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EDUCATIONAL REVIEW

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Current understanding and perioperative management of pediatric pulmonary hypertension

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Summary

Pediatric pulmonary hypertension is a complex disease with multiple, diverse etiologies affecting the premature neonate to the young adult. Pediatric pulmonary arterial hypertension, whether idiopathic or associated with congenital heart disease, is the most commonly discussed form of pediatric pulmonary hypertension, as it is progressive and lethal. However, neonatal forms of pulmonary hypertension are vastly more frequent, and while most cases are transient, the risk of morbidity and mortality in this group deserves recognition. Pulmonary hypertension due to left heart disease is another subset increasingly recognized as an important cause of pediatric pulmonary hypertension. One aspect of pediatric pulmonary hypertension is very clear: anesthetizing the child with pulmonary hypertension is associated with a significantly heightened risk of morbidity and mortality. It is therefore imperative that anesthesiologists who care for children with pulmonary hypertension have a firm understanding of the pathophysiology of the various forms of pediatric pulmonary hypertension, the impact of anesthesia and sedation in the setting of pulmonary hypertension, and anesthesiologists' role as perioperative experts from preoperative planning to postoperative disposition. This review summarizes the current understanding of pediatric pulmonary hypertension physiology, preoperative risk stratification, anesthetic risk, and intraoperative considerations relevant to the underlying pathophysiology of various forms of pediatric pulmonary hypertension.

KEYWORDS

anesthesia, bronchopulmonary dysplasia, cardiology, congenital heart defect, persistent pulmonary hypertension of newborn, pulmonary hypertension, right ventricular dysfunction

1 | INTRODUCTION

Pediatric pulmonary hypertension (PH) is an uncommon disorder with diverse etiologies. In most forms of persistent pediatric PH, the underlying pulmonary hypertensive vascular disease (PHVD) is characterized by pulmonary vascular inflammation and remodeling. This leads to elevated pulmonary vascular resistance (PVR) and pulmonary artery pressure (PAP), with eventual right ventricular (RV) failure and significant morbidity and mortality. Evolving knowledge of the fundamental mechanisms of pediatric PH, especially pulmonary arterial hypertension (PAH), has led to targeted therapies and significantly improved outcomes in recent years; however, PH remains a life-threatening condition across all age groups. Management of pediatric PH is challenging due to lack of prospective pediatric PH trials, as well as the complex heterogeneity of pediatric PH etiologies and possible coexisting congenital anomalies.

Pulmonary arterial hypertension, a subset of PH, remains without a cure despite significant advances in the current understanding of the disease, the advent of novel PAH-targeted therapies, and prolonged survival and quality of life in the modern era. With increased survival, a child with PAH will typically require multiple anesthetics,

including recurrent cardiac and noncardiac procedures. It is well documented that the risk of perioperative cardiac arrest and death is at least 20-fold higher compared to all children undergoing anesthesia or sedation.[1] It is thus imperative that anesthesiologists who care for children with PH have a firm understanding of the pathophysiology of the various forms of pediatric PH, the impact of anesthesia and sedation in the setting of PH, and the anesthesiologist's role as perioperative experts in managing the child's care from preoperative planning to postoperative disposition.

2 | DEFINITIONS AND CLASSIFICATION

Pulmonary hypertension is defined as a mean pulmonary artery pressure (mPAP) ≥25 mm Hg in individuals >3 months of age at sea level, diagnosed by cardiac catheterization. The mPAP in healthy people is 14 ± 3 mm Hg, rarely exceeds 20 mm Hg, and is relatively unchanged regardless of gender, age, or ethnicity.[2] Note that the definition of PH does not include PVR; rather, it simply denotes an elevated PAP from any cause. However, when PH is characterized by progressive structural pulmonary vascular changes, predominantly in precapillary vessels, the disease is termed PAH. PAH is defined hemodynamically by a mPAP ≥25 mm Hg, pulmonary artery wedge pressure (PAWP) ≤15 mm Hg, and indexed pulmonary vascular resistance (PVRi) >3 Wood units (WU) m^2, meaning that the restriction to blood flow is predominantly in the pulmonary precapillary bed. Most forms of pediatric PAH are either idiopathic or associated with congenital heart disease (CHD). Pediatric PHVD is a recently adopted pediatric-specific term to define children with mPAP ≥25 mm Hg and PVR >3 WU m^2, regardless of PAWP, as this is more inclusive of some pediatric subpopulations.[3]

In contrast to the precapillary PHVD that characterizes pediatric PAH, postcapillary PH occurs in the setting of left heart disease due to left atrial or pulmonary venous hypertension. The differentiation of precapillary (PAH/PHVD) vs postcapillary PH is crucial in children because treatment differs in many ways, and implementation of improper treatment may worsen symptoms. However, even among this most basic of classifications, most forms of pediatric PH involve elements of both precapillary and postcapillary pathology as the disease eventually progresses.[4,5] Several other subgroups of pediatric PH are recognized; definitions are listed in Table 1, and detailed discussion follows.

There are numerous etiologies of adult and pediatric PH with considerable phenotypic heterogeneity and varied treatment responses. In recognition of this, the World Health Organization's (WHO) World Symposium on Pulmonary Hypertension update in Nice in 2013 expanded specific pediatric PH subgroups to create a comprehensive classification for both adults and children.[6] A summary of the WHO classification highlighting only the pediatric-specific subgroups is in Table 1. Given concerns regarding the applicability of an adult-centric classification system for children, the

TABLE 1 Classification and definitions of the most common causes of pediatric pulmonary hypertension

PH type	WHO group	Definition
PH		mPAP ≥25 mm Hg in children >3 mo of age at sea level
Group 1	PAH	mPAP ≥25 mm Hg PAWP ≤15 mm Hg PVRi >3 WU m^2
Group 1.1	Idiopathic PAH	PAH with no underlying disease known to be associated with PAH
Group 1.2	Heritable PAH	PAH with no underlying disease but with positive family history or known genetic abnormality
Group 1.4.4	PAH-CHD	Biventricular hearts: mPAP ≥25 mm Hg and PVRi >3 WU m^2 Univentricular hearts: mean TPG >6 mm Hg or PVRi >3 WU m^2
Group 1″	PPHN	Delay or failure of normal PVR reduction postnatally
Group 2	PH due to left heart disease	mPAP ≥25 mm Hg PAWP >15 mm Hg
Group 3	PH due to lung diseases and/or hypoxia	mPAP ≥25 mm Hg PAWP ≤15 mm Hg Presence of chronic lung disease
Group 3.7	BPD-PH	Chronic lung disease in premature infants born ≤32 wk GA who require oxygen after 36 wks GA
Group 4	Chronic thromboembolic PH (CTEPH)	Rare form of PH following acute or recurrent pulmonary embolus
Group 5	PH with unclear multifactorial mechanisms	PH due to mitochondrial diseases, thyroid disorders, neonatal hemochromatosis, chronic hemolytic anemia (sickle cell disease), myeloproliferative disorders, and segmental PH (associated with pulmonary atresia)

WHO classification as per the 2013 Nice updated clinical classification: Simonneau *et al.*[6]
BPD, bronchopulmonary dysplasia; GA, gestational age; mPAP, mean pulmonary artery pressure; PAH, pulmonary arterial hypertension; PAH-CHD, pulmonary arterial hypertension associated with congenital heart disease; PAWP, pulmonary artery wedge pressure; PH, pulmonary hypertension; PHVD, pulmonary hypertensive vascular disease; PPHN, persistent pulmonary hypertension of the newborn; PVR, pulmonary vascular resistance; PVRi, indexed pulmonary vascular resistance; TPG, transpulmonary gradient.

Pulmonary Vascular Research Institute developed the pediatric-specific 2011 Panama classification, which uses 10 major groups and over 100 subgroups to highlight the considerable heterogeneity of pediatric PH.[3] Notwithstanding, the WHO classification remains the predominant standard for both adult and pediatric PH.[7]

Throughout this review, the term "PAH" will be used when referring specifically to WHO group 1 PH, and "PH" will be used for pulmonary hypertension in general.

