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CONTEMPORARY REVIEW

Patent Ductus Arteriosus: A Contemporary Perspective for the Pediatric and Adult Cardiac Care Provider

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ABSTRACT: The burden of patent ductus arteriosus (PDA) continues to be significant. In view of marked differences in preterm infants versus more mature, term counterparts (viewed on a continuum with adolescent and adult patients), mechanisms regulating ductal patency, genetic contributions, clinical consequences, and diagnostic and treatment thresholds are discussed separately, when appropriate. Among both preterm infants and older children and adults, a range of hemodynamic profiles highlighting the markedly variable consequences of the PDA are provided. In most contemporary settings, transcatheter closure is preferable over surgical ligation, but data on longer-term outcomes, particularly among preterm infants, are lacking. The present review provides recommendations to identify gaps in PDA diagnosis, management, and treatment on which subsequent research can be developed. Ultimately, the combination of refined diagnostic thresholds and expanded treatment options provides the best opportunities to address the burden of PDA. Although fundamental gaps remain unanswered, the present review provides pediatric and adult cardiac care providers with a contemporary framework in PDA care to support the practice of evidence-based medicine.

Key Words: patent ductus arteriosus ■ pediatric cardiology ■ treatment

The ductus arteriosus (DA) is a vascular structure that bridges the 2 major arteries leading from the heart, connecting the proximal descending aorta to the pulmonary artery near the origin of the left branch pulmonary artery. The DA is an essential component of fetal circulation, diverting cardiac output away from the lungs toward the placenta to support systemic oxygenation. At birth, the placental circulation is clamped and removed, resistance in the pulmonary vascular bed decreases, and the lungs become the source of oxygenation and gas exchange; thus, the DA is no longer necessary. In normal term infants, the DA closes in >90% by 48 hours and in 100% by 96 hours of age.[1] In preterm infants, structural and physiological immaturity of the ductus is associated with later closure of the DA and increasing the probability that the DA will remain patent at the equivalent of term gestation.[2,3] For example, among infants born at <26 weeks' gestation, the median age at spontaneous DA closure is 66 days, and at term equivalent age the DA remains patent in >25%,[2] referred to as a *patent DA* (PDA). In a few individuals, a PDA will remain open into later childhood or adult life.

The clinical consequences of a PDA are dependent on its size and the cardiopulmonary status of the patient. Although fundamental questions on best treatment practices for the PDA remain unanswered, the present review is intended to provide pediatric and adult cardiac care providers with a contemporary framework to support the practice of evidence-based

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Nonstandard Abbreviations and Acronyms

DA	ductus arteriosus
HSPDA	hemodynamically significant patent ductus arteriosus
IE	infective endocarditis
PAH	pulmonary arterial hypertension
RD	risk difference

medicine. In view of marked differences in preterm infants and more mature, term counterparts (viewed on a continuum with term infants beyond the first months of life, older children, and adult patients), the mechanisms regulating ductal patency, genetic contributions, clinical consequences, and diagnostic and treatment approaches are discussed separately, when appropriate.

NORMAL EMBRYOLOGY, ANATOMY, AND PHYSIOLOGY

In normal cardiovascular development, the sixth embryonic aortic arches undergo morphological transformations that result in bridges between the main pulmonary artery and the descending aorta distal to the left subclavian artery (Figure 1).[4] The proximal portions of the sixth embryonic arches form the branch pulmonary arteries, whereas the distal left sixth arch forms the DA.[4] This transformation occurs in the first 8 weeks of fetal development in humans. Although an essential fetal structure, the DA is abnormal if it remains patent beyond the neonatal period. The DA may persist in a wide variety of sizes and configurations, with variable relationships to adjacent structures (Figure 2). These anatomic considerations provide insight into pathophysiologic consequences (*discussed below*).

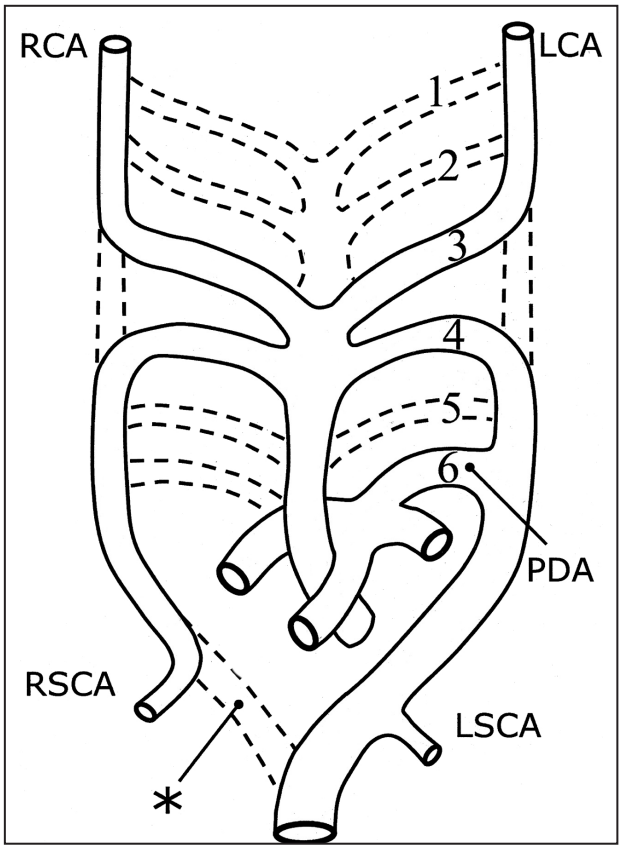


Figure 1. Schematic of embryonic aortic arch system.
The 6 pairs of embryonic aortic arches are shown (left-sided arches are numbered). Broken-lines represent portions that involute in normal development. The distal left sixth embryonic arch normally persists and becomes the PDA, bridging the left pulmonary artery to the proximal descending aorta. The right distal sixth arch normally involutes, as does the eighth segment of the right dorsal aorta (*), which results in a leftward aortic arch. PDA indicates patent ductus arteriosus; LCA, left carotid artery; LSCA, left subclavian artery; RCA, right carotid artery; and RSCA, right subclavian artery. Reproduced from Schneider and Moore [4] with permission. Copyright ©2006, American Heart Association, Inc.

MECHANISMS REGULATING FETAL DUCTAL PATENCY AND CLOSURE

The fetal DA has intrinsic tone, which requires dilating factors to maintain patency in utero (Figure 3A). During early fetal development, endothelially derived nitric oxide (NO) is the primary relaxing agent and acts through cyclic guanosine monophosphate (cGMP)/protein kinase G signaling.[5] As the fetus approaches term gestation, the burden of keeping the DA patent shifts to prostaglandin E_2, originating from the placenta,[6] which interacts with the G-protein–coupled receptor, prostaglandin E_2 receptor 4 (EP_4), to initiate the cyclic adenosine monophosphate (cAMP)/protein kinase A signaling cascade.[7] Irrespective of the initiating signaling molecule, these pathways cooperatively decrease the concentrations of intracellular calcium, thereby preventing DA smooth muscle cell contraction during fetal life.[8,9]

MECHANISMS REGULATING NORMAL POSTNATAL DUCTAL CLOSURE

Postnatally, the DA functionally closes and permanently remodels into the fibrous *ligamentum arteriosum*. Several molecular, structural, hemodynamic, and maternal environmental/infection factors have been described that contribute to postnatal ductal closure.

Molecular Factors

Postnatal DA closure is facilitated by sharp reductions in dilating factors and increases in intracellular calcium levels (Figure 3B). The onset of respiration dramatically

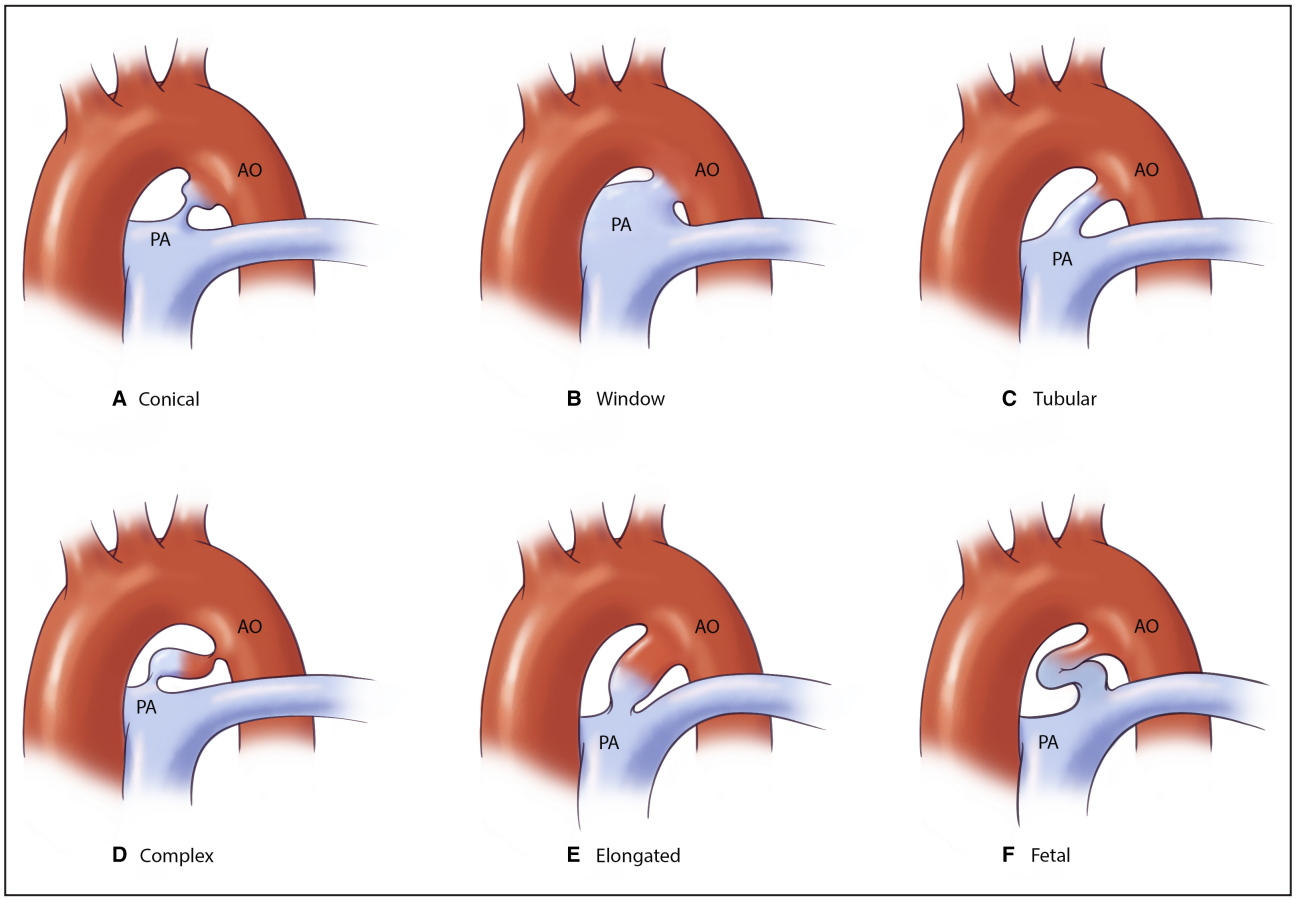


Figure 2. Variations in patent ductus arteriosus (PDA) configuration.
Illustration of multiple configuration of PDAs: type a ("conical") ductus, with defined aortic ampulla and constriction near the pulmonary artery (PA) end; type b ("window") ductus, with short length and constriction at the aortic end (wide PA end); type c ("tubular") ductus, without constrictions at the aortic or pulmonary ends; type d ("saccular") ductus, with constricted aortic and pulmonary ends and a wide center; type e ("elongated") ductus, which is narrow with a constricted pulmonary end; and type f ("fetal") ductus, which is found largely in premature infants and is long, wide, and tortuous. AO indicates aorta.

increases the alveolar PaO_2, which acts as a principal regulator of DA closure. Emerging evidence suggests that immature biochemical oxygen-sensing mechanisms contribute to maintenance of ductal patency in preterm infants.[10]

Structural Factors

Compared with term infants, rudimentary or absent intimal cushions, fewer mature contractile smooth muscle cells, and lack of *vasa vasorum* are structural components that contribute to sustained ductal patency in preterm infants.

