Recent Advances in Pulmonary Hypertension

Clinical Evaluation and Management of Pulmonary Hypertension in the Adult With Congenital Heart Disease

Alexander R. Opotowsky, MD, MPH

Pulmonary hypertension (PH) refers to elevated pulmonary artery (PA) pressure (PAP), defined as mean PAP ≥25 mm Hg. PH is not synonymous with pulmonary arterial hypertension (PAH), which specifies resistive PH characterized by elevated pulmonary vascular resistance (PVR) and normal pulmonary venous pressure. Approximately 5% to 10% of adults with congenital heart disease (CHD) have PH, and this subset of CHD patients is at higher risk of hospitalization and death.1–3 Understanding the epidemiology of PH associated with CHD (PH-CHD) is not straightforward, however, because definitions of PH-CHD and diagnostic techniques vary. Appropriate diagnosis and the management of PH-CHD rest on identifying the cause of elevated PAP: high pulmonary venous pressure, high pulmonary vascular resistance, high pulmonary flow, or some combination of these factors, which are referred to throughout this review as passive, resistive, hyperkinetic, and polygenic PH, respectively (Table 1).

Prognosis in PH-CHD depends on the underlying cause, pulmonary vascular pathophysiology, and the interaction between the right heart and pulmonary circulation. Adult CHD is heterogeneous, with myriad permutations of underlying defects, previous interventions, and associated comorbidities. Although comprehensive understanding of clinical context is a prerequisite, identifying the optimal therapy for a patient with PH-CHD depends more heavily on an understanding of pathophysiology than it does on the underlying diagnosis. Therefore, the goal of this review is to frame an understanding of PH-CHD in terms of fundamental cardiovascular hemodynamic pathophysiology and to emphasize the clinical assessment and management of situations commonly encountered by adult cardiologists caring for patients with PH-CHD.

Classifications of PH and PH-CHD
Classification schemes in PH represent clinical perspectives of underlying pathophysiology and tend to parallel fundamental hemodynamic relationships of the pulmonary circulation. PVR is defined: $PVR = \frac{\text{mean PAP} - \text{PAOP}}{Q_p}$. Pulmonary artery occlusion pressure (PAOP) approximates pulmonary venous pressure and $Q_p$ is pulmonary blood flow. Rearranging this equation gives $\text{mean PAP} = \left( PVR \times Q_p \right) + \text{PAOP}$. Elevated PAP, therefore, can result from an increase in PVR, $Q_p$, or PAOP.

World Health Organization Classification
The most recent World Health Organization classification describes 5 groups: (1) PAH, defined as PH attributable to elevated PVR with normal pulmonary venous pressure; (2) PH owing to left heart disease; (3) PH attributable to lung diseases and hypoxia; (4) chronic thromboembolic PH; and (5) PH with unclear/multifactorial mechanisms.3 Until 2013, PH-CHD was listed exclusively under group 1 according to 4 clinical phenotypes observed in congenital systemic-to-pulmonary shunt lesions: Eisenmenger syndrome (ES), PAH associated with systemic-to-pulmonary shunts, PAH with small cardiac defects, and PAH after corrective surgery. The 2013 update recognizes a broader spectrum of PH-CHD; for example, congenital left-sided obstructive lesions such as Shone complex (the combined presence of parachute mitral valve, supravalvular mitral ring, subaortic stenosis, and coarctation of the aorta) are classified as group 2.3 Importantly, CHD anatomy does not necessarily dictate what type of PH will develop; for example, a repaired ventricular septal defect may be associated with either PAH or pulmonary venous hypertension as a consequence of chronic left-sided volume overload.

Modified Wood Classification
Paul Wood described 5 types of PH based on hemodynamics and pulmonary vascular pathophysiology, along with a sixth category designating mixed etiology.4 Two categories are particularly relevant to PH-CHD: (1) PH attributable to high pulmonary blood flow (hyperkinetic PH) and (2) PH with multiple causes (polygenic PH). Because there should be no assumption that a specific anatomic CHD diagnosis will correspond to a designated pathophysiology, this classification approach is useful when caring for patients with PH-CHD, and will serve as the framework of the current review (Table 1; Figures 1 and 2).5 For clinical purposes, obstructive, obliterator, and vasoconstrictive pulmonary vasculopathies are reasonably considered together as resistive PH for several reasons. First, these frequently coexist, as is often the case for ES. Second, it is difficult in clinical practice to distinguish the contribution of each etiology to PH-CHD, and, with the exception of chronic thromboembolic PH, current therapy does not depend on differentiating between these pathological substrates.

From the Department of Cardiology, Boston Children’s Hospital, Boston, MA; and Department of Medicine, Brigham and Women’s Hospital, Boston, MA. Correspondence to Alexander R. Opotowsky, MD, MPH, Assistant Professor, Harvard Medical School, Boston Children’s Hospital, 300 Longwood Avenue, Boston, MA 02115. E-mail alexander.opotowsky@chboston.org (Circulation. 2015;131:200-210. DOI: 10.1161/CIRCULATIONAHA.114.006976.)

© 2015 American Heart Association, Inc.

