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Recent Advances Concerning the Molecular Mechanism of Patent Ductus Arteriosus

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1. Introduction

The ductus arteriosus (DA), a fetal arterial shunt between the main pulmonary artery and the descending aorta, is a normal and essential fetal structure. Normally, the DA begins to close immediately after birth, but in some cases it remains patent after birth. Postnatal patent DA (PDA) is a major cause of morbidity and mortality in premature infants, leading to severe complications including pulmonary hypertension, right ventricular dysfunction, postnatal infections, and respiratory failure (Hermes-DeSantis & Clyman, 2006). The incidence of PDA among full-term newborns has been estimated at one in 500, and in preterm newborns it accounts for the majority of all congenital heart disease cases (Mitchell, 1971). The incidence of PDA exceeds 30% in preterm babies with birth weights <1,500 g (Van Overmeire, 2004). Curiously, patent DA can be essential for patients with complex congenital heart diseases in which the systemic or pulmonary circulation is dependent on the passage of blood through the DA. Therefore, a thorough understanding of the precise molecular mechanism underlying DA closure is very important in pediatric cardiovascular medicine.

Closure of the human DA occurs in two phases: functional closure of the lumen within the first hours after birth by smooth muscle constriction, and anatomic occlusion of the lumen over the next several days due to extensive neointimal thickening and vascular remodelling. Although this overall process is similar among all mammals, the time course of the two phases varies among species.

DA constriction after birth is induced by an increase in arterial oxygen tension, a dramatic decline in circulating prostaglandinE_2 (PGE_2), and a decrease in blood pressure within the DA lumen (Smith 1998; Clyman 2006). Anatomical closure of the DA is associated with a unique system of differentiation of the vessel wall. The most prominent phenotypic change is intimal thickening, a process characterized by (a) an area of subendothelial deposition of extracellular matrix, (b) the disassembly of the internal elastic lamina and loss of elastic fiber in the medial layer, and (c) the migration of undifferentiated medial smooth muscle cells (SMCs) into the subendothelial space. The DA later undergoes permanent closure through structural remodelling and fibrosis. The resulting fibrous band with no lumen persists in the adult as the ligamentum arteriosum (Fay & Cooke 1972). The cascade of events is thought to orchestrate the activation of subsequent signalling pathways, leading finally to the complete obliteration of the DA. In this chapter, we focus on reviewing the current state of knowledge regarding the mechanisms by which vascular remodelling of the DA is regulated.

2. Anatomical closure of the DA

After birth, extensive remodelling of the DA wall occurs, leading to permanent closure of the DA. Although these rapid changes are readily apparent after birth, the structural remodelling of the DA has already begun in late gestation, under the control of the abovementioned unique differentiation system. Therefore, the DA has a distinct structural character from its neighboring arteries. For example, smooth muscle myosin isoform SM2, which is predominantly expressed in adult arteries, is highly expressed in the fetal DA (Kim, 1993).

2.1 Physiological intimal thickening of the DA

Intimal thickening, though often observed in pathological arteries, such as injured or atherosclerotic arteries, is also a characteristic developmental structural change in the DA. The intimal thickening that occurs in the DA is physiological in nature and is required for postnatal DA closure (Rabinovitch, 1996; Yokoyama. 2006a). In rats, intimal thickening can be observed in the mature DA on the 21st day of gestation, though it is not observed in the immature DA on the 19th day of gestation. Intimal thickening starts with a lifting of the endothelial cells. Accumulations of hyaluronan and other extracellular matrices in the subendothelial region and fragmention of the inner elastic lamina provide optimal conditions for the migration of SMCs into the subendothelial region (De Reeder, 1988). These changes in DA structure have been well investigated both in rodents and in humans. Given that intimal thickening is poorly developed in patients with PDA and in animal models of PDA (Gittenberger-de Groot, 1980; Gittenberger-de Groot,1985; Tada,1985), this process must play a critical role in permanent closure of the DA after birth. Therefore, a common molecular mechanism must underlie the development of intimal thickening of the DA in humans and animals alike.

2.2 Molecular mechanisms underlying intimal thickening

Intimal thickening is associated with many characteristic phenomena such as the proliferation and migration of SMCs, the accumulation of extracellular matrix in the subendothelial region, and the fragmention of the inner elastic lamina. Analysis of the causal genes of this complex process in patients with PDA and animal models of PDA is resulting in significant progress toward understanding the molecular mechanism underlying it.

