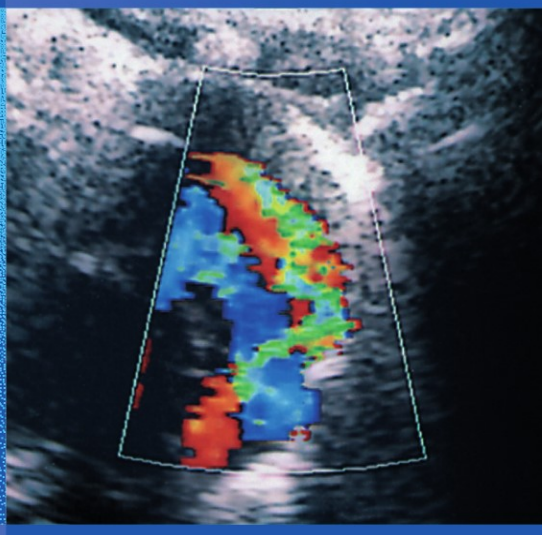
M. Obladen
P. Koehne
(Eds.)



Interventions for Persisting Ductus Arteriosus in the Preterm Infant

Springer

M. Obladen

P. Koehne

Interventions for Persisting Ductus Arteriosus in the Preterm Infant

M. Obladen (Editor)
P. Koehne (Editor)

Interventions for Persisting Ductus Arteriosus in the Preterm Infant

With 51 Figures and 7 Tables

Springer

Prof. Dr. Michael Obladen
Director, Department of Neonatology,
Charité Universitätsmedizin Berlin,
Campus Virchow/Campus Benjamin Franklin,
Augustenburger Platz 1, 13353 Berlin
michael.obladen@charite.de

Dr. Petra Koehne
Head Physician, Department of Neonatology,
Charité Universitätsmedizin Berlin,
Campus Virchow,
Augustenburger Platz 1, 13353 Berlin
petra.koehne@charite.de

ISBN 3-540-24511-1
Springer Medizin Verlag Heidelberg

Cataloging-in-Publication Data applied for
A catalog record for this book is available from the Library of Congress.

Bibliographic information published by Die Deutsche Bibliothek
Die Deutsche Bibliothek lists this publication in the Deutsche Nationalbibliografie;
detailed bibliographic data is available in the Internet at <http://dnb.ddb.de>.

Springer Medizin Verlag.
A member of Springer Science+Business Media
springer.de

Printed in The Netherlands

SPIN 11384281
Cover Design: deblik, Berlin, Germany
Typesetting: TypoStudio Tobias Schaedla, Heidelberg, Germany

Printed on acid free paper 18/3160/yb – 5 4 3 2 1 0

Preface

»Nature knows in advance that the fetal lung, an organ in development and without movement, does not have the same needs as the mature, breathing lung. Nature has therefore connected the pulmonary artery with the aorta.« This was written by Galen in the second century after Christ <opera omnia IV:243>, confirmed by Giulio Cesare Aranzio <de humano foetu> in 1564 and later falsely attributed to Leonardo Botallo who became famous by this error. By connecting the pulmonary artery with the aorta, nature had not foreseen that in Europe most infants born at 25–27 weeks gestation would survive at the beginning of the 21st century. Over the past few years we have witnessed a remarkably rapid evolution in the professional level of neonatology and in the survival of immature infants. Sadly, many of these survivors later have neurodevelopmental handicaps, and presently there is not too much the neonatologist can do to prevent them. Avoiding ventilation, pneumothorax, and hypocarbia are the best choice. Closure of the ductus is another option, but many uncertainties exist concerning indication, approach, best time, and side effects. These issues were discussed in a European workshop in Fulda, Germany, on April 4 and 5, 2004. Not only the speakers but most participants were experts either in neonatology or in pediatric cardiology, and this small book contains the abstracts of the workshop, which, as we hope, will help to define the level of evidence and to develop standards of intervention for persisting ductus arteriosus in Europe. With survival of more and more immature infants, adequate dealing with the ductus will become a challenge for every perinatal center. We are deeply indebted to the many talented and dedicated contributors, we thank the staff of Springer publishers for good advice and for help in editing this volume, and we thank Dr. Barbara Donnerstag and Mr. Eberhard Kroll from Orphan Europe, not only for sponsoring this meeting but also for developing evidence based therapies for specific and small patient groups in whom little money can be earned.

Berlin, December 2004

Michael Obladen, MD
Petra Koehne, MD

Table of Contents

Part I: Basics

Part II: Clinical Features

Part III: Diagnostics

Part IV: Interventions

List of Contributors

Dr. Regina Bökenkamp
Department of Anatomy
and Embryology,
Leiden University Medical Center,
Wassenaarsenweg 62,
Postbox 9602, 2300, RC Leiden,
The Netherlands

Prof. Dr. Karl-Heinz Deeg
Director, Children's Hospital,
Klinikum Bamberg,
Buger Straße 80, 96049 Bamberg,
kinderklinik@klinikum.bamberg.de

Dr. Marie-Christine Fortun
Regulatory Affairs Director,
Orphan Europe (France) SARL,
Immeuble »Le Wilson«,
70, avenue du General de Gaulle, F-92058 Paris, France,
mcfortun@orphan-europe.fr

Dr. Véronique Gournay
Division of Pediatric Cardiology,
University Hospital of Nantes,
Hôpital Mère Enfant,
7, quai Moncousu,
44093 Nantes Cedex 1, France,
veronique.gournay@chu-nantes.fr

Prof. Dr. Michael Hofbeck
Director, Division of Pediatrics II,
Universitätsklinikum Tübingen,
Hoppe-Seyler-Straße 3,
72070 Tübingen,
michael.hofbeck@
med.uni-tuebingen.de

Dr. Michael Hübler
Attending Surgeon,
Department of Cardiothoracic
and Vascular Surgery,
German Heart Institute Berlin,
Augustenburger Platz 1,
13353 Berlin,
huebler@dhzb.de

Prof. Dr. Walter Kachel
Director, Department of Pediatrics/
Perinatalzentrum,
SLK-Kliniken Heilbronn GmbH,
Am Gesundbrunnen 18–20,
74067 Heilbronn,
walter.kachel@slk-kliniken.de

Dr. Petra Koehne
Head Physician, Department of
Neonatology, Charité Universitäts-
medizin Berlin, Campus Virchow,
Augustenburger Platz 1,
13353 Berlin,
petra.koehne@charite.de

Prof. Dr. Rolf F. Maier
Director, Department
of Neonatology and Pediatric
Neurology, Klinikum der
Philipps-Universität Marburg,
Deutschhausstr. 12,
35033 Marburg,
rolf.maier@med.uni-marburg.de

Prof. Dr. Ingo Morano
Director, Division of Molecular
Muscle Physiology,
Max-Delbrück-Center Berlin,
Robert-Rössle-Straße 10,
13092 Berlin,
imorano@mdc-berlin.de

Prof. Dr. Michael Obladen
Director, Department of
Neonatology, Charité Universitäts-
medizin Berlin, Campus Virchow/
Campus Benjamin Franklin,
Augustenburger Platz 1,
13353 Berlin,
michael.obladen@charite.de

Dr. Christiane Pees
Department of Congenital
Heart Defects, German Heart
Institute Berlin,
Augustenburger Platz 1,
13353 Berlin,
chrpees@yahoo.de

Prof. Dr. Karsten Schrör
Director, Institute for Pharmacology
and Clinical Pharmacology,
Heinrich-Heine-Universität,
Universitätsstr. 1, 40225 Düsseldorf,
kschroer@uni-duesseldorf.de

Prof. Dr. Helmut Singer
Director, Department of Pediatric
Cardiology, Klinik für Kinder und
Jugendliche der Universität
Erlangen-Nürnberg,
Loschgestr. 15, 91054 Erlangen,
htsinger@
kinder.imed.uni-erlangen.de

PD Dr. Josef Sonntag
Department of Pediatrics,
Städtisches Klinikum Lüneburg,
Bögelstraße 1, 21339 Lüneburg,
josef.sonntag@
klinikum-lueneburg.de

Dr. Burkhard Trusen
Head Physician, Children's Hospital,
Klinikum Bamberg,
Buger Straße 80, 96049 Bamberg,
kinderklinik@klinikum.bamberg.de

Prof. Dr. Berndt Urlesberger
Department of Neonatology,
Universitätsklinik für Kinder- und
Jugendheilkunde, Auenbrugger
Platz 30, A-8036 Graz, Austria,
Bernd.urlesberger@kfunigraz.ac.at

Prof. Dr. Bart van Overmeire
Department of Pediatrics, Division
of Neonatology, University Hospital
of Antwerp, Wilrijkstreet 10,
B-2650 Edegem, Belgium,
Bart.Van.Overmeire@uza.uia.ac.be

Dr. Axel von der Wense
Department of Neonatology
and Pediatric Intensive Care,
Altonaer Kinder-Krankenhaus,
Bleickenallee 38, 22763 Hamburg,
wense@akker.net

List of Abbreviations

BPD	Bronchopulmonary dysplasia
CBF	Cerebral blood flow
CI	confidence interval
CLD	Chronic lung disease
CHD	Congenital heart defect
COX	Cyclooxygenase (isoforms -1 and -2)
ELBW	Extremely low birth weight (<1000 g)
IVH	Intraventricular hemorrhage
MHC	Type II myosin heavy chain
MLC	Type II myosin light chain
MLCK	Myosin light chain kinase
NEC	Necrotizing enterocolitis
NICU	Neonatal intensive care unit
NNT	Number needed to treat
NO	Nitric oxide
NSAID	Nonsteroidal anti-inflammatory drug
OR	odds ratio
PaO_2	Arterial oxygen partial pressure
PCO_2	Carbon dioxide partial pressure
PGE2	Prostaglandin type E2
PDA	Persisting ductus arteriosus
PVL	Periventricular leukomalacia
Q	Volume flow
RBF	Renal blood flow
RDS	Respiratory distress syndrome = surfactant deficiency
RI	Resistance index
ROP	Retinopathy of prematurity
RVSP	Right ventricular systolic pressure
SaO_2	arterial oxygen saturation
SMC	Smooth muscle cells
TAV	Time averaged flow velocity
TR	Tricuspid regurgitation
UBC	Unbound bilirubin concentration
Ved	End diastolic flow velocity
Ves	End systolic flow velocity
Vs	Peak systolic flow velocity
VEGF	Vascular endothelial growth factor
VLBW	Very low birth weight (<1500 g)
VSMC	Vascular smooth muscle cell

Part I Basics

1

Developmental Anatomy of the Ductus Arteriosus

Regina Bökenkamp

Introduction

The ductus arteriosus is a unique, dynamic vascular structure functioning as a prenatal bypass between pulmonary artery and aorta. The uniqueness of this fetal structure was already described in antique medicine by Galen [1]. Understanding of the functional significance of the ductus became possible after the discovery of circulation by Harvey in the 17th century [2]. Virchow is credited with being the first to note the histological difference between ductus arteriosus and other great arteries and to point out the clinical significance of his findings for postpartum closure [3].

Embryogenesis

The vascular system of the embryo starts from endothelial precursors forming an endothelial plexus in the splanchnic mesoderm. During development extensive remodelling takes place. After folding of the embryo the endothelial plexus in the heart region becomes incorporated within the myocardium [4]. The omphalomesenteric vessels enter the heart at the venous pole, while the arterial pole becomes connected to the dorsal aortae by the symmetric pharyngeal arch arteries.

The development of the arteries starts with the recruitment of cells which differentiate into smooth muscle cells. Differences in matrix production and growth are responsible for the development of the phenotype of elastic and muscular arteries [5].

Pharyngeal arch patterning (Figure 1.1, and title page) [6] is influenced by neural crest cells, by smooth muscle cells and by the neural system surrounding the arches [7]. The ductus arteriosus derives from the sixth pharyngeal arch artery on the left side in normal human development [7]. During pharyngeal arch remodelling the ductus acquires a muscular vessel wall, whereas the surrounding great arteries become elastic arteries. The reason for this unique and ductus-specific differentiation program, starting early in development, is not known.

Ductal Maturation

Significant structural changes of the vascular morphology preparing the ductus for postnatal closure start in late gestation [7, 9, 10] (Fig. 1.2).

In the second trimester of the human fetus the ductus is a muscular artery with a single or locally duplicated internal elastic lamina and a very thin intima. With further development intimal cushions appear. At term the internal elastic lamina

has become fragmented and the intimal cushions are pronounced. Intimal thickening together with oxygen-dependent constriction functionally closes the ductus during the first hours after birth [11, 12, 13]. Anatomic closure with dedifferentiation and apoptosis of smooth muscle cells and reorientation of endothelial cells leads to the definitive morphology of the ligamentum arteriosum [14, 15].

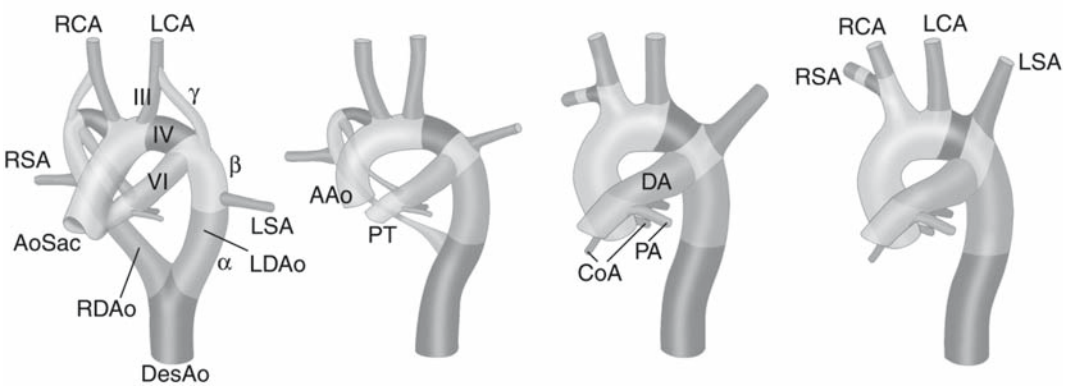


Fig. 1.1 Pharyngeal arch patterning from branchial arches to mature arteries (with permission from [6])
AAo = ascending aorta, AoSac = aortic sac, CoA = coronary arteries, DA =ductus arteriosus, DesAo = descending aorta, PA = pulmonary artery, PT = pulmonary trunk, LDAo = left descending aorta, LCA = left carotid artery, LSA = left subclavian artery, RCA = right carotid artery, RDAo = right descending aorta, RSA = right subclavian artery; III, IV, and VI refer to the branchial arches.

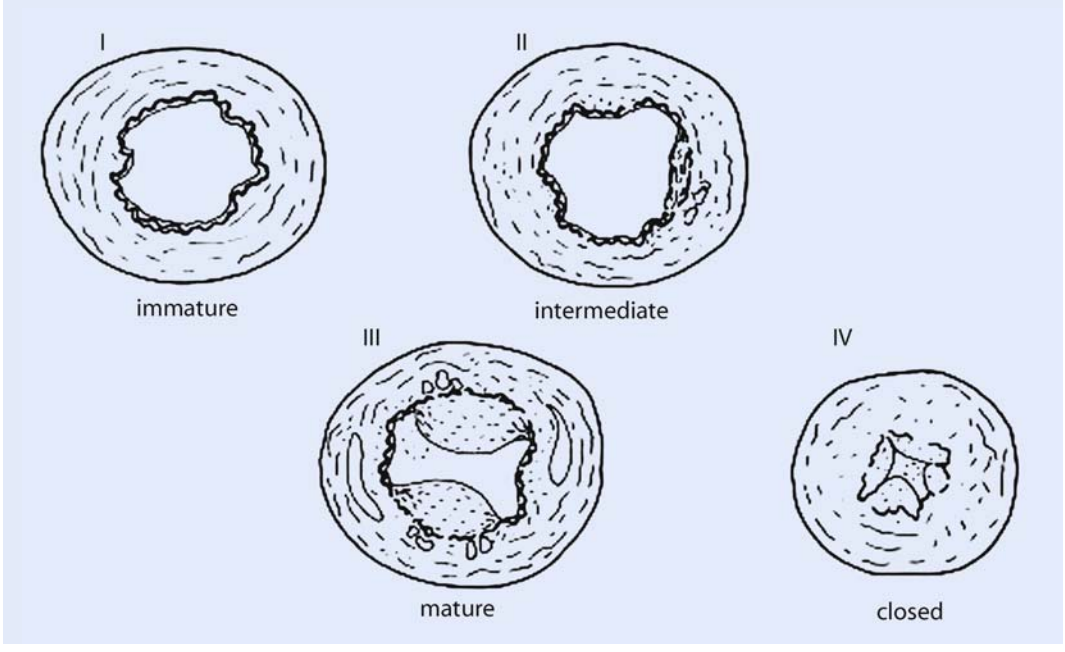


Fig. 1.2 Ductal maturation stages (modified after [11, 16]). Maturation starts in the second trimester of pregnancy. There is no strict relation between gestational age or birth weight and histological maturation of the ductus.

Patent Ductus Arteriosus in Premature Infants

The ductus arteriosus of a premature infant will generally not have passed through all stages of maturation. It can be assumed that closure, anatomical or functional, will not be completed in just a few days [16]. From histological studies in immaturely born fetuses, preterm infants and full-term newborns it is concluded that one cannot predict whether a ductus is likely to be mature at the time of birth [10]. The observation that there is no strict relation between gestational age or birthweight and histological maturation explains that early spontaneous closure of the ductus is possible even in a young premature infant.

Persistent Ductus Arteriosus (PDA)

A patent ductus arteriosus beyond the age of three months after full gestation is defined as persistent ductus arteriosus. From epidemiological studies in newborns the proportion of PDA was reported to be as high as 13.5% of all congenital heart defects [17]. This figure is debatable, as physiological closure may be delayed until the age of three months.

Ductal patency in mature infants and children has to be considered as primary congenital malformation of the vessel wall [9]. In persistent ductus the structural changes associated with physiological ductal closure do not occur. The endothelium remains attached to the internal elastic lamina; invagination of endothelium or migration of smooth muscle cells from the abnormally structured media is not observed [10, 11].

Rubella infection is a well-known teratogenic factor resulting in PDA in humans [18]. From studies in dogs with hereditary patent ductus arteriosus a multigenic cause of the structural anomaly of the vessel wall is suggested [19]. Patients with Char syndrome have an inherited form of PDA due to the mutation of the transcription factor TFAP 2B [20].

Summary

Differentiation and maturation of the ductus arteriosus start early in gestation and prepare its rapid postnatal closure. Delayed closure of an immature ductus arteriosus in premature infants has to be differentiated from the vascular anomaly of persistent ductus arteriosus.

This structural difference between immature and persistent ductus explains in part why prostaglandin-synthesis inhibitors are effective in preterm neonates with patent ductus and cannot be used to treat patients with persistent ductus.

The lecture gives an overview of findings obtained at the Department of Anatomy and Embryology, Leiden University Medical Center (Head: Prof. AC Gittenberger-de Groot)

References

1. Galenus, Opera Omnia IV:243 (131 A.D.).
2. French RK. The thorax in history: Circulation of blood. Thorax 1978. 33: 714–27.
3. Gräper L. Die anatomische Verhältnisse kurz nach der Geburt. III. Ductus Botalli. Z Anat Entwicklungsgesch. 1921. 61: 312–29.
4. DeRuiter MC, Poelman RE, VanderPlas-de Vries I, Mentink MMT, Gittenberger-de Groot AC. The development of the myocardium and endocardium in mouse embryos. Anat Embryol. 1992. 185: 461–73.
5. Bergwerff M, DeRuiter MC, Gittenberger-de Groot AC. Comparative anatomy and ontogeny of the ductus arteriosus, a vascular outsider. Anat Embryol. 1999. 200: 559–71.
6. Molin DGM, DeRuiter MC, Wisse LJ, Azhar M, Doetschman T, Poelmann RE, Gittenberger-de Groot AC. Altered apoptosis pattern during pharyngeal arch artery remodelling is associated with aortic arch malformations in Tgfbeta2 knock-out mice. Cardiovasc Res. 2002. 56: 312–22.
7. Silver MM, Freedom RM, Silver MD, Olley PM. The morphology of the human newborn ductus arteriosus: a reappraisal of its structure and closure with special reference to prostaglandin E1 therapy. Hum Pathol. 1981. 12: 1123–36.
8. Congdon ED. Transformation of the aortic arch system during development of the human embryo. Contrib Embr Carnegie Instit. Washington. 1922. 14: 47–110.
9. Gittenberger-de Groot AC. Persistent ductus arteriosus: most probably a primary congenital malformation. Brit Heart J. 1977. 39: 610–8.

10. Gittenberger-de Groot AC, van Ertbruggen I, Moulaert AJMG, Harinck E. The ductus arteriosus in the preterm infant: Histological and clinical observations. J Pediatrics. 1980. 90: 88–93.
11. Gittenberger-de Groot AC, Strengers JL, Mentink M, Poelmann RE, Patterson DF. Histologic studies on normal and persistent ductus arteriosus in the dog. J Am Coll Cardiol. 1985. 6: 394–404.
12. Clyman RI, Mauray F, Wong L, Heymann MA, Rudolph AM. The developmental response of the ductus arteriosus to oxygen. Biol Neonate. 1978. 34: 177–81.
13. Hornblad PY. Embryological observations of the ductus arteriosus in the guinea pig, rabbit, rat and mouse. Studies on closure of the ductus arteriosus. IV. Acta Physiol Scand. 1969. 76: 49–57.
14. Slomp J, Gittenberger-de Groot AC, Glukhova MA, van Munstern C.J, Kockx MM, Schwartz SM, Koteliansky VE. Differentiation, dedifferentiation, and apoptosis of smooth muscle cells during the development of the human ductus arteriosus. Arterioscler Thromb Vasc Biol. 1997. 17: 1003–9.
15. Momma K, Ito T, Mori Y, Yamamura Y. Perinatal adaptation of the cardiovascular system. Early Hum Dev. 1992. 29: 167–70.
16. Strengers JLM. Fetal and postnatal behaviour of the ductus arteriosus 1988, thesis Leiden.
17. Crawford, Di Marco and Paulus. eds, Cardiology 2E, textbook, 2004, Elsevier Ltd.
18. Gittenberger-de Groot AC, Moulaert AJ, and Hitchcock JF. Histology of the persistent ductus arteriosus in cases of congenital rubella. Circulation 1980; 62: 183–6.
19. Patterson DF, Pyle RL, Buchanan JW, Trautvetter E, Abt DA. Hereditary patent ductus arteriosus and its sequelae in the dog. Circ Res 1971; 29: 1–13
20. Satoda M, Zhao F, Diaz GA, Burn J, Goodship J, Davidson HR, Pierpont ME, Gelb BD. Mutations in TFAP2B cause Char syndrome, a familial form of patent ductus arteriosus. Nat Genet. 2000; 25: 42–6.

2

Regulation of Smooth Muscle Contraction

Ingo Morano

The tone of vascular smooth muscle cells (VSMC) determines organ perfusion and the filtration rate of glomeruli, as well as the peripheral resistance of the circulatory system, the main determinant of blood pressure in adults. Dysregulation of the vascular smooth muscle tone therefore causes a variety of pathophysiological states, e.g. hypertension with subsequent end-organ damage such as renal and cardiac failure, as well as delayed closure of the ductus arteriosus.

Type II myosin is the molecular motor which causes SMC contraction and movement by cyclic interaction with actin and hydrolysis of ATP. It consists of two heavy chains (MHC) with around 200 kDa each, which revealed a 140nm alpha-helical »rod« domain and a pear-shaped N-terminal »head« domain around 20nm in length (Fig. 2.1). Two pairs of light chains (MLC) with 17 kDa (essential MLC) and 20 kDa (regulatory MLC) are non-covalently associated with each MHC close to the head domain. Proteolytic cleavage experiments defined a subfragment 1 (S1) consisting of the head and MLC binding domains. The three-dimensional structure of S1 determined by X-ray crystallography of both striated [1] and smooth muscle (SM) [2] is almost identical. The head contains the actin- and ATP-binding domains (catalytic domain). An alpha-helical »neck« domain 8.5 nm down-stream of the head binds the MLC non-covalently. In a contemporary model, the neck domain acts as a mechanical lever arm which amplifies small conformational changes in the head into a power stroke of around 10nm [1, 2]. The C-terminal rod domain of both smooth muscle (SM) and non-muscle (NM) MHC isoenzymes contains a small non-helical tailpiece which is absent in sarcomeric myosins.

Type II myosin has the ability to convert chemical energy (ATP) into mechanical work by cyclic interactions with F-actin which is considered to be similar in striated and smooth muscle [3]. Transition from non-force-generating to force-generating states (attachment reaction) is associated with the release of inorganic phosphate from the actomoysin complex. ADP release from the catalytic domain of force-generating myosin causes the transition from the force-generating into the non-force generating cross-bridge states (detachment reaction) [4] and determines the maximal shortening velocity [5].

Myosin of smooth muscle cells (SMC) has some unique properties. MLC20 phosphorylation is a key event in the initiation of smooth muscle contraction [6] and the extent of MLC20 phosphorylation determines shortening velocity and tension development [7] (Fig. 2.2). In vivo phosphorylation of SM- and NM-MLC20 isoforms is accomplished by raising free intracellular Ca^{2+}

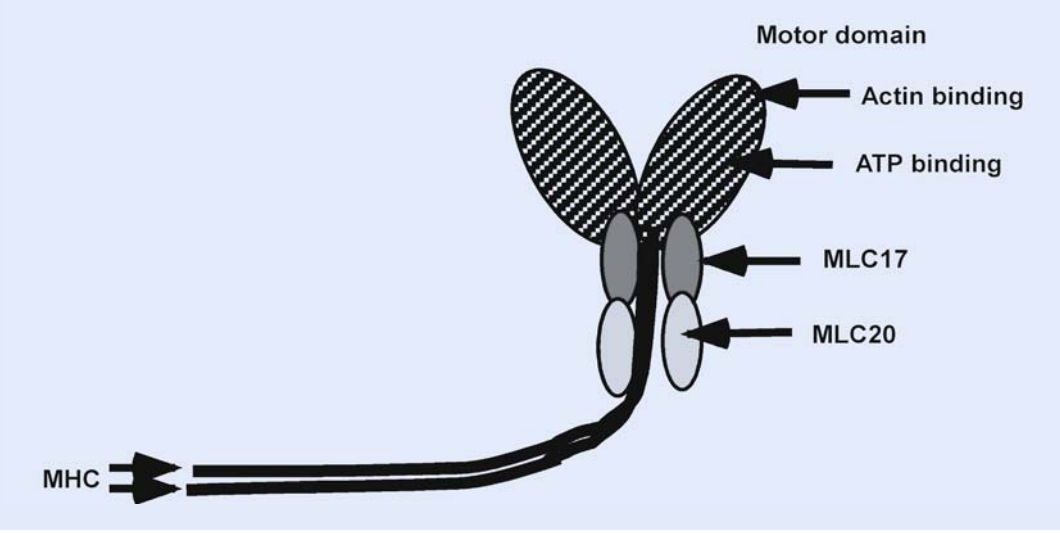


Fig. 2.1 The type II myosin motors of smooth muscle cells. They consist of two heavy chains (MHC) (200 kDa each), with a 140nm alpha-helical »rod« domain and a pear-shaped N-terminal »head« domain with around 20nm length (motor domain). Two pairs of light chains (MLC) with 17 kDa (essential MLC) and 20 kDa (regulatory MLC) are non-covalently associated with each MHC.

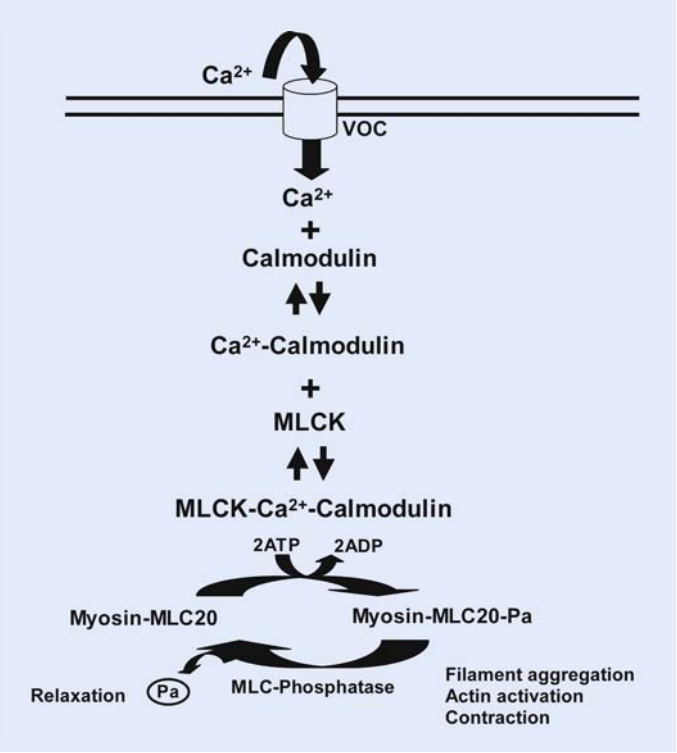


Fig. 2.2 Contraction regulation of smooth muscle cells. Raising free intracellular Ca^{2+} and subsequent formation of Ca^{2+}-calmodulin complexes activate myosin light chain kinase (MLCK). MLCK phosphorylates MLC20, thus activating the smooth muscle myosin motors. A MLC20 phosphatase dephosphorylates MLC20 and transforms SM- and NM-myosin into an inactive form, causing smooth muscle relaxation.

and subsequent activation of Ca^{2+}-calmodulin dependent myosin light chain kinase (MLCK) [8], which predominantly targets Ser19 [9]. MLC20 phosphorylation causes the transition of myosin from a folded, enzymatically inactive structure (10S) to an elongated structure (6S) of the myosin having a 500fold higher actin-activated ATPase activity [10, 11]. MLC20 phosphorylation by MLCK on Thr18 has only a small effect on ATPase activity and velocity of actin translocation in the in vitro motility assay [12]. MLC20 is also phosphorylated by protein kinase C, CaM-kinase II, Rho-kinase, and p21-activated kinase (c. f. [13]). Integrin-linked kinase (ILK) [14] and ZIP-kinase [15] also phosphorylate MLC20 in the absence of Ca^{2+}, at Ser19 and Thr18, thus activating myosin activity.

A MLC20 phosphatase (MLCP), a type PP1 form, dephosphorylates MLC20 and transforms SM- and NM-myosin into an inactive form thus causing smooth muscle relaxation ([16, 17] for review). Inhibition of MLCP represents a Ca^{2+}-independent mechanism of smooth muscle contraction regulation [17]. Hence RhoA-kinase phosphorylates the regulatory M110-130 subunit of MLCP and inhibits its catalytic activity, thereby raising MLC20 phosphorylation levels of both SM- and NM myosin [18]. Likewise, ZIP/MYPT-1 kinase [15] and ILK [19] phosphorylate the regulatory subunit of MLCP. A strong MPLC inhibitor is the small protein CPI-17 which is phosphorylated and thereby activated by PKC [20] and PKN [21].

Shortening velocity of smooth muscle preparations and the actin sliding velocity of smooth muscle myosin in the in vitro motility assay [22] were at least one order of magnitude slower than those of skeletal muscle myosin. Economy of tension maintenance is high during smooth muscle compared to striated muscle contraction ([23] for review). The time in which SM-myosin generates force or displacement during actomyosin interactions (duty cycle) was 5 times longer compared to striated muscle myosin [24]. The fraction of force-generating cross-bridges, therefore, should be much higher in smooth compared to striated muscle. In fact, SMC contain only about 20–30% of the myosin found in skeletal muscle but they develop similar forces [25]. Average unitary force (1.2–3.7pN) and actin filament displacement per cross-bridge stroke (around 10nm) of smooth and skeletal muscle myosin, however, were equal [24].

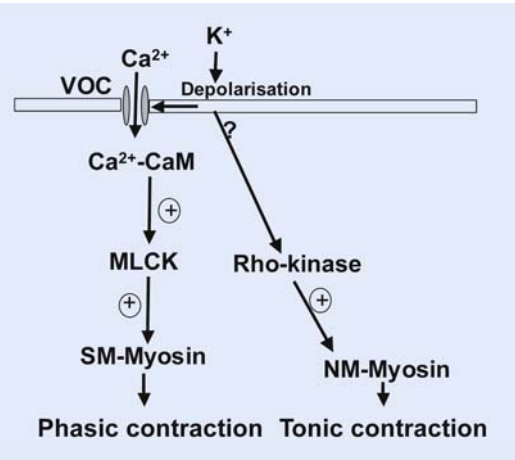
Three different MHC genes are expressed in SMC, namely SM-MHC (exclusively expressed in SMC) [26], NM-MHCA and NM-MHCB (also expressed in non-muscle cells) [27, 28, 29, 30], located on chromosome 16p13.13 [31], 22 [32] and 17 [33], respectively in human. NM-MHCB is expressed in the embryonic SMC (designated SMemb) [26, 28], in proliferating SMC during the formation of vascular lesions [34] and in culture [36]. In the adult state, myometrial cells [36] as well as smooth muscle cells of blood vessels, including aorta [30] and ductus arteriosus [37], expressed NM-MHCA in addition to SM-specific MHC isoforms. NM-MHC isoenzymes revealed a high degree of homology with SM-MHC [38]. In addition, they can form filaments and are activated by phosphorylation of the regulatory 20kDa MLC similar to SM-MHC (for review [13]). Genscan predictions indicate the presence of an additional myosin gene with broad homology to NM-MHCB on chromosome 19 [39], but its expression and function needs to be elucidated.

The SM-MHC gene transcript is alternatively spliced at both the 3´- (carboxy-terminal myosin tail) and at the 5´- end (amino-terminal head domain). Inclusion of a 39 nucleotide exon which encodes 9 amino acids at the outmost 3´-terminus generates the translation of a SM-MHC isoenzyme with 1443 amino acids and around 200 kDa (SM2) with a shortened tail region. Exclusion of this exon causes the translation of an elongated tail with 1477 amino acids and around 204 kDa (SM1), containing a non-helical tailpiece domain with a phosphorylatable serine residue which is absent in SM2 [40, 41, 42]. 5´-splicing of SM-MHC is accomplished by excision of a highly conserved exon with 21 nucleotides (7 amino acids) causing a shortened flexible surface loop (loop 1) close to the ATP-binding 25K/50K-junction [43, 44, 45]. SM-MHC without the 5´-insert were designated as »SMA«-forms (SM1A and SM2A), those with 5´-insert as »SMB« forms (SM1B and SM2B).

Potassium depolarization of intact smooth muscle preparations caused a rapid transient phasic contraction with high force generation and high Vmax (around 0.4 ML/s), and a subsequent

tonic state of contraction with both low force (around 1/3 of the initial phasic force) and low Vmax (ca. 0.15 ML/s). The initial phasic contraction of SMC of mice with mutated SM-MHC gene, however, was absent. Tonic contraction with both low Vmax and low isometric force could still be elicited in mice with ablated SM-MHC gene, i.e. with NM-MHC alone [46, 47]. Intracellular free calcium ion transients in SM-MHC knock-out remained normal (a rapid and transient increase of free Ca^{2+} which declines to almost basal levels during sustained contraction) [47]. These experiments demonstrated the presence of distinct contractile systems in SMC: During early activation, SM-myosin is recruited for phasic contraction, while during sustained tonic contraction NM-myosin is active [46, 47] (■ Fig. 2.3).

Differential recruitment of distinct contractile systems during activation observed in SMC could well explain the unique functional and biochemical properties of smooth muscle observed during prolonged activation, i.e. drop in Vmax, ATP consumption, and MLC phosphorylation levels, denoted as »latch« state [48, 49]. In fact, the rapid decline of intracellular Ca^{2+} after activation causes a rapid inactivation of MLCK with subsequent dephosphorylation and inactivation of the SM-myosin system, a process which is ML-7 sensitive. This explains the rapid drop of MLC20 phosphorylation upon prolonged activation [48, 49], since the inactivated SM-myosin represents the predominant isoenzyme in SMC. Remaining MLC phosphorylation levels during sustained contraction of SMC then reflect the phosphorylated MLC20 of NM-myosin, the minor isoenzyme in SMC. NM-myosin activation by MLC20 phosphorylation in the presence of almost basal intracellular Ca^{2+} during prolonged activation could be achieved and maintained by the Rho-kinase system, which is also activated upon membrane depolarization by KCl [50]. Interestingly, the specific Rho-kinase inhibitor Y-27632 preferentially inhibited the depolarization-induced tonic contraction rather than the initial phasic contraction [50, 51]. Transient activation of the SM-myosin system and the recruitment of NM-myosin upon prolonged activation could also explain the drop in ATPase consumption and Vmax observed during sustained SMC contraction. In fact, Vmax [46, 47] and the velocity of actin filament sliding in the in vitro motility assay [52] of NM-myosin is lower than that of SM-myosin. The NM-MHC, therefore, may form the latch cross-bridges.



■ **Fig. 2.3** Regulation of phasic and tonic contraction of smooth muscle. Activation of smooth muscle cells e.g. by potassium depolarization (K+), initially recruits smooth muscle specific myosin upon Ca^{2+}-calmodulin-MLCK dependent pathways, causing phasic contraction. Prolonged activation recruits non-muscle myosin, probably by the Rho-kinase system, causing tonic contraction.

Endothelial cells and SMCs of the ductus arteriosus differ from those of adjacent vessels in their ability to form neointimal cushions. Ductus arteriosus SMCs also secrete more fibronectin and chondroitin sulfate than those of the aorta or pulmonary artery. Slow tonic contraction generated by NM-MHC alone was not sufficient for normal smooth muscle organ function in neonatal SM-MHC knock-out mice. Thus, failure of micturition caused an atonic huge bladder in these mice. In addition, closure of the ductus arteriosus was retarded [46]. In normal mice, ductus arteriosus was closed after 3 hours post partum. However, SM-MHC knock-out mice revealed a patent ductus arteriosus between 6 and 12 hours after birth. The delayed closure of the ductus arteriosus could be the cause of the observed ventricular dilatation in neonatal SM-MHC knock-out mice [46].

This work was supported by a grant from the Deutsche Forschungsgemeinschaft Mo 362/16-2.