Circulation is available at http://circ.ahajournals.org

DOI: 10.1161/CIRCULATIONAHA.114.006976

200
Diagnosis: History and Physical Examination

PH can be asymptomatic, but it is often associated with exertional dyspnea or fatigue; hemoptysis, angina, presyncope, and syncope suggest severe disease. Symptoms, however, are not specific for PH in patients with CHD. Likewise, symptoms are of variable value in identifying PH type. Orthopnea and paroxysmal nocturnal dyspnea suggest left heart failure; hemoptysis is more often a feature of severe PAH or thromboembolic disease (case, Figure 3A), but may be present with mitral stenosis.

Physical examination may reveal a parasternal lift, high-pitched tricuspid regurgitation murmur, widely split S2 (in the absence of right bundle-branch block, large atrial septal defect [ASD], or other cause), pulmonary ejection sound, or loud P2. An extended or square-wave blood pressure response to the Valsalva maneuver suggests elevated left-sided filling pressures among patients with suspected PH. Elevated jugular venous pressure itself and sustained abdominojugular reflux are less specific, and may be present with any type of PH-CHD or even with left heart failure not associated with PH. Anatomic peripheral pulmonary artery stenosis may cause a systolic or continuous murmur over the back or precordium.

Clinical Assessment of PH-CHD

Assessment of PH-CHD involves: (1) making a diagnosis, (2) defining pathophysiology, and (3) evaluating prognosis and response to therapy. Although many of the same clinical tests are used to address these distinct objectives, the pertinent variables will differ depending on the aim. Although history, physical examination, ECG, and echocardiography are the most commonly used tests in the initial evaluation of PH-CHD (Figure 3), a definitive diagnosis of the underlying (patho) physiology requires invasive hemodynamic catheterization. Exercise testing, submaximal and maximal, allows objective functional monitoring. Chest radiography, V/Q scan, computed tomography angiography, cardiovascular magnetic resonance, circulating biomarkers, and pulmonary function testing also play an important role in specific situations.

Diagnosis: Echocardiography

PH is often suspected based on echocardiography demonstrating elevated tricuspid regurgitation peak velocity that suggests elevated right ventricular (RV) systolic pressure. RV systolic pressure, however, is not equal to PA systolic pressure (PASP) in the presence of RV outflow obstruction. PASP estimates must therefore account for any RV outflow gradient (eg, congenital pulmonary stenosis). Furthermore, PASP correlates strongly with mean PAP, but caution is warranted in patients with high flow (eg, shunt or pulmonary regurgitation), because, under these conditions, systolic pressure increases to a proportionally greater extent than mean pressure (high pulse pressure; case, Figure 3C). RV dysfunction is common with CHD, even in the absence of PH, and consequently does not reliably identify PH. For
example, abnormal RV function are often unrelated to pulmonary vascular disease in patients with Ebstein anomaly or repaired tetralogy of Fallot with pulmonary regurgitation.

Echocardiography is also helpful for understanding PH-CHD pathophysiology beyond the estimation of PAP, and may provide guidance on whether invasive evaluation is merited. This situation is commonly encountered following ASD repair; despite favorable overall prognosis, echocardiography suggests a high prevalence of PH. Elevated PASP in this situation may be attributable to (1) high PVR (ie, true PAH-CHD); (2) a spurious finding, because echocardiographic and invasive PAP correlate only moderately ($r = 0.7$) with wide limits of agreement; (3) elevated pulmonary venous pressure, which is common after ASD closure owing to noncompliant atria or septal patch/device; or (4) high pulse pressure due to stiff, noncompliant pulmonary arteries secondary to chronic pulmonary overcirculation.

Late systolic ventricular septal flattening and abnormal RV outflow tract Doppler flow (short acceleration time and notch attributable to reflected pressure waves) are consistent with elevated pulmonary impedance causing prolonged RV contraction and elevated PVR, respectively (case, Figure 3A), and help to distinguish resistive from passive PH-CHD; there are also quantitative echocardiographic methods to estimate PVR; Left atrial size, tissue Doppler, and mitral inflow velocity patterns may identify elevated left atrial pressure (case, Figure 3B), although this does not preclude coexisting increases in PVR.

**Diagnosis: Cardiac Catheterization**

Symptomatic patients suspected of having PH attributable to elevated PVR should undergo cardiac catheterization to confirm PH and define underlying pathophysiology. It is less clear when to pursue invasive assessment in asymptomatic patients or for patients with PH believed attributable to isolated left heart disease (passive PH). If invasive diagnosis is not pursued, a high index of suspicion for alternative causes of PH is prudent with reconsideration of catheterization for patients who do not improve with empirical therapy for passive PH.

Cardiac catheterization is the reference standard for the diagnosis of PH, but several pitfalls merit consideration, especially in CHD. First, the Fick principal is often applied to determine cardiac output by the use of an estimate of $O_2$ uptake. This introduces important error, and $O_2$ uptake should be measured directly at the time of catheterization; dilution methods are appropriate only in the absence of intracardiac shunting. Second, catheterization data represent a snapshot of supine resting hemodynamics at a single moment in time. In patients with borderline or mixed physiology, dynamic maneuvers (eg, upright position, exercise, nitric oxide, nitroprusside, volume loading) can better establish the predominant pathophysiology. Finally, ensuring valid pulmonary artery and vein saturations is not a trivial task for complex CHD or even for simple shunt lesions (eg, PDA). Shunt calculations and pulmonary blood flow estimates depend on accurate measurement and appropriate interpretation fully cognizant of implicit assumptions and limited precision. Even appropriately collected accurate data can unwittingly be misinterpreted. As such, catheterization should be performed by an experienced PH-CHD specialist.