2.2.1 Cyclooxygenase (COX): The generator of PGE_2

The cyclooxygenases COX1 and COX2 catalyze the synthesis of prostaglandin H, a precursor of biologically active prostaglandins including PGE_2, from arachidonic acid. Therefore COX inhibitors such as indomethacin are often used for treatment of PDA to induce vasoconstriction of the DA by attenuating the synthesis of PGE_2. Exposure *in utero* to indomethacin induces premature closure of the DA. Interestingly, it has been reported that infants of mothers who received indomethacin tocolysis are susceptible to symptomatic PDA. These contradictory observations suggest that a relatively complex mechanism underlies the role of COX1 and COX2 in the DA. Furthermore, genetic disruption of COX1 and COX2 results in postnatal PDA (Loftin, 2001). As seen in COX-deleted mice, COX2 plays a primary role in DA closure after birth, and its effect is attenuated in cases of preterm gestation. In addition to COX2, COX1 also contributes to DA closure in a gene dosage-dependent manner (Loftin, 2001; Loftin, 2002). Although it is not apparent from the

literature why COX deletion causes PDA in mice, we assume that the same mechanism should work as described below in mice harboring deletion of the EP4 gene, a predominant PGE_2 receptor in the DA. Trivedi et al. have demonstrated that COX2 expression is attenuated in EP4-deleted mice (Trivedi,. 2006), suggesting the existence of a positive feedback loop in COX-PGE_2 cascades.

2.2.2 Prostacyclin (PGI_2)

Dogs have been studied as an animal model of inherited PDA because their histological features of normal DA and PDA closely resemble those of humans. Through such studies, De Reeder et al. have demonstrated that the expression of PGI_2 synthase is high in the endothelium and low in vascular SMCs in PDA and other patent neighboring arteries. In normally closing DA, in contrast, high amounts of PGI_2 are found in the vascular SMCs of the intimal cushions, suggesting that PGI_2 plays a role in the onset of intimal thickening (de Reeder, 1989).

2.2.3 PGE_2 – EP4: A critical player in regulating intimal thickening

PGE_2, the most potent vasodilator affecting the DA, is produced in the placenta (Smith 1998) and in the DA itself (Clyman, 1978; Coceani, 1978). During gestation, PGE_2 contributes to DA patency *in utero*. Stimulation of PGE_2 receptors activates adenylyl cyclases (ACs). The resulting increased intracellular concentrations of cyclic AMP (cAMP) inhibit myosin light chain kinase, inducing DA relaxation (Smith 1998). The dilator effect of PGE_2 on the mammalian DA is mediated mainly by the PGE_2 receptor, EP4. After birth, the concentration of circulating PGE_2 declines dramatically as the placenta is removed and PGE_2 is rapidly catabolised through lung circulation. Furthermore, the expression levels of PGE_2 receptors are decreased in the DA wall (Smith 1998).

Although PGE_2 plays a primary role in maintaining the patency of the DA, previous studies have demonstrated that genetic disruption of EP4 paradoxically results in fatal PDA in mice (Nguyen, 1997; Segi, 1998). We have found that intimal thickening was completely absent in DA from EP4-disrupted neonatal mice (Yokoyama, 2006a). Moreover, a marked reduction in hyaluronan production was found in EP4-disrupted DA, whereas a thick layer of hyaluronan deposit was present in wild-type DA. PGE_2-EP4-cAMP-protein kinase A (PKA) signalling up-regulates hyaluronan synthase type 2 mRNA, which increases hyaluronan production in the DA. Accumulation of hyaluronan then promotes SMCs migration into the subendothelial layer to induce intimal thickening (Yokoyama, 2006a). Therefore, signalling through PGE_2-EP4 plays two essential roles in DA development, namely, vascular dilation and intimal thickening.

