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Arterial Duct in Health and Disease

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Summary

Jaiyesimi O, Baichoo V. Arterial Duct in Health and Disease. *Nigerian Journal of Paediatrics* **1998; 25:29.** Publications on the arterial duct are legion. But they are dispersed in several specialty and subspecialty journals, and it is therefore often very difficult for busy clinicians to access them instantly or obtain a balanced overview of advances in that area of paediatric practice. This review article attempts to remedy that situation. It is a synopsis of some topical issues related to the arterial duct, including its role in foetal circulation, the consequences of its persistent patency after birth, and management of persistent ductus arteriosus in neonates and older children, including advances in endovascular PDA closure. The concluding section focuses on attempts at prolonging ductal patency in neonates whose immediate and short term survival depends on the PDA.

In a figurative sense, the arterial duct enjoys a vascular status that is unrivalled by that of any other structure, of comparable size, in the human body. This is a reflection of its immense importance, which derives largely from its crucial role in the foetal circulation and in the transition from foetal to postnatal circulation. Interest in the arterial duct is also hinged on its ambivalent potential in newborn infants: its prolonged patency can be fatal in some and yet life-saving in others.

This review article focuses on some topical issues related to the duct. The opening section deals briefly with the duct in health, that is, its role in foetal circulation and the changes that occur at birth. Subsequent sections examine the clinical implications of a persistent ductus arteriosus (PDA) and its management in preterms, term infants, and older children. The concluding section summarises methods of maintaining ductal patency in infants whose lives depend on a PDA.

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Foetal circulation

Detailed accounts of the foetal circulation are available in many standard text books [1-3] and will not be repeated here. Rather, this section will focus on those aspects which illustrate the essence of the arterial duct.

It will be recalled that the oxygen tension in foetal blood is quite low, the highest value (in the inferior vena cava blood) being only 25-30 mmHg (saturation, 60-70 percent). But this is largely offset by a very high cardiac output, the combined output from both ventricles being approximately 220ml/kg/min. About a third of the relatively 0_2 - rich blood from the inferior vena cava is guided through the foramen ovale into the left atrium and ventricle, and is destined for distribution mainly to the coronary, carotid and subclavian arteries.

The right ventricle pumps about 65 percent of the combined cardiac output; but less than 10 percent of the blood it ejects goes into the lungs. The rest, amounting to approximately 60 percent of the combined output, is channelled through the duct into the descending aorta. This is clearly a large-volume flow, and the duct is correspondingly large; indeed, it is larger than the aortic isthmus and the pulmonary arteries (Fig. 1).

Another remarkable aspect of the duct is that it is one of only two links between the parallelly arranged pulmonary and systemic circulations, the other being the foramen ovale. These two links are

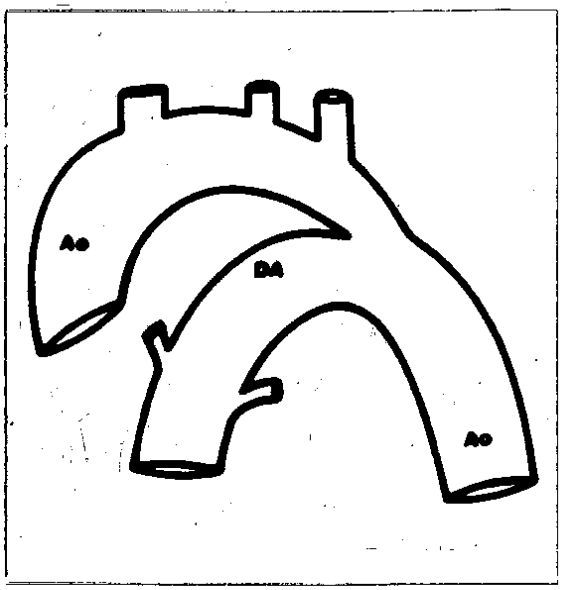

Fig. 1 *Schematic illustration of the relative sizes of the aorta (AO), ductus arteriosus (DA) and pulmonary arteries in the foetus. Note that the ductus arteriosus is larger than the left and right pulmonary arteries.*

indispensable for foetal well-being and survival. Quite predictably, antenatal constriction of the duct, which can be induced by maternal indomethacin therapy, is associated with disorders ranging from persistent pulmonary hypertension of the newborn and hydrops fetalis to intrauterine death.[4]