Hemodynamic Factors

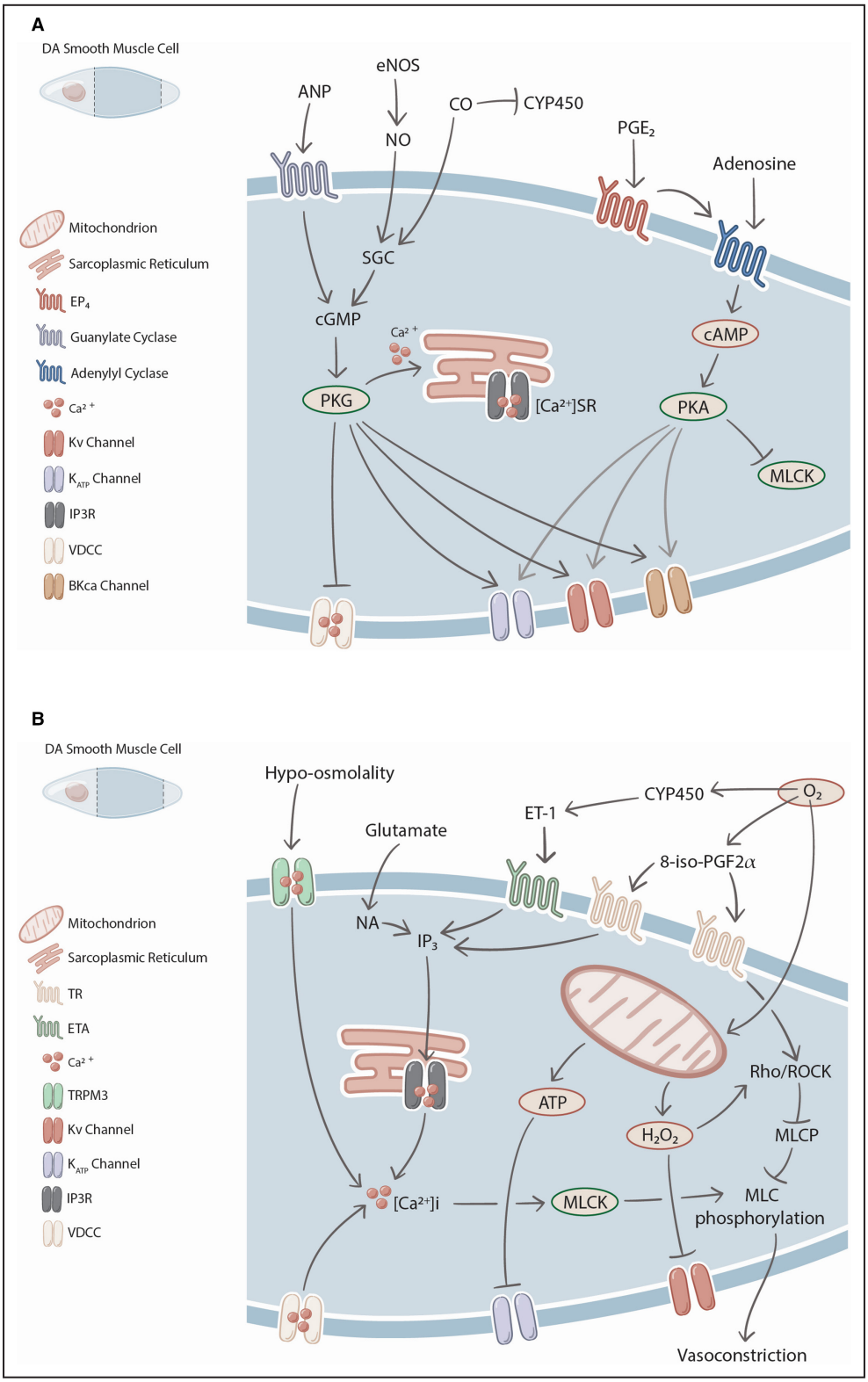
Recent evidence suggests PDA tone may also be regulated by biomechanical factors, particularly among preterm infants. Although data are mixed,[11] some investigators have observed an association between thrombocytopenia and delayed ductal closure in very preterm infants.[12] Interestingly, among thrombocytopenic premature infants, platelet transfusions fail to accelerate PDA closure. These observations have led some health care providers to postulate that platelet function, not platelet number, may be a regulator of preterm PDA status.[13]

Maternal Environmental/Infection Factors

Congenital rubella syndrome may contribute to postnatal ductal patency.[14] Zika virus is emerging as another potential infectious cause of PDA.[15] In addition to infectious origins, prenatal teratogens are associated with increased incidence of PDA. For example, tetrahydrocannabinol concentrations secondary to cannabis use among pregnant women have been associated with a greater incidence of PDAs.[16,17]

GENETIC CONTRIBUTORS

PDA has a complex and multifactorial genetic cause. Evidence suggests that the PDA is likely 2 overlapping



disorders, wherein preterm PDA arises from structural and physiological immaturity, and term PDA arises from genetic alterations.[18] PDA is a common finding in dysmorphic syndromes associated with congenital heart disease, with an estimated 10% of PDA cases associated with chromosomal abnormalities (Table 1). PDA exists in syndromic and nonsyndromic forms; syndromic cases of PDA, more common in term infants, are associated with chromosomal aneuploidy (eg, trisomy 21), chromosomal microdeletion (eg,

Figure 3. Molecular pathways involved in intrauterine ductus arteriosus (DA) relaxation (A) and molecular pathways involved in postnatal DA constriction (B).
A, Endothelial NO synthase (eNOS)–derived NO, CO, and atrial natriuretic peptide (ANP) initiate the cGMP signaling cascade by activating membrane-bound or soluble guanylate cyclase (sGC). cGMP subsequently activates protein kinase G (PKG), which decreases the intracellular calcium concentration by inhibiting voltage-dependent calcium channels (VDCCs) and promoting calcium uptake into the sarcoplasmic reticulum. PKG also activates voltage-gated potassium channel (K_v), ATP-gated potassium channel (K_{ATP}), and large conductance calcium-activated potassium channel (BK_{Ca}), which trigger potassium efflux and membrane hyperpolarization, resulting in VDCC inhibition. In addition, prostaglandin E_2 (PGE_2), working through the prostaglandin E_2 receptor 4 (EP_4), activates adenylyl cyclase. Adenosine also activates adenylyl cyclase, which, in turn, activates the cAMP/protein kinase A (PKA) signaling cascade. PKA activates K_v, K_{ATP}, and BK_{Ca} and inhibits myosin light chain kinase (MLCK), which subsequently reduces phosphorylation of myosin light chains (MLCs), thereby preventing vasoconstriction. **B**, Increased O_2 tension increases the concentration of intracellular calcium via several pathways. First, O_2 stimulates mitochondrial production of ATP and H_2O_2, which inhibit vasodilating K_{ATP} and K_v. H_2O_2 also activates the ras homologous protein (Rho)/rho-associated protein kinase (ROCK) cascade, which promotes constriction by inhibiting MLC phosphatase (MLCP)–mediated MLC dephosphorylation. In addition, O_2 upregulates the production of 8-iso-prostaglandin F2α (8-iso-PGF2α), which signals through thromboxane receptor (TR) to activate Rho/ROCK and inositol trisphosphate (IP_3) signaling cascades. Furthermore, O_2 promotes constriction by cytochrome P450 (CYP450)–mediated binding of endothelin-1 (ET-1) to endothelin receptor A (ET_A), which subsequently activates the IP_3 pathway. Similarly, glutamate activates IP_3 signaling via noradrenaline (NA) production. Once activated, IP_3 then binds to IP_3 receptor (IP_3R) on the sarcoplasmic reticulum, causing movement of calcium into the cytoplasm. Intracellular calcium concentrations are also regulated by transient receptor potential melastatin-3 channel (TRPM3), which becomes activated under hypo-osmotic conditions. Accumulation of intracellular calcium facilitates activation of MLCK, which phosphorylates MLC, allowing for myosin and actin interaction and subsequent muscle contraction. $[Ca^{2+}]i$ indicates concentration of intracellular calcium; and $[Ca^{2+}]SR$, concentration of calcium in the sarcoplasmic reticulum.

