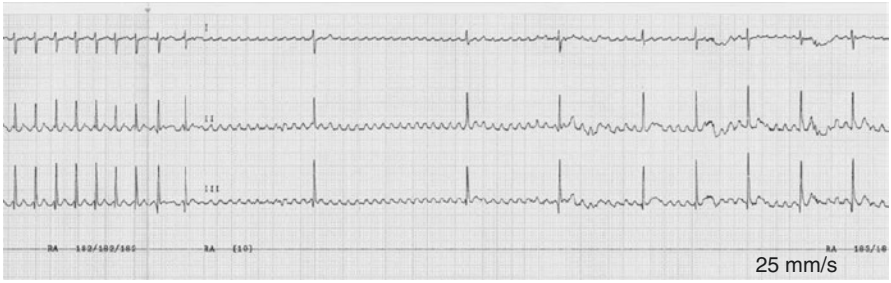


Fig. 11.9 Atrial flutter. Adenosine blocks AV nodal conduction and unmasks the existing atrial flutter

Intraatrial reentry tachycardia occurs in particular in patients following cardiac surgery of the atrial region. This involves circulating electrical impulses around anatomical zones of electrical insulation, such as atriotomy scars or plastic patches (after ASD closure). IART are associated with increased rates of late postoperative morbidity and mortality. These tachycardias frequently exhibit a slower rate than typical atrial flutter and are therefore frequently conducted 2:1 to the ventricles, but also 1:1, so that the ensuing ventricular rate is often not tolerated hemodynamically.

Diagnosis in atrial flutter/IART
Atrial flutter/IART can most clearly be unmasked after administration of an adenosine bolus – the typical "sawtooth pattern" (see Fig. 11.9) is visible in the surface ECG as a result of the short-term AV block. Similarly, very fast regular atrial activation can be detected by means of an atrial electrode.

Treatment is based on the hemodynamic status
In the event of hemodynamic impairment, synchronized electrical cardioversion with an energy dose of 1–2 J/kg BW should be given with a biphasic defibrillator under analgosedation. If the hemodynamics are stable, atrial overdrive pacing can also be applied transesophageally or via a temporary pacemaker. To this end, the atrium is stimulated via the atrial electrode at a rate that is about 20% faster than the tachycardia and as a result "overtaken." As a result, the atrial myocardium becomes refractory to the next flutter wave so that the circular stimulation is blocked. The next sinus action can then step in again. Atrial overdrive pacing usually succeeds only with high output (10–20 mV and 1–2 ms) and requires patience.

Note In the presence of atrial flutter >48 h, intracardiac thrombi must be excluded by transesophageal echocardiography before electrical cardioversion or overdrive pacing.

After electrical cardioversion or atrial overdrive pacing, the risk of relapse in patients with healthy hearts is low, so that in the early stages it is possible to refrain from drug therapy. If, however, long-term success cannot be achieved by electrical

cardioversion or atrial overdrive pacing, the next step would be to delay conduction to the ventricles for rate control. Administration of beta-blockers, digoxin, propafenone, class III antiarrhythmics (sotalol, amiodarone), and also verapamil as an CID (Cont. Intravenous Drip Infusion) in older children/adolescents is possible for this purpose. Repeat electrical cardioversion following drug saturation is usually more promising.

In patients with congenital heart defects and known large atria, atrial flutter/IART often cannot be terminated in the long term. In these patients, adequate anticoagulation is urgently required.

Atrial fibrillation, paroxysmal or persistent

Atrial fibrillation is considerably less common than atrial flutter in children and can be paroxysmal or persistent. At a fibrillation rate of 350–450/min, conduction occurs very irregularly depending on the refractory period of the AV node and results in atrial fibrillation with a very variable heart rate. In atrial fibrillation, the very rapid and irregular fibrillation waves are often not detectable in the surface ECG. An atrial ECG recording is very helpful for diagnosis. Spontaneously occurring atrial fibrillation in patients with healthy hearts not infrequently also terminates spontaneously. In persistent atrial fibrillation, treatment is equal to that of atrial flutter.

Caveat In patients with preexcitation syndrome, fast conduction to the ventricles can occur in the presence of a fast-conducting accessory pathway in atrial fibrillation. Very fast, broad, irregular ("FBI") QRS complexes can be observed in the ECG, which are not tolerated hemodynamically. These require electrical cardioversion. Adenosine is contraindicated as it simply promotes conduction further via the accessory pathway.

11.4.2 Ventricular Tachycardia (VT), Ventricular Flutter and Ventricular Fibrillation

VT is present if more than three successive depolarizations occur below the bundle of His that are at least 20% faster than the base rhythm and exhibit a different QRS morphology from it. The ventricular rate is usually between 150 and 300/min. There is frequently a widening of the QRS complex beyond the age-specific normal range (infants > 80 ms, young children > 90 ms, older children > 120 ms), while in neonates narrow QRS complexes can also occur in VT. Depending on the QRS morphology, a distinction is drawn between monomorphic (QRS complexes all appear the same) and polymorphic ventricular tachycardias. AV dissociation with intermittent capture beats (normally conducted sinus beats) is evidence of a VT. However, in infants and children, retrograde 1:1 ventriculoatrial conduction is occasionally present due to the good conduction properties of the AV node. As a result of the high ventricular rate and the usually absent atrial contraction, there is a reduction in CO. Coronary perfusion deteriorates as a result, which in turn reduces myocardial perfusion so that the VT is perpetuated further. VT therefore requires immediate and consistent treatment.

Ventricular tachycardia transitions seamlessly into ventricular flutter and ventricular fibrillation. Ventricular flutter usually has a rate of 200–300/min and typical hairpin-shaped QRS complexes on the ECG without an isoelectric line. Ventricular fibrillation is faster; the fibrillation waves of different morphologies usually oscillate around the baseline at low amplitude.

Caveat Increased risk of VT with electrolyte variations, pH variations, hypoxia, pharmacologic causes, myocardial damage/cardiomyopathies, cardiac tumors, and ion channel disorders

Differential diagnosis

- SVT with preexisting bundle branch block: difficult to differentiate; adenosine is helpful here.
- SVT with preexcitation syndrome with antidromic regular conduction: also difficult to differentiate, here again adenosine is helpful – preexcitation is then detectable during sinus rhythm.
- Accelerated idioventricular rhythm: rate < 20% of the base rhythm, usually well-tolerated hemodynamically, disappears immediately on acceleration of sinus rhythm, and usually does not require treatment (see Fig. 11.10).

Treatment of VT

Therapeutic measures are based on the patient's clinical status and the underlying disease, if known.

Measures in stable patients:

- As a general rule: collect as much information as possible. Medical history? Medication? Triggers? Underlying disease? Evidence of infection? Family history?
- If possible, immediate 12-channel ECG recording.
- In parallel: blood sample with blood gas analysis and determination of electrolytes (incl. magnesium), cardiac enzymes (troponin I, CK = creatine kinase, CK-MB), coagulation with D-dimers, where necessary drug levels.
- Echocardiogram: assessment of heart function, tumor? Pericardial effusion?
- In hemodynamically stable patients, adenosine can be administered initially for further diagnostic investigations. This can frequently terminate right ventricular

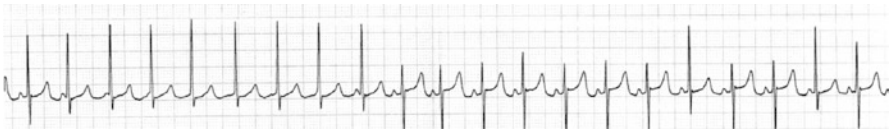


Fig. 11.10 Accelerated ventricular rhythm in an neonate. Ventricular rhythm with narrow QRS complexes

outflow tract tachycardia (monomorphic, left bundle branch block morphology and inferior axis [neg. QRS complex in aVF]) but also SVT with wide QRS complexes. Adenosine, however, must not be administered in patients with atrial fibrillation and preexcitation syndrome with fast conduction ("FBI" morphology; see above).
- If the hemodynamics are impaired but perfusion pressures are still adequate, amiodarone (5 mg/kg BW over 2–3 min i.v.) should be injected as long as cardioversion facilities are available. Alternatively lidocaine i.v. (more rarely: beta blockers) can also be administered.
- If unsuccessful: electrical (if monomorphic, VT-synchronized) cardioversion with 1–2 J/kg BW/energy dose.

Measures in unstable patients:

- Precordial thump: can be successful immediately after the observed onset of circulatory arrest (Do it!).
- CPR and bag-valve-mask ventilation: 30, 2 older children; 15, 2 infants, always start with 5 ventilations.
- First defibrillation: 2–4 J/kg BW, then CPR; if necessary second defibrillation with 4 J/kg BW followed by CPR; then, if still unsuccessful:
  - Adrenaline i.v. or intraosseous: 0.01 mg/kg (= 0.1 ml/kg of 1:10000 diluted solution).
  - Then 3rd defibrillation immediately. If unsuccessful: amiodarone 5 mg/kg BW over 2–3 min i.v. or with G5% as CID and 4th defibrillation immediately.
- If the previous measures are still unsuccessful: adrenaline 0.01 mg/kg every 3–5 min, if necessary repeat administration of amiodarone (5 mg/kg) or switch to lidocaine 2 mg/kg; if hypomagnesemia, magnesium replacement 0.3–0.5 mmol/kg BW i.v.
- Elimination of other triggers: hypoxia, pericardial effusion, electrolyte disturbances, hypovolemia.
- If VT is not terminated successfully: continue CPR until, e.g., ECMO is ready for use.

Caveat Do not defibrillate in asystole or slow pulseless electrical activity! If > 5 defibrillations: myocardial depression!

Note Apart from the fastest possible electrotherapy, sufficient CPR is the most important measure.

Special forms of VT

Idiopathic VT

Idiopathic VT occur in children with normal cardiac anatomy, although myocarditis or cardiomyopathy should be excluded. Idiopathic VT exhibit monomorphic QRS complexes. With frequent persistent tachycardiac episodes, a tachycardia-induced

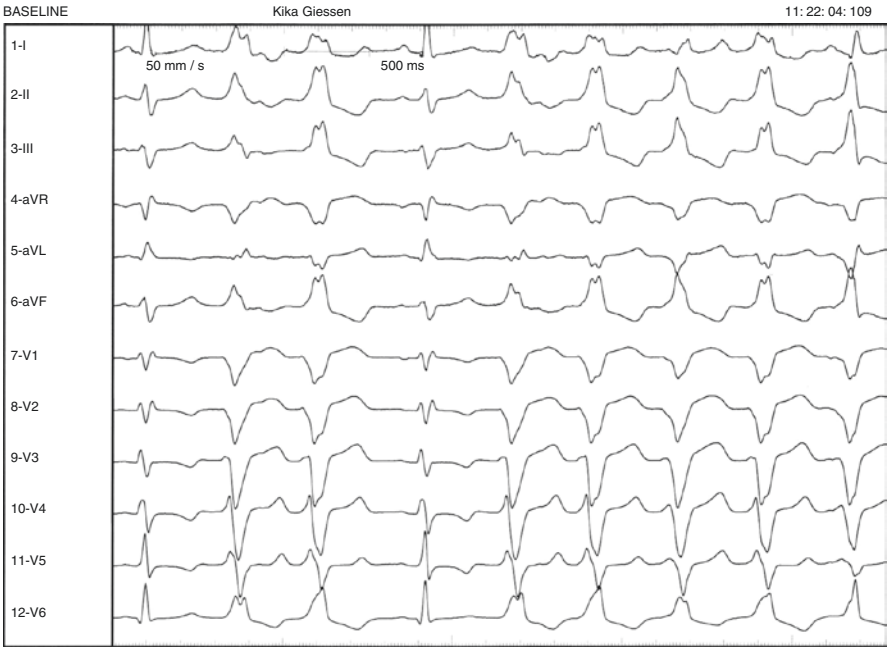


Fig. 11.11 RVOT-VT

cardiomyopathy can develop. In children, this usually involves an outflow tract tachycardia, which can originate from both the right (more common) (see Fig. 11.11) and the left outflow tract. The ECG usually displays a left bundle branch block morphology with inferior axis (positive in aVF). These outflow tract tachycardias have a trigger mechanism and can usually be readily terminated with adenosine. Treatment with a beta-blocker is usually sufficient for relapse prophylaxis.

Idiopathic VT also include *left ventricular fascicular VT* (also called Belhassen VT) (see Fig. 11.12). This is a reentry tachycardia involving the apical posterior fascicle. This tachycardia usually onsets abruptly. The ECG displays QRS complexes with a right bundle branch block morphology and superior axis (negative QRS complex in aVF). LV fascicular tachycardia is the only VT that can be terminated by verapamil i.v., so that verapamil can also be used as long-term therapy. In infants, however, medication with propranolol should be tried. Catheter ablation has a high success rate.

VT based on ion channel diseases This usually involves autosomal dominant inherited gene mutations in ion channels that affect the ion balance of the cardiomyocytes. Depending on the localization of the gene mutation, disorders occur to the potassium or sodium channels in the cell wall (long QT syndrome [LQTS], short QT syndrome [SQTS], Brugada syndrome [BrS]) or disorders of calcium exchange within the cell (CPVT, *c*atecholamine-sensitive *p*olymorphic *VT*). These changes cause prolongation (LQTS; QTc > 440 ms) or shortening of the action

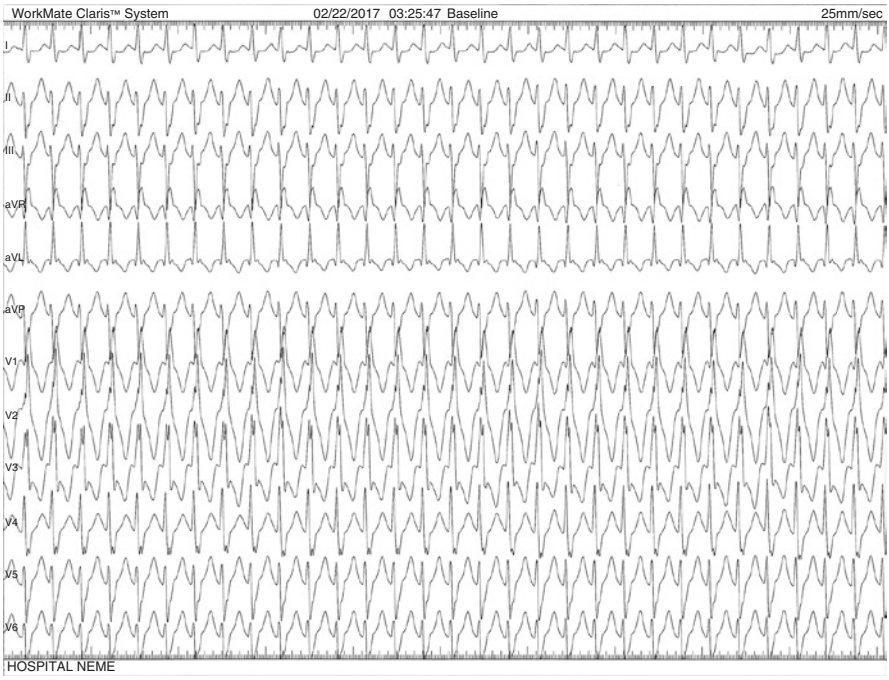


Fig. 11.12 Fascicular VT

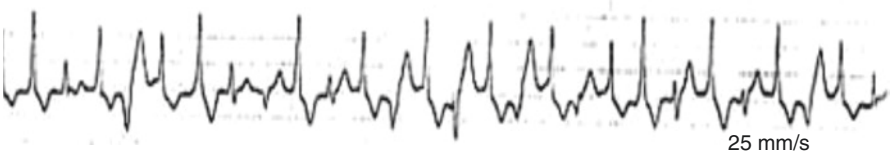


Fig. 11.13 Bidirectional VT in CPVT (change of QRS complex axis top-bottom, sinus capture beats in-between)

potential (SQTS; QTc $\leq$ 340 ms and Brugada syndrome), or a calcium overload of the cell in CPVT, which result in ventricular tachyarrhythmia as a result of early or late afterdepolarizations and changes in refractory periods. This usually involves polymorphic ventricular tachycardia or ventricular fibrillation (see Figs. 11.13 and 11.14).

Particular trigger mechanisms for ventricular tachycardia in the presence of an ion channel disorder:

- Increased sympathetic tone (sport, emotional stress): typical for LQTS type 1 and 2, CPVT
- Sudden loud acoustic phenomena: LQTS type 2

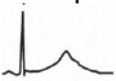
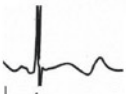
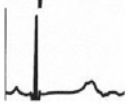
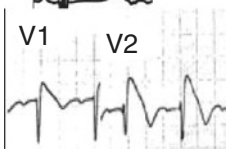
Typ	Ion-channel	Prevalence	T-wave-morphology	Trigger
LQT1	K / potassium	54 %		exercise / emotional stress
LQT2	K / potassium	35 %		sudden noise / swimming
LQT3	Na / sodium	10 %		sleep/rest wake up
BrS	Na / sodium			fever

Fig. 11.14 ECG features in LQT and Brugada syndrome

- Swimming: particularly strong trigger in LQTS type 1
- Occurrence of arrhythmia in sleep: LQTS type 3, Brugada syndrome
- In fever: Brugada syndrome (see Fig. 11.14)

Acute therapeutic measures:

- Defibrillation/cardioversion as soon as possible (2–4 J/kg)
- Further acute treatment depending on the specific diagnosis:
  - LQTS type 1 and 2: beta-blockers (e.g., esmolol, metoprolol i.v.), magnesium i.v., in existing bradycardia, temporary ventricular stimulation
  - LQTS type 3: lidocaine i.v. together with temporary ventricular stimulation
  - CPVT: high-dose beta-blockers (esmolol, metoprolol i.v.)
  - Brugada syndrome: isoprenaline or orciprenaline i.v. for acute stabilization; if fever is present, aggressive antipyretic treatment additionally

Note Because of the very different acute pharmacologic treatment of LQTS and CPVT (beta-blockers) and Brugada syndrome (isoprenaline), a correct ECG interpretation or knowledge of the precise diagnosis is mandatory. The administration of other antiarrhythmic drugs is ineffective and even proarrhythmic (e.g., amiodarone in LQTS or CPVT)!

Torsade de pointes This special form of VT is characterized on the ECG by a wavelike or spindle-shaped arrangement of different QRS complex morphologies that appear to twist about the baseline (Fig. 11.15). The torsades often cease spontaneously; more rarely they progress to ventricular fibrillation.

Predisposing factors for torsades are:

- Prolongation of the QTc duration by
  (a) Congenital LQTS
  (b) Drugs (class Ic and class III antiarrhythmics, antibiotics, neuroleptics, etc.)

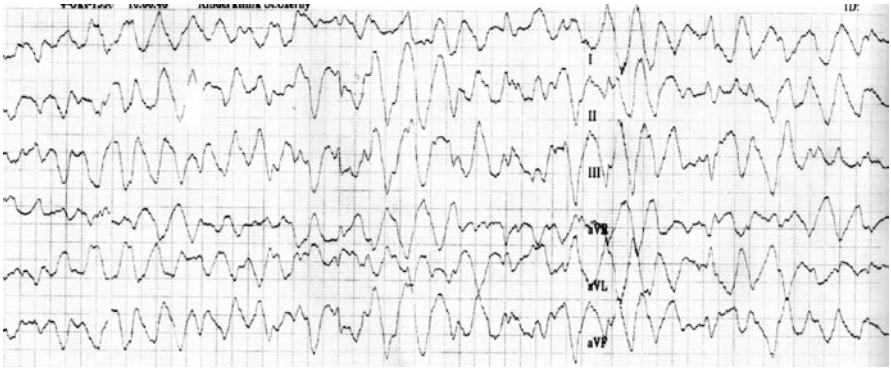


Fig. 11.15 Torsade de pointes

(c) Electrolyte fluctuations (hypomagnesemia, hypokalemia)
(d) Electric shock
(e) Hypertrophic cardiomyopathy
(f) Bradycardia
(g) Hypoxia

Treatment of torsade de pointes

- In cases of persistent tachycardia: electrical cardioversion.
- Magnesium (1.5 mL/kg 10% over 5 min) and potassium i.v. (aim for high-normal values – for membrane stabilization).
- In the acute situation: increase in HR (e.g., orciprenaline or temporary pacemaker) prevents development of bradycardia-induced tachycardia.

Caveat Amiodarone exacerbates the situation.

Incessant VT This is a rare permanent form of VT (> 10% of the time). In most cases it is induced by intracardiac tumors (hamartomas, rhabdomyomas). It usually occurs within the first 3 years of life, when it is relatively well-tolerated hemodynamically, but can result in tachycardia-induced cardiomyopathy. It is difficult to control pharmacologically. Beta-blockers or sotalol is used in acute treatment. In the long term, however, surgical removal of the pathological substrate by catheter ablation is successful.

11.5 Pharmacologic Antiarrhythmic Therapy for Frequent Cardiac Arrhythmias

Apart from the avoidance of pro-arrhythmogenic substances (e.g., betamimetics, adrenaline, and theophylline) and close monitoring of serum electrolytes, only a few specific antiarrhythmics play a role in clinical practice.

11.5.1 Class II Antiarrhythmics (Beta-Blockers)

The myocardium is very sensitive after cardiac surgery, so that beta-adrenergic impulses can result in cardiac arrhythmias. The use of beta-blockers is then frequently indicated. Beta-blockers reduce sinus rate by blockade of the β_1 adrenoceptors in the heart muscle (negative chronotropic), delay AV conduction (negative dromotropic), and reduce contractility of the heart (negative inotropic) and myocardial excitability (negative bathmotropic).

They can therefore be used in:

- Sinus tachycardia (after excluding other treatable causes)
- Increased extrasystoles (SVES and VES)
- Supraventricular reentry tachycardia (to block AV conduction times)
- Atrial flutter, atrial fibrillation, and FAT to reduce ventricular rate

Beta-blocker therapy is not indicated in the event of bradycardia, AV blocks, and existing severely impaired ventricular function.

Propranolol (particularly in infants and young children; patients with LQTS, CPVT, unifocal VT), metoprolol succinate (sustained release preparation), and esmolol are frequently used for antiarrhythmic therapy. From experience, bisoprolol has a weaker antiarrhythmic effect, particularly in children and especially in the treatment of supraventricular reentry tachycardia, monomorphic VT, CPVT, and LQT.

Note About 5–10% of patients are nonresponders to metoprolol.

Oral dosage:

- Propranolol 1–4(–8) mg/kg BW/day (3–4 single doses)
- Metoprolol 1–3 mg/kg BW/day (2 single doses)

11.5.2 Class III Antiarrhythmics (Amiodarone, Sotalol)

Amiodarone belongs to the class III antiarrhythmics with sotalol. These block Na and Ca channels as well as β-receptors and inhibit fast K efflux. As a result, there is a prolongation of the action potential duration in a wide variety of types of heart cell. This results in a cardiac conduction disorder as well as QTc prolongation. Amiodarone has only a weak negative inotropic effect, so that it can be used even when ventricular function is impaired. It is a very potent antiarrhythmic and can be used both in supraventricular tachycardia and in ventricular tachycardia and fibrillation. Because of the numerous side effects in long-term therapy (irreversible pulmonary fibrosis, thyroid function disorders, corneal deposits, etc.), amiodarone is only exceptionally used for long-term therapy.

Caveat Amiodarone has a long half-life, which needs to be borne in mind on the first signs of side effects! Marked interaction with other drugs, in particular, increased digoxin levels!

Note The risk of torsade de pointes tachycardia is increased by prolongation of the QTc time! Contraindicated in LQTS.

Oral dosage:

- Amiodarone: 2–5 mg/kg BW/d
- Sotalol: 90–200 mg/m^2 body surface area/day (2–3 single doses)

11.5.3 Class I antiarrhythmics

These antiarrhythmics block the fast Na influx into the cell with varying effects on the action potential. Class IC is most frequently used in children.

Class IA: quinidine and ajmaline
Prolongation of the action potential with prolongation of the QRS width and QTc, anticholinergic effect on the sinus node and AV node HR increases, AV conduction accelerates.

Indication: Brugada syndrome (ajmaline as challenge test).

Class IB: lidocaine (i.v. only) and mexiletine (orally only)
Shortening of the action potential of the ventricular myocardium, little effect on atrium and AV node.

Indication: Ventricular tachycardia, LQTS type 3.

Class IC: propafenone, and flecainide
No effect on action potential duration results in rate reduction in the atrium and ventricle and a conduction delay in the AV node and ventricular myocardium, hence possibility of QRS widening.

Indication: FAT, SVT with reentry mechanism (if adenosine and beta-blocker refractory), atrial flutter, atrial fibrillation.

Caveat If QRS widening > 20%, reduce propafenone dosage.

Oral dosage:

- Propafenone: 150–max. 300 mg/m^2 body surface area/day in 3 single doses or 8–20 mg/kg in 3 single doses (approx. 1 h before or after food, never with milk)
- Flecainide: 80–200 mg/m^2 body surface area/day in 2 single doses

11.5.4 Digoxin

Digoxin inhibits Na-K-ATPase, causing an increase in the intracellular Na concentration. This results in equalization of the intra- and extracellular Na concentration, lowering the concentration gradient necessary for calcium transport out of the cell, which depends on the Na-Ca exchanger. Calcium remains in the cell to an increased

Table 11.4 Digoxin dosage

Age group	Saturation dose	Maintenance dose
Neonates	0.01 mg/kg BW three times a day	0.0025 mg/kg BW twice daily
<25 kg	0.01 mg/kg BW three to four times a day	0.01 mg/kg BW twice daily
>25 kg	0.25 mg/m^2 BSA i.v. four times a day	0.2 mg/m^2 BSA once daily

BSA body surface area, *BW* body weight

extent and thus increases contractility (positive inotropic). Digoxin also has a negative chronotropic and negative dromotropic effect by a direct action on the central nuclei of the vagus nerve. This property enables digoxin to be used in patients with focal atrial tachycardia but also in atrial flutter or atrial fibrillation to reduce the conduction rate to the ventricle. The positive bathmotropic effect of digoxin should be noted, as this results in a reduction in the stimulation threshold, in addition to which it is proarrhythmic if overdosed and can result in ventricular fibrillation (cf. Table 11.4).

Caveat Do not use digoxin in patients with known ventricular arrhythmias.

Note Slow i.v. administration always by physician and always diluted. Beware of dose calculation error!

The following also are important:

- Strict establishment of the indication, only in combination with other antiarrhythmics (beta-blockers or sotalol).
- Regular determination of serum levels, target: 0.8–1.2 ng/mL.
- Elimination is entirely via the kidneys (Caution: renal failure!).
- Keep potassium constantly above 4 mmol/L.
- Where possible, do not give with amiodarone.
- Do not give in WPW syndrome (shortens antegrade effective refractory period of the accessory pathway, therefore increases risk of 1:1 conduction in atrial fibrillation).

11.5.5 Dosage of Antiarrhythmics in Acute Treatment of Cardiac Arrhythmias

See Table 11.5.

Figure 11.16 depicts a flow chart for the diagnosis and treatment of hemodynamically *unstable* tachycardia in children.

Figure 11.17 depicts a flow chart for the diagnosis and treatment of hemodynamically *stable* tachycardia in children.

Table 11.5 Dosage of antiarrhythmics in acute treatment of cardiac arrhythmias

Medicines	Dosage initial i.v. bolus	Drip infusion
Adenosine	0.1–0.3 mg/kg (rapid administration, as close to the heart as possible)	
Ajmaline	1.0 mg/kg over 5 min	
Amiodarone	5 mg/kg over 30 min	10–30 mg/kg/day
Atropine	0.01–0.04 mg/kg	
Esmolol	0.5 mg/kg over 1 min	50–200 µg/kg/min
Flecainide	1.0 mg/kg over 5 min	
Isoprenaline		0.01–0.5 µg/kg/min
Lidocaine	1 mg/kg (max. 4×)	20–50 µg/kg/min
10% Magnesium	0.1 ml/kg BW	1–2 ml/kg/day
Metoprolol	005–0.1 mg/kg BW	1–2 mg/kg/d
Orciprenaline	1.5–3.0 µg/kg slow i.v.	0.15–0.5 µg/kg/min
Propafenone	0.2–1.0 mg/kg over 5 min	4–10 µg/kg/min
Propranolol	0.1–0.2 mg/kg	
Verapamil	0.1 mg/kg BW i.v. max. 5 mg	(Children > 5 years)

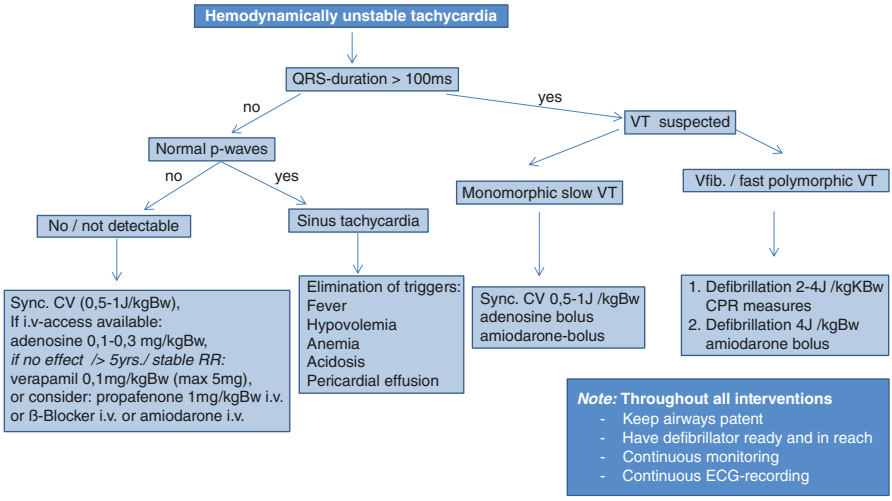


Fig. 11.16 Flow chart of diagnosis and treatment of hemodynamically unstable tachycardia in childhood

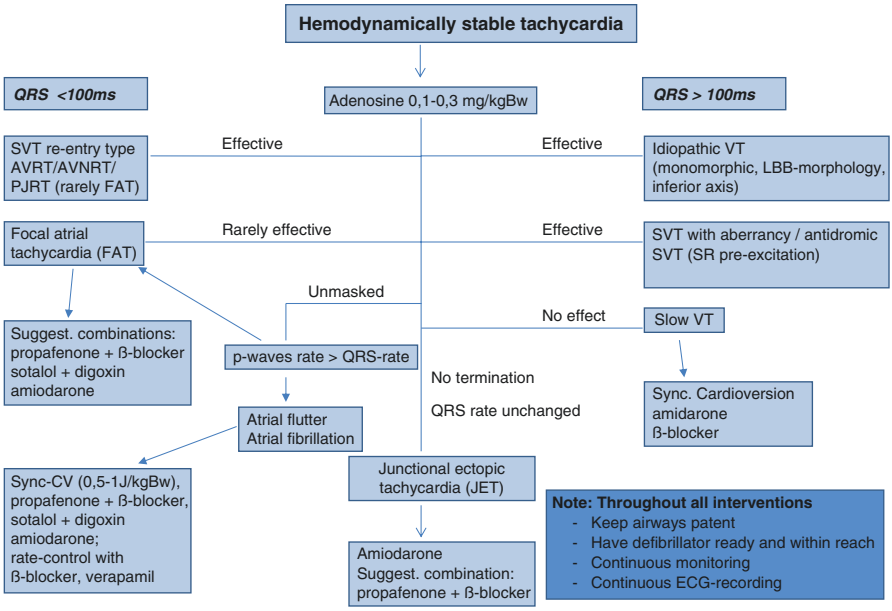


Fig. 11.17 Flow chart of diagnosis and treatment of hemodynamically stable tachycardia in childhood

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Resuscitation

12

Christoph Neuhaeuser and Dietrich Klauwer

Cardiopulmonary resuscitation (CPR) on the ICU usually involves patients with relevant risk factors (see Sect. 12.2), so that in many cases, preventive measures can be taken (e.g., rescue medication at the bedside, defibrillator and resuscitation board within reach, intubation material prepared, etc.). In addition, these patients are permanently on a monitor, so that developing resuscitation situations can be detected at an early stage.

12.1 Resuscitation: General Part

The latest recommendations are issued by the European Resuscitation Council (ERC) for children >1 month (pediatric life support, PLS) date from 2015 (update every 5 years).

In any emergency the *ABC rule* should be followed in principle (A = clear and maintain an **A**irway, B = maintain **B**reathing or ventilation, C = maintain or restore **C**irculation) and *call for assistance immediately!*

Basic life support (BLS) measures are not discussed further here (see ERC guidelines). CPR measures in the pediatric ICU correspond basically to the ERC guidelines for advanced life support (ALS).

(Note: any adaptations here are given in italics.)

C. Neuhaeuser (✉)
Pediatric Intensive Care Unit, Pediatric Heart Center of Giessen, Children's Heart Transplantation Center, UKGM GmbH, Giessen, Germany
e-mail: christoph.neuhaeuser@paediat.med.uni-giessen.de

D. Klauwer
Department of Pediatrics, Singen Medical Center, Gesundheitsverbund Landkreis Konstanz, Krankenhausbetriebsgesellschaft Hegau-Bodensee-Klinikum, Singen, Germany

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D. Klauwer et al. (eds.), *A Practical Handbook on Pediatric Cardiac Intensive Care Therapy*, https://doi.org/10.1007/978-3-319-92441-0_12

12.1.1 Chest Compression

- Rate:
  - 100–120/min
- Site:
  - Lower half of sternum (using xyphoid as a guide)
- Method:
  - Neonates, infants (<10 kg): two-thumb technique encircling the chest
  - Young children, school children: one-handed or two-handed technique
  - Adolescents/adults: two-handed technique
  - Alternation of compression and ventilation (two-rescuer method for all non-intubated patients)
  - Initial care for neonates: alternation of three compressions and one breath (3:1)
  - Children 1 month to 16 years: alternation of 15 compressions and 2 breaths (15:2)
  - Patients >16 years: alternation of 30 compressions and 2 breaths (30:2)
- Depth:
  - $^1/_3$ of the anteroposterior chest diameter (infants/young children, 4 cm; school-children, 5 cm; adolescents/adults, 5–6 cm)
- How to proceed:
  - Push hard and fast.
  - Complete relaxation of the chest at the end of the individual chest compression.
  - Do not interrupt if possible (except at moment of defibrillation).
  - CPR in bed only with resuscitation board.

12.1.2 Ventilation

- FiO_2:
  - Always 100% during CPR
  - Reduction after return of spontaneous circulation
  - Target SpO2 according to clinical features and previous disease, normally 94–98% (exception, cyanotic defects, hypoplastic left heart syndrome [HLHS], etc.)
- $PaCO_2$:
  - 35–55 mmHg, no hyperventilation (except pulmonary hypertensive crisis)
- Non-intubated patient:
  - Bag-valve-mask ventilation, where necessary with Guedel airway (during CPR, 10–12 breaths/min; after return of spontaneous circulation, 12–20 breaths/min)
  - Synchronization of compressions and ventilation (children >1 month, 15:2; > 16 years, 30:2)
  - Ensure effective chest excursions and complete relaxation
  - *No fear of aspiration in pediatric patients (children die of hypoxia, not of aspiration)*

- Intubated patient:
  - *Where necessary, switch to volume-controlled ventilation (and adapt pressure alarm, e.g., 35–40 mmHg)*
  - *Respiratory rate: as a guide for compression rate, RR can be set as follows:*
  - *Neonates/infants: e.g., RR 40/min (Ti = 0.5 s, Te = 1.5 s); 3 × compressions per breath = rate 120/min*
  - *Young children: e.g., RR 40/min (Ti = 1.0 s, Te = 2.0 s); 5–6 × compressions per breath = rate 100–120/min*
  - *Adolescents: e.g., RR 40/min (Ti = 1.5 s, Te = 2.5 s); 7 × compressions per breath = rate 105/min*
  - *Tidal volume: about 10 mL/kg*
  - Non-synchronized CPR possible
  - If necessary, manual ventilation by ventilation bag
- $etCO_2$:
  - Helpful in confirming the correct position of the tube and as a trend parameter of circulation during CPR (e.g., PetCO2 increases with increasing CO).
  - The displayed PetCO2 can differ considerably from the measured PaCO2 (PetCO2 < PaCO2) during CPR and is therefore not suitable for adapting the ventilation.

12.1.3 Airway Management

- Endotracheal Intubation:
  - In an emergency: oral.
  - Continuous CPR with bag-valve-mask ventilation is better than interrupting CPR for intubation for more than 1–2 min.
  - Intubation has the advantage of maintaining the airway and the possibility of "non-synchronized" CPR and ventilation with higher FiO2 as well as PEEP.
  - The Sellick maneuver to close the esophagus is no longer generally recommended.
- Tube:
  - Uncuffed tubes: <8 years.
  - Cuffed tubes: >8 years.
  - Cuffed tubes (e.g., Microcuff) can be used from the neonatal period onward (from ID 3.0) (correct choice, standard tube internal diameter (ID) – 0.5 = ID of Microcuff tube).
- Alternatives:
  - Laryngeal mask (LM 1, < 5 kg; LM 1.5, 5–10 kg; LM 2, 10–20 kg; LM 2.5, 20–30 kg; LM 3, 30–50 kg)
  - Guedel airway and bag-valve-mask ventilation (Guedel airway only in unconscious child; correct size; measured from incisors to angle of the jaw)

12.1.4 Defibrillation

- Indication:
  - Pulseless ventricular tachycardia and ventricular fibrillation
- Energy:
  - 4 J/kg (max. 360 J)
  - Monophasic or, better, biphasic
- Paddles:
  - <10 kg (<1 year): small defib paddles (Ø 4.5 cm)
  - >10 kg (<1 year): large defib paddles (Ø 8–12 cm)
  - Small or large adhesive pads, if available
  - If in doubt: largest possible contact area
- Position:
  - Anterior posterior position (when using adhesive pads in children <8 years, one adhesive patch on the chest and one on the back)
  - Anterolateral position (1. when using adhesive pads in children >8 years, one beneath the right clavicle and one beneath the left axilla; 2. when using age-commensurate defibrillator paddles at any age)
- Technique:
  - Apply good amount of gel to paddles and press down firmly for shock.
- Time:
  - Immediately in the case of pulseless ventricular tachycardia (VT) and ventricular fibrillation (CPR should be administered until defibrillator is ready and charged).
  - The prospect of successful defibrillation recedes with each minute lost (reduction in probability of survival by 7–10% per minute lost).
  - According to the guideline, the application of only one shock is recommended, followed by the immediate resumption of CPR (without checking circulation after defibrillation).
  - *As an alternative to this recommendation, it may be useful if a "shockable rhythm disorder" occurs on the ICU to defibrillate up to three times in succession (without intervening CPR) to increase the success of defibrillation and to restore spontaneous circulation as rapidly as possible.*

12.1.5 Intravenous/Intraosseous Access

- An i.v. access is generally present in ICU patients.
- Intraosseous (i.o.) access:
  - If there is no i.v. access, the creation of an i.o. access is the quickest, most effective, and safest procedure (achievable within 1 min).
  - Children <6 years: proximal, medial, tibial plateau, 1.5–2.0 cm below the tibial tuberosity.
  - Children >6 years: distal, medial tibia, 2.0–3.0 cm superior to the malleolus.
  - I.o. drill: 3–39 kg, 15 G 15-mm needle; ≥40 kg, 15 G 25-mm needle.
  - Cook i.o. needle: >1 month, 18–20 G; 1–6 months, 16–14 G; 6–18 months, 14 G; >18 months, 14 G.

12.1.6 Medications

- All medications should be administered i.v. (alternatively i.o.)!
- Adenosine (1 mL = 3 mg):
  - Bolus of 100–200–400 µg/kg BW i.v./i.o. (in 3–5 mL 0.9% NaCl).
  - In supraventricular tachycardia.
  - In this scenario, the circulation is generally maintained (i.e., no CRP).
  - Where possible, administer via CVC or as rapid peripheral bolus.
  - Caution should be exercised when using adenosine in asthmatics, 2nd or 3rd degree AV block, long QT syndrome, and heart transplant patients.
- Adrenaline (1 mL = 1000 µg):
  - Bolus of 10 µg/kg BW (max. 1 mg) i.v./i.o. every 3–5 min.
  - In *shockable* (pulseless VT, ventricular fibrillation) and in *non-shockable* circulatory arrest (asystole, pulseless electrical activity).
  - *In patients on the ICU, who are usually resuscitated immediately after the onset of circulatory arrest and who have therefore not yet developed severe acidosis, the dose of 10 µg/kg BW is often too high and (particularly on repeated administration) can result in (sometimes extreme) hypertension and tachycardia after return of spontaneous circulation.*
  - *Therefore, on the ICU: 2–5–(10) µg/kg BW i.v. every 3–5 min (draw up in larger volume, e.g., 5–10 mL).*
- Amiodarone (1 mL = 50 mg):
  - Bolus of 5 mg/kg BW i.v./i.o.
  - In pulseless VT or ventricular fibrillation after the 3rd (unsuccessful) shock.
  - *In our experience, early administration of amiodarone, e.g., already after the first unsuccessful defibrillation, is beneficial in ventricular fibrillation.*
  - As i.v. bolus in circulatory arrest.
  - In tachycardiac arrhythmia (supraventricular tachycardia [SVT] or VT) in which the circulation is maintained, as a short-term infusion over 20 min. This is because a bolus dose can cause severe hypotension.
- Atropine (1 mL = 500 µg):
  - According to the guideline, *only* recommended now in vagus-induced bradycardia or cholinergic intoxication (*no longer* in non-shockable circulatory arrests)
  - Bolus of 25 µg/kg BW (max. 2 mg)
- 10% Magnesium sulfate (1 mL = 100 mg $MgSO_4$):
  - According to the guideline, *not* for routine use
  - Can be administered in patients with confirmed hypomagnesemia or a torsade de pointes VT (dose, 25–50 mg/kg BW i.v./i.o.)
- 8.4% Sodium bicarbonate (1 mL = 1 mmol):
  - According to the guideline, *not* for routine use.
  - In cases of prolonged CPR (after >20 min or more than 3–4 doses of adrenaline), severe acidosis (BE < −15 mmol/l), hyperkalemia (K > 5 mmol/L), intoxication with tricyclic antidepressants, and hemodynamic instability, sodium bicarbonate can be given (dose, 0.5–1.0 mmol/kg BW i.v./i.o.).
  - *In patients on the ICU, "early" buffering may also be useful in mild acidosis (BE < −2 mmol/L) in specific situations (e.g., PHT).*

- Lidocaine (1 mL = 10 mg):
  - According to the guideline, *not* the drug of 1st choice in pulseless VT or ventricular fibrillation (dose, 1–2 mg/ kg BW i.v./i.o.)
- Vasopressin (Pitressin 1 mL = 20 IU):
  - According to the guideline, *not* for routine use
  - Can be used in circulatory arrest if repeated doses of adrenaline demonstrate no effect (dose, 0.2–0.5 IU/kg BW (max. 40 IU) i.v./i.o.)

12.1.7 Monitoring

- ECG, SpO_2, noninvasive BP measurement, and $etCO_2$ (usually present in intensive care patients, including arterial BP measurement)
- *In patients on the ICU also always: CVP, BGA* (*with electrolytes, blood glucose*, *and lactate*), *echocardiography,* and *chest X-ray*

12.1.8 Exclusion of Reversible Causes (4 Hs and 4 Ts)

- 4 Hs:
  - *H*ypoxia
  - *H*ypovolemia
  - *H*ypo- or hyperkalemia
  - *H*ypothermia
- 4 Ts:
  - Cardiac *t*amponade
  - Drug *t*oxicity (e.g., digitalis)
  - *T*hromboembolism (pulmonary or coronary)
  - *T*ension pneumothorax
- Incidence: high during resuscitation on the ICU

12.1.9 Extracorporeal Membrane Oxygenation (ECMO)

- To be considered in treatment-refractory circulatory failure during or after CPR
- Prompt notification of cardiac technician (perfusionist) and heart surgeon

12.1.10 Algorithms

According to the current ERC guideline for ALS, the procedure in an unconscious child with suspected circulatory arrest is as follows:

- *If* the child does not respond to stimulation (or pain stimuli):
  - *Then* call for assistance immediately in the hospital (e.g., resuscitation team).
  - Subsequently establish a clear airway (remove foreign material under visual control, slightly overextend head, Esmarch maneuver, suctioning of secretions, etc.).
- *If* no breathing or agonal respiration:
  - *Then* 5 (initial) breaths with the ventilation bag (if necessary Guedel airway) and ventilation bag with O_2 reservoir and high O_2 flow (e.g., 15 L/min).
- *If* no signs of life or central pulse (e.g., axillary artery, carotid artery) observable within 10 s:
  - *Then* start CPR with 15 chest compressions (cardiac massage, see above), followed by 2 breaths (two-rescuer method with 15:2).
- At the earliest possible moment: defibrillator rhythm diagnosis (ECG lead via paddles, adhesive pads, or ECG electrodes possible).

If the ECG shows *pulseless electrical activity (PEA)* or *asystole* (in three leads), the procedure depicted in Fig. 12.1 (PALS = pediatric advanced life support) is followed (simplified outline).

In other words, continuous CPR (15:2) is performed, and the rhythm is checked every 2 min on the ECG (see Fig. 12.2). In PEA/asystole, an i.v./i.o. access should be created immediately and in parallel with CPR by a 3rd person to allow early administration of 10 µg/kg BW adrenaline i.v./i.o. (repeated every 3–5 min). Intubation can be performed at any time but should not entail prolonged interruption of CPR (max. 1–2 min).

If the ECG shows *ventricular fibrillation* (VF) or *pulseless VT*, the procedure depicted in Fig. 12.3 is followed (simplified outline).

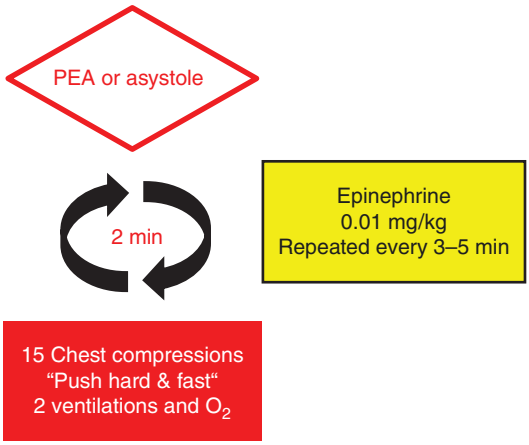

Fig. 12.1 Pediatric advanced life support: "Nonshockable Rhythm": Asystole/PEA

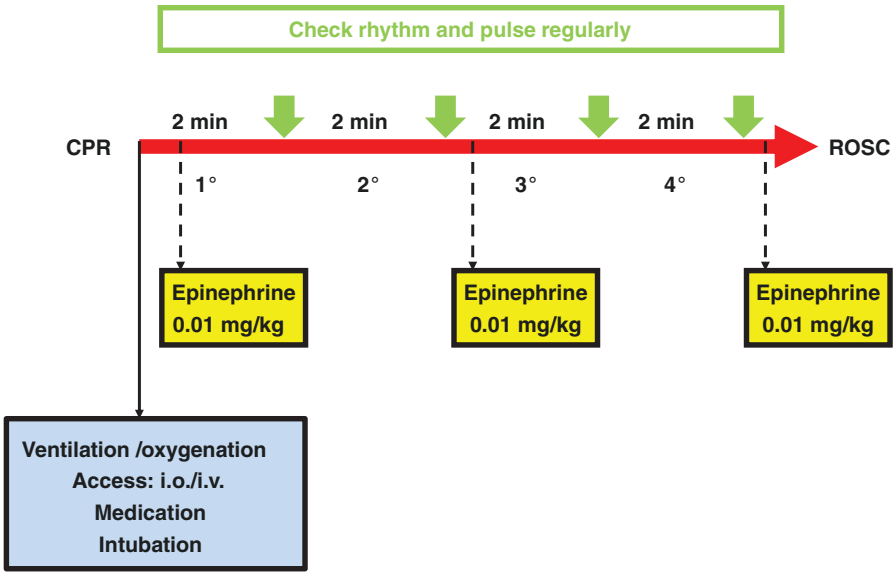

Fig. 12.2 Cardiac arrest: "Nonshockable Rhythm"

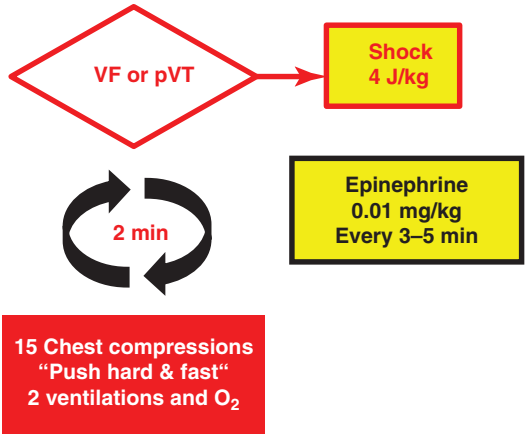

Fig. 12.3 Pediatric advanced life support: "Shockable Rhythm": VF/ Pulseless VT (pVT)

As soon as ventricular fibrillation or VT is diagnosed, CPR (15:2) is interrupted, and a shock of 4 J/kg is delivered immediately by defibrillator (ensure the assistant is safe). CPR is then continued without checking the circulation further. The rhythm should be checked every 2 min on the ECG and a shock given if ventricular fibrillation/VT persists (see Fig. 12.4). After the 3rd unsuccessful defibrillation, the 1st dose of adrenaline (10 µg/kg BW i.v./i.o.) and the 1st dose of amiodarone (5 mg/kg i.v./i.o.) are administered an i.v./i.o. access should therefore be created immediately and in parallel with the CPR by a 3rd person. The dose of adrenaline is repeated every 3–5 min, while the resuscitation is continued. After the 5th unsuccessful defibrillation, the 2nd dose of amiodarone is given. Intubation

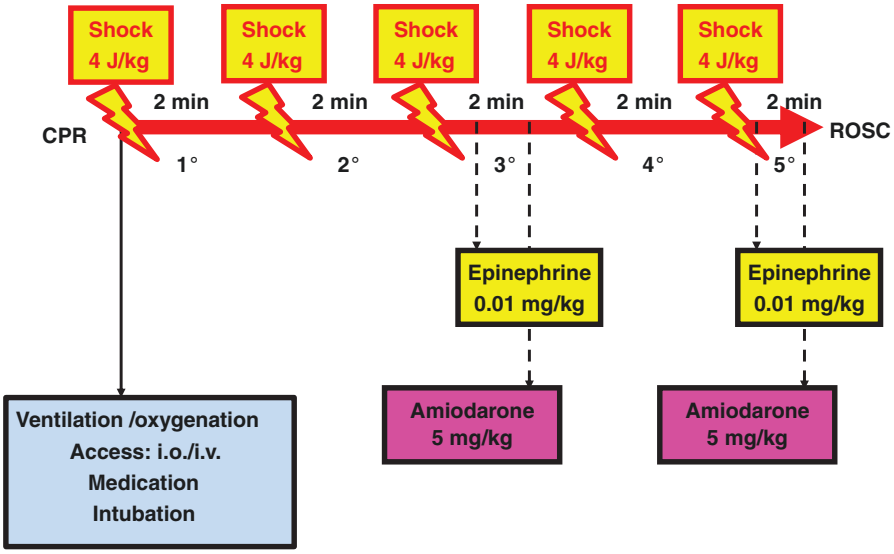

Fig. 12.4 Cardiac arrest: "Shockable rhythm"

can be performed at any time but should not entail prolonged interruption of CPR (max. 1–2 min).

Cessation of the resuscitation measures may be considered in the following situations:

- Spontaneous circulation could not be achieved after 45–60 min (reversible causes excluded, ECMO not an option).
- A poor (neurologic) prognosis is likely, e.g., after "warm" hypoxia or asphyxia >10 min, SIDS (sudden infant death syndrome), or CPR following trauma.
- The patient's prior neurologic conditions or general prognosis is unfavorable (case-by-case decision).
- On no account should the resuscitation measures be ended prematurely in patients who have suffered a hypothermic circulatory arrest (i.e., in a hypothermic environment) (rewarming with a heart-lung machine if necessary).
- By hypothermia is not meant the poikilothermia that often also develops during resuscitation (e.g., at room temperature of 18–20 °C).
- If circulatory arrest persists despite a core body temperature > 30–32 °C and sufficient resuscitation measures for >45 min (see above), the possibility of ceasing may be considered.

12.2 Resuscitation: Special Part

In patients in the pediatric cardiac ICU, special measures frequently have to be taken to prevent resuscitation situations arising because of the specific anatomic and pathophysiologic features. The CPR itself may also differ from the ERC guidelines in some aspects. Some of the typical situations in pediatric cardiology are discussed below.

12.2.1 Information that Must Be Known About Every Cardiological Patient

- What is the underlying cardiac condition?
- What surgical correction was performed?
- When did the patient undergo surgery?
- What cardiovascular treatment is already present?
- What preceded the emergency situation (context)?
- Which medicines might be responsible (e.g., digitalis)?
- What additional diseases are present (organ insufficiency?)?
- Is the patient anticoagulated (PTT-effectively? Marcumar?)
- Is the patient wearing a pacemaker or ICD (implantable cardioverter-defibrillator)?
- Are there any limiting factors for the prognosis?

Some specific causes of a resuscitation situation and the related measures are discussed below.

12.2.2 Pulmonary Hypertensive Crises (See Also Chap. 9)

Children with already pathologically increased pulmonary vascular resistance (PVR) have a tendency to pulmonary hypertensive crises in situations of stress and/or hypoxemia (e.g., deep oral suctioning without precautions). Occasionally the episodes occur without any identifiable stimulus.

Acute right heart failure develops as a result of massive pulmonary vasoconstriction. The high pulmonary afterload prevents the RV from being able to eject adequately, as a result of which the right ventricular end-diastolic volume (EDV) increases dramatically and the interventricular septum is displaced to the left (ventricular interdependency). Left ventricular filling is obstructed, and left ventricular stroke volume falls (internal tamponade), resulting in arterial hypotension. Critically reduced coronary perfusion pressure and pathologically increased wall tension can cause myocardial ischemia with circulatory arrest (VT/ventricular fibrillation possible, but bradycardia/asystole more common).

In hospital, the acute pulmonary hypertensive crisis usually presents as a sudden fall in SpO_2 and arterial blood pressure (with a concomitant increase in PAP and CVP). If treated promptly, circulatory arrest usually does not occur.

Measures

Most patients who exhibit these problems are still intubated and ventilated. The resuscitation situation is usually provoked (i.e., staff are at the bedside) and of short duration (1–20 min).

Minor crises can be controlled by sedation alone (e.g., 1–2 mg/kg BW propofol bolus and 1–2 mg/kg BW ketamine bolus; relaxation if necessary) and hyperventilation (bag ventilation if necessary) with high FiO_2 (if the patient is receiving NO, the bag should be connected to the NO source in the case of bag ventilation: 15 L/min O_2 ~ 10 ppm NO depending on the type of bottle).

In severe episodes with impending circulatory arrest, the primary concern is to maintain coronary perfusion pressure and cardiac output. Therefore, following a critical fall in blood pressure, cardiac compression should be started in addition, and vasopressors should be given (5 µg/kg BW noradrenaline or adrenaline bolus i.v.). Vasopressin may be of benefit here as it causes systemic but not pulmonary vasoconstriction. I.v. pulmonary vasodilators (e.g., iloprost (Ilomedin), PGI2 (Flolan), adenosine (Adrekar), etc.) should be avoided here because of their systemic effects in the resuscitation situation. However, they can be used subsequently in the stabilization phase. In addition, NO should be initiated at 20–40 ppm (if not already administered). There is a generous indication for the use of sodium bicarbonate in pulmonary hypertensive crises.

To prevent further crises, analgosedation must also be deepened (additional relaxation if required), particularly before manipulations on the patient.

12.2.3 Decompensation in Cardiomyopathy (See Also Chap. 14)

Decompensation of dilated cardiomyopathy

Patients with DCM frequently have a dramatically low ejection fraction (e.g., EF <10%) and a very large left ventricular EDV with high wall tension. If acute decompensation develops, this usually results in a state of shock with arterial hypotension. In this context, malignant arrhythmias frequently occur (e.g., runs, torsades, VT, ventricular fibrillation), which may result in the development of a resuscitation situation.

This also applies to patients with severe myocarditis.

Measures

Patients with pulseless arrhythmias must be defibrillated immediately. In circulation-depressing arrhythmias in which pulses are still palpable, synchronized cardioversion (i.e., R wave triggered) with 1–2 J/kg is performed in SVT or VT. The determination and, where required, correction of electrolytes (particularly potassium, magnesium, and calcium) are also necessary, as for any resuscitation. In terms of antiarrhythmics, amiodarone may be considered and also magnesium in the event of torsades.

Circulatory stabilization is sometimes difficult in patients with DCM. In a resuscitation situation, adrenaline boluses (5–10 µg/kg BW) are given, followed by a drip infusion (if necessary milrinone, levosimendan – *beware*: hypotension!). Monitoring (echocardiogram, CVP) is required if volume replacement is performed in order to prevent an increase in wall tension.

The cardiac surgeon should be informed in good time in order to stabilize the patient if necessary by ECMO or CPB. The benefit of an assist device (e.g., Berlin Heart) should then be discussed.

Decompensation of hypertrophic cardiomyopathy with dynamic obstruction of the left ventricular outflow tract

In patients with hypertrophic obstructive cardiomyopathy (HOCM), a hypercontractile state of the heart can occur in a stressful situation. Because of the high

muscle mass and the small, pin-shaped left ventricular cavity, filling is impaired. If the contractility of the heart increases, a reduction in LV filling and hence in SV occurs because of the massive relaxation disorder. In addition, the dynamic obstruction in the left ventricular outflow tract impairs the ejection of the heart (obstruction becomes larger with increased contractility). This results in arterial hypotension with a decrease in coronary perfusion pressure. As the inner layers of the hypertrophic myocardium are already borderline perfused at rest, myocardial ischemia develops rapidly as perfusion pressure falls.

Measures
Resuscitation after circulatory arrest in HOCM is difficult and often unsuccessful. Everything must therefore be done to ensure it does not come to that point.

If a minimal circulation is still present, administration of betamimetic catecholamines must be strictly avoided (contraindication!). Instead, sedation (e.g., 0.1 mg/kg BW morphine) and a beta-blocker (e.g., 0.5 mg/kg esmolol), or alternatively sedation and a Ca antagonist (e.g., 0.1 mg/kg BW verapamil), should be given to try to abolish the hypercontractility of the heart muscle. In addition, an attempt must be made to increase left ventricular SV and stabilize blood pressure by volume administration and vasopressors (e.g., noradrenaline or phenylephrine) (*caution*: risk of pulmonary edema!). Defibrillation is performed in pulseless VT or ventricular fibrillation, or else amiodarone can be given. As a low SVR with hypotension is unfavorable in these patients, administration of vasopressin (0.1–0.5 U/kg BW) provides an option for raising SVR without a positive inotropic (side) effect. (Similar considerations also apply to patients with ventricular hypertrophy with outlet stenoses.)

12.2.4 ST Segment Changes with Presumed Myocardial Ischemia

1. Because of incomplete air removal from the heart, air embolisms can occur postoperatively in the coronary arteries (typically moving into the right coronary artery with ST elevation in II, III, aVF, and V5–V6).
2. In surgery on the coronary arteries (Ross procedure, switch surgery, surgery for Bland-White-Garland syndrome) or coronary anomalies (intramural trajectory, atypical outlet, stenoses, etc.), myocardial ischemia can occur following a fall in perfusion pressure. Thromboembolic closures are also possible.
3. Low diastolic blood pressure (<20–25 mmHg) with, e.g., a systemic-to-pulmonary artery shunt, PDA, aortic insufficiency, or arterial hypotension can also result in myocardial ischemia.

Measure
Re 1: In the event of an air embolism (air possibly in the left atrial auricle detectable by echocardiography), arterial blood pressure must be raised, for example, by 1–5 µg/kg BW noradrenaline. In addition, FiO_2 can be increased to 100% to obtain more rapid resorption of the pulmonary embolism. ST elevations usually resolve within the next 12–24 h.

Re 2: In the event of ischemic ST segment changes (elevations, depressions) following surgery on the coronary arteries, the blood pressure should also be adjusted to high-normal levels (e.g., noradrenaline drip). In addition, the surgeon must be informed in order to discuss the subsequent procedure (e.g., surgery, anticoagulation, etc.). ECMO therapy can provide an option in circulatory collapse.

Treatment by intraaortic balloon pump (counterpulsation) (IABP) represents an option in larger children as long as the heart is still ejecting (the effect is to increase diastolic blood pressure and hence coronary perfusion while at the same time reducing afterload).

Re 3: If ST segment changes occur in conjunction with low diastolic blood pressure, this can be increased by means of a noradrenaline drip. In the case of a systemic-to-pulmonary artery shunt, a discussion is required as to whether too large a shunt has been chosen and needs to be revised. In aortic insufficiency and PDA, noradrenaline is counterproductive in the longer term. Surgical correction should be the aim here as well.

Short-term resuscitation situations also occur not infrequently in conjunction with a low output syndrome with hypotension. Although catecholamines are already running, coronary perfusion pressure is insufficient in the short term, and brief CPR and a catecholamine bolus (adrenaline or noradrenaline) are required to "jump-start" it. The circulatory and ventilatory conditions must be reassessed in these patients once the acute situation has been resolved (echocardiography).

12.2.5 Acute Pericardial Tamponade (See Also Chap. 8)

A progressively developing hypotension (paradoxical pulse, where applicable) with sinus tachycardia and a (usually) pathologically high CVP should point to pericardial tamponade. This is frequently preceded by the cessation of drain flow (blockage or thrombosis of the drains with the simultaneous persistence of bleeding or effusion formation). The presumptive diagnosis is confirmed by echocardiography.

Measure
"Milking" can be employed to try to relieve tamponade via the drains. The treatment of acute pericardial tamponade with circulatory collapse is immediate surgical relief. In an emergency, this can be done on the ward by opening the chest (cutting the sutures or using a wire cutter to cut through the sternum wires). With a serous effusion, obviously the ultrasound-guided insertion of a pigtail catheter may be sufficient. Before unloading, as well as volume replacement, adrenaline can be used as a catecholamine for circulation stabilization, as SV is relatively fixed in cardiac tamponade and CO is therefore rate-dependent.

12.2.6 Cardiac Arrhythmias

Tachycardiac arrhythmias (see also Chap. 11)
A distinction is drawn between pulseless tachycardia (VT, ventricular fibrillation) and tachycardia in which the circulation is preserved. For a detailed description of

Table 12.1 Overview of resuscitation measures in ventricular tachycardia (VT)

VT – residual circulation maintained	VT – residual circulation depressed	VT/fibrillation without circulation
Monitoring: ECG, BP, SpO_2, BGA, electrolytes	ABC measures, defibrillator, and ECG	ABC measures, CPR, until defibrillator charged
Amiodarone, initially: 5 mg/kg BW as short-term infusion; drip: 10–20 mg/kg/d	Cardioversion in sedation: 1–2 J/kg BW synchronized (i.e., R wave triggered)	Immediate defibrillation: 4 J/kg (up to 3 times), then continue CPR as per algorithm (adrenaline boluses)
Defibrillator and readiness for CPR	Amiodarone, initially: 5 mg/kg BW as short-term infusion; drip: 10–20 mg/kg/d	Amiodarone, initially: 5 mg/kg BW as short-term infusion; drip: 10–20 mg/kg/d
Electrolyte therapy (KCl, magnesium)	Electrolyte therapy (KCl, magnesium)	Electrolyte therapy (KCl, magnesium)

tachycardiac arrhythmias, see Chap. 11 (e.g., junctional ectopic tachycardia [JET], SVT, atrial fibrillation with rapid conduction, torsade de pointes, etc.).

It may generally be assumed in cardiology patients that any sudden loss of consciousness (syncope) or any sudden circulatory collapse is caused by a malignant arrhythmia until proven otherwise. Therefore, in these cases, the defibrillator must be used immediately (Table 12.1).

Measures

Until the defibrillator is ready for use (apply gel to paddles or position adhesive electrodes, charge defibrillator), the ABC rule should be followed and CPR performed (as described above). In patients on the ICU who exhibit a pulseless VT or ventricular fibrillation on monitoring, the most effective measure for restoring spontaneous circulation is immediate and repeated defibrillation (up to three times). In our experience, it is helpful in these situations to initiate amiodarone early (right after the first unsuccessful defibrillation).