**Prognosis and Response to Therapy**

Severity of symptoms and functional impairment are the most direct markers of prognosis and response to therapy; not only does symptomatic and functional improvement itself constitute an important therapeutic goal, it also is associated with overall prognosis. There is no definitive evidence that treatment decreases the incidence of hard clinical end points in PH-CHD (eg, death), and one might argue that symptomatic improvement is the only reasonable target of therapy. Symptoms, however, are insensitive markers of ventricular dysfunction or physiological change. Despite a lack of supportive data, it is presumed that treatment-related physiological improvement (eg, increase in RV ejection fraction, decrease in circulating B-type natriuretic peptide concentration) should correspond to meaningful benefit for the patient. Therefore, physiological correlates of prognosis and response to therapy play an essential clinical role.

Exercise testing, most commonly the 6-minute walk test, provides an objective, reproducible measure of functional status. Although maximal cardiopulmonary exercise testing with measurement of gas exchange provides detailed information on ventilatory efficiency and dynamic shunting, the 6-minute walk test is more convenient for frequent follow-up of functionally limited patients.

Once the diagnosis of PH is made, the absolute level of PAP elevation deserves little attention; it does not accurately predict prognosis or response to therapy. Instead, prognosis corresponds more closely to variables that reflect the extent of right heart dysfunction. For example, changes in echocardiographic markers of venous pressure (eg, inferior vena cava size, pericardial effusion) and RV function (eg, RV fractional area change) are of greater value than changes in estimated PASP.

Physical examination informs prognosis based on the same principles. Sinus tachycardia, low systemic pulse pressure, and hypotension suggest low cardiac output, whereas elevated jugular venous pressure corresponds to high right heart filling pressure. Circulating biomarkers that reflect disease severity, such as ventricular wall tension (eg, B-type natriuretic peptide concentration), can provide additional information on disease severity and response to therapy.
### Figure 3

**A**, Resistive PH: a 38-year-old woman was diagnosed at 26 years of age with a large primum atrial septal defect. Catheterization revealed mildly elevated PVR (4WU) with $Q_s/Q_p = 1.6$. She underwent surgical fenestrated patch repair with symptomatic improvement, but developed increasing dyspnea 7 years later. Echocardiogram demonstrated severe RA and RV enlargement with ventricular septal flattening causing LV compression (Top). RV outflow tract Doppler flow demonstrated short acceleration time and midsystolic notching (Top Middle), consistent with elevated PVR. Subsequent catheterization demonstrated mean PAP=70 mm Hg, PAOP=12 mm Hg, TPG=58 mm Hg, $Q_s/Q_p = 3.8$ L/min, PVR=15WU. Right lower lobe wedge angiogram (Bottom Middle) showed dilated more proximal arteries rapidly tapering to tortuous distal vessels with suggestion of patchy early background blush. The patient later presented with hemoptysis, and CT angiography (Bottom) showed extensive pulmonary artery thrombus (*=thrombus, †=lumen) and consolidation (arrows).

**B**, Passive PH: a 60-year-old woman was first diagnosed with a large primum atrial septal defect and cleft mitral valve at 16 years of age. Catheterization at the time showed $Q_s/Q_p = 4:1$, with normal PAP and PVR. Soon thereafter, she underwent surgical atrial septal defect closure and suture repair of the mitral valve. She was lost to follow-up and remained symptomatically well until developing paroxysmal atrial fibrillation at 60 years of age. An echocardiogram demonstrated severe left atrial enlargement (Top) and important mitral regurgitation (Middle). RVOT Doppler flow was normal (Bottom), consistent with normal PVR. Catheterization demonstrated mean PAP=30 mm Hg, PAOP=24 mm Hg, TPG=6 mm Hg, $Q_s/Q_p = 5$ L/min, PVR=1.2WU.

**C**, Hyperkinetic PH: a 44-year-old man with Noonan syndrome status post pulmonary valvotomy for valvar pulmonary stenosis in childhood presented with exertional cyanosis and dyspnea. Evaluation revealed moderate pulmonary regurgitation and a previously undiagnosed inferior sinus venosus defect (Top, dotted oval). Echocardiography estimated systolic PAP>100 mm Hg (Middle) and showed diastolic ventricular septal flattening (Bottom). Invasive hemodynamics: PAP=88/17, mean=41; PAOP=12; TPG=29 mmHg; $Q_s/Q_p = 4.8$ L/min; $Q_p=11$ L/min, PVR=2.6WU. Intermittent right-to-left shunting in the setting normal PVR can be caused by streaming effects, eccentric tricuspid regurgitation, or alternative causes of decreased right heart compliance such as pulmonary regurgitation. PA indicates pulmonary artery; PAH, pulmonary arterial hypertension; PAOP, pulmonary artery occlusion (or wedge) pressure; PAP, pulmonary artery pressure; PVR, pulmonary vascular resistance; R/LA, right/left atrium; R/LV, right/left ventricle; RVOT, right ventricular outflow tract; $Q_p$, pulmonary blood flow; $Q_s$, systemic blood flow; S/IVC, superior/inferior vena cava; TPG, transpulmonary gradient; and WU, Wood units.
peptide) or end-organ perfusion (eg, uric acid, sodium, creatinine), provide additive information.21,22