References

1. Rayment, I., Rypniewski, W.R., Schmidt-Bäse, K., Smith, R., Tomchick, D.R., Benning, M.M., Winkelmann, D.A., Wesenberg, G., Holden, H.M. (1993) Three-dimensional structure of myosin subfragment 1: a molecular motor. Science 261: 50–58
2. Dominguez, R., Freyzon, Y., Trybus, K.M., Cohen, C. (1998) Crystal structure of a vertebrate smooth muscle myosin motor domain and its complex with the essential light chain: visualization of the pre-power stroke state. Cell 94: 559–571
3. Marston, S.B., Taylor, E.W. (1980) Comparison of the myosin and actomyosin ATPase mechanisms of the four types of vertebrate muscles. J. Mol. Biol. 139: 573–600
4. Brenner, B., Eisenberg, E. (1987) The mechanism of muscle contraction. Biochemical, mechanical, and structural approaches to elucidate cross-bridge action in muscle. Basic Res. Cardiol. 82 Suppl 2: 3–16
5. Siemankowski, R.F., Wiseman, M.O., White, H.D. (1985) ADP dissociation from actomyosin subfragment 1 is sufficient slow to limit the unloaded shortening velocity in vertebrate muscle. Proc. Natl. Acad. Sci. 82: 658–662
6. Sobieszek, A. (1977) Ca^{2+} linked phosphorylation of a light chain of vertebrate smooth muscle myosin. Eur. J. Biochem. 118: 533–582
7. Hai, C.M., Murphy, R.A. (1989) Ca^{2+}, cross-bridge phosphorylation, and contraction. Ann. Rev. Physiol. 51: 285–298
8. Dabrowska, R., Sherry, J.M.F., Aromatorio, D.K., Hartshorne, D.J. (1978) Modulator protein as a component of the myosin light chain kinase from chicken gizzard. Biochem. 17: 253–258
9. Ikebe, M. and Hartshorne, D. J. (1985) Phosphorylation of Smooth Muscle Myosin at Two Distinct Sites by Myosin Light Chain Kinase. The Journal of Biological Chemistry 260: 10027–10031
10. Cross, R.A. (1988) What is 10S myosin for? J. Muscle Res. Cell Mot. 9: 108–110
11. Trybus, K.M. (1996) Myosin regulation and assembly. In Biochemistry of smooth muscle contraction, Barany, M., ed. Academic Press, pp 37–46
12. Bresnick, A.R., Wolff-Long, V.L., Baumann, O., Pollard, T.D. (1995) Phosphorylation of threonine-18 of the regulatory light chain dissociates the ATPase and motor properties of smooth muscle myosin II. Biochemistry 34: 12576–12583
13. Bresnick, A.R. (1999) Molecular mechanisms of nonmuscle myosin-II regulation. Current Opinion in Cell Biology 11: 26–33
14. Deng, J.T., VanLierop, J.E., Sutherland, C., Walsh, M.P. (2001) Ca^{2+}-independent smooth muscle contraction. A novel function for integrin-linked kinase. J. Biol. Chem. 276: 16365–16373
15. Niiro, N., Ikebe, M. (2001) Zipper-interacting protein kinase induces Ca^{2+}-free smooth muscle contraction via myosin light chain phosphorylation. J. Biol. Chem. 276: 29567–29574
16. Alessi, D., MacDougall, L.K., Sola, M.M., Ikebe. M., Cohen, P. (1992) The control of protein phosphatase-1 by targeting subunits: the major myosin phosphatase in avian smoth muscle is a novel form of protein phosphatase-1. Eur. J. Biochem. 210: 1023–1035
17. Somlyo, A.P., Somlyo, A.V. (2000) Signal transduction by G-proteins, Rho-kinase and protein phosphatase to smooth muscle and nonmuscle myosin II. J. Physiol. 522: 177–185
18. Kimura, K., Ito, M., Amano, M., Chihara, K., Fukata, Y., Nakafuku, M., Yamamori, B., Feng, J., Nakano, T., Okawa, K., Iwamatsu, A., Kaibuchi, K. (1996) Regulation of myosin phosphatase by Rho and Rho-associated kinase (Rho-kinase). Science 273: 245–248
19. Muranyi, A., MacDinald, Deng, J.T., Wilson, D.P., Haystead, T.A.J., Walsh, M.P., Erdödi, F., Kiss, E., Wu, Y., Hartshorne, D.J. (2002) Phosphorylation of the myosin phosphatase target subunit by integrin-linked kinase. Biochem. J. 366: 211–216
20. Eto, M., Ohmori, T., Suzuki, M., Furuya, K., Morita, F. (1995) A novel protein phosphatase-1 inhibitory protein potentiated by protein kinase C. Isolation from porcine aorta media and characterization. J. Biochem. 118: 1104–1107
21. Hamaguchi, T., Ito, M., Feng, J., Seko, T., Koyama, M., Machida, H., Takase, K., Amano, M., Kaibuchi, K., Hartshorne, D.J., Nakano, (2000) Phosphorylation of CPI-17, an inhibitor of myosin phosphatase, by protein kinase N. Biochem. Biophys. Res. Comm. 274: 825–830
22. Warshaw, D.M., Desroisiers, J.M., Work, S.S., Trybus, K.M. (1990) Smooth muscle myosin cross-bridge interactions modulate actin filament sliding velocity in vitro. J. Cell Biol. 111:453–463
23. Paul, R.J. (1989) Smooth muscle energetics. Ann. Rev. Physiol. 51: 331–349
24. Guilford, W.H., Dupuis, D.E., Kennedy, G., Wu, J., Patlak, J.B., Warshaw, D.M. (1997) Smooth and skeletalk muscle myosins produce similar unitary forces and displacements in the laser trap. Biophys. J. 72: 1006–1021
25. Murphy, R.A., Herlith, J.T., Mergerman, J. (1974) Force generation capacity and contractile protein content of arterial smooth muscle. J. Gen. Physiol. 64: 691–705
26. Aikawa, M., Sivam, P.N., Kuro-o, M., Kimura, K., Nakahara, K., Takewaki, S., Ueda, M., Yamaguchi, H., Yazaki, Y., Periasami, M., Nagai, R. (1994) Human smooth muscle myosin heavy chain isoforms as molecular markers for vascular development and atherosclerosis. Circ. Res. 73: 1000–1012
27. Gaylinn, B.D., Eddinger, T.J., Martino, P.A., Monical, P.L., Hunt, D.F., Murphy, R.A, (1989) Expression of nonmuscle myosin heavy and light chains in smooth muscle. Am. J. Physiol. 257: C997–C1004
28. Kuro-o, M., Nagai, R., Nakahara, K., Katoh, H., Tsai, R.C., Tsuchimochi, H., Yazaki, Y., Ohkubo, A., Takaku, F. (1991) cDNA cloning of a myosin heavy chain isoform in embryonic smooth muscle and its expression during vascular development and in artheriosclerosis. J. Biol. Chem. 266: 3768–3773
29. Phillips, C.L., Yamakawa, K., Adelstein, R.S. (1995) Cloning of the cDNA encoding nonmuscle myosin heavy chain-B

and analysis of human tissues with isoform-specific antibodies. J. Muscle Res. Cell Mot. 16 : 390–400
30. Packer, C.S. (1997) Arterial muscle myosin heavy chains and light chains in spontaneous hypertension. Comp. Biochem. Physiol. 117B: 19–28
31. Deng, Z., Liu, P., Claxton, D.F., Lane, S., Callen, D.F., Collins, F.S., Siciliano, M.J. (1993) Genomics 18: 156–159
32. Saez, C.G., Myers, J.C., Shows, T.B., Leinwand, L.A. (1990) Human nonmuscle myosin heavy chain mRNA: generation of diversity through alternative polyadenylation. Proc. Natl. Acad. Sci. 87: 116
33. Simons, M., Wang, M., McBride, O.W., Kawamoto, S., Yamakawa, K., Gdula, D., Adelstein, R.S., Weir, L. (991) Human non-muscle myosin heavy chains are encoded by two genes located on different chromosomes. Circ. Res. 69: 530–539
34. Schwartz, S.M., Campbell, G.R., Campbell, J.H. (1986) Replication of smooth muscle cells in vascular disease. Circ. Res. 58: 427–444
35. Kawamoto, S., Adelstein, R.S. (1991) Chicken nonmuscle myosin heavy chains: differential expression of two mRNAs and evidence for two different polypeptides. J. Cell Biol. 112: 915–924
36. Morano, I., Erb, G., Sogl, B. (1993) Expression of myosin heavy and light chains changes during pregnancy in the rat uterus. Pflügers Arch. 423: 434–441
37. Giuriato, L., Scatena, M., Chiavegato, A., Guidolin, D., Pauletto, P., Sartore, S. (1993) Rabbit ductus arteriosus during development: anatomical struicture and smooth muscle cell composition. Anat. Rec. 235: 95–110
38. Adelstein, R.S., Sellers, J.R. (1996) Myosin structure and function. In: Barany M ed. Biochemistry of smooth muscle contraction. Academic Press Inc. San Diego, California, pp 3–19
39. Berg, J.S., Powell, B.C., Cheney, R.E. (2001) A millennial myosin census. Mol. Biol. Cell 12: 780–794
40. Rovner, A.S., Thompson, M.M., Murphy, R.A. (1986) Two different myosin heavy chains are found in smooth muscle. Am. J. Physiol. 250: C861–C870
41. Nagai, R., Kuro-o, M., Babij, P., Periasamy, M. (1989) Identification of two types of smooth muscle myosin heavy chain isoforms by cDNA cloning and immunoblot analysis. J. Biol. Chem. 264: 9734–9737
42. Hamada, Y., Yanagisawa, M., Katsugarawa, Y., Coleman, J.R., Nagata, S., Matsuda, G., Masaki, T. (1990) Distinct vascular and intestinal smooth muscle myosin heavy chain mRNAs are encoded by a single-copy gene in the chicken. Biochem. Biophys. Res. Commun. 170: 53–58
43. White, S., Martin, A., Periasamy, M. (1993) Identification of a novel smooth muscle myosin heavy chain cDNA: isoform diversity in the S1 head region. Am. J. Physiol. 264: C1252–C1258
44. Babij, P. (1993) Tissue-specific and developmentally regulated alternative splicing of a visceral isoform of smooth muscle myosin heavy chain. Nucl. Ac. Res. 21: 1467–1471
45. Kelley, C.A., Takahashi, M., Yu, J.H., Adelstein, R.S. (1993) An insert of seven amino acids confers enzymatic differences between smooth muscle myosins from the intestines and vasculature. J. Biol. Chem. 268: 12848–12854
46. Morano, I., Chai, G.X., Baltas, L.G., Lamounier-Zepter, V., Lutsch, G., Kott, M., Haase, H., Walther, T., Bader, M. (2000) Smooth muscle contraction without smooth muscle myosin. Nature Cell Biol. 2: 371–375
47. Löfgren, M., Ekblad, E., Morano, I., Arner, A. (2003) Nonmuscle myosin motor of smooth muscle. J. Gen. Physiol., in press
48. Dillon, P.F., Aksoy, M.O., Driska, S.P., Murphy, R.A. (1981) Myosin phosphorylation and the cross-bridge cycle in arterial smooth muscle. Science 211: 495–497
49. Kamm, K.E., Stull, J.T. (1985) The function of myosin and myosin light chain kinase phosphorylation in smooth muscle. Ann. Rev. Pharmacol. Toxicol. 25: 593–620
50. Mita, M., Yanagihara, H., Hishinuma, S., Saito, M., Walsh, M.P. (2002) Membrane depolarization-induced contraction of rat caudal arterial smooth muscle involves Rho-associated kinase. Biochem. J. 364: 431–440
51. Kupittayanant, S., Burdyga, R., Wray, S. (2001) The effects of inhibiting Rho-associated kinase with Y27632 on force and intracellular calcium in human myometrium. Pflügers Arch 443: 112–114
52. Umemoto, S., Bengur, A.R., Sellers, J.R. (1989) Effect of multiple phosphorylations of smooth and cytoplasmic myosins on movement in an in vitro motility assay. J. Biol. Chem. 264: 1431–1436

3

Prostaglandin Metabolism and Effects of Inhibitors

Karsten Schrör

For more than 20 years it has been known that prostaglandins, such as PGE_2 and PGI_2 (prostacyclin), relax the ductus arteriosus (Morris et al. 20003). More recently, it was shown that this effect is mediated via specific receptors, including prostaglandin EP_2 and perhaps other G_s-coupled prostaglandin receptors (Fig. 3.2), such as EP_4 and the prostacyclin receptor IP (Hahn et al. 2000). The significance of prostaglandins for maintenance of ductus patency is exemplified by the delay of ductus closure in COX-2 deficient mice (Baragatti et al. 2003) and by the failure of ductus closure in knockout mice lacking both cyclooxygenase (COX)–1 and COX-2 (Loftin et al. 2002). It is likely but not yet proven in humans that additional mediators are involved in the regulation of ductus tone and remodelling, including nitric oxide (NO) and vascular endothelial growth factor (VEGF) which are also related to prostaglandin metabolism and, therefore, changed after inhibition of prostaglandin generation.

Inhibition of both COX isoforms results in closure of the ductus, the efficacy being dependent on gestational age. Several drugs are available to induce ductus closure in preterm infants, including indomethacin and ibuprofen, both being non-selective inhibitors of COX-1 and COX-2. However, in particular indomethacin is associated with a number of severe side effects in preterm infants, such as necrotizing enterocolitis, transient or permanent renal dysfunction, reduction of renal, gastrointestinal and cerebral perfusion and gastrointestinal and intracranial hemorrhage, in particular if the mothers have been pretreated with the compound (tocolysis) (Norton et al. 1993). This might also result in therapeutic failure of ductus closure after postnatal treatment. These side effects appear to be less frequent and less severe with ibuprofen at an efficacy equal to that of indomethacin. It should also be considered that the half-life of indomethacin and ibuprofen in (preterm) neonates amounts to about 20 and 30 hours, respectively, being about 10 times longer than in adults.

From a pharmacological point of view, the treatment of persisting ductus arteriosus may be improved and requires more detailed knowledge of prostaglandin-related metabolic pathways and their interaction with other pathways in human metabolism.

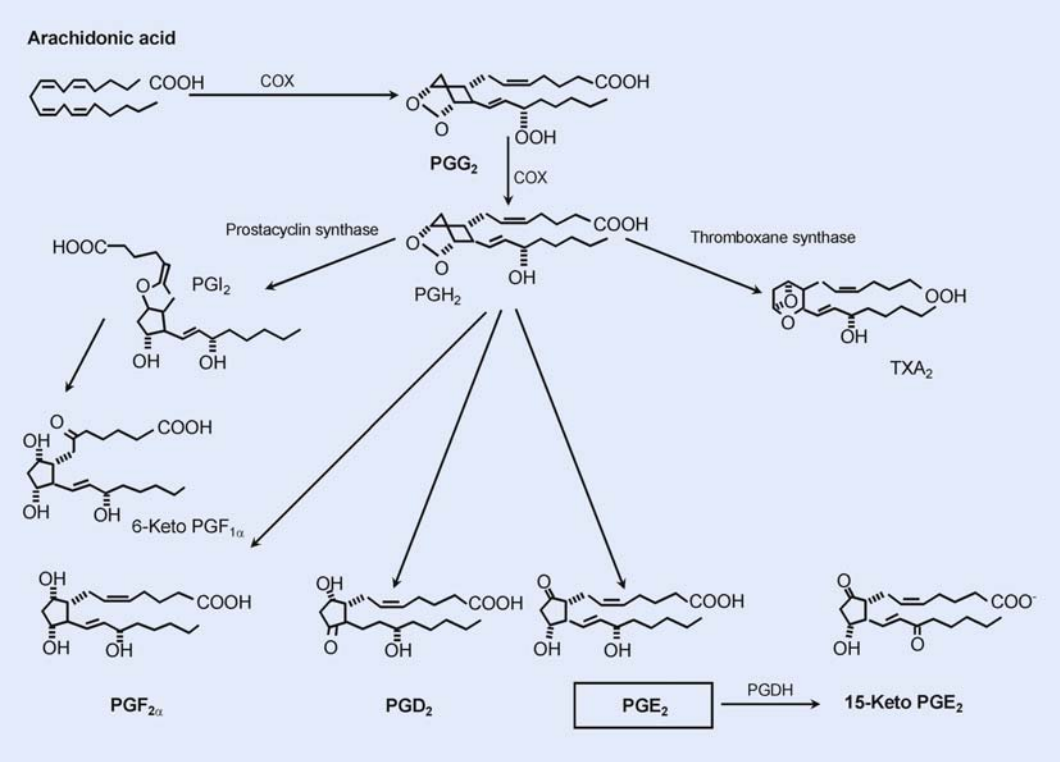


Fig. 3.1 Biosynthesis and metabolism of prostaglandins in humans. Various prostaglandins exist, all sharing a similar chemical structure characterized by 20-carbon unsaturated carboxylic acids with a cyclopentane ring. Arachidonic acid is the precursor not only for prostaglandins but for other chemically related biologically active molecules such as prostacyclin, thromboxanes, and leukotrienes. The committed step of prostaglandin biosynthesis, the conversion of arachidonic acid (substrate) to prostaglandin H_2, the common precursor for biosynthesis of the various prostanoids, is regulated by the enzyme cyclooxygenase (also termed prostaglandin H synthase). The synthesis of prostaglandin H_2 is the point of differentiation in prostanoid production, with individual cell types possessing predominantly different terminal synthases. The terminal synthases generate the various effector prostaglandins, among which prostaglandin E_2 plays a major role. With regard to the ductus arteriosus, prostaglandin E_2 is essential for maintaining ductus patency in utero. Prostaglandin E_2 is inactivated to 15-keto-PGE_2 by the nicotinamide adenine dinucleotide-dependent (NAD^+) enzyme PDGH and than further catabolized. Metabolism of PGE_2 by PGDH contributes to the characteristic fall in PGE_2 levels after birth that are crucial for remodelling of the ductus arteriosus. For a more complete background and synthesis pathways showing the interrelationships among the above compounds, see Campbell and Halushka (1996). COX, cyclooxygenase; PGG_2, prostaglandin endoperoxide; TXA_2, thromboxane; PGI_2, prostacyclin; PGE_2, prostaglandin E_2; PGD_2, prostaglandin D_2; $PGF_{2\alpha}$, prostaglandin $F_{2\alpha}$; PGDH, prostaglandin 15-hydroxyprostaglandin dehydrogenase.

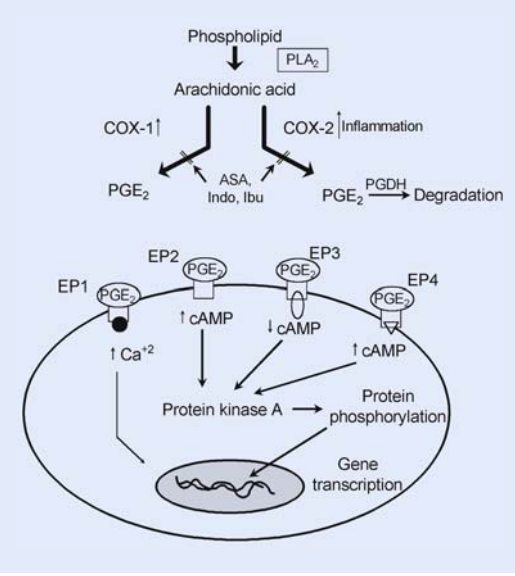


Fig. 3.2 Prostaglandin E_2 synthesis and receptor binding. Prostaglandin E_2 is synthesized from arachidonic acid via the constitutively expressed cyclooxygenase-1, and the inducible cyclooxygenase-2 enzymes. The bioavailability of arachidonic acid from phospholipids and the activity of phospholipase A_2 regulate prostaglandin production. The inducible cyclooxygenase-2 has been localized in many cell types and appears to be activated under conditions of physiologic and pathologic stress. Inflammatory disease states like sepsis induce a cascade of inflammatory and anti-inflammatory mediators that regulate cyclooxygenase-2 activity and gene expression, thereby leading to elevated plasma concentrations of prostaglandin E_2. This mechanism contributes to the clinical phenomenon of reopening of functionally closed ductuses during infection in preterm infants. Once synthesized, prostaglandin E_2 can exert its multiple effects by interacting with one of four classes of prostaglandin receptors, EP1, EP2, EP3, or EP4. Interactions with these receptors elevate (EP2 and EP4) or depress (EP3) intracellular levels of cAMP or increase intracellular calcium (EP1). PLA_2, phospholipase A_2; COX, cyclooxygenase; COX-1, cyclooxygenase-1; COX-2, cyclooxygenase-2; PGE_2, prostaglandin E_2; EP1, EP2, EP3 and EP4, prostaglandin E2 receptor subtypes; Ca, calcium; cAMP, cyclic adenosine 3′, 5′-monophosphate; PGDH, prostaglandin 15-hydroxyprostaglandin dehydrogenase; ASA, aminosalicylic acid; Indo, indomethacin; Ibu, ibuprofen.

References

Morris JL, Rosen DA, Rosen KR: Nonsteroidal anti-inflammatory agents in neonates. Pediatr Drugs 2003; 5: 385–405.

Hahn EL, He LK, Gamelli RL: Prostaglandin E_2 synthesis and metabolism in burn injury and trauma. J Trauma 2000; 49: 1147–54.

Loftin CD, Tiano HF, Langenbach R: Phenotypes of the COX-deficient mice indicate physiological and pathophysiological roles for COX-1 and COX-2. Prostaglandins Other Lipid Mediat 2002; 68–69: 177–85.

Baragatti B, Brizzi F, Ackerley C, Barogi S, Ballou LR, Coceani F: Cyclooxygenase-1 and cyclooxygenase-2 in the mouse ductus arteriosus: individual activity and functional coupling with nitric oxide synthase. Br J Pharmacol 2003; 139: 1505–15.

Norton ME, Merrill J, Cooper BA, Kuller JA, Clyman RI: Neonatal complications after the administration of indomethacin for preterm labor. N Engl J Med 1993; 329: 52–63.

Campbell WB, Halushka PV: Lipid-derived autoacids: Ecosanoids and platelet-activating factor. In Goodman and Gilman's the pharmacological basis of therapeutics, 9th edition 1996: 601–616, (eds. Hardman JG et al.), McGraw-Hill, New York, NY.

Postnatal Circulatory Adaptation

Michael Hofbeck

Basic cardiac development is complete and **fetal circulation** is established by the end of the first trimester. Animal studies form the basis of our understanding of the circulation at this age.

Blood returning from the umbilical vein has a relatively high PO_2 (30–35 mmHg). One third of the inferior caval vein blood crosses the foramen ovale to the left atrium to reach the left ventricle, the aorta and the cerebral vessels (Fig. 4.1). Blood returning from the superior caval vein has a low PO_2 (12–14 mmHg); most of this blood enters the right ventricle while < 3% of this desaturated blood crosses the patent foramen ovale. The right ventricle ejects and receives 2/3 of the combined cardiac output. However, most blood entering the pulmonary artery is shunted away from the high resistance pulmonary vascular bed into the ductus arteriosus which is connected to the descending aorta: While 65% of the combined cardiac output enters the pulmonary artery, only 8% passes the lungs (Fig. 4.1). Pulmonary artery and aorta are at identical pressures due to a widely patent ductus arteriosus. While both the right and left ventricle support the systemic circulation, both ventricles function in parallel.

Immediately **after birth**, following inflation and oxygenation of the lungs, there is a dramatic decrease in pulmonary vascular resistance and a dramatic increase in pulmonary blood flow. Removal of the placental circulation from the systemic circuit leads to an increase of systemic vascular resistance. These changes result in an immediate decrease of ductal right-to-left shunting (Fig. 4.2). Following the increase in pulmonary blood flow there is an increase in left atrial presure, and reduced flow in the inferior caval vein results in a reduced pressure in the right atrium – both factors resulting in functional closure of the flap valve of the foramen ovale with cessation of shunting at atrial level.

Following cessation of shunting at atrial and ductal level the ventricles start to function in series. The ductus arteriosus closes shortly after birth in response to increased oxygen tension and vasoactive substances. While functional closure usually occurs within 10–96 hours, anatomical closure is complete after 2–3 weeks.

The **transitional circulation** consists of a low-resistance pulmonary circuit and a high-resistance systemic circuit separated by a functionally but not anatomically closed foramen ovale and ductus arteriosus. Failure to establish and maintain low pulmonary vascular resistance can lead to persistence of the transitional circulation in the newborn: Low arterial oxygen tension and/or stress may prevent closure of the ductus arteriosus with left-to-right shunting and, in the presence of elevated pulmonary vascular resistance,

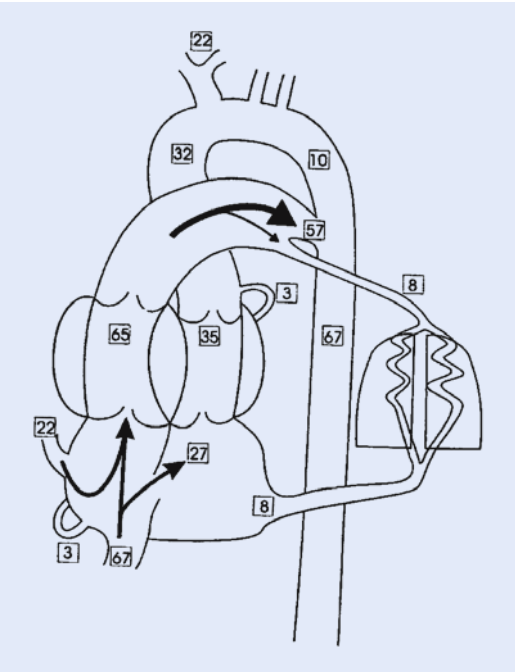


Fig. 4.1 Fetal circulation showing percentages of the combined cardiac output. Note that 57% of the combined cardiac output passes the ductus arteriosus.

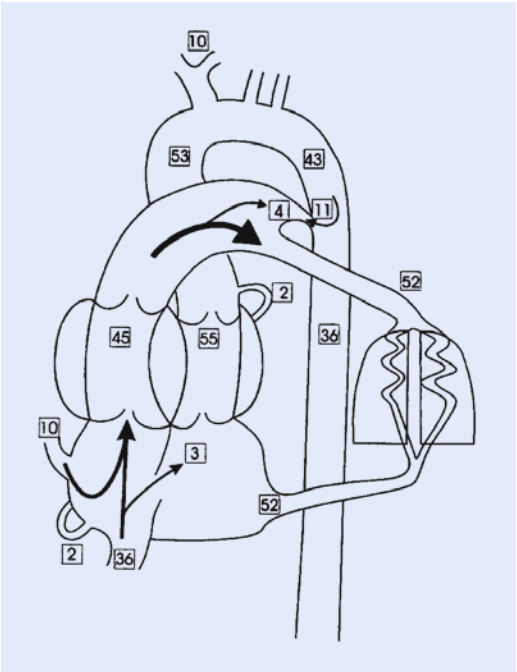


Fig. 4.2 Postnatal circulation showing percentages of the combined cardiac output. Ductus flow fell to 4% of combined cardiac output.

may result in right-to-left shunting at the level of the ductus arteriosus. With a wide open PDA, the pulmonary vascular bed is exposed to systemic blood pressure and increased pulmonary blood flow. Because the preterm infant often has low plasma oncotic pressure and increased capillary permeability, PDA may increase interstitial and alveolar lung fluid. Elevated pulmonary arterial, right ventricular and right atrial pressures can result in right-to-left shunting at the level of the foramen ovale.

The **circulatory consequences** of a PDA depend on the degree of left-to-right shunt and on cardiac and pulmonary responses to the shunt. Before term, the myocardium has more water and less contractile mass. This makes the ventricles less distensible and generates less force per sarcomere than in the term infant.

It seems that failure of the DA to close in preterm infants is not primarily an abnormality of the ductus but rather due to abnormal stimuli (such as acidosis and continuing high circulating prostaglandin levels) or due to the absence of normal stimuli (such as an increase in oxygen tension). Prematurity in the absence of respiratory distress syndrome does not prolong the initial duration of physiologic shunting. Failure of the ductus to close is associated with a more immature status of the lungs, more severe RDS, and more aggressive ventilation.

Oxygen has been shown to have greater constrictive effects on the ductus arteriosus in term than in preterm human infants. This difference is not due to increased muscle development in the ductus wall towards term, but to a developmental alteration in the sensitivity of the vessel to locally produced vasodilators. This difference in reactivity makes the preterm infant more prone to reopening of the ductus, e.g. as a reaction to proinflammatory cytokines in systemic infection. On the other hand, antenatal administration of corticosteroids causes a

significant reduction in the incidence of PDA in premature human infants. This is probably due to decreased sensitivity of the ductus to PGE2 following cortisol exposure. Although, maternal administration of corticosteroids did not reduce EP3 and EP4 receptor gene expression of ductus arteriosus tissue in animal models (Smith et al. 2001). In healthy premature infants physiologic closure of the ductus arteriosus occurs by the 4th day of life – ductal patency beyond day 4 is abnormal. The majority of premature infants ≥ 30 weeks will have normal closure of the ductus by day 4 even in the presence of an uncomplicated RDS. Spontaneous closure of the ductus within a physiologic time frame (< day 4) is significantly reduced (52%) in infants < 30 weeks with relevant RDS.

The degree of ductus patency is regulated by **dilating and contracting factors** (Fig. 4.3). Vasodilating prostaglandins, especially PGE2, play a major role in maintaining ductus patency both in fetal and in postnatal life. In addition to prostaglandins, an increase in PO2 stimulates the release of nitric oxide (NO), which also exerts vasodilating action on the ductus.

Factors causing constriction of the ductus are not yet fully understood. Endothelin 1 (ET-1) seems to maintain fetal vessel tone and is a potent vasoconstrictor for the ductus after birth. At fetal oxygen tensions, ET-1 is produced by both luminal endothelial cells and the muscle media of the ductus arteriosus. The rise in oxygen tension after birth is responsible for constricting the ductus arteriosus, and members of the cytochrome P450 family have been suggested as potential receptors for the oxygen induced events in the ductus (Coceani 1994). ET-1 appears to be a downstream mediator for the oxygen / cytochrome P450 interaction. ET-1 synthesis in the ductus increases with increasing oxygen tension. If ET-1 synthesis

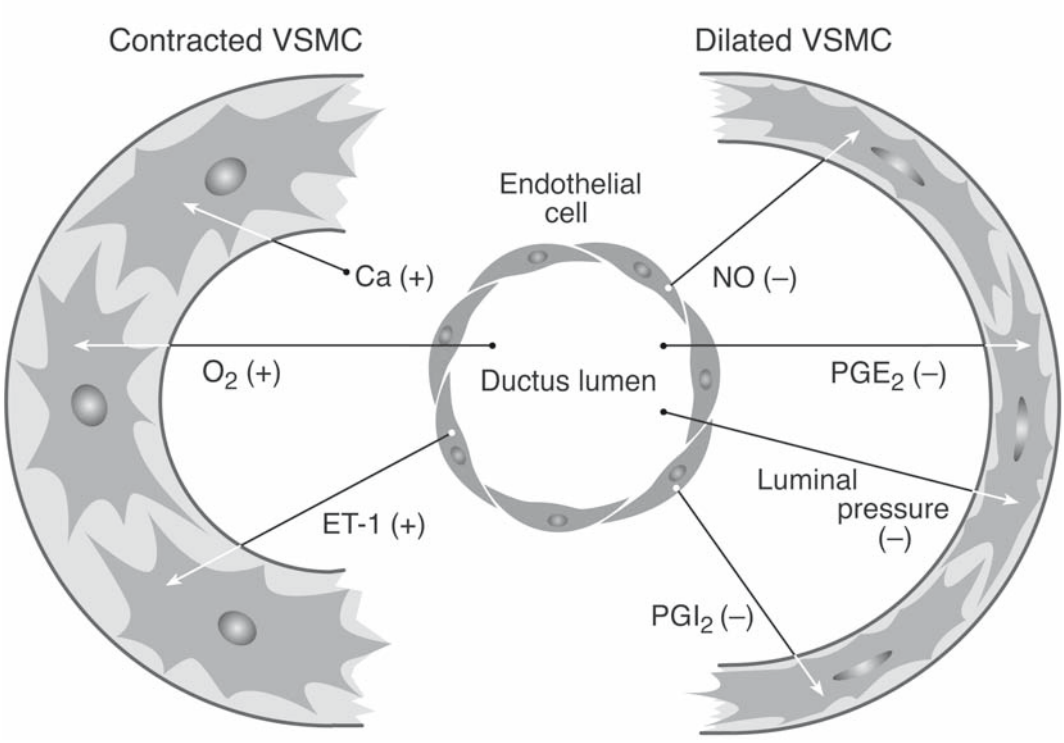


Fig. 4.3 Dilating (-) and contracting (+) mediators involved in the closure of the ductus arteriosus at birth. Ca, calcium; ET1, endothelin-1; NO, nitric oxide; O_2, oxygen; PG, prostaglandin; VSMC, vascular smooth muscle cell.

is blocked, the oxygen-induced contraction of the ductus does not occur (Nakanishi 1993).

Closure of the ductus at birth occurs due to alterations in the balance between dilating and contracting factors. The postnatal increase in PO_2 augments the local formation of the vasoconstrictor ET-1, which then becomes more influential than the vasodilating effects of PGE2 and NO. With the onset of air breathing, pulmonary vascular resistance and pressure drop markedly. This produces a drop in the mean intravascular pressure (which opposes ductus arteriosus constriction) and thereby facilitates closure of the ductus. Patency of the ductus is not necessarily associated with clinical problems. Clinical problems depend on ductal shunting, which in turn depends on size and length of the ductus, systemic and pulmonary blood pressure and pulmonary vascular resistance.

References

Coceani F, Kelsey L. Endothelin-1 release from lamb ductus arteriosus: Relevance to postnatal closure of the vessel. Can J Physiol Pharmacol 1991; 69: 218–21.

Coceani F, Kelsey L, Ackerley C Rabinovitch M, Gelboin H. Cytochrome P450 during ontogenic development: Occurrence in the ductus arteriosus and other tissues. Can J Physiol Pharmacol 1994; 72: 217.

Coceani F, Liu Y, Seidlitz E, Kelsey L, Kuwaki T, Ackerley C, Yanagisama M. Endothelin A receptor is necessary for O(2) constriction but not closure of ductus arteriosus. Am J Physiol 1999; 277: H 1521–31.

Clyman RI, Mauray F, Heymann MA, Ballard PL, Rudolph AM, Payne B. Effects of antenatal glucocorticoid administration on ductus arteriosus of preterm lambs. Am J Physiol 1981; 241: H415–20.

Clyman RI, Waleh N, Black SM, Riemer RK, Mauray F, Chen YQ. Regulation of ductus arteriosus patency by nitric oxide in fetal lambs: The role of gestation, oxygen tension, and vasa vasorum. Pediatr Res 1998; 43: 633–44.

Clyman RI, Chen YQ, Chemtob S, Mauray F, Kohl T, Varma DR, Roman C. In utero remodeling of the fetal lamb ductus arteriosus: The role of antenatal indomethacin and avascular zone thickness on vasa vasorum proliferation, neointima formation, and cell death. Circulation 2001; 103: 1806–12.

Hinek A, Rabinovitch M: The ductus arteriosus migratory smooth muscle cell phenotype processes tropoelastin to a 52 kDa product associated with impaired assembly of elastic laminae. J Biol Chem1993; 268: 1405.

Kandzora J, Köster S, Möller JC. Bedeutung der Kreislaufumstellung für das perinatale Management angeborener Herzfehler. Gynäkologe 1997; 30: 249–59.

Kajino H, Chen YQ, Chemtob S, Waleh N, Koch CJ, Clyman RI. Tissue hypoxia inhibits prostaglandin and nitric oxide production and prevents ductus arteriosus reopening. Am J Physiol Regul Integr Comp Physiol 2000; 279: R278–86.

Nakanishi T, Gu H, Hagiwara N, Momma K: Mechanisms of oxygen-induced contraction of the ductus arteriosus isolated from the fetal rabbit. Circ Res 1993; 72: 1218.

Reller MD, Ziegler ML, Rice MJ, Solin RC, McDonald RW. Duration of ductal shunting in healthy preterm infants: An echocardiographic color flow Doppler study. J Pediatr 1988; 12: 441–6.

Reller MD, Buffkin DC, Colasurdo MA, Rice MJ, McDonald RW. Ductal patency in neonates with respiratory distress syndrome. A randomized surfactant trial. Am J Dis Child 1991; 145: 1017–20.

Reller MD, Rice MJ, McDonald RW. Review of studies evaluating ductal patency in the premature infant. J Pediatr 1993; 122: S59–62.

Richard C, Gao J, LaFleur B, Christman BW, Anderson J, Brown N, Reese J. Patency of the preterm fetal ductus arteriosus is regulated by endothelial nitric oxide synthase and is independent of vasa vasorum in the mouse. Am J Physiol Regul Integr Comp Physiol 2004; 287: R652–60.

Smith GC, Wu WX, Nijland MJ, Koenen SV, Nathanielsz PW: Effect of gestational age, corticosteroids, and birth on expression of prostanoid EP receptor genes in lamb and baboon ductus arteriosus. Pediatr J Cardiovasc Pharmacol 2001; 37: 697–704.

Taniguchi T, Azuma H, Okada Y, Naiki H, Hollenberg MD, Muramatsu I. Endothelin-1-endothelin receptor type A mediates closure of the rat ductus arteriosus at birth. J Physiol 2001; 537: 579–85.

Yanowitz TB, Yao AC, Pettigrew KD, Werner JC, Oh W, Stonestreet BX: Postnatal hemodynamic changes in very-low-birthweigth infants. J Appl Physiol 1993; 87: 370–80.

Epidemiology of Persisting Ductus in Preterm Infants

Christiane Pees, Michael Obladen

In the normal population, the incidence of congenital heart defects is approximately one in every 200 births [Mitchell et al. 1971]. More recent statistics show a total prevalence of 12–14 congenital heart defects per 1000 live births [Hoffmann et al. 2002]. The patent ductus arteriosus as a single inborn error in newborns accounts for 5–10% of all congenital heart diseases, not considering the persistence of the ductus in premature infants [Myung 2002]. However, due to the metabolic immaturity, patency of the ductus arteriosus is a more or less common physiological phenomenon in preterm infants, who account for as many as 5–7% of all liveborn neonates.

Congenital Anomaly or Prolonged Adaptation?

To give a figure for the prevalence of persisting ductus arteriosus in premature infants one must take into account different problems associated with the inhomogenous group of patients and the overall changes in this population during recent years due to improved prenatal care, postnatal therapy, and new diagnostic possibilities. Before establishment of the Doppler technique as an integral part of echocardiography, the ductus was diagnosed mainly by clinical symptoms such as a systolic or continous murmur, bounding pulses and an active precordium as well as increased vascular markings and an increased cardiothoracic ratio on chest x-ray films. Studies showed a poor sensitivity of these clinical signs compared to Doppler echocardiography, with only 43% for pulse quality and 42% for a murmur. The radiological examination did not improve the diagnosis of a patent ductus arteriosus at all [Davis et al. 1995]. In a study by Hirsimäki et al. [1990], the incidence of a patent ductus would have been 18% when diagnosed only by clinical signs, but 47% had ductal shunting during the first two days of life as shown by Doppler echocardiography. Studies based on echocardiography a few days after birth usually record a larger number of infants with PDA than studies done after three weeks [Ooshima et al. 1995]. Many infants have phases of intermittent patency of the ductus, especially during phases of respiratory instability or infection [Lim et al. 1992]. Reller et al. [1985] found a hemodynamically significant PDA early (during the first week of life) in 75% of the neonates by echocardiography, whereas a murmur was not heard in 66% of these 32 infants. This study revealed that there is a high incidence of »silent ductal shunts« during the first days of life, which is also postulated by Zanardo et al. [1991], who favored an immediate intervention for a »silent« ductus. The incidence of silent ductus has been estimated to be 1 per 500 to 1000 in the total population [Lloyd et al. 1994].

Clinical Relevance

In previous years, the ductus was usually searched for when the neonate could not be weaned from the ventilator or when cardiac failure occurred. More recently, the patent ductus became thought to cause intraventricular hemorrhage and therefore worsen neurological outcome in the premature infant. Several studies suggested that PDA contributes to the development of bronchopulmonary dysplasia and necrotizing enterocolitis, which further increased motivation to prevent these diseases by closure of the PDA. This explains why the assessment age recently tends to be much earlier. This issue leads to the next problem: the definition of a patent ductus arteriosus. Is a patent ductus in a premature infants only sign of a prolonged circulatory adaptation and will close spontaneously later, or is it a real persistent patency without closure and with the features of a disease?

Frequency Depends on Immaturity and Echocardiography

Reller et al. [1988] found spontaneous closure of the ductus in healthy preterm infants of 30–37 gestational weeks in 50–58% on the second and in 81–87% on the third day of life. All except one infant had a patent ductus closed at the postulated age of four days and the one still open ductus closed on the ninth day of life. The same group evaluated ductal patency in premature infants of similar gestational age but with RDS and found that the timing of spontaneous functional closure of the ductus arteriosus in these infants was comparable to healthy infants without RDS. By the fourth day of life, only 4 of 36 (11.1%) of the infants continued to have evidence of ductal patency (Reller et al. 1990). Other studies evaluating the ductal closure in very low birth weight (VLBW) infants described delayed spontaneous closure in 79% of preterms with an average age of 3.1 months [Siassi et al. 1976]. Dudell et al. [1984] described a risk of 75% for prolonged ductal shunting in VLBW infants (mean gestational age 28.7 +/- 1.7 weeks), with a therapy indication for permanent patency later on in 63% of these cases. During the past 30 years, the prevalence of persisting ductus arteriosus has increased, while the infants' mean birth weight has decreased (Table 5.1). As Reller et al. [1990] stated, most of the patent ductuses close spontaneously in infants born with a gestational age of more than 30 weeks. The readiness to intervene therapeutically once PDA has been diagnosed has increased to over 50%: In the EPICURE study performed in the UK and Ireland in 1999, PDA was reported in 202 of 313 survivors born before 26 weeks of gestation (65%). Of these infants with PDA, 116 (57%) were treated with indomethacin alone, 26 (13%) with indomethacin and ligation, and 6 (3%) with ligation alone [Costeloe et al. 2000].

Figures 5.1 and 5.2 show the same effect for our department: Figure 5.1 shows the management of PDA in 1404 VLBW infants admitted from 1987 to 2003. It can be seen that with the introduction of the »neuroprotective« indication in 1999, the frequency of PDA intervention increased, and indomethacin was replaced by ibuprofen in April 2001.

Figure 5.2 shows that in the years 1992–1997, when echocardiography was not yet a routine procedure in the first days of life, 63% of the VLBW infants in our unit remained without any intervention for PDA. In these years, PDA was mainly treated in order to facilitate weaning from artificial ventilation, and median age at the first intervention was 9 days. In the years 1998–2003, when early echocardiography had been established and the intervention became more and more oriented towards the brain, the percentage of VLBW infants without intervention had dropped to 57%, and the median age at the first intervention to 5 days.

Individual Variability

Little is known on constitutional or genetic factors making the individual infant more susceptible for PDA. In the present era of prenatal corticoids, postnatal surfactant substitution, and replacement of prolonged positive pressure ventilation by early nasal CPAP, most infants in neonatal intensive care units with ventilatory problems are those below 28 weeks of gestation.

Table. 5.1 Comparison of references reporting the incidence of PDA in preterm infants during the past 30 years. @, with; BW, birth weight (g); GA, gestational age (completed weeks); DOL (day of life); n.a., not available. Data are [mean] and ranges.

