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Chapter 1

General introduction
Introduction

Historical background

“Nature’s destruction of fetal structures that are superfluous in the adult seems to me something much greater than her original creation of those structures” wrote Galen when he recognized the fetal structures of the ductus arteriosus (DA) and the foramen ovale in the second century AD.¹ In countries under German influence the first description of the ductus arteriosus is erroneously attributed to the late-renaissance Italian surgeon Leonardo Botallo. Working in France he gave his name to the foramen ovale “le trou de Botal”.² Due to a mistake in the German edition of Botallo’s work his name became associated with the DA. The understanding of the functional role of the fetal arterial connection between pulmonary artery and aorta was possible after the discovery of the blood circulation by William Harvey, who in 1628 described ductus arteriosus and foramen ovale in “unripe births of mankind” in Exercitatio Anatomica De Motu Cordis et Sanguinis in Animalibus.³ But still it took many years until the transitional circulatory changes at birth were described and graphically demonstrated in vivo by Barclay et al ⁴ and the disturbances of this physiological process noted by Lind.⁵ Virchow is credited with being the first to note the histological differences between DA and the surrounding arteries and to point out the clinical significance of his findings for postpartum closure.⁶

Figure 1.1 The ductus arteriosus as depicted in „de formatu fetu“ Tab VI, Fig XV, Hieronymus Fabricius ab Aquapendente (1537-1619). Source: Venice edition 1600, Bibliotheca Universitaria, Bologna: Aula-A VIII HH I 5 Legends: A: descending aorta, B: heart, C: left lung, D: ascending aorta, E: ductus arteriosus originally described as „propago magnae arteriae in venam arterialem, que in foetibus ampla apparet: in natis ut funiculus fit“ F: pulmonary trunk, G: left pulmonary artery, H: aortic arch branches.
In the second half of the last century physiological studies of fetal cardiovascular development and the transition to postnatal life by Rudolph together with biochemical studies, and histological studies enormously increased our knowledge of this unique process. From the appreciation of the two main regulators of DA dilatation and constriction (i.e. prostaglandin and oxygen) it was a small step to use synthetic prostaglandins and prostaglandin-synthesis inhibitors for the medical treatment of DA related pathology in neonates.

The DA and the development of pediatric cardiac surgery and pediatric cardiology

In view of the development of pediatric cardiac surgery and pediatric cardiology the persistent DA (PDA) was ascribed the role of a pathfinder by RM Marquis. The first successful pediatric cardiac surgical procedure was the ligation of a PDA performed on an eight year old girl at Children's Hospital Boston in 1938 by Robert E. Gross. In 1944 the concept of Helen Taussig to create an artificial DA hereby improving pulmonary perfusion in deeply cyanosed children with a tetralogy of Fallot opened a new era in pediatric cardiology and pediatric cardiac surgery. The introduction of synthetic prostaglandins in 1975 was the beginning of the next new era, which enabled pediatric cardiologists to keep neonates with complex cardiac defects alive and pediatric cardiac surgeons to treat them. With an open DA most critically ill ductus-dependent neonates can be stabilized before surgical treatment is offered. A better preoperative condition of the patients and the development of more sophisticated surgical techniques made that nowadays more than 15% of the cardiac defects are treated at neonatal age. Not only pediatric cardiac surgery but also pediatric cardiology was stimulated by new treatment options for the DA. In 1967 Porstmann demonstrated with the first closure of a PDA by catheter technique that congenital cardiac defects could be “corrected” in the catheterization lab. This took place just one year after pediatric interventional cardiology was founded by the first palliative procedure, the balloon atrial septostomy, reported by Rashkind and Miller. In 1979 Rashkind reported the first successful catheter interventional treatment of a PDA in an infant. Since then various devices have been invented for closure of small and larger PDA and catheter treatment has become the method of choice for treatment of PDA beyond neonatal age. Later catheter techniques have been developed to palliate neonates with complex DA-dependent anomalies by DA-stenting. The stented DA functions as a substitute for a (modified) Blalock-Taussig shunt or guarantees the
systemic circulation in infants palliated with the staged hybrid procedure for hypoplastic left heart syndrome or its variants. After stenting the combination of physiological and stent-related remodeling of the DA puts the patient at risk for occlusion of the DA. As procedural and long-term success of DA stenting techniques depend on reliable DA patency in the first months of life it is important to increase the knowledge of the underlying molecular mechanisms of physiological DA closure in the neonate.

Patent or persistent DA – not only a matter of definition

In clinical practice the expression “patent DA” is often used synonymously with persistent DA and both are abbreviated as PDA although they differ in morphology, causes and clinical implication. Definition, morphology and physiological changes during process of normal DA closure are extensively reviewed in chapter 2.

