Review

Biology of the Neonate

Biol Neonate 2006;89:330–335
DOI: 10.1159/000092870

Published online: June 1, 2006

© Free Author Copy – for personal use only

ANY DISTRIBUTION OF THIS ARTICLE WITHOUT WRITTEN CONSENT FROM S. KARGER AG, BASEL IS A VIOLATION OF THE COPYRIGHT.

Written permission to distribute the PDF will be granted against payment of a permission fee, which is based on the number of accesses required. Please contact permission@karger.ch

Mechanisms Regulating the Ductus Arteriosus

Ronald I. Clyman

School of Medicine, Cardiovascular Research Institute, University of California, San Francisco, Calif., USA

Key Words

Ductus arteriosus patency, regulation · Ductus arteriosus, anatomic closure-histologic changes · Ductus arteriosus, hemodynamic and pulmonary alterations

Abstract

A patent ductus arteriosus (PDA) results in increased pulmonary blood flow and redistribution of flow to other organs. Several co-morbidities (i.e., necrotizing enterocolitis, intracranial hemorrhage, pulmonary edema/hemorrhage, bronchopulmonary dysplasia, and retinopathy) are associated with the presence of a PDA, but whether or not a PDA is responsible for their development is still unclear. In this review, comparative physiology between the full term and preterm newborn and the barriers preventing the necessary cascade of events leading to permanent constriction of the PDA are reviewed.

Copyright © 2006 S. Karger AG, Basel

Pulsed Doppler echocardiographic assessments of full term infants indicate that functional closure of the ductus has occurred in almost all by 72 h. Essentially all healthy preterm infants of 30 weeks' gestation or greater will have closed their ductus by the fourth day after birth. Respiratory distress syndrome (RDS) delays ductus closure; however, in most infants who are 30 weeks' gestation or greater, the actual impact of RDS on ductal shunting may be less than commonly assumed (only 11% are still open after 4 days). On the other hand, preterm infants of less than 30 weeks' gestation with severe RDS have a 65% incidence of persistent patent ductus arteriosus (PDA).

The introduction of exogenous surfactant therapy has altered both the incidence and the presentation of the PDA. Although surfactant has no effect on the contractile behavior of the ductus, its effects on pulmonary vascular resistance lead to an earlier clinical presentation of the left-to-right shunt in preterm animals [1, 2] and humans [3–6]. Infants who receive excessive fluid administration during the first days of life also are more likely to develop a clinically symptomatic PDA [7].

Regulation of Ductus Arteriosus Patency

In the full term infant, closure of the ductus arteriosus occurs in two phases: (1) 'functional' closure of the lumen within the first hours after birth by smooth muscle constriction, and (2) 'anatomic' occlusion of the lumen over the next several days due to extensive neointimal thickening and loss of smooth muscle cells from the inner muscle media.

Patency of the fetal ductus arteriosus is regulated by both dilating and contracting factors. The ductus nor-

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

© 2006 S. Karger AG, Basel
0006–3126/06/0894–0330$23.50/0

Accessible online at:
www.karger.com/bon

Prof. Ronald I. Clyman
Box 0544, HSW 1408, University of California, San Francisco
San Francisco, CA 94143-0544 (USA)
Tel. +1 415 476 4462, Fax +1 415 502 2993
E-Mail clymanr@peds.ucsf.edu

mally has a high level of intrinsic tone during fetal life [8]. The factors that promote ductus constriction in the fetus have yet to be identified. The intrinsic ductus tone is due to components that are both dependent on and independent of extracellular calcium [8]. Permeabilized smooth muscle from the fetal ductus is significantly more sensitive to the contractile effects of calcium than is smooth muscle from the aorta and the pulmonary artery [9]. Endothelin-1 also appears to play a role in producing the basal tone of the ductus [10].

