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REVIEW ARTICLE

Common shunt lesions with pulmonary hypertension—who will benefit from surgery?

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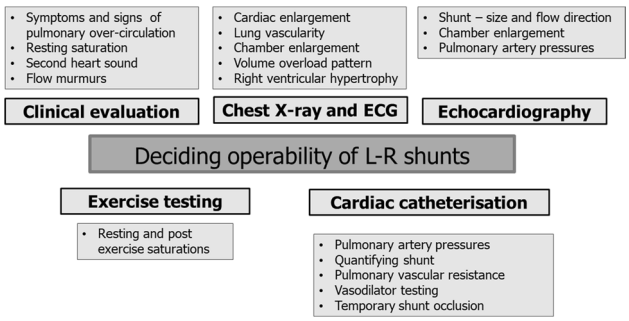
Abstract

Left to right shunts comprise a specific group of congenital heart disease, when identified and treated on time result in excellent outcomes. However, a proportion of these defects do not receive the timely intervention and often present late posing the question of safe operability especially in low- and middle-income countries. The lack of ample evidence and standardised guidelines often poses an enigma to the treating physician preventing appropriate and patient-friendly decision-making. Moreover, no single test or clinical feature can accurately define operability in this subset of patients. In this review, we aim to address this issue in a comprehensive and holistic manner and formulate a simplified guideline based on current evidence to help the physician to arrive at an appropriate decision.

Graphical Abstract

ECG, electrocardiogram; L-R left to right



Keywords Left to right shunt · Congenital heart disease · Pulmonary hypertension · Operability · Eisenmenger syndrome

Introduction—problem statement

Shunt lesions are among the commonest of congenital heart defects (CHD). Late presentation of CHD is common in most low- and middle-income countries (LMICs) because of deficiencies across the CHD care continuum that include poor detection in early infancy, limited access to accurate diagnosis, ill-defined referral pathways, and substantial shortfall of centres with comprehensive paediatric cardiac services [1]. Shunt lesions with pulmonary arterial hypertension (PAH) are at an elevated risk of right cardiac failure and death in the early postoperative period [2]. Decision on whether to operate is crucial because early and late outcomes are worse for patients with postoperative PAH compared to those who remain unoperated including those who develop the Eisenmenger syndrome (ES) [3]. The question of operability most commonly arises in older children and adults with common left to right shunts like ventricular septal defect (VSD), patent ductus arteriosus (PDA), and atrial septal defect (ASD) when associated with elevated pulmonary vascular resistance (PVR) [4].

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In this review, we seek to develop a framework for decisions on operability in shunts with PAH by blending contemporary understanding on development and progression of PAH with available evidence on patients operated for large shunt lesions at an older age.

Pulmonary vascular disease associated with CHD: essential concepts

The term *pulmonary vascular disease* (PVD) associated with CHD generally refers to abnormal pathological changes in pulmonary vasculature resulting from increased pulmonary blood flow due to CHD over a period of time causing elevated PVR and resultant PAH. This should be distinguished from *hyperkinetic PAH* which is essentially a reflection of increased flow due to the left to right shunt with early pulmonary vascular changes and reverses completely after shunt closure. These patients have symptoms and signs of large left to right shunts and are almost always operable. On the other hand, when the disease progress beyond the stage of reversibility, the PVR become fixed and hence inoperable. PVR when used in adults is often not indexed to body surface area (BSA) and the unit is Wood units (Wu). When used in paediatric population and often in context of CHD, it is indexed to BSA (pulmonary vascular resistance index (PVRI)) and the unit is $Wu \times m^2$, i.e., $Wu.m^2$. It must be remembered that for indexing PVR to BSA, one needs to multiply PVR with BSA rather than dividing (a common misconception!) since in the formula for PVR only the pulmonary blood flow in the denominator is indexed, the pressure difference in numerator is not, hence resulting in multiplication than division [5].

The histopathological changes and haemodynamic correlates associated with PVD have been well characterised. The *morphometric grading by Rabinovitch* et al. seeks to provide a pathologic classification that correlates with haemodynamic changes [6]. This correlated well with preoperative pulmonary haemodynamic findings. Grades A and B (mild) correlated with increased pulmonary blood flow but normal or minimal elevation in mean pulmonary arterial (PA) pressure; grade B (severe) correlated with increased pulmonary blood flow and elevated mean PA pressure (usually at least half systemic level) but normal PVRI and in grade C (mild) PVRI was usually 3.5 $Wu.m^2$ or greater but less than 6 $Wu.m^2$ and with grade C (severe) PVRI was often 6 $Wu.m^2$ or greater.

The *Heath-Edwards classification* includes six grades and lesions with grade 4 and above are in general considered irreversible [7]. In children between 1 and 10 years of age with VSD, there was immediate reduction in PA systolic pressure to less than 50 mmHg soon after shunt closure in Heath-Edwards grade up to III [8]. The pulmonary vasculature was labile up to grade III even though with high PVR and often reversible. The grades V and VI were considered non-labile and irreversible, grade IV being transitional [9].

It should be remembered that these morphological classifications favouring operability are not discrete compartments and overlaps are noted with elevated PVR and abnormal exercise responses after shunt closure in seemingly operable grades, mandating long-term follow-up.

