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Review Article

Paediatric pulmonary hypertension due to congenital heart disease in non-cardiac surgery: Anaesthetic implications

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ABSTRACT

Paediatric patients with pulmonary hypertension associated with Congenital Heart Disease (PH-CHD) are frequently encountered in non-cardiac surgical settings. Although the pharmacological and surgical management of the underlying CHD in the group has improved yet its management remains challenging due to associated high morbidity and mortality. The dilemma prevails more so because of the dearth of adequate literature describing its pathophysiology and management in non-cardiac surgical settings. There are no specific guidelines pertaining to paediatric PH-CHD care, and the precepts have been extrapolated from adult studies and guidelines. This review article intends to apprise the pathophysiology of PH-CHD, its management, and its perioperative care with special emphasis on pulmonary vascular hypertensive crisis in these patients posted for non-cardiac procedures.

1. Introduction

Pulmonary Hypertension (PH) in paediatric population is associated with diverse etiology, mostly either idiopathic or associated with congenital heart disease (CHD).

CHD occurs approximately 6-10 per 1000 live births, and 4-5% of these patients go in to develop PH. About 30% among these might require surgery during the first year of life due to extracardiac anomalies such as tracheoesophageal fistula, anorectal anomalies, cleft lip, cleft palate, renal and skeletal pathologies.[1,2]

The improvements in diagnosis and management of CHD have not just led to improved survival rates but also increased prevalence of various associated cardiac sequelae, such as arrhythmias, postoperative valvar and vascular structural defects, ventricular dysfunction, and PH. But despite advances in diagnosis, and management; prognosis remains poor in surgical settings, especially in the PH group.[3]

The established preoperative risk assessment guidelines may underestimate the associated risks and calls for a meticulous and vigilant anaesthetic management in paediatric CHD patients with PH (PH-CHD) posted for surgical procedures.[4] This article focusses on CHD associated PH; and the perioperative management of this paediatric cohort in non-cardiac surgical settings.

2. Materials and Methods

A comprehensive search was performed on PUBMED search engine for articles having the following key words 'pulmonary hypertension', 'pulmonary arterial hypertension', paediatric pulmonary hypertension', 'congenital heart disease', 'treatment/management of pulmonary hypertension', 'surgical procedures', 'non cardiac surgery', 'cardiac catheterization' "perioperative

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care in PH". A total of 379 articles were identified in the paediatric cohort of PH-CHD within the last score. After excluding duplicate articles, drug trials, articles focusing on specific subgroup of CHD, and personal perspectives; a total of 62 articles comprising of systematic review and meta-analyses, review articles, scientific statements, and randomized controlled trials were included in the review. Because of the paucity of data on standard management guidelines in the paediatric pulmonary hypertension cohort; data from adult literature emphasizing on management guidelines and risk stratification has been incorporated.

3. Epidemiology

The Netherlands data reports the annual incidence and point prevalence of PAH-CHD cases per million children as 2.2 and 15.6 respectively.[5] Registry to Evaluate Early and Long Term Pulmonary Arterial Hypertension (PAH) Disease (REVEAL) and the French Registry approximate PAH-CHD to be 10-11% of all cases of paediatric PH,[6] while the Tracking Outcomes and Practice in Paediatric Pulmonary Hypertension registry (TOPP) estimates 36% of 362 patients to be due to PAH-CHD.[6] According to a 20-years report based on experience by National Paediatric Pulmonary Hypertension Service, UK; the median age of diagnosis of PH was 2.6 years with 51.0% being females. CHD was the underlying etiology in 62.9%, followed by idiopathic PAH in 22.3% cases.[7]

4. Definition

The Paediatric Task Force follows the newly proposed adult definition, defined PH as a mean pulmonary arterial pressure (mPAP) >20 mm Hg measured during right heart catheterization at rest while abandoning the previous definition of mPAP >25 mmHg at 3 months of age. The impact of mPAP between 21-24mm Hg is unknown in paediatric age group. Hemodynamically, PH is broadly categorized into pre-capillary and postcapillary PH based on pulmonary vascular resistance (PVR) and pulmonary arterial/capillary wedge pressure (PAWP or PCWP) values. (Table 1)[8] In PH-CHD, it is also vital to distinguish pulmonary arterial hypertension (PAH) with low PVR from high PVR, as vasoconstriction and arteriolar remodelling in the latter has a bearing on management strategy.[9,10] The threshold value for PVR is >2 Wood Units and PCWP ≤15 mm Hg.[9] It is recommended to use PVR indexed to body surface area (PVRI).[11] PVRI value ≥3 WU·m2 indicates pulmonary vascular disease (PVD).[8,9,12]

But the above definition may also be erroneous in view of the lack of standardization of provocative challenges to assess vasoreactivity, ideal preload and accurate pulmonary capillary wedge pressure across respiratory cycle.[13]

Table 1: Haemodynamic definitions of pulmonary hypertension[8]

Pulmonary Hypertension (PH)	mPAP >20 mmHg
Pre-capillary Pulmonary Hypertension (PAH)	mPAP >20 mmHg; PAWP ≤15 mmHg; PVR >2 WU
Isolated post-capillary Pulmonary Hypertension (PVH)	mPAP >20 mmHg; PAWP >15 mmHg; PVR ≤2 WU
Combined post & pre-capillary Pulmonary Hypertension	mPAP >20 mmHg; PAWP >15 mmHg; PVR >2 WU
Unclassified Pulmonary Hypertension	mPAP >20 mmHg; PAWP ≤15 mmHg; PVR ≤2 WU

PH: pulmonary hypertension; mPAP: mean pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure; PVR: pulmonary vascular resistance; WU: Wood units

5. Classification

According to 2022 ECS (European Society of Cardiology)/ ERS (European Respiratory Society) Guidelines for the diagnosis and treatment of pulmonary hypertension,[8] and 6th World Symposium on Pulmonary Hypertension (WSPH) of 2019,[9,12] paediatric PH is classified into 5 categories as depicted in Table 2. The subgroup 1.4.4 PH associated with CHD includes patients with volume overload to the pulmonary arteries (PA). Transient PH may occur following closure of a shunt defect and accounts for one of the commonest, and difficult to manage forms of PH in children. Group 2 comprises of PH due to left heart disease (post capillary obstructive lesion) while Group 5.4 includes complex congenital heart diseases with congenital anomalies of the pulmonary vasculature having differential pulmonary blood flow (segmental PH), single ventricle physiology and scimitar syndrome.