The factors that oppose ductus arteriosus constriction in utero are better understood. The elevated vascular pressure within the ductus lumen (due to the constricted pulmonary vascular bed) plays an important role in opposing ductus constriction [11]. The fetal ductus also produces several vasodilators that oppose the ability of the intrinsic ductus tone to constrict the vessel. Vasodilator prostaglandins (PGs) appear to be the dominant vasodilators that oppose ductus constriction in the later part of gestation [12]. Inhibitors of PG synthesis constrict the fetal ductus both in vitro and in vivo. Both isoforms of the enzyme responsible for synthesizing PGs (cyclooxygenase (COX)-1 and COX-2) are expressed in the fetal ductus [13]. PGE_2 is the most potent PG produced by the ductus [14, 15] and appears to be the most important prostanoid to regulate ductus patency. The response of the ductus to PGE_2 is unique among blood vessels in that it is extraordinarily sensitive to this vasodilating substance. PGE_2 produces ductus relaxation by interacting with several of the PGE receptors (EP_2, EP_3, and EP_4) [16]. In the ductus, all three of the EP receptors participate in vasodilation by activating adenylate cyclase [16]. The increased intracellular concentrations of cAMP inhibit the sensitivity of the ductus' contractile proteins to calcium [9]. In addition, one of the EP receptors (EP_3) also relaxes the ductus smooth muscle by opening KATP channels which hyperpolarize the muscle and inhibit ductus tone [16].

In addition to the PGs that are made within the ductus, the fetal ductus is also under the influence of circulating concentrations of PGE_2. Circulating concentrations of PGE_2 appear to be of placental origin [17]. Circulating concentrations of PGE_2 (approximately 1 n*M*) in the late gestation fetal lamb are close to those that produce maximal relaxation of the ductus [18]. PGE_2 concentrations are particularly high in the fetus because of the reduced pulmonary clearance of circulating PGs due to the low fetal pulmonary blood flow [19].

Nitric oxide (NO) is made by the fetal ductus arteriosus and appears to play an important role in maintaining ductus patency in rodent fetuses early in gestation [12]. Although NO is also made in the ductus of larger species, its importance in maintaining ductus patency under normal in utero conditions has not been conclusively demonstrated [20] (see below for the role of NO in fetuses exposed to indomethacin tocolysis and in premature newborns).

Carbon monoxide relaxes the ductus arteriosus and both hemoxygenase-1 and -2 (the enzymes that make carbon monoxide) are found within the endothelial and smooth muscle cells of the ductus. Under physiological conditions the amount of carbon monoxide made by the ductus does not seem to affect ductus tone; however, in circumstances where its synthesis is upregulated, e.g., endotoxinemia, it may exert a relaxing influence on the ductus [21].

Following delivery there are several events that promote ductus constriction in the full term newborn: (1) an increase in arterial PO_2, (2) a decrease in blood pressure within the ductus lumen (due to the postnatal decrease in pulmonary vascular resistance), (3) a decrease in circulating PGE_2 (due to the loss of placental PG production and the increase in PG removal by the lung), and (4) a decrease in the number of PGE_2 receptors in the ductus wall [16]. Although the newborn ductus continues to be sensitive to the vasodilating effects of NO, it loses its ability to respond to PGE_2 [22, 23]. All of these factors promote ductus constriction after birth.

The postnatal increase in arterial PaO_2 plays an important role in ductus constriction. A cytochrome P_{450} hemoprotein, that is located in the plasma membrane of the vascular smooth muscle cells, appears to act as a receptor for the oxygen-induced events in the ductus [24, 25]. Oxygen inhibits K^+ channels [26, 27]. This is associated with membrane depolarization, an increase in smooth muscle intracellular calcium [28], and formation of the potent vasoconstrictor, endothelin-1 [29]. However, the role of endothelin-1 in postnatal ductus closure has recently been questioned [10, 27, 30] and the pathways through which oxygen alters membrane potential are still unclear [26, 31].

In contrast with the full term ductus, the premature ductus is less likely to constrict after birth. The most important mechanism that prevents the preterm ductus from constricting after birth is its increased sensitivity to the vasodilating effects of PGE_2 and NO [32]. The increased sensitivity is not due to an increased number of PGE_2 receptors but rather to enhanced coupling between the receptors and the downstream signaling pathways. As a result, inhibitors of PG production (e.g., indomethacin,

ibuprofen, and mefanamic acid) are usually effective agents in promoting ductus closure in the premature infant. It follows that drugs interfering with NO synthesis or function also could become useful adjuncts, especially in situations where indomethacin has proven to be ineffective [33].