Special Considerations in PH-CHD
A comprehensive knowledge of initial CHD diagnosis, previous procedures, and diagnostic testing, and current anatomy is vital to caring for adults with CHD. Three additional considerations of special note in PH-CHD are further reviewed.

Anatomic Lesions Amenable to Repair
Anatomic lesions can either cause or simulate PH. Lesions that actually cause PH (ie, elevated distal PAP) include left-sided obstructive lesions such as mitral stenosis, cor triatriatum, or pulmonary vein compression. Conversely, lesions such as pulmonary valve stenosis, infundibular pulmonary stenosis, double chamber RV, branch PA stenosis, or kinking at the site of a previous systemic-to-pulmonary palliative anastomosis do not result in PH, but can cause elevated RV systolic pressure and thereby simulate the clinical presentation of PH-CHD with right heart failure and high systolic transtricuspid flow velocity by echocardiography. The distinction is challenging but essential, because anatomic lesions are often readily repairable.

Pulmonary and Chest Wall Disease
Pulmonary disease, both parenchymal lung disease and chest wall deformity, is a common comorbidity associated with a number of congenital heart defects.23,24 Scoliosis, for example, is prevalent among patients with cyanotic heart disease, and can also result from previous cardiothoracic surgery. Such chest wall deformities are a risk factor for hypercapnic and hypoxemic respiratory failure, which, in turn, may increase PVR. This is often ameliorated by positive-pressure ventilation and should be considered another potentially reversible cause of elevated PVR in this population.

Distinguishing Clinically Relevant Pathology From an Abnormal Variant
There are no normative hemodynamic data for asymptomatic adults with CHD at rest or during exertion, and it is unclear if mild abnormalities relative to the general population are clinically important. Even in patients with excellent long-term prognosis, subtle pulmonary vascular remodeling of both large and small vessels may persist after the repair of a shunt lesion25,26; this is associated with lower exercise capacity, but the prognostic significance is unknown.

In symptomatic patients, we risk attributing symptoms to abnormal hemodynamic values that may have been stable, albeit unmeasured, for decades. As noninvasive tools become increasingly sensitive for defining pulmonary vascular remodeling, it will important to define the expected range of cardio-pulmonary hemodynamics in asymptomatic CHD patients to better understand whether a given finding is likely to be the cause of progressive symptoms.

Therapy for PH-CHD by Class
Passive and Hyperkinetic PH
For patients with a specific anatomic cause of passive or hyperkinetic PH, appropriate treatment may be apparent (eg, mitral valve repair for severe mitral regurgitation). In the absence of a surgical option, management for passive PH-CHD generally aligns with left heart failure therapy used in adults without CHD, although this approach rests on first principles and extrapolation from the understanding of acquired heart failure rather than specific empirical evidence.

Resistive PH, PAH-CHD
Several supportive interventions and approaches should be part of the care for all patients with PAH-CHD. International expert consensus recommendations (class of recommendation in parentheses) include ensuring regular care by a specialist PAH-CHD provider (I), administering appropriate immunizations such as an annual influenza vaccine (I), assessing oxygen saturation and response to supplemental oxygen in patients with ES (I), providing psychosocial support resources as needed (IIa), counseling on contraception to prevent pregnancy (I/III), and considering the use of anticoagulation (IIb).20,27 Although some types of activity should be avoided (ie, intense isometric activity or exercise associated with concerning symptoms, III),27 patients are encouraged to remain active and fit. Individualized education and counseling is an integral part of PAH-CHD specialist care.

PAH-CHD in the setting of a congenital shunt lesion presents in 1 of 4 scenarios,2 and specific therapy for each is individually reviewed below.

Eisenmenger Syndrome
Progressive pulmonary vascular disease can develop in any patient with a congenital defect of the heart or great arteries associated with large volume left-to-right shunting; ES refers to the development, in such patients, of PH with PAP at a systemic level attributable to high PVR (>10 Wood units) and consequently reversed or bidirectional shunt.28

Prognosis
Despite chronic cyanosis, the prognosis in ES is better than for PAH in the absence of a patent shunt, although it is markedly worse than in the general population.30,31 Many predictors of outcome overlap with those in PAH patients without CHD: cardiac index, right atrial pressure, uric acid, 6-minute walk distance, and B-type natriuretic peptide.21,22,32

Specific Supportive Care for Patients With ES
There is a diverse array of multisystem manifestations of chronic cyanosis and erythrocytosis in ES (Table 2). A holistic perspective, rather than a narrow focus on cardiac function and pulmonary vascular disease, is therefore central to the care of patients with ES.33 The management of iron status and aerobic conditioning represent areas of evolving understanding.