3 | EPIDEMIOLOGY

The overall incidence of pediatric PAH ranges from 2 to 4 cases per million children per year with a prevalence of 20-30 cases per million children.[8–12] The overall incidence is much higher when neonates and infants with typically "transient" forms of PH are included, such as persistent pulmonary hypertension of the newborn (PPHN). This was demonstrated by the Netherlands national PH registry, which found that 82% of children had transient PH, 8% had PH due to lung disease/hypoxemia, 5% had progressive PAH, 5% had PH due to left heart disease, and <1% had chronic thromboembolic PH.[9] When transient cases of PH were removed, the calculated incidence of progressive PAH was three cases per million children, matching other registry reports. When studying PH etiologies that extend beyond infancy, idiopathic pulmonary arterial hypertension (IPAH) and PAH-CHD represent the majority of pediatric PH cases.[8–12]

Children with PH have vastly improved survival compared to past decades. Across recent registries, survival rates at 1 and 3 years are 80%-83% and 74% for all pediatric PH (WHO group 1-5)[8,13] and 73%-92% and 63%-85% for PAH (WHO group 1), respectively, with overall better survival for group 1 (PAH) children compared to groups 2, 3 and 5.[9–12] IPAH and PAH associate with congenital heart disease (PAH-CHD) have similar survival in most registries.

4 | NEONATAL PH

The most common form of pediatric PH is that present during the neonatal period. In the majority of cases, ongoing growth into infancy leads to complete resolution of PH, and most do not require anesthesia prior to resolution; however, early mortality is significant with severe disease. Two general classes of neonatal PH are recognized and exist in different groups in the WHO classification: PPHN (WHO group 1.1) and bronchopulmonary dysplasia-related PH (BPD-PH, WHO group 3). The underlying etiologies of PPHN and BPD-PH are diverse, yet there is considerable overlap between these two groups in cellular and clinical manifestations, leading to inconsistent classification of several of the specific underlying etiologies.

4.1 | Persistent pulmonary hypertension of the newborn

Persistent pulmonary hypertension of the newborn is an umbrella term that includes noncardiac causes of cyanosis and elevated PVR in term or near-term neonates. It is defined as a failure of the normal postnatal reduction of PVR, thereby resulting in right-to-left shunting of deoxygenated blood across fetal shunts with resultant hypoxemia. PPHN occurs due to intrauterine or immediate postnatal insults to the pulmonary system and as such presents at or shortly after birth.[3] PPHN is occasionally idiopathic but more commonly associated with an underlying pulmonary pathology. The clinical course may range from mild, transient respiratory distress to severe respiratory failure with hypoxemia, cardiac instability, and organ failure.[14] The incidence is approximately 2 per 1000 live births,[15,16] which makes PPHN the most common form of pediatric PH, with an incidence approximately 500-1000-fold higher than pediatric PAH. Echocardiography is the diagnostic procedure of choice to rule out congenital cardiac anomalies and glean evidence of elevated PAP/PVR.[16]

While no classification system or inclusion criteria exists for PPHN, three pathophysiologic categories can be used to characterize the underlying pathobiology[3,17,18] and help guide understanding during perioperative management.

1. *Maladaptation PPHN* is seen in neonates with normal pulmonary vasculature but with perinatal factors that produce active pulmonary vascular constriction and impaired vasodilation. Causes include sepsis, asphyxia, pneumonia, or respiratory distress syndrome. PPHN will resolve in this group with treatment of the underlying disease. PVR is likely modifiable pharmacologically.
2. *Maldevelopment PPHN* refers to normal lung development but with abnormal pulmonary vasculature characterized by pulmonary arteriole luminal hyperplasia. It may be idiopathic or due to underlying pulmonary pathology, such as meconium aspiration syndrome, excessive in utero pulmonary blood flow, or prenatal exposure to medications. During the first 2 weeks of rapid pulmonary vascular growth, PVR will often decrease commensurate with growth and treatment of any underlying etiology. PVR is likely modifiable pharmacologically.
3. *Lung hypoplasia PPHN* is an overall reduction in the sum cross-sectional area of the pulmonary vasculature. PVR and PAP are elevated due to the reduced number and size of the pulmonary vasculature, and PVR is likely less modifiable compared to the groups above. Etiologies include congenital diaphragmatic hernia (CDH), alveolar capillary dysplasia, oligohydramnios, cystic adenomatoid malformation of the lung, omphalocele/gastroschisis, and renal agenesis. This group is at greatest risk of PPHN-related morbidity and mortality.

Persistent pulmonary hypertension of the newborn is reversible when the cause itself is reversible, such as meconium aspiration syndrome or sepsis; however, other forms are not transient, such as alveolar capillary dysplasia or severe lung hypoplasia.[14] In addition to treating the underlying cause, supportive care focuses on maintaining appropriate oxygenation (pre-ductal SaO_2 91%-95%), biventricular support, as well as appropriate ventilation strategies with avoidance of excessive inspiratory pressures. Mild permissive hypercapnia may be employed as long as systemic pH remains within normal limits to prevent escalating PVR. The use of sildenafil or inhaled

nitric oxide (iNO) may improve acute management.[19] Neonates with CDH have been shown to have coexisting biventricular dysfunction, which may require inotropic or extracorporeal life support (ECLS).[20]

The early mortality in neonates with moderate to severe PPHN is about 10% and is considerably higher in the setting of CDH or other forms of lung hypoplasia.[15] For the majority of infants with PPHN who survive the acute phase, most will have complete resolution, and most have few residual respiratory symptoms after 1 year of age, with sequelae predominantly confined to those who required ECLS.[21]

4.2 | Bronchopulmonary dysplasia-related PH

Among the developmental lung diseases, BPD is the most common and important cause. BPD is the most common morbidity of children born <30 weeks' gestation and remains the most common lung disease of infancy.[22] BPD is diagnosed in roughly 40% of infants born ≤28 weeks gestational age, which results in 10 000-15 000 new cases in the USA each year.[22–26] While knowledge of the pathophysiology and pathobiology of BPD continues to evolve, BPD is defined as a chronic lung disease in preterm infants born ≤32 weeks' gestation who require ongoing oxygen therapy at 36 weeks' postconceptual age.[23,27] The pathophysiology is characterized by a uniform arrest of lung development and dysmorphic pulmonary capillaries.[28] Postnatal factors may further injure the already fragile pulmonary system, such as oxygen toxicity, volutrauma, infection, and pulmonary overcirculation.[27]

About 25%-35% of infants with BPD will develop PH (BPD-PH), including nearly 50% of infants with severe BPD.[29] However, this number may significantly underestimate the true incidence due to lack of diagnostic codes for BPD-PH and high early mortality rates. The presence of pulmonary veins stenosis is increasingly recognized as a lethal contributing factor.[27,30] Therefore, echocardiography is recommended in preterm infants with sustained need of respiratory support, which also means that a diagnosis of PH in this cohort may be delayed until fulfilling screening criteria at an older age.[27] The genesis of elevated PVR in BPD-PH is a combination of "fixed" PVR due to arrested lung growth, as well as "reactive" PVR due to pulmonary vascular remodeling, which is amenable to acute vasodilator therapy.[22] The cornerstone of treatment is ensuring adequate ventilation and treating the underlying causes of hypoxia and lung disease.[27] BPD-PH has a mortality rate of 10%-70%, depending on inclusion criteria and length of followup.[22,27,30–32] Those who survive generally demonstrate resolution of PH concordant with pulmonary vascular growth; however, longitudinal studies of BPD survivors suggest the presence of lifelong compromised pulmonary function, as well as risk of RV dysfunction and possible recurrent PH in adulthood.[22]

5 | IDIOPATHIC PULMONARY ARTERIAL HYPERTENSION/HEREDITARY PULMONARY ARTERIAL HYPERTENSION

Idiopathic pulmonary arterial hypertension and hereditary pulmonary arterial hypertension (HPAH) are defined by a mPAP ≥25 mm Hg, PAWP ≤15 mm Hg, and PVRi >3 WU m^2 with no known underlying cause. HPAH, which is further defined as IPAH that has documented presence in the family lineage, is phenotypically identical to IPAH, and represents 6% of IPAH/HPAH cases.[33] IPAH/HPAH, as well as PAH-CHD, represent the vast majority of non-neonatal, non-transient pediatric PH, with the incidence of IPAH/HPAH being roughly equal to PAH-CHD.[8–11] In the Netherlands registry, the incidence and prevalence of pediatric IPAH was 0.7 and 4.4 per million children, respectively.[9] IPAH is a progressive disease with no cure, and until relatively recently, survival after diagnosis was usually measured in months. Advances in PAH-specific therapies in recent decades have afforded children with PAH an improved quality of life and 5-year survival rates of 62%-97%, which exceeds that of adults with IPAH.[34–37]

The pathogenesis of IPAH is characterized by a vascular proliferative process that shares many cellular features with malignancies: dysregulated angiogenesis, unopposed cellular growth, resistance to apoptosis, clonal expansion of endothelial cells, and inflammation.[38] The elevation of PVR occurs gradually. At first, the pulmonary vasculature retains the ability to vasodilate and vasoconstrict by endogenous and exogenous mediators of pulmonary vascular tone. As the disease course advances, chronic remodeling ultimately leads to obliteration of the precapillary bed and development of "plexiform lesions" that hallmark severe PAH, leading to relatively "fixed" PVR. The degree of elevated PVR (ie, reduced cross-sectional area of the pulmonary vasculature) ultimately dictates the degree of right heart failure, which in turn determines the child's functional capacity and mortality.