22q11.2 deletion), and single-gene defects (eg, *Char*). Among term infants, epidemiologic studies report an increased recurrence risk in siblings of 2% to 4% for PDA.[19] Interestingly, among preterm infants, the incidence of PDA (requiring therapy) in monozygotic twins is higher than in dizygotic twins.[20] However, most cases of nonsyndromic PDA are attributable to multifactorial inheritance, wherein underlying genetic predispositions and environmental triggers at vulnerable times are likely contributory.[21,22] Lack of available human DA tissues precludes studies on the mechanisms of DA function, but mouse models have been developed that provide insight on pathways in DA regulation.[23]

EPIDEMIOLOGY

PDA represents the most common cardiovascular condition of preterm infants,[24] and the incidence of PDA is inversely related to gestational age at birth.[3] Recent evidence suggests that >50% of infants born at <26 weeks of gestation have an open ductus beyond 2 months postnatal.[3] Data among term infants suggest that PDAs are observed in ≈1 in 2000 births, accounting for 5% to 10% of all congenital heart disease.[24] Longitudinal cohort studies suggest that the incidence of "silent" PDA, those cases discovered by cardiac imaging in the absence of clinical manifestations, approach 1 in 20 births.[25]

PATHOPHYSIOLOGY

The hemodynamic consequences of PDA are markedly variable. In infants whose pulmonary vascular resistance decreases at birth and PDA remains patent, a continuous left-to-right shunt develops. Shunt flow, according to the Poiseuille Law, is proportional to the pressure gradient between the aorta and pulmonary artery and inversely related to the resistance to flow. The impact of changes in pulmonary and systemic resistances is greater among patients with a larger ductus and less resistance to flow than in those with a smaller ductus and greater resistance to flow. Modifiable determinants of pulmonary vascular resistance (eg, PaO_2 and pH) also modulate transductal flow.[26]

A left-to-right ductal shunt results in excessive pulmonary blood flow. The magnitude of the PDA shunt and its associated cardiopulmonary interactions dictate the pathophysiologic features of this lesion in clinical care. Specific features of cardiovascular mechanics associated with prematurity predispose neonates, in particular, to greater PDA-associated cardiorespiratory compromise. A left-to-right ductal shunt results in increased pulmonary blood flow and left heart dilatation, culminating in higher left ventricular end-diastolic pressures, upstream pulmonary venous pressure, and pulmonary congestion, a pathophysiology exacerbated among preterm neonates because of greater elastance of immature ventricles.[27] Unlike in adults, in whom pulmonary vascular distention and capillary bed recruitment assist in managing increased pulmonary blood flow without associated changes in capillary hydrostatic pressure, the pulmonary vascular bed in neonates is already nearly fully recruited and poorly compliant.[28] PDA-associated increases in pulmonary blood flow therefore result in increased pulmonary arterial pressure and a shift in the pulmonary pressure head to downstream capillary filtration sites, leading to pulmonary interstitial edema, reduced lung compliance, and impaired oxygenation.[29,30] Additional increases in left atrial and volume and pressure overload associated with larger ductal shunts may further worsen pulmonary venous pressure and culminate in

Table 1. PDA Associated With Genetic Syndromes (Selected)

Syndrome	Gene(s)	Location	Additional cardiac lesions
Trisomy 21[1]	3 Copies of chromosome 21		Atrioventricular septal defect; atrial septal defects; ventricular septal defect; tetralogy of Fallot
Trisomy 18[2]	3 Copies of chromosome 18		Atrial and ventricular septal defects; nonspecific cardiovascular morphologic abnormalities
Trisomy 13[3]	3 Copies of chromosome 13		
22q11.2 deletion[4]	*TBX1*, *CRKL*	22q11.2	Interrupted aortic arch (type B); tetralogy of Fallot; truncus arteriosus; ventricular septal defects; aortic arch abnormalities
Wolf-Hirschhorn[5]	*NSD2*, *WHSC1*, *LETM1*, *CTBP1*, *CPLX1*, *FGFRL1*	4p Deletion	Atrial and ventricular septal defects; nonspecific cardiovascular morphologic abnormalities
Char[6]	*TFAP2B*	6p12.3	Ventricular septal defect
Cantu[7]	*ABCC9*, *KCNJ8*	12p12.1	Bicuspid aortic valve; hypertrophic cardiomyopathy
Carpenter[8]	*RAB23*, *MEGF8*	6p12.1-p11.2, 19q13.2	Nonspecific cardiovascular morphologic abnormalities
CHARGE[9]	*SEMA3E*, *CHD7*	7q21.11, 8q12.2	Tetralogy of Fallot; ventricular septal defect; atrioventricular septal defect; aortic arch abnormalities
Holt-Oram[10]	*TBX5*	12q24.1	Atrial and ventricular septal defects; hypoplastic left heart syndrome
Loeys-Dietz (forms 1–5)[11]	*TGFBR1* (1), *TGFBR2* (2), *SMAD3* (3), *TGFB2 (4), TGFB3 (5)*	9q22.33 (1), 3p24.1 (2), 15q22.33 (3), 1q41 (4), 14q24.3 (5)	Aortic aneurysm; aortic dissection; arterial dissection
Mowat-Wilson[12]	*SMAD1P1*, *ZEB2*	2q22.3	Tetralogy of Fallot; ventricular septal defect
Noonan[13]	*PTPN11* (1), *LZTR1* (2, 10), *KRAS* (3), *SOS1* (4), *RAF1* (5), *NRAS* (6), *BRAF* (7), *RIT1* (8), *SOS2* (9), *MRAS* (11), *RRAS2* (12), *MAPK1* (13)	12q24.13 (1), 22q11.21 (2, 10), 12p12.1 (3), 2p22.1 (4), 3p25.2 (5), 1p13.2 (6), 7q34 (7), 1q22 (8), 14q21.3 (9), 3q22.3 (11), 11p15.2 (12), 22q11.22	Dysplastic/stenotic pulmonary valve; pulmonary artery stenosis, atrial septal defect; cardiomyopathy
Periventricular heterotopia (X linked)[14]	*FLNA*	Xq28	Bicuspid aortic valve
Rubinstein-Taybi (forms 1 and 2)[15]	*CREBBP* (1), *EP300* (2)	16p13.3 (1); 22q13.2 (2)	Nonspecific cardiovascular morphologic abnormalities

ABCC9 indicates ATP-binding cassette, subfamily C member 9 (aka, sulfonylurea receptor 2) encoding gene; *BRAF*, B-Raf encoding gene; CHARGE, coloboma of the eye, heart defects, atresia of the choanae, retardation of growth and/or development, genital hypoplasia, and ear abnormalities (eg, deafness); *CHD7*, chromodomain–helicase–DNA-binding protein 7 (aka, ATP-dependent helicase CHD7) encoding gene; *CPLX1*, complexin-1 encoding gene; *CREBBP*, CREB-binding protein encoding gene; *CRKL*, Crk-like protein encoding gene; *CTBP1*, C-terminal–binding protein 1 (aka, CtBP1) encoding gene; *EP300*, histone acetyltransferase p300 (aka, p300 HAT, adenovirus early region 1A–associated protein p300) encoding gene; *FGFRL1*, fibroblast growth factor receptor-like 1 encoding gene; *FLNA*, filamin A, α encoding gene; *KCNJ8*, potassium inwardly rectifying channel, subfamily J, member 8; *KRAS*, K-Ras encoding gene; *LETM1*, leucine zipper-EF-hand containing transmembrane protein 1 encoding gene; *LZTR1*, leucine–zipper-like transcriptional regulator 1 encoding gene; *MAPK1*, mitogen-activated protein kinase 1 (aka, MAPK1, p42MAPK, ERK2) encoding gene; *MEGF8*, multiple epidermal growth factor-like domains 8; *MRAS*, Ras-related protein M-Ras (aka, muscle RAS oncogene homolog, R-Ras3) encoding gene; *NRAS*, neuroblastoma RAS viral oncogene homolog encoding gene; *NSD2*, nuclear receptor binding SET domain protein 2 encoding gene; PDA, patent ductus arteriosus; *PTPN11*, tyrosine-protein phosphatase nonreceptor type 11 (aka, protein-tyrosine phosphatase 1D, Src homology region 2 domain-containing phosphatase-2, protein-tyrosine phosphatase 2C) encoding gene; *RAB23*, Ras-related protein Rab-23 encoding gene; *RAF1*, RAF proto-oncogene serine/threonine-protein kinase (aka, proto-oncogene c-RAF, c-Raf, Raf-1) encoding gene; *RIT1*, GTP-binding protein Rit1 encoding gene; *RRAS2*, Ras-related protein R-Ras2 encoding gene; *SEMA3E*, semaphorin 3E encoding gene; *SMAD*, mothers against decapentaplegic homolog (aka, SMAD family member) encoding genes; *SOS*, son of sevenless homolog encoding genes; *TBX*, T-box transcription factor encoding genes; *TFAP2B*, transcription factor AP-2 β (aka, AP2-β) encoding gene; *TGFB*, transforming growth factor encoding genes; *TGFBR*, transforming growth factor-β receptor encoding genes; *WHSC1*, probable histone-lysine N-methyltransferase nuclear receptor binding SET domain protein 2 encoding gene; and *ZEB2*, zinc finger E-box–binding homeobox 2 encoding gene.

alveolar edema and further deterioration in respiratory mechanics and function. Preterm neonates with respiratory distress syndrome are more sensitive to increases in microvascular perfusion pressure and demonstrate exaggerated increases in interstitial and alveolar lung fluid accumulation, resulting in secondary surfactant dysfunction.[31,32] Diastolic flow reversal in the descending aorta attributable to ductal shunting to the pulmonary artery can occur and is associated with reduced abdominal organ blood flow.[33] Absent or reverse end-diastolic flow may occur in the celiac, superior mesenteric, and middle cerebral arteries, although only middle cerebral artery flow aberrations have been associated with neonatal morbidity.[34]

DEFINING THE HEMODYNAMICALLY SIGNIFICANT PDA

Among preterm infants, health care providers are often unable to clearly discern if the PDA is causal of, or merely associated with, adverse outcomes. Thus, contemporary definitions of a hemodynamically significant PDA (HSPDA) are not simply echocardiographic-derived markers of atrial or ventricular chamber enlargement, but rather various clinical and echocardiographic parameters aimed at identifying preterm infants in whom ductal shunt volumes are estimated to be primary pathological contributors to physiologic instability (Table 2).[35] In contrast, among term infants, older children, and adults, general consensus is that echocardiographic evidence of left atrial or left ventricular enlargement attributable to the ductus constitutes an HSPDA (Table 3).[36]

CLINICAL CONSEQUENCES IN PRETERM INFANTS

In the setting of unique developmental vulnerabilities, PDA among preterm infants is associated with several adverse outcomes, including death, that are not typically observed in older, more mature patients.[37-39] Despite decades of investigation, clarity on the relative contributions to short- and longer-term sequelae of a persistent ductus, including treatments used to close the ductus, have not been resolved.[40-43]

Respiratory

The potential pathological effects of left-to-right ductal shunting include an association with increased respiratory support, mechanical ventilation, and chronic lung disease (notably, bronchopulmonary dysplasia [BPD]). PDA exposure has been associated with pulmonary hemorrhage, with estimates suggesting an incidence of 3% to 23%, depending on the gestational age, ductal size, and associated PDA treatments.[44,45] However, a recent meta-analysis of early treatment (defined as treatment initiated by postnatal day 7) compared with expectant management for an HSPDA among infants at <37 weeks of gestation observed no differences between the 2 groups in rates of pulmonary hemorrhage (relative risk [RR], 0.58 [95% CI, 0.30–1.11]; 5 studies; N=332).[46]