Many ES symptoms, including fatigue, weakness, and headache, have been attributed alternatively to hyperviscosity or iron deficiency. Phlebotomy, long standard therapy for secondary erythrocytosis, depletes iron stores, which affects blood viscosity and lowers hemoglobin concentration; the latter compromises oxygen-carrying capacity. Despite acute benefits, chronic phlebotomy is associated with reduced functional capacity and increased stroke risk.34,35 Further, iron may play a role in normal pulmonary vascular function, including hypoxic response.36 Iron supplementation in adults with ES and iron deficiency is associated with improved quality of life and exercise capacity.37 Phlebotomy is recommended only in rare cases for hyperviscosity symptoms with markedly
Table 2. Systemic Noncardiovascular Consequences of Eisenmenger Syndrome and Other Cyanotic Congenital Heart Disease

<table>
<thead>
<tr>
<th>1. Hematologic</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Abnormal cell components</td>
</tr>
<tr>
<td>i. Secondary erythrocytosis</td>
</tr>
<tr>
<td>ii. Thrombocytopenia</td>
</tr>
<tr>
<td>b. Propensity to thrombosis and hemorrhage</td>
</tr>
<tr>
<td>i. Cerebrovascular accident</td>
</tr>
<tr>
<td>ii. In situ pulmonary thrombosis</td>
</tr>
<tr>
<td>iii. Hemoptysis and pulmonary hemorrhage</td>
</tr>
<tr>
<td>iv. Menorrhagia, epistaxis</td>
</tr>
<tr>
<td>2. Infectious</td>
</tr>
<tr>
<td>a. Cerebral abscess</td>
</tr>
<tr>
<td>b. Pneumonia</td>
</tr>
<tr>
<td>c. Subacute bacterial endocarditis</td>
</tr>
<tr>
<td>d. Acne, sinusitis</td>
</tr>
<tr>
<td>3. Renal, endocrine and metabolic</td>
</tr>
<tr>
<td>a. Decreased renal plasma flow with increased filtration fraction</td>
</tr>
<tr>
<td>b. Decreased renal clearance of uric acid</td>
</tr>
<tr>
<td>c. Albuminuria</td>
</tr>
<tr>
<td>d. Renal tubular acidosis</td>
</tr>
<tr>
<td>e. Impaired capacity to dilute or concentrate urine</td>
</tr>
<tr>
<td>f. Gallstone disease (calcium bilirubinate)</td>
</tr>
<tr>
<td>g. Pheochromocytoma and paraganglioma</td>
</tr>
<tr>
<td>4. Musculoskeletal</td>
</tr>
<tr>
<td>a. Scoliosis</td>
</tr>
<tr>
<td>b. Clubbing/hypertrophic osteoarthropathy</td>
</tr>
<tr>
<td>c. Gout</td>
</tr>
</tbody>
</table>

elevated hematocrit (>65%; American Heart Association/American College of Cardiology class I recommendation).39

For ES patients, current American Heart Association/American College of Cardiology guidelines advise against, “moderate and severe strenuous activity, particularly isometric exercise,”19 (class I) given the risks of systemic vasodilation in the context of markedly limited pulmonary vasodilator reserve. However, recent evidence suggests almost universal benefit from regular aerobic conditioning in associated diseases, including other types of PAH and left heart disease.38,39 A small nonrandomized cohort study of a mixed PAH-CHD sample, half with ES, reports that conditioning is safe and may be effective;40 European guidelines support a possible role for supervised exercise rehabilitation in deconditioned patients with PAH, without a distinction based on the presence of CHD (class IIa).27 Recommendations defining optimal exercise type, intensity, and potential efficacy await further investigation (eg, NCT01397110 at clinicaltrials.gov).

Medical and Interventional Approaches to Pulmonary Vascular Disease in ES

Observational studies and several randomized controlled trials in ES support the benefit from pulmonary vasodilator medications including prostanoids,41 endothelin receptor antagonists,42,43 and phosphodiesterase 5 inhibitors.44,45 The largest double-blind placebo controlled trial to date, the Bosentan Randomized Trial of Endothelin Antagonist Therapy-5 (BREATHE-5) study, randomly assigned 54 functional class III ES patients to bosentan or placebo (2:1 bosentan:placebo). Bosentan did not exacerbate hypoxemia, as some had worried it might, and subjects receiving bosentan demonstrated improved pulmonary vascular resistance and 6-minute walk distance (+53.1 m in comparison with placebo).46 Although bosentan has been most extensively studied in randomized trials, and European Society of Cardiology guidelines recommend its use (class I),46-49 there is no specific evidence or a priori reason suggesting that other agents are less safe or effective. Intravenous therapy is often avoided because of the potential for paradoxical embolism, but the risk must be weighed against the benefit in each case. Vasodilators are generally indicated for markedly functionally limited patients (class IIa for pulmonary vasodilator therapy “because of the potential for improved quality of life” without specification of functional class, American Heart Association/American College of Cardiology; in World Health Organization functional class III patients, class I bosentan and IIa other vasodilator medications, European Society of Cardiology).19,49 The role for these drugs in less symptomatic patients is less well defined, but they are used commonly in this setting. One retrospective study suggested improved survival in ES patients treated with advanced PAH medications (initial therapy bosentan, sildenafil, and epoprostenol in 73.5%, 25%, and 1.5%, respectively); over a median follow-up of 4 years, 50 of the 161 patients who did not receive advanced PAH medications died, in comparison with only 2 of the 68 patients who were so treated (unadjusted hazard ratio, 0.21; 95% confidence interval, 0.05-0.86; P=0.03).48 The applicability of this encouraging result to contemporary practice may, however, be limited because early patients were likely started on therapy as part of clinical trials and by the dramatic shift in clinical approach over the study period. Recent studies that included a larger proportion of treated patients and longer follow-up support that advanced PAH therapy provides sustained functional benefit,32,47,51 but they do not corroborate a mortality benefit.32 Few studies have investigated the benefit of combination therapy, adding a second pulmonary vasodilator medication, in ES. A randomized, placebo-controlled crossover trial found that adding sildenafil to bosentan provided no significant benefit in the 6-minute walk distance; observational studies, however, suggest a benefit of adding a second class of medication for patients on a single medication who experience clinical functional decline.51,55 As such, combination therapy is considered a reasonable option for World Health Organization functional class III ES patients (class IIb, European Society of Cardiology guidelines).49

