Congenital heart disease and pulmonary hypertension: pharmacology and feasibility of late surgery
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Abstract
Pulmonary arterial hypertension (PAH) with increased pulmonary vascular resistance (PVR), previously termed pulmonary vascular obstructive disease or pulmonary vascular disease is a frequent complication of congenital heart disease (CHD). While there have been advances in the medical treatments available for classic Eisenmenger syndrome patients who are not suitable for repair, the sub-group of patients with moderate sized congenital systemic to pulmonary shunts and mild to moderately elevated PVR remains challenging. With the development of targeted medical treatments for pulmonary arterial hypertension (PAH), the concept of a combined medical and interventional/surgical approach for patients with PAH associated with CHD (APAH-CHD) has emerged. Careful evaluation and an understanding of the predominant physiologic features will help guide the management of these complex patients and whether late surgical repair is feasible. (Prog Cardiovasc Dis 2012;55:128-133)

Keywords: Congenital heart disease; Pulmonary hypertension; Vasodilator therapy; Pulmonary vascular disease; Operability

Pulmonary arterial hypertension (PAH) with increased pulmonary vascular resistance (PVR), previously termed pulmonary vascular obstructive disease or pulmonary vascular disease is a frequent complication of congenital heart disease (CHD). As more patients with structural heart disease survive into adulthood, PAH has become an important medical management issue particularly with respect to late operability. Further, with the development of targeted medical treatments for PAH, i.e. PH with increased PVR but without pulmonary venous hypertension (PVH), the concept of a combined medical and interventional/surgical approach for patients with PAH associated with CHD (APAH-CHD) has emerged. Determining the appropriate treatment course including whether the patient is a suitable candidate for targeted PAH medical therapy or surgery is extremely challenging. Just because we “can” close a defect successfully does not mean that it is in the patient’s best interests long-term. By closing the defect, the patient with borderline PVR, who un-operated would progress to Eisenmenger syndrome (ES), is converted physiologically into a patient with idiopathic PAH (IPAH; previously termed primary pulmonary hypertension) with an outcome often worse than if the patient had been left unrepaired. In this article we review current strategies for evaluating patients with CHD for repair and the available pharmacologic/interventional and surgical options.

PH is not a disease but merely reflects that the patient’s mPAP ≥ 25 mm Hg at rest. More specifically, PAH is defined as mean PAP ≥ 25 mm Hg, PCWP ≤ 15 mm Hg and an increased PVR. PAH has different clinical implications than PVH defined as mPAP ≥ 25 mm Hg, PCWP > 15 mm Hg without an increased PVR which is often associated with left sided congenital heart defects. In certain situations of CHD and PH, “mixed” PH occurs, defined as mPAP ≥ 25 mm Hg, PCWP > 15 mm Hg and an increased PVR. The only way to definitively distinguish between the hemodynamic subtypes is by performing a
complete cardiac catheterization. Determining whether a patient has PAH, PVH or “mixed” PH is critical as the treatments for these various forms of PH can vary significantly—from being safe and effective for one form of PH-CHD and unsafe without efficacy and with potential deleterious outcomes in other forms.

An overall understanding of the defect-specific natural history, including the likelihood of developing irreversible pulmonary vascular obstructive disease, is critical in evaluating the adult with CHD with PH, i.e. certain defects are more frequently associated with pulmonary vascular disease. In these cases, pharmacologic intervention may be more appropriate than an interventional or surgical approach. Table 1 illustrates defects with the likelihood of developing pulmonary vascular disease if the congenital defect is not repaired within the optimal time frame as shown.

Even though these recommendations apply to the young child with CHD, they are important for the physician caring for adults with CHD to understand in order to determine a patient’s anticipated outcome especially if the patient was repaired later than recommended. If defects are not repaired in a timely fashion or are diagnosed late, patients are considered at risk for pulmonary vascular disease. This can be present immediately following surgical repair or may only become clinically apparent years later. Not infrequently patients repaired late feel better for 3–5 years following repair but then become progressively more symptomatic, e.g. dyspnea with exertion, from progressive pulmonary vascular disease. It is at this stage that it becomes readily apparent that in hindsight the defect should not have been closed or at least not closed completely. Again, the authors want to emphasize that just because we can close the hole does not mean we should. The onus falls on the clinician to rule out pulmonary vascular disease prior to any intervention. In order to fully assess PAH in a CHD patient, cardiac catheterization is necessary. Cardiac catheterization will enable assessment of disease severity, degree of systemic to pulmonary shunting, the presence of post-capillary disease and presence or absence of acute pulmonary vasoreactivity. Assessment of pulmonary to systemic blood flow (Qp/Qs) and PVR is not readily or reliably available from non-invasive testing and are critical in the determination of operability.