Clinical classification of PAH associated with CHD

This aims at the ease of clinically classifying the patients for practicality [10] and is as follows:

1. Eisenmenger syndrome: This is characterised by reversal of shunt and cyanosis at rest. Closure of defect is contraindicated.
2. PAH associated with prevalent systemic to pulmonary shunts
   - Correctable
   - Non-correctable

The shunting is exclusively left to right and cyanosis at rest is not a feature.

3. PAH with small/coincidental defects

This includes PAH in defects not large enough to result in PVD (usually ASD < 20 mm and VSD < 10 mm in adults with disproportionately high PAH expected of the defect size. However, mere size alone may not reflect the haemodynamic significance of the lesion and often require detailed evaluation). The defect is likely to be coincidental and vascular changes are secondary to non-CHD aetiology.

4. PAH after shunt correction: Here PAH persists or develops later at any point of time after correction of CHD in the absence of haemodynamically significant residual lesions.

Determinants of PVD in shunt lesions

There are well-defined determinants of PVD accounting for the troublesome variability which we encounter in clinical practice. Understanding the determinants helps in evaluating the pathophysiologic basis for PVD and aiding in appropriate decision. It should be kept in mind that there are unknown factors as well. The known factors that initiate and perpetuate the pathology are discussed below.

Location and size of defect

The pulmonary vasculature is directly exposed to systemic pressures in addition to flow-related stress in post-tricuspid shunts resulting in early progression towards vascular changes. In contrast in pre-tricuspid shunts, it is the flow-related stress that results in vascular changes and tends to be late. The increased pressure and flow are potent stimulators for vascular changes than either alone. The size of the shunt logically is expected to influence the propensity of developing PVD. In his classical manuscript, Paul Wood reasonably concludes that ES is unlikely in VSDs < 10 mm and PDAs < 5 mm, the smaller diameter PDAs which resulted in ES being often short in length [11]. If the PVR were normal, these defects would effect a pulmonary to systemic blood flow ratio (Qp:Qs) of at least 3.5, usually varying between 4 and 6. Interestingly, the size of ASD had little bearing on propensity for ES with significant overlap between ES and non-ES subset especially when > 30 mm. However, there are contrasting reports of incremental risk for PVD with increase in size of ASD [12, 13]. With the lesions more than the above-mentioned size, it is worth observing that the percentage of defects progressing to ES are 53%, 52%, and 9%, respectively, for PDA, VSD, and ASD. Thus, ES is not always the inevitable destination in large shunts not closed in a timely manner and this is supported by the observation that we often see older patients with large shunts that are operable [14, 15].

Another subset of patients is those with smaller defects (especially ASD) with disproportionate PAH and often associated with comorbidities. These defects usually are incidental, innocent lesions not contributing to PAH. They typically behave like idiopathic pulmonary arterial hypertension (IPAH) and closure of these defects are contraindicated.

Age and gender

The onset of ES occurs in late infancy in 83% of VSD, 79% of PDA, and 8% of ASD [5]; 92% of ASD destined to develop shunt reversal do so in adulthood with significant female preponderance (male to female ratio of 1:4). This suggests that the pathophysiology in ASD is different from post-tricuspid shunts. While many older patients with ASD remain operable until late adulthood, there is an overall increased risk for development of PVD with age. Therefore, all adults with ASD should be carefully screened for PAH [12, 13].

Rabinovitch et al. noted that closure of post-tricuspid left to right shunts in general within 9 months of age resulted in normalisation of PA pressure and PVR on evaluation at 1 year post surgery irrespective of severity of pulmonary vascular changes identified by histology at the time of repair [6]. Beyond 9 months, the PA pressures and PVR were raised in half of the patients (morphometric grade B (severe) with Heath-Edwards grade II or morphometric grade C with Heath-Edwards grade I or II). All patients beyond 2 years of age with morphometric grade C or Heath-Edwards grade III had elevated PA pressures (up to severe) and PVR. Friedli et al. noted that PA concentration (density of pulmonary vasculature) tends to decrease and the degree of PA concentration decrease that can be recovered with PA growth is restricted in children with VSD repair beyond 2 years of age [16].

Thus, it is evident that age plays an important role in deciding operability. Post-tricuspid shunts are ideally repaired in infancy and beyond 2 years of age has significant risk for residual PAH. Any PAH should be viewed with concern in patients with ASD and a careful assessment is merited.

Associated comorbidities

In addition to PVD, there can be other comorbid conditions which can influence the pulmonary vasculature independently affecting operability. These include known common syndromes like Down syndrome, DiGeorge syndrome, Scimitar syndrome, and Noonan syndrome. The identification of these syndromes in a child with CHD should alert towards a propensity for inherent PVD. Those with bronchopulmonary dysplasia, post congenital diaphragmatic hernia repair, significant upper airway obstructions, interstitial lung disease, chronic liver diseases, congenital portocaval shunts (Abernathy malformations), and connective tissue disorders are at risk for PAH independent of CHD. Very often it is impossible to quantify PAH related to comorbidity unless it is a potentially treatable condition like airway issues and liver diseases.

Genetic determinants

The exact genetic basis for vulnerability to develop PVD is undetermined. It is often intriguing to see lesions of similar characteristics behaving differently in different patients. The commonly identified gene mutations causing PAH and associated with CHD are bone morphogenetic protein receptor 2 and transcriptional factor SRY-related box 17 (SOX 17) mutations [17, 18]. In addition, there are other mutations which though not directly associated with CHD are causative of PAH [10]. Disproportionate PAH or residual PAH after timely closure of shunt or family history of PAH should prompt for evaluation for alternate basis for PAH-like gene mutations.

