Challenges in the Patient With Pulmonary Hypertension and Atrial Septal Defect: Understanding When and How to Close the Defect

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Atrial septal defects (ASDs) are common congenital heart defects in children and adults. Pulmonary arterial hypertension (PAH) is found in subsets of both pediatric and adult patients with atrial defects under varied clinical contexts. The pulmonary hypertension specialist is often faced with questions surrounding timing and method of defect closure, which may have significant impact on procedural and long-term morbidity and survival. This review highlights important differences in management between children and adults with ASDs associated with PAH, highlighting indications for closure, operability, types of closure, and long-term outcomes.

BACKGROUND AND BASELINE EVALUATION

Atrial septal defects (ASDs) are commonly diagnosed structural heart lesions occurring in about 2 per 1,000 live births.[1] Pulmonary arterial hypertension (PAH)—defined by mean pulmonary artery (PA) pressure ≥25 mm Hg, pulmonary capillary wedge pressure (PCWP) ≤15 mm Hg, and pulmonary vascular resistance (PVR) ≥3 Wood units (WU)—is a significant complication in adults with ASDs with reported prevalence of 8% to 10%.[2-4] PAH in patients with ASD is linked to specific anatomic defects. There is a higher prevalence of PAH among patients with sinus venosus defects than secundum ASDs.[3] Other risk factors for PAH in the setting of ASDs include residence at altitude,[5] older age, female sex, larger size of defect, and presence of at least moderate tricuspid regurgitation.[6] Patients with small hemodynamically inconsequential ASDs may have clinical presentation similar to idiopathic PAH. Significant PAH occurs less frequently in pediatric patients with ASDs (2.2%) and may be found particularly in children with underlying genetic cause of PAH.[7] ASDs are additionally associated with pulmonary hypertension (PH) in

ex premature infants with bronchopulmonary dysplasia, perhaps reflecting effects of increased pulmonary blood flow on pulmonary vascular remodeling.[8]

ASDs are often repaired in order to optimize cardiovascular function. Benefits of ASD repair include decreased right ventricular volume overload, improved right ventricular function, and decreased PA pressure.[6-9] However, closure of ASDs associated with PAH must be carefully considered to avoid both perioperative and long-term morbidity and mortality related to progression of PAH and right heart failure. In some cases preoperative assessment may calculate that no intervention with ensuing right to left shunt, Eisenmenger syndrome, and polycythemia may carry a better prognosis than potential perioperative complications, right heart failure, and progressive pulmonary vascular disease associated with high-risk ASD closure.[10]

Prior to consideration of closure, patients with PAH and ASDs should be evaluated, and if necessary and possible, treated for associated processes such as obstructive sleep apnea, chronic thromboembolism, and interstitial lung disease. Echocardiography should be performed to characterize the size, number of defects, and atrial septal

anatomy (Figure 1).[11] Exercise testing, or 6-minute walk test, if feasible, should be completed to measure preoperative functional capacity and ascertain whether there is right to left shunting with exertion. Adult and pediatric
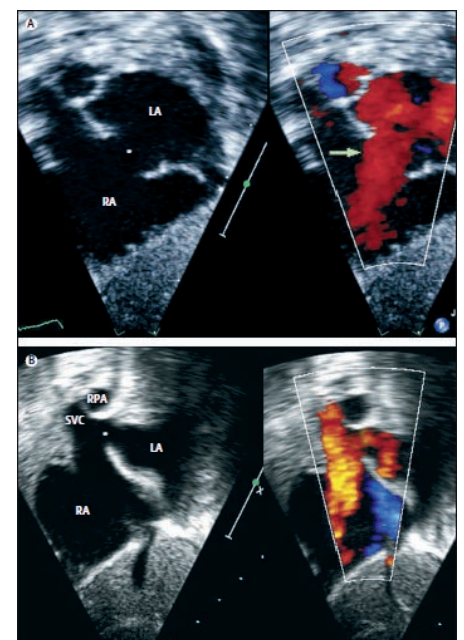

Figure 1: Echocardiographic imaging of atrial defects. (A) Secundum atrial septal defect in the centre of the fossa ovalis (*). Note the left-to-right flow imaged by colour Doppler (arrow). (B) Superior vena cava (SVC)-type sinus venosus defect located above the fossa ovalis between the SVC and the right upper pulmonary vein as it enters the left atrium (LA). RA=right atrium. RPA=right pulmonary artery. Reprinted from Geva T, Martins JD, Wald RM. Atrial septal defects. *Lancet*. 2014;383(9932):1921-1932. Copyright 2014, with permission from Elsevier.