First Author	Year	N	BW (g) [mean]	GA (weeks) [mean]	Assessment method	Age (DOL)	PDA % Prevalence
Kitterman	1972	111	<1750 [1258]	[30.9]	clinical (16 catheters)	6–33	**15.3** (17.5 @ RDS)
Siassi	1976	150 100 50	 [1559] [2248]	28–40 [33] [36]	clinical	> 3rd	**21** 36 12
Brown	1979	47 64 118 676	<1000 –1250 –1750 >1751	n.a.	n.a.	n.a.	47 38 13 1
Ellison	1983	1689 319 824 546	<1750 500–999 1000–1499 1500–1750		clinical and echocardiography	< 14	**20.2** 42 20.6 7
Dudell	1984	191 119 72	 [1060] [2166]	 [28.7] [36.0]	aortic contrast echocardiography	1 –4 3 3	**56** 65.5 40.3
Reller	1985	50 13 18 19	750–1500 750–1000 1001–1250 1251–1500	27–33 [29.4]	clinical and echocardiography	< 5	**64** 77 56 63
Mouzinho	1991	636	[1037] 500–750 750–1000 1001–1250 1251–1500	[27.9] 25–27 28–29 30–31 > 32	clinical and echocardiography	10+/–6	**19** 33 / 41 30 / 18 22 / 12 8 / <1
Zanardo	1991	175	640–1750 [1256]	25–33 [29.2]	Doppler echocardiography	3	**20.5** (@ RDS)
Hack	1991	1765 349 382 1034	<1500 500–750 751–100 1001–1500	[28.1]	echocardiography n.a.	n.a	**21.5** 32 41 17
Trus	1993	76	[650]	[25.3]	clinical and LA/Ao	n.a.	**55.3**
Vermont Oxford Network	1993	2961 526 726 820 889	501–1500 501–750 751–1000 1001–1250 1251–1500	[28]	echocardiography n.a.	n.a.	**31** 42 42 29 19
Davis	1995	100	[1269]	[29.5]	clinical + Doppler	3–7	**23**
Rojas	1995	119	500–1000 [802]	[26.8]	clinical or Doppler	early <7 late >7	**58** **28.6**
Lee	2000	13317	n.a.	28–37	n.a.	n.a.	**28**
Costeloe	2000	313	360–1040	22.–25.	n.a.	n.a.	**64.5**

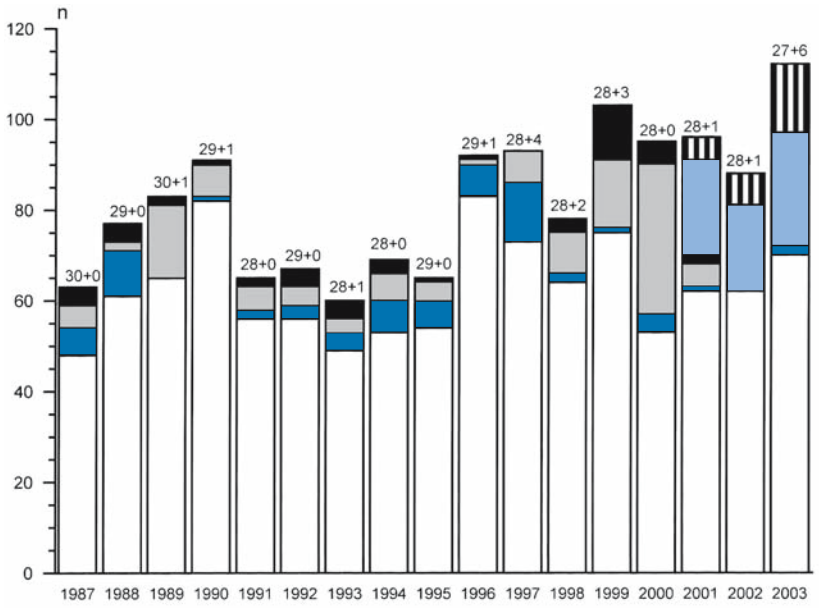


Fig. 5.1 Management of PDA in 1404 VLBW infants admitted from 1987 to 2003. White, no intervention. Dark blue, first line surgery. Grey, first line indomethacin. Bright blue, first line ibuprofen. Black, indomethacin failure followed by surgery. Dashed, ibuprofen failure followed by surgery. It can be seen that, with the introduction of the »neuroprotective« indication in 1999, the frequency of PDA intervention increased, and indomethacin was replaced by ibuprofen in 2001.

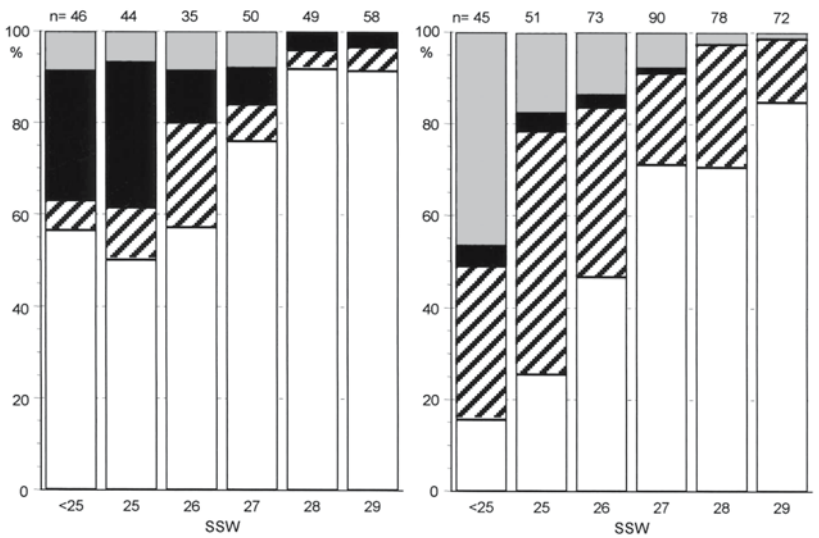


Fig. 5.2 Management of PDA by gestational age in 691 survivors of less than 30 weeks gestation at Charité-Virchow, Dept. of Neonatology. Left panel: 282 infants admitted 1992–1997, right panel: 409 infants admitted 1998–2003. White, no intervention. Dashed, closure by pharmacotherapy. Black, first line surgery. Grey, surgery after failure of pharmacotherapy. Between the two six-year periods, the rate of PDA intervention in this gestational age group increased from 28% to 43% ($p < 0.001$), the median age at the first intervention decreased from 9 to 5 days, and surgery as first line approach has been virtually abandoned.

So if one looks at a study group of this age today, one will find much higher prevalences of ductal patency than even a few years ago (Fig. 5.2). In our own department, the prevalence of the patent ductus in infants below 28 weeks gestation is 72% assessed between 24 and 72 hours of life by Doppler echocardiography (unpublished data).

Conclusions

The incidence of hemodynamically relevant PDA highly depends on the diagnostic tools established. In the era of surfactant substitution, PDA is rarely a clinical problem in infants of 28 weeks gestation or more. Most infants of less than 28 weeks gestation will have some ductal patency during the first three days of life. However, many of theses ductuses will close spontaneously. Echocardiography allows a timely diagnosis of a PDA. However, neonatologists should be aware of the dangers inherent in regarding a prolonged physiological adaptation as a disease.

References

1. Brown ER. Increased risk of pulmonary dysplasia in infants with patent ductus arteriosus. J Pediatr 1979; 95: 865–6.
2. Costeloe K, Hennessy E, Gibson AT, Marlow N, Wilkinson AS. The EPICure Study: Outcomes to discharge from hospital for infants born at the threshold of viability. Pediatrics 2000; 106: 659–71.
3. Davis P, Turner-Gomes S, Cunningham K, Way C, Roberts R, Schmidt B. Precision and accuracy of clinical and radiological signs in premature infants at risk of patent ductus arteriosus. Arch Pediatr Adolesc Med 1995; 149: 1136–41.
4. Dudell GG, Gersony WM. Patent ductus arteriosus in neonates with severe respiratory disease. J Pediatr 1984; 104; 915–20.
5. Ellison RC, Peckham GJ, Lang P, Talner NS, Lerer TJ, Lin L, Dooley KJ, Nadas AS. Evaluaion of the preterm infant for patent ductus arteriosus. Pediatrics 1983; 71: 364–72.
6. Hack M, Horbar JD, Malloy MH, Tyson JE, Wright E, Wright L. Very low birth weight outcomes of the National Institute of Children Health and Human Development Neonatal Network. Pediatrics 1991; 87: 587–97.
7. Hirsimäki H, Kero P, Wanne O. Doppler ultrasound and clinical evaluation in detection and grading of patent ductus arteriosus in neonates. Crit Car Med 1990; 18: 490–3.
8. Hoffmann JIE, Kaplan S. The incidence of congenital heart disease. J Am Coll Cardiol 2002; 39: 1890–900.
9. Kitterman JA, Edmunds LH, Gregory GA, Heymann MA, Tooley WH, Rudolph AM. Patent ductus arteriosus in premature infants. Incidence, relation to pulmonary disease management. New Engl J Med 1972; 287: 473–7.
10. Lee SK, McMillan DD, Ohlsson A, Pendray M, Synnes A, Whyte R, Chien L-Y, Sale J and the Canadian NICU Network. Variations in practice and outcomes in the Canadian NICU Network: 1996–1997. Pediatrics 2000; 106: 1070.
11. Lim MK, Hanretty K, Houston AB, Lilley S, Murtagh EP. Intermittent ductal patency in healthy newborn infants: Demonstration by colour Doppler flow mapping. Arch Dis Child 1992; 67: 1217–8.
12. Lloyd TR, Beekman RH, 3rd. Clinically silent patent ductus arteriosus (letter). Am Heart J 1994; 127: 1664–5.
13. Mitchell SC, Korones SB, Berendes HW. Congenital heart diseases in 56,109 births. Incidence and natural history. Circulation 1970; 43: 323–32.
14. Mouzinho AI, Rosenfeld CR, Risser R. Symptomatic patent ductus arteriosus in very-low-birth-weight infants: 1987–1989. Early Hum Dev 1991; 27:65–77.
15. Myung K Park. Pediatric Cardiology for Practitioners, 4th Edition, Mosby 2002.
16. Ooshima A, Fukushige J, Ueda K. Incidence of structural cardiac disorders in neonates: An evaluation by colour Doppler echocardiography and the results of a 1-year follow-up. Cardiology 1995; 86: 402–6.
17. Reller MD, Lorenz JM, Kotagal UR, Meyer RA, Kaplan S. Hemodynamically significant PDA: An echocardiographic and clinical assessment of incidence, natural history, and outcome in very low birth weight infants maintained in negative fluid balance. Pediatr Cardiol 1985; 6: 17–24.
18. Reller MD, Ziegler ML, Rice MJ, Solin RC, McDonald RW. Duration of ductal shunting in healthy preterm infants: An echocardiographic color flow Doppler study. J Pediatr 1988; 112: 441–6.
19. Reller MD, Colasurdo MA, Rice MJ, McDonald RW. The timing of spontaneous closure of the ductus arteriosus in infants with respiratory distress syndrome. Am J Cardiol 1990; 66: 75–8.
20. Rojas MA, Gonzalez A, Bancalari E, Claure N, Poole C, Silva-Neto G. Changing trends in the epidemiology and pathogenesis of neonatal chronic lung disease. J Pediatr 1995; 126: 605–10.
21. Siassi B, Blanco C, Cabal LA, Coran AG. Incidence and clinical features of patent ductus arteriosus in low-birthweight infants: A prospective analysis of 150 consecutively born infants. Pediatrics 1976; 57: 347–51.
22. Trus T, Winthrop AL, Pipe S, Shah J, Langer JC, Lau GYP. Optimal management of patent ductus arteriosus in the neonate weighing less than 800 g. J Pediatr Surg 1993; 28: 1137–9.
23. The Vermont-Oxford Trials Network: Very low birth weight outcomes for 1990. Pediatrics 1993; 91: 540–5.
24. Zanardo V, Milanesi O, Trevisanuto D, Rizzo M, Ronconi M, Stellin G, Cantarutti F. Early screening and treatment of »silent« patent ductus arteriosus in prematures with RDS. J Perinat Med 1991; 19: 291–5.

Part II Clinical Features

6

Persisting Ductus Arteriosus and Respiratory Problems

Walter Kachel

The relation between persisting or reopened ductus arteriosus and respiratory complications has been recognized since successful ventilatory support became available with the introduction of continuous positive airway pressure in the early seventies. Infants with PDA showed especially severe course and unfavorable outcome, and bronchopulmonary dysplasia has been linked to patency of the ductus arteriosus.

Association with Pulmonary Immaturity / Surfactant Deficiency

PDA is associated with respiratory distress syndrome and therefore both with pulmonary immaturity and with the degree of respiratory insufficiency. Various prevalences have been reported and the studies are difficult to compare, as different definitions for »relevant« or »significant« PDA have been used. The high prevalence in premature infants with respiratory distress syndrome (RDS) is probably related to diminished oxygen availability and augmented response to PGE2, since a major source for PGE2 is the lung. Nevertheless spontaneous ductus closure occurs in 65% of premature infants with birth weight below 1500 g. In 19% the ductus arteriosus reopens and in 16% it remains patent from birth on (Evans et al. 1995). In other cohorts, different prevalence data were reported. Margot van de Bor et al. (1988) found that occurrence of a patent ductus arteriosus in no way increases linearly with decreasing gestational age and suggested that birth weight and nutritional status play equally important roles. RDS is the condition mostly associated with PDA. In Birmingham (Alabama) about 1/3 of all infants suffering from RDS simultaneously had PDA. Also in van de Bor's cohort study the co-occurrence of PDA and RDS was shown to be highly significant. In the same way this was true for septicemia. The occurrence of RDS increased the chance for PDA sevenfold. The chance for PDA increases twofold in twins, and fivefold in twins with birth weight below 1750 g, which probably contributes to the augmented mortality of premature twins. The following reasons may be responsible for the increased risk for PDA in premature infants with RDS: (1) More frequent phases of hypoxia and apnoic spells, (2) Need for artificial ventilation, (3) Shear stress of lung tissue, (4) Release of arachidonic acid and prostacyclin, (5) PGE release along with apneic spells.

Association with Pulmonary Infection / Inflammatory Response

Inflammatory processes are associated with PDA and may lead to reopening of the ductus. They also

are major players in the pathogenesis of chronic lung disease, as shown for Ureaplasma urealyticum and other pulmonary contaminants. Increased concentration of platelet activating factor has been demonstrated in the tracheal aspirate of neonates with PDA (Koyama et al 1993). Following successful closure of the PDA, polymorphonuclear cell counts fell significantly both in peripheral blood and tracheal aspirate (Nakamura et al. 2002), and myeloperoxidase activity was found to decrease in tracheal aspirates of preterm infants, in whom pharmacologic closure of the PDA was successful (Varsila et al 1995, Nakamura et al. 2002). These anti-inflammatory changes after closure of the PDA probably are caused not only by indomethacin, but by PDA closure itself and one mechanism by which closure of the ductus may reduce infants' respiratory dysfunction may be amelioration of the pulmonary inflammation caused by activated neutrophils (Varsila et al. 1995).

Impact of prostaglandins

Neonatal platelets are able to augment the release rate of arachidonic acid; asphyxia und hypoxia stimulate prostaglandin and thromboxane synthesis. Hutchinson et al. (1985) demonstrated increased 6-keto-$PGF_{1\alpha}$ levels immediately after birth in premature infants who later suffered from PDA. T_xB_2 levels were also significantly elevated in this group. In preterm infants without PDA, the presence of RDS was associated with higher 6-keto-$PGF_{1\alpha}$ levels. Kluckow et al. demonstrated in 1999 that premature infants suffering from RDS have increased 6 $KPGF_{1\alpha}$ levels at 12 and 24 hours of age.

X-Ray Opacities

In a systematic evaluation of X-ray studies, Odita showed (2001) that non-clearance of reticulogranular lung pattern may accompany, but cannot be strongly associated with, PDA. However, a significant proportion of the persisting lung opacities were associated with pulmonary interstitial emphysema or with chronic lung disease. Figure 6.1 shows that lung opacities may clear rapidly following ductus ligation, even in infants with late surgery for PDA.

PDA, Lung Water, and Pulmonary Hemorrhage

Alpan et al. (1989) investigated in an animal experiment with lambs the extent to which increased lung blood flow and increased prostaglandin expression lead to protein leakage. After

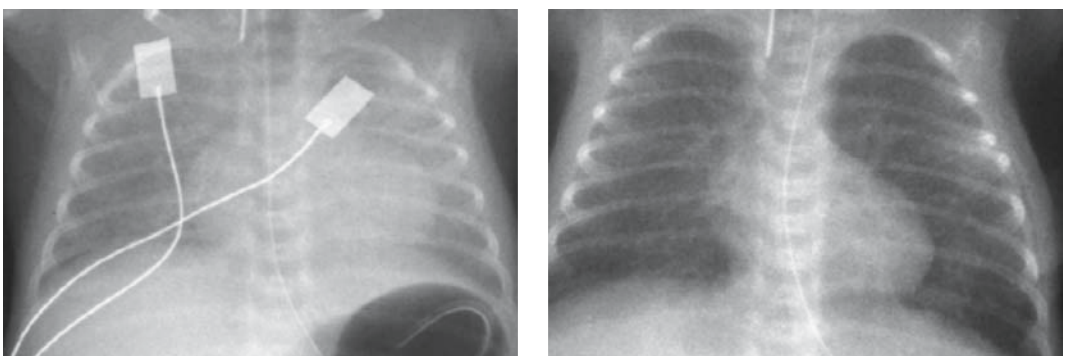


Fig. 6.1 Consecutive chest X-rays of a 1215g girl of 27 weeks gestation referred from an outside hospital for ductus ligation after unsuccessful treatment with indomethacin. The left image, taken on the 17th day of life one hour before surgical ligation, shows hazy lungs and cardiomegaly. The right image, taken one hour after the operation, shows how rapidly the lung has cleared and cardiomegaly diminished. Seven days after the PDA ligation, however, the infant developed necrotizing enterocolitis which she survived following enterostomy.

an experimental course of only 3 hours they could neither demonstrate water accumulation within the left sided lung (wet : dry weight), nor substantiate larger quantities of labeled albumin in lung tissue or eluate. In additional experiments with a similar animal model, Alpan et al. (1991) addressed lymphatic clearance of the lung. When the ductus was open, pulmonary blood flow duplicated as compared to phases with closed ductus. Simultaneously lymph flow exceeded 68% and protein-content decreased by 17% in the open ductus situation as compared to the closed ductus condition. Protein clearance, which can be calculated from these measurements, was 39% when the ductus was open. These data suggest a protective mechanism with regard to lung tissue and circulatory regulation. Finally a clinical example may be added: Kluckow and Evans (2000) published several cases with pulmonary hemorrhage. By echocardiography, the authors could demonstrate especially large ductal diameters and a significantly increased ductal flow in the infants in whom pulmonary hemorrhage occurred.

Lung Mechanics

As early as 1978, Naulty showed that lung mechanics were altered in infants with persisting ductus arteriosus even when lung failure was not clinically prominent. Compliance was measured 24 h before and 24 hours after ductus ligation and was found to increase markedly. Nevertheless some patients died from BPD during the further course. Also Gerhard and Bancalari (1980), who examined lung function in ten infants undergoing surgical ligation of the ductus in the first 48 hours, found a clear inverse-linear relation between basic compliance and percent improvement. Yeh et al. (1981) published lung function parameters measured within a blinded study with indomethacin for ductal closure in unventilated infants. Also in this study a significant increase in compliance became apparent along with the pharmacological ductus closure. In a similar way the results by Balsan et al. (1991) may be interpreted, who recorded lung mechanics days before appearance of a PDA and days after intervention. These data differ from the results presented by Kraus et al. (1989): They studied three groups of ventilated premature infants, one with PDA and following intervention with indomethacin, a second group with PDA without pharmacological intervention, and a third group without PDA. The study could not find any differences regarding the course of lung function among the three groups. In 11 infants with mean gestational age of 27.1 weeks and severe respiratory insufficiency, Farstad and Bratlid (1994) found no improvement in lung mechanics or oxygenation up to 48 hours after ductus ligation at age 14 days and concluded that structural changes in the lung were already established. A recent study of 16 infants with mean gestational age 27.6 weeks reported significant increases in dynamic compliance of 77%, in tidal volume of 29%, and in minute ventilation of 17% (Szymankiewicz et al. 2004).

Surfactant Substitution

The additional influence of surfactant was analyzed in a controlled study conducted by Heldt et al. (1989), who explored lung function in infants with PDA for 30 hours. Compliance was much higher when spontaneous ductus closure occurred. Interventional ductal closures did not simulate such a favorable development. In the early years of surfactant substitution, there was some concern that this treatment may augment the risk for PDA. However, the studies dealing with effects and side effects of exogenous surfactant showed that the beneficial effects of exogenous surfactant were not associated with either an increased risk for delayed closure of the ductus or a greater need for indomethacin treatment (Reller et al. 1991).

Chronic Lung Disease

It is difficult to study the association of PDA and chronic lung disease (CLD) of the preterm infant, as the basic risks for CLD and PDA are

finally the same. In 1984 Peckham already found no differences in CLD prevalence at one year of age among three distinct intervention strategies for PDA. Recent studies dealing with CLD distinguish between ventilator therapy or oxygen dependency at the age of 28 days and the need for ventilation or oxygen therapy beyond 36 weeks corrected gestational age. Usually the second definition is seen to be more relevant for the population of very immature infants, in whom PDA is frequent. In very immature infants, an early form of chronic lung disease (»new BPD«) is frequent, which is more associated with inflammation than with artificial ventilation. The four PDA reviews listed in the Cochrane Library (Malviya et al. 2003, Shah et al. 2003, Cooke et al. 2003, Herrera et al. 2004) which focus on different forms of PDA interventions (surgical, indomethacin, ibuprofen) have shown no reduction of CLD prevalence in early or late intervention.

Conclusions

Persisting ductus arteriosus impairs lung function in a very early stage and seems to activate processes which influence lung growth and structural differentiation very early. Inflammatory processes contribute both to reopening of the ductus and to the development of chronic lung disease. Surgical or pharmacological closure, even when executed very early or prophylactically, does not reverse this process in all cases.

References

Evans N, Iyer P. Longitudinal changes in the diameter of the ductus arteriosus in ventilated preterm infants: Correlation with respiratory outcomes. Arch Dis Child Fetal Neonatal Ed. 1995; 72: F156–61.

Van de Bor M, Verloove-Vanhorick SP, Brand R, Ruys JH. Patent ductus arteriosus in a cohort of 1338 preterm infants: a collaborative study. Paediatr Perinat Epidemiol. 1988; 2: 328–36.

Koyama N, Ogawa Y, Kamiya K, et al: Increased platelet activating factor in the tracheal aspirates from neonates with patent ductus arteriosus. Clin Chim Acta 1993; 215: 73–9.

Nakamura T, Takasaki J, Ogawa Y. Inflammatory changes in the lungs of premature infants with symptomatic patent ductus arteriosus. Pediatrics International 2002; 44: 363–7.

Varsila E, Hallman M, Venge P, Andersson S. Closure of patent ductus arteriosus decreases pulmonary myeloperoxidase in premature infants with respiratory distress syndrome. Biol Neonat 1995; 67: 167–71.

Hutchison AA, Ogletree ML, Palme CJ, Leheup BP, Barrett JM, Fleischer AC, Stahlman MT, Brigham KL. Plasma 6-keto prostaglandin F1 alpha and thromboxane B2 in sick preterm neonates. Prostaglandins Leukot Med. 1985; 18: 163–81.

Kluckow M, Evans N, Leslie G, Rowe J. Prostacyclin concentrations and transitional circulation in preterm infants requiring mechanical ventilation. Arch Dis Child Fetal Neonatal Ed. 1999; 80: F34–7.

Odita JC. The significance of recurrent lung opacities in neonates on surfactant treatment for respiratory distress syndrome. Pediatr Radiol. 2001; 31: 87–91.

Alpan G, Scheerer R, Bland R, Clyman R. Patent ductus arteriosus increases lung fluid filtration in preterm lambs. Pediatr Res. 1991; 30: 616–21.

Alpan G, Mauray F, Clyman RI. Effect of patent ductus arteriosus on water accumulation and protein permeability in the lungs of mechanically ventilated premature lambs. Pediatr Res. 1989; 26: 570–5.

Kluckow M, Evans N. Ductal shunting, high pulmonary blood flow, and pulmonary hemorrhage.J Pediatr 2000; 137: 68–72.

Naulty CM, Horn S, Conry J, Avery GB. Improved lung compliance after ligation of patent ductus arteriosus in hyaline membrane disease. J Pediatr 1978; 93: 682–4

Gerhardt T, Bancalari E. Lung compliance in newborns with patent ductus arteriosus before and after surgical ligation. Biol Neonate 1980; 38: 96–105.

Yeh TF, Thalji A, Luken L, Lilien L, Carr I, Pildes RS. Improved lung compliance following indomethacin therapy in premature infants with persistent ductus arteriosus. Chest 1981; 80: 698–700.

Balsan MJ, Jones JG, Guthrie RD. Effects of a clinically detectable PDA on pulmonary mechanics measures in VLBW infants with RDS. Pediatr Pulmonol 1991; 11: 161–5.

Krauss AN, Fatica N, Lewis BS, Cooper R, Thaler HT, Cirrincione C, O'Loughlin J, Levin A, Engle MA, Auld PA. Pulmonary function in preterm infants following treatment with intravenous indomethacin. Am J Dis Child 1989; 143: 78–81.

Farstad T, Bratlid D. Pulmonary effects of closure of patent ductus arteriosus in premature infants with severe respiratory distress syndrome. Eur J Pediatr 1994; 153: 903–5.

Szymankiewicz M, Hodgman JE, Siassi B, Gadzinowski J. Mechanics of breathing after surgical ligation of patent ductus arteriosus in newborns with respiratory distress syndrome. Biol Neonat 2004; 85: 32–6.

Heldt GP, Pesonen E, Merritt TA, Elias W, Sahn DJ. Closure of the ductus arteriosus and mechanics of breathing in preterm infants after surfactant replacement therapy. Pediatr Res 1989; 25: 305–10.

Reller MD, Buffkin DC, Colasurdo MA, Rice MJ, McDonald RW. Ductal patency in neonates with respiratory distress syndrome. Am J Dis Child 1991; 145: 1017–20.

Peckham GJ, Miettinen OS, Ellison RC, Kraybill EN, Gersony WM, Zierler S, Nadas AS. Clinical course to 1 year of age in premature infants with patent ductus arteriosus: results of a multicenter randomized trial of indomethacin. J Pediatr 1984; 105: 285–91.

Malviya M, Ohlsson A, Shah S. Surgical versus medical treatment with cyclooxygenase inhibitors for symptomatic patent ductus arteriosus in preterm infants. Cochrane Database Syst Rev. 2003;(3):CD003951.

Shah SS, Ohlsson A. Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants. Cochrane Database Syst Rev. 2003;(2): CD004213.

Cooke L, Steer P, Woodgate P. Indomethacin for asymptomatic patent ductus arteriosus in preterm infants. Cochrane Database Syst Rev. 2003; (2): CD003745.

Herrera C, Holberton J, Davis P. Prolonged versus short course of indomethacin for the treatment of patent ductus arteriosus in preterm infants. Cochrane Database Syst Rev. 2004;(1):CD003480.

Influence on Mesenteric Perfusion and Necrotizing Enterocolitis

Josef Sonntag

Introduction

Since understanding of the circulatory physiology in the developing intestine may provide insight into the roles of patent ductus arteriosus (PDA) and mesenteric ischemia for the etiology of necrotizing enterocolitis (NEC), this review summarizes first of all what is currently known about the regulation of blood flow and oxygenation in the immature gut.

Mesenteric Perfusion

Oxygen consumption is the product of blood flow and the arteriovenous oxygen content difference [6]. The developing intestine is unable to autoregulate blood flow under falling pressure. A young intestine fails to demonstrate vasodilation in response to arterial pressure reduction; indeed, vascular resistance increases after pressure reduction. Collateral circulation within the superior mesenteric artery network is functionally immature as well. Nonetheless, under physiologic conditions it can maintain oxygen uptake by increasing oxygen extraction without increase in blood flow. However, the reserve during periods of stress is minimal, resulting in the young intestine having an increased risk for tissue hypoxia. The tolerance for ischemic insult decreases if the intestine is simultaneously exposed to the lipid component of luminal nutrients [6].

Patent Ductus Arteriosus and Mesenterial Perfusion

Left-to-right shunting through a PDA is associated with reduced postductal organ blood flow through the »ductal steal« phenomenon (Table 7.1). Infants with PDA showed a significant decrease of the endsystolic velocity (31 vs. 15 cm/sec) and enddiastolic velocity (18 vs. –5 cm/sec) in the truncus coeliacus, whereas the pulsatility index (0.75 vs. 1.08) was significantly increased in comparison to that of a healthy control group [7].

Necrotizing Enterocolitis

With a mortality rate of 24% and a frequently impaired neurodevelopmental outcome NEC is one of the most severe diseases of premature infants [17, 18]. The pathogenesis of NEC remains unknown, but contributing factors have been postulated, including prematurity, mesenteric ischemia/hypoxia, enteral alimentation and infection (Fig. 7.1). Ischemia is one of the main

Table 7.1 Mesenteric perfusion in preterm infants with and without PDA.

	Preterm newborns with PDA (n = 12)	Preterm newborns without PDA (n = 24)
Maximal systolic velocity	72 ± 21 cm/sec	77 ± 16 cm/sec
Velocity endsystolic	15 ± 14 cm/sec	31 ± 10 cm/sec
Velocity enddiastolic	-5 ± 8 cm/sec	18 ± 9 cm/sec

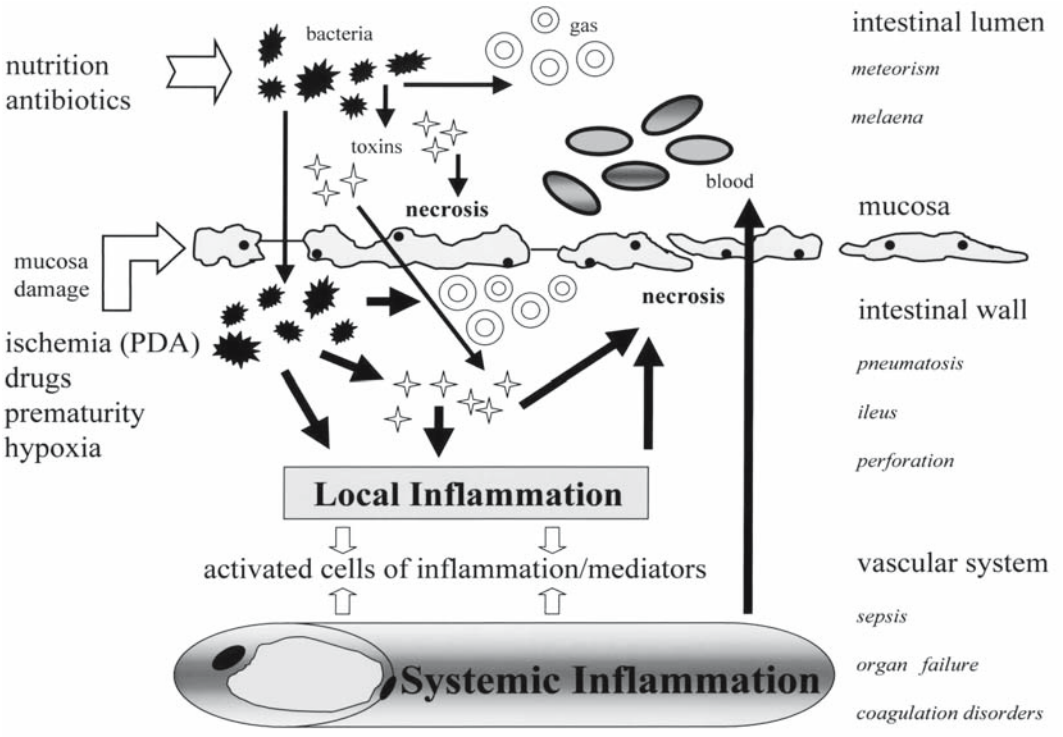


Fig. 7.1 Circulatory and inflammatory mechanisms involved in the pathogenesis of necrotizing enterocolitis. PDA triggers or contributes to multiple vicious cycles by decreasing perfusion of the intestinal wall.

risk factors, which was shown by Coombs et al. [4, 5] in Doppler studies of neonates at risk of NEC by reduced mesenterial blood flow. Growth retarded fetuses with diminished enddiastolic frequencies in the fetal aorta have been shown to be more likely to develop NEC [10].

Patent Ductus Arteriosus and Necrotizing Enterocolitis

Hypoperfusion of the gastrointestinal tract appears to be an important factor contributing to the development of NEC in premature infants with a hemodynamically significant ductus arteriosus. In an epidemiological study of all infants born at less than 32 weeks and/or weighing less than 1500 g NEC occurred more frequently in infants with PDA (11.2 vs. 5.0%, p =0.0058) [19]. PDA must be considered a risk factor for NEC

with an OR of 2.5 (95% CI: 1.4–4.7) regardless of gestational age and birth weight. In newborns who weighed 1000 g or less at birth and required supplemental oxygen, the incidence of NEC was reduced in the group that underwent prophylactic ligation on the day of birth (8%) compared to a control group (30%) without ligation on day one [2]. This result also shows the high risk for NEC in preterm infants with PDA. On the other hand, recent trials failed to show that PDA has an effect on NEC incidence.

Indomethacin Intervention

Coombs et al. [4, 5] found a severe disturbance in gut perfusion in infants with patent ductus, which was exacerbated by indomethacin. The mean peak systolic low velocity in the superior mesenteric artery fell from 74 cm/sec before to 38 cm/sec after indomethacin administration. This reduction provided the rationale for the assumed association between PDA, gastrointestinal complications, and the use of indomethacin. These reports of complications, particularly concerning NEC and isolated gastrointestinal perforation, have generated concerns about the use of this medication [8, 9]. Although this rationale seems compelling, recent studies, including Cochrane reviews of indomethacin prophylaxis and therapy, have failed to identify any increased risk for NEC caused by indomethacin [1, 3, 12, 13]. Additionally, early enteral feeding seems to be as well tolerated in preterm infants treated for PDA with indomethacin as in their matched controls without indomethacin therapy [1]. Persisting ductus as well as indomethacin treatment increase the risk of intestinal ischemia. It could be hypothesized that the positive effect of indomethacin on ductus closure with increased intestinal perfusion is counterbalanced by its negative effect on intestinal perfusion. Consequently, PDA therapy failed to reduce NEC incidence.

Ibuprofen

Clinical studies did not show an association between ibuprofen prophylaxis or therapy and NEC or other gastrointestinal complications [16]. Additionally, ibuprofen did not adversely affect the feeding tolerance [20].

Indomethacin Versus Ibuprofen

Pezzati et al. [15] evaluated the effects of ibuprofen and indomethacin on mesenteric blood flow velocity in preterm newborns using Doppler ultrasonography. Indomethacin (0.2 mg/kg) caused a significant reduction of the blood flow velocity 30 minutes after drug administration which did not return to the pre-treatment levels after 120 minutes. Ibuprofen did not reduce mesenteric blood flow after treatment; on the contrary, this was increased 120 minutes after treatment. Compared to indomethacin, ibuprofen did not significantly reduce mesenteric blood flow velocity (Table 7.2). The Cochrane analysis showed no differences in NEC incidence or the time to full enteral feeds between preterm infants treated for PDA with indomethacin or with ibuprofen [14].

Table 7.2 Action of frequently used cyclooxygenase inhibitors on mesenteric perfusion and necrotizing enterocolitis.

	Indomethacin	Ibuprofen
Mesenteric blood flow	reduced blood flow velocity	without effects
Feeding tolerance	without problems	without problems
Isolated intestinal perforation	few casuistic reports	no reports
Increased NEC incidence	no	no

Surgical Ligation

Knight [11] showed no difference in NEC between infants treated with indomethacin or surgical ligation in a review of randomized studies. Obviously there is no advantage for surgical ligation of PDA as initial treatment, unless indomethacin is contraindicated.

Conclusions

PDA compromises the mesenteric perfusion in preterm infants. This could be exacerbated by treatment with indomethacin but not with ibuprofen. Without a doubt, older trials showed that a PDA leads to higher incidence of NEC. Early PDA closure, which represents the treatment practices in present-day neonatal intensive care units, is no longer associated with a higher incidence of NEC.

References

1. Bellander M, Ley D, Polberger S, Hellström-Westas L. Tolerance to early human milk feeding is not compromised by indomethacin in preterm infants with persistent ductus arteriosus. Acta Paediatr 2003; 92: 1074–1078.
2. Cassady G, Crouse DT, Kirklin JW, Strange MJ, Joiner CH, Godoy G, Odrezin GT, Cutter GR, Kirklin JK, Pacifico AD et al. A randomised, controlled trial of very early prophylactic ligation of the ductus arteriosus in babies who weighed 1000 g or less at birth. N Engl J Med 1989; 320: 1511–1516.
3. Cooke L, Steer P, Woodgate P. Indomethacin for asymptomatic patent ductus arteriosus in preterm infants (Cochrane Review). In: The Cochrane Library, Issue 1, 2004
4. Coombs RC, Morgan ME, Durbin GM, Booth IW, McNeish AS. Gut blood flow velocities in the newborn: Effects of patent ductus arteriosus and parenteral indomethacin. Arch Dis Child 1990; 65: 1067–1071.
5. Coombs RC, Morgan ME, Durbin GM, Booth IW, McNeish AS. Abnormal gut blood flow velocities in neonates at risk of necrotising enerocolitis. J Pediatr Gastroenterol Nutr 1992; 15: 13–19.
6. Crissinger KD. Regulation of hemodynamics and oxygenation in developing intestine: Insight into the pathogenesis of necrotizing enterocolitis. Acta Paediatr Suppl. 1994; 396: 8–10.
7. Deeg KH, Gerstner R, Bundscherer F, Harai G, Singer H, Gutheil H. Doppler sonographic detection of reduced flow velocity in the celiac trunk of the newborn infant with patent ductus arteriosus Botalli compared to a healthy control group. Monatsschr Kinderheilkd 1987; 135: 24–29.
8. Fujii AM, Brown E, Mirochnik M, O`Brien S, Kaufman G. Neonatal necrotizing enterocolitis with intestinal perforation in extremely premature infants receiving early indomethacin treatment for patent ductus arteriosus. J Perinatol 2002; 22: 535–540.
9. Grosfeld JL, Chaet M, Molinari F et al. Increased risk of necrotizing enterocolitis in premature infants with patent ductus arteriosus treated with indomethacin. Ann Surg 1996; 224: 350–355.
10. Hackett GA, Campell S, Gamsu H, Cohen-Overbeck T, Pearce JM. Doppler studies in the growth retarded fetus and prediction of neonatal necrotising enterocolitis, haemorrhage, and neonatal morbidity. Br Med J 1987; 294: 13–6.
11. Knight DB. The treatment of patent ductus arteriosus in preterm infants. A review and overview of randomised trials. Semin Neonatol 2001; 6: 63–73.
12. Koehne PS, Bein G, Alexi-Meskhishvili V, Weng Y, Bührer C, Obladen M. Patent ductus arteriosus in very low birthweight infants: complications of pharmacological and surgical treatment. J Perinat Med 2001; 29: 327–34.
13. O`Donovan DJ, Baetiong A, Adams K, Chen A, O`Brian Smith E, Adams JM, Weisman LE. Necrotizing enterocolitis and gastrointestinal complications after indomethacin therapy and surgical ligation in premature infants with patent ductus arteriosus. J Perinatol 2003; 23: 286–90.
14. Ohlsson A, Walia R, Shah S. Ibuprofen for the treatment of patent ductus arteriosus on preterm and/or low birth weight infants (Cochrane Review). In: The Cochrane Library, Issue 1, 2004
15. Pezzati M, Vangi V, Biagiotti R, Bertini G, Cinanciulli D, Rubaltelli FF. Effects of indomethacin and ibuprofen on mesenteric and renal blood flow in preterm infants with patent ductus arteriosus. J Pediatr 1999; 135: 733–8.
16. Shah SS, Ohlsson A. Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants (Cochrane Review). In: The Cochrane Library, Issue 1, 2004
17. Sonntag J, Grimmer I, Scholz T, Metze B, Wit J, Obladen M. Growth and neurodevelopmental outcome of very low birthweight infants with necrotizing enterocolitis. Acta Paediatr 2000; 89: 528–32.
18. Sonntag J, Wagner MH, Waldschmidt J, Wit J, Obladen M. Multisystem organ failure and capillary leak syndrome in severe necrotizing enterocolitis of very low birth weight infants. J Pediatr Surg 1998; 33: 481–4.
19. Van de Bor M, Verloove-Vanhorick SP, Brand R, Ruys JH. Patent ductus arteriosus in a cohort of 1338 preterm infants: A collaborative study. Pediatr Perinatal Epidemiol 1988; 2: 328–36.
20. Varvarigou A, Bardin CL, Beharry K, Chemtob S, Papageorgiou A, Aranda JV. Early ibuprofen administration to prevent patent ductus arteriosus in premature newborn infants. JAMA 1996; 275: 539–44.

Persisting Ductus Arteriosus and Intraventricular Hemorrhage

Rolf F. Maier

Particular morphological and functional conditions of the immature brain predispose preterm infants to intraventricular hemorrhage (IVH).