Duct Patency *in utero*

Patency of the arterial duct in the foetus is an active process, mediated mainly through the dilator effects of PGE_2, PGE_1, and PGI_2.[5,6] Poised against these vasodilators are the duct constrictors notably oxygen, PGF_2 and corticosteroids. Glucocorticoids promote duct constriction through, at least, three mechanisms. First, they inhibit prostaglandin synthesis by blocking the release of arachidonic acid from cell phospholipids. Secondly, they increase ductile tissue responsiveness to the constrictory effects of oxygen while decreasing its sensitivity to the vasodilator effects of PGE_2.[4,6] Furthermore, corticosteroids promote the conversion of PGE_2 to its inactive analogue, 15-keto PGE_2.[4]

Change in the Circulation at Birth

Many complex changes occur in the circulation at birth. With the establishment of alveolar ventilation the oxygen tension increases, pulmonary vascular resistance decreases, and pulmonary blood flow increases, as does the venous return to the left atrium. Consequently, the left atrial pressure rises. Concomitantly, with the clamping of umbilical cord and hence severance of the low-resistance placenta, the systemic vascular resistance rises, flow ceases in the umbilical vein, venous return to the right atrium decreases, and the right atrial pressure falls. Thus, a pressure gradient develops between the left and right atria, and this results in flap-closure of the foramen ovale.

With this, the "in parallel" foetal circulatory pattern is converted to one in which the pulmonary and systemic circulations are sequential. The arterial duct becomes redundant; and it is functionally closed by age 50 hours in about 50 percent of healthy term infants and in practically all of them by 100 hours.[7-10] In the first few days of life, however, the duct remains labile; and intermittent patency may occur especially during hypoxaemic episodes in preterm infants. This is a phenomenon which is commonly observed in units that care for sick low-birth-weight (LBW) infants.

Perhaps, the most remarkable feature of the transition from foetal to postnatal circulation is the 'fine programming' which ensures that as the arterial duct closes the pulmonary vascular resistance falls and the pulmonary arteries open up to accommodate the right ventricular output. The lowering of pulmonary vascular resistance is mediated by several interactive factors, including a change in the shape of the pulmonary arterioles induced by lung inflation, direct vasodilator effect of oxygen, and the effects of PGI_2, PGE_2, nitric oxide, adenosine, acetycholine and ß-adrenergic stimulation.[4,8,11] Failure of this 'fine programming' results, among other things, in the syndrome of persistent pulmonary hypertension of the newborn.[11,12]

Duct Closure at Birth

Normal closure of the duct at birth is believed to result from several complex interactive factors, prime among which is the increase in oxygen tension which accompanies the establishment of normal alveolar ventilation. Oxygen exerts a direct

constrictory effect on the duct, and also blunts its sensitivity to PGE_2.[9] There also appears to be a net decrease in prostaglandin E series, brought about by reduced synthesis of PGE_2, cessation of the placental supply, and increased inactivation in the lungs as a result of increased pulmonary blood flow.[13] A contributory role has also been attributed to endothelin-1.[13] Normally, functional closure of the duct is followed four to eight weeks later by anatomical, irreversible closure. This second phase is dependent on the cessation of intraluminal flow and ischaemic damage to duct structure.[9]

Postnatal Persistence of the Arterial Duct in Preterm Infants

Failure of the adaptive processes outlined above, especially inadequate tissue oxygenation after birth, results in persistence of the duct. Apart from birth asphyxia and respiratory distress syndrome (RDS), other factors that may be associated with prolonged duct patency in very immature neonates include hypervolaemia, phototherapy, administration of frusemide, surfactant therapy, and sepsis.[4,14-17] Owing to differences in study methodology and patient populations, the incidence of PDA reported by various authors has varied very widely, from 9-80 percent.[7,10,18-21] However, an inverse relationship between birth weight and PDA incidence has been a consistent feature and highest figures (40-80 percent) have accrued from studies of infants who weighed less than 1000g,[7,18,19] in whom RDS was an invariable coexisting risk factor. Indeed, some authors[8,10] have stated that RDS - induced hypoxaemia, rather than prematurity *per se*, is the critical aetiologic factor because, in the absence of RDS, the duct closes within the normal time frame even in very-low-birth-weight (VLBW) infants. It is happy to note that not every PDA in these very immature infants causes clinical morbidity as only 30-40 percent of them actually develop a haemodynamically significant left-to-right shunt.[18,22]

Haemodynamic Consequences

Not only do preterm infants have the highest incidence of PDA, its haemodynamic consequences are most severe in them, largely because of an interplay of factors which are peculiar to such infants. An early and sharp decline in pulmonary vascular resistance facilitates a large left-to-right ductal shunt. This increases the pulmonary blood flow, reduces the pulmonary compliance, aggravates any concurrent RDS, and increases the need for supplemental oxygen and ventilatory assistance. It thus predisposes to bronchopulmonary dysplasia.[4,23]

Equally notable is that the increased pulmonary blood flow presents the left heart chambers with an increased volume load which the inadequately compliant neonatal myocardium may be unable to handle efficiently. This may result in heart failure which, apart from its adverse effects on tissue perfusion and cellular metabolism, will further reduce the pulmonary compliance, as well as predispose to pulmonary haemorrhage.