Altitude

The hypoxic stimulus in high altitude is a potent pulmonary vasoconstrictor causing secondary PAH. The incidence of PAH among CHD is noted to increase with altitude [19]. It might be highly advisable to reassess PAH at sea level to eliminate a reversible cause precluding operability.

When to suspect PVD and borderline operability

The clinician should be conscious of the red flags where the operability in a left to right shunt can be truly borderline. The following scenarios warrant a thorough evaluation before recommending shunt closure:

1. Older age of presentation—typically beyond 2 years in post-tricuspid shunt
2. Clinical features of PAH overshadowing shunt haemodynamics including symptom status
3. PAH disproportionate to the size of defect
4. Associated comorbid conditions including known syndromes

Assessment of operability

The assessment of operability must be comprehensive and multidimensional. To date, there is no single specific measurement threshold or clinical feature that reliably predicts operability in borderline subjects. The decision must be a summation of all information gathered meticulously that must include clinical examination and all relevant investigations.

Symptoms

The presence of symptoms suggestive of left to right shunt usually favours operability. Typically in infancy suck rest suck cycle, head sweating, persistent fast breathing with lower chest indrawing resulting in Harrisson's sulcus (happy tachypnoea) and failure to thrive predominates. Older children are likely to have recurrent respiratory infections and failure to thrive. A relatively asymptomatic child for size of the defect or a recent history of resolution of previous symptoms from increased pulmonary blood flow may indicate development of elevated PVR due to onset of PVD.

Physical examination

Clinically apparent cardiomegaly with hyperdynamic precordium and apex points towards a large resting left to right shunt favouring closure. Clubbing indicates chronic hypoxia from shunt reversal usually signalling inoperability. A pulse oximetry saturation (SpO_2) of > 95% is usually reassuring. One should always rule out primary lung diseases like bronchiectasis and chronic tuberculosis as an alternative source of desaturation when associated with CHD in setting of LMIC. However, a normal saturation does not always favour operability since the patient might have established PVD, not yet resulted in shunt reversal. Conversely, mild desaturation (often normalises with neck extension and oxygen supplementation) from upper airway issues may be seen in operable situations when associated with conditions like Down syndrome. A relatively silent chest with no cardiomegaly, right parasternal heave, palpable and loud second heart sound, and absence of flow murmurs are ominous signs. The presence of malar rash, joint symptoms (connective tissue disorders), jaundice (liver diseases), telangiectasias with epistaxis (hereditary haemorrhagic telangiectasia), and dysmorphism (known syndromes) may provide clue for underlying comorbid conditions contributing to PVD.

Exercise

An exercise-induced fall in SpO_2 to < 95% is usually a warning sign and can be assessed by a 6-min walk test (6MWT) in children > 5 years. It should be noted that in PDA the lower limb saturation should be mandatorily checked at baseline and after exercise to detect systemic desaturation. A drop in PaO_2 in arterial blood gas of > 10 mmHg at peak treadmill exercise has been well correlated with a PVR of > 7 Wu in adult patients with ASD and borderline operability [20].

Chest X-ray

The chest X-ray is an extremely useful tool in assessing operability. Cardiomegaly, end on vessels of > 3 per lung field or 5 bilaterally, end on vessels at least 1.5 times larger than the adjacent bronchus, increased peripheral vasculature in lateral 1/3 of lung fields and pulmonary plethora favours significant left to right shunt (Fig. 1). Proximal dilation of branch pulmonary arteries with abrupt tapering of distal branches (pruning), oligemic peripheral lung fields, and absence of cardiomegaly usually suggest abolishing left to right shunt from onset of PVD (Fig. 2).

Electrocardiogram (ECG)

In general, the ECG findings are of very limited value in assessing operability. Prominent left ventricular (LV) or biventricular forces (Katz-Wachtel phenomenon), presence of q waves in lateral precordial leads V5/V6 (suggesting LV volume overload), and left atrial enlargement (Fig. 3) point towards a large resting L-R shunt. A rightward deviation of QRS axis, predominant right ventricular (RV) forces with strain pattern and right atrial prominence may be a warning sign towards inoperability (Fig. 4). In ASD, the findings are very likely to overlap with changes due to PAH and is therefore of limited incremental value.

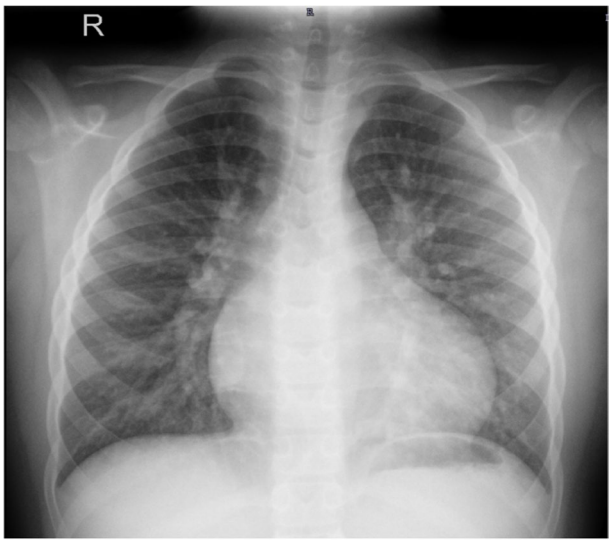

Fig. 1 Chest X-ray—operable. Chest X-ray of an 8-year-old child with large VSD, saturation of 98% shows cardiomegaly, dilated MPA and branch PAs without peripheral pruning, multiple end on vessels, and increased vascularity. Mean PA pressure was 28 mmHg with Qp:Qs of 3.9, PVR of 1.7 Wu, and PVR to SVR ratio of 0.07, defect closed successfully. VSD, ventricular septal defect; MPA, main pulmonary artery; PA, pulmonary artery; Qp:Qs, ratio of pulmonary to systemic blood flow; PVRI, pulmonary vascular resistance index; Wu, wood units; SVR, systemic vascular resistance