The endogenous factors that alter the ability of the preterm ductus to constrict with advancing gestation are unknown. Prenatal administration of vitamin A has been shown to increase both the intracellular calcium response and the contractile response of the preterm ductus to oxygen [34]. During normal fetal development, circulating cortisol concentrations increase near the end of gestation. Elevated cortisol concentrations in the fetus have been found to decrease the sensitivity of the ductus to the vasodilating effects of PGE_2 [35]; consistent with these findings, prenatal administration of glucocorticoids causes a significant reduction in the incidence of PDA in premature humans and animals [36–40]. The postnatal administration of glucocorticoids also has been shown to reduce the incidence of PDA [41]. However, postnatal glucocorticoid treatment also seems to increase the incidence of several of the other neonatal morbidities [41].

Anatomic Closure-Histologic Changes

In normal, full term animals, loss of responsiveness to PGE_2 shortly after birth prevents the ductus arteriosus from reopening once it has constricted [22, 23]. The loss of responsiveness is accompanied by rapid histologic changes that ultimately lead to obliteration of the vessel's lumen and loss of smooth muscle cells from the inner muscle media. In the full term newborn there is progressive intimal thickening and fragmentation of the internal elastic lamina after delivery. As the intima increases in size, it ultimately forms mounds that occlude the already constricted lumen. The increase in intimal thickening is due (1) to migration of smooth muscle cells from the muscle media into the intima and (2) to proliferation of luminal endothelial cells.

The process that initiates the permanent closure of the ductus has recently been elucidated. Both the loss of vasodilator regulation and the anatomic events that lead to permanent closure appear to be controlled by the degree of ductus smooth muscle constriction. Experimental models that alter the ability of the ductus to constrict at term also prevent the normal histologic changes that occur after birth [11, 42–46]. Constriction produces ischemic hypoxia of the vessel wall [47]. In the full term newborn ductus, the ischemic hypoxia that accompanies constriction occurs even before luminal flow has been eliminated. This is due to alterations in intramural vasa vasorum blood flow [48]. With advancing gestation, the thickness of the ductus wall increases in size to a dimension that requires the presence of intramural vasa vasorum to provide nutrients to its outer half. These collapsible, intramural vasa vasorum provide the ductus with a unique mechanism for controlling the maximal diffusion distance for oxygen and nutrients across its wall. In the full term newborn, ductus constriction obliterates vasa vasorum flow to the outer muscle media; this turns the entire thickness of the muscle media into a virtual avascular zone. The profound ischemic hypoxia that follows the compression of the vasa vasorum inhibits local production of PGE_2 and NO, induces local production of growth factors (e.g., TGF-β and vascular endothelial growth factor (VEGF)), and produces smooth muscle apoptosis in the ductus wall. VEGF plays a critical role in the migration of the ductus smooth muscle cells into the neointima and in the proliferation of intramural vasa vasorum [49].

In preterm infants, the ductus frequently remains open for many days after birth. Even when it does constrict, the premature ductus frequently fails to develop profound hypoxia and anatomic remodeling. The preterm infant seems to require a greater degree of ductal constriction, than the full term infant, in order to develop a comparable degree of hypoxia. In contrast with the full term ductus, the thin-walled preterm ductus does not depend on intramural vasa vasorum to provide oxygen and nutrients to its wall. The absence of intramural vasa vasorum leaves the preterm ductus without a mechanism to rapidly increase the diffusion distance across its wall during postnatal constriction. As long as there is any degree of luminal patency, the thin-walled preterm ductus fails to become profoundly hypoxic and fails to undergo anatomic remodeling after birth. As a result, the preterm ductus requires that there be complete cessation of luminal flow before it can develop the same degree of hypoxia as found at term. If this degree of hypoxic ischemia can be induced in the preterm ductus, then most of the anatomic changes seen at term will occur [8, 38]. If the premature ductus does not develop the degree of ischemic hypoxia necessary to induce anatomic remodeling and smooth muscle death, it remains essentially fetal in appearance and is still susceptible to vessel reopening.

