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Interventions for Persisting Ductus Arteriosus in the Preterm Infant

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With 51 Figures and 7 Tables

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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
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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