Can “Inoperable” Congenital Heart Defects Become Operable in Patients with Pulmonary Arterial Hypertension? Dream or Reality?

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ABSTRACT

The decision whether to repair congenital heart defects in patients with raised pulmonary vascular resistance to alleviate pulmonary hypertension is a complex one. The degree of pulmonary vascular disease is of paramount importance. Operating on patients with pulmonary vascular resistance above a certain threshold runs the risk of postoperative persistent pulmonary hypertension and a worse long-term prognosis. This review focuses on patients deemed “borderline inoperable” or “inoperable” due to pulmonary vascular disease and asks whether they can be “converted to an operable status” with pulmonary arterial hypertension-specific drugs that potentially modify the pulmonary vascular lesions and resistance.

Key Words. Pulmonary Arterial Hypertension; Congenital Heart Defects; Bosentan; Sildenafil Nitrate; Prostacyclin

Introduction

Advances in pediatric cardiac surgery now enable successful corrective surgery for congenital heart defects that are associated with increased pulmonary blood flow to take place in very early infancy. These procedures aim to prevent a whole plethora of sequelae, including the development of pulmonary arterial hypertension (PAH) and pulmonary vascular disease (PVD). However, in some individuals with systemic-to-pulmonary shunts, such defects may pass undetected until childhood or even adulthood and are diagnosed late when pulmonary vascular lesions have developed. Additionally, in developing countries, due to a previous lack of opportunity to close defects during infancy, PAH in children with congenital heart disease (CHD) is common. This situation is now becoming a very current issue, as health care in these countries is starting to improve. Therefore, worldwide, there is a need for guidance concerning complete surgical repair or palliative surgery of heart defects in patients that, as a result of their hemodynamic condition, develop PAH or some degree of PVD.

When discussing the best strategy for managing patients with congenital heart defects and high pulmonary arterial pressures (PAP) and high pulmonary blood flow, it is important to be clear about the difference between the terminologies “pulmonary vascular disease” and “pulmonary arterial hypertension,” as they are not interchangeable. Patients with moderate to large defects can have PAH but not necessarily irreversible PVD in terms of a permanently and extensively remodeled pulmonary vascular bed. In cases where PAP and blood flow are high, but pulmonary vascular resistance (PVR) is within normal limits or slightly elevated, the patient can be considered a suitable candidate for operation. In this scenario, pulmonary vascular lesions are likely not to be extensive. Conversely, high PAP and very high PVR means an unfavorable operating indication as the patient will most likely have extensive PVD. When PVR increases in patients with...
systemic-to-pulmonary shunts to the extent that it exceeds that of the systemic circulation, blood flow through the shunt becomes bidirectional or reversed. At this point, the condition has progressed to Eisenmenger’s syndrome, and, at this advanced stage, the patient is considered virtually inoperable due to irreversible obstructive lesions of the pulmonary vasculature.

While PAH and pulmonary vascular lesions are reversed after surgery in some patients and a successful long-term outcome is achieved, in others, PAH becomes irreversible and the prognosis is often worse than if surgery had not taken place. In a 5-year retrospective study of children with PAH in the United Kingdom, the subpopulation with postoperative PAH following surgical intervention of the defect (PVR: 13.8 Wood units \(\times\) m\(^2\)) fared far worse than those with PAH associated with complex (unoperated) heart defects (PVR: 12.7 Wood units \(\times\) m\(^2\)) and Eisenmenger’s syndrome (PVR: 22.7 Wood units \(\times\) m\(^2\)). Almost one-quarter of the children with postoperative PAH-CHD died (11 out of 47). Children with Eisenmenger’s syndrome had a greater cumulative survival time by 1.3 years, indicating that surgical repair is not necessarily always the best option.