Anatomic and physiologic classification of CHD

Anatomic and physiologic classification of CHD is an important part of the evaluation of the patient with CHD and PH. Anatomically, there are 5 features that should be evaluated including defect type, dimension, net directionality of the shunt, associated cardiac or extracardiac anomalies, and repair status (Table 2).

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### Abbreviations and Acronyms

- **APAH**: associated pulmonary arterial hypertension
- **CHD**: congenital heart disease
- **ES**: Eisenmenger syndrome
- **IPAH**: idiopathic pulmonary arterial hypertension
- **QP/QS**: pulmonary/systemic blood flow
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<table>
<thead>
<tr>
<th>Defect Type</th>
<th>Likelihood of Developing PV Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Truncus arteriosus</strong></td>
<td>100%</td>
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<tr>
<td><strong>AVC</strong></td>
<td>100%</td>
</tr>
<tr>
<td><strong>TGV</strong></td>
<td>100%</td>
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<tr>
<td><strong>Large VSD</strong></td>
<td>50%</td>
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<tr>
<td><strong>Large PDA</strong></td>
<td>50%</td>
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<tr>
<td><strong>Large ASD</strong></td>
<td>10%</td>
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**Table 1**

The likelihood of developing pulmonary vascular disease if not repaired within the designated time frame.

- **Infancy**: 100% (all defects)
- **2 years old**: 70% (large defects, small defects)
- **Adulthood**: 10% (small defects, large defects)

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**Anatomic and Physiologic Classification of CHD**

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**Overall, four physiologic subtypes exist for patients with APAH-CHD:**

1. Eisenmenger physiology which includes all unrepaired systemic-to-pulmonary shunts resulting from large, unrestrictive defects leading to a severe progressive increase in PVR, bi-directional shunting and ultimately reversed (pulmonary-to-systemic) shunting with central cyanosis; 2) PAH with moderate to large defects. PVR is mildly to moderately increased, systemic-to-pulmonary left or right shunt is still prevalent, and no cyanosis is present at rest; 3) small defects.
(usually ventricular septal defects ≤ 1 cm and atrial septal defects ≤ 2 cm effective diameter assessed by echocardiography) with the clinical picture similar to IPAH; and 4) PAH after corrective cardiac surgery where the CHD has been corrected, but PAH is still present immediately after surgery or recurs several months or years after surgery in the absence of significant postoperative residual shunts. The latter two categories are physiologically more analogous to the patient with IPAH with respect to lack of an adequate “pop-off” valve for the failing right ventricle (RV) to decompress when an increase in venous return occurs such as with exertion; otherwise this can result in acute right heart failure that can be catastrophic. These patients are at an increased risk for more rapidly progressive right heart failure and a worse outcome than had they not been repaired. The medical approach for patients with small restrictive defects or pulmonary vascular disease following complete repair of a CHD is the same as for other forms of Group 1 PAH although there is less controlled data available for such patients.

For patients with the first physiologic subtype, “classic Eisenmenger syndrome” and those with the second subtype, “un-repaired moderate sized defects” management is more challenging and is the focus of the remainder of this article.

**Management of the patient with Eisenmenger physiology**

In patients who have a large unrepaired systemic to pulmonary communications with associated cyanosis, elevated PVR and absence of a large left to right shunt, surgical intervention can be fatal even if the patient survives the surgery. And not unexpectedly, if a patient has been taken to the operating room to close a shunt and cannot come off bypass, merely taking down the repair will not necessarily prevent a fatal outcome as the patient may still not be able to come off bypass. Similarly, just because a patient tolerates a test closure of a defect in the cardiac catheterization laboratory while lying on the cardiac catheterization table at rest, does not mean the defect should be closed. With exertion, the PVR could easily increase with the patient acutely decompensating.