Cerebral Perfusion

As a source of neuronal and glial precursors the subependymal germinal matrix is a proliferative tissue, which is richly vascularized. Cerebral autoregulation, which provides constant cerebral blood flow over a broad range of arterial blood pressure in adults, is not as effective in preterm infants (Fig. 8.1). Therefore, alterations in arterial blood pressure provoke fluctuations in the cerebral blood flow of preterm infants, which may lead to rupture of the vulnerable capillaries of the subependymal germinal matrix resulting in IVH.

Patent ductus arteriosus (PDA) is well known to influence the arterial blood pressure and to alter cerebral blood flow. Thus, the question arises whether PDA is capable of causing IVH in preterm infants. This assumption is highly suggestive because PDA and IVH occur within the same population. Incidence of both PDA and IVH increases with decreasing birth weight and decreasing gestational age [8, 9]. However, about 50% of all IVH occur during the first day of life, a period before PDA usually becomes clinically symptomatic (Fig. 8.2). Osborn et al. [11] determined distinct and different risk factors for early and late periventricular/intraventricular hemorrhage in two large prospective cohort studies with a total of 254 infants born before 30 weeks gestation. Low superior vena cava flow (SVC) in the first 24 hours of life was the only independent risk factor associated with IVH in both cohorts. Adjusted for the perinatal risk factors, low SVC flow was associated with a large ductus diameter in the first cohort [12].

PDA, Lung Maturity, and IVH

Both PDA and IVH are associated with respiratory distress syndrome (RDS) in preterm infants. Prenatal corticosteroid therapy in order to prevent RDS has been shown to reduce the incidence of both PDA and IVH in preterm infants of 26–34 weeks gestation [1]. Natural surfactant given prophylactically to preterm infants of less than 30 weeks gestation effectively reduces neonatal mortality and the incidence of pulmonary air leaks, but does not significantly reduce the rate of PDA and IVH [10]. Thus, prevention of RDS by prenatal steroids but not by surfactant is combined with lower incidence of both

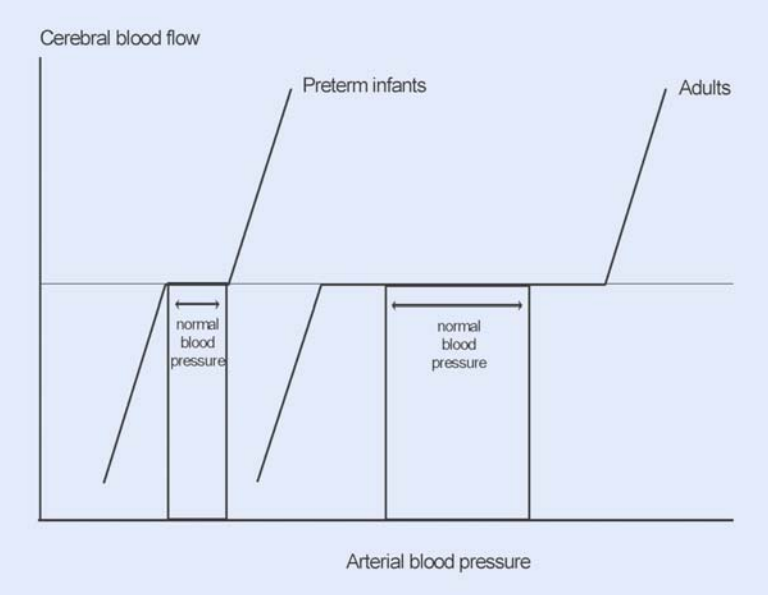


Fig. 8.1 Cerebral autoregulation is the ability of the brain to maintain normal perfusion when blood pressure changes. It is less effective in preterm infants (left) than in adults (right).

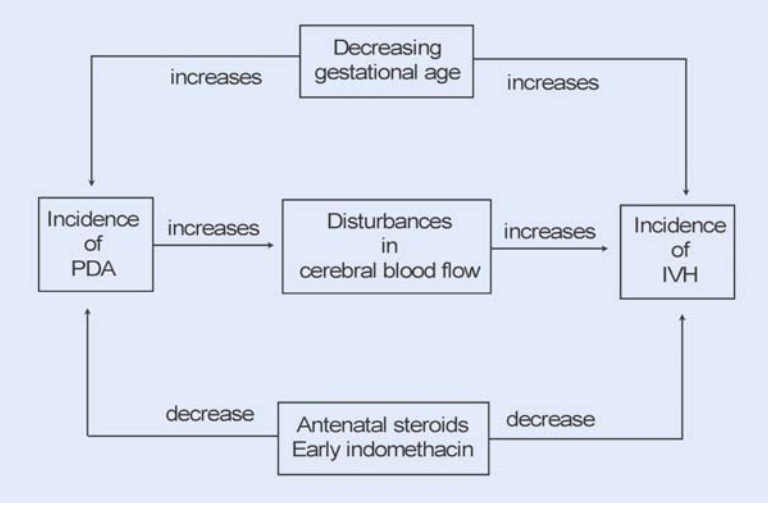


Fig. 8.2 Schematic drawing of the associations between persisting ductus arteriosus (PDA) and intraventricular hemorrhage (IVH).

PDA and IVH. Early ductal shunting proven by echocardiography before occurrence of IVH has been shown to be associated with later IVH in ventilated infants with birth weights below 1500 g [4]. However, prophylactic ligation of PDA on the day of birth in infants with birth weights less than 1000 g has not succeeded in lowering the rate of IVH [2].

Pharmacological Interventions

Prophylactic administration of indomethacin given 6–24 hours after birth to preterm infants of less than 37 weeks gestation lowers the rate of both PDA (symptomatic and asymptomatic) and IVH (all IVH and severe IVH) [5]. In contrast, indomethacin given for asymptomatic PDA in preterm

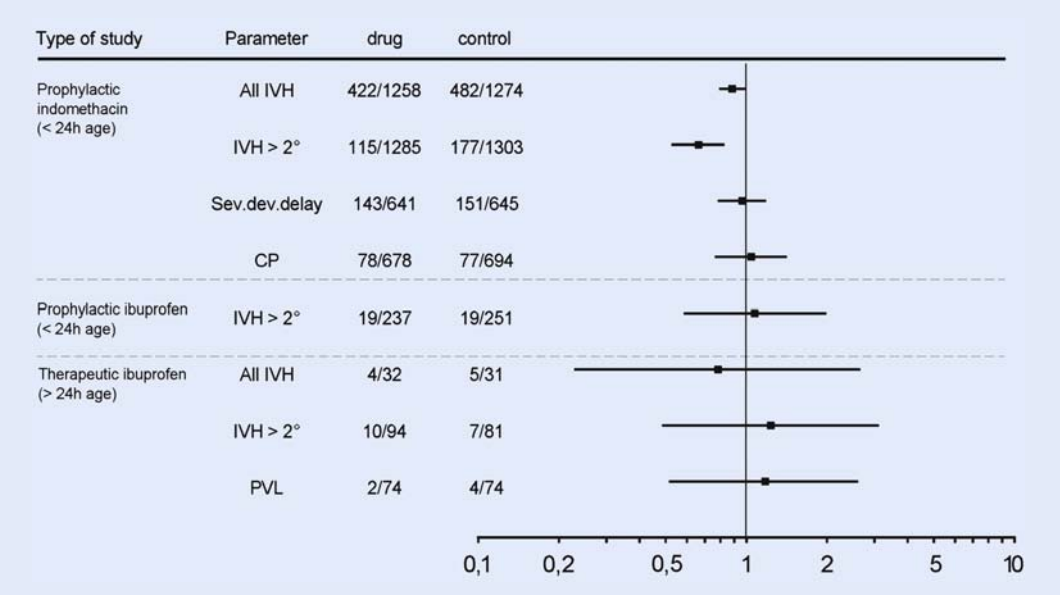


Fig. 8.3 Effects of pharmacologic interventions for PDA on the occurrence of intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), severe developmental delay, and cerebral palsy (CP). Bars depict risk reduction and 95% confidence intervals. Modified from Fowlie et al. [5], Ohlsson et al. [6] and Shah et al. [7].

infants with birth weights less than 1750 g later than 24 hours after birth significantly reduces the incidence of symptomatic PDA, but not of IVH [3]. Ibuprofen administered early in life (2–24 hours after birth) reduces the rate of PDA on day 3 of life, but does not significantly influence the incidence of severe IVH [7]. The effect of ibuprofen given later than 24 hours after birth in preterm (less than 37 weeks gestation) or low birth weight (less than 2500 g) infants does not differ significantly from that of indomethacin with respect to closure of PDA or occurrence of IVH [6]. Thus, early and late administration of indomethacin as well as early and late administration of ibuprofen induces closure of PDA. In contrast, IVH can be prevented by early administration of indomethacin, but not by late indomethacin nor by ibuprofen (Fig. 8.3).

Conclusions

Both PDA and IVH are closely associated within the same population and can be prevented by prenatal steroids and by indomethacin given early in life. However, PDA has not definitively been shown to cause IVH.

References

1. Amorim MM, Santos LC, Faúndes A. Corticosteroid therapy for prevention of respiratory distress syndrome in severe preeclampsia. Am J Obstet Gynecol 1999; 180: 1283–8.
2. Cassady G, Crouse DT, Kirklin JW, Strange MJ, Joiner CH, Godoy G, et al. A randomized, controlled trial of very early prophylactic ligation of the ductus arteriosus in babies who weighed 1000 g or less at birth. New Engl J Med 1989; 320: 1511–6.
3. Cooke L, Steer P, Woodgate P. Indomethacin for asymptomatic patent ductus arteriosus in preterm infants. Cochrane Database Syst Rev 2003; CD003745.
4. Evans N, Kluckow M. Early ductal shunting and intraventricular haemorrhage in ventilated preterm infants. Arch Dis Child 1996; 75: F183–6.
5. Fowlie PW, Davis PG. Prophylactic intravenous indomethacin for preventing mortality and morbidity in preterm infants. Cochrane Database Syst Rev 2002; CD000174.
6. Ohlsson A, Walia R, Shah S. Ibuprofen for the treatment of a patent ductus arteriosus in preterm and/or low birth weight infants. Cochrane Database Syst Rev 2003; CD003481.

7. Shah SS, Ohlsson A. Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants. Cochrane Database Syst Rev. 2003; CD004213.
8. Sheth RD. Trends in incidence and severity of intraventricular hemorrhage. J Child Neurol 1998; 13: 261–4.
9. Siassi B, Blanco C, Cabal LA, Coran AG. Incidence and clinical features of patent ductus arteriosus in low-birthweight infants: A prospective analysis of 150 consecutively born infants. Pediatrics 1976; 57: 347–51.
10. Soll RF. Prophylactic natural surfactant extract for preventing morbidity and mortality in preterm infants. Cochrane Database Syst Rev 2000; CD000511.
11. Osborn DA, Evans N, Kluckow M. Hemodynamic and antecedent risk factors of early and late periventricular/intraventricular hemorrhage in premature infants. Pediatrics 2003; 112: 33–39.
12. Kluckow M, Evans N. Low superior vena cava flow and intraventricular haemorrhage in preteme infants. Arch Dis Child Fetal Neonatal Ed 2000; 82: F188–F194.
13. Su PH, Chen JY, Su CM, Huang TC, Lee HS. Comparison of ibuprofen and indomethacin therapy for patent ductus arteriosus in preterm infants. Pediatr Int 2003; 45: 665–70.

Part III Diagnostics

9

Echocardiographic Assessment

Helmut Singer

The high incidence of persistent ductus arteriosus (PDA) and the high rate of serious complications necessitate immediate and safe diagnosis of the PDA in preterm infants with very low birth weight. Clinical signs are of limited accuracy for the diagnosis of a PDA, particularly in the first 3 to 4 days of life [1, 4]. Echocardiography together with Doppler and color Doppler is a diagnostic tool that allows accurate and timely diagnosis of a PDA. The clinical relevance of an echocardiographically detected PDA, however, remains unclear.

Before a PDA intervention is planned, congenital heart defects, especially those with PDA-dependent pulmonary or systemic circulation must be excluded by echocardiography. Estimation of size, morphology and hemodynamic relevance are mandatory requirements for the correct indication of treatment. As a major effect, a hemodynamically relevant PDA leads to fluid overload of the lungs and left heart. In these cases the two dimensional B-mode technique shows left atrial and ventricular enlargement and bowing of the interatrial septum fromthe left into the cavity of the right atrium in the apical four chamber view. Although the measurement of left atrium to aortic root diameters bears severe methodical uncertainties (i.e. LA enlarged in other directions than anterior-posterior, cardiac rotation, unusual transducer positions) determination of the LA/Ao ratio with the M-mode technique is still widely used to evaluate fluid overload by a hemodynamically relevant PDA. The direct visualization of the PDA is performed in different sectional cuts, especially with high parasternal or suprasternal position of the transducer. Color Doppler examination gives important information about direction and size of the shunt flow within the ductus and both great arteries. Color Doppler codes blood according to the direction of blood flow relative to the transducer. In general, red (orange) color codes for flow directed towards the transducer and blue colour codes for flow away from the transducer whereas a turbulent flow appears either light green or yellow. The Doppler examination allows estimation of pressure and resistance in pulmonary or aortic circulation by measuring flow velocities, pressure gradient over the PDA, and by analysis of the flow curves in the PDA, pulmonary artery, and aorta. Additional information can be gained by analysis of the flow profiles in the A. cerebri anterior, truncus coeliacus and A. renalis. Size, length, and anatomical features of the ductus arteriosus may vary considerably from infant to infant. PDA in preterms should not be confused with aorto-pulmonary window, major aorto-pulmonary connecting anastomoses, or arteria lusoria. Increased

flow velocity may be absent in large PDA, which carries the risk of confusing the ductus with the aorta on the color Doppler. Fatal consequences will result from pre- and intraoperative confusion of the PDA with the aortic arch, which may have a smaller diameter than the PDA in many cases (◘ Figures 9.1–9.6).

The exclusion of a ductus-dependent circulation is most important in this field of diagnosis, especially when surgical or medical closure is planned. Systemic circulation can be ductus-dependent in cases with coarctation, critical aortic valve stenosis, and hypoplastic left heart. The exclusion of severe coarctation may be difficult when a large ductus prevents direct visualization of the stenosis. In this special situation flow pattern in the truncus coeliacus may be normal and femoral pulses are of normal quality when the ductal shunt from the pulmonary artery to the descending aorta is sufficient. Ductus-dependent pulmonary perfusion exists in various forms of pulmonary atresia, in tetralogy of Fallot and in critical pulmonary valve stenosis. The forward-backward flow in the main pulmonary artery (if present) between atretic valve and PDA is the main diagnostic echocardiographic finding. In transposition of the great arteries systemic arterial saturation is also ductus-dependent. Before closure of the PDA this malformation must be excluded in preterm infants.

Early diagnosis and assessment of the ductus in preterms is necessary to ensure benefit of the intervention and to prevent serious complications. Echocardiography is the method of choice to diagnose the PDA, to judge its hemodynamic severity, to exclude cardiac malformations with ductus-dependent systemic or pulmonary perfusion, and to indicate and monitor treatment. Initial echocardiography assessment should be performed by a pediatric cardiologist familiar with very small infants. In order to ensure longitudinal follow up examination in the neonatal intensive

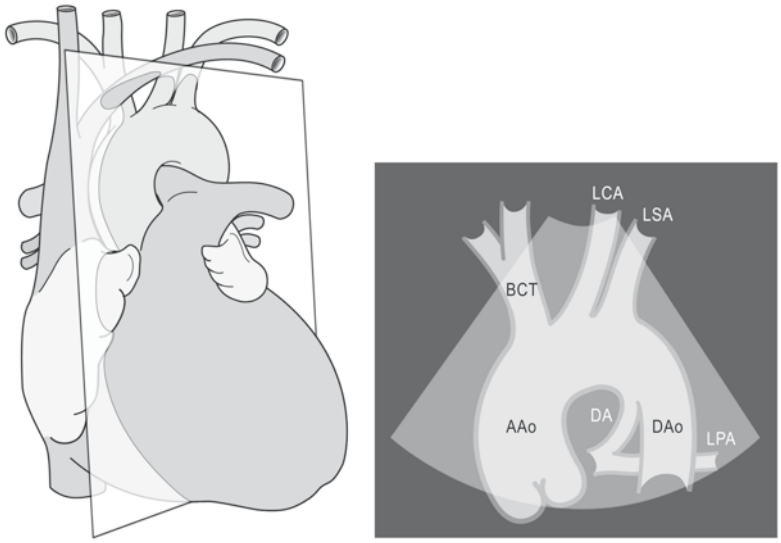


Fig. 9.1 Echocardiography in PDA: Schematic diagram of suprasternal notch long-axis view (left) and sketch of two-dimensional image obtained (right). For the suprasternal long-axis view the transducer is placed into the jugulum or in the left second intercostal space along an axis from the right mamilla to the left shoulder. This axis is best to visualize shunt direction and anatomic features (e.g. shape and length) of a persistent ductus arteriosus from the pulmonary artery to the descending aorta. This view is also important for the evaluation of anomalies in the ascending and descending aorta (e.g. to some extent, coarctation of the aorta can be excluded) and the aortic arch (e.g. interruption). A Ao, ascending aorta; D Ao, descending aorta; BCT, brachiocephalic trunk; LCA, left carotid artery; LSA, left subclavian artery; DA, ductus arteriosus; LPA, left pulmonary artery

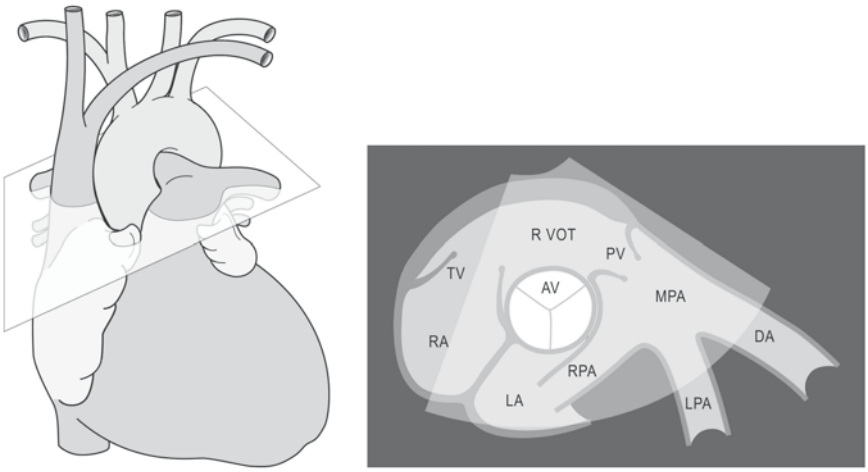


Fig. 9.2 Echocardiography in PDA: Schematic diagram of parasternal short-axis view in the upper part of the sweep (left) and sketch of two-dimensional image obtained (right). The transducer position for this view is the left parasternal third or fourth intercostal space along an axis from the right hip to the left shoulder. This projection provides a cross-sectional image of the heart and the great arteries and is important in the evaluation of the aortic valve (e.g. bicuspid or tricuspid), pulmonary valve, main pulmonary artery and its branches, right ventricular outflow tract, and the right atrioventricular valve. The PDA is usually visualized as a third branch emerging from the main pulmonary artery. This axis is preferred to measure the anatomic diameter of the ductus. AV, aortic valve; MPA, main pulmonary artery; DA, ductus arteriosus; LPA, left pulmonary artery; RPA, right pulmonary artery; LA, left atrium; RA, right atrium; RVOT, right ventricular outflow tract; PV, pulmonary valve; TV, tricuspid valve.

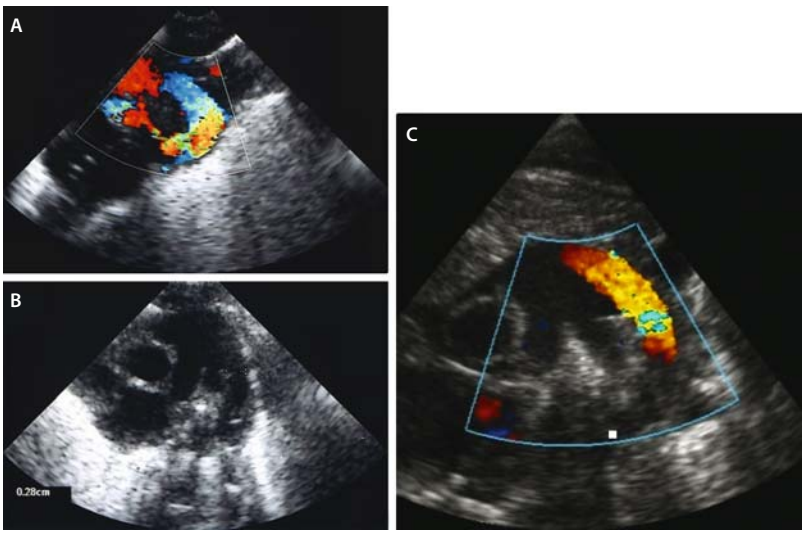


Fig. 9.3 Suprasternal view A (upper left): The color Doppler image in the suprasternal long axis shows the whole course of a PDA with a pure left-to-right shunt symbolized by the red color coded blood flow moving towards the main pulmonary artery. The blood flow in the distal aortic arch and in the descending aorta (blue color coding) is directed away from the transducer. Parasternal short axis view: B-mode image (B – lower left) demonstrates a 2.8 mm patent ductus arteriosus. Three branches of similar size emerge from the main pulmonary artery of which the upper branch next to the LPA represents the PDA, leading to the typical »three finger sign«. The corresponding color coded Doppler image (C – lower right) obtained with the same transducer position shows a pure left-to-right shunt within the PDA. After ductus closure, pulsed Doppler measurements often show accelerated flow velocity in the left pulmonary artery.

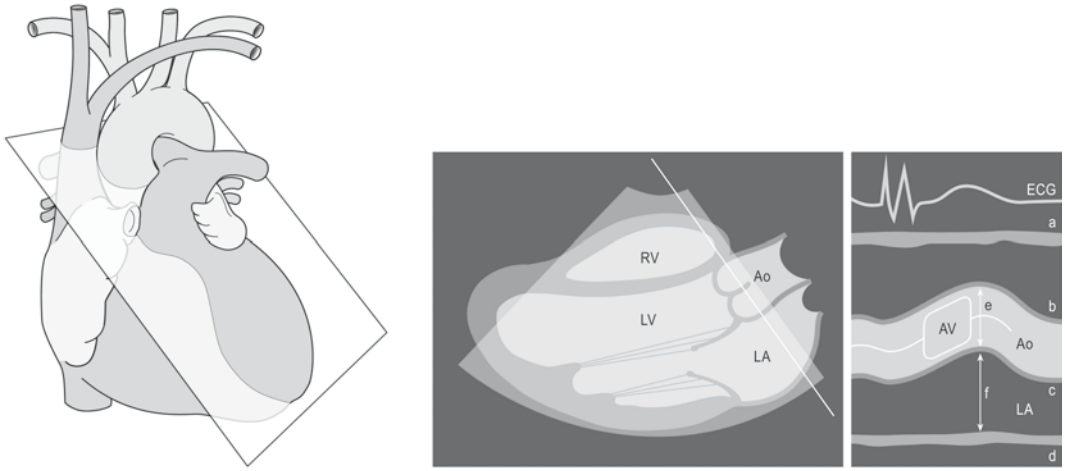


Fig. 9.4 Echocardiography in PDA: Schematic diagram of parasternal long-axis view (left), corresponding cross-sectional sketch of the left side of the heart (center), and M-mode obtained (right). To obtain this view, the transducer is positioned in the left parasternal third or fourth intercostal space along an axis from the left hip to the right shoulder. As the most basic view the parasternal long-axis shows the left ventricular inflow and outflow tracts. This view is important in evaluating abnormalities of the mitral valve, left atrium, left ventricle, left ventricular outflow tract, aortic valve, aortic root, ascending aorta, and ventricular septum. This axis allows measurement of the dimension of the aortic root and the left atrium (B-mode image center) and to determine LA/Ao ratio (M-mode recording right, along white line of center image). Ao, aorta; AV, aortic valve; LV, left ventricle; LA, left atrium; RV, right ventricle; ECG, electrocardiogram; a, RV free wall; b, anterior Ao wall; c, posterior Ao wall; d, LA posterior wall; e, aortic root diameter in systole; f, left atrial dimension in systole.

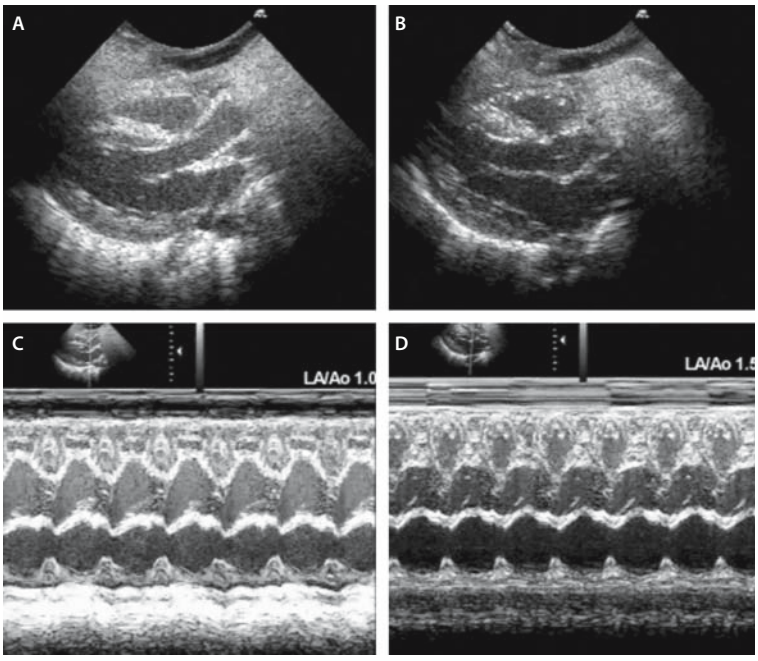


Fig. 9.5 Two-dimensional image along the parasternal long-axis showing normal left atrium size (upper left – A) and dilated left atrium in large PDA (upper right – B). Corresponding M-mode echo recordings show M-mode recording with normal LA/Ao ratio of 1.0 (lower left – C) and M-mode in large PDA with elevated LA/Ao ratio of 1.5 (lower right – D).

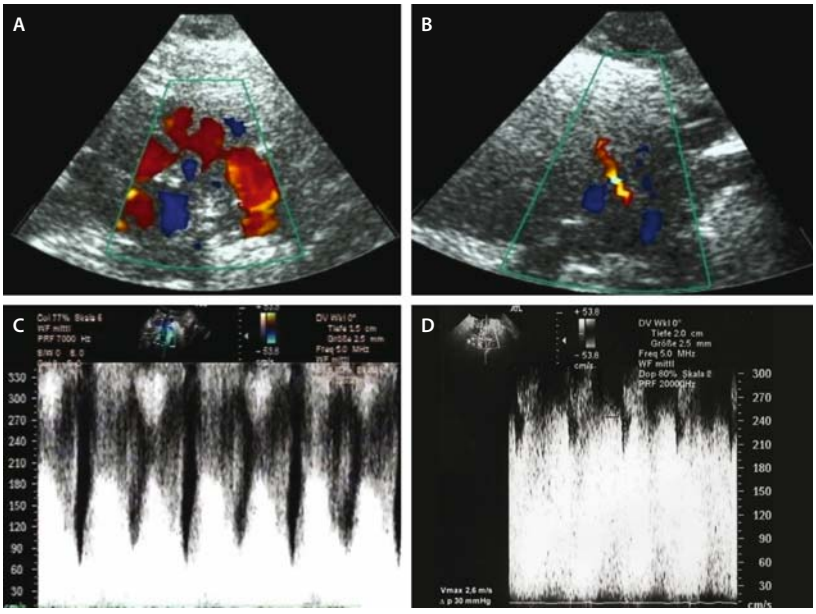


Fig. 9.6 Contrasting color Doppler studies show (A – upper left) a ductus with poor constriction and a large shunt of blood moving through it as opposed to (B – upper right) a ductus with good constriction. The corresponding pulsed Doppler appearance of both ductus reveals different ductal flow patterns, as shown below. Doppler echocardiographic studies of the ductus provide important functional information, such as ductal shunt patterns (pure left-to-right, bidirectional, or predominant right-to-left shunt) and magnitude of the ductal shunt. The Doppler cursor is placed at the pulmonary end of the PDA in the parasternal short-axis view. The continuous positive flow indicates a pure left-to-right shunt with the pulmonary artery pressure lower than the aortic pressure. The maximum flow velocity is 210 cm/second in the large nonconstricted PDA (C – lower left) and around 260 cm/second in the closing pattern of the constricted PDA (D – lower right).

care unit, neonatologists should be familiar with the principles of echocardiography [3]. With this rapidly executed protocol serious complications of the large ductus arteriosus can be prevented in the majority of very small preterms.

References

1. Davis P, Turner-Gomes S, Cunningham K, Way C, Roberts R, Schmidt B: Precision and accuracy of clinical and radiological signs in premature infants at risk of patent ductus arteriosus. Arch Pediatr Adolesc Med 1995; 149: 1136–41.
2. Evans N, Iyer P: Longitudinal changes in the diameter of the ductus arteriosus in ventilated preterm infants: Correlation with respiratory outcomes. Arch Dis Child 1995; 72: F156–61.
3. Schmidt B, Davis P, Moddemann D, Ohlsson A, Roberts RS, Saigal S, Solimano A, Vincer M, Wright LL. Trial of Indomethacin Prophylaxis in Preterms Investigators. Long-term effects of indomethacin prophylaxis in extremely-low-birth-weight infants. N Engl J Med 2001; 344: 1966–72
4. Skelton R, Evans N, Smythe J: A blinded comparison of clinical and echocardiographic evaluation of the preterm infant for patent ductus arteriosus. J Pediatr Child Health 1994; 30: 406–11.
5. Park MK: Pediatric cardiology for practitioners. 4th ed., St. Louis, Missouri, Mosby 2002.

Cerebral Doppler Sonographic Measurements

Karl-Heinz Deeg, Burkhard Trusen

The most sensitive method for the diagnosis of a patent ductus arteriosus (PDA) is color Doppler imaging of the blood flow in the pulmonary artery. When the pulmonary vascular resistance decreases postnatally, the increasing left to right shunt from the aorta to the pulmonary artery can be displayed by color Doppler within the pulmonary trunk. The shunted blood is »stolen« from the systemic circulation especially during diastole. This diastolic steal may cause hypoperfusion of the peripheral circulation. The increased incidence of severe intracranial hemorrhage and periventricular leucomalacia reported in the literature could be the result of hypoperfusion of the brain [1, 2, 13, 14]. Prophylactic treatment of preterm infants with indomethacin caused closure of the ductus and was associated with the reduction of severe intracranial hemorrhage [3, 4, 5, 6].

Intracranial Arteries

With the help of pulsed Doppler sonography blood flow can be measured in all large intracranial arteries such as the anterior cerebral artery and the basilar and internal carotid artery but also in small arteries such as the lenticulostriate arteries and Heubner's artery. Pulsed Doppler sonographic flow measurements in intracranial arteries of infants without a PDA demonstrate a systolic and diastolic forward flow. The high diastolic amplitude in intracranial arteries is caused by the low peripheral vascular resistance of the brain and the »Windkessel« function of the aorta. PDA causes a leakage of the aortic Windkessel. According to the pulmonary vascular resistance blood is shunted away from the aorta to the pulmonary circulation. This may lead to a decrease of the diastolic amplitude in the cerebral arteries.

From the flow profile the flow velocities and the resistance index can be measured. The peak systolic flow velocity, the endsystolic (shoulder in the declinig part of the flow profile), the enddiastolic and time average flow velocities can be measured. A PDA with significant left to right shunt causes a significant decrease of the endsystolic and enddiastolic flow velocities (see figures 10.2, 10.3) [4]. Alterations in PDA are most pronounced in the internal carotid and basilar arteries as compared with the anterior cerebral arteries.

Doppler Parameters

The peak systolic (Vs), endsystolic (Ves), enddiastolic (Ved) and time averaged (TAV) flow velocities can be measured. Additionally the

resistance index (RI) can be calculated according to the equation

$$RI = \frac{Vs - Ved}{Vs}$$

The advantage of the RI is the independence of the angle of incidence. The disadvantage is the fact that different alterations of the numerator and denominator can cause similar alterations of the RI. As the preterm infant's skull is soft, RI is influenced by the pressure with which the transducer is applied, especially in transfontanellar measurements.

The advantage of the flow velocities, especially the time averaged velocity, is the correlation with volume flow and organ perfusion. With decreasing enddiastolic and endsystolic flow velocities the time average velocity decreases. The volume flow Q can theoretically be calculated by Doppler sonography according to the equation:

Q = A x TAV x 60
Q = volume flow (ml/min);
A = cross sectional area of the vessel (mm^2)
TAV = time average velocity (m/sec.)
60 = multiplier (flow over 60 seconds).

Unfortunately the cross sectional area of the tiny intracranial arteries cannot be measured sonographically. However, as the diameter of the intracranial arteries does not change significantly, the cross sectional area A of the vessels can be assumed to be constant. Volume flow therefore is directly proportional to the time averaged velocity (TAV) which can be measured by Doppler sonography. Therefore qualitative changes of brain perfusion can be registered Doppler sonographically.

PDA-Specific Flow Patterns

In infants with a patent ductus arteriosus fluctuating blood flow in the intracranial arteries can be found (Fig. 10.1). The peak systolic flow velocities as well as the other flow velocities change from beat to beat, causing fluctuating cerebral perfusion. Fluctuating flow, possibly caused by a PDA, may be associated with an increased incidence of intracranial hemorrhage [7, 8, 9].

Beside fluctuating cerebral blood flow a PDA significantly affects the diastolic amplitude in the cerebral arteries. The diastolic blood flow velocities (endsystolic and enddiastolic) and the time average velocities decrease depending on the amount of left to right shunting [10] (Fig. 10.2). These changes can be found in all intracranial arteries and in the mesenteric and renal arteries too. According to literature the flow alterations

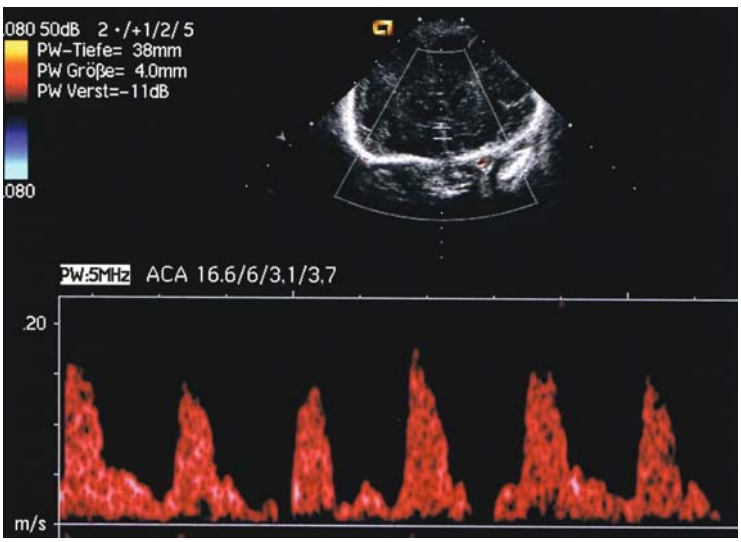


Fig. 10.1 Fluctuating blood flow in the anterior cerebral artery of a preterm infant with a gestational age of 25 weeks and patent ductus arteriosus.

are more pronounced in the larger intracranial arteries such as the internal carotid and middle cerebral arteries than in the anterior and basilar arteries [11, 12]. However in our experience similar changes can be found in all intracranial arteries. Therefore flow measurements for the judgement of a PDA can be performed in any intracranial artery which can easily be measured.

The blood flow changes in the peripheral circulation allow qualitative judgement of the hemodynamic relevance of a patent ductus (Fig. 10.3). A decreased diastolic forward flow is typical for a small left to right shunt, lack of enddiastolic flow can be found in a moderate left to right shunt and a retrograde diastolic flow is typical for a large hemodynamically relevant left to right shunt. In infants with lacking or negative diastolic flow the PDA should be closed either by drugs or surgery.

Figure 10.4 shows the flow velocities and resistance indices of premature infants with PDA

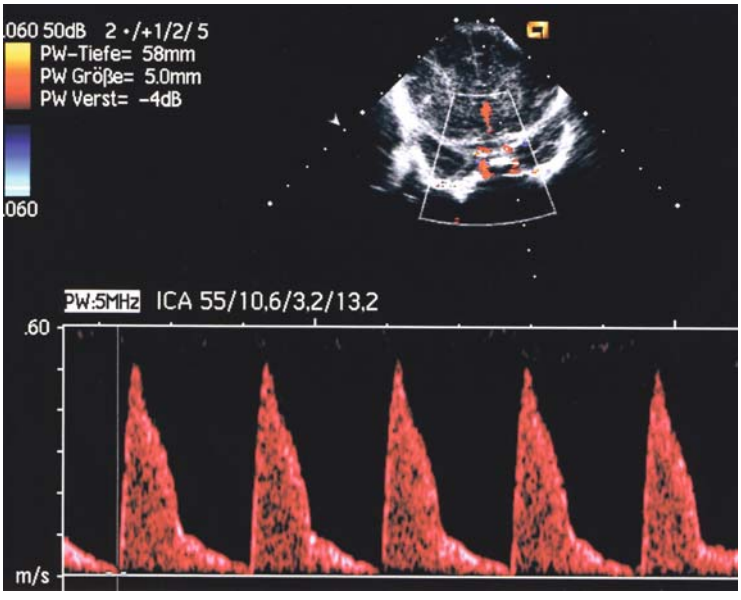


Fig. 10.2 Decreased diastolic amplitude in the internal carotid artery of a preterm infant with a hemodynamically relevant PDA.

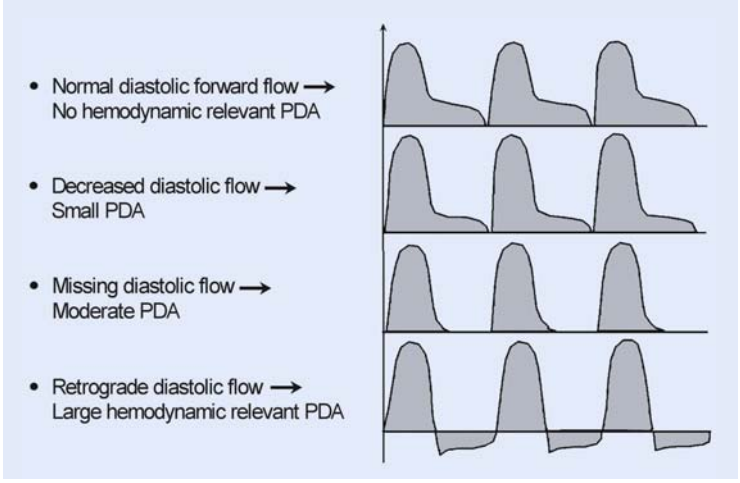


Fig. 10.3 Qualitative assessment of persisting ductus in dependency of the magnitude of the left to right shunt.

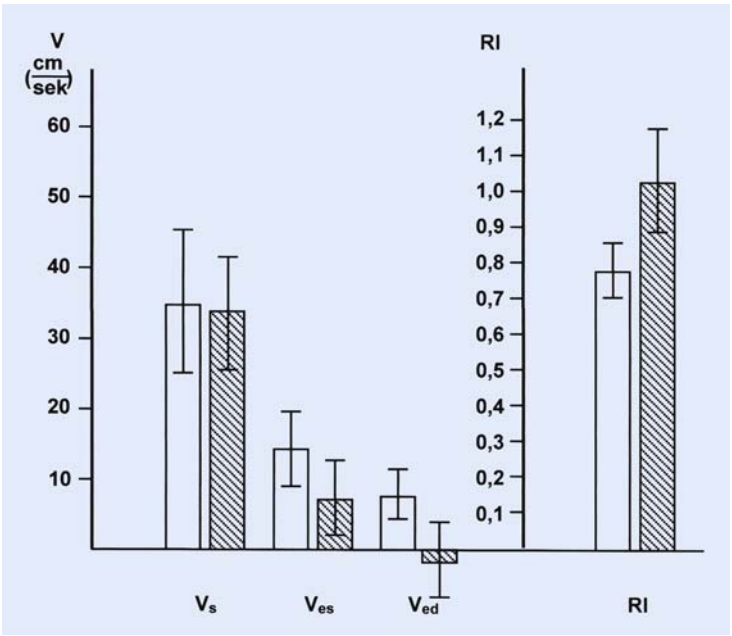


Fig. 10.4 Flow velocities in the anterior cerebral arteries of 32 preterm infants with patent ductus (hatched columns) in comparison with a healthy control group (empty columns). The endsystolic (Ves) and enddiastolic (Ved) flow velocities are significantly reduced in the ductus group and the resistance index (RI) is increased.

in comparison with a healthy control group. The endsystolic and enddiastolic velocities were significantly reduced in the ductus group, whereas the resistance index was increased. Other conditions causing a decreased diastolic flow have to be ruled out, especially hypovolemia, hypocarbia, increased intracranial pressure and other congenital heart diseases causing leakage of the aortic »Windkessel« (Table 10.1).

