Treatment of Severe Pulmonary Hypertension in the Setting of the Large Patent Ductus Arteriosus

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KEY WORDS
pulmonary hypertension, patent ductus arteriosus, catheterization, occlusion

ABBREVIATIONS
ASD—atrial septal defect
PA—pulmonary arterial
PDA—patent ductus arteriosus
PH—pulmonary hypertension
PVR—pulmonary vascular resistance
RV—right ventricular
SBP—systolic blood pressure
SVR—systemic vascular resistance
RVEDP—right ventricular end diastolic pressure

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abstract

Treatment of the large patent ductus arteriosus (PDA) in the setting of pulmonary hypertension (PH) is challenging. Left patent, the large PDA can result in irreversible pulmonary vascular disease. Occlusion, however, may lead to right ventricular failure for certain patients with severe PH. Our center has adopted a staged management strategy using medical management, noninvasive imaging, and invasive cardiac catheterization to treat PH in the presence of a large PDA. This approach determines the safety of ductal closure but also leverages medical therapy to create an opportunity for safe PDA occlusion. We reviewed our experience with this approach. Patients with both severe PH and PDAs were studied. PH treatment history and hemodynamic data obtained during catheterizations were reviewed. Repeat catheterizations, echocardiograms, and clinical status at latest follow-up were also reviewed. Seven patients had both PH and large, unrestricted PDAs. At baseline, all patients had near-systemic right ventricular pressures. Nine catheterizations were performed. Two patients underwent 2 catheterizations each due to poor initial response to balloon test occlusion. Six of 7 patients exhibited subsystolic pulmonary pressures during test occlusion and underwent successful PDA occlusion. One patient did not undergo PDA occlusion. In follow-up, 2 additional catheterizations were performed after successful PDA occlusion for subsequent hemodynamic assessment. At the latest follow-up, the 6 patients who underwent PDA occlusion are well, with continued improvement in PH. Five patients remain on PH treatment. A staged approach to PDA closure for patients with severe PH is an effective treatment paradigm. Aggressive treatment of PH creates a window of opportunity for PDA occlusion, echocardiography assists in identifying the timing for closure, and balloon test occlusion during cardiac catheterization is critical in determining safety of closure. By safely eliminating the large PDA, this treatment algorithm can halt the perilous combination of the large shunting from the PDA and PH in a population at high risk of morbidity and mortality. Pediatrics 2013;131:e1643–e1649
Treatment of the large patent ductus arteriosus (PDA) in the setting of severe pulmonary hypertension (PH) poses a unique challenge. Like other large communications between the systemic and pulmonary circulations,1,2 large PDAs expose the pulmonary arterial (PA) bed to high pressure and flow. Over time, remodeling of the pulmonary vasculature occurs. Progressive morphologic changes, from arteriolar medial hypertrophy, intimal proliferation, and fibrosis to obliteration of pulmonary arterioles and capillaries, result in increased pulmonary vascular resistance (PVR). When the PVR approaches and exceeds systemic vascular resistance (SVR), initial left-to-right ductal shunting reverses and becomes right-to-left, leading to cyanosis and Eisenmenger syndrome.5,6 Whereas early repair can mitigate the development of PH4 and likely permit reversal of vasculopathy in those with more advanced disease,5,6 some patients with severe irreversible PH will not tolerate ductal closure. When PVR exceeds SVR, closure of the PDA leads to suprasystemic PA pressures and even to low cardiac output and right ventricular (RV) failure.5,7–10 Therefore, determining the reversibility of changes in the pulmonary vasculature is critical in judging the safety of permanent shunt closure.

Our center has developed a staged medical and interventional management strategy for patients with both large PDAs and PH. This strategy has been particularly important in determining the timing and safety of ductal closure in patients with PH.