Emerging data suggest that duration of exposure, rather than simply the presence or absence of a ductal shunt, may contribute more to observed outcomes. Among infants born at <28 weeks of gestation, the risks of the composite outcome of BPD or death were greater after 7 to 13 days of exposure to moderate-to-large PDAs than in infants who closed their ductus in their first postnatal week (odds ratio [OR], 2.12 [95% CI, 1.04–4.32]).[47] For the outcome of increased BPD alone, PDA exposure ≥14 days was associated with increased BPD (OR, 4.08 [95% CI,

Table 2. Comprehensive Grading Schema for HSPDA Among Preterm Infants

Clinical	Echocardiography	
Asymptomatic	No PDA	No evidence of ductal flow on 2D or Doppler interrogation
Mild symptoms • MAP <8 mmHg (on respiratory support of NCPAP or mechanical ventilation) • Feeding intolerance	Small, non-HSPDA	• Transductal diameter <1.5 mm • Restrictive continuous transductal flow (DA V_{max} >2.0 m/s) • No signs of left heart volume loading (eg, mitral regurgitant jet >2.0 m/s or LA:Ao >1.5:1) • No signs of left heart pressure loading (eg, E/A ratio <1.0 or IVRT <50)
Moderate symptoms • MAP 9–12 mmHg (ventilation requirement) • Evidence of abdominal distention and/or persistent emesis	Moderate, HSPDA	• Transductal diameter 1.5–3.0 mm • Unrestrictive pulsatile transductal flow (DA V_{max} <2.0 m/s) • Mild-moderate left heart volume loading (eg, LA:Ao 1.5–2.1) • Mild-moderate left heart pressure loading (eg, E/A ratio ≥1.0 or IVRT 50–60) • Decreased or absent diastolic flow in the superior mesenteric, middle cerebral, and/or renal arteries
Severe symptoms • MAP >12 mmHg (high ventilation requirements or HFOV) • Marked abdominal distention and/or erythema	Large HSPDA	• Transductal diameter >3.0 mm • Unrestrictive pulsatile transductal flow • Severe left heart volume loading (eg, LA:Ao >2.1, mitral regurgitant jet >2.0 m/s) • Severe left heart pressure loading (eg, E/A ratio >1.5 or IVRT >60) • Reversal of end-diastolic flow in superior mesenteric, middle cerebral, and/or renal arteries

2D indicates 2 dimensional; DA V_{max}, transductal maximal fluid velocity; E/A (ratio), peak velocity blood flow from the left ventricular relaxation in early diastole (E-wave) to peak velocity flow in late diastole caused by atrial contraction (A-wave); HFOV, high-frequency oscillatory ventilation; HSPDA, hemodynamically significant PDA; IVRT, isovolumic relaxation time; LA:Ao, left atrial diameter to aortic root diameter ratio; MAP, mean airway pressure; NCPAP, nasal continuous positive airway pressure; and PDA, patent ductus arteriosus.

Table 3. Comprehensive Grading Schema for HSPDA Among Older Children and Adults

PDA size	Physiological symptoms
Silent or trivial	• "Silent" (inaudible) PDAs are asymptomatic* • No hemodynamic or anatomic sequelae • Normal exercise capacity • Normal renal, hepatic, and pulmonary function
Small	• Small left-to-right shunt, not HSPDA • No restrictions of exercise capacity
Mild/moderate	• Mild-moderate left-to-right or bidirectional shunt, HSPDA • Mild-moderate hemodynamic or anatomic sequelae (mild/moderate LAE and/or LVE, mild-moderate left ventricular dysfunction) • Mild or moderate hypoxemia/cyanosis • Mild or moderate PH • Potential for mild renal, hepatic, and pulmonary dysfunction
Large	• Large left-to-right, bidirectional, or right-to-left shunt • Severe hemodynamic or anatomic sequelae (severe LAE and/or LVE, moderate to severe left ventricular dysfunction) • Moderate or severe hypoxemia/cyanosis • Severe PH • Risk of Eisenmenger syndrome with PH and right-to-left shunting

HSPDA indicates hemodynamically significant PDA, defined as left atrial/ventricular enlargement and/or sustained pulmonary blood flow to systemic blood flow ratio (Qp/Qs) ≥1.5; LAE, left atrial enlargement; LVE, left ventricular enlargement; PDA, patent ductus arteriosus; and PH, pulmonary hypertension.
*Not all asymptomatic PDAs are silent.

2.32–7.22]) compared with infants whose ductus closed in the first postnatal week.[47] However, duration of ductal patency may be a biomarker of increased pulmonary or systemic illness, rather than causal, for development or progression of observed outcomes (BPD or death).[48]

Neurologic

Independent of the presence of PDA, prematurity is associated with intraventricular hemorrhage, periventricular leukomalacia, and compromised school-aged performance.[49-51] Most intraventricular hemorrhage occurs in the first postnatal week, coincident with decrease of pulmonary vascular resistance and emergence of a left-to-right PDA shunt in some preterm infants. Prophylactic indomethacin is provided in the first postnatal days and often before a diagnosis of a PDA. Compared with placebo, administration of prophylactic indomethacin after preterm birth reduces the incidence of symptomatic PDA (risk difference [RD], −0.24 [95% CI, −0.28 to −0.21]; RR, 0.44 [95% CI, 0.38–0.50]) and surgical PDA ligation (RD, −0.05 [95% CI, −0.08 to −0.03]; RR, 0.51 [95% CI, 0.37–0.71]).[52] In addition, prophylactic indomethacin reduces the incidence of severe periventricular and intraventricular hemorrhage more effectively than does placebo (RD, −0.05 [95% CI, −0.07 to −0.02]; RR, 0.66 [95% CI, 0.53–0.82])[52]; however, these early neurological benefits may be unrelated to closure of the ductus.[53] However, prophylactic indomethacin is not associated with reduced mortality or improved neurodevelopment at 18 months of age (RD, 0.01 [95% CI, −0.04 to 0.06]; RR, 1.02 [95% CI, 0.90–1.15]).[52,54] In view of these observations, rates of indomethacin use in the first 24 hours postnatal is ≈7% across US hospitals.[55] In the absence of clear evidence, controversies persist on the benefits (or lack thereof) and optimal use of indomethacin prophylaxis for preterm infants.[42,56,57,58,59,60] Some investigators have called for the abandonment of *routine* prophylactic indomethacin to all preterm infants,[42] whereas others have suggested a nuanced approach that takes into consideration an individual center's baseline risk of intraventricular hemorrhage.[56] Surgical ductal ligation has been associated with neurodevelopmental impairment in early childhood,[61] but failure to account for confounding effects because of patient illness limits data interpretation.[62]

Intestinal Injury

Diastolic flow reversal in the abdominal aorta and systemic arteries (renal, celiac, and superior mesenteric) is common among preterm infants with PDA.[63] Although data are mixed, contemporary randomized clinical trials have not observed differences in rates of necrotizing enterocolitis following ductal closure compared with nonclosure.[64,65] More important, simultaneous administration of early systemic hydrocortisone and indomethacin for intraventricular hemorrhage prophylaxis increases the risk of spontaneous intestinal perforation and is contraindicated.[66]

CLINICAL CONSEQUENCES AMONG OLDER PATIENTS (TERM INFANT THROUGH ADULTHOOD)

Pulmonary Arterial Hypertension and Eisenmenger Syndrome

Although the precise pathophysiological mechanisms are not completely understood, long-standing left-to-right shunting exposes the pulmonary arterial system

to higher pressures and greater blood flows. Over time, this leads to progressive morphological changes in the pulmonary vasculature, including arteriolar medial hypertrophy, intimal proliferation and fibrosis, and eventual obliteration of pulmonary arterioles and capillaries, characterized by increased pulmonary vascular resistance with development of pulmonary arterial hypertension (PAH).[67] When pulmonary vascular resistance approaches and exceeds systemic vascular resistance, ductal shunting reverses and becomes right to left, classically described as Eisenmenger syndrome. Clubbing of toenails and spared (or mild) clubbing in the fingers is pathognomonic for Eisenmenger syndrome in the setting of a PDA.[68] In this setting, patients may develop right ventricular systolic failure, the most common cause of death among patients with Eisenmenger syndrome.[69]

Infective Endocarditis

Historical estimates suggest an incidence of infective endocarditis (IE) of ≈1% among patients with a PDA.[70,71] Sadiq et al observed that, among 2908 children aged <16 years admitted to a single pediatric cardiology center over a 6-year time frame, 96 (3.3%) fulfilled diagnostic criteria for IE; PDA was the cardiac lesion in 14 children with IE (14.6%).[72] Alternatively, of nearly 3 million deaths in Sweden (1960–1993), Thilen and Astrom-Olsson reported 2 cases of IE as a complication of PDA.[73] Historically, risk of IE was commonly cited as an indication for ductal closure beyond infancy[74]; however, recent guidelines from the American Heart Association no longer support use of antibiotic prophylaxis (outside the first 6 months following definitive ductal closure) among patients with PDA to prevent IE.[75]

DIAGNOSTIC ASSESSMENT OF THE PDA

Diagnostic assessments vary according to the hemodynamic significance of the ductus.

Unique Considerations in the Diagnosis of PDA Among Preterm Infants

In contemporary medical settings, transthoracic echocardiography is the preferred noninvasive modality to assess ductal significance in preterm infants (Table 4). Interrogation of ductal flow using 2-dimensional and color flow Doppler can determine ductal size and shunt direction (Figure 4A), as well as shunt volume (Figure 4B).[76,77]

ASCERTAINMENT OF HEMODYNAMIC SIGNIFICANCE

To target infants with the highest probability of deriving benefits following ductal treatment (*described below*), health care providers have attempted to define subgroups of preterm infants, based on clinical or sonographic criteria, with HSPDAs. However, lack of a standardized or validated definition of HSPDA has led to medical uncertainty about which infants with a diagnosis of PDA should receive treatment. This may relate, at least in part, to the lack of consistency in the definitions of HSPDA used to date in published randomized clinical trials. A systematic review of the definition of HSPDA used in published trials highlighted marked variance with the use of arbitrary echocardiographic thresholds, which were not validated against relevant clinical outcomes.[78]

Historical Determinants of Ductal Significance: An Oversimplification

The measurable physiological impacts of PDAs in preterm infants are related to shunt volumes, intrinsic cardiopulmonary adaptive mechanisms, and duration of exposure; therefore, arbitrary subjective or single-point estimates of PDA sizes are unlikely to define hemodynamic significance accurately. However, many trials relied solely on PDA diameters to adjudicate hemodynamic significance, which represents an evaluative and physiological oversimplification. This is attributable to the high likelihood of measurement error related to geometric assumptions (circular in cross-section) or operator-dependent factors in echocardiographic-based measurements of ductal size.[45,79,80,81] A PDA diameter of ≥1.5 mm is often used to define hemodynamic significance, but the data to support this practice are not evidence based.[82] Moreover, several studies have demonstrated the poor reliability of individual imaging measures and the weak relationship of ductal diameter to echocardiographic indices of pulmonary or systemic blood flow.[83-85] Although left atrial/aortic ratios are also commonly used to determine ductal significance, the metric is prone to significant operator-dependent error and may be falsely normal in the context of a large interatrial left-to-right shunt decompressing the left atrium.[84] In a comparative evaluation using magnetic resonance imaging, holodiastolic flow reversal in the postductal arch was the most accurate and reliable echocardiographic estimate of PDA shunt volume.[86]