The onset of symptoms manifests as progressive exercise intolerance. Diagnosis is not typically made until well into the disease process, when signs of heart failure and shortness of breath are present. Syncope is also not uncommon prior to diagnosis in children with PAH. Notwithstanding this, three quarters of children with IPAH at diagnosis have a relatively preserved cardiac index (CI) and low right atrial (RA) pressure, despite a high PAP and PVR. This suggests that RV function remains preserved in the majority of children at diagnosis, although RV function deteriorates over time.[39] Definitive diagnosis of PAH requires cardiac catheterization with demonstration of elevated PVR, as will be discussed later.

6 | PULMONARY ARTERIAL HYPERTENSION-CONGENITAL HEART DISEASE

Pulmonary vascular disease is a well-recognized complication of many forms of CHD, and the prevalence and survival of childhood PAH-CHD is roughly similar to childhood IPAH.[40,41] As with IPAH, PAH-CHD is a progressive disease, characterized by escalating PVR, RV remodeling and failure, and ultimately death, unless the provoking cardiopulmonary physiology can be corrected prior to irreversible pulmonary vascular injury. Risk factors for progression to PAH-CHD include chronic volume and pressure overload of the pulmonary circulation from left-to-right shunts, chronic hypoxia, and anatomic

factors. Genetic mutations, including syndromes such as trisomy 21, may amplify the risk.[42]

Five subcategories of PAH-CHD are recognized:

1. *Left-to-right shunts* category includes those with moderate to large shunts and an elevated PVR that has not yet progressed to Eisenmenger syndrome. Shunt closure may be considered based upon specific hemodynamic findings.
2. *Eisenmenger syndrome* is the development of PAH in the setting of large left-to-right shunt(s), whereby escalating PAP has become suprasystemic and precipitated shunt reversal. Cyanosis and multi-organ involvement are usually present, and morbidity and mortality are high. Shunt closure is contraindicated.
3. *PAH with coincidental CHD* is the presence of PAH with no shunt or a small shunt that does not itself account for the development of PAH. This clinical picture is very similar to IPAH, and closure of an existing shunt is likely contraindicated.
4. *Postoperative PAH* is characterized by persistent (>6 months postsurgery) or recurrent PAH after appropriate and timely repair of CHD. This form has the overall worst outcome among the PAH-CHD cohort.[43]
5. *PHVD following staged surgery for single ventricle* is a unique category in children whose pulmonary artery perfusion is modified by pulmonary artery banding, aortopulmonary shunt, Norwood, Glenn, or Fontan palliation. Particularly after Glenn and Fontan palliation, pulmonary blood flow is supplied solely from systemic venous return, and PVR can be pathologically elevated despite little to no increase in mPAP.

Children born with a large post-tricuspid left-to-right shunt (eg, ventricular septal defect [VSD], truncus arteriosus, patent ductus arteriosus) and without pulmonary stenosis will have mPAP >25 mm Hg due to transmission of systemic pressure and flow to the pulmonary vasculature. This qualifies as PH but not PAH because PVR is not yet elevated and the pulmonary vasculature has not undergone significant histologic changes, as this typically takes time. Timely closure of the shunt will negate the lifetime risk of PAH in most cases. If closure is delayed, PVR will begin to increase during a stage of early PVHD, which is characterized by medial hypertrophy yet remains potentially reversible. Ongoing presence of the left-to-right shunt will eventually provoke an irreversible advanced phase, characterized by significant pulmonary vascular narrowing. At this point, the child is considered to have PAH-CHD. Closure of an existing shunt at this stage is generally contraindicated, as it will likely worsen outcomes. The rate of advancement from reversible to irreversible disease is variable and poorly understood.[9,44]

Pulmonary arterial hypertension-congenital heart disease not associated with left-to-right shunts or PAH-CHD persisting or recurring following complete surgical repair is associated with significant mortality.[45] Certain lesions are associated with a higher risk of persistent PAH-CHD, including truncus arteriosus, aortopulmonary window, dextro-transposition of the great arteries (dTGA), and some forms of double outlet RV.[46] Postnatal left-to-right shunting certainly plays a role in these lesions, but histologic changes and elevated PVR can already be present at birth. For instance, up to 12% of babies with dTGA (particularly with intact ventricular septum) have PPHN in the first week of life,[47] suggesting that genetic or fetal hemodynamic factors play a role. In other cases, PAH is not present after successful arterial switch operation for dTGA but appears years later with poor prognosis. Lastly, children with trisomy 21 are at higher risk for PPHN and PAH-CHD both before and after surgical correction, which translates to higher mortality in this population.[48,49]

7 | PH DUE TO LEFT HEART DISEASE

Some children develop PH solely or mostly from left heart disease (WHO group 2), which is differentiated from PAH by a PAWP >15 mm Hg rather than <15 mm Hg. Data for this group are very limited, despite PH due to left heart disease representing perhaps 15% of all pediatric PH cases.[8] Characteristic lesions in this category include pulmonary vein stenosis, total anomalous pulmonary venous return, cor triatriatum, supravalvular mitral ring, mitral stenosis, subaortic stenosis, aortic valve stenosis, cardiomyopathies, and coarctation of the aorta associated with increased left ventricular end-diastolic pressure.[7] Targeted PAH therapies, which promote pulmonary blood flow, are relatively contraindicated in this cohort as they may provoke pulmonary edema and clinical deterioration in the setting of downstream obstruction. Best therapy entails repairing or palliating the obstructive lesion. Diuresis and respiratory support may be needed. Of note, chronic pulmonary venous hypertension may eventually provoke "precapillary" PAH over time, or PAH may develop after successful repair of left-sided obstruction (eg, successful pulmonary venous stenosis repair).[4,10]

8 | OTHER FORMS OF PEDIATRIC PH

World Health Organization group 4 PH includes chronic thromboembolic PH and represents just 1% of children with PH. Group 5 includes PH with unclear multifactorial mechanisms and represents <5% of children with PH.[8] The most common underlying etiologies of group 5 in one registry included mitochondrial diseases, thyroid disorders, and neonatal hemochromatosis,[8] but chronic hemolytic anemia (including sickle cell disease), myeloproliferative disorders, and segmental PH (usually associated with forms of pulmonary atresia) are additional pediatric etiologies.[6] Limited overall data are available for group 4 and 5 pediatric PH.

9 | DIAGNOSIS AND CARDIAC CATHETERIZATION

Echocardiography is the primary diagnostic tool to screen for the presence of PH and associated cardiac malformations, and it is usually the only test for diagnosis in neonates with transient forms of PH.[22] Spectral Doppler analysis of the tricuspid regurgitation velocity, when present, allows an estimate of RV pressure and thus the

PA systolic pressure, assuming absence of stenosis between the RV and PA. The ratio of peak tricuspid regurgitation velocity to the time-velocity integral of the RV outflow tract provides a reliable estimation of PVR, especially when PVR is not significantly elevated.[50] Septal flattening may be used as a surrogate of elevated RV pressures when tricuspid regurgitation is insufficient to estimate RV pressure. Evaluation of PDA or VSD shunt direction and velocity, when present, can estimate right heart pressures. Once PH is definitively diagnosed, serial echocardiograms are recommended every 3-6 months and to routinely assess efficacy and optimization of medical management.[51,52]