2.2.4 Specific adenylyl cyclases regulate intimal thickening of the DA

Chronic PGE_2-EP4-AC-cAMP-PKA signalling during gestation induces vascular remodelling of the DA and thereby promotes hyaluronan-mediated intimal thickening and structural closure of the vascular lumen. Both PGE_1 and PGE_2 also induce vasodilation in the DA. Since intracellular cAMP is synthesized by ACs, which are transmembrane enzymes activated by G protein-coupled receptors, including PGE receptors, ACs must play an important role in regulating vasodilation and remodelling in the DA. To date, nine different isoforms of membrane-bound forms of ACs (AC1 through AC9) have been identified in vertebrate tissues. Most tissues express several AC isoforms, which exhibit remarkable diversity in their biochemical properties (Sunahara & Taussig 2002). Since SMCs in the DA exhibit biological

properties distinct from those of SMCs in other vessels such as the aorta, it is possible to identify specific AC isoforms that play a distinct role in the DA. Recent advances concerning AC isoform-selective activation or inhibition have allowed us to investigate the role of AC isoforms and the availability of AC isoform-selective activators in regulating DA vascular tone and remodelling. AC2 and AC6, for example, are more highly expressed in rat DA than in the aorta during the perinatal period (Yokoyama, 2010). AC6-targeted siRNA counteracts PGE-induced hyaluronan production in rat DA SMCs. Overexpression of AC6 enhances PGE-induced hyaluronan production and induces intimal thickening in DA explants. Furthermore, intimal thickening of the DA is less marked in mice lacking AC6 than in wild-type mice. Interestingly, stimulation of AC2 attenuates AC6-induced hyaluronan production via inhibition of the p38 mitogen-activated protein kinase pathway and AC6-induced intimal thickening of the DA. The AC2/6 activator 6-[N-(2-isothiocyanatoethyl) aminocarbonyl] forskolin (FD1) does not induce hyaluronan-mediated intimal thickening in DA explants, though the AC5/6 activator 6-[3-(dimethylamino)propionyl]-14 15-dihydroforskolin (FD6) does. Therefore AC6 must be responsible for hyaluronan-mediated intimal thickening of the DA, while AC2 inhibits AC6-induced hyaluronan production. It should be noted that the DA is dilated by stimulation with both FD1 and FD6, the effect of which is longer than that of stimulation with PGE_1 (Yokoyama, 2010). These data suggest that the activation of both AC2 and AC6 induces vasodilation, although the effectiveness of AC2 and AC6 activation has not yet been directly investigated. Administration of FD1 induces vasodilation without intimal thickening of the DA, suggesting that combinative stimulation with AC2 and AC6 or AC2-specific stimulation may be a novel alternative therapy to current PGE therapy for patients with DA-dependent congenital heart disease.

2.2.5 Epac (Exchange Protein Activated by cAMP): A novel target of cAMP

A new target of cAMP, i.e., a new exchange protein activated by cAMP, has recently been discovered and is called Epac. Epac has been known to utilize a distinct cAMP signalling pathway that is independent of PKA (Bos 2006). Epac is a guanine nucleotide exchange protein that regulates the activity of small G proteins. There are two variants: Epac1 is expressed in most tissues, including the heart and blood vessels, whereas Epac2 is expressed in the adrenal gland and the brain. Although both Epac1 and Epac2 are up-regulated during the perinatal period, Epac1, but not Epac2, acutely promotes SMC migration and thus intimal thickening in the DA (Yokoyama, 2008). Since Epac stimulation does not increase hyaluronan production, the effect of Epac1 on SMC migration is independent of that of hyaluronan accumulation, which operates through a mechanism different from that underlying PKA stimulation. Epac stimulation improves the organization of actin stress fibers and enhances focal adhesion of DA SMCs. Therefore, the EP4-cAMP signal pathway can induce intimal thickening in the DA via a PKA-dependent mechanism or an Epac-dependent mechanism.

2.2.6 Oxygen and reactive oxygen species

The DA is an oxygen-sensitive tissue, and oxygen is its most potent vasoconstrictor. The DA senses the change in oxygen tension through the change in redox status. Redox and reactive oxygen species are known to play an important role in vascular remodelling of pathological arteries. Therefore, the change in oxygen tension that occurs after birth should affect postnatal vascular remodelling of the DA. In this regard, Clyman's group has demonstrated that muscular constriction produces a region of ischemic hypoxia in the middle of the ductus muscle media and that intense hypoxia within the constricted vessel wall of the DA

induces vascular endothelial cell growth factor (VEGF), which in turn stimulates neointimal proliferation and vasa vasorum ingrowth (Waleh, 2010; Clyman, 2002). They have also emphasized that hypoxia in the vessel wall plays a role in permanent DA closure. Yet before the blood flow through the DA is completely obstructed, the DA is exposed to blood containing higher oxygen content after birth compared to the blood passing through it during the fetal period. Recently we have found that oxygenation promotes migration of DA SMCs followed by intimal thickening of the rat DA (unpublished data). Accordingly, oxygenation, in addition to inducing contraction, plays an important role in completing DA closure through promoting intimal thickening after PGE_2 removal. Further investigation is warranted to elucidate the molecular mechanism by which oxygenation promotes intimal thickening of the DA.