Table 1. Recommendations for Closure of Simple Shunt Defects in Adults With PAH

Recommendation for Closure of ASD	ESC/ERS 2015[13]	ACC 2018[14]
YES	PVRi <4 WU m^2	Systolic PA pressure <one-half systemic PVR / SVR <0.3
INDIVIDUALIZE	PVRi 4 to 8 WU m^2	Systolic PA pressure one-half to two-thirds systemic PVR / SVR 0.3 to 0.66
NO	PVRi >8 WU m^2	Systolic PAP >two-thirds systemic PVR / SVR >0.66 and Qp/Qs <1.0

patients with echocardiographic evidence of PAH considering ASD repair warrant full hemodynamic evaluation with cardiac catheterization to assess baseline physiological measurements including right atrial pressure, mean PA pressure, PVR, cardiac index (CI), and shunt determination (Qp/Qs).[12] During catheterization, patients should undergo acute vasodilator testing as recommended in guidelines with reassessment of hemodynamic parameters to determine pulmonary vasoreactivity. Also at catheterization, angiography should be considered to exclude the presence of peripheral pulmonic stenosis, aortopulmonary collateral vessels, and pulmonary venous anomalies.

ASD CLOSURE IN ADULTS WITH PAH

Indications for closure in adults with ASD and PAH in adults have been reviewed in consensus guidelines and are summarized in Table 1. The European guidelines generated by the Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS) state that moderate to large defects with prevalent systemic to pulmonary shunting and without cyanosis at rest are correctable when indexed PVR (PVRi) is <4 WU m^2 but due to operative risk should not be repaired when PVRi is >8 WU m^2.[13] Repair of ASDs with PVRi between 4-8 WU m^2 may be considered individually in specialized PH centers, carefully weighing risks and benefits of the procedure, particular patient characteristics, institutional expertise, and local postoperative care resources.

Additionally, recent American College of Cardiology/American Heart Association (AHA) Guidelines for the Management of Adults with Congenital Heart Disease include recommendations for ASD closure in patients with PAH.[14] Indications for closure include impaired functional capacity, right atrial or right ventricular enlargement, and net left to right shunt (Qp:Qs) ratio >1.5:1 without cyanosis at rest or with exercise. Closure is recommended for adults with systolic PA pressure less than 50% of systemic pressure and PVR less than one-third systemic vascular resistance (SVR). ASD closure may be considered for adults with net left to right shunt of 1.5:1 or greater, systolic PA pressure 50% or more of systemic arterial pressure, and/or PVR greater than one-third of the systemic resistance. However, these guidelines caution that ASD closure should not be performed in adults with systolic PA pressure greater than two-thirds systemic, PVR greater than two-thirds systemic, and/or a net right to left shunt.[14]