6. Prognosis

Paediatric PH entails significant morbidity and mortality. A systematic review and meta-analysis by Ploegstra et al.[14] highlighted that WHO-Functional Classification (WHO-FC), NT-proBNP, mean right atrial pressure (mRAP), PVRI, cardiac index (CI), and acute vasoreactivity testing (AVT) determine prognosis. AVT has a potential role in calcium channel blocker (CCB) therapy, and in assessment of CHD operability.[8,12] Few studies report mPAP (mean pulmonary arterial pressure)/mSAP (mean systemic arterial pressure) ratio >0.75, mRAP (mean right atrial pressure) >10 mmHg, and PVRI >20 WU·m2 affecting prognosis.[8,15–17] Failure to thrive predicts mortality,[9] while unlike adults baseline 6-min walk distance has a limited role.[5] Since the treatment relies on risk stratification, the current guidelines utilize certain risk assessment tools as analyzed in retrospective observational studies viz. right ventricular (RV) failure,

Table 2: Clinical classification of pulmonary hypertension (PH)[8,9,11]

Group 1 Pulmonary arterial hypertension (PAH)	
1.1 Idiopathic	
1.2 Heritable	
1.3 Associated with drugs and toxins	
1.4 Associated with:	
1.4.1 Connective tissue disease	
1.4.2 HIV	
1.4.3 Portal hypertension	
1**.4.4 Congenital heart disease**	**Group 1.4.4 Clinical classification of pulmonary hypertension associated with congenital heart disease**
	Eisenmenger syndrome: Closing the defects is contraindicated.
	PAH (with prevalent systemic-to-pulmonary shunts)
	PAH (with small/coincidental defects)
	PAH (with small/coincidental defects)
1.4.5 Schistosomiasis	
1.5 PAH with features of venous/capillary (PVOD/PCH) involvement	
1.6 Persistent PH of the new-born	
Group 2 PH associated with left heart disease	
2.1 Heart failure with preserved ejection fraction	
2.1 Heart failure with preserved ejection fraction	
2.2 Heart failure with reduced ejection fraction	
2.3 Valvular heart disease	
2.4 Congenital/acquired cardiovascular conditions leading to post-capillary PH	**Group 2.4 Congenital post-capillary obstructive lesions**
	Pulmonary vein stenosis
	Cor-triatriatum
	Obstructed total anomalous pulmonary venous return
	Mitral/aortic stenosis (including supra/sub-valvular)
	Coarctation of the aorta
Group 3 PH associated with lung diseases and/or hypoxia	
3.6 Developmental lung disorders (e.g., Downs Syndrome)	
Group 4 PH associated with pulmonary artery obstructions	
4.1 CTEPH	
4.2 Other pulmonary artery obstructions (e.g. congenital pulmonary stenosis)	
Group 5 PH with unclear and/or multifactorial mechanisms	
5.2 Systemic disorders	
Segmental pulmonary hypertension	
5.3 Metabolic disorders	
Isolated pulmonary artery of ductal origin	
5.4 Complex congenital heart disease	**5.4 Complex congenital heart disease**
5.5 Pulmonary tumour thrombotic microangiopathy	Absent pulmonary artery
5.6 Fibrosing mediastinitis	Pulmonary atresia with ventricular septal defect and major aorto-pulmonary collateral arteries
	Single ventricle Unoperated/ Operated
	Scimitar syndrome

PH: Pulmonary hypertension; PAH: Pulmonary arterial hypertension; PVR: Pulmonary vascular resistance; PVOD: Pulmonary veno-occlusive disease; PCH: Pulmonary capillary haemangiomatosis; CTEPH: Chronic thromboembolic pulmonary hypertension, HIV: Human immunodeficiency virus syndrome

progress in symptoms, WHO Functional Class III-IV, Echocardiography, elevated serum NT-proBNP, and certain hemodynamic values.[8,9,13]

7. Congenital Heart Disease-associated Pulmonary Hypertension (PH-CHD)

Classification of PH-CHD is challenging due to its dynamic nature, multifactorial etiology, including genetics. Diller et al. have presented PH-CHD classification as depicted in Figure 1.[18]

PH-CHD can also be classified depending on hemodynamics and basic pathophysiology accounting for the increase in pulmonary pressures, as depicted in Figure 2.[19]

PH in CHD can be either due to increased pulmonary flow (hyperkinetic PH/ pre-capillary PH) as in ventricular septal defect (VSD), patent ductus arteriosus (PDA); or due to increased pulmonary venous congestion (postcapillary PH) as in disorders of the left side of the heart eg. mitral stenosis.[1,20,21]Table 3 briefly highlights the differences between pre-capillary and post capillary PH.[22,23]

In hyperkinetic PH, vasoconstriction protects transmission of high systemic pressure to pulmonary arteries preventing congestive heart failure (CHF). Eisenmenger Syndrome develops after a persistent period of hyperkinetic PH in patients with large left to right shunts, resulting in supra systemic pulmonary pressures and irreversible Pulmonary Vascular Disease. Nevertheless, pre-tricuspid shunts display right ventricular (RV) volume overload, and PAH develops beyond the fourth decade in about 6-17% of the patients, while Eisenmenger Syndrome in <2.0% of cases with atrial septal defect (ASD).[18,20,21,24]

Post-tricuspid lesions are high-pressure shunts, leading to volume load on the left ventricle and pulmonary circulation. Eventually, PA pressure increases to systemic pressure and if untreated, ≈50% will progress to Eisenmenger Syndrome.[18,20,21]

Decreased pulmonary blood flow e.g. pulmonary atresia (PA) with intact interventricular septum (IVS), Tetralogy of Fallot (TOF), is also associated with PH. The major reasons being increased resistance due to restricted alveolar development, pulmonary arterial hypoplasia, inflammation, thrombosis, postoperative residual VSD, postoperative relief of pulmonary stenosis, and presence of aortopulmonary collaterals.[25]

The complexity of underlying CHD, and other associated co-morbidities such as prematurity, lung hypoplasia, chromosomal abnormalities often make the diagnosis, evaluation and management of elevated PVR confusing and difficult.[11]

8. Patho-physiology of PH in CHD

PH is characterized by vasoconstriction, vascular remodeling, and thrombosis. The high flow and pressure across the pulmonary vasculature disturbs the endothelial barrier function causing pulmonary vascular endothelial dysfunction.[26] There is an imbalance between the vasoconstrictors (such as endothelin, thromboxane) and vasodilators (such as prostacyclin, nitric oxide) causing remodelling of the vascular bed.[20,26,27] An increased turnover of serotonin in paediatric CHD cohort has also been implicated.[20] Inflammation and thrombosis ensue with eventual smooth muscle cell hypertrophy and proliferation, neo-intima proliferation, plexiform lesions, and rarefaction of the pulmonary vascular tree, and failure of endothelial cell apoptosis.[1,17]

In 1958, Heath and Edwards classified PH based on histology into six grades of which Grade I to III is reversible while Grade IV to VI is irreversible. (Table 4)[28]

Rabinovitch M et al. presented a morphometric approach to classification based on lung biopsy that correlated with clinical severity of PAH-CHD. They suggested that despite surgical correction of the obliterative PVD (paediatric pulmonary hypertensive vascular disease- PPHVD), the disease process is irreversible and will progress in clinical severity.[29]

9. Clinical Presentation and Diagnosis

The presentation depends on the underlying CHD, age, repair status, direction, and severity of shunt.[29] In the paediatric cohort, PH is usually identified during evaluation of underlying CHD or any intercurrent illness.