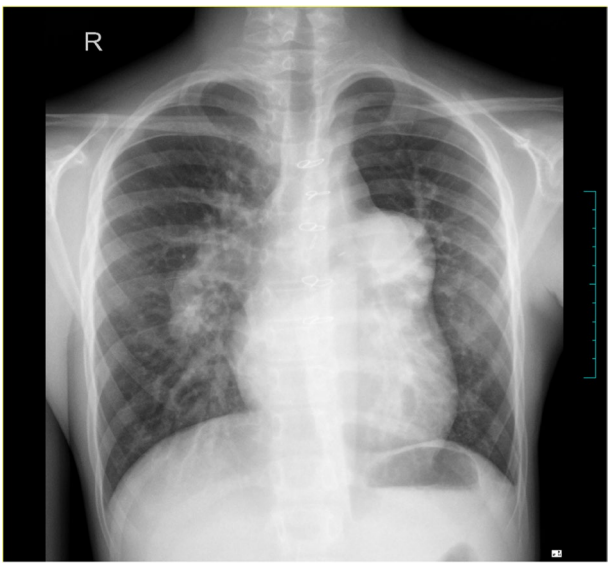

Fig. 2 Chest X-ray—borderline operability. Chest X-ray of a 15-year-old with apical muscular VSD shows absence of cardiomegaly, dilated MPA and proximal branch PAs with abrupt tapering, and absence of vasculature towards lateral 1/3 of lung fields. The child had resting aortic saturation of 96% with Qp:Qs of 1.2 and baseline PVR of 16 Wu, PVR to SVR ratio 0.7, AVT with iNO was negative. VSD, ventricular septal defect; MPA, main pulmonary artery; PA, pulmonary artery; Qp:Qs, ratio of pulmonary to systemic blood flow; PVR, pulmonary vascular resistance; Wu, wood units; SVR, systemic vascular resistance; AVT, acute vasodilator test; iNO, inhaled nitric oxide

Laboratory investigations

A subtle reversal of shunt and clinically inapparent cyanosis may reflect as elevated haemoglobin levels from secondary erythrocytosis. The presence of anaemia, thrombocytopenia, and elevated inflammatory markers may point towards connective tissue disorders. Abnormal liver function tests and ammonia levels can indicate chronic liver disease or associated Abernathy malformations.

Ultrasound of the abdomen

In a small proportion of patients with left to right shunts particularly those who have heterotaxy, may have Abernathy malformation that can contribute to disproportionate PAH [21]. This is often missed unless specifically looked for. It is our institutional protocol to perform an ultrasound of the abdomen for all patients with left–right shunts who have disproportionate PAH.

Echocardiography

Echocardiography is of immense value in enabling decisions on operability. Predominant left to right direction of shunt and chamber enlargement downstream to the shunt (e.g., left atrium and LV in VSD) favours operability in post-tricuspid shunts. It must be recognised that at times transient right to left shunting is noted in operable patients with large VSDs. It is also important to recognise that pulmonary artery systolic pressures are likely to be at near systemic levels in large post-tricuspid shunts despite the patient being operable. Accurate estimation of pulmonary artery systolic pressure using the tricuspid regurgitation jet is of value in patients with ASD. At times, it is possible to estimate pulmonary artery diastolic and mean pressure from the jet of pulmonary regurgitation when present. However, good-quality Doppler traces may not be consistently obtainable. Additional features that suggest elevated PVR include the pulmonary artery acceleration time of less than 105 ms and mid systolic notch in the pulse wave Doppler of the pulmonary valve [10].

Cardiac catheterisation

Cardiac catheterisation is usually indicated when assessment of operability is inconclusive from symptoms, clinical examination, and baseline investigations. It is not indicated in straightforward situations (e.g., young infant with a large VSD) where operability is clear. Similarly, in established cases of ES with systemic desaturation at rest, it is unnecessary. Cardiac catheterisation should be done ideally in awake state under local anaesthesia. If sedation is required, effort should be made to maintain a uniform plane of sedation

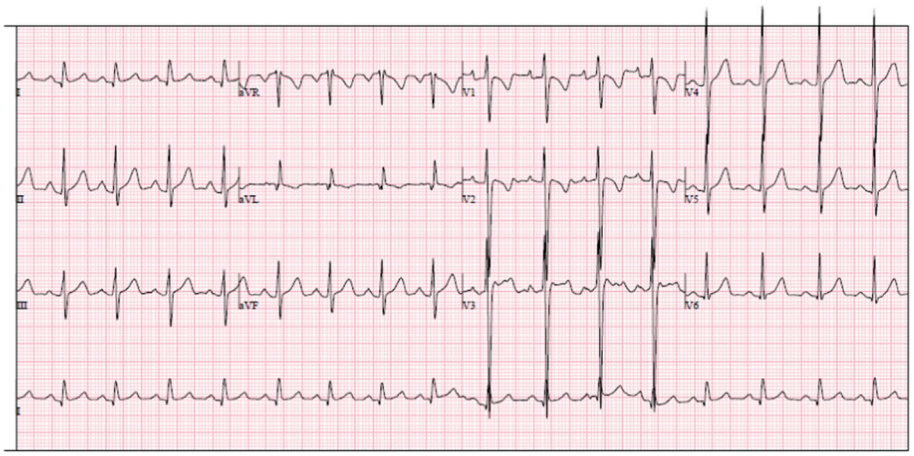

Fig. 3 ECG—operable. ECG of the patient in Fig. 1 shows normal axis, left atrial prominence, predominant LV forces, and small q wave in V6