Severe haeomodynamic derangements may also occur in the systemic circulation. With a haemodynamically significant PDA, blood leaks from the aorta into the pulmonary artery during systole and diastole. In <1000g infants especially, the systolic and diastolic blood pressure falls,[24] organ perfusion is compromised, and there may in fact be a diastolic reversal of blood flow, thus producing a diastolic "steal" phenomenon. This was demonstrated in the anterior cerebral arteries by Perlman, Hill and Volpe[25] many years ago and, later, in the mesenteric artery by Coombs and his colleagues.[26] The deranged haemodynamics in the brain, kidney and intestine may manifest as cerebral ischaemia, intraventricular haemorrhage, periventricular leukomalacia, renal dysfunction, and necrotizing enterocolitis.[4,26,27,28]

Diagnosis and Shunt Quantification

Because a PDA has the potential for grave consequences in preterm infants it is essential that the diagnosis be made early so that effective management can be instituted promptly. Regrettably, however, the clinical signs are 'soft' and their early recognition may be thwarted by factors related to the patient or to ongoing treatment (Table I). For instance, in about 15 percent of the patients the peripheral pulses are not bouncy. Besides, the shunt murmur is commonly systolic, and it may be sufficiently loud at the lower left sternal border to arouse a suspicion of a ventricular septal defect. However its ductal origin is easily recognizable in approximately 20 percent of the infants in whom the murmur is evanescent. Furthermore, some extremely immature (<1000g) infants may have an echocardiographically demonstrable PDA without showing any of the usual clinical signs. This has

been termed a 'silent ductus'. [19 22 29 30]

If the clinical recognition of a PDA in a preterm is fraught with so many potential pitfalls how, then, can the shunt through the duct be quantified? This is often a difficult problem; the issue is best decided by a careful consideration of the clinical signs and results of relevant investigations. A hyperactive precordium, bouncy pulses, and an increasing need for ventilatory support in the absence of deteriorating lung parenchymal disease usually denote a significant shunt. Echocardiography with Doppler/colour imaging (Fig 2) is, however, the gold standard for diagnosis and shunt quantification: an increase in the ratio of the left atrial to aortic root dimension beyond 1.3, a deep and broad PDA jet on colour imaging and/or reversal of blood flow in

Table I

Clinical Signs of PDA in Preterms, and their Obscurers

Sign		*Obscurer*
Hyperactive precordium		Ventilator therapy; pulmonary interstital emphysema; pneumothorax
Bounding peripheral pulses		Fluid depletion; VLBW
Cardiac murmur		Absent/Evanescent in 15 - 20% of VLBW infants
Cardiac enlargement		Fluid depletion: high-pressure ventilation; parenchymal lung disease
Increasing need for ventilatory support (oxygen, pressure, rate)		—
Echocardiography:	Direct imaging (2D/ Colour)	Technical constraints
	Doppler	
	Increased LA/AO ratio	
	Diastolic flow reversal in descending aorta	