### TABLE 1 Baseline Demographic and Clinical Characteristics

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age</th>
<th>Weight, kg</th>
<th>Gender</th>
<th>Additional Diagnoses</th>
<th>SaO2 on Presentation on RA, %</th>
<th>Oxygen Requirement</th>
<th>Direction of Ductal Flow by Echo at Presentation</th>
<th>Medications at Presentation</th>
<th>Medication Adjustments Before Cardiac First Catheterization</th>
<th>Direction of Ductal Flow by Echo Before Cardiac Catheterization</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.2 mo</td>
<td>2.5</td>
<td>Male</td>
<td>Prematurity, 22 wk, BPD, Triplet</td>
<td>88</td>
<td>Mechanical ventilation (tracheostomy) FiO2: 0.35%–0.5%</td>
<td>Left to right</td>
<td>O2, Furosemide Prednisolone</td>
<td>Added: sildenafil (0.25 mg/kg q6)</td>
<td>Left to right</td>
</tr>
<tr>
<td>2</td>
<td>1.7 mo</td>
<td>3</td>
<td>Male</td>
<td>Prematurity, 32 wk, BPD, CDH, repaired</td>
<td>80</td>
<td>Mechanical ventilation (intubated) FiO2: 0.3%</td>
<td>Bidirectional</td>
<td>O2, InO, Sildenafil (1 mg/kg q8)</td>
<td>Furosemide</td>
<td>Left to right</td>
</tr>
<tr>
<td>3</td>
<td>22 mo</td>
<td>10.2</td>
<td>Female</td>
<td>Trisomy 21, RDS, PPHN, CAVC</td>
<td>68</td>
<td>Mechanical ventilation (tracheostomy) 1 L/min</td>
<td>Right to left</td>
<td>O2, Sildenafil (0.5 mg/kg q8)</td>
<td>Bosentan (15.6 mg QD), Furosemide, Spironolactone, Albuterol</td>
<td>Increased: sildenafil (1 mg/kg q8)</td>
</tr>
<tr>
<td>4</td>
<td>2.5 y</td>
<td>13.4</td>
<td>Female</td>
<td>CDH, residual deficit after repair, Systemic hypertension</td>
<td>90</td>
<td>1/4 L/min NC</td>
<td>Bidirectional</td>
<td>O2</td>
<td>None</td>
<td>Bidirectional</td>
</tr>
<tr>
<td>5</td>
<td>3.6 y</td>
<td>15.9</td>
<td>Male</td>
<td>DOM, Right-heart failure, Pleural effusions, Prematurity, 36 wk, CAVC</td>
<td>100</td>
<td>2 L/min NC</td>
<td>Left to right</td>
<td>O2, Furosemide</td>
<td>None</td>
<td>Left to right</td>
</tr>
<tr>
<td>6</td>
<td>12.2 y</td>
<td>36</td>
<td>Female</td>
<td>Prematurity, 36 wk, CDH, repaired</td>
<td>86</td>
<td>2 L/min NC</td>
<td>Bidirectional</td>
<td>Nifedipine</td>
<td>None</td>
<td>Bidirectional</td>
</tr>
<tr>
<td>7</td>
<td>1.2 y</td>
<td>7.2</td>
<td>Female</td>
<td>RDS</td>
<td>88</td>
<td>1 L/min NC</td>
<td>Right to left</td>
<td>Sildenafil (1 mg/kg q6)</td>
<td>None</td>
<td>Bidirectional</td>
</tr>
</tbody>
</table>

**BID, twice daily; BPD, bronchopulmonary dysplasia; CAVC, complete atrioventricular canal; CDH, congenital diaphragmatic hernia; DOM, dilated cardiomyopathy; Echo, echocardiogram; FiO2, fraction of inspired oxygen; InO, inhaled nitric oxide; NC, nasal cannula; PPHN, persistent pulmonary hypertension of the newborn; q6, every 6 hours; q8, every 8 hours; QD, every day; RA, room air; RDS, respiratory distress syndrome; SaO2, arterial oxygen saturation.**
caused by their PDA and coincident primary parenchymal pulmonary disease. We describe our experience with these patients.