The general signs and symptoms include exertional dyspnea, lethargy, fatigue/failure to thrive, syncope, peripheral oedema, congestive heart failure and angina as PH progresses to right ventricular failure (RVF).[27] Angina is a consequence of subendocardial ischemia following RV wall stress and compression of left main coronary artery by the enlarged pulmonary artery.

Progressive RV uncoupling to its afterload (pulmonary circulation) occurs resulting in high RV end diastolic pressures, RV dilation, and eventually failure as depicted in Figure 3. Cyanosis and clubbing are visibly present in patients developing Eisenmenger physiology. There might also be associated multiorgan complications such as bleeding diathesis, thrombotic episodes, risk of bacterial endocarditis, cerebral abscess, hepatic and renal dysfunction, even risk of sudden death.

On clinical examination, there may be RV hypertrophy with parasternal heave; a prominent P2, a tricuspid regurgitation murmur, S3 or S4 heart sound might be heard. The chest radiograph can display cardiomegaly, an enlarged main pulmonary artery and enlarged hilar vessels with peripheral pruning. Electrocardiogram shows a right axis

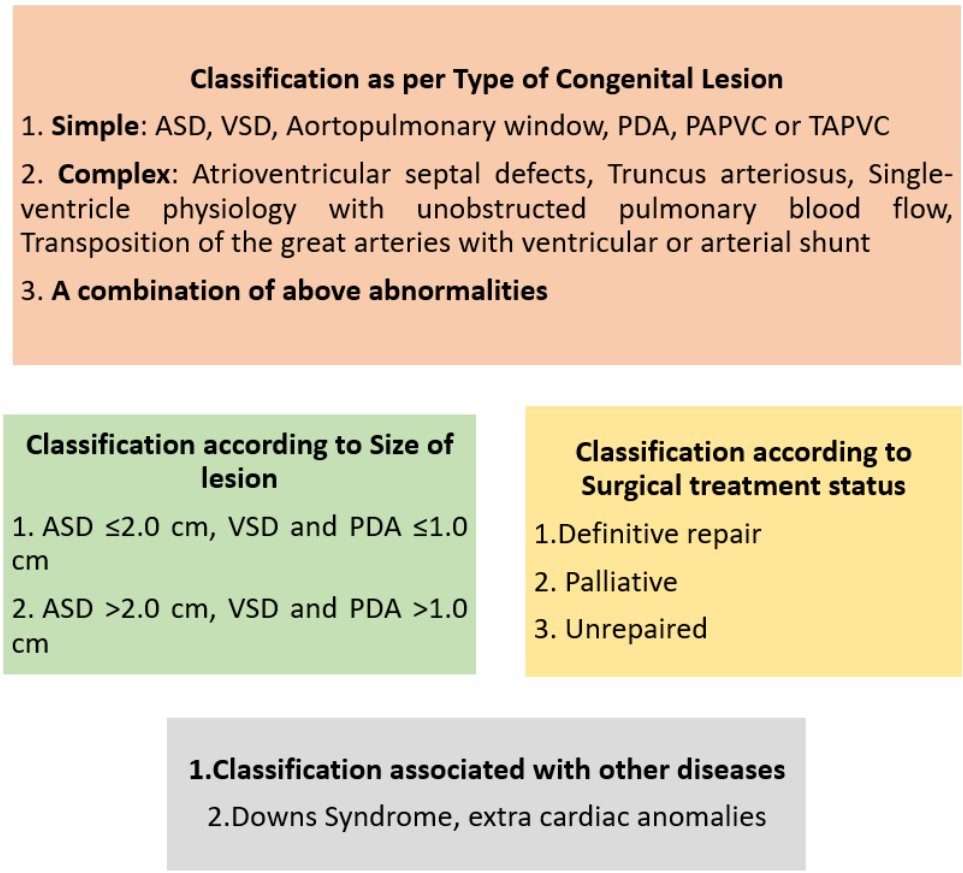

Figure 1: Classification of PH-CHD
ASD: Atrial Septal Defect, PDA: Patent Ductus Arteriosus, PAPVC: Partial Anomalous Pulmonary Venous Connection, TAPVC: Total Anomalous Pulmonary Venous Connection, VSD: Ventricular Septal Defect.

Table 3: Overview of pre-capillary and post-capillary hypertension

	PAH (Pre-capillary Hypertension) in congenital heart disease	**PVH (Post-capillary Hypertension) in congenital heart disease**	
Causes	PAH due to left-to-right shunts	e.g., Cor-Triatriatum, Obstruction in LV inflow and outflow	
		Passive	**Reactive**
Mean PA Pressure (mPAP)	>20	>20	>20
Pulmonary Capillary Wedge Pressure (PCWP)	≤15	>15	>15
Trans-pulmonic Gradient (mPAP-PCWP)	≥10	<10	≥10
PA End Diastolic Pressure- PCWP	≥10	<10	≥10
Diastolic Dysfunction Grade	None/ 1	1	2-4
Right ventricle size	Increased	Normal/ increased	
Right atrium: left atrium size ratio	>1	Normal or <1	
Interatrial septum	Shifted to left	Shifted to right	
RVOT notching	Common	Rare	
Lateral E/e´	<8	>10	
Treatment	Corrective Surgery, Diuretics, Pulmonary Vasodilators.	Corrective surgery, Diuretics.	

E/e': Trans-mitral doppler early filling velocity/ tissue doppler early diastolic mitral annular velocity; LV: Left ventricle; PAH: pulmonary arterial hypertension; PVH: Pulmonary venous hypertension; RVOT: Right ventricular outflow tract