VLBW: Very low birth weight; AO: Aorta; LA: Left atrial

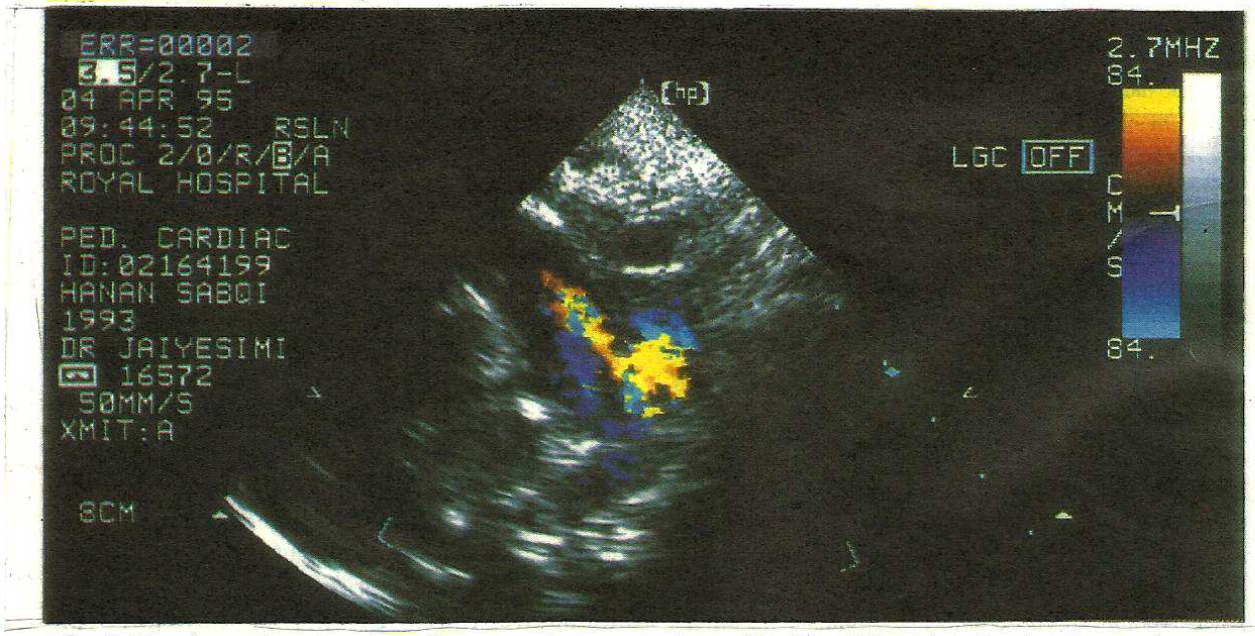

Fig. 2 *Doppler colour imaging of a patent ductus arteriosus. The jet of blood from the duct (in mosaic colour) appears as a retrograde flow in the main pulmonary artery.*

the descending aorta during diastole usually indicate a large shunt. And once that is established, indomethacin therapy or other measure aimed at effecting duct closure should be instituted.

Use of Indomethacin in Preterm Infants

In the last two decades indomethacin has been widely employed to effect PDA closure in preterm infants. [4 31 32] The success rate varies between 60 and 90 percent, depending on the weight of the patient, the postnatal age at the time of treatment, and the treatment protocol. [4 33 34] Best results are obtained in infants who weigh between 1000g and 1750g, and when treatment is given early after birth. Reopening of the duct occurs in 20-40 percent of treated preterms, especially in those weighing <1000g, whose ducts seem to be very sensitive to circulating dilator prostaglandins (PGE_2, PGE_1, PGI_2). [33] In 20-50 percent of the infants treated with indomethacin the efficacy may be associated with adverse effects including impaired cerebral perfusion, renal dysfunction, necrotizing enterocolitis, platelet dysfunction, and increased susceptibility to sepsis. [4 28 32 34 35 36] Concerns generated by these adverse effects have given rise to controversies about certain aspects of the use of the drug; at the core of which are critical clinical issues pertaining to patient selection, timing of treatment, drug dosage and mode of administration. These issues will be examined below.

Who should receive Indomethacin, and when?

Rescue Use

A haemodynamically significant PDA in a preterm, LBW infant deserves to be closed promptly. But this does not automatically translate into immediate indomethacin therapy. There are, broadly, two medical-management options: I) immediate treatment with indomethacin; or ii) trial of a regimen of fluid restriction plus or minus frusemide therapy, with recourse to indomethacin only if this regimen is ineffective. Both options have their merits and demerits. Indomethacin therapy is more efficacious but, as indicated above, it also has the potential for serious adverse effects. The frusemide/fluid-restriction regimen is simpler, and safer, but the efficacy is modest; the success rate in our experience is approximately 15-20 percent. Besides, it must be noted that the regimen is anchored on frequent and meticulous monitoring of the clinical status and, especially, renal function. Any deterioration in these parameters should be taken as an indication to discontinue that mode of treatment.

This is an area that demands prompt and astute clinical judgement. For example, it will be unwise to prolong the fluid restriction regimen if it is ineffective within a stipulated period. Injudicious prolongation will almost certainly aggravate the renal hypoperfusion that a symptomatic PDA entails, and may therefore precipitate overt renal failure. Should that happen, the patient will no longer be suitable for indomethacin therapy. Besides, prolonged trial of an ineffective fluid-restriction regimen will reduce the chances of successful closure with indomethacin because, as stated earlier, the efficacy of indomethacin decreases as the patient's postnatal age increases.