If the tachycardia persists with depressed but preserved circulation (e.g., VT, SVT), synchronized cardioversion should be performed (according to ERC guideline with 1 J/kg). If consciousness is still preserved, short analgosedation (e.g., 0.5–1 mg/kg BW propofol i.v., 1–2 mg/kg BW ketamine i.v.) should be given for cardioversion.

Bradycardiac Arrhythmias

Circulatory collapse in association with bradycardia occurs in particular with 3rd degree AV block and vagus-induced asystole.

Measures

Bradycardiac arrhythmias can easily be controlled in the postoperative phase by means of a pacemaker via the thoracic pacing wires (see Chap. 11). The time until the pacemaker is ready should be bridged by CPR (in neonates CRP may be started, if the HR drops <60/min). Atropine and/or adrenaline helps in vagus-induced bradycardia/asystole.

12.2.7 Thromboembolic Complications (See Also Chap. 8)

1. In acute thromboembolic systemic-to-pulmonary artery shunt closure, the lung is no longer sufficiently perfused (residual perfusion possibly via original pulmonary vessel or collaterals) and severe life-threatening hypoxia results.
2. Acute pulmonary embolisms (PE) are fairly rare in children (risk factors, central catheter, immobilization, postpubertal age, thrombophilia, sickle cell anemia, cyanotic heart defects, infections, and malignancies). The diagnosis can be made by ultrasound or spiral CT. In acute PE, the sudden increase in right ventricular afterload (with >60% displacement of the cross section of the pulmonary circulation) results in acute right heart failure. The same vicious circle occurs as that already described in Sect. 12.2.2.
   Circulatory collapse usually occurs with Fontan circulation, whereas with a hemi-Fontan, there is upper inflow congestion and severe cyanosis (with possible preservation of the circulation).

Measures
Re 1: If the circulation is still preserved, blood pressure can be increased by means of noradrenaline (e.g., 5 µg/kg BW i.v.) in order, where necessary, to obtain pulmonary perfusion via collaterals or a residual lumen in the systemic-to-pulmonary artery shunt. A heparin bolus (50–100 IU/ kg BW i.v.) should be given to prevent further thrombosis. Lysis by r-tPA may be considered (but not within the first few days postoperatively). Following circulatory collapse, intubation and ventilation with FiO_2 = 100% should be undertaken together with prolonged CPR. Immediate emergency surgery with a heart-lung machine or ECMO treatment can also be lifesaving.

Re 2: In PE with circulatory collapse, on the one hand, coronary perfusion pressure and right ventricular function must be maintained (adrenaline, noradrenaline, if necessary vasopressin), and on the other hand, the obstruction in the pulmonary circulation must be removed (lysis with r-tPA, e.g., alteplase 0.5 mg/kg BW/h over 6 h; total dose <100 mg). In this case too, a heparin bolus is given.

Since lysis is dangerous in the immediate postoperative period, surgical embolectomy should be discussed with the surgeon in such cases.

12.2.8 Postoperative Electrolyte Disorders (See Also Chap. 5)

Hyperkalemia (>6.0 mmol/L) and hypokalemia (<3.0 mmol/L) are particularly dangerous, and further risk factors also need to be borne in mind (e.g., digoxin). Hypokalemia is often combined with hypomagnesemia.

Measures
Correction is best performed according to the measured value (BGA). In malignant arrhythmias associated with severe hypokalemia (<2.5 mmol/L), a potassium bolus of 0.1–0.5 mmol/kg BW can be given by slow i.v. infusion (over 10–20 min)

Table 12.2 Treatment of hyperkalemia

Causes	Tumor lysis, hemolysis, rhabdomyolysis	Anuria	Adrenal insufficiency	Tubular acidosis	Iatrogenic
ECG changes	High T	Long PR interval	Missing P	QRS wide	VT asystole
Treatment	Calcium gluconate 10% 0.5–1 ml/kg BW i.v.	10 IU insulin in 500 ml 10% glucose: 5 ml/kg i.v. = 0.1 IU/kg BW insulin and 0.5 g/kg glucose		Beta-2-mimetics, Sodium bicarbonate, Lasix, Resonium	CVVHDF

followed by a potassium drip. It is also useful to correct the usually concurrent magnesium deficiency (e.g., 10% magnesium sulfate 25–50 mg/kg BW i.v. over 10 min) (Table 12.2).

In hyperkalemia with arrhythmias, calcium should be administered initially to antagonize the electrophysiological effects at the myocardial cell membrane (no effect on potassium levels). The most effective measure for reducing potassium levels is then an insulin-glucose bolus (see below) followed by a drip infusion. In patients with renal impairment, only CVVHDF is of any use in the longer term.

Calcium In prolonged resuscitation with asystole of uncertain origin, calcium should be given because of the suspicion of hyperkalemia (preferably after BGA).

12.2.9 Fontan Circulation (See Also Chap. 15)

The resuscitation of children with Fontan or Glenn circulation presents a particular challenge. A determining factor in the restoration of minimal circulation with CPR in this situation is probably the thoracic pressure difference between inspiration and expiration on bag ventilation. In inspiration, the blood is forced out of the lung and fills the univentricular heart, whereas in expiration blood can flow into the lung. Obviously in this case, a negative intrathoracic pressure would be ideal (e.g., by active compression-decompression resuscitation or negative pressure ventilation). In practice, however, this is rarely achievable in children with CPR. Alternatively, to optimize filling of the lung during expiration, peripheral venous pressure can be increased (increase in the pressure gradient between peripheral and central veins). Alternating massage of the chest and abdomen, for example, has been proposed to this end. As coordination is difficult, complications are frequent, and the effectiveness is questionable, this procedure (however) is no longer recommended.

Measures
Volume replacement is used to try to improve filling (e.g., very large quantities of fluid are necessary; possibly also raising the legs in larger children). Additionally,

noradrenaline (5–10 µg/kg BW) or vasopressin (0.1–0.5 U/kg BW) can be given for centralization to increase the perfusion pressure. Otherwise, CPR is performed according to the ERC guidelines, ensuring good coordination between chest compression and ventilation (probably always better here to resuscitate in synchronized fashion).

12.2.10 Tetralogy of Fallot (See Also Chap. 16)

Tetralogy of Fallot (TOF) children with critical pulmonary stenosis or dynamic obstruction of the right ventricular outflow tract can (prior to surgical correction) suffer cyanotic attacks in conjunction with stress, hypoxemia, or infections (increase in PVR, decrease in SVR). In addition to the acute R/L shunt via the VSD (into the aorta), the hypertrophic RV can exhibit a relaxation disorder with insufficient filling and a decrease in CO. During the cyanotic attack, the otherwise loud systolic murmur becomes softer.

Measure
As with the management of a crisis in HOCM, action must be taken rapidly and decisively in the child with a cyanotic crisis to prevent a resuscitation situation. Betamimetic catecholamines are also contraindicated here. Mild sedation with morphine (0.1 mg/kg BW i.v.) or ketamine (1 mg/kg BW i.v.) and a squatting position (legs on the abdomen) usually help. It is essential to administer high concentration oxygen, even if the effect can initially be slight or delayed (as long as the blood flows past the lung). In severe cases esmolol (0.5 mg/kg BW i.v.) and sodium bicarbonate (0.5–1 mmol/kg BW i.v.) can help. A vasopressor may also be necessary (noradrenaline or vasopressin) to increase SVR (decrease in R/L shunt).

In a resuscitation situation, emergency surgery with extracorporeal circulation (creation of an AP shunt if necessary) should be considered.

12.2.11 Duct–Dependent Defects (See Also Chap.15)

A distinction is drawn between defects with duct-dependent pulmonary perfusion (e.g., TAT, PAT, TOF, critical PS), duct-dependent mixing (e.g., TGA), and duct-dependent systemic perfusion (e.g., HLHS, CoA, IAA, critical AST). Following closure of the ductus, severe cyanosis occurs in the first two cases, while in the latter a state of shock develops.

Measure
As the individual heart defects are discussed in detail in the specific part of the book, the importance of immediate PGE1 administration (50–100 ng/kg/min) is referred to again here only briefly. In HLHS, hyperventilation also should be avoided, and FiO_2 should be adapted to the situation (if possible, no additional O_2: target SpO_2 75–85%).

12.2.12 Hypoxia

Out-of-hospital resuscitation in children (particularly infants and young children) is to a large extent due to hypoxic dysoxia (i.e., respiratory arrest occurs before cardiac arrest). As the dysoxic tolerance of the brain is lower (about 5 min in normothermia) than that of the heart, the neurologic prognosis is poor if (the) children are discovered in circulatory arrest (primary resuscitation success possible, secondary resuscitation success uncertain). Patients who become hypothermic before the onset of hypoxemia (e.g., near-drowning victims in winter) represent an exception. The dysoxic tolerance of the brain is prolonged as core body temperature decreases (up to about 45 min at a core body temperature of 18 °C).

The prognosis for children who develop hypoxia in hospital is considerably better (monitoring, more rapid action possible). The crucial factor here is that hypoxia can be abolished rapidly by decisive airway management (A and B) and oxygen administration.

Hypoxia-induced resuscitation situations tend to be rare in the pediatric cardiac ICU. Children under 6 years of age and patients with Down's syndrome are particularly affected:

- Postextubation apnea due to obstruction of the upper airway (e.g., muscle hypotonia in the oropharynx or hypopharynx, swelling, membranes, malacia, stenoses) or spastic reactions (e.g., laryngospasm)
- Apnea and/or hypoventilation (particularly premature infants and neonates; as a result of opioids or PGE1 therapy)
- Acute status asthmaticus or allergic reactions
- Tension pneumothorax
- Aspiration
- Ventilation difficulties in the intubated patient in a "DOPE" situation (D = dislocation, O = obstruction, P = pulmonary problem (pneumothorax, unilateral intubation), E = equipment failure).

Measures

Establishment of an airway (remove foreign material under visual control, slightly overextend head, Esmarch maneuver, suctioning, etc.) and bag-valve-mask ventilation with a high O_2 concentration (O_2 reservoir) are the most important measures. The great majority of difficult situations can be controlled in this way. Oxygenation and not intubation takes priority. In hypoxia-induced bradycardia (e.g., as a result of apnea), heart rate subsequently increases very rapidly, and circulation is restored.

If ventilation problems occur in an intubated patient (see above), always proceed "from patient to ventilator" (and not vice versa!). In other words, listen to the patient first of all and in the event of doubt disconnect from the ventilator and ventilate by bag. On suspicion of obstruction or dislocation of the tube, immediate extubation with temporary bag-valve-mask ventilation and subsequent reintubation may even be necessary.

Tension pneumothorax must obviously be relieved by puncture or drainage (e.g., Bülau or pigtail drainage), while asthmatic and allergic reactions should be treated as usual.

Patients with obstructions of the upper airway may present particular problems. In croup-like swelling in the area of the cricoid (e.g., postextubation croup), there is in some cases severe inspiratory stridor. In this case, administration of 0.5 mg/kg BW dexamethasone i.v., repeated inhalation with adrenaline (0.1–0.5 mg/kg BW [max. 6 mg]), and BIPAP ventilation via a face mask can be helpful. If reintubation proves necessary, smallish (possibly cuffed) tubes should be available. Laryngospasm must usually be controlled by means of bag-valve-mask ventilation. If that does not work, the spasm can be abolished by short-term anesthesia (e.g., 3–4 mg/kg BW propofol, and if necessary 1–2 mg/kg BW succinylcholine).

In neonates with duct-dependent defects, the required PG1 infusion can result in central apnea. This usually occurs at the beginning of infusion. Treatment of this apnea is sometimes difficult, and the underlying heart disease must be taken into consideration, as well as possible side effects of treatment:

- In defects with duct-dependent pulmonary perfusion or duct-dependent mixing, nasal CPAP with additional O2 is usually helpful. Analeptics (e.g., caffeine or theophylline) can also be tried. Intubation with controlled ventilation should be avoided whenever possible because of the negative effects on the circulation (fall in CO).
- The situation is more difficult in the case of defects with duct-dependent systemic perfusion. In these children it is essential to avoid a fall in PVR due to hyperventilation and increased FiO2, as this can lead to pulmonary hypercirculation and systemic hypoperfusion. A reduction of the PGE1 infusion to a minimal dose (e.g., 5 ng/kg BW/min) may be helpful here (with regular ultrasound monitoring to check whether the ductus is still sufficiently open). CPAP and analeptics must be used carefully as they can induce an increase in breathing (*caution*: strict indication and monitoring!). Here too it is better to avoid ventilation.

12.3 Intensive Care After Primarily Successful Resuscitation

Even with optimal chest compression, CO during CPR is only 20% of normal. Administration of adrenaline serves to centralize the blood flow in favor of the vital organs: the heart and brain. The longer the resuscitation continues, the more likely organ damage is to occur and the more serious it is. Added to this are hypoxia- and ischemia-related injuries that occurred as a result of the initial respiratory or cardiac arrest and those that may occur in conjunction with reperfusion.

Following the return of spontaneous circulation (ROSC) and pharmacologic stabilization, intensive care therapy is then undertaken to maintain and restore organ functions, particularly those of the brain (see Table 12.3).

An assessment of the neurologic prognosis is difficult during the first 24 h after CPR. Everything should therefore be done initially for the patient's survival.

Evidence of irreversible hypoxic-ischemic brain damage can be found from evoked potentials, EEG and MRI 24–72 h after resuscitation.

Even if brain death is established subsequently, the continuation of treatment may be justified from the perspective of a possible organ donation (consent of parents or guardians).

In adults with circulatory arrest as a result of ventricular fibrillation, the neurologic outcome can be improved by mild therapeutic hypothermia for 24 h. However, a more recent study found no difference between patients receiving hypothermal (33 °C) and normothermal (36 °C) treatment. These data possibly point to the fact that consistent temperature monitoring and the avoidance of fever are more important than the temperature target per se. Comparable data have also been found for children (from neonatal age up to 18 years). There is therefore no general recommendation for therapeutic hypothermia following cardiocirculatory arrest with persistent coma. By contrast, the treatment of hypothermia (target temperature, 33–34 °C; treatment duration, 72 h) is recommended for neonates following neonatal asphyxia (Sarnat stage II–III).

As mild therapeutic hypothermia is the only method for reducing secondary lesions (arising from reperfusion), in our view the indication should be established fairly generously following any resuscitation involving a suspicion of hypoxic-ischemic brain injury (for indications see Table 12.3).

However, following fairly short-lasting resuscitation (<2 0 min), rapid return of spontaneous circulation (without previous severe hypoxemia), and signs of awakening, as frequently occur on the ICU, the application of mild therapeutic hypothermia is usually avoided (case-by-case decision).

Table 12.3 Aims of intensive care therapy after resuscitation

Ventilation	$PaCO_2$ = 40 ± 5 mmHg Avoid hyperventilation SpO_2 94–99% (except with, e.g., cyanotic defects, in which case, 75–85%) Avoid hyperoxia
BP	(High) normal
Liquid	Normovolemia (e.g., CVP 8–12 mmHg) Balance: ±0
Myocardial dysfunction (stunning)	Adrenaline, dobutamine, milrinone Follow-up by echocardiography
Positioning	30° upper body elevation Head in mid-position (free venous outflow)
Mild therapeutic hypothermia (within 6 h after CPR)[a]	32–34 °C (taken rectally or better esophageally) for 24–72 h Analgosedation (morphine drip or fentanyl ± midazolam drip) aEEG monitoring if necessary Rewarming: (0.25–0.5 °C/h)
Indication for therapeutic hypothermia[a]	If coma persists after CPR Always initiate in case of doubt (e.g., if CPR > 20 min and unclear neurological situation)
Temperature	<37.5 °C (outside therapeutic hypothermia)

Table 12.3 (continued)

Blood glucose (BG)	Blood glucose 100–180 mg/dL Minimum glucose supply: Neonates: 5 g glucose/kg BW/d Infants: 4 g glucose/kg BW/d Young children: 3–4 g glucose/kg BW/d Adults: 1–2 g glucose/kg BW/d Otherwise insulin drip Avoid blood glucose <60 and > 200 mg/dL
Gastric protection	0.5–1 mg/kg omeprazole b.i.d.
Seizures (prophylaxis)	Midazolam, phenobarbital, phenytoin
Organ function	Maintenance of organ function: Kidney, coagulation, enteral nutrition, etc. Laboratory tests Treatment adjustment for renal or hepatic impairment
Additional monitoring	Cerebral NIRS, aEEG
Evaluation of prognosis	EEG Evoked potentials after 24 h NSE after 48 h MRI after 72 h
Unclear origin	Intoxication screening, genetics, metabolism tests, myocardial biopsy, etc.

aEEG amplitude-integrated EEG, *NSE* neuron-specific enolase
[a]Please see text for further explanation

Suggested Reading

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Part II

Management of Specific Pediatric Cardiac Problems

Preoperative Diagnostic Procedures

13

Dietrich Klauwer and Christian Jux

13.1 Introduction

The aims of this chapter are manifold: (1) to describe a hemodynamically based classification of heart defects, (2) to consider heart defects and heart defect entities in conjunction with subordinate extracardiac findings, and (3) to provide an overview of those findings that need to be obtained in a patient with a specific heart defect and analyzed preoperatively so that optimal and rational therapy can be rendered and no relevant details are overlooked.

In the first place, this involves the medical arsenal of any pediatrician dedicated to the care of children with cardiac issues. However, it is known from everyday clinical practice that seemingly banal things like case history and clinical data recede ever further into practitioners' mental background as their specialization increases. And yet it is the simplest things that actually continue to be pivotal. Secondly, there are heart defect-specific data that must be recorded during preoperative diagnostic studies to ensure the planning, performance, and follow-up of the surgical procedure/intervention.

The central part of the history-taking, however, remains the immediate reason for presentation, which, in the case of elective surgery, should include the indication for surgery. Previous diagnostic procedures and treatment must also be recorded, as well as the decision paths and the decision-makers. During the course of the history-taking itself, it must be checked whether these interrelationships seem plausible to the parents, to the patient, but also to the healthcare professional taking the history (see Table 13.1).

D. Klauwer (✉)
Department of Pediatrics, Singen Medical Center, Gesundheitsverbund Landkreis Konstanz, Krankenhausbetriebsgesellschaft Hegau-Bodensee-Klinikum, Singen, Germany

C. Jux
Pediatric Intensive Care Unit, Pediatric Heart Center of Giessen, Children's Heart Transplantation Center, UKGM GmbH, Giessen, Germany

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D. Klauwer et al. (eds.), *A Practical Handbook on Pediatric Cardiac Intensive Care Therapy*, https://doi.org/10.1007/978-3-319-92441-0_13

Table 13.1 History-taking

Pregnancy history	Birth history	Family history	Pediatric history	Pediatric cardiological history	Review of systems
Gestational age	Birth mode	Names Family status	Illnesses	Failure to thrive Nutritional disorder	Drinking Vomiting Reflux
Mother's diseases previously	Complications	Height Weight (BMI)	Vaccinations	Cyanosis	Sweating
Mother's diseases during pregnancy Infections Drugs	APGAR Umbilical artery pH	Occupations Smoking Alcohol	Growth to date	Dyspnea edema	Micturition
Induction of labor	Weight Height Head circumference	Previous diseases	Milestones	Exercise intolerance	Bowel movements
Examinations: Echo, laboratory tests, etc.	Adaptation Discharge from maternity hospital	Familial diseases, Miscarriages Unexplained sudden deaths	Previous noncardiologic examinations	Syncopes Unexplained exceptional conditions Arrhythmias	Sleep behavior Apnea
Number of previous pregnancies, births and their outcome	Further observations	Siblings	Documentation	Initial diagnosis	Allergies
				Drugs Previous therapy	Drug interactions

13.2 Clinical Examination

In addition to the basic examination measurements (height, weight, head circumference, and SpO_2 were necessary with pre- and postductal gradient, where an aberrant right subclavian artery is not present, the right hand is considered the preductal reference) the examination of the cardiovascular system must be given particular attention. Blood pressure should be taken on all extremities as well as resting heart rate and respiratory rate. Even if the symptoms are not always clearly clinically apparent, every effort must be made to divide them into those of cardiac forward failure, backward failure, and pulmonary impairment and symptoms not associated with cardiac decompensation. In addition, symptoms due to possible adverse drug reactions, syndromal stigmata, local and generalized growth abnormalities, skin and hair abnormalities, movement deficits, and an outline of the developmental status should be recorded.

Besides the pediatric cardiological examination, the examiner should gain an overview of the main organ systems (neurology, gastrointestinal tract, renal function, and locomotor apparatus).

It is only from a clear understanding of the disease history, a careful physical examination, and the patient's overall situation that it is possible to establish a reliable diagnosis and treatment plan later.

Following the history-taking and the physical examination, echocardiography and ECG are then available as initial diagnostic methods. If needed, these examinations are supplemented by chest X-rays and laboratory analyses. If the findings fail to elucidate complex heart defects or functional disorders sufficiently, diagnostics are supplemented by cardiac catheterization, exercise or long-term ECG examinations, and radiological studies like MRI, CT angiography, or rare special investigations. Nowadays, CT radiation exposure is often less than with diagnostic cardiac catheterization. Alongside an understanding of hemodynamics and the collected findings, the "many eyes" principle is paramount for patient safety and rationality, enhanced by the learning effect from the structured presentation of patients and findings (see Table 13.2).

13.2.1 Structured Echocardiography

The analysis should include the planes and images mentioned below as adapted from the Echocardiography Working Subgroup of the Pediatric Cardiology Working Group of the Austrian Society of Pediatrics and Adolescent Medicine (see Table 13.3).

Quantitative Measurements

M-mode. Parasternal short axis or long axis at papillary muscle level: RVAWD, RVEDD, IVSD, LVEDD, LVPWD, LVESD, LWPWS, shortening fraction, and ejection fraction.

Table 13.2 Clinical examination

Baseline data	Baseline investigations	Forward failure	Backward failure	Pulmonary symptoms	Stigmata	Assessment of heart sounds	Rhythm
Size	SpO_2	Microcirculation/ recapillarization prolonged	Hepatomegaly	Tachypnea	Tall/short stature	In the cardiac cycle	Heart rate
Weight	BP (all 4 extremities)	Pallor	Ascites	Dyspnea	Facial dysmorphias	In loudness	Palpated rhythm: Regular, periodically irregular, irregularly irregular arrhythmia/ gallop rhythm
Head circumference	Resting HR	Vigilance	Nausea, vomiting	Pleural effusions	Chest deformities	In tonal quality	Pulse deficit regular
BSA, BMI	Resting breathing rate	Groggily or agitated	Edema	Stridor	Limb deformities	In terms of localization	
	Pulse status	Cold hands/ extremities	Congested veins	Cyanosis	Genitals, abdominal wall defects	In terms of conduction	
		Peripheral cyanosis	Collateral circulations	Wet rales	Vertebral column malformations	In terms of body position	
		Oliguria (wet diaper?)		Cardiac asthma	Connective tissue, skin and hair abnormalities	Heart sounds: Second heart sound singular, widely and fixedly split or drumming/ prominent	
		Moist mucosae				Third and fourth heart sounds	

HR heart rate; *BP* blood pressure; *BSA* body surface area; *BMI* body mass index

Table 13.3 Structured echocardiography

	2DE	CD	MM	SD
Four-chamber view: AV valves	●	●		PW E and A
Four-chamber view: Coronary sinus	●			
Four-chamber view: PV inflow				PW curve LVOT
Five-chamber view	●	●		LVOT
Three-chamber view/apical axis	●	●		
Two-chamber view optionally				
Left ventricle	●	●	● LA/AO and left ventricle study	
Left ventricular inflow tract	●	●		CW: PV, tilted also TV
Left ventricular outflow tract	●	●		
Heart base	●	●	● LA/AO and left ventricle study	CW: PV
Coronary arteries	●			
Mitral valve	●	●	●	
Papillary muscles	●	●	Left ventricular study/right ventricle size/dilation?	
Left ventricular apex	●	●		
Abdomen transverse view	●			
IVC and abdominal aorta lengthwise	●	●		PW: Abdominal aorta; celiac trunk
Atrial septum and pulmonary veins	●	●		
Left ventricle and aorta	●	●		
Right ventricle inflow and outflow	●	●		
Caval veins (bicaval view)	●	●		
Right ventricle outflow and left ventricle	●	●		
Right and left ventricles	●	●		
High parasternal sections				
Pulmonary artery bifurcation	●	●		
Ductus view	●	●		
Long axis ascending aorta	●			
High right parasternal optional				
Long axis aortic arch	●	●		CW: Ascending and descending aorta
Short axis/frontal plane	●	●		(LA with pulmonary veins = crab view)

Parasternal short axis or long axis at aortic annulus level: LAs and AOs and LA/AO.

However, in principle, valvular and vascular structures should be measured at the time of their greatest expansion, i.e., the diameters of the semilunar valves and great arteries in systole and the diameters of the AV valves and veins in diastole or in expiration (e.g., inferior vena cava). Vessel diameters must always be measured perpendicularly to their longitudinal axis (= direction of blood flow).

Four-chamber view – tricuspid annular plane systolic excursion (TAPSE) and mitral annular plane systolic excursion (MAPSE).

Spectral Doppler:

- MV: E, A, E/A, (PW)
- LVOT/MV (PW): IVRT
- TV: tricuspid insufficiency V_{max} (CW)
- PV: V_{max}, PI V_{max}, and end-diastolic (CW)
- LVOT V_{max}
- Aortic arch, descending aorta V_{max} (CW) – description of flow profile
- Abdominal aorta V_{max} (PW) – description of flow profile
- Where necessary, view of ASD/PFO, VSD, PDA, shunts, stenoses, etc.

In patients with (complex) heart defects, the problem not infrequently arises that an adequate, if any, three-dimensional visualization or understanding of the anatomy cannot be achieved with routine views only. It is therefore always important to consider a structure from various viewpoints. An attempt should be made to achieve this three-dimensional visualization by integrating "nonstandard views." As an example, the coronary arteries can also often be traced better in the five-chamber view.

13.3 Functional Classification of Heart Defects

In order to consider each heart defect within its context, a simple grouping can be undertaken on the basis of hemodynamic aspects, where subgroups can then also be distinguished from one another on the basis of parallels and differences (Table 13.4).

In order not to "overlook" anything in the preoperative and diagnostic phase for individual heart defects, the necessary diagnostic details will be presented in table form in addition to the superordinate hemodynamics.

The first group comprises heart defects with an intra- or extracardiac L/R shunt.

13.3.1 Heart Defects with Intra- or Extracardiac L/R Shunt

Common to these defects is the fact that the basic intracardiac anatomy remains largely preserved with the presence of two atria and two ventricles. However, as there are short-circuit connections between the cardiac cavities and the high-pressure and low-pressure system of the circulation, a cardiac output required for

Table 13.4 Classification of heart defects in terms of hemodynamics

Heart defects with intra- or extracardiac L/R shunt	ASD (Partial) anomalous pulmonary venous connections VSD AVSD PDA AV malformation Aortopulmonary window TAC
Heart defects with right heart obstruction	TAT PST PAT/IVS PAT/VSD Peripheral PST TAC TOF DORV of the Fallot type
Heart defects with left heart obstruction	MS Supravalvular MS, Cor triatriatum AST, sub- and supravalvular AST HLHS CoA
Univentricular hearts	Large VSD AV canal subtypes DILV DOLV Special forms DORV, etc.
TGA	d-TGA, l-TGA, MGA
Total anomalous pulmonary venous connection	
Complex defects	Heterotaxia, “undefined” ventricles, MGA, etc.

TAC Truncus arteriosus communis

sufficient organ perfusion must be provided by additional cardiac work. In other words, if the systemic perfusion requirement is unchanged, this means that the quantity of blood lost through the shunt must be pumped severalfold by the heart. A significant difference, however, lies in whether the shunt is found in the high-pressure area of the circulation, i.e., after the tricuspid valve, or in the low-pressure area of the circulation, in other words upstream from the tricuspid valve.

With shunts in the high-pressure area, the flow of the shunt volume occurs (predominantly) during systole. In the example of VSD, this means that the shunt flow occurs via the defect with the right ventricle contracted and the pulmonary valve open thus mainly overloading the right ventricle with pressure (resulting in hypertrophy), but not volume (therefore no RV dilatation in VSDs). By contrast, the pulmonary vascular bed and the left ventricle are volume overloaded with blood that has to be pumped additionally. This causes pressure overload of the right ventricle with corresponding hypertrophic consequences, where the pulmonary vascular system is volume- and pressure-overloaded and the left half of the heart remains solely volume overloaded (see Table 13.4).

These contrast with pre-tricuspid shunts (ASD, anomalous pulmonary venous connections), in which a volume overload of the right half of the heart (resulting in dilatation) and the pulmonary vascular bed occurs. Here, the shunt flow begins in late ventricular systole but continues to about the middle of diastole, principally because of the usually markedly higher compliance of the right ventricle and hence stronger "suction effect" in the ventricular inflow. At the end of diastole, hardly any shunt flow occurs. Since "too little blood" is made available to the left ventricle, deficient cardiac output can only be provided by an increase in heart rate and to a limited extent by an increase in contractility (see Table 13.5).

Against this backdrop, the shunt volume is determined not only by the size of the defect, but also by the compliance of the downstream system. Apart from increased volume overload with high compliance of the right ventricle and in particular of the pulmonary vascular bed, pulmonary hypertension hardly develops at all or only at a very late stage in the case of a pre-tricuspid L/R shunt. In post-tricuspid shunts, by contrast, pulmonary hypertension is a dreaded early complication. The systolic systemic pressure acts here directly on the pulmonary vascular bed, which protects itself by precapillary vasoconstriction, medial hypertrophy, and lastly a fixed increase in resistance.

AV fistulas and atrioventricular septal defects (AVSD) have a special place in this respect.

In the case of AV fistulas, the shunt exists between branches of the systemic arterial and the systemic venous system. Since the terminal arterial vessels and the capillary bed are circumvented in the area of the fistula, vascular resistance decreases so that volume overload of both halves of the heart (increase in stroke volume and blood pressure amplitude) and the pulmonary vascular bed occurs. In this case, also, pulmonary hypertension can develop at an early stage. Both the high flow through the lung as well as the increased left-sided filling pressures (LVEDP = LAP) in left atrial volume overload play a role here.

In AVSD, the findings and problems of pre- and post-tricuspid L/R shunt are combined, and furthermore patients with trisomy 21 in particular tend to develop early PHT.

Table 13.5 Atrial septal defect (ASD)

Clinical features	Anatomy	Shunts	ECG	Rationale for cardiac catheterization	Surgical options	Surgical aims	Special features
Often no symptoms, heart murmur from relative pulmonary stenosis with right-sided volume overload Wide and fixed split 2nd heart sound	ASD II in and around oval fossa – Small defects (<6 mm) tend to close spontaneously by school age	L/R shunt at atrial level	RV volume overload incomplete RBB (rSR type)	For defect closure, visualize defect location, and rims before by echo	ASD closure directly, with patch, Warden procedure	Closure and thus elimination of volume overload of the right heart and pulmonary circulation	ASD is a frequent accompanying other malformations
Rare diastolic murmurs of relative tricuspid stenosis	ASD I adjacent to AV valve level (MV cleft?)	Increase with postnatally increasing RV compliance	Right atrial enlargement Atrial arrhythmias	If sufficient defect margins exist	With (partial) sternotomy From right laterally	Necessary to leave a residual defect?	Frequently associated malformation: PDA, PST
Recurrent pulmonary infections Failure to thrive with large shunt	Upper *sinus venosus* defect with PAPVR – Usually right upper pulmonary vein. Tends earlier to PHT	Volume assessable via RV dilation and septal movement	ASD I with leftward superior ("northwest") axis	Possible if mm Ø ≤ body weight in kg (rule of thumb)	With symptoms, with RV dilation and paradoxical septal movement		

(continued)

Table 13.5 (continued)

Clinical features	Anatomy	Shunts	ECG	Rationale for cardiac catheterization	Surgical options	Surgical aims	Special features
Late PHT	Lower *sinus venosus* defect less common with PAPVR	With upper anomalous pulmonary venous connection, the shunt also occurs through the pulmonary vein		Indication as for surgery: With symptoms, with RV dilation, and with paradoxical septal movement			
Late atrial arrhythmia	Very rarely CS defect with unroofed CS and l-SVC	ASD left open or newly generated as "pop-off" in PHT					
Heart failure only with very large shunt or PHT	Look for atrial septal aneurysm and its perforations (multiple defects)	ASD as obligatory shunt in left and right heart obstructions					
	RV, RA, and PA – Volume overload						
	Paradoxical septal movement						

Table 13.6 VSD

Clinical features	Anatomy	Shunts	ECG	Rationale for cardiac catheterization	Surgical options	Surgical aims	Special features
Systolic murmur Later possibly aortic insufficiency Relative MS Lastly, loud 2nd heart sound in PHT	Inlet septum Outlet septum Muscular trabecular septum Membranous septum Subaortic septum	Initially, always L/R shunt With PHT or right ventricle obstruction possibly R/L shunt	The larger, the more: High R left, significant Q left, Deep S right, LVH, biventricular hypertophy, infants with large VSD sometimes also only RVH (right ventricular hypertrophy)	Interventional closure	No neonatal surgery if possible – Pharmacological therapy temporarily	Closure – Shunt elemination and hence volume underloading of the left heart and pulmonary circulation Pressure unloading of right ventricle and pulmonary vessels	VSD is common, sometimes a hemodynamically necessary accompanying malformation
Trill, apex beat	Malalignment of ventricular septum or septal dislocation	"Post"-tricuspid L/R shunt can increase right ventricular pressure and generates precapillary PHT more rapidly	Prolonged P duration	For PHT testing, operability?	Surgery always in symptomatic children	AoI treatment necessary (?)	Sometimes syndrome-associated malformation

Table 13.6 (continued)

Clinical features	Anatomy	Shunts	ECG	Rationale for cardiac catheterization	Surgical options	Surgical aims	Special features
Signs of heart failure (forward and backward)	Measurements of extension along cardiac axes Visualize localization in all axes Note outflow tracts, chordae tendineae, and valve insufficiencies	Classification hemodynamically into restrictive, partially restrictive, nonrestrictive	Resting tachycardia		VSD size and LA/LV dilation	Patch closure, direct suture	PHT more rapidly in trisomy children
Recurrent pulmonary infections	Size relative to AVV – Frequently relevant if $>^1/_2$ AVV Ø Always determine dP in Doppler	Perimembranous and outlet VSDs with AoI (?)			AoI and avoidance of irreversible PHT	No residual shunt and VOTO	
	LA, LV, and lung volume overload, right ventricle and PA pressure overload (in larger defects)						

Table 13.7 Atrioventricular canal or septal defects (AVSD)

Clinical features	Anatomy	Shunts	ECG	Rationale for cardiac catheterization	Surgical options	Surgical aims	Special features
ASD I same as ASD – Relatively early PHT Caution: AV valve insufficiency (cleft)	Complete form: Common undivided fibrous AVV ring. Partial form: ASD I with 2 separate fibrous AVV rings	ASD I and AV valve cleft with partial AV canal	Marked axis deviation (superior-leftward)	PHT testing	ASD patch and "MV" cleft suture	Corrective surgery	Association with trisomy-21
Complete AV canal with forward-backward failure and pulmonary congestion with AVV insufficiency	ASD I adjacent to AV valve level	ASD I and restrictive VSD with intermediate type	First degree AV block		ASD and VSD closure with one or two patches as well as AV valve reconstruction	Rarely PA banding (and CoA resection) if not primarily correctable	Fallot with AV canal
Usually systolic heart murmur	Inlet VSD	ASD I and large inlet VSD with complete type with only one AV valve opening and AV valve ring	Right hypertrophy with rSR RBB, LA, and LV overload		Prevention of LVOTO	Shunt elemination and volume unloading of the whole heart and pressure unloading of the right heart as well as of pulmonary vessels	DORV with AV canal

Table 13.7 (continued)

Clinical features	Anatomy	Shunts	ECG	Rationale for cardiac catheterization	Surgical options	Surgical aims	Special features
	AV valves on one level with no off-set and not (completely) separated	Univentricular heart with very large VSD			Timed for first months of life Caution: CoA and PHT		Frequently CoA with hypoplastic left ventricle
	Right and left lateral leaflet, right anterior-superior leaflet, anterior and posterior bridging leaflet with variable "cleft"	Ventricular imbalance, e.g., in Rastelli type B with small left ventricle			Time depends on efficacy of anticongestant therapy		Many other complex malformations
	Division of the anterior bridging leaflet +/− chordae tendineae attachments*	Varying degrees of right and left-sided AVV insufficiency			Tends to be earlier with T21		
	AV node displaced ventrally	Subaortic stenosis due to left-sided AVV valve material (?)					
	Aortic valve ring displaced ventrally – LVOTO (?)						

*Rastelli classification based on *anterior bridging leaflet* (*ABL*) morphology: type A – ABL predominantly assigned to left ventricle and usually attached to IVS crest (often associated with T21); type B – ABL extends more to right ventricle and chordae tendineae cross the septal crest to an atypical right ventricle papillary muscle at the septomarginal trabeculation; type C – ABL extends further right, "floats" freely over the septal crest, and is attached to an anterior papillary muscle (often associated with asplenia syndrome)

Table 13.8 Patent ductus arteriosus (PDA)

Clinical features	Anatomy	Shunts	ECG	Rationale for cardiac catheterization	Surgical options	Surgical aims	Special features
In newborns systolic, later systolic-diastolic heart murmur	"Normal" PDA between PA bifurcation and aortic arch distal to left subclavian artery	As single defect L/R shunt	Prolonged P duration ("P mitrale")	Closure	Silent duct can remain open	Ligature and clipping from left lateral	Additional anomalies
Precordial thrill	Assess width, length, ampulla, shape, stenosis?	Left-sided volume overload	Left ventricular hypertrophy	PHT testing (trial closure)	Premature neonates if not pharmacologically treatable		Important for survival with obstructive defects and TGA
Large BP amplitude	Atypical PDA particularly with pulmonary atresia	Pressure overload of pulmonary vascular bed (post-tricuspid shunt)	Left-sided repolarization disorders		Untreatable PDA by catheterization	Volume unloading of pulmonary circulation and left heart, pressure unloading of pulmonary vessels	
Heart failure		Shunt ratios in cardiac cycle	Right-sided involvement in PHT		Symptomatic PDA and early with PHT		
Not audible but visualizable (Echo). Audible. Audible with clinical or Echo signs of overload. PDA with PHT		Reduced organ perfusion with loss of Windkessel and diastolic runoff			On suspicion of advanced PHT with testing		

Table 13.9 AV malformation – arteriovenous fistulas

Clinical features	Anatomy	Shunts	ECG	Rationale for cardiac catheterization	Surgical options	Surgical aims	Special features
Comparable to PDA with high BP amplitudes, tachycardia, biventricular heart failure, and pulmonary congestion with pre- and postcapillary PHT Flow-related PHT	AV short-circuit connections with shunt due to low resistance. AV malformation congenital. AV fistulas sometimes iatrogenic	No or only small capillary vascular bed in nidus induces a greater extracardiac L/R shunt	Biventricular hypertrophy	Embolization	If embolization not promising or successful: Surgical vessel clipping	Elimination/ reduction of shunt volume. Volume unloading of whole heart and pulmonary circulation	Kasabach-Merritt phenomenon
Flow murmur	Congenital or (puncture-related) traumatic			Increase in size of remaining fistula branches possible, if afferent flow not completely abolished	Surgery sometimes possibly after radiotherapy or neoadjuvant chemotherapy	Excision with smaller vessels convolutes	Association with Osler's disease
Organ perfusion disorders	Brain, liver, lung, etc.					Bleeding relief on rupture	Beta-blockers with cutaneous and visceral hemangiomas
Local symptoms in affected organs – Megaly, oxygenation disorder, or neurology. With intrapulmonary AV malformations: Cyanosis	Enlarged cardiac cavities and body veins						

Table 13.10 Aortopulmonary window

Clinical features	Anatomy	Shunts	ECG	Rationale for cardiac catheterization	Surgical options	Surgical aims	Special features
If PVR falls, shunt increases Heart failure depending on shunt volume and PVR	Two semilunar valves present, but aortopulmonary connection often without significant restriction	L/R shunt with reduction in PVR in systole and diastole	First left, then also right, ventricular overload	If uncertain, PAH testing followed by late correction	Closure – Direct or with patch	Corrective	ASD, VSD, PDA, CoA, and TOF (conotruncal malformation)
Systolic-diastolic heart murmur as in PDA	Sometimes with right pulmonary artery (rPA) from aorta. Defect of varying size but usually nonrestrictive	Distal arteries with sometimes negative diastolic flow (runoff)		Rarely for intervention	Sometimes with rPA transplant	Volume unloading of left heart and pulmonary circulation, pressure unloading of pulmonary vessels	Coronary anomalies as in all patients with microdeletion syndrome 22q11

Table 13.11 Persistent truncus arteriosus

Clinical features	Anatomy	Shunts	ECG	Rationale for cardiac catheterization	Surgical options	Surgical aims	Special features
Heart failure in event of decrease in PVR and truncal valve insufficiency – Less with anatomical PA stenoses	Truncal valve overrides VSD types A1–A4 according to van Praagh (see Fig. 13.1a–d)	VSD not "pressure separating"	Biventricular hypertrophy. Atrial dilation	Rarely with unclear anatomy, later correction (fixed PHT?)	VSD closure	Correction surgery/AO (= truncal) valve reconstruction	Conotruncal malformation. Frequently right arch. Frequently coronary artery anomalies and CoA
With type A4, duct-dependent perfusion of the lower half of the body – BP gradient	Typing dependent on origin of pulmonary arteries		Tachycardia in heart failure	Coronary artery anomalies	Two-stage surgery with arch reconstruction and PA banding	Volume unloading of the left heart and pulmonary circulation, pressure unloading of pulmonary vessels	Associated malformations (LSVC, TAPVR/ PAPVR, ASD)
Cyanosis (slight) with mixed blood More severe with PA stenoses	Truncal valve frequently "dysmorphic" and insufficient/more rarely stenotic, sometimes quadricuspid valve	PDA with flow to the lung (type A3) or PDA with perfusion of lower half of the body (type A4)	Repolarization disorders	For PHT testing	RV–PA conduit	Good semilunar valve function, unobstructed aortic arch	Frequently 22q11
With type A3, duct-dependent perfusion of the (usually) left lung	PA stenoses (?) Right-sided aortic arch frequent				Early timing of surgery essential because of PHT		

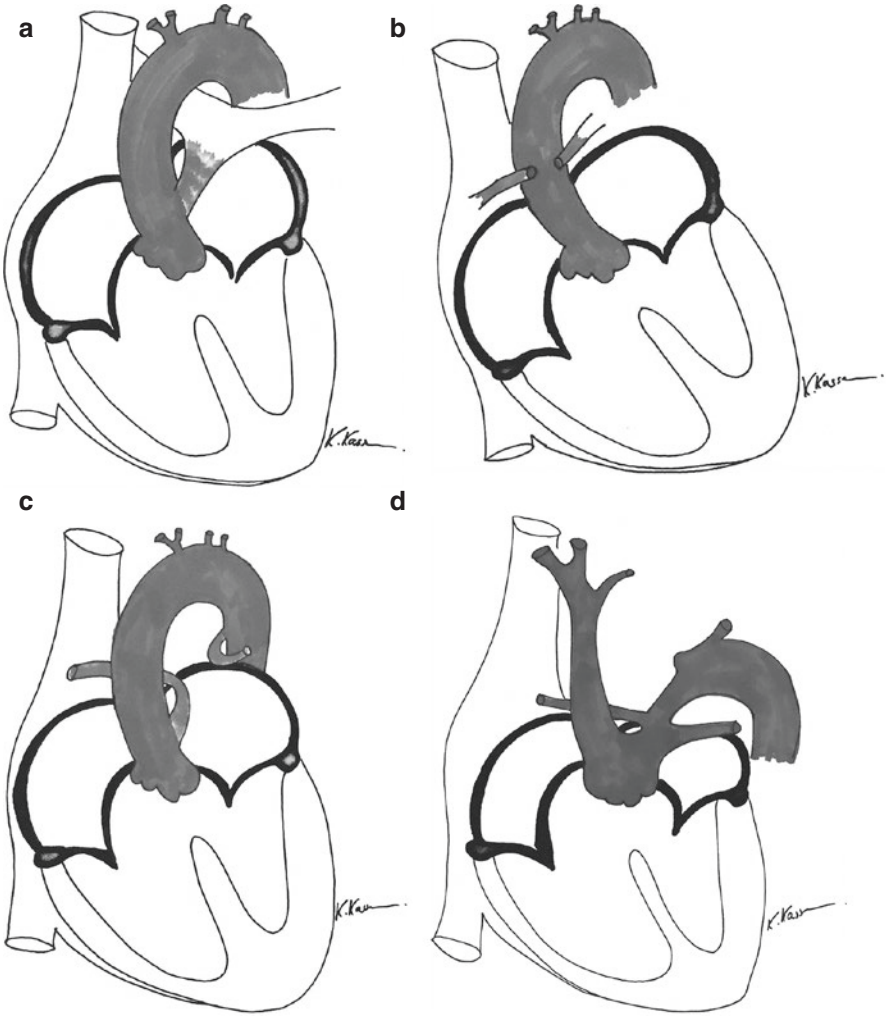

Fig. 13.1 (**a**–**d**) Forms of persistent truncus arteriosus types A1–A4 according to van Praagh

13.3.2 Defects with Right Heart Obstruction

Starting with a cor triatriatum dextrum (not described here), the blood flow through the right heart can be obstructed along its whole path or completely impeded. The anatomical obstruction can be of a fibrous nature or can be due to valve dysplasia, atresia, or commissural fusion. Muscular obstructions can also very frequently be found and lastly hypoplasia and dysplasia of the pulmonary arterial vascular bed. Reduced pulmonary perfusion is usually observed in right heart obstructions. Pulmonary stenosis (noncritical), tricuspid stenosis, pink Fallot, and tricuspid atresia with TGA here constitute fairly rare exceptions (see Table 13.12).

Table 13.12 Pulmonary valve stenosis

Clinical features	Anatomy	Shunts	ECG	Rationale for cardiac catheterization	Surgical options	Surgical aims	Special features
Deep cyanosis followed by circulatory insufficiency with critical stenosis (duct-dependent)	With critical PST, usually dysplastic valve with narrow ring and variable PA size	Critical PST is a cyanotic defect with R/L PFO/ASD shunt and PDA-dependent pulmonary perfusion	Right ventricular hypertrophy	Always balloon dilation with critical PST	Valve reconstruction	Elimination of gradient and hence pressure unloading of right ventricle	Caution: Relative stenosis with L/R shunts
Systolic heart murmur, ejection click and thrill in pediatric stenosis (usually with dP > 40 mmHg)	Purely valvular form with normal ring, commissural fusion, and poststenotic dilation	With high-grade stenosis and PFO/ASD, RAP can be > LAP and thus often some cyanosis	In children, signs of hypertrophy correlate with gradient	In symptomatic children, with reduced RV function, or gradient >50 mmHg for treatment	Commissurotomy, partial valvectomy, transannular patch with hypoplastic valve ring	Prevention of PI	RVOT hypoplasia with conotruncal malformations
No ejection click with dysplastic form	Dysplastic form usually without poststenotic dilation/more often with sinotubular supravalvular constriction			Elective from gradient of 40–50 mmHg on echo	Myectomy with obstructive subvalvular hypertrophy	If necessary, valve replacement	With absent PV dysplasia without RVOTO and with PI-wide PA due to regurgitant blood

Mild to moderate stenoses are clinically unapparent apart from the heart sound	Bicuspid valve? Three-partid right ventricle? Right ventricle hypoplastic?						Look for peripheral pulmonary stenoses
	Tricuspid insufficiency (TI) for assessing right ventricular pressure						
	TV valve size?						
	PFO/ASD size, shunt, gradient						
	Reactive RVOTO						

Table 13.13 Peripheral pulmonary stenoses

Clinical features	Anatomy	Shunts	ECG	Rationale for cardiac catheterization	Surgical options	Surgical aims	Special features
Often postoperatively, e.g., after TOF, PAT, PTA correction, or in conjunction with syndromes	Definition: Stenoses distal to PA trunk	In ASD/PFO or VSD, R/L shunt dependent on extent of stenosis	Right ventricular hypertrophy, possibly RA hypertrophy	Reduction of right ventricular pressure	Possible only as far as lung hilum	Reduction of right ventricular pressure	Syndrome-associated, e.g., Noonan, Alagille, Williams-Beuren, elastin defects
Systolic murmur with conduction to affected lung	Often multiple		Possibly secondary atrial arrhythmias	Balloon angioplasty (possibly high-pressure balloons, possibly cutting balloons)	Patch reconstruction, possibly with aortopulmonary shunt	Growth of distal pulmonary arteries	
Often asymptomatic for long time	Often with hypoplastic vessels distally			Possibly stent insertion	Possibly as hybrid intervention (intraoperative balloon dilation, stenting)	Equal bilateral pulmonary perfusion	
Increasing exercise impairment with high-grade stenoses	Usually only assessable by angiography or CT			Particularly significant with “passive” pulmonary perfusion (Glenn, Fontan)			

With high-grade stenoses, cyanosis in presence of ASD/ PFO and/or VSD								
With tricuspid insufficiency, possibly secondary atrial arrhythmias								
Right backward failure (hepatic congestion)								

Table 13.14 Pulmonary atresia with intact ventricular septum

Clinical features	Anatomy	Shunts	ECG	Rationale for cardiac catheterization	Surgical options	Surgical aims	Special features
Cyanosis	Configuration of "valve?" Diameter and dysplasia	PFO/ASD obligatory	"P-pulmonale" +/− "mitrale"	Sinusoids Fistulas	Commissurotomy, valvectomy	Biventricular with TV *Z* score >−3 without right ventricle-dependent coronary circulation	RV-dependent coronary circulation must be investigated prior to any intervention
Heart murmur due to ductus, MAPCAs, or fistulas	Three-partid right ventricle? Size? Hypertrophy?	Gradient across ASD/PFO	Left ventricular hypertrophy	Possibilities of intervention on the valve (PV perforation)?	RVOT reconstruction (transannular)	1½ circulation	The more pronounced the tricuspid insufficiency, the fewer the sinusoids
Backward failure with restrictive ASD	Size of tricuspid valve ring? (*Z* score and comparison with mitral valve)	PDA	Right-sided repolarization disorders	PDA stent	PA reconstruction	Univentricular path	The thicker/ hypoplastic or more stenotic the tricuspid valve, the more sinusoids
Left-sided volume overload usually not determining factor	Tricuspid valve opening?	MAPCAs			Right ventricle-PA conduit		
	Tricuspid insufficiency?						
	Coronary sinusoids? Coronary fistulas?						

Starting with valvular pulmonary stenosis, the hemodynamic and anatomical consequences of right heart obstruction can be elucidated.

To maintain sufficient cardiac output, there is an increase in contractility with pressure hypertrophy. Tachycardia induced in parallel by sympathetic counterregulation causes almost no increase in cardiac output and frequently even reduces it. The more hypertrophic the ventricle, the longer should be the diastolic filling phase of the ventricle, as a relaxation disorder interferes with filling and thus reduces stroke volume (preload dependency of the hypertrophic ventricle).

In addition, with concentric hypertrophy (specifically of the right ventricle), a narrowing of the outflow tract occurs over time, which increases the gradient further and increasingly interferes with ejection. This regresses following successful relieve of pulmonary stenosis.

With valvular constrictions of the outlet valves, there is frequently poststenotic dilation of the following section of the artery. If supravalvular stenosis is present additionally, dilatation does not occur. This is the case, for example, with dysplastic valves with sinotubular constriction (typical in Noonan syndrome).

The higher the degree of stenosis, the more likely there is to be exertion intolerance with a cardiac output that can barely be increased at all. If, in addition, any parallel intracardiac shunts are present (PFO, ASD, VSD), then cyanosis also occurs as soon as RVP > LVP or RV compliance < LV compliance or RVP > LVP, respectively.

Intracardiac shunts must be present in the case of complete or almost complete atresia of the pulmonary valve (= critical stenosis) in order then to be able to ensure pulmonary perfusion from the systemic side via PDA/MAPCAs. Critical PS is defined as duct (or MAPCA)-dependent pulmonary circulation. Anatomically, a distinction is drawn between critical pulmonary valve stenosis on the one hand and pulmonary atresia with intact ventricular septum and conotruncal malformations with a Fallot-like anatomy (see Tables 13.15 and 13.16).

In critical pulmonary stenosis, a three-partid right ventricle is usually present which is hypertrophied and in rare cases also dilated. As the cardiac output cannot flow serially (antegrade flow into the pulmonary circulation is considerably impaired), mixing with an R/L shunt occurs at the level of the atrial septum. Pulmonary perfusion is partly or wholly dependent on the L/R shunt via the PDA. If this connection becomes smaller, increasing arterial hypoxemia occurs with cyanosis and tachypnea, in addition to symptoms of backward failure (organomegaly).

In the case of pulmonary atresia with an intact ventricular septum (PAT/IVS), the whole of the pulmonary blood flow is derived from the systemic circulation (PDA or MAPCA) and the whole systemic venour return must reach the left heart side through the atrial septal defect. If there is transtricuspid blood flow in utero and a three-partid right ventricle can develop, in systole, this blood either reaches the coronary circulation via myocardial sinusoids or it has to escape via tricuspid insufficiency. The more severe the tricuspid insufficiency, the fewer are the sinusoids and vice versa. Fortunately, the central pulmonary arteries are usually of a good-size caliber in PAT/IVS (as in the various forms of tricuspid atresia as well [9]).

Table 13.15 Pulmonary atresia with VSD

Clinical features	Anatomy	Shunts	ECG	Rationale for cardiac catheterization	Surgical options	Surgical aims	Special features
Cyanosis (PDA- or MAPCA-dependent pulmonary circulation)	Atresia of PV with dysgenesis of pulmonary arteries. Genuine central pulmonary arteries present? Confluent or discontinuous?	PDA- or MAPCA-dependent pulmonary perfusion with L/R shunt	RV and RA hypertrophy	Anatomical visualization/ determination of exact size and indexing of PAs. Visualization of pulmonary perfusion, with MAPCAs: Single or double supply of segments? Look for source of perfusion of all lung segments	From membranous via muscular RVOT atresia to lung perfusion by MAPCAs without central pulmonary vessels	VSD closure and right ventricle-PA conduit	Conotruncal malformation
Heart failure with pulmonary hypercirculation with only slight cyanosis	RVOT hypoplasia	From pulmonary flooding to severe cyanosis	Biventricular hypertrophy with pulmonary flooding	PDA stent with PDA-dependent pulmonary circulation	AP shunt, unifocalization, single- versus multiple-stage correction, uni- vs. biventricular procedure	Sometimes only after PA growth by AP shunt or PDA stent	Coronary anomalies, fistulas, sinusoids
Increase in cyanosis (and decrease in HF) with MAPCA stenoses	VSD (malalignment)			MAPCA coiling with pulmonary flooding and double supply		Sometimes after previous unifocalization	Right arch

PDA or MAPCA murmur	Pulmonary blood supply via PDA and/or MAPCAs			Treatment of distal stenoses of PAs		With hypoplastic PAs, possibly initially leave/ reduce VSD, fenestrated patch	22q11
	Extent of pulmonary artery hypoplasia determines procedure and prognosis						PFO/ASD
	Visualize MAPCAs and tortuous vertical PDA from aortic arch						

Table 13.16 Tetralogy of Fallot

Clinical features	Anatomy	Shunts	ECG	Rationale for cardiac catheterization	Surgical options	Surgical aims	Special features
Cyanosis and systolic heart murmur	Malalignment VSD, usually not restrictive	Pink Fallot with relatively little RVOTO	Right ventricular hypertrophy (RVH)	Anatomy unclear	The higher the SpO_2, the later the surgery	Pulmonary valve ring should remain intact where possible	ASD, PDA
Slight/no cyanosis and heart murmur in "pink Fallot"	Infundibular septum shifted anteriorly and superiorly	Blue Fallot with right outlet resistance > left outlet resistance	Possibly right atrial hypertrophy (RAH)	Rarely stenting of RVOT or PDA to gain time	Usually primary corrective surgery	If transannular patch, then possibly with monocuspid valve reconstruction	AV canal association
Episodes of cyanosis with SVR ↓ or RVOT spasm	RVOTO, Additive gradients possible at various positions (sub- and/or supra-/valvular)			Surgically relevant coronary artery anomalies	Rarely AP shunt required for growth of hypoplastic PAs	Some residual stenosis and slight PI better than free PI without PS	Conotruncal malformations with right arch, coronary artery anomalies, and 22q11 association
	Right ventricular hypertrophy enhances RVOTO			Possibly balloon valvuloplasty (BVP) if predominantly valvular stenosis			The less orthograde the pulmonary perfusion, the more MAPCAs develop

	Bicuspide PV						Tendency to endocarditis/ paradoxical embolism, as with all cyanotic defects
							Differential diagnosis: Double-chambered right ventricle (DCRV) with (restrictive) VSD

Table 13.17 Absent pulmonary valve syndrome

Clinical features	Anatomy	Shunts	ECG	Rationale for cardiac catheterization	Surgical options	Surgical aims	Special features
Systolic-diastolic heart murmur	Pulmonary valve not formed	Pronounced R/L shunt via VSD with marked pulmonary valve ring stenosis	Right axis deviation	Bronchial stenting experimentally	Valve replacement (Contegra)	Surgery where possible before severe bronchial complications	High mortality rate with severe bronchial symptoms
Massive airway problems from bronchial compression due to ectatic PAs	Only fibrous margin	Hypoplastic peripheral pulmonary arteries (variable) ± relative hypercapnia (compression of airways) in summary → cyanosis of differing degrees	Right atrial hypertrophy (RAH)		VSD closure with baffle patch	Reduction of aneurysmal parts of PA and reanastomosis, plicature	
	Pulmonary (valve) ring usually stenotic to varying degrees		Right ventricular hypertrophy (RVH)		PA reduction plasty		
Stridor heart- and possibly lung-related cyanosis	Variable pulmonary (valve) stenosis						
	Primarily insufficiency, however						

	Central pulmonary arteries usually massively dilated and space occupying						
	Peripheral PA branches often hypoplastic						
	Malalignment VSD						

Table 13.18 Double outlet right ventricle (DORV)

Clinical features	Anatomy	Shunts	ECG	Rationale for cardiac catheterization	Surgical options	Surgical aims	Special features
Subaortic VSD with PST clinical features as with TOF	Both great vessels from the right ventricle – Usually side by side	VSD "directs" blood to outlet valve	Right axis deviation	Anatomy unclear	VSD position? Vessel position? Outflow tract obstruction? Associated malformation?	Corrective surgery	Conotruncal malformation
DORV with subpulmonary VSD with (conal septum)-related subaortic stenosis – As for left heart obstruction	Bilateral infundibular conal septum – muscle tissue interrupts fibrous aortomitral continuity	Vessel position determines flow direction functionally	1st degree AV block	PDA stent	Fallot-type DORV similar to TOF surgery	Sometimes DKS plus right ventricle-PA Conduit required	DORV with subpulmonary VSD Taussig-Bing anomaly: With subaortic stenosis as for left heart obstruction, with free flow as with TGA
Without outlet stenosis, heart failure results together with pulmonary flooding – As with large VSD	Large VSD is left ventricular outlet	With subaortic stenosis and CoA-PDA required for lower half of body	Right ventricular hypertrophy (RVH)	Coronary artery anomaly	If RVOT is inoperable: Rastelli surgery with extracardiac conduit	In rare cases univentricular path if VSD too large or too far from outlet/ non-contractile tunnel patch	As well as malalignment VSD and malposition of great arteries, also AV canal, pulmonary atresia, AV valve anomalies, coronary artery anomalies

Clinical features of TGA with cyanosis and heart failure with subpulmonary VSD and TGA without obstruction ("Taussig-Bing")	VSD position, outflow tract obstruction, and vessel position are determining factors for clinical features and treatment			Rashkind with subpulmonary VSD and insufficient mixing	ASO with TGA plus VSD closure	PA banding can be bridged to decision	Association with syndromes
	Balanced ventricles for biventricular correction			Balloon pulmonary valvuloplasty			

Table 13.19 Tricuspid atresia

Clinical features	Anatomy	Shunts	ECG	Rationale for cardiac catheterization	Surgical options	Surgical aims	Special features
Can be PDA-dependent pulmonary perfusion (IIa), reduced pulmonary perfusion (IIb), or reduced systemic perfusion (IIc) Heart failure with slight cyanosis	Fibromuscular or fibrous membrane	ASD R/L with total cardiac output	Extreme left axis deviation	Gradient at atrial level with clinical signs of backward failure – Rashkind/ stent	DKS reconstruction with open PV and LVOTO	All follow the univentricular palliation path	Caution type II with AST or CoA have hemodynamics as for left heart obstruction
	Type I with normal position of arteries II with d-TGA III with l-TGA		LVH (with left-sided Q waves) RAH/LAH	Gradient via VSD and precise anatomy in case of doubt Older children: PHT testing with c types without restrictive pulmonary flow	Arteriopulmonary shunt in type a and possibly also b		Always VSD except type Ia
Systolic heart murmur through VSD +/– PST	a = PAT – no VSD required b = PST c = free PA flow			Rarely PST for balloon valvuloplasty	Rarely VSD intervention required with DKS		Persistent left superior vena cava

Restrictive VSD in type II can be LVOTO	Size of right ventricle and (muscular) VSD correlate			PDA stent with a types			Associations with syndromes
	RA, LA, left ventricle large, right ventricle often small						

Table 13.20 Ebstein anomaly

Clinical features	Anatomy	Shunts	ECG	Rationale for cardiac catheterization	Surgical options	Surgical aims	Special features
Neonatal cyanosis with (sometimes) PDA-dependent pulmonary circulation	Displacement of septal and posterior TV leaflet to cardiac apex (>8 mm/m^2 BSA)	Regurgitant flow via tricuspid insufficiency – RA volume overloaded	RA dilation and right bundle branch block	PDA stent with duct-dependent pulmonary perfusion	With minimal right ventricle: Modified BT shunt with additionally high-grade/ unreconstructable tricuspid insufficiency, Starnes procedure (=fenestrated TV closure + atrioseptectomy + main PA ligation + BT-Shunt)	Attempt biventricular repair, if needed PVR reduction with medication, tolerance of cyanosis	Rarely associated malformations
Possibly pharmacological PVR reduction and tolerance of cyanosis		Reduced flow to lung	PQ time long (RA dilation) or short (WPW)	ASD closure		Ensure sufficient pulmonary perfusion SpO_2 75%)	WPW/recurrent SVT
Heart failure (primarily backward failure) – Also left ventricular failure with reduced preload, compression/septal shift	Basal right ventricle portions "atrialized," functional right ventricle sometimes small				With dominant tricuspid insufficiency: Valve reconstruction, e.g., Danielson procedure, Cone procedure		History with "difficult" start and improvement thereafter

Heart murmur (tricuspid insufficiency)	Extent of tricuspid insufficiency hemodynamically significant	Neonatal forms require the ASD and are often cyanotic	RA + RV dilatation with large pendulum volume		TV replacement if repair is not feasible	In intermediate cases, consider 1½ circulation	
		Cyanosis, right heart failure, and clinical congestive signs decrease with reduction in PVP			AP shunt with intolerable cyanosis		
SVT (WPW)	Fibrous AV valve ring interrupted (WPW)				ASD reduction or closure		
					Tightening, plicature, size reduction of RA		
Exertional cyanosis in heart failure	Mobility of anterior leaflet, functional right ventricle size and contractility, and RVOTO hemodynamically decisive						
Sometimes respiratory insufficiency, tachydyspnea							

Fallot-like malformations (TOF, PAT/VSD, DORV of the Fallot type) frequently exhibit additional problems at this point. The dysgenesis emanates from the infundibular septum, which is displaced forward and upward. This gives rise to variable constrictions (to the extent even of atresia) of the pulmonary valve and the (proximal) pulmonary arteries, which already compromise the pulmonary circulation in utero and require alternative (= aortopulmonary) pathways of pulmonary perfusion (atypical PDA/MAPCAs). In such cases – as well as in other so-called conotruncal malformations – coronary anomalies, a right-sided aortic arch, and an microdeletion syndromes (21q11) are found more commonly.