Undeniably, the decision to operate on patients with medium to large defects shunting left to right who have moderate increases in PVR is difficult as the extent of pulmonary vascular lesions is unknown and there is no guarantee of long-term success. In the absence of an evidence-based treatment algorithm, such patients are currently managed on a case-by-case basis, according to almost arbitrary decisions of physicians, resulting in wide variations of acceptable hemodynamic limits for assessing operability between centers. These patients require very careful assessment to determine operability and gauge the level of risk of irreversible PAH after surgery. In this review, we shall briefly describe the investigations, protocols, and measurements currently used to assess operability in patients with congenital heart defects who have a high risk of irreversible PAH after surgery. Having established criteria for operability, it is a natural progression to question whether patients outside of these limits would benefit from drugs that prevent, slow down, or even reverse pulmonary vascular lesions and decrease PVR, that is, “Is there anything in our current medical treatment strategy that can be used to ‘convert’ patients deemed inoperable to a status where surgery is possible?”

Assessing Operability of Patients with PAH Associated with Congenital Heart Defects

At present, clinical examination and hemodynamic assessments form the basis of evaluating patients for operability. In the past, the evaluation of histopathologic changes of the pulmonary vasculature by means of lung biopsy was used to assess operability. However, these days, the reliability of the results is not considered sufficient to justify the invasive nature and risks involved in obtaining a lung tissue sample. Lung biopsy is limited in that it provides a snapshot of one randomly selected area of the lung. As such, it is not possible to completely evaluate the nature and extent of lesions across the entire lung. Patients without intimal thickening of the distal pulmonary arteries and considered to have reversible PVD can still develop irreversible postoperative PAH. Moreover, younger children (less than 2 years of age) are often operable despite advanced changes on lung biopsy.

Clinical examination is conducted for signs of congestive heart failure and cyanosis. Echocardiography will detect signs of increased pulmonary blood flow. However, although echocardiography is useful for showing dilated left cavities and pulmonary overflow in patients that fit the criteria for operability, it is not accurate enough to assess operability in borderline patients. For patients who are equivocal, right heart catheterization, which is considered the current gold standard of measurements to assess hemodynamic parameters and vasoreactivity, is necessary.

Empirical thresholds using hemodynamic data from right heart catheterization and vasoreactivity are used to best predict which patients would have a positive or negative surgical outcome. In a recent article, Lopes and O’Leary, from the available literature and by seeking expert opinion from recognized centers of excellence, suggested hemodynamic criteria based on both PVR and the ratio of PVR to systemic vascular resistance (SVR) and the way these values change during acute vasodilator challenge. It was proposed that:

- A baseline PVR index less than 6 Wood units \(\times\) m\(^2\) associated with a PVR : SVR ratio <0.3 without a vasoreactivity test may be considered indicative of a favorable outcome following operations resulting in a biventricular circulation.
- Acute vasodilator challenge using oxygen and nitric oxide has been strongly encouraged if baseline PVR index is between 6 and 9 Wood units \(\times\) m\(^2\) in the presence of a PVR:SVR ratio.
of about 0.3 to 0.5. Although there is no absolute consensus, operability with a favorable outcome is considered likely if all the following criteria are met:

- A decrease of 20% in the PVR index
- A decrease of about 20% in the ratio of PVR:SVR
- A final PVR index < 6 Wood units × m⁻²
- A final ratio of PVR:SVR < 0.3.

Acute vasodilatory testing, regardless of whether nitric oxide alone or in combination with oxygen, is used to test the reactivity of the pulmonary vascular bed. However, when assessing the operability of a patient with a congenital heart defect and high PVR, there is no consensus as to whether vasoreactivity testing is accurate enough to discriminate between patients who will or will not have a good surgical outcome. In addition, technical difficulties leading to calculation errors and other medical conditions need to be considered when undertaking vasodilatory testing.

The proposal by Lopes and O’Leary⁶ is a conservative one and may be considered quite restrictive. However, this is justified given the lack of solid evidence and variation between centers of what are considered acceptable hemodynamic limits for operability. In an equally thorough review of the literature, with subsequent multidisciplinary analysis, Giglia and Humpl⁷ reported a consensus statement that precise values of hemodynamic measures of PVD to determine level of risk of death or persistent PVR following biventricular repair cannot be derived. In fact, it is unclear which preoperative pulmonary hemodynamic parameters correlate best with outcomes; another unknown is the influence of individual patient factors such as cardiac lesion type and genetic predisposition.