Cardiac catheterization remains the diagnostic gold standard for PH. Consensus statements maintain cardiac catheterization is indicated prior to initiating PAH-targeted therapy to confirm the diagnosis, evaluate PH severity, and perform acute vasoreactivity testing (AVT).[37,51–55] An exception is those children presenting gravely ill who should begin empirical therapy prior to undergoing the anesthetic and procedural risk of catheterization.[52] Right heart catheterization should be performed during the initial evaluation, including an evaluation for the presence of intra- or extracardiac shunts. It is optimal to perform the catheterization under basal conditions, meaning normoxia, normocapnia, and normal pH. A diagnosis of PH is confirmed with mPAP ≥25 mm Hg, and PAH is diagnosed with mPAP ≥25 mm Hg, PAWP ≤15 mm Hg, and PVRi >3 WU m^2. If PAWP is >15 mm Hg, which signifies PH due to left heart disease, then a left heart catheterization is required to investigate the underlying etiology. In children with single ventricle physiology and post-Glenn or Fontan procedure, the lack of a subpulmonary ventricle directly pressurizing the pulmonary arteries requires modification of the above criteria. In such cases, the term PHVD is used and is diagnosed when the diastolic transpulmonary gradient is >6 mm Hg or PVRi >3 WU m^2, even if the mPAP is <25 mm Hg.[55]

Acute vasoreactivity testing is indicated to assess reversibility of PVR in PAH, including PAH-CHD, and thus indicate which children will benefit from treatment with a calcium channel blocker. Depending on the criteria used, 6%-50% of children are positive responders to AVT at the time of diagnosis, meaning they retain vascular reactivity and thus improved prognosis with targeted PAH therapy.[53,55] AVT is performed comparing basal hemodynamics to those after administration of pulmonary dilators, usually iNO with or without oxygen. Several criteria exist to judge positive response to AVT. Each criteria differs in predictive value in the response to treatment, and thus various centers may use different criteria and vasodilatory strategies.[53,55] The 2016 modified "Barst criteria" defines a positive response to AVT as follows[52,55]:

- In children with no shunt: >20% fall in mean PAP and indexed pulmonary vascular resistance (PVRi)/indexed systemic vascular resistance (SVRi) ratio without a decrease in cardiac output.
- In children with shunt: >20% fall in PVRi and PVRi/SVRi ratio with respective final values <6 WU m^2 and <0.3.

Acute vasoreactivity testing should be cautiously performed in children with PH due to left heart disease (group 2) because increased pulmonary blood flow in the setting of downstream obstruction may provoke pulmonary edema, worsening ventilation-perfusion matching, and acute clinical deterioration. Subsequent cardiac catheterizations with or without AVT are performed to assess response to a change in therapy, for routine surveillance, or to assess worsening clinical course.[52]

Other tests are indicated during the diagnostic workup and possibly routinely thereafter to supplement clinical decisions, including brain natriuretic peptide (BNP) or N-terminal (NT) proBNP as an indication of ventricular function, 6-minute walk test to follow changes in exercise tolerance, imaging to assess underlying pulmonary pathology, cardiopulmonary exercise testing (CPET), polysomnography in those at risk for sleep disordered breathing, and cardiac magnetic resonance imaging (CMR).[52] Compared to echocardiography, CMR accurately measures parameters that correlate with severity and prognosis in children with PH, particularly RV volume and function.[56] Consensus statements recommend the use of CMR during diagnostic evaluation and routine followup in those who do not require anesthesia. For those who require anesthesia for CMR, the team must weigh the perceived risk of anesthesia vs the perceived benefit of data obtained by CMR rather than echocardiography.[51,52] Additional disease states may need to be ruled out, such as autoimmune disease, coagulopathy, human immunodeficiency virus, and thyroid disease.

10 | CONTEMPORARY TREATMENT OF PAH

The approach to treatment is not the same across the various subsets of pediatric PH; however, given the disproportionally high prevalence and chronicity of PAH in children, this section will focus on treatment of PAH, understanding that PAH-CHD has additional considerations that influence treatment. The treatment strategy for pediatric PAH entails pulmonary arterial vasodilation, treatment of RV failure, avoidance of coronary ischemia and biventricular failure, and optimizing functional capacity and survival. Underlying disease states that may exacerbate PH, such as obstructive sleep apnea, must be aggressively treated. Despite lack of pediatric studies and thus regulatory approval for the vast majority of PAH-targeted pharmaceuticals, many are used as mono- or combination therapy in children, which underscores the importance of treatment in centers with specialized pediatric pulmonary hypertension programs.[7,46]

A major putative mechanism of pediatric PAH is overexpression of endogenous vasoconstrictors, such as endothelin, as well as under-expression or reduced sensitivity to endogenous vasodilators, such as NO and prostacyclin. Elucidation of these pathways has led to the development of PAH therapies that target these pathways. The major classes of PAH-targeted therapies used in children are listed in Table 2.[7,46,57]

Initiation of PAH pharmacotherapy depends on the diagnostic cardiac catheterization results and the child's risk stratification. Acute responders to AVT who are over 1 year of age are started on a trial of oral calcium channel blocker therapy and observed closely for

TABLE 2 Commonly used pediatric pulmonary arterial hypertension-targeted therapies

Medication class	Medications	Pharmacology
Calcium channel blockers	Diltiazem Nifedipine Amlodipine	Cause relaxation of vascular smooth muscle but will also result in systemic vasodilation and reduced inotropy; restricted to positive acute vasoreactivity testing responders
Endothelin receptor antagonists (ERAs)	Bosentan Ambrisentan	Block endothelin, a potent pulmonary vasoconstrictor
Phosphodiesterase type 5 (PDE5) inhibitors	Sildenafil Tadalafil	Reduce breakdown of cGMP, resulting in pulmonary vasodilation; may limit cellular hypertrophy within the vasculature
Prostacyclin analogs (prostanoids)	Epoprostenol Treprostinil Iloprost Beraprost	Replete under-expressed endogenous prostacyclin and are potent pulmonary and systemic vasodilators; have antiplatelet, antithrombotic, antiproliferative, and anti-inflammatory properties

potential clinical deterioration as a result of the negative inotropic effects of calcium channel blockade. AVT nonresponders or those who fail calcium channel blocker therapy are then risk stratified. Lower risk children may be initiated on oral therapy with endothelin receptor antagonists (ERA) or phosphodiesterase (PDE5) inhibitors. Addition of inhaled prostacyclin (iloprost, treprostinil) may be considered. Children who are high risk (WHO functional class IV) (Table 3) or experiencing acute deterioration on oral therapy are initiated on aggressive combination therapy, often including an intravenous or subcutaneous prostanoid (epoprostenol, treprostinil, iloprost, beraprost).[7,46,52] New oral prostanoids have become available and are under investigation. Additional treatment modalities may be required concomitant with PAH-targeted therapy, including heart failure management, anticoagulation, and outpatient administration of oxygen for oxygen saturation <92%.[52] Modifiable factors must be identified, such as sleep apnea/disordered breathing or relocation to a lower altitude when applicable.

Children with drug-refractory PAH and deteriorating functional status should be assessed for definitive treatment with lung transplantation, which itself carries a high rate of morbidity and mortality. An atrial septostomy may be considered prior to lung transplant in children without current shunt; an ASD will augment LV preload in the setting of acute and chronic RV failure. A downside of the atrial septostomy is that the right-to-left shunt worsens coronary, cerebral, and systemic hypoxia, and it may worsen the clinical course in those who are already hypoxemic (<80%-90%) or have mean RA pressure >20 mm Hg.[58,59] Upon recognition that adults with Eisenmenger syndrome survive longer than those with IPAH and no shunt, creation of an aortopulmonary anastomosis (Potts shunt) via interposition graft between the proximal descending aorta and the left pulmonary artery was proposed in those with suprasystemic PAP. The Potts shunt allows direct RV afterload reduction while maintaining systemic blood flow. Shunting of deoxygenated blood into the descending aorta allows LV oxygenated outflow to preferentially perfuse the coronary and cerebral circulations, which is a potential advantage over intracardiac shunts. Early data in children and adults are encouraging, suggesting that it may become a valid palliative procedure pre-lung transplantation or perhaps even an indefinite alternative to lung transplantation.[59,60] Anesthetic considerations for children undergoing Potts shunt are complex and have been reviewed elsewhere.[61]

11 | PHYSIOLOGY OF PEDIATRIC PAH

Pulmonary arterial hypertension is hallmarked by progressive elevation of PVR during the course of the disease. There are two important categories to appreciate, while understanding that progression of PVR occurs on a continuum, and overlap necessarily exists between the two categories. In the early stages of PAH, the PVR is increased but remains responsive to the normal triggers of pulmonary vascular dilation and constriction. Given the somewhat reduced cross-sectional area of the pulmonary vasculature, an acute rise in PVR causes an exaggerated decrease in pulmonary blood flow. If the RV is not capable of adequately compensating for the acutely increased afterload, acute RV failure may occur, hallmarking a PH crisis. Bronchoconstriction can accompany a PH crisis and worsen the ability to effectively oxygenate and ventilate.[52]