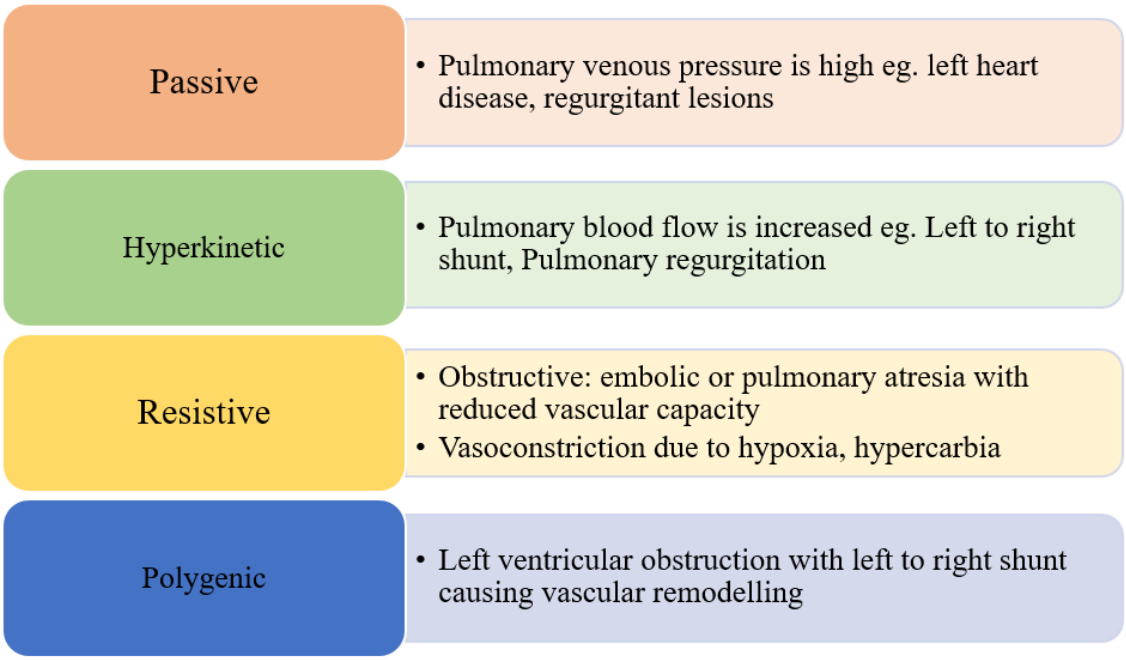

Figure 2: Modified wood classification of pulmonary hypertension

Table 4: Heath and Edwards histological classification of PH[28,29]

Grade of PAH	Histological Feature
I	Medial hypertrophy with retention of fetal type pulmonary arteries
II	Cellular intimal hyperplasia in abnormal muscular artery
III	Fibrous intimal lumen occlusion with some generalized medial dilation
IV	Arteriolar dilation with medial thinning with onset of intimal plexiform lesion
V	Plexiform lesion with angiogenesis, medial pulmonary haemosiderosis
VI	Fibrinoid and necrotizing arteritis

PH; Pulmonary hypertension

deviation suggesting RV hypertrophy. TOPP registry data on 456 children suggest that it is very unlikely for children with catheterization proven PH to have normal chest x-ray, ECG, and echocardiogram.[3]

Specific to the evaluation of PH, following recommendations have been put forth by the European Paediatric Pulmonary Vascular Disease Network: (Table 5)[8,12]

The various specific diagnostic modalities employed are:

1. **Transthoracic echocardiography (TTE):** The first investigation of choice for delineating cardiac structure, defect size (if restrictive or not), direction of flow and pressure gradient, ventricular size, and function.[30]
2. **Cross-sectional imaging:** Underlying cardiovascular lesions can affect the severity of PH. Thus, the ability to Three-dimensional viewing of cardiac structures as well as extra cardiac anomalies simultaneously makes Computed Tomography/Magnetic Resonance Imaging valuable in delineating complex congenital heart disease and deciding further management.
3. **Cardiac magnetic resonance phase contrast imaging:** It can measure the degree and direction of pulmonary to systemic flow (Qp:Qs) non-invasively.
4. **Cardiac catheterization:** It is the gold standard for diagnosing PH with and without PVD.[6] It helps in shunt evaluation, pathophysiology, vasoreactivity, and response to treatment and suitability for device or surgical closure. Dynamic maneuvers, such as inhaled nitric oxide (iNO) challenge, volume loading, and exercise, will help determine the prevailing pathophysiology in borderline or mixed PH cases.
5. **Evaluation for coexisting diseases** in other organs viz. lung, abdomen that increase the risk of PPHVD.[12]

A comprehensive paediatric diagnostic and management algorithm is elucidated in Figure 4:

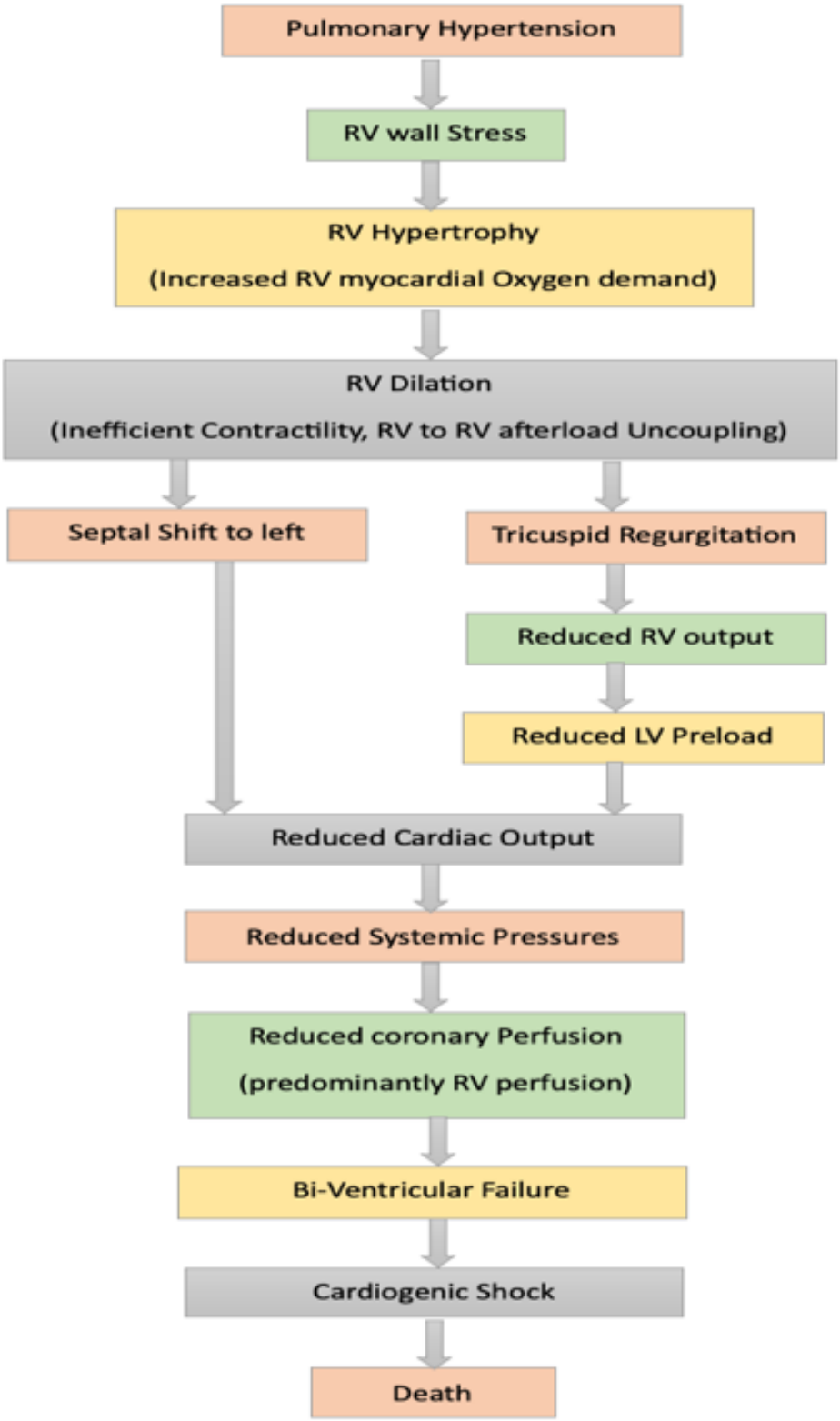

Figure 3: Pathophysiology of RV failure in pulmonary hypertension

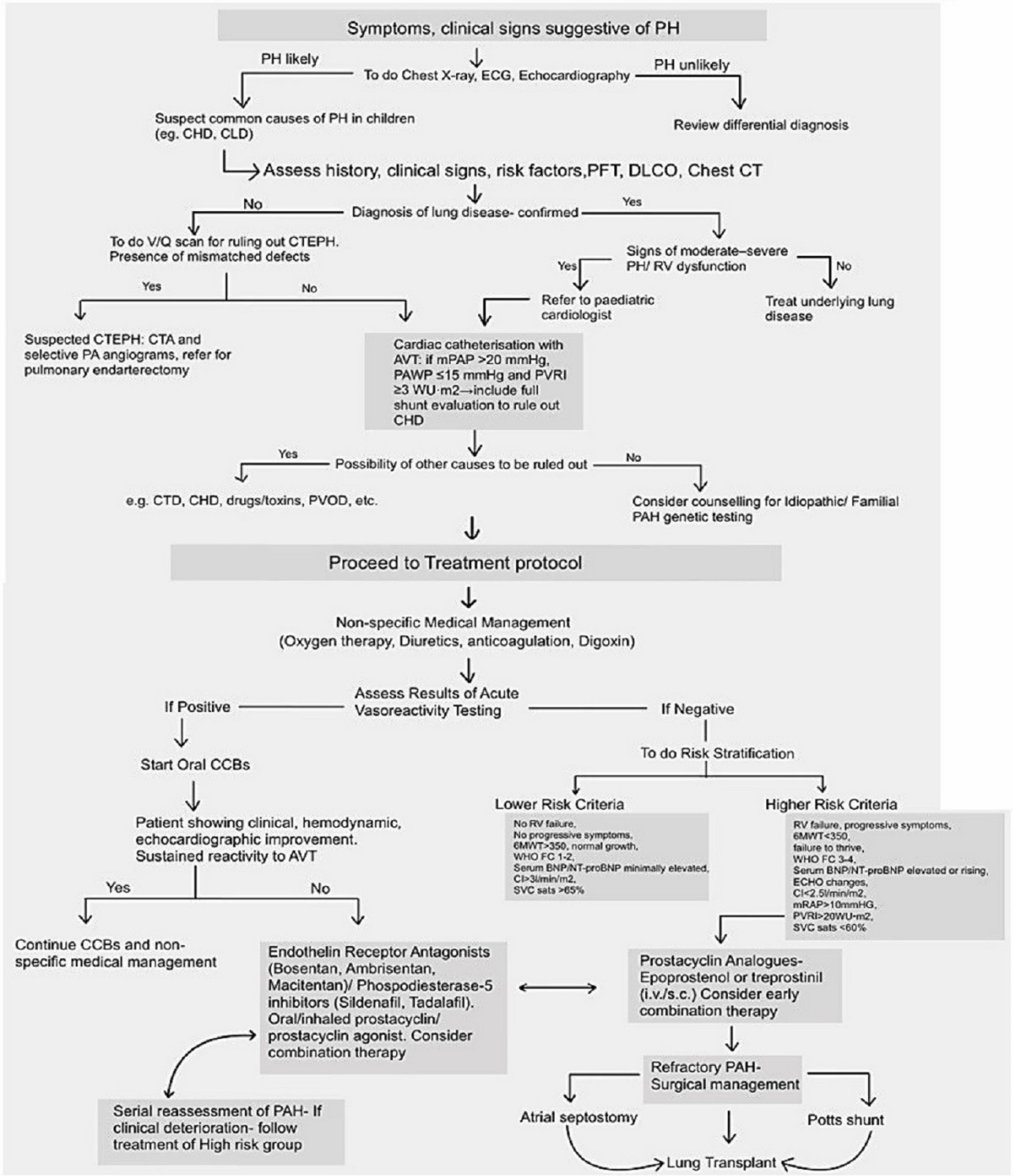

Figure 4: Diagnostic and management algorithm in paediatric pulmonary hypertension[9] Diagnostic and management algorithm in paediatric pulmonary hypertension$

PH: Pulmonary hypertension; ECG: Electrocardiogram; CLD: Chronic lung disease; CHD: Congenital heart disease; PFT: Pulmonary function test; DLCO: Diffusing capacity of the lung for carbon monoxide; CT: Computed tomography; V/Q: Ventilation/perfusion; CTEPH: Chronic thromboembolic PH; CTA: CT angiography; PA: Pulmonary artery; RV: Right ventricle; AVT: Acute vasoreactivity testing; mPAP: Mean pulmonary arterial pressure; PAWP: Pulmonary arterial wedge pressure; PVRI: Pulmonary vascular resistivity index; WU: Wood units; CTD: Connective tissue disease; PAH: Pulmonary arterial hypertension; CCB: Calcium channel blocker; 6MWT: 6-min walk test; WHO FC: World health organization functional class; BNP: Brain natriuretic peptide; NT-proBNP: N-terminal pro-BNP; CI: Cardiac index; mRAP: Mean right atrial pressure

Table 5: Recommendation by European pulmonary vascular disease network for PH-CHD

Recommendation	Class of recommendation	Level of evidence
Specific transthoracic echocardiography (TTE) to evaluate for PH and/or ventricular dysfunction in CHD patients. However, PAH with increased PVR cannot be distinguished from normal PVR by TTE	Class I	C
If PAH/PPHVD-CHD present, a thorough diagnosis is necessary to determine whether PAH is associated or causally related to concomitant CHD	Class I	C
Right heart catheterization and acute vasodilator testing is recommended before starting any definitive therapy.	Class I	C

PAH: Pulmonary arterial hypertension; PPHVD: Paediatric pulmonary hypertensive vascular disease; PVR: Pulmonary vascular resistance

10. Management

Treatment of PH in paediatric cohort has been extrapolated from the adult algorithm with the aim to improve survival and facilitate optimal child development.