CASES

Baseline Findings

Between January 2005 and December 2011, 7 patients with PDAs and PH underwent combined medical and interventional therapy (Table 1). Six patients had additional diagnoses associated with intrinsic lung disease. All patients were treated with supplemental oxygen; 3 patients were mechanically ventilated at the time of initial evaluation.

The diagnosis of PH was determined by echocardiography and given to patients with bidirectional or right-to-left shunting at the PDA or low-velocity left-to-right shunting with 1 or both of the following: elevated RV systolic pressures (estimated by the maximal velocity of the tricuspid regurgitation jet) or flattening of the interventricular septum. In our series, the direction of ductal flow was right-to-left in 2 patients, bidirectional in 3 patients, and left-to-right in 2 patients. All patients were seen by the PH service (G.B.M. and F.E.R.). In these patients, PH pharmacotherapy was either initiated or intensified. The goal of PH therapy was to decrease PVR to a point at which the PDA might be closed safely. At presentation, 5 patients were already receiving PH pharmacotherapy (Table 1). In 2 of these patients, intensification of PH therapy was associated with a change in the direction of ductal blood flow on repeat echocardiography before cardiac catheterization (Fig 1).

Patients with right-to-left shunting did not undergo invasive testing. Catheterization of patients for possible PDA closure was deferred until PH therapy resulted in bidirectional or left-to-right ductal shunting.

Cardiac Catheterization

At catheterization, all patients exhibited either bidirectional or left-to-right shunting (Fig 1). In total, 9 cardiac catheterizations (initial and repeat) were performed in the 7 patients over

FIGURE 1

Echocardiograms in patients 2 (A), 3 (B), and 5 (C). Before PDA occlusion, the left ventricle (LV) is D-shaped due to flattening of the septum (A1, B1, C1). After PDA occlusion, the LV has a normal, circular configuration (A2, B2, C2). PH therapy led to changes in the direction of flow in the PDA from bidirectional (A3) to left-to-right (A4) and from right-to-left (B3) to left-to-right (B4).
The study period (Tables 2 and 3). The median PVR was 11.7 U·m\(^2\). At the time of catheterization, the PA pressure was near-systemic in all patients. A balloon test occlusion of the PDA was performed in 6 patients to evaluate the effects of PDA closure on cardiac output (Fig 2). In 1 patient (patient 2), Balloon test occlusion of the PDA was performed after the addition of bosentan and iloprost to medical regimen. In this setting, the PDA was primarily closed without test occlusion. Three patients experienced an increase in systemic pressure, a decrease in PA pressure, and an improvement in cardiac output. Interestingly, 2 patients experienced a decrease in heart rate during balloon inflation. Although initially worrisome, the decrease in heart rate was associated with increases in systemic blood pressure and cardiac output and improved hemodynamics.

Two patients (patients 4 and 6) failed balloon test occlusion (Table 2): that is, the PA pressure increased to suprasystemic levels during test occlusion. These patients did not undergo PDA device occlusion and had their PH therapy escalated after catheterization. Patient 4 also underwent surgical repair for residual diaphragmatic herniation to eliminate additional factors contributing to PH. Both patients were later brought back for repeat cardiac catheterization. At repeat catheterization 22 months later, the PVR in patient 4 had significantly diminished. Repeat test occlusion resulted in sub systemic PA pressures, which permitted successful occlusion of the large PDA.

Unfortunately, there was no reduction in her PVR, and balloon occlusion resulted in suprasystemic PA pressures. As a result, her PDA was not occluded.