Changes of the tricuspid valve also count as obstructions of the right heart. While congenital tricuspid stenosis can occur in isolation, the whole cardiac output in fibromuscular atresia of the tricuspid valve (TAT) must also pass though an atrial septal defect to the left half of the heart and then also via the mitral valve. If the great vessels are normally related (TAT type I), the blood intended for pulmonary perfusion must overcome two possible bottlenecks. More rarely, a restrictive interventricular communication is found (a VSD always exists in TAT, except in type IA), but more frequently there is an atretic (TAT type A) or stenotic (TAT type B) pulmonary valve. These cases, therefore, involve potentially PDA- or MAPCA-dependent forms of pulmonary perfusion. Only rarely is the flow to the lung completely unobstructed (TAT type C).

Normally related great arteries are most frequently found in TAT forms (TAT type I, 69%). d-TGA occurs less frequently (TAT type II, 27%), and l-TGA (TAT type III, 4%) is also found, albeit more rarely. If, however, a constriction is found in the subsystemic outlet in transposed great arteries from a functional hemodynamic perspective, this is a left heart (= subsystemic) obstruction, which in terms of nomenclature and anatomy belongs to the right heart obstructions.

The Ebstein anomaly assumes a further special position. This can result in a functional right heart obstruction due to defective right ventricular ejection that depends essentially on PVR. Thus, forms are frequently found that exhibit a (partial) PDA-dependent pulmonary perfusion postnatally but which then pump increasingly more blood via the right ventricle into the lung in the first weeks of life following physiological PVR reduction. This continues until the cyanosis ultimately disappears, and the formerly vital ASD then shunts left to right.

Overall, in right heart obstructions, clinical signs of backward failure, pulmonary hypoperfusion, and central cyanosis should be sought in addition to heart sounds. As with any patient with aortopulmonary connections, there is a need to be aware of low diastolic blood pressures due to runoff and hence a possibly compromised coronary perfusion. In all patients in whom the pulmonary vascular bed does not act as a “filter,” there is also an increased risk of paradoxical arterial embolism with ensuing microcirculatory problems (caution with central venous catheters).

Table 13.21 Aortic valve stenosis

Clinical features	Anatomy	Shunts	ECG	Rationale for cardiac catheterization	Surgical indications and options	Surgical aims	Special features
Left ventricular forward failure	Incomplete valve opening	PDA with shunt direction	Left ventricular hypertrophy	For intervention (balloon valvuloplasty (BVP))	Instantaneous echo gradient >60 mmHg, mean echo gradient >40 mmHg, (=catheter gradient)	Commissurotomy	Critical AST with left ventricular hypoplasia
Left ventricular backward failure	Valve ring too small	PFO/ASD with significant shunt?	Left-sided repolarization disorders	Critical AST and poor condition	Symptomatic patients	Valve reconstruction	Endocardial fibroelastosis (EFE)
PHT (postcapillary)	Commissural fusion		Ventricular arrhythmias on long-term ECG	Indications as for surgery	Impaired left ventricular function irrespective of gradients	Valve replacement	Shone complex
Systolic heart murmur	Bicuspid valve, unicuspid valve, pinhole opening				Pathological exercise ECG: inadequate increase in HR or fall in BP	Ross procedure	Left ventricle apex-forming? Size?
Ejection click	Valvular dysplasia, thickening		With critical AST (duct-dependent) right ventricular overload and left ventricular ischemia possible				Left ventricular length >20 mm neonatally?

(continued)

Table 13.21 (continued)

Clinical features	Anatomy	Shunts	ECG	Rationale for cardiac catheterization	Surgical indications and options	Surgical aims	Special features
Jugular thrill, syncopes, sudden cardiac death, angina pectoris	Left ventricular hypertrophy (concentric) Left ventricular dilation(?) Critical AS in neonates with right ventricular dilation Critical stenosis has PDA-dependent systemic perfusion EFE?						2 papillary muscles?

Table 13.22 Supravalvular AST

Clinical features	Anatomy	Shunts	ECG	Rationale for cardiac catheterization	Surgical indications and options	Surgical aims	Special features
Heart murmur (without click), thrill	Hourglass-shaped narrowing of STJ due to wall abnormality or supravalvular crest	Rarely associated	Left ventricular hypertrophy	On suspicion of coronary stenoses	Instantaneous echo gradient >60 mmHg, mean gradient >40 mmHg (=catheter gradient)	Eliminate (reduce) gradient	Frequently elastin gene defect (Wiliams-Beuren-syndrome (WBS))
Angina pectoris	Coronary ostia included (?)		Left ventricular repolarization disorders	For visualization of further arterial stenoses	Symptomatic patients	Inspect aortic valve	WBS or Eisenberg type
Very late left ventricular failure	Valve mobility affected (?)		Signs of ischemia	CT angiography frequently sufficient	(Exercise) ECG changes	Coronary osteoplasty, rarely bypass	Hypercholesterolemia?
	Prestenotic dilation of sinus?		Right ventricular hypertrophy with pulmonary stenosis		New or increasing aortic insufficiency		Pulmonary stenoses?
	Left ventricular hypertrophy				LV dilatation or loss of function irrespective of gradient		Outlet stenoses of great arteries requiring meticulous anesthesia because of fall in blood pressure
	Great arteries elsewhere involved?						
	Pulmonary arteries involved?						
	Renal artery stenosis?						

Table 13.23 Coarctation of aorta

Clinical features	Anatomy	Shunts	ECG	Rationale for cardiac catheterization	Surgical indications and options	Surgical aims	Special features
Critical COA with PDA-dependent perfusion of lower half of body Caveat: LV failure	Usually circumscribed narrowing at the isthmus	PDA with preferential R/L shunt downward	Left ventricular hypertrophy	Emergency therapy in neonatal shock	Neonatal critical COA	End-to-end anastomosis after resection	Significantly more boys
Blood pressure gradient Saturation gradient	Rarely also further distally or extended	Shunts with accompanying anomalies	Repolarization disorders	Balloon angioplasty (BAP) up to about 20 kg BW, with >20 kg BW with re-dilatable stents	Gradients >20 mmHg systolicResting or exertional hypertension	End-to-side anastomosis	Frequently in Ullrich-Turner syndrome (UTS)
Heart murmur more in larger children	Frequently with aortic arch hypoplasia Stenosis of proximal subclavian artery			Restenoses for treatment (BAP, stent)	Symptomatic patients	Patch enlargement	Frequent in Williams-Beuren-syndrome (WBS)
Continuous collateral flow murmurs	Left ventricular hypertrophy Bicuspid AV Sawtooth curve on the stenotic aortic Doppler				Morphologically circumscribed narrowing	Interposition graft	Frequently associated malformation with other left heart obstructions (Shone complex)

Hypoperfusion symptoms of lower half of the body, absent or attenuated pedal pulses, unmeasurable leg blood pressure					Treatment of hypoplastic aortic arch where necessary		Association with TGA and DORV
Arterial hypertension (right arm)							Look for aberrant subclavian artery, arterial stenoses, and cerebral aneurysms, differential diagnosis mid-aortic syndrome

Table 13.24 Shone complex

Clinical features	Anatomy	Shunts	ECG	Rationale for cardiac catheterization	Surgical indications and options	Surgical aims	Special features
Heart murmur systolic > diastolic	Supravalvular mitral stenosis Mitral valve malformations (parachute mitral valve/hammock valve)	ASD with L/R shunt in mitral stenosis Strong pulmonary hypercirculation and congestion	LA predominance	If unclear, possibly hemodynamic relevance of MS, postcapillary PAH	Severity and morphology of mitral stenosis determine prognosis	COA resection	Look for PDA, ASD, VSD
Hypertension, heart failure with forward and backward failure	Left ventricular hypoplasia and/or VSD	PDA with R/L shunt in critical neonatal CoA	Left ventricular and possibly also right ventricular overload			Subaortic stenosis resection	
	Subaortic stenosis, aortic valve malformations (with stenosis)	VSD?	Tachycardia			MV reconstruction and resection of supravalvular MS	
	Aortic arch hypoplasia, coarctation of aorta						

Table 13.25 Subvalvular aortic stenosis

Clinical features	Anatomy	Shunts	ECG	Rationale for cardiac catheterization	Surgical options	Surgical aims	Special features
Systolic murmur without click	Subvalvular fibrous crest	Increases VSD shunt	Left ventricular hypertrophy	Possibly with complex anatomy/in association with complex defect	Transaortic resection	Reduction of stenosis	Can be part of obstructive HOCM
Progressive stenosis with late clinical features	Fibromuscular ring		Left ventricular repolarization disorders		Myotomy	Inspection of AV	Caution AoI during subsequent course
Syncopes	Local muscle hypertrophy				Myectomy	Inspection of mitral apparatus	
Angina pectoris	Parts of mitral valve involved				(Modified) Rastan Konno procedure	Avoidance of AOI	
Left ventricular insufficiency	Hypoplastic LVOT (tunnel)				Possibly DKS if complex anatomy		
Postoperative stenosis with compromised left ventricle reduces cardiac output	With Shone complex				Ross-Konno if tunnel-shaped SAS with aortic hypoplasia		
Heaving apex beat	As part of a complex defect						
	Postoperative (e.g., after AVSD correction, VSD tunnel patch)						
	AoI due to jet flow						

13.3.3 Left Heart Obstructions

The group of left heart obstructions also includes types in which the serial hemodynamics are not eliminated but only obstructed (most commonly valvular aortic stenosis, subaortic stenosis, and coarctation of the aorta (CoA)). These are distinguished from those that are dependent on shunt connections between pulmonary circulation and systemic circulation in the event of insufficient systemic perfusion through the subsystemic ventricle. There are sometimes borderline cases between these two clearly definable entities in which it may be difficult to decide therapeutically between a biventricular procedure and (primary) univentricular palliation (see Tables 13.21 and 13.22).

Starting with aortic stenosis, the hemodynamic and anatomical changes can be elucidated. As the blood flow is obstructed but flows serially, this results in prestenotic myocardial hypertrophy, sometimes with additional muscular obstruction of the left ventricular outflow tract (LVOT), in the form of asymmetrical septal hypertrophy and later (following decompensation) of left ventricular dilation. Valvular aortic stenosis may also lead to poststenotic aortic dilatation, and clinically at a relatively late stage to exercise intolerance or angina pectoris, as the coronary circulation is impaired by the increased left ventricular wall tension. In combination with pressure overload of the left ventricle, fatal cardiac arrhythmias can occur. Cardiac output can no longer be increased. In some cases, CO can even be decreased following a sympathetically induced increase in heart rate leading to left ventricular forward failure. Secondly, an emergent diastolic dysfunction interferes with ventricular filling as diastole becomes shorter. As this is usually a slowly progressive process, the increasing LAP ultimately results in a postcapillary pulmonary arterial hypertension (pulmonary edema is more the consequence of an acute increase in LAP). In most cases, however, treatment is given in good time so that this complication is rare.

By contrast, supravalvular aortic stenoses, having similar effects on hemodynamics, exhibit some specific features. They frequently occur in connection with overriding connective tissue disorders (thus necessitating a search for further arterial stenoses) and are more or less unamenable to interventional catheter therapy. As the coronaries are in the prestenotic blood supply region, a hypertension-induced vasculopathy can develop here at an early stage, or the coronaries are themselves part of the disease and exhibit ostial stenoses. There is also the risk in the case of severe left ventricular hypertrophy of inducing relative underperfusion and hence myocardial ischemia postoperatively as a result of a reduction in blood pressure obtained in this area by eliminating the stenosis.

The aortic isthmus is located further distally at the transition of the aortic arch to the thoracic aorta (behind the origin of the left subclavian artery). Isthmic stenosis or coarctation of the aorta (CoA) causes flow acceleration of the blood as well as a relevant fall in distal blood pressure and the previously described consequences of left ventricular hypertrophy. Coarctation of the aorta may be associated with various syndromes e.g., Ullrich-Turner syndrome (UTS) and bicuspid aortic valve, Williams-Beuren syndrome (WBS), borderline small left-sided structures, and Shone complex. The association with a hypoplastic aortic arch is important because it usually exerts an influence on the surgical procedure (median versus lateral thoracotomy).

In "critical" forms of CoA, the lower half of the body following ductus closure is no longer (sufficiently) perfused, and left ventricular failure develops, since this now has to pump all pulmonary venous blood against a massively increased resistance and decompensates.

Older children with coarctation of the aorta are usually identified by a systolic heart murmur or arterial hypertension. A marked blood pressure gradient needs not to present if there is sufficient collateralization. Cardiac consequences of resistance-related hypertrophy and vascular damage may already have occurred in the area of the prestenotic high-pressure region (eyes, brain). If untreated or treated late, CoA can cause the target value for arterial wall tension to be displaced (probably due to changes in the baroreceptors in the aortic arch) and thus in the long-term result in arterial hypertension, which can then persist despite an anatomically perfect surgical or interventional treatment.

In Shone complex, obstructions (and hyperplasia) are present at various levels of the left heart. Many combinations are possible, ranging from a supravalvular (= prevalvular) fibrous constriction of the mitral inflow (= supravalvular mitral stenosis), via valvular mitral stenosis ("parachute mitral valve"), borderline left ventricular size, and left ventricular outflow tract obstruction (LVOTO) with a fibromuscular subaortic stenosis, to aortic valve malformations (bicuspid, dysplastic, stenotic), aortic arch hypoplasia, and CoA. It is always necessary to look for a VSD.

Several aspects are clinically suggestive in the assessment of this very heterogeneous group of patients.

- In the first place, an answer is required to the question of whether elimination of the CoA sufficiently unloads the left ventricle, permitting the patient to thrive and allowing for a sufficient LV growth stimulus. The same applies to a hypoplastic aortic arch.
- This is dependent secondly on the extent of the mitral stenosis. If this is too severe and requires an ASD with L/R shunt as a pop-off, marked pulmonary hypercirculation and congestion occur. With this there is the risk that left ventricular filling is insufficient for its growth and for adequate systemic perfusion. In addition, there is also the threat of congestive right heart failure.

The problem is much more pronounced in hypoplastic left heart syndrome. In this case, the right ventricle must ensure the pulmonary and the systemic perfusion by means of an R/L shunt via the ductus. In aortic and mitral atresia, perfusion of the aortic arch to the coronaries is retrograde only. An additional CoA can be fatal here (paradoxical blood pressure difference). In forms in which the left ventricle makes a (small) contribution to systemic perfusion (mitral stenosis and aortic stenosis, arch hypoplasia, and small left ventricle), antegrade flow occurs into the ascending aorta and arch, and the extent of this can partially determine the therapeutic options over the course of time. This hypoplastic left heart complex thus includes variants without the potential for integrating the small left ventricle into the circulation, as well as borderline cases in which a wait-and-see procedure (by PA banding and ductal stent with restrictive interatrial communication) can potentially also allow subsequent biventricular treatment if left ventricular growth occurs (see Table 13.26).

Table 13.26 Hypoplastic left heart

Clinical features	Anatomy	Shunts	ECG	Rationale for cardiac catheterization	Surgical options	Surgical aims	Special features
Cyanosis decreases with reduction in PVR	Borderline left ventricule: Left ventricular length > 20 mm? Apex-forming? Left ventricle with 2 papillary muscles? MV *Z* score >−3? Severe endocardial fibroelastosis (EFE)? Antegrade perfusion up to PDA (?) or completely retrograde perfusion of ascending aorta	PFO or ASD with L/R shunt	Right hypertrophy, low/absent left ventricular potentials	For PDA stent in conjunction with hybrid procedure	Neonatal surgery without CPB in conjunction with hybrid procedure (bilateral PA banding)	Hybrid situation with bilateral PA banding and PDA stent	Association with syndromes
Systemic hypoperfusion and pulmonary hyperperfusion/ heart failure increases with reduction in PVR, forward/backward failure and pulmonary edema	Complete pulmonary venous return via ASD? Left ventricle without contribution to systemic cardiac output?	PDA with (systolic) R/L shunt and diastolic L/R shunt	RA predominance	For Rashkind or ASD stent with restrictive PFO (mean gradient >4 mmHg)	Neonatal major CBP procedure (Norwood)	Norwood procedure with DKS and aortic arch reconstruction as well as AP shunt (modified BT shunt) or right ventricle-PA shunt (Sano)	Extracardiac malformations, microcephaly

PDA closure results in shock and MOF, acidosis, and pulmonary flooding in tachypnea and pulmonary edema	MST and aortic atresia with sinusoids? Retrograde coronary perfusion, EFE (?)	Retrograde arch perfusion	Tachycardia			Elimination of any CoA	Restrictive atrial communication results in pulmonary congestion and edema, pulmonary (lymph-) angiectasis, remodeling/ arterialization of pulmonary veins
No definite heart murmur	Aortic arch anomalies and CoA, arch width in all segments? TI quantified?	PDA closure with shock and increasing SpO_2	Signs of ischemia?				VSD, coronary artery anomalies, persistent left SVC
	With high SpO_2 ASD can be "relatively restrictive"						

Table 13.27 Aortic insufficiency

Clinical features	Anatomy	Shunts	ECG	Rationale for cardiac catheterization	Surgical indications and options	Surgical aims	Special features
Exercise intolerance	Valve morphology (hole, coaptation defect, vegetations, paravalvular leak), cusp prolapse, position of insufficiency jet, central, between which cusps?	Mainly none	Left ventricular hypertrophy	Possibly visualization of coronaries in aortic root surgery	Always if symptomatic	Valve reconstruction	Cardiomegaly on X-ray – Diagnostically obsolete
Dyspnea	Jet width measured relative to LVOT Vena contracta		Prominent Q (V5, V6)		LVEDD exceeding normal range	Ross procedure	MRI quantifies regurgitation and left ventricular volume well
Chest pain	Determine/describe depth of penetration of jet into left ventricle		Repolarization disorder (late)		Reduced EF	AV replacement	Early therapy, if AoI mechanically induced with VSD or subaortic stenosis
Syncope	Measure pressure half time						Afterload reducing medication with caution
Tachycardia	LVEDD enlarged		Tachycardia with acute aortic insufficiency				Preferably not beta-blockers

Diastolic heart murmur	Diastolic backflow into left ventricle starting where?						Common in Marfan, connective tissue disorders
Low diastolic BP with large amplitude (water hammer pulse)	SF decreases late						

Table 13.28 Mitral insufficiency

Clinical features	Anatomy	Shunts	ECG	Rationale for cardiac catheterization	Surgical options	Surgical aims	Special features
Forward failure and backward failure Pulmonary edema in acute MI	Dilated valve ring, (residual) cleft, MV prolapse	Pendulum volume	"P mitrale" (LAH)	Possibly diagnostic with PHT monitoring	If anticongestive therapy with afterload reduction and spironolactone is insufficient	Reconstruction	Congenital – Cleft with AV canal + MI with TGA
Chronic heart failure and PHT with slow decompensation, "cardiac asthma"	Leaflet dysplasia	Systolic backflow into the pulmonary veins	LVH		MV plication and sometimes maze procedure	Reduction/ elemination of insufficiency without creating stenosis	Ischemia
Caution supraventricular arrhythmias	Rupture of chordae tendineae		RVH (with PAH)		MV replacement (from 15 mm to larger)		Postoperatively
Systolic heart murmur conducted to axilla	Papillary muscle abnormality		Supraventricular arrhythmias/SVT				Connective tissue diseases/storage diseases – Esp. Marfan syndrome
Tachycardia as compensation mechanism	LA and left ventricular dilation						Postinflammatory, e.g. after endocarditis

	Even with significant MI, SF can still be normal						With left ventricular volume overload/very late with pressure overload
	Dilated LA indicates significant MI						(slight) MI with prolapse
	Look for coaptation defect/vena contracta						

Table 13.29 Transpositions of great arteries (TGA)

Clinical features	Anatomy	Shunts	ECG	Rationale for cardiac catheterization	Surgical options	Surgical aims	Special features
Progressive cyanosis with PDA closure	d-TGA with aortic origin at RVOT	Parallel circulation with obligate shunt via ASD R/L and PDA L/R	Right ventricular hypertrophy (RVH)	Rashkind with deep cyanosis	Anatomical correction (= arterial switch operation (ASO) with Lecompte), i.e., aorta completely behind PA	Surgery only with trained left ventricle (PVR falls rapidly), i.e., in the first 10–14 days	ASD and PDA required for shunt
Severe cyanosis with ASD restriction or PHT	Coronary arteries arise from sinus, lying directly opposite the pulmonary valve (“facing sinus”)	VSD with increasing R/L shunt		Possibly PDA stent with VSD (and septal deviation) to postpone corrective surgery	With LVOTO, possibly Rastelli with extraanatomical conduit	Later surgery with larger VSD or after PA banding (“LV training”)	VSD with outflow tract obstructions
Heart murmur with VSD or outlet stenosis	Coronary anomalies not infrequent, intramural course?				Alternative complex surgical procedures Nikaido and REV with outflow tract and valve reconstruction	ASD closure, stenosis-free outflow tracts, coronary arteries without distortion/ torsion	l-TGA without cyanosis
	Small VSD insignificant						Double outlet ventricle with malpositioned great vessels

	Large VSD with good preoperative mixing, but greater surgical risk							
	Malalignment VSD with outflow tract obstruction and straddling of AV chordae tendineae							
	Anterior septal deviation results in RVOTO (= subaortic stenosis) and AO arch hypoplasia							
	Posterior septal deviation results in LVOTO, possibly with additional pulmonary stenosis							

Many criteria are incorporated in the assessment of borderline left ventricles. As well as anatomical features (mitral valve annulus, left ventricular volume, aortic valve annulus, EFE, number of papillary muscles, etc.), these also include hemodynamic parameters (e.g., antegrade perfusion of the head, neck and right arm? evidence of PHT in restrictive ASD?) and parameters of dynamic development, such as the thriving of the child on therapy, and left ventricular growth over time (see Table 13.26).

In some cases, a clear decision on the best type of treatment (uni- versus biventricular) is not possible at the outset, so that in the end the disease course determines the choice of best treatment. Particularly in such borderline cases, a hybrid procedure (ductal stent plus bilateral PA banding) can offer the advantage of delaying the time of the ultimate decision.

The hemodynamics of classic HLHS spare the left ventricle, and pulmonary venous blood reaches the right ventricle (in some cases with a gradient) via the atrial septum, from where it is pumped on the one hand into the lung and on the other via a PDA into the systemic circulation. The distribution ratio between pulmonary and systemic perfusion depends on many influencing factors, some of which are difficult to balance. On the pulmonary side, PVR and the L/R shunt gradient at the atrial level play the main roles, whereas systemic perfusion depends on the resistance of the PDA and systemic vascular resistance. In addition, the perfusion areas of the heart and head lie in the area of retrograde aortic arch perfusion, so that CoA here can have a deleterious effect. Diastolic runoff is frequently the deciding factor, which then "draws" the blood retrogradely in diastole via the PDA into the pulmonary perfusion with decreasing PVR, where in particular it compromises the already reduced coronary perfusion.

Left heart hypoplasia is associated with about 10% of children with syndromal and extracardiac diseases (e.g., of the gastrointestinal tract and the CNS, including microcephaly).

13.3.4 TGA

d-TGA represents a largely independent entity in terms of hemodynamics. The aorta – together with the aortic valve and coronaries with a frequently show an abnormal distribution pattern – arises from the right ventricle, which is located in the typical position. Admittedly, the aorta also arises to the right of the pulmonary artery in d-TGA but very far to the front. The large vessels do not cross over in the vicinity of the heart (PA in front of aorta is normal) but follow a parallel course; and after this parallel course to the pulmonary trunk, the aorta then proceeds beyond the r-PA to the left into the posterior mediastinum. In simple forms of this malformation, "only" transposition of the vessels occurs, whereas in more complex forms, there can be in particular VSD (about 40% of all TGA), outflow tract obstructions to the lung, AV valve anomalies, and constrictions in the aortic isthmus, which considerably affect the hemodynamics and also especially the surgical procedure.

The hemodynamics can be elucidated initially on the basis of a simple TGA: on the one hand, oxygen-rich blood must reach the subsystemic right ventricle. On the other hand, while blood from the systemic circulation must also be made available to the pulmonary perfusion via the PDA. When circulations are connected in parallel, the net

shunt amount must be equalized. The patient is therefore dependent on an interatrial communication for oxygenated PV blood to reach the right ventricle. Only a very large atrial communication with sufficient bidirectional shunt can do without a PDA.

A smaller VSD also has no effect in this situation, since with lower PVR a lower pressure now prevails in the subpulmonary left ventricle, and therefore no enriched blood passes to the right. Only a larger VSD allows for adequate mixing here, thus resulting in sufficient SpO_2 values. On postnatal adaptation – PVR decreases and PDA is reduced in size with the (in this case minor) O_2 stimulus – there is the threat of functional closure of the interatrial communication from the now higher LAP. However, the TGA patient is at this point dependent on an L/R shunt, and thus, restrictive atrial communication simultaneously means deep cyanosis. This can be enhanced if metabolic acidosis develops as a result of peripartum problems or a hypoxemia-induced anaerobic metabolic situation, and pulmonary arterial resistance increases above systemic resistance. As well as a sufficient interatrial communication (Rashkind) and an open PDA (PGE1), a reduction in PVR must also be induced to increase arterial saturation (O_2 administration, buffer, iNO). Reflexive reinforcement of ventilation therapy (in the ventilated child) tends to be counterproductive with increasing mean airway pressure. If chest X-ray findings and pulmonary compliance are normal, a maximal respiratory minute volume (RMV) of 200–300 mL is fully sufficient.

It is apparent from what has gone before that life-threatening hypoxia can develop in simple TGA because of "inefficient" shunts. Therefore, in the preoperative diagnostic investigations, particular attention must be paid to the shunt situation as well as to the basic anatomy. As well as size and direction of flow, gradients must also be estimated. It is only when an overall picture has been established that it is possible to decide how prostaglandin therapy, fluid volume administration, and respiratory situation should be adjusted.

So-called "complex TGA" exhibits relevant VSD and/or additional malformations. These can affect the preoperative management as much as the surgery itself. Large ventricular septal defects, stenoses in the inflow to the pulmonary circulation, coronary anomalies, coarctation of the aorta, and AV valve pathologies are of particular significance. Vice versa, TGA or malposition of the great vessels relative to the ventricles can constitute part of many complex heart defects. While anomalies of the coronaries are important for surgical planning (no contraindication for surgery), large VSD, for example, may simplify preoperative management – without prostaglandins, no deep hypoxemia and no need for Rashkind. Additionally, surgery can be postponed to early infancy on grounds of neuroprotection, among others, since the left ventricle continues to be trained by pressure equalization. On the other hand, large VSD in small hearts frequently represents a particular surgical challenge that can result postoperatively in reduced heart function, AV valve problems, or heart blocks. In addition, with pressure-equalizing VSD, there is a particular risk of a postoperative PHT crisis.

If the pulmonary valve (left ventricular outlet valve and later neoaortic valve) should be too small, stenotic, or dysplastic or the pulmonary blood flow is reduced by intracavitary left ventricular constriction, the patient is all the more dependent on the L/R shunt via the PDA. However, the intraoperative procedure in particular can be considerably more complicated and then have considerable consequences for the postoperative intensive phase (myocardial stunning, LCOS, etc.).

13.3.5 Total Anomalous Pulmonary Venous Connections

Total anomalous pulmonary venous connections also constitute a group of cardiovascular malformations in their own right, since in this case specific hemodynamics come into play. PV blood usually reaches the vena cava (= supra- or infracardiac type) from a retrocardiac confluence either via connecting veins or reaches the RA directly in the area of the coronary sinus (= cardiac type), which accordingly conveys mixed blood. Filling of the left half of the heart is dependent on the R/L shunt at the atrial level. Accordingly, an apparently small left ventricle is frequently found.

In this situation, the reduction in PVR results in an increasing right-sided volume overload with pulmonary hypercirculation and developing global heart failure. If the connection of the pulmonary veins to the right-sided circulation is obstructed (stenoses of draining venes, extravascular compression by diaphragm, or adjacent structures), even more complex hemodynamics result: in existing postcapillary PHT, considerably less, and considerably lowered saturated blood is available to the systemic circulation, so that severe cyanosis and circulatory insufficiency are combined. Therapeutic approaches such as pulmonary vasodilation (exacerbates pulmonary edema) and vasopressors (tend to reduce cardiac output) are more or less unable to stabilize the patient in this situation so that an emergency surgical intervention is required.

In addition to the anatomy of the pulmonary venous drainage and any stenoses (flow acceleration to more than 1.6 m/s is usually significant), the ASD with the R/L shunt gradient, the comparative dimensions of the ventricle, and the direction of flow in the PDA must be reliably documented. A more precise elucidation of the anatomy is often better possible with CT angiography/MRI. Not infrequently, especially in compex heart defects one or all of the pulmonary veins do not flow orthotopically, which means that here such anomalies should be looked for specifically (see Table 13.30).

13.3.6 Functionally Univentricular Hearts

The range of functionally univentricular hearts extends from types in which only a very large ventricular septal defect precludes a biventricular correction, via unbalanced ventricles in which the excessively small ventricle cannot assume the circulatory function, to double-inlet ventricles in which the ventricular morphology may or may not be definable. The common feature of this entity is that treatment requires a palliation pathway via a Glenn anastomosis (PCPC) to Fontan circulation (TCPC) and thus in the end “passive” pulmonary circulation. Pulmonary blood flow in the total cavo-pulmonary connection (TCPC) is driven by the breathing pump (blood is sucked into the lungs during inspiration) and the diastolic “suction effect” of the systemic ventricle, supplemented by the sceletal muscles during walking and exercise. These mechanisms replace the right heart, and the existing ventricle connected in series after the pulmonary circulation bears the systemic circulation. Without additional malformations, although these are very common in this very heterogeneous group, both great arteries arise from ventricles that function as one, which conveys mixed blood prior to the TCPC (see Tables 13.31, 13.32, 13.33 and 13.34).

Table 13.30 Total anomalous pulmonary venous connection

Clinical features	Anatomy	Shunts	ECG	Rationale for cardiac catheterization	Surgical options	Surgical aims	Special features
Without obstruction, rapid heart failure with pulmonary hypercirculation, systolic heart murmur (relative pulmonary stenosis), fixed and widely split 2nd heart sounds, possibly 3rd heart sound	Pulmonary venous blood drains into large RA – Via coronary sinus (CS) or via collecting vessel and connecting veins to vena cava	Complete cardiac output must pass via R/L shunt into LA and ASD can be restrictive	Right atrial hypertrophy (RAH), right ventricular hypertrophy (RVH)	Rarely preoperative balloon atrial septostomy (BAS) before correction surgery with restrictive ASD	Connection of confluence to LA	Stenosis-free pulmonary vein connection to LA	Sometimes with univentricular hearts
With obstruction, white lung with oxygenation disorder and forward failure	Supracardiac to SVC via confluence and vertical vein	Dilated systemic veins can be part of the circulation		Rarely retrograde stenosis stenting in TAPVR with pulmonary venous drainage stenosis	ASD closure	Surgery on pulmonary veins themselves with risk of restenosis, sutureless technique	Association with syndromes
	Cardiac to CS	Sometimes CT or MRI required to visualize the anatomy and obstruction			Closure of "bypass vein"		Heterotaxia syndromes

(continued)

Table 13.30 (continued)

Clinical features	Anatomy	Shunts	ECG	Rationale for cardiac catheterization	Surgical options	Surgical aims	Special features
	Infracardiac (diaphragmatic) via collecting vessel to IVC/hepatic veins/ portal vein (frequently with obstruction)				With direct pulmonary vein connection to RA, baffle patch in atrium		Left ventricle can be small if ASD restricts flow
	Left ventricle frequently appears borderline small						

Table 13.31 Large VSD/AV canal subtypes

Clinical features	Anatomy	Shunts	ECG	Rationale for cardiac catheterization	Surgical options	Surgical aims	Special features
Heart failure type if no PST	Normal vessel position	Increasing L/R shunt on reduction in PVR	Biventricular hypertrophy	For PHT testing	PA banding – If there is a later option for biventricular correction	Reduction of pulmonary blood flow with hypercirculation	Rarely
Cyanosis type if PST	VSD so large that closure appears impossible	With later increase in PVR, then decrease in L/R shunt			If univentricular: AP shunt and DKS anastomosis or PAB to balance pulmonary flow	Prevent PHT	CoA more likely in LVOTO
Heart murmur and forward-backward failure as well as pulmonary congestion	AV canal with one hypoplastic ventricle ("imbalanced") or severe septal hypoplasia	Look for PDA			PDA closure and possibly CoA treatment	Preparation for PCPC	In PST, the hemodynamics may possibly self-balance as "autologous banding"
	Mostly no LVOTO	Cyanosis in Eisenmenger's reaction (but sometimes also without Eisenmenger! – Intraventricular mixing in large VSD)					

Table 13.32 Double inlet left ventricle (DILV)

Clinical features	Anatomy	Shunts	ECG	Rationale for cardiac catheterization	Surgical options	Surgical aims	Special features
Univentricular circulation → PVR determines clinical features	Both atria drain into the morphologically left ventricle	Frequently no ASD	Usually marked LVH	Usually only before Glenn	Univentricular	Free outlet to systemic circulation of both ventricles	Look for CoA
Restrictive bulboventricular foramen (RBF) can act like subaortic stenosis in TGA	Right ventricular rudiment mainly left – Ventricular inversion is then present (about 40%)	VSD with flow to aorta (l-TGA) or PA (normal position – Rare)	Look for Qs in III, aVF, and V1	Before TCPC	DKS anastomosis and modified BT shunt	Pulmonary perfusion by aortopulmonary shunt	Caution: Spontaneous AV block even without surgery (l-TGA)
If PA from right ventricle, pulmonary perfusion can be limited by RBF/VSD (rare)	Usually with l-TGA → right-sided left ventricular pumps into aorta	PDA required?			AV valve reconstruction if insufficiency	Glenn	Heterotaxia?
Subpulmonary stenosis can also restrict pulmonary flow – Mild cyanosis (“autobanding”)	VSD (here bulboventricular foramen) can be restrictive				Surgery on septum in RBF highly disputed (preferably DKS)	TCPC	
Systolic murmur with subpulmonary stenosis or RBF	AV valve dysmorphism?						
(Mild) cyanosis and heart failure							

Table 13.33 Double outlet left ventricle (DOLV)

Clinical features	Anatomy	Shunts	ECG	Rationale for cardiac catheterization	Surgical options	Surgical aims	Special features
Cyanosis dependent on PVR and PST	Both great arteries (predominantly) from the left ventricle	VSD channels right ventricle blood to outlet valves	Left ventricular hypertrophy (LVH)	Precise anatomy – Preferably MRI	Mostly biventricular	VSD closure with baffle patch	Rare malformation
Systolic murmur in PST	75% suitable for biventricular procedure	PDA for pulmonary perfusion rarely necessary		Stenosis gradient?		VSD closure plus valve reconstruction	Segmental approach to classification mandatory
HF with pulmonary hypercirculation	With TAT or severe right ventricular hypotrophy, inoperable OTO only univentricular					RV-PA conduit	
	VSD position relative to outlet valves?					DKS, aortopulmonary shunt until Glenn/ TCPC	
	Positional relationships of outlet valves to one another						
	(Sub)valvular stenoses?						

Table 13.34 Diagnostic procedures before Glenn anastomosis

Clinical features	Anatomy	Shunts	ECG	Rationale for cardiac catheterization	Surgical options	Surgical aims	Special features
Cyanosis – Severe in the event of reduced pulmonary perfusion	DKS and/or Norwood/ Sano shunt	PDA or AP shunt	Hypertrophy	Measurement of PVR and PAP	Shunt closure +/− aortic arch reconstruction	Volume unloading of ventricle	Hybrid procedure delays aortic arch surgery until infancy
Heart failure with pulmonary hypercirculation	Bilateral PA banding plus PDA stent	MAPCAs	Otherwise unspecific	Measurement (L) VEDP, or PC wedge, calculation of transpulmonary gradient	SVC to central PA +/− central PA reconstruction	Partial (50–60%) "passive" pulmonary perfusion	Right isomerism with 2 sinus nodes (possibly alternating P-axis/ shape)
Heart murmur plus shunt murmur	AP shunt "only"			Visualization and possibly intervention on PAs	Closure of azygos vein (if IVC present)	"Free" aortic arch	Left isomerism without sinus node (deep atrial rhythm, possibly junctional replacement, bradycardiac arrhythmia)
Heart not yet volume unloaded – Only balanced				Visualization of aortic arch			
Organ damage after neonatal phase or interstage (?)				Closure of collaterals (venovenous, MAPCAs)			

With "uninhibited" parallel circulation, the physiological reduction in PVR results in the first days to weeks of life in massive pulmonary hypercirculation, which on the one hand is accompanied by forward failure as a result of the inability of systemic perfusion to be increased and on the other by congestive heart failure with pulmonary flooding and congestion in the body's veins. Increasing transcutaneous saturation and an increase in respiratory rate are frequently the first symptoms to be observed clinically.

In addition to the history-taking and the clinical examination, echocardiography usually suffices for a preliminary classification. This involves an evaluation of the atria, AV valves, ventricles and their outlets, as well as the great vessels near the heart, in terms of morphology and position, and, if additional abnormalities are present, assessing their effects on hemodynamics.

As some malformations, including some that are serious, such as an anomalous pulmonary venous connections and major large septal defect, are less relevant from a hemodynamic aspect and tend to be more important from the point of view of planning surgery, other associated anomalies exert a considerable impact.

While AV valve insufficiencies, for example, exacerbate the in any case already considerable volume overload of the ventricle, outlet stenoses to the pulmonary vessel bed can act as congenital PA banding and reduce, and sometimes even persistently balance, the pulmonary circulation. These contrast with outlet stenoses to the systemic circulation which can trigger forward failure or, in the worst-case scenario, even engender PDA-dependent systemic perfusion. Obstructions to the systemic circulation can be found at the valve level or in the area of the aortic arch but can equally be due to muscle bundles or restrictive interventricular communication in the case of double-inlet ventricles (restrictive bulboventricular foramen) (see Table 13.32).

In sum, the hemodynamics must be investigated morphologically (segmental approach) and pathophysiologically. In this case, the position of the unpaired abdominal organs, the connection of the great veins to the atria, the orifice of the pulmonary veins, and the disposition of the arteries in the vicinity of the heart are of particular importance. What information for treatment planning cannot be obtained from the basic diagnostic investigations must be established by additional diagnostic procedures as necessary (MRI, CT, catheter).

13.3.7 Univentricular Palliation

Following the first step of separating the circulations connected in parallel, which, depending on the cardiac defect and the clinical and anatomical situation, consists of controlled pulmonary perfusion (PA banding, aortic/systemic to pulmonary shunt, Sano shunt, PDA stent, or PGE1 therapy) on the one hand and the best possible, unobstructed perfusion of the systemic circulation on the other. The univentricular heart, which has to feed both circulations, is still volume overloaded.

In the first step of volume unloading, pulmonary perfusion is then provided by anastomosis of the superior vena cava to the (usually right) pulmonary artery. The preexisting pulmonary perfusion pathway is interrupted surgically. Major vessels between the body's veins above and below the Glenn anastomosis (in particular azygos vein, venovenous collaterals) are closed.

A particular situation pertains in the case of left heart obstructions with preexisting PDA-dependent systemic perfusion, as in status-post hybrid procedure. Here, the ventricular outlet must first be constructed by DKS anastomosis and aortic arch reconstruction in addition to the Glenn procedure (comprehensive stage II, CBP surgery with aortic clamping).

As the driving forces of the "passive" pulmonary perfusion are on the one hand the preload before the Glenn anastomosis and the diastolic "suction effect" of the systemic ventricle and on the other and the subatmospheric intrathoracic inspiratory pressure in spontaneous breathing, the Glenn procedure can only be performed after a complete fall in PVR after several months of life and only with unobstructed flow into the pulmonary arteries. Diagnostically, echocardiography alone is usually insufficient here; hence anatomy, pressure, and flow relationships must be evaluated by cardiac catheterization. This is done in order to document a sufficient reduction in PVR to allow surgery but also in order to manage preexisting problems in the pulmonary supply area therapeutically, if needed. Such problems can include circumscribed constrictions in the pulmonary arterial system, collaterals connecting body veins of the upper and lower half of the body or with pulmonary venous or intracardiac cavities, as well as a competing pulmonary flow from the systemic arterial territory (MAPCAs) (see Table 13.35).

The preoperative diagnostic investigations prior to complete circulatory separation (TCPC) generally involve not only history-taking and clinical and echocardiographic examinations but also cardiac catheterization. Similar to as before a Glenn anastomosis, primary importance is attributed to achieving optimal conditions for the (single) ventricle with AV valves, outflow tract and anastomoses, unobstructed pulmonary arteries, and venous problems and collaterals. MAPCAs, connections of the systemic veins to the pulmonary veins or the atrium, and venous and pulmonary arterial stenoses can be managed therapeutically. The invasively measured hemodynamics (transpulmonary gradient between PA pressure and end-diastolic pressure in the single ventricle) as well as the patient's clinical status provide indications, for example, of the need for fenestration of the proposed TCPC to the atrium.

Table 13.35 Diagnostic procedures before TCPC (Fontan completion)

Clinical features	Anatomy	Shunts	ECG	Rationale for cardiac catheterization	Surgical options	Surgical aims	Special features
Heart murmur rarer (AV insufficiency/outlet stenosis, residual CoA/anastomotic narrowing?)	Mostly unilateral and bidirectional Glenn	MAPCAs	Cardiac arrhythmias	Pressure measurement and flow calculation before complete circulatory separation	TCPC with extracardiac conduit	Complete circulatory separation	Even small gradients in PA region with major consequence for pulmonary flow
Cyanosis (SpO_2 70–85%)	Unobstructed flow through PAs?	Venovenous collaterals?	Otherwise unspecific	Closure of collaterals	Fenestration with high TPG and MAPCAs	Maximum volume unloading of the univentricular heart	Particularly in heterotaxia, visualization of hepatic veins
Venous congestion (particularly upper half of body)	Collateral veins to pulmonary veins, atrium or lower half of body	Aorto-pulmonary collaterals?/ residual MAPCAs?		Opening, dilation, or stenting of flow obstructions in PA vascular territory	Enlargement/ reconstruction of central PAs		
Heart failure improved	MAPCAs	Intrapulmonary shunts?			Intervention on aortic arch narrowing		
However, performance impairment/failure to thrive/edema					Rarely intracardiac tunnel		
Bronchial infections							
Neurological problems after difficult neonatal phase?							

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Considerations for Hemodynamics

14

Dietrich Klauwer and Christoph Neuhaeuser

14.1 Preliminary Considerations

The energy required for the cardiomyocytes to contract is provided in the healthy heart at rest by free fatty acids, glucose, and lactate in approximately equal proportions. With increased load and unchanged force-frequency coupling (Bowditch effect), increasingly more glucose and lactate are consumed proportionately until ultimately the limit of aerobic metabolism is reached, and, with little possibility of increasing O_2 extraction (>65% of the delivered O_2 is already extracted at rest), the heart itself produces lactate (= lactate reversal). In the process, mechanical systole (= phase of isovolumetric contraction plus the ejection phase) requires about three quarters of the energy, while diastole (= isovolumetric relaxation plus the ventricular filling phase) also requires about 25% of the energy. This energy is used essentially for structural maintenance, regeneration of membrane potentials, and atrial systole.

As energy supply is critical only in exceptional situations (severe hypoglycemia/metabolic defects), O_2 provision takes precedence. Coronary blood flow is therefore a crucial variable in this process: This can be enhanced by an increase in rate, coronary vasodilation, opening of precapillary sphincters with an enhanced blood supply requirement, and increased perfusion pressure. In this respect, two mechanisms must be considered critically from an economic perspective:

D. Klauwer (✉)
Department of Pediatrics, Singen Medical Center, Gesundheitsverbund Landkreis Konstanz, Krankenhausbetriebsgesellschaft Hegau-Bodensee-Klinikum, Singen, Germany

C. Neuhaeuser
Pediatric Intensive Care Unit, Pediatric Heart Center of Giessen, Children's Heart Transplantation Center, UKGM GmbH,
Giessen, Germany
e-mail: christoph.neuhaeuser@paediat.med.uni-giessen.de

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D. Klauwer et al. (eds.), *A Practical Handbook on Pediatric Cardiac Intensive Care Therapy*, https://doi.org/10.1007/978-3-319-92441-0_14

Firstly, an increase in rate can increase coronary O_2 delivery only up to a certain point – once this is exceeded, there is an O_2 delivery mismatch as a result of a reduction in the duration of diastole with a concurrent rate-dependent increase in contraction.

Secondly, adrenergic coronary vasodilation (predominantly mediated by β_1 receptors) is also exhausted by increases in rate and contractility, and, as a result of additive adrenergic effects (α-receptor-mediated vasoconstriction), a disproportionate increase in O_2 consumption occurs as heart rate increases.

In addition to the previously described preload dependency of ventricular filling and the reduction in contractility on overdistension (see Starling curve), the afterload and the muscular condition of the myocardium itself naturally play important roles. Kinetically, the afterload describes how much energy must be used for isovolumetric contraction until the aortic valve opens in order to build up wall tension that overcomes systemic vascular resistance.

By increasing contractility and wall tension within limits, the healthy left ventricle can overcome a higher afterload – under exertion, systolic blood pressure rises (increased contractility) far more than diastolic. In resistance-induced concentric hypertrophy of the ventricle (the contractile elements of the individual muscle cells proliferate), a higher ventricular pressure can be generated with unchanged wall tension. According to Laplace's law, wall tension is inversely proportional to wall thickness. Wall tension (κ) = ventricular pressure × ventricular radius/2 × wall thickness.

This compensation mechanism is acquired on the other hand at the expense of reduced diastolic compliance – the hypertrophic ventricle requires a comparatively longer diastole for optimal filling and is highly dependent on the active component of ventricular filling due to atrial systole (A wave of transmitral inflow or A wave of the atrial pressure curve). Therefore, compared with a ventricle with normal wall strength, cardiac output can barely be increased at all in a (hypertrophic) ventricle trained against resistance, even at lower heart rates or following loss of sinus rhythm.

In a dilated ventricle with a comparatively thin ventricular wall (= high wall tension), all compensation mechanisms are compromised in parallel. In order to be able to maintain cardiac output when contractility is impaired, the heart slips into the distension range on the Starling curve by a neuroendocrine, primarily RAAS-triggered, mechanism. As a result of sympathomimetic stimulation, the (overdistended) ventricle approaches the limit of its contractility reserves, while the heart rate also increases to maintain organ perfusion. An increase in afterload here can then rapidly overburden the heart. In this case, therapeutic afterload reduction must be accomplished carefully so as not to compromise coronary perfusion.

This yields a range for the optimal, i.e., most economic, cardiac output for each heart in relation to the physiological requirements of the circulation that depends on contractility, filling pressures and volumes, wall thickness, and wall tension of the overloaded ventricle, as well as on the physiological demands that the body places on the system (= O_2 requirement).

On the venous side of the circulation, various mechanisms cause the return of blood from the capillary venous branch (capillary filling pressure about 15–25 mmHg) to the heart.

The well-contracting right ventricle generates a suction effect in the venous system in systole by displacing the AV valve level with the AV valves closed (valve level mechanism identifiable by the X wave of the atrial curve = lowest pressure level) and draws the returning blood to the heart. The negative intrathoracic pressure of inspiration in spontaneous breathing acts on venous blood flow in a similar fashion. The effect of the muscle pump (with preserved venous valves) is slight in immobile patients. However, atrial systole with an opened AV valve contributes up to 20–25% to ventricular filling (particularly in tachycardia) and thus to the forward transport of the venous blood into the ventricle.

All these mechanisms can only work if diastolic ventricular function is unimpaired:

In the case of diastolic dysfunction, on the one hand, energy-consuming (isovolumetric) ventricular relaxation can be impaired – in the short term, β_1 stimulants can then improve lusitropy (= capacity of the cardiomyocytes to relax). On the other hand, a high wall tension on relaxation (ventricular hypertrophy) and an increased end-diastolic ventricular pressure due to a systolic function disorder can obstruct filling of the ventricle with venous blood.

The mechanism of interventricular interaction (interventricular dependency) comes into play to only a limited extent following cardiac surgery with opened pericardium, but it is certainly important following pericardial closure.

RV and LV share the space within the pericardium. The pericardium is distensible only to a very limited extent (exponential distension curve). Acute volume changes in one ventricle therefore also act directly on the other. If, for example, right heart dilation occurs in association with an acute increase in pulmonary afterload (e.g., PHT crisis), the septum is shifted to the left, and the LV is compressed (the position of the septum is dependent on the respective pressures in the right and left ventricle). If a ventricle is compressed from the "outside," ventricular compliance decreases (ventricular filling disorder), thereby causing the end-diastolic volume (EDV) and stroke volume (SV) to decrease as well. As a result of the unloading of a dilated ventricle, therefore, the filling of the other ventricle is improved, which can lead to a "paradoxical" increase in cardiac output.

Echocardiographic measurement methods

Extensive experience is required for purely visual identification of the systolic function of the ventricles (eyeballing). If no regional wall movement disorders are detected here, the method of determining ventricular fractional shortening (FS) by measuring the diastolic and systolic internal diameter of the left ventricle in the parasternal long axis orthogonally in the area of the tendinous cords or in the parasternal short axis below the mitral valve level can be of use. (Paradoxical septal movements are also always found after arterial switch surgery in Bland-White-Garland syndrome or in patients with large atrial septal defects (ASD), so that FS is not 1:1 transposable, but nevertheless LV function can be estimated in this way.) At both levels, the right ventricle can also be assessed at the same time.

Formula 43

$FS = [(Diam_{ed} - Diam_{es})/Diam_{ed}] \times 100\%$

Normal: ≥28–30%

Using the multislice summation method (biplanar) or other approximation procedures (including monoplanar), the ejection fraction (EF) can also be estimated from the ratio of the end-diastolic ventricular area to the end-systolic ventricular area if the endocardium is clearly identifiable.

Formula 44

$$EF\,in\% = \left[\left(Vol_{ed} - Vol_{es}\right) / Vol_{ed}\right] \times 100$$

or

$$EF\,in\% = SV / EDV \times 100$$

Normal: >50% (<30% severely impaired)

Example:

1. Where EDV = 100 mL and SV = 60 mL → EF = 60%
2. Where EDV = 200 mL and SV = 60 mL → EF = 27%

Example 2 shows that a "weakly" dilated ventricle can still generate normal cardiac output despite a reduced ejection fraction (at rest). During exertion (increased VO_2) or stress (higher systemic vascular resistance [SVR]), however, systolic function sometimes is insufficient to cover the increased need (= sign of heart failure).

To measure this, the diameter of the lumen (= endocardium-to-endocardium) is determined. The dimensions mentioned are particularly important for ongoing monitoring in myocardial diseases of the left ventricle and in patients with biventricular anatomy and must be considered strictly in relation to the patient's clinical situation.

An absolute estimation of stroke volume as would be required to determine cardiac output (CO = SV × HF) is more or less impossible by echocardiography. By way of approximation, the VTI (velocity-time integral), measured by pulsed-wave Doppler via the LVOT, for example, can be multiplied by the cross-sectional area instead. Most ultrasound devices provide algorithms for this purpose, as well as for the measurement of rates of pressure rise via valve regurgitations. When assessing FS and EF, it should be borne in mind that in patients with significant mitral or aortic insufficiency as a result of regurgitant blood flow, there is a high FS or EF as long as ventricular function is good. A borderline left ventricular FS/EF in these cases is already a sign of pump failure.

14.2 Managing Heart Defects

14.2.1 "Hypertrophy" Versus "Dilation"

As described earlier, concentric myocardial *hypertrophy* serves to overcome increased resistances with relatively little increase in wall tension at the expense of

reduced diastolic compliance, which is dependent on a sufficiently long diastole and adequate filling pressure. In simplified terms, *hypertrophied ventricles* ("compliance disorder") are preload-sensitive and afterload-insensitive and react early to tachycardia and loss of *atrioventricular coordination* with a decrease in cardiac output.

This means they react *sensitively* to an increase in preload with an increase in SV, whereas a reduction in afterload results in *no* increase in SV. This is so because such ventricles usually eject a large proportion of their EDV even under normal conditions (high EF).

Therefore, hypertrophied hearts respond well to an increase in preload by volume replacement, as well as to a reduction in heart rate with beta-blockers or central alpha-stimulants and to an increase in blood pressure, e.g., with noradrenaline. Increased blood pressure therefore tends to be beneficial for these hearts, since this prevents "hypercontractility" while maintaining an adequate perfusion pressure for the coronary arteries. With low diastolic blood pressure, there is a risk of intimal ischemia because of the long diffusion distance and the high end-diastolic pressure. A striking example is sudden cardiac death (SCD) in patients with hypertrophic cardiomyopathy under exertion.

Opposing the hypertrophied ventricle is a dilated, thin, and weak heart (e.g., dilative cardiomyopathy [DCM]). The weak contraction of these ventricles results in an increase in EDV and hence wall tension. As only a small percentage of the EDV can be ejected during systole (low EF), these hearts are working at an already high end-diastolic filling level. A further increase in preload can therefore provide little further contribution to an increase in SV (there is also a threat of acute decompensation on overdistension of sarcomeres). The main problems of these ventricles are the limited contractility and the "structural dilation" (as the contractile filaments no longer overlap optimally and therefore can produce less force). As a result of a reduction in afterload, there is an increase in stroke volume in this situation, as the ventricle can again eject more despite reduced contractility. Accordingly, EDV decreases again (*caution*: reduction in afterload beyond the limit of minimal organ perfusion pressures, particularly of diastolic coronary perfusion pressure).

In simplified terms, *dilated ventricles* ("contractility disorder" with low EF = SV/EDV) are *afterload-sensitive* and *preload-insensitive*. This means these hearts react sensitively to a reduction in afterload with an increase in SV, whereas an increase in preload results in a significant increase in SV only within a very limited range.

As well as a reduction in afterload, dilated, weak ventricles obviously also benefit from increased contractility. Inodilators such as milrinone (Corotrop®) or the calcium sensitizer levosimendan (Simdax®) are best suited to this purpose. Higher-dosed betamimetics (e.g., adrenaline, dobutamine), which result in an increase in O_2 consumption and tachycardia, are better avoided in our opinion. On the basis of earlier arguments (see also Chap. 3), a (excessively) high HR (in the form also of a demand-tachycardia) is not beneficial and does not result in any improvement of the O_2 balance (target: age-commensurate normal HR).

The strengthening of systolic function also contributes to improved diastolic filling through the higher stroke volume and the decrease in EDV. The transmitral inflow profile is normalized and the interventricular interaction can improve as a result (see Fig. 14.1).

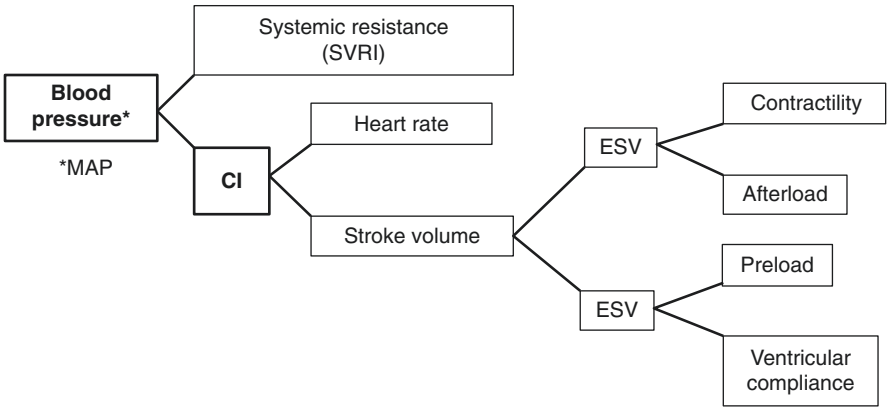

Fig. 14.1 Factors influencing arterial blood pressure

14.3 Classification of Cardiac Output and O_2 Balance

Cardiac output is of the greatest importance for the body's O_2 supply (DO_2). Usually only cardiac output can be altered acutely, whereas Hb and SpO_2 are usually relatively "fixed" parameters (see also Chap. 1).

Formula 45

$DO_2 = CO \times Hb \times SaO_2$

The factors in oxygen supply (in the order of their importance for DO_2) are:

- Cardiac output
- Hb concentration
- SaO_2

Theoretically, it should be possible for cardiac output to continue to increase constantly through an increase in heart rate and ventricular filling (with appropriate contractility). However, there are limits:

- The Frank-Starling curve becomes increasingly flatter as filling increases (see Fig. 3.1).
- Ventricular volume is constrained by the pericardium.
- As HR increases, SV (at high rates) decreases again (shorter diastole).
- With excessive filling pressure (= preload), pressures at the venous capillary end also increase, which can result in edema.

The previous sections have described how cardiac output can be increased (see also above and Chap. 3) and how significant an inadequate oxygen supply (critical DO_2) is for the body.

The clinical parameters are checked to establish sufficient oxygen delivery (DO_2):

- Arterial blood pressure (perfusion pressure, afterload, heart function, see Fig. 14.1.)
- Central venous pressure (filling, preload, compliance disorder, heart function)
- Capillary filling (microcirculation)
- Urine output (perfusion pressure – kidney particularly pressure-sensitive)
- Temperature difference between body core and shell (microcirculation, afterload)
- Arterial blood gas analysis (pH, BE, lactate, SaO_2, pO_2, Hb)
- Ventilation parameters
- Venous blood gas analysis (SvO_2)
- Vigilance

As well as the abovementioned function and measurement parameters, causes of postoperative function disorders (residual defect, outlet stenoses, leaking valves or valve stenoses, etc.) should be identified by echocardiography so that a therapeutic decision is rapidly possible from the combination of previous history, clinical features, and supplementary technical examinations (see Table 14.1).

In rare exceptional cases and only in biventricular serial circulation without relevant shunts, PICCO technology can provide vital prompts for therapeutic action by continuous pulse contour analysis combined with (repeated) static thermodilution: Benefits here can include detection and quantification of pulmonary edema, quantification of cardiac preload and cardiac output, measurement of volumetric preload parameters instead of filling pressures, and determination of afterload, contractility, or volume reactivity.

Table 14.1 Hemodynamic effects

Influencing factors	Normal ventricle	Dilated ventricle	Hypertrophic ventricle	
Preload ↑	Cardiac output ↑	Cardiac output ↓ on overdistension	Cardiac output ↑, requires a lot of preload	Diseased ventricles work at higher preload level
Afterload ↑	Cardiac output (↓)	Cardiac output ↓↓	Cardiac output ↔	Laplace
Atrioventricular coordination	Cardiac output ↑	Cardiac output ↑	Cardiac output ↑↑	
Contractility ↑	Cardiac output ↑	Cardiac output ↑	Cardiac output ↓, outflow tract, obstruction, filling on relaxation ↓	
HR	Cardiac output ↑	Cardiac output ↑, reflex tachycardia, note HR_{max}	Cardiac output (↓) with poor filling	

14.4 Postoperative Differential Diagnosis of Arterial Hypotension

One of the most common postoperative problems is arterial hypotension, which always raises the question: Is the hypotension due to

- Low cardiac output = reduced cardiac output (preload deficiency, anemia, poor contractility, high afterload, cardiac arrhythmia, pHT, etc.) or
- Reduced peripheral resistance (vasodilation; see Fig. 14.1)?

SvO_2 provides further help here:

- The combination of hypotension with low SvO_2 indicates a low cardiac output (preload deficiency, poor contractility, etc.).
- The combination of hypotension with normal or fairly high SvO_2 indicates a sufficient cardiac output with low afterload (vasodilation).

Typical constellations:

- BP low, HR high, CVP "low", SvO_2 low to normal, volume-responsive (BP increases more strongly than CVP): hypovolemia
- BP low, HR high, CVP "high", SvO_2 low, volume-nonresponsive (CVP increases more strongly than BP): tamponade, lower ventricular compliance, pump failure
- BP low, HR high, CVP "normal," SvO_2 normal to high: vasodilation

As well as the clinical examination, echocardiography in particular can also be used for rapid differentiation. As depicted in Fig. 14.1, blood pressure is related to cardiac output.

No flow, no pressure (macrocirculation) – no pressure, no flow (organ circulation).

If organ functions are normal and cardiac output (oxygen delivery/VO_2) and perfusion pressure are therefore adequate, the numerical value of the blood pressure is of no interest ("Don't care about the numbers").

While flow and hence the supply of nutrients and oxygen to the organs are the most important parameters overall, a certain minimum perfusion pressure must also be maintained at the organ level (best example: in the absence of adequate diastolic blood pressure, myocardial ischemia, pump dysfunction, etc. occur!).

In *critical* situations, therefore, *pressure comes before flow* ("centralization" in favor of organs such as the brain and heart that are vital to survival); in *stabilized* situations, *flow comes before pressure* (best example: severe heart failure in which afterload reduction results in an increase in cardiac output). (In cardiac arrest, it is obvious that flow must be generated first in this situation before there can be pressure.)

14.4.1 Tamponade ("Wet" and "Dry" Due to Myocardial Edema)

When the pericardium is filled with fluid (usually blood – more rarely chyle or serious fluids), diastolic filling of the heart can very rapidly be impaired with the resultant development of symptoms of acute heart failure. Retrosternal and intrapericardial drains are therefore usually put in place at the end of surgery. Similarly, and with similar symptoms (tachycardia, LOCS, increase in CVP, etc.), postoperative swelling of the myocardium is manifested after prolonged ischemia or insufficient myocardial protection in the form of a ventricular filling disorder. An acute diastolic function disorder develops in which the ventricle is able to receive the delivered blood only at high preload pressures – in the case of this filling disorder, which can be differentiated clinically and by echocardiography, it is usually possible to provide sufficient physical assistance by opening the chest (left open postoperatively or reopened) and to try to close it when filling pressures fall and there is sufficient urine output (caution: increased risk of infection).

14.5 Considerations for Shunt Defects

In deviations from the normal (serial) anatomy of the blood circulation, the blood chooses the path of least resistance.

As the right ventricle exhibits considerably greater compliance than the left and pulmonary vascular resistance (PVR) is markedly lower than systemic vascular resistance (SVR), an L/R shunt normally occurs in defects at the vascular level (anomalous pulmonary venous return, AV fistula, or aortopulmonary window) and at the cardiac level (VSD/ASD). If there is an additional (pathological) change, this rule may not apply:

- *RV compliance reduced and PVR still* high (postnatally with physiological pulmonary hypertension and a still "trained" ventricle). In this case, ASD can lead to an R/L shunt.
- If the resistance of an *RV outlet stenosis* (e.g., pulmonary stenosis) is higher than the peripheral systemic resistance, this results in an R/L shunt (Fallot with hypoxemia).
- *Similarly with PVR* (hypoxia/pneumonia/acidosis/Eisenmenger syndrome) – in this case also a shunt reversal can occur.
- *SVR ↓↓ (as in sepsis)*: Here also the blood can be conducted more to the systemic circulation and less to the pulmonary circulation.

The ratio describing the relationship between pulmonary and systemic perfusion is known as the Qp/Qs ratio. In serial circulation, the ratio is about 1:1; in L/R shunts, it reflects the degree of hyperperfusion of the lung relative to systemic perfusion and therefore contributes to the degree of heart failure of the LV and the risk of development of an increase in PVR.

In all *noncyanotic heart defects* Qp/Qs is 1 or greater, i.e., there is *no* mixing of deoxygenated blood in the systemic ventricle (or the atrium), and only "saturated" blood is ejected into the systemic circulation.

Conversely, in *cyanotic defects,* an R/L shunt occurs with the mixing of nonoxygenated blood with the systemic perfusion: As a result, organ perfusion may be compromised; this tends to be due more to reduced oxygen delivery rather than to low cardiac output.

In the univentricular heart (a mixing chamber) with a constant SvO_2 and $SpvO_2$ (= pulmonary venous saturation), SaO_2 varies according to the Qp/Qs ratio ($SpO_2 \approx SaO_2$).