In contrast with the full term newborn ductus, the preterm newborn ductus continues to respond to PGE_2 after birth. In addition to its persistent responsiveness to PGE_2,

the premature ductus produces an increased amount of NO after birth. This is due to the ingrowth of new intramural vasa vasorum that expressly synthesize NO [49]. As a result, there is a change in the relative balance of the vasodilators that maintain ductus patency after birth. Ductus patency becomes less dependent on PG generation and more dependent on other vasodilators during the first weeks after birth. This could explain why the effectiveness of indomethacin wanes with increasing postnatal age [50, 51]. In premature baboons, the combined use of a NO synthase-inhibitor and indomethacin produces a much greater degree of ductus constriction than indomethacin alone [33]. It follows that drugs that interfere with NO synthesis could become a useful adjunct, especially in situations where indomethacin has been found to be ineffective.

Hemodynamic and Pulmonary Alterations

The pathophysiologic features of a PDA depend both on the magnitude of the left-to-right shunt and on the cardiac and pulmonary responses to the shunt. Studies in preterm lambs and human newborns [52, 53] have shown that preterm newborns are able to increase left ventricular output, and maintain their 'effective' systemic blood flow, even with left-to-right PDA shunts equal to 50% of left ventricular output. With shunts greater than 50% of left ventricular output, 'effective' systemic blood flow falls, despite a continued increase in left ventricular output. The increase in left ventricular output associated with a PDA is accomplished not by an increase in heart rate, but by an increase in stroke volume [52, 53]. Stroke volume increases primarily as a result of the simultaneous decrease in afterload resistance on the heart and the increase in left ventricular preload. Despite the ability of the left ventricle to increase its output in the face of a left-to-right ductus shunt, blood flow distribution is significantly rearranged. This redistribution of systemic blood flow occurs even with small shunts [52]. Blood flow to the skin, bone, and skeletal muscle is most likely to be affected by the left-to-right ductus shunt. The next most likely organs to be affected are the gastrointestinal tract and kidneys. These organs receive decreased blood flow due to a combination of decreased perfusion pressure (due to a drop in diastolic pressure) and localized vasoconstriction. These organs may experience significant hypoperfusion before there are any signs of left ventricular compromise [53, 54]. This decrease in organ perfusion contributes to some of the morbidities caused by a PDA: necrotizing enterocolitis and decreased glomerular filtration rate [50, 55].

The decreased ability of the preterm infant to maintain active pulmonary vasoconstriction [56] may be responsible in part for the earlier presentation of a 'large' left-to-right PDA shunt [57, 58]. In addition, therapeutic maneuvers (e.g., surfactant replacement) that lead to a more rapid drop in pulmonary vascular resistance can exacerbate the amount of left-to-right shunt in preterm infants with RDS and lead to pulmonary hemorrhage [6, 59]. Although the mechanisms responsible for pulmonary hemorrhage after surfactant are uncertain, a retrospective cohort study found that a clinically detectable PDA was associated with the onset of the hemorrhage [60]. Early ductus closure has been shown to decrease the incidence of significant pulmonary hemorrhage [50, 61]. With a wide-open PDA, the pulmonary vasculature is exposed to systemic blood pressure and increased pulmonary blood flow. While it is true that preterm animals with a PDA have increased fluid and protein clearance into the lung interstitium, due to an increase in pulmonary microvascular filtration pressure, a simultaneous increase in lung lymph flow appears to eliminate the excess fluid and protein from the lung. This compensatory increase in lung lymph acts as an 'edema safety factor', inhibiting fluid accumulation in the lungs. As a result, there is no net increase in water or protein accumulation in the lung and there is no change in pulmonary mechanics [1, 50, 62–64]. This delicate balance between the PDA-induced fluid filtration and lymphatic reabsorption is consistent with the observation, made in human infants, that closure of the ductus arteriosus, within the first 24 h after birth, has no effect on the course of the newborn's hyaline membrane disease. However, after several days of lung disease and mechanical ventilation, the residual functioning lymphatics are more easily overwhelmed by the same size ductus shunt that could be accommodated on the first day after delivery. As a result, it is not uncommon for infants with a persistent PDA to develop pulmonary edema and alterations in pulmonary mechanics at 7–10 days after birth. In these infants, improvement in lung compliance occurs following closure of the PDA [50, 65–69]. Factors responsible for these alterations in pulmonary mechanics have recently been identified. Using a baboon model of premature chronic lung disease, Drs. McCurnin, Yoder, Seidner, Ikegami, Chang, Waleh and Clyman (unpubl. results) have found that there are no differences in surfactant secretion, epithelial protein permeability, or increase in surfactant inhibitory proteins when the preterm infant is exposed to an open PDA for 2 weeks after birth.