Doppler sonography of the flow in intracranial arteries can also demonstrate the effect of ductus closure on systemic blood flow. A dramatic increase of the diastolic flow velocities and a decrease of the resistance indices could be shown after ductus ligation.

Table 10.1

Leakages of the aortic Windkessel:
- Patent ductus arteriosus
- Truncus arteriosus communis
- Aortic insufficiency
- Aorto-pulmonary window
- Aorto-pulmonary shunt
- Large arteriovenous fistulas

Figure 10.5 demonstrates that the time average velocity increases more than 100% in a preterm infant after 5 doses of indomethacin. This means that the volume flow after ductus closure increased more than 100%. On the other hand before ductus closure volume flow had fallen below 50%.

A decrease of the time average velocity causes a reduction of volume flow to the brain and may lead to hypoperfusion of the brain. This may cause or augment ischemic brain injury and may contribute to periventricular leucomalacia.

Conclusions

PDA causes fluctuating cerebral blood flow and decreases enddiastolic and time averaged flow velocities. This may lead to hypoperfusion of the brain, causing intracranial hemorrhage and hypoxic-ischemic brain injury. The quantification of the flow velocities allows the hemodynamic relevance of a PDA (small, moderate, large) to be judged. Quantification of the flow velocities is superior to the calculation of the resistance index expecially for serial controls. The decrease of the time average flow velocity

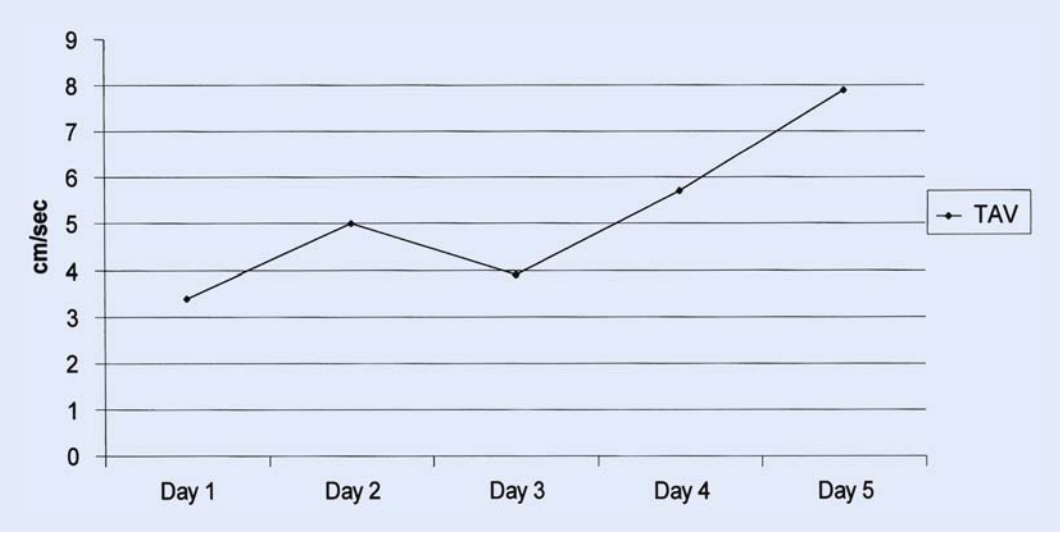


Fig. 10.5 Influence of treatment of an open ductus arteriosus with indomethacin on the time averaged flow velocities (TAV) in the intracranial arteries. Note significant increase of the time averaged velocity after 5 doses of indomethacin of over 100% of the initial value.

is a strong indicator of hypoperfusion of the brain.

References

1. Martin CG, Snider, AR, Katz SM. Abnormal cerebral blood flow patterns in preterm infants with a large patent ductus arteriosus. J Pediatr 1982; 101: 297–9.
2. Shortland DB, Gibson NA, Levene MI. Patent ductus arteriosus and cerebral circulation in preterm infants. Dev Med Child Neurol 1990; 32: 386–93.
3. Bandstra ES, Montalvo BM, Goldberg RN, Pacheco I, Ferrer PL, Flynn J, Gregorios JB, Bancalari E. Prophylactic indomethacin for prevention of intraventricular hemorrhage in premature infants. Pediatrics 1988; 82: 533–42.
4. Ment LR, Oh W, Ehrenkranz RA, Phillip AG, Vohr B, Allan W, Makuch RW, Taylor KJ, Schneider KC, Katz KH, et al. Low-dose indomethacin therapy and extension of intraventricular hemorrhage: a multicenter randomized trial. J Pediatr 1994; 124: 951–5.
5. Schmidt B, Davis P, Moddemann D, Ohlsson A, Roberts RS, Saigal S, Solimano A, Vincer M, Wright LL. Trial of Indomethacin Prophylaxis in Preterm Infants. Long-term effects of indomethacin prophylaxis in extremely-low-birth-weight infants. N Engl J Med. 2001; 344: 1966–72.
6. Fowlie PW, Davis PG. Prophylactic indomethacin for preterm infants: a systematic review and meta-analysis. Arch Dis Child Fetal Neonatal Ed. 2003; 88: F464–6.
7. Calvert SA, Ohlsson A, Hosking MC, Erskine L, Fong K, Shennan AT. Serial Measurements of Cerebral Blood Flow Velocity in Preterm Infants during the First 72 Hours of Life. Acta Paediatr Scand 1988; 77: 625–31.
8. Mullaart RA, Hopman JC, De Haan AF, Rotteveel JJ, Daniels O, Stoelinga GA. Cerebral blood flow fluctuation in low-risk preterm newborns. Early Hum Dev 1992; 30: 41–8.
9. Coughtrey H, Rennie JM, Evans, DH. Variability in cerebral blood flow velocity:; observations over one minute in preterm babies. Early Hum Dev. 1997; 47: 63–70.
10. Deeg KH, Gerstner R, Brandl U, Brundscherer F, Zeilinger G, Harai G, Singer H, Gutheil H. Dopplersonographic Flow Patterns in the Anterior Cerebral Arteries in Patent Ductus Arteriosus of Premature Babies in Comparison to a Healthy Control Group. Klin. Pädiat. 1986; 198: 463–70.
11. Wilcox WD, Carrigan TA, Dooley KJ, Giddens DP, Dykes FD, Lazzara A, Ray JL, Ahmann PA. Range-gated pulsed Doppler ultrasonographic evaluation of carotid arterial blood flow in small preterm infants with patent ductus arteriosus. J Pediatr 1983; 102: 294–8.
12. Wright LL, Baker KR, Hollander DI, Wright JN, Nagey DA. Cerebral blood flow velocity in term newborn infants: Changes associated with ductal Flow. J Pediatr 1988; 112: 768–73.
13. Dykes FD, Lazzara A, Ahmann P, Blumenstein B, Schwartz J, Brann AW. Intraventricular Hemorrhage: A Prospective Evaluation of Etiopathogenesis. Pediatrics 1980; 66: 42–9.
14. Evans N, Kluckow M. Early ductal shunting and intraventricular haemorrhage in ventilated preterm infants. Arch Dis Child 1996; 75: F183–6.

Part IV Interventions

11

Therapeutic Options

Axel von der Wense

Persisting ductus arteriosus Botalli (PDA) is one of the most frequent problems complicating the clinical course of very low and especially extremely low birth weight infants (VLBW, ELBW). Thus a large number of preventive, prophylactic and therapeutic strategies have been developed over the last 30 years to minimize the incidence of PDA and its potentially harmful consequences such as bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC) and intracerebral hemorrhage (ICH).

Therapeutic decisions are based on different sources of evidence. Numerous studies of varying designs have been published since 1975 (986 articles in Medline using search items PDA and therapy). Ten systematic reviews from The Cochrane Library at least partially address aspects of prevention or treatment of PDA [1–6]. The evidence, however, cannot be only derived from the classical methods of evidence based medicine. Experimental and pathophysiological studies, as well as individual results of neonatological centers and the personal experience of neonatologists have influence on the therapeutic strategy.

Prevention of PDA

Preventive efforts include prenatal corticosteroid therapy probably via the reduction of severe respiratory distress syndrome [7]. As oxygen is the major factor mediating the contraction of ductus arteriosus, adequate oxygenation and avoidance of hypoxic episodes should reduce the incidence of PDA [8]. However, there is a lack of clinical data defining PO_2 or SaO_2 levels related to the risk of PDA. Mechanically ventilated infants have higher plasma levels of PGE2, PGF_2, and PGI_2 [9]. From a pathophysiological point of view avoidance of mechanical ventilation or new »gentle« ventilation strategies such as INSUREX (intubation, surfactant, extubation) or early nasopharyngeal CPAP may also reduce the incidence of PDA. Controlled studies have not shown clear evidence up to now.

Excessive fluid administration (associated with the care under overhead radiant heaters) has been shown to be one factor associated with the development of PDA [21]. There is no evidence from randomized trials to support the routine use of early volume expansion in very preterm infants without cardiovascular compromise [22]. Moderate fluid restriction during the first days of life has been shown to reduce the risk of mortality, NEC and PDA in VLBW infants [10]. Closed incubator care and daily review of body weight, parenteral volumes administered, and output and specific gravity of urine may help to make high fluid intake during the first days of life unnecessary. Administration of furosemide should be

avoided because of its interference with prostaglandin catabolism leading to higher circulating PGE2 levels.

Prophylactic Administration of Cyclooxygenase Inhibitors

Indomethacin reduces cerebral blood flow [2, 8, 9, 11]. A number of trials have been performed aiming primarily at the reduction of ICH in VLBW infants. The majority of these trials also showed a lower incidence of PDA in the treatment group. In spite of the partly promising short-term outcome data, long-term neurological outcome results are disappointing [11–14]. Although indomethacin slightly reduces the incidence of ICH grade IV (Fig. 11.1), there is no advantage for the treatment group concerning IQ levels, incidence of cerebral palsy or other long-term developmental problems (Fig. 11.2). This leads to speculation whether indomethacin could compromise cerebral white matter differentiation via hypoperfusion. Number needed to treat (NNT) for avoidance of PDA is 4 and for avoidance of severe ICH 20, so that there is a high number of overtreated infants [2].

Ibuprofen has no influence on cerebral blood flow. Thus it was also studied in order to reduce the incidence of PDA. NNT for this purpose is 3. There are no statistically significant differences in mortality, severe ICH, CLD or NEC favoring

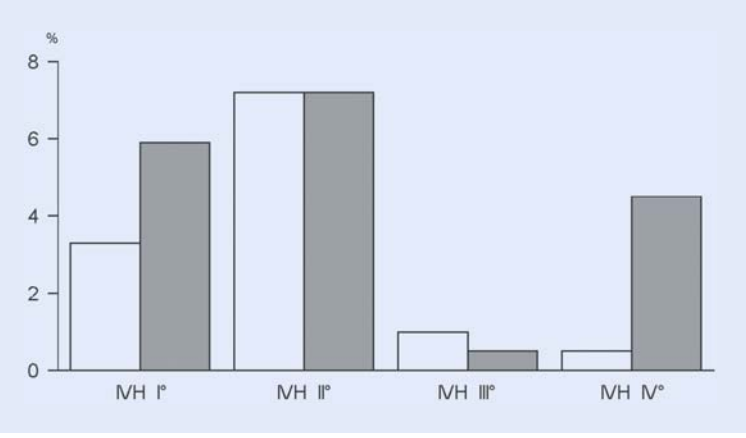


Fig. 11.1 Prophylactic indomethacin and incidence (%) in IVH. White: Indomethacin, grey: placebo (with permission from L. Ment, Pediatrics 1994, 93:543)

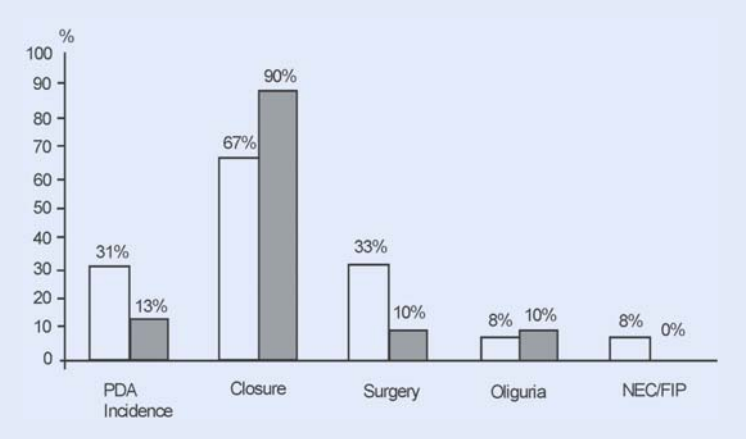


Fig. 11.2 Incidence (%) of adverse outcomes 18 months after prophylactic indometacin. White: Indometacin, grey: Placebo (with permission from B. Schmidt, NEJM 2001, 344:1966)

the ibuprofen treatment group [4]. One trial was stopped after 3 infants developed severe pulmonary hypertension responsive to NO in the treatment group [15]. Although a rare event, this supports concern about the safety of very early administration of cyclooxygenase inhibitors.

Indomethacin

Indomethacin was introduced for pharmacological closure of PDA in the 1970s [18]. Since then several thousand premature infants have been treated in controlled trials. Efficacy for closure of PDA has been 60–90%, with differences due to different study populations and trial designs. Closure rates in ELBW infants are lower compared to VLBW infants. The serum half-life of indomethacin is 20 hours. Several dosing regimens (classical dose 0.2 mg/kg every 12–24 h, low dose 0.1 mg/kg, continuous infusion) and time schedules (early vs. late, short vs. prolonged therapy) have been proposed over the last 30 years [9]. Slow infusion over at least 30 minutes causes fewer renal side effects than bolus injection. Although indomethacin has been the drug of choice for many years, its possibly harmful long-term side effects are still of concern. Acute side effects include decreased cerebral, mesenteric and renal blood flow, impaired renal function and altered platelet function. As PDA itself causes reduction of cerebral blood flow, further reduction via indomethacin is an issue of serious concern. Metaanalyses have not shown an increase of cystic PVL in indomethacin treated infants. However cystic PVL is only the tip of the iceberg, as more diffuse forms of white matter disease due to hypoperfusion and/or inflammatory processes are being intensively studied in present research.

Ibuprofen

Experimental investigations on alternative cyclooxygenase inhibitors have been performed since the late 1970s [19]. Ibuprofen emerged as a substance with potentially fewer side effects and equal efficacy. It was introduced into clinical trials in 1995 [16]. Ibuprofen has been shown to close PDA effectively without reducing cerebral, mesenteric or renal blood flow. At up to 30 hours, its serum half-life exceeds that of indomethacin (20 hours). Ibprofen usually is started with a dose of 10 mg/kg given as slow infusion, and is continued by two doses of 5 mg/kg in 24 hour intervals. No data on maintenance treatment are available yet. A recent metaanalysis [5] identified 509 patients in 8 studies comparing ibuprofen and indomethacin. Effectiveness in closing the PDA was equal and ibuprofen had a lower incidence of oliguria with a NNT of 9. Oxygen dependency on day 28 was slightly higher in the ibuprofen treated infants (relative risk 1.37). The authors concluded that indomethacin should remain the drug of choice and propose a four arm trial including both drugs in a treatment and prophylaxis strategy. The concern about a higher risk of BPD seems to be questionable, because clinically relevant BPD is better defined as O_2 dependency at 36 weeks postmenstrual age and the lower confidence interval for the odds ratio was only 1.01. Furthermore there were no statistically different results for BPD in prophylactic trials using ibuprofen as compared to indomethacin [4].

Hamburg Ibuprofen Study

Stimulated by the publication of van Overmeire in September 2000 [17], we performed a prospective, non-controlled cohort study from January 2001 to December 2002 in two neonatological centers (Hamburg-Barmbek: R. Laux, Hamburg-Altona: A. von der Wense) [20]. A total of 398 infants were enrolled during the 2 year period (230 VLBW, 168 ELBW). Echocardiography was performed in all infants on days 3–5. PDA was treated with ibuprofen 10–5–5 mg/kg every 24 hours. Closure of PDA was checked by repeated echocardiography. A second course of ibuprofen or prolonged treatment was allowed for partial response or reopening. Surgery was indicated if primary contraindications to ibuprofen or treatment failure were present.

Eighty-one infants (20.3%) developed PDA, 52 of them (31%) in the ELBW group and 29 (13%) in the VLBW group. Surgical closure was performed in 3 patients of the ELBW group, so that 78 infants received ibuprofen. The mean birth weight of the treated infants was 901 g, gestational age 26.5 weeks. In the population studied by van Overmeire [17] these data were 1230 g and 29.0 weeks, respectively.

The main results are shown in Figures 11.3 and 11.4. The rate of closure was comparable to that of van Overmeire et al. [17] in spite of lower gestational age and birth weight. Not surprisingly, the effectiveness of ibuprofen was lower in ELBW infants than in the VLBW group. The 9% incidence of oliguria was reasonably low, as were abdominal complications with a rate of 5% for NEC or focal intestinal perforation, all cases in the ELBW group. The need for surgical closure was higher than in the van Overmeire trial, probably due to the higher proportion of extreme prematurity (52% of infants <27 weeks versus 18%). No bleeding complications were observed, especially no progression of IVH. We did not find cases of severe pulmonary hypertension. Oxygen dependency at 36 weeks GA was present in 6% of the treated infants.

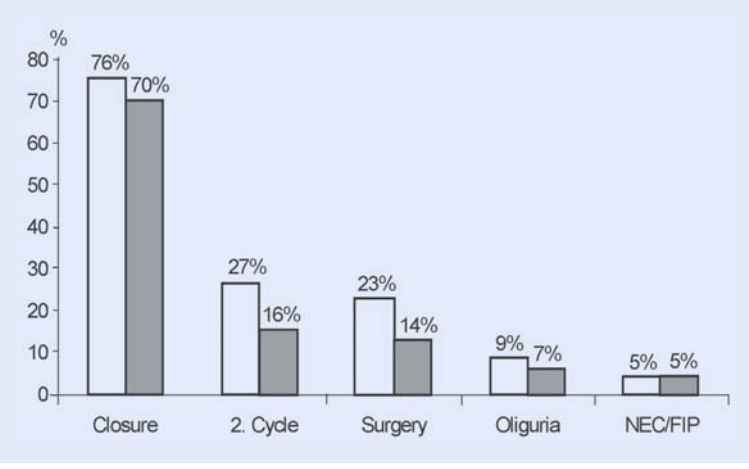


Fig. 11.3 Results of ibuprofen therapy: Comparison of data from Hamburg Ibuprofen study with published results by van Overmeire et al. 2001. White: Hamburg data, n=78, grey: Belgium data, n=74

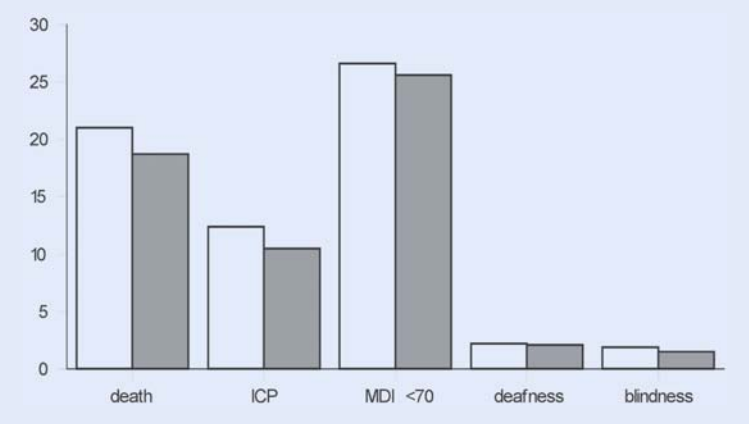


Fig. 11.4 Hamburg Ibuprofen study: Adverse outcome (%) according to birth weight. White: ELBW infants, birth weight <1000g (n=49), grey: VLBW, birth weight 1000-1499 g (n=29). ICP, intracranial pressure MDI, mental developmental index

Current Hamburg Concept of PDA Treatment

Derived from currently available evidence and our own data the actual approach to PDA in VLBW and ELBW infants is as follows:

- No prophylactic treatment with cyclooxygenase inhibitors.
- Echocardiography to rule out or prove PDA on day 3 in all infants independent of the presence of symptoms.
- Treatment of PDA with ibuprofen 10–5–5 mg/kg every 24 hours; echocardiographic evaluation of ductal closure.
- Second course of ibuprofen for reopening, prolonged course of 5–5–5 mg/kg for partial closure.
- On-ward surgery for the definitive closure of every hemodynamically relevant PDA not responding to ibuprofen, or in the rare case of primary contraindications (e.g. preexisting renal failure).

References

1. Barrington K, Brion LP. Dopamine versus no treatment to prevent renal dysfunction in Indomethacin-treated preterm newborn infants. The Cochrane Library 1, 2002.
2. Fowlie PW, Davis PG. Prophylactic intravenous Indomethacin for preventing mortality and morbidity in preterm infants. The Cochrane Library 2, 2002.
3. Cooke L, Steer P, Woodgate P. Indomethacin for asymptomatic patent ductus arteriosus in preterm infants. The Cochrane Library 3, 2002.
4. Shah SS, Ohlsson A. Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants. The Cochrane Library 1, 2003.
5. Ohlsson A, Walia R, Shah S. Ibuprofen for the treatment of patent ductus arteriosus in preterm and/or low birth weight infents. The Cochrane Library 1, 2003.
6. Malviya M, Ohlsson A, Shah S. Surgical versus medical treatment with cyclooxygenase inhibitors for symptomatic patent ductus arteriosus in preterm infants. The Cochrane Library 2, 2003.
7. Crowley P. Prophylactic corticosteroids for preterm birth. The Cochrane Library 1, 1996.
8. Hammerman C. Patent Ductus Arteriosus. Clinical relevance or prostaglandins and prostaglandin inhibitors in PDA pathophysiology and treatment. Clin Perinatol 1995; 22: 457–79.
9. van Overmeire B, Suys B. Pharmacological manipulation of patent ductus arteriosus. In: Les medicaments en reanimation neonatale. Springer Verlag 1999, 141–71.
10. Bell EF, Acarregui MJ. Restricted versus liberal water intake for preventing morbidity and mortality in preterm infants. The Cochrane Library 2, 2001.
11. Ment LR, Oh W, Ehrenkranz RA, Philip AG, Allan W, Duncan CC, Scott DT, Taylor KJ, Katz KH. Low-Dose Indomethacin and prevention of intraventricular hemorrhage: A multicenter randomized trial. Pediatrics 1994; 93: 543–50.
12. Ment LR, Vohr B, Scott DT, Allan WC, Westerveld M, Duncan CC, Ehrenkranz RA, Katz KH, Schneider KC, Makuch RW. Neurodevelopmental outcome at 36 months´ corrected age of preterm infants in the Multicenter Indomethacin Intraventricular Hemorrhage Prevention Trial. Pediatrics 1996; 98: 714–18.
13. Vohr BR et al. School-age outcomes of very low birth weight infants in the Indomethacin intraventricular hemorrhage prevention trial, Pediatrics 2003; 111: e340–e346.
14. Schmidt B, Davis P, Moddemann D, Ohlsson A, Roberts RS, Saigal S, Solimano A, Vincer M, Wright LL, for the Trial of Indomethacin Prophylaxis in Preterms Investigators. Long-term effects of indomethacin prophylaxis in extremely-low-birth-weight infants. New Engl J Med 2001; 344: 1966–72.
15. Gournay V, Savagner C, Thiriez G, Kuster A, Rozé JC. Pulmonary hypertension after ibuprofen prophylaxis in very preterm infants. Lancet 2002; 359: 1486–1488.
16. Patel J Roberts I, Azzopardi D, Hamilton P, Edwards AD. Randomized double-blind controlled trial comparing the effects of Ibuprofen with Indomethacin on cerebral hemodynamics in preterm infants with patent ductus arteriosus. Pediatr Res 2000; 47: 36–42.
17. Van Overmeire B, Smets K, Lecoutere D, Van de Broek H, Weyler J, De Groote K, Langhendries JP. A comparison of ibuprofen and indomethacin for closure of patent ductus arteriosus. New Engl J Med 2000; 343: 674–681.
18. Heymann MA, Rudoph AM, Silverman NH: Closure of the ductus arteriosus in premature infants by inhibition of prostaglandin synthesis. New Engl J Med 1976; 295: 530–533.
19. Coceani F, White E, Bodach E, Olley PM. Age-dependent changes in the response of the lamb ductus arteriosus to oxygen and Ibuprofen. Can J Physiol Pharmacol 1979; 57: 825–31.
20. von der Wense A, Laux R, Süßenguth R. Ibuprofentherapie des persistierenden Ductus arteriosus Botalli bei Frühgeborenen mit sehr niedrigem Geburtsgewicht. Z Geburth Neonatol 2003; 207, Suppl 1: 17.
21. Stevenson JG. Fluid administration in the ssociation of patent ductus arteriosus complicating respiratory distress syndrome. J Pediatr 1977; 90: 257–61.
22. Osborn DA, Evans N: Early volume expansion for prevention of morbidity and mortality in very preterm infants. The Cochrane Database of Systematic Reviews 2004; Issue 2: CD002055.

Surgical Closure

Michael Hübler

History

On August 26, 1938, Robert Gross performed the first successful surgical correction of a congenital heart defect when he ligated a patent ductus arteriosus in a seven year old child at the Boston Children's Hospital (Gross et al. 1939). In 1946, Alfred Blalock described triple ligation (Blalock 1946) and in 1963 DeCanq reported the ligation of a PDA in a 1417 g preterm infant (DeCanq 1963). Surgery was the only treatment for patent ductus arteriosus until pharmacological approaches became available in 1976 (Heymann et al. 1976). The thoracoscopic technique for interrupting the PDA in infants was developed in Paris in the early 1990s (Laborde et al. 1993). Today, in most instances PDA surgery in preterm infants is a second line approach in patients in whom pharmacotherapy fails. About one third of both indomethacin and ibuprofen interventions fail to close the PDA permanently (Su et al. 2003, Little et al. 2003). Among the factors making surgical PDA interventions in immature infants successful are: (1) appropriate indication, (2) optimal timing, (3) perfect cooperation of the teams involved, (4) skill of the cardiac surgeon.

Transport to the Operating Room

Like others (Mortier et al. 1996, McKee 2004), we believe that transporting an unstable, artificially ventilated infant of extremely low birth weight is more threatening for the infant than the PDA ligation itself, and strongly advocate to perform the operation within the neonatal intensive care unit (NICU). Elaborate organization must precede a thoracotomy within the NICU, and aseptic surroundings similar to the operating room cannot be achieved. However, these difficulties are outweighed by the risks associated with the transfer of a highly unstable, artificially ventilated preterm infant: The infant must be moved from the ICU ventilator to different ventilators during transport and anesthesia before returning to the ICU ventilator during a phase of repeated and large changes in lung function. An even greater risk is loss of continuity and information if different teams care for the baby on the ward, during transit, and in the operating room. An experienced neonatologist thoroughly informed about the individual problems and a nurse who is familiar with the baby should stay with the infant during transfers and surgery. The infant's temperature, blood pressure and oxygenation should be continuously monitored. Unnecessary changes in intravenous volume supply or composition and

bolus injections should be avoided. Blood gases should be checked repeatedly.

Preparation for Operation in the NICU

The major goal is to perform PDA closure with as little trauma to the infant as possible, especially with regard to the brain. This includes avoiding hypo- and hyperthermia, hypo- and hypervolemia, hypo- and hyperoxia, hypo- and hypercarbia, and hypo- and hyperglycemia. As these risks increase with time, a gentle, safe, and rapid intervention must be planned. Also when the procedure is done in the NICU, general anesthesia should be performed by a pediatric anesthetist who is familiar with extremely low birth weight infants.

1. Essential information:
   - Coagulation study (minimum: thromboplastin time, platelet count)
   - Ultrasound scan of the brain (hemorrhages, echodensities)
   - Echocardiography to exclude ductus dependent cardiac defects, right-to-left shunting, and to assess the anatomical situation
   - Chest X-ray to ascertain tube position
   - Parental consent.
2. Information for cardiac surgeon and pediatric anesthetist:
   - Size of the PDA, degree of shunt, anatomic peculiarities
   - Lung function, ventilator settings, recent blood gas measurements
   - Accompanying disorders, especially renal insufficiency, and concomitant medication.
3. Requirements in the intervention room:
   - Open intensive care bed with overhead heater and full NICU equipment
   - Entire room is heated to 32–35° C two hours before surgery, if necessary with the use of an additional mobile heater
   - Enough space must be available for six persons
   - Sufficient light source or mobile operation room lamp
   - Ventilator with settings adapted to the infant's needs
   - Electrocauterizer
   - Complete NICU documentation including ventilator charts and recent X-rays.
4. Mobile equipment required by the surgeon:
   - Sterile towels to support positioning
   - Instrument set
   - Clips and forceps
   - Pleural drains, size 8 and 10.
5. Mobile equipment required by the pediatric anesthetist:
   - End expiratory CO2 monitor
   - Set of standard rescue medication
   - Colloidal fluids or blood transfusions are rarely needed but must be present
   - Mobile ventilator (should be present, but usually manual ventilation is preferred in order to adapt to the rapid changes in pulmonary distensibility when the lung is compressed by the surgeon)
   - General anesthesia is performed with Nimbex® (GlaxoSmithKline, Brentford, UK).

Perioperative Management

The infant is placed in the right lateral position (Fig. 12.1A); the final positioning is chosen by the surgeon. For parenteral fluids we initially continue the infant's individual infusion. Sometimes the glucose concentration in the infusion must be reduced. Postoperative pain control is achieved with morphine infusion. During the intervention, monitoring must be provided for electrocardiogram, blood pressure, O_2 saturation, transcutaneous PO_2 and PCO_2, rectal temperature, blood gases especially when ventilator settings are changed, and blood sugar.

Surgical Management

The approach is similar to that in older infants, but the size and tissue stiffness of the ductus make the triple ligature technique dangerous. The ductus is approached by a small left lateral thoracotomy (Fig. 12.1B), the cut following the latissimus

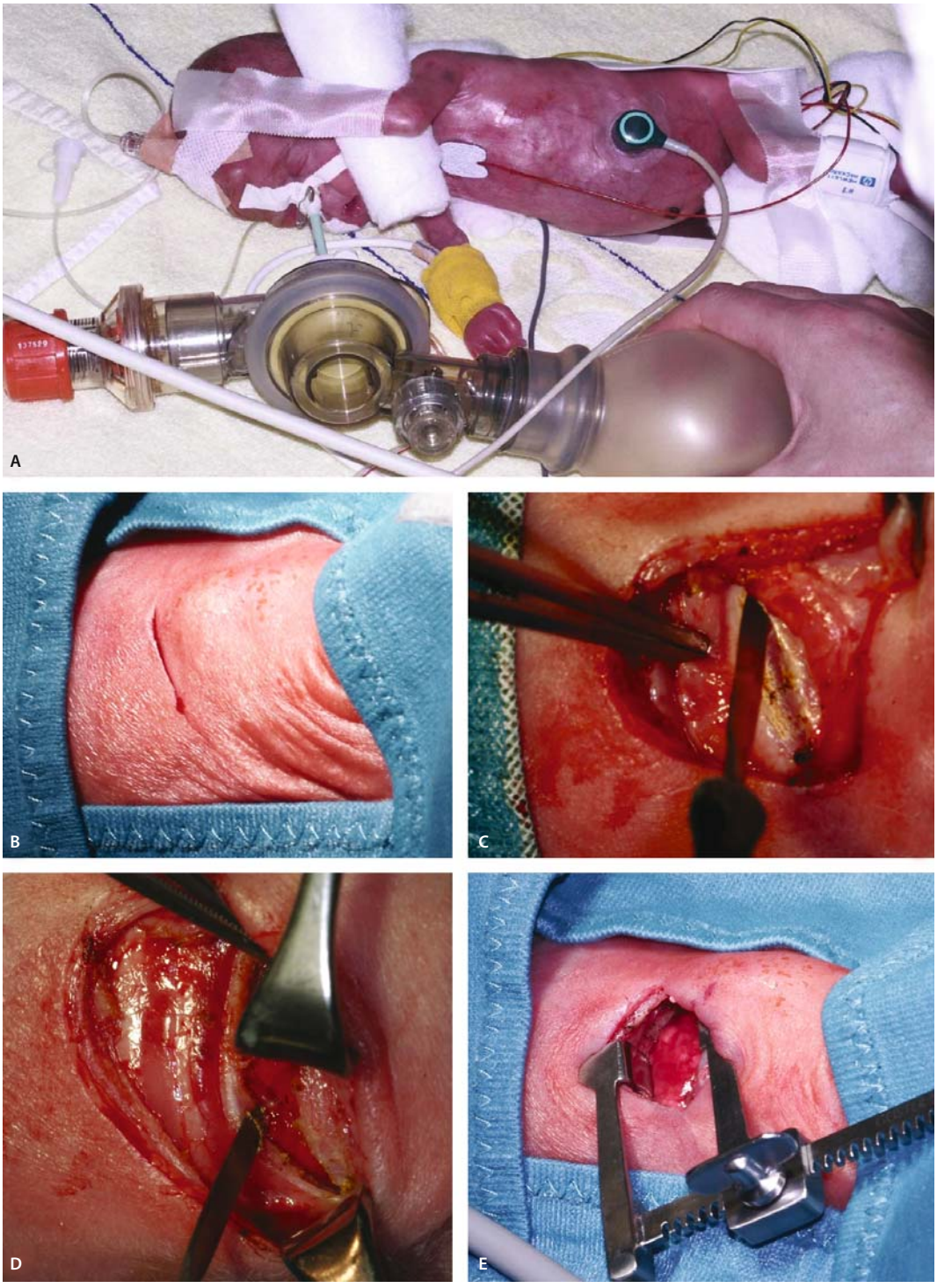


Fig. 12.1 Preoperative positioning of the infant (A), skin (B) and intercostal cut (C), opening of the pleura (D) and retraction of the ribs (E).

dorsi and opening the third or fourth intercostal space by electrocautery (Fig. 12.1C). A miniaturized rib retractor (Mini-Finiochetto, Geister, Tuttlingen Germany) is placed and opened only partially at first, then gradually opened further to obtain adequate exposure (Fig. 12.1D). A malleable retractor (brain retractor, Aesculap, Tuttlingen, Germany) is gently placed on the lung and a vertical incision is made in the mediastinal pleura over the proximal descending aorta (Fig. 12.1E). The PDA is completely dissected from the soft tissue (Fig. 12.2G) and meticulous care is taken to identify all structures (Fig. 12.2F), as the PDA may be larger than the aorta. The left recurrent laryngeal nerve is visualized (but not isolated) just inferior and posterior to the PDA (Fig.12.2H). A single central ligature (5–0 PTFE impregnated Polyester) (Tevdek®, Genzyme, Cambridge, USA) is performed after circumferential dissection. In many cases, the friable vascular tissue may make the complete dissection of the ductus unadvisable. An equally effective alternative is a titanium ligating clip (Horizon®, Pilling Weck, Markham, Canada) (Fig. 12.2I–K), especially in cases in which circumferential dissection is regarded to be difficult or dangerous. Both diameter and length of the PDA vary widely and two clips may become necessary (Fig. 12.3L). The clip is placed with a forceps completely across the aortic end of the PDA, making sure that its tip does not grasp the recurrent laryngeal nerve or other soft tissue. The rib retractor is removed and a 8F catheter (Vygon®, Ecouen, France) is inserted into the posterior part of the pleural space (Fig. 12.3P). The use of pleural catheters is controversial and especially with extrapleural approaches regarded as unnecessary (Miles et al. 1995). However, as postoperative tension pneumothorax is a rare but catastrophic complication, which may lead to severe intracerebral hemorrhage, and as the placement of a thoracic catheter is more traumatic if done after the operation, we routinely insert a small low suction pleural drainage catheter which may be removed after 12 to 24 hours. The ribs on either side of the incision are gently approximated with two or three absorbable 3–0 interrupted sutures (Vicryl® Ethicon, Piscataway, USA), taking care not to connect the ribs tightly (Figs. 12.3M and 12.4). The muscular und subcutaneous layers are closed with absorbable running sutures (Biosyn®, Tyco Healthcare, Gosport, UK) (Fig. 12.3N,O). Usually, the thorax is closed within 30 minutes after onset of the operation. Immediately after return to the regular NICU place a chest x-ray is taken (Fig. 12.3Q) in order to exclude pneumothorax and atelectasis.

Postoperative Management

Repeated blood gas analyses are required to find the appropriate ventilator settings, which may be more ore less aggressive than before the operation. A chest x-ray should be taken to assure bilateral ventilation and to exclude air leak. The chest drain usually remains clamped and can be removed after 12–24 hours. Weaning from the ventilator is usually not feasible during the first 24 hours after the operation. Pain control should be achieved with short acting opiates. We prefer morphine 10 µg/kg/h by infusion, and try to avoid midazolam due to its side effects and long half life. Oxygenation, blood pressure, fluid intake and excretion should be closely monitored until the infant is stable, at least for 48 hours.

Complications

Ligation of a patent ductus arteriosus in the preterm infant can be performed with very litle morbidity and mortality directly related to the surgical procedure (Koehne et al. 2001). In low birth weight infants, severe thoracic deformity and even scoliosis may occur after thoracotomy (Jaureguizar et al. 1985, Seghaye et al. 1997). A severe complication is vocal palsy (Fig. 12.4), which has also been described after minimally invasive thoracoscopic surgery (Burke et al. 1999). Due to the high degree of immaturity and lung damage in these infants, considerable postoperative mortality and morbidity remains. In a non-randomized comparison within the international trial of indomethacin prophylaxis, Kabra et al. found a significant direct correlation between the rates of surgical PDA closure in the individual study centers

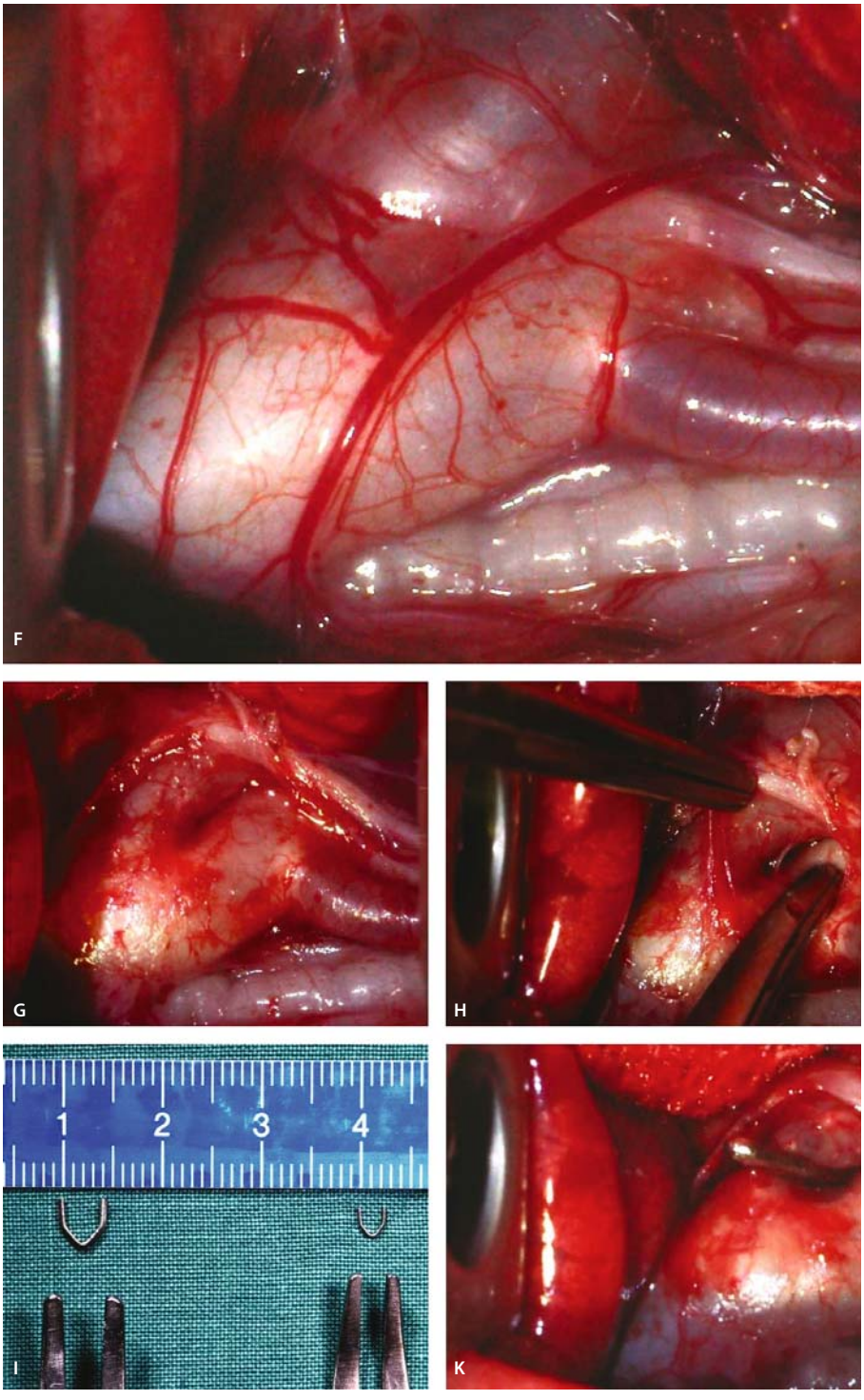


Fig. 12.2 Operation situs showing (from top) PDA, N. vagus, aortic arch, subclavian artery, vertebral column (F); ductus after preparation (G), pushing aside N. vagus and N. recurrens (H), selecting clip (I), clip in position (K).