Treatment and prognosis of PH-CHD has improved owing to evolving and aggressive strategies. The general measures are avoiding strenuous activities, oxygen supplementation. Digoxin, diuretics, and salt restriction are recommended in presence of CHF. Specific management involves attenuation of reactive vasoconstriction by vasodilators, diminishing vascular remodelling by antiproliferative agents (Table 6), and anticoagulation to prevent thrombosis.[8,31]

For patients in whom pulmonary changes have a potential to be reversed, Beghetti et al. suggest a PVR< 6 Wood units along with a PVR/SVR ratio of 0.3 following a year of treatment for PH as the hemodynamic upper limit for operability.[32] As for closure of congenital heart defect, it is contraindicated in the presence of severe PH (i.e. PAP > two-thirds systemic arterial pressure; PVR > two-thirds of SVR as per the AHA/ACC guidelines and PVR >5 WU as per the European guidelines) and/or a net right-to-left shunt.[9,33,34]

11. Perioperative Considerations in Non-cardiac Settings

A comprehensive perioperative risk assessment and management of this group of patients involving a multidisciplinary team comprising of paediatric specialists in the field of cardiology, surgery, cardiovascular surgery, and cardiac anaesthesia should be the standard of care, especially in the paucity of any guidelines.[35] In the event of intermediate or high risk non-cardiac surgery, it should be performed at specialized PH centre with the facility of emergency mechanical circulatory support because perioperative complications are of a common occurrence even in non-severe PH[13,36] PH-CHD paediatric patient cohort impose a significant risk of cardiovascular complications such as arrhythmias, paradoxical embolism, cardiac defect specific complications, pulmonary hypertensive crisis, right heart failure, and even death; irrespective of patients' demography, underlying aetiology and type of surgical procedure or anaesthetic technique (general v/s regional).[37,38] There is a scarcity of literature on paediatric PH and associated complications, both in the cardiac and non-cardiac settings[35] and procedure-specific estimates of cardiovascular risk may underestimate the actual risks in this cohort of patient population.[39]

Cardiac catheterizations (39.2%), and, abdominal (29.1%) and central venous access (8.9%) form the most common procedures in paediatric PH patients, and most common perioperative complications in the non-cardiac settings include failed planned extubation (5.6%), postoperative cardiac arrest (4.7%), induction or intraoperative cardiac arrest (2%), and postoperative death (1.4%).[40,41] Incidence of perioperative cardiac arrest in children with PH is 1.6% and 10.0% in all types of procedures and major surgeries respectively as opposed to 0.014% in children without PAH,[37] while the incidence of perioperative death is as high as 1.5%.[42] Taylor et al. in their retrospective analysis of 70 children undergoing cardiac catheterization under general anaesthesia, found 6% rate of major complications including death.[43] Similarly, a retrospective analysis by Ramakrishna et al. revealed 42% morbidity, and 7% early mortality in adult patients with PH undergoing non cardiac surgery. In their study, a history of pulmonary embolism, NYHA > II, anaesthesia duration > 3 hours, and intermediate to high-risk surgery were independent predictors of 30-day morbidity.[44] Warner et al. also found that PH predicted enhanced morbidity in 276 CHD patients, both adult and paediatric, undergoing non cardiac procedure.[37] In a study by Stein et al., 26% of noncardiac procedure were associated with serious adverse events.[45]

Therefore, a meticulous preoperative risk assessment is necessary which should include NYHA /WHO FC, the grading and severity of PH, underlying disease and CHD specific risks as well as the type of surgery. Carmosino et al., evaluated the child's clinical status, recent

Table 6: Medications for pulmonary hypertension

Drug Class	Drug	Mechanism/ Site of Action	European Medicines Agency approval for use in children with PAH
Phosphodiesterase 5 inhibitors (oral)	Sildenafil (selective inhibitor)	Increased half-life of cGMP, promoting vasodilation.	Recommended for ≥1 year of age. Recommended dosing: <20kg:30mg/day (3 divided doses). ≥20kg:60mg/day (3 divided doses).
	Tadalafil		Suggested dosing: 0.5-1mg/kg/day in 1dose. Evaluated in children>3yrs age.
Endothelin receptor antagonists (oral)	Bosentan	Competitive antagonist at ETa & ETb1/ETb2 receptors.	Recommended for ≥1 year of age. Recommended dosing: 4mg/kg/day in 2 doses.
	Ambrisentan	Selective ETa receptor antagonist.	Recommended for >8 years of age Recommended dosing: 2.5-10 mg/day in 1 dose.
	Macitentan	Dual Eta & ETb1/ETb2 receptor blocker	Not recommended
Prostacyclin analogues (i.v./s.c.)	Epoprostenol i.v.	Pulmonary & systemic vasodilation, Inhibition of vascular remodelling, Antiplatelet aggregation.	Not recommended Suggested dosing: Starting dose 1-2ng/kg/min. In children, avg dosing 40-80 ng/kg/min, dose increase may be required.
	Treprostinil i.v./s.c.		Not recommended Suggested dosing: Starting dose 2ng/kg/min. In children, avg dosing 50-100 ng/kg/min, dose increase may be required
	Iloprost (inhaled)		Not recommended
Selective Prostacyclin receptor agonist	Selexipag (oral)	Anti-proliferative, anti-thrombotic, anti-inflammatory	Not recommended
Soluble guanylate cyclase stimulator	Riociguat (oral)	Sensitizes Soluble guanylate cyclase to endogenous Nitric oxide.	Not recommended
Calcium Channel Blockers	Nifedipine (Dihydropyridine CCB)	Inhibition of calcium	Initial dose: 0.6–0.9 mg/kg/day (3 divided doses) Maintenance dose: 2–5 mg/kg/day
	Diltiazem (Benzothiazepine derivative)		Initial dose: 1.5–2 mg/kg/day (3 divided doses) Maintenance dose: 3–5 mg/kg/day (3 divided doses)
	Amlodipine (Dihydropyridine CCB)		Initial dose: 2.5–5 mg/day Maintenance dose: 2.5–5 mg/kg/day (2 divided doses)

cGMP: Cyclic guanosine monophosphate; Et: Endothelin; i.v.: Intravenous; CCB: Calcium channel blocker.

electrocardiogram (ECG), TTE, and cardiac catheterization reports as a part of pre anaesthetic check-up.[37] Preoperative laboratory investigations should include routine laboratory tests, blood gas analysis, TTE, effort tolerance assessment, pulmonary function testing (PFT), and catheterization study. Serum NT-ProBNP and uric acid are emerging biomarkers in risk assessment.[9,13,46]