Qp/Qs = 1 with SpO_2 about 80%, as long as $SpvO_2 \approx 100\%$ is the case:

Formula 46

$Qp/Qs = (SaO_2 - SvO_2)/(SpvO_2 - SpaO_2)$

Calculation: (80–60) / (100–80) = 1

(Since $SpvO_2$ can only be determined by cardiac catheterization, the only clinical option remains an approach by means of SpO_2/SaO_2 and pulmonary function.) An ideal pulmonary venous saturation ($SpvO_2$) of 100% is assumed in the calculation:

Qp/Qs = 2 with SaO_2 90%, "good" SvO_2 (70%): (90–70)/(100–90) = 2. (This condition does not persist for long since, with predominant pulmonary circulation, systemic cardiac output is insufficient in the long term for a "good" SvO_2.)

- Instead, with SpO_2 of 90%, a SvO_2 of 40% or less is seen:
- Qp/Qs = 5: (90–40)/(100–90) = 5 → threat of massive heart failure from pulmonary flooding.
- With low systemic arterial saturation (60% and good lung), cardiac output may be fine, but pulmonary flow is impaired. Example $SvO_2 = 40$
- Qp/Qs = 0.5 with a calculation: (60–40)/(100–60) = 0.5

If there is a decrease of $SpvO_2$ ("pulmonary disorder") or SvO_2 (fall in cardiac output, Hb, SaO_2, or increase of VO_2), the resultant SaO_2 naturally also falls accordingly, and the actual values would have to be used in the formula:

Qp/Qs = 3 with SpO_2 80% SvO_2 50%, but $SpvO_2$ only 90%

It is clear from this example that the ratio of pulmonary to systemic perfusion in univentricular circulation can be deduced not just from the transcutaneously measured saturation.

14.6 Considerations for Pressure Gradients

Pressure gradients develop at stenoses, vascular connections, or septal defects. The pressure gradient at a stenosis or a defect depends on various factors:

1. The extent of the constriction or the size of the defect
2. The amount of blood flow via the stenosis
3. The pressure or resistance conditions before and after the stenosis or the defect

These conditions can be described by means of a VSD. If the VSD is large (non-pressure-separating), the pressures of both ventricles equal out (LVP = RVP). With a relatively small VSD (pressure-separating), there is a pressure gradient. If left ventricular systolic pressure decreases (reduced SVR, reduced contractility), the pressure gradient also is reduced without any change occurring in the defect. When RV pressure is high (e.g., neonatally or in association with pulmonary hypertension), the gradient also is lower if LV pressure is unchanged.

14.7 Classification of Heart Defects

Table 14.2 contains a simplified classification of heart defects, while Chap. 13 discusses them in greater detail.

If we look at non-cyanotic heart defects with an L/R shunt taking VSD as an example, the blood recirculating in the pulmonary circulation generates a pressure and volume overload of the pulmonary vascular bed and a volume overload of the left heart. The higher the pulmonary hypercirculation, the less volume is available for the systemic circulation (Qs). This not only impairs peripheral organ perfusion (resulting in activation of the renin-angiotensinaldosterone system = RAAS ↑), but also limits LV reserves.

In the presence of hypercirculation and poor left ventricular function, left atrial pressure, and hence PCWP, also increases in parallel and generates an increase in post-capillary pulmonary resistance with a tendency to pulmonary edema. This in turn results in a compensatory increase in precapillary pulmonary vascular resistance to protect against pulmonary edema.

Right ventricular afterload is thereby increased with the possible consequence of RV failure (hepatic congestion and peripheral edema) and a further reduction in organ perfusion (RAAS ↑↑). The increase in pulmonary vascular resistance becomes established in the second 6 months of life, so that in the event of a severe (particularly post-tricuspid) L/R shunt, surgery should be performed by that time.

In cyanotic defects, nonoxygenated blood is mixed with the blood in the systemic ventricle. This is possible through various shunts and hence different types of circulatory anatomy, which need to be treated differently (particularly in the preoperative phase).

In the case of cyanotic *heart defects with reduced pulmonary perfusion*, the right ventricle is obstructed, e.g., at the inlet (tricuspid valve) or outlet (pulmonary valve). An ASD or VSD is essential in order to conduct the caval blood to the systemic side (R/L shunt). The same applies to univentricular hearts. In these patients, Qp is < Qs, and massive hypoxemia develops as soon as pulmonary perfusion is limited by closure of the ductus arteriosus (*PDA-dependent pulmonary perfusion*).

These patients are at risk from hypoxemic acidosis, although the systemic perfusion is initially wholly sufficient; obviously, acidosis and reduced O_2 delivery (DO_2↓) also affect ventricular function secondarily. The focus of preoperative therapy thus lies on keeping the PDA open, administering O_2 (as long as a pulmonary component plays a role in hypoxia), and providing sufficient O_2 transporters (Hb > 12–14 g/dL). Naturally the channeling of blood to the systemic ventricle must

Table 14.2 Simplified classification of heart defects

Acyanotic heart defects	Cyanotic heart defects (= R/L shunt)
With L/R shunt	With reduced pulmonary perfusion
With valve dysfunction	With increased pulmonary perfusion
With ventricular dysfunction	Univentricular heart defects
	Transpositions of great arteries (TGA)

not be obstructed in these heart defects either (e.g., restrictive ASD), since otherwise this results in inflow congestion and an excessively low cardiac output.

A good balance between systemic perfusion and pulmonary perfusion is achieved in the patient with PDA-dependent circulation (assuming constant pulmonary ventilation and pulmonary perfusion) with arterial saturation of about 80% (Qp/Qs about 1:1).

This contrasts with *left heart obstructions with reduced systemic perfusion*. In this case, structures of the left heart or aorta are malformed so that the right ventricle is entirely or largely responsible for systemic perfusion via the open PDA (PDA-dependent systemic perfusion in HLHS, *critical* aortic stenosis, high grade CoA, or hypoplastic aortic arch).

Oxygenation of the blood in this case is initially unproblematic, but the systemic supply is compromised by reduced perfusion on PDA closure or decreasing pulmonary vascular resistance and the associated pulmonary hypercirculation. As well as maintaining PDA and ensuring the outflow of the oxygenated blood from the left to the right atrium (a highly restrictive atrial septum here results in pulmonary congestion), the primary measures here are those that improve systemic perfusion (careful afterload reduction), that *do not reduce pulmonary vascular resistance* (no O_2, no ventilation if not clinically necessary, and no hyperventilation), and that improve the heart function of the right ventricle, which now carries the systemic circulation.

With other univentricular heart defects in which there is no inflow obstruction of the pulmonary or systemic circulation, the postnatally high PVR balances the pulmonary to systemic perfusion ratio. However, with decreasing resistance in the pulmonary vascular bed, this leads here to pulmonary hypercirculation with the aforesaid consequences for pulmonary and systemic perfusion. Restricting the blood flow to the pulmonary vascular bed is of primary importance here in the initial therapy.

In any understanding of the preoperative approaches to treatment (including TGA, the circulatory conditions of which are addressed in detail later), knowledge of the possibilities of influencing the pulmonary/systemic vascular bed, heart function, and pulmonary function are vital.

14.8 Influencing Pulmonary Artery Resistance

For details on how to influence pulmonary artery resistance, refer to Table 14.3 and Chap. 9.

Table 14.3 Influences on pulmonary arterial and systemic vascular resistance

PVR ↑ (1st quarter)	*SVR* ↑ (2nd quarter)
$PaCO_2$ ↑	Alphamimetics
pH ↓	Pain
Excessive PEEP increase (overdistension)	Agitation
Ventilation disorder	
Pain	Negative intrathoracic pressure
Agitation	
Alphamimetics	
PVR ↓ (3rd quarter)	*SVR* ↓ (4th quarter)
$PaCO_2$ ↓	Milrinone (Corotrop)
pH ↑	Dobutamine
FiO_2 ↑	Analgesia
Optimized lung ventilation (adequate PEEP)	Sedation
NO	Positive pressure ventilation (PPV)
Analgesia	
Sedation	Afterload reducers (ACE inhibitors, Nipruss, etc.)
Relaxation	
Milrinone	
Minprog (PGE1), prostaglandin, etc.	

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Heart Defects with Indication for Neonatal Surgery

15

Dietrich Klauwer

Unless intrauterine decompensation of fetal hemodynamics have already occured, neonates with heart defects will usually become increasingly symptomatic during the first few days of life (sometimes even within hours!). In some heart defects, the physiologic postnatal cardiopulmonary adaptation processes can become a serious threat to the neonate within a very short time. This is manifested by:

- Decrease in pulmonary artery resistance
- Closure of patent ductus arteriosus (PDA)
- Functional closure of the foramen ovale

These adaptation processes frequently take between hours and days. That means, there is usually time to plan the diagnostic procedures and treatment, particularly when the heart defects are known antenatally. Clinical and echocardiographic investigations are performed initially to ascertain whether PGE1 therapy (Minprog therapy) is indicated postnatally.

However, rare exceptions to this rule are given when there is a direct threat to life: e.g., total anomalous pulmonary venous return (TAPVR) with pulmonary venous outflow obstruction, right or left heart obstruction with restrictive atrial communication, or transposition of great arteries (TGA) without sufficient mixing of blood.

D. Klauwer
Department of Pediatrics, Singen Medical Center, Gesundheitsverbund Landkreis Konstanz, Krankenhausbetriebsgesellschaft Hegau-Bodensee-Klinikum, Singen, Germany

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D. Klauwer et al. (eds.), *A Practical Handbook on Pediatric Cardiac Intensive Care Therapy*, https://doi.org/10.1007/978-3-319-92441-0_15

Other than the previously mentioned emergency indications immediately postnatally, the most important neonatal heart defects requiring intervention consist of cyanotic defects with PDA-dependent systemic or pulmonary perfusion, TGA, total anomalous pulmonary venous return (with obstruction but without decompensation), the various forms of univentricular heart, and defects with a left-sided obstruction.

In the case of persistent high pulmonary vascular resistance (PVR) and wide-open PDA immediately postnatally, an "apparent" clinical discrepancy will frequently exist between the cyanotic skin color (SpO_2 < 93%) and the patient's eupnea. When postnatal cyanosis only involves the lower half of the body (aortic arch anomalies) but the inguinal pulses are (still) readily palpable, then cyanosis is frequently difficult to detect. Initial postnatal misinterpretations in cases where a diagnosis has not been established prenatally are not uncommon.

The pointers for further diagnostic investigations and treatment can be established by echocardiography.

The hemodynamics and the main details of the heart defects have already been described in Chap. 13. Those tending to require an interventional catheterization procedure are distinguished from those usually involving a surgical procedure. The latter are discussed here, some by way of example. Although this may involve repetition, all the main points required for a rapid understanding of the procedure will also be mentioned here.

15.1 Heart Defects with Right-Sided Obstruction

15.1.1 Pulmonary Atresia (PAT) with Intact Ventricular Septum (IVS)

Further details are provided in Table 15.1 and Chap. 13 (PAT/IVS).

Table 15.1 Differentiation of pulmonary atresia (PAT)

PAT with intact ventricular septum (IVS)	PAT with ventricular septal defect (VSD)
Disorder lies at the valve level or proximally = RV developmental disorder	Disorder lies at the valve level or distally = more of a vascular developmental disorder
Ranges from membranous valve septum with well-developed RV to hypoplastic RV with coronary fistulas to RV – Very rarely MAPCA	The RV is usually well developed, maldevelopment of pulmonary vascular bed – Usually MAPCA
Distal to the atretic pulmonary valve, the vascular bed is normal!	RV OK (hypertrophied), pulmonary vascular bed hypoplastic, or maldeveloped

IVS intact ventricular septum

15.1.1.1 Anatomy of PAT with IVS in Keywords

Hypoplastic valve root; highly muscled and frequently hypoplastic RV (lack of tripartite division into inlet, muscular, and outlet chambers), sometimes fibroelastic restructuring of the myocardium and coronary fistulas to the ventricular lumen; hypoplastic tricuspid valve (the degree of tricuspid insufficiency is inversely proportional to the flow in the sinusoids), widened RA, usually nonrestrictive atrial septal defect (ASD).

Coronary hypoperfusion can also occur in the LV at the time of pressure unloading (opened RV-PA connection) in the case of coronary artery to right ventricle fistulas.

15.1.1.2 Procedure

In PAT with IVS, the degree of hypoxia determines the degree of initial intensive care treatment.

Where severe generalized tissue hypoxia with organ involvement (left heart function ↓, renal function disorder, metabolic acidosis, pulmonary function disorder with tachydyspnea) has already occurred, the following procedure can be recommended:

- Two i.v. accesses and initiation of PGE1 (Minprog: 30–50 ng/kg BW/min or higher)
- Blood sampling for blood count, coagulation, cross matching (for cardiac catheterization), electrolytes, creatinine, liver function parameters, TNI, BGA
- Intubation where necessary, careful sedation (reduction of O_2 consumption and lowering of PVR with NO)
- Correction of acidosis by buffering (assumes sufficient pulmonary perfusion)
- Placement of CVC (or umbilical venous catheter) plus treatment with vasopressors and possibly inotropic drugs; volume therapy depending on clinical picture, CVP, and ultrasound

An assessment of the atrial septal defect is important at this point: in the event of a – fairly rare – restriction, an immediate catheter intervention may be necessary.

As long as there are no signs of organ hypoxemia, treatment with low-dosed prostaglandin therapy (10–20 ng/kg BW/min) is initiated in the presence of cyanosis to maintain a patent ductus.

Depending on the size and structure of the right ventricle (tripartite division present?) and the morphology of the tricuspid valve and pulmonary artery, it needs to be established whether an initial biventricular procedure or an initial univentricular procedure or "$1^1/_2$ circulation" can be planned for the individual patient. The solution, however, often lies between these options or can only be given over the course of time, since for a transitional period (RV growth is still possible postnatally), right ventricular ejection is not yet sufficient to ensure adequate pulmonary perfusion against the still high postnatal pulmonary vascular resistance (see Table 15.2).

A cardiac catheter examination is usually performed in the first week of life to visualize the anatomy and in particular to exclude RV-dependent coronary

Table 15.2 Pulmonary atresia (PAT) with intact ventricular septum (IVS) – treatment options

I	II	III	IV
Interventional balloon valvuloplasty and dilatation suffice	Interventional opening of valve and dilatation do not suffice	RV does not grow sufficiently; intervention and PDA stent	RV too small, primarily univentricular procedure
	Pulmonary perfusion additionally via PDA (stent rather than prostaglandin)	Possibility of simultaneous pulmonary perfusion via superior cavopulmonary anastomosis (usually right) and via RV (inferior vena cava blood)[a]	1. Reliable provision of pulmonary perfusion (ductal stent/AP shunt) 2. Glenn anastomosis 3. Total cavopulmonary connection (TCPC)
If good RV function and good intervention outcome, no intensive therapy	Monitoring of CVP (RV insufficiency), blood pressure, particularly diastolic because of pulmonary runoff via PDA	Monitoring of RV function, PAP, and CVP	
Monitoring of RV function, SpO_2, clinical signs of RV failure	Monitoring of RV growth, SpO_2; from what point is it OK, even without PDA?		

[a]In this procedure in which the vena cava blood competes for access to the pulmonary circulation bed, i.e. on the one hand the superior vena cava blood (approx. $^1/_3$) which flows passively (without "supportive pressure" via the cavopulmonary anastomosis, and on the other hand the inferior vena cava blood which is pumped by the right ventricle, banding between the two pulmonary circulation territories can be beneficial for hemodynamic reasons. As distinct from a Glenn anastomosis, the circulation remains serial (complete circulation separation – "$1^1/_2$ circulation")

perfusion. Where there is an option for interventional valve opening (where necessary with an RVOT stent), this can be tried, in addition to which there are alternative possibilities of implantation of a ductal stent or balloon atrioseptostomy. Before any attempt at pressure unloading of the right ventricle, check for the presence of RV-dependent coronary perfusion that would preclude this procedure. Instead of the often difficult stent implantation in PAT + IVS, there is the possibility of surgical shunt creation if necessary (see Sect. 15.1.4 and Chap. 13).

15.1.1.3 Procedure in the Event of Planned Univentricular Circulation

Where the possibility of using the right ventricle for pulmonary perfusion does not exist in the case of an unsuitable or excessively small right ventricle or RV-dependent coronary perfusion, the option of functional univentricular correction still remains. As this is a constantly recurring procedure – with modifications – in various heart defects, the intention of this definitive palliation will be described here using the example of PAT with IVS.

The underlying principle is that the existing ventricle takes over the pump performance for both circulations, and pulmonary perfusion is "dosed" surgically to compensate for the decreasing pulmonary vascular resistance. In *right heart obstruction*, a PDA is required initially (= PDA-dependent pulmonary perfusion) and subsequently a PDA stent or a systemic-to-pulmonary artery shunt. In the case of right heart obstruction, the systemic venous blood must reach the subsystemic ventricle freely (via the atrial septum), which may in some cases require an intervention (atrioseptostomy).

Conversely, in the case of heart defects with *inadequate systemic perfusion, i.e. left heart or aortic arch obstruction*, communication between the functioning right ventricle and the aorta must be maintained to ensure systemic perfusion. This is done by means of:

- PDA with a prostaglandin infusion always at the beginning of treatment and PDA stent – in both cases of PDA-dependent systemic perfusion, the existing ventricle pumps into the pulmonary artery and from there via the ductus antegrade into the lower half of the body and retrograde into the aortic arch. Caveat: "retrograde" coarctation of the aorta.
- Since pulmonary flooding with simultaneously inadequate systemic flow could occur in the case of physiologic reduction of pulmonary arterial resistance – PVR ↓ in the first few weeks of life and latest after about 3 months – with parallel circulation and unobstructed flow to the pulmonary vascular system (blood flows along the path of least resistance), the flow to the pulmonary vascular bed must be reduced if required (PA banding – surgically – if a "natural" pulmonary stenosis does not protect the pulmonary vascular system).

Alternatively, following a fall in PVR in the first few days of life, the circulations can be balanced by means of aortic arch reconstruction and the creation of a systemic-to-pulmonary artery shunt – usually an AP shunt or modified Blalock-Taussig shunt (*Norwood or Damus-Kaye-Stansel [DKS] procedure*). By analogy with right heart obstruction, in left heart obstruction there must be free communication between the atria to allow the pulmonary venous blood to reach the right atrium.

Placement of the ductal stent usually does not require intensive care treatment – the important intensive care aspects in the case of PA banding or aortic arch repair (Norwood or DKS anastomosis) are discussed there in detail.

For the various treatment options for different anatomic and functional preconditions in pulmonary atresia with intact ventricular septum, see Table 15.2.

As is apparent from the flow chart (Fig. 15.1), there are various heart defects in which definitive univentricular palliation is indicated:

- *Right heart obstruction*:
  - PAT with IVS (for a very hypoplastic RV, see above)
  - Tricuspid atresia (TAT)
  - Ebstein's anomaly (some forms)
- *Left heart obstruction*:
  - Hypoplastic left heart syndrome (HLHS)

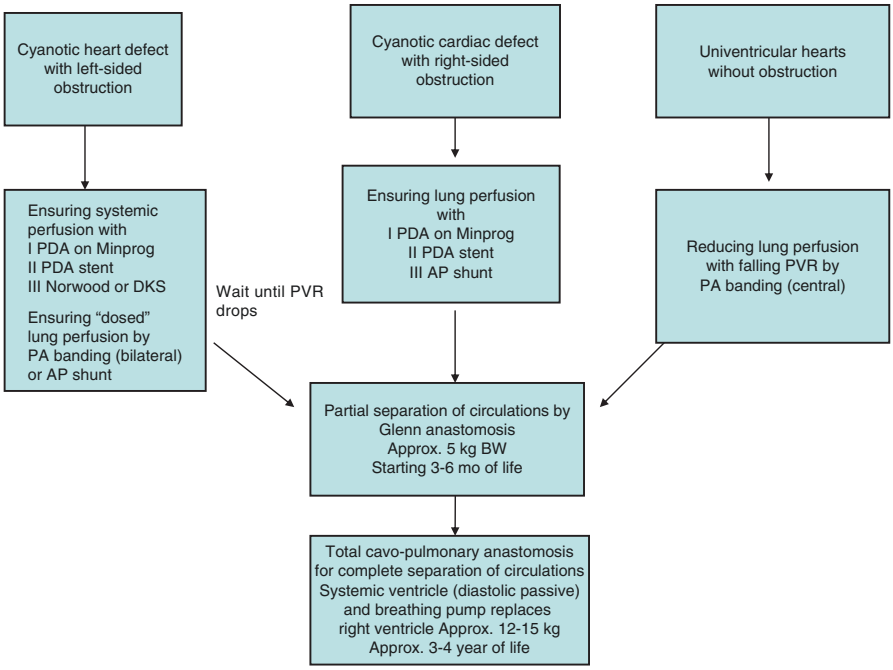

Fig. 15.1 Procedure for univentricular correction

- Aortic atresia with VSD
- Mitral atresia

- *Univentricular hearts*:
  - Unbalanced AV canal
  - DORV with hypoplastic LV
  - Double inlet left ventricle (DILV)
  - Some complex defects with functionally or anatomically univentricular hearts

Common to these strategies is the fact that a balanced circulatory situation is established until complete reduction of PVR, allowing the creation of a Glenn anastomosis so that the subsystemic ventricle is volume unloaded and pulmonary perfusion can occur "passively" (explanations below). Complete separation of the circulations then occurs in a third step, when the complete systemic venous blood of the body is channeled to the pulmonary arteries, and, as a result, the right heart is "replaced" by the respiratory pump and suction effect of the subsystemic ventricle.

15.1.2 Tricuspid Atresia

In tricuspid atresia, pulmonary blood flow can be both reduced and increased. For the vena cava blood to pass into the LA, there must be an atrial communication. A mean ASD gradient of > 3–4 mmHg is considered here to be an indicator of excessively restrictive communication. After mixing of blood in the LA, the blood

reaches the left ventricle via an enlarged mitral valve (10% are significantly insufficient). The position of the great arteries and the presence of a either a large or a restrictive VSD and pulmonary stenosis/atresia determine the distribution of the blood to the systemic or pulmonary circulation.

In most cases, pulmonary perfusion is reduced by pulmonary stenosis/atresia and/or a restrictive VSD if the great arteries are normally positioned. In such cases, the patient is at risk of increasing hypoxia and acidosis on postnatal ductus closure.

The greater the VSD and the lesser the blood flow that is limited by the presence of a pulmonary stenosis, the more likely is pulmonary hypercirculation to occur. Pulmonary hypercirculation is greatest in TAT if the LV blood is pumped unrestricted into the PA in the case of (d)-transposition of the great vessels, while a restrictive VSD (or an outflow tract stenosis) impairs the blood supply to the aorta (which is now above the small RV). This then tends to result in the same hemodynamics as those that occur in left heart obstruction (Table 15.3).

Treatment in the neonatal period also depends on the ratio of pulmonary to systemic blood flow.

Since pulmonary inflow is restricted in the overwhelming majority of patients and therefore oxygenation is PDA-dependent, in these patients there is a risk, following PDA closure, of the scenario described previously for PAT, involving hypoxia and acidosis and ensuing organ failure and the resultant emergency treatment.

PGE1 treatment can be initiated in non-decompensated patients and PDA-dependent pulmonary perfusion (e.g. 10 ng/kg BW/min). Perfusion of the lung is maintained subsequently by means of a systemic-to-pulmonary artery shunt or PDA with stent until the first stage of palliation (Glenn) with separation of the circulations. In these cases of parallel circulation also, the point of reference is considered to be Qp/Qs = 1 with a transcutaneous saturation of 75–80% (with a healthy lung).

This contrasts with those patients in whom the flow to the pulmonary vascular bed is not limited by pulmonary stenosis or in whom a restrictive VSD inhibits flow to the RV. Following a fall in PVR, there is then the risk of increasing pulmonary hypercirculation with congestive heart failure, pulmonary edema, and low cardiac output to the systemic circulation.

Table 15.3 Classification of forms of tricuspid atresia (TAT) according to Edwards and Burchell, accounting for the differences

TAT I (70%) normal-sized arteries	A with pulmonary atresia	B with restrictive ventricular septal defect (VSD) ± pulmonary stenosis	C without restrictive VSD, without pulmonary stenosis
TAT II (30%) with d-transposition of the great arteries (TGA)	A VSD/ pulmonary atresia	B VSD/pulmonary stenosis	C VSD without pulmonary stenosis
TAT III, l-TGA very rare			

A + *B* pulmonary hypoperfusion
C possibly pulmonary hypercirculation

In these patients, careful reduction of systemic afterload should be considered where there is sufficient organ perfusion pressure (MAP 35 mmHg). In ventilated patients, O_2 is administered to prevent a fall in PVR only when SpO_2 is <70% and simultaneous permissive hypercapnia ($PaCO_2$ 60 mmHg) is used to increase PVR therapeutically.

In concrete terms, that means:

- Careful volume administration, milrinone up to 1 µg/kg BW/min in the case of poor ventricular function
- NaBic only from pH < 7.2
- Ventilation: CO_2 > 55 mmHg, SpO_2 < 80%
- Furosemide for anticongestant treatment
- MAP > 35 mmHg, otherwise noradrenaline with caution
- Where MAP allows → careful afterload reduction
- Bear in mind potential consequences of the temporary hypoperfusion (NEC, PVL = periventricular leukomalacia)

In the non-decompensated state – or after recompensation – there is an indication in patients with pulmonary hypercirculation to reduce pulmonary blood flow by PA banding, in this case centrally, in order to balance pulmonary and systemic blood flow and to await a reduction in pulmonary vascular resistance and thus prepare for Glenn anastomosis.

A special case of TAT is present when (d-)TGA is combined with a subaortic obstruction. Although by definition this involves a right-sided obstruction, systemic flow is obstructed to such an extent, as a result of the lack of flow into the aorta (which now lies above the RV), that only an open PDA with shunt from the pulmonary to the systemic circulation can ensure organ perfusion.

In these patients, it may be necessary – until the first stage of separation of the circulations – to construct a common trunk from the aorta and the PA trunk (DKS repair) which conveys the blood to the systemic circulation, while the lung is perfused by means of a “modified” BT/AP shunt that conducts the blood into the pulmonary artery which is detached from the heart. Subsequently, both ventricles pump the blood into the aorta, and the lung is perfused exclusively via the systemic-to-pulmonary artery shunt. After 3–4 months, following the physiologic decrease in PVR, this procedure also culminates in “definitive palliation” by a Glenn procedure and at a later stage TCPC.

Therefore, to gain an idea of which treatment is useful and indicated in a neonatal cyanotic heart defect, certain questions need to be answered:

- Are there clinical signs of hypoxemia (reduced pulmonary perfusion) or is there more or less normal (in this case too high) transcutaneous saturation with clinical signs of low cardiac output?
- Is hypoxia the manifestation of inadequate mixing (TGA) or inadequate pulmonary perfusion (right heart obstruction)?

- In the presence of clinical signs of low cardiac output, is there deep cyanosis or is saturation rather too high and indicating pulmonary hypercirculation?

As soon as the diagnosis can be established by echocardiography, the question arises as to whether prostaglandin (PGE1) is required for sufficient pulmonary perfusion (in right-sided obstruction) or to maintain systemic perfusion (in left-sided obstruction). It must also be established whether there is a sufficient R/L shunt (in right-sided obstruction) or L/R shunt in left-sided obstruction at the atrial level.

15.1.3 Pulmonary Atresia with Ventricular Septal Defect

In this case, the RV is usually well developed, and the malformation involves the RVOT and, above all, the pulmonary arteries (see Tables 15.1 and 15.4 and Chap. 13) (Table 15.5).

The degree of cyanosis again indicates the ratio of pulmonary-to-systemic perfusion (Qp/Qs). In the event of high saturation (e.g. > 85% measured transcutaneously), a Qp/Qs of 2:1 or more is present, indicating (a risk of) hypercirculation with congestion. With a SpO_2 of about 75–80%, Qp/Qs is about 1:1 (assuming the lung is healthy).

Following the initial treatment, which involves the maintenance of a patent PDA in the event of severe cyanosis, the precise anatomy of the pulmonary perfusion must be elucidated for treatment planning.

This requires visualizing the sections of the pulmonary arterial vascular bed that are supplied by the "normal pathway," i.e., from centrally to peripherally, via PA

Table 15.4 Pulmonary atresia (PAT) with ventricular septal defect (VSD) – anatomy-based treatment options

I	II	III	IV
Central pulmonary vessels well developed	Central pulmonary vessels slightly hypoplastic, absence of main PA trunk	Central pulmonary vessels highly hypoplastic	No central pulmonary vessels
Pulmonary perfusion via PDA	PDA ↑ and MAPCAs ↓ provide for pulmonary perfusion	MAPCAs ↑ and PDA ↓ provide for pulmonary perfusion	Only MAPCAs provide for pulmonary perfusion
As needed, interventional valve opening or systemic-to-pulmonary artery shunt (PDA stent)	Systemic-to-pulmonary artery shunt, closure or coiling of major aortopulmonary collateral arteries (MAPCA)	Systemic-to-pulmonary artery shunt, MAPCAs closure or unifocalization	Unifocalization, connection of PA confluence to RV without correction
Corrective surgery in 1st year of life	Corrective surgery after 1st year of life	Corrective surgery after 1st year of life	Surgery corrective?

Table 15.5 Checklist for the management of Memo on aortopulmonary (AP) shunt

Central AP shunt	Coagulation	Ventilation	SpO_2 ↑	SpO_2 ↓
3.5 mm PTFE	Initiation of heparin when bleeding ↓	O_2 affects oxygenation by means of PVR ↓	BP ↓, PEEP ↑, PVR ↑ (by means of ventilation)	BP ↑ (noradrenaline), PVR ↓ (by means of ventilation)
Saturation ↑ excessive shunt flow	PTT target 60 s, AT III 80%	Well-developed lung (PEEP 5 cmH_2O)		NO as needed, shunt monitoring
Saturation ↓ too little shunt flow	Heparin bolus on suspicion of shunt closure	Vti about 6–8 mL/kg BW (PIP 22 cmH_2O)		Pulmonary edema? Ventilation disorder?
Saturation initially ↑, then falling: Pulmonary edema?	Revision surgery or cardiac catheter if shunt closure	Ti 0.4–0.5 s, RR 20–25/min		Diffusion disorder? Does O_2 help?
		Ventilation until next day, X-ray before extubation		

branches, the sections perfused solely via major aortopulmonary collateral arteries (MAPCAs, frequently with stenoses), and the pulmonary regions with a "dual" supply.

This anatomic investigation is performed by cardiac catheter and by MRI/CT angiography. For pulmonary sections with a dual supply, MAPCA closures are indicated now or perioperatively to prevent pulmonary flooding and to promote the growth of the genuine pulmonary vessels. The choice of treatment strategy depends on the anatomic requirements.

In some patients with short-segment atresia of the pulmonary valve/RVOT and with the presence of a PA trunk, serial circulation can be created by a catheter intervention to open the valve, where necessary with the closure of individual MAPCAs and dilation of any existing central PA constrictions. In the process, the access to the pulmonary vascular system remains stenotic, so that the pulmonary vascular bed continues to be protected against hypercirculation via the VSD (as in Fallot's tetralogy) → correction usually in the second 6 months of life.

Where interventional restoration of continuity between RV and central pulmonary arteries is not possible, pulmonary perfusion and the growth of genuine pulmonary arteries can be achieved by a surgically created systemic-to-pulmonary artery shunt. As described above, the aim is to perform corrective surgery with elimination of the VSD and reconstruction of the RVOT/central pulmonary vessels in the second 6 months of life, as in Fallot's tetralogy.

The more hypoplastic the central pulmonary arteries are, the more pulmonary perfusion occurs via MAPCAs – in some cases independently of the pulmonary artery vascular bed. Planning for whether to perform an initial unifocalization of the

MAPCAs and the genuine peripheral PAs with the central pulmonary arteries in connection with a systemic-to-pulmonary artery shunt or whether to perform corrective surgery (unifocalization, VSD closure, RV-PA connection) at the outset must be undertaken on an individual basis.

Overall, the patient's prognosis improves with the quality of central pulmonary artery development. The more MAPCAs and the less favorable the anatomy of the central PA sections, the more likely it is following corrective surgery that there will be a persistent increase in pulmonary artery resistance, (regional) developmental disorders in the pulmonary vascular bed, increasing cyanosis, and the risk of RV failure with excessive afterload.

The postoperative management of corrective surgery is described under Fallot's tetralogy (see Sect. 15.4).

15.1.4 Systemic-to-Pulmonary Artery Shunt

In PDA-dependent pulmonary perfusion, a surgical creation of a systemic-to-pulmonary artery shunt has receded into the background because of the possibility of interventional PDA stent implantation. In principle, *PAT with VSD* – since it is usually *not associated with a PDA* – remains one of the few indications for the creation of a surgical systemic-to-pulmonary artery shunt (see above).

For a systemic-to-pulmonary artery shunt in neonates, a PTFE shunt with a diameter of about 3.5 mm and a length of about 2–3 cm is interposed between the ascending aorta and PA trunk (central AP shunt) – alternatively, a shunt connecting the right subclavian artery with the central pulmonary vessels (modified Blalock-Taussig shunt, BT shunt) can also serve the same purpose.

Perfusion of the lung is dependent on free passage, the diameter and length of the shunt, the (primarily diastolic) blood pressure in the aorta, and the pulmonary artery resistance (PVR). However, PVR is affected overall not only by the resistance in the distal small pulmonary arteries but also and in particular by anatomically related changes in caliber between individual proximal pulmonary artery sections (branch stenoses in PAT + VSD), by stenoses related to the shunt, e.g. the anastomoses, and by the development of pulmonary vascular capacity.

Postoperative handover after systemic-to-pulmonary shunt: as surgery is performed without heart-lung machine, significant myocardial depression is usually not to be expected. Generally, there is no lung function disorder either. Thus, hyposaturation of the patient with normal blood pressure (BP) (e.g. saturation < 65% transcutaneously) can be attributed primarily to a perfusion problem of the shunt. Where a shunt sound can be heard on auscultation or the shunt can be visualized on ultrasound, diastolic blood pressure should be increased (with noradrenaline as long as there is no volume deficiency). With an open shunt, this should result in increased saturation. A reduction in pulmonary artery PVR by means of ventilation (effect on CO_2, pH, O_2, or also with inhalational NO) can be diagnostically and therapeutically helpful if the vascular PVR is the cause of the hyposaturation.

The most problematical aspect is a thrombotic shunt closure, which usually occurs immediately postoperatively and does not respond to any of the measures mentioned, i.e. BP ↑ and PVR ↓.

Lysis cannot be used because of the risk of bleeding, but a heparin bolus (100 IU/kg BW/single dose) with simultaneously raised blood pressure can eliminate the problem. If that is not the case, a revision of the shunt (by cardiac catheterization or surgically) is required.

This contrasts with the situation in which saturation is initially too high (e.g., $SpO_2 > 90\%$) but decreases constantly in the first few postoperative hours. The increased pulmonary blood flow obtained by the AP shunt – conveyed to the pulmonary vascular system with insufficiently reduced pressure – can overwhelm the pulmonary vascular bed and result in pulmonary edema.

With this disproportion between pulmonary and systemic perfusion ($Qp >> Qs$), a significant disturbance of organ perfusion can occur. A reduction in afterload in the arterial system is usually no longer helpful here – the shunt already causes low diastolic blood pressure through a hole in the aortic Windkessel – caveat: coronary artery and head perfusion.

An increase in PEEP (e.g. to 10 cmH_2O) and hypoventilation (CO_2 60 mmHg) can be tried in an attempt to reduce the perfusion of the shunt. If the problem persists, however, a revision of the shunt with banding or repositioning will be necessary to eliminate the flow-related problem.

Therefore, in assessing AP shunt function and postoperative adaptation following AP shunt, the time course of SpO_2 is always important.

A balanced situation ($Qp/Qs \approx 1$) may be assumed with arterial saturation of about 75–80%, as long as the lung is well ventilated. For any oxygenation disorder, a brief test can be performed by administering O_2 (hyperoxia test) to ascertain whether there is either a pulmonary problem – in which case saturation should increase significantly – or a flow-related problem (little or no change in SaO_2). Where the cause is flow-related, the blood pressure should be increased – volume (primarily) or noradrenaline – and the shunt monitored clinically (auscultation) and echocardiographically.

If saturation remains persistently too high, pulmonary edema or congestive heart failure may be expected to develop. When a reduction of arterial afterload does not help here (or is not possible because of runoff), the shunt must be made smaller.

Saturation that is persistently too low with a healthy lung indicates inadequate shunt flow. The causal factors here may be anatomic, partial thrombosis or kinking, insufficient shunt size, or a high PVR.

Investigations: (1) ultrasound, (2) cardiac catheterization, (3) surgical revision.

So far, in heart defects with “parallel circulation” of the pulmonary and systemic circulation, the Qp/Qs ratio has been derived from SpO_2 and the concept of “healthy lung.”

Since complete mixing of venous blood from the caval and pulmonary veins (with a healthy lung, saturation here is about 100%), is generally assumed in such heart defects, the aortic blood and that of the pulmonary artery (or shunt) have the same saturation. If the saturation of this blood is higher, the more the pulmonary venous

blood contributes to the mixing, i.e. a large proportion of the mixed ventricular blood is pumped through the lung and proportionally less into the systemic circulation. With a reduced systemic blood supply, this results in increased peripheral O_2 exhaustion of the blood ($SvO_2 \downarrow$). Therefore, in addition to arterial oxygen saturation (alternatively: SpO_2) and the assessment of pulmonary function – caveat: intrapulmonary shunts in the case of atelectases! – saturation of the central venous blood (superior vena cava) is also important for assessing the Qp/Qs ratio.

Calculation using the Fick principle for cardiac output, where the uptake or release of a substance by an organ equals the product of blood flow to that organ times the arterial-venous concentration differential (gradient) of that substance:

Formula 47

$$\frac{Qp}{Qs} = \frac{\left(SaO_2 - SvO_2\right)}{\left(SpvO_2 - SpaO_2\right)}$$

$SpvO_2$ with a healthy lung 100% and $SaO_2 = SpaO_2$ with complete mixing of venous and pulmonary venous blood.

15.2 Cyanotic Heart Defects with Left-Sided Obstruction

15.2.1 Hypoplastic Left Heart Syndrome

Further details on this topic are also provided in Sect. 15.11 and Chap. 13.

HLHS is a complex of underdeveloped structures of the left heart of varying degrees of severity, central among which are aortic valve atresia or stenosis and hyperplasia of ascending aorta and aortic arch (diameter 2–4 mm vs. 6–10 mm normally), hypoplastic left ventricle, and hypoplastic and stenotic or atretic mitral valve. There are functional and anatomic overlaps across borderline hypoplastic left heart (HLH), Shone complex, and extend to defects with VSD and relative LV hypoplasia.

Common to these lesions is the fact that the venous (systemic and pulmonary venous) blood is mixed in the right atrium and then reaches the RV via the TV (tricuspid valve), from where it proceeds to the main PA trunk. Here, the blood flow divides into that to the lung (via right and left PA) and that to the systemic circulation by means of an R/L shunt at PDA level. In this case, the flow is "downward," i.e., antegrade into the descending aorta, while the aortic arch and the ascending aorta (and hence also the head and neck vessels and coronary arteries) are perfused predominantly retrogradely via a usually hypoplastic aorta.

Perfusion of the systemic circulation is dependent on several factors:

Width of the PDA and the aorta (caveat: coarctation of the aorta; *can be missed on ultrasound; always measure blood pressure postductally as well*).

PVR – this falls dramatically in the first 1–2 weeks of life, so that the blood tends to be recirculated via the pulmonary vessels rather than flow into the systemic circulation (PVR < < SVR). This results in congestive heart failure due to hypercirculation with a coexisting reduction in coronary and head perfusion due to hypoplasia of the aortic arch.

If there is a relative flow restriction of the PV blood from the left to the right atrium, PVR may not decrease so markedly because of congestion (post-capillary component) in the PV, and this therefore limits the pulmonary hypercirculation.

The flow gradient can be determined echocardiographically by the pressure differential across the ASD (or patent foramen ovale [PFO]) (LAP = CVP + ΔP). The extent of the diastolic L/R shunt via the PDA also provides an indication of the ratio of SVR to PVR.

As with all heart defects exhibiting univentricular circulation, the ratio of pulmonary-to-systemic perfusion distinctively determines the clinical picture. Thus, in patients with decreasing PVR and increasing SVR, pulmonary hypercirculation develops increasingly on PDA closure: SpO_2 increases, while systemic blood flow decreases progressively. The clinical consequences of this are poor microcirculation, tachycardia, shallow pulse, hepatomegaly, oliguria, subsequently falling blood pressure and tachypnea (acidosis), and ultimately signs of multiorgan failure (MOF).

More rarely, if interatrial communication is massively impaired, there is so little mixing of blood that generalized hypoxemia with MOF occurs. This hypoxemic process begins immediately after birth due to the *anatomically* related interatrial communication impairment. Even if the emergency balloon atrioseptostomy that must be performed straight away in such cases is successful, the prognosis for these children remains dubious, for example due to the intrauterine development of intrapulmonary lymphangiectasia.

A good balance between systemic and pulmonary blood flow is essential to stabilize patients with HLHS. As blood mixing occurs in the RA, PA and arterial saturation (estimated from transcutaneously deduced saturation or measured) are identical (if there is no antegrade flow across the aortic valve). PV saturation can be assumed as 100% (with an otherwise healthy lung), so that Qp/Qs can be deduced from the ratio of the systemic arteriovenous saturation differential to the pulmonary (venoarterial) saturation differential (see above Formula 47).

To guide the therapy of these patients in particular, placement of a CVC is therefore very helpful in determining SvO_2 (for CVC positioning, see below under coarctation).

Rule of thumb: With SpO_2 of 75–80% and an arterial-(central) venous saturation differential of 25%, Qp/Qs is about 1:1.

In this optimal situation, the RV needs to generate “only” about twice its normal volume output.

15.2.1.1 Preoperative Management

The patients need their PDA (R/L shunt) to maintain the systemic circulation.

Therefore PGE1 (dosage between 10 and 30 ng/kg BW/min, depending on width).

(PGE1, where necessary with Fluimucil [acetylcysteine] 10 mg/kg BW/single dose t.i.d. – to liquefy viscous "Minprog" mucus)

As long as the organ perfusion pressure (kidney, coronary arteries) does not fall below the critical level (reference values: MAP 40 mmHg and diastolic > 28–30 mmHg), it is possible to try to conduct the blood flow from the pulmonary to the systemic circulation by careful reduction of systemic arterial afterload.

Example
Start titrating sodium nitroprusside 0.5 μg/kg BW/min (or phentolamine), or administer oral ACE inhibitors cautiously.

Because of the right ventricular overload immediately at the start of a decompensation, initiate milrinone 0.25–1 μg/kg BW/min where necessary; blood pressure usually does not fall, and systemic blood flow improves.

If decompensation has already occurred, ventilation often cannot be avoided (for intubation, see section on HLHS). At the same time, hyperventilation with a reduction in PVR must be strictly avoided. Aim for SpO_2 of 75–80% (see above). Therapeutic management involves close monitoring of urine output, lactate, SvO_2, if possible near-infrared spectroscopy (NIRS; of the head), and ultrasound. In this context, the documentation of intracerebral and intraabdominal Doppler flows in particular is also of special importance, as this is where the main consequences of hypoperfusion become manifest (development of PVL and risk of NEC).

15.2.1.2 Giessen Procedure

The complexity of the classical Norwood procedure and the necessary surgical steps early in life result in significant peri- and postoperative mortality and long-term morbidity. Whether in this respect the hybrid procedure ("Giessen procedure") produces better long-term neurologic outcomes remains to be established. However, patients who are no longer conventionally operable can also be rendered amenable to univentricular palliation by the hybrid procedure. In addition, the initial hybrid intervention provides the possibility of offering children with defects that are not initially suitable for biventricular correction (borderline HLH) a biventricular strategy over the course of time. Furthermore, the most recently evaluated data analyses indicate >80% survival until complete separation of the circulations in an unselected population of patients with HLHS.

With the Giessen procedure, pulmonary perfusion is restricted surgically by bilateral PA banding (a more gentle procedure than Norwood I in neonatal patients). In a second stage, the PDA is provided with a stent so as to maintain the systemic circulation without prostaglandin. It is critical in this stage to look for and where necessary to eliminate a coarctation of the aorta (= retrograde obstruction) so as to ensure free retrograde perfusion of the head and neck vessels and the coronary arteries. In the presence of restrictive interatrial communication, balloon atrioseptostomy should be performed supplementally, preferably after the PA banding.

The second surgical stage of the hybrid strategy is the combination of cavopulmonary anastomosis, pulmonary artery debanding with or without pulmonary artery

reconstruction, and connection of the RV and the reconstructed neoaorta, corresponding to the Norwood I procedure. This "comprehensive stage II" usually occurs at the age of 3–6 months. In the last stage, the hybrid strategy is completed at the age of about 1.5–2.5 years with the classical total cavopulmonary anastomosis and hence in the same end result as the classical Norwood procedure.

Stenoses in the pulmonary vessels that potentially need to be reconstructed and possible myocardial damage – e.g. due to impairment of coronary perfusion after the first stage – are unlikely to significantly impair the long-term prognosis in the hybrid strategy.

Bilateral pulmonary artery banding corresponds to extracardiac surgery without the use of a heart-lung machine. The aim of the constriction produced proximally in the right and left pulmonary artery is to reduce the pressure to about semisystemic level and to reduce the flow as a result.

Cardiac function is unlikely to be impaired, at least in comparison with the preoperative situation. Inotropics are not usually necessary. With uncomplicated ventilation (e.g., PEEP 4–5 cmH_2O; Vti 6–8 mL/kg BW; Ti about 0.4 s; flow about 12 L/min, e.g., with flow-controlled pressure-limited ventilation; FiO_2 about room air or just above; target CO_2 about 50 mmHg arterially – see Chap. 2 Ventilation), it should be possible to extubate the patient on the day of surgery. Particular attention must be paid to any tendency to bleeding and apnea during prostaglandin therapy. In addition, neonates not infrequently exit the operating room cold – in which case do not extubate immediately.

PDA stent insertion by cardiac catheterization is then performed shortly after PA banding. Following discontinuation of PGE1 (shortly before the performance of the intervention), it is essential to look for the development of a flow obstruction (retrograde) into the aortic arch, among other reasons because dispersed ductal tissue in the aortic wall can result in local constriction and hence retrograde flow obstruction to the head and coronary arteries. Caveat: strictly and regularly as in all aortic arch interventions: monitoring of blood pressure in the right arm and (non-catheter) leg.

The classical Norwood I procedure is described later.

15.2.2 Left Ventricular Outflow Tract Obstructions (LVOTO)

Closure of the ductus arteriosus in children with LVOTO can jeopardize systemic perfusion and intensify left ventricular failure. In some cases, however, right ventricular decompensation may be the cardinal symptom, at least on ultrasound, as a result of pulmonary hypertension (see below). In most cases an isolated valvular aortic stenosis is responsible in the neonatal period, but transitional forms to HLHS and sub- or supravalvular obstructions in the neonatal period itself can both also be causal factors.

Where there is a coexisting mitral stenosis (MST)/borderline left ventricular hypoplasia/hypoplasia and stenosis of the subvalvular LVOT and borderline small aorta or CoA (= hypoplastic left heart complex), a decision must be taken as to whether a univentricular or biventricular procedure is more sensible for the individual patient or whether a hybrid approach (see 14.2.1) initially keeps both options open. Echocardiographic parameters, among others, can be used here to reach a decision (see also Chap. 13):

- LV length and muscle mass (reference point: length < 20 mm: univentricular)
- Aortic root and mitral valve ring Ø
- Subendocardial scars (fibroelastosis)

The compliance disorder due to severe LV hypertrophy in LVOTO is of major significance. This results in the fact that, if LVEDP is high, then LAP is also high – unless an ASD can divert the blood to the RA. The increase in LAP results in an increase in post-capillary pulmonary resistance which – as in other heart defects with LAP ↑ – can result reactively in an increase in pulmonary artery resistance that can also persist postoperatively or postinterventionally (protective mechanism against pulmonary edema).

15.2.2.1 Critical Aortic Stenosis Neonatally

Where the heart defect is not known antenatally or becomes apparent as a result of a heart murmur, shock develops on "physiologic" postnatal closure of the PDA as well as pulmonary edema in the event of pulmonary hypercirculation and LAP ↑.

Actions

- Initiation of PGE1 (10–30 ng/kg BW/min [higher in shock]) – together with Fluimucil *[acetylcysteine]* (10 mg/kg BW/single dose t.i.d.); is the ASD large enough?
- Usually intubation and ventilation with PEEP, e.g. 6 cmH_2O, target CO_2 dependent on pulmonary hypercirculation and Qp/Qs ratio.
- Milrinone – if RV function is impaired – also improves LV compliance (0.5–1 µg/kg BW/min).
- (Nor)adrenaline where necessary to establish sufficient organ perfusion pressure.
- Buffer where necessary in severe acidosis – it must also be possible for CO_2 to be exhaled.
- Furosemide in the absence of urine output and established renal perfusion pressure and for the treatment of pulmonary edema.

Decision

Is a catheter intervention indicated for valve dilation or is surgery the first-line procedure?

The patient (75% boys) should be stabilized before either measure, unless atrial restriction is so severe that massive hypoxia is present (much rarer and then – as in HLHS – tending to occur more immediate postnatally).

The compliance disorder of the LV persists after both catheter intervention and surgical valvulotomy, i.e. the increase in LAP regresses only slowly. In these patients, therefore, extubation should be undertaken only if there is reliably sufficient urine output, good pulmonary function on the respirator, and good heart function of both ventricles on ultrasound. If there is a marked reactive increase in pulmonary resistance (normal pulmonary compliance with a transparent X-ray image and poor SpO_2 despite ventilation), inhalational NO is an option.

With both treatment options, secondary injury (surgery tends to be associated more with aortic stenosis/BAP more with insufficiency) is to be expected. Therefore LV function and dilation must be assessed by careful follow-up, and the timing of the subsequent valvular surgery (e.g. Ross procedure) must be defined.

15.2.2.2 Coarctation of the Aorta

Table 15.6 presents a list of aortic arch anomalies.

As the aorta near the ductal orifice also contains contractile ductal tissue, there is usually no significant aortic constriction until closure of the aortic ductal ends. Caveat: CoA develops on ductal closure. As a result, the LV afterload increases very rapidly so that there is no time for a left ventricular compensation mechanism to intervene and the LV can become acutely decompensated. This results in the cycle already described for the other left heart obstructions of increasing LVEDP (with possible exhaustion of the coronary reserve), increasing LAP, increasing PVR, and L/R shunt at atrial level. This results in RV overload and, in the case of hypercirculation, RV failure.

The LV can be unloaded by a VSD, but pulmonary hypercirculation and systemic hypoperfusion are further exacerbated (Qp/Qs ↑↑).

As a result, the previously described clinical picture of left heart obstruction with systemic hypoperfusion (shock and acidosis), combined with pulmonary hypercirculation (pulmonary edema and congestive RV failure), develops on PDA closure.

Acute therapy should be guided by these symptoms (see Table 15.7).

In shock: Initiation of prostaglandin (PGE1) 30–50 ng/kg BW/min. The possibility of a left heart obstruction must be considered in any neonate with shock of unknown origin who has low blood pressure and poor perfusion, congestive heart failure, and poor lung function (pulmonary edema).

Table 15.6 Aortic arch anomalies

Coarctation (most common form)	Aortic arch hypoplasia	Aortic arch atresia	Interrupted arch	Common to all
Hemodynamically significant narrowing of the thoracic aorta	Less than 40% of the diameter of the ascending aorta	Lumenless band joins two ends	No ligament	PDA supplies system “downwards”
Proximal to, distal to, or opposite the ductus	Luminal narrowing proximal to the ductus			Frequently associated with ventricular septal defects
Infolding of media into aorta	Normal vascular structure			Mostly bicuspid aortic valve
Adult form is post-ductal (downward collaterals)				Many other intra–/extracardiac vascular malformations

Table 15.7 Checklist for the management of coarctation of the aorta (CoA)

Keywords	Stable CoA	Unstable CoA – medication rescue works	Unstable CoA medication rescue does not work
PGE1 (Minprog)	10 ng/kg BW/min	30–50 ng/kg BW/min	30–50 ng/kg BW/min
Ultrasound	Caution with VSD!	Immediately	Immediately
Blood pressure gradient, documentation	1–2 ×/shift	Preferably arterially	Preferably arterially
Intubation	No	Yes	Yes
Inotropics	No	Milrinone, adrenaline	Milrinone, adrenaline
Volume restriction	Yes	Yes – In shock 1 × volume	Yes
Preparation for surgery, blood tests	Soon	If stabilized, PGE1 opens ductus	If no ductus, cardiac catheterization (BAP)
SpO_2	Pre−/ post-ductal	Pre−/post-ductal	Pre−/post-ductal

In the event of tachydyspnea, intubate or at least be prepared for acute intubation if the diagnosis is confirmed and the clinical status is still acceptable (particularly because of prostaglandin-related apnea and PVR ↓ – in this case a severe L/R shunt with pulmonary deterioration can occur, especially with a coexisting VSD).

The decision about volume therapy in neonatal shock can be a difficult one. Volume therapy may be contraindicated in congestive heart failure, whereas in septic shock "nothing goes" without volume. Therefore, a CVC should be established rapidly to measure CVP, and, following echocardiography, circulatory therapy should be managed with inotropics (milrinone up to 1 µg/kg BW/min) and adrenaline/noradrenaline as necessary (caveat: if there is a significant L/R shunt at the atrial level, SvO_2 can be deceptively high because of an increase in LAP due to left heart obstruction, in which case SvO_2 may be unsuitable for assessing the circulation.)

The situation in patients with aortic arch obstruction and VSD is particularly difficult. In this case, PVR can be reduced by prostaglandin therapy and ventilation to such an extent that pulmonary flooding results in pulmonary edema. Postductal SpO_2 of about 85% – with normal preductal saturation – indicates a Qp/Qs of about 1:1. The ventilation strategy with low FiO_2, permissive hypercapnia, and fairly high PEEP can reduce pulmonary blood flow.

15.2.2.3 Postoperative Management

As surgical correction should only be performed if there is good heart function, the function should not provide any problems postoperatively. However, significant bleeding (not into the pericardium) may occur because of the aortic suture or perfusion disturbance in the spinal cord because of the intraoperative perfusion disruptions (does the patient move his/her legs?). Vocal cord nerve palsy or postoperative

Table 15.8 Surgery for coarctation of the aorta (CoA)

Coarctation of the aorta (CoA)			
Ventilation: PEEP 4–5 cmH_2O, Vti 6–8 ml/kg BW, CO_2 40–50 arterially, extubation usually on day of surgery. Caveat: Pulmonary hypertension!	Analgosedation: Lateral thoracotomy very painful, morphine single dose, paracetamol every 4–6 h, do not force extubation	Complications: Bleeding, spinal cord perfusion disorder, recurrent nerve lesion, thoracic duct lesion, phrenic nerve lesion, restenosis – Highly amenable to treatment with BAP	Post-coarctation syndrome in older children (necrotizing angiitis of the abdominal vessels from relative hypertension after preexisting hypoperfusion), 2–6 days postoperatively
		Common: Paradoxical hypertension (baroreceptors displaced), atenolol 2 × 0.5–1 mg/kg BW/ single dose postoperatively	For postoperative blood pressure monitoring, it is decisive to exclude any aberrant subclavian artery

chylothorax can also occur. An aortic residual postoperative pressure gradient can be documented by pre- and postductal (invasive) blood pressure measurements and by echocardiography.

If a VSD is also present, LV afterload can fall as a result of PDA closure and elimination of CoA. The LV must now receive all the blood that previously supplied the lower half of the body from right to left via the PDA and as a result is volume overloaded. If the VSD is closed at the same time, the LV can be overburdened by this volume overload – large VSD can in this case require a two-stage process, with a central PA banding until full correction.

Borderline small or severely hypertrophic ventricles can also be overburdened if a volume overload newly occurs. This is found in particular if there is a coexisting aortic valve stenosis (bicuspid valve) or borderline small ventricle in Shone complex. An ASD as an atrial pop-off can be helpful here (see Table 15.8).

15.2.2.4 Interrupted Aortic Arch

Types (described distally to proximally relative to the left subclavian artery):

- Type A = All arch defects are proximal to the interruption – most common type.
- Type B = Only the left subclavian artery lies distal to the interruption.
- Type C = The left common carotid artery also lies distal to the interruption (rarity).

Most patients have a VSD, many have a valvular aortic stenosis, and some have additional complex malformations (TGA, aortopulmonary window, DORV). A microdeletion on chromosome 22 is often present.

The combination with a VSD can cause the pressure-unloaded left ventricle to shunt to the right, resulting in the previously described situation of RV overload,

and, in the case of decreasing PVR and PDA closure postnatally, to pulmonary hypercirculation with congestive heart failure can develop.

Preoperatively: Similar to critical CoA, the patient requires prostaglandin to maintain the perfusion of the lower half of the body (start with 10–20–50 ng/kg BW/min depending on the status). If the PDA closure is already advanced – hence pulmonary hypercirculation and RV failure – inotropic therapy (milrinone/adrenaline) and ventilation may also be necessary. Since ventilation can increase pulmonary hypercirculation by dint of a reduction in PVR if there is a coexisting VSD, supplemental oxygen should be avoided as far as possible. A further attempt should be made to restrict pulmonary perfusion by means of high PEEP (6–10 cmH_2O) and slight hypercapnia (CO_2 60 mmHg arterially) and to achieve a balanced Qp/Qs with an SpO_2 of about 85% postductally.

A complete correction should be aimed for intraoperatively. Subsequently – as already described for coarctation – the left ventricle may be overburdened by the resultant volume overload. This occurs in particular if the ventricle is small, the VSD was large, or a LVOTO (subaortic stenosis) is present, and LV compliance remains poor because of hypertrophy. In these cases, the diastolic LV functional disorder can result in low output and also in backward failure with pulmonary edema.

In therapeutic terms, the focus postoperatively lies on maintaining sufficient perfusion pressure (noradrenaline where necessary) alongside treatment with milrinone, as well as antitachycardiac therapy (clonidine/dexmedetomidine, esmolol with caution). In LVOTO, beta-mimetics should be avoided wherever possible. If there is a severe diastolic functional disorder, the chest should remain open postoperatively.

15.3 Transpositions of Great Arteries

In complete transposition of the major vessels (d-TGA), the aorta – and with it the coronary arteries – arises from the right ventricle, so that on ultrasound, the aortic root and coronary arteries are located at the front, close to the sensor. Where the normal anatomy of the blood conduction from the atria to the ventricles is preserved (AV concordance), two separate circulations result. The pulmonary circulation circles on itself (LV → PA → LA → LV), while the blood in the systemic circulation is conveyed past the lung (RV → aorta → caval veins → RA → RV) and is not oxygenated. Massive cyanosis develops if there is no mixing of blood at atrial level – PFO/ASD – and/or the PDA does not contribute to pulmonary perfusion with an L/R shunt.

In most cases, cyanosis is already apparent in the early postnatal period; this increases with PDA closure and presence of only a minor shunt at atrial level If untreated, this results in hypoxia-induced organ and circulatory insufficiency. Furthermore, the LV, which has to pump “only” through the pulmonary circulation, loses muscle mass and contractility with decreasing PVR postnatally, so that even with compensated mixing of blood by means of an open atrial communication and a PDA, surgical treatment is required within the first 10–14 days in order that the less trained LV is not overburdened by the comparatively high SVR following arterial switch.

The simplest and most common form of (d)-TGA has no further malformations, but in 20–30% of cases, a VSD, coronary anomaly, coarctation of the aorta, or pulmonary stenosis can also be present.

A sufficiently large VSD promotes the mixing of blood and the training status of the left (subpulmonary) ventricle preoperatively. However, surgery is complicated and prolonged – longer ischemic time and more frequent arrhythmias (early and late postoperatively). Coronary anomalies also can complicate surgery, but usually do not preclude switch surgery.

15.3.1 Preoperative Procedure

In most cases, cyanosis is rapidly detectable postnatally. The poorer the mixing of blood via ASD/PFO and the additive pulmonary perfusion via PDA, the more severe the cyanosis. At critical arterial saturation values < 60–65% (PaO_2 30 mmHg), an undersupply of oxygen to the organs, energy deficiency, lactate formation, and lastly shock and MOF can occur.

Therefore, two venous accesses should be established, PGE1 should be initiated in the case of a narrow ductus (30–50 ng/kg BW/min), and where necessary O_2 should be administered. Intubation and ventilation with PEEP is necessary in hypoxemic and metabolically acidic, i.e. critically ill, patients. In a context of hypoxemia, a marked increase in PVR can occur that prevents pulmonary perfusion even if the shunt size is sufficient (O_2 ventilation, mild hyperventilation, and where necessary inhalational NO as treatment options). Volume administration to improve mixing at atrial level can improve oxygenation.

With SpO_2 < 65% and systemic signs of hypoxemia, balloon atrioseptostomy is performed in the case of narrow atrial communication (PDA alone is not sufficient for mixing); as a rule, this improves oxygenation and should result in regression of the acidosis and in the ability to extubate the patient with low doses (10 ng/kg BW/min) of, or in rare cases entirely without, prostaglandin therapy.

By contrast, in TGA patients with a very wide PDA and saturation values of more than 87–90%, consider presence of hypercirculation (PVR ↓ through ventilation, PGE1, improvement of acidosis, and expiration of CO_2) and tailor the treatment to a congestive overload of the subpulmonary LV, which should be avoided preoperatively (target preoperative SpO_2 values in patients with TGA: 75–85%).

15.3.2 Arterial Switch Operation (ASO)

In order to ensure a good training status of the LV, PVR should not fall excessively preoperatively, since postoperatively the LV has to pump the whole CO through the systemic circulation (with a correspondingly high SVR). It is not only the physiologic fall in PVR in the first days of life that plays a limiting role; overly intensive prostaglandin therapy in conjunction with “good” saturation can also negatively impact on LV function preoperatively (via volume overload). Surgery should therefore generally be timed to occur between the 3rd and 10th (−14th) day of life.

Aorta and PA are switched intraoperatively above the semilunar valves, and the coronary arteries are transplanted and re-inserted into the neoaorta – which can result in distortions with an ensuing perfusion impairment.

Because of the often relatively long aortic clamp time in neonates, there is often a significant capillary leak and postoperative myocardial function impairment after ASO. Postoperatively there is generally a substantial volume demand, and in most cases, inotropics are also required.

Ventilation
PEEP 5–6 cmH_2O, normoventilation, Vti 6–10 ml/kg BW, RMV 150–200 mL/kg BW.

Sedation
Low-dose analgosedation with a fentanyl/midazolam drip is usually needed for postoperative pain therapy and tube tolerance. This sedation should not be intensified to deep anesthesia.

Circulatory monitoring
Ultrasound, SvO_2, lactate, urine output, microcirculation, ΔT, NIRS, in addition to blood pressure and CVP.

Rhythm monitoring
JET not uncommon, ischemia-related arrhythmias in coronary perfusion disorder possible.

If sinus tachycardia is present despite good sedation (pain), temperature monitoring (fever) and high normal CVP (10–12 cmH_2O), a diastolic functional disorder is particularly likely. In this case, following trial pharmacological rate reduction (dexmedetomidine), delayed chest closure should be considered.

If MAP is too low – despite sufficient preload – adrenaline and noradrenaline can be used with caution. Urine output not infrequently comes to a halt, so that higher doses of furosemide (consider drip) may be needed (see Table 15.9).

Table 15.9 Checklist for the management of surgery for transposition of the great arteries (TGA)

Blood pressure	MAP 40 mmHg, 35 mmHg if SvO_2 good/ no lactate	Inotropics	Milrinone always, noradrenaline if capillary leak, adrenaline if systolic function disorder
CVP	Up to 14 cmH_2O	JET	Cooling, amiodarone
Urine output	Lasix single dose/drip		
Tachycardia (Ø fever, Ø pain)	JET/diastolic function disorder, dry tamponade	Tachycardia	Caveat: Dry tamponade!
Lactate	CO↓, glucose utilization disorder	Coronary arteries	Nitro drip 0.5–1 µg/kg BW/min, heparin 300 IU constantly; pay attention to ST segment changes
SvO_2	≥ 60%		
Capillary leak	Dexamethasone? Factor XIII (?)		

Good flow with low normal blood pressure is the best left ventricular protection

15.3.3 At-Risk Transpositions of Great Arteries

The surgical risk in simple TGA (early mortality) is about 1%. Mortality is increased markedly if additional anomalies are present, such as relevant VSD or aortic arch obstructions, and slightly increased with coronary anomalies – in this case due in particular to an intramural course.