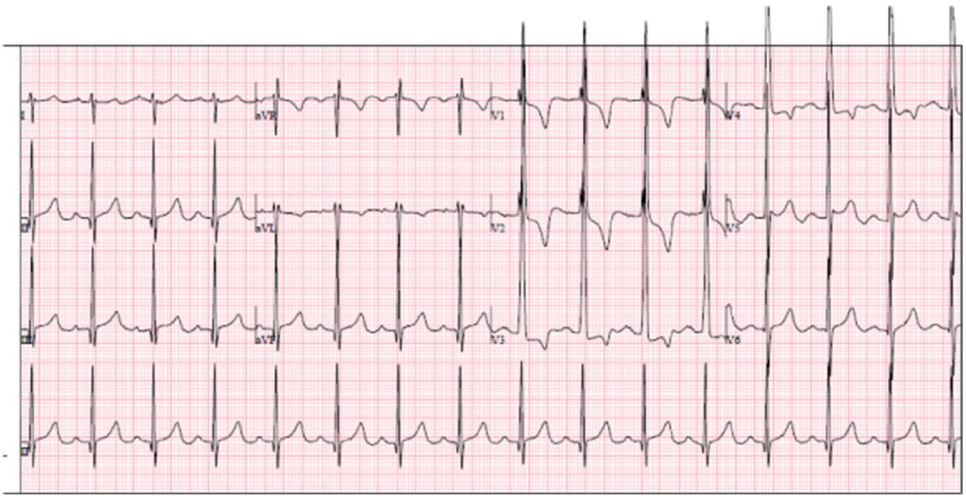

Fig. 4 ECG—borderline operability. ECG of the patient in Fig. 2 shows right axis deviation with significant RV hypertrophy with strain pattern

to obtain optimal haemodynamic measurements. General anaesthesia is indicated only in uncooperative or sick subsets of patients.

The primary purpose of cardiac catheterisation in assessing operability is to quantify the baseline shunt and PVR. The acceptable level of baseline shunt and PVR according to latest 2022 European Society of Cardiology/European Respiratory Society (ESC/ERS) guidelines [10] is given in Table 1. Acute vasodilator testing to assess the reactivity of pulmonary vascular bed can be done in available centres but however has not conclusively predicted the operability and may be useful in individual cases. The consensus statement defines operability as fall in PVRI to < 4 Wu.m^2 and PVRI to systemic vascular resistance index (SVRI) ratio of < 0.3 from the baseline value [22]. The standard agent recommended is inhaled nitric oxide at 20 parts per million for 10 min. Other currently recommended agents include inhaled

Table 1 PVR levels for operability in shunt lesions[a]

Lesion Qp:Qs > 1.5	Operable (PVR Wu)	Possibly operable (PVR Wu)	Inoperable/expert opinion (PVR Wu)
ASD	< 3	3–5 < 5 with treatment	> 5 despite treatment
VSD	< 3	3–5	> 5
PDA	< 3	3–5	> 5

ASD atrial septal defect, *VSD* ventricular septal defect, *PDA* patent ductus arteriosus, *PVR* pulmonary vascular resistance, *Wu* wood units, *Qp;Qs* ratio of pulmonary to systemic blood flow

[a]Humbert M, Kovacs G, Hoeper MM, Badagliacca R, Berger RMF, Brida M, et al. 2022 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Respir J*. 2023 Jan;61(1):2200879. https://doi.org/10.1183/13993003.00879-2022

iloprost (5–10 µg for 15 min) and intravenous epoprostenol 2–12 ng/kg/min for 10 min). Recently, we evaluated intravenous sildenafil (0.25 mg/kg in children and 10 mg in adults as slow iv infusion over 10 min followed by measurement of haemodynamics after 20 min) and was shown to be a promising agent in comparison with inhaled nitric oxide [23]. Vasoreactivity testing with oxygen has inherent fallacies and is not recommended [24].

Cardiac catheterisation offers the opportunity for temporarily occluding shunts and recording its effects on PA pressure. Generally, it is only feasible for PDA and selected cases of ASD. It is extremely difficult to temporarily balloon occlude VSD because of the contracting ventricles. A few studies have shown promising results in test occlusion of PDA. Zhang et al. closed 135 PDA with mean size of 10 ± 3 mm (> 12 years old, mean PA pressure ≥ 45 mmHg, Qp:Qs > 1.5, and PVR:SVR (systemic vascular resistance) < 0.7) and after median follow-up of 5 years detected residual PAH by echo in 13%. They correctly identified post-trial occlusion systolic PA to systolic aortic pressure ratio of > 0.5 as a predictor of residual PAH [25]. Zhou et al. in 134 patients with PDA (mean age 35 ± 10.2 years, mean diameter 11.7 ± 2.2 mm, mean PA pressure > 50 mmHg) noted that all patients with total PVR > 4 Wu had residual PAH and immediate post closure mean PA pressure of > 35 mmHg was an independent risk factor (odds ratio 1.06 (1.003–1.140), $p = 0.04$) for residual PAH by echo after median follow-up of 1 year [26]. Balloon occlusion in ASD in predicting operability is not well validated and may be considered in a case-to-case basis.