An already compromised RV homeomeric autoregulation is further disturbed in the presence of sympathetic blockade, vasovagal stimuli, anaesthetic drugs, positive pressure ventilation, and cytokine release precipitating severe RV dysfunction, and death.[47] Therefore preoperative optimization of fluid balance, RV function, adjustment of PH therapy, treatment of comorbidities and any intercurrent illness specifically respiratory infection which has a bearing on PVR, is the cornerstone for successful outcome, and elective surgery should be deferred if the patient status demands amelioration.[13,24]

Intraoperatively a meticulous titration and maintenance of hemodynamic stability is the goal. Apart from standard American Society of Anaesthesiologists (ASA) monitoring, invasive arterial pressure, central venous pressure (CVP), TEE, Bispectral Index (BIS), arterial blood gas analysis is recommended. An increase in CVP along with hypotension suggests impending RV compromise and failure. Pulmonary pressure lowering agents should be kept at hand including the iNO delivery device. If blood loss is anticipated, an early cross-match is recommended. As with any shunt lesion, infusion lines should be air bubble free.

Ideal anaesthetic regimen should dilate pulmonary vasculature, maintain systemic vascular resistance and cardiac output to boot. In Carmosino et al. study, balanced anaesthetic technique and sub-anaesthetic doses of a mix of drugs were used to maintain hemodynamic balance.[37]

It is imperative to consider the balance between systemic vascular resistance (SVR) and pulmonary vascular resistance (PVR) as in the presence of uncorrected lesions increase in PVR and fall in SVR will result in desaturation at the cost of maintaining systemic output, while the reduction in PVR with the increase in SVR will result in pulmonary congestion with fall in cardiac output.

The drug of choice for premedication was midazolam while a combination of midazolam, fentanyl, propofol and sevoflurane was used for induction and maintenance along with muscle relaxants either vecuronium or rocuronium. Hickey et al. demonstrated relative stability of PVRI in infants with left to right shunt and PVR ~ 3 Wood units who were administered fentanyl.[48] Williams et al. reported propofol decreased Qp:Qs leading to further desaturation.[49] Propofol may cause shunt reversal due to propensity to lower SVR. However low dose infusion propofol or ketamine with propofol may be used.[47] Ketamine may be safely used if carbon dioxide levels are maintained. Shah et al. suggest use of induction agents that maintain perfusion pressures- e.g., etomidate, ketamine or high dose fentanyl.[24]

Taylor et al. emphasize on maintaining systemic pressures as a strained right ventricle is more likely to fail under anaesthetic drugs induced depression.[43] As for inhalational agents, Isoflurane at 1 MAC and Sevoflurane that cause pulmonary vasodilation may be part of the strategy with due consideration that they may directly impair RV contractility and reduce CO; while desflurane increased PAP.[10,24,27,47] The existing studies do not demonstrate significant direct effects of nitrous oxide on pulmonary hemodynamics.[47] Dexmedetomidine may be used if postoperative sedation is desirable. Shah et al. suggest induction in the presence of vasopressor if RV dysfunction is already present.[24] In another study by Bennet et al. addition of a vasopressor during induction, irrespective of the induction agent used decreased the incidence of hypotension in Eisenmenger Syndrome patients.[50]

Tracheal intubation was the preferred technique of choice while supraglottic devices were used as appropriate in Carmosino et al. study.[37] Intubation should be performed only when the patient is deeply sedated, and by an experienced anaesthesiologist to avoid pulmonary hypertensive crisis either by sympathetic stimulation or inadvertent endobronchial intubation. Twite et al. also preferred tracheal intubation.[38] However tracheal suctioning is an important cause in precipitating pulmonary vascular hypertensive crisis and should be done prudently. Intraoperatively surgeon should perform meticulous positioning, careful creation of pneumoperitoneum or lung/diaphragmatic compression if required. Anaesthesiologist is also responsible for smooth extubation, prevention and prompt treatment of airway obstruction, agitation and pain.

Pulmonary arterial constriction is associated with bronchoconstriction, and airway resistance increases commensurately along with a reduction in tidal volumes (TV) in pulmonary vascular hypertensive crisis. A high plateau pressure should be avoided to minimize the effects on RV function. A low TV strategy with low positive end expiratory pressure (PEEP) is recommended.[47,51]

In a comparative study between general anaesthesia (GA) and regional anaesthesia (RA), patients were more haemodynamically stable under GA, with a significantly lower PAP and PVRI with improved cardiac index. However, RA may be preferred in appropriate cases keeping in mind it may compromise RV perfusion and cause reversal of shunting.[47]

Patients with Eisenmenger Syndrome are preload dependent, require high haemoglobin concentration, and a fall in SVR should be avoided.[51]

12. Pulmonary Vascular Hypertensive Crisis

It can be precipitated by any event that causes sudden increase in PVR. The pulmonary vascular hypertensive

crisis heralds RVF; and two major principles to manage it are reducing PVR, and maintaining RV function to restore both coronary and systemic perfusion pressures.[24,27,52]

13. Treatment of Pulmonary Vascular Hypertensive Crisis

13.1. General measures for reducing PVR

1. Administer 100% oxygen, moderate hyperventilation, correction and prevention of acidosis. Hyperoxia may cause increase in systemic resistance, while hypocarbia may cause a reduction in cardiac output. Therefore, maintain $PaCO_2$ at 30-35 mmHg, and PaO_2 between 100-120mm Hg.[47] But there are studies that support that oxygen is a pulmonary vasodilator and that hyperoxia decreases PVR supporting oxygen therapy as well.[53,54]
2. Avoid ventilation-perfusion mismatch. Both high and low lung volumes are detrimental owing to alveolar and extra-alveolar pulmonary vessel compression respectively.[55] Use PEEP judiciously as it may narrow capillaries in well ventilated areas.
3. Prevent sympathetic stimulation e.g. treat pain, adequate sedation, prevent shivering. Avoid oversedation, and airway obstruction.