Nifedipine and other calcium channel blockers are considered contraindicated in ES because of the risk of worsening hypoxemia if systemic vascular resistance decreases to greater degree than pulmonary vascular resistance (with consequently greater right-to-left shunting and lower pulmonary blood flow; class III, European Society of Cardiology guidelines).49 Interestingly, however, small studies suggest that nifedipine improves exercise capacity without lowering resting or exercise arterial oxygen saturation in ES.54,55 This could be explained by improvement in systemic blood flow while maintaining pulmonary blood flow resulting in improved systemic oxygen delivery and higher mixed venous O₂ saturation which offset the effect
of concomitantly increased shunting. On balance, there are insufficient data to guide clinical care or substantively dispute the contraindication of calcium channel blocker therapy in ES conveyed by consensus guidelines, but the role of cautious chronic (not acute) systemic vasodilators used in concert with pulmonary vasodilator therapy deserves further study.

Interventional therapies for subsets of ES and other severe PAH-CHD have been reported: pulmonary artery banding, atrial baffle placement to optimize streaming of oxygenated blood, and targeted medical therapy followed by subsequent shunt closure. Reported acute and short-term results of such interventions at experienced centers are hopeful, but the long-term consequences remain unknown. Lung or heart-lung transplantation remains an option for selected patients in whom posttransplantation prognosis is expected to be better than the native prognosis; the availability of pulmonary vasodilator medications may influence the optimal timing of transplantation.

**PAH with Left-to-Right Shunt and Elevated PVR**

If not repaired early in childhood, large posttricuspid shunt lesions (ventricular septal defect, patent ductus arteriosus) almost invariably present with ES. As such, most clinical decision making in adults with CHD and sizable left-to-right shunts involves patients with pretricuspid shunt lesions, mainly ASD. Only a minority of adults with a large pretricuspid shunt presents with elevated PAP or PVR. Conversely, small defects can be associated with severe PAH. Known clinical risk factors such as defect size and type (eg, sinus venous defects are associated with higher risk of PH) have modest predictive value, and the development of PAH in patients with pretricuspid shunts is largely idiosyncratic.

**Identifying Patients Who Would Benefit From ASD Closure**

ASD closure is indicated for those with right heart dilation and normal PVR. Under these circumstances prognosis is excellent, especially if repair is performed earlier in life (eg, <25 years of age). Repair later in life is associated with symptomatic improvement and possibly improved prognosis, but may not obviate the increased risk of premature death. A subset of patients may also have subclinical residual right heart and pulmonary vascular dysfunction that limits RV stroke volume augmentation during exercise after ASD closure.

Clinical decision making is more difficult for patients with evidence for mild or moderate pulmonary vascular disease (eg, immediately elevated PVR), because a subset will develop PAH after closure, and it is preferable not to perform closure in that group. One study reported that most patients who developed PAH late after ASD or ventricular septal defect closure had baseline PVR >5 Wood units (n=18/22), PVR:SVR>0.33 (n=21/22), or Qp:Qs<1.5 (n=11/22). The number of patients who did not develop PAH in the context of equivalent hemodynamics was not reported. Expert consensus guidelines propose strikingly different criteria to inform clinical decision making in ASD patients with moderately increased PVR (Table 3). Despite the distinctions, published guidelines base this decision on a single resting hemodynamic study. In clinical practice, a personalized patient-specific approach is preferable, integrating data from resting catheterization, noninvasive exercise testing, sequential assessment of response to medical therapy, and dynamic invasive hemodynamic response to exercise and acute pulmonary vasodilator administration.