Resource availability, local experience and other relevant considerations will obviously influence the choice of one or the other management strategy. Our practice, predicated on a desire to avoid indomethacin-related adverse effects whenever possible, is to give a trial of fluid restriction (by 20 - 25 percent), plus or minus frusemide, (depending on the baby's blood chemistry and overall clinical status) for 24 - 36 hours. If this regimen fails to close the duct we switch to indomethacin, provided there are no contraindications to its use (Table II). By and large we tend to give the drug, whenever it is indicated, within the first week of life, mostly between postnatal days five and seven.

Table II
Contraindications to the use of Indomethacin in Neonates

Poor renal function	- Urine output < 1ml/kg/hr - Serum creatinine > 120umol/L - Blood urea > 8 mmol/L
Bleeding disorder	- Haematuria; gastro intestinal, pulmonary or intracranial haemorrhage
Thrombocytopenia	Platelet count < 60 000/mm^3
Necrotizing enterocolitis	
Sepsis	
Hyperbilirubinaemia necessitating exchange blood transfusion	

Prophylactic Use

Infants weighing <1000g are a slightly different management issue. These very immature neonates have a very high risk (about 80 percent) of developing large left-to-right shunts once a PDA murmur becomes audible. [34] It has therefore been suggested that they should be treated with indomethacin once the murmur is heard, and the diagnosis confirmed by echocardiography, well before other clinical signs develop. There are reports which suggest that this strategy of early intervention reduces the need for subsequent surgical duct ligation; but there is no clear evidence that it improves the overall outcome significantly. [4]

A more truly prophylactic regimen is the routine administration of indomethacin shortly after birth to infants weighing <1000g. From all available accounts, there is still widespread reservation about this form of intervention, [34 36] which stems from concerns about the drug's adverse effects, some of which (e.g. the gastrointestinal, renal and CNS complications) can be so serious that trading off a PDA for indomethacin therapy leaves the patient with little, if any, benefit.

Paediatricians who advocate restraint in the use of indomethacin in VLBW infants will doubtlessly feel vindicated by two recent reviews of the subject. [34 37] In a paper based on a meta-analysis of over 40 publications Clyman [34] recommended that use of the drug should be limited to VLBW infants with at least an apparent PDA. Similarly, Fowlie[37] cautioned that though prophylactic indomethacin had several immediate benefits, more data were needed on the incidence of adverse effects before its routine use could be recommended. We also share this view of cautious approach.

How should Indomethacin be administered?

There tends to be a resurgence in PGE_2 level some five to seven days after cessation of indomethacin therapy,[4] and this may be associated with duct reopening in about 20 - 40 percent of patients, particularly <1000g infants whose ducts are more sensitive to the vasodilator prostaglandins. [4 33] This observation and the desire to minimize the adverse effects of indomethacin therapy have stimulated trials of alternative treatment strategies ('extended protocols'), all characterized by a low dose given over a much longer period. It was hypothesized that if duct closure was maintained for several days ischaemic damage to its structure, which comes with cessation of intraluminal flow, will render it unresponsive to any further PGE influence. Several workers have tested and, to varying degrees, validated this hypothesis. [33 38 39] In the study by Rennie and Cook [33] a low-dose extended course (IV indomethacin, 0.1mg/kg Q24 hr x 6) appeared to be more efficacious than the conventional course (0.2mg/kg Q 12 hr x 3 doses, the duct closure rates being 90 vs 77 percent and the recurrence rates 21 vs 40 percent respectively. But there were more deaths among infants who received the extended course and, as the authors cautioned, this and any other new treatment strategy must be carefully evaluated. Similarly, there is need for critical appraisal of reports[4] which suggest that continuous infusion of indomethacin virtually eliminates its adverse effects on the brain and kidney. Quite understandably, most centres still use the conventional 3-dose regimen. [37]

Trial of other Prostaglandin Synthesis Inhibitors

Unallayed concerns about the adverse effects of indomethacin have also prompted trials of other prostaglandin synthesis inhibitors, including acetyl salicylic acid, mefenamic acid, ethamsylate, and ibuprofen. Acetyl salicyclic acid [31 40] and mefenamic acid [41] were found unsuitable because of low efficacy and high toxicity profile, respectively. Ethamsylate was initially evaluated in connection with the prevention of periventricular haemorrhage in preterm infants, [42-45] but in one of the studies, Benson *et al* [44] noted a reduced incidence of PDA in the babies. Subsequently, Amato, Huppi and Markus [16] specifically studied the use of the drug for the prevention of PDA in babies treated with surfactant. The preliminary report by these workers suggested that IV ethamsylate (12.5mg/kg given within 4 hours after birth, and repeated Q6 hrly x 4 days) effectively reduced the incidence of symptomatic PDA. However, the number of patients in the study was small, and much larger studies are needed to fully evaluate the efficacy and safety of the drug. Of the prostaglandin synthesis inhibitors so far evaluated ibuprofen has received the most, and still continuing, attention; [28 36 46 47] and the results to date suggest that the drug is as effective as indomethacin. More importantly, the renal side-ef-