A Comprehensive Approach to Defining HSPDAs

Rather than a unidimensional approach (eg, ductal diameter), contemporary definitions of HSPDA integrate a comprehensive echocardiographic assessment (Table 5). The evaluative goal is to identify preterm infants in whom ductal shunt volumes are estimated to be primary pathological contributors

Table 4. Diagnostic Assessments

Preterm infant*	Diagnostic modalities*	Term infant/adult†
Continuous, "machinery" murmur diastolic rumble; prominent LV impulse; tachycardia, tachypnea, abdominal distention; prediastolic and postdiastolic hypotension; postductal systolic hypotension	Physical examination‡	Differential cyanosis (clubbing of the toes, not the fingers)§; high-frequency, diastolic decrescendo murmur; holosystolic; peripheral edema
Cardiomegaly with LA and LV enlargement, pulmonary artery dilation, and increased pulmonary vascular markings	Chest radiograph‡	Calcifications on the ductus; clear lung fields; dilated pulmonary arteries without significant cardiomegaly
Findings are highly variable and lack sensitivity/specificity	ECG‡	Ventricular hypertrophy, and ST-segment or T-wave depression
Diastolic flow reversal in postductal arch; LA dilation (LA:Ao); ductal diameter indexed to LPA diameter; PDA V_{max} (CW); ductal left-to-right diastolic flow; LVO; pulmonary vein diastolic (PVD) V_{max}; IVRT	Echocardiogram	Right-to-left ductal shunting in systole can be difficult to separate from adjacent LPA; transesophageal echocardiogram may be useful
…	CT	Faster imaging and breath holding to identify thromboembolic disease; cardiac gated CT can identify calcifications; may reveal PDA not seen on echocardiogram
…	Magnetic resonance imaging	Gold standard for noninvasive flow, function, quantification, and anatomic evaluation without ionizing radiation for adults; may reveal PDA not seen on echocardiogram
Safety and feasibility of device closure demonstrated in infants weighing 700 g; venous-only approach increasingly adopted	Cardiac catheterization	Test occlusion to assess tolerance to closure (change in PAP, systemic BP); pulmonary vascular reactivity testing can identify response to vasodilators
Lower values (cerebral, renal) may be markers of ductal significance; may be beneficial for longitudinal assessment	Near-infrared spectroscopy	Unclear diagnostic value in PDA assessment, but used in other cardiovascular conditions and perioperative settings
Unclear diagnostic value; insufficient evidence to support universal monitoring	Biomarkers	Unclear diagnostic value in PDA assessment, but used in other cardiovascular conditions and perioperative settings

… indicates gold standard for diagnosing PDA in preterm infants is transthoracic echocardiography; BP, blood pressure; CT, computed tomography; CW, continuous wave; IVRT, isovolumetric relaxation time; LA, left atrial; LA:Ao, left atrial diameter to aortic root diameter ratio; LPA, left pulmonary artery; LV, left ventricular; LVO, LV output; PAP, pulmonary arterial pressure; PDA, patent ductus arteriosus; and V_{max}, maximum velocity.

*Findings described for preterm infants with hemodynamically significant PDA.

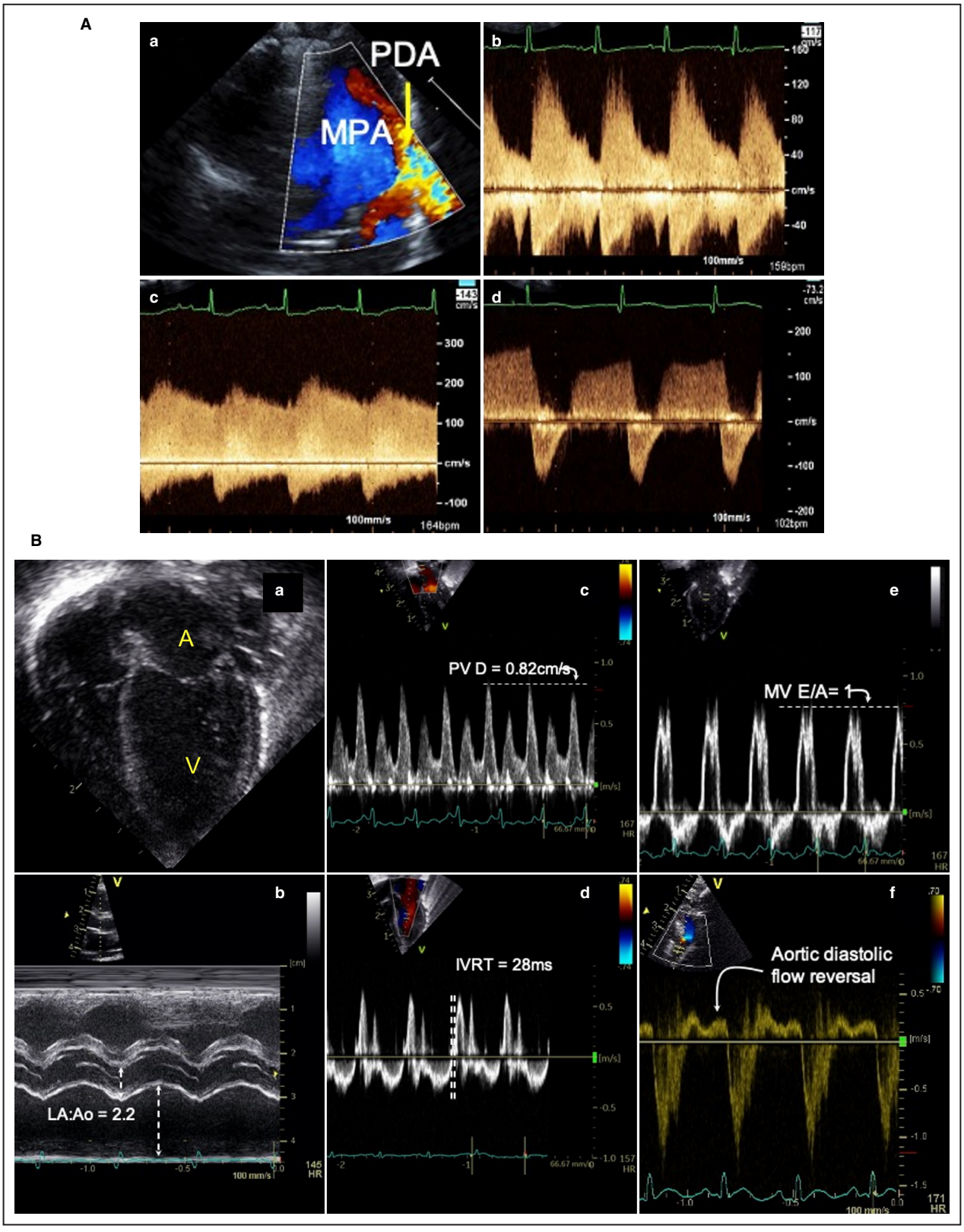
†Findings described for adult patients with PDA and associated pulmonary arterial hypertension.

‡Findings are highly variable and lack sensitivity/specificity.

§Recommend measurement of oxygen saturation in upper and lower extremities in adults to assess for the presence of right-to-left shunting (differential cyanosis).

to current physiologic instability, considering other concurrent pathologies (eg, lung immaturity and/or ventilator-associated injury). The process of adjudication of hemodynamic significance should incorporate clinical and echocardiographic parameters in a manner that helps health care providers recognize a hierarchal model of shunt volume (small or large), rather than mere ductal patency. The McNamara PDA staging system proposed adjudicating hemodynamic significance based on a composite of clinical and echocardiographic criteria (see Table 2, above).[35] Prolonged exposures to higher-volume shunts are associated with greater risks of prolonged oxygen dependency[87] or the composite outcome of death or BPD.[88] The PDA scoring system recently proposed by El-Khuffash et al, derived from a prospective evaluation of an untreated cohort, combined gestational age with 4

Figure 4. Ductal size and shunt direction evaluation (A) and ductal shunt volume evaluation (B).
A, Echocardiographic verification of patent ductus arteriosus (PDA) presence, with PDA size and shunt direction assessment. a, Color flow of PDA. b, Pulsatile pattern with left-to-right low-velocity flow with wide differential between systole and diastole. c, Restrictive pattern with higher velocity in both systole and diastole. d, Bidirectional pattern with right-to-left ductal flow during systole. **B**, Echocardiographic examination of left atrial and left ventricular enlargement and quantification of ductal impact on cardiac performance. a, Dilated left atrium (A) and ventricle (V). b, M-mode measurement, demonstrating a dilated left atrium indexed to the aortic diameter. c, Elevated and pulsatile pulmonary venous flow, demonstrating high pulmonary venous diastolic flow. d, Shortened isovolumetric relaxation time. e, Transmitral flow, demonstrating an early/atrial flow ratio of 1. f, Reversal of diastolic flow in the postductal descending thoracic aorta. IVRT indicates isovolumetric relaxation time; LA:Ao, left atrial diameter to aortic root diameter ratio; MPA, main pulmonary artery; MV E/A, mitral valve early/atrial flow ratio; and PV D, pulmonary vein diastolic velocity.



echocardiographic characteristics derived on postnatal day 2, which provided accurate predictions of the composite outcome of death or BPD (area under the curve, 0.92 [95% CI, 0.86–0.97]).[89] However, benefit from ductal closure based on these criteria has not yet been demonstrated.