Lung biopsy

Histopathological analysis and grading systems aiding in assessment of reversibility in PVD are well documented in yesteryears. However, this is not routinely recommended due to the risks associated with invasive procedures, non-uniform involvement of pulmonary vasculature posing difficulty in identifying the ideal biopsy site, and inconsistent correlation with immediate and long-term pulmonary haemodynamics after shunt closure.

Bridging strategies in borderline operability

Pulmonary artery banding

The rationale of interim PA banding is to reduce the pulmonary shear stress from increased flow and allow reversible changes in pulmonary vasculature so that the patient may become operable later. This strategy has been nearly abandoned due to requirement of an invasive procedure, difficulty in attaining appropriate banding haemodynamics, and dismal long-term outcomes after complete repair post banding [27, 28].

Treat re-evaluate repair treat (*T2RT*) strategy

This aims at treating patients with elevated PVR who do not meet the criteria for operability with targeted pulmonary vasodilators and reassessing them for repair based on the response after treatment. It is essential to obtain the pre-treatment haemodynamic data before initiating therapy. Dual pulmonary vasodilator therapy (phosphodiesterase 5 inhibitor (PDE5i) with endothelin receptor antagonist (ERA), ideally tadalafil and ambrisentan) for a period of at least 12 weeks (majority of the drug trials of pulmonary vasodilators give a treatment period of at least 12 weeks before repairing defect) may be ideal. The patient may be reassessed clinically for evidence of operability and then subjected to catheterisation if deemed appropriate. A post-treatment reduction in PVR to < 3 Wu with a Qp:Qs ratio of at least > 1.5 ideally qualify for a fenestrated shunt closure [10].

Few recent meta-analyses concluded possible favourable outcomes at short-term follow-up for treat-repair-treat strategy. Wang et al. analysed outcomes of patients with left to right shunts predominantly (ASD and VSD) with PVR ≥ 5 Wu or mean PA pressure of > 45 mmHg naïve to treatment who were treated with pulmonary vasodilators and operated later [29]. The study analysed nine patient series from 2010 to 2021 meeting the criteria. The duration of treatment before surgery varied from 5 days to 10 months and nearly all were treated with a combination of PDE5i and ERA (selected studies in Table 2). After medication and surgery, there was significant reduction in PA pressure and PVR with significant improvement in 6 MWT and SpO_2 from baseline. Patients < 18 had better reduction in PA pressures when compared to those > 18 years. Interestingly, regarding criteria for selecting patients for surgical repair after treatment, SpO_2 improvement had better efficacy than conventional cardiac catheterisation or acute vasodilator testing. However, at last follow-up, percentage of patients requiring medications for residual PAH after surgery varied from 42 to 100%. Additional follow-up is most certainly needed as progression of PAH can happen after several years.

Another recent meta-analysis examined 11 major patient series from 2012 to 2023 with ASD > 18 years of age having PVR ≥ 5 Wu, Qp:Qs of > 1.5, and absence of Eisenmenger physiology and compared treat-repair-treat group with straight to repair group [30]. The duration of treatment before intervention varied from 3 to 12 months and often was with combination of PDE5i and ERA (selected studies in Table 2). The former group outperformed the latter in terms of improvement in functional and haemodynamic parameters. The study population was heterogenous, the criteria for operability was

non-uniform and estimate of residual PAH was not analysed in most of the studies. They concluded that prior to closure, assessment by acute vasodilator testing and or balloon occlusion is advisable to fine tune the decision on operability.

As per the currently available data, *T2RT strategy* seems to hold some promise for selected cases with borderline operability. The long-term outcomes of those with residual PAH being worse than IPAH, this strategy reinforces the selection of more appropriate candidate for shunt closure by proving at least short-term vasoreactivity. It is prudent to repair these defects surgically enabling to leave behind at least 10-mm circular defect in the atrial septum which can function as a pop off for RV and can be easily closed by transcatheter option in the future. Creating artificial fenestration in ASD or PDA devices do not last long term and tend to occlude with time. The patients should be continued on dual vasodilator therapy with regular follow-ups for progression of PAH.

Valved or fenestrated patch closure of VSD with borderline operability

In patients with VSD and borderline operability, valved or fenestrated patch closure has been attempted. Unidirectional valved patch closure in a small subset ($n=17$) with preoperative PVRI of 10.2 ± 2.9 Wu.m^2 had acceptable immediate post-surgical outcomes and after mean follow-up of nearly 3 years had nil mortality with decrease in PVRI to 5.8 ± 2 Wu.m^2 and absent flow across the valve [31, 32]. Double patch flap valve closure of VSD in early years demonstrated higher short-term mortality of nearly 15% [33]. In a recent review of double patch technique with long-term follow-up (median 19 years), 40 patients with demonstrable pre-surgical vasoreactivity (median baseline PVR 10.1 Wu (interquartile range (IQR) 7.6–12.8), post-acute vasodilator test median PVR 6.2 Wu (IQR 3.4–8.8)) showed normalisation of PA pressures in 20% and more than half systemic PA pressure in 40% with flap valve being functional only in < 50% [34]. Moreover, there was no survival difference between double patch technique and traditional closure of VSD in those with PVR to SVR ratio > 0.6. Overall, the fenestration techniques seem a low-risk procedure in immediate postoperative period but the long-term outcomes tend to be determined primarily by baseline PVR. On follow-up, the non-predictability of regression of PAH and lack of patency of fenestration were seriously concerning along with confounding by insufficient sample size. As of now, there is no sufficient evidence to recommend these techniques as a standard of practice. We would recommend an appropriate fenestration in atrial septum instead of VSD patch fenestration which is likely to be durable and can be easily closed by device if PVR normalises in future.