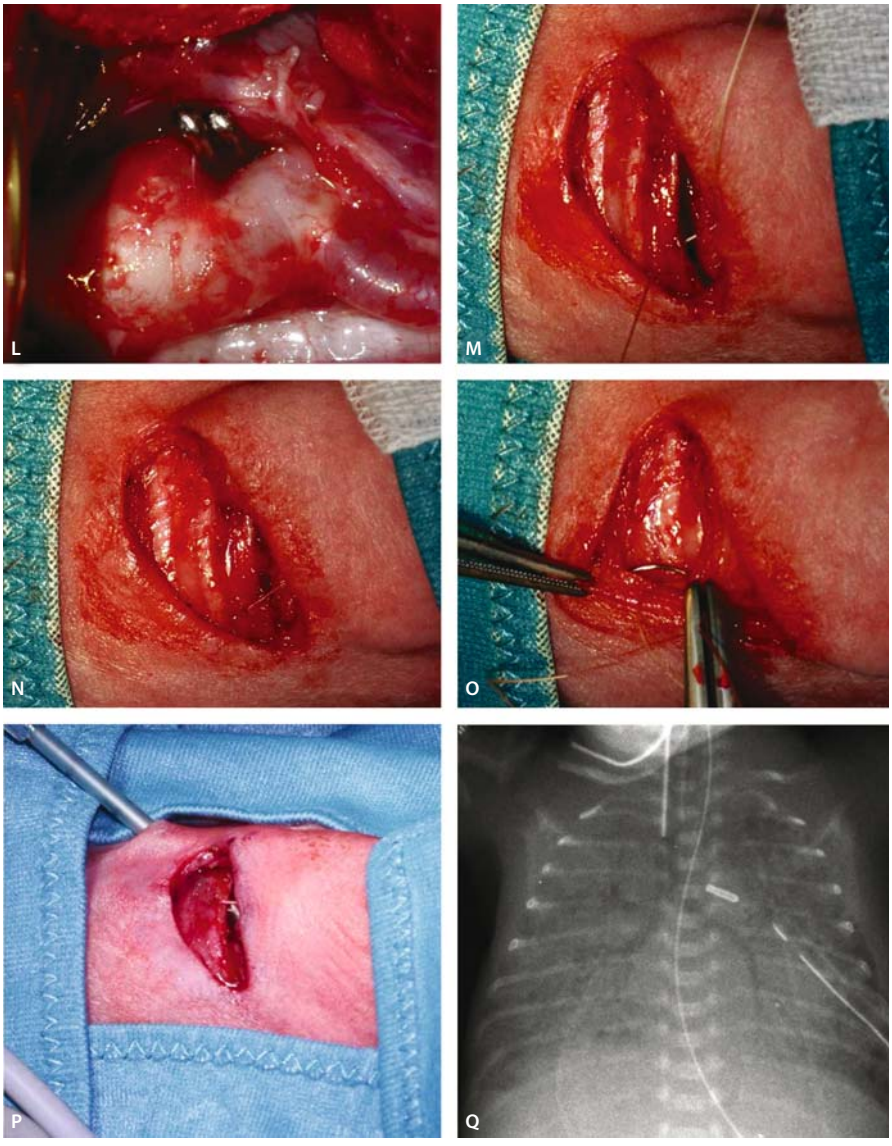


Fig. 12.3 Large duct occluded with two clips (L), closure of chest wall (M,N), closure of soft tissues in two layers (O), insertion of pleural drain (P), postoperative chest x-ray (Q).

and the prevalence of neurosensory impairments in survivors (Kabra et al. 2004). As among the infants undergoing intervention for PDA, those requiring surgery were the sickest and the most immature, it remains unclear whether PDA ligation is a cause or a marker of adverse long-term outcome in this population. When compared to medical treatment, the major burden of surgical intervention is pneumothorax (Fig. 12.5). Misidentification of the ductus is much more likely in premature infants because of the limited surgical exposure and the emphasis on shortening the procedure. We have not experienced gross misidentifications, but unintentional ligations of the pulmonary artery, the aorta, and even a main stem bronchus have been described.

Outcome and Complications in our Center

Between January 1989 and March 2004 we performed 119 PDA ligations in very low birth weight infants. Mean birth weight of the infants was 740 g (range 470/1300), gestational age 25.8 weeks (23.1/31.5). Mean age at surgery was 9 days (range 4/22) and mean procedural time was 26 min (23–31). Postoperative echocardiography revealed complete closure in 113 of the 119 infants. We observed 3 cases of tension pneumothorax, 2 cases each of intraoperative bleeding and wound infection, and 1 case of vocal fold palsy due to lesion of the N. recurrens (Koehne et al. 2001). No intraoperative mortality, no phrenic palsy and no chylothorax occurred, no severe scoliosis was detected at the regular follow up examination.

Minimally Invasive Approaches

Recently and with the development of smaller instruments, less invasive surgical approaches already established in older and larger patients have been extended to PDA interventions in preterm infants (Georgeson et al. 2004), among them

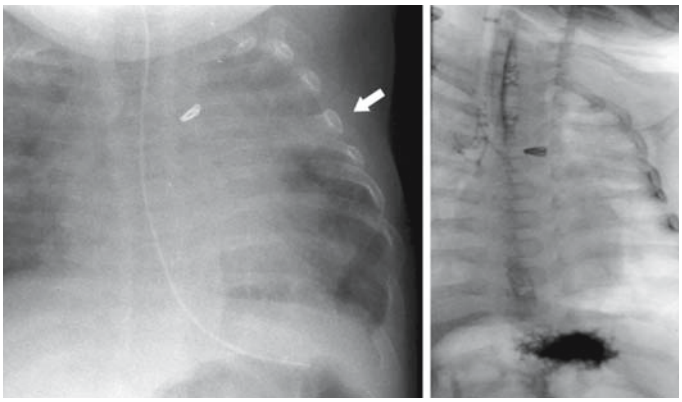


Fig. 12.4 Chest deformity (arrow) due to intercostal suture (left panel) and vocal palsy leading to gastrografin aspiration (right panel) are rare but serious complications of ductus ligation in preterm infants.

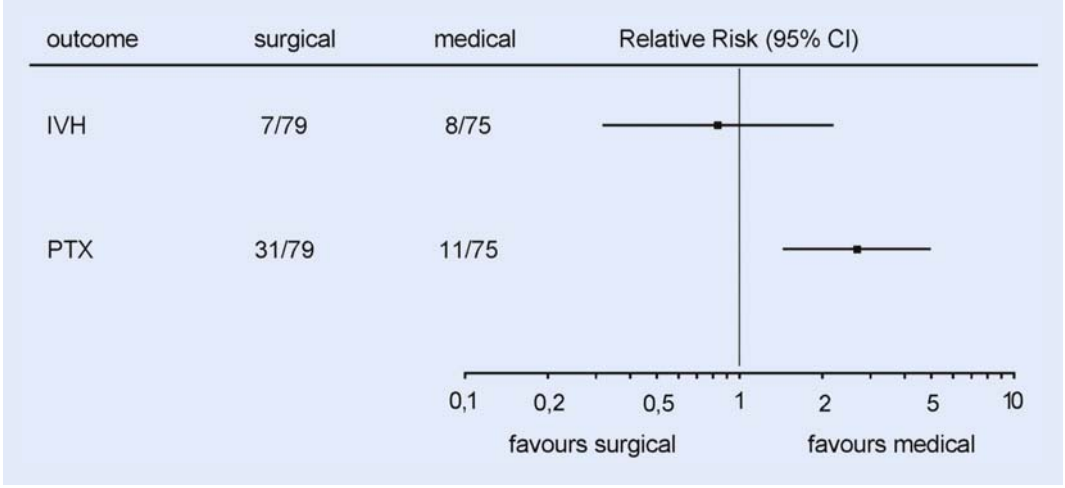


Fig. 12.5 Metaanalysis showing elevated rates of pneumothorax (PTX) but not intraventricular hemorrhage (IVH) in preterm infants with surgical vs. medical treatment with cyclooxygenase inhibitors in preterm infants with symptomatic PDA. Adapted from Malviya et al. 2003.

the superior extrapleuric approach (Mazzera et al. 2004), dorsal minithoracotomy (Vicente et al. 2004) and video assisted thoracoscopic surgery (VATS), which reduces trauma, metabolic stress and risk of thoracic deformations (Hines et al. 2003, Jacobs et al. 2003). As VATS necessitates transport from the NICU to the operating room, and as intervention and therefore anesthesia last longer, it cannot be presently regarded as an alternative to thoracotomy, but possibly it may become a complementary approach in the future.

References

Blalock A: Operative closure of the patent ductus arteriosus. Surg Gynecol Obstet. 1946; 82: 112.

Burke RP, Jacobs JP, Cheng W, Trento A, Fontana GP: Video-assisted thoracoscopic surgery for patent ductus arteriosus in low birth weight neonates and infants. Pediatrics 1999; 104: 227–30.

DeCanq HE Jr. Repair of patent ductus arteriosus in a 1417 g infant. Am J Dis Child 1963; 106: 402–5.

Georgeson KE, Robertson DJ: Minimally invasive surgery in the neonate: Review of current evidence. Seminars in Perinatology 2004; 28: 212–20.

Gould DS, Montenegro LM, Gaynor JW, Lacy SP, Ittenbach R, Stephens P, Steven JM, Spray TL, Nicolson SC: A comparison of on-site and off-site patent ductus arteriosus ligation in premature infants. Pediatrics 2003; 112: 1298–301.

Gross RE, Hubbard JP: Surgical ligation of a patent ductus arteriosus: A report of first successful case. JAMA 1939; 112: 729–31.

Heymann MA, Rudolph AM, Silverman NH: Closure of the ductus arteriosus in premature infants by inhibition of prostaglandin synthesis. N Engl J Med. 1976; 295: 530–3.

Hines MH, Raines KH, Payne RM, Covitz W, Cnota JF, Smith TE, O'Brien JJ, Ririe DG: Video-assisted ductal ligation in premature infants. Ann Thorac Surg. 2003; 76: 1417–20.

Jacobs JP, Giroud JM, Quintessenza JA, Morell VO, Botero LM, van Gelder HM, Badhwar V, Burke RP: The modern approach to patent ductus arteriosus treatment: complementary roles of video-assisted thoracoscopic surgery and interventional cardiology coil occlusion. Ann Thorac Surg. 2003; 76: 1421–7; discussion 1427–8.

Jaureguizar E, Vasquez J, Murcia J, Diez Pardo JA: Morbid musculoskeletal sequelae of thoracotomy for tracheoesophageal fistula. J Peditr Surg 1985; 20: 511–4.

Kabra NS, Schmidt B, Doyle L, Papile L, Fanaroff A: Surgical closure of a patent ductus arteriosus (PDA) is associated with increased neurosensory impairment in extremely low birth weight (ELBW) infants: Results from the trial of indomethacin prophylaxis in preterms. Pediatr Res. 2004; 56: 503A.

Kinouchi K: Anaesthetic considerations for the management of very low and extremely low birth weight infants. Best Pract Res Clin Anaesthesiol. 2004; 18: 273–90.

Koehne P, Bein G, Alexi-Meshkishvili, V, Weng Y, Bührer C, Obladen M: Patent ductus arteriosus in very low birthweight infants: Complications of pharmacological and surgical treatment. J Perinat Med 2001; 29: 327–334.

Laborde F, Noirhomme P, Karam J, Batisse A, Bourel P, Sain Maurice O: A new video-assisted thoracoscopic surgical technique for interruption of patent ductus arteriosus in infants and children. J Thorac Cardiovasc Surg 1993; 105: 278–80.

Küster A, Jouvet P, Bonnet D, Flandin C, Lenclein R, Hubert P, Jan D: Feasibility of surgery for patent ductus arteriosus of premature babies in a neonatal intensive care unit. Eur J Pediatr Surg. 2003; 13: 294–7.

Limpert JN, Limpert PA, Weber TR, Bower RJ, Trimble JA, Micelli A, Keller MS: The impact of surgery on infants born at extremely low birth weight. J Pediatr Surg. 2003; 38: 924–7.

Little DC, Pratt TC, Blalock SE, Krauss DR, Cooney DR, Custer MD: Patent ductus arteriosus in micropreemies and full-term infants: the relative merits of surgical ligation versus indomethacin treatment. J Pediatr Surg. 2003; 38: 492–6.

Malviya M, Ohlsson A, Shah S: Surgical versus medical treatment with cyclooxygenase inhibitors for symptomatic patent ductus arteriosus in preterm infants. Cochrane Database Syst Rev. 2003; (3): CD003951

Mazzera E, Brancaccio G, Feltri C, Michielon G, Capolupo I, Costa D, Di-Donato R:: [A new approach to the closure of patent ductus arteriosus in premature infants]. Ital Heart J Suppl. 2004;5: 205–8.

McKee M: Operating on critically ill neonates: The OR or the NICU. Seminars in Perinatology 2004; 28: 234–9.

Miles RH, DeLeon SY, Muraskas J, Myers T, Quinones JA, Vitullo DA, Bell TJ, Fisher EA, Pifarre R: Safety of patent ductus arteriosus closure in premature infants without tube thoracostomy. Ann Thorac Surg. 1995; 59: 668–70.

Mortier E, Ongenae M, Vermassen F, Van Aken J, Van Haesebrouk P, Vandeveire B, Rolly G: Operative closure of patent ductus arteriosus in the neonatal intensive care unit. Acta Chir Belg. 1996; 96: 266–8.

Seghaye MC, Grabitz RG, Alzen G, Trommer F, Hörnchen H, Messmer BJ, Von Bernuth G. Thoracic sequelae after surgical closure of the patent ductus arteriosus in preterm infants. Acta Paediatr 1997; 86: 213–6.

Su PH, Chen JY, Su CM, Huang TC, Lee HS: Comparison of ibuprofen and indomethacin therapy for patent ductus arteriosus in preterm infants. Pediatr Int. 2003; 45: 665–70.

Szymankiewicz M, Hodgman JE, Siassi B, Gadzinowski J: Mechanics of breathing after surgical ligation of patent ductus arteriosus in newborns with respiratory distress syndrome. Biol Neonate. 2004; 85: 32–6.

Vicente WV, Rodrigues AJ, Ribeiro PJ, Evora PR, Menardi AC, Ferreira CA, Alves L Jr, Bassetto S: Dorsal minithoracotomy for ductus arteriosus clip closure in premature neonates. Ann Thorac Surg. 2004; 77: 1105–6.

Comparison of Indomethacin and Ibuprofen

Bart van Overmeire

Ibuprofen is not a new drug: it has already been used for more than 40 years. The first patent on ibuprofen was filed by Sir Stewart Adams in 1962 for the relief of pain, fever, and inflammation. Only recently has its application been expanded to include use in the most vulnerable and smallest preterm infants. Ibuprofen has been studied as an alternative treatment for patent ductus arteriosus (PDA) because serious concerns remain about the side effects of the conventional treatment of PDA with indomethacin.

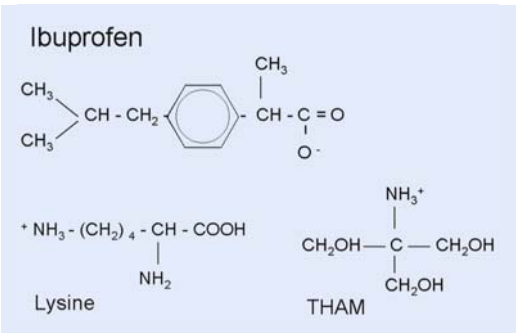


Fig. 13.1 Structure of ibuprofen lysine and THAM (tris-hydroxymethyl-aminomethane).

Properties of Ibuprofen

Ibuprofen is a nonsteroidal anti-inflammatory agent with a 2-arylpropionic acid structure, which exerts its pharmacological effect in the S(+)isomer configuration by inhibiting cyclo-oxygenase [1]. Unidirectional conversion of almost 60% from the R form to the S form has been reported in adults. In preterm infants who received three doses of prophylactic i.v. ibuprofen, the serum half life (95% CI) was 25.5 (21.5–31.2) hours for the S and 10.0 (8.7–11.0) hours for the R enantiomers [22]. Indomethacin and ibuprofen are nonselective cyclooxygenase (COX) inhibitors reducing the activity of both COX 1 and COX 2. Ibuprofen is insoluble in water and therefore has been attached to lysine or to tris-hydroxymethyl-aminomethane (THAM) buffer to obtain a formulation suited for intravenous infusion (Fig. 13.1). Very recently it has been shown that oral administration might also be effective for inducing ductal closure in preterm infants [2].

Therapy and Prophylaxis of Patent Ductus Arteriosus

Publications on the use of ibuprofen for treatment of PDA have appeared since 1995 [3–6] (Fig. 13.2). Recent evidence from 8 studies

including 509 patients demonstrates that ibuprofen is equally effective as indomethacin for inducing closure of PDA in preterm infants [RR 0.92 (95% CI 0.69, 1.22)] [7]. The occurrence of oliguria (urine production < 1 mL/kg/h) was significantly lower in the ibuprofen group than in the indomethacin group (Fig. 13.3). Mortality, surgical ligation of the ductus, duration of ventilatory support, intraventricular hemorrhage, and necrotizing enterocolitis did not differ between the two drugs [7] (Fig. 13.4).

Prophylaxis with ibuprofen also reduces the development of a PDA [8]. Acute pulmonary hypertension was observed immediately after the infusion of ibuprofen-THAM solution in 3 infants [9]. Although there is no clear explanation for this observation, it has not been reported in the trials using the ibuprofen-lysine formulation. This »adverse effect« is possibly not unique for ibuprofen, as an increase in oxygen requirement has also been observed after the prophylactic administration of indomethacin [10]. Prophylaxis with ibuprofen seems not to reduce the occurrence of intraventricular haemorrhage [11], in contrast with a pronounced and statistically significant reduction of severe intraventricular hemorrhage after early indomethacin administration [12, 13].

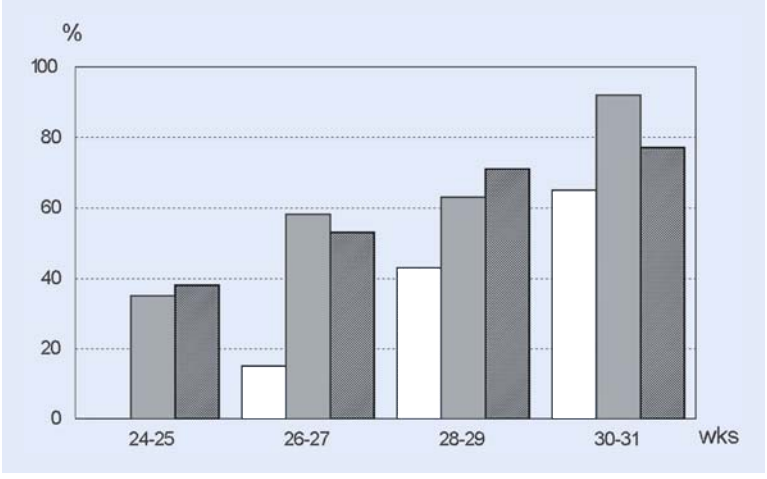


Fig. 13.2 Closure rate (%) on day 3 vs. gestational age in 211 preterm infants with PDA. White, controls; striped, ibuprofen; grey, indomethacin. Adapted from van Overmeire et al. [11].

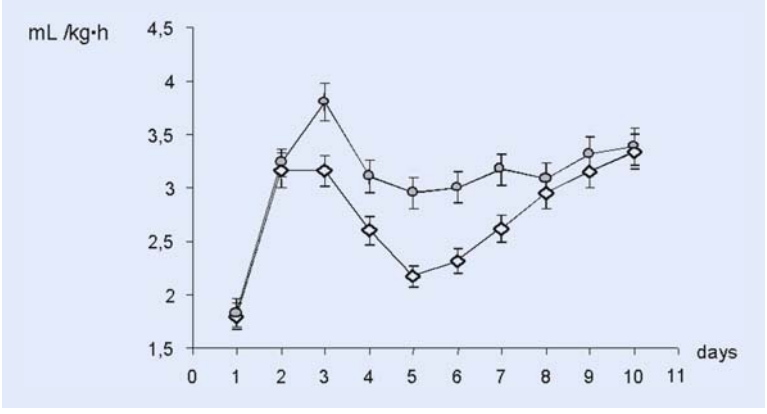


Fig. 13.3 Striking difference in urine production after indomethacin (squares) and ibuprofen (circles) treatment for PDA in 148 infants. Adapted from van Overmeire et al. [6].

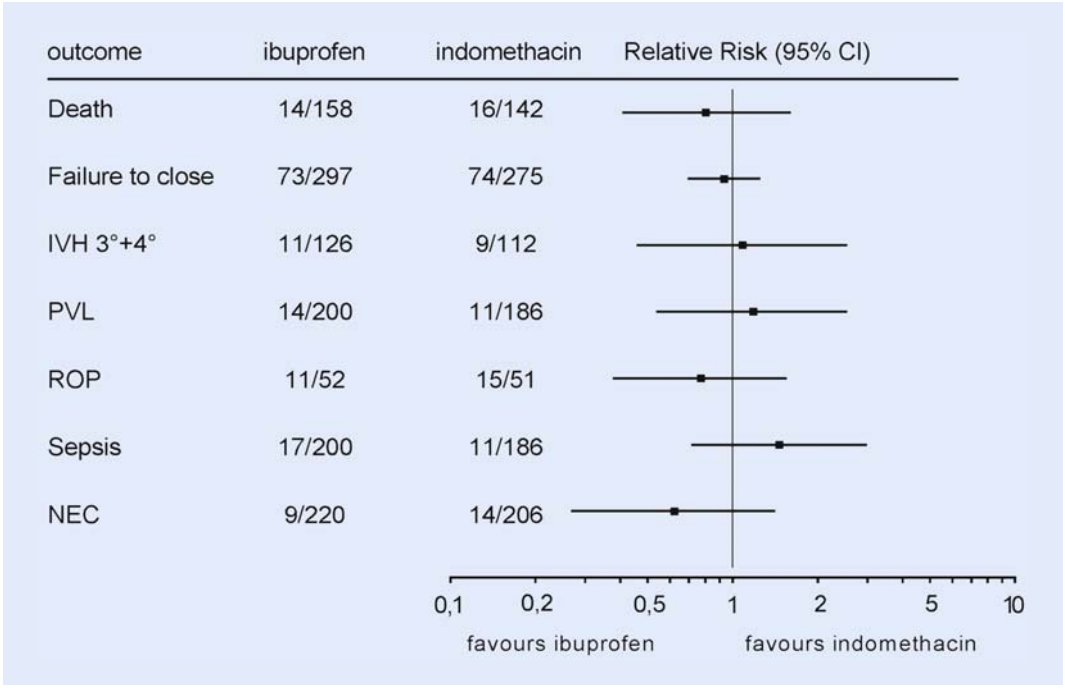


Fig. 13.4 Metaanalysis of adverse events observed in controlled trials with ibuprofen and indomethacin. IVH, intraventricular hemorrhage; PVL, periventricular leukomalacia; ROP, retinopathy of prematurity. Adapted from Ohlsson et al. [7] and Su [21].

Effects on Regional Circulation

Renal and mesenteric perfusion was less influenced by ibuprofen than by indomethacin [14]; however, animal experiments could not confirm these observations [15]. Ibuprofen causes no reduction of cerebral blood flow. Cerebral oxygen delivery was not significantly altered, which contrasts with the effects of indomethacin [3, 16]. After ibuprofen prophylaxis the minimal changes that were observed in cerebral blood volume or blood flow were comparable to those provoked with saline infusion [17].

Pharmacokinetics

Few data are available on the pharmacokinetics of ibuprofen. Compared to indomethacin, ibuprofen has a prolonged serum half-life. Marked age related differences and a wide interpatient variability in plasma concentrations and in pharmacokinetics are reported [18]. Serum half-life decreased from 43 h (SD 7.8) on the third day to 26.8 h (SD 6.5) on the fifth day of life. In very low birth weight infants the clearance of ibuprofen is slower and serum half-life is significantly longer than in older children.

Ibuprofen is highly bound to albumin and has the potential to increase the free fraction of bilirubin thereby increasing the risk of kernicterus [19, 20]. More data are needed to evaluate the extent of this effect in relation to ibuprofen plasma levels that are obtained in very low birth weight infants.

Conclusions

Available data indicate that ibuprofen(-lysine) is as efficacious as indomethacin in promoting ductal closure and that it has less adverse renal effect. Its effect on the cerebral and gastrointes-

tinal circulations are also different but a clear explanation is still lacking. Although ibuprofen seems promising, more studies are needed to define the optimal dose/effect relationship and the properties of the different formulations that are being studied.

References

1. Adams SS, Bresloff P, Mason CG. Pharmacological differences between the optical isomers of ibuprofen: Evidence for metabolic inversion of the (-)-isomer. J Pharm Pharmacol 1976; 28:256–7.
2. Heyman E, Morag I, Batash D, Keidar R, Baram S, Berkovitch M. Closure of patent ductus arteriosus with oral ibuprofen suspension in premature newborns: A pilot study. Pediatrics 2003; 112:e354–8.
3. Patel J, Marks KA, Roberts I, Azzopardi D, Edwards AD. Ibuprofen treatment of patent ductus arteriosus. Lancet 1995; 346:255.
4. Varvarigou A, Bardin CL, Beharry K, Chemtob S, Papageorgiou A, Aranda JV. Early ibuprofen administration to prevent patent ductus arteriosus in premature newborn infants. JAMA 1996; 275:539–44.
5. Van Overmeire B, Follens I, Hartmann S, Creten WL, Van Acker KJ. Treatment of patent ductus arteriosus with ibuprofen. Arch Dis Child 1997; 76:F179–84.
6. Van Overmeire B, Smets K, Lecoutere D, Van de Broek H, Weyler J, De Groote K, Langhendries J-P. A comparison of ibuprofen and indomethacin for closure of patent ductus arteriosus. N Engl J Med 2000; 343:674–81.
7. Ohlsson A, Walia R, Shah S. Ibuprofen for the treatment of a patent ductus arteriosus in preterm and/or low birth weight infants (Cochrane Review). The Cochrane Library 2003; Issue 2, Oxford.
8. Shah SS, Ohlsson A. Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants (Cochrane Review). The Cochrane Library 2003; Issue 2, Oxford.
9. Gournay V, Savagner C, Thiriez G, Kuster A, Rozé J-C. Pulmonary hypertension after ibuprofen prophylaxis in very preterm infants. Lancet 2002; 359: 1486–8.
10. Schmidt B, Wright LL, Davis P, Solimano A, Roberts RS. Ibuprofen prophylaxis in preterm neonates. Lancet 2002; 360: 492.
11. Van Overmeire B, Casaer A, Allegaert K, Debauche C, Decaluwe W, Jespers A, Weyler J, Langhendries JP. Multicenter randomized double-blind placebo controlled trial of ibuprofen prophylaxis in very preterm infants. Pediatr Res 2002; 51: 379A.
12. Fowlie PW, Davis PG. Prophylactic intravenous indomethacin for preventing mortality and morbidity in preterm infants (Cochrane Review). The Cochrane Library 2003; Issue 1 2003. Oxford.
13. Schmidt B, Davis P, Moddemann D, Ohlsson A, Roberts RS, Saigal S, Solimano A,Vincer M, Wright LL, for the Trial of Indomethacin Prophylaxis in Preterms Investigators. Long-term effects of indomethacin prophylaxis in extremely-low-birth-weight infants. N Engl J Med 2001; 344: 1966–72.
14. Pezzati M, Vangi V, Biagiotti R, Bertini G, Cianciulli D, Rubaltelli FF. Effects of indomethacin and ibuprofen on mesenteric and renal blood flow in preterm infants with patent ductus arteriosus. J Pediatr 1999; 135: 733–8.
15. Guignard JP. The adverse renal effects of prostaglandin-synthesis inhibitors in the newborn rabbit. Semin Perinatol 2002; 26: 398–405.
16. Mosca F, Bray M, Lattanzio M, Fumagalli M, Tosetto C. Comparative evaluation of the effects of indomethacin and ibuprofen on cerebral perfusion and oxygenation in preterm infants with patent ductus arteriosus. J Pediatr 1997; 131: 549–54.
17. Naulaers G, Delanghe G, Allegaert K, Casaer P, Devlieger H, Van Overmeire B. Randomized double-blind controlled trial comparing the effects of ibuprofen with placebo on cerebral hemodynamics. Pediatr Res 2002; 51: 338A.
18. Van Overmeire B, Touw D, Schepens PJC, Kearns GL, van den Anker JN. Ibuprofen pharmacokinetics in preterm infants with patent ductus arteriosus. Clin Pharmacol Ther 2001; 70: 336–43.
19. Cooper-Peel C, Brodersen R, Robertson A. Does ibuprofen affect bilirubin-albumin binding in newborn infant serum?. Pharmacol Toxicol 1996; 79: 297–9.
20. Ahlfors CE. Effect of ibuprofen on bilirubin-albumin binding. J Pediatr 2004; 144: 386–8.
21. Su, PH, Chen JY, Su CM, Huang TC, Lee HS. Comparison of ibuprofen and indomethacin therapy for patent ductus arteriosus in preterm infants. Pediatr Int 2003; 45: 665–70.
22. Gregoire N, Gualano V, Geneteau A, Millerioux L, Brault M, Mignot A, Roze JC. Population pharmacokinetics of ibuprofen enantiomers in very premature naonates. J Clin Pharmacol 2004; 44: 1114–24.

Indomethacin Effects and Side Effects

Berndt Urlesberger

Effects

Indomethacin is a non-selective cyclooxygenase inhibitor that reversibly blocks the cyclooxygenase pathway of prostaglandin (PG) synthesis. Since the 1970s indomethacin has been used effectively in preterm infants to close a patent ductus arteriosus (PDA) [1, 2]. Since then a number of randomized controlled trials have been performed to analyze the various aspects of the use of indomethacin. Indomethacin may be used in the management of either symptomatic or asymptomatic PDA, as well as in the prophylaxis of PDA. To give a short overview of these three management strategies, review articles of randomized trials were used.

Management of Symptomatic PDA

In a metaanalysis of seven randomized trials, Nehgme et al. [3] came to the conclusion that indomethacin improved the cardiorespiratory status of preterm neonates with symptomatic PDA, when administered either every 24 or every 8–12 hours (for a maximum of three doses). No clinically significant complications were reported. A significant decrease in the mortality rate was noted only with the more frequent administration schedule (8–12 hours) of indomethacin compared to placebo. Furthermore, indomethacin was more effective in the treatment of PDA than standard medical treatment (consisting of fluid restriction and diuretics, with or without digoxin). The effects on the course of RDS were conflicting; a potential preventive effect on the incidence of bronchopulmonary dysplasia (BPD) was reported. No effect on mortality was noted in the comparison to standard medical treatment. The dose schedules used were 0.2mg/kg iv (given every 24 h or 8–12 h, with a maximum of three doses).

Management of Asymptomatic PDA

Treatment of an asymptomatic PDA with indomethacin significantly reduced the incidence of symptomatic PDA and the duration of supplemental oxygen requirement. There was no evidence of effect on mortality, chronic lung disease (CLD), intraventricular hemorrhage (IVH), retinopathy, or length of ventilation. One trial reported a significant reduction in the duration of supplemental oxygen in a subgroup of infants with a birth weight less than 1000 g. All these conclusions were drawn on the basis of five [3] or three [4] randomized trials. There is a lack of data for evaluation of long-term consequences. The dose

schedules used were 0.2mg/kg as single dose, or every 12 h (with a maximum of three doses).

Prophylactic Indomethacin

For metaanalysis of prophylactic use of indomethacin, ten [3] and nineteen [5] randomized trials were used. There was a significant reduction in the incidence of symptomatic PDA and the need for surgical PDA ligation. There was a significant reduction in the incidence of severe IVH (IVH grade 3 ± periventricular hemorrhage). There is no evidence of differences in rates of necrotizing enterocolitis, sepsis, or excessive clinical bleeding. There is no evidence for any reduction in long-term neurosensory impairment (cognitive delay, cerebral palsy, blindness, or deafness). There was an increased incidence of oliguria with the use of prophylactic indomethacin, but this was not associated with major renal impairment. The dose schedules used were 0.1–0.2mg/kg iv, followed by the same dose every 12–24h (with a maximum of 3–6 doses).

Conclusions Regarding Effects

Indomethacin is effective in closure of asymptomatic and symptomatic PDA, and its prophylaxis. However, there is considerable lack of knowledge of: (1) the ideal dose (range in literature 0.1–0.3mg/kg), (2) the ideal administration mode (e.g. early versus late administration), and (3) the ideal duration of indomethacin administration (short versus prolonged course). In a metaanalysis of the latter question, Herrera et al. [6] came to the conclusion that there is not enough evidence to prefer either a short course (three or fewer doses) or a long course (four or more doses).

Side Effects

Since indomethacin inhibits the synthesis of all prostaglandins, whether active in vasoconstriction or vasodilation, a wide variety of effects are expected, including adverse effects. The main side effects are: (1) impairment of renal function, (2) impairment of cerebral perfusion, (3) impairment of intestinal perfusion, (4) reduction of blood glucose level, and (5) platelet dysfunction.

Impairment of Renal Function

Indomethacin administration acutely decreases renal blood flow (RBF), possibly resulting in acute renal failure. Indomethacin administration is associated with suppression of PG synthesis and a fall of plasma renin activity (from the high levels that are attributed to renal hypoperfusion due to PDA) [7]. Furthermore, there is decreased free water clearance with dilutional hyponatremia (due to increased corticomedullary gradient and enhanced hydroosmotic effect of antidiuretic hormone), and a decrease in renal K^+ excretion (possibly due to hyporeninemic hypoaldosteronism, and/or decreased Na^+ delivery to the distal tubule) [8]. The reduction of RBF was proven by numerous studies using either Doppler measurements or fluorescent microspheres. Indomethacin led to a sharp decrease in peak systolic flow velocity and temporal mean flow velocity in the renal artery. This effect began maximally 10 minutes after indomethacin application, and lasted at least 1 hour [9] (dosage: 0.1mg/kg iv). Using microspheres a significant decrease in blood flow in both renal cortex and medulla was observed 40 and 60 minutes after indomethacin injection [10]. Different strategies were used to improve RBF during indomethacin administration, including a continuous infusion of indomethacin [11] (0.3mg/kg within 36 hours infusion time), extracellular volume expansion [12], dopamine infusion [13], and furosemide administration [14]. Concerning the latter two, there has even been a Cochrane Review [13, 14] of the available studies, which came to the conclusion that in both cases there was not enough evidence to recommend the procedure.

Impairment of Cerebral Perfusion

A reduction of cerebral blood flow (CBF) in association with indomethacin administration was proven by different methods, using Doppler

measurements [15, 16], the 133-xenon technique [17], near infrared spectroscopy [18], and fluorescent microspheres [10]. Using Doppler a significant decrease of cerebral blood flow velocity was seen with doses of 0.2mg/kg [15] and 0.1mg/kg [16], whereas the duration of CBF decrease was 90–120 minutes. Using near infrared spectroscopy [18] a reduction of CBF, cerebral blood volume, and cerebral oxygen delivery was seen. Furthermore a reduction in CBF response to changes in pCO_2 was observed. Using microspheres [10] it was seen in animal experiments that there was a significant reduction of CBF in all brain regions. The reasons for this reduction of cerebral perfusion are not known in detail; there is some effect of inhibition of PG synthesis, but this is thought not to be the only reason. There may be an increase of endothelin levels due to indomethacin administration, thus suggesting an indirect vasconstrictive effect of indomethacin [19]. There were no differences in changes of cerebral perfusion between rapid (5 min) and slow (30 min) infusion rates of indomethacin, using near infrared spectroscopy [18] and Doppler technique [20]. There was a significant difference between bolus and continuous infusion (36h) in one recent study [11]. The problem now is that on the one hand a reduction of cerebral perfusion in association with indomethacin administration was proven in numerous studies using different techniques, but on the other hand the clinical consequences and interpretation of these observations are unclear. In contrast, there is even a protective effect of prophylactic indomethacin with a significant reduction in the rate of severe intraventricular hemorrhage [5, 21].

Abdominal Side Effects

The abdominal side effects of indomethacin administration include impairment of intestinal perfusion (seen with Doppler technique and fluorescent microspheres), and possibly an increased risk for development of necrotizing enterocolitis (NEC). Using Doppler a reduction in blood flow and an increase in vascular resistance of the superior mesenteric artery and coeliac axis were seen in association with indomethacin administration [22, 23]. The duration of this effect was 10–60 minutes. Using microspheres [10] it was seen in animal experiments, that there was a significant decrease in blood flow in the duodenum/jejunum, the ileum, and the colon. The reasons for these observations are unclear in detail. There is some effect of inhibition of PG synthesis, but it cannot be made responsible for all observed aspects. Using different administration schedules it was seen, that there was no significant fall of systolic velocity in the superior mesenteric artery and coeliac axis after slow infusion (30 min) versus a significant fall after rapid administration (20 sec) [23]. There was also no fall of intestinal perfusion after continuous infusion (36h) [11]. Concerning the increased risk of development of NEC, the literature is still controversial. In a retrospective study, Grossfeld at al. [24] showed an increased risk of NEC and bowel perforation with use of indomethacin in the presence of PDA. Furthermore, in ELBW infants (<27 weeks of gestation), indomethacin during the first 48 hours of life was associated with increased risk of NEC and bowel perforation [25]. On the other hand, there was no increased incidence of NEC in any study investigating prophylactic indomethacin [5], and no differences in NEC incidence or bowel perforation in premature infants after indomethacin (13%) versus surgical ligation (14%) [26] were found.

Interference with Blood Glucose

Yeh et al. [27] showed significantly lower blood glucose values 24h and 48h after indomethacin application. Hosono et al. [28] observed a significant reduction in blood glucose values between 12 and 96h following iv indomethacin therapy in ELBW-infants. The mechanisms for decrease of blood glucose level in association with indomethacin administration are unclear in detail, but seem to be complex. The pancreatic islets of indomethacin-treated rats secreted insulin at a higher rate, combined with attenuated hormone responsiveness to insulin and noradrenaline [29].

Platelet Dysfunction

In platelets, nonsteroidal antiiflammatory drugs interfere with cyclooxygenase, thus influencing thromboxane A_2 production (which stimulates platelets, resulting in shape change, adhesion, and aggregation). Like aspirin, indomethacin can interfere with cyclooxygenase function but, unlike aspirin, it does not form a covalent complex with the enzyme, and its antiplatelet effects therefore disappear with falling indomethacin serum levels. However, in no studies was excessive clinical bleeding observed in association with indomethacin administration.

Contraindications

Because of the described side effects, a number of contraindications for indomethacin therapy, and/or indications for discontinuing indomethacin treatment have been proposed (Tab. 14.1).

Conclusions

The effects and side effects of indomethacin are well known and well documented, although not understood in all pathophysiological aspects. Indomethacin is effective in the closure of asymptomatic and symptomatic PDA and its prophylaxis. There is a clear need for studies concerning different administration schedules to control effects and side effects.

References

1. Heymann MA, Rudolph AM, Silverman NH. Closure of the ductus arteriosus in premature infants by inhibition of prostaglandin synthesis. N Engl J Med 1976; 295:530–533
2. Friedman WF, Hirschklau MJ, Printz MP, et al. Pharmacologic closure of patent ductus arteriosus in premature infants. N Engl J Med 1976; 295:526–529
3. Nehgme RA, O'Connor TZ, Lister G, et al. Patent Ductus Arteriosus. In Sinclair and Bracken (Eds.) »Effective Care of the Newborn« Oxford University Press 1992
4. Cooke L, Steer P, Woodgate P. Indomethcin for asymptomatic patent ductus arteriosusin preterm infants. Cochrane Database 2003
5. Fowlie PW, Davis PG. Prophylactic intravenous indomethacin for preventing mortality and morbidity in preterm infants. Cochrane Database 2002
6. Herrera C, Holberton J, Davis P. Prolonged versus short course of indomethacin for treatment of patent ductus arteriosus in perterm infants. Cochrane Database 2004
7. Seyberth HW, Rascher W, Hackenthal R, et al. Effect of prolonged indomethacin therapy on renal function and selected vasoactive hormones in very-low-birth-weight infants with symptomatic patent ductus arteriosus. J Pediatr 1983; 103:979
8. John EG, Vasan U, Hastreiter AR, et al. Intravenous indomethacin and changes of renal function in premature infants with patent ductus arteriosus
9. van Bel F, Guit GL, Schipper J, et al. Indomethacin-induced changes in renal blood flow velocity waveform in premature infants investigated with color Doppler imaging. J Pediatr 1991; 118:621–626
10. Speziale MV, Allen RG, Henderson CR, et al. Effects of ibuprofen and indomethacin on the regional circulation in newborn piglets. Biol Neonate 1999; 76:242–252
11. Christmann V, Liem KD, Semmekrot BA, et al. Changes in cerebral, renal and mesenteric blood flow velocity during continuous and bolus infusion of indomethacin. Acta Pediatr 2002; 91:440–446

Table 14.1 Contraindications for indomethacin therapy and/or indications for discontinuing indomethacin: Summary of the criteria most frequently used in different studies [3, 5, 6, 21].