Table 5. Comprehensive Echocardiographic Assessment of Ductal Significance in Preterm Infants

Echocardiographic measures	Significant PDA	Limitations	Measurement technique	Normal range
Size of ductus				
Indexed to LPA diameter	PDA/LPA >1.0	LPA dilation, high-volume shunt	High-PS view in 2D	…
Systemic blood flow (postductal aorta, celiac, MCA)				
Flow patterns: antegrade, absent, retrograde diastolic flow	Flow reversal for diastolic steal; abnormal end organ flow pattern	Accuracy determined by measurement location angle of insonation	Aorta: high-PS, PW Doppler parallel to angle of flow (diaphragm) Celiac: sagittal view, midabdominal MCA: axial view, temporal fossa	Forward diastolic flow
Markers of pulmonary overcirculation				
1. LVO	LVO ↑ [>300] secondary to increased preload	Dependent on LVOT morphology; minimize angle correction	LV-VTI and Aorta: PW at hinge points of aortic valve	150–300 mL/min per kg
2. Mitral valve E/A ratio	E/A ≥1 indicates ↑ LA pressure	Both unreliable in the setting of severe mitral valve regurgitation	Apical 4Ch; PW Doppler perpendicular to the MV; at tips of the leaflets	<1
3. IVRT	IVRT <40		Apical 5Ch; PW at intersection of inflow and outflow on color Doppler	40–60 ms
Left heart volume loading				
1. LA:Ao	≥1.6	Abnormality could be secondary to LV dysfunction	PS, long-axis M-mode through aortic valve annulus (LA:Ao)	LA:Ao <1.6
2. PV D-wave velocity	↑ PV diastolic wave velocity [>0.5 m/s] indicates ↑ PV return	Peak velocity decreases as PV dilates with larger shunts	Apical 4Ch PW Doppler parallel to the RUPV inflow	0.2–0.50 m/s
3. LPA end-diastolic velocity	↑ PBF leads to ↑ mean and end-diastolic flow velocity	LPA dilation commonly occurs concurrently with ↑ volume shunt	High-PS parallel to flow in the LPA, distal to the ductal insertion	<0.2 m/s

2D indicates 2 dimensions; 4Ch, 4 chamber; 5Ch, 5 chamber; E/A, ratio of peak velocity blood flow from left ventricular relaxation in early diastole (E) to peak velocity flow in late diastole caused by atrial contraction (A); IVRT, isovolumetric relaxation time; LA, left atrial; LA:Ao, left atrial diameter to aortic root diameter ratio; LPA, left pulmonary artery; LV, left ventricular; LVO, LV outflow; LVOT, LVO tract; MCA, middle cerebral artery; MV, mitral valve; PBF, pulmonary blood flow; PDA, patent ductus arteriosus; PS, parasternal (view); PV, pulmonary vein; PW, pulse wave; and RUPV, right upper PV; VTI, velocity time integral.

UNIQUE CONSIDERATIONS IN THE DIAGNOSIS OF PDA AMONG OLDER PATIENTS (TERM INFANT THROUGH ADULTHOOD)

Transthoracic echocardiography provides adequate imaging in term infants, but poor acoustic windows in older patient populations may limit utility. Transesophageal echocardiography can be used with views in the upper esophagus using a clockwise rotation from the aortic views.[90] However, color flow Doppler assessment can be misleading, particularly in the presence of elevated pulmonary vascular resistance, wherein right-to-left shunting in systole at the ductus can be difficult to separate from adjacent structures, including the left pulmonary artery. These observations have led health care professionals to consider diagnostic modalities for PDA in older patients beyond echocardiography, including magnetic resonance imaging or computed tomography.

Among adolescent and adult patients with PAH, cardiac magnetic resonance imaging or computed tomographic imaging may illuminate a PDA that was not revealed during echocardiography. Cardiac magnetic resonance imaging has long been considered the gold standard for noninvasive flow assessments, function quantification, and anatomic evaluation, providing useful information on ductal morphology and characteristics, without ionizing radiation. Alternatively, computed tomography provides faster imaging and allows breath holding, preferable for identifying in situ thromboembolic disease that is prevalent in older patients with long-standing PDA and associated PAH.[91] In addition, cardiac-gated multidetector computed tomography scans can identify and track the extent of calcifications found in subsets of adults with PDA. This is particularly important to identify when considering definitive closure (*discussed below*).[92]

In the setting of long-term ductal exposure, hemodynamic assessment by cardiac catheterization provides critical information on the risk/benefit profile of ductal closure (Figure 5). A 2018 joint statement from the American Heart Association and American College of Cardiology recommended, on the basis of consensus expert opinion, that cardiac catheterization can be useful in adult patients with PDA and suspected PAH.[36] In the setting of elevated pulmonary vascular resistance, the PDA may serve as a physiologic "pop-off" for the right ventricle, allowing for egress of blood, albeit deoxygenated blood, from the right ventricle to the systemic circulation. In this setting, closure of the PDA may precipitate right ventricular failure. Test occlusion of the ductus during the catheterization can evaluate physiologic tolerance of the right ventricle to shunt closure.[93] In addition, in the setting of concerns for PAH, performance of pulmonary vascular reactivity testing during cardiac catheterization can identify responsiveness to pulmonary vasodilators.[94]

PDA TREATMENTS IN PRETERM INFANTS

Indomethacin

Indomethacin, a cyclooxygenase inhibitor (*see above*) targeting prostaglandin synthesis, is the prototypical NSAID and is the most extensively studied medical treatment for ductal closure among preterm infants. Thirty-nine randomized trials (23 as prophylaxis,[52] 4 for early treatment of an asymptomatic PDA,[95] and 12 for treatment of a symptomatic PDA[96]) demonstrate consistent efficacy for achievement of ductal closure (RR for persistent patency, 0.39 [95% CI, 0.35–0.44], 0.41 [95% CI, 0.26–0.65], and 0.40 [95% CI, 0.32–0.50]), at mean ages at treatment of <1, 2.5, and 6 days, respectively. Despite efficacy in closing the ductus, randomized trials have not identified benefits with respect to most other outcomes (including mortality, BPD, necrotizing enterocolitis, and neurodevelopment).[40-42] Indomethacin treatment is often followed by oliguria and increases in serum creatinine levels, which have

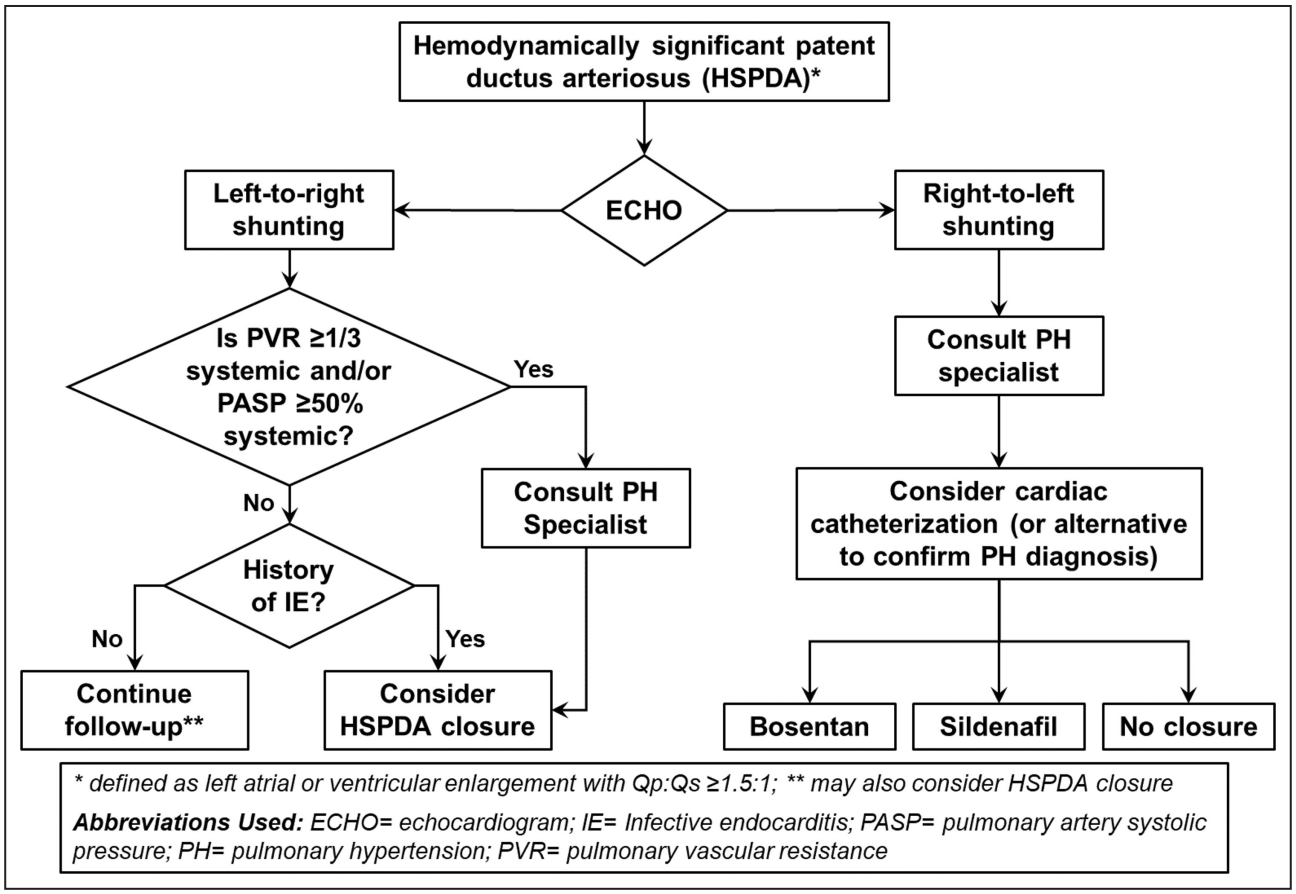


Figure 5. American Heart Association guideline for management of noninfant patients with hemodynamically significant patent ductus arteriosus (HSPDA).
Flowchart and guideline for the management of older patients and adults with HSPDA. Adapted from and based on recommendations in Stout et al[36]. ECHO indicates echocardiography; IE, infective endocarditis; PASP, pulmonary arterial systolic pressure; PH, pulmonary hypertension; and PVR, pulmonary vascular resistance.

been linked to increased risks of spontaneous intestinal perforation, particularly in infants also exposed to postnatal corticosteroids.[97,98]

Ibuprofen

Ibuprofen has been compared with placebo or nontreatment in 15 randomized controlled trials (6 as prophylaxis[99] and 9 as treatment[64]). Collectively, these trials demonstrated efficacy for PDA closure comparable to that of indomethacin (RR, 0.45 [95% CI, 0.40–0.51]). Oral dosing appears to be more effective than intravenous dosing (RR, 0.38 [95% CI, 0.26–0.56]).[64] Direct comparisons to indomethacin also support comparable efficacy[64,99] and suggest that oliguria and necrotizing enterocolitis are less likely in infants treated with ibuprofen.[64] Other outcomes, with the exception of ductal patency (and "rescue" NSAID treatment or ligation), are not changed by ibuprofen prophylaxis[99] or treatment.[64] Comparable efficacy for ductal closure and the lower risk of adverse effects have led some reviewers to designate ibuprofen as the NSAID of choice for medical PDA closure.[64]