It should be noted that the above criteria specified by Lopes and O’Leary⁶ do not apply to patients with single ventricle physiology who are being assessed for the creation of a Fontan circulation. These patients should ideally have near-normal levels of PVR and, certainly, it should be no more than 3 Wood units × m⁻².⁵ A preoperative mean PAP of greater than 15 to 19 mm Hg is a likely risk factor for poor outcome after the Fontan operation. Moreover, obtaining accurate hemodynamic measurements can be even more difficult in patients with single ventricle physiology.⁶,⁷

Although right heart catheterization measurements of hemodynamics are helpful, and are indeed the best tools available at present, they are not completely reliable. Patients that fall within the ranges deemed appropriate from determining a good operable outcome may still present with persistent postoperative PAH. Even in patients with moderately elevated PVR (mean preoperative PVR of 7.63 ± 1.8 Wood units) one study showed that 21% (eight out of 38 patients) either died or had persistent severe PAH following corrective surgery for ventricular septal defect (VSD).⁸ Conventional hemodynamic evaluation is far from optimal. To be as certain as possible of a good outcome, limits of a “safe” PVR have to be within a restrictive range, which consequently excludes many patients. Better, more accurate, and preferably less invasive evaluation tools are needed, and especially in patients considered uncertain for operability due to their hemodynamic profile. Identifying biomarkers that can define the degree of PVD, potential for reversal and confirm operability, would represent a real breakthrough in the decision-making process for the management of these patients. Circulating endothelial cells which are already recognized as a noninvasive marker of vascular damage and remodeling have recently emerged as a putative biomarker.⁹ Patients with irreversible PAH post-surgery, in addition to showing pulmonary arterial intimal thickening and a corresponding high expression of the antiapoptotic marker Bcl-2 in the endothelial cells on lung biopsy,¹⁰ also had significantly higher circulating endothelial cell levels in the peripheral blood than those with reversible PAH.⁹ In contrast, other biomarkers of endothelial activation, regeneration and injury, have not been able to discriminate between reversible and irreversible PAH following surgery.¹¹ These data are promising as they suggest a link between a biomarker that can be measured by taking a blood test with cellular and intracellular changes strongly associated with irreversible postoperative PAH that can only be measured by invasive biopsy. It is hopeful that long-term studies will confirm circulating endothelial cells as an appropriate marker for predicting reversibility of PAH and a simple blood test could replace the need for catheterizations and lung biopsies.

Role of Medical Treatment in Preparing Patients with PAH Associated with Congenital Heart Defects for Operability

In the past 10 years, prostanoids, endothelin receptor antagonists, and phosphodiesterase type-5 inhibitors have all shown to be effective...
in treating PAH by targeting the obstructive changes of the distal pulmonary arteries. In fact, experimental work has indicated that prostanoids, endothelin receptor antagonists, and phosphodiesterase-type 5 inhibitors exert antiproliferative activities on vascular endothelial and smooth muscle cells.\(^{12,13}\) Hypothetically, these molecules could have beneficial “de-remodeling” properties in cases where lesions of the pulmonary vascular bed are not fixed or irreversible, thus allowing surgical repair.

Drugs approved for PAH have been extensively tested in idiopathic PAH,\(^{14-18}\) and there is also good evidence that some of them are effective in treating PAH-CHD.\(^ {19-22}\) The mechanisms of PAH in patients with large heart defects are partially known; it is thought that the pressure and volume load on the pulmonary vascular bed leads to pulmonary vascular remodeling and lesions. These changes may have a different level of severity in each individual. So by reducing PVR in patients where vascular lesions are not extensive, the possibility arises that pretreatment with PAH-specific drugs can be used to improve a patient’s condition and an inoperable case could be considered operable. This may not, however, always be the case in patients where lesions are extensive and PVD is established. Although drugs can reduce PVR in these patients, PAH could remain postoperatively and a worse prognosis could result. If PAH-specific therapies are found to have a place in reducing PVR and preparing patients for operation by remodeling the pulmonary vascular bed, they could also be used to treat pre-Fontan patients, with a PVR >3 Wood units \(\times\) m\(^2\), attributed to mild pulmonary vascular lesions either after banding of the pulmonary artery (in the presence of increased pulmonary blood flow at birth) or systemic-to-pulmonary shunt (in the presence of decreased pulmonary blood flow at birth).

