Pulmonary Arterial Hypertension Associated With Bronchopulmonary Dysplasia and Congenital Heart Disease in Preterm Infants

A Case Report of a Preterm Infant With Recurrent Pulmonary Hypertension After Corrective Cardiac Surgery and Review of the Literature

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SUMMARY

In preterm infants with congenital heart disease, concomitant bronchopulmonary dysplasia (BPD) is associated with relatively poor clinical outcomes because of the increased pulmonary vascular resistance and adverse effects of inflammation on the damaged lungs, even after surgery. We present herein a 1-year-old female who developed recurrent pulmonary arterial hypertension 6 months after closure of a ventricular septal defect. She was born at 26 weeks of gestation (birth weight, 470 g), and developed BPD requiring oxygen supplementation. Her systemic-to-pulmonary blood flow ratio was 2.1 preoperatively and 1.0 postoperatively, pulmonary arterial pressure was 61/15 (mean 39) mmHg preoperatively and 41/17 (mean 24) mmHg postoperatively, and pulmonary vascular resistance was 4.2 mmHg/L·minute·m² preoperatively and 3.6 mmHg/L·minute·m² postoperatively. At 1 year of age, echocardiography showed an increase in her estimated right ventricular pressure, indicating worsening pulmonary hypertension. After 3 years of treatment with oxygen supplementation, prostacyclin, and bosentan, her pulmonary arterial pressure improved to the normal range. The pathophysiology of pulmonary arterial hypertension is heterogeneous in preterm infants with congenital heart disease and concomitant BPD. Careful management of these patients is warranted even after corrective cardiac surgery. (Int Heart J 2015; 56: S22-S25)

Key words: Pulmonary vascular resistance, Home oxygen supplementation, Bosentan, Prostacyclin, Extremely low birth weight, Ventricular septal defect, Chronic lung disease, Left-to-right shunt, Prematurity, Intensive care

Bronchopulmonary dysplasia (BPD) continues to cause serious morbidity in preterm infants, in spite of improvements in neonatal management such as exogenous surfactant therapy, decreased oxygen toxicity, expanded options for ventilatory support, improved fluid management, and improved nutrition. BPD occurs in 8% to 25% of preterm infants, and 40% of infants with BPD also have pulmonary arterial hypertension (PAH). Unfortunately, infants with BPD related to PAH have a high mortality rate of 14% to 50%. The risk factors for BPD include prematurity, initial oxygen supplementation, mechanical ventilation, infection, and patent ductus arteriosus (PDA). BPD also occurs in many infants with congenital heart disease (CHD) because CHD is occasionally associated with prematurity. Among preterm infants with CHD, those who have concomitant BPD have worse clinical courses because of the increased pulmonary vascular resistance and adverse effects of inflammation on the damaged lungs, even after surgery. However, the specific clinical features of these infants remain difficult to determine. We review the literature regarding CHD with BPD, and present a preterm infant who developed recurrent PAH after corrective cardiac surgery.

Incidence of CHD and BPD: Preterm infants are known to be at risk of both CHD and BPD. The incidence of CHD is 12.5 per 1000 births in preterm infants and 2.5 per 1000 births in other infants. Sixteen percent of all infants with CHD are born before term. As 8% to 25% of preterm infants have BPD, we estimate that at least 1.2% to 4% of infants with CHD have concomitant BPD. In the clinical setting, however, it is difficult to determine the precise incidence of BPD in preterm infants with CHD because of the confounding clinical factors.

Although ventricular septal defects (VSDs) and atrial septal defects are common in both preterm and term infants, preterm infants are more likely to have pulmonary atresia with VSD, complete atrophicventricular defect, aortic coarctation, and tetralogy of Fallot. Early repair of CHD avoids damage to other organs including the lungs. However, early repair may be less tolerated in preterm neonates because of prematurity or...
body weight. The most frequent corrective procedure is VSD closure (20%), followed by aortic arch repair (18%). Preterm infants with univentricular heart and concomitant BPD have high postoperative mortality.\(^8\)

**Pathophysiology of BPD in infants with CHD:** The pathophysiology of BPD is related to the mechanical forces of ventilation, oxygen exposure, maldevelopment of the lungs, persistent inflammation, nutrition, and genetic factors.\(^9\) In preterm infants with left-to-right shunt, excessive pulmonary blood flow and shear stress to the vasculature are also associated with development of BPD.