As in our review we will use “patent DA” in this thesis as umbrella term for all situations in which the DA is open either physiologically or pathologically. The structurally normal DA in neonates is at risk to remain patent mostly due to immaturity and altered environmental conditions. An open DA in children beyond the age of three months after full gestation is defined as “persistent DA”. The persistent DA is a structural anomaly, characterized by an abnormal amount of elastin in its wall and the presence of a subendothelial elastic lamina. In chapter 2 various causes of structural anomalies of the DA are discussed such as perinatal viral infections (i.e. rubella) and diverse genetic syndromes (i.e. Char, CHARGE, Noonan, Cri-du-chat, Holt-Oram syndrome). A structurally abnormal DA is also found in association with other congenital heart diseases (CHD), heritable disorders of connective tissue and mutations in contractile proteins. These associations, documented in families (chapter 6), indicate that under certain circumstances a PDA is part of a more complex cardiac or systemic vascular disorder. Recently the strict distinction between functional anomalies of the immature DA and structural anomalies of the DA has been challenged by studies on the genetic influence on patency of DA in premature babies. Genetic variations in the TFAP2B gene, also affected by a dominant-negative mutation in patients with Char-syndrome, were identified as genetic risk factors for patency of the DA in premature infants suggesting a functional role for this transcription factor during normal DA closure in neonates. By comparing gene expression in the DA and aorta in fetal rats we identified the DA-dominant expression of the rat
analogue of TFAP2B in endothelial (EC) and smooth muscle cells SMC at the end of gestation (chapter 5).

Remodeling of the DA and similar vascular remodeling processes

In all air-breathing vertebrates the DA can be traced back to a specific segment of the 6th pharyngeal arch that matures and remolds different from all adjacent vascular structures. As reviewed in chapter 2 the unique remodeling process of the DA starts already during the second trimester of pregnancy when intimal thickening regulated by prostaglandins develops. At birth contraction of SMC in response to rising oxygen partial pressure and prostaglandin withdrawal closes the DA and initiates its degeneration by apoptosis and cytolytic necrosis. Intimal thickening and loss of SMC are histological features that are comparable between DA remodeling, the arteries of children with Hutchinson-Gilford progeria syndrome (HGPS) and ageing individuals. This similarity and the knowledge that progerin, the truncated lamin A protein causing HGPS, is also expressed in genetically normal aged individuals, triggered us to study (chapter 4) lamin A/C and progerin expression in the neonatal DA. Because of the mutually exclusive spatiotemporal expression of lamin A/C and progerin in the neonatal DA we propose that activation of alternative splicing of the lamin A/C gene is involved in the circulatory system during neonatal DA closure. The relation between DA closure and ageing needs further clarification.
Aim and chapter outline of the thesis

In this thesis we have studied various aspects of physiological DA closure and PDA in animal models and humans. We were intrigued by the fact that the DA reacts completely different to the postnatal change in environmental conditions than the adjacent vessels. Therefore we aimed to identify genes and molecular mechanisms, which give the DA a specific genetic signature and might explain some of its characteristic morphological features. As all current therapeutic approaches to the DA have major side effects we hope that knowledge of genes that maintain fetal ductal patency and promote closure of the DA will help to develop new therapeutic strategies. These strategies might be tailored to individual genomes in order to improve the present approach targeting the prostaglandin pathway, using implantable intravascular devices or surgery. Furthermore we studied PDA-patients and their extended families with the aim to identify patients in whom the PDA is a heritable structural anomaly either of the DA or a more general vasculopathy.

In chapter 2 we give insights into the pathogenesis and genetic background of patency of the DA. For this purpose normal DA closure, animal models of PDA and genetic syndromes with PDA are reviewed in this chapter.

In chapter 3 we introduce a new model of a small laboratory animal with PDA. In the BN-inbred rat strain a small PDA and aortic fragility are associated and the implications of this association are discussed.

In chapter 4 we studied progerin and lamin A/C expression in the neonatal human DA considering that activation of alternative splicing of the lamin A/C gene might be involved in human neonatal DA closure.

In chapter 5 we analyzed DA- and aorta-specific transcriptional profiles selectively in ECs and SMCs harvested by laser-capture microdissection from the fetal DA and aorta of Wistar-rats. Using microarray and quantitative RT-PCR technique we identified genes that have not earlier been described in relation with DA-specific remodeling.

In chapter 6 data of a retrospective patient-based study assessing the prevalence of PDA and other cardiovascular disease in families of PDA-patients are presented. These data provide evidence for a genetic association of PDA and aortic disease in these families.
Finally, chapter 7 presents concluding considerations of the topics covered by the chapters 2 to 6. It brings the data from basic research in the clinical context of all medical specialties that deal with problems related to the process of closure of the normal neonatal DA and the presence of a PDA.
Chapter 1

References