Acetaminophen

Recent reports have suggested that acetaminophen (paracetamol) might be a less toxic, but similarly effective, alternative to indomethacin or ibuprofen for inducing ductal closure. Most reports are anecdotal, without controls, and there are few randomized trials.[100] The 2 randomized trials comparing acetaminophen with placebo[101] or no treatment[102] enrolled a combined total of 80 subjects and found that treatment reduced the RR of ductal patency after 4 to 5 days of treatment by 51% (RD, −0.21; RR, 0.49 [95% CI, 0.24–1.00]).[100] No differences in mortality, oxygen use at 36 weeks' postmenstrual age, or other outcomes were observed. Several small trials comparing acetaminophen with ibuprofen or indomethacin found no differences in rates of ductal closure between the treatments,[100] suggesting therapeutic equivalence. However, prospective nonrandomized data from the Early Treatment Versus Delayed Conservative Treatment of the Patent Ductus Arteriosus (PDA-TOLERATE) trial indicate that acetaminophen is no more effective than conservative treatment and is less effective than indomethacin in inducing ductal closure.[103]

Pharmacogenetics of Drug Treatment for PDA

Recent evidence has shown that unpredictable responses to pharmacological PDA treatments (eg, indomethacin and ibuprofen) may reflect differences in developmental trajectory (ontogeny), genetic variability of drug-metabolizing enzymes, and drug targets.[22] For example, current weight-based dosing of indomethacin leads to variable drug exposures, with up to 14-fold variation in drug concentrations 24 hours after identical intravenous drug dosing.[104] To that end, genetic variability in indomethacin metabolism may explain the variability observed in drug exposures. Indomethacin is metabolized by the cytochrome P450 enzymes, primarily CYP2C9,[105] and uridine 5'-diphospho-glucuron osyltransferase (UGT) enzymes.[106] Infants have low expression levels of CYP2C9 in fetal and early neonatal life, and UGT enzymes are also expressed at relatively low levels.[107,108] For both enzymes, expression matures rapidly during infancy.

In addition, CYP2C9 genotype has been associated with response to indomethacin in preterm infants with PDA.[109] The G allele of *rs2153628* was associated with increased odds of response to indomethacin in the case-control analysis (OR, 1.918 [95% CI, 1.056–3.483]). Moreover, the polymorphism CYP2C92 was associated with drug failure in a multicenter cohort study of preterm infants receiving indomethacin for PDA.[110] The mechanisms by which variants in these and other genes alter NSAID responses have not been established, but may relate to the complex molecular network regulating ductal patency before and after birth.

Surgical Closure

Surgical ligation of the ductus, usually performed by application of a surgical clip via a left posterolateral thoracotomy,[111] has the advantage of virtually universal achievement of ductal closure (although rare cases of ligation of the left pulmonary artery or mainstem bronchus have been reported). Only 4 procedural PDA-closure trials have been conducted in preterm infants.[65,112,113,114,115,116] All trials evaluated open surgical ligation, rather than minimally invasive transcatheter closure (*discussed below*), and were conducted before the 1980s, before modern intensive neonatal care advances (eg, antenatal corticosteroids and surfactant) that have allowed many preterm infants with PDAs to survive.[117] Prophylactic ligation of the ductus on the day of birth for infants <1000 g in weight was associated with lower rates of necrotizing enterocolitis, more frequent oxygen use and mechanical ventilation at 36 weeks, and no difference in mortality.[65] Despite the clear differences in ductal patency, ligation for symptomatic PDA did not demonstrably decrease any adverse outcome.[40] The landmark National Collaborative Study, comparing ligation with indomethacin for treatment of persistent PDA, found that ligation was more likely to produce ductal closure (RR, 0.04 [95% CI, 0.01–0.27]), but was associated with higher rates of pneumothorax and retinopathy of prematurity, without affecting mortality, chronic lung disease, or other

outcomes (by study design, the ductus was closed in all subjects before study completion).[113]

Ductal ligation is often followed within hours by cardiorespiratory deterioration (postligation syndrome), apparently attributable to altered afterload, leading to impaired left ventricular systolic performance[118]; this complication is more likely in infants who undergo ligation at <30 postnatal days.[119] Surgical ligation has also been associated with increased risks of BPD[114,120] and neurodevelopmental impairment.[121] Long-term complications of surgical ligation include left vocal cord paresis[122] and scoliosis.[123] In view of these observations, rates of surgical ligation across US hospitals have decreased markedly over the past decade (8.4% in 2006 to 1.9% in 2015).[55]

Transcatheter Closure

Transcatheter closure is the procedure of choice for definitive PDA occlusion in adults, children, and infants ≥6 kg, but application in smaller, preterm infants is a more recent development.[124] Availability of devices specifically designed to address the unique ductal morphology of preterm infants, including several with the type F (fetal) PDA (see Figure 2), coupled with increasing experience among interventional teams, has led to growing interest and use of this approach (Figure 6A). A multicenter, nonrandomized, single-arm trial performed under the auspices of a US Food and Drug Administration investigational device exemption protocol and continued access program evaluated safety and effectiveness of the Amplatzer Piccolo Occluder device in 200 patients, including 100 weighing ≤2 kg and 33 weighing ≤1 kg. The trial demonstrated high implant success rates (191/200 [95.5%] and 99/100 [99%] at ≤2 kg) and low major complication rates (4/194 [2.1%]), with effective ductal closure documented in 172 of 173 (99.4%) at 6 months. Five infants were observed to have new evidence of moderate tricuspid regurgitation on echocardiography following transcatheter closure, likely related to catheter manipulation across the tricuspid valve.[126] Following review of these results, the device was approved by the US Food and Drug Administration for transcatheter PDA closure in infants who weighed ≥700 g and were aged ≥3 postnatal days.[127]

Evidence that the risk of an adverse event following transcatheter PDA closure is inversely related to postnatal age or procedural weight remains unclear.[124,128] However, heterogeneity across studies in definitions for complications, timing (intraprocedural or postprocedural) of event reporting, and adjudication of procedural-related adverse events limits the interpretation of available data on the risks of complications following transcatheter PDA closure. Recent procedural modifications, including adoption of vascular access using femoral venous, rather than femoral arterial, approaches, have led to marked reductions in the incidence of postprocedure limb ischemia (Figure 6B).[129] Moreover, consensus-based guidelines outlining contemporary strategies to prevent and manage complications associated with transcatheter closure will likely contribute to improved safety profiles.[130]

In the absence of direct comparisons, the optimal treatment to achieve definitive ductal closure among preterm infants remains unknown. Despite promising short-term data, longer-term outcomes following transcatheter PDA closure are lacking. Whether the greater certainty of achieving ductal closure with this approach will be associated with increased benefits to treated infants (compared with NSAID treatment or conservative management, described below) also remains to be determined.[124,129]

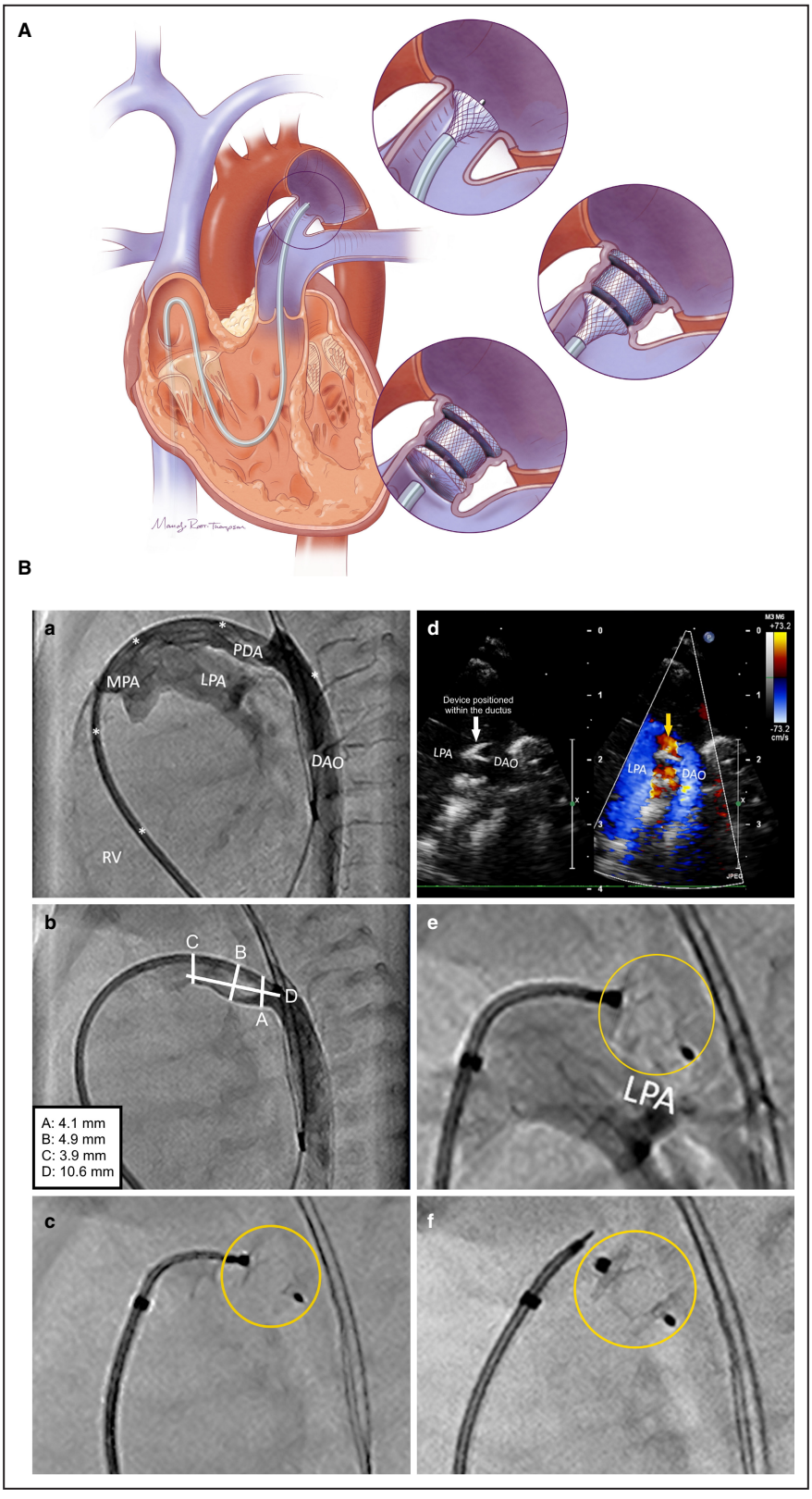
Conservative Management

Despite evidence that a persistent ductus is associated with worse outcomes, including death, randomized trials of both pharmacological and surgical ligation treatments to close persistent PDAs in preterm infants have not demonstrated long-term benefits.[40,41,43] To that end, trials of treatment to close the ductus have provided evidence that those measures, at least when applied nonselectively, do not improve outcomes.[40] These observations have led to increasing adoption of conservative approaches to PDA management. In conservative management, health care providers avoid definitive (transcatheter or surgical) closure, while awaiting the possibility of spontaneous closure.[131]

With conservative management, several strategies to manage consequences of the ductus are often used, including fluid restriction, diuretics, systemic afterload reduction, increases in positive airway pressures, or maintenance of higher hematocrits; however, these approaches have not been evaluated in systematic randomized trials.[41,131] Although data are mixed,[132,133] adoption of conservative management has not been found to be associated with differences in outcomes.[131] However, among "high-risk" subgroups, such as infants born at <26 weeks' gestation, with evidence of HSPDAs producing demonstrable circulatory compromise, or with persistent patency well beyond the expected age of spontaneous closure, questions on the safety and effectiveness of conservative management versus alternative treatments (definitive closure) remain unanswered.[3,132,133]

Timing of Therapy

Because a speculative analysis of experiences with oral or rectal indomethacin from the 1970s suggested that treatment after 12.5 days of age may be less effective than treatment at an earlier age,[134] considerations of



treatment approaches for PDA have been influenced by concerns that deferral of early treatment might result in missed opportunities for effective NSAID treatment. However, that analysis did not account for the expected frequency of early spontaneous closure, which is common.[3] Data from randomized clinical trials, including those of indomethacin, do not support declining efficacy with advancing postnatal age; trials that randomized

Figure 6. Percutaneous patent ductus arteriosus (PDA) closure (A) and intraprocedural imaging of percutaneous PDA closure (B).