In the later stages of PAH, loss of appreciable vasodilation of the pulmonary vasculature results in a more rigid pulmonary circulation with persistently elevated PVR. The compensatory RV hypertrophy eventually progresses to dilation and failure, with subsequent reduced pulmonary blood flow and cardiac output. These children are at less risk for sudden increases in PVR, although small rises in PVR that may occur can be catastrophic given the minimal cross-sectional area of the pulmonary arteriole bed and limited RV functional reserve. Of note, children at this stage may still experience acute rises in PVR as progression of PHVD may not be homogenous throughout the lung; some pulmonary vascular segments can have fixed resistance with nearly destroyed vasculature, while other areas maintain reactivity and are susceptible to stimuli that provoke acute rises in PVR. Notwithstanding, the primary risk at this stage is acute on chronic RV failure in the setting of coronary hypoperfusion or small increases in PAP. Coronary perfusion to the RV normally occurs in both systole and diastole; however, in children with acute or chronic severe PH, systolic coronary perfusion is reduced or eliminated and diastolic perfusion is limited, which gravely reduces the RV's metabolic reserve.[62] Acutely elevated PAP, reduced cardiac output, and resultant aortic hypotension with worsening coronary perfusion pressure risk overwhelming the chronic adaptive mechanisms of the RV, leading to ischemia, arrhythmias, and cardiac arrest. Such children with chronically near-systemic or suprasystemic PAP pose significant risk of morbidity and mortality under anesthesia.

TABLE 3 Functional classification of pediatric pulmonary hypertension

WHO Classification of adult PH		PVRI Classification of Pediatric PH (2 of 5 age categories noted)	
Class	**Symptoms**	**Class/Age**	**Symptoms**
I	PH but without limitation of physical activity. Ordinary physical activity does not cause undue dyspnea, fatigue, chest pain or near syncope	I (1-2 yo)	Asymptomatic, growing along own centiles, no limitation of physical activity. Standing, starting to walk/walking, climbing
		I (2-5 yo)	Asymptomatic, growing normally, attending nursery/school regularly, no limitation of physical activity, playing sports with his/her classmates
II	PH resulting in slight limitation of physical activity. Comfortable at rest. Ordinary physical activity causes undue dyspnea, fatigue, chest pain or near syncope	II (1-2 yo)	Slight limitation of physical activity, unduly dyspneic and fatigued when playing. Delayed physical development. Comfortable at rest. Continues to grow along own centiles
		II (2-5 yo)	Slight limitation of physical activity, unduly dyspneic and fatigued when playing with classmates. Comfortable at rest. Continues to grow along own centiles. Nursery/school attendance 75% normal. No chest pain
III	PH resulting in marked limitation of activity. Comfortable at rest. Less than ordinary activity causes dyspnea or fatigue, chest pain or near syncope	IIIa (1-2 yo)	Marked limitation of physical activity. Regression of learned physical activities. Reluctant to play. Quiet and needs frequent naps. Hesitant and unadventurous. Comfortable at rest. Less than ordinary activity causes undue dyspnea, fatigue, or syncope and/or presyncope. Growth compromised. Poor appetite
		IIIa (2-5 yo)	Marked limitation of physical activity Regression of learned physical activities. Not climbing stairs, reluctant to play with friends. Hesitant and unadventurous. Comfortable at rest. Less than ordinary activity (dressing) causes undue dyspnea, fatigue, syncope and/or presyncope or chest pain. Nursery/schooling compromised <50% normal attendance
		IIIb (1-2 yo)	Growth severely compromised. Poor appetite. Supplemental feeding. Less than ordinary activity causes undue fatigue or syncope. Plus features of Class IIIa
		IIIb (2-5 yo)	Unable to attend nursery/school, but mobile at home. Wheelchair needed outside home. Growth compromised. Poor appetite. Supplemental feeding. Less than ordinary activity causes undue fatigue, syncope or chest pain. Plus features of Class IIIa
IV	PH resulting in inability to carry out any physical activity without symptoms. These patients manifest symptoms of right heart failure. Dyspnea and/or fatigue may be present even at rest. Discomfort is increased by any physical activity undertaken. Syncope or near syncope can occur	IV (1-2 yo)	Unable to carry out any physical activity without undue dyspnea, fatigue or syncope, not interacting with family. Syncope and/or right heart failure. Plus features of Class III
		IV (2-5 yo)	Unable to carry out any physical activity without undue dyspnea, fatigue, syncope or chest pain, unable to attend school, wheelchair dependent, not interacting with friends. Syncope and/or right heart failure. Plus features of Class III

Summarized from Lammers et al.[66] The PVRI Classification contains different definitions for ages 0-0.5, 0.5-1, 1-2, 2-5, and 5-16. Only definitions for age groups 1-2 and 2-5 yo shown here as an example.
PH, pulmonary hypertension; PVRI, Pulmonary Vascular Research Institute; WHO, World Health Organization; yo, years old.

Right ventricular diastolic dysfunction and RV failure play a central role in morbidity and mortality of pediatric PH and are thus a key prognostic factor. Due to effective remodeling and perhaps improved metabolic efficiency of the pediatric RV under chronic strain, it is not infrequent for children, especially compared to adults, to have high PAP, nearsyncope, and exertional dyspnea yet remain in functional class II for a prolonged period due to preserved RV systolic and diastolic function.[39,63] The mechanism of syncope is not understood but likely relates to a transient elevation of the PAP to aortic pressure ratio, resulting in an acute reduction in cerebral blood flow.[64] Physical limitations in the setting of preserved RV function stem from the child's limited reserve capacity to provide cardiac output and adequate oxygen delivery (DO_2) in times of increased demand. Another increasingly recognized and important impact of RV dysfunction is adverse ventricular interdependence leading to biventricular mechanical discoordination with reduced LV diastolic function and contractile efficiency.[65] Cardiac arrhythmias are poorly tolerated due to loss of atrial contraction to fill the stiff RV, atrioventricular synchrony, ventricular coordination, and adequate filling times during tachydysrhythmias, with clinical symptoms worsened by the degree of RV dysfunction and tenuous oxygen supply:demand relationship of coronary perfusion.

Functional status classifications are used to stratify the clinical severity of PH in children and adults, thus creating a common

TABLE 4 Summary of patient, procedural, and anesthetic risk factors that confer incremental risk of perioperative morbidity and mortality

Hemodynamic factors
CI <2.5 L/min/m^2
mPAP/mSAP ratio or sPAP/sSAP ratio >0.75
Mean RA pressure >10-15 mm Hg
PVRi >15 WU m^2
Severe right ventricular enlargement, dysfunction, or failure
TAPSE <10 mm (>1 y old)
S/D ratio >1.4 (TR jet)
Pericardial effusion
Patient factors
Treatment naïve or recent progressions/exacerbation of disease
Younger age, especially <1 y of age
History of syncope
Clinical evidence of right ventricular failure
Failure to thrive
WHO functional class III or IV
Elevated BNP >59.5 pg/mL; elevated NT-proBNP
Comorbidities: significant sleep disordered breathing, obesity, reactive airway disease, chronic aspiration, neuromuscular dysfunction, sickle cell disease, coronary anomalies, congenital/acquired cardiac disease, or other major organ dysfunction
Chronic lung disease
Abrupt withdrawal of PH-specific therapy
Intercurrent illness (eg, acute lung injury, infection)
Surgical/procedural factors
Major surgery associated with major fluid shifts, significant systemic inflammatory response, extreme sympathetic tone, compromise of lung vessels, risk of embolization of surgical materials
Airway, abdominal, cardiac, or interventional cardiac catheterization surgery/procedures
Higher risk infant procedures: central venous line insertion, airway, or thoracic surgery (congenital diaphragmatic hernia repair, diaphragm plication, video-assisted thoracoscopic surgery)
Long procedural length
Emergent surgery
Postsurgical risks
Hypovolemia and fluid shifts, bleeding, vomiting
Systemic inflammatory response, reperfusion injury, excessive pain
Potential for airway compression or compromise, airway bleeding/tracheal secretions
Anesthetic factors
Use of general anesthesia
ASA status ≥III
Unstable intraoperative course: hemodynamic lability, appearance or worsening of arrhythmias, intraoperative vasoactive agent use; difficulties with oxygenation or ventilation
Difficult airway
Increased requirement for long-acting opioids
Difficult postoperative recovery with escalated cardiopulmonary support
Difficult postoperative pain management