**TABLE 2**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age</th>
<th>Weight, kg</th>
<th>Duration of Escalated Pulmonary Vasodilator Therapy Before Catheterization</th>
<th>Baseline</th>
<th>Balloon Test Occlusion</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>SBP, mm Hg</td>
<td>PAP, mm Hg</td>
<td>PVR, U·m(^2)</td>
<td>PAP:SBP, %</td>
</tr>
<tr>
<td>1</td>
<td>3.2 mo</td>
<td>25</td>
<td>2 d</td>
<td>59/26 (40)</td>
<td>48/26 (35)</td>
<td>10.2</td>
</tr>
<tr>
<td>2</td>
<td>13.7 mo</td>
<td>9.6</td>
<td>12 mo</td>
<td>89/45 (65)</td>
<td>65/30 (38)</td>
<td>4.9</td>
</tr>
<tr>
<td>3</td>
<td>2.8 y</td>
<td>10.7</td>
<td>11.6 mo</td>
<td>82/44 (60)</td>
<td>80/46 (65)</td>
<td>9.6</td>
</tr>
<tr>
<td>4</td>
<td>2.9 y</td>
<td>14.3</td>
<td>4.8 mo</td>
<td>74/42 (58)</td>
<td>74/36 (57)</td>
<td>17</td>
</tr>
<tr>
<td>4a</td>
<td>4.8 y</td>
<td>18.6</td>
<td>2.3 y</td>
<td>94/43 (66)</td>
<td>90/44 (64)</td>
<td>10.3</td>
</tr>
<tr>
<td>5</td>
<td>3.0 y</td>
<td>15.9</td>
<td>None</td>
<td>97/56 (72)</td>
<td>69/15 (60)</td>
<td>13.2</td>
</tr>
<tr>
<td>6</td>
<td>12.4 y</td>
<td>37.4</td>
<td>2.4 mo</td>
<td>84/40 (50)</td>
<td>92/42 (64)</td>
<td>28.4</td>
</tr>
<tr>
<td>6a</td>
<td>17.5 y</td>
<td>52.3</td>
<td>5.3 y</td>
<td>83/45 (60)</td>
<td>118/48 (64)</td>
<td>50</td>
</tr>
<tr>
<td>7</td>
<td>12 y</td>
<td>7.2</td>
<td>6 mo</td>
<td>72/41 (63)</td>
<td>69/41 (69)</td>
<td>11.2</td>
</tr>
</tbody>
</table>

ADO, Amplatzer duct occluder (St Jude Medical, St Paul, MN); N/A, not applicable; PAP, PA pressure; PAP:SBP, ratio of systemic pulmonary to systemic flow ratio; SBP, systemic blood pressure; VSD, ventricular septal defect; —, not measured.

a Repeat cardiac catheterization on patient 4 performed after repair of residual CDH and the addition of bosentan and iloprost to medical regimen.

b Repeat cardiac catheterization on patient 6 performed after the addition of bosentan and iloprost to medical regimen.
In total, 6 of 7 patients underwent successful PDA closure. The median age and weight for patients at the time of successful closure were 2 years and 10.2 kg, respectively. The median PVR was 10.2 U·m⁻², and the median PA to systemic ratio was 0.88 before PDA occlusion. There were no complications or adverse events associated with balloon occlusion or PDA closure.

Follow-up

At follow-up, all patients are alive. Six patients have clinically improved (Table 3 and Fig 1). Patient 6, who twice failed balloon test occlusion, continues to have severe PH. PH therapy was continued after catheterization in all patients. Two patients (patients 1 and 5) were weaned off PH medications after clinical and echocardiographic variables suggested complete resolution of PH (Fig 1). The remaining 5 patients continue to exhibit evidence of elevated RV pressures by echocardiography and remain on PH therapy. Three patients, who had been chronically ventilator-dependent at the time of the catheterization, tolerated discontinuation of mechanical ventilation after PDA occlusion.

Two patients underwent additional cardiac catheterization during follow-up. Patient 3 had her PVR reassessed to determine how she would tolerate surgical repair of her intracardiac defects. Her PVR was mildly elevated at 5.6 U·m⁻² but lower than previously measured (9.6 U·m⁻²). Three months later, she underwent successful surgical repair of her ostium primum atrial septal defects (ASDs) with an uncomplicated postoperative course. Seven months after surgery, there was no evidence of RV hypertension or PH by echocardiography (ie, normal interventrical septal motion, interval decrease in RV hypertension, low-velocity regurgitant jet through the tricuspid valve).