TGA with subvalvular and/or valvular pulmonary stenosis allows the timing of surgery to be delayed but requires a substantially more complex surgical strategy, often associated with long-term sequelae (e.g. Rastelli procedure, translocation).

15.4 Total Anomalous Pulmonary Venous Return (TAPVR)

In total anomalous pulmonary venous return (TAPVR), the oxygenated blood is not returned to the LA but communicates directly with the venous system of the body's systemic circulation. There is often an obstruction in the area of the pulmonary venous drainage.

The pulmonary venous confluence can drain into the right atrium via the innominate vein (supracardiac type – 50%) or via the coronary venous sinus or via direct connections (cardiac type 30%). With the infracardiac type (20%), there is usually a supracardiac confluence, but this is not connected to an atrium but transdiaphragmatically via a vertical vein to the portal circulation (as a relic of the umbilical vein connection) (see also Chap. 13).

The TAPVR variants mentioned necessarily entail an L/R shunt from the pulmonary veins to the systemic venous circulation on the one hand and on the other hand an intracardiac R/L shunt at atrial level. The pathophysiology derives hemodynamically from the increased pulmonary blood flow and a possible obstruction in the opening of the pulmonary veins (= post-capillary pulmonary hypertension with a reactive precapillary component).

Although these are rare conditions, a total anomalous pulmonary venous return should be considered in the differential diagnosis of any severely ill neonate with cyanosis and "white lung." If pulmonary compliance is still good, but the lung X-ray is already white, this is a clinical sign.

15.4.1 Preoperative Management

Since in cases of TAPVR with a severe obstruction there is the possibility of pulmonary edema occurring with hypoxemia and, at the same time, low cardiac output as a result of the reduced return to RA → LA → systemic circulation (the whole systemic CO must pass via the R/L shunt through the atrial septum!). This produces a situation in which there is a volume deficit in the systemic circulation and excess volume in the pulmonary circulation. The increasing acidosis exacerbates the precapillary component of the increase in pulmonary resistance. When, therefore, the circulation is obstructed by a severe pulmonary venous obstruction (PVO), this is a

Table 15.10 Total anomalous pulmonary venous return (TAPVR)

TAPVR	Severe stenosis of PV drainage (PVO)	Moderate PVO	No PVO
PVR	PVR ↑↑	PVR ↑, but PBF ↑	PVR slightly increased
Lung	PBF ↓, PHT, pulmonary edema, PDA past the lung	PBF increases because PVR decreases postnatally (pulmonary edema) in PVO	PBF ↑, little pulmonary edema because no PVO
Blood flow + oxygenation	Severe hypoxia, CO ↓	Moderate cyanosis, pulmonary hypercirculation	Slight cyanosis, late congestive HF
Clinical features	Hypoxemic MOF	Congestive heart failure	As ASD

PVO pulmonary venous obstruction, *PBF* pulmonary blood flow

surgical emergency; catheter interventional treatment of the obstruction can allow stabilization and elective surgical correction, although valuable time can be lost on cardiac catheterization, particularly with severe hypoxemia. Inhalational NO can help as a bridging measure but ultimately exacerbates the pulmonary edema. In extreme cases, it is necessary to achieve sufficient systemic perfusion and organ regeneration by ECMO preoperatively.

In moderate PVO, PVR↑ and increased pulmonary blood flow balance one another out, so that hypercirculation through the lung results in congestive right heart failure. In these patients, PPV together with diuretic and inotropic treatment (furosemide, milrinone, where necessary adrenaline/noradrenaline with caution if MAP <35 mmHg) can bridge the time to surgery.

Patients without PVO can remain relatively asymptomatic for a long time (see Table 15.10).

15.4.2 Surgery

A connection between the PV confluence and the LA is created by the surgical procedure. Depending on the anatomy, various techniques can be used, which have in common the fact that they can result in distortions of the anastomoses and consequently to pulmonary venous stenoses.

The extent of the postoperative problems depends to a large extent on factors such as preoperative circulatory insufficiency, pulmonary hypertension, pulmonary edema, and operation time.

If the outflow via the new PV opening is uncomplicated, as described previously for other heart defects, the precapillary component of the increase in PVR can initially persist and result in PA crises. In severe cases analgosedation (fentanyl/midazolam drip) as well as inhalational NO can be used to treat postoperative PHT.

As the correction of TAPVR involves surgery on a heart-lung machine in the neonatal period, severe capillary leak, postoperative vascular failure, and pump failure after a prolonged aortic clamp time can occur, particularly in cases involving problematic anatomy and with a long operation time. In this case, milrinone

(routinely), catecholamines, a furosemide drip, and lastly postoperative ECMO may be required for stabilization. This contrasts with uncomplicated cases (without pulmonary venous obstruction), in which very rapid postoperative extubation is desirable.

15.5 Patent Ductus Arteriosus in Mature Neonates

The ductus arteriosus closes physiologically – triggered by the high O_2 tension (PaO_2) with a postnatal L/R shunt via the ductus – in the first 24 h of life in functional terms. The reversal of the shunt relative to the fetal situation occurs because of the dramatic decrease in PVR postnatally while SVR is increasing. Irreversible fibrous ductal obliteration usually occurs in the first 2–3 weeks of life. Ductal closure is precluded if PaO_2 and pH are low and blood prostaglandin levels are high.

In symptomatic patent ductus arteriosus (PDA) patients, the extent of the L/R shunt is determined in the first place by the decreasing PVR. The shunt results in a pressure and volume overload of the pulmonary vascular bed and a volume overload of the left side of the heart (LA + LV).

Depending on the size of the PDA, symptoms may develop within the first few weeks of life in the form of congestive heart failure with pulmonary edema. A reduction in diastolic flow in the organ arteries occurs as a result of the loss of the Windkessel function of the aorta and subsequent diastolic pulmonary runoff to the detriment of organ perfusion. The volume overload of the left heart causes LA and LV dilation, an increase in LAP, and possibly also ensuing pulmonary edema. The pulmonary vascular bed reacts to this increase in LAP by precapillary vasoconstriction, which, together with the pressure overload via the nonpressure-separating PDA, results in pulmonary hypertension.

In the rare cases of decompensation, treatment is provided in the form of PPV and permissive hypercapnia, diuretics, and where necessary inotropics. As a rule, PDA closure can be achieved by catheter intervention.

15.6 Patent Ductus Arteriosus in Premature Infants

Compared with mature children, a PDA of hemodynamic relevance is found in premature infants increasingly frequent with decreasing gestational age, albeit without an exact correlation with maturity.

Intrauterinely, the RV, which accounts for about $^2/_3$ of cardiac output, pumps only about 10% of its blood through the lung. The remaining proportion of the right ventricular blood is available for systemic perfusion via the ductus. As PVR decreases rapidly postnatally as a result of spontanous pulmonary ventilation and SVR increase following closure of the umbilical artery, the direction of the shunt via the ductus is reversed in the first few hours of life from R/L to L/R. In addition, an increase in left atrial pressure and hence functional closure of the foramen ovale occur with increasing pulmonary perfusion and increased LV afterload.

In preterm infants, O_2-dependent vasoconstriction, the vessel-occluding intimal cushion, and degeneration of the elastic fibers of the ductal wall are relatively underdeveloped as physiologic closure mechanisms. Further factors that may lead to a PDA are a severe respiratory distress syndrome and secondary infection.

If there is an increased risk of renal impairment, NEC or PVL, ductal closure is strictly indicated. In other cases, clear and validated criteria for assessing hemodynamic relevance and the indication for surgery are lacking.

Pharmacological PDA closure is highly promising in the first few days of life because of the high response rate to COX inhibitors (in some cases also paracetamol). Later treatment is most likely to be indicated if the following criteria are present:

1. Very small preterm infants who cannot be extubated after consolidation of lung function (surfactant therapy) or who exhibit other relevant organ perfusion problems
2. Preterm infants with a large PDA who, despite extubation, still exhibit lung function disorders or kidney or GI function disorders after more than 1–2 weeks

In the patients described under 1 and 2, greater focus is placed on surgical PDA closure, since COX inhibitors frequently are no longer effective here. In addition, the possible side effects of the nonselective COX inhibitors indomethacin and ibuprofen are a primary consideration. These include kidney function and intestinal perfusion disorders in particular. However, whether COX therapy used as late treatment (after 1–2 weeks of life) additively increases the risk of NEC in subjects whose intestinal perfusion is already impaired by PDA remains a subject of debate.

Surgical PDA closure – example of preparation and corresponding procedure:
Child often referred from externally:

- Preoperative laboratory findings, microbial situation, current chest X-ray, current antibiotic therapy, nutritional status, parental situation (in particular, explanation by referring hospital can sometimes cause irritation)
- Clinical status, ventilation status, signs of NEC, or sepsis
- Surgery feasible: no signs of infection, platelets >100,000/μL, Hb > 10 g/dL, order 1 unit packed RBC (filtered and free from CMV (cytomegalovirus); cefuroxime as long as there is no particular microbial situation
- Accesses: tube – X-ray assisted, Silastic catheter, volume access (24 G peripheral i.v. access), preferably artery (radial)
- Surgery. Packed RBC on ward or in the OR
- Fentanyl (single dose up to 5 μg/kg BW)
- Midazolam (2–3 single doses, about 0.1 mg/kg BW)
- Vecuronium (1–2 × 0.1 mg/kg BW)
- Operation time about 30 min, MAP as a rule increases on clamping of PDA (Windkessel works again)

Poor oxygenation frequently develops following dissection of the PDA due to external procedural lung compression, therefore adapt PEEP/PIP and FiO_2,

preferably measuring Vti (6 mL/kg BW/breath). Ask surgeons about pulmonary ventilation before lateral chest closure.

After closure, place the patient in supine position, request chest X-ray, and follow up ultrasound. Ensure sufficient analgesia for painful lateral thoracotomy wound. Afterwards, do not extubate until following day; then, if needed, take blood sample in the presence of signs of inflammation. Do not return patients directly to the referring hospital after extubation. If a rapid transfer is desired or necessary, it is safer for the child to remain intubated for the transport.

15.7 Aortopulmonary Window

With an aortopulmonary window, there is hemodynamically a post-cardiac L/R shunt with volume overload of the left heart structures, loss of the Windkessel function of the aorta, and pressure and volume overload of the pulmonary circulation.

The connection is located shortly distal to the semilunar valves, sometimes in the immediate vicinity of the orifice of the left coronary artery and sometimes also slightly further distally between aorta and RPA. Usually the connection consists simply of a transition of the vessel walls of the aorta and pulmonary artery into one another; a tubular arrangement is less common.

If PVR is still high neonatally, there is initially only a weak L/R shunt, the volume of which increases as PVR ↓ and therefore can result in a hemodynamic compromise (= congestive heart failure), pulmonary hypercirculation, and hence the risk of pulmonary arterial hypertension. An aortopulmonary window can be associated with malformations, especially VSD and interrupted arch, as well as coronary anomalies, so that preoperative cardiac catheterization and/or an MRI scan can be helpful.

Surgical correction is usually performed in the first few weeks of life.

Where no other malformations are present, the postoperative complications of pulmonary hypercirculation – high PVR, PA crises, and RV failure most likely immediately postoperatively – are only to be expected if there is already a long-term increase in PVR. However, it is usually possible to extubate early.

Therapeutically, the following measures are used as necessary:

- Sedation
- Ventilation strategies with CO_2 40 mmHg, pH 7.4, where necessary slight alkalinization, NO
- Prevention and treatment of PA crises (where necessary also with oral sildenafil)
- Treatment with sufficient preload and milrinone for RV support

15.8 Persistent Truncus Arteriosus (PTA), Truncus arteriosus communis (TAC)

The main anatomic feature common to the heterogeneous forms of this heart defect is a single major vessel arising from the heart and supplying both the systemic and pulmonary circulation with blood (see Fig. 13.1a–d). The common vessel usually straddles a VSD, which deviates to the right from the normal axis of the septum

Table 15.11 Truncus arteriosus communis (TAC)

Type I	Type II	Type II	Type IV	TAC with VSD and MAPCA
Main PA trunk present	No main PA trunk	No main PA trunk	Main PA trunk supplies RPA/LPA and ductus for lower half of body	No main PA trunk
RPA and LPA arise from main PA trunk	RPA and LPA arise jointly from the aorta	RPA and LPA arise separately – further distally – from the aorta	Interrupted aortic arch	Pulmonary perfusion very diverse

RPA/LPA right/left pulmonary artery

(malalignment). Different variants of pulmonary artery origins can be found distal to the common outlet valve – which can be insufficient and stenotic to different degrees and in some cases also can comprise more than three semilunar valve leaflets (see Table 15.11 and Fig. 13.1a–d).

As coronary anomalies and malformations of the aortic arch may be present, cardiac catheterization and/or MRI/CT angiography should be performed for precise visualization of the anatomy. As there is frequently a microdeletion on chromosome 22, appropriate genetic testing should be requested.

In persistent truncus arteriosus, the systemic blood pressure acts on the pulmonary vascular bed. There is a substantial L/R shunt that is often already symptomatic of heart failure in the neonatal phase. Caveat: Watch out for an increase in shunt following postnatal decrease in PVR!

In most cases biventricular correction is possible. To this end, the VSD is closed in such a way that the LV blood is channeled to the trunusk valve and the RV is anastomosed by means of an allograft – or else by means of foreign material – with the main PA trunk (type I) or the PA bifurcation (type II). Reconstruction of the insufficient and/or stenotic trunk valve may be required. Postoperative risks include a tendency to pulmonary hypertensive crises and result from residual anatomic defects or stenoses.

Postoperative treatment following biventricular correction must be approached in the knowledge of these risk factors.

Ventilation aims in the event of signs of postoperative pulmonary hypertension:

- Normoventilation, $SpO_2 > 95\%$, pH > 7,4, where necessary NO and where necessary early postoperative sildenafil
- Extubation only following improvement of the PHT situation – until which time sedation may be required

Improved RV performance can be achieved with milrinone, relatively high CVP (*caveat:* volume deficiency!), RV afterload reduction by ventilation strategy (see above), where necessary open chest to improve filling, where necessary treatment of tachycardia in the event of a diastolic function disorder (clonidine/dexmedetomidine).

Improved LV performance (CO) can be achieved with afterload reduction (with sufficient perfusion pressure), i.e. milrinone, where necessary sodium nitroprusside

early postoperatively – as long as the systemic blood pressure allows – and initiation of ACE inhibitor, particularly in the case of trunk valve insufficiency.

Pacing (caveat: baffle-patch at the margin of the VSD in the vicinity of the AV node → risk of block) to maintain atrial and ventricular coordination.

15.9 Pulmonary Artery Banding

As PVR falls from the systemic level to about $^1/_4$ of the systemic level in the first weeks after birth, in the case of defects in which pulmonary and systemic circulation are connected in parallel and not serially (HLHS, univentricular hearts, TAT, etc.) as well as with large interventricular connections, there is an unequal distribution of pulmonary (↑) to systemic (↓) blood flow. This is associated on the pulmonary side with the risk of permanent damage to the vascular bed (PHT due to pressure- and volume-related shear stress) and on the systemic side with the risk of heart failure. While both can be influenced by therapeutic measures to control blood flows and improve Qp/Qs, long-term protection against volume and pressure overloading of the pulmonary vascular bed and heart failure can only be achieved by surgical narrowing of the flow/flows to the lung.

Various hemodynamic situations are distinguished in which two "comparable" outflows are supplied with blood from the ventricle/ventricles (large, pressure-equalizing VSD, AVSD, DOLV, TAT without pulmonary stenosis). In such cases the vessel leading to the lung needs to be restricted by central PA banding if a biventricular process is not possible. The patient gains time as a result of the protection from pulmonary arterial injury and the improvement of heart failure.

This contrasts with defects in which pulmonary and systemic perfusion are supplied with blood from only one outlet (HLHS and PTA III). In this case, the right and left pulmonary artery must then each be restricted bilaterally after the bifurcation (= bilateral PA banding) in order to balance the blood flows of the systemic and pulmonary artery perfusion territories when the pulmonary arterial resistance decreases.

15.9.1 Bilateral Pulmonary Artery Banding

(As Described in Sect. 15.2.1)

15.9.2 Central Pulmonary Artery Banding

(Large, Pressure-Equalizing VSD, Unbalanced AVSD, DOLV, TAT Without Pulmonary Stenosis, Etc.)

Taking the example of tricuspid atresia without pulmonary stenosis, it can be seen that without a surgical intervention the mixed blood of the left atrium reaches the LV via the mitral valve and the RV via the VSD. As PVR decreases, an

imbalance in the blood flows into the lung (↑) and the systemic circulation (↓) increasingly develops. This results in the scenario of heart failure with relatively high SpO_2. In the case of this heart defect, separation of the circulations (Glenn → TCPC) is indicated for definitive palliation. Although the Glenn procedure is possible (after reduction of PVR) from a body weight of as low as 3 kg, ideally it is performed at a weight of 5 kg and above. Therefore, with increasing arterial saturation (= pulmonary hypercirculation) in the neonatal period, the flow to the PA needs to be reduced surgically by central PA banding.

The aim of postoperative therapy is in turn to balance the blood flows in the pulmonary and systemic circulations (see above Formula 47).

All variables in the equation, with the exception of PV saturation, are known ($SaO_2 = SpaO_2 \approx SpO_2$), and SvO_2 is measurable. Therefore, in this case also, the assessment of lung function – X-ray, ventilation parameters with tidal volume, PEEP, PIP (compliance) – is a precondition for the meaningful tailoring of circulatory therapy.

With a saturation of about 75–80% and a "good" lung, Qp/Qs is about 1:1, so that incipient heart failure is optimally treated.

With a diseased lung, an SpO_2 of 75–80% may already be the manifestation of substantial pulmonary hypercirculation, and heart failure may be present.

Tip

In this case, SvO_2 as an indirect parameter for estimating CO also falls, and transcutaneously measured saturation increases markedly in the hyperoxia test (sudden "dramatic" increase in FiO_2).

Surgically the main PA trunk is ligated with a band without a heart-lung machine so as to result in a fall in pressure in the PA to about $^1/_2$ of the systemic level.

15.9.2.1 Postoperative Management

Since the preload delivery to the LV (and RV) is decreased by the reduction in pulmonary hypercirculation, patients regularly require postoperative volume. The LVOT must be assessed by echocardiography as an outlet obstruction (LVOTO) may develop following unloading of the ventricle.

Extubation should then be attempted promptly if at

- (approximately) room air and
- tolerable pH values (from about 7.3 venous) at
- low ventilation rates
- safe circulatory conditions are obtained.

Fine-tuning after extubation is performed by treatment with ACE inhibitors, furosemide, and spironolactone to manage congestive heart failure while monitoring lung function (clinical features) and SpO_2.

A further surgical option for balancing systemic-to-pulmonary flows in hemodynamically univentricular hearts is offered by the DKS (Damus-Kaye-Stansel) procedure with a systemic-to-pulmonary shunt (see Tables 15.12 and 15.13).

Table 15.12 Checklist for the management of therapy PA banding

Ventilation	Circulation	Ultrasound	Possible effects
PEEP 4–5 cmH_2O	MAP > 40 mmHg	Good function	Afterload reduction with sufficient MAP improves systemic perfusion
PIP 22 cmH_2O	Urine output 2 mL/kg BW/min	Δ P band: about 50% SAP	CO_2 ↑ with tolerable pH improves systemic perfusion
Vti 6–8 ml/kg BW	CVP 6–8 mmHg	No outflow tract obstruction	PEEP after extubation keeps lung open
CO_2 50–60 mmHg	SvO_2 55–65%, $avDO_2$ about 20–30%		Uncontrolled O_2 administration after extubation can mask heart failure
X-ray: Lung free?	Good MC?		

Table 15.13 Checklist for the management of Treatment Damus-Kaye-Stansel (DKS) procedure with shunt

Objectives	Ventilation	Possible effects	What to do?
SpO_2 ≈75–80%	Neonatal respirator	Saturation ↑	BP ↓ (afterload ↓), FiO_2 ↓, CO_2 ↑
SvO_2 50–60%	PEEP 4–5 cmH_2O	Saturation ↓	Converse – Caveat: Shunt thrombosis!
MAP ≈40 mmHg	PIP about 20–22 cmH_2O	Increase organ perfusion	Milrinone, pulmonary perfusion ↓
Urine output 2 mL/kg BW/h	Vti 6–8 ml/kg BW	O_2 consumption ↓	Sedation, normothermia, BG monitoring, ventilation
PTT 60 s	CO_2 50–60 mmHg (venous)		

15.10 Damus-Kaye-Stansel Procedure

In cardiac defects with (sub-)aortic stenosis, e.g.

- DILV with TGA and aortic stenosis
- TAT with TGA and subaortic stenosis
- DORV with subaortic stenosis

the blood supply to the system is (predominantly) PDA-dependent. The aortic arch and hence also the coronary arteries are perfused in some cases retrogradely.

As a result of the DKS anastomosis, the ventricular outlets (stenotic aortic outlet and PA outlet) are anastomosed, so that the mixed blood is channeled via both outlets to the aorta, which is now completely antegradely perfused again (where necessary with widening of the aortic arch) (see Fig. 15.2).

To ensure pulmonary perfusion, a systemic-to-pulmonary shunt (diameter 3.5–4 mm) is now put in place to allow the development of a parallel circulation with ejection from the ventricle(s) into the aorta and pulmonary perfusion that is slowed and dosed by the shunt (modified BT shunt in Fig. 15.2).

Fig. 15.2 Univentricular circulation with modified Blalock-Taussig shunt

As with (almost) all univentricular circulations, free atrial communication is required.

Postoperatively – as with almost all neonatal CBP surgery – a myocardial function disorder and a significant capillary leak is likely to occur.

Many of the patients benefit from milrinone therapy; excessive volume replacement therapy can be limited if necessary by low doses of noradrenaline (target MAP about 40 mmHg, ensure sufficient urine output with furosemide). As the pulmonary and systemic circulations are connected in parallel postoperatively, the previously mentioned treatment aims apply.

Urgent consideration must be given to the perfusion through the AP shunt (saturation, auscultation, ultrasound, cardiac catheter; if necessary: revision surgery!) and additionally to any sign of myocardial ischemia (EKG changes, arrhythmias, reduced contractility). As with any defect in the aortic Windkessel, coronary perfusion can be compromised by low diastolic blood pressures.

As myocardial depression often does not reach its peak until about 6 h postoperatively and the circulatory conditions need to adapt first because of the markedly altered hemodynamics, postoperative analgosedation in the first night is recommended (e.g. fentanyl/midazolam drip). This can be discontinued once the above-mentioned target parameters have been reached at the end of the first night so that weaning can be attempted after a further evaluation of hemodynamics, lung function, laboratory values, and echocardiography.

15.11 Norwood I Procedure for Hypoplastic Left Heart Syndrome

The anatomical and physiological circumstances and the Giessen procedure have already been described in Sect. 14.2.1. Besides aortic atresia/stenosis, hypoplastic LV, and mitral atresia/stenosis, hyperplasia of the aortic arch is also found in HLHS (see Fig. 15.3). In the absence of treatment, RV overload, tachycardia, exhaustion of coronary reserves, and systemic low cardiac output with MOF develop as a result of the pulmonary hypercirculation, induced by PDA closure in conjunction with low systemic perfusion. Caveat: coronary arteries, brain, intestine, and kidneys!

A common echocardiographic manifestation of the RV overload is the development of tricuspid insufficiency.

Mechanisms for recompensation:

- Prostaglandin (PGE1) to open the PDA (systemic flow ↑, PVR ↓)
- Milrinone for positive inotropic treatment and afterload reduction
- Sodium nitroprusside or phentolamine for afterload reduction and improvement of systemic perfusion
- Sodium hydrogen carbonate for treatment of acidosis (*caveat:* can further reduce PVR)
- As needed, ventilation to reduce O_2 consumption (*caveat:* do not hyperventilate)
- Vasopressors and beta-mimetics in shock (administration of thyroid hormone and steroids where necessary)

Fig. 15.3 Hypoplastic left heart syndrome (HLHS)

- Analgosedation (O_2 consumption ↓, tube tolerance, ventilation control)
- Temperature about 35–36 °C (to reduce O_2 consumption)

It is important in this context to be aware of the effect of blood flow via the atrial septum. If atrial communication is unimpeded, there is no increase in post-capillary pulmonary resistance, and blood flow to the lung is unobstructed (scenario of high SpO_2 in shock). With restrictive ASD, less blood flows into the lung, restricting pulmonary hypercirculation, and the patient has lower saturations, to the extent even of hypoxemia – this scenario occurs already shortly after birth because of the anatomic flow restriction (massive cyanosis in HLHS → PVR ↑↑ because of LAP ↑ with a lack of atrial communication and congestion before the hypoplastic LV). These patients must be ventilated and transferred immediately for atrioseptostomy to the cardiac catheter laboratory. Attempts at surgical opening usually have a fatal outcome; the long-term prognosis can be clouded by pulmonary lymphangiectasia.

If PVR decreases, a "restriction" in the atrial septal defect (ASD/PFO) can develop with increasing flow. This prevents unrestricted pulmonary arterial flow and can, if the child's respiratory function is unproblematic, constitute an very useful compensation mechanism for balancing the circulation until surgery.

Alongside the Giessen procedure, the Norwood I procedure is also an option as long as decompensation has not developed or recovery has occurred. As many preoperative, operative, and postoperative difficulties accumulate in these patients, particular demands are placed on the team.

In the preoperative phase, the existing right ventricle is frequently already volume overloaded due to pulmonary hypercirculation, while the pressure overload to maintain the systemic arterial blood pressure also continues to persist. In the event of insufficient systemic CO, latent hypoperfusion of various organs can develop, thereby preoperatively compromising cardiac, cerebral, and intestinal perfusion. The following are therefore determining factors in this phase:

- Optimal Qp/Qs balance by afterload reduction or optimization of ventilation, milrinone therapy, minimum meaningful prostaglandin dose.
- Optimal provision of O_2 transporters (Hb 12–14 g/dL, Hct > 40%).
- Cautious handling of drugs that affect the circulatory situation.
- Sufficient treatment of any emergent septic complications (status post bowel ischemia).
- A CVC should be present guide the treatment based on SvO_2.

Hyperventilation (which would lead to acute pulmonary flooding if PVR ↓ and resultant acute coronary ischemia) should be strictly avoided, particularly at the time of intubation.

Proposed regimen: Etomidate 0.3 mg/kg slowly i.v.; supportive manual bag ventilation, where necessary via a nasopharyngeal airway without the addition of O_2 about 20 times per min, monitoring of chest excursions and SpO_2, and then intubation once the patient has relaxed.

Initial ventilation: PEEP 4 mmHg, PIP 20 mmHg (depending on excursion), Ti 0.4 s, RR 20/min (Vti: 6–8 ml/kg BW; flow 12 L/min with flow-controlled and pressure-limited ventilation).

There is one other point on which the Norwood procedure differs from most other forms of cardiac surgery. The procedure does not provide the patient with any immediate hemodynamic benefit. Instead, the RV must continue to bear the systemic load, is damaged functionally by the surgical trauma, and is protected from pulmonary flooding and volume overload to only a limited extent by the AP shunt placement.

Surgical steps:

The interatrial septum is removed and the PA is transected and closed at the pulmonary end.

- The aorta is reconstructed by means of an (allo)graft and connected to the PA.
- A 3.5–4 mm PTFE (polytetrafluorethylene) systemic-to-pulmonary artery shunt is connected (see Fig. 15.4).

The alternative "Sano shunt" between RV and PA offers the advantage of more favorable coronary artery perfusion during diastole. Shunt stenoses and surgical trauma to the RV are disadvantages of this method.

This is reflected in a preventive and protective approach in the postoperative management.

- Reduction in O_2 consumption:
  - Analgosedation, normothermia about 36 °C, Ca_{ion} > 1.1 mmol/L, Hb 12–14 g/dL, milrinone (0.5–1 µg/kg BW/min), pH > 7.3

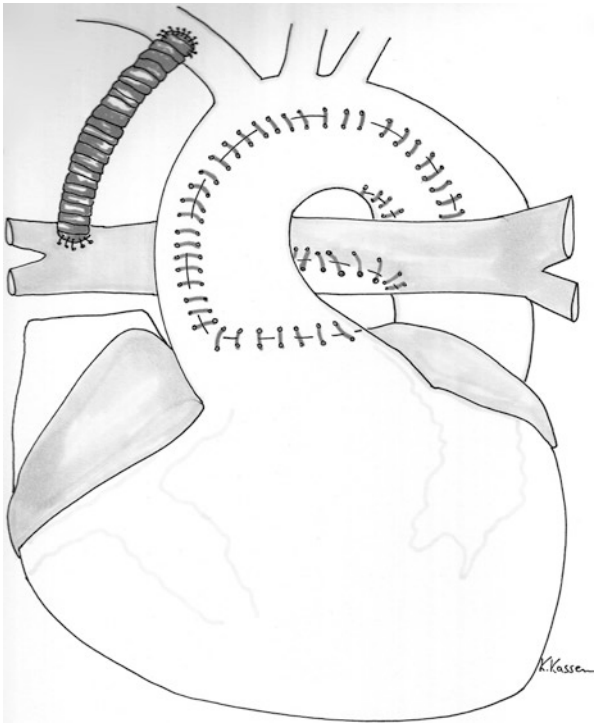

Fig. 15.4 Norwood I procedure with modified Blalock-Taussig shunt

- Ventilation:
  - Neonatal respirator: PEEP 4–5 cmH_2O – higher if pulmonary flooding, PIP 22–24 cm H_2O, Vti 6–8 mL/kg, RR according to ventilation, Ti 0.6 s
- Coagulation:
  - Following deep hypothermia there is usually a risk of hypocoagulability, therefore platelets >100,000 and fibrinogen >1.5 g/L.

In the event of bleeding, determine ACT (most probably heparin effect if platelets normal), TEG, or ROTEM because of hyperfibrinolysis.

15.11.1 Circulatory Therapy

To be able to determine where a modification of treatment might prove successful, many considerations must be addressed in parallel in the course of a Norwood I procedure:

- Heart function: Pump function, non-leaking AV valve? Tamponade, arrhythmia (coronary arteries?), which preload level? Aortic anastomosis without gradient?
- Circulation: Important parameters to monitor CO are SvO_2 (Caveat: position of CVC! If the blood sampling location is in the right atrium, there is a risk that pulmonary venous blood that has passed through the ASD is included in the sample and not exclusively the deoxygenated blood from the body's circulation, thus causing the determination of a false high SvO_2), lactate, peripheral MC (this is also a measure of afterload), ΔT, NIRS of the patient's head, urine output (late). Perfusion pressure: MAP >40 mmHg, strictly monitor amplitude/diastole (b/o shunt), EKG with signs of ischemia?
- Qp/Qs: If PV saturation is normal – which cannot be measured, therefore lung function and the X-ray must be used indirectly – an equal distribution of pulmonary-to-systemic perfusion is obtained with an arterial saturation of 75–80%. A value of about 50–55% in the SvO_2 measurement ($avDO_2$ about 20–30%) should then be reached if peripheral organ perfusion is sufficient.

If transcutaneous saturation is too high (>85%), pulmonary flooding is responsible, and treatment consists of a reduction of FiO_2 and ventilation – PEEP remains, first of all rate ↓ then PIP ↓ (note Vti) – end NO rapidly, if used.

In this case, a high blood pressure amplitude with low diastolic blood pressure can also frequently be seen, which is indicative of pulmonary runoff. This can critically reduce the perfusion pressure (coronary arteries). If pressures are then increased by the use of vasopressors, for example, a vicious circle can develop, since shunt perfusion increases further with higher blood pressure, while afterload increases and CO to the systemic circulation decreases further.

If arterial saturation is low – e.g. less than 65% SaO_2 – there may be various causes, and SvO_2, lung function parameters, and ultrasound can be of help in assessing these.

Pulmonary causes (PV saturation low) can be parenchymal in nature: pulmonary edema, infiltrate, compliance disorder.

However, an increase in PVR due to hypothermia, acidosis, or a PV obstruction can also be present. In this case, the lung function parameters on the respirator and the X-ray image are normal; in this case there is insufficient flow via the shunt because the PVR of the pulmonary vascular bed is too high. The situation can be assessed by a brief increase in blood pressure, by ultrasound and auscultation. If in the process the circulatory parameters (MAP, lactate, $avDO_2$) are acceptable and the low pulmonary perfusion is not due to low blood pressure, ventilation can be intensified to reduce pulmonary resistance:

- FiO_2 ↑, CO_2 reduction by improving ventilation (RR↑, if Vti OK, otherwise PIP ↑).
- If this already generates high mean respiratory pressures (MAP >10 cmH_2O), NO may be used.

Otherwise, if there is a good pulmonary function and sufficient oxygenation of the blood in the PV, low arterial saturation can also be caused by very low central venous saturation, as PV blood and vena cava blood mix in the common atrium.

Causes of low SvO_2 may be:

- On the one hand, excessive oxygen consumption:
  - Fever, tachycardia, pain, insufficient sedation, work of breathing
- On the other hand, low O_2 delivery due to insufficient flow (CO ↓):
  - Relative bradycardia, leaking AV valve, SVR ↑ (BP too high), and Qp/Qs imbalance
- Arrhythmia (= coronary perfusion disorder)
- Tamponade

Important

Always consider a dysfunction of the shunt itself!

Before changes can be made to the treatment, it is necessary to be clear about the following:

- Is the heart pumping "forwards" or is the AV valve very leaky?
- Consideration about Qp/Qs: CO more pulmonary or systemic?
- Organ perfusion sufficient? Perfusion pressure sufficient?
- Improvement through PVR ↑↓ or SVR ↑↓?
- Surgically: Shunt too large? Obstructed? Tamponade? Aortic anastomosis stenotic?

Generally the patient should be stabilized in the operating room following a Norwood procedure. In the event of major postoperative problems and an acceptable surgical outcome, temporary mechanical circulatory support should be to hand. Any further changes to be made in the ICU should only be minor, since the complexity of the interactions can be associated with serious unforeseen changes, which can be extremely difficult to manage (see Table 15.14).

Table 15.14 Checklist for the management of Norwood I procedure

Circulatory parameter	Lung (Qp/Qs)	Ultrasound	Coagulation	Aortic surgery
BP, CVP	Ventilation parameters	Ventricular function	Platelets > 100,000/µL	Blood pressure difference
Amplitude	X-ray	AV valve	Fibrinogen > 1.5 mg/dL	Coronary perfusion
SvO_2	Pleural effusion	Effusion	Drainage amount?	Rhythm complications
MC	SpO_2	Shunt detectable?	Effusion?	
Δ T	SvO_2	Neoaorta detectable?	ACT?	
Lactate	Blood pressure amplitude	Doppler flow (abdomen/head)	Hyperfibrinolysis?	
Urine output	Shunt function			
Near-infrared spectroscopy (head)				

15.12 Definitive Palliation

15.12.1 Partial Cavopulmonary Anastomosis (Glenn Shunt)

Defects with hypoplasia and maldevelopment of a ventricle (these has already been described):

- Tricuspid atresia
- Hypoplastic left heart syndrome (HLHS)
- Mitral atresia
- PAT with intact ventricular septum and hypoplastic RV
- Unbalanced AV canal with hypoplasia of a ventricle
- DILV
- Borderline cases of Ebstein's anomaly

With these defects, long-term congestive heart failure develops if the existing ventricle has to "parallel service" both circulations. Its function deteriorates as a result of the subsequent dilation of the ventricle, and the AV valve is at risk of becoming leaky.

After the surgery the patient has to rely on a passive pulmonary perfusion, requiring a low PVR, which is overcome only by the negative intrathoracic pressure of spontaneous inspiration and the suction effect of the systemic ventricle.

This also yields the opportunities and limits of the procedure:

The better

- the "breathing pump" can generate negative intrathoracic pressure (trained breathing muscles, normal respiratory drive, elastic chest cage),
- the function of the systemic ventricle is (contractility, non-leaking AV valves, sinus rhythm, diastolic function),
- the PVR can be overcome (PVR ↓),

the better this concept works.

The surgical procedure is such that after the usually right-sided anastomosis of the SVC (superior vena cava), the blood from the upper half of the body flows "bidirectionally" into the pulmonary arteries. The flow of blood from the subpulmonary ventricle to the pulmonary circulation is suppressed.

This results in the systemic venous blood of the lower half of the body mixing together with the pulmonary venous blood of the lung (communication between LA and RA must not be impeded) in the atrium, flowing via the AV valve(s) into the systemic ventricle and from there to the aorta with a physiologic O_2 saturation of about 70–85%.

Existing anatomic anastomoses (in particular the azygous vein) between SVC and IVC (inferior vena cava) and acquired venovenous collaterals must be closed surgically in order to prevent circumvention of the lung and hence impaired oxygenation of the venous blood of the upper half of the body.

This also defines the optimal preconditions for cavopulmonary anastomosis:

- Good ventricular function with a non-leaking AV valve ensures sufficient CO with low CVP (pressure in the inferior vena cava as a surrogate for ventricular filling pressure).
- A well-ventilated lung (kept open only if absolutely necessary by means of ventilation with low PEEP [4–5 cmH_2O]) is the basis for a low PVR and hence for a low "transpulmonary gradient": differential of superior vena cava pressure (PAP) – inferior vena cava pressure (CVP).
- The pulmonary blood flow must also not be disrupted by anatomic obstructions (vascular compression externally or distortions), in addition to which thromboses can form intraluminal obstructions that impede the pulmonary blood flow.
- Preoperatively, PVR can be reactively increased (due to pulmonary hypercirculation or high LAP) and prevent free flow through the pulmonary vasculature. Cardiac catheterization is performed regularly before the Glenn anastomosis, so that the preconditions for surgery can be determined and tested by pressure measurements and visualization, and where necessary therapeutic measures can be initiated at an early stage (see Chap. 13).

Postoperative problems usually result from a combination of different causes that should be minimized by appropriate basic treatment and detected by early and immediate diagnostic investigations.

Where the patient has not already been extubated during surgery, SIMV + PS ventilation should be chosen immediately postoperatively, as discussed in Chap. 2 (ventilation), with a low PEEP of about 4 cmH_2O. The respiratory rate should be 8–12/min with a Vti of about 10 mL/kg BW. The pressure-supported breaths should

also be sufficient for a Vti of 4–6 mL/kg BW. This can be achieved by suitable pressure support and regulation of the "end-inspiratory cycle" (see Chap. 2 Ventilation). The aim of this strategy is an appropriate RMV (e.g. 150 mL/kg BW/min) with a low MAP that produces as little resistance to passive pulmonary perfusion as possible.

If, nevertheless, a higher PAP is required in the presence of good pulmonary ventilation and sufficient tidal volume with low PIP (= good pulmonary compliance), this is due to increased PVR (e.g. persisting reactively following pulmonary hypercirculation), poor ventricular function (or AV valve insufficiency/outlet stenosis) of the systemic ventricle, or anatomic stenoses at the pulmonary vessels.

The cause can usually be established with the aid of intraoperative or postoperative echocardiography and an assessment of the pressure values, allowing therapeutic measures to be initiated. If ventricular function is good and the AV valve is not leaky, a reduction in PVR is the primary consideration and can be achieved by measures including: Administration of O_2, reduction of the mean airway pressure, prompt initiation of oral sildenafil, and whenever possible extubation – where this is not possible, inhalational NO. In these patients, increasing "preload before the Glenn" (PAP ↑) by means of a suitable sitting position (such as in a bathtub) and volume administration to improve oxygenation is particularly important.

Whether increased cerebral perfusion – induced by slight permissive hypercapnia – improves oxygenation by an increased blood supply cranially or whether instead the CO_2-mediated pulmonary vasoconstriction worsens oxygenation needs to be determined individually.

In the case of moderate ventricular function, impaired diastolic function, e.g. due to tachycardia, or high CVP due to AV valve insufficiency, an effect on the circulation should be exerted primarily by reducing overload and optimizing HR. Clonidine/dexmedetomidine as first-line treatment, ACE inhibitors if there is sufficient blood pressure reserve, or sodium nitroprusside (very rarely used under these circumstances) are available for this purpose.

Ensure that there is sufficient urine output – where necessary by initiating an intravenous drip infusion of furosemide 1–2 mg/kg BW/day and theophylline 5 mg/kg BW/day in combination from the outset. However, excessive urine output resulting in a repeated requirement for volume replacement should be avoided.

Where there is no need for the immediate treatment of poor ventricular function (AV valve insufficiency or severe tachycardia), extubation (if possible immediately postoperatively) is very much the priority in terms of treatment aims. Thereafter, the focus should be on pain therapy. This constitutes paracetamol (i.v.) and, as long as tolerated in terms of blood pressure, should consist of a clonidine/dexmedetomidine drip (1–2 µg/kg BW/min) combined, for example with single doses of ketamine, until extubation.

Carefully dosed opiates (e.g. morphine 0.03–0.05 mg/kg BW/single dose) should not suppress the respiratory drive or delay extubation. Prior to extubation, a clinical assessment of respiratory drive and the pain situation, pulmonary ventilation and compliance, as well as airway obstruction, is important.

In accordance with the procedure described in Chap. 8 (coagulation system), the aim in the case of passive pulmonary perfusion is PTT-effective heparinization – 300 IU heparin/kg BW/day as a drip infusion should be established already during the first night. Long-term anticoagulation is administered on the basis of the

preoperative diagnostic investigations for thrombophilia and the obtained pulmonary hemodynamics.

Despite good (systolic) heart function, a non-leaking AV valve, and a developed lung with low transpulmonary gradient, a ventricular outlet obstruction (subvalvular, valvular, or supravalvular) would massively impair the circulation in similar fashion to an excessive systemic afterload.

The resultant reflex tachycardia with a low stroke volume will attenuate diastolic function in the case of a hypertrophic ventricle. CVP and PAP increase to higher ranges, resulting in both systemic (ascites, congested head, poor renal perfusion, digestive disorders) and pulmonary (effusion, ventilation disorders) congestions. Functional outflow obstructions can be treated by reducing afterload and monitoring heart rate (e.g. clonidine/dexmedetomidine). In muscle-induced flow obstructions, the combination of an i.v. beta-blocker (esmolol) and noradrenaline can be helpful. However, structural outflow obstructions usually require surgical revision (should be looked for and excluded by TEE in the OR).

Depending on the patient's clinical status, particularly the transpulmonary gradient and SpO_2, the Glenn anastomosis should be visualized by contrast medium (CM), particularly in order to demonstrate a homogeneous CM outflow, to visualize stenoses and perfusion gaps or, in the case of low PAP values and poor saturation, to look for anastomoses between the superior and inferior vena cava.

In terms of postoperative treatment following extubation, administration of diuretics (furosemide + spironolactone) is indicated, as well as cautious afterload reduction (ACE inhibitor). Try to eliminate furosemide in long-term therapy to prevent triggering RAAS (see Memory Chart in Table 15.15).

Complete separation of the circulations is then performed at the age of 2–3 years by total cavopulmonary anastomosis. Because of increased activity and stronger growth of the lower half of the body, the patient would otherwise become increasingly cyanotic (Glenn, Qp/Qs about 0.6). Moreover, exclusion of the hepatic venous blood from the pulmonary perfusion encourages the development of intrapulmonary arteriovenous fistulas.

15.12.2 Total Cavopulmonary Connection

In Giessen in recent years, following completion of the serial circulation, an extracardiac PTFE conduit with a diameter of 18–20 mm has usually being anastomosed from the inferior vena cava – separated from the RA – to the right PA at the level of the SVC. Depending on the individual risk constellation, this conduit is provided with a 4–5 mm fenestration as an overflow valve to the common atrium (free wall).

This results in pulmonary perfusion that is determined by the level of preload (PAP should be equal to the CVP/IVC pressure, otherwise a constriction of the anastomosis must be excluded), PVR, and heart function, including AV valve competence and systemic arterial afterload.

Table 15.15 Checklist for the management of Glenn anastomosis

PAP	Caution > 18 mmHg!	PVR ↑, poor heart function, ventilation disorders, MAP ↑, pleural effusion	NO, sildenafil, optimize ventilation, look for effusions, visualize Glenn anastomosis, extubation
CVP	Caution > 10 mmHg!	Poor heart function, leaking AV valve(s), tachycardia, outlet stenosis	Milrinone drip, reduce afterload, optimize HR
Transpulmonary gradient	Caution > 10 mmHg!	PVR ↑, bronchial obstruction, atelectases, effusion	NO, sildenafil, O_2 and optimal ventilation strategy
SpO_2	Caution < 70%, always arterial monitoring!	Volume deficiency, atelectases, PVR ↑ (poor flow)	Volume administration, blood as volume? X-ray, optimal ventilation?
HR	Caution > 160/min!	Heart function ↓, beta-mimetics (inhalational?) ↓, pain, fever, volume deficiency, outlet stenosis	Clonidine/ dexmedetomidine, esmolol; digoxin
Blood pressure	MAP > 45–50 mmHg, MAP < 60–70 mmHg	Volume deficiency, capillary leak, afterload still reducible?	Volume administration? Minimally dosed noradrenaline (femoral CVC)
Urine output	Minimum 2 mL/kg BW/h	Furosemide drip, blood pressure higher?	
SvO_2 (superior caval vein)	Caution < 40%, $avDO_2$ max. 30%!	Afterload reducible, HR optimized, blood as volume? Oxygenation can be improved on the pulmonary side or by preload before the Glenn anastomosis?	Sodium nitroprusside

In the presence of good heart function (arrhythmia?), competent AV valve, low PVR, and low PAP (e.g. < 14 mmHg), the patient should be rapidly extubated.

Otherwise, in the event of poor cardiac output, the hemodynamics must be evaluated as for the Glenn anastomosis. The following parameters are easily available (see Table 15.16):

- Pressures: PAP (= CVP), BP, and also, if clearly visualizable, atrial pressure (RAP) measured via the fenestration
- Heart rate, ventricular function, and AV valve competence on ultrasound, as well as SvO_2 and arterial saturation

Where cardiac and lung function permit, an attempt should be made to extubate a patient with increased PVR immediately postoperatively.

Table 15.16 Checklist for the management of total cavopulmonary connection (TCPC)

Low cardiac output			
PAP ↓	AP ↓	Hypovolemia, mostly associated with tachycardia	Volume replacement – Primarily FFP, Hb above 12 g/dL. Caveat: Effusion formation, initiate noradrenaline in case of massive volume requirement! Do not titrate volume based on negative BE
PAP ↑	AP ↔	PVR ↑, functionally or anatomically (PA too narrow/ obstructed) →	X-ray – Ventilation disorder? Effusion? PVR ↑ – NO ventilation or preferably extubation – Uses negative inspiratory pressure, early sildenafil, cardiac catheterization
> PAP ↑	AP ↑	Poor heart function, valve insufficiency, tachycardia/arrhythmia, outflow tract obstruction →	Milrinone, afterload reduction, DDD pacing, esmolol, revision surgery

AP arterial pressure

15.12.2.1 Ventilation Strategy

By analogy with the Glenn procedure, MAP should be adjusted by a moderate PEEP (4 cmH_2O) and low-rate (e.g. 10 breaths of 10 mL/kg BW) SIMV ventilation with pressure support, e.g. in PRVC mode with pressure support (PS). The PS breaths should be configured in such a way that they make a significant contribution to RMV (select PS so that 4–5 mL/kg BW Vti is generated – the length of the breath can be determined by the setting of the end-inspiratory cycle). This will rapidly produce completely synchronized ventilation with the lowest possible mean airway pressure.

Because of the marked tendency of TCPC patients to develop a scites and pleural effusion (which can interfere with ventilation), these should be the subject of ultrasound investigation, and drainage should be performed promptly.

To obtain early extubation, pain medication should be given initially with paracetamol, clonidine/dexmedetomidine, and ketamine, where necessary limited opiates, and midazolam cautiously prior to extubation. Urine output, supported by furosemide, should be checked to ensure it is sufficient (SvO_2 about 60%, MAP > 50–55 mmHg). As in the Glenn procedure, PTT-effective heparinization must be given.

Particularly in passive pulmonary perfusion, the negative intrathoracic pressure in spontaneous ventilation and the suction effect of a properly contracting ventricle (with unimpaired filling) are the determining factors (see Memory Chart in Table 15.17 and Chap. 18).

Table 15.17 Memory chart on total cavopulmonary connection (TCPC)

Low cardiac output	Volume deficiency PVR ↑ Impaired heart/valve function High afterload
Ventilation problem	MAP too high Effusions Hyperpnea associated with metabolic acidosis due to volume deficiency Lung disease
Effusion formation	PAP too high Sufficient volume replacement? (hypoproteinemia, fibrinogen ↓, IgG ↓)
Analgesia	Clonidine/dexmedetomidine Paracetamol Ketamine Low-dose opiates
Heparin	PTT about 60 s AT III > 70%
Urine output	MAP > 50–55 mmHg Preferably start furosemide drip early
Dietary buildup	Frequently protracted due to ascites and high CVP

Suggested Reading

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Heart Defects with Therapy after the Neonatal Phase

16

Dietrich Klauwer

16.1 Atrial Septal Defect

An atrial septal defect (ASD) leads to a volume overload of the right heart and the pulmonary circulation. If the pulmonary vascular bed is exposed to volume overload due to recirculation alone, PHT usually develops relatively late, in contrast to the situation when additional pressure overload is present, e.g. with a large ventricular septal defect (VSD). It is only if additional defects (primarily obstruction and malfunction of the left heart, such as mitral stenosis, aortic stenosis or cardiomyopathy, or of the pulmonary veins) or an imbalance of the ventricles is present that children become symptomatic as early as in the first 2 years of life. Infants with concomitant lung disease, e.g., premature infants with BPD, can also become symptomatic relatively early. Therefore, children with heart failure due to an ASD should generally be examined for additional causes.

An ASD II can usually be closed interventionally, and patients do not subsequently require intensive care therapy. The anomalous pulmonary vein must be surgically redirected to the LA in cases of ASD with partial anomalous pulmonary venous return (where the ASD is usually a sinus venosus defect).

An ASD I, i.e. a defect situated directly above the level of the atrioventricular valves, is frequently associated with a cleft in the mitral valve with mitral insufficiency. Operative correction typically involves ASD closure, usually with a patch, as well as closure of the cleft. Due to the short aortic clamp time with mild hypothermia, postoperative ventricular function impairment is rare, and postoperative intensive care therapy over and above the usual monitoring measures is not required.

Tables 16.1 and 16.2 present classifications and features of atrial and ventricular septal defects (ASD and VSD).

D. Klauwer
Department of Pediatrics, Singen Medical Center, Gesundheitsverbund Landkreis Konstanz, Krankenhausbetriebsgesellschaft Hegau-Bodensee-Klinikum, Singen, Germany

© Springer International Publishing AG, part of Springer Nature 2019

D. Klauwer et al. (eds.), *A Practical Handbook on Pediatric Cardiac Intensive Care Therapy*, https://doi.org/10.1007/978-3-319-92441-0_16

Table 16.1 Atrial septal defects (ASD)

	ASD II	Upper SVD	Lower SVD	ASD I	CSD
Position	Fossa ovalis surrounded by atrial myocardium	Transition area of SVC to atrial myocardium (area of upper right PV)	Transition area of IVC to atrial myocardium (area of lower right PV)	Defect directly above valve level	Area of coronary venous sinus below tricuspid valve
Surgery	Usually interventional, otherwise surgical: suture or patch	Patch directs PV blood to LA, SVC augmentation	Patch directs PV blood to LA, IVC dilation	Surgical closure and mitral cleft suture	Direct suture
Complications	Arrhythmias, particularly sinus node dysfunction	Sinus node dysfunction and upper inflow congestion, right upper PV obstruction	AV node dysfunction, lower inflow congestion, right lower PV obstruction	AV node dysfunction, mitral insufficiency/ stenosis	AV node dysfunction, coronary venous obstruction
				Corresponds to partial AV canal	

Indication for surgery if Qp/Qs > about 1.5/1, RV dilation on ultrasound and clinically split 2nd heart sound (HS) and apical murmur
SVD sinus venosus defect, *PV* pulmonary vein, *CSD* coronary sinus defect

Table 16.2 Memory chart on ventricular septal defects (VSD)

Risk factor	PVR ↑, PAP > 25% of SAP	Trisomy 21	Large defect	Straddling with tendinous cords	Malalignment	Multiple defects
Effect/ consequence	PA crises	PA crises, RV failure, hypothyroidism, status post infections	Low output	Incomplete closure	Impaired ventricular geometry	Long surgery, incomplete closure (not all closed), ventriculotomy, low output

PAP pulmonary artery pressure, *PVR* pulmonary arterial resistance, *RV* right ventricle, *SAP* systemic arterial pressure

16.2 Ventricular Septal Defect

An isolated ventricular septal defect (VSD) results in a L/R shunt with pressure overload of the RV and the pulmonary circulation, depending on the size of the defect, as well as volume overload of the left-sided heart structures. If the hole is small, the LV pressure does not directly impact the RV and the pulmonary

circulation – such VSDs are called restrictive and "separate" the blood pressure between the pulmonary and systemic circulation. With a larger VSD, pressure separation no longer occurs, and the pressure of the systemic circulation (LV pressure) is transmitted to the right and thus to the RV and the pulmonary circulation. In post-tricuspid L/R-shunts, this leads to simultaneous pulmonary hypercirculation and pressure overload, and without early correction the risk of a permanently elevated pulmonary resistance increases rapidly.

The previously explained ratio of pulmonary to systemic blood flow (Qp/Qs) – calculated from the ratio of systemic (SaO_2 – SvO_2) to pulmonary ($S_{pulm}vO_2$ – $S_{pulm}aO_2$) saturation differences – reflects the extent of pulmonary hypercirculation. The volume load is less, while the PVR is still elevated in the neonatal period and increases with the physiological decrease in PVR up to the 3rd month of life. Permanent damage to the pulmonary circulation can occur if larger shunts persist beyond the 6th month of life; therefore larger VSDs should be closed by that point. Patients with trisomy 21 are at higher risk to develop persistent PVR ↑ at an even younger age, and the surgical risk can be increased considerably by PA crises and RV function disorders.

Different defect types are distinguished according to the position of the defect; the most important of which are mentioned below:

- Perimembranous VSD: Opening(s) in the membranous ventricular septum, near the tricuspid valve and/or the aortic valve.
- Muscular VSD: Single or multiple ("Swiss cheese") defects, only in the muscular part of the septum (situated centrally or apically).
- VSD in the outflow tract and as part of complex defects is classified according to their position to the semilunar valves into subpulmonary, subaortic, doubly committed, and non-committed.
- Malalignment/subaortic VSD (e.g. in tetralogy of Fallot, TOF).
- AV canal type (inlet type): Opening in the area of the inlet septum.

A malalignment VSD is present if the parts of the ventricular system are shifted from their actual axis and parts of the valve override the defect, as, for example, in TOF. In these types of VSD, the patch must be fitted in such a way that the blood flow is functionally correctly redirected to the semilunar valve, while the patch and septal portions may deviate from the anatomical axis of the septum.

Where an interventional closure is not possible, VSDs with a Qp/Qs >1.5/1.0 are managed surgically by means of suture (rarely) or patch. In perimembranous VSDs situated inferior to the membranous portion of the aortic and tricuspid valve, the septal tricuspid leaflet must sometimes be detached in order to insert the patch. In this case, there is the risk of postoperative tricuspid insufficiency (TI). In addition, an AV block (which can also be permanent) can develop postoperatively due to irritation of the bundle of His.

As well as the general postoperative risks with tamponade and severe bleeding, typical complications of VSD repair include AV block, tricuspid insufficiency, residual VSD (in some cases due to a rupture of sutures), and temporary

JET (markedly less frequent following the introduction of dexmedetomidine intraoperatively).

Depending on the degree of preoperative pulmonary hypercirculation and preoperative PVR, there is the risk of postoperative PA crises and RV failure. Trisomy 21 is a particular risk factor here.

In postoperative management, therefore, awareness of the preoperative increase in PVR is particularly important. Postoperative (or preferably intraoperative transesophageal) echocardiography serves to assess the PAP/RV pressure, to exclude a significant residual defect, and to assess ventricular function and pericardial effusion, as well as the degree of TI. Normally, patients without the abovementioned risk factors and with an appropriate ultrasound result and good pulmonary ventilation should be weaned and extubated rapidly following sufficient analgesia. In the presence of risk factors, particularly any predisposition to PA crises, it needs to be assessed whether exceptionally the patient should be ventilated longer (targets: $SpO_2 > 95\%$, $PaCO_2 < 45–50$ mmHg arterially) while receiving adequate analgosedation (fentanyl/midazolam). Maneuvers that are irritating for the patient, particularly suctioning of the tracheal tube and airways, should be performed with additional prophylactic sedation and in the presence of a physician. Furthermore, early use of sildenafil has proved useful as soon as it is possible to reintroduce an oral diet. PA crises should be treated as described in the chapter on pulmonary hypertension.

16.3 Atrioventricular Septal Defect

Similar to ASD and VSD, the degree of heart failure in atrioventricular septal defect (AVSD) depends on the magnitude of pulmonary hypercirculation. Moreover, in AVSD there are AV valve function disorders that can additionally impair ventricular function and ejection fraction. These heart defects are characterized by a developmental disorder of the septum and AV valves. The septal maldevelopment toward the atria (no closure of the ostium primum) results in an atrial gap, while an inlet VSD is found on the ventricular side (no closure of the inlet septum). The extent of the AV valve anomaly ranges from individual small clefts (mitral valve leaflet cleft) to the presence of a rudimentary common AV valve with severe insufficiency (see Chap. 13).

A partial AVSD involves an ASD I as well as a mitral cleft, which results in MI (mitral insufficiency) of varying degrees. This heart defect can be recognized based on the position of the ASD and the attachment of the tricuspid leaflet in relation to the mitral leaflet. Whereas normally the anterior mitral leaflet attaches above the tricuspid valve (the tricuspid valve lies closer to the apex of the heart), in patients with an AVSD, the attachments lie on the same level. A partial AVSD does not tend to close spontaneously, and interventional closure is not possible in the absence of a septal rim near to the valve. Preoperative intensive care therapy is not necessary. Surgery should be performed before the onset of significant atrial enlargement with possible arrhythmias – usually before the 4th year of life.

A complete AVSD is characterized by the previously mentioned ASD I as well as an inlet VSD. Furthermore, the AV valves are malformed to varying degrees. AV valve defects can range from the formation of two separate valves with clefts to the formation of a single cohesive AV valve without separation of the AV valve apparatus. In this case, the aortic root is displaced ventrally and is not located between the anterior portions of the AV valves.

Hemodynamically, with falling PVR, the L/R shunt causes severe pulmonary hypercirculation. In addition, the leaking AV valve can potentiate heart failure, particularly of the left heart. In this context, it should be borne in mind that the supporting apparatus of the mitral valve can be substantially altered and attached in the area of the LVOT. Positive inotropic therapy in LVOTO can therefore further adversely affect hemodynamics.

There is an increase in congestive heart failure as PVR decreases after the neonatal period, so that surgery needs to be planned. Preoperative anticongestive therapy is limited to ACE inhibitors to decrease afterload and to reduce the negative effects of the activated RAAS, as well as beta-blockers and spironolactone and, in rare cases, diuretics (= usually severe pulmonary congestion). Caution should be exercised when reducing afterload in the presence of an existing LVOTO.

As with VSD, there is a postoperative risk of PA crises, whereby children with trisomy 21 are particularly affected.

Table 16.3 presents the particular risks associated with AV canal surgery, listing clinical features of note, proposed treatments, and preventive methods.

Table 16.3 Particular risks after AV canal surgery

Risks	Clinical features	Treatment	Prevention
PA crisis	CVP ↑, BP ↓, oxygenation ↓	Sedation (relaxation), hyperventilation with O_2 ↑, noradrenaline if necessary, buffering (small bolus)	Analgosedation, CO_2 monitoring, good oxygenation, lung "open"
Volume status	CVP usually 8–10 cmH_2O	If possible, no volume "manually"	Sufficient furosemide at early stage
Mitral insufficiency	Pulmonary edema, cardiac output ↓	PEEP ventilation, afterload reduction	
Tricuspid insufficiency	CVP ↑, cardiac output ↓, PHT?	RV afterload reduction (normoventilation, NO?, oxygenation ↑)	
Infection	CrP, gray coloring	In Down's children, consider extended antibiotic therapy (cefuroxime and tobramycin)	
JET	Lack of atrioventricular coordination, ECG (P wave runs through)	Amiodarone, AAI pacing, hibernization (cooling)	Caution: Beta-mimetics!
AV block	Cardiac output ↓	DDD pacing	
Hypothyroidism			Caution: Down's patients!

16.3.1 Postoperative Management in Complete AVSD

Where it has been possible to perform a complete correction of the AVSD, i.e. ASD and VSD closure as well as valve reconstruction, the heart is hemodynamically unloaded postoperatively. Preoperatively, compensated heart failure will usually have been present, and depending on the complexity of the procedure, the duration of the surgery (aortic clamp time) can be long and may cause postoperative myocardial dysfunction. Some patients also have a susceptibility to PA crises. In severe cases, the patient often needs to be analgosedated postoperatively for at least one night and should not be extubated (fentanyl/midazolam, e.g. 5–10 µg/kg BW/h + 0.2 mg/kg BW/h). However, rapid extubation may be possible in such cases if the circumstances are uncomplicated (see Chap. 18).

Risk Patients

Due to a previously dilated RV, a higher preload (CVP 10–12 cmH_2O) may be necessary. In the presence of peripheral vascular failure and low perfusion pressures (with sufficient volume status), low-dose noradrenaline can be used. Because of the often prolonged machine time in small patients and the large volume requirement, consideration should be given to ensure sufficient diuresis at an early stage.

The susceptibility to PA crises can be best monitored online if a PA pressure catheter is placed. However, patients are mostly treated without a PA catheter. As the resting state provides only a snapshot, clinical observation with gentle manipulations is important in addition to the echocardiographic assessment. Treatment should be undertaken with extreme caution if increases in CVP with a simultaneous fall in BP and poorer oxygenation become apparent.

In addition to controlled ventilation (SpO_2 > 95% and $PaCO_2$ not more than 45 mmHg) and unproblematic, dystelectasis-free pulmonary ventilation – PEEP 5–6–7 cmH_2O and Vti about 8–10 ml/kg BW/breath – major manipulations such as suctioning of the ET tube and nursing interventions should be performed only under additional oxygenation and sedation and occasionally also with relaxation. PA crises also often occur “spontaneously,” which mandates frequent monitoring as to whether the sedation is sufficient.

Patients with Down’s syndrome are particularly difficult with regard to sedation. In these patients, it is often not possible to use the less respiratory depressant ketamine for better tube tolerance because of pronounced secretion. Single opioid doses, otherwise highly efficacious, may have an insufficient effect, cumulate with repeated use, and cause the patient to fall back into a deep sleep.

In these situations, it is recommended to combine non-opioid analgesics with, e.g. clonidine/dexmedetomidine and to try low-potency neuroleptics additively (promethazine 0.5–1 mg/kg BW as a short-term infusion). Because of the previously described on-off phenomenon, Down’s patients with a concurrent susceptibility to PA crises, pulmonary infections, and severe mucus formation should preferably be extubated under controlled conditions. If, following extubation, acute hypopnea sets in, naloxone can be used in exceptional cases with assisted bag ventilation.

However, the better the patient is prepared for extubation and the fewer opiates are used cumulatively, the less frequently this treatment will be required. Pretreatment with steroids is also recommended because of a tendency to develop stridor postextubation.

16.4 Tetralogy of Fallot

Tetralogy of Fallot (TOF), also referred to as Fallot's tetralogy, is a malformation characterized by the components of pulmonary stenosis, RV hypertrophy as well as a VSD that is "overridden" by the aorta. Coronary anomalies are not infrequent either. Depending on the extent of the increase in structural central pulmonary resistance, cyanosis develops due to a substantially decreased pulmonary perfusion (blue Fallot). If there is only a minor pulmonary stenosis component, rarely the patients may be at risk of hypercirculation and heart failure (pink Fallot).

As already described for PAT with VSD, an obstruction of the pulmonary circulation in TOF can involve the muscular infundibulum, the valve, the PA, and the peripheral branches of the PA (usually extending as far as to the hilum of the lung). MAPCAs can additionally convey blood to the lung too. The boundaries between the different types of TOF to PAT with VSD are fluid.