A, Illustration of percutaneous device release for closure of a PDA. An end hole catheter is used to cross the tricuspid valve into the right ventricle (RV), then a soft, floppy-tipped wire is advanced across the PDA and into the descending aorta (DAO) (*data not shown*). At this point, the catheter in the right ventricle is removed over the wire, and a delivery catheter is advanced over the wire through the venous sheath into the PDA and descending aorta (*data not shown*). The device is advanced to the tip of the catheter (a). The device is deployed under fluoroscopic and transthoracic echocardiography guidance within the PDA with careful attention to avoid device protrusion into the aorta or pulmonary artery (b). When position is satisfactory, the device is released from the delivery cable (c). **B**, Radiographs illustrating steps and final result of a percutaneous PDA closure procedure. a, Following femoral vein access, a 4F catheter is introduced and advanced to the RV under fluoroscopic guidance, wherein a floppy-tipped wire is guided via this catheter through the PDA and into the descending aorta, after which a 4F delivery catheter is exchanged. b, An angiogram is obtained for configuration and dimensional data of the PDA, which permits selection of the most appropriate device for closure. c, The device is then advanced through the delivery catheter and deployed, but not fully released. d, Additional echocardiographic imaging is obtained to confirm placement of the device. e, Additional angiographic imaging to evaluate for aortic or left pulmonary obstruction attributable to the device. f, Device is released; additional imaging to evaluate postrelease positioning and stability, residual shunting, and other clinical parameters (eg, presence of new or increased tricuspid valve regurgitation) may be warranted. Reproduced from Barcroft et al[125] with permission. Copyright ©2022 Elsevier. LPA indicates left pulmonary artery; and MPA, main pulmonary artery.

subjects at a mean postnatal age >7 days (range, 7.4–20.1 days) demonstrated PDA-closure efficacy (RR, 0.35 [95% CI, 0.25–0.48]) equivalent to trials of treatment at earlier ages. In the PDA-TOLERATE trial, NSAID treatment was followed by PDA closure in 46% of subjects in the early (8±2 days) treatment group and in 44% of those in the conservative treatment group who received rescue treatment (at 21±8 days of age).[80,103] The age at which medical therapy becomes ineffective therefore remains uncertain, but deferral of treatment into the fourth postnatal week does not appear to compromise its utility for achievement of ductal closure.

Postdischarge Treatment

At present, data on the posthospital outcomes of preterm infants who are discharged home with a persistent PDA are lacking. Herrman et al reported that, among 21 infants discharged with an open ductus, 86% (18/21) underwent spontaneous closure.[135] This is consistent with a recent report of spontaneous closure in 52 of 68 (76%) infants discharged with an open PDA, with continued evidence of closure beyond 2 years postnatal.[136] In a recent prospective multicenter study of 201 premature infants discharged home with a PDA and followed up at 6-month intervals through 18 months of age, the authors observed spontaneous ductal closure occurred in 47% and 58% of infants at 12 and 18 months, respectively.[137] In the absence of data, optimal outpatient surveillance among preterm infants discharged with a persistent PDA remains unknown.[135,136]

PDA TREATMENTS IN OLDER PATIENTS (TERM INFANT THROUGH ADULTHOOD)

Beyond the first postnatal months, term infants are outside the window when pharmacological therapy (indomethacin and ibuprofen) to close the ductus is effective. Although diuretics may be used to treat pulmonary overcirculation among term infants with a PDA in the first months of life, decisions about the need for ductal closure are largely driven by presence (or absence) of HSPDA, with consideration to the direction of ductal shunting and pulmonary artery systemic pressure and/or pulmonary vascular resistance indexed to systemic pressure (see Figure 5). The frequency and timing of outpatient follow-up are determined on the basis of PDA classification (Table 6).

Management of HSPDA

Transcatheter PDA closure remains the mainstay for definitive ductal closure in older patients.[138] In patients weighing >6 kg, most PDAs are amenable to transcatheter occlusion, with the notable exception of the type B ductus (see Figure 2). According to 2011 guidelines from the American Heart Association on cardiac catheterization in pediatric heart disease, based on consensus expert opinion, transcatheter PDA occlusion is indicated in older patients for the treatment of an HSPDA with "left-to-right shunt that results in any of the following: congestive heart failure, failure to thrive, pulmonary overcirculation, or an enlarged left atrium or left ventricle, provided the anatomy and patient size are suitable" (class I recommendation, level of evidence B).[139]

Management of PDA With Associated PAH in Term Infants and Older Children

Among term infants and older children, high levels of pulmonary artery pressure associated with unrestrictive ductal shunting may relate to excessive flow, and not high pulmonary vascular resistance indicative of pulmonary vascular disease. In this context, health care providers may consider transcatheter closure following short-term pulmonary vasodilator testing (eg, decrease of ≥20% in mean pulmonary artery pressure

Table 6. Recommended Frequency of Outpatient Follow-Up and Treatment Among Term Infants, Older Children, and Adults With PDA

Classification	Assessment intervals and treatment options					
	Pediatric/ACHD cardiologist	ECG	TTE	Pulse oximetry	Exercise test*	Treatment
"Silent" or trivial PDA†	36–60 months	36–60 months	36–60 months	As needed	As needed	None
Small PDA‡	24 months	24 months	24 months	As needed	As needed	None
HSPDA§ or PDA with mild or moderate PH	6–12 months	12 months	12 months	Each visit	12–24 months	Closure is recommended if PDA causing LAE/LVE with net left-to-right shunt, PASP <50% of systemic, and PVR <1/3 systemic‖
PDA with severe PH and/or Eisenmenger syndrome	3–6 months	12 months	12 months	Each visit	6–12 months	Closure is NOT recommended with net left-to-right shunt and PASP or PVR ≥2/3 systemic

ACHD indicates adult congenital heart disease; HSPDA, hemodynamically significant PDA; LAE, left atrial enlargement; LVE, left ventricular enlargement; PASP, pulmonary artery systolic pressure; PDA, patent ductus arteriosus; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; and TTE, transthoracic echocardiography.

*Six-minute walk test or cardiopulmonary exercise test.

†No hemodynamic or anatomic consequences of the PDA.

‡Small shunt that is not HSPDA and is asymptomatic.

§HSPDA = LAE/LVE and/or sustained pulmonary blood flow to systemic blood flow ratio (Qp/Qs) ≥1.5.

‖PDA closure considered: net left-to-right shunt if PASP ≥50% systemic and/or PVR is ≥1/3 systemic.

after administration of 100% oxygen and/or 80 parts per million of inhaled NO) and a favorable hemodynamic response to test occlusion.[140] In a study by Niu et al, the authors describe that younger patients with pulmonary artery/systolic blood pressure ratios (cardiac index) <0.8 during test occlusion were considered to have favorable hemodynamics and underwent successful PDA closure, despite many in the cohort having met historical thresholds for being poor candidates for intervention (pulmonary vascular resistance index, >6 Wood units m^2).[94]

Management of PDA With Associated PAH in Older Patients and Adults

Recent American Heart Association/American College of Cardiology guidelines emphasize that considerations for ductal closure among older patients be made in the context of evaluation of left-to-right shunting and hemodynamic assessment for PAH (see Figure 5).[36] Correspondingly, European guidelines suggest pulmonary/systemic shunt ratios of <1.5 and pulmonary vascular resistances of >5 Wood units as prohibitive for ductal closure in adults.[69] Supportive pharmacologic treatments (eg, endothelin receptor antagonists and phosphodiesterase-5 inhibitors) have been shown to improve functional capacities in adult patients with Eisenmenger syndrome, including marked increases in survival advantage for those on PAH therapies versus not on PAH therapies (97% versus 69%; $P<0.01$).[141] Before transcatheter closure, balloon test occlusion provides insight on risk/benefit profiles, which are particularly valuable for patients with evidence of PAH.

Definitive Closure (Transcatheter or Surgical Ligation)

Transcatheter PDA closure in older patients remains the mainstay for definitive ductal closure.[138] Following hemodynamic assessment, for patients with unfavorable ductal morphology for transcatheter closure, surgical intervention remains feasible via both video-assisted thoracoscopic or open thoracotomy, with high degrees of success and low complication rates.[142,143]

Management of "Silent" or Small PDAs

Since the first surgical PDA ligation by Gross in 1939, thresholds for intervention on the basis of IE risk have been appropriately recalibrated as a function of the advent of antibiotic treatment and the ability to offer transcatheter PDA occlusion.[144,145] In other words, previous indications to close were based on prevention of endarteritis, wherein closing the PDA would curtail the need for long-term antibiotic prophylaxis. Because "silent" or small PDAs are not considered HSPDA (see Table 2, above), societal guidelines no longer recommend antibiotic prophylaxis; thus, the rationale for closing "silent" or small PDAs no longer exists.[36,75]

CONCLUSIONS

PDA is a complex pathophysiology, resulting in markedly variable clinical consequences. To provide more targeted, individualized treatments, a better understanding of the molecular mechanisms of ductal closure, the effect of each patient's clinical and echocardiographic biomarkers on both treatment success and improved outcomes, as well as genetic variants

in drug metabolism and drug targets should be prioritized.[146] Irrespective of patient age, incorporating clinical and cardiac imaging parameters that recognize a hierarchal model of adverse ductal sequalae is recommended. The critical need for contemporary, pragmatic clinical trials that evaluate the impact of existing PDA treatments on important patient outcomes is acknowledged.

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