Patient 4 underwent repeat cardiac catheterization to assess symptoms of exertional chest pain. The baseline PA pressure was near-systemic, and the PVR was 14 U·m⁻². Administration of isoproterenol to elicit an exercise response resulted in suprasystemic PA pressures and evidence of myocardial ischemia inferiorly on electrocardiogram tracings. Pulmonary vasodilator testing while receiving 100% O₂ and 40 ppm of inhaled nitric oxide did not reveal additional vasoreactivity. The patient recovered from catheterization without issues and subsequently had her PH medications intensified. Clinically, she is self-restricting her activities but has remained stable during follow-up.

DISCUSSION

We describe our experience using a combined medical and interventional approach in treating PH in the presence of a large PDA. To our knowledge, this is the first pediatric series in the English-language literature reporting such a staged paradigm. Although there have been case reports describing success in closing the PDA in patients with PH, the application of this approach has more frequently been described in patients with combined ASDs and PH.⁵,⁷,⁸,¹¹–¹３ Of course, ASD physiology is not associated with pressure-loading.

To encourage reversal of vascular remodeling, our team treats PH aggressively with pharmacotherapy when

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**TABLE 3** Follow-up Data

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age at Last Follow-up</th>
<th>Time Since PDA Closure</th>
<th>Interval Events and Findings</th>
<th>PH Medications at Follow-up</th>
<th>Clinical Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>36 mo</td>
<td>35 mo</td>
<td>Successfully weaned from PPV and decannulated</td>
<td>None</td>
<td>Doing well; no O₂ requirement</td>
</tr>
<tr>
<td>2</td>
<td>38 mo</td>
<td>25 mo</td>
<td>Successfully weaned from PPV and decannulated</td>
<td>Sildenafil</td>
<td>Doing well; no O₂ requirement</td>
</tr>
<tr>
<td>3</td>
<td>6.5 y</td>
<td>32 mo</td>
<td>Successfully weaned from PPV and decannulated; successful complete CAVC repair</td>
<td>Sildenafil, aspirin</td>
<td>Doing well; new-onset autoimmune disease; no O₂ requirement</td>
</tr>
<tr>
<td>4</td>
<td>8.6 y</td>
<td>46 mo</td>
<td>Repeat catheterization 8.5 mo after PDA occlusion secondary to exertional chest pain</td>
<td>Sildenafil</td>
<td>Mild exercise intolerance, exertional chest pain; no O₂ requirement</td>
</tr>
<tr>
<td>5</td>
<td>5.1 y</td>
<td>19 mo</td>
<td>Near normalization of RV and LV systolic function by echocardiography; improvement in LV ejection fraction from 25% to 57%; sildenafil discontinued</td>
<td>Bosentan, treprostinil (inhaled)</td>
<td>Doing well with minimal exercise restriction; no O₂ requirement</td>
</tr>
<tr>
<td>6</td>
<td>18.7 y</td>
<td>N/A</td>
<td>Persistent systemic RV pressures estimated by echocardiography</td>
<td>Enalapril, carvedilol, amiodarone</td>
<td>No exercise intolerance; nonadherent to inhaled treprostinil; transitioned to adult care; no O₂ requirement</td>
</tr>
<tr>
<td>7</td>
<td>1.8 y</td>
<td>0.3 y</td>
<td>Remains on sildenafil, off O₂ therapy</td>
<td>Sildenafil</td>
<td>Doing well</td>
</tr>
</tbody>
</table>

CAVC, complete atrioventricular canal; LV, left ventricular; N/A, not applicable; PPV, positive pressure ventilation; SaO₂, arterial oxygen saturation; s/p, status post.
it is first identified. Successful treatment of PH in the setting of a large PDA will necessarily promote a left-to-right shunt; yet, none of our patients developed symptoms of heart failure or left-heart enlargement. Before closure of the large PDA, pulmonary pressures remain systemic by definition, regardless of success of PH medication to modulate PVR.