fects seem to be milder, [28 36 47] and it apparently does not impair mesenteric [46 48] or cerebral haemodynamics. [47] All in all, the drug seems to hold out some promise, and results of further studies are keenly awaited.

Surgical Ligation of PDA in Preterm Infants

For babies with failed medical intervention the recourse is to surgery. It is therefore cheering to note that considerable advances have also occurred in the area of surgical treatment. The surgical mortality is virtually nil. Besides, minimal access techniques are being increasingly employed, and with satisfactory results. [49] Quite recently, Burke and Jacobs[50] reported on their experience with video-assisted thoracoscopic surgery in 24 LBW neonates and infants. The mean weight of the patients at the time of surgey was 1.18kg, and 14 of them weighed <1000g. The duct was successfully clipped through a thoracostomy opening in 22 of the 24 babies, and at open thoracotomy in the remaining.

PDA in Term Infants and Older Children

Term infants and older children may have a PDA as a lone defect, or in combination with other cardiovascular defects. Its reported incidence varies in different countries, due perhaps to differences in the study populations and methodology; but in general it occurs in about 4-8 per 10,000 live births [34 51] and ranks among the top five cardiovascular defects in various parts of the world (Table III).

Table III

Relative Prevalence of PDA in Chidlren with Congenital Heart Defects

Country	*Author(s)*	*Year*	*Percent of Total*	*(Ranking)*
USA	Ellison [52]	1981	8.6	(5)
UK	Dickinson, Arnold & Wilkinson [53]	1981	12	(2)
Japan	Nakazawa, Sequchi & Takao [54]	1988	3.6	(5)
Saudi Arabia	Jaiyesimi, Ruberu & Misra [55]	1993	8	(4)
Zimbabwe	Bannerman & Mahalu [56]	1998	11.9	(3)

Its manifestations beyond the newborn period are well-known and will therefore not be recounted here. Suffice it to stress that the compounding effects of RDS and pulmonary haemorrhage are usually not an issue in term infants and older children. Furthermore, these older patients tolerate the aortic leak better and, ordinarily, it does not cause necrotizing enterocolitis, renal failure or intracranial haemorrhage. However, while a small duct may produce no symptom at all, and may indeed be 'silent', i.e. without any associated murmur, [57 58] a large duct may cause recurrent pulmonary infections, heart failure, growth failure or pulmonary hypertension.[59]

In theory, all PDAs pose a risk of infective endarteritis. In practice, however, the picture is different. We have not enountered a single case of PDA-related infective endarteritis in our last 1000 consecutive cardiac patients. Fukushige, Igarashi and Ueda[60] encountered only two cases over a 20 year period in a university hospital in Japan. Similarly, data reviewed recently by Sullivan[58] also indicate that PDA-related endocarditis is indeed rare, with an incidence which ranged from around 1 per 9000 in London to nil among 270 Swedish patients who were followed up for an aggregate of 1196 'at risk' years. The management implication of these findings is that need to prevent endocarditis may no longer be a strong indication for early PDA closure.

PDA Closure in Older Children

Transcatheter PDA Closure

As stated earlier, the term infant or older child with a PDA cannot hope for rescue through indomethacin therapy. For such patients the choice is between surgery and transcatheter closure using an occluder device. Endovascular PDA closure via a catheter was first reported in 1967 by Portsmann *et al*, [61] but the high cost of the occluder device, coupled with the technical complexities, prevented a wide acceptance of the procedure. However, the concept of transcatheter occusion prevailed and, 12 years later, Rashkind and Cuaso[62] reported on a refined occluder, subsequently named Rashkind device (synonym: disk, umbrella device). Again technical constraints precluded the use of the earliest devices in small children (weight<10kg) but, with

advances in device design and improved operator expertise the device soon became applicable in young children.[57 63 - 65]

Transcatheter PDA closure has many attractions. It requires no thoracotomy and therefore avoids the cosmetic blemish of a thoracotomy scar. The hospital stay is shortened (to 1-2 days in most centres), thus saving on cost while also minimising the emotional trauma suffered by hospitalized children. The procedure is effective. In most centres with the appropriate expertise the duct closure rate in patients with successful device implantation is 80-90 percent for the Rashkind device and close to 100 percent for occluder coils.[65-68] A small residual shunt is common immediately after the first implantation, but most of such shunts get obliterated subsequently, either spontaneously through thrombogenesis or by repeat device implantation.