Adapted from Refs. ([1,39,51,52,63,67]).
ASA, American Society of Anesthesia; CI, cardiac index, mPAP, mean pulmonary artery pressure; mSAP, mean systemic arterial pressure; PH, pulmonary hypertension; PVRI, indexed pulmonary vascular resistance; RA, right atrial; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation; WHO, World Health Organization.

lexicon for diagnosis, treatment, and research. The functional status correlates, to a degree, to risk stratification for anesthesia. The WHO functional class is most commonly used, although it is an adult PH classification. The Pediatric Task Force of the Pulmonary Vascular Research Institute (PVRI) further subdivided the functional classifications for children, and two of the five age groups are summarized in Table 3.[66]

12 | STRATIFYING ANESTHETIC RISK

Children with PH have a significantly elevated risk of perioperative morbidity and mortality, with rates perhaps 20-fold greater than all children undergoing anesthesia. Several pediatric studies have reported an incidence of perioperative cardiac arrest ranging from 0% to 5% and perioperative death up to 1.5%.[1,39,67–72] However, defining precise risk stratification for anesthesia in the child with PH is problematic.[1] First, pediatric PAH is very uncommon, and thus the overall incidence of perioperative major morbidity and mortality is low. Second, most pediatric studies are retrospective and comparatively heterogeneous in regard to inclusion criteria, types of procedures and surgeries included, time frame inclusive of postoperative complications, changes to classification and management of pediatric PH over time, and institutional practice variation.[1,39,67–72] Third, the various subgroups of pediatric PH may confer differing perioperative risk. As a testament to this, statistical analyses of risk factors in different studies have often conflicted with each other. However, some commonalities exist and are summarized in Table 4. Factors associated with perioperative risk with some consistency across studies include systemic or suprasystemic PAP, presence of syncope, elevated mean RA pressure, decreased RV function, young age (especially <1 year old), and home oxygen use. These factors are intuitive, as they all reflect the severity of the child's PH, except young age, which is an independent anesthetic risk in general. The etiology of PH is inconsistently associated with risk.[1,39,67–72] Anecdotally, newly diagnosed children presenting for cardiac catheterization are also at significant risk, perhaps because most have yet to be medically optimized until after the catheterization results.

The factors summarized above and in Table 4 predominantly represent children with PAH, meaning IPAH and PAH-CHD. Data are lacking to delineate perioperative risk in the neonatal/infant PH population, predominantly those with PPHN or BPD-PH. An exception is a recent study focusing on 77 infants with PH undergoing 148

procedures at a median of 6 months of age.[67] The cohort included infants with BPD-PH (50%), PAH-CHD (30%), and CDH (14%; thus representing PPHN) undergoing cardiac and noncardiac procedures, including repair of CDH. Complications included postoperative cardiac arrest (4.7%), intraoperative cardiac arrest (2%), and postoperative death (1.4%). Multivariate analysis demonstrated more frequent complications in children with severe baseline PH, but PH etiology was not associated with risk. Overall, the risk of major complications in this infant cohort mirrors the gravity of risk in older children with PAH; however, it must be noted that this patient population had high rates of severe cardiopulmonary and other systemic disease in addition to the presence of PH, limiting the applicability to other patient populations.

13 | PREOPERATIVE EVALUATION

What level of anesthesia expertise is required to anesthetize a child with PH/PAH? The answer to this question has not been directly studied. However, given the serious risk anesthetizing children with PH and the uncertainty of classifying an individual child's risk of perioperative complications, the American Heart Association and American Thoracic Society guidelines on Pediatric Pulmonary Hypertension state that "elective surgery for patients with pediatric PH should be performed at hospitals with expertise in PH and in consultation with the pediatric PH service and anesthesiologists with experience in the perioperative management of children with PH."[52] It is the authors' opinion that children at risk of perioperative deterioration be anesthetized at hospitals with pediatric ECLS available. In the event of a child requiring urgent surgery at a hospital without pediatric PH expertise, phone consultation with a pediatric PH center should occur, and transfer to that center should be considered if feasible.

The preoperative evaluation should include case discussion between the anesthesiologist and the child's cardiologist.[52] Prior to a procedure, the anesthesiologist must ensure that the child's PH status is optimized (not experiencing acute PH exacerbation), has no acute comorbidity that might worsen PH (infection, reactive airway exacerbation, gastrointestinal illness with dehydration), and all PH medications are taken per schedule. The factors in Table 3 should be carefully assessed to both understand the severity of the child's disease as well as understand risk stratification for preoperative, intraoperative, and postoperative management. Children with moderate, severe, or poorly responsive PH deserve preoperative multidisciplinary planning and aggressive pharmacologic optimization prior to surgery. Strong consideration should be given to preoperative hospital admission and overnight intravenous hydration during fasting in children at higher perioperative risk. Postoperative disposition planning should occur before the day of surgery, including a planned postoperative intensive care admission or the ability to escalate to intensive care if perioperative factors change on the day of surgery.

A history and physical examination will reveal many of the factors listed in Table 4. Recall that the presence of syncope or near syncope is an ominous sign, regardless of the listed WHO functional class. A BNP value >59.5 pg/mL has been shown to be an indicator of high risk for future clinical deterioration in pediatric PAH, as it reflects the severity of RV dysfunction.[63] The most recent echocardiogram should be reviewed, while appreciating that the test is a snapshot of the child at one moment in time and may not represent the cardiopulmonary status on the day of surgery. In most cases, an echo should be available within the past 3-6 months, as that is the recommended surveillance interval in children with active disease.[51] The same is true of the most recent cardiac catheterization. Furthermore, echocardiography and catheterization results must be interpreted in light of the overall cardiopulmonary status of the child. For instance, the PAP should be interpreted together with the underlying RV function. Consider the child with systemic PAP and preserved RV function; sudden deterioration of RV function will lead to less pulmonary blood flow and potentially lower PAP, yet this child is sicker despite a lower PAP. Overall, RV adaptation to the chronically elevated PAP, rather than the absolute PAP or PVR, determines symptoms and risk for acute deterioration. The interpretation of PAH and RV function in the setting of CHD with residual shunts is complex, and discussion with the child's cardiologist is recommended. If any child with PH has not been recently assessed by their cardiologist or is in the midst of an acute change in clinical status, consideration should be given to delaying surgery until gaining assurance that the child is optimized.

14 | ANESTHETIC CONSIDERATIONS SPECIFIC TO NEONATES AND INFANTS WITH PPHN AND BPD-PH

Due to coexisting issues of prematurity, pulmonary dysfunction, or persistence of fetal circulation, neonates with PAH/PH have unique characteristics that deserve specific mention. Some issues will be most relevant shortly after birth, while others will persist through the neonatal period and into infancy while acute disease remains. In addition, the intraoperative considerations discussed in later sections are also relevant to this population.

14.1 | Persistent pulmonary hypertension of the newborn

Neonates with PPHN and reactive PVR (eg, sepsis, asphyxia, pneumonia) are at risk for perioperative PH crises. Those with predominantly fixed PVR (eg, CDH, lung hypoplasia) are at risk for profound hypoxemia and low cardiac output in the setting of significantly elevated RV afterload. Goal-directed oxygenation and ventilation are paramount. Normoxia and normocapnia (relative to the patient's baseline) are key components to maintaining baseline PVR and thus overall DO_2. However, hyperoxia (PaO_2 >100 mm Hg) does not provide further pulmonary vasodilation, it promotes free radical formation with resultant inflammation and pulmonary vasoconstriction, and hyperoxia lessens the vasodilator response to endogenous and exogenous NO.[14,73] Although the optimal SaO_2 in this setting is unknown, data suggest that a preductal SaO_2 between 92% and

95% strikes an appropriate balance between ensuring adequate DO_2 while avoiding oxidative stress to the lungs.[52,74] Overall, hyperoxia and hypocapnia are associated with increased morbidity and mortality in this cohort.[75]

Intraoperative mechanical ventilation should be carefully managed. The neonatal lung, especially in the setting of CLD, is susceptible to volutrauma with resultant morbidity. Data are lacking to suggest optimal tidal volumes in neonates; however, a lower tidal volume strategy (eg ~6 mL/kg) with "permissive hypercapnia" has gained some acceptance in neonates and children, particularly those with CDH.[76] The first risk with low tidal volumes is resultant atelectasis with increased intrapulmonary shunting and increased PVR. Judicious use of positive end-expiratory pressure will assist maintaining recruitment throughout the ventilatory cycle. The second risk is hypercapnia. Severe hypercapnia and subsequent systemic acidosis risk elevated PVR and cardiopulmonary decompensation. However, mild permissive hypercapnia can be tolerated chronically if systemic pH remains neutral.[77] Conversely, acutely reducing P_aCO_2, even if that number falls within a "normal" range, will be relative hypocapnia to that child. While an ideal endtidal CO_2 cannot be stated, ventilation to a habitual endtidal CO_2 of 35 mm Hg in a chronically hypercarbic child may well induce relative hypocapnia with risks of cerebral hypoperfusion and subsequent periventricular leukomalacia. Overall, the balance is to effectively ventilate and oxygenate with acceptably low tidal volumes, thus avoiding volutrauma, while also avoiding relative hypocapnia or severe hypercapnia.