On the basis of our experience, we believe that early treatment of PH in these patients is essential in creating a window of opportunity for eliminating left-to-right shunts. For 3 of our patients (patients 2, 3, and 7), pretreatment with PH pharmacotherapy was associated with a change in the directionality of ductal flow. We postulate that reverse remodeling in the PA vascular bed was the mechanism driving the change in the flow between the systemic and pulmonary vasculature. Interestingly, the patient who twice failed test occlusion of the PDA was the oldest patient in our series. These cases support the notion of early and aggressive treatment of PH as a bridge to PDA closure in this challenging population.

The unique aspects of this population deserve emphasis. Large, unrestricted PDAs are found in many infants and neonates; these patients have, by definition, systemic PA pressures. However, the flow through the PDA in these patients is left-to-right and the physiology is that of a left-to-right shunt, with attendant left-heart enlargement; these patients present with cardiomegaly, poor weight gain, and congestive heart failure. In patients with elevated PVR, the pressures are exactly the same as above, yet the flow is different: right-to-left due to the high (or higher) PVR compared with SVR. It is this aspect that imperils straightforward PDA closure. When PVR exceeds SVR, the pressures will be equal but once the PDA is closed in this scenario the PA pressures become suprasystemic, and RV failure and a decrease in cardiac output can occur.

Eligibility for catheterization is predicated on the direction of PDA flow by echocardiography. When bidirectional or left-to-right shunting is seen, patients are referred for cardiac catheterization to determine the hemodynamic effects of PDA occlusion. Predominant right-to-left shunting at the PDA indicates that PVR exceeds SVR, and therefore PDA occlusion in this scenario is potentially risky. In the 6 patients who underwent successful PDA closure, there was evidence of ongoing PH well after PDA occlusion. For another patient with dilated cardiomyopathy (patient 5), the addition of oral sildenafil after transcatheter ductal closure resulted in improved right-heart function over time. One additional patient (patient 1) recovered completely from PH as a result of transcatheter ductal occlusion, somatic growth, and subsequent medical PH therapy.

In the PH milieu, primary PDA occlusion can be a precarious undertaking. Whereas baseline PVR, reactivity testing with oxygen and inhaled nitric oxide, brain natriuretic peptide, and RV end diastolic pressure (RVEDP) may be surrogates for pulmonary hypertension severity, none are predictive of the pulmonary vascular response to ductal closure. Patients 2 and 7 (Table 2)
illustrate this point. In both, the RVEDP and PVR were elevated beyond what would typically be considered “reversible.” With test occlusion, the RVEDP decreased by at least two-thirds, and the duct was identified as a significant conduit through which pressure was transmitted. In the presence of a PDA, transcatheter test occlusion is a reliable means to predict and identify patients who will tolerate PDA closure.

During test occlusion, the decision to proceed with ductal closure was guided by the PA to SBP ratio, cardiac index. Although there was no absolute threshold PA to SBP ratio used to exclude patients from ductal closure, our experiences reveal that during test occlusion, patients who had a PA:SBP of <0.8 were deemed favorable and underwent PDA closure.

In all of our patients, causes of PH outside of the large PDA were present (eg, prematurity, chromosomal abnormalities, cardiomyopathy, lung hypoplasia, congenital diaphragmatic hernia). Moreover, all patients had clinical and echocardiographic indicators of advanced PH (eg, hypoxemia, bidirectional shunting). Although early primary closure of the PDA might seem an attractive therapy in salvaging the pulmonary vascular bed, our experience highlights the imprudence of such an approach. With test occlusion, 2 of our patients developed suprasystemic pulmonary pressures. Closing the PDA without test occlusion would have placed these patients at risk of right-heart failure and hemodynamic collapse.

Conventionally, patients with a measured PVR >6 U·m² have been thought to be inoperable for treatment of left-to-right shunts or, at best, poor candidates for intervention. In our series, PDA occlusion was achieved in patients with a PVR between 5 and 13 U·m². Our experience adds to the growing evidence that patients with more advanced PH may in fact tolerate closure of left-to-right shunts after aggressive pre-treatment of their PH. PDA occlusion, when tolerated, is critical in treating PH and allows for reversal of pulmonary vascular disease.

REFERENCES

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