One problem that may arise by decreasing PVR with PAH-targeted therapies is that an increase in pulmonary blood flow, due to an increase in shunt volume, reestablishes the propensity toward lesion occurrence. Thus, paradoxically, the reversal of vascular remodeling and lesion formation, leading to an initial decrease in PVR, could actually result in pulmonary vascular damage later on. Fitting an adjustable pulmonary band to regulate blood flow once PVR starts to decrease should protect the pulmonary vasculature from pressure and flow stress. Partial closure of the defect may also be a protective measure, so should the PVR rise postoperatively, the right ventricle is able to decompress. Techniques that can be used include leaving a small hole which can be closed via catheterization once PVR has shown to be stabilized or a VSD flap. This latter technique enables right-to-left shunting only. While these are established surgical techniques in managing PAH-CHD, their use in combination with PAH therapies is experimental and their effectiveness in this situation has not been determined. There have been several case reports of pretreatment with prostanoids, or endothelin receptor antagonists, and one report with a phosphodiesterase type-5 inhibitor being used prior to surgical correction of a heart defect to prepare equivocal or “inoperable patients” (Table 1).\(^ {23-30}\) These reports suggest the possibility of using PAH-specific therapies to improve hemodynamics and make conditions more favorable for repair. However, there are several very important elements that need to be considered: (1) In these cases, most patients had simple atrial septal defects (ASDs) so it is not certain that they would have developed Eisenmenger’s syndrome late in life. In the Dutch CONCOR registry, 79% of patients with VSDs compared with 29% of those with ASDs had Eisenmenger’s syndrome; (2) How was operability defined? In the case of Hoetzenecker et al.,\(^ {24}\) even before PAH therapy, the patient was more or less within the safety limits of operability as defined by Lopes and O’Leary; (3) For all but two of these studies, the follow-up time of the patients when outcomes were reported was short—1 year or less. To confidently declare a successful outcome, data over a minimum of 5 to 10 years would be required; (4) While these isolated cases show success with pretreatment prior to operability, we do not know how many cases have failed and have not been reported. A retrospective analysis of surgical registries on these types of data would be required in order to gain a complete picture. The report of the patient with Eisenmenger’s syndrome who underwent closure of her ASD following a decrease in PVR with sildenafil treatment should be considered with caution.\(^ {29}\) The PVR and PAP were still not within normal range and it is impossible to know whether the operation will/will not have improved her long-term prognosis.

Huang and colleagues\(^ {32}\) used a “diagnostic treat and repair” strategy to select 49 PAH-CHD patients who had PAPs close to that of systemic pressures and who were previously considered inoperable for surgical correction. Patients who had improved transcutaneous oxygen saturation after treatment with either conventional pulmonary hypertension therapies (digoxin,
### Table 1. Case Studies of Patients with PAH Who Have Undergone Surgical Correction for Congenital Heart Defects Following Treatment with PAH-specific Therapies