**The Role of Acute Pulmonary Vasoreactivity Testing in Guiding Therapy**

Acute hemodynamic response to inhaled nitric oxide or other pulmonary vasodilator agents provides insight into the extent of active pulmonary vasoconstriction. PAP response should not be considered in isolation, especially in the presence of shunting; PVR may decrease markedly without any change in PAP if there is also an increase in pulmonary blood flow. Robust declines in PVR suggest pharmacological salvage therapy would be effective if needed acutely after ASD closure and is also associated with favorable medium-term survival. There is no universally accepted definition of positive vasodilator response in the context of intracardiac shunting. In the Inhaled Nitric Oxide as a Preoperative Test (INOP-1) Study, which focused on pediatric patients, criteria for a positive vasodilator response were the ratio of pulmonary-to-systemic vascular resistances (Rp:Rs) <0.33 and a ≥20% decrease in Rp:Rs from baseline with a combination of oxygen and inhaled nitric oxide. Of note, however, 18% of ES patients enrolled in another study demonstrated a decrease in total pulmonary resistance of >20% in response to nitric oxide (80 ppm). The presence of such a response in ES patients implies that intermediate degrees of preserved vasoactivity to acute challenge may not reliably predict whether repair or chronic pulmonary vasodilator therapy will be preferable over the long term for a given patient with a patent shunt and PAH-CHD. In addition, the chronic use of pulmonary vasodilator medications may have pleiotropic benefits not related directly to vasodilatation (ie, reverse remodeling) that are not captured by acute testing. Thus, the relationship between acute response and long-term reversibility or progression of PAH-CHD requires clarification. Likewise, hemodynamic responses to exercise and acute balloon occlusion of shunt lesions may help predict the risk of immediate postclosure RV failure (ie, increasing right-sided filling pressure or decreased cardiac output), but the implications for long-term outcomes remain undefined.

**Histopathologic Assessment to Direct Management of PH-CHD**

Investigators have studied pulmonary vascular histopathology from lung biopsy specimens and surrogate assessment of pulmonary arterial remodeling by using pulmonary wedge angiography (see case, Figure 3A) to distinguish reversible from fixed PH. Histopathology corresponds only moderately well with hemodynamics, cannot inform our understanding of dynamic vasoconstriction, and does not reliably identify the potential for reverse remodeling in response to mechanical (eg, PA banding) or medical therapies. Consequently, lung biopsy is rarely performed for this purpose in clinical practice.

**Medical Therapy as a Bridge to Shunt Closure and Other Intermediate Approaches**

Case reports have described a treat-and-repair approach for patients with borderline hemodynamics, with neoadjuvant pulmonary vasodilator medication followed by defect repair. Although short- and medium-term outcomes appear...
Table 3. Atrial Septal Defect Closure Recommendations Related to Pulmonary Vascular Disease From 3 Recent Consensus Documents

<table>
<thead>
<tr>
<th>Indicated</th>
<th>Possibly Indicated</th>
<th>Contraindicated</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ESC GUCH Guidelines, 2010</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td>PVR&lt;5 WU with significant shunt regardless of symptoms (class I)</td>
<td>PVR&gt;5 WU but &lt;2/3rd SVR, or PAP&lt;2/3rd systemic blood pressure (baseline or with vasodilator), and net L-to-R shunt (Q&lt;sub&gt;L&lt;/sub&gt;:Q&lt;sub&gt;R&lt;/sub&gt; &gt;1.5; class IIb)</td>
</tr>
<tr>
<td><strong>AHA/ACC ACHD Guidelines, 2008</strong>&lt;sup&gt;3&lt;/sup&gt;</td>
<td>All with RA or RV enlargement, with or without symptoms (class I; no mention of PVR)</td>
<td>Net L-to-R shunting, PAP&lt;2/3rd systemic, PVR&gt;2/3rd SVR, or when responsive to either pulmonary vasodilator therapy or test occlusion of the defect (class IIb)</td>
</tr>
<tr>
<td><strong>Updated Clinical PH Classification, 2013</strong>&lt;sup&gt;3&lt;/sup&gt;</td>
<td>PVR&lt;2.3 WU (&lt;4WU×m&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>PVR 2.3–4.6 WU (4–8 WU×m&lt;sup&gt;2&lt;/sup&gt;)</td>
</tr>
</tbody>
</table>

Notes:

- Class I, IIb, and III refer to the level of recommendation as described in the respective documents, with I representing agreement that this recommendation is beneficial, IIb that usefulness is less well established, and III that the treatment is either not useful or harmful. ACHD/GUCH indicates adult/grown-up congenital heart disease; AHA/ACC, American Heart Association/American College of Cardiology; ESC, European Society of Cardiology; L-to-R, left-to-right; PAH, pulmonary arterial hypertension; PAP, pulmonary artery pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; Q<sub>L</sub>:Q<sub>R</sub>, ratio of pulmonary to systemic flow; RA, right atrial; RV, right ventricular; SVR, systemic vascular resistance; and WU, Wood units.

Reassuring based on a small number of case reports, most patients remain symptomatic with elevated PAP/PVR requiring continued medical therapy. Partial defect closure, using a flap-valve or fenestrated patch or device, is also reported. Identifying optimal fenestration size is challenging, however, because the residual shunt must be small enough to provide benefit but large enough to serve as an effective relief valve and prevent obstruction by thrombosis or endothelialization.