Impaired renal function:	Urine output <0.5 (–1.0) mL/kg/h
	Serum creatinine >1.5 (–2.0) mg/dL
	Blood urea nitrogen >20 (–40) mg/dL
Low platelet count <50.000 (–75.000) /µL	
Sonographic evidence of acute intra/periventricular hemorrhage	
Evidence of abnormal bleeding (e.g. venipuncture, lung, gastrointestinal)	
Clinical or radiographic evidence of necrotizing enterocolitis	
Hyperkalemia (>6 mMol/L)	
Hyponatremia (<120 mMol/L)	

12. Leititis JU, Burghard R, Gordjani, et al. Effect of modified fluid therapy on renal function during indomethacin therapy for persistent ductus arteriosus. Acta Pediatr Scand 1987; 76:789–94
13. Barrington K, Brion LP. Dopamine versus no treatment to prevent renal dysfunction in indomethacin-treated preterm newborn infants. Cochrane Database 2002
14. Brion LP, Campbell DE. Furosemide for prevention of morbidity in indomethacin-treated infants with patent ductus arteriosus. Cochrane Database 2001
15. van Bel F, van de Bor M, Stijnen, et al. Cerebral blood flow velocity changes in preterm infants after a single dose of indomethacin: duration of ist effect. Pediatrics 1989; 84:802–7
16. Mardoum R, Bejar R, Merritt A, et al. Controlled study of the effects of indomethacin on cerebral blood flow velocities in newborn infants. J Pediatr 1991; 118:112–115
17. Pryds O, Greisen G, Johansen KH. Indomethacin and cerebral blood flow in premature infants treated for patent ductus arteriosus. Eur J Pediatr 1988; 147:315–316
18. Edwards AD, Wyatt JS, Richardson C, et al. Effects of indomethacin on cerebral haemodynamics in very preterm infants. Lancet 1990; 335:1491–1495
19. Therkelsen K, Jensen KA, Freundlich M, et al. Endothelin-1 and cerebral blood flow: influence of hypoxia, hypercapnia and indomethacin on circulating endothelin levels in healthy volunteers. Scand J Clin Lab Invest. 1994; 54:441–51.
20. Simko A, Mardoum R, Merritt, et al. Effects on cerebral blood flow velocities of slow and rapid infusion of indomethacin. J Perinatol 1994; 14:29–35
21. Ment LR, Oh W, Ehrenkranz RA, et al. Low-dose indomethacin and prevention of intraventricular hemorrhage: a multicenter randomized trial. Pediatrics 1994; 93:543–50
22. van Bel F, van Zoeren D, Schipper J, et al. Effect of indomethacin on superior mesenteric artery flow velocity in preterm infants. J Pediatr 1990; 116:965–70
23. Coombs RC, Morgan ME, Durbin GM, et al. Gut blood flow velocities in the newborn: effects of patent ductus arteriosus ant perenteral indomethacin. Arch Dis Child 1990; 65:1067–71
24. Grosfeld JL, Chaet M, Molinari F, et al. Increased risk of necrotizing enterocolitis in premature infants with patent ductus arteriosus treated with indomethacin. Ann surg 1996; 224:350–57
25. Fujii Am, Brown E, Mirochnick M, et al. Neonatal necrotizing enterocolitis with intestinal perforation in extremely premature infants receiving early indomethacin treatment for patent ductus arteriosus. J Perinatol 2002; 22:535–40
26. O'Donovan DJ, Baetiong A, Adams K, et al. Necrotizing enterocolitis and gastrointestinal complications after indomethacin therapy and surgical ligation in premature infants with patent ductus arteriosus. J Perinatol 2003; 23:286–90
27. Yeh TF, Raval D, Lilien LD, et al. Decreased plasma glucose following indomethacin therapy in premature infants with patent ductus arteriosus. Pediatr Pharmacol 1982; 2:171–77
28. Hosono S, Ohono T, Kimoto H, et al. Reduction in blood glucose values following indomethacin therapy for patent ductus arteriosus. Paediatr Int 1999; 41:525–528
29. Wasner HK, Weber S, Partke HJ, et al. Indomethacin treatment causes loss of insulin action in rats: Involvement of prostaglandins in the mechanism of insulin action. Acta Diabetol 1994;31:175–82

15

Complications of Cyclooxygenase Inhibition in Preterm Infants

Véronique Gournay

A persisting ductus arteriosus (PDA) resulting in hemodynamically significant left-to-right shunting of blood remains a common problem in sick premature infants, increasing the risk for intraventricular hemorrhage, necrotizing enterocolitis, bronchopulmonary dysplasia, and death. Medical treatment with cyclooxygenase (COX) inhibitors is effective in closing the ductus in about 70% of the patients. However, concerns have been raised about the safety of this therapeutic class in neonates. Indomethacin, the conventional pharmacologic treatment, affects renal, gastro-intestinal, and cerebral blood flow, and may lead to complications such as transient renal dysfunction, necrotizing enterocolitis, gastrointestinal hemorrhage, and reduced cerebral intracellular oxygenation. More recently, the use of ibuprofen to promote ductal closure has been reported, with efficacy similar to that of indomethacin and lesser renal effects. In animal and human studies, ibuprofen, in contrast to indomethacin, does not affect peripheral organ perfusion to the same extent as indomethacin. On the other hand, ibuprofen may increase the risk of kernicterus because of its interference with bilirubin-albumin binding at therapeutic plasma levels.

Pharmacology

Two COX isoforms have been described. COX-1 is constitutively expressed in almost all tissues and has characteristics of a housekeeping enzyme whose activity depends solely on the availability of its substrate. COX-1 supplies tissues with prostaglandins required to maintain physiological organ function, such as cytoprotection of the gastric mucosa and regulation of renal blood flow. Conversely, COX-2 behaves as an immediate early gene and is subject to rapid regulation at the transcriptional level. COX-2 is up-regulated in peripheral tissues in response to injury. Both indomethacin and ibuprofen inhibit the two isoforms of COX, thereby leading to reduced synthesis of vasodilating prostaglandins such as prostacyclin (PGI_2) and prostaglandin E_2 by the arachidonic acid metabolic pathway. The resulting vasoconstriction, and thus decreased organ blood flow, may explain some of the side-effects that have been reported with the use of those two nonsteroidal anti-inflammatory drugs (NSAIDs) to close the ductus in neonates. However, some of these effects may not be related to inhibition of prostaglandin synthesis. Indeed, several studies have demonstrated unequivocally that certain NSAIDs cause effects independent of COX activity and prostaglandin synthesis inhibition [1]. These effects, which are probably mediat-

ed predominantly through alterations of the activity of cellular kinases, differ from one COX inhibitor to another. For example, ibuprofen inhibits the activity of several transcription factors and kinases that are not altered by indomethacin. These differences in COX-independent mechanisms may have consequences for the specific toxicity of these drugs. Recently, ibuprofen has been shown to prolong the half-life of amikacin [36] and to suppress apoptosis in neonatal neutrophils [37], but the clinical significance of these findings is unclear.

Cerebral Effects of COX Inhibitors

Indomethacin causes a marked decline in cerebral blood flow, cerebral oxygen delivery, and cerebral blood volume, and may also reduce cerebral intracellular oxygenation [2, 3]. Furthermore, data from animal studies showed an indomethacin-induced impairment of the normal compensatory effects that protect cerebral perfusion during hypoxia and hypotension [4, 5]. Conversely, ibuprofen causes no significant reduction of cerebral blood flow, cerebral blood volume, cerebral oxygen delivery, and cerebral vasoreactivity to changes in arterial carbon dioxide tension [6, 7, 8, 9] (Fig. 15.1). In addition, ibuprofen increases the range of cerebral blood flow autoregulation in newborn piglets [10]. These different effects of indomethacin and ibuprofen on cerebral vascular regulation suggest that they may not be due solely to prostaglandin synthesis inhibition. A specific action of indomethacin on the vascular endothelium is possible. The long-term consequences of these effects of indomethacin are not well known. One animal study reported abnormal brain development and neurobehavioral deviations in adult rats treated with indomethacin during the neonatal period, with different patterns of abnormalities depending on the ontogenic stage at drug exposition [11]. This study was only descriptive and the mechanisms of injury were not discussed.

Several clinical trials showed that prophylactic indomethacin, consisting in treating all premature infants regardless of their ductal status within a few hours after birth, significantly decreases the incidence of all intraventricular hemorrhage (IVH) and the incidence of severe IVH (grades 3 and 4). However, long-term studies failed to demonstrate significant improvements in long-term neurodevelopmental outcome and survival that could be expected from this reduced incidence of IVH [12, 13, 14]. This may be due to the counteracting cerebral effects of indomethacin, as abnormalities of cerebral perfusion play an important role in the development of cerebral injury in newborn infants. We recently compared prophylactic ibuprofen, which does not affect cerebral hemodynamics, with placebo in a large randomized trial in France [15]. The study design included a back-up treatment, first by curative ibuprofen at day 3, and then by indomethacin at day 6 if medical treatment had failed to close the ductus. The trial showed a trend to decreased incidence of severe IVH and no effect on the incidence of periventricular leukomalacia. Surprisingly, looking back at our data, we found that the incidence of ventriculomegaly increased with the number of courses of medical treatment administered (either ibuprofen or indomethacin): from 15% in the patients who received no medical treatment, to 28% in the patients who received a course of either prophylactic or curative ibuprofen, up to 55% in the patients who received either two courses of ibuprofen or one course of ibuprofen followed by one course of indomethacin. This analysis being only retrospective and not the primary aim of our study, it needs further investigations. Furthermore, the long-term follow-up of these patients is not available yet.

In conclusion, indomethacin and ibuprofen have different effects on cerebral hemodynamics. These cerebral effects are probably not mediated only by prostaglandin inhibition. Although prophylactic indomethacin, and maybe also ibuprofen, decrease the risk of severe IVH in preterm infants, further long-term evaluations are necessary to ensure the safety of prophylactic treatment with these drugs.

Pulmonary Effects of COX Inhibitors

During late fetal development, pulmonary vascular resistance is high and pulmonary blood flow is limited to less than 10% of combined ventricular

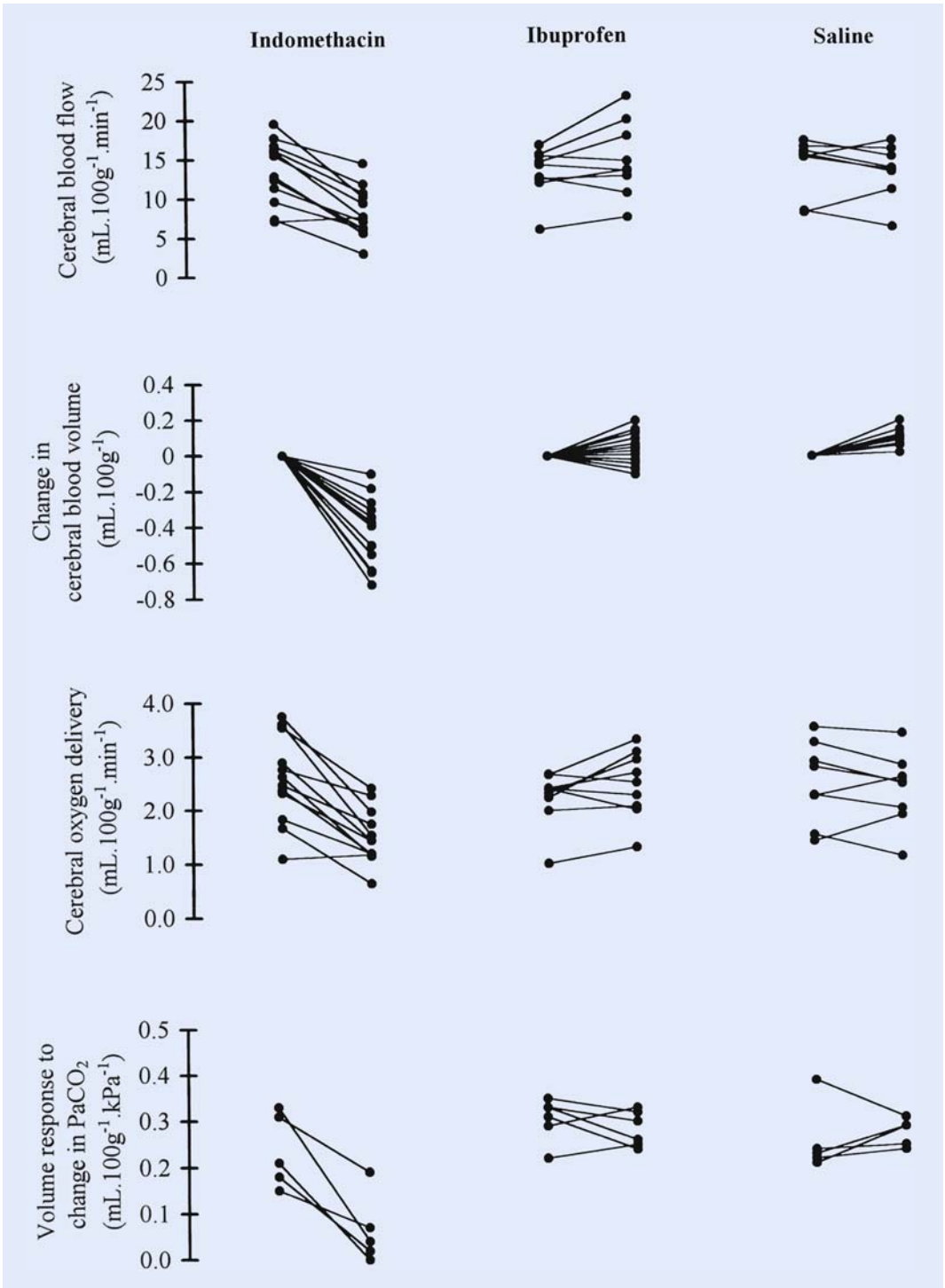


Fig. 15.1 Individual mean values for cerebral circulation variables before and after either indomethacin, ibuprofen or saline administration. (With permission from Patel et al., Pediatr Res 2000; 47: 36–42).

output. At birth, mechanical distension of the lungs, increased oxygen tension, and increased shear stress result in a precipitous decrease in pulmonary vascular resistance and increase in pulmonary blood flow to 100% of cardiac output. Studies in fetal lambs showed that an increase in prostacyclin synthesis plays a major role in the vasodilatation caused by initiation of rhythmic breathing, in addition to the increased vessel radius due to mechanical distension (Fig. 15.2), and that COX inhibition by indomethacin prevents the normal decrease in pulmonary vascular resistance associated with rhythmic lung distension at birth [16, 17]. In addition, the normal left-to-right ductal shunting during the first hours of life increases diastolic blood flow and may thus contribute significantly to the rise in pulmonary blood flow induced by shear stress. These physiologic mechanisms may explain why we observed three cases of severe hypoxemia secondary to pulmonary hypertension occurring after the administration of ibuprofen before 6 hours of life in very premature infants in the setting of our multicenter clinical trial [18]. Hypoxemia resolved rapidly on nitric oxide administration in all three neonates (Fig. 15.3). This severe side-effect prompted the premature discontinuation of the trial after 135 enrollments. Although this type of event had never been reported previously with indomethacin, one author mentioned in a letter that »prophylactic indomethacin adversely affected gas exchange in the first week of life« in a retrospective analysis of data from a trial on prophylactic indomethacin [19].

Although the use of COX inhibitors to promote ductal closure in premature infants does not improve long-term respiratory outcome, it does not seem to cause long-term deleterious effects either. However, one meta-analysis of trials comparing the effectiveness of ibuprofen with that of

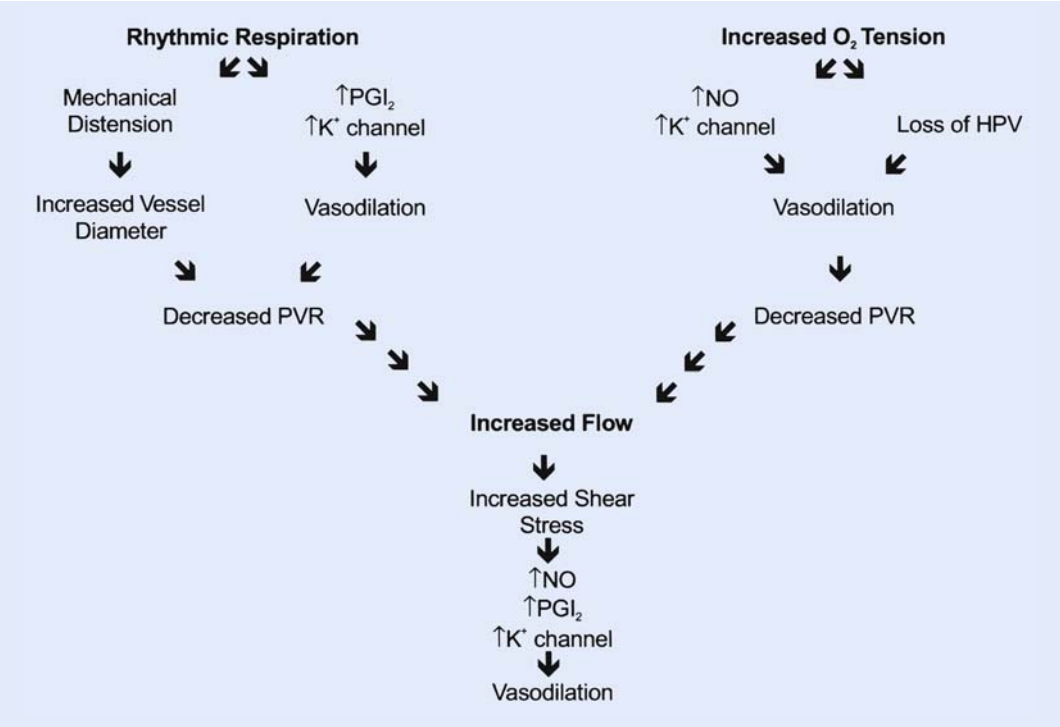


Fig. 15.2 Birth-related stimuli that lead to decreased pulmonary vascular resistance (PVR). (With permission from Ghanayem et al., Respir Res 2001; 2: 139–44). HPV, hypoxic pulmonary vasoconstriction.

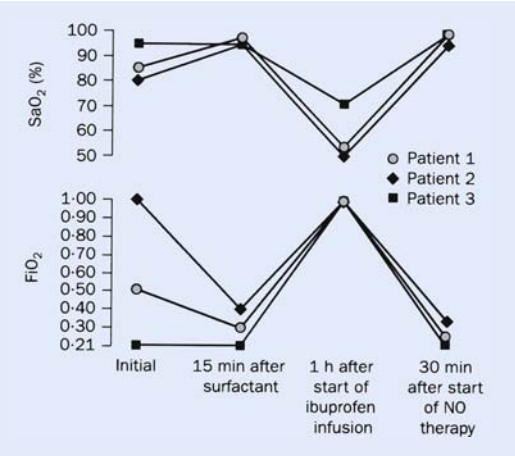


Fig. 15.3 Evolution of fractional concentration of oxygen in inspired gas (FiO_2) and pulse oxymetry (SaO_2) before surfactant therapy, after surfactant therapy, in 3 patients with pulmonary hypertension after administration of the loading dose of ibuprofen, and after inhaled nitric oxide (NO) therapy. (With permission from Gournay et al., Lancet 2002; 359:1486–88).

indomethacin found that chronic lung disease was more likely to occur in the ibuprofen group [20].

In conclusion, COX inhibition in the immediate postnatal period may interfere with normal cardiopulmonary adaptation involving prostacyclin synthesis and cause pulmonary hypertension. It may be safer not to administer COX inhibitors, at least ibuprofen, within the first 6 hours in newborns at risk for pulmonary hypertension (premature rupture of the membranes, maternal use of NSAIDs, group B streptococcal neonatal sepsis).

15

Renal Effects of COX Inhibitors

Animal studies in rodents showed that COX-2 and the renin-angiotensin-aldosterone system, by complex and intricate mechanisms, play major roles in the late stages of kidney development. During the postnatal period, COX-2 stimulates intrarenal renin secretion, and lack of COX-2 activity induced by selective COX-2 blockade leads to pathological change in cortical architecture and eventually to renal failure [21]. In addition to their potential direct effects on intrarenal prostaglandin synthesis, COX inhibitors affect renal hemodynamics. Numerous animal and human studies demonstrated that prophylactic ductal closure by indomethacin decreases renal blood flow and almost invariably causes renal failure, leading to oliguria and mild elevation in serum creatinine [22]. In contrast to indomethacin, ibuprofen does not affect renal hemodynamics in newborns, as shown by two authors using Doppler ultrasonographic measurement of renal blood flow [23, 24]. Furthermore, comparative clinical trials of early curative indomethacin versus ibuprofen showed similar effectiveness in closing the ductus, but less severe renal side-effects with ibuprofen [25, 26]. However, in our French multicenter clinical trial of prophylactic ibuprofen versus placebo, we did observe mild and transient renal effects, such as oliguria and elevation of serum creatinine, quite similar to those of indomethacin [15] (Fig. 15.4). Finally, we should mention one study that found that acute intravenous doses of ibuprofen have significant renal hemodynamic and functional side-effects in the neonatal rabbit, not less than reported previously with indomethacin [27].

In conclusion, COX inhibitors impair renal function, mostly by hemodynamic effects on renal perfusion, but may also alter kidney development by direct effects on local prostaglandin synthesis and interference with the renin-angiotensin-aldosterone system. These effects were observed mostly with indomethacin, and are undeniably less severe with ibuprofen. However, there is a need for other studies comparing ibuprofen with placebo to evaluate the real impact of ibuprofen on renal function.

Intestinal Effects of COX Inhibitors

Poor mesenteric perfusion secondary to diastolic blood steal from the aorta below the ductus is one of the clinical consequences of left-to-right ductal shunting in a premature infant, increasing the risk of necrotizing enterocolitis. Unfortunately, indomethacin, by its vasoactive effects, also decreases mesenteric perfusion [28] (Fig. 15.5), and its use has been associated with digestive complications such as necrotizing enterocolitis, isolated bowel perforation [29], and gastroin-

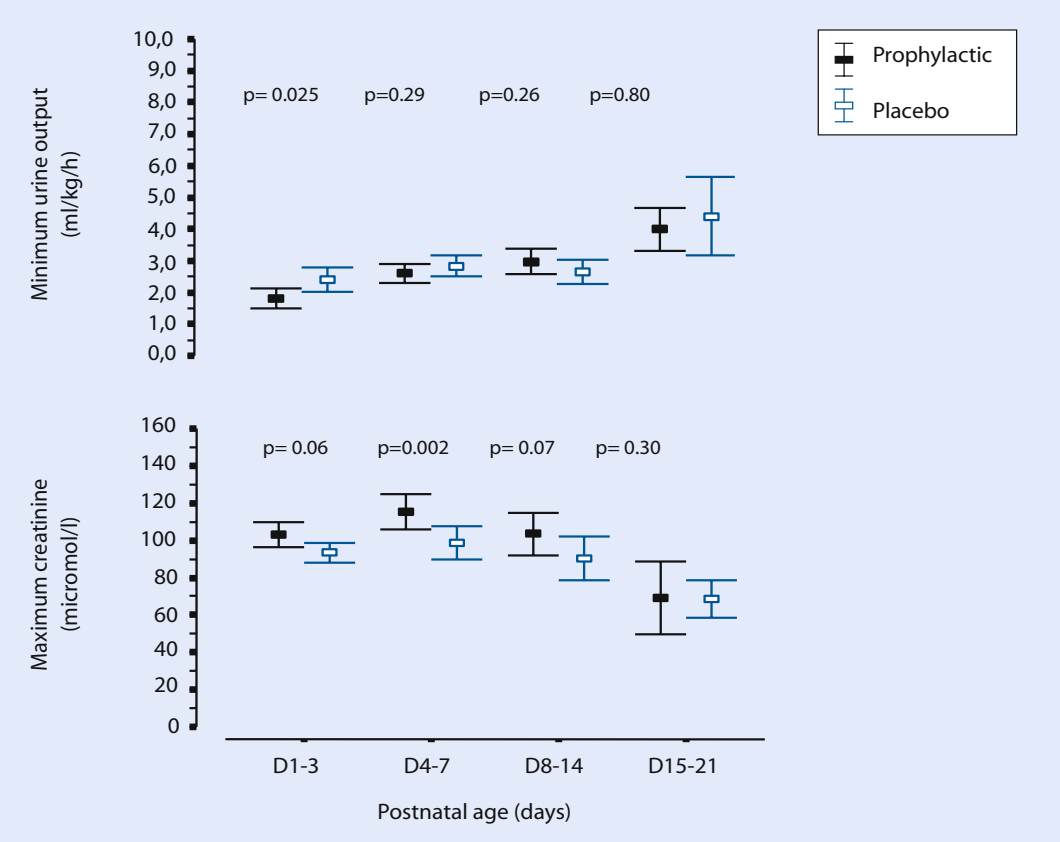


Fig. 15.4 Results of a comparative trial of prophylactic ibuprofen versus placebo.
A (upper pannel): Minimum urine output during four follow-up periods (median and interquartile range). Minimum urine output was significantly lower in newborns receiving prophylactic ibuprofen only during the first treatment period (day 1 to day 3). **B** (lower pannel): Maximum creatinine concentration during four follow-up periods (median and interquartile range). Maximum creatinine, which already tended to be higher during the first treatment period (day 1 to day 3), became significantly higher during the next period (day 4 to day 7) in newborns receiving prophylactic ibuprofen. (With permission from Gournay et al. Lancet 2004; 364: 1939–44).

testinal hemorrhage [30]. However, large randomized controlled trials found that prophylactic indomethacin did not significantly alter overall digestive outcome either way [13, 14].

Ibuprofen, in contrast to indomethacin, does not affect mesenteric blood flow [23] (Fig. 15.6). Comparative trials of indomethacin versus ibuprofen did not show significantly different rates of digestive complications between the two drugs. However, adverse digestive effects of ibuprofen have been described in at least two publications. In our multicenter French comparative trial of prophylactic ibuprofen versus placebo, we did observe that the incidence of NEC was higher in the ibuprofen group than in the placebo group (11/65 versus 3/66, p=0.025) and, likewise, that the incidence of bowel perforation tended to be higher in the ibuprofen group (5/65 versus 1/66, p=0.11) [15]. Another publication reported two cases of spontaneous intestinal perforation after oral ibuprofen treatment of PDA in very low birth weight infants, which did not occur in the setting of a clinical trial [31].

In conclusion, indomethacin causes vasoconstriction of the mesenteric arteries and may cause bowel ischemia. Although ibuprofen does

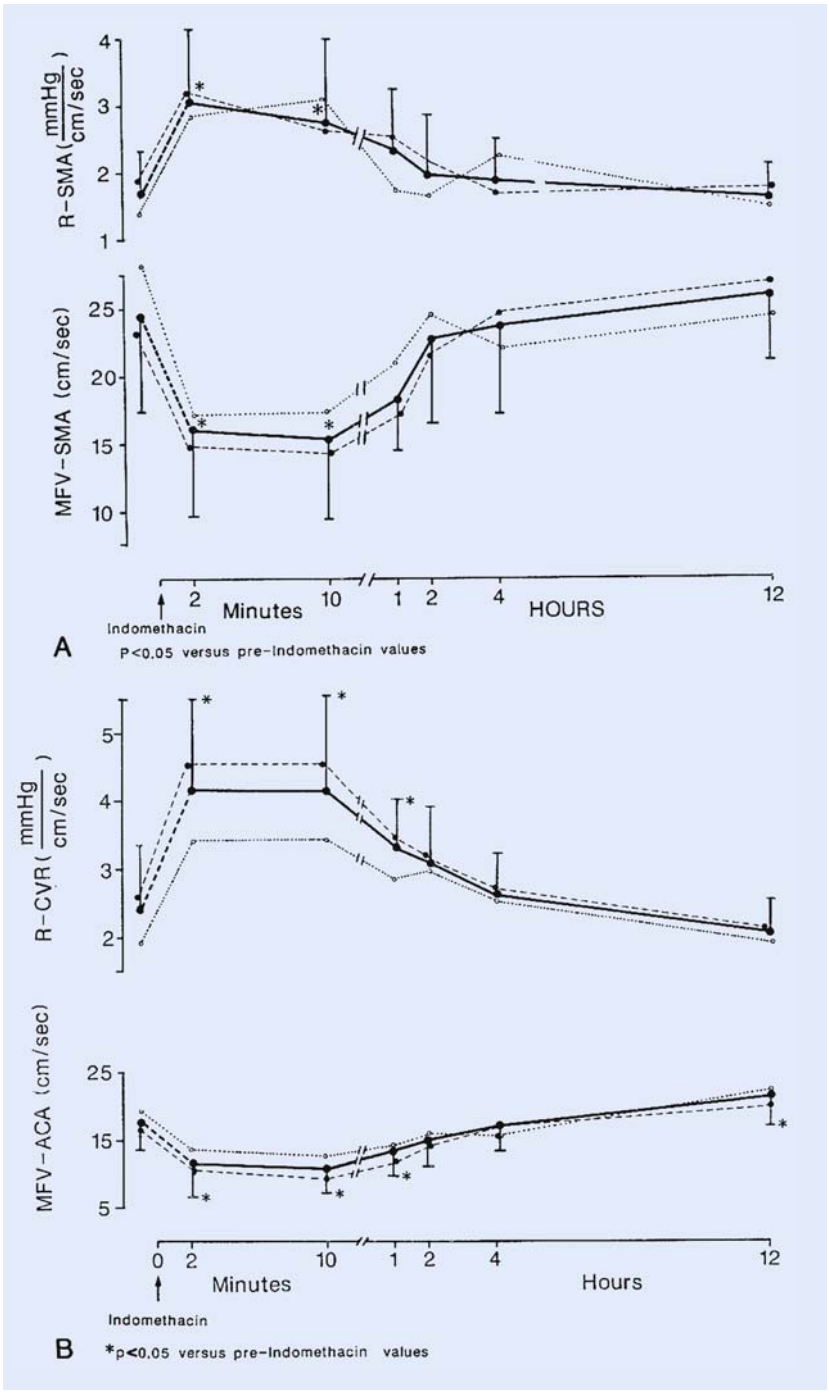


Fig. 15.5 **A** Mean values (±SD) of temporal mean flow velocity in superior mesenteric artery (MFV-SMA) and relative resistance in perfusion region of superior mesenteric artery (R-SMA) as function of time. **B** Mean values (±SD) of temporal mean flow velocity in anterior cerebral artery (MFV-ACA) and relative cerebral vascular resistance (R-CVR) as function of time. Total study group is indicated by solid line. Infants with clinical ductus closure: dashed line with full circles; infants whose ductus remained open: dotted line with open circles. (With permissiom from Van Bel et al., J Pediatr 1990; 116: 965–70).

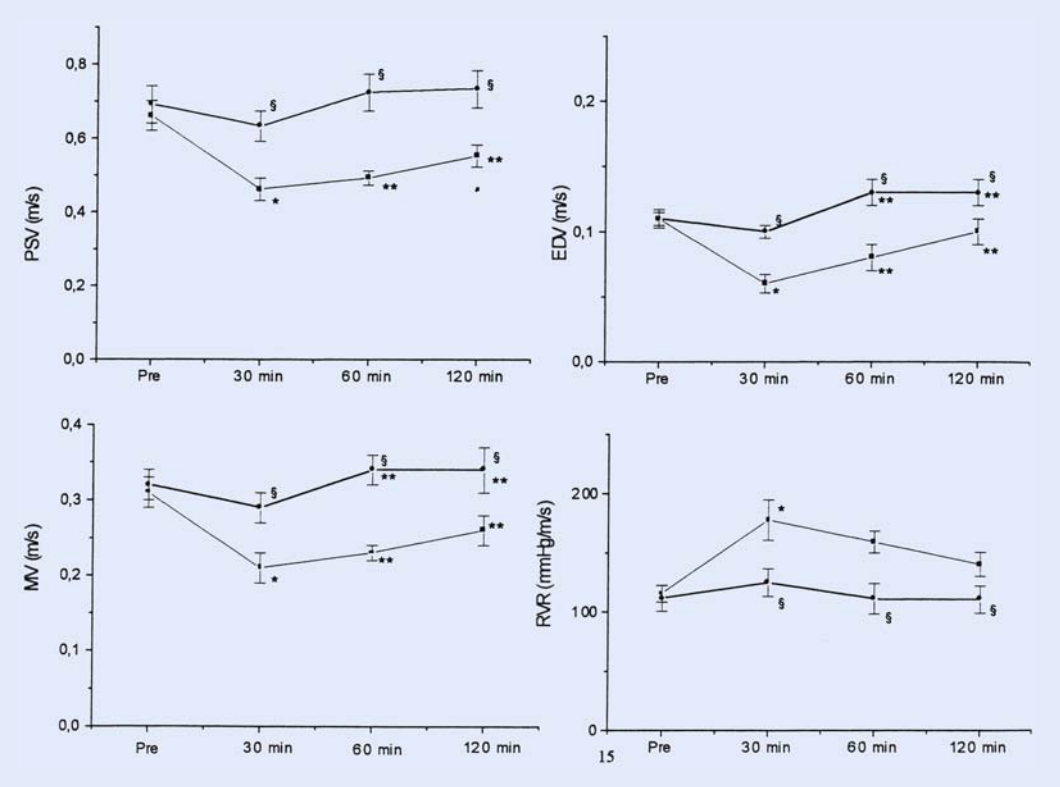


Fig. 15.6 Doppler measurements (peak systolic velocity (PSV), mean velocity (MV), end diastolic velocity (EDV)) and relative vascular resistance (RVR) in superior mesenteric artery before and 30, 60, and 120 minutes after either indomethacin (squares) or ibuprofen (circles) administration. (With permission from Pezzati et al., J Pediatr 1999; 135: 733–8).

not seem to have a similar effect on mesenteric blood flow, digestive complications have been described with both drugs. Therefore caution should be taken when COX inhibitors are administered to infants at high risk for NEC, such as infants with intrauterine growth retardation and/or perinatal birth asphyxia.

Effect of Ibuprofen on Bilirubin-Albumin Binding

The individual variation in ibuprofen pharmacokinetics in premature infants is considerable, with mean 1-hour postdose (10 mg/kg) plasma ibuprofen levels ranging from 181 µg/mL (approximately 879 µmol/L) on day 1 to 33 µg/mL (approximately 160 µmol/L) on day 3 [32]. Since this drug is given in the first few days of life and competes with bilirubin for albumin binding sites, babies receiving it could be at risk for bilirubin encephalopathy (kernicterus). The risk of drug-induced kernicterus depends on the plasma concentration of drug and albumin, the intrinsic ability of albumin to bind the drug and bilirubin (i.e., the equilibrium association binding constants), and the size of the baby's bilirubin load when the drug is given. Indomethacin, for example, also interferes with bilirubin-albumin binding but only at plasma indomethacin levels far in excess of those that occur clinically. Two studies aimed at evaluating the effect of the clinically relevant plasma levels of ibuprofen on the unbound bilirubin concentration (UBC), a measure of bilirubin-albumin binding [33, 34]. The authors found that ibuprofen, at a plasma level between 50 and 100 µg/mL,

increased the UBC by 1.5-fold (50%). Even more worrisome, this increase went as high as 3.9-fold at an ibuprofen level of 200 µg/mL. Total serum bilirubin concentration has been shown to correlate with neurodevelopmental and hearing impairment in extremely low birth weight infants [35]. Therefore, if ibuprofen is used in newborns, it would seem prudent to ensure that bilirubin loads are as low as possible during the administration of the drug. It could also be recommended to monitor the bilirubin-albumin binding during ibuprofen use. Unfortunately, no officially approved method is currently available in most countries for routine measurement of the UBC.

Conclusions

COX inhibitors constitute a reasonably effective and attractive therapeutic alternative to surgery to close the ductus arteriosus in premature infants. However, they do have significant adverse renal, digestive, pulmonary, and cerebral effects, related to both prostaglandin synthesis inhibition and COX-independent mechanisms. Therefore, concerns remain over their safety in specific clinical situations, such as renal failure or pulmonary hypertension. In these situations, which should be considered as contra-indications to COX inhibitors, surgery represents a safer option.

References

1. Tegeder I, Pfeilschifter J, Geisslinger G. Cyclooxygenase-independent actions of cyclooxygenase inhibitors. FASEB J. 2001;15:2057–2072.
2. Edwards AD, Wyatt JS, Richardson C, Potter A, Cope M, Delpy DT, Reynolds EO. Effects of indomethacin on cerebral haemodynamics in very preterm infants**.** Lancet. 1990;335:1491–5.
3. McCormick DC, Edwards AD, Brown GC, Wyatt JS, Potter A, Cope M, Delpy DT, Reynolds EO**.** Effect of indomethacin on cerebral oxidized cytochrome oxidase in preterm infants. Pediatr Res. 1993;33:603–8.
4. Leffler CW, Busija DW, Fletcher AM, Beasley DG, Hessler JR, Green RS**.** Effects of indomethacin upon cerebral hemodynamics of newborn pigs. Pediatr Res. 1985;19:1160–4.
5. Leffler CW, Busija DW, Beasley DG, Fletcher AM. Maintenance of cerebral circulation during hemorrhagic hypotension in newborn pigs: Role of prostanoids. Circ Res. 1986;59:562–7.
6. Chemtob S, Beharry K, Barna T, Varma DR, Aranda JV. Differences in the effects in the newborn piglet of various nonsteroidal antiinflammatory drugs on cerebral blood flow but not on cerebrovascular prostaglandins. Pediatr Res. 1991;30:106–11.
7. Mosca F, Bray M, Lattanzio M, Fumagalli M, Tosetto C. Comparative evaluation of the effects of indomethacin and ibuprofen on cerebral perfusion and oxygenation in preterm infants with patent ductus arteriosus. J Pediatr. 1997;131:549–54.
8. Pellicer A, Aparicio M, Cabanas F, Valverde E, Quero J, Stiris TA. Effect of the cyclo-oxygenase blocker ibuprofen on cerebral blood volume and cerebral blood flow during normocarbia and hypercarbia in newborn piglets. Acta Paediatr. 1999;88:82–8.
9. Patel J, Roberts I, Azzopardi D, Hamilton P, Edwards AD. Randomized double-blind controlled trial comparing the effects of ibuprofen with indomethacin on cerebral hemodynamics in preterm infants with patent ductus arteriosus. Pediatr Res. 2000;47:36–42.
10. Chemtob S, Beharry K, Rex J, Varma DR, Aranda JV. Prostanoids determine the range of cerebral blood flow autoregulation of newborn piglets. Stroke. 1990;21: 777–84.
11. Benesova O, Tejkalova H, Kristofikova Z, Husek P, Nedvidkova J, Yamamotova A. Brain maldevelopment and neurobehavioural deviations in adult rats treated neonatally with indomethacin. Eur Neuropsychopharmacol. 2001;11:367–73
12. Couser RJ, Hoekstra RE, Ferrara TB, Wright GB, Cabalka AK, Connett JE. Neurodevelopmental follow-up at 36 months's corrected age of preterm infants treated with prophylactic indomethacin. Arch Paediatr Adolesc Med 2000;154:598–602.
13. Schmidt B, Davis P, Moddemann D, et al. Long-term effects of indomethacin prophylaxis in extremely-low-birth-weight infants. N Engl J Med 2001;344:1966–72.
14. Fowlie PW, Davis PG. Prophylactic indomethacin for preterm infants: A systematic review and meta-analysis. Arch Dis Child 2003;88:F464–66.
15. Gournay V, Roze JC, Kuster A et al. Multicenter prospective randomized double blind trial comparing prophylactic ibuprofen versus placebo in very premature infants. Lancet 2004; 364: 1939–44.
16. Tod ML, Yoshimura K, Rubin LJ. Indomethacin prevents ventilation-induced decreases in pulmonary vascular resistance of the middle region in fetal lambs. Pediatr Res 1991;29:449–54.
17. Velvis H, Moore P, Heymann MA. Prostaglandin inhibition prevents the fall in pulmonary vascular resistance as a result of rhythmic distension of the lungs in fetal lambs. Pediatr Res 1991;30:62–8.
18. Gournay V, Savagner C, Thiriez G, Kuster A, Roze JC. Pulmonary hypertension after ibuprofen prophylaxis in very preterm infants. Lancet 2002;359:1486–88.