Although there are numerous changes in the genes that regulate inflammation and tissue remodeling in the preterm lung after birth, the presence of an open ductus does not appear to alter the expression pattern of these pro-inflammatory genes, or of the genes involved in lung remodeling. The main differences in the animals with an open ductus were the amount and the distribution of water in their lungs. In contrast with the full term lung, which mobilizes fluid quite rapidly after birth, the preterm lung mobilizes lung fluid much more slowly. A persistent PDA leads to a small but significant increase in lung water at 2 weeks after delivery. Closure of the PDA with a COX inhibitor, like ibuprofen, leads to increased expression of epithelial sodium channels and increased removal of fluid from the alveolar compartment. In addition, the presence of a persistent PDA significantly alters alveolar growth and leads to alveolar simplification with decreased alveolar surface area. The question now is: what does this alveolar growth arrest mean for long-term gas exchange beyond the neonatal period?

References

1 Shimada S, Raju TNK, Bhat R, Maeta H, Vidyasagar D: Treatment of patent ductus arteriosus after exogenous surfactant in baboons with hyaline membrane disease. Pediatr Res 1989;26:565–569.

2 Clyman RI, Jobe A, Heymann MA, Ikegami M, Roman C, Payne B, Mauray F: Increased shunt through the patent ductus arteriosus after surfactant replacement therapy. J Pediatr 1982;100:101–107.

3 Kaapa P, Seppanen M, Kero P, Saraste M: Pulmonary hemodynamics after synthetic surfactant replacement in neonatal respiratory distress syndrome. J Pediatr 1993;123:115–119.

4 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;145:1017–1020.

5 Reller MD, Rice MJ, McDonald RW: Review of studies evaluating ductal patency in the premature infant. J Pediatr 1993;122:S59–S62.

6 Alpan G, Clyman RI: Cardiovascular effects of surfactant replacement with special reference to the patent ductus arteriosus; in Robertson B, Taeusch HW (eds): Surfactant Therapy for Lung Disease: Lung Biology in Health and Disease. New York, Dekker, 1995, pp 531–545.

7 Bell EF, Acarregui MJ: Restricted versus liberal water intake for preventing morbidity and mortality in preterm infants. Cochrane Database Syst Rev 2001;3:CD000503. Review.

8 Kajino H, Chen YQ, Seidner SR, Waleh N, Mauray F, Roman C, Chemtob S, Koch CJ, Clyman RI: Factors that increase the contractile tone of the ductus arteriosus also regulate its anatomic remodeling. Am J Physiol 2001; 281:R291–R301.

9 Crichton CA, Smith GC, Smith GL: Alpha-toxin-permeabilised rabbit fetal ductus arteriosus is more sensitive to Ca^{2+} than aorta or main pulmonary artery. Cardiovasc Res 1997;33: 223–229.

10 Coceani F, Liu Y, Seidlitz E, Kelsey L, Kuwaki T, Ackerley C, Yanagisawa M: Endothelin A receptor is necessary for O_2 constriction but not closure of ductus arteriosus. Am J Physiol 1999;277:H1521–H1531.

11 Clyman RI, Mauray F, Heymann MA, Roman C: Influence of increased pulmonary vascular pressures on the closure of the ductus arteriosus in newborn lambs. Pediatr Res 1989;25: 136–142.

12 Momma K, Toyono M: The role of nitric oxide in dilating the fetal ductus arteriosus in rats. Pediatr Res 1999;46:311–315.

13 Takahashi Y, Roman C, Chemtob S, Tse MM, Lin E, Heymann MA, Clyman RI: Cyclooxygenase-2 inhibitors constrict the fetal lamb ductus arteriosus both in vitro and in vivo. Am J Physiol 2000;278:R1496–R1505.

14 Clyman RI, Mauray F, Roman C, Rudolph AM: PGE_2 is a more potent vasodilator of the lamb ductus arteriosus than either PGI_2 or 6-keto-$PGF_1\alpha$. Prostaglandins 1978;16:259–264.