ASD CLOSURE IN CHILDREN WITH PAH

In pediatric patients with PH and shunt lesions, younger age at repair is an important predictor of operative survival and freedom from long-term PAH.[15] A modified algorithm from the AHA/American Thoracic Society (ATS) pediatric PH guidelines[16] provides guidance for operability (Figure 2). Young patients (<1 to 2 years) with pulmonary over circulation, failure to thrive, oxygen saturation >95%, and only systemic to pulmonary shunting should undergo repair without necessarily requiring invasive preoperative catheterization. Older patients (>1 to 2 years) or those with bidirectional shunts should, how-
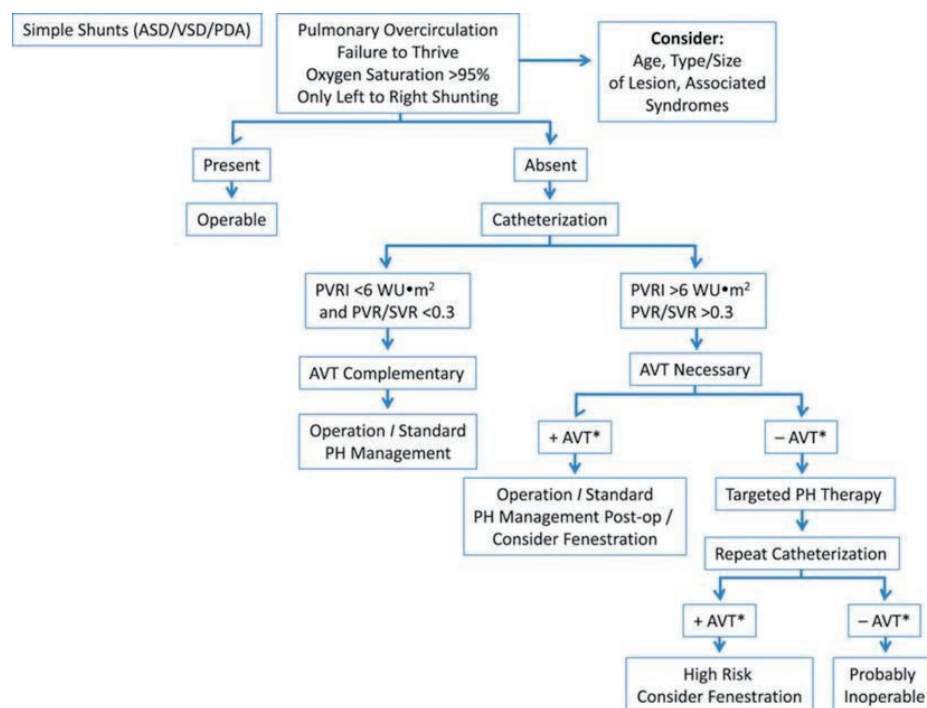

Figure 2: Algorithm for Management of Simple Shunts (ASD) in Pediatric Patients With PH. Reprinted from Abman SH, Hansmann G, Archer SL, et al. Pediatric Pulmonary Hypertension: Guidelines From the American Heart Association and American Thoracic Society. *Circulation*. 2015;132(21):2037-2099.

ever, undergo hemodynamic assessment through cardiac catheterization. ASD repair is recommended for patients with PVRi <6 WU m^2 and PVR/SVR <0.3. For patients with PVRi >6 WU m^2 and PVR/SVR >0.3, acute vasodilator testing is indicated. Those with positive acute vasodilator testing response showing reversibility of PAH may undergo repair with careful postoperative PH management and consideration of closure with atrial fenestration. Repair is contraindicated for children with PVRi >6WU m^2 and PVR/SVR >0.3 who do not respond to acute vasodilator testing because of unacceptable operative risk related to their severe PH. These patients may, however, be considered for a treat-and-repair strategy with targeted PH therapy for a period of time followed by repeat catheterization to assess operability.[17] Treated patients who subsequently show improved PVRi and positive acute vasodilator testing are considered high-risk for ASD closure, but may undergo repair with consideration of fenestration. Patients who have not improved after a period of targeted PH therapy and remain unresponsive to acute vasodilator therapy are likely inoperable with unacceptable risks of closure.

Important differences between current adult and pediatric guidelines include the use of acute vasodilator therapy to determine operability in children, as well as the potential deployment of a treat-and-repair approach in pediatric patients who were previously deemed inoperable. This strategy creates the possibility for repair in patients with significantly unfavorable initial hemodynamics who demonstrate improvement and/or response to acute vasodilator testing after a course of targeted PH therapy. It must be acknowledged that additional data are needed in support of this approach,[18,19] and optimal vasodilator strategy and timing of therapy are yet to be determined. High-risk patients embarking on a "treat-and-repair" approach need careful postoperative follow-up to evaluate mid- and long-term results.

DEFECT CLOSURE
The mode of ASD closure, a critical choice between surgery and transcatheter approaches for PH patients with ASDs, is no less important than the decision on whether to repair the defect at all. Transcatheter closure avoids cardiopulmonary bypass as well as surgical postoperative complications. With regard to candidacy for either approach, attention to type of defect is important as anatomy precludes transcatheter closure of ostium primum, sinus venosus, or coronary sinus defects. The size of the defects must be carefully measured. Transcatheter closure may be successfully performed for balloon stretched secundum defects <35 mm when sufficient rims of atrial tissue are available.[20] Additional contraindications to a transcatheter approach may include small patient size, vascular access, infectious issues, or contraindications for antiplatelet therapy post-catheterization.