2.2.7 Calcium channel

A growing body of evidence has demonstrated that voltage-dependent calcium channels (VDCCs), in addition to their role in determining the contractile state, play an important role in regulating differentiation, proliferation, migration, and gene expression in vascular SMCs. VDCCs are classified according to their distinct electrophysiological and pharmacological properties into low-voltage-activated (T-type) and high-voltage-activated (L-, N-, P-, Q-, and R-type) VDCCs. VDCCs consist of different combinations of α1 subunits and auxiliary subunits. Among the α1 subunits, α1C and α1G are the most predominant isoforms in the rat DA (Yokoyama, 2006b). In addition to a conventional α1C subunit, a novel alternatively spliced variant of the α1C isoform is highly expressed in the neointimal cushion of the rat DA, although the role of the spliced variant of the α1C isoform in neointimal cushion formation has not yet been investigated (Yokoyama, 2006b). Interestingly, α1G, a T-type VDCC, is significantly up-regulated in oxygenated rat DA tissue and in the region of intimal thickening in the DA (Akaike, 2009). α1G plays a role in migration of DA SMCs and neointimal cushion formation. *R(-)*-efonidipine, a T-type VDCC-specific antagonist, delays the closure of the rat DA through inhibiting the contraction and neointimal formation of the DA (Akaike, 2009). Therefore, isoform-specific inhibition of VCDD may be an alternative therapeutic strategy to regulate the patency of the DA.

2.2.8 Cytokines

Inflammatory responses to vascular injury or atherosclerosis are known to be associated with the pathogenesis of neointimal thickening. Given that several proinflammatory cytokines are known to play an essential role during vascular remodelling, it is reasonable to assume that cytokines might contribute to physiological vascular remodelling processes as well, in particular, the permanent closure of the DA. Accordingly, it is likely that VEGF stimulates neointimal proliferation and vasa vasorum ingrowth during permanent DA closure, as described above (Waleh, 2010; Clyman, 2002). In addition, transforming growth factor-beta (TGF-β) 1 in endothelial cells and SMCs probably regulates vascular remodelling of the DA, though the function and expression of TGF-β 1 in the DA are controversial (Tannenbaum, 1996; Zhou, 1998).

Clyman's group has demonstrated that the expression levels of vascular cell adhesion molecule (VCAM)-1 (an important ligand for the mononuclear cell adhesion receptor VLA4), E-selectin, IL-8, macrophage colony stimulating factor-1, CD154, interferon-gamma, IL-6, and tumor necrosis factor-alpha are increased in the ductus wall. They have also found that VLA4+ monocytes/macrophages (CD68+ and CD14+) and, to a lesser extent, T-lymphocytes adhere to the postnatal DA (Waleh, 2005).

The expression of IL-15 mRNA is significantly higher in rat DA than in the aorta. IL-15 immunoreactivity is detected predominantly in the internal elastic laminae, and to a lesser extent in SMCs, in the rat DA. IL-15 attenuates PDGF-BB-mediated SMC proliferation and PGE_1-induced hyaluronan production in a dose-dependent manner. Accordingly, IL-15 might have an inhibitory effect on the physiological vascular remodelling processes involved in closing the DA (Iwasaki, 2007).
Moreover, growth hormones promote the migration of DA SMCs, thus enhancing intimal cushion formation in the DA. Growth hormones also regulate the expression of cytoskeletal, genes in DA SMCs, which may retain a synthetic phenotype in the smooth muscle-specific cytoskeletal genes (Jin, 2011).