<table>
<thead>
<tr>
<th>Age and Sex</th>
<th>Defect</th>
<th>Drug Treatment</th>
<th>Hemodynamics Pre-drug Treatment</th>
<th>Hemodynamics Post-drug Treatment</th>
<th>Operation</th>
<th>Outcome at Last Follow-up</th>
<th>Reference</th>
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<tbody>
<tr>
<td>31-year-old female</td>
<td>ASD</td>
<td>Intravenous epoprostenol for 3 years prior to operation</td>
<td>Mean PAP: 58 mm Hg Qp:Qs: 1.5 PVR: 824 dyn/s/cm² (10.3 Wood units)</td>
<td>Mean PAP: 51 mm Hg Qp:Qs: 2.0 PVR: 471 dyn/s/cm² (5.9 Wood units)</td>
<td>Transcatheter ASD closure with continued epoprostenol</td>
<td>1 year postoperation Mean PAP: 39 mm Hg Qp:Qs: 1.0 PVR: 256 dyn/s/cm⁵ (3.2 Wood units)</td>
<td>23</td>
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<tr>
<td>71-year-old female</td>
<td>ASD (Large type II [15 × 36 mm]) with bidirectional shunt</td>
<td>Bosentan 125 mg/day increased to 250 mg/day after 1 month for 10 months prior to operation</td>
<td>Mean LAP: 17 mm Hg Mean RAP: 16 mm Hg Mean PAP: 54 mm Hg Qp:Qs: 2.7 PVR: 460 dyn/s/cm² (3.9 Wood units)</td>
<td>Mean LAP: 11 mm Hg Mean RAP: 10 mm Hg Mean PAP: 30 mm Hg Qp:Qs: 2.2 PVR: 352 dyn/s/cm² (2.6 Wood units)</td>
<td>Closure with Dacron patch and continued bosentan therapy</td>
<td>8 months postoperation Mean LAP: 13 mm Hg Mean RAP: 7 mm Hg Mean PAP: 35 mm Hg Qp:Qs: 1 PVR: 538 dyn/s/cm⁵ (4.2 Wood units)</td>
<td>24</td>
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<tr>
<td>39-year-old female</td>
<td>PDA</td>
<td>Bosentan 125 mg/day for 2.5 years prior to operation</td>
<td>Systolic PAP: 112 mm Hg Mean PAP: 75 mm Hg Qp:Qs: 2.8 PVR: 9.5 Wood units PVR:SVR: 0.31</td>
<td>Systolic PAP: 106 mm Hg Mean PAP: 76 mm Hg Qp:Qs: 4.3 PVR: 6.1 Wood units PVR:SVR: 0.15</td>
<td>Closure using a 16F Foley catheter and Goretex patch under circulatory arrest. Bosentan therapy was continued</td>
<td>9-months post-operation Systolic PAP: 42 mm Hg Mean PAP: 29 mm Hg Qp:Qs: 1 PVR: 5.3 Wood units PVR:SVR: 0.14</td>
<td>25</td>
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<tr>
<td>63-year-old male</td>
<td>PDA</td>
<td>Bosentan, 62.5 mg/twice daily for 30 days then 125 mg/twice daily for 3 month prior to operation</td>
<td>Mean RAP: 8 mm Hg Mean PAP: 65 mm Hg</td>
<td>Mean RAP: 10 mm Hg Mean PAP: 55 mm Hg</td>
<td>Percutaneous closure with amplatz duct occluder. Bosentan therapy continued</td>
<td>3-months post-operation Mean RAP: 7 mm Hg Mean PAP: 35 mm Hg</td>
<td>26</td>
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<tr>
<td>38-year-old female</td>
<td>ASD (large 20 mm)</td>
<td>Intravenous epoprostenol for 2.5 years prior to operation</td>
<td>Mean SAP: 92 mm Hg RAP: 3 mm Hg Mean PAP: 75 mm Hg Qp:Qs: 0.88 PVR: 8.8 Wood units (reducing to 4.2 Wood units with vasodilation response)</td>
<td>Systolic PAP: 65–80 mm Hg RAP: 3 mm Hg Mean PAP: 32 mm Hg PVR: 2.8 Wood units</td>
<td>Percutaneous shunt closure with continued epoprostenol therapy for 1 year and 7 months and then bosentan therapy</td>
<td>3 months postoperation Systolic PAP: 50–55 mm Hg</td>
<td>27</td>
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<tr>
<td>29-year-old female</td>
<td>ASD</td>
<td>Intravenous epoprostenol for 4 years prior to operation</td>
<td>PAP: 105/40 mm Hg RAP: 12 mm Hg LVP: 96/10 mm Hg CO: 6 L/min</td>
<td>PAP: 40–50 mm Hg Qp:Qs: 2</td>
<td>Closure of ASD, receiving amiodrine and warfarin since cessation of epoprostenol</td>
<td>8 years postoperation PAP: 45 mm Hg CO: 3.7 L/min</td>
<td>28</td>