14.2 | Bronchopulmonary dysplasia-related PH

The risk of anesthesia in infants with BPD-PH will depend on the severity of underlying factors. These include the severity of PH and parenchymal lung disease, as well as the presence of any airway disease or associated comorbidities. Most infants with BPD-PH will have reactive PVR, and they are at risk for PH crisis under anesthesia.[29] As such, attention to normoxia, normocapnia relative to the neonate's baseline, normal acid-base status, and normothermia is important to limit escalations in PVR, particularly during induction and emergence from anesthesia. Parenchymal lung disease with alveolar dysfunction and poor pulmonary compliance may hinder oxygenation and ventilation. Continued use of the intensive care unit ventilator in the operating room may be required in the child with poor pulmonary reserve. This population may require ophthalmologic procedures to treat retinopathy of prematurity, and phenylephrine eye drops should be used with caution due to a risk of PH crisis under anesthesia.[78]

Bronchopulmonary dysplasia is also associated with large airway obstruction due in part to prolonged tracheal intubation and mechanical ventilation, and tracheo-bronchomalacia are also common.[79] Perioperatively, the child should be closely monitored for acute airway obstruction, which may provoke elevated PVR and decompensation. Airway hyperreactivity with the risk of bronchospasm and subsequent cardiopulmonary collapse is possible in the neonatal age, and reactive airway disease becomes an increasingly important morbidity in survivors of BPD months to years after birth.[29]

15 | INTRAOPERATIVE MANAGEMENT

15.1 | Preparation

The overarching goal of anesthetic management is to provide adequate anesthesia and analgesia for the procedure, while avoiding RV failure, increased PVR, low SVR, and coronary ischemia. There is currently no reported "best" anesthetic that achieves these goals; rather, the needs of the patient and procedure will influence the appropriate anesthetic plan, and a complete understanding of all potential hemodynamic effects of each anesthetic agent is mandatory to avoid complications. Given the limited cardiopulmonary reserve of many of these children, the operating room/anesthetizing site should be carefully prepared before beginning anesthesia. All equipment and medications that may be required should be immediately accessible, including those for emergent resuscitation. An iNO machine on standby in the OR is encouraged to rescue a PH crisis in high-risk children. Any continuously administered pulmonary vasodilator (inhaled or intravenous) must be maintained, and a central venous line for infusion of continuous prostacyclin analogs should be considered a dedicated line and never used for intraoperative venous access. All oral PH medications should be taken on schedule with a small sip of water. The decision of whether to continue administration of oral diuretics and antihypertensive agents, as well as anticoagulation management, should occur in consultation with the child's cardiologist. If the child requires prolonged NPO status or bowel prep, then preoperative transition to intravenous therapy (ie, sildenafil) may be required.

The decision to premedicate the child with PAH carries risks and benefits. Premedicating an anxious child can alleviate the increased PVR and oxygen consumption associated with agitation preinduction; however, oversedation and resultant hypoventilation and hypercapnia should be avoided, especially in children with baseline airway obstruction. Use of pulse oximetry is essential after premedication.

15.2 | Induction, maintenance, and emergence

Induction of anesthesia is arguably the riskiest time of the anesthetic. It is a period of potential hypoxia, hypercapnia, decreased SVR from induction agents, and noxious stimulus during airway instrumentation, all of which risk clinical deterioration as previously discussed. The goal is an induction with minimal changes to SVR and PVR, while ensuring adequate ventilation. During general anesthesia, the choice of endotracheal intubation, supraglottic airway device, or natural airway is dependent on the needs of the child and the procedure. Preparation for intubation requires a balance between sufficient analgesia to blunt the noxious stimulus while also maintaining adequate SVR and myocardial performance. The trachea should be intubated quickly without allowing significant hypoxia and hypercapnia. A supraglottic airway may reduce the need for as deep an

induction compared to endotracheal intubation, but one must consider inherent risks, including difficulty managing a laryngospasm or bronchospasm and adequately supporting ventilation in the setting of significant laryngeal leak. Likewise, spontaneous ventilation through a natural airway limits the ability to accurately measure endtidal CO_2 or rapidly detect hypoventilation.

Most anesthetic drugs have significant cardiopulmonary effects. Anesthetic gases reduce SVR and myocardial contractility in a dose-dependent fashion; however, they attenuate hypoxic pulmonary vasoconstriction and may provide a small amount of pulmonary vasodilation. Opioids blunt the response to noxious stimuli and as such limit the risk of PH crisis from that provocation; long-acting opioids should be used carefully given the risk of postoperative respiratory depression. Ketamine, which previously was thought to cause pulmonary vasoconstriction, has been shown to have little to no pulmonary vascular effects.[80] Its properties of combined anesthesia and analgesia with little impact on respiratory drive makes it an attractive choice in children with PH. Etomidate has a long track record of cardiac stability. Propofol, on the other hand, significantly reduces SVR and has a more limited role in fragile cardiac states. Excellent detailed reviews of the effect of anesthetic medications in children with PH/PAH are available.[80,81]

Ventilation is an important consideration. Outside of the newborn/neonatal period, oxygen may be used liberally if acceptable for the procedure. Oxygenation will decrease PVR, mildly increase SVR, and may even reduce oxygen consumption and maintain higher mixed venous saturations in the event of right-to-left shunt physiology.[82] When the child is breathing spontaneously, the child must be closely monitored for hypoventilation, atelectasis, and hypercapnia, with immediate measures to support ventilation as indicated. During mechanical ventilation, excessive positive end-expiratory pressure (PEEP) or prolonged inspiratory times will increase PVR and reduce preload conditions to the LV.

Akin to induction, emergence from anesthesia may provoke spikes in PVR if the child has a catecholamine surge (coughing, tracheal stimulation, pharyngeal suctioning) or postsurgical pain. Deep extubation can be considered in children without difficult airways, but the risk of hypoventilation should be balanced against the risk of noxious stimulus from awake extubation. An option is to deep extubate but remain in the operating room with proximity to resuscitation supplies until the patient has sufficiently emerged from anesthesia and is demonstrating adequate ventilation and airway patency.

15.3 | Pulmonary hypertensive crisis

A PH crisis occurs when there is an acute insult to baseline cardiopulmonary mechanics (eg, rise in PVR), compensatory mechanisms of chronic PH fail, RV function decompensates, and LV preload acutely decreases resulting in inadequate cardiac output and coronary perfusion. This cycle of deterioration, as shown in Figure 1, can quickly lead to biventricular ischemia and cardiac arrest. Anesthesia may be additive by blunting compensatory mechanisms. Hypoxia, hypercapnia, acidosis, hypothermia, and noxious stimuli increase PVR and are known causes of acute PH crisis under anesthesia, particularly in children who retain modifiable PVR. A precipitous fall in SVR during induction or maintenance of anesthesia also risks increasing the PAP/systemic arterial pressure ratio and provoking PH crisis. Early signs of increased PVR or decreased SVR must be treated quickly and aggressively to avoid morbidity. Other mechanism may instigate a PH crisis, especially in children with advanced PAH and relatively fixed PVR. These include reduced preload with subsequently reduced RV output, anesthesia-induced myocardial depression, coronary hypoperfusion and ischemia, arrhythmias, pneumothorax, pulmonary embolism, sepsis, pericardial effusion, bronchospasm, anaphylaxis, etc. In the event of ongoing crises, the differential diagnosis must be sought during ongoing resuscitation, while at the same time alerting personnel to ready ECLS support.