15 Coceani F, Bodach E, White E, Bishai I, Olley PM: Prostaglandin I_2 is less relaxant than prostaglandin E_2 on the lamb ductus arteriosus. Prostaglandins 1978;15:551–556.

16 Bouayad A, Kajino H, Waleh N, Fouron JC, Andelfinger G, Varma DR, Skoll A, Vazquez A, Gobeil F Jr, Clyman RI, Chemtob S: Characterization of PGE_2 receptors in fetal and newborn lamb ductus arteriosus. Am J Physiol 2001;280:H2342–H2349.

17 Thorburn G (ed): The Placenta, PGE_2 and Parturition. Amsterdam, Elsevier, 1992, pp 63–73.

18 Clyman RI, Mauray F, Roman C, Rudolph AM, Heymann MA: Circulating prostaglandin E_2 concentrations and patent ductus arteriosus in fetal and neonatal lambs. J Pediatr 1980;97: 455–461.

19 Clyman RI, Mauray F, Heymann MA, Roman C: Effect of gestational age on pulmonary metabolism of prostaglandin E_1 and E_2. Prostaglandins 1981;21:505–513.

20 Fox JJ, Ziegler JW, Dunbar DI, Halbower AC, Kinsella JP, Abman SH: Role of nitric oxide and cGMP system in regulation of ductus arteriosus tone in ovine fetus. Am J Physiol 1996; 271:H2638–H2645.

21 Coceani F, Kelsey L, Seidlitz E, Marks GS, McLaughlin BE, Vreman HJ, Stevenson DK, Rabinovitch M, Ackerley C: Carbon monoxide formation in the ductus arteriosus in the lamb: implications for the regulation of muscle tone. Br J Pharmacol 1997;120:599–608.

22 Abrams SE, Walsh KP, Coker SJ, Clarkson MJ: Responses of the post-term arterial duct to oxygen, prostaglandin E_2, and the nitric oxide donor, 3-morpholinosydnonimine, in lambs and their clinical implications. Br Heart J 1995;73: 177–181.

23 Clyman RI, Mauray F, Roman C, Heymann MA, Payne B: Factors determining the loss of ductus arteriosus responsiveness to prostaglandin E_2. Circulation 1983;68:433–436.

24 Coceani F, Wright J, Breen C: Ductus arteriosus: involvement of a sarcolemmal cytochrome P_{450} in O_2 constriction? Can J Physiol Pharmacol 1989;67:1448–1450.

25 Coceani F, Kelsey L, Ackerley C, Rabinovitch M, Gelboin H: Cytochrome P_{450} during ontogenic development: occurrence in the ductus arteriosus and other tissues. Can J Physiol Pharmacol 1994;72:217–226.

26 Reeve HL, Tolarova S, Nelson DP, Archer S, Weir EK: Redox control of oxygen sensing in the rabbit ductus arteriosus. J Physiol 2001; 533:253–261.

27 Michelakis E, Rebeyka I, Bateson J, Olley P, Puttagunta L, Archer S: Voltage-gated potassium channels in human ductus arteriosus. Lancet 2000;356:134–137.

28 Nakanishi T, Gu H, Hagiwara N, Momma K: Mechanisms of oxygen-induced contraction of ductus arteriosus isolated from the fetal rabbit. Circ Res 1993;72:1218–1228.

29 Coceani F, Armstrong C, Kelsey L: Endothelin is a potent constrictor of the lamb ductus arteriosus. Can J Physiol Pharmacol 1989;67:902–904.