Nevertheless, in the absence of early surgical repair, CHD patients who develop ES have significant morbidity and a reduced life-span. There is emerging evidence that targeted PAH medical therapy can offer these patients an improvement in clinical status. In the first randomized, double-blinded placebo controlled trial of the endothelin receptor antagonist (ERA) bosentan for the treatment of ES patients (BREATHE-5), the active treatment group had no worsening in systemic arterial
oxygen saturation at rest with a concomitant improvement in PVR and in exercise capacity (as assessed by the six minute walk test) at week 16 versus baseline. The placebo group in this trial had worsening in PVR and exercise capacity during the 16 weeks which suggests that even patients with longstanding ES progress more quickly than previously appreciated. This lends further support to medical intervention for these patients. Additional small observational series with another ERA, ambrisentan, for ES have also demonstrated maintenance of systemic oxygen saturation with improvement in exercise capacity as measured by the 6 minute walk test. In addition to uncontrolled case series with the PDE-5 inhibitor sildenafil in classic ES patients, Zhang et al reported efficacy in patients with ES over 12 months. In this open-label prospective study 84 Eisenmenger patients in WHO Class II–IV were treated with sildenafil 20 mg tid. The patients demonstrated improvements in hemodynamic parameters: PAPm $-4.7 \text{ mmHg (p=0.001)}$ and PVR $-474 \text{ dyn s cm}^{-2} \text{ m}^{-2} (p<0.0001)$. There were also reported improvements in WHO functional class and 6 minute walk distance. While the exact mechanism of benefit of targeted PH therapies has not been well-described in ES patients, one might attribute clinical improvements to improved pulmonary blood flow with decrease in right to left shunting at rest or with exertion, and stabilization of the effects of secondary erythrocytosis.

Patients in the second physiologic subgroup with APAH-CHD and mild to moderately elevated PVR and moderate to large systemic to pulmonary shunting with no cyanosis at rest are the most challenging to manage with respect to preferred therapeutic approach. Although there are no validated criteria for preoperative hemodynamics that would predict early or late morbidity, there are several important features that require evaluation including a complete cardiac catheterization with acute vasodilator testing and possible temporary balloon occlusion, exercise testing, and a careful and thorough medical history. For example a patient may seem “operable” at rest but with an associated minor respiratory illness and hypoxic pulmonary vasoconstriction, it may become clear that the shunt should not be closed or at least not completely closed. The evaluation often requires observation of response to medical therapy overtime and sometimes multiple catheterizations following a medical intervention. This group is so variable in type of defects, degree of shunting and symptoms that careful serial evaluation is necessary before performing an interventional procedure that could potentially worsen right heart function with resultant progressive right heart failure and an earlier death than if not repaired.

In general, when discussing IPAH, the most prognostic hemodynamic features are indices of right heart function, i.e. mean right atrial pressure (mRAP) and cardiac index. It turns out that mPAP is less useful for assessing disease severity as the PAP may in fact decrease when the patient is deteriorating due to the patient no longer being able to generate a higher PAP with progressive right heart failure. In contrast, when evaluating a patient with shunt physiology one should be most focused on PVR, PVR/ systemic vascular resistance ratio, and QP/QS as PAP alone and even transpulmonary gradient are less indicative of the underlying severity of the pulmonary vascular disease. By the very nature of having a large VSD or PDA, the PAP will be at systemic levels regardless of the PVR. One needs to determine whether the primary pathology is due to pulmonary arterial vasculopathy with elevated “irreversible” PVR or due to a large shunt (elevated QP/QS) with potential for reversibility of the PH if the shunt is eliminated. Unfortunately there is a gray zone where the predominant physiology is unclear or “mixed” and one might consider targeted medical therapy for some period of time with close serial re-evaluation before deciding whether ultimately repair is indicated, both from a short-term and long-term standpoint. It is clearly hard to not intervene but “benign neglect” is still most appropriate in some patients.