In the preoperative phase, previously unknown triggers can result in an additional increase in resistance in the pulmonary vessels and provoke severe hypoxemic episodes. If the PVR exceeds the SVR, there is a marked R/L shunt via the VSD. These children appear restless and turn blue, in addition to which they become unconscious if the condition is prolonged and severe hypoxia is present.

Effective treatment in this case involves increasing the SVR (press legs to the belly) and reducing the PVR (administration of oxygen and sedation). If the measures described do not have a rapid and satisfactory effect, the SVR can be increased instantly with a minibolus of noradrenaline 1 μg/kg BW to assure blood flow to the lungs. Hypoxemic episodes can be minimized in TOF by preoperative administration of beta-blockers; the occurrence of such episodes constitutes an indication for surgery.

16.4.1 TOF Procedure

Where "only" a tetralogy of Fallot is present, a corrective procedure can usually be performed in the first 6 months of life. Depending on the anatomy, this involves widening of the infundibulum and commissurotomy of the valve or widening it with a transannular patch. In addition, it may be necessary to surgically remove any obstructions of the central pulmonary vessels. If larger MAPCAs are present and surgically accessible, these are ligated. The VSD is closed by means of a patch so that the LV blood is now directed only to the aortic valve. Given a good surgical outcome, patients can usually be rapidly extubated – patients at risk of postoperative problems tend to be the exception.

Risk Patients

In the postoperative phase, problems tend to frequently occur if the hypertrophic and therefore compliance-impaired RV has to pump the total cardiac output through the pulmonary circulation, requiring very high filling pressures. In this case, it is of particular importance that the contraction of atria and ventricles is coordinated in *normofrequent* sinus rhythm. However, TOF patients, in particular, have a tendency to tachycardia, which can considerably reduce cardiac output if ventricular filling is impaired. On the one hand, the preoperatively discontinued beta-blocker therapy may play a role (rebound phenomenon); on the other hand, JETs frequently occur specifically in TOF.

The consequence of this is:

- To note the rhythm!
- JET: Amiodarone, cooling, AAI pacing
- Sinus tachycardia: Clonidine/dexmedetomidine, beta-blocker (if RV compliance is reduced)
- Milrinone (avoid tachycardia and high PEEP and ventilation-related PVR ↑)

If the pulmonary circulation is overburdened by the whole cardiac output, this may result in the development of pleural effusions, making ventilation more difficult and ultimately culminating in oxygenation disorders (atelectasis leading to blood flow without contact with the alveoli) and to an increase in PVR (Euler-Liljestrand mechanism). Therefore, regular checks should be made for effusions, particularly in TOF.

Furthermore, effusions can be due in some degree to transient left ventricular failure, resulting in an increased risk of pulmonary edema with high LAP. Sinus rhythm, if needed, pacing (JET therapy and antitachycardia therapy) is also important in this case, and if in doubt, both ventricles can benefit from an "open chest." Although afterload-reducing therapy is in principle sensible for the LV, it is often impossible due to low output, capillary leak, and postoperative myocardial dysfunction.

16.4.2 Ventilation

During the TOF procedure, various problems can come to the fore, and the ventilation strategies need to be adapted to these. In rare cases with poor LV function due to impaired compliance of the comparatively less muscular left ventricle, ventilation with high PEEP can be useful in treating the resultant pulmonary edema. In this situation, although the postcapillary component of the PVR increases, specific ventilatory measures to reduce the PVR (such as hyperventilation, O2 administration, or NO) are contraindicated because they can exacerbate the pulmonary edema.

In contrast, when RV compliance is impaired with a "good left ventricle," a reduction in PVR induced by ventilation optimization can be very helpful, since the RV can be unloaded as a result.

Table 16.4 Ventilation in tetralogy of Fallot

Mode	Ventilation Rate	PEEP	Vti	Objectives	Caution
PC	18–20/min	5 cmH_2O	8 ml/kg BW/breath	Normoventilation (CO_2 40–50_{art})	Postcapillary PVR ↑ with hypotrophic LV
				Tc saturation > 95%	With "good" LV: PVR ↓ through ventilation

LV left ventricle, *PVR* pulmonary arterial resistance

Beneficial for the lung in all cases:

- Short diffusion distance (early furosemide therapy and fluid balancing)
- Atelectasis-free: PEEP 5 cmH_2O, Vti 8–10 mL
- Normoventilation with good LV function

As the pulmonary vascular bed in TOF patients is normally protected from hypercirculation by the pulmonary stenosis, and hence from PA crises, persistent morphologic obstructions in the RVOTO and the pulmonary arteries must be considered when there is a marked increase in RV pressure. It is important to exclude obstructions postoperatively by echocardiography, as the flow of the total cardiac output through the lung can overburden the RV if relevant obstructions are still present while the VSD is now closed. RVP (right ventricular pressure) > 65–70% of SAP is regarded as critical here (Table 16.4).

16.5 Double Outlet Right Ventricle (DORV)

DORV occurs in multiple forms. A feature common to all of them is that both major arteries arise predominantly from the right ventricle and that the pulmonary venous blood (LA) passes via the mitral valve into the LV and then via a VSD to the subarterial right ventricle. Here, VSD is the only outlet from the LV.

The hemodynamics in DORV are essentially determined by three anatomical structures:

- Pulmonary stenosis or not
- Position of the VSD relative to the aorta and the pulmonary artery (subaortic, subpulmonary, both continuous [doubly committed or non-committed] and restrictive)
- Position of the major arteries

In addition, aortic arch anomalies (CoA and hypoplastic aortic arch [up to 20%]) can also have a major impact on hemodynamics.

This determines the preoperative clinical presentation and the surgical options:

If the VSD is near to the aortic arch (subaortic VSD, the most common variant, constituting about 50% of cases), the LV blood flows preferentially into the

aorta, and the extent of the heart failure is dependent on the ratio of pulmonary/systemic resistance. The VSD can be closed in such a way that the patch diverts the LV blood to the aortic valve. The time of surgery is essentially dependent on whether pulmonary hypercirculation is precluded by an accompanying pulmonary stenosis or whether the decreasing PVR in the first few months of life leads to a risk of pulmonary hypercirculation with the development of heart failure.

Where no pulmonary stenosis is present, the procedure resembles a VSD closure. However, as a result of the patch insertion between the septal VSD and subaortic VSD margins, distortions of ventricular geometry can occur, which manifest functionally in an LVOTO (LVP ↑, risk of hypertrophy). Depending on the extent and duration of the existing pulmonary hypercirculation prior to surgery, in rare cases symptoms of an increase in PVR with RV failure and PA crises can appear postoperatively.

If a PST is present, the vessels are in a normal position, and the VSD is subaortic; the procedure can be performed similar to Fallot's correction. This involves a VSD patch to divert the flow and a widening of the LVOT (with/without a transannular patch). Postoperatively, the left ventricle may be too small relative to the new volume load, potentially resulting in a low output syndrome, which must then be treated by afterload reduction (for ventilation and weaning when LAP is increased, see section 16.4 TOF procedure).

The situation becomes more difficult if there is an associated transposition of the great arteries (TGA).

If the VSD lies close to the aortic valve, the VSD can be closed in such a way that the LV blood can be diverted to the aortic valve by means of a Goretex tunnel (Rastelli tunnel, see Fig. 16.1). This canal obstructs RV blood flow to the pulmonary valve. Therefore, an (in this case extracardiac) valve-bearing conduit conveys the blood from the RV to the surgically detached pulmonary bifurcation (see Fig. 16.2).

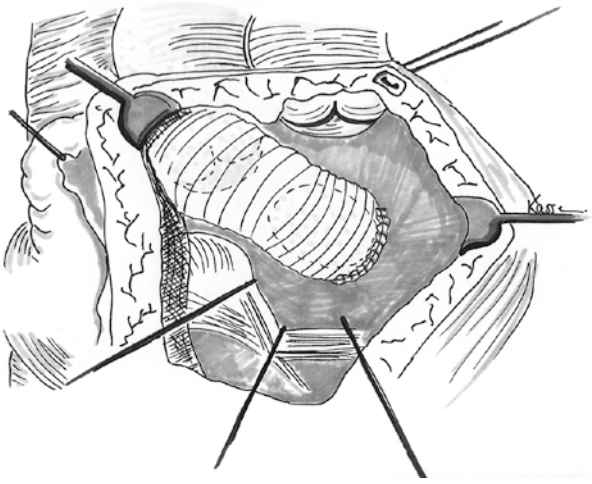

Fig. 16.1 Rastelli procedure. The Rastelli tunnel channels the left ventricular blood from the ventricular septal defect to the aorta

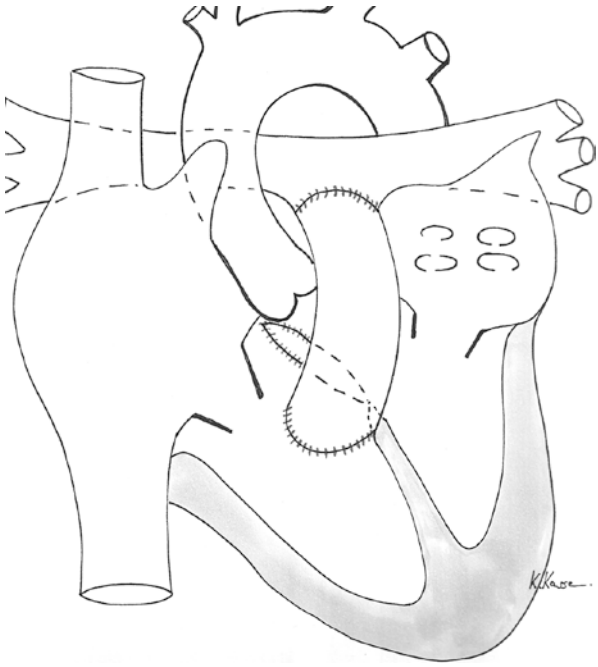

Fig. 16.2 Hemodynamics following Rastelli procedure

As a result, a serial circulation is maintained with the LV as the systemic ventricle and the coronary arteries do not need to be transposed. However, the more distant the aortic valve is to the VSD, and the greater the distance to be bridged by a tunnel is, the more LV dysfunction (tunnel does not contract) and distortion of ventricular geometry are to be expected postoperatively, potentially leading to a LVOTO.

It is also possible that, in a TGA situation, the VSD lies near the pulmonary valve subpulmonary, called "Taussig-Bing anomaly." Surgical correction includes a combination of:

- VSD closure by patch, which channels LV blood to the PA
- Arterial switch surgery

In this case, the serial circulation is also preserved, but the coronary arteries must be transplanted (in the Giessen center → 300 IU/kg BW/d heparin, coronary protective approach with postoperative nitro therapy). In terms of heparinization, it should be noted that the approach is somewhat historical in nature; in the event of postoperative distortions, kinking or obstructions of the coronary arteries, these must be treated as mechanical obstructions. In addition, a long ischemia time and postoperative myocardial depression are to be expected.

Postoperative intensive care therapy is geared essentially to the surgical outcome; therefore in this case no standard procedure can be recommended.

The same general treatment principles apply as after the Rastelli procedure, involving cardiac output optimization, maintenance of sufficient perfusion pressure, good urine output and fluid balance, optimized SvO2, and monitoring and treatment of rhythm complications. In addition, open lung ventilation, normoventilation, and extubation should be performed as soon as the circulatory situation allows. Postoperative echocardiography, in particular, is also essential because it can detect LVOTO, a residual VSD or, in the case of a Rastelli procedure, obstructions in the extracardiac tunnel and thereby guide intensive care management.

Therefore, in the various forms of DORV correction, it is essential to distinguish between low cardiac outputs due to LV failure (small LV, long procedure, JET, LVOTO, coronary ischemia) and RV failure, particularly in patients with status post severe pulmonary hypercirculation. This problem can only be properly assessed by intra- and postoperative echocardiography in conjunction with pressure measurements, e.g. in the LA – high LAP indicates LV failure – and postoperative X-rays.

It is only then that postoperative management can be established.

Lastly, severe LV hypoplasia may also occur in DORV, as well as other very rare variants, necessitating a univentricular approach.

16.6 Ebstein Anomaly

This malformation (0.5% of heart defects) is characterized by displacement of the septal and posterior tricuspid valve leaflets towards the right ventricle to a very variable degree. In addition, the valve leaflets are malformed to a variable degree, in some cases even fusing with the RV wall. The anterior atrioventricular valve inserting at the valve ring is enlarged and can obstruct the RVOT. An ASD is usually also present and often a pulmonary stenosis.

If the so called “atrialization” of the RV is only slightly pronounced and the tricuspid insufficiency is minor, there are hardly any clinical symptoms.

Even with severe TI and a relatively small RV cavity (resulting in a reduced pump function), it is possible to maintain “normal hemodynamics.” Neonatally, however, the right ventricle may be overburdened by the elevated PVR, so that central cyanosis develops if the ASD is sufficiently large and compensated right heart failure if the ASD is too small. This situation clinically improves with the reduction of the PVR when the impaired RV manages to pump the whole cardiac output through the lung (the only abnormality that may remain in the medical history of undetected cases is a “difficult” neonatal history).

Significant heart failure can develop neonatally, which often improves in the first weeks of life following a decrease in PVR but which can result in RV failure over the first few years of life (as well as LV failure if there is a substantial change of ventricular geometry) with enlargement of the RA and development of predominantly supraventricular arrhythmias. In addition to this, the *Ebstein anomaly is frequently associated with accessory conduction pathways* in the form of a WPW syndrome (see Table 16.5).

Table 16.5 Ebstein anomaly

Ebstein	Severe form in neonatal phase	Moderate form in neonatal phase	Postneonatal period, infancy
Heart function	Hypoxia and acidosis jeopardize heart and circulation	Cyanosis less severe	RV moderately restricted, LV OK
RV	Almost no function	Induces antegrade flow, improvement with PVR ↓	Dilated, function can be improved with medication
Tricuspid valve	Massive TI	TI variable	Moderate insufficiency
ASD	R/L shunt required	Not urgent	Not necessary
PDA	L/R shunt required	Initially	Not necessary
RA	Giant → pulmonary compression + arrhythmias	Large, pulmonary compression, arrhythmias	Grows with time, pulmonary compression + arrhythmias
Treatment	PGE_1 + ventilation, positive inotropes, PVR ↓, univentricular (pulmonary perfusion through AP shunt/ductal stent)	PGE_1 + ventilation, positive inotropic, PVR ↓, biventricular after stabilization	Anticongestive, valve reconstruction

ASD atrial septal defect, *PDA* patent ductus arteriosus, *PVR* pulmonary arterial resistance, *RA* right atrium, *RV* right ventricle

In the critical neonatal form of this heart defect, the RV has no relevant function because of its minimal residual size and massive TI. There is no antegrade perfusion of the pulmonary valve, which remains functionally atretic. In some cases, differentiation from anatomical pulmonary atresia by echocardiography can be difficult (consider NO test). The lung is perfused via the PDA. As a result, an ASD without restriction is required (Rashkind/BAS maneuver to be performed if necessary), and massive cyanosis develops once the PDA is no longer patent (= PDA-dependent pulmonary perfusion). At the beginning of treatment, the main considerations are to ensure atrial communication (R/L shunt) and maintain PDA-dependent pulmonary perfusion by PGE1. An enlarged heart (the extreme variant being a wall-to-wall heart) with pulmonary compression and severe cyanosis constitutes an indication for ventilation. If any sequelae of hypoxia have already occurred (lactate formation, LV function impairment, acidosis, and vascular failure), positive inotropic therapy (milrinone, noradrenaline), buffering, as well as beta-stimulation may be necessary. Beta-mimetics should be avoided, whenever possible, since they are a substantial trigger of arrhythmias. An improvement in pulmonary perfusion can be achieved with inhalational NO. Over the subsequent clinical course it must be checked whether a sufficient antegrade pulmonary flow can be established following the drop in PVR. Since a large PDA might maintain increased pulmonary pressure, controlled partial pharmacological ductal closure (prostaglandin reduction) should be considered. It will only become apparent over the course of time whether an additional aortopulmonary connection is required or even whether a univentricular approach needs to be pursued.

If the TI and the hemodynamic impairment were already present antenatally, these patients are frequently found to have a massive atrial enlargement, which may already be associated with pulmonary problems (pulmonary hypoplasia) due to compression of the lung/airways, preventing the patient initially from being extubated.

In patients with minor atrialization of the RV and mild TI, the situation may stabilize over time following the postnatal decrease in PVR. Also, the antegrade flow through the pulmonary valve may be sufficient (PVR ↓ → RVP ↓ → RAP ↓ → R/L shunt at atrial level↓). In this case, an improvement of the cyanosis can be observed clinically. As long as the postoperative course is not complicated by symptoms due to pulmonary compression, the patient can be expected to thrive on anticongestive therapy (spironolactone, ACE inhibitor); frequent echocardiographic assessments are mandatory. If TI, RA size, and heart failure increase subsequently, a surgical procedure should be considered (TV reconstruction or, where necessary, volume unloading by cavopulmonary anastomosis).

With a biventricular correction, the foremost considerations are the reconstruction and tightening of the tricuspid valve (without replacement) and the associated enlargement of the right ventricular cavity. *Caveat*: the now "ventricularized" atrial tissue does not contract (well)!

Accordingly, the postoperative problems that may arise is that of a poorly functioning small RV with clinically relevant TI. For this reason, the following measures are often useful:

- Positive inotropic therapy (milrinone).
- Sensitive volume therapy with borderline high CVP (12–14 cmH_2O, no volume by hand).
- Combination with suitable ventilation: Normoventilation, pH > 7.4, NO, and low MAP – sildenafil should be considered.

Because of the marked susceptibility to supraventricular tachycardia, all triggers such as beta-mimetics, hypothermia, or electrolyte fluctuations should be avoided.

As these patients often have prior pulmonary damage and a compromised RV, an increase in PVR is often poorly tolerated, and therefore extubation should be attempted only under close supervision after 2–3 days of ventilation.

An alternative to biventricular correction is the $1^1/_2$ circulation. In this approach, the circulations are separated by ASD closure, and while the SVC blood is directed via a Glenn anastomosis to the pulmonary circulation, the IVC blood flows physiologically through the tricuspid valve into the RV, which – now volume unloaded – maintains a pulsatile circulation through the lung. This may require separation of the two established pulmonary arterial circulations due to the different pressure levels (e.g. by banding).

As with the Glenn anastomosis, postoperative treatment goals include a reduction in mean airway pressure, right ventricular afterload (NO, oxygen), and positive inotropic RV support with milrinone.

16.7 Pediatric Aortic Stenosis and Aortic Valve Insufficiency

As long as a critical aortic stenosis does not cause low output neonatally, an aortic stenosis may be compensated for years by the development of concentric left ventricular hypertrophy. Symptoms are usually impaired exercise capacity, syncope, or chest pain on exercise.

With high-grade aortic stenosis, two therapeutic approaches are established:

In the case of a stenosis due to valvular adhesions, an attempt to treat the stenosis can be made interventionally by balloon angioplasty or surgically by commissurotomy. As the procedure results in the unloading of the ventricle which was previously "well-trained," there are rarely major problems following the procedure.

However, since the strongly muscled (hypertrophic) LV no longer has to work against a stenosis, it must be ensured postoperatively that there is no relevant muscular constriction of the LVOT. In this case, positive inotropic agents must be viewed with suspicion; treatment should primarily be directed at increasing preload (volume administration) and the use of beta-blockers.

Where an interventional approach is not possible and surgical commissurotomy or reconstruction is insufficient, a Ross procedure (see Fig. 16.3) is performed for an isolated valvular aortic stenosis or a Ross-Konno procedure in the case of an aortic stenosis with muscular LVOTO.

The Ross-Konno procedure, required when there is an additional subvalvular stenosis in the LVOT, involves implanting the pulmonary valve into the aortic position. A "tongue" of the RVOTO is carried over and used to widen the LVOT

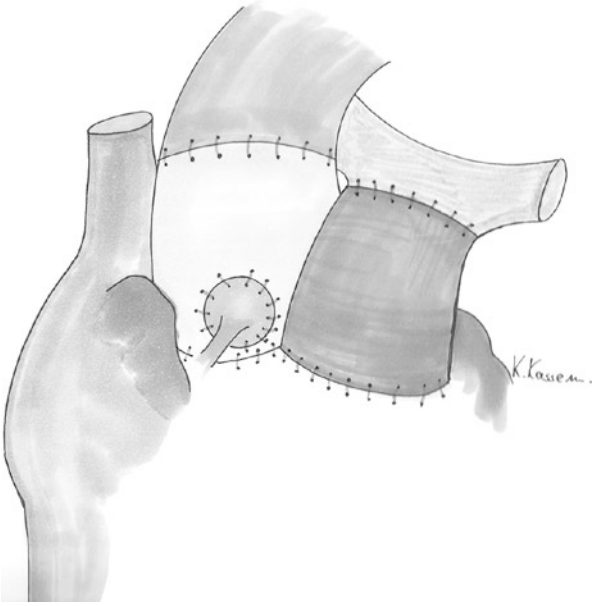

Fig. 16.3 Ross procedure

(alternatively patch widening of an incision of the interventricular outflow septum), while the resultant gap in the RVOT is closed with patch or graft material.

The main complications of the procedure are:

- Postoperative bleeding (tamponade)
- Arrhythmias (block and VES and JET)
- Coronary ischemia
- Neurological complications (always use NIRS)

After prolonged ischemia, postoperative therapy generally includes milrinone; catecholamine therapy is often not necessary if the volume status is sufficient (CVP 8–10 cmH_2O). If the fluid balance is strongly positive, volume should be avoided as much as possible with low doses of noradrenaline; beta-mimetics should not be used because of the increased susceptibility to arrhythmias and outflow tract obstruction.

As with all surgery involving the reimplantation of coronary arteries, 300 IU/kg BW/d heparin should be administered. Nitro may be used to improve coronary perfusion (start with 0.5 µg/kg BW/min) if blood pressure allows.

With suitable pain medication (pethidine and piritramide potently prevent shivering in older children), the patient can usually be extubated very promptly if bleeding and ECG changes can be excluded and the echocardiography results are good.

16.7.1 Ross Procedure

In the Ross procedure, the patient's own pulmonary valve is implanted in the aortic position, and coronary arteries are reimplanted, while a valve-bearing homograft or xenograft is used in the pulmonary artery position. This xenograft can be chosen slightly larger in children but will need to be exchanged at some point depending on growth of the patient. Although the biological valve prosthesis does not grow with the child, it does not require immunosuppression or prolonged anticoagulation. Table 16.6 summarizes the key aspects of complications, ventilation and circulation, coronary protection, and weaning for the Ross procedure.

16.8 Supravalvular Stenosis

Supravalvular stenosis can occur as a familial condition and is sporadically associated with, e.g., Williams-Beuren syndrome. As the obstruction lies on the distally from the coronary ostia, the high pressure is present in the coronary arteries proximally to the stenosis. Over the long term, this can result in coronary damage and tortuosities, which then can lead to problems in the postoperative phase, as the coronary arteries are now "used" to high pressure.

The narrow part of the aorta is widened surgically by means of a patch, resulting in LV unloading (caveat: LVOTO!) and a reduction in myocardial O_2 consumption. However, mean arterial pressure must be kept high-normal postoperatively to

Table 16.6 Ross procedure

Complications	Ventilation	Circulation	Coronary protection	Weaning
Bleeding, suture rupture Avoid of BP peaks!	PC	Close electrolyte monitoring	300 IU/kg BW/day heparin, as long as there is no bleeding and PTT < 60 s	PRVC + SIMV
Cardiac arrhythmias	Vti = 10 ml/kg BW	Rather "high" CVP about 8 cmH_2O	Nitro, if tolerated	Pain medication piritramide + low dose benzodiazepine
Neurology	RR 12–18/min	Milrinone, no beta-mimetics		PCA if necessary
Coronary ischemia	PEEP 5 cmH_2O	Because of hypertrophic ventricle + arrhythmias: Beta-blocker		
	Ti 0.8–1.1 s			

CVP central venous pressure, *PCA* patient-controlled analgesia, *PRVC* pressure-regulated volume controlled, *SIMV* synchronized intermittent mandatory ventilation

prevent myocardial hypoperfusion. Where the stenosis is very severe, an increase in LAP and consequently PHT, primarily postcapillary, may be present preoperatively; postoperatively, an elevated PVR and PHT with its precapillary component may persist and can cause RV overload. Therefore, RV function should also be assessed following surgery on the LVOT, and pulmonary arterial pressure should be measured or estimated by echocardiography.

16.9 Miscellaneous

While not all forms of pediatric heart surgery have been addressed in the previous chapters, the principles of monitoring and treatment described can be applied to most cases. An understanding of whether and to what extent hemodynamic changes have occurred as a result of surgery and whether the preload and pressure level of the ventricles have changed significantly is important in successfully initiating appropriate postoperative treatment. In addition, aortic clamp time and preoperative heart function (degree of existing heart failure) play important roles. An evaluation of these ensures the safe management of foreseeable problems and challenges.

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Heart Transplantation

17

Josef Thul and Dietrich Klauwer

17.1 Indication, Listing, and Waiting Phase

To date, complex heart defects have predominated among the indications for listing neonates and infants for HTx, while cardiomyopathies have been the prevailing indication in children >1 year of age. The proportion of children and adolescents on the waiting list for HTx who develop end-stage heart failure after early surgical palliation of a congenital heart defect is growing constantly. Approx. 5% of all HTx involve a retransplantation.

The allocation of donor hearts usually is regulated by nationwide or international organizations such as Eurotransplant (Central Europe region) and UNOS (USA). According to the current listing criteria of Eurotransplant (ET), all children <16 years of age are automatically listed as "high-urgency" status. Adolescents >16 years of age can likewise be assigned to this urgency level by demonstrating that their skeletal maturity is not yet complete (X-ray of the left wrist). After submitting an informal application to ET, among the children listed as "high-urgency," those are given preference, who have been receiving inpatient treatment during the waiting period ("hospitalization" status). Within these groups the allocation depends on waiting time and does not consider urgency or chances for success after transplantation. After submitting a center-specific treatment protocol to ET, all children of that center up to the age of 2 years are automatically considered for a possible ABO-incompatible HTx. Each center itself is responsible for appraising the individual's suitability and for compliance with the logistical prerequisites of ABO-incompatible HTx.

J. Thul (✉)
Pediatric Intensive Care Unit, Pediatric Heart Center of Giessen, Children's Heart Transplantation Center, UKGM GmbH, Giessen, Germany
e-mail: josef.m.thul@paediat.med.uni-giessen.de

D. Klauwer
Department of Pediatrics, Singen Medical Center, Gesundheitsverbund Landkreis Konstanz, Krankenhausbetriebsgesellschaft Hegau-Bodensee-Klinikum, Singen, Germany

© Springer International Publishing AG, part of Springer Nature 2019

D. Klauwer et al. (eds.), *A Practical Handbook on Pediatric Cardiac Intensive Care Therapy*, https://doi.org/10.1007/978-3-319-92441-0_17

During the waiting phase, in addition to human leukocyte antigen (HLA) typing, screening for preformed HLA antibodies should be carried out by lymphocyte cytotoxicity testing (LCT) against a test panel; if the finding is positive, it is then verified by the more specific Luminex® (Luminex, USA) method. In high-risk patients, i.e., with homografts and blood transfusions or on the ventricular assist device (VAD), these tests should be repeated during waiting times of several months. It may turn out that a restriction to donors with matching HLA type is indicated or that virtual crossmatching and a pre- and intraoperative reduction in antibodies (apheresis, rituximab) are needed. In potential ABO-incompatible candidates, the isoagglutinin titers should be tested repeatedly.

Given the threat of right heart failure in the donor organ, pulmonary hypertension fixed at a certain level is a contraindication for heart transplantation. Help in the assessment of transplantability is provided by excursions from numerical limit values – transpulmonary gradient (TPG) (PAP_m – $PCWP_m$ and/or LAP_m: < 15 mmHg) and a pulmonary vascular resistance index (PVRI <6 WE × m^2) – and evidence of pulmonary vascular reactivity to vasodilators. The diastolic TPG (PAPdiast – PCWPm or LAP) is independent of cardiac output and is designed to better delineate the precapillary component from the postcapillary portion that is essentially reversible by the HTx. Transplantability becomes questionable at levels >7 mmHg (out-of-proportion pulmonary hypertension). However, no singular of the aforementioned criteria is sufficiently valid for rendering the indication. Therefore, the individual risk assessment should at least consider the patient's age and the underlying cardiac disease alongside the possibility for temporary mechanical circulatory support.

If an offer from ET is telephoned in, the ET number and the donor's basic data (blood group, age, weight, cause of death, donor hospital) should be obtained on the telephone and reported to the supervising resident without delay. In general, more detailed particulars are quickly made available by fast fax transmission from ET, or they can be viewed electronically on the ET homepage via the donor's ET number. It may be necessary to additionally contact the transplantation coordinator of the donor center in advance to clarify any further questions in detail (e.g., myocardial function). The decision about accepting the organ is rendered mutually with the cardiac surgeons. If there are several competitive offers, e.g., organ offers from countries outside of the territory supplied by ET, an expedient decision is of the essence. If an organ offer has been accepted, the explant and transportation of the donor heart and the preparation of the recipient have to be started simultaneously.

17.2 Preparing the Recipient

Current Infection Status Take smears from the nasopharyngeal and anal regions. Perform new serology (CMV IgG, EBV IgG, HBsAG, HCV antibodies and/or CMV PCR, EBV PCR)

Blood Bank Have at ready 2–3 units of packed red blood cells (leukocytes – depleted), 2 units of fresh frozen plasma (FFP), and 1–2 units of platelet concentrate. If an ABO-incompatible HTx is planned, notify the blood bank as early as possible (see below).

Preoperative Medication (see Table 17.1)

Extending Preoperative Immunosuppression in the presence of special indications (e.g., presumed rejection risk after previous transfusions, prior surgeries including VAD, known preformed antibodies, retransplantation):

IL-2 Receptor Blocker Basiliximab (Simulect ® Novartis/Switzerland)

- First dose within 2 h before HTx
- Second dose on postop. day 4
- Dosage: Children <35 kg BW, 10 mg; children >35 kg BW, 20 mg

Note: Basiliximab is an off-label use in HTx and may be arrhythmogenic.
Optionally: Measure the effects by anti-CD25-positive lymphocyte-staining assay.

Antibodies Neutralization by Intravenous Immunoglobulins (IVIG) 0.5–1 g/kg pre- and postoperative.

If necessary, prepare for intraoperative *plasmapheresis* and/or blood/plasma exchange on the extracorporeal circulation.

Preoperative antimicrobial prophylaxis and/or therapy standard:

- Teicoplanin 8 mg/kg (adults: 6 mg/kg) (next dose after 24 h), CrCl <40 mL/min: half a dose
- Ceftazidime 50 mg/kg (next dose at the earliest postoperatively on the ICU)
- Adjust according to specific microbial situation

Table 17.1 Immunosuppression

Cyclosporine A	Azathioprine	Prednisolone
5 mg/kg BW p.o.	2 mg/kg p.o. daily	
Alternative:	Alternative:	Not on the ICU
0.1 mg/kg BW/h continuous drip infusion, as soon as the heart has been accepted, until extracorporeal circulation initiated	1 mg/kg i.v. as short-term infusion	Take 10 mg/kg along with transfer to operating room, administer prior to opening aortic clamp
CsA should run alone, but peripheral also allowed, is compatible with catecholamines		

Table 17.2 Pre-and post-heart transplantation (HTx) hygiene protocol

Pre-HTx: repeat immune status	Pre-HTx microbiology	Post-HTx: on the day of surgery and twice weekly until discharge	Ventilation	Physical measures
CMV, EBV, HCV, HBV	Cultures: Nasotracheal, urine, CVC blood; replace CVC if needed	Tracheal secretion + urine + blood (anaerobic + aerobic)	Change ventilator/ tubing twice weekly	Face mask and lab coat (no sterile lab coats) until discharge, stringent disinfection of hands and equipment (ultrasound transducers)
				Limit visits to a minimum; no children

Table 17.2 contains a hygiene protocol of aspects to be observed pre-and post-heart transplantation.

17.3 Crossmatching

Pieces of the donor's spleen should be available (EDTA blood is less suitable) for crossmatching and serum for possible completion of serology (CMV, EBV, HBV, HCV), and EDTA blood is recommendable for a repeated check of the blood group. The aim of crossmatching is to obtain functional evidence of HLA antibody specificities in the recipient's serum against HLA markers from isolated donor lymphocytes – the complement-dependent cytotoxicity test (CDC-CM assay) performed for this purpose identifies antibodies against the donor's HLA antigens that could trigger acute rejection.

After receipt of the materials (donor spleen, recipient's native blood), the crossmatch should be reported immediately to the HLA laboratory. The local circumstances may make it necessary to contact an external HLA laboratory.

A virtual crossmatch must be reported to Eurotransplant if the recipient has (known) preformed anti-HLA antibodies: ET undertakes efforts to HLA type the donor as early as possible. Next, the transplanting center must compare the HLA type with the recipient's antibody status. A true prospective crossmatch before HTx is hardly feasible for the understandable logistic reasons (primarily maximum ischemia time of the explanted organ of not more than 4–6 h).

17.4 Surgical Procedures

The two classic surgical techniques are schematically illustrated in the diagram in Fig. 17.1. Modifications are common, depending on the anatomy of the congenital heart defects. Depending on the anatomical prerequisites, vessels near the donor's

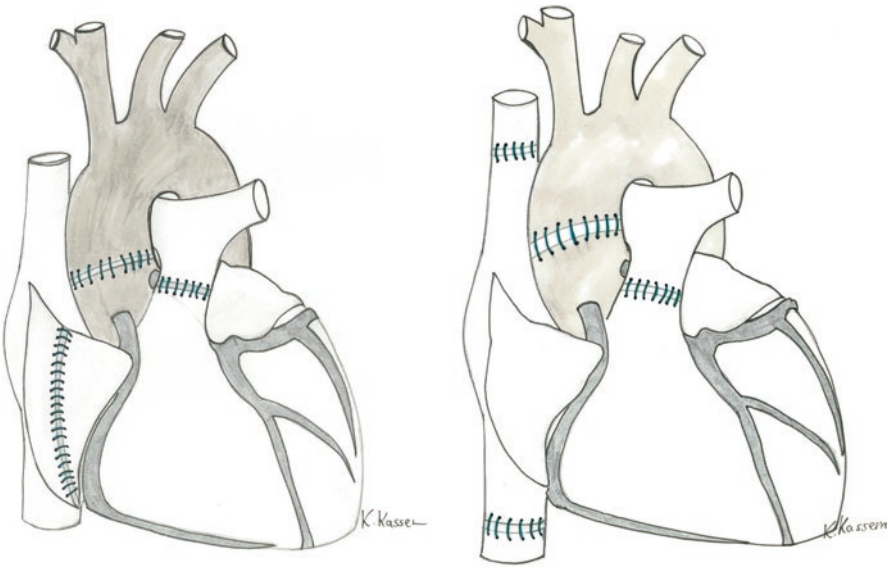

Fig. 17.1 Transplantation technique as described by Lower and Shumway (left) and "bicaval, bipulmonary venous technique"

heart must be sometimes used for reconstruction; this is an issue that must be planned in advance before any a multi-organ removal.

The fact that the patient has undergone prior surgeries may critically complicate the procedure. Since it is anticipated that the number of children with congenital heart defects, who have undergone prior surgeries in whom HTx is indicated will grow, it can likewise be expected, that the very low post-HTx perioperative mortality rate characterizing the past 10 years will start to rise.

17.4.1 Routine Intraoperative Measures

Stop any preoperatively initiated continuous cyclosporine A (CsA) drip infusion once extracorporeal circulation is started.

Decortin H 10 mg/kg i.v. before opening the aortic clamp.

Pulmonary vein catheter (continuous oximetry and PAP monitoring).

Normally, prophylactic pulmonary arterial vasodilatation is accomplished by a continuous drip infusion with iloprost (Ilomedin® Bayer, Germany) and/or inhaled NO.

17.5 Early Postoperative Measures and Medication

17.5.1 Heart Transplant-Specific Postoperative Problems

Primary failure of the donor heart can be the result of prior injury (sustained before or after organ removal) or hyperacute rejection. The latter can be triggered by preformed HLA antibodies of the recipient or by an inadvertent blood group

incompatibility. Primary right heart failure in recipients with pulmonary hypertension is one of the most common early postoperative causes of death. The stimulation frequency of the donor heart and its adaption to different workload are impaired by the surgical interruption of innervation. Postoperatively, the renal function of usually already-impaired kidneys will often fail, especially due to the early high-dose use of CsA or tacrolimus (TAC). Faced with this risk, induction with antithymocyte globulin (ATG) can be considered an alternative option (see below).

17.5.2 Immunosuppression

Initial standard immunosuppression is introduced with cyclosporine A (CsA) + azathioprine (AZA) + prednisolone. In the first 3 postoperative weeks, CsA is normally replaced with tacrolimus (TAC) and AZA with mycophenolate (MMF). In infants, CsA can be administered for longer given its simpler dosability.

Cyclosporine A
Among others, it causes reversible inhibition of the release of IL-2 from activated T-helper cells.

Side effects of long-term CsA therapy: Arterial hypertension, nephrotoxicity, neurological symptoms (neuropathy, cerebral seizures), gingival hyperplasia, impaired liver function, lymphoma development, and multiple drug interactions.

Start: Postoperatively, not until after onset of diuresis (!). Continuous drip infusion with 1 mg/kg BW/24 h varies according to diuresis (0,5–3 mg/kg BW/24 h as continuous drip).

Target levels on continuous drip and trough levels on p.o. administration (same target levels despite the pharmacokinetic difference!):

- Weeks 1–4: 200–300 ng/mL
- From week 5: 150–200 ng/mL
- From month 3: > 100 ng/ml

The monoclonal EMIT (enzyme-multiplied immunoassay) method on a COBAS-Analyzer® (Roche, Switzerland) only measures native CsA, no metabolites.

As soon as possible, switch to oral CsA:

- Stop continuous drip approx. 2 h before first p.o. administration.
- Generally, start with 20 mg/kg/d in 3 (up to 3 years) or 2 single doses.

In renal failure: Lower target levels, possibly a CsA holiday, transient ATG

Do not measure CsA levels from the CVC tubing that the continuous CsA drip was infused through.

Tacrolimus (FK506)
Like CsA, it inhibits the expression of T-cell activator genes for certain cytokines, like IL2, by binding to the calcineurin-calmodulin complex.

The doses are given i.v. or p.o. Due to its fluctuating resorption rates, the active levels of TAC must also be measured daily. The spectrum of adverse reactions is similar to that of CsA. Fungal infection and diabetes mellitus appear to be more frequent than with CsA.

Dosed i.v. as a continuous drip infusion: 0.01–0.05 mg/kg BW/d

0.3 mg/kg/d p.o. in 2 single doses (3 single doses <4 years) or 0.15 mg/kg/d in adults

Target levels:

- Weeks 1–4: 10–15 ng/mL
- Weeks 6–10: 10–12 ng/mL
- > Week 10: 8–10 ng/mL

Azathioprine (AZA)

It inhibits protein biosynthesis and thereby the proliferative capacity of T lymphocytes.

Initial: 1 mg/kg/d i.v. 1 single dose/d; thereafter, vary dose based on differential blood count

Target: Weeks 1–10 – Total number of lymphocytes and monocytes <3.0 10^9/L

The p.o. switch usually requires double the dose.

Mycophenolate Mofetil (MMF)

It inhibits the proliferation of T and B lymphocytes by intervening in purine synthesis; supplied as syrup or capsules.

Dosage: 40 mg/kg i.v. or p.o. twice daily or: 1200 mg/m^2 in 2 single doses (infants 3 single doses)

The differential blood count is the primary orientational parameter for monitoring therapy. Unfortunately, there are no predictable dose-level correlations; therefore, attention should be paid to the peak levels that are reached approx. 2–3 h after administration. Here, plasma levels of >2.5–4 µg/mL should be used for guidance.

Frequently, gastrointestinal intolerance problems occur. Therefore, a switch from AZA to MMF is unfavorable buildup of oral nutrition.

Prednisolone

Dosage:

Day of surgery: 1 intraoperative dose of 10 mg/kg + 10 mg/kg/d in 3 single doses

Postoperative days 1–3: 5 mg/kg/d

Thereafter, incremental reduction:

- Up to 1 mg/kg/d on postop. Day 10
- Up to 0.2 mg/kg/d at the end of week 4
- Up to 0.1 mg/kg/d at the end of week 10

Patient-specific: Stop steroids after 10 weeks or continue for the long term.

Target of Rapamycin (TOR) Inhibitors: Sirolimus and Everolimus

TOR inhibitors disrupt the post-receptor response at the IL-2 receptor and thereby similarly inhibit lymphocyte proliferation. Due to their ubiquitous inhibition of proliferation, mTOR inhibitors are presumed to have advantages for preventing the risk of transplant vasculopathy. Moreover, they are less nephrotoxic. It is still unclear whether mTOR inhibitors can replace the verified standards CsA/TAC to achieve an immunosuppressive effect in the early post-HTx phase.

Everolimus (Certican®, Novartis, Switzerland): dose guideline, 0.1 mg/g/d in 2 single doses, trough: 4–8 ng/mL); adverse reactions, angioedema, cytopenia, hyperlipidemia, and wound healing disorders.

Induction Therapy

Induction with basiliximab (see above) is undertaken in patients with a higher rejection risk (prior surgeries, multiple transfusions, VAD, retransplantation).

Induction therapy with antilymphocyte globulin (here ATG) is not the standard at our center: ATG is only given in patients with therapeutically refractory rejection or as a substitute for calcineurin inhibitors in renal failure.

ATG: e.g., Grafalon® – Fresenius, Germany – 3–5 mg/kg as short-term infusion over 1 h (caution: alternative medication – the dose will vary depending on the drug).

Combination with ranitidine, steroid bolus, and dimethindene maleate, as needed: immunoglobulins, antifungals, and virus prophylaxis with ganciclovir (5 mg/kg BW/d).

ATG dose adjustments:

ATG dose reduction if total leukocytes <2000/µl or platelets <50,000/µl.

At a total lymphocyte count <100/µl, ATG is paused.

The ATG dose can (best) be monitored by flow cytometry:

- Here, the T-helper cell target is <200/µl.
- The dose is reduced between 50 and 100/µl.
- At <50/µl a holiday is taken.

Duration: as a rule, 1 single dose daily over 3–5 days

If there is a high risk of humoral rejection (case history, preformed antibodies against the test panel, positive crossmatch) and additionally for standard immunosuppression:

Immunoglobulins 1–2 weekly, rituximab as needed (375 mg/m^2 – once weekly over 4 weeks, i.e., 4 once-weekly doses in total.

Upon initial evidence of donor-specific HLA antibodies:

Plasmapheresis or – even better – immune apheresis (adsorption of IgG on extracorporeal adsorber columns) and rituximab.

Alternatively or supplementally: eculizumab (Soliris® Alexion, USA), specific anti-complement C5 antibody, inhibits terminal complement activation; off-label use in HTx; dose: 600 mg over 30 min, twice weekly; increased susceptibility to infection, especially to meningococci.

17.6 Cytomegalovirus (CMV)

The risk of a CMV infection directly triggered by the transplantation is of varying seriousness for many recipient (R)/donor (D) constellations. If the donor has already come into contact with CMV, but the recipient has not, this is the easiest way for the disease to become manifested. In cases of primary infection of the recipient under immunosuppression (D+/R–), the clinical course is often more difficult than in constellations with secondary infections (D+/R+), where the recipient's immune system had already reacted to the virus before induction of immunosuppression (= immunological memory). Now, the immune system is only confronted with a new virus strain – albeit now in an immunosuppressed state. The risk is even lower, when it is only the organ recipient who carries the virus (D−/R+). In this case, immunosuppression can reactivate the CMV (of the previously known strain). The most favorable constellation is when neither recipient nor donor organ has had any in contact with CMV (D−/R−). In this context, a primary infection can be triggered by the ambient surroundings. Therefore, a serology panel on donor and recipient is required preoperatively for risk assessment.

17.6.1 Diagnostics

CMV PCR once weekly and then every 2–3 weeks from weeks 5 to 10

17.6.2 Standard Postoperative CMV Prophylaxis

In negative recipient and positive donor (R−/D+):

Ganciclovir 5 mg/kg/d in 1 single dose for 3 weeks (adapted to impaired renal function)

Thereafter, valganciclovir for 2 months

Valganciclovir (Valcyte® Roche/Switzerland) dosage guide:

Daily dose in mg = 7 × BSA × CrCl (modified Schwartz formula):

- CrCl = mL/min/m2/1,73 m2 = k × height (cm)/serum creatinine (mg/dl)
- K = 0.45 for children <2 J
- K = 0.55 for boys 2–12, girls 2–16 years
- K = 0.7 for boys >13 years

Daily dose in adults and adolescents: 900 mg

Preemptive therapy in the event of seroconversion in the recipient or positive CMV PCR findings:

Ganciclovir: 10 mg/kg/d in 2 single doses for not less than 14 days or 2 weeks beyond PCR negativity.

Symptomatic CMV infection with fever, lymphadenopathy, hepatitis, neutropenia, and/or organ-related symptoms (e.g., endocarditis, invasive colitis).

Management as with preemptive therapy.

If necessary, supplementally: CMV – hyper-immunoglobulin (Cytotect® Biotest, Germany 1 ml/kg every 3 weeks)

17.7 Antibiotic Therapy

Teicoplanin 8 mg/kg once daily (adults: 6 mg/kg); adapted to impaired renal function; see Chap. 19 (alternative: linezolid)

Ceftazidime (100 mg/kg/d).

After CVC removal, switch to cefuroxime or no antibiotic therapy (see below for exceptions).

Diagnostic tests: Blood culture and tracheal secretion twice weekly.

Starting with the buildup of oral nutrition:

- Amphotericin B oral suspension (1–)2 mL p.o. six times daily
- Miconazole oral gel 1 mL p.o. four times daily
- Co-trimoxazole (TMP) 5 mg/kg p.o. every 2 days

17.8 Organ Rejection

A singular rejection episode tends to be the rule rather than the exception (see Table 17.3). The first rejections mostly occur in postoperative weeks 2 to 4.

None of the clinical findings and apparatus-based tests are specific. A myocardial biopsy can be considered if the findings are ambiguous and after weighing the risk of rejection therapy. The same applies if probationary rejection therapy fails to produce any effect. The biopsy can additionally provide evidence for a humoral or antibody-mediated rejection, which means there is an extended need for therapy.

The biopsies undergo a histological and molecular pathological workup. Cellular rejection is classified according to the grading system of the International Society for Heart & Lung Transplantation (ISHLT) (see Table 17.4). *Among others*, one marker for a humoral component is complement Cd4 deposition immunohistochemically detected in the capillary endothelium.

Table 17.3 Signs and symptoms of rejection

ECG (recorded daily)	Echocardiography	Clinical exam	Lab tests
Overall amplitudes ↓I, II, III, $V_1 + V_6$	Systolic and diastolic dysfunction	Resting heart rate ↑	TNI ↑, BNP ↑
Arrhythmia	New effusions	Appetite ↓	No inflammation
New conduction disturbances	Septal thickness ↑. Changes in septal echogenicity	Fever, patient "not doing so well"	(genomics ?)

BNP brain natriuretic peptide, *TNI* troponin I

Table 17.4 International Society for Heart & Lung Transplantation (ISHLT) Cellular rejection grading scheme (revised version, 2004)

Grade 0	None
Grade 1 R mild	Interstitial and/or perivasculkar infiltrate with up to one focus of myocyte damage
Grade 2 R moderate	Two or more foci of infiltrate with associated myocyte damage
Grade 3 R severe	Diffuse infiltrate with multifocal myocyte damage +/– edema +/– hemorrhage +/– vasculitis
	The presence or absence of acute antibody-mediated rejection(AMR) may additionally be recorded as AMR 0 or AMR1

Limitation:

- Any positive immunohistological findings should always be weighed against the clinical status.
- A negative Cd4 finding does not exclude humoral rejection.

17.8.1 Rejection Therapy

Prednisolone
10 mg/kg/d over 3 days, thereafter incremental reduction to the original dose

CsA/TAC: Aim for high-normal levels, CsA: > 250 ng/mL elevate, or continuous drip infusion

In initial rejection with a severe clinical course (need for catecholamine, intubation, etc.) or with a failure to improve after prednisolone shock therapy: ATG (see above)

Humoral Rejection
Typical biopsy findings (C4d+) and/or clinical status (lack of response to conventional rejection therapy) and/or evidence of donor-specific HLA antibodies in the peripheral plasma (Luminex® single antigen method) may indicate an antibody-mediated rejection.

Give IVIG

Plasmapheresis

More specific and effective than plasmapheresis: Immune apheresis (TheraSorb® Miltenyi Biotec, Germany): specific adsorption of IgG in columns, e.g., ten cycles under IgG monitoring and/or monitoring of the donor-specific HLA antibodies in the peripheral blood (Luminex®)

Rituximab: Once weekly 375 mg/m^2 over 4 weeks (CD-19 monitoring)

As a last resort: Bortezomib (Velcade® Pharmaceuticals, Inc., USA): Proteasome inhibitor directly targets plasma cells.

Eculizumab (Soliris® Alexion, USA): Anticomplement C5 antibody (see Sect. 17.5).

17.9 Antihypertensive Therapy

Normally, systemic arterial hypertension will develop within a few days. This is particularly attributable to the immunosuppressive therapy with steroids and CsA and mandates rigorous management to additionally prevent damage to the transplanted heart through an elevated afterload and avoid further complications from hypertension.

Among others, the following antihypertensive drugs have become established for therapeutic management, in part, because of their synergistic effect on pulmonary arterial resistance:

- Amlodipine
- ACE inhibitors / Angiotensin II receptor antagonists
- Sildenafil
- α - Adrenoreceptor-blockers

17.10 Pulmonary Hypertension Post-Heart Transplantation

As described in Chap. 9, persistently poor LV function causes an increase in LAP and results in an elevation of postcapillary pulmonary resistance. As a protective mechanism against pulmonary edema, a precapillary elevation in pulmonary resistance can result over the long term; this precapillary component of PAH may progress and turn out to be irreversible to a certain extent when poor LV function persists. Because LV worsening takes place as a process-like chain of events, the recipient's RV can be adapted to elevated pulmonary vascular resistance (PVR). The elevated PVR continues up to immediately post-HTx. If left untreated, it can lead to RV decompensation of the grafted heart that is not accustomed to the high PVR. That means that each preoperative improvement in LV function (likewise the use of a mechanical LV assist device) positively impacts PVR (↓) and can thus mitigate the risk of acute RV failure post-HTx.

Weaning from cardiopulmonary bypass can be hampered by an acute elevation in resistance in the pulmonary circulation. Accurate monitoring is accomplished with a PA catheter (at best with an additional oximetry function). The patient is routinely weaned from bypass with inhaled NO. Additionally, each patient receives post-HTx milrinone (continuous drip infusion with 1 μg/kg BW/min) to lower the afterload of LV and RV and improve contractility.

The ventilation regimen (see Table 17.5) consists of an open lung (PEEP 5–6–7 cmH_2O or higher) and tidal volumes of approx. 8–10 mL/kg BW with an arterial CO_2 target of approx. 40 mmHg and a pH of 7.4. The ventilation mode is primarily selected with pressure-regulated volume control (PRVC = safe tidal volume at a decelerated gas flow and minimized PIP) or pressure control (PC).

Table 17.5 Post-heart transplantation ventilation (not in neonates)

Mode	PEEP	Vti	PIP	CO_2 target	pH target
PRVC or PC	5–7 cmH_2O	8–10 mL/kg BW	Max. 30 cmH_2O	40 mmHg	7.4

PRVC pressure-regulated volume control, *PC* pressure control

If the primary aim is to rapidly extubate these patients, safety frequently dictates that an observation and adaptation phase of approx. 24 h under analgosedation initially follow postoperatively (fentanyl 5–10 µg/kg BW/h or higher, midazolam 0.2 mg/kg BW/h).

- At the first signs of pulmonary arterial resistance (PAP > 25% of SAP), check whether the problem is attributable to a pulmonary cause (atelectasis → Euler-Liljestrand), a genuine vascular cause, or an anatomical cause. In this regard, X-ray, pulmonary sonogram, but also the end-expiratory CO_2 can provide hints. In the case of atelectasis, there will be a discrepancy between low levels in the expiratory air and higher levels in the BGA. The normal value here would be a difference of 2–4 mmHg with higher levels in the BGA (see also Mismatch in Sect. 2.2.7 Ventilation). In the event of pulmonary problems, the ventilation regimen must be adapted, i.e., as a rule, by raising the mean arterial pressure (MAP) through PEEP elevation or careful recruitment (this can be risky if the RV is impaired). Additionally, it should take place briefly in the presence of sufficient preload (CVP) and under monitoring of blood pressure and PAP.

If a vascular cause is presumed, the coagulation status (including ACT) should be checked before starting a continuous drip infusion with iloprost (Ilomedin®). This is because iloprost can lead to reversible inhibition of platelet aggregation associated with a tendency to early postoperative bleeding.

Dosage: Start iloprost at a dose of 0.5 ng/kg BW/min, and then increase to 1–2 ng/kg BW/min.

In the case of an acute, critical increase in PAP: Sedation, as needed, relaxation, 100% FiO_2, careful hyperventilation, as needed, noradrenaline bolus (1–10 µg/kgBW). A patient on pacemaker therapy may have no ejection fraction (measured arterially or by echocardiography) while showing a "normal" heart rate – in this situation cardiac resuscitation must not be delayed. As part of this process, a low PAP in the presence of decreasing blood pressure and increasing central venous pressure as well as a drop in heart rate may not exclude the diagnosis of a pulmonary artery hypertensive crisis, because if there is severe pulmonary artery resistance of the RV, this can no longer be overcome and the PAP can no longer be built up.

If the aforementioned measures fail or it is not possible to end CPB because of RV failure, ECMO can be used to bridge over the time until the PVR is reduced and/or RV has adapted.

17.11 ABO-Incompatible Heart Transplantation

The Eurotransplant allocation rules allow ABO-incompatible heart transplantation into infants and small children up to of 2 years of age.

In small children and infants, HTx has become established as a very successful method for treating the most serious cases of congenital heart defects and acquired myocardial diseases. Indeed, especially in this age group, the scarcity of donor organs is particularly dramatic, with many children dying while on the waiting list. In 1996, North America introduced the concept of blood group-incompatible heart transplantation in infants to take efficient and equitable advantage of the pool of donor hearts and utilize otherwise not immediately allocatable organs for transplantation. Presently in place at numerous centers worldwide, this policy has meanwhile been successfully implemented in small children as well. In Canada, the introduction of ABO-incompatible HTx has lowered waiting times in this youngest age group. Like in the USA, at Eurotransplant, the allocation of ABO-incompatible organs still is subordinated to blood group-compatible ones. Accordingly, the influence of this policy on waiting time mortality and morbidity under these circumstances can be questioned. Based on currently available data, long-term survival and the risk of rejection and the development of transplant vasculopathy in this cohort do not appear to differ from children undergoing ABO-compatible HTx. The absence of normal redevelopment of isoagglutinins against the blood group of the donor heart occurring after an ABO-incompatible HTx cannot solely be attributed to immunosuppression but more likely suggests that a tolerance to these foreign antigens develops. Moreover, there is evidence that under these circumstances, the simultaneous development of a tolerance to HLA antigens is promoted and that thereby the long-term prognosis for the transplant recipient may even be improved. The experience gained to date in our center on a few patients suggests a hitherto unverifiable but suspicious trend toward an excessively elevated susceptibility to infection.

The introduction of ABO-incompatible HTx at our Pediatric Heart Center has been linked to a number of medical and organizational measures. The practice guidelines listed below are founded on the experience gained at pediatric heart centers in Toronto, Newcastle, and Munich while taking the structural circumstances at Giessen into consideration.

17.11.1 Inclusion Criteria

Whether a child can be proposed as a candidate for an ABO-incompatible HTx is dictated by age, risks of a possible sensitization (triggered by transfusions, prior surgeries, mechanical circulation support), HTx urgency, and – above all – the quantitative levels of isoagglutinins to be measured in screening tests. At the Giessen Pediatric Heart Center, this policy was initially limited to children up to the age of 2 years and with preoperative isoagglutinin titers up to 1:32. Maternal antibody titers do not count as exclusion criteria in young infants. Only children who are

already ET-listed by utmost urgency (high-urgency + hospitalization status) can be considered. It is not necessary to separately register a potential recipient of an ABO-incompatible organ with ET.

17.11.2 Preoperative Measures

If an ABO-incompatible HTx comes into question, the essential patient data including all findings from previous antibody tests should be available and kept up to date during the clinical course.

While waiting for a donor heart, the isoagglutinin titers should be checked every 4 weeks. This is done to monitor the inclusion criteria and make it easier to judge the elimination measures to be expected perioperatively. The method of gel card centrifugation should be preferred over optically assessable dilution series in test tubes. The gel card test is less rater-dependent and takes approx. 45–60 min to carry out. When ordering the test, there should be explicit instructions regarding the intent to perform an ABO-incompatible HTx and the necessity to test for IgG antibodies.

As far as possible, the transfusions of blood products should be avoided during the waiting period. If they should nevertheless become necessary, Table 17.6 provides guidance for blood product selection. Group O recipients should not be administered O plasma (or O platelet concentrates). This is because these products can contain very high anti-A-isoagglutinin titers, which are accordingly difficult to remove and, depending on the situation, may require repeated intraoperative blood exchanges. If the isoagglutinin titers are low at the time of the transfusion, transfusions are primarily given with AB plasma or AB platelet concentrates. When doing so, the – probably age-dependent – risk of sensitization to platelets of a blood group different than the recipient's must be accepted. After the transfusion, the isoagglutinin titer assay should be repeated. If an O recipient is registered for an ABO-incompatible HTx, the blood bank ensures that any potentially required AB platelet concentrates are made available. The production of washed platelet concentrates is not presently regarded as effective.

Table 17.6 Matrix for transfusions to recipients after ABO-incompatible heart transplantation

Recipient blood group	Donor blood group	Packed red blood cells	FFP	Platelet concentrate[a]
O	A	O	A or AB	A or AB
O	B	O	B or AB	B or AB
O	AB	O	AB	AB
A	B	A	AB	AB
A	AB	A	AB	AB
B	A	B	AB	AB
B	AB	B	AB	AB

[a]When ordering blood products, special instructions must be given by phone or in writing with regard to the individual requirements

While waiting for a donor organ, screening for preformed HLA antibodies should be performed parallel to the isoagglutinin assay (current method: LCT test = complement-dependent microlymphocytotoxicity test). This test should be repeated around every 8–12 weeks – especially after exposure to transfusions, homografts, VAD, or the likes.

If a candidate organ from an ABO-incompatible donor is offered, the blood bank should be given advance notice without delay. That way, they will be able to start coordinating the organizational prerequisites for the impending tests and the provision of specially selected blood products as early as possible. Once this donor organ is accepted, an assay for isoagglutinin titers against the donor's blood group must also be performed at the earliest possible time. This immediately preoperative check may only be refrained from if the most recent screening produced no evidence of isoagglutinins, the test is not older than 4 weeks, and no transfusion of blood products has taken place in the interim.

At the time of transfusion, the donor's blood group should be tested once again in the blood bank at the place of receipt by performing the fastest possible test on the EDTA blood of the donor at the in-house blood bank. Either way, this double-checking of the recipient's blood group constitutes the standard.

17.11.3 Intraoperative Measures

Intra- and postoperatively, it is imperative to avoid adding ABO antibodies against the donor's organ because of their depleting effect. Therefore, rigorous attention must be paid to the proper selection of blood and blood components. Normally, recipient-identical erythrocytes and donor-compatible plasma and platelet concentrates are used. Guidance on the selection particulars is given in Table 17.6. Filling of the HLM is based on the same criteria. For filling, account must be taken of the fact that an approx. 1.5 times greater volume of blood is needed due to the impending blood exchange. After an ABO-incompatible HTx, over the further clinical course – e.g., in the event of future surgeries or emergencies – the blood products must be selected strictly according to the aforementioned diagram. Nevertheless, the combination of erythrocytes from group 0 with plasma/platelet concentrates from group AB can be generally considered safe for every possible recipient/donor combination.

17.11.4 Intraoperative Exchange of Blood/Plasma

The blood/plasma exchange commences immediately after connection to the HLM. Initially, an amount of approx. 1.5 times the calculated recipient's blood volume is exchanged. The blood/plasma exchange takes place by drawing the recipient's blood through the venous tubing on the HLM while, at the same time, substituting erythrocytes of the recipient's blood group and plasma of the donor's blood group (see above). If necessary, the Cellsaver can be employed to extract the

recipient's erythrocytes and wash and then reinfuse them into the patient over the further course of the operation. This procedure can help mitigate the risk of transfusion incidents.

If a targeted assay of isoagglutinin titers against donor antigens is performed immediately before the surgery and measured a max. Titer of 1:4, this will obviate the intraoperative need for a further blood exchange and repeated titer assays. If these titers are >1:4, then a quantitative titer test must be repeated immediately after the first blood exchange. Thereafter, further blood exchanges and titer monitoring may be necessary until the target is reached (titer: max. 1:4). Not until the titer is negative and/or reaches a max. 1:4 should the aortic clamp be released and the donor organ perfused. It is therefore essential to avoid any time delays in titer monitoring in order to limit ischemia in the donor heart.

If – according to the above criteria – immediate preoperative titers were not measured, it is mandatory to check the titers against the donor's blood group after the first blood exchange and before opening the aortic clamp. Depending on the result, further exchanges and titer checks may follow (see above).

Offers for donor organs often are made in the evening after 6 p.m. In such cases, it has to be anticipated that at least one titer assay will have to take place between 6 p.m. and 8 a.m. A close organizational coordination with the blood bank is therefore indispensable.

At present, the blood bank is committed to a titer test turnaround time of 45–60 min for the actual workup. It is paramount that all kinds of time delays are eliminated (e.g., blood courier) as these would otherwise extend the ischemia time for the donor organs and could jeopardize the graft outcome.

17.11.5 Postoperative Measures

Within the first week, quantitative titer assays should be performed daily; thereafter, once weekly for 4 weeks; and then once monthly as whenever clinically indicated.

There are many different elimination methods available in the event that significant (> 1: 4) postoperative evidence of isoagglutinins against the blood group of the donor emerges. Non-specific immune apheresis (e.g., TheraSorb® Miltenyi Biotec, Germany) and ABO-specific immune apheresis (e.g., Glycosorb®ABO Glycorex, Sweden) are to be preferred over plasmapheresis, because they are markedly more effective. Supportively, the administration of immunoglobulins and the early adjustment to mycophenolate can be considered. The CD-20 antagonist rituximab should be considered in the event of therapeutic resistance or recurrences.

17.11.6 Immunosuppression

At the Giessen Pediatric Heart Center, perioperative immunosuppression is accomplished according to the described institutional standards that entail a combination of CsA, AZA, and steroids. In at-risk patients (HLA sensitization after prior

surgeries or on mechanical circulatory support), an IL-2 receptor antagonist is added to therapy. In ABO-incompatible HTx, immunoglobulins are moreover administered in the early postoperative stage (day 1). This measure must be accounted for in isoagglutinin titer assay (rise in titers by 1–2 levels, without being clinically relevant). The switch from CsA to TAC and from AZA to mycophenolate should also take place expediently (< 1 week). In ABO-incompatible HTx as well, the routine induction with antilymphocytic antibodies is not necessary.

Suggested Reading

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Ultrafast Tracking in Pediatric Cardiac Surgery

18

Christoph Schmidt and Edward Malec

18.1 Definition

Fast tracking is defined as a multidisciplinary, interprofessional, systematic concept for the care of cardiac surgery patients. Its aim is to save costs by early postoperative extubation, rapid mobilization, immediate transfer from the ICU, and prompt discharge from hospital without jeopardizing the quality of treatment outcomes. The central aspect of any fast-track concept is early postoperative extubation – either while the patient is still on the operating table or during the first few hours after their admission to the ICU.