19. Schmidt B. Ibuprofen prophylaxis in preterm neonates. Lancet 2002;360:492.
20. Ohlsson A, Walia R, Shah S. Ibuprofen for the treatment of a patent ductus arteriosus in preterm and/or low birth weight infants. Cochrane Database Syst Rev 2003;(2): CD003481.
21. Jensen BL, Stubbe J, Madsen K, Nielsen FT, Skott O. The renin-angiotensin system system in kidney development: Role of COX-2 and adrenal steroids. Acta Physiol Scand 2004;181:549–59.
22. Betkerur MV, Yeh TF, Miller K, Glasser RJ, Pildes RS. Indomethacin and its effect on renal function and urinary kallicrein excretion in premature infants with patent ductus arteriosus. Pediatrics 1981;68:99–102.
23. Pezzati M, Vangi V, Biagiotti R, Bertini G, Cianciulli D, Rubaltelli FF. Effects of indomethacin and ibuprofen on mesenteric and renal blood flow in preterm infants with patent ductus arteriosus. J Pediatr 1999;135:733–8.
24. Romagnoli C, De Carolis MP, Papacci P, Polimeni V, Luciano R, Piersigilli F, Delogu AB, Tortorolo G. Effects of prophylactic ibuprofen on cerebral and renal hemodynamics in very preterm infants. Clin Pharmacol Ther 2000;67:676–83.
25. Van Overmeire B, Smets K, Lecoutere D, Van de Broek H, Weyler J, De Groote K, Langhendries JP. A comparison of ibuprofen and indomethacin for closure of patent ductus arteriosus. N Engl J Med 2000;343:674–81.
26. Lago P, Bettiol T, Salvadori S, Pitassi I, Vianello A, Chiandetti L, Saia OS. Safety and efficacy of ibuprofen versus indomethacin in preterm infants treated for patent ductus arteriosus: A randomised controlled trial. Eur J Pediatr 2002;161:202–7.
27. Chamaa NS, Mosig D, Drukker A, Guignard JP. The renal hemodynamic effects of ibuprofen in the newborn rabbit. Pediatr Res 2000;48:600–5.
28. Van Bel F, Van Zoeren D, Schipper J, Guit GL, Baan J. Effect of indomethacin on superior mesenteric artery blood flow velocity in preterm infants. J Pediatr 1990;116:965–70.
29. Fuji AM, Brown E, Mirochnick M, O'Brien S, Kaufman G. Neonatal necrotizing enterocolitis with intestinal perforation in extremely premature infants receiving early indomethacin treatment for patent ductus arteriosus. J Perinatol 2002;22:535–40.
30. Rennie JM, Doyle J, Cooke RW. Early administration of indomethacin to preterm infants. Arch Dis Child 1986;61:233–8.
31. Tatli MM, Kumral A, Duman N, Demir K, Gurcu O, Ozkan H. Spontaneous intestinal perforation after oral ibuprofen treatment of patent ductus arteriosus in two very-low-birthweight infants. Acta Padiatr 2004;93:999–1001.
32. Aranda JV, Varvarigou A, Beharry K, Bansal R, Bardin C, Modanlou H, Papageorgiou A, Chemtob S. Pharmacokinetics and protein binding of intravenous ibuprofen in the premature newborn infant. Acta Pediatr 1997;86:289–93.
33. Cooper-Peel C, Brodersen R, Robertson A. Does ibuprofen affect bilirubin-albumin binding in newborn infant serum? Pharmacol Toxicol 1996;79:297–9.
34. Ahlfors CE. Effect of ibuprofen on bilirubin-albumin binding. J Pediatr 2004;144:386–8.
35. Oh W, Tyson JE, Fanaroff AA, Vohr BR, Perritt R, Stoll BJ, Ehrenkranz RA, Carlo WA, Shankaran S, Poole K, Wright LL. Association between peak serum bilirubin and neurodevelopmental outcomes in extremely low birth weight infants. Pediatrics 2003; 112: 773–9.
36. Allegaert K,Cossey V, Langhendries JP, Naulaers G, Vanhole C, Devlieger H, Van Overmeire B. Effects of co-administration of ibuprofen-lysine on the pharmacokinetics of amikacin in preterm infants during the first days of life. Biol Neonate 2004; 86: 207–11.
37. Hanna N, Graboski S, Laskin DL, Weinberger B. Effects of ibuprofen and hypoxia on neutrophil apoptosis in neonates. Biol Neonate 2004; 86: 235–9.

16

Ibuprofen in Infants Below 28 Gestational Weeks

Petra Koehne

The Timing of PDA Intervention

Following a retrospective data analysis of pharmacological and surgical treatment for patent ductus arteriosus performed over a 12 year period from 1987 until 1998, we began to standardize our own PDA intervention regime (Koehne et al. 2001). During this time period 931 VLBW infants were admitted to our neonatal intensive care unit, of whom 156 (16.8%) underwent treatment for PDA (for patient demographics see chapter 5). Treatment of PDA was initiated only in infants dependent on ventilatory support if the PDA was hemodynamically significant, as judged by echocardiography (increased left atrial diameter compared to aortic root) and Doppler flow measurements in the anterior cerebral artery (low or negative end-diastolic flow). To a large extent, the type of first-line intervention was left to the discretion of the attending physician unless contraindications, present in 9 (6%) infants, ruled out the use of indomethacin. First-line pharmacological treatment of PDA was performed in 101 infants by administration of indomethacin with a successful closure rate of 63% (n = 64). Three doses of 0.2 mg/kg indomethacin were given at 12-hour intervals, followed by a maintenance dose of 0.1 mg/kg every 24 hours for a maximum of 6 days. The dosage of indomethacin was adjusted when trough serum concentrations 12 hours after administration were outside the range of 0.5 – 1 µg/ml (Yeh et al. 1989). Indomethacin was not discontinued upon closure of PDA, and not extended beyond 6 days in the case of non-closure. Treatment was discontinued when NEC was suspected (n = 7), in infants with renal impairment (n = 11) or severe thrombocytopenia (n = 3), and when toxic serum levels occurred (n = 2). Surgical treatment of PDA was performed in a total of 89 infants. Primary surgical PDA closure was carried out in 55 infants, whereas 34 infants who had adverse reactions to indomethacin or failed to show a persistent response to pharmacotherapy underwent ligation as secondary approach.

Our reluctance to screen for the presence of a significant PDA, which meant that echocardiography was not employed until clinical symptoms from volume overload of the heart and the lungs developed and infants were difficult to wean from the ventilator, resulted in an advanced age at diagnosis. Simultaneously this policy led to a late intervention age, which correlated with a prolonged duration of a significant PDA. The age at primary intervention ranged from 2 to 21 days of life (median 8 days) in the indomethacin group, 4 to 27 days (median 11 days) in the surgery group, and 4 to 23 days (median 9 days) in the indomethacin followed by surgery group.

The 34 infants of the latter group underwent surgery 0 – 44 (median 5) days after initiation of indomethacin. Although prolonged patency of a significant PDA resulted in a higher median duration of ventilatory support (28 days, range 5 – 185 days) in the primary surgery group than in the indomethacin group (17 days, range 0 – 74 days), incidence of BPD, defined as need for supplemental oxygen at 36 weeks of gestation, was similar in the two groups with 24% (16 infants) and 22% (12 infants), respectively.

Based upon the data from this retrospective analysis of our patient population and in concordance with published recommendations encouraging a strategy of »early symptomatic« pharmacological treatment (Kluckow et al. 1995, 2000) we established a more standardized PDA regime for our very premature patients (Fig. 16.1). We performed routine echocardiography in all very low birth weight infants between 24 and 48 hours of life and used the presence of one or more of the following criteria to define a hemodynamically significant PDA: left atrium/aortic root ratio > 1.4 (Johnson et al. 1983), reduced diastolic flow in the anterior cerebral artery (RI, resistance index > 0.86) or respiratory step back (required $FiO_2 \geq 0.3$ and/or positive pressure ventilation). We reserved surgical treatment for infants with contraindications to cyclooxygenase inhibitors and for those not responding to pharmacological treatment. These changes in the intervention policy with earlier echocardiographic screening and diagnosis of a hemodynamically relevant PDA lead to higher PDA intervention rates (for illustration see Figs. 5.1 and 5.2, chapter 5). After the publication of data by Patel et al. (2000) we changed our medical management from indomethacin to ibuprofen in April 2001. Our subsequent management was directed towards earlier intervention in order to shorten the duration of cerebral hypoperfusion and to decrease the degree of cerebral blood flow variation. It is important to emphasize that this was an empirical rather than a controlled protocol. Controversial opinions regarding the optimal time of PDA intervention exist and up to now different treatment approaches have not proven to improve long term neurodevelopmental outcome.

Parameters Characterizing the Hemodynamic Significance of a PDA

The timing of PDA intervention greatly depends on the diagnostic criteria used to define a »hemodynamically relevant PDA«. Reliance on clinical signs will eventually make the diagnosis of a PDA but only after left to right shunt through the ductus has been significant for some days. Blinded comparison of clinical signs to echocardiographic criteria of ductal hemodynamic significance (discussed below), have shown that it is normal for a hemodynamically significant ductus to be clinically silent for the first 2 to 3 days of life (Skelton et al. 1994). Therefore, accurate and early diagnosis of significant ductal shunting depends on echocardiography.

Echocardiography aims to identify markers allowing early prediction of a subsequent significant ductal shunting, thereby allowing treatment to be targeted to defined at-risk infants who are likely to benefit from timely PDA treatment. Most groups rely on the presence of more than one echocardiographic parameter before treatment of a PDA is initiated. Table 16.1 tries to give an overview of the echocardiographic parameters available for evaluation of the hemodynamic relevance of a PDA with respect to the evidence gained from the literature.

Early Ibuprofen for Symptomatic PDA in Infants under 28 Weeks Gestational Age

Three cases of pulmonary hypertension with severe hypoxemia were reported in 2002 after ibuprofen administration during the first six hours of life in a randomized controlled trial of prophylactic PDA treatment in very preterm infants (Gournay et al. 2002). On the basis of this report we set up a monocenter open study to investigate whether curative treatment with ibuprofen for a hemodynamically significant PDA induced pulmonary hypertension when it was administered to infants under 28 weeks of gestational age (GA) on the second or third day of life.

During a six month period from July 2003 we screened 29 infants below 28 weeks of GA

Table 16.1 Parameters determining hemodynamic relevance of PDA
Limiting the analysis to infants younger than 29 weeks of gestation further improved the predictive accuracy of ductal diameter in the study of Kluckow et al. (1995). For Doppler parameters of cerebral arteries see chapter 10. DA, ductus arteriosus; DAo, descending aorta; SVC, superior vena cava flow; CI, confidence interval; OR, odds ratio; n.a., not available.

Diagnostic feature	Total N (assessed patients)	GA (wks) mean [range]	BW (g) mean [range]	Mean age at assessment [range]	N (patients developed significant PDA)	Mean age at PDA diagnosis/ treatment [range]	Assessment method	Cut-off value for »hemodynamic relevance«	First author and year	Value for hemodynamic relevance	Limitation
LA/Ao root-Ratio	116	27.4 [24-34]	1028 [512-1490]	19 hrs [7-31]	42	5 days [1-15 days]	parasternal long-axis view at the level of the aortic valve (Sahn 1978)	average of 3 measurements; ≥ **1.5**	Kluckow 1995	sensitivity of 29% and specificity of 91% to predict a significant PDA; positive likelihood ratio was 3 (95% CI, 1.32 to 7.24)	
	26	[27-35]	[770-2400]	serial assessment day 1 to 3 of life	13	5 days [2-8 days]	left atrial dimension and aortic root diameter were measured as recommended by Sahn 1978	> **1.3**	Mellander 1987	sensitivity to predict symptomatic PDA was 18, 46 and 100% at 1, 2 and 3 days of age. Specificity was 80, 92 and 85% and total error rate was 52, 32 and 8%.	
Ductal diameter (internal)	116	27.4 [24-34]	1028 [512-1490]	19 hrs [7-31]	42	5 days [1-15 days]	minimum diameter (i.e. point of maximum constriction) of color Doppler signal within course of the duct in left high parasternal view	average of 3 to 5 measurements ≥ **1.5 mm**	Kluckow 1995	predicts requirement to treat with 85% (95% CI, 77% to 93%) specificity and 81% (95% CI, 69% to 93%) sensitivity	width of color jet can be altered by the color settings of the machine
	126	27 [23–29]	991 [420-1630]	5 hrs	35	48 hrs [12-365 hrs]		> **1.6 mm**	Kluckow 2000	predicts later symptomatic PDA with 67% specificity and 89% sensitivity	
Diastolic turbulence in MPA	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	MPA is imaged from the low parasternal window; Doppler range gate is placed in MPA beyond the pulmonary valve and flow recorded	diastolic turbulence	Evans 2004	provides no information on the significance of the shunt	will not detect a PDA with right-to-left shunt

Table 16.1 *Continued*

Diagnostic feature	Total N (assessed patients)	GA (wks) mean [range]	BW (g) mean [range]	Mean age at assessment [range]	N (patients developed significant PDA)	Mean age at PDA diagnosis/ treatment [range]	Assessment method	Cut-off value for »hemodynamic relevance«	First author and year	Value for hemodynamic relevance	Limitation
Direction of postductal diastolic flow in the descending aorta	116	27.4 [24-34]	1028 [512-1490]	19 hrs [7-31]	42	5 days [1-15 days]	high left parasternal or suprasternal position; pulsed Doppler range gate placed distal to the duct insertion in the DAo and flow velocity time signal recorded	altered flow (unclear direction to diastolic flow or retrograde flow)	Kluckow 1995	sensitivity of 68% and specificity of 85% to predict a significant PDA; positive likelihood ratios of 4 (95% CI, 2.5 to 8.0)	
Left ventricular output	116	27.4 [24-34]	1028 [512-1490]	19 hrs [7-31]	42	5 days [1-15 days]	imaged from the modified apical view with Doppler range gate placed distal to aortic valve (Mandelbaum 1991); maximum velocity time integral averaged from 5 consecutive complexes with laminar flow	Calculated as left ventricular stroke volume x heart rate > 300 ml/kg per minute	Kluckow 1995	sensitivity of 26% and specificity of 92% to predict a significant PDA	interpretation of ventricular outputs can be confounded by shunts within the adapting herat (Evans 1994)
pulmonary /systemic flow ratio Qp/Qs	51	27.3 [24–33]	994 [512–1490]	3 days [1–7]	ca. 19	n.a.	calculated from right and left ventricular stroke volume ratio	in PDA diameter >2 mm, Qp/Qs is likely to exceed 1–1.5	Evans 1994	Accurate measure of PDA shunt size when no interatrial shunt is present	interpretation of ventricular outputs can be significantly confounded by intracardiac shunts (Evans 1994)
Superior vena cava flow (SVC)	126	27 [23–29]	991 [420-1630]	serial assessment at 5, 12, 24 and 48 hrs of life	35 18 late IVH (after initial ultrasound)	48 hrs [12-365 hrs]	measured as previously described (Kluckow 2000)	low SVC flow (< 41 ml/kg/min) at any time in the first 24 hrs	Kluckow 2000	DA > 1.6mm (OR: 2.56; 95% CI: 1.10 – 5.99). Low SVC flow on first day of life was independent risk factor for late IVH (adjusted OR: 20.39; 95% CI: 2.54-163.89).	SVC flow is a measure for upper body systemic blood flow less confounded by intracardiac shunts
	128	26.8 [n.a.]	988 [n.a.]	serial assessment at 3, 5 to 10 and 24 hrs of life	80 19 late IVH	within first 24 hours of life	measured as previously described (Kluckow 2000)	low SVC flow (< 41 ml/kg/min) at any time in the first 24 hrs	Osborn 2003	logistic regression for prediction of low SVC flow in the first 24 hours:no association with large DA. Low SVC flow on first day of life was independent risk factor for late IVH (adjusted OR: 5.16; 95% CI: 1.59-16.71).	

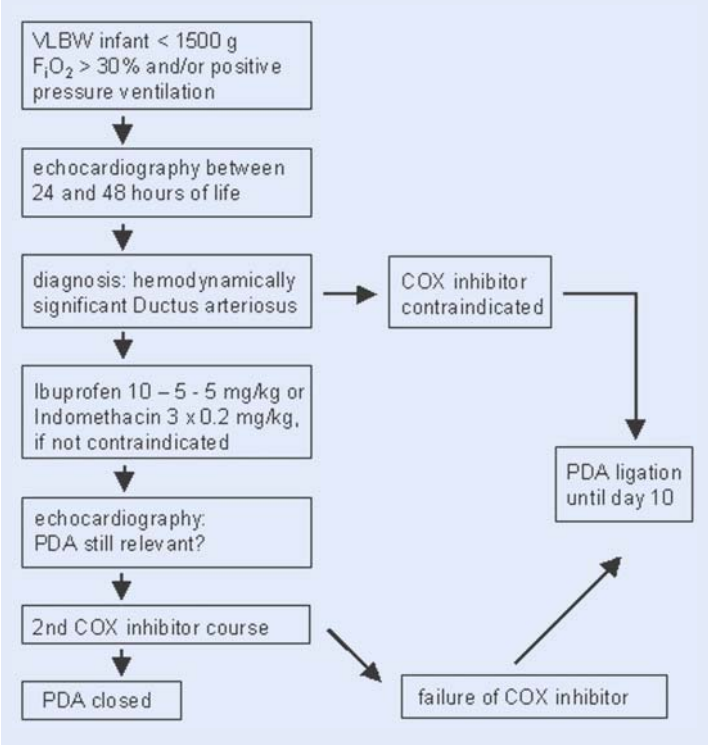


Fig. 16.1 Flow chart for the management of PDA in very low birth weight infants at Charité-Virchow, Department of Neonatology.

between 24 and 72 h of life for the presence of a significant PDA. The confirmed presence of one or more of the following criteria was necessary to diagnose a hemodynamically significant PDA: (1) left atrium/aortic root ratio > 1.4, (2) reduction in diastolic flow in the anterior cerebral artery (resistance index > 0.8), or (3) respiratory step back (increased oxygen supply > 15% = required FiO_2 > 0.36). Main exclusion criteria were: ductus-dependent cardiopathy, right-to-left shunt through the PDA, severe intra-ventricular hemorrhage (Papile grade III or IV) or thrombocytopenia < 50.000/nl. Intravenous ibuprofen was started after confirmation of a hemodynamically significant PDA with 10 mg/kg body weight and was continued with two doses of 5 mg/kg in 24 h intervals, infused continuously over 15 minutes.

Besides determination of a hemodynamically significant PDA echocardiographic measurements included the following parameters for the evaluation of pulmonary vascular resistance: shunt direction and flow velocity via the ductus and foramen ovale, estimation of the right systolic ventricular pressure (RSVP) in the presence of tricuspid regurgitation (TR) and systolic pulmonary artery pressure (Figs. 16.2 and 16.3). Cerebral ultrasound and echocardiography were performed daily in the 29 preterm infants until 72 h of life. In the treated infants these measurements were obtained during the first ibuprofen administration, just before the second dose and 24 h after the third dose. During every ibuprofen infusion pre-ductal (right upper limb) and post-ductal (left upper or lower limb) oxygen saturation was recorded continuously to rule out occurrence of right-to-left ductal shunting, evident by a sudden increase of the maximal saturation difference.

Of the 29 screened patients 14 were excluded from the study: 3 patients with severe IVH, 3 with pulmonary hypertension, and 8 due to non-relevant PDA (Fig. 16.4). Among the 15 treated infants 8 showed tricuspid regurgitation before the first ibuprofen dose with an estimated pulmonary vascular pressure below systemic systolic

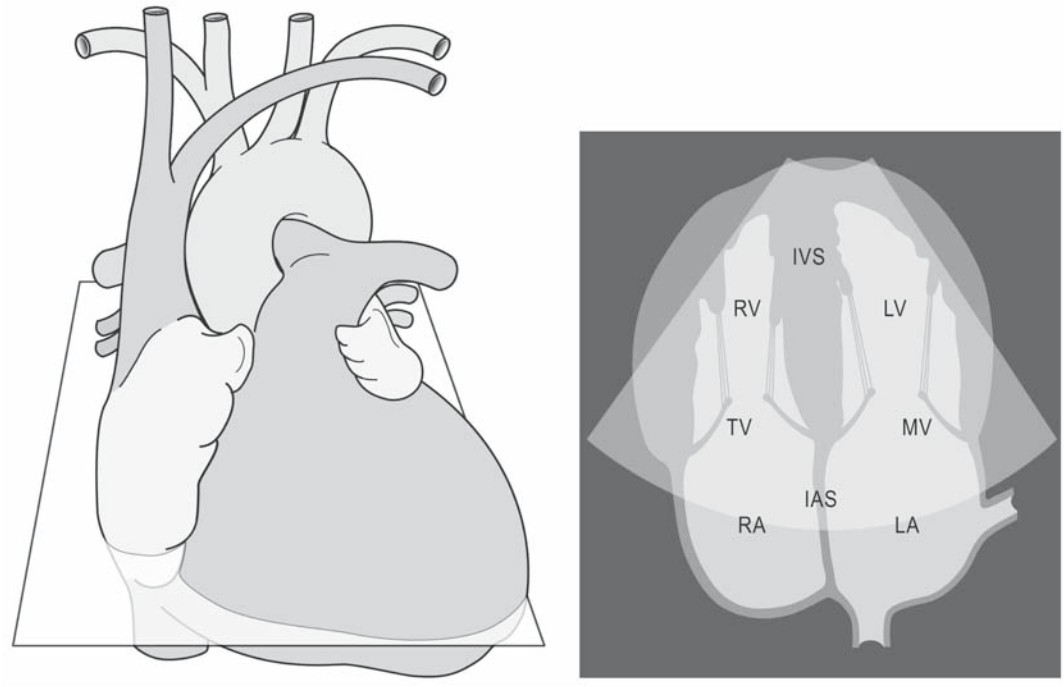


Fig. 16.2 Schematic diagram of the heart during echocardiography in the apical position. To obtain the apical four-chamber view, the transducer is placed above the apex of the heart along an axis from the left shoulder to the right mammilla. This view allows evaluation of the atrial and ventricular septa, atrial and ventricular chambers, AV valves, and pulmonary veins, as well as identifying tricuspid regurgitation, when present. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle; TV, tricuspid valve; MV, mitral valve; IVS, interventricular septum; IAS, interatrial septum.

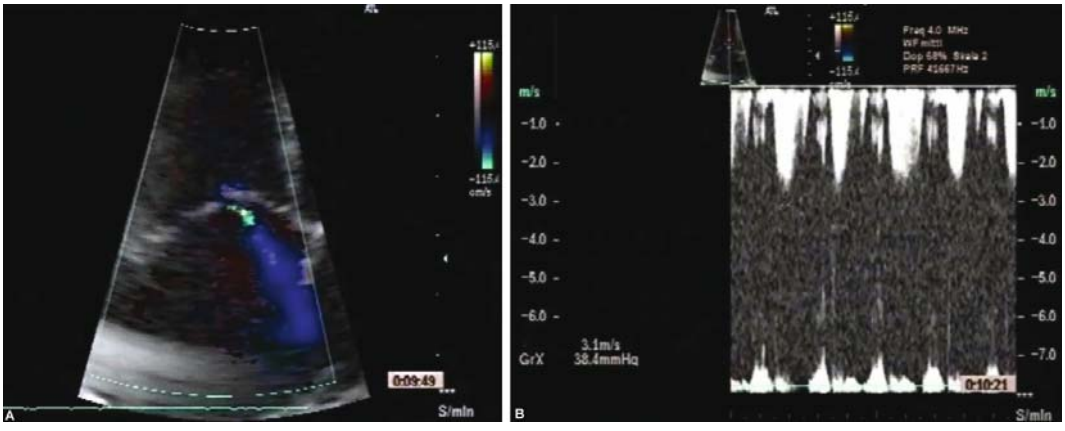


Fig. 16.3 Color doppler echocardiography in the apical four-chamber view. The blue color coded blood flow represents the presence of tricuspid regurgitation (left). Estimation of the systolic pulmonary artery pressure is most accurately obtained from the peak velocity of the tricuspid regurgitation (TR Vmax, green color coding). In this example (right) TR Vmax was 310 cm/second and estimated right ventricular systolic pressure (RVSP) 43 mmHg (including 5 mmHg central venous pressure).

pressure (Table 16.2). This elevation of pulmonary pressure did not increase above supra-systemic levels and instead resolved during ibuprofen administration. PDA closure rate 24 h after the third ibuprofen dose was 53.3% in the treatment group. The closure rate is comparable to that described by others (Van Overmeire 2000). Detailed echocardiographic and pharmacokinetic data will be published elsewhere.

Conclusion

Curative treatment with ibuprofen for a hemodynamically significant patent ductus arteriosus in preterm infants below 28 weeks GA was not associated with the occurrence of pulmonary hypertension when it was administered beyond 24 h of life and after prior echocardiographic exclusion of supra-systemic pulmonary hypertension.

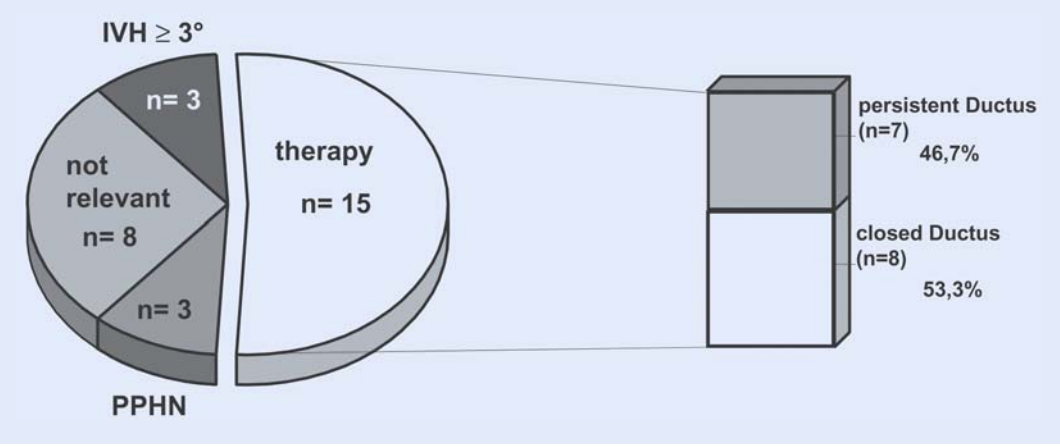


Fig. 16.4 Study population. Infants screened and studied (left) and outcome of ibuprofen treatment (right). PPHN, persistent pulmonary hypertension.

Table 16.2 Tricuspid regurgitation (TR) with an estimated pulmonary vascular pressure (RVSP median 31 mmHg; range 23 – 43 mmHg) below systemic systolic pressure (median 41 mmHg; range 32 – 51 mmHg) in 8 patients of the therapy group before the first ibuprofen dose.

TR Vmax [cm/s]	RVSP mmHg [incl. 5 mmHg ZVD]	systolic blood pressure [mmHg]
260	32	41
290	39	45
210	23	32
240	28	37
260	32	44
250	30	38
250	30	41
310	43	51

References

Evans N, Iyer P: Assessment of ductus arteriosus shunting in preterm infants requiring ventilation: effect of inter-atrial shunting. J Pediatr 1994; 125: 778–85.

Evans N, Malcolm G, Osborn D, Kluckow M: Diagnosis of patent ductus arteriosus in preterm infants. Neo Reviews 2004; 5: e86–e97

Gournay V, Savagner C, Thiriez G, Kuster A, Rozé J-C: Pulmonary hypertension after ibuprofen prophylaxis in very preterm infants. Lancet 2002; 359: 1486–88.

Johnson GL, Breart GL, Gewitz MH, Brenner JI, Lang P, Dooley KJ, Ellison RC: Echocardiographic characteristics of premature infants with patent ductus arteriosus. Pediatrics 1983; 72: 864–71.

Kluckow M, Evans N. Early echocardiographic prediction of symptomatic patent ductus arteriosus in preterm infants requiring mechanical ventilation. J Pediatr 1995; 127: 774–79.

Kluckow M, Evans N. Ductal shunting, high pulmonary blood flow, and pulmonary hemorrhage. J Pediatr 2000; 137: 68–72.

Kluckow M, Evans N. Superior vena cava flow in newborn infants: a novel marker of systemic blood flow. Arch Dis Child Fetal Neonatal Ed 2000; 82: F188–F187.

Kluckow M, Evans N. Low superior vena cava flow and intraventricular haemorrhage in preterm infants. Arch Dis Child Fetal Neonatal Ed 2000; 82: F182–F194.

Koehne PS, Bein G, Alexi-Meskhishvili V, Weng Y, Bührer C, Obladen M: Patent ductus arteriosus in very low birthweight infants: complications of pharmacological and surgical treatment. J Perinat Med 2001; 29: 327–34.

Mandelbaum Isken VH, Linderkamp O: Cardiac output by pulsed Doppler in neonates using the apical window. Pediatr Cardiol 1991; 12: 13–6.

Mellander M, Larsson LE, Ekström-Jodal B, Sabel KG: Prediction of symptomatic patent ductus arteriosus in preterm infants using Doppler and M-mode echocardiography. Acta Paediatr Scand 1987; 76: 553–559.

Osborn DA, Evans N, Kluckow M: Hemodynamic and antecedent risk factors of early and late periventricular/intraventricular hemorrhage in premature infants. Pediatrics 2003; 112: 33–39.

Patel J, Roberts I, Azzopardi D, Hamilton P, Edwards AD: Randomized double- blind controlled trial comparing the effects of ibuprofen with indomethacin on cerebral hemodynamics in preterm infants with patent ductus arteriosus. Pediatr Res 2000; 47: 36–42.

Sahn DJ, DeMaria A, Kisslo J, Weyman A: Recommendations regarding quantitation in M-mode echocardiography: results of a survey of echocardiographic measurements. Circulation 1978; 58: 1072–83.

Skelton R, Evans N, Smythe J: A blinded comparison of clinical and echocardiographic evaluation of the preterm infant for patent ductus arteriosus. J Paeds Child Health 1994; 30: 406–11.

Van Overmeire B, Smets K, Lecoutere D, Van de Broek H, Weyler J, Degroote K, Langhendries JP: A comparison of ibuprofen and indomethacin for closure of patent ductus arteriosus. N Engl J Med 2000; 343: 674–81.

Yeh TF, Achanti B, Patel H, Pildes RS: Indomethacin therapy in premature infants with patent ductus arteriosus – determination of therapeutic plasma levels. Dev Pharmacol Ther 1989; 12: 169–78.

Intravenous Ibuprofen: State of Registration

Marie Christine Fortun

The European Commission granted an orphan designation for ibuprofen in the indication of treatment of patent ductus arteriosus (PDA) in February 2001 (registered as n° EU/3/01/20 in the European Register of Orphan Medicinal Products). Registration is planned under the trade name Pedea®.

At that time, the COMP (Committee of Orphan Medicinal Products) located at the EMEA in London estimated the prevalence of the condition as being 2.13 in 10,000 persons.

PDA is a rare disorder. As no appropriate formulation of ibuprofen was available, there was an unmet medical need. Therefore, Orphan Europe, specialized in orphan drugs, decided more than 6 years ago to develop an appropriate formulation of ibuprofen to treat premature infants safely and efficiently.

This would lead to the first intravenous formulation of ibuprofen.

Pharmaceutical development work linked to the route of administration was performed. Special requirements were needed such as dedicated facilities and sterile atmosphere. Even though the toxicological profile of ibuprofen was already known for more than 40 years, Orphan Europe put in place additional studies related to the target population and the route of administration.

The following animal studies were conducted:

- A local tolerance study conducted in rabbits comparing ibuprofen to placebo, using the iv route.
- An acute toxicity study using the iv route in newborn rats comparing the effects of ibuprofen, saline solution and placebo.

Therefore after compilation of all the data, an application for marketing authorization was submitted to the European Agency (EMEA) in May 2003.

The European registration of Pedea® is currently on-going using the so-called centralized procedure (driven by Ireland acting as rapporteur and the UK acting as co-rapporteur).

The CPMP (scientific committee responsible for the evaluation of quality, safety and efficacy of medicinal products submitted for registration) located at the EMEA has now released a positive opinion towards the registration (on 22 April 2004).

The European marketing authorization, applicable in the 25 countries of the enlarged European Union, is expected during summer (August 2004).

The therapeutic indication will be: »Pedea® is indicated for the treatment of hemodynamically significant patent ductus arteriosus in preterm newborn infants of less than 34 weeks of gestational age«.

Pedea® will be presented as a box of 4 ampoules of 2ml containing 5mg/ml of ibuprofen.

Part V Perspectives

Summary and Perspectives

Michael Obladen

A major conclusion of the Fulda conference was that there is no clear definition of clinically relevant ductus arteriosus in the preterm infant. Even more worrisome is the fact that, despite a high rate of activities, little or no long-term benefit has been established for ductus oriented interventions.

Basics

Related to better definitions, terminology should be clarified: Prolonged – patent – persisting ductus are not clearly distinguishable. Anatomically, persisting is different from patent ductus, as no separation of endothelium from the basal lamina occurs. During the phase of ductal closure, cushion formation is essential. Preterm infants vary from one to the other, and little is known about those 50% of immature infants in whom the ductus closes easily and spontaneously. PDA is associated with respiratory distress syndrome. However, at least in some infants, inflammatory mechanisms contribute to reopening of the ductus. Both COX-1 and COX-2 are required to close the ductus arteriosus functionally. Interventions must act on both tonic and phasic components of contraction. Besides prostaglandins, nitric oxide and endothelin-1 are involved in ductus contraction. Little is known about prostaglandin metabolism after indomethacin or ibuprofen treatment. The role of angiogenic factors, such as vascular endothelial growth factor (VEGF) involved in the definitive ductal closure, as well as their interaction with the cyclooxygenase and prostaglandin pathways, remains to be clarified. Following birth, transitional circulation with right-to-left shunting persists in some infants for hours, which fails to establish and maintain low pulmonary resistance. During this phase ductus intervention is unfavorable.

Consequences for practice: Antenatal glucocorticoid administration reduces the risk for PDA.

Implications for research: Either exogenous (e.g. anti-inflammatory) or endogenous (e.g. genetic polymorphisms) mechanisms must be present, the knowledge of which will improve understanding of PDA pathophysiology and may help to develop strategies to prevent PDA. The interaction of oxygen, nitric oxide, endothelin, and prostaglandins during the initial phase of ductal closure as well as the role of angiogenic factors during remodelling and obliteration of the ductus need to be further addressed.

Clinical Features

PDA is associated with respiratory failure, but no causal relation to BPD has been established. PDA compromises mesenteric perfusion, is associated

with NEC, and early closure may decrease NEC risk. No causal relation of indomethacin and NEC has been established. PDA and intraventricular hemorrhage are associated but a causal relation has not been established. Prophylactic early indomethacin, but not late treatment of symptomatic PDA has been shown to prevent intraventricular hemorrhage. Most randomized controlled trials had a backup treatment option, and most are 10–25 years old. Long-term benefit of PDA intervention has never been established by randomized controlled trials.

Consequences for practice: IVH prevention and PDA closure can be achieved with prophylactic indomethacin administration. Especially when performed in the first 12 hours of life, right-to-left shunting and pulmonary hypertension must be ruled out before this approach is chosen. The prophylacic approach, however, is devaluated by the fact that many infants will unnecessarily receive a potentially toxic drug.

Implications for research: To demonstrate benefit for treatment of symptomatic PDA, randomized controlled trials with untreated controls and with a longterm neurodevelopmental outcome still are needed.

Diagnostics

There is no satisfactory definition of relevant PDA and an urgent need for predictors indicating which infant will be harmed by the ductus and will benefit from PDA intervention. Before any PDA intervention, echocardiography should be performed to exclude PDA dependent heart malformation, and, perhaps more important, to exclude transitory circulation with right-to-left shunting. As decisions must be reached within a relatively short time and around the clock, neonatologists must be familiar with echocardiography – at least to such a degree that they can evaluate size and shunt direction of the ductus arteriosus. Echocardiography has been widely used to define hemodynamic »significance« of the PDA, but turns out to be a two edged sword with the inherent risk to overdiagnose and overtreat ductuses in a prolonged but physiological phase of postnatal adaptation. Anatomic measurements (LA, LV size) indicate cardiac failure more reliably than LA/Ao ratio. Ductus diameter can be easily measured with color Doppler and seems to be more reliable than flow rate (Qp/Qs). It is the large ductus which will fail to close spontaneously, but the optimal threshold limit is unknown. A diameter of 3mm is surely relevant, but what about 2 mm?

Brain perfusion ist best measured by Doppler flow in ICA or ACA; time averaged flow velocity (TAV) or absent or negative enddiastolic flow (Ved) is more valuable than resistance index (RI), which may be influenced by the pressure exerted on the transducer.

Consequences for practice: The diagnosis of a relevant PDA should not be based on sonographic findings alone. Especially in stable infants, neonatologists should mistrust echocardiographic indicators of hemodynamic significance. Brain perfusion should be assessed by time averaged or enddiastolic flow velocity instead of resistance index.

Implications for research: With highly standardized echocardiography, fluid administration, and oxygenation, reference values for ductus closure and diameter should be obtained in both stable preterm infants and those with RDS, but without PDA intervention.

Indomethacin

Indomethacin is registered in the US, but not in all European countries. For indomethacin, more studies are available and the evidence regarding its effects is higher. Side effects are renal failure, reduced CBF, intestinal hypoperfusion, but not NEC. Renal failure may be severe, but is usually reversible during several days after discontinuation of treatment. Preventive use of indomethacin has been found to be effective in reducing the incidence of cerebral hemorrhage. This effect, however, has not been established for curative treatment in symptomatic PDA.

Consequences for practice: Most frequently used dosages are 0.1–0.2 mg/kg, repeated after 12–24 hours for a maximum of 3–6 doses. When

renal failure, pulmonary hypertension, acute bleeding, or thrombocytopenia are present, indomethacin is contraindicated and surgery represents a safer option.

Implications for research: The optimal administration schedule and duration of the treatment need to be clarified by controlled trials.

Ibuprofen

With the European registration of ibuprofen a complicated situation arises: A new drug is registered despite the absence of extensive efficacy and safety studies, whereas the well studied indomethacin is not registered in most countries. Ibuprofen has two enantiomers, the S form with serum half life of 26 hours and the R form with serum half life of 10 hours. Two different galenic preparations of ibuprofen have been used, ibuprofen lysine and ibuprofen THAM, and it is unknown whether there are differences in the action of these two preparations. Most studies have used ibuprofen lysine rather than THAM, which is the registered formula. Ibuprofen causes less circulatory disturbance and less oliguria than indomethacin. However, reduced incidence of intraventricular hemorrhage (as established for indomethacin) has not yet been shown for ibuprofen. Severe pulmonary hypertension has been observed in three infants when used during the first six hours of life, but not in infants >24 hours of age, in whom right-to-left shunting had been excluded. Ibuprofen has been shown to displace bilirubin from albumin at high serum levels, which places the immature brain at risk for kernicterus especially in jaundiced infants. Amikacin half-life is prolonged by ibuprofen. What about other aminoglycosides, e.g. gentamicin? Ibuprofen decreases neutrophil apoptosis and the clinical significance of this finding for infants treated during infection is unclear.

Consequences for practice: Don't run to the drugstore – yet. Benefits and risks of ibuprofen are poorly known, and presently the drug should be used only in controlled clinical trials. Most frequently studied dosage was initial 10 mg/kg, followed by two dosages of 5 mg/kg every 24 hours.

Implications for research: Highest priority must be given to ibuprofen safety concerning the brain. As unbound bilirubin is difficult to measure in vivo, brain stem acoustic potentials may help to recognize if there is clinically relevant bilirubin toxicity during ibuprofen treatment.

Surgery

PDA clipping by the cardiac surgeon in the NICU has been the treatment of choice in infants, in whom pharmacotherapy failed. Operation in the NICU avoids the severe problems associated with transfer of an unstable infant. However, many of these infants had severe brain problems. It is probable that the most immature and sickest infants were those ligated, and it may well be that prolonged PDA and not the surgical intervention itself caused the problems. Some concern, however, remains. Surgery associated complications include pneumothorax, vocal palsy, and thoracic deformity. Catheter interventions are not available for preterm infants, and, due to the risks of cardiac catheterization in infants under 1000 g birthweight, also are not likely to be developed for this population. In most centers minimally invasive thoracoscopic techniques presently are devaluated by the need for transfer to the operation room.

Consequences for practice: Elaborate organization provided, thoracotomy can be performed safely in the neonatal intensive care unit and is preferable to the transfer of the ventilated infant to the operating room. Prophylactic insertion of a pleural catheter helps to minimize the risk of postoperative pneumothorax.

Implications for research: In appropriate setting and design, randomized controlled trials may clarify if there is a benefit of video assisted thoracoscopic versus conventional surgery. If the technique is shown to have significant advantages over thoracotomy, mobile equipment must be developed to avoid transfer of the unstable infant.

Perspectives

Research is warranted into more physiologic approaches to prevent or treat PDA. Presently, there is no consensus regarding adequate oxygenation, fluid intake, or incubator versus open radiant heater care – all three being factors associated with persistence of ductus arteriosus. In order to understand safety and risks of the two cyclooxigenase inhibitors, large head-to-head trials with long-term endpoints are needed. If efficacy and benefit for the quality of life are to be studied, an untreated control group is required, possibly with a late emergency rescue escape arm. Endpoints in these trials will be difficult to define, but certainly should include standardized neurodevelopmental testing, assessment of hearing threshold, chronic lung disease, and renal function at an age of at least two years.

Subject Index

D

E

F

G

H

I

K

L

M

N

O

P

R

S

T

U

V

X