**Clinical Monitoring to Identify Development of PAH**

Patients at increased risk for developing progressive PAH, including those with elevated PVR, should be assessed regularly with cardiopulmonary exercise testing to identify indicators of early pulmonary arteriolar remodeling (eg, elevated V<sub>E</sub>/V<sub>CO</sub>, slope, excertional hypoxemia) and echocardiography with a focus on quantitative markers of RV dysfunction, systolic ventricular septal flattening, and abnormal RV outflow Doppler flow. This is true for those with patent shunts and those who have undergone defect closure. Ongoing intervention studies and national registries are anticipated to clarify strategies for identifying suitable defect closure candidates in the context of PH status and managing those at highest risk for development of PAH after repair (eg, clinicaltrials.gov NCT01548950, NCT01659411, and NCT01218607).

**PAH With Coincidental CHD and PAH after Defect Closure**

In patients with PAH and small intracardiac shunts, the structural defect is generally considered incidental and unrelated. Some small defects, however, presumably represent partially closed larger lesions. Defect closure is contraindicated; otherwise, treatment of PAH in this situation and when PAH develops after defect closure should parallel recommended management of PAH among patients without CHD.

**Polygenic PH**

The historical observation that “it is...clear that almost any form of PH may become polygenic in one way or another....” is particularly true for adults with PH-CHD because of the common comingle of left heart disease and pulmonary vascular remodeling, the presence of pertinent comorbidities, and the lifelong course of heart disease that allows full expression of compensatory processes. Two well-studied types of polygenic PH are discussed below.

**Primarily Hyperkinetic PH With Elevated or Borderline PVR**

Presumably, all patients with ES pass through a period of high flow and increasing PVR before developing markedly elevated PVR and bidirectional or right-to-left shunting. The flow dependence of PVR (Figure 4) confounds the relationship between PVR and the severity of underlying pulmonary vascular pathology in high- or low-flow states. For example, PVR should be low in the setting of markedly elevated pulmonary blood flow. This phenomenon underlies the observation that PVR =2.3 to 3 Wood units, lower than the PVR level required for a clinical diagnosis of PAH, may be associated with pulmonary vascular disease in patients with left-to-right shunting (Table 3).<sup>3</sup>

**Primarily Passive PH-CHD With Elevated PVR**

Mitral stenosis, congenital or acquired, is the classic lesion of passive PH-CHD with a subsequent increase in PVR. Elevated pulmonary venous pressure is ubiquitous and may be associated with any level of PVR. The key clinical question, after the determination of acute procedural risk, is whether PVR will improve with relief of the valvular lesion. Acute vasodilator administration generally induces a marked decline in PVR in children and adults with mitral stenosis, although sometimes at the expense of increasing left atrial pressure and pulmonary edema in older patients.<sup>82,83</sup> Although postoperative management of patients with mitral stenosis (or regurgitation) with associated elevation in PVR is often complicated by residual PH and right heart failure, PVR usually improves in the months following intervention and may normalize.<sup>84</sup>

**Emerging Roles for Pulmonary Vasodilator Therapy**

Several clinical scenarios in CHD are characterized by pathological pulmonary vascular remodeling and variable degrees of right heart dysfunction despite normal PAP or PVR. Pulmonary atresia and other conotruncal defects, for example, are associated with abnormal pulmonary arterial arteriobization.
Pulmonary vasodilator therapy may also have a role in the management of CHD patients with ventricular-arterial uncoupling despite an absence of pulmonary vascular disease or PH. Examples include patients with severe subpulmonary ventricular dysfunction or tricuspid regurgitation (eg, Ebstein anomaly). This is somewhat analogous to the defined role of pulmonary vasodilators in acute RV failure after cardiac surgery or acute RV myocardial infarction, irrespective of PVR. It is unknown, however, whether chronic pulmonary vasodilator therapy improves symptoms or long-term outcomes in right heart failure without elevated PVR in patients with CHD.

Summary

PH is common among adults with CHD. PH-CHD comprises several distinct pathophysiologic causes, and may be attributable to elevated PVR (PAH-CHD), high pulmonary flow, high pulmonary venous pressure, or a combination of these. There have been notable recent advances in medical therapy for patients with PAH-CHD including ES; less research has focused on other types of PH-CHD. The cause of PH for any given CHD patient cannot be inferred from the underlying heart defect. Rather, identifying the optimal therapeutic approach in PH-CHD requires the definition of the underlying physiologic, as well as a comprehensive understanding of each patient’s CHD and its associated natural and modified history.

Acknowledgments

Dr Opatowsky is grateful to Eric Krieger, Lilamari Moko, Aaron Waxman, Britanni Loukas, Martin St. John Sutton, Andrew Leventhal, Bradley Maron, and Michael Landzberg for insightful review of the manuscript.

Disclosures

Dr Opatowsky has received research grant funding from Actelion Pharmaceuticals US Inc and Merck & Co Inc. Dr Opatowsky is supported by the Dunlevie Family Fund.

References


Clinical Evaluation and Management of Pulmonary Hypertension in the Adult With Congenital Heart Disease
Alexander R. Opotowsky

Circulation. 2015;131:200-210
doi: 10.1161/CIRCULATIONAHA.114.006976

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2015 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/131/2/200

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/