Important demographic characteristics include age, time of CHD diagnosis, type of CHD and circumstances of the diagnosis. Whether there have been any previous interventions and other risk factors is also important. Was the patient diagnosed in infancy? If so, was it an incidental diagnosis by murmur or did the infant have failure to thrive, signs of congestive heart failure or frequent severe respiratory infections? If any of these features are present, it is likely that the congenital systemic to pulmonary shunt was large in early childhood predisposing the development of pulmonary vascular hypertensive changes if not treated early. In the case of a patient diagnosed incidentally by murmur or in adulthood with no symptoms, there are two possibilities: the shunt is small or the patient already has high PVR preventing heart failure symptoms from a large left to right shunt. With advancing age there are also some patients who may not have previously been symptomatic, but will develop respiratory symptoms related to an increase in left to right shunting related to decreases in left ventricular compliance. With respect to age at presentation, in general the earlier a congenital to systemic shunt is discovered, the more likely the patient is operable. By operability, we are referring to whether the PAH will improve or progress after repair. The window of operability, however, varies between defects with lesions associated with high sheer stress and high flow being most likely to lead to early pulmonary vascular disease. Other important historical features include asking questions about cyanosis. Has the patient ever noticed blue nail beds or lips particularly with exertion? Is there a history of dyspnea or exercise limitation? All of these questions help to frame the case for whether a patient is operable and/or PAH-targeted medical therapy should be considered. Defect specific management is essential as
certain combinations particularly those in association with left sided defects (e.g. mitral stenosis, mitral regurgitation, aortic stenosis), do not lend well to targeted medical therapy alone. Cardiac catheterization becomes a critical tool in assessing defect-specific operability.

During the cardiac catheterization for evaluation of a congenital systemic to pulmonary shunt, the data that is required includes baseline room air hemodynamics including three complete oxygen saturation shunt runs (high and mid superior vena cava, RA lateral wall, RV, PA and aortic (pre and post ductal if a patent ductus arteriosus is present). The measures should be obtained in the absence of respiratory or metabolic acidosis, anemia or agitation. Once baseline data is obtained, if there is no evidence of post-capillary pulmonary hypertension, acute vasodilator testing should be performed if the PVR is >3 Wood units. Another full assessment including complete shunt runs should be obtained while on the acute vasodilator using either inhaled nitric oxide or intravenous prostacyclin (epoprostenol). A separate assessment with the addition of 100% O2 can be performed as well. Preferably, oxygen consumption should be measured and not assumed. But regardless, the hemodynamic parameters must be assessed using the Fick method as opposed to thermo-dilution unless there is already severe ES with only a right to left reversed shunt in which case the cardiac catheterization may not be needed to assess operability. One example of a treatment strategy for an adult with an atrial septal defect is illustrated in Fig. 1.

In addition to hemodynamic and history assessment, exercise capacity and in particular the presence of cyanosis at rest or with exertion should preclude closure of the defect. In the case of cyanosis with exertion or at rest, and late discovery of the defect with the PVR above 6 Wood units*m^2 the preferable approach to management would be medical with targeted PAH therapy and reassessment within 6–12 months if criteria was initially borderline operable at prior cardiac catheterization. While data exists for the use of ERAs for classic Eisenmenger patients, there is less data on the use in patients with moderate sized shunts. However our experience is growing that this approach can be done in these types of cases if the patient is being closely monitored and serially re-evaluated. In the event that a defect is repairable, the patient should be counseled that there may be perioperative pulmonary hypertensive crises and complications including the need for inhaled nitric oxide or extracorporeal membrane oxygenator bridging as well as the need for long term PAH medical therapy. In addition, a conversation with the surgeon about leaving a small fenestration in the patch repair that would permit a “pop-off” valve may be beneficial (even if just used in the peri-operative period when the patient may be at a higher risk of acute postoperative PH crises).

In summary, while PAH and CHD are classified with many other subgroups of PH Group 1, i.e. PAH, the group is very heterogeneous in terms of anatomic, physiologic and clinical features. A combined medical/interventional

![Fig. 1. CHD/PH (ASD) Clinical management algorithm: Individualized case approach.](image-url)
approach may be indicated for the patient with borderline pulmonary vascular hemodynamics. Future clinical trials should be designed to evaluate these approaches in patients with APAH–CHD so that we can best predict who will have the best early and late post-operative outcome and in cases where surgery is not feasible, what is the best medical therapeutic approach.

Statement of Conflict of Interest

Dr. Erika Berman Rosenzweig has received honoraria from Actelion, Gilead and United Therapeutics for attending scientific advisory board meetings and presenting CME lectures in the past, and has received research/grant support from Actelion, Bayer, Gilead, GSK, Eli Lilly, Novartis and United Therapeutics. None of these relationships are relevant to the content of this manuscript.

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References