18.2 Terminology

In pediatric cardiac surgery, the following terminological definitions are becoming accepted as binding:

- Early extubation: Extubation within 24 h of the end of surgery
- Fast-track pediatric cardiac surgery: Extubation within 6 h of the end of surgery
- Ultrafast-track pediatric cardiac surgery: Extubation on the operating table

C. Schmidt (✉)
Department of Anesthesiology, Surgical Intensive Care Medicine and Pain Therapy, Münster University Medical Center, Münster, Germany
e-mail: christoph.schmidt@ukmuenster.de

E. Malec
Division of Pediatric Cardiac Surgery, Münster University Medical Center, Münster, Germany

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D. Klauwer et al. (eds.), *A Practical Handbook on Pediatric Cardiac Intensive Care Therapy*, https://doi.org/10.1007/978-3-319-92441-0_18

18.3 Historical Development

Until the beginning of the 1990s, it was regarded as an undisputed maxim in adult cardiac surgery that all patients be sedated after cardiac surgical procedures and placed on controlled ventilation for a few days. Numerous arguments based on pathophysiological considerations were advanced to elevate this practice to an irrefutable standard of care. In particular, prolonged postoperative controlled ventilation in combination with high-dose opioid administration appeared to be the only way to effectively counteract the surgically induced activation of the neurohumoral systems. As an adverse consequence of any neurohumoral stress response, a disturbance in the delicate balance between myocardial oxygen consumption and delivery and the associated increase in the occurrence of perioperative myocardial ischemia were particularly feared. Moreover, the whole-body inflammatory response with the associated multiple organ dysfunction syndrome, impairment of pulmonary gas exchange by ventilation-perfusion inhomogeneities, disorders of plasma coagulation and platelet function, capillary leak syndrome following cardiopulmonary bypass, postischemic myocardial dysfunction, atrial fibrillation, ventricular rhythm disorders, or delirious neurologic syndromes were advanced as convincing pathophysiologic arguments to justify postoperative sedation and ventilation after cardiac procedures (see also Chap. 10).

From the mid-1980s, the socioeconomic environment then changed. Fixed sum-based billing procedures and an increasing shortage of medical resources, such as a lack of qualified staff, intensive care beds and operating rooms, placed doctors and hospitals under pressure to work more efficiently and to reduce costs effectively. It was against this backdrop that the first fast-track protocols were developed. Primarily thanks to a dramatic reduction in the total opioid dose, the precondition was created for the early extubation of patients, thereby enabling the duration of stay of cardiac surgery patients on the ICU to be decisively reduced. Relative to the conventional procedure, the ICU costs in fast-track treatment are reduced by about 50%. The overall costs of hospital treatment are also markedly reduced by about 15% per patient. At the same time, hospital capacities can be utilized more efficiently since there are fewer postponements of elective surgery. Moreover, a greater proportion of patients can be channeled through the system per unit of time, because the treatment period for each individual patient is markedly reduced.

While the “economic outcome” is improved by fast tracking, patient safety is not jeopardized. There is no increased incidence in perioperative myocardial infarctions or other complications, as had been the initial concern of many authorities in the field. As a consequence of improved resource utilization, cost savings and the same good outcome for patients, fast-track protocols became very rapidly and universally established in adult cardiac surgery. Today, they represent the new global standard in treatment and quality of care.

Figure 18.1 provides an exemplary flowchart of a fast-track protocol.

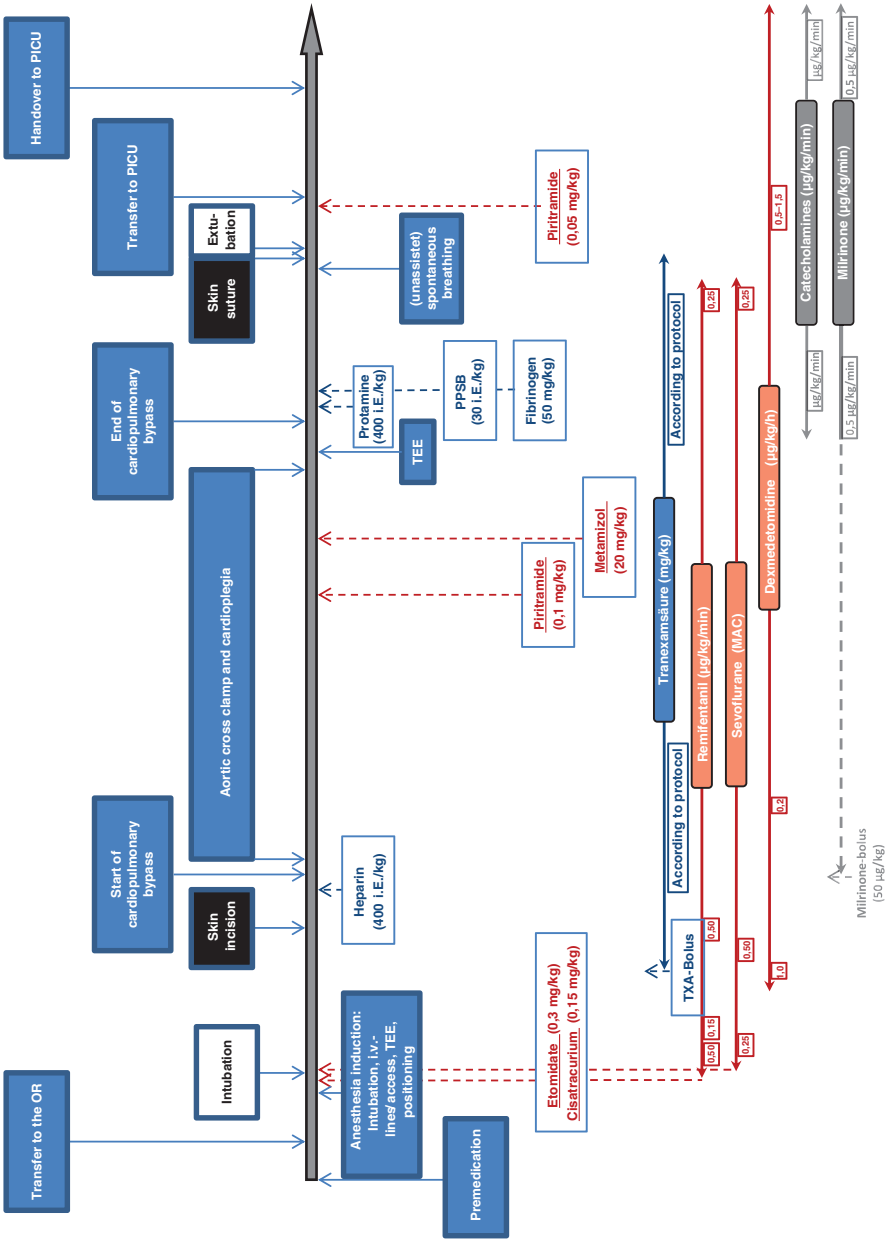

Fig. 18.1 Flowchart of the ultrafast-track protocol presented here

By contrast, fast tracking in pediatric cardiac surgery is only just now beginning to evolve. Data on the practical feasibility, costs and safety of fast-track concepts derive overwhelmingly from retrospective analyses of individual centers or relate to a few populations with precisely defined heart defects. There is, at present, no study in children with a broad spectrum of congenital heart defects that undertakes a comparison of an integrated fast-tracking strategy with a control group treated conventionally over the same period. It appears astonishing from a current perspective that, at the beginnings of pediatric cardiac surgery in the 1970s, children were routinely extubated immediately after cardiac surgical procedures and with remarkably good results. In those pioneering years, the prevailing state of development in perioperative medicine was responsible for that approach. The hypnotics, sedatives, analgesics, and muscle relaxants then available were associated with severe adverse cardiodepressant effects. Given the then existing state of ventilator technology and knowledge of respiratory physiology, mechanical ventilation in neonates, infants or young children was associated with both considerable hemodynamic impairment and a high risk of functional, biochemical, and mechanical lung injury. The prevailing opinion was that extubation on the operating table had benefits over routine continuation of analgosedation and ventilation, without these benefits being specified any further.

At the beginning of the 1990s, academic opinion changed abruptly in response to a single study published by Anand and Hickey in 1992 in 45 children undergoing cardiac surgery. The study, published in the authoritative *New England Journal of Medicine*, compared neonates who had received high doses of an ultrapotent opioid intraoperatively and during the first 24 h postoperatively (5–15 μg/kg sufentanil in fractionated doses intraoperatively and then 2 μg/kg sufentanil per hour as continuous infusion postoperatively) with one group treated with halothane-morphine anesthesia and postoperatively with intermittent doses of morphine and diazepam. In the sufentanil group, the neuroendocrine stress response and the body's metabolic reaction were markedly attenuated—a finding which was interpreted as a cause for the excess mortality in the halothane-morphine group. In response to the results of this study, high-dose opioid anesthesia with postoperative mechanical ventilation was raised to a universally observed rule despite the absence of further validation. This stipulation was supported by simultaneous progress in the field of ventilator technology. It therefore appeared for a long time as if the perioperative care of cardiac surgery children was firmly established.

The greater economic pressure then heralded in a new movement in the area of pediatric cardiac surgery, in the same way as it had happened in adult cardiac surgery around two decades before. In addition to this, the revival of the fast-track concept was prompted by other developments, e.g., the increasingly sophisticated evaluation of the potential risks of mechanical ventilation. No longer was consideration merely given to the detrimental effects of positive-pressure ventilation on resistance and blood flow in the pulmonary circulation. Rather, serious complications such as laryngotracheal trauma, barotrauma, dystelectasis and atelectasis

formation, ventilator-associated pneumonia, accidental extubation, or the triggering of pulmonary hypertensive crises by airway manipulations were also regarded in a critical light. Furthermore, the forced introduction of modern substances such as sevoflurane, remifentanil, dexmedetomidine, or cisatracurium into the practice of pediatric cardiac anesthesia provided new impetus to the fast-track movement. Unlike traditionally used anesthetics, the modern alternative agents facilitate the exact control of anesthetic depth by virtue of their precisely predictable elimination kinetics. Moreover, they offer a pharmacodynamic profile that raises the possibility of breaking the previously apparently indissoluble link between stress reduction and high-dose opioid anesthesia.

18.4 State of Research

Between 40 and 50 pertinent publications on the subject of fast tracking in pediatric cardiac surgery have appeared during the last decade and a half. These also include some very topical articles that show how fast tracking can be transposed to the group of neonates undergoing surgery for complex congenital heart defects. A slowly increasing number of centers are implementing (ultra)fast-track protocols with the aim of using (ultra)fast tracking as a primary therapeutic strategy across all age ranges and surgical categories. By contrast, the majority of centers remain bound to the traditional approach. In many respects, these approaches are placed in direct opposition to one another, rather than allowing room for "context-sensitive" decision-making and a comparison of the benefits and disadvantages of early extubation and prolonged postoperative mechanical ventilation with one another in individual cases without any preconceptions. The fundamental feasibility of (ultra)fast tracking, however, is now undisputed; in the great majority of studies, it is credited with greater cost effectiveness and optimized resource utilization. The current interest in clinical practice and research is focused primarily on investigating the safety of rapid extubation and the reduced duration of intensive care and hospital stays. Whether, in addition, there are even benefits for children in terms of morbidity and mortality is increasingly becoming the subject of dispute.

18.4.1 Economic Aspects

Savings gained from (ultra)fast tracking are generated predominantly by a reduction in the duration of stay on the ICU and in hospital. This must be weighed against costs generated by longer overlap periods in the operating room if the child does not awake promptly at the end of the procedure. Many papers from recent years have strikingly demonstrated in various patient populations and also in the neonatal sector that fast-track concepts can contribute to substantial cost reductions and to a reduction in the duration of ICU stays.

18.4.2 Safety

As already described in adults, current study data demonstrate that fast-track protocols do not jeopardize patient safety in pediatric patients either. Even the reintubation rate – a recognized marker of postoperative morbidity and mortality in pediatric intensive care medicine – is lower with fast tracking than in conventional therapeutic regimens. Forms of deliria such as postoperative delirium have been identified as a frequent cause of reintubation. Attempts are made to take account of this finding through the integration of antidelirium interventions, such as early mobilization, multimodal pain therapy, and administration of specific active substances, for example, selective α_2 agonists, but also by the early inclusion of parents ("kangaroo care").

18.4.3 Big Data Analyses

The scientific evaluation of large data registries established by specialist societies, public bodies, or state institutions allows insights and findings that go beyond the progress reports of specialized treatment centers. There are a growing number of big data analyses in pediatric cardiac surgery from which certain key messages can be extracted:

- The clinical practice of early extubation varies considerably according to the complexity of the surgical procedure and the frequency of surgery in the center concerned.
- The prevalence of extubation in the operating room is low at the current time and equates to about 25%.
- Extubation in the operating room has a low complication rate and may be regarded as safe.
- The probability of prolonged postoperative positive-pressure ventilation is higher for children in general pediatric ICUs than in specialist pediatric cardiology units.
- Indicators of an increased reintubation rate include the degree of complexity of the surgical procedure, deep hypothermic circulatory arrest, surgery in neonates, and institutional experience with the handling of fast tracking.

18.5 Learning How to Fast Track

An initiative of the American Pediatric Heart Network Investigators describes how fast tracking can be learned systematically as institutional practice. Collaborative learning strategies have been used for the development and introduction of fast-track protocols at various centers. Such strategies are employed in the production industry to identify processes or procedures with poor results and then to adapt them substantively and structurally to those that exhibit the best performance.

Collaborative model learning within the initiative was based primarily on reciprocal team visits for the purpose of exchanging experiences and concepts and on the advice of expert anesthesiologists from a model center possessing a track record of many years in the successful practice of early extubation. As a result of collaborative learning, the rate of early extubation increased rapidly without any increase in the occurrence of complications. The model learning project emphasized a considerable number of interesting perspectives:

- Over the course of 12 months following the implementation of an early extubation guideline, there was a continuous and significant increase in the early extubation rate.
- Following the introduction of fast tracking, the time to resumption of enteral nutrition decreased markedly.
- Intravenous analgesics were administered over a significantly shorter period.
- The postoperative pain score remained low following the introduction of fast-track and was in the mild discomfort range.
- Fast tracking was not associated with an increased occurrence of hypertensive crises.
- The proportion of children treated with dexmedetomidine increased substantially following the implementation of a fast-track guideline.
- The postoperatively administered cumulative doses of both opioids and benzodiazepines decreased markedly and highly significantly.
- The duration of stay in the ICU was unchanged. For Fallot children, there was a trend to a shorter duration of stay.

18.6 The Pros and Cons of (Ultra)Fast Tracking

Even now a search for the term "fast tracking" in standard pediatric cardiac surgery or cardiac anesthesia textbooks will prove fruitless, despite the fact that nowadays at major centers about 25% of children are extubated after cardiac surgery while still in the operating room. The topic is probably still too much a subject of dispute in specialist circles.

18.6.1 Pros: Fast Tracking Probably Improves Patient Outcomes

In contrast to adults, children with a congenital heart defect usually come for surgery in a compensated cardiac state. Apart from pharmacologically controlled heart failure and possibly cyanosis and a failure to thrive, an absence of extracardiac morbidities is characteristic of these children. Except with specific defects and in rare circumstances, there are no impairment of cardiac contractility and no myocardial ischemia. The surgical procedure then usually corrects both pressure and volume overload and intra- and extracardiac shunt flows, which then restores the functional integrity of the cardiorespiratory system. Hence, surgery confers

immediate hemodynamic benefit for the child. Against this background, there is a whole series of other arguments and justifications for fast tracking.

Mechanical ventilation is burdened by complications:

- Ventilator-associated pneumonia
- Ventilator-induced lung injury (VILI)
- Atelectasis and dystelectasis formation with subsequent intrapulmonary right-to-left shunting
- Ventilation-perfusion inhomogeneities with increased resistance in the pulmonary circulation by activation of hypoxic pulmonary vasoconstriction (HPV)
- Barotrauma
- Volutrauma
- Localized pulmonary and generalized systemic inflammatory response

Mechanical ventilation entails further invasive therapeutic measures:

- Continuous intravenous administration of analgesics and sedatives
- Regular endotracheal suctioning associated with respiratory tract irritation, stress, and pulmonary hypertensive crises
- Arterial catheter for sampling for blood gas analyses
- Central venous catheter for hemodynamic monitoring
- Fixation and immobilization to protect from tube dislocation and accidental extubation
- Chest X-rays for monitoring tube position and pulmonary pathologies

Spontaneous respiration normalizes pressure/volume relationships of the respiratory system immediately after surgery:

- Negative intrapleural pressure fosters venous return to the heart and increases cardiac output, which has a beneficial effect on diastolic filling in the event of a restrictive physiology of the right ventricle, e.g., in children with tetralogy of Fallot.
- Spontaneous respiration promotes pulmonary blood flow compared to positive-pressure ventilation, which is of benefit, for example, to children with a univentricular heart and passive pulmonary perfusion following Glenn anastomosis or Fontan completion or even children with Blalock-Taussig shunt.
- Restoration of spontaneous respiration results in a reduction in pulmonary vascular resistance and thus causes an increase in cardiac output in cases of compromised right ventricular function.
- Following early extubation, spontaneously breathing children usually exhibit mild respiratory acidosis with improved cerebral perfusion and increased blood return via the superior vena cava, which is manifested following a Glenn procedure, for example, in an improved neurological outcome.

Fast tracking opens the way to rapid restoration of normal physiological conditions following surgical trauma:

- Enteral nutrition can be resumed within just a few hours of the procedure.
- Early mobilization serves as effective prophylaxis against numerous consequences of surgery and intensive care therapy (including catabolism, pressure sores, delirium, infections).
- Conscious awareness of parents, caregivers, and the immediate circle prevents the development of psychological and emotional disorders.
- Early contact with the child reduces parental stress and increases treatment satisfaction.
- Unnecessarily long and unnecessarily deep analgosedation in children of neonatal age probably impairs central nervous development processes.

Fast tracking reduces the total amount of analgesics, sedatives, and muscle relaxants administered perioperatively:

- The depressant effects of analgesics, sedatives, and muscle relaxants on cardiac mechanics, autonomic nervous system, and neuroendocrine functions are more moderate, so that catecholamines and other positive inotropic substances are either not needed at all or only at a reduced dose.
- Systemic vascular resistance remains largely unaffected, rendering the use of vasopressors unnecessary.
- Optimization of left and/or right ventricular preload is achieved by intravascular delivery of a lower fluid volume, limiting the accumulation of interstitial fluid in patients with impaired capillary permeability.
- Smaller quantities of analgesics and sedatives, accurately tailored to alleviate pain and discomfort of the individual child, reduce the probability of occurrence of postoperative agitation states or a withdrawal syndrome or delirium.
- The avoidance of benzodiazepines, for example, during postoperative treatment reduces the frequency of withdrawal syndromes.

Early extubation in children with, for instance, pulmonary hyperperfusion and pulmonary artery hypertension was a subject of particular dispute. For many years academic opinion held that anesthesia must be continued postoperatively, in some cases for several days, to prevent pulmonary hypertensive crisis. The good clinical experience with early extubation in this well-defined group of patients as well has prompted watchful reconsideration.

Conversely, growing clinical practice advises caution in certain subtypes of heart defects in which the subsystemic ventricle continues to remain exposed to severe pressure and volume overload after initial surgical correction or where the latter develops as an outcome of surgery. Examples of this are hypoplastic left heart syndrome and transposition of the great arteries. In the patients with these defects, positive-pressure ventilation produces a clinically significant afterload reduction for

the subsystemic ventricle, while extubation immediately after surgery with an abrupt transition to spontaneous respiration can provoke an acute low cardiac output syndrome by ventricular failure. Early extubation of patients with severe pressure and volume overload of the subsystemic ventricle must therefore be viewed with some reservation.

18.6.2 Cons: Fast Tracking Probably Worsens the Patient Outcome

The central hypothesis of opponents of fast tracking states that the stress response of the body to surgical trauma, heart-lung machine, and intensive care therapy must be suppressed by the administration of high-dose opioids to improve the outcome in pediatric cardiac surgery. Although there are only few and limited data confirming this assumption, they have left a lasting impression in the development of pediatric cardiac surgery and pediatric cardiology.

- Mechanical ventilation reduces systemic afterload. Afterload reduction is important following surgery with cardiopulmonary bypass since transient heart failure frequently develops postoperatively as a result of myocardial ischemia and systemic inflammation.
- Respiratory work is normally already high in neonates, in addition to which there are limited possibilities for it to increase further. An increased ventilation requirement, as is the case following pediatric cardiac surgery, therefore cannot be compensated by spontaneous respiration.
- Following pediatric cardiac surgery, the proportion of oxygen consumption by the respiratory muscles can increase to up to 20% of the oxygen consumption for the whole body. Mechanical ventilation relieves the heart from increased oxygen demand, thus preventing any possible decompensation of the systemic ventricle.
- On pathophysiological grounds, early extubation following specific pediatric cardiac surgical procedures, e.g., stage I Norwood procedure, arterial switch operation, or common arterial trunk repair, must be viewed with some criticism.
- Extubation of a child in the operating room triggers a catecholamine storm. This can then lead to the development of life-threatening arrhythmias, pulmonary hypertensive crises, or cardiogenic shock.
- Episodic, critical increases in pulmonary artery pressure occur frequently in children with preexisting pulmonary hyperperfusion. They can only be treated effectively by controlled mechanical hyperventilation, where necessary with the addition of nitrogen monoxide to the respiratory gas mixture.
- Cardiopulmonary bypass, ischemia-reperfusion injury, and transfusion of blood and blood products induce an inflammatory response with a capillary leak syndrome. The degree of impairment of vital organ functions, particularly lung function, is unpredictable. In individual cases, acute lung failure can occur.

- Reduced functional residual capacity and lowered elastic recoil forces of lung and chest wall in neonates and small infants predispose to the development of airway obstructions and atelectasis on spontaneous respiration. Postoperative mechanical ventilation serves to prevent pulmonary complications.
- Pulmonary compliance can be severely reduced following pediatric cardiac surgery. Mechanical ventilation relieves patients of the associated increase in respiratory work in the vulnerable postoperative period.
- Glomerular filtration rate is low in neonates at about 20 mL/min, and the concentrating capacity of the renal tubules is restricted. Many metabolic functions of the liver are not yet fully developed at birth. The immaturity of the kidneys and liver affects the elimination kinetics of most anesthetics, particularly those of opioids. The particular sensitivity to anesthetics, especially to opioids, is associated with a high risk of unexpected respiratory arrest in the postoperative period.

It is important when assessing the various arguments to be aware of the heart-lung interactions in various functional states of the cardiorespiratory system:

- Spontaneous inspiration increases venous return, right ventricular preload and right ventricular stroke volume. At the same time, left ventricular afterload increases and left ventricular stroke volume decreases. The relationships are reversed in spontaneous expiration. However, the absolute change in intrapleural and intrapulmonary pressures in spontaneously breathing healthy patients is generally slight.
- With mechanical ventilation, the relationships are reversed, and the absolute change in intrapleural and intrapulmonary pressures becomes greater.
- In forced spontaneous inspiration of agitated or stridorous patients, intrapleural pressures can fall to extremely negative values of less than 50 cm H_2O. The intraventricular pressure must increase by the corresponding amount for an unchanged stroke volume to be ejected. Agitation and stridor therefore represent an immediate threat to hemodynamic stability, irrespective of whether they occur in intubated patients with spontaneous respiratory efforts or in extubated patients. They must be treated immediately.

18.7 Ultrafast-Track Cardiac Surgery as a Practical Clinical Strategy

The following section will introduce a multidisciplinary protocol developed by pediatric cardiac surgery, pediatric cardiology, and anesthesia, designed essentially to extubate all children on the operating table. There are four exceptions:

- Prematurity with incomplete development of the lungs
- Mechanical ventilation already prior to pediatric cardiac surgery
- Difficult airway with genetic defects and syndromes with craniofacial dysmorphia
- Status post Norwood stage I operation, arterial switch operation, and common arterial trunk repair or heart transplantation

The key aspect of the protocol is the avoidance of postoperative mechanical ventilation. Prolonged ventilation is the only variable in perioperative management that affects all aspects of the care of cardiac surgery children without exception: Adjustments at this point affect the restoration of physiological organ functions, the morbidity and mortality, and the efficiency of resource consumption simultaneously.

18.7.1 Preparation and Pharmacological Premedication

In order to prevent dehydration and hypoglycemia, children are given clear fluids such as tea, water, or fruit juice up until 2 h before surgery. The intake of breast milk or breast milk substitutes is discontinued 4 h before initiation of anesthesia and other solid food 6 h beforehand. A continuous intravenous infusion is initiated on the pediatric cardiology ward no later than the time at which fluids are withdrawn, covering the maintenance requirements for water, electrolytes, and glucose. The principles of pharmacological premedication are presented in Table 18.1.

18.7.2 Anesthesia Induction

Anesthesia is typically induced intravenously. In the event of a difficult venous access, transnasal induction with S-ketamine and midazolam or inhalational induction with sevoflurane are alternative options. The choice of method of anesthesia induction is governed by the type of congenital defect, direction of intra- or extracardiac shunt flows, and cooperativeness of the child. Transnasal induction is preferred in uncooperative and young children and is undertaken with 5 mg/kg S-ketamine and 0.5 mg/kg midazolam (Mucosal Atomization Device, MAD®). Loss of consciousness occurs slowly over the course of about 15 min. On inhalational induction with sevoflurane, rapid uptake and distribution is obtained with a high concentration in the inspired gas mixture of between 6 and 8%. Loss of consciousness occurs after a few breaths. Thereafter the concentration of the volatile anesthetic can be adapted individually.

Table 18.1 Premedication

	Age under 6 months	Age over 6 months
Premedication	None	0.5 µg/kg dexmedetomidine (transnasally)
Time		45 min before induction
Justification	Are not afraid of strangers	Are not afraid of strangers, traumatic experience of separation from parents
Advantage		No respiratory depression, marked anxiolytic, and antidelirium effect
Disadvantage		Bradycardia and hypotension more pronounced than with midazolam premedication
Monitoring		Connection of pulse oximeter and ECG after administration of premedication

In the context of the ultrafast-track protocol, S-ketamine or etomidate is used for intravenous anesthesia induction. Etomidate is preferred if decompensated heart failure is present.

S-Ketamine

The cardiovascular effects of S-ketamine can be summarized under the keyword "sympathomimetic." They are triggered by central activation of the sympathetic nervous system. Peripheral inhibition of noradrenaline and dopamine reuptake at the synaptic end plates of the sympathetic varicosities acts synergistically in this respect. The result is an amplification of the action of endogenous and exogenous catecholamines. It is important to be aware that S-ketamine itself exerts a negative inotropic effect on the myocardium. In vivo, however, this effect normally does not play a primary role, since it is overridden by central and peripheral sympathetic activation. With repeated injections of S-ketamine, however, the negative inotropism becomes more obvious and manifests itself as reductions in heart rate, mean arterial blood pressure, and cardiac output. For this reason, follow-up injections should be strictly avoided in those cases, where ventricular function is already compromised. S-ketamine should generally be omitted in the presence of decompensated heart failure with exhausted sympathetic/adrenergic reserves. Such a condition fully unmasks the negative inotropic action of S-ketamine and is associated with the implicit danger of experiencing severe hypotension after administration the drug.

S-ketamine at a dosage of 2 mg/kg is the intravenous induction agent of first choice in ultrafast-track anesthesia (see Table 18.2).

Table 18.2 S-ketamine facts

S-ketamine	Duration of action	Hemodynamics	Usability	Adverse effects
Allosteric inhibition of central NMDA receptors	10–20 min	Heart rate and MAP increase significantly, SVR less so	With serial and univentricular circulation	Bronchial dilation (desired)
Activation of GABA receptors and of opioid receptors in the spinal cord and brain	Terminal elimination half-life about 3 h	PVR relatively unaffected	Negatively inotropic in decompensated heart failure	Oral and bronchial hypersecretion
Sympathomimetic action (central and peripheral catecholamine reuptake inhibition)		No histamine release	Preferably avoid further injections – Blood pressure and heart rate can drop	Not in decompensated heart failure
Substantially more potent than racemate or R-ketamine				

GABA gamma-aminobutyric acid, *MAP* mean arterial pressure, *NMDA* N-methyl-D-aspartate, *PVR* pulmonary vascular resistance, *SVR* systemic vascular resistance

Etomidate

Etomidate is a pure hypnotic that lacks the analgesic component of S-ketamine. Etomidate acts via GABAergic receptors in the reticular formation. Because of the lack of analgesic effect, etomidate only inadequately depresses the stimulus of endotracheal intubation. In ultrafast-track anesthesia, therefore, continuous infusion of the highly potent opioid remifentanil at a dose of 0.5 μg/kg/min is initiated prior to the administration of etomidate. Following endotracheal intubation, the dosage of remifentanil is reduced to 0.15 μg/kg/min.

The great benefit of etomidate lies in the fact that, of all induction anesthetics, this compound is associated with the least pronounced cardiovascular adverse effects. The only marginal depression of myocardial contractility and the stability of systemic vascular and pulmonary vascular resistance after injection of an induction dose should be particularly emphasized. The beneficial cardiovascular effects of etomidate are faced with a whole series of partly serious adverse effects that previously precluded the more widespread use of the substance in pediatric cardiac anesthesia. The suppression of adrenal cortisol and aldosterone synthesis must be regarded in a particularly critical light. After a single dose of etomidate, cortisol biosynthesis ceases almost completely as a result of the blockade of adrenocortical 11β-hydroxylase, which is related to worse outcomes in adult patients.

There are only a few reports describing the effects of etomidate in children with congenital heart defects. The sporadic communications unanimously confirm the neutral hemodynamic profile of etomidate and the suppression of adrenocortical function. Hard outcome data on the use of etomidate in pediatric cardiac surgery are completely lacking to date.

Etomidate at a dose of 0.3 mg/kg is the induction hypnotic of choice in decompensated heart failure with exhausted sympathetic/adrenergic reserve (cf. Table 18.3).

Table 18.3 Etomidate facts

Etomidate	Duration of action	Hemodynamics	Usability	Adverse effects
Purely hypnotic	Onset after 1 min	Contractility remains practically unaffected	Single	Adrenal suppression for 24 h even after a single injection
GABAergic	Duration 3–10 min	PVR and SVR unaffected	Indicated in heart failure	Injection pain, nausea, vomiting, hiccup, myoclonus – Duration about 1 min
Lipid emulsion better than glycol solution	Elimination half-life is 2 to 5 h	No histamine release	Almost no respiratory depression	
Reduce remifentanil after intubation has been performed				

PVR pulmonary vascular resistance, *SVR* systemic vascular resistance

Cisatracurium

Cisatracurium at a dose of 0.15 mg/kg is the muscle relaxant of first choice in ultrafast-track anesthesia. Muscle relaxation is given only to facilitate endotracheal intubation. Muscle relaxants are not routinely administered intraoperatively. Repeated doses are administered only if hiccup occurs during surgery that cannot be suppressed by increasing the depth of anesthesia and/or by moderate hyperventilation. The repeat dose of cisatracurium is 0.03 mg/kg.

Cisatracurium acts as a competitive antagonist at the nicotinergic receptors of the motor end plate. Although the agent stimulates cardiac muscarinic receptors and nicotinergic receptors of the autonomic ganglia as well, there are hardly any cardiovascular adverse effects. In contrast to other nondepolarizing muscle relaxants, cisatracurium does not result in histamine release, and thus does not give rise to any negative effects on heart rate or blood pressure. As elimination occurs organ-independently by spontaneous pH- and temperature-dependent degradation (= Hoffman elimination), the duration of action is absolutely predictable. It is 15–20 min. Postoperative residual curarization is virtually excluded.

Overview of Induction Medications

Premedication:

- Dexmedetomidine 0.5 μg/kg transnasally (from the sixth month of life)

Anesthesia induction:

- S-ketamine 2 mg/kg intravenously
- Cisatracurium 0.15 mg/kg intravenously

Anesthesia induction in decompensated heart failure:

- Etomidate 0.3 mg/kg intravenously
- Remifentanil 0.5 μg/kg/min until endotracheal intubation
- Cisatracurium 0.15 mg/kg intravenously
- Remifentanil 0.15 μg/kg/min after endotracheal intubation

With a left/right shunt, there is a reduction in the effective systemic and cerebral blood flow as a result of pulmonary recirculation with a delayed increase in the concentration of intravenously administered drugs in the brain. Conversely, their onset of action is accelerated with a right/left shunt, as the shunt volume reaches the systemic circulation directly, circumventing the pulmonary circulation. With a left/right shunt, intravenous induction agents are dosed about 25% higher. On the one hand, this is done to compensate for the slower increase in concentration in the systemic circulation and, on the other, to compensate for the pulmonary first-pass uptake that affects, e.g., S-ketamine and opioids.

18.8 Monitoring and Instrumentation

Monitoring and instrumentation follow the established standards of pediatric cardiac anesthesia. However, all vascular accesses – central venous, arterial, and peripheral venous – are positioned under ultrasound guidance. Ultrasound helps avoid complications and shorten anesthetic induction times.

18.8.1 Transesophageal Echocardiography

Under the ultrafast-track protocol, it is mandatory to use transesophageal echocardiography (TEE) in all intracardiac procedures and in extracardiac procedures if there are special issues. The precondition is that the child weighs more than 2.5 kg. The TEE probe is advanced into the esophagus at the end of anesthesia induction. In rare cases, the probe can obstruct the major airways, impair pulmonary venous return, compress the ascending aorta or aortic arch, or trigger supraventricular arrhythmias by mechanical irritation of the left atrium. The TEE probe remains in situ until the end of surgery.

The use of intraoperative TEE essentially seeks to achieve two aims:

Intraoperative diagnostic procedures:

- Change of preoperative diagnosis in 3–5% of cases
- Modification of the surgical procedure in 5–15% of cases
- Return-to-bypass in 3% of cases
- Fundamental effect on the surgical outcome in 10–15% of cases

Extended hemodynamic monitoring:

- Global and regional ventricular function
- Preload and afterload
- Stroke volume and cardiac output
- Intravascular volume status and volume responsivity
- Intracardiac pressures
- Stenosis and/or insufficiency of the heart valves

Intraoperative TEE findings are discussed and interpreted by pediatric heart surgeons and anesthetists and analyzed with a view to the surgical procedure and hemodynamic management.

18.8.2 Cerebral Oximetry

The ultrafast-track protocol provides for the measurement of regional cerebral oxygen saturation ($rScO_2$) by near-infrared spectroscopy (NIRS), although there are as yet no systematic studies documenting a better outcome with NIRS or NIRS-triggered interventions. Usually only one electrode is used for reasons of cost.

Bilateral monitoring is considered if techniques for selective cerebral perfusion are used during cardiopulmonary bypass, if there is a persistent left superior vena cava, and if vascular anomalies of the aortic arch or the supraaortic branches are addressed surgically. The NIRS monitor shows the proportion of oxygenated hemoglobin in the blood pool of the frontal lobe up to a depth of 6 mm as a percent. The cerebral blood volume detected by the sensor is 75% composed of venous blood, 20% of arterial blood, and 5% of capillary blood, which implies that the oxygen saturation measured by the NIRS method predominantly records the venous capillary circulation of the oxygen transport chain.

The ultrafast-track protocol dictates that the $rScO_2$ value obtained during anesthesia induction under ventilation with a FiO_2 of 0.21 and a $PaCO_2$ of 40 mmHg with stable hemodynamics be defined as the individual normal value. Any relative decrease in $rScO_2$ by more than 20% of this normal value and any absolute value less than 50% is regarded as jeopardizing the cerebral oxygen supply. The therapeutic interventions for correction of the cerebral oxygen balance that are then initiated are dependent on whether or not the child is connected to the heart-lung machine at the time in question. The individual measures are aimed either at increasing cerebral oxygen delivery or decreasing cerebral oxygen consumption. The simplest and most rapidly implementable measures are taken first of all.

Hierarchy of Measures Following an NIRS Reduction

Interventions with a critical reduction in $rScO_2$ during spontaneous circulation:

- Improvement of venous return from the brain (upright position of upper body, head held straight)
- Increase in FiO_2
- Increase in end-tidal PCO_2 to 45 mmHg according to capnography
- Increase in cerebral perfusion pressure (absent contraindications, α_1-receptor agonists, e.g., phenylephrine 1–5 μg/kg administered as an IV bolus)
- Increase in cardiac output (possibly volume administration, inotropic agents, vasodilators)
- Increased depth of anesthesia
- Reduction in body temperature to 36 °C
- Increase in hemoglobin concentration by transfusion

Interventions with a critical reduction in $rScO_2$ during cardiopulmonary bypass:

- Ensuring unimpeded drainage of venous blood to the heart-lung machine
- Increase in pump flow of the heart-lung machine
- Increase in perfusion pressure (phenylephrine 1–5 μg/kg)
- Increase in $PaCO_2$
- Increase in PaO_2
- Reduction in body temperature depending on type of surgery
- Increase in hemoglobin concentration by transfusion
- Repeated control of the position of aortic cannula and reassurance of adequate venous return

Irrespective of the widespread use of cerebral oximetry and regardless of the great popularity that this method enjoys despite its high costs, it is not possible at the present time to avoid two conclusions that arise from a variety of case reports, case series, and studies:

- There is no definite evidence that the measurement of $rScO_2$ results in an improvement in the outcome of cardiac surgery patients.
- Systematic reviews have not revealed any correlation between perioperative interventions for correction of $rScO_2$ and an improvement in the short-term neurological outcome of children undergoing cardiac surgery.

Despite all the reservations and concerns, however, it is nonetheless the case that in Germany the Competence Network for Congenital Heart Defects requires NIRS monitoring to be performed in pediatric cardiac surgery in connection with quality assurance.

18.9 Anesthesia Maintenance

Anesthesia is maintained by sevoflurane, remifentanil, and dexmedetomidine.

18.9.1 Sevoflurane

Sevoflurane is vaporized in ultrafast-track anesthesia at a minimum alveolar concentration (MAC) of 0.5. The MAC expresses the anesthetic potency of an inhalational anesthetic. A MAC of 1.0 is defined as the alveolar concentration at which 50% of all patients exhibit no pain response after a skin incision. A MAC of 0.5 in a neonate corresponds to a sevoflurane concentration in the inspiratory gas mixture of 1.6 vol%. As the MAC is age-dependent, the corresponding concentration decreases in young children to 1.2 vol%. During the cardiopulmonary bypass phase, sevoflurane is delivered via the HLM oxygenator in the identical concentration. At core body temperatures of less than 32 °C, the sevoflurane concentration is halved. As a delivery device for sevoflurane, a conventional anesthesia vaporizer (Vapor) is connected to the gas circuit of the HLM oxygenator. A technical arrangement of this nature is permitted under the German Medical Devices Act and certified by the German Technical Inspection Association (TÜV).

In young children, the ratio of alveolar ventilation per minute to functional residual capacity is 5, while in adults it is 1.5. The large ratio is one of the reasons for the relatively more rapid uptake of inhalational anesthetics in children. Modern volatile anesthetics have low blood-gas partition coefficients. That coefficient for sevoflurane, for example, is 0.65 and therefore only slightly above that of nitrous oxide. The lower the blood/gas partition coefficient is, the more rapidly the partial

pressures of a volatile anesthetic equilibrate between inspired air, alveolar space, blood, and central nervous system. In other words, a volatile anesthetic with a low blood/gas partition coefficient is taken up and is eliminated very fast. Thus, the hypnotic effect emerges quickly and recedes just as quickly: This constitutes excellent controllability. It is apparent from what has been said that consciousness is very rapidly lost following the start of sevoflurane delivery, but that it is also equally rapidly restored after the end of delivery.

Volatile anesthetics exert a cardioprotective effect by preventing myocardial ischemia or reperfusion injury. By analogy with the phenomenon of ischemic preconditioning (= improvement in ischemia tolerance of the myocardium by prior short periods of ischemia followed by reperfusion), the term anesthetic-induced pharmacological preconditioning has been coined. Pharmacological preconditioning with volatile anesthetics imitates ischemic preconditioning and, as there, the interaction with mitochondrial and sarcolemmal ATP-sensitive potassium channels is here the most important molecular mechanism of action.

A right/left shunt delays the uptake of volatile anesthetics because the shunt volume reaches the systemic circulation without taking up anesthetic from the alveolar space. The delay is proportional to the ratio of the pulmonary to the systemic blood flow (Qp/Qs). In contrast to right/left shunts, left/right shunts have only a minor effect on the uptake of volatile anesthetics. Although pulmonary blood flow is increased in a left/right shunt, which accelerates uptake, on the other hand, the partial pressure difference between venous blood and alveolar space decreases, as the shunt blood recirculating in the pulmonary circulation has already taken up the anesthetic. For clinical practice, it may be assumed that the two effects balance one another out in respect of the speed of anesthesia induction (see Tables 18.4 and 18.5).

Depression of contractile properties by volatile anesthetics is very well documented experimentally. With halothane, myocardial depression assumes dangerous proportions, whereas with sevoflurane the effect is moderate and only appears clinically at concentrations above 1.5 MAC. Myocardial depression is induced by inhibition of the calcium flux through the voltage-dependent L-type calcium channels of the surface membrane and the membrane of the sarcoplasmic reticulum.

Table 18.4 Effects profile of sevoflurane

Mechanism of action	Pharmacodynamics	Pharmacokinetics	Benefits	Adverse reactions
Unspecific effects on excitable membranes	Hypnotic Minor analgesic effect Minor relaxant effect	Rapid onset of action (loss of consciousness) Rapid excretion (fast recovery from anesthesia)	Well controllable Cardioprotective	Nausea Vomiting Intracranial pressure increase at higher doses

Table 18.5 Cardiovascular effects of sevoflurane

Myocardial contractility	Blood pressure	CO	HR	Arrhythmia	Qp/Qs	Coronary artery perfusion
Dose-dependent negative inotropic effect, particularly in neonates and young infants (decrease in contractility by about 25% at 1 MAC)	Dose-dependent decrease in DAP by about 15% at 1 MAC and by about 20% at 1.5 MAC	Dose-dependent decrease in CO in children by 17% at 1 MAC and by 21% at 1.5 MAC	Rarely drop in HR	Ventricular arrhythmias only at very high concentrations No sensitization to catecholamines (as is known with other volatile anesthetics)	Decrease in pulmonary artery pressures and PVR	Dose-dependent decrease in coronary blood flow and myocardial O_2 consumption
Dose-dependent diastolic dysfunction	Decrease in MAP resulting from a reduction in SVR (direct effect on vascular smooth muscle cells), from an inhibition of the central sympathetic nervous system, and from direct negative inotropic effects	Decrease in myocardial O_2 consumption		Atrial or junctional arrhythmias in 10% of all children Junctional bradycardia <80/min common in children in the first year of life	No change in Qp/Qs ratio in children with biventricular morphology or left/right shunt	Coronary vasodilation with subsequent reduction in coronary vascular resistance No coronary steal effect

CO cardiac output, *DAP* diastolic arterial pressure, *HR* heart rate, *Qp/Qs* pulmonary to systemic blood flow ratio, *MAC* minimum alveolar concentration, *MAP* mean arterial pressure, *O_2* oxygen, *PVR* pulmonary vascular resistance, *SVR* systemic vascular resistance

18.9.2 Remifentanil

During surgery remifentanil is administered by continuous intravenous infusion at a dosage of 0.5–1.0 µg/kg/min in ultrafast-track anesthesia.

Remifentanil holds a special rank among opioids by virtue of its extreme potency and extraordinarily good controllability that resembles the behavior of an "on/off light switch." Its elimination takes place by extremely rapid- and organ-independent degradation of the molecule resulting from hydrolysis of the ester bond by ubiquitous nonspecific serum and tissue esterases. Thanks to its very rapid onset and equally immediate cessation of action and because it does not accumulate even after sustained infusions, remifentanil is particularly suited for abolishing neurohumoral stimuli during the surgical procedure whenever extubation is planned immediately after surgery. This rapid decline in effect, however, requires the overlapping addition of long-acting opioid analgesics in order to ensure effective postoperative pain suppression (see Table 18.6).

Opioids are characterized by their minor cardiovascular adverse effects and therefore are among the standard substances used in cardiac anesthesia. Most of the acute actions of opioids on the cardiovascular system can be attributed to three effects.

- Central sympathicolysis
- Central parasympathomimetic effect with increase in vagal tone
- Direct vasodilating effects

The effects of remifentanil on the cardiovascular system are summarized in detail in Table 18.7.

Tolerance, withdrawal symptoms or hyperalgesia can occur peracutely after just a single high-dose administration of remifentanil.

18.9.3 Dexmedetomidine

In ultrafast-track anesthesia, dexmedetomidine is initiated at a dosage of 1.0 µg/kg/h during anesthesia induction. The dosage is reduced to 0.2 µg/kg/h after a cumulative loading dose of 1.0 µg/kg has been reached. In children under 3 months of age, the infusion rate is reduced to 0.1 µg/kg/h after a cumulative loading dose of 0.5 µg/kg has been reached.

As a result of the rapid redistribution in tissue, dexmedetomidine is considerably more easily controlled than clonidine and the required depth of sedation can be achieved rapidly by adapting the infusion rate (see Table 18.8).

The effects and adverse effects of dexmedetomidine with respect to the different organs and organ systems are summarized in detail in Table 18.9.

In the ultrafast-track concept presented here, dexmedetomidine holds the key position among the pharmacological components despite its off-label use.

Table 18.6 Special features of remifentanil

Site of action	Mechanism of action	Potency	Kinetics	Positive	Negative
Highly selective μ-agonistic activity	Analgesia via μ_1 receptors	Analgesic effect 200 times stronger than that of morphine	Immediate onset of action	Switch-on/switch-off kinetics	Chest rigidity
To a much lesser extent agonistic at κ receptors	Respiratory depressant effect via μ_2 receptors	Mild sedation	Temperature-dependent ester hydrolysis = no dose adjustment except in neonates	Safe suppression of neurohumoral stress responses	Emergence delirium shortly after termination Psychotropic substance causing withdrawal symptoms after termination Rapid tolerance development Hyperalgesia after termination
No intrinsic activity at δ and σ receptors	Sedative via cortical κ receptors	Marked respiratory depression	Half-life 5–10 min No accumulation with hypothermia during cardiopulmonary bypass or following long-term infusion	Cessation of typical gastrointestinal opioid side effects (nausea and vomiting, opioid-induced obstipation, paralytic ileus, constriction of the sphincter of Oddi) immediately after termination of continuous infusion	
				No bronchoconstriction	Rapid development of tachyphylaxis

Table 18.7 Cardiovascular effects of remifentanil

Myocardial contractility	Blood pressure	Cardiac output	Heart rate	Coronary circulation
Slightly negatively inotropic	Moderate hypotension	Largely unaffected	Bradycardia	Balanced reduction of myocardial O_2 consumption and O_2 demand (adapted to minor drops in pressure and cardiac output and to a pronounced decline in heart rate)
Reduction in contractility following reduction in heart rate (Bowditch effect = force-frequency coupling)	Causes venous pooling (caveat: positioning)		Vagotonic Sympatholytic	
	Centrally mediated vagotonic			
	Centrally mediated sympatholytic			

Table 18.8 Dexmedetomidine: Memo

Site of action	Kinetics	Positive	Negative	Dose
Presynaptic α_2 receptors	Distribution half-life 6 min	Sympathicolysis	Initial increase in blood pressure	Children >6 mon nasally: 0.5 μg/kg (premedication)
Virtually no agonistic effects due to stimulation of peripheral α_1 receptors	Elimination half-life 2 h	Vagotonia	Drop in blood pressure and heart rate after a few minutes	Anesthesia induction 1.0 μg/kg/h
Inhibition of release of various neurotransmitters in the central nervous system: dopamine, serotonin, GABA, noradrenaline	Hepatic elimination (Caveat: liver function)	Well controllable		From loading dose of 1 μg/kg, reduction in flow rate to 0.2 μg/kg/h
	Renal impairment does not affect dosage			In infants younger than 3 months, loading dose of 0.5 μg/kg and thereafter flow rate of 0.1 μg/kg/h

GABA gamma-aminobutyric acid

Table 18.9 Profile of dexmedetomidine

	Effects	Adverse effects
CNS	Sedation without affecting the ability to cooperate	Hallucinations
	Anxiolysis	Nightmares
	Dose-dependent amnesic effect	Unreliable amnesia
	Co-analgesic effect (opioid-saving)	Awareness
	Delayed development of opioid tolerance	
	Antidelirium effect	
	Autonomic inhibition in withdrawal symptoms	
	Suppression of emergence delirium	
	Neuroprotection and rapid postoperative restoration of neurocognitive functions	
Hemodynamics	No negative inotropism	Symptomatic bradycardia
	Antiarrhythmic effect/suppression of junctional ectopic tachycardia	AV block
	Reduction of myocardial O_2 consumption	Sinus arrest
	Cardioprotection (increased resistance to ischemia and ischemia/reperfusion injury)	Vasodilation
	Depression of neurohumoral stress response to pain stimuli	Biphasic effect on blood pressure with increase initially and hypotension thereafter
	Bradycardia and fall in blood pressure usually very predictable	Decrease in cardiac output
Respiration	Bronchodilation	
	No respiratory depression, unchanged responsiveness of the medullary respiratory center to $PaCO_2$	
	No increase in respiratory depressant effect of opioids	
	Protective and defensive reflexes unaffected	
Gastrointestinal tract	Antiemetic effect	Dry mouth
		Increased thirst
		Constipation
		Delayed gastric emptying
Kidney	Increased urine output	Polyuria
	Increased renal blood flow	
	Increased glomerular filtration rate	
	Inhibition of ADH release	
Blood	Increased platelet aggregability	Increased risk of thromboembolism
	Reduced intraoperative blood losses	
Muscles	Reduction of postoperative shivering	Hypothermia
	Inhibition of opioid-induced muscle rigidity	
Endocrine system	Inhibition of stress hormone release (noradrenaline, adrenaline, ACTH, cortisol, etc.)	Hyperglycemia
	Inhibition of insulin release	Suppression of corticoadrenal function
	Inhibition of renin release	
	Inhibition of lipolysis	

ACTH adrenocorticotropic hormone, *ADH* antidiuretic hormone

Dexmedetomidine is successfully used preoperatively for anxiolysis; intraoperatively for suppression of neuroendocrine stress response, rapid restoration of neurocognitive functions, and initiation of early extubation; and postoperatively for adjustment of the required depth of sedation, analgesia, and delirium prophylaxis. The particular benefits consist of more stable hemodynamics, including the prevention of tachycardiac cardiac arrhythmias (*caveat***:** pacemaker-dependent bradycardia), a reduction in ventilation duration, lower total opioid doses and prevention and treatment of withdrawal symptoms, lower blood glucose and cortisol levels, and a reduced incidence of postoperative delirium.

Because of the delayed hepatic degradation in neonates, it is advisable to halve the dose in the first 2–4 weeks of life, whereas, after a Glenn anastomosis, for example, a slight increase in dosage is conversely indicated (25% because of systemic recirculation of the shunt volume including the liver). Dexmedetomidine and etomidate are chemically related to one another (imidazole derivatives). That explains why both substances suppress adrenocortical function. In the case of dexmedetomidine the effect is weak. However, combined use of the two substances could be harmful. There are to date no consistent data on the matter.

Overview of Medication for Anesthesia Maintenance
Sevoflurane:

- Vaporization of 0.5 MAC during the whole surgical operation
- Delivery of 0.5 MAC via the oxygenator during the cardiopulmonary bypass phase
- Cessation of delivery about 10 min before the end of surgery

Remifentanil:

- Intravenous infusion of 0.5 μg/kg/min during endotracheal intubation on induction with etomidate; after intubation, reduction of dosage to 0.15 μg/kg/min
- Continuous intravenous infusion of 0.15 μg/kg/min, starting about 10 min after intubation with induction by S-ketamine
- Increase in dosage to 0.5–1.0 μg/kg/min, starting about 5 min before skin incision until the start of skin suture

Dexmedetomidine:

- Start of continuous intravenous infusion at a dosage of 1.0 μg/kg/h during anesthesia induction
- Reduction of dosage from 1.0 μg/kg/h to 0.2 μg/kg/h after achievement of a cumulative loading dose of 1.0 μg/kg in children over 3 months of age
- Reduction of dosage from 1.0 μg/kg/h to 0.1 μg/kg/h after achievement of a cumulative loading dose of 0.5 μg/kg in children under 3 months of age

18.10 Intraoperative Coagulation Management

The need for blood transfusion can be reduced or even avoided by effective coagulation management. Blood transfusions increase morbidity and mortality in cardiac surgery because they are associated with many immunologically and nonimmunologically mediated complications, such as infections, hemolytic reactions, allergic reactions, transfusion-associated acute lung injury (TRALI), graft-versus-host reactions, and immunosuppression.

The procedures for coagulation management and transfusion strategy, which for the most part have been developed on an empirical basis, differ markedly between the various pediatric cardiac surgery centers. The ultrafast-track procedure presented here also includes an algorithm for the rapid restoration of coagulability following cardiopulmonary bypass:

18.10.1 Tranexamic Acid

Tranexamic acid has been demonstrated to reduce bleeding complications and hospital mortality more effectively than other antifibrinolytics such as aprotinin and ε-aminocaproic acid. The improved outcome is due not only to the effects on blood coagulation but also to the anti-inflammatory properties of tranexamic acid.

- At low plasma concentrations, tranexamic acid inhibits fibrinolysis by complexing with plasminogen.
- At intermediate concentrations, it also inhibits platelet activation (by tissue thromboplastin) and at high to very high concentrations it inhibits the intrinsic activation of thrombin (by factor XIIa).

Whether low, intermediate, or high drug levels should be aimed for in the prophylactic use of tranexamic acid continues to be the subject of research. However, high plasma levels of 150 µg/mL are associated with an unacceptably high risk of seizures and are therefore placed in parentheses in the dosage regimen proposed here, even though they have been shown to be more effective in adults with severe bleeding complications. The ultrafast-track protocol stipulates low plasma concentrations of 20 µg/kg for cardiopulmonary bypass procedures under normothermia or mild hypothermia and mean concentrations of 60 µg/mL for surgery under deep hypothermia and for all reoperations. As well as the type of procedure, the dosage regimen based on pharmacokinetic studies takes into account the priming volume of the heart-lung machine and the child's age, which is of vital importance for the plasma concentration-time curve as a function of the administered dose (see Table 18.10).

The pharmacokinetic properties of tranexamic acid alter rapidly, particularly in the first year of life, as a result of which a lower loading dose can be administered with increasing age for the age group of 2- to 12-month-old infants: Start with

Table 18.10 Plasma level-targeted dosing of tranexamic acid in certain age groups

	Low plasma levels (normothermia/ mild hypothermia) (20 µg/mL)	Mean plasma levels (deep hypothermia/revision surgery) (60 µg/mL)
0–2 months	Loading: 15 mg/kg	Loading: 50 mg/kg
	Infusion: 2.5 mg/kg/h	Infusion: 7 mg/kg/h
	HLM prime: 20 µg/mL prime volume	HLM prime: 60 µg/mL prime volume
2–12 months	Loading: 9 (6–12) mg/kg	Loading: 25 (20–30) mg/kg
	Infusion: 2 mg/kg/h	Infusion: 6 mg/kg/h
	HLM prime: 20 µg/mL prime volume	HLM prime: 60 µg/mL prime volume
> 12 months	Loading: 4 mg/kg	Loading: 13 mg/kg
	Infusion: 2 mg/kg/h	Infusion: 5.5 mg/kg/h
	HLM prime: 20 µg/mL prime volume	HLM prime: 60 µg/kg prime volume

HLM heart-lung machine

12 mg/kg at 2 months to 6 mg/kg at 12 months. The loading dose is always administered intravenously over about 5 min. Toward the end of anesthesia induction. A continuous infusion is then initiated. The infusion is continued until the end of surgery.

18.10.2 Coagulation Factor Concentrates

Following cardiac surgery with cardiopulmonary bypass, a hemostatic disorder that requires treatment frequently occurs as a result of blood loss, dilution and consumption coagulopathy, hyperfibrinolysis, thrombocytopenia, platelet function disorder, hypothermia, and excess citrate. It is a confirmed fact that transfusion rate and volume can be reduced by coagulation factor concentrates. The high effectiveness of fibrinogen concentrate compared with fresh frozen plasma in the treatment of bleeding complications after cardiopulmonary bypass is demonstrated not only in adults but now also in children undergoing cardiac surgery. Four-factor prothrombin complex concentrates (PPSB), which contain the vitamin K-dependent coagulation factors prothrombin (factor II), proconvertin (factor VII), Stuart-Prower factor (factor X), and antihemophilic factor B (factor IX), are known to optimize the generation of thrombin in neonatal plasma after cardiopulmonary bypass, to contribute effectively to hemostasis, and to represent a reliable treatment option for persistent bleeding losses, although they have rarely been used to date in children. Under the ultrafast-track protocol, all children who have undergone a procedure under deep hypothermia or reoperations receive fibrinogen and PPSB without further previous diagnostic studies once the heparin effect has been antagonized by protamine. The escalation regimen, which is based on a literature search and our own experience, provides specifically for the following procedure:

Antagonism of Heparin

- Administration of protamine over a period of 5 min
- Administration of protamine in a ratio of 1:1 to the total heparin dose
- Monitoring of activated clotting time (ACT)
- With higher values than before cardiopulmonary bypass, repeat protamine dose where necessary

→ In the case of interventions under deep hypothermia with reoperations and in cases with a persistent clinical bleeding tendency, antagonism of heparin as described and in addition.

Coagulation Factor Concentrates

- Without prior diagnostic investigations
- Fibrinogen 50 mg/kg over a period of 5 min
- Four-factor prothrombin complex concentrate 30 IU/kg over a period of 5 min

Platelet Concentrate

- Without prior diagnostic investigations
- From automatic platelet apheresis
- Initially 5 ml/kg
- Where necessary, repeat dose of 5 mL/kg

→ In the event that bleeding persists

Point-of-Care Testing (POCT)

- Rotational thromboelastometry (ROTEM®)
- Impedance aggregometry (Multiplate®)
- Targeted replacement of platelets, fibrinogen, PPSB, fresh frozen plasma, antifibrinolytics, and protamine on the basis of analytical results

→ With ever-persistent bleeding – extremely rarely

Rescue Therapy

- Recombinant activated factor VII (factor VIIa concentrate, Novoseven®)
- Initially 90 μg/kg
- Where necessary, repeat dose of 90 μg/kg after 2 h

The flanking supportive measures in coagulopathic bleeding include normothermia, calcium levels in the high normal range, normal pH values and hematocrit levels over 30%. The principle of "platelets first" that normally applies in pediatric

cardiac surgery after procedures under deep hypothermia is reversed in the escalation plan to "coagulation factors first." It has been shown empirically that there is only rarely now a need to resort to platelet transfusion if fibrinogen and PPSB are administered initially. The establishment of a strict indication for platelet concentrates enables not only costs to be saved but also infectious complications to be avoided. Fresh frozen plasma is used only very rarely. In contrast to other protocols, intraoperative POCT is considered only if a diffuse bleeding tendency still persists clinically after fibrinogen, PPSB and an initial administration of platelets. This is extremely rarely the case. As POCT results are not available until after 15 min at the earliest, the outlined approach will save time.

An escalation regimen as described here has not yet been reported in the literature. In particular, administration of PPSB is not widely used in congenital heart surgery. Our experience over several years in numerous interventions has demonstrated that the regimen is very safe and extraordinarily effective. Thrombotic complications have yet to been noted. Only once has a factor VIIa concentrate been resorted to.

18.10.3 Extracorporeal Circulation

The use of extracorporeal circulation is accompanied by considerable adverse effects, such as hypothermia, full heparinization, nonpulsatile blood flow, hemolysis, or platelet degranulation and aggregation. Contact of the blood with nonepithelial surfaces and ischemia-reperfusion processes trigger activation of the coagulation and fibrinolysis cascades, the complement system, and complex immunological mechanisms. The different processes are interlinked and culminate as a common endpoint in the release of a number of pro-inflammatory mediator substances that induce a systemic inflammatory response syndrome (SIRS). SIRS is a major contributor to morbidity and mortality in cardiac surgery.

A reduction of the inflammatory reaction (SIRS; see also Chap. 10) is naturally of considerable importance in the context of fast tracking. The established measures for attenuating the postperfusion syndrome are firstly implemented in the technical design of the system for extracorporeal circulation and secondly are borne in mind in the conduct of the cardiopulmonary bypass. The details are given in the following list.

Cardiopulmonary Bypass

- Roller pump
- Pump flow of 2.4 L/min/m^2 even under hypothermic conditions
- Hollow-fiber oxygenator
  - Quadrox NEO® with $^1/_4$ inch tube system with flow rates of up to 1.5 L/min
  - Quadrox PAED® with $^1/_4$ inch tube system with flow rates of 1.5–2.8 L/min
  - Quadrox Small Adult® with $^3/_8$ inch tube system with flow rates of 2.8–4.5 L/min

- Prime volume of the system for neonates and infants is 250 mL
- Prime volume of the system for neonates and infants including ultrafilter is 330 mL
- Composition of the prime volume
  - Balanced crystalloid solution 150 mL
  - Human albumin 5% 250 mL
  - Mannitol 15% 3 mL/kg
- Adding packed red blood cells to the prime volume in case of a calculated reduction in hematocrit to less than 24% after connecting the child's circulation to the heart-lung machine
- Balanced ultrafiltration during cardiopulmonary bypass for quantitative removal of the volume of cardioplegia and for hemoconcentration with the aim of an equilibrated crystalloid fluid balance
- Antegrade crystalloid cardioplegia; Bretschneider Custodiol 30 ml/kg
- pH-stat regulation of the acid-base balance up to a temperature of 30 °C, α-stat regulation at temperatures <30 °C

Techniques for selective antegrade or retrograde cerebral perfusion are not used, as they do not yield any improvement in the neurological outcome and are associated with a higher rate of thromboembolic cerebral infarcts. Where duly indicated, surgery is instead performed under deep hypothermic circulatory arrest at core body temperatures of between 18 and 20 °C.

18.10.4 Emergence from Anesthesia

As remifentanil is eliminated within a few minutes, it is necessary to switch to an alternative pain therapy in good time before the continuous remifentanil infusion is stopped. This involves the use of a multimodal strategy aimed at combining the analgesic effects of a long-acting opioid, a nonsteroidal anti-inflammatory drug, and dexmedetomidine.

Pain Treatment Concept for Switching from Remifentanil
Long-acting opioid:

- Piritramide 0.1 mg/kg intravenously before the end of extracorporeal circulation

Nonopioid analgesic:

- Metamizole 20 mg/kg intravenously before the end of extracorporeal circulation

Co-analgesia:

- Dexmedetomidine 0.1–1.5 μg/kg/h intravenously depending on the degree of sedation

Piritramide is preferred to morphine as an opioid, as it has a relatively greater sedative effect.

The continuous remifentanil infusion is stopped on the start of subcutaneous suturing. With a skin suture, the delivery of sevoflurane is also stopped. The ventilator is switched to an assisted spontaneous ventilation mode with inspiratory pressure support of 10 cm H_2O and PEEP of 5 cm H_2O. Sufficient spontaneous respiration usually becomes established within a few minutes. Extubation occurs before the child is transferred from the operating table to the incubator or the intensive care bed.

After sevoflurane and/or remifentanil, unfocused states of agitation (emergence delirium) can occur that jeopardize hemodynamic stability. Emergence delirium is treated consistently according to a well-defined staged plan.

Step Plan for the Treatment of Emergence Delirium
Piritramide:

- Bolus administration of 0.025–0.05 mg/kg intravenously in case of tachypnea and clinical signs of incomplete analgesia

Dexmedetomidine:

- Bolus administration of 0.1–0.25 μg/kg intravenously over 30 s for severe unfocused agitation
- Continuous infusion of 1–1.5 μg/kg/h intravenously for states of restlessness and uncooperativeness

Propofol:

- Bolus administration of 0.1–0.5 mg/kg as rescue medication for difficult-to-control emergence delirium

Midazolam:

- Bolus administration of 0.05–0.1 mg/kg intravenously as rescue medication

If the child is sleeping peacefully and pain-free, they are transferred from the operating table and transported to the pediatric ICU. During transport and the first hours after extubation, it is particularly important to continuously record end expiratory CO_2 partial pressure. Special nasal cannulas are available for the purpose. These nasal cannulas have a separate prong for each nostril. Oxygen is delivered via one of the prongs, while the second serves for capnographic recording of the carbon dioxide concentration in the expired breathing gas.