2.3 Vascular smooth muscle differentiation

SMCs retain the ability to reversibly alter their phenotype in response to various environmental and physiological changes (McDonald and Owens 2007). This property has been termed phenotypic switching or SMC plasticity. Contractile SMCs express high levels of contractile proteins involved in establishing and maintaining myofilament structure and function, including SM22α, SMA and SMMHC. In contrast, synthetic SMCs express lower levels of contractile muscle proteins and have higher rates of proliferation, migration and production of extracellular matrix components. The DA is a very specialized blood vessel, with a vascular wall composed of highly differentiated and contractile smooth muscle (Slomp, 1997). A unique transcriptional program is probably responsible for generating this particular artery during fetal development (Ivey, 2008). A growing body of evidence has demonstrated that maturation and differentiation of DA SMCs is essential for postnatal DA closure. Deletion of several factors that are required for DA SMCs to adopt a contractile phenotype results in PDA. It should be noted, however, that neointimal thickening is induced by migrating and proliferating vascular SMCs, which are characterized as a dedifferentiated (synthetic) phenotype. Therefore, the DA must consist of SMCs exhibiting phenotypic heterogeneity.

2.3.1 Myocardin

Myocardin is a remarkably potent transcriptional coactivator that regulates SMC contractile proteins. Myocardin-null mouse embryos exhibit a block in vascular SMC differentiation as well as defects in the yolk sac vasculature (Li, 2003). Importantly, mice generated after selective myocardin ablation of cardiac neural crest-derived vascular SMCs exhibit PDA and die at postnatal day 3 (Huang, 2008). In these mutant mice, the *myocardin*-deficient vascular SMCs populating the DA exhibit ultrastructural features generally associated with the synthetic, rather than the contractile, SMC phenotype. In addition, the architecture of the neointima and tunica media of the DA is markedly disturbed in association with a dramatic increase in extracellular matrix and a relative decrease in vascular SMC volume. These data demonstrate that myocardin regulates the expression of genes required to induce the contractile phenotype in neural crest–derived SMCs and provide new insights into the molecular and genetic systems that underlie the vascular remodeling of the DA.

2.3.2 TFAP2B

Identifying gene mutations in TFAP2B, a neural crest cell-specific transcription factor involved in Char syndrome, is one of the most important discoveries regarding the

molecular mechanism of PDA. Char syndrome is a genetic syndrome consisting of PDA in association with facial anomalies and minor skeletal anomalies (Chen, 2011; Satoda, 2000; Khetyar, 2008). In addition, Ivey et al. has demonstrated that TFAP2B disruption affects the development of vascular SMCs in the DA (Ivey, 2008), although they did not observe morphological differences between TFAP2B$^{-/-}$ and wild-type mice at embryonic days 13.5, 15.5 and 18.5. It will be intriguing to examine in future studies whether TFAP2B plays a role in neointimal formation of the DA.

2.3.3 Jag1

The evolutionarily conserved Notch signaling pathway plays a major role in vascular development in mammals and other vertebrates (Kurpinski, 2010; High, 2008). Mice with SMC-specific deletion of Jag1, which encodes a Notch ligand, die postnatally from PDA (Feng, 2010). These mice exhibit defects in contractile SMC differentiation in the medial vascular wall of the DA, which therefore fails to express contractile SMC proteins. However, the differentiation of contractile vascular SMCs is confined to the region adjacent to the endothelial cell layer in the DA. Therefore, propagation of the Jag1-Notch signal throughout the width of the vascular wall is required for contractile SMC differentiation of the DA.

2.4 Extracellular matrix involved in vascular remodelling of the DA

Vascular cells are defined by the ways in which they regulate their extracellular matrix, and changes in the extracellular matrix, in turn, determine vascular cell phenotype, i.e. the ability to differentiate, proliferate, and migrate (Rabinovitch, 1996). As described in section 2.2.3, PGE-induced hyarulonan plays a critical role in the onset of intimal thickening of the DA (De Reeder, 1988; Yokoyama, 2006a). In addition, it has been reported that DA SMCs produce twice as much fibronectin as aortic SMCs do (Rabinovitch, 1996). Mason et al. have demonstrated that preventing fibronectin-dependent intimal thickening would be a feasible manipulation to cause PDA as a mode of treatment of congenital heart diseases (Mason, 1999). TGF β and nitric oxide induce extracellular matrix, including hyaluronan and fibronectin, in DA SMCs (Rabinovitch, 1996). Future studies will be needed to determine the other constituents of extracellular matrix that play a role in vascular remodelling of the DA.