Operability in CHD beyond simple shunts

Left to right shunts like endocardial cushion defect, aortopulmonary window, and truncus arteriosus tend to have earlier onset with more progressive PVD. The principles of assessment for operability are the same as the simple shunts of similar physiology.

Total anomalous pulmonary venous connection (TAPVC) is ideally repaired in infancy. The development of PVD tends to be late and outcomes in late survivors are encouraging

Table 2 Summary of studies with treat-repair-treat strategies[a,b]

Author	Year	*N*	Age (years)	Diagnosis	Medication	Duration of treatment (median)	Follow-up (months, median)	Deaths
Takaya et al	2021	42	51 ± 18	ASD	ERA, PDE5i SGc, PC	9 months	33	1
He et al	2020	14	27.9 ± 7.4	ASD	ERA, PDE5i	10.7 months	21.1	0
Bradely et al	2018	19	37 ± 23	ASD	ERA, PDE5i SGc, PC	24 months	52.8	0
Kijima et al	2015	8	37 ± 15	ASD	ERA, PDE5i PC	-	19	0
Thomaz et al	2019	33	0.8 (median)	VSD,PDAAVSD	PDE5i	6 months	6	3
Hu et al	2015	31	29.1 ± 8.1	VSD	ERA, PDE5i PC	7.3 months	37.9	2
Liu et al	2014	56	17.2 ± 9.3	VSD	ERA, PDE5i	4.4 months	27.9	0
Huang et al	2011	38	3.04 ± 1.9	ASD,VSDPDA	ERA, PDE5i PC	5–120 days	117	0

ASD atrial septal defect, *VSD* ventricular septal defect, *PDA* patent ductus arteriosus, *AVSD* atrioventricular septal defect, *PDE5i* phosphodiesterase 5 inhibitor, *ERA* endothelin receptor antagonist, *SGc* soluble guanylate cyclase stimulator, *PC* prostacyclin

Adapted from [a]Wang Z, Li X, Li M, Peng J, Zhang H. The efficacy of the treat-repair-treat strategy for severe pulmonary arterial hypertension associated with congenital heart disease: a meta-analysis. *BMC Cardiovasc Disord*. 2023 Nov 20;23(1):569. https://doi.org/10.1186/s12872-023-03606-z

[b]Cool CJ, Kamarullah W, Pranata R, Putra ICS, Khalid AF, Akbar MR, et al. A meta-analysis of atrial septal defect closure in patients with severe pulmonary hypertension: is there a room for poking holes amid debate? *Curr Probl Cardiol*. 2024 Jan;49(1 Pt C):102121. doi:https://doi.org/10.1016/j.cpcardiol.2023.102121

[35]. The operability status in this subset can be assessed in line with that of ASD. Being an admixture physiology, a $SpO_2 > 85\%$ may indicate reasonable shunt signifying evaluation towards operability.

VSD when associated with complex CHD like d or l transposition of great artery (TGA), double outlet right ventricle, etc. are well known for rapid progression of PVD. In d TGA with VSD, this was noted especially beyond 7 months of age in lung biopsy specimens [36]. A preoperative mean PA pressure < 50 mmHg was associated with good immediate postoperative outcomes in patients with d TGA VSD and PAH [37]. In children beyond 6 months of age with d TGA and large VSD/Taussig-Bing anomaly with severe PAH (mean PA pressure 64.9 ± 13 mmHg), reversibility of PAH was defined as an increase in SpO_2 by at least 5% from baseline after 2 weeks of continuous inhaled NO (20–40 ppm) along with sildenafil and bosentan [38]. This subset after arterial switch operation and mean follow-up of 42 months had modest outcomes (mean PA pressure of 22.4 ± 8.7 mmHg) with mortality of 17.3%. Echocardiographic assessment of pulmonary venous return post oxygen inhalation for assessment of operability has been reported in small subset of patients with d TGA VSD [39]. In inoperable cases, a palliative arterial switch with no or partial closure of VSD resulted in significant improvement in quality of life on short-term follow-up [40].

In patients with single ventricle physiology planned for Fontan surgery, consensus recommends a mean PA pressure ≤ 15 mmHg, mean transpulmonary gradient (mean PA pressure − mean pulmonary vein pressure) ≤ 6 mmHg, and PVRI ≤ 3 Wu.m^2 for operability [41]. With the recent 2022 ESC/ERS guidelines [10] bringing down the upper limit of normal PVR to ≤ 2 Wu, the same value may be applicable in this subset of patients.