13.2. Optimizing RV function

Both hypovolemia as well as hypervolemia tend to be detrimental to RV function. While hypovolemia will compromise RV perfusion, hypervolemia will cause RV overload and increased RV wall tension and decompensation.[13]

1. Maintain RV preload; CVP should be <10 cm H_2O; or more specifically by assessing dynamic measures of fluid status such as passive leg raising (PLR).
2. Reducing RV after load by decreasing PA pressure:
   (a) iNO decreases PAP in diverse clinical settings viz. COPD, ARDS, CHD, after cardiopulmonary bypass. It is a selective pulmonary vasodilator that improves oxygenation as well in a dose of 5-40ppm. It is devoid of systemic side effects but requires specialized delivery system, and is associated with rebound PAH after discontinuation, methemoglobinemia, and increased bleeding time. A Cochrane systematic review however fails to validate postoperative treatment effect of iNO on PAH in paediatric CHD.[56] It is suggested to give a trial with iNO for 30 minutes in patients with significant perioperative PAH. The trial can be terminated if no response.[57]
   (b) Phosphodiesterase (PDE)-III inhibitors e.g. milrinone either intravenous (50mg/kg bolus followed by 0.375-0.75mg/kg/min) or in aerosolized form. Another advantage of PDE III inhibitors is positive effect on contractility. Levosimendan may also be used.
   (c) Phosphodiesterase (PDE)-V inhibitors e.g. sildenafil (i.6mg/kg/day).
   (d) Prostaglandin analogues such as PGI_2 or its stable analogue iloprost (1-5ng/kg/min), Alprostodil (PGE_2). The biggest disadvantage is lack of pulmonary selectivity, and hence may cause a decline in systemic pressures as well. PGI2 is also available in aerosolized form, and can be directly delivered into the pulmonary circulation to any systemic effects.
3. Systemic vasoconstrictor such as norepinephrine, phenylephrine maintains RV coronary pressures. Increasing systemic pressures also prevent septal bowing thereby improving left ventricular filling and contractility that in turn supports RV haemodynamics. However, a cautious use is warranted only in the face of systemic hypotension otherwise may worsen PA pressure due to vasoconstrictive effects.
4. Inotropes such as epinephrine, dobutamine help in maintain systemic haemodynamics and biventricular contractility.

Pulmonary vascular hypertensive crisis may be a harbinger of difficult to treat cardiac arrest, and emergent use of extracorporeal membrane oxygenation (ECMO) may be required.[58]

Preoperative pulmonary vasodilator therapy can prevent precipitation of such crisis.[43] The odds of developing complications was 0.31 in children treated preoperatively for PAH.[59]

13.3. Postoperative care

Routine post-operative monitoring in PICU/HDU is recommended for at least 48-72 hours.[47] PH-CHD patients lie at a precarious balance of haemodynamics following anaesthesia in view of increased pulmonary vascular tone, pulmonary thromboembolism, cardiac arrhythmias, and fluid shifts. Factors that may precipitate a hypertensive crisis should be avoided while iNO if administered should be gradually tapered to avert any rebound hypertension. Wheezing may increase PVR and should be avoided. Pain should be adequately controlled while avoiding excessive sedation. Early extubation is preferable to reduce intrathoracic pressures and eventual RV dysfunction.

A brief summary of perioperative care of PH-CHD paediatric patients is illustrated in Table 7.[10,60,61]

14. Future Directions

As an improvement in understanding of pathophysiology, and advanced diagnostic and treatment options become

Table 7: Brief illustration of management of PH-CHD patients posted for non-cardiac surgery

Pre-op Checklist	Multidisciplinary management. Discussion with cardiologist for diagnostic evaluation, need for cardiac catheterization, risk stratification, optimization of PH medications. Senior paediatric Anaesthesiologist to assess patient (history and clinical evaluation). Risk disclosure, Counselling of family, Very High-Risk Consent for procedures, prolonged ICU stay, transfusion, ECMO. Preferably post patient in Cardiac Surgery Theatre.
Pre-operative care	Continue PH medications, and supportive management. Pre-medication. Calm environment to minimize stress / anxiety. Limit pre-operative waiting time.
Intraoperative Care	ASA standard monitoring, arterial line, arterial blood gases, central line, ScvO2, PA catheter/ other cardiac output monitoring devices, TEE Avoid Hypoxemia, Anxiety, Hypercapnia, Acidosis, Hypothermia, Vasoconstriction, Noxious stimulus. Selection of Balanced Anaesthetic technique (Regional Vs General). Good pain management. Optimize RV preload, minimize RV afterload. FiO2 at higher settings. Avoid lung hyperinflation and atelectasis, limit peak and plateau pressure
Warning signs of deterioration	Patient restless or showing signs of discomfort, desaturation, systemic hypotension, sinus tachycardia or bradycardia, pallor, poor peripheral perfusion, elevated central venous pressure (CVP).
Management of cardiac decompensation intra-operatively	100% oxygen. Call for assistance. Correct Acidosis, Hypoxia, Hypercarbia, Hypothermia, deepen plane of anaesthesia. Maintain sinus rhythm, right ventricular preload, arterial pressures and cardiac output. Reduce right ventricular afterload. Use of Inodilators (Milrinone, Levosimendan), Inotropic support (Dobutamine, Adrenaline), Vasopressors (Nor-adrenaline, Vasopressin), Pulmonary Vasodilators (nitric oxide, prostacyclin, Iloprost, sildenafil). Consider ECMO support. Notify ICU.
Post-operative care	Continuous monitoring of ECG, BP, SpO2. Continue PH medications. Lower risk patient: Recovery room, then transfer to High Dependency Unit when hemodynamically stable. Higher risk patient: Direct transfer from theatre to ICU, observe for warning signs of acute PH crisis/ cardiac decompensation. Ensure adequate analgesia. IV hydration till tolerating oral fluids post-operative. Patient to return back to pre-procedure baseline prior to discharge or ward transfer.
Discharge	To assess patient prior to discharge with appropriate follow-up arrangements.

PH: Pulmonary hypertension; ECMO: Extra-corporeal membrane oxygenator; IV: Intravenous; EtCO2: End tidal carbon dioxide, CVP: Central venous pressure; ScvO2: Mixed venous oxygen saturation, PA: Pulmonary artery; TEE: Trans oesophageal echocardiography; RV: Right ventricle

available, more opportunities may come way in the care of PH-CHD patients eg. development of echocardiogram score and cross-sectional imaging techniques are promising avenues in the evaluation of PVR and an eventual tailored treatment. However, the treatment modalities are yet to include those with PH after shunt closure or complex CHD. The paediatric data available is mostly extrapolated from the adult data, and it still calls for guidelines set for paediatric patients. Recent research emphasizes on interference with the molecular pathways involved in vascular remodelling eg. drug selonsertib, imatinib and seralutinib.Pediatr Research is also developing in areas that target on prevention of RV dysfunction eg evaluation of the role of famotidine in improving 6MWD, NYHA functional class, and decreasing BNP levels. Results of various ongoing trials may guide in the better management and improving quality of life of PH-CHD patients.

15. Conclusion

Despite an evolution in the understanding of pathophysiology and treatment of PH, anaesthetic management is still challenging in paediatric patients with PH-CHD, especially in the paucity of well-defined research and guidelines. The delicate hemodynamic balance can be easily disturbed even in the face of normal physiological changes due to anaesthesia. Therefore, a comprehensive understanding of pathobiology, scrupulous preoperative multidisciplinary planning, meticulous perioperative management with early anticipation, recognition and management of complications can mitigate the challenges and risks in this insubstantial group of patients.

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17. Conflict of Interest

None.

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