30 Fineman JR, Takahashi Y, Roman C, Clyman RI: Endothelin-receptor blockade does not alter closure of the ductus arteriosus. Am J Physiol 1998;275:H1620–H1626.
31 Clyman RI, Saugstad OD, Mauray F: Oxygen metabolites stimulate prostaglandin E_2 production and relaxation of the ductus arteriosus. Clin Res 1988, p 228A.
32 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;43:633–644.
33 Seidner SR, Chen YQ, Oprysko PR, Mauray F, Tse MM, Lin E, Koch C, Clyman RI: Combined prostaglandin and nitric oxide inhibition produces anatomic remodeling and closure of the ductus arteriosus in the premature newborn baboon. Pediatr Res 2001;50:365–373.
34 Wu GR, Jing S, Momma K, Nakanishi T: The effect of vitamin A on contraction of the ductus arteriosus in fetal rat. Pediatr Res 2001;49:747–754.
35 Clyman RI, Mauray F, Roman C, Heymann MA, Ballard PL, Rudolph AM, Payne B: Effects of antenatal glucocorticoid administration on the ductus arteriosus of preterm lambs. Am J Physiol 1981;241:H415–H420.
36 Collaborative Group on Antenatal Steroid Therapy: Prevention of respiratory distress syndrome: effect of antenatal dexamethasone administration. National Institutes of Health, Publ No 85-2695, 1985, p 44.
37 Clyman RI, Ballard PL, Sniderman S, Ballard RA, Roth R, Heymann MA, Granberg JP: Prenatal administration of betamethasone for prevention of patent ductus arteriosus. J Pediatr 1981;98:123–126.
38 Momma K, Mishihara S, Ota Y: Constriction of the fetal ductus arteriosus by glucocorticoid hormones. Pediatr Res 1981;15:19–21.
39 Thibeault DW, Emmanouilides GC, Dodge ME: Pulmonary and circulatory function in preterm lambs treated with hydrocortisone in utero. Biol Neonate 1978;34:238–247.
40 Waffarn F, Siassi B, Cabal L, Schmidt PL: Effect of antenatal glucocorticoids on clinical closure of the ductus arteriosus. Am J Dis Child 1983;137:336–338.
41 Group VONSS: Early postnatal dexamethasone therapy for the prevention of chronic lung disease. Pediatrics 2001;108:741–748.
42 Mason CA, Bigras JL, O'Blenes SB, Zhou B, McIntyre B, Nakamura N, Kaneda Y, Rabinovitch M: Gene transfer in utero biologically engineers a patent ductus arteriosus in lambs by arresting fibronectin-dependent neointimal formation. Nat Med 1999;5:176–182.
43 Nguyen M, Camenisch T, Snouwaert JN, Hicks E, Coffman TM, Anderson PA, Malouf NN, Koller BH: The prostaglandin receptor EP4 triggers remodelling of the cardiovascular system at birth. Nature 1997;390:78–81.
44 Loftin CD, Trivedi DB, Tiano HF, Clark JA, Lee CA, Epstein JA, Morham SG, Breyer MD, Nguyen M, Hawkins BM, Goulet JL, Smithies O, Koller BH, Langenbach R: Failure of ductus arteriosus closure and remodeling in neonatal mice deficient in cyclooxygenase-1 and cyclooxygenase-2. Proc Natl Acad Sci USA 2001;98:1059–1064.
45 Jarkovska D, Janatova T, Hruda J, Ostadal B, Samanek M: Effect of prostaglandin E_2 on the ductus arteriosus in the newborn rat. An ultrastructural study. Physiol Res 1992;41:323–330.
46 Fay FS, Cooke PH: Guinea pig ductus arteriosus. II. Irreversible closure after birth. Am J Physiol 1972;222:841–849.
47 Clyman RI, Chan CY, Mauray F, Chen YQ, Cox W, Seidner SR, Lord EM, Weiss H, Wale N, Evan SM, Koch CJ: Permanent anatomic closure of the ductus arteriosus in newborn baboons: the roles of postnatal constriction, hypoxia, and gestation. Pediatr Res 1999;45:19–29.
48 Kajino H, Goldbarg S, Roman C, Liu BM, Mauray F, Chen YQ, Takahashi Y, Koch CJ, Clyman RI: Vasa vasorum hypoperfusion is responsible for medial hypoxia and anatomic remodeling in the newborn lamb ductus arteriosus. Pediatr Res 2002;51:228–235.
49 Clyman RI, Seidner SR, Kajino H, Roman C, Koch CJ, Ferrara N, Waleh N, Mauray F, Chen YQ, Perkett EA, Quinn T: VEGF regulates remodeling during permanent anatomic closure of the ductus arteriosus. Am J Physiol 2002;282:R199–R206.