Patients with ASD and elevated PVR may benefit from fenestrated ASD closure in order to preserve a residual shunt for decompression of the right ventricle and to maintain cardiac output in the event of acute rise in PVR postoperatively.[21] This strategy may be particularly advantageous for patients with preoperative right ventricular dysfunction. The use of a fenestrated patch during surgical ASD repair has been demonstrated to be feasible in patients with severe PAH.[22] Several studies have explored the use of fenestrated, commercially available transcatheter devices.[23,24] Recently, a novel fenestrated transcatheter device, the Occlutech® Fenestrated ASD device, showed promise in a multicenter compassionate use trial of ASD closure in patients with PAH.[25] Additional studies of these devices will be required to determine optimal timing of fenestrated closure, effective size of fenestration, and long-term results.

BEYOND CLOSURE: CAN WE PREDICT LATE OUTCOMES?
The reported prevalence of PAH after ASD closure varies between 5% and 50%.[21] Persistent PAH after ASD closure is associated with significant morbidity and mortality, making it important to identify patients at increased risk for progressive disease. Yong and colleagues studied a group of 215 consecutive adults undergoing transcatheter ASD closure.[6] At 15 months
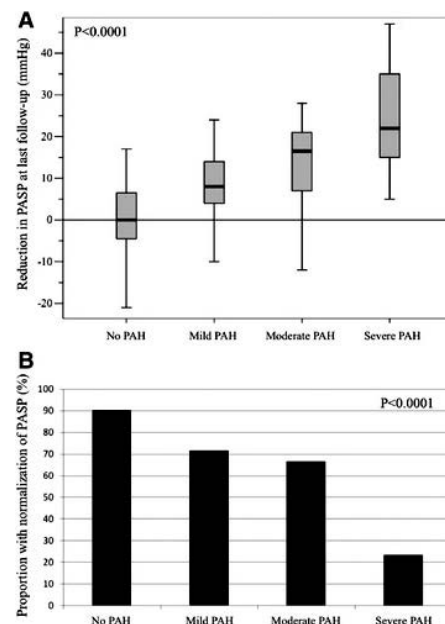

Figure 3: Outcomes After Transcatheter ASD Closure in Patients With PAH. Reprinted with permission from Yong G, Khairy P, De Guise P, et al. Pulmonary arterial hypertension in patients with transcatheter closure of secundum atrial septal defects: a longitudinal study. *Circ Cardiovasc Interv*. 2009;2(5):455-462. https://doi.org/10.1161/CIRCINTERVENTIONS.108.826560. Reduction in PASP (A) and normalization of pressures (B) after transcatheter closure of ASD. A, Degree of reduction in PASP after transcatheter ASD closure according to whether patients had no, mild, moderate, or severe PAH at baseline. B, Proportion of patients with normalization of PASP (<40 mm Hg) after ASD closure, as stratified by the baseline degree of PAH.[6]

post procedure, patients with higher baseline PA pressures were more likely to experience decreased PA pressure after closure (Figure 3, Panel A) but also less likely to normalize PA pressure (Figure 3, Panel B). Among patients with moderate to severely increased PA pressures before closure, normalized pressures were associated with lower baseline pressures and no more than mild tricuspid regurgitation. Additional independent factors for normalization of PA pressures after closure included younger age and small ASD size. In a separate study, D'Alto and colleagues found high baseline value of PVRi >6 WU m^2 or PVR/SVR >0.33 to be associated with progressive PAH after shunt closure.[26] An association between age and higher PA pressures after ASD closure was also observed by Humberger

and colleagues.[27] A multivariate logistic regression analysis of a case control cohort from a Dutch adult congenital heart disease registry additionally found pre-closure New York Heart Association functional class >1 strongly predictive of PH development after ASD closure.[28] In the future, novel biomarkers and genetic characteristics may prove useful for determining patients at risk for irreversible, progressive PAH after shunt closure.[29,30]

The approach to ASDs in patients with PH involves careful preoperative clinical, imaging, and hemodynamic assessment. Guidelines have been developed to assess risk of closure in adults and childhood and may require individualized approach. A treat-and-repair strategy may be considered for patients with less favorable hemodynamics; additional data are needed to determine optimal therapies for such patients. Options for surgical and transcatheter closure should be carefully planned and the use of fenestrated surgical or transcatheter device closure may be beneficial for high-risk patients. Persistent PAH has been associated with preoperative variables including higher pressures, older age, and decreased functional class. Close clinical and echocardiographic follow-up of patients after ASD closure is essential. Following repair, clinicians should have a low threshold to reassess hemodynamics at cardiac catheterization and initiate or augment targeted PAH therapy.

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