On the child's arrival on the pediatric ICU, its handover to the intensive care team is documented in a structured report. This involves a detailed report by the pediatric cardiac surgeons of the type and outcome of the surgical procedure and any conclusions that can be drawn from this for the subsequent treatment. The

cardiac anesthetist summarizes the course of the anesthesia and describes the current functional status of the vital organs. As it is well known that the causes of medical errors and fatal losses of information are frequently to be found in patient handovers, the handover process follows a defined protocol. The whole surgical team remains together until the handover is completed and does not leave the pediatric ICU until there are no further questions and cardiorespiratory stability is present.

Conclusion

Fast tracking only works if the surgical procedure proceeds rapidly and precisely and the preoperative treatment plan is followed closely in terms of a successful surgery. There is no point in extubating on the operating table after complex surgery in a neonate, only to have to reintubate 2 h later because of a complication. The essential prerequisite for fast tracking is therefore a surgical procedure that leaves behind no significant functional or anatomical lesions and does not engender any foreseeable acute complications. For this reason it is also understandable why the time of extubation is starting to become a significant internal and external assessment criterion in cardiac surgery and especially in pediatric cardiac surgery.

Fast tracking combines economic benefits with a striving for continuous improvement of the patient outcome. If fast tracking were burdened with more complications than the traditional approach, the costs would offset the theoretical potential savings. Fast tracking therefore has incorporated its own built-in counterbalance.

Alongside its economic rationale, fast tracking has now also been attested with a good physiological justification. Modern substances allow complete suppression of the neurohumoral response during surgery without necessarily precluding prompt awakening and adequate spontaneous respiration at the end of the procedure. Nowadays there are many conceivable anesthetic techniques that circumvent the previous incompatibility of stress protection and early restoration of physiologic organ functions. In conclusion, this chapter has mapped out a feasible path and, above all, one that is easily learned in the multidisciplinary team. As practice and familiarity increasingly grow, fast tracking can develop into one of many building blocks for improving outcomes in pediatric cardiac surgery.

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Drug List

19

Josef Thul and Dietrich Klauwer

Chapter 19 presents a list of 111 substances administered in treatment of pediatric cardiac intensive care patients. Relevant pharmacokinetic and pharmacodynamic details are given for the categories active compound, drug name, efficacy, adverse drug reactions (ADR), indications, contraindications and recommended dosage. Additional tables provide more specifics on the subjects of beta-blockers, nausea, and phenprocoumon.

The drug list below (Table 19.1) does not claim to be exhaustive. Many of the products are not licensed for pediatrics or the cited indication (off-label). Irrespective of potential differences in pharmacokinetics and pharmacodynamics, many recommendations are oriented on the adult dosages. Exemplary instructions for adjusting dosages in patients with renal impairment or undergoing dialysis can be found [in German] at www.dosing.de or www.uniklinik-ulm.de/arzneimitteldosierung or (in English) at "Pediatric Drug Book-Kidney Disease Program" (https://kdpnet.kdp.louisville.edu/drugbook/pediatric/) or at http://www.globalrph.com/renaldosing2.htm. Recommended reading on questions concerning any potential hepatotoxicity of certain compounds can be found at https://livertox.nih.gov. The memory chart on beta-blockers in Table 19.2 containes a list of selective and nonselective beta-blockers both with and without intrinsic sympathomimetic activity (ISA). An annotated overview of anti-nausea drugs is presented in Table 19.3. The key clinical and pharmacological particulars of the anticoagulant phenprocoumon are summarized in Table 19.4.

J. Thul (✉)
Pediatric Intensive Care Unit, Pediatric Heart Center of Giessen, Children's Heart Transplantation Center, UKGM GmbH, Giessen, Germany
e-mail: josef.m.thul@paediat.med.uni-giessen.de

D. Klauwer
Department of Pediatrics, Singen Medical Center, Gesundheitsverbund Landkreis Konstanz, Krankenhausbetriebsgesellschaft Hegau-Bodensee-Klinikum, Singen, Germany

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D. Klauwer et al. (eds.), *A Practical Handbook on Pediatric Cardiac Intensive Care Therapy*, https://doi.org/10.1007/978-3-319-92441-0_19

Table 19.1 Drug list

Active compound	Trade name (German)	Pharmacological action	Adverse drug reactions	Indications/ contraindications	Dosage
Acetylcysteine	ACC Bromuc Fluimucil	Cleaves disulfide bonds	Allergic or gastrointestinal effects unusual	Reduction of mucous viscosity during mechanical ventilation, hepatoprotective action (high dose), paracetamol poisoning	10 mg/kg t.i.d.i.v.; 40 mg/kg t.i.d. in hepatopathy, 300 mg/kg in 20 h in PCT – poisoning
Acetylsalicylic acid (ASA)	Aspirin	Analgesic, anti-inflammatory, platelet aggregation inhibiting	Bleeding tendency, ulcers, hyperuricemia, acidosis (intoxication), asthma, PDA closure, Reye's syndrome	Antipyresis, Kawasaki's syndrome (acute/ long-term therapy), platelet aggregation inhibiting/caveat: ideally, discontinue or replace 10 days prior to surgery (life span of platelets is approx. 8 days)	Antipyretic 10–15 mg/kg i.v. (max. 100 mg/kg/d), Kawasaki's syndrome –100 mg/kg/d for 14 days, thereafter 5 mg/kg/d for 3 months; inhibition of platelet aggregation – 2–4 mg/kg/d orally; "ASA resistance": prevalence 30% (diagnostic challenge)
Adenosine	Adrekar	Ion channel blocker, slow Ca inflow ↓, AV blockade	Vasodilatation, bronchospasm, nausea caveat: AV block (external pacemaker available?), arrhythmia induction	Paroxysmal re-entry SVT with AV node involvement, diagnostic: e.g. unmaskes atrial flutter	0.1–0.3 mg/kg (rapid bolus)
Alprostadil prostaglandin E1	Minprog	Prostaglandin E1 receptor agonist	Hypotension, apneas, hyperirritability, temperature ↑↓, bleeding tendency	Keep a PDA open; lowering of PVR/caveat: in cases of profuse bleeding (inhibits platelet aggregation)	5–50 ng/kg/min; supportive: acetylcysteine; look for lowest effective dose; consider blood pressure above and below in PDA-dependent systemic perfusion

Alteplase r-tPA	Actilyse	Plasminogen activation (at the thrombus site), fibrinolysis	Induction of bleeding, allergic reactions	Impending loss of limbs/ loss of organs, severe embolic cerebral infarction (signed parental consent)/ *not* in status postoperative surgery, status post cerebral hemorrhage coumarin therapy, status post vascular punctures at non-compressible sites	0.5 mg/kg/h over 6 h or 0.1–0.2 mg/kg bolus in 2 min, followed by 0.05–0.1 mg/kg/h over 24 h; in life-threatening thrombosis: 0.2 mg/kg as a bolus followed by 0.8 mg/kg over 2 h; always simultaneously with heparin; partial thromboplastin time > 40 s (if appropriate, ascertain plasminogen level or combine with FFP)
Amiodarone	Cordarex	Class III antiarrhythmic agent, anti-adrenergic, delay of action potential and effective refractory period of atrium and ventricle; sinus and atrioventricular node functions ↓	Hypotension, blocks, myocardial depression, hyper−/ hypothyroidism, fibrosis of the lungs, liver toxicity, visual disorders, blood count and coagulation disorders; interactions: digitalis, antiarrhythmic agents, phenprocoumon, and phenytoin (among others)	SVT and VT as well as JET; prior to long-term therapy: Ophthalmologist, check lung function, thyroid function, and metabolic status	In ventricular tachycardia (VT): 5 mg/kg bolus; in pulseless ventricular tachycardia, begin with defibrillation, if appropriate, bolus prior to repeated cardioversion and/or defibrillation; in JET, begin with 10–20–30 mg/kg/d; under PM therapy always monitor sinus nodes and natural frequency; oral: ascertain the minimum effective dose (1–8 mg/kg/d, 1 single dose/d)

(continued)

Table 19.1 (continued)

Active compound	Trade name (German)	Pharmacological action	Adverse drug reactions	Indications/ contraindications	Dosage
Amlodipine	Norvasc	Calcium channel blocker (calcium antagonist), direct action on the vascular smooth muscle cells, improves coronary perfusion, has little effect on the cardiac conduction system	Drop in blood pressure, flushing, palpitations, fatigue, nausea, changes in blood count; caveat: in postcapillary pulmonary arterial hypertension, there is a risk of pulmonary edema	Hypertension – effective on the pulmonary vascular bed	0.05–0.15 mg/kg/d (increase every 5 days) up to 0.5 mg/kg/d
Antithymocyte globulin (ATG)	ATG Grafalon Thymoglobulin	Antithymocyte antibody (rabbit), ATG has a cytotoxic effect (primarily) against T-lymphocytes	Fever, chills, gastrointestinal complaints; monitor blood count, kidneys, circulation	Early postoperative rejection prophylaxis (induction); treatment of acute, severe rejection episodes	2–5 mg/kg over 2–4 h - dosage according to lymphocyte-platelet count; beforehand: dimethindene, paracetamol, steroid bolus
Argatroban	Argatra	Direct thrombin inhibitor	Bleeding; caveat: reduction of dosage in liver function disorders; no specific antidote – if appropriate, F VII a	HIT II (approved by pos. HIPAA test), ECLS, CRRT	0.5–2 µg/kg/min, PTT target: 1.5 to 2 times baseline PTT (steady state after 1–3 h)
Atenolol	Tenormin	β1 Selective blocker with a long half-life (6 h)	Bradycardia, hypotension, cardiac output ↓, asthma, detrimental to metabolic syndrome; caveat: combining with digitalis and calcium antagonists	Hypercontractile heart failure, myocardial hypertrophy, hypertension, congestive heart failure; protective against ventricular extrasystole and ventricular tachycardia	0.3–1 mg/kg/day p.o. in 2 single doses

Atropine	Atropin	Parasympatholytic	Tachycardia, dilatation of bronchi and pupils, saliva, and sweat ↓	As an antidote in toxicity with parasympathomimetics; have atropine ready in the event of succinylcholine intubation	10 µg/kg i.v., less than 50 µg/ single dose is not appropriate
Azathioprine	Imurek	DNA and RNA synthesis ↓ – especially of B lymphocytes	Liver and kidney function disorders, changes in blood count; monitor: blood count (diff), creatinine, bilirubin, transaminases, protein, coagulation, infections (fungus), gastrointestinal side effects	Immunosuppression, additive to CsA/TAC/ unsuitable for combination with angiotensin-converting enzyme inhibitors; interaction with several medications	Initially 2–3 mg/kg, later 1–2 mg/kg p.o.; i.v., 0.5–1 mg/kg, titrate the dosage according to monocytes and lymphocytes (Chap. 17)
Basiliximab	Simulect	Anti-interleukin-2 (IL-2) receptor antibody/ Anti-CD25+ lymphocytes	Allergic reactions, bradydysrhythmia, susceptibility to infection ↑	Before and after HTx in presumed elevated rejection risk (previous transfusions, implantation of VAD, surgeries, HLA antibodies)	First dose within 2 h prior to HTx, < 35 kg BW –10 mg, > 35 kg BW – 20 mg; second dose on the fourth postoperative day
Bisoprolol	Concor	β1 Selective blocker with long half-life (10 h)	Bradycardia, hypotension, dizziness, bronchospasm, hypoglycemia or hyperglycemia	Congestive heart failure, supraventricular tachycardia	0.1–0.3 mg/kg/day p.o. (1 single dose)

(continued)

Table 19.1 (continued)

Active compound	Trade name (German)	Pharmacological action	Adverse drug reactions	Indications/ contraindications	Dosage
Bosentan	Tracleer	Endothelium-1 antagonist	Hypotension, increase in transaminases, interaction with e.g., CsA	Pulmonary arterial hypertension; anti-remodeling properties suspected	2–3 mg/kg/d in 2 single dose p.o.
Butylscopolamine	Buscopan	Parasympatholytic	Sweating ↓, tachycardia, dryness of the mouth	Colic-like visceral problems	0.3 – 0.5 mg/kg/single dose i.v. or orally (hardly any resorption) max. 3 ×/day
Captopril	Lopirin	Angiotensin-converting enzyme (ACE) inhibitor, lowers peripheral resistance, increases venous capacity preload ↓, afterload ↓↓	Cough, allergy, hypotension, salt deficiency, few instances of reflex tachycardia; caveat: hyperkalemia	Hypotension, heart failure/never given in obstructive cause for heart failure (valvular stenosis, hypertrophic obstructive cardiomyopathy); never administer in bilateral renal artery stenosis	2–3 single doses infants: 0.1–0.5–1 mg/kg/d; small children: 1–5 mg/kg/d; adults: 12.5–100 mg/d, always administer utilizing low starting doses with a schedule of slow up-titration!
Carvedilol	Dilatrend	α1- and β-blocker	Hypotension, bradycardia (up to AV block), hyperglycemia, bronchial obstruction, orthostasis	Congestive heart failure – alternative or additive to angiotensin-converting enzyme inhibitors	0.1–0.8 mg/kg/d p.o. in 2 single doses, in good tolerance, double every 2 weeks; reduction in liver function disorders
Clonazepam	Rivotril	Benzodiazepine (GABAergic)	Drop in blood pressure and respiratory depression as with benzodiazepine	Anticonvulsant, status epilepticus	0.1–0.2–0.5 mg/kg i.v. per single dose depending on the patient height; 1–2 repeat administrations; reckon with respiratory depression in neonates

Clonidine	Catapresan, Paracefan	α2-agonist, central sympathicolysis, partial morphine agonist	Drop in blood pressure, drop in heart rate, drop in cardiac output, atrioventricular (AV) block, optimize volume status in advance, can cause withdrawal effects on its own	Sedation, heart rate control, drug withdrawal (analgesia); at optimized heart rate, cardiac output can be improved by increasing stroke volume	Single dose (anesthetic induction): 4–5 μg/kg i.v.; sedation 0.5–1–2–3 μg/kg/h (low initial dose and slow up-titration); for tapering off: divide the i.v. dose into 6 individual oral daily doses, reduced every 2–3 days
Clopidogrel	Plavix	Adenosine diphosphate (ADP)-dependent platelet adhesion and aggregation inhibition	Bleeding, ulcers; do not administer with macrolides, rifampicin, thrombolytics, statins	In combination with ASA in Kawasaki's syndrome and with major coronary aneurisms; in stenotic aortopulm, shunts, PDA stent and in Berlin Heart®	0.2–1 mg/kg/day (1–2 single dose) monitored by TEG or Multiplate analyzer
Chloralhydrate	Chloralhydrate	Mechanism of action unknown	Nausea, sensitized to catecholamine-induced arrhythmias, uncertain duration of action and strength	Sedation caveat: while using catecholamines, not in liver damage	30 mg/kg/single dose; can be repeated once or twice duration of action cannot be predicted

(continued)

Table 19.1 (continued)

Active compound	Trade name (German)	Pharmacological action	Adverse drug reactions	Indications/ contraindications	Dosage
Cyclosporin A (CsA)	Sandimmune	IL-2 transcription inhibitor, calcineurin inhibitor	Anuria with hyperkalemia, arterial hypertension, nephrotoxicity, neurological complaints (tremors, seizures), gingival hyperplasia, impaired liver function; development of lymphomas, hirsutism. In uncertain drug interactions, please always check these, since there are several interactions; frequently: macrolides, anticonvulsants, NSAIDs, and conazole fungicides, among others	After (H)Tx, cannot be dialyzed in intoxication	Before HTx: 1 × 5 mg/kg orally or 0.1 mg/kg/h as CID –start with explantation of the donor heart, up to start of bypass; after Tx: (0.5-) 2 mg/kg/day as CID – depending on diuresis and target level, 250–300 ng/ml during the first week, thereafter approx. 200 ng/ml, in the long term 100–150 ng/ml (blood level test prior to the next dose); oral conversion, stop CID about 2 h before first p.o. administration; as a rule, start with 20 mg/kg/d in 3 single doses (up to 3 yr) or 2 single doses
Desmopressin DDAVP	Minirin	Vasopressin	Overdosage: syndrome of inappropriate antidiuretic hormone secretion (hyponatremia cerebral edema)	1. Increase of the VIII activity and the vWF concentration 2. Diabetes insipidus	1. 0.3 µg/kg short infusion (once only, since vWF reservoir is empty thereafter) 2. 0.4–1 µg/kg i.v./i.m. in 1–2 single doses or by nasal administration

Dexmedetomidine	Precedex	Clonidine derivative	In comparison to clonidine, less vasodilation, stronger sedative effect, lower bradycardia induction	Sedation; withdrawal from opiate addiction	Short-term sedation, 0.5–1 μg/kg in 10 min; CID, 1–3 μg/kg/h
Diazepam	Diazepam	Benzodiazepine (GABAergic)	Hypopnea, arterial hypotension (primarily in volume deficiency), accumulation risk	Sedation, anxiolysis, anterograde amnesia, withdrawal therapy for drugs (alcohol); anticonvulsive; "softener" prior to extubation/ potentially, paradox reaction in trisomy 21 – patients	0.1–0.2 mg/kg/single dose, onset of action 2–4 min., duration of action: a few hours
Digoxin	Lanicor Lanitop	Cardiac glycoside, inhibition of the Na/K adenosine triphosphatase (ATPase), Ca ↑ intracytoplasmatic; parasympathomimetic effect up to the atrioventricular nodes	Never in hypokalemia, caveat: renal failure, drug level increased by drug interaction; not in ventricular outflow stenosis	Sinus tachycardia, congestive heart failure (no longer the first choice); chronic atrial fibrillation blood level: 0.9–2 ng/ml	1 drop = 0.013 mg methyldigoxin; neonates saturation dose, 0.03 mg/kg/d in 3 single doses; maintenance, 0.005 mg/kg/d in 1–2 single dose; infants – saturation, 0.04 mg/kg/d in 3 single doses; maintenance, 0.01 mg/kg/d in 2 single doses; children – saturation, 1 mg/m^2 of total body surface/d; maintenance, 0.2 mg/m^2 of total body surface/d

(continued)

Table 19.1 (continued)

Active compound	Trade name (German)	Pharmacological action	Adverse drug reactions	Indications/ contraindications	Dosage
Diltiazem	Dilzem	Ca antagonist with medium strength effectiveness on the conductive system	AV blocks, post-cap. Pulmonary hypertension (PHD) and severe heart failure (reduction of ability to contract), monitoring lung edemas and liver values caveat: combining with beta-blockers and digitalis	Antihypertensive (primarily pulmonary); for slowing down of AV transition in SVT, atrial fibrillation/flutter	0.5 mg/kg/t.i.d.p.o. increase every 5 days; i.v., 0.15–0.45 mg/kg bolus; CID: 2 µg/kg/min
Dimethindene	Fenistil	Antihistamine	Somnolence, anticholinergic	Allergic reaction, anaphylaxis	i.v.: 0.1 mg/kg
Dimenhydrinate	Vomex	Antiemetic	Central, competitive H_1 receptor blocker	Nausea, vomiting	i.v. 0.5–1–2 mg/kg/single dose every 8 h; suppository, < 6 yr., 40 mg; > 6 yr., 70 mg; adolesc,150 mg
Disopyramide	Rytmodul	Class 1a antiarrhythmic	AV blockade, extension of QT	SVT – atrial ectopic	i.v. bolus 2 mg/kg as a short infusion; CID, 0,4 mg/kg/h; orally <2 years, 20–30 mg/kg/d; > 10 yr., 5–10 mg/kg/d
Dipyridamole	Persantin	Inhibition of ADP dependent adhesion and aggregation of thrombocytes; vasodilatation	Bleeding, hypotension, rare bronchospasm, arrhythmia, combination with other anticoagulants only under close monitoring	Long-term anticoagulation - in Berlin Heart®, - after valve replacement	2–4–6 mg/kg/day (4 single doses) monitor by TEG (reduction of the MA to <50%) or Multiplate analysis

Dobutamine	Dobutrex	Synthetic β1+ β2 agonist	Tachycardiac arrhythmia	Right heart failure, bradycardia	CID: 1–20 µg/kg/min
Dopamine	Dopamine	Depending upon dosage: dopa < beta < alpha	Increase of afterload → O_2 consumption↑ caveat: poor heart function; prolactin↓, arrhythmia (tachycardia)	Low dose: vasodilatation (heart/head/kidney); medium dose (5 µg/kg/min): CO ↑, contractility↑, blood pressure (RR) ↑; high doses, as for noradrenaline	2.5–5–20 µg/kg/min high doses have the same effect as noradrenaline (stronger tendency to arrhythmias); "kidney dose": controversial
Dronabinol	Marinol	Tetrahydrocannabinol (THC/Cannabis)	Sympathomimetic, psychotropic	Analgesic, nausea, anorexia	Starting does 0.1–0.25 mg/kg/d, increase according to its effect
Enalapril	Xanef	ACE inhibitor, lowers peripheral resistance, increases venous capacity (preload ↓, afterload ↓↓) caveat: hyperkalemia	Cough, allergy, hypotension, salt deficiency, rarely reflex tachycardia	In hypotension and heart failure/ never in obstructive causes of heart failure (valve stenosis hypertrophic obstructive cardiomyopathy) never in bilateral renal artery stenosis	p.o. 0.05 mg/kg in 2 single doses (low initial doses with slow up-titration)

(continued)

Table 19.1 (continued)

Active compound	Trade name (German)	Pharmacological action	Adverse drug reactions	Indications/ contraindications	Dosage
Enoxaparin	Clexane	Low-molecular heparin			Subcutaneous (s.c.) therapy: 1 mg/kg every 12 h Anti-Xa after 4 h: 0.5–1.0 IU/ml a) < 2 months: 1.5 mg/kg/dose every 12 h – max. 3.0 mg/kg/dose b) > 2 months: 1.0 mg/kg/dose every 12 h – max. 2,0 mg/kg/dose; prophylaxis: a) < 2 months: –0.75 mg/kg/dose every 12 h b) > 2 mo – 0.5 mg/kg/dose every 12 h neonates: preferably higher doses
Epoprostenol	Flolan	Vasodilatation especially in pulmonary arteries; inhibition of platelet aggregation; half-life: about 6 min	Drop in blood pressure, tendency to bleed; mismatch in state of dystelectasis	PHT – long-term therapy with pump; heparin-induced HIT for anticoagulation	5–20 ng/kg/min > > 20 ng/kg/min in long-term therapy
Esmolol	Brevibloc	Selective β1-blocker with rapid onset of action and short duration of action	Bradycardia (block), bronchial obstruction, hyperglycemia, concealing hypoglycemia symptoms, deterioration of heart failure, constipation; caveat: combination with digitalis and Ca antagonists + amiodarone	Heart failure primarily with impaired ventricle relaxation, tachycardia, outlet obstruction, hyperdynamic tachycardia, hypertension; improved cardiac output by lowering heart rate; possibly combination with noradrenaline/caveat: combination with digitalis/Ca antagonists	10–25–200 µg/kg/min following bolus 500 µg/kg over 1 min Possibly clonidine preferable in the postop. period: heart rate reduction in (almost) stable cardiac output

Ethacrynic acid	Reomax	Loop diuretic, inhibits Na/Cl resorption in the ascending part of the loop of Henle, additive to Lasix	Hypokalemia, hypocalcaemia, hypomagnesemia, hyponatremia, hypovolemia, met. alc alosis, vit. K antagonist's effect strengthened, glucose tolerance ↓	Support of furosemide therapy; prevention of dialysis; reserve diuretic	1–2–3 mg/kg/d i.v. 1–3 doses (authors' empirical experience)
Etomidate	Etomidate-Lipuro, Hypnomidate	GABAergic, especially at the brain stem, not analgesic, good cardiovascular stability, cerebral perfusion pressure is maintained, ICP decreases	Vomiting, myoclonic twitches initially, relatively little hypoventilation, adrenocortical insufficiency, pain due to injection	Intubation of unstable patients, short anesthesia (onset of action. 10 s, end 10 min); can be combined well, e.g., with an opioid	0.2–0.4 mg/kg/single dose; CID:5–8 µg/kg/min for short anesthesia, not usable for longer duration anesthesia due to risk of adrenocortical insufficiency
Everolimus	Certican	m-TOR inhibitor, antiproliferative	Wound healing disorder, hyperlipidemia, pneumonitis, kidney failure (among others)	After HTx with CsA or TAC in reduced doses for prophylaxis of kidney failure; after posttransplant lymphoproliferative disease; reportedly beneficial in transplant vasculopathy	2 × 0.05 mg/kg/d starting dose; trough level, 4–8 ng/ml interactions: among others, CsA elevates everolimus levels; dose adjustment in hepatic dysfunction

(continued)

Table 19.1 (continued)

Active compound	Trade name (German)	Pharmacological action	Adverse drug reactions	Indications/ contraindications	Dosage
Flecainide	Tambocor	Class Ic antiarrhythmic, no influence on duration of action potential, extremely low therapeutic breadth	Myocardial depression, poor heart function, blocks; do not administer in kidney or liver disorders or hepatic dysfunction; monitoring of blood count (BB), liver, and kidney values as well as blood level	Supraventricular tachycardia arrhythmia (at the first atrial ectopic tachycardia) ventricular tachycardia arrhythmias/ flecainide intoxication: sodium bicarbonate infusion	po, 3–6 mg/kg/d in 3 single doses, up to a max. 8 mg/kg/d (increase every 4–5 days); i.v., 0.5 mg/kg short infusion repeat after 10 min CID, 0.2–0.5 mg/kg/h
Fludrocortisone	Astonin-H	Mineral corticosteroid			p.o. 0.005 mg/kg/d; long-term therapy: 0.001–0.002 mg/kg/d
Furosemide	Lasix	Loop diuretic, inhibits Na/Cl resorption in ascending part of the loop of Henle	Hypokalemia, hypocalcaemia, hypomagnesemia, hyponatremia, hypovolemia, met. alc alosis; not so effective in combination with NSAIDs; effect of vit. K antag. may increase, glucose tolerance ↓	Postoperative diuresis induction, congestive heart failure, renal failure, hyperkalemia/ caveat: hypokalemia and digitalis	i.v., 0.2–0.5–5 mg/kg/single dose up to 6 times/d CID: 6–(10) mg/kg/d; duration of oral action 6 h i.v.: duration of action 2–3 h; CID must be administered alone!
GHB, gamma-hydroxybutyrate	Somsanit Xyerem	Progenitor of endogenous neurotransmitter, GABAergic; no respiratory depression	Narcolepsy	Anesthesia, continuous sedation	10–20 mg/kg/h CID

Glucose-insulin				Hyperkalemia	15 IU regular – insulin + in 100 ml G 40%; CID, 3 ml/kg/h; if necessary: bolus, 1 ml/kg
Glyceryl trinitrate	Nitrolingual Perlinganit	Vascular NO donator, venous pooling	Hypotension, reflex tachycardia, headaches, methemoglobin (HB) formation, tachyphylaxis; do not administer in obstructive heart diseases (AST, MST, HOCM), do not administer in elevated ICP	Primary preload ↓, improved peripheral microcirculation, particularly coronary, surgery: improved coronary perfusion	Neonates (e.g., TGA) 0.1–2 µg/kg/min, older, 0.5–1 µg/kg/min, always titrate
Glycopyronium bromide	Robinul 1 ml = 200 µg	Synthetic anticholinergic agent (hardly central action)	Anticholinergic, mouth dryness, tachycardia, mydriasis, vomiting	In pharyngeal/bronchial hypersecretion; avoidance of complication by vagal stimulation; antidote against physostigmine/neostigmine	4–10 µg/kg/single dose i.v. works almost immediately, titration (e.g., in bronchoscopy)
Granisetron	Kevatril	5-HT_3 antagonist antiemetic	Reduces intestinal motility, cardiac arrhythmia, reduces the effectiveness of paracetamol	Prophylactic in chemotherapy, postop nausea	40 µg/kg/single dose 1 to 2 times/d, also possible orally

(continued)

Table 19.1 (continued)

Active compound	Trade name (German)	Pharmacological action	Adverse drug reactions	Indications/ contraindications	Dosage
Hydrochlorothiazide	Esidrix	Reversibly inhibits the NaCl cotransporter in the luminal cell membrane at the tubule, as a result of which NaCl is fully eliminated along with the excreted water, while Ca excretion ↓; Mg excretion ↑	Massive electrolyte shift blood pressure ↓, crea + urea ↑, blood count changes	Edema in heart failure, combining with Aldactone ± Lasix, bronchopulmonary dysplasia, mild hypertension	1–2–4 mg/kg/d in 2 single doses, lower doses are preferable for older children
Hydrocortisone	Hydrocortisone			For lowering the catecholamine requirements in septic/ cardiogenic shock	Bolus 5 mg/kg i.v., maintenance dose, 2 mg/kg/d i.v. in 3–4 single doses
Ibuprofen	Ibuprofen	Nonselective COX inhibitor	Gastrointestinal bleeding, transaminase ↑, severe renal failure, liver damage can be aggravated	Postop pain; antipyresis in switching with paracetamol – no combining with other NSAID; not with MTX; CSA, tacrolimus; phenytoin, digitalis	3 to 4 times/day: 7 mg/kg

Iloprost	Ilomedin	Synthetic prostacyclin, especially pulmonary vasodilatation, platelet aggregations inhibition; half-life 30 min	Fall in blood pressure, bleeding, mismatch in dystelectatic lungs	Lowering of the pulmonary arterial resistance in precapillary pulmonary hypertension; as by inhalation in PHT and in the postoperative adaptation phase in Glenn/TCPC; status post large L/R shunt with reactive pulmonary arterial high blood pressure; arterial occlusive disease; Raynaud's	CID, 0.5–1–2 ng/kg/min; by inhalation, 0.25–0.5 µg/kg/ single dose in NaCl 0.9% (10 µg on 10 or 20 ml NaCl) – up to 9 ×/d inhalator: drops <7 µm (adjustment of dosage in accordance with effect)
Indomethacin	Indocin	Anti-inflammatory agent; i.v. administration for PDA closure; IVH prophylaxis	Oliguria, electrolyte variations, bleeding in preexisting coagulation disorder/platelets <100,000/µl; food intolerance, necrotizing enterocolitis (NEC) and perforations with simultaneous administration of steroids, frequent hypoglycemia (no combination with other NSAID)	Premature neonates: IVH prophylaxis; pharmacological PDA closure/ do not administer with steroids, in coagulation disorders, thrombocytopenia, recent bleeding, NEC, kidney failure	PDA: 0.2 mg/kg t.i.d. at intervals of 12 h short infusion more than 30 min IVH prophylaxis 0.1 mg/kg every 24 h over 3 days, starting <6 h postnatal

(continued)

Table 19.1 (continued)

Active compound	Trade name (German)	Pharmacological action	Adverse drug reactions	Indications/ contraindications	Dosage
Irbesartan	Aprovel	Selective angiotensin receptor-II receptor antagonist (Type AT1)	Headaches, fatigue dizziness, angioedema; caveat: hyperkalemia primarily in combination with aldactone	Hypertension, congestive heart failure – afterload reduction (if ACE inhibitors are not tolerated, e.g., due to cough)	0.5–1–6 mg/kg/d in 1 single dose
Ketamine	Ketanest	NMDA receptor antagonist, sedation, hypnosis, analgesia (cataleptic dissociative anesthesia)	In healthy individuals: blood pressure ↑; sympathicotonia ↑; in combination with benzodiazepine preferably neutral; in ill people, also myocardial depression; PAP ↑, only blood pressure ↑; heart rate can increase; psychedelic effects	Short anesthesia with preserved ventilation; bronchospasmolytic with hypersecretion, pharyngeal hyperreflexia, long-term sedation	1–2 mg/kg/single dose (effect after 1–2 min) CID. 1–5 mg/kg/h intra-nasal: 2 mg/kg
Levomepromazine	Neurocil Nozinan	Medium-strength neuroleptic, analgesic, sedative, antiemetic, antiallergic, depression-relieving, local anesthetic, inhibits central temperature regulation	Dyskinesia, enhancement of the effect of analgesics, sedatives; anticholinergic adverse reactions, arrhythmia, hypotension	Intractable fever; acute psychosis (do not administer in intoxicated state)	0.1–0.5 mg/kg/single dose (short infusion over 15 min)

Levosimendan	Simdax	Ca sensitizer, selective phosphodiesterase III inhibitor, increases ability to contract with good relaxation, (slight) peripheral vasodilatation	Rarely:hypotension, arrhythmia, nausea, hypokalemia	Severe heart failure, pre-op prophylaxis, postop LCO; prior to ending CPB (ECMO, Berlin Heart®)	0.1–0.2 µg/kg/min every 4–9 days; bolus not recommended (children off-label); dilution 5 ml Simdax 500 ml G5%, then peripheral is also workable (1:100)
Lidocaine	Xylocaine	Local anesthesia, class I antiarrhythmic	Arrhythmia, negative inotropy, AV block formation, respiratory depression; in case of intoxication, eurol. adverse reactions (coma, seizures)	CPR (see also Chap. 12) ventricular flutter/ fibrillation/ lidocaine intoxication: use sodium bicarbonate	CPR 1–2 mg/kg, loading dose 1 mg/kg, then 20–50 µg/kg/min, reduction of dose in heart failure; endotracheal 2–10 times more; lipid emulsion (lipid rescue therapy): – 1–2 ml/kg intralipids 20% as a bolus – then 6–8 ml/kg as short infusion
Lisinopril	Lisinopril	Angiotensin-converting enzyme (ACE) inhibitor lowers peripheral resistance, increases venous capacity (preload ↓, afterload ↓↓)	Cough, allergy, hypotension, salt deficiency, few instances of reflex tachycardia; caveat: hyperkalemia	Hypertension and congestive heart failure/ do not administer in obstructive causes of heart failure (valve stenosis hypertrophic obstructive cardiomyopathy), do not administer in bilateral renal artery stenosis	Small children, 0.05–0.1 mg/kg 1 single, low initial dose with slow up-titration! older children 1–2.5–5 mg low initial dose with slow up-titration

(continued)

Table 19.1 (continued)

Active compound	Trade name (German)	Pharmacological action	Adverse drug reactions	Indications/ contraindications	Dosage
Lorazepam	Tavor	Benzodiazepine GABAergic sedative, anxiolytic, antiepileptic	Hypotension, respiratory depression, paradoxical reaction, rapid onset of dependency	Panic situations, anxiolytic effective for a longer period (12–16 h)	Small children 0.5 mg (in this case, nonuse would be preferable); older children 1–2.5–5 mg as a tablet or short infusion; Tavor Expidet in seizures (oral emergency therapy)
Magnesium	Magnesium chloride, Magnesium sulfate			Arrhythmia, torsade de pointes	Mg-Sulfate 10 %: 10 ml = 1g = 4 mmol bolus, 0.1 - 0.2 ml/kg slowly or as a short infusion CID: 1-3ml/kg/d
Metamizole	Novalgin	Unclear working mechanism analgesic/ antipyretic, slightly anti-inflammatory and also spasmolytic	Drop in blood pressure, heart failure in rapid administration; bronchial obstruction, ulcers, agranulocytosis	Analgesia, antipyresis/ use only after the third month of age	10 mg/kg t.i.d. to q.i.d. CID: 40 mg/kg/d
Methadone (levomethadone)	L-Polamidon	Strong opioid	Including extension of QT intervals	Opiate withdrawal; analgesia in chronic pains	0.1 mg/kg - 2-6x/d, reduce every 3 days
Metoclopramide	Paspertin	Dopamine antagonist, prokinetic agent, antiemetic	Dizziness fatigue, cholinergic, extrapyramidal (biperiden antagonizes this)	Nausea, vomiting; postoperatively/not in mechanical ileus, epilepsy; accumulation in renal failure	2 yr. onward: 0.1–0.2 mg/kg every 4 h p.o. or i.v.

Metoprolol	Beloc Beloc Zok	Selective β1-blocker, low-level membrane-stabilizing properties	Bradycardia (block), bronchial obstruction, hypoglycemia, concealing symptoms of hypoglycemia, aggravation of heart failure, constipation; caveat: combination with digitalis and Ca antagonists + amiodarone	Congestive heart failure, lowering of blood pressure	Orally, 0.5–2 mg/kg/d in 2–3 single doses; i.v., single dose 0.1 mg/kg; CID, 1–5 µg/kg/min
Midazolam	Dormicum	Benzodiazepine (GABAergic)	Hypopnea, arterial hypotension (especially in volume deficiency), accumulation risk lower than that of diazepam	Sedation, anxiolysis, anterograde amnesia, combined preparation with ketamine in CID, anticonvulsive, "softener" prior to extubation, short anesthesia + ketamine (drainage tubes ex), paradoxical reaction in patients with trisomy 21 possible	0.05–0.1 mg/kg/single dose onset of action 2–4 min duration of action 30–90 min suitable for CID: 0.1–0.2 mg/kg/h intra-nasal, 0,2 mg/kg

(continued)

Table 19.1 (continued)

Active compound	Trade name (German)	Pharmacological action	Adverse drug reactions	Indications/ contraindications	Dosage
Milrinone	Corotrop	Inodilator, inhibits degeneration of cyclic adenosine monophosphate (cAMP), stroke volume ↑, O_2 consumption quite constant	Hypotension, arrhythmias, thrombocytopenia, liver enzymes, renal excretion (see dosing. de), bronchospasm	Heart failure, ending CPB; acute, intermittent, and long-term therapy	0.2–0.5–1 µg/kg/min; lower dosages in young people/ adults (hypotension) and renal insufficiency
Morphine	Morphin	µ-Receptor; analgesia, euphoria, meiosis, respiratory depression, antitussive effect, vomiting (early), antiemetic (later), bradycardia, constipation, spasms of the sphincter of Oddi	Respiratory depression, hypotension in hypovolemia, early vomiting, meiosis, drug addiction	Analgesia, sedation/ do not administer in ileus (obstruction of the ileum or other part of the intestine), biliary tract problems	0.05–0.1 mg/kg/single dose, in neonates and preemies approx. 50%; onset of action 2–5 min maximum effectiveness 30 min, duration of action about 2–3 h, CID, 0.02–0.2 mg/kg/h; possible without concomitant benzodiazepine due to its sedative effect
Mycophenolate mofetil (MMF)	CellCept	T/B cell proliferation ↓ → T-cytotox. ↓ and antibody formation ↓	Nausea, fever, headaches, gastrointestinal side effects – less in gradual dosage, antacids reduce MMF concentration; virostatic agents increase MMF concentration	After (heart) Tx, alternative to azathioprine (AZA)	2 × 40 mg/kg i.v. or p.o. (or 1200 mg/m^2) in 2 single doses (infants 3 single dose); juice or capsules; dose orientation primarily along blood count, no predictable dose-level correlation, indicative trough level: 2.5–4 µg/ml

Nalbuphine	Nalpain	Opioid analgesic, partial μ-antagonist (see Chap. 6)		Analgesic, opiate antagonist (alternative to naloxone); compared to morphine: lower respiratory depressive effect/lower grade of intestinal atony/do not combine with opiates for analgesia (partial antagonist)	0.1–0.2 mg/kg i.v. duration of action 2–3 h
Naloxone	Narcanti	Central opioid antagonist	Pains, sweating, tachycardia, vomiting, cardiac arrest	Postoperative respiratory depression, respiratory depression caused by other opiates	10 μg/kg/single dose; to avoid adverse reactions of the overdose: under bag-valve-mask ventilation fractionated 1:10 in NaCl; babies in 1 ml increments; small children 2 ml increments; adults in 5 ml increments, then repetitively every 2 min
Sodium nitroprusside	Nipruss	Reduction of the systemic vascular resistance via NO donation, arterial > > venous, (only) with fine-meshed, most preferably invasive blood pressure monitoring	Acts immediately and is broken down within minutes, reflex tachycardia; cyanide intoxication possible (Na thiosulfate dialysis); CID for max. 3–5 days, light-protected syringe	Drop in post-load, reduced LV wall tension improves Starling level, intensive therapy for hypertensive crises/ do not administer in LV obstructions and isthmus stenosis	0.3–10 μg/kg/min; in suspected intoxication, monitoring of cyanide level (if necessary Na thiosulfate if suspected: e.g., 50 mg/kg as a short infusion)

(continued)

Table 19.1 (continued)

Active compound	Trade name (German)	Pharmacological action	Adverse drug reactions	Indications/ contraindications	Dosage
Nifedipine	Adalat Nifical drops 1 drop = 1 mg	Ca channel blocker in smooth musculature and heart muscle cells, vasodilatation and low negative inotropic	Hypotension, reflex tachycardia, edema, flushing, liver values ↑, blood count changes	Hypertensive crises, HOCM (sustained release form), Norvasc (amlodipine) is preferable in PHT	i.v., 0.25–0.5 mg/kg/single dose in hypertensive crisis; CID, 0.2–1 µg/kg/min; sublingual, 0.2–0.7 mg/kg; p.o., 0.5–1 mg/kg/d in 4 single doses
Novo VII recombinant factor VIIa	Novoseven	Formation of thrombin activators on activated platelets	Effective only with functioning platelets and fibrinogen levels >1.0 g/dl, clotting, embolisms, and thromboses	Otherwise untreatable postop bleeding; Glanzmann's disease; bleeding in liver failure; bleeding after NOAD	50–90 µg/kg/single dose (=4500 IE/kg/single dose) not simultaneously with other coagulation products, FFP, platelets
Octreotide	Sandostatin	Growth hormone (GH), insulin, and glucagon inhibitor, reduction of the splanchnic nerve perfusion, reduction of chyle formation	Vomiting, diarrhea, pulmonary artery hypertension, hyperglycemia	Chylothorax (postoperative or congenital), acute GI bleeding, hyperinsulinism	5–10 µg/kg/h protect from light and always administer in separate infusion and via separate access
Ondansetron	Zofran	Serotonin 5-HT_3 receptor antagonist	Headache, constipation, cardiac arrhythmias, reduction of the effect of paracetamol	Chemotherapy, postoperative nausea	0.1 mg/kg or 5 mg/m^2 slowly i.v.; most preferably as prophylactic; never give more than 4 mg b.i.d. to children <10 yr

Orciprenaline	Alupent	β1+ β2 mimetic	Cardiac arrhythmias, obstructive cardiomyopathy	Bradycardia, cardiac arrhythmias such as sinus bradycardia, bradycardia caused by digitalis, bradycardiac absolute arrhythmia in atrial fibrillation, second-degree AV blocks with Wenckebach periodicity, for bridging prior to pacemaker application, antidote in overdosing of beta-blockers	0.1–2 µg/kg/min, adjust dosage according to effect
Paracetamol	Perfalgan	Analgesic, lowering of temperature	Nausea, transaminases ↑, changes in blood count	Short-term use in mild pains or additive antipyresis	15 mg/kg/single dose; daily maximum q.i.d.; intoxication from 100 mg/kg/day onward
Pethidine	Dolantin	Preferably µ-receptor agonist; analgesia, euphoria, (slight) meiosis, respiratory depression, antitussive effect, vomiting (early on), antiemetic (later), bradycardia, constipation, spasms of the sphincter of Oddi rarely	Respiratory depression, hypotension in hypovolemia, vomiting, tachycardia and seizures	Pain (postoperative), muscle tremors, analgesic in cholestatic disorders	0.5–1 mg/kg/single dose, onset of action 2–3 min, maximum effect: 20–30 min, duration of action 2–4 h

(continued)

Table 19.1 (continued)

Active compound	Trade name (German)	Pharmacological action	Adverse drug reactions	Indications/ contraindications	Dosage
Phenobarbital	Luminal	GABAergic Sodium channel blocker	Myocardial depression, drop in blood pressure; enzyme induction (osteopathy?), coagulation disorder, respiratory depression	Anticonvulsant; long-term sedative/ do not administer immediately postoperatively, preferably not in severe heart failure	First day 2 × 10 mg/kg, then 2 × 3–5 mg/kg/d, from the fourth day onward. level monitoring (20–40 µg/ml); anticonvulsive: 2–3 times 10 mg/kg; adults, 50–200 mg i.v. slowly
Phentolamine	Regitine	α Blocker, also "central sympathectomy"; pulmonary artery pressure (PAP) somewhat ↓	Reflex tachycardia, shock, nausea, vomiting, stomach ache, diarrhea, angina pectoris	Arterial hypertension; as with sodium nitroprusside due to reduction of the afterload improvement of the starling level; increase in cardiac output/caveat: not in case of outflow tract obstruction	0.2–1–10 µg/kg/min half-life 3–4 h; only with intensive monitoring of blood pressure
Piritramide	Dipidolor	µ-Receptor agonist: analgesia, euphoria, meiosis (mild), respiratory depression, antitussive effect, vomiting (early on), antiemetic (later), bradycardia, constipation	Respiratory depression, hypotension in hypovolemia, early vomiting, meiosis, drug addiction	Postoperative pain, frequently has an euphoric effect, in shivering *PCA	0.1–0.2 mg/kg/single dose; onset of action 2–5 min; maximum time of onset of action 30–40 min; duration of action 2–6 h; CID,10–30 µg/kg/h; also by PCA* pump, e.g., max. 10 boluses/4 h; bolus of 2–3 mg; blocking interval 10 min
Prazosin	Minipress	α-Adrenoceptor blocker		Arterial hypertension	0.5–1 mg/kg/d in 3–4 single doses

Promethazine	Atosil	Mild neuroleptic agent strong antihistaminergic, sedative	Sedation, antiemetic; do not administer in cardiac arrhythmias; extrapyramidal side effects; frequent paradoxical effects	Sedative, frequently effective even if effect of benzodiazepine is poor	0.5–1 mg/kg/single dose iv or orally max. every 6 h
Propafenone	Rytmonorm	Class Ic antiarrhythmic agent, Na channel blocker	Reduced impulse generation and depressed conduction of stimuli generated in the sinus node and AV node – bradycardiac dysrhythmia and AV blocks, myocardial contractility ↓, nausea, fever	SVT (especially atrial ectopic heart beats, less effective in reentry SVT)	i.v. dosage, 0.2–0.5 mg/kg, repeat after 10 min, max. 2 mg/kg; CID, 4–7 µg/kg/min; i.v. – application only under ECG monitoring; stop if QRS width exceeds 20%; orally: 150–200 – max. 300 mg/m^2 total body surface/d in 3 single doses or 10–20 mg/kg/d in 3 single doses (about 1 h after meals, never together with milk)
Propranolol	Dociton	Nonselective β-blocker	Fatigue, bradycardia, drop in blood pressure (initially, sometimes rise in blood pressure), asthma, peripheral arterial perfusion disorders, AV blocks, aggravates metabolic syndrome	SVT, SVES, VES, HOCM; heart failure (suppressed by means of β1 selective medications); right ventricular outflow tract obstruction in patients with Fallot's/ caution: combination with digitalis and/or ca antagonists	Orally: 1–5–10 mg/kg/d in 3–4 single doses, i.v.: 0.02–0.2 mg/kg single dose as a short infusion (SVT, hypoxic seizure)

(continued)

Table 19.1 (continued)

Active compound	Trade name (German)	Pharmacological action	Adverse drug reactions	Indications/ contraindications	Dosage
Propofol	Propofol-Lipuro Disoprivan	GABAergic	Hypotension, bradycardia, respiratory depression, pain due to injection. Do not give to patients w/allergies, particularly, food, i.e., soy, peanuts etc., rarely: propofol, infusion syndrome (bradycardia, lactate acidosis, hyperlipidemia, rhabdomyolysis)	Short anesthesia, sleeping agent until extubation (fast-acting)/ no combining with cardiac depressing medications (caveat: volume deficiency)	Infants, 2.5–3.5 mg/kg i.v., older children, 1.5–2.5 mg/kg i.v. (the heavier the patient, the lower the initial dosage); CID 3–5 mg/kg/h (as short as possible, not more than 6 h in infants)
Protamine	Protamine	Heparin complexation, AT III inhibition thrombin inhibitor, action form about 5 min after administration (not immediately)	Acute hypotension, acute allergic reactions, PHT crisis (thromboxane induced) – more likely in surgery – rather rarely on the ICU; protamine itself inhibits coagulation, i.e., bleeding induced by overdose Half-life: 5 min (High molecular heparin: half time 1–5 h)	Postoperative heparin deactivation; antagonization in heparin overdose	1 mg neutralizes 100 IU heparin; 1 ml = 10 mg; heparin administration: < 30 min ago → antagonize 100% of the heparin dose; 30–60 min → 75–50%, 60–120 min → 50%, > 120 min → 25–30%; if needed repeated dosage due to different half time of heparin; low molecular weight heparin can be antagonized only to about 60%; slow i.v. or short infusion

Ranitidine	Zantic	H_2 blocker reversible	Constipation, allergies, bradycardiac cardiac arrhythmias	Gastric protection, postoperatively or in steroid therapy	0.5 mg/kg i.v. t.i.d. 1 mg/kg orally t.i.d.
Remifentanil	Ultiva	Exclusively μ-receptor agonist, analgesia, euphoria, meiosis, respiratory depression, antitussive effect, vomiting (early), antiemetic (later), bradycardia, constipation, spasms of the sphincter of Oddi	Respiratory depression, hypotension (especially in volume deficiency)	For rapid extubation, in Glenn and Fontan surgery due to the short half-life – should be terminated only when an opiate or ketamine with a longer action is given with overlap	Application only in CID (half-life): 0.1–0.3 μg/kg/min, immediate onset of action, duration of action 2–5 min; therefore, consider before termination of alternative painkillers (morphine/ piritramide, etc.)
Reproterol	Bronchospasmin	β2 Mimetic	Tachycardiac arrhythmias	Bronchial obstruction; on a trial basis: in combination with beta-blockers in acute heart failure	CID: 0.1 μg/kg/min
Sildenafil	Revatio Viagra Sildenafil	Phosphodiesterase-5 (PDE-5) inhibitor, cyclic guanosine monophosphate (cGMP) degeneration-inhibition, raises endogenous NO concentration, vasodilatation, can improve NO effect	Flushing, visual disturbance, dyspepsia, headaches, rhinitis	Pulmonary arterial hypertension/ do not administer with nitro (hypotension)	Orally: 2–3 mg/kg in 3–4 single doses; CID: 0.02–0.04 mg/kg/h

(continued)

Table 19.1 (continued)

Active compound	Trade name (German)	Pharmacological action	Adverse drug reactions	Indications/ contraindications	Dosage
Sotalol	Sotalex	Type III antiarrhythmic + nonselective beta-blocker – extends refractory period and duration of action potential	Bradycardia, hypotension, heart failure deterioration, arrhythmia: especially with long QT intervals, tendency to *torsades de pointes*; fatigue, metabolic deterioration, asthma	SVT, ventricular tachycardia (VT)/ do not administer in case of long QT intervals; do not administer in blocks	90 mg/m^2 of total body surface in 3 single doses, if necessary gradually double the dosage; dose ↓ in renal failure. i.v., 1 mg/kg as short infusion; CID, 1 mg/kg/h
Spironolactone	Aldactone	Aldosterone antagonist	Hyperkalemia, hyponatremia, gynecomastia	Combining with other diuretics, edema in hepatic cirrhosis, kidney, and heart failure/ careful with angiotensin-converting enzyme (ACE) blockers and NSAIDs	Neonates, 1–3 mg/kg/d in 1–2 single doses small children, 1.5–4 mg/kg/d in 1–2 single doses adults, 25–200 mg/d in 1–2 single doses
Succinylcholine	Succinylcholine	Depolarizing muscle relaxant	Vagotonia (keep atropine in readiness), allergic reactions, blood pressure ↓, arrhythmia, malignant hyperthermia	Crush intubation, e.g., in aspiration risk	1–1,5 mg/kg i.v. onset of action 30–60 s duration of action 2–6 min
Sucralfate	Ulcogant	Protective film on the esophagus/stomach/ duodenal mucous membrane	Constipation, feeling of abdominal distension	Prevention of aspiration pneumonia, reflux esophagitis, ulcer therapy	Small children 0.25–0.5 g q.i.d., > 10 kg BW: 1 g q.i.d.

Sufentanil	Sufenta	Stronger sedation effect, in identical analgesia, 5–10 times that of fentanyl or 500–1000 times that of morphine; lower respiratory depressive effect compared to fentanyl; additional effective on kappa receptors, i.e., can induce anxiety	Respiratory depression, hypotension in hypovolemia, vomiting, meiosis	Strong analgesia less respiratory depression; effective for a somewhat shorter period than fentanyl	0.2–0.3 µg/kg/single dose; CID, 0.5–1.5–5 µg/kg/h; as far as possible, do not administer to neonates; according to literature, better for extubation after long-term opiate use
Tacrolimus	Prograf	Inhibits calcineurin effect → interleukins ↓	Nephro–/ neurotoxicity, high blood pressure, seizures, hypomagnesaemia, diabetes, anorexia, nausea, hyperglycemia, carcinogenic (e.g., lymphomas)	CsA – alternative in HTx; blood level monitoring: 10–15 ng/ml first week, 7–10 ng/ml first year, 5–7 ng/ml later on; constant monitoring of the liver, kidney, and neurological status	p.o., 0.1–0.2 mg/kg/d in 2 (> 2 yr) and/or 3 single doses (<2 yr) i.v., 0.02–0.05 mg/kg/d (rarely used); some antibiotics (especially macrolides) and antiarrhythmic influence levels
Terbutaline	Bricanyl	β2 Mimetic	Tachycardia, arrhythmia	Bronchospasm	i.v./sc. 5–10 µg/kg; CID, 1–10 µg/kg/h; inhaled, 0.5 drops/kg in 2 ml NaCl
Terlipressin	Haemopressin	Increases vascular toning of the arterioles, effective for longer period than vasopressin, antidiuretic hormone secretion effect	Hypertension, LV afterload failure, water intoxication, peripheral circulatory disorder to the extent of organ loss	Intractable hypotension; alternative to noradrenaline in tachycardia; bleeding from esophageal varices (splanchnic nerve perfusion ↓)	5–10–20 µg/kg/single dose every 4 h; CID, begin with 5–10 ng/kg/min, thereafter, increase according to effectiveness

(continued)

Table 19.1 (continued)

Active compound	Trade name (German)	Pharmacological action	Adverse drug reactions	Indications/ contraindications	Dosage
Theophylline	Euphylline Solosin	Methylxanthine, phosphodiesterase inhibitor	Caveat: in tachycardia cardiac arrhythmias, never in seizures	Respiratory analepsis, bronchodilation (from about 20 mg/kg BW/d onward); intended sinus tachycardia, improvement of diuresis	5 mg/kg/d in furosemide – CID; 10 mg/kg/d in respiratory analepsis; 20 mg/ kg/d as bronchodilator
Thiopental	Trapanal	GABAergic, sodium channel blocker	Myocardial depression, drop in blood pressure, respiratory depression, enzyme induction (osteopathy?), bronchospasm, laryngospasm (in this case use atropine), susceptibility to infection in long-term use	Intubation in patients with stable blood pressure and without circulatory compromises; cerebral compression therapy, anesthesia in status epilepticus caveat: cardiodepressant, in volume deficiency; accumulation in repetitive administration, muscle tremors, vascular irritation	4–5 mg/kg/single dose as short anesthesia (duration of action 5–10 min); cerebral edema 1–3 mg/kg/single dose; under EEG check CID: 1–10 mg/kg/h after bolus administration until burst suppression; elimination half-life 3–8 h (fat storage)
Tolvaptan	Samsca	Competitive arginine vasopressin receptor - 2 - antagonist	Avoid excessively rapid increase of Na (risk of demyelination)	Hyponatremia SIADH/ not in case of hyponatremic hypohydration	No verified doses for children; “reduced titration” of the adult dose; 15 mg per day in adults

Tramadol	Tramal	Morphine receptor-agonist, anxiolysis as well as antidepressive effect, approx. 0.1 times the effect of morphine	Nausea, vomiting, no analgesic effect in approx. 30% of cases, constipation, sphincter of Oddi dysfunction	Slight respiratory depression, pain medication drip in spontaneous breathing/ never in diseases of the CNS, in combination with phenprocoumon or antidepressants	Orally, 1 mg/kg/single dose every 4 h, i.v., 0.5–1 mg/kg/ single dose every 4 h, CID, 1–8 mg/kg/d
Tranexamic acid	Cyklokapron	Inhibits fibrin depletion by means of plasmin complexing	Nausea/vomiting hypotension in excessively rapid infusion, thromboses in thrombophilia	In verified (TEG/ ROTEM) or suspected state of hyperfibrinolysis, suspected local hyperfibrinolysis, (postoperative hematoma), locally in epistaxis (impregnated tamponade)	10–20 mg/kg/single dose short infusion of 5 min; CID, after bolus: 1 mg/kg/h
Urapidil	Ebrantil	Peripheral α1-blocker, central sympatholysis	Slight reflex tachycardia, orthostasis, vomiting, do not administer with cimetidine and/or in obstructive cardiac function disorders	Arterial hypertension, heart failure (afterload reduction), improves bronchial obstruction, similar to sodium nitroprusside, but less controllable, less potent	CID, 0.2–1 mg/kg//h; bolus, 0.2–0.5 mg/kg (short infusion over 10 min)
Vasopressin	Pitressin	Vasopressor (direct) as well as antidiuretic hormone (ADH), half-life 1 min	Hypertension, bradycardia, vasospasms, seizures, fever, necrosis, bronchial spasms, water intoxication	Shock with vasoplegia, caveat: cardiogenic shock, GI bleeding; in CPR (?)	Shock with vasoplegia 0.0005–0.001 IU/kg/min, increase as required; CPR, 0.5 IU/kg/single dose

(continued)

Table 19.1 (continued)

Active compound	Trade name (German)	Pharmacological action	Adverse drug reactions	Indications/ contraindications	Dosage
Verapamil	Verapamil Isoptin	Calcium antagonist, pronounced myocardial effect, vascular effect weaker	Drop in blood pressure, conduction block, transaminases ↑, not combining with digitalis and β-blockers	Atrial flutter/atrial fibrillation and SVT for control of the ventricular rate/ not in WPW syndrome, blocks, shock, poor pump function; muscular diseases and respiratory exhaustion	i.v. 0.1–0.2 mg/kg/single dose, repetition not earlier than 20 min later, antidote: Ca; CID, 5 μg/kg/min; orally, 1.5–2 mg/kg t.i.d.; HOCM 5–10 mg/kg/d in 3 single doses
Vecuronium	Norcuron	Non-depolarizing muscle relaxant	No vagolytic reaction, no histamine release, hypotension in hypovolemia (volume deficiency)	Potent muscle relaxant, onset of action after 2 min, 30–60 min duration of action, accumulation in renal impairment	0.05–0.1 mg/kg/single dose; CID, 0.1 mg/kg/h
Vitamin K	Konakion	Vitamin K1, carboxylation of factors II, VII, IX, X testing via Quick/INR (proteins S + C are also dependent on vitamin K)	Very rare instances of compromised circulation	Postnatal prophylaxis 1, 3, 28 day of life; vitamin K deficiency – bleeding, renal impairment	Prophylaxis preemies 0.4 mg/kg i.v. or i.m.; neonates: 1–2 mg orally absolute; in resorption disorders: 1–2 mg i.v.; in vitamin K deficiency – bleeding, 1–10 mg i.v. (laboratory check 4 h later); store away from light

CPB Cardiopulmonary bypass (heart-lung machine), *CNS* Central nervous system, *CPP* Cerebral perfusion pressure *CRRT* Continuous renal replacement therapy, *CID* Continuous intravenous drip infusion, *CsA* Cyclosporin A, *CRC* Concentrated red cells, *CPR* Cardiopulmonary resuscitation, *ECLS* Extracorporeal life support, *FFP* Fresh frozen plasma, *ICP* Invasive intracranial pressure, *GABAergic* Gamma-aminobutyric acid-ergic, *h* Hour(s), *HIT II* Heparin-induced thrombocytopenia II, *HLA* Human leukocyte antigen, *HTx* Heart transplant, *HOCM* Hypertrophic obstructive cardiomyopathy, *IU* International units, *IVH* Intraventricular hemorrhage, *JET* Junctional ectopic tachycardia, *LCO* Low cardiac output, *MMF* Mycophenolate mofetil, *mo* Month(s), *NOAD* New oral anticoagulant drugs, *NSAIDs* Nonsteroidal anti-inflammatory drugs, *PCA* Patient-controlled analgesia, *PDA* Patent ductus arteriosus, *PHT* Pulmonary hypertension, *PM* Pacemaker, *PTT* Partial thromboplastin time, *yr* Years of age, *SIADH* Syndrome of inappropriate antidiuretic hormone secretion, *SVES* Supraventricular extra systole(s), *SVT* Supraventricular tachycardia, *TAC* Tacrolimus, *TCPC* Total cavopulmonary connection, *TEG* Thrombelastography, *VAD* Ventricular assist device, *VES* Ventricular extra systole(s), *VT* Ventricular tachycardia, *WPW* Wolff-Parkinson-White

Table 19.2 Memory chart on beta-blockers

Beta-blockers	Without ISA	With ISA
β1 Selective	Atenolol, bisoprolol, metoprolol, esmolol, betaxolol, nebivolol	Celiprolol, acebutolol
Nonselective	Propranolol, timolol, sotalol, carvedilol	Alprenolol, oxprenolol, pindolol

ISA intrinsic sympathomimetic activity

Table 19.3 Memory chart on nausea

Drug	General remarks
Vomex A = dimenhydrinate	Sugar-coated tablets or suppositories, good against less severe nausea, as i.v. medication administration 0.5–1 mg/kg/single dose every 6–8 h, good postoperatively
Dexamethasone = Fortecortin	Standard steroid against nausea: infants 1–2 mg, small children 2–4 mg, adults 8 mg i.v., hyperglycemia, sensitization to beta-receptors (sympathomimetic adverse effects)
Granisetron = Kevatril	5-HT3 antagonist, 1 mg i.v. or 2 mg p.o., duration of action about 24 h, headache, constipation as adverse effect, can usefully be combined with dexamethasone
Ondansetron = Zofran	Very similar to granisetron (5-HT3 antagonist); shorter-acting, must be higher dosed, but there is an orally mouth-dissolving tablet
Metoclopramide = MCP	First in drop form p.o., definitely from 12 years of age because of dyskinetic movement disorders, these can be readily antagonized
Lorazepam, diazepam, midazolam	Benzodiazepines exhibit a synergistic effect with the usual antiemetic therapy, as nausea is reduced in anxiolysis
Haloperidol	Neuroleptics can also reduce nausea by suppressing the autonomic nervous system and are therefore suitable as comedication (albeit more from adolescence onward)

BW body weight

Table 19.4 Memory chart on phenprocoumon (Marcumar)

Phenprocoumon	
Effect	Inhibition of γ-carboxylation of vitamin K-dependent factors II, VII, IX, and X and protein C + S
Indications	Artificial valves
	Bypasses with foreign materials
	Thrombosis prophylaxis
	Extracorporeal devices
	Arrhythmias rarely
Control	Prothrombin time and INR Target 2–3.5
Adverse effects	Hemorrhages GI adverse effects
	Reduction in bone density
	As inhibition of procoagulatory factors persists for longer than that of anticoagulatory factors, always start by overlapping with heparin
	Interactions with various drugs

(continued)

Table 19.4 (continued)

Phenprocoumon						
Doses	0.1 mg/kg/day					
	Infants and small children					
		Day				
	INR	2	3	4	5	6
	<1.5	100%	100%	125%	150%	150%
	1.5–1.7	75%	100%	100%	100%	125%
	1.8–2.0	50%	50%	75%	75%	75%
	2.1–2.5	50%	50%	50%	50%	50%
	2.6–3.0	25%	25%	25%	25%	25%
	> 3.0	0	0	12.5%	12.5%	12.5%
Pharmacology	Oral dose almost 99% absorbed					
	Metabolites predominantly excreted renally					
	Half-life 3–6 days					
	Onset of action 2–3 days					
	Caveat: liver disease, cardiac decompensation, GI infections					

GI gastrointestinal, *INR* international normalized ratio
Reference: http://www.staff.uni-mainz.de/goldinge/dosmatrx.htm

Suggested Reading

1. Munoz R, et al. Handbook of pediatric cardiovascular drugs. Heidelberg: Springer; 2008.
2. Brunton L, et al. Goodman and Gilman's the pharmacological basis of therapeutics – 13th edition. New York: McGraw Hill education; 2017.
3. Vincent J. Dugs and the Kidneys. Clin Pharmacol Ther. 2017;102(3):368–72.