There is substantial lack of evidence to formalise recommendations for operability in complex CHD. One should be more aggressive in timely repair of the defect before the onset of PVD and less aggressive in repairing those with borderline operability. In general, the principles of

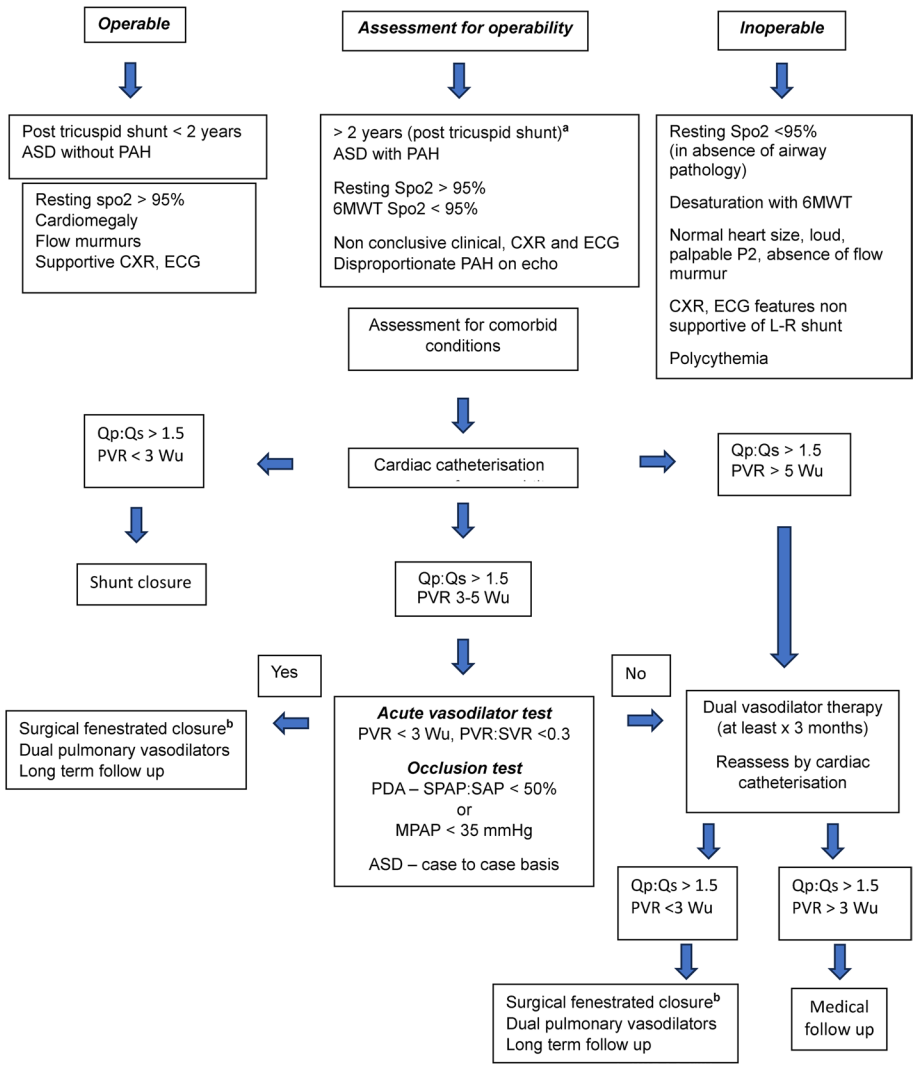

Fig. 5 Novel algorithm for assessment of operability in simple left to right shunts. Beyond 2 years of age those who fulfil operable criteria can safely undergo shunt closure (superscript a). Ten-millimetre circular fenestration is desirable in the atrial septum while closing ASD and VSD (superscript b). PDA may be closed by device or surgery depending on size for practical ease since atrial septum is inaccessible during PDA closure for creating fenestration. VSD, ventricular septal defect; ASD, atrial septal defect; PDA, patent ductus arteriosus; CXR, chest X-ray; MPAP, mean pulmonary artery pressure; Qp:Qs, ratio of pulmonary to systemic blood flow; PVR, pulmonary vascular resistance; Wu, wood units; SVR, systemic vascular resistance; 6MWT, 6-min walk test; PAH, pulmonary arterial hypertension; SPAP, systolic pulmonary artery pressure; SAP, systolic aortic pressure

operability may be extrapolated from simple lesions of similar physiology but with more rigorous screening.

Advances in assessing operability

There is very preliminary information on new modalities that include assessment of vascular distensibility of PA by intravascular ultrasound [42], main pulmonary artery dilatation and assessment of fractal branching of pulmonary vascular tree by specialised computed tomography imaging [43], and specific biomarkers like circulating endothelial cells, asymmetric dimethyl arginine, ghrelin, etc. [44–46]. These studies have not been tested adequately to predict operability.

The latest 2022 ESC/ERS guidelines in pulmonary hypertension have revised the guidelines for operability in CHD with PAH updating the existing 2020 ESC and 2018 American Heart Association guidelines on adult CHD. Still there is significant paucity of clear-cut evidence to formulate a definite guideline in addressing this unique subset of patients. We propose a novel practical algorithm for assessment of operability in common shunt lesions in setting of LMICs and is depicted in Fig. 5.

Conclusions

The assessment of shunts with borderline operability is comprehensive and multidimensional. There are no specific features or tests that pinpoint towards operability. With evolving evidence of dismal outcomes with residual PAH, the aggressiveness to treat those with borderline operability has given way to overall conservative approach. The *treat-re-evaluate-repair-treat* strategy appears promising by mandating more rigorous screening with short-term vasoreactivity and long-term follow-ups. *When in doubt, don't close!!, would be an ideal corollary for do no harm, if not cure.*

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Declarations

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