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<tr>
<td>41-year-old female</td>
<td>ASD</td>
<td>Sildenafil, 25 mg/twice daily for 9 months increasing to 50 mg/twice daily for 2 years prior to operation</td>
<td>PAP: 87/20 mm Hg RAP: 1 mm Hg Mean PAP: 75 mm Hg Qp:Qs: 0.87 PVR index: 25 Wood units × m² (23.7 Wood units × m² with vasodilation response)</td>
<td>PAP: 128/32 mm Hg RAP: 10 mm Hg Mean PAP: 75 mm Hg Qp:Qs: 1.73 PVR index: 12.63 Wood units × m² (12.1 Wood units × m² with vasodilation response)</td>
<td>Partial temporary occlusion of defect with 34 mm diameter test balloon with subsequent surgical repair of the ASD. Sildenafil therapy was continued for 3 years</td>
<td>6 months after repair echocardiography showed mild tricuspid regurgitation with peak velocity 3.8 m/s</td>
<td>29</td>
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<tr>
<td>31-year-old female</td>
<td>Sinus venous ASD</td>
<td>Bosentan 125 mg/twice daily for approximately 1 year prior to surgery</td>
<td>Mean PAP: 42 mm Hg PAPWP: 5 mm Hg PVR: 4.09 Woodunits Pulmonary artery oxygen saturation 84% Mean PAP and PVR decreased on adenosine challenge but pulmonary artery oxygen saturation did not.</td>
<td>Mean PAP: 47 mm Hg (decreasing to 44 mm Hg on vasoactivity challenge) RAP: 13 mm Hg LAP: 14 mm Hg RVP: 16 mm Hg LVP: 12 mm Hg Qp:Qs: 1.9 CO: 5.0 L/min</td>
<td>ASD closed and the PAPVD redirected to the left atrium with a superior vena cava baffle, with the patent foramen ovale left open as an escape route. Bosentan therapy was maintained</td>
<td>1 year after surgery Mean PAP was 25 mm Hg</td>
<td>30</td>
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ASD, atrial septal defect; CO, cardiac output; LAP, left atrial pressure; LVP, left ventricular pressure; PAP, pulmonary arterial pressure; PAPVD, partial anomalous pulmonary venous drainage; PVR, pulmonary vascular resistance; PVR:SVR, pulmonary vascular resistance : systemic vascular resistance; Qp:Qs, pulmonary-to-systemic blood flow ratio.
hydrochlorothiazide, captopril, or iv prostaglandin; 16 to 150 days) or advanced pulmonary hypertension therapies (nitrogen oxide, bosentan, or sildenafil; 5 to 21 days) underwent radical surgical repair during which lung biopsy samples were taken. Using the Heath–Edwards histology classification system of hypertensive PVD, the lung biopsies showed the majority of patients (78%) to have grade I change and 10.2% to have grade II change, which technically, according to this classification, are suitable levels of PVD to consider corrective surgery. Despite this, more than half of the patients (59%) had high postoperative PAH. The two patients who had grade IV change with plexiform lesions, and therefore considered to have irreversible PAH, actually showed reversal of PVD. However, without repeated lung biopsy, it is not quite clear how this reversal was judged. Although the population mean PAP and PVR were significantly decreased (P < 0.001) postoperatively vs. preoperatively (mean PAP 69.4 ± 11.6 mm Hg vs. 30.8 ± 11.0 mm Hg and PVR 1640.8 ± 712.2 dyn/s/cm² vs. 736.1 ± 290.4 dyn/s/cm², respectively), they were still higher than normal range. Some patients in this study may have benefitted in the short- to midterm, but the high number of patients with persistent PAH postoperatively and the lack of long-term survival outcomes for the whole cohort caution against this approach. The role of PAH therapy in preparing these patients for operability is unclear, and it is possible that they were “operable” even before treatment.