50 Clyman RI: Commentary: Recommendations for the postnatal use of indomethacin. An analysis of four separate treatment strategies. J Pediatr 1996;128:601–607.
51 Schmidt B, Davis P, Moddemann D, Ohlsson A, Roberts RS, Saigal S, Solimano A, Vincer M, Wright LL: Long-term effects of indomethacin prophylaxis in extremely-low-birth-weight infants. N Engl J Med 2001;344:1966–1972.
52 Clyman RI, Mauray F, Heymann MA, Roman C: Cardiovascular effects of a patent ductus arteriosus in preterm lambs with respiratory distress. J Pediatr 1987;111:579–587.
53 Shimada S, Kasai T, Konishi M, Fujiwara T: Effects of patent ductus arteriosus on left ventricular output and organ blood flows in preterm infants with respiratory distress syndrome treated with surfactant. J Pediatr 1994;125:270–277.
54 Meyers R, Alpan G, Lin E, Clyman RI: Patent ductus arteriosus, indomethacin, and intestinal distension: effect of intestinal blood flow on oxygen consumption. Pediatr Res 1991;194:569–574.
55 Cassady G, Crouse DT, Kirklin JW, Strange MJ, Jonier CH, Godoy G, Odrezin GT, Cutter GR, Kirklin JK, Pacifico AD, Collins MV, Lell WA, Satterwhite C, Philips JB: A randomized, controlled trial of very early prophylactic ligation of the ductus arteriosus in babies who weighed 1,000 g or less at birth. N Engl J Med 1989;320:1511–1516.
56 Lewis AB, Heymann MA, Rudolph AM: Gestational changes in pulmonary vascular responses in fetal lambs in utero. Circ Res 1976;39:536–541.
57 Jacob J, Gluck G, DiSessa T, Edwards D, Kulovich M, Kurlinski J, Merritt TA, Friedman WF: The contribution of PDA in the neonate with severe RDS. J Pediatr 1980;96:79–87.
58 Gersony WM, Peckham GJ, Ellison RC, Miettinen OS, Nadas AS: Effects of indomethacin in premature infants with patent ductus arteriosus: results of a national collaborative study. J Pediatr 1983;102:895–906.
59 Raju TNK, Langenberg P: Pulmonary hemorrhage and exogenous surfactant therapy – a meta-analysis. J Pediatr 1993;123:603–610.
60 Garland J, Buck R, Weinberg M: Pulmonary hemorrhage risk in infants with a clinically diagnosed patent ductus arteriosus: a retrospective cohort study. Pediatrics 1994;94:719–723.
61 Domanico RS, Waldman JD, Lester LA, McPhillips HA, Catrambone JE, Covert RF: Prophylactic indomethacin reduces the incidence of pulmonary hemorrhage and patent ductus arteriosus in surfactant treated infants <1,250 grams. Pediatr Res 1994;331A.
62 Krauss AN, Fatica N, Lewis BS, Cooper R, Thaler HT, Cirrincione C, O'Loughlin J, Levin A, Engle MA, Auld PAM: Pulmonary function in preterm infants following treatment with intravenous indomethacin. Am J Dis Child 1989;143:78–81.
63 Alpan G, Mauray F, Clyman RI: Effect of patent ductus arteriosus on water accumulation and protein permeability in the premature lungs of mechanically ventilated premature lambs. Pediatr Res 1989;26:570–575.
64 Pérez Fontán JJ, Clyman RI, Mauray F, Heymann MA, Roman C: Respiratory effects of a patent ductus arteriosus in premature newborn lambs. J Appl Physiol 1987;63:2315–2324.
65 Gerhardt T, Bancalari E: Lung compliance in newborns with patent ductus arteriosus before and after surgical ligation. Biol Neonate 1980;38:96–105.
66 Johnson DS, Rogers JH, Null DM, DeLemos RA: The physiologic consequences of the ductus arteriosus in the extremely immature newborn. Clin Res 1978;826A.
67 Naulty CM, Horn S, Conry J, Avery GB: Improved lung compliance after ligation of patent ductus arteriosus in hyaline membrane disease. J Pediatr 1978;93:682–684.
68 Stefano JL, Abbasi S, Pearlman SA, Spear ML, Esterly KL, Bhutani VK: Closure of the ductus arteriosus with indomethacin in ventilated neonates with respiratory distress syndrome. Effects of pulmonary compliance and ventilation. Am Rev Respir Dis 1991;143:236–239.
69 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.