The clinical signs of a PH crisis may range from gradually deteriorating oxygenation and cardiac output to sudden cardiopulmonary collapse. Signs of PH crisis under anesthesia include decreased endtidal CO_2, arterial desaturation, cerebral near infrared spectroscopy desaturation, sinus tachycardia that is often followed by bradycardia, ECG changes consistent with RV strain, and hypotension. A PH crisis provoked by a noxious stimulus may be immediately preceded by hypertension and tachycardia prior to decompensation. In a structurally normal heart, echocardiography during a crisis will likely demonstrate a dilated, poorly contractile RV and underfilled LV; tricuspid regurgitation may increase in the setting of increase RV afterload, but it may be unchanged or even decreased in the setting of RV failure.[83] The presence of a pre-tricuspid or post-tricuspid shunt allows improved LV filling in the setting of PH crisis, but this is at the expense of worsening hypoxemia that can further contribute to ongoing deterioration.

If a PH crisis occurs, immediate treatment includes administration of 100% oxygen, mild hyperventilation, administration of a selective pulmonary vasodilator (iNO), ventricular support (epinephrine, vasopressin), systemic alkalinization (sodium bicarbonate and/or hyperventilation), and deepening of anesthesia if noxious stimuli are a possible trigger.[77,84] RV function is preload dependent in pediatric PH, and a fluid bolus may be beneficial if hypovolemia is suspected; however, conditions may worsen in the setting of decompensated RV failure.[77] Administration of pulmonary vasodilators should be considered during a crisis, understanding that their efficacy may be notably less in children with long-standing PAH and nonreactive pulmonary vasculature. iNO is the first choice in mechanically ventilated patients. iNO may be rapidly delivered, and it selectively reduces PVR without a significant decrease in SVR. Many other pulmonary vasodilators (sildenafil, milrinone, prostanoids) also undesirably decrease SVR. Along with the obvious benefit of organ perfusion, maintenance of SVR is important for coronary perfusion and interventricular septal positioning in the setting of acute RV strain. As such, vasopressin may be a useful adjunct during PH crisis. Vasopressin and terlipressin increase SVR while also decreasing PVR, thus beneficially decreasing the PVR:SVR ratio; this is in contrast to phenylephrine and norepinephrine, which increase PVR.[77,85] A

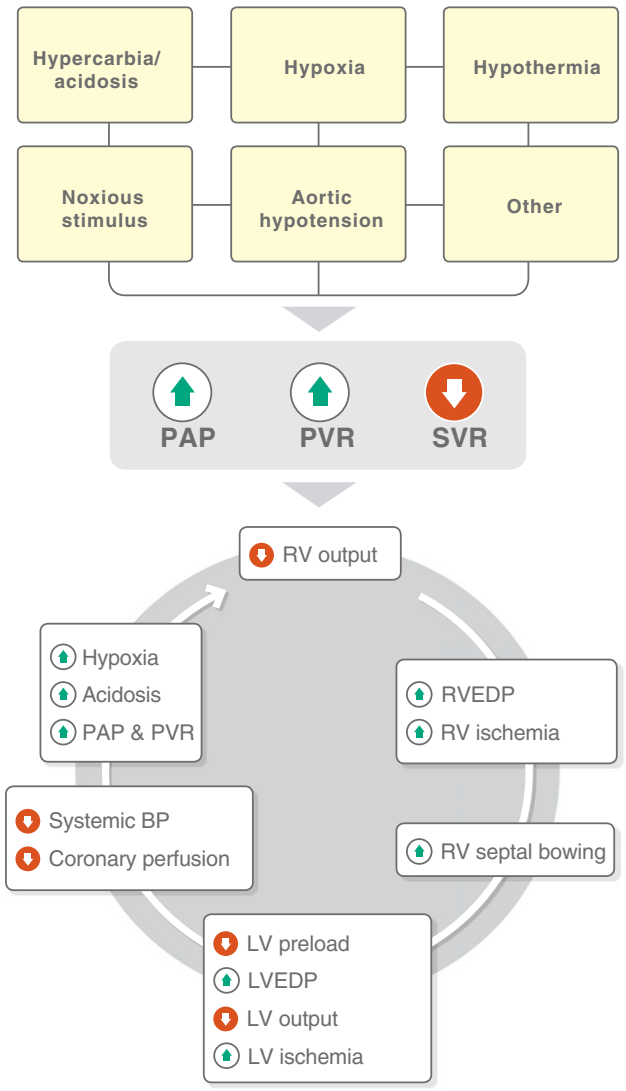

FIGURE 1 The cycle of pulmonary hypertensive crisis. Examples of "other:" hypovolemia, anesthesia-induced myocardial suppression, arrhythmias, pneumothorax, pulmonary embolism, sepsis, pericardial effusion, bronchospasm, anaphylaxis, ventilation-perfusion mismatch. BP, blood pressure; LV, left ventricle; LVEDP, left ventricular enddiastolic pressure; PAP, pulmonary artery pressure; PVR, pulmonary vascular resistance; RV, right ventricle; RVEDP, right ventricular enddiastolic pressure; SVR, systemic vascular resistance. Figure courtesy of Tom Latham

benefit of norepinephrine, despite the risk of increasing PVR, is concurrent beta agonism to support ventricular function in the setting of the increased afterload. The impact of afterload manipulation in the setting of a post-tricuspid shunt must be considered, and the use of echocardiography during resuscitation is highly recommended in this setting.

Evidence of ongoing RV or LV failure justifies the addition of inotropic support. Dobutamine, dopamine, or epinephrine may be acutely required to improve biventricular inotropy, while being mindful that tachycardia limits ventricular filling and increases myocardial oxygen consumption. Milrinone and levosimendan are useful inotropes as they also reduce PVR and avoid tachycardiac; however, the necessity of a loading dose in the acute phase that also decreases SVR is less appealing. If PH crisis culminates with circulatory collapse, early use of ECLS is warranted because resuscitation of cardiac arrest in children with PH is difficult and associated with poor outcomes.[77] Insufficient data are available to estimate the perioperative mortality rate in children with PH who require ECLS. A large multicenter retrospective review of 14 880 children with PH admitted to intensive care revealed a 3.8% rate of ECLS, with a subsequent 45% mortality rate.[86] Of note, the cohort in this study included all age groups, all forms of PH, and high rates of CHD, cardiac failure, respiratory failure, and sepsis, thus limiting applicability to the perioperative setting. In another multicenter study of 4401 children undergoing 6339 cardiac catheterizations, 1416 procedures were conducted in children with IPAH. Of these, 1.8% of children underwent ECLS, and 36% (9 of 16) of those requiring ECLS died prior to discharge.[87]

16 | POSTOPERATIVE DISPOSITION

Careful consideration must be given to postoperative disposition in children with PH because the risk of PH crisis, morbidity, and mortality remains even after emerging from anesthesia. Recent recommendations by Chau et al[1] provide an excellent framework to guide disposition planning for an individual child. In brief, the postanesthetic setting should proactively minimize the risk of PH crisis, ventricular failure, and myocardial ischemia until the child has returned to their preoperative baseline. Children with a lower risk status who underwent uneventful procedures may be considered for outpatient status with or without extended monitoring in the postanesthesia care unit. Postoperative admission to the ward or intensive care unit is warranted with increasing risk factors in Table 4. Data in infants after congenital heart surgery have demonstrated that routine use of iNO reduces the rate of postoperative PH crises, although data are lacking outside of the cardiac surgery cohort.[88] Factors that delay a child's return to their baseline status include need for ongoing sedation, pain control, hydration (eg, ongoing nausea and vomiting), airway/pulmonary support, cardiac support, and ability to resume oral PH medications. Airway obstruction and hypoventilation are significant risk factors for postoperative decompensation and cardiac arrest in the immediate postoperative setting. There are no studies suggesting criteria for discharge or de-escalation of care in children with PH; notwithstanding, a conservative approach in these children is warranted.[1]

17 | SUMMARY

Anesthetizing the child with PH is clearly associated with significantly heightened morbidity and mortality. This requires a thoughtful approach for the entire perioperative period. Effective multidisciplinary communication will help identify those at higher risk and allow ample time to plan potential preoperative admission for hydration and optimization, assigning an anesthesiologist with appropriate

expertise, and postoperative disposition. The goal of anesthesia is to provide adequate anesthesia and analgesia as required by the procedure, while maintaining baseline PVR, SVR, and biventricular function. If cardiopulmonary instability or pulmonary hypertensive crisis occurs, treatment must be swift to avoid cardiopulmonary collapse.

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ETHICAL APPROVAL

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CONFLICT OF INTEREST

The authors report no conflict of interest.

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