There has been one case series reported for prostacyclin and one case report of bosentan being used postsurgery to improve the surgical results. The results from these studies should be put into context with the natural course of PAH after closure of the defect. This will vary between individuals and it may take weeks or even months for PAP to return to normal after closure of the defect. Three female patients aged 13, 27, and 35 years old and one male patient aged 57 years old, all with ASDs, were considered borderline for operability with mean PAP ranging from 45 to 65 mm Hg, PVR ranging from 6 to 12 Wood units × m², and pulmonary-to-systemic blood flow ratios (Qp:Qs) ranging between 1.2 and 1.4 inclusive. All patients had a decrease in PAP immediately after complete closure of the ASD. Following long-term oral prostacyclin therapy, 60 to 20 μg/day, PVR below preoperative levels was observed over the follow-up period of 1.5 to 6.2 (mean 3.4) years.

Eicken et al. reported on a 35-year-old woman with a patent ductus arteriosus. She had a mean PAP of 66 mm Hg, a mean right atrial pressure of 9 mm Hg and a mean left atrial pressure of 10 mm Hg. Her PVR was 17 Wood units × m², which reduced to 7.5 Wood units × m² and 5.4 Wood units × m² on vasoreactivity testing with oxygen and nitric oxide, respectively. Her baseline Qp:Qs was 2.2 and increased to 4.3 and 6.0 with oxygen and nitric oxide challenge. Following hemodynamic evaluation, the patient underwent patent ductus arteriosus occlusion. However, at 4 months, her PAP and PVR were still high at 50 mm Hg and 11.6 Wood units × m². She was still vasoreactive with PVR of 9.2 and 8.2 Wood units × m² when challenged with oxygen and nitric oxide. Her Qp:Qs remained at 1 on challenge. She was treated with bosentan and nocturnal oxygen with apparent symptomatic improvements, but no hemodynamic and long-term data are provided.

The long-term efficacy of PAH-specific drugs in patients with residual PAH after corrective surgery for congenital heart defects is not established. The predicted survival of patients with CHD and postoperative PAH who were subsequently treated with bosentan was 3.67 years out of a possible 4.88 years with a 26% mortality rate in nonoperated patients. In view of these data, it needs to be asked whether borderline patients or those in high-risk situations would be best managed with pharmacologic therapy and no operation. This question will only be resolved in future studies with appropriate follow-up.

Conclusion

For patients with PAH-CHD defects who are borderline for surgery, there are no evidence-based recommendations of how best to proceed, and careful evaluation, especially hemodynamic assessment using right heart catheterization, of each patient is required. A risk–benefit assessment is required for each individual based on type of defect and the natural course of PAH, risks of procedure, and risk of developing right heart failure should a high PVR persist. Future areas of research that could potentially advance this field would be the identification and validation of prognostic biomarkers for reversibility of PAH, analyses of surgical patient registries examining correlations between perioperative parameters and short- and long-term outcomes, and well-designed prospective, case-controlled or cohort studies from experienced international centers.

So far, treatment that can convert inoperable patients to operable is far from a reality. No large-
scale studies have been conducted, and there are no definitive data available to be able to construct an algorithm to give guidance on a “treat and repair” strategy. Consideration can be given to key aspects that should be included into a clinical study assessing the effects of PAH-specific drugs on reducing PVR to levels compatible to shunt closure and subsequent long-term outcomes, although survival remains a difficult end point in this population. Which drug should be used for this approach is a pertinent question as several are currently available. Should a single oral therapy be used, and, if so, which one? Or should more aggressive combination treatment, including the use of parenteral prostanooids be considered? Based on current knowledge, we suggest a PVR < 6 Wood units/m² and a PVR:SVR ratio of 0.3 to be the hemodynamic limit following 12 months of targeted PAH therapy. Patients should be assessed by right heart catheterization at baseline, and after 12 months of therapy. Beyond 12 months, it seems unlikely that a patient would reach the PVR limit and so should not undergo the procedure. The end point of such a study needs particular thought especially in light of preliminary data showing that patients who have undergone corrective surgery have worse 10-year survival rates than patients with Eisenmenger’s syndrome or open systemic-to-pulmonary shunts. While a long-term survival trial is the ideal, we believe that it is an unrealistic primary end point. Therefore, we suggest a study which has a short-term primary end point of postoperative survival and a PVR < 3 Wood units/m² 1 year postoperatively with or without the need for continued PAH therapy. Annual long-term follow-up of patients to assess long-term outcomes in terms of sustained low PVR and survival should be conducted. While a trial of this kind is a major undertaking, it is the only way to scientifically answer the question of whether shunt closure, even within conservative preoperative PVR limits, is ultimately the best option for the patient. This is an important question that needs resolution.

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