Equally important, the procedure is safe. The complications, including device embolization, haemorrhage, haemolysis and partial obstruction of the left pulmonary artery near its origin, are fairly easy to manage. The risk of infective endocarditis is small, but it is not nil.[58] Predictably, the complications rates vary from one centre to another, and also within the same centre at different periods, depending on such variables as operator expertise, type of occluder device used, and size of the duct. These and other technical aspects of the procedure have been detailed in many publications,[57 62-66] and were summarized in a very recent review by Rothman.[69]

Coil, Disk, or Surgery?

Where the requisite resources are available, the child who needs to have his PDA closed can now be offered one of three effective treatment options: coil, disk (Rashkind device), or surgery. In general, coils are most suited for small ducts (narrowest diameter≤ 4mm) and small children (weight<6kg), and Rashkind device for small to medium-sized ducts (< 8mm) and bigger children. Large ducts (> 8mm) may be occluded by implanting two Rashkind devices or multiple coils, but multiple implantation tends to increase the risk of device embolization and obstruction of the left pulmonary artery. Surgery is probably the best treatment option for such large ducts, as well as for symptomatic young infants.. Surgical PDA closure via a thoracotomy now entails nil mortality and negligible morbidity in most centres;[58 67] and the application of muscle-sparing techniques[70] has increased its attractiveness. In addition the successful closure of PDA in recent years using video-assisted thoracostomy techniques[70-73] has further enhanced the competitiveness of, and rekindled interest in surgical closure.

In the final analysis, though, the selection of any of these treatment modalities will depend on such variables as prevailing expertise in the centre, age and weight of the patient, duct size, presence or absence of other significant cardiovascular defects, as well as cosmetics and cost considerations. In Europe and the US, surgery is currently the most expensive of the three options, and coil implantation the most cost-effective.[66 - 68] But the economics are bound to be different in countries where physician

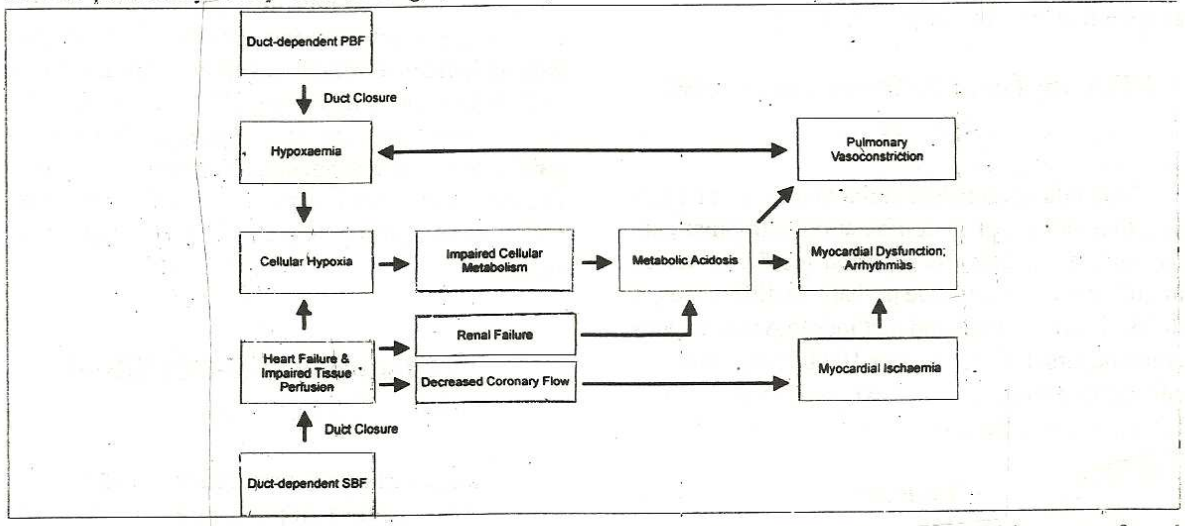

Fig. 3 *Consequences of inappropriate duct closure in patients with duct dependent circulations. (PBF: pulmonary blood flow; SBF: Systemic blood flow)*

remuneration is low and cost of imported items is high. In such countries it may still be cheaper to open (the chest) and close (the duct).