2.5 Disassembly of the internal elastic lamina and loss of elastic fiber in the medial layer of the DA

The disassembly and fragmentation of the internal elastic lamina and sparse elastic fibers in the middle layer of the DA is a hallmark of vascular remodelling in the DA. In the normally closing DA, impaired elastogenesis coincides with increased SMC migration and proliferation, contributing to physiological occlusion. The reduced elasticity of the DA wall may help its structure collapse easily as a prelude to postnatal permanent closure of the DA. In PDA, in contrast, an abundance of elastin lamellae in the intima, a subendothelial elastic lamina, and a failure of intimal SMC migration are found in humans and animal models (de Reeder, 1990; Hinek, 1991; Slomp, 1992). In humans and in animal models such as canine puppies and the inbred Brown-Norway (BN) rat (Bokenkamp, 2006), the subendothelial elastic lamina is thought to limit the passage of SMCs from the media to the intima. In PDA in BN rats, the media of elastin lamellae are absent, and the intima contains many elastic fibers. The abnormal distribution of elastin in the PDA of BN rats suggests that impaired elastin metabolism is related to the persistence of the DA and implicates a genetic factor that may link the PDA with aortic fragility. In this regard, recent studies have identified a new

aortic aneurysm syndrome that is due to mutations in the TGF β receptors 1 and 2 and is associated with PDA and ductal aneurysm (Loeys, 2005). Further investigation is required to identify the molecular mechanism underlying the impaired elastogenesis in cases of DA.

3. Conclusion

Ductal closure occurs in two phases. In full-term newborns, the first few hours after birth see acute and functional closure as a result of smooth muscle contraction of the DA, which is triggered by an increase in oxygen tension and a decline in levels of circulating PGE_2. Importantly, prior to this, anatomical vascular remodelling occurs under the control of highly conserved yet complex molecular mechanisms. This remodelling requires a specific sequence of processes, which includes the differentiation of vascular SMCs and endothelial cells, the accumulation of extracellular matrix, vascular SMC migration into the subendothelial region, impaired elastogenesis, and eventually fibrotic changes due to apoptosis and necrosis. Recent advances in high-throughput genetic screening for human diseases and genetically manipulated animal models of PDA have facilitated the identification of pathways and genes involved in development and closure of the DA. As seen in the PGE_2-EP4-cAMP signal pathway as well as in the oxygen and calcium channels, multiple vasoreactive stimulations can serve as an important modulator of vascular remodelling of the DA. In this regard, endothelin-1, nitric oxide, and other vasoreactive factors in the DA that we have not discussed here in detail may play a role in vascular remodelling of the DA. Thus, it is reasonable to infer that endothelial cells in the DA may also play an important role in the differentiation of vascular SMCs, which are considered to be a pivotal cellular structure in the pathogenesis of PDA. In addition to its role in controlling vascular tone in the functional closure of the DA, the vascular remodelling of the DA is now attracting considerable attention as a target for novel therapeutic strategies for patients with PDA and DA-dependent cardiac anomalies.

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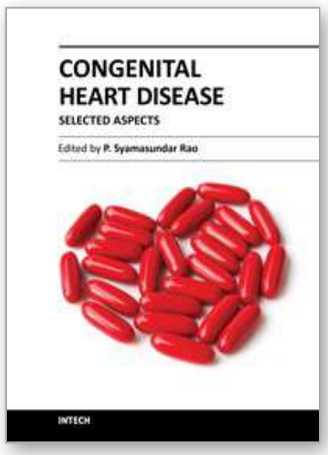
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Congenital Heart Disease - Selected Aspects

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There are significant advances in the understanding of the molecular mechanisms of cardiac development and the etiology of congenital heart disease (CHD). However, these have not yet evolved to such a degree so as to be useful in preventing CHD at this time. Developments such as early detection of the neonates with serious heart disease and their rapid transport to tertiary care centers, availability of highly sensitive noninvasive diagnostic tools, advances in neonatal care and anesthesia, progress in transcatheter interventional procedures and extension of complicated surgical procedures to the neonate and infant have advanced to such a degree that almost all congenital cardiac defects can be diagnosed and "corrected". Treatment of the majority of acyanotic and simpler cyanotic heart defects with currently available transcatheter and surgical techniques is feasible, effective and safe. The application of staged total cavo-pulmonary connection (Fontan) has markedly improved the long-term outlook of children who have one functioning ventricle. This book, I hope, will serve as a rich source of information to the physician caring for infants, children and adults with CHD which may help them provide optimal care for their patients.

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