Essential PDA

In the clinical scenarios considered thus far a PDA is a disadvantage. However, there are babies in whom either the pulmonary or the systemic circulation is dependent on patency of the arterial duct (Table IV). In such situations a PDA is essential for immediate and short-term survival. Similarly, in babies with transposition of the great anteries and intact intracardiac septa (atrial, ventricular) a PDA is the main life-line. Yet, even in such babies the arterial duct may close at a variable time after birth, thereby precipitating potentially fatal haemodynamic and biochemical disturbances (Fig 3).

Table IV
'Essential' Ductus Arteriosus

Duct - dependent pulmonary circulation	Critical pulmonary valve stenosis Severe tetralogy of Fallot Pulmonary atresia Tricuspid atresia with intact ventricular septum Hypoplastic right heart.
Duct - dependent systemic circulation	Critical aortic stenosis Severe coarctation of aorta
Interrupted aortic arch	Hypoplastic left heart
Transposition of great arteries with intact atrial/ventricular septum	

Maintaining Ductal Patency with PGE

Infusion of PGE_1 maintains ductal patency in about 70-80 percent of neonates treated with the drug, and it has become a vital ingredient of the pre-operative management of neonates with a duct-dependent circulation. However, certain practical points need be kept in mind. First, there is an inverse relationship between the infant's postnatal age and the ability of PGE_1 to keep the duct patent; it works best when started within 72 hours of birth. Second, it is more effective in maintaining ductal patency than in re-opening a closed duct. And third, it is more effective in hypoxaemic infants (P_aO_2 <30mm Hg). PGE_2 is equally effective, cheaper, and is generally more widely available because of its use in obstetric practice. Initial doses of PGE_1 vary considerably (0.05-0.20 ug/kg/min), depending on institutional preferences. Some centres, like ours, start with a high dose and then gradually scale down to the smallest dose that maintains ductal patency. Some others start with a low dose and gradually increase it until the desired objectives are obtained. High doses alleviate hypoxaemia/acidaemia faster, but they are also associated with a higher incidence of apnoea and hence the need to provide mechanical ventilation. In most patients a maintenance dose of 0.01-0.02 ug/kg/min will achieve the desired effects.

Adverse effects are rather common with PGE_1 infusion and, as indicated above, they are partly dose-related. Apnoea, fever, skin flushing and tachycardia occur in up to 20 percent of the patients. Bradycardia can also occur, as can hypotension. Other adverse effects include diarrhoea, jitteriness, seizure-like movements, and cortical hyperostosis of long bones. There are also reports which suggest that after prolonged prostaglandin therapy the ductal tissue may become less contractile and more friable, raising the risk of haemorrhage should surgical ligation of the duct become necessary later.[74]

But the major constraint to the use of PGE_1 (and PGE_2) is its short half-life (<1 minute). Thus, to maintain a therapeutic plasma concentration the drug is usually given as a continuous infusion. That virtually limits its use to short-term applications aimed at alleviating or averting severe hypoxaemia or metabolic acidosis while preparations are made for surgery. On a few occasions we had to give PGE_2 orally, in a dose of 25-50 pg/kg given 2 hourly. But the difficulties and inconvenience of such around-the-clock administration are considerable; and the absorption is unpredictable.

Achieving Prolonged Ductal Patency

Finally, we wish to comment on attempts at maintaining prolonged ductal patency in unoperated babies with a duct-dependent circulation. Quite a few interventional modalities have been tried. They include infiltrating the duct wall with formalin, thermal treatment, balloon dilation and, lately, stent insertion. Attempts at fixing the duct wall with formalin [75] were largely unsuccessful, as were attempts at thermal fixation using laser or radiofrequency energy.[76] Balloon dilation has been tried both in experimental animals and human newborns, [77 78] but the need to repeat the procedure, and consequently repeat cardiac catheterization, obviously limits its

use in clinical practice. More recently, and drawing from experience with the use of metal stents to dilate stenosed vessels, [79] attempts have been made to keep ducts patent by inserting stents. [80] This form of intervention is still in its infancy and cannot be described as tested. The technical difficulties are formidable, but these will probably be overcome with time, with improvement in stent design, operational techniques, and increase in operator expertise. Meanwhile the arterial duct remains a medical paradox: so small structurally and yet so immense in terms of its health implications especially in neonates and young infants. It also remains the subject of what would probably appear to a casual observer as an inconsistency in clinical practice: clinicians are often either busy closing it when it is patent, or striving to open it when it is closed.

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