The optimal level of oxygen supplementation to minimize the risk of BPD has not yet been determined, and oxygen supplementation often confounds the clinical course of preterm infants with CHD and BPD. Askie, et al\(^11\) reported that initial oxygen toxicity was related to the development of BPD. However, oxygen supplementation may occasionally be tolerated in the management of preterm infants with cyanotic CHD. Hypoxia also delays alveolar development, which may lead to BPD.\(^12\) In preterm infants with left-to-right shunt, increased pulmonary blood flow resulting from oxygen supplementation leads to deterioration of respiratory symptoms and possible requirement for mechanical ventilation, which increases the risk of BPD. Oxygen supplementation may also result in excessive pulmonary blood flow causing pulmonary vascular obstructive disease, and oxygen toxicity may result in BPD, which may be followed by improvement in respiratory symptoms due to increased pulmonary vascular resistance. Preterm infants with CHD occasionally have airway problems such as microgastria, tracheomalacia, or compression of the airways by the great vessels, and may therefore require oxygen supplementation or mechanical ventilation. These factors may result in a confusing clinical presentation for neonatologists and pediatric cardiologists.

BPD is associated with arrested development of the alveoli and abnormal organization of vascular structures including abnormal endothelial cell differentiation, proliferation, migration, tube formation, branching, and vessel remodeling and maturation.\(^10\) Vascular endothelial growth factor plays a pivotal role in the capillary development and alveolarization of the lungs.\(^15\) As patients with CHD have abnormal expression of vascular endothelial growth factor in the pulmonary vasculature, preterm infants with CHD have a higher risk of BPD than those without CHD.\(^13-15\) In addition, increased levels of inflammatory cytokines including TNF-alpha, TGF-beta, IL-1, IL-6, and IL-8 influence the development and severity of BPD in preterm infants.\(^16\) If lung damage and exposure to inflammatory mediators occurs during a critical period of alveologenesis, the lungs may not completely recover their growth potential, even in the long term.\(^17\) In preterm infants with CHD and concomitant BPD who need surgery, cardiopulmonary bypass can cause further damage to the lungs because of their susceptibility to inflammatory mediators.\(^22\) These patients have an ongoing risk of deterioration of BPD even after corrective cardiac surgery.

Drossner, et al\(^23\) reported that inflammatory responses in patients with BPD may result in abnormal development and remodeling of the pulmonary veins, leading to pulmonary venous stenosis. It is assumed that acquired pulmonary venous stenosis is one of the causes of PAH in preterm infants with CHD and BPD.

**Postoperative morbidity and mortality:** Advances in perioperative intensive care have enabled the performance of open heart surgery in preterm infants, even those weighing less than 2 kg. However, prematurity is still a risk factor for mortality in cardiac surgery. Preterm infants have high overall mortality, and the odds ratio for death during the first years of life compared with term infants is 4.4.\(^14\) McMahon, et al\(^17\) reviewed the morbidity and mortality of preterm infants with CHD and concomitant BPD. They found that the 30-day survival rate was 84%, and only 68% of these infants achieved hospital discharge after surgery. Postoperative ventilation and duration of stay in the intensive care unit were significantly prolonged. Home oxygen supplementation or mechanical ventilatory support was required in 25% of infants after hospital discharge. Palliative surgery is likely to be safe in infants with CHD and BPD.\(^19\) However, infants with high pulmonary vascular resistance have a high mortality rate even if they only undergo palliative procedures. Ambalavanan, et al\(^20\) reported that 45% of extremely premature infants were rehospitalized by 18 to 22 months, and 15% were rehospitalized for respiratory causes during the first years of life. These findings suggest that respiratory problems may recur even after the treatment of CHD.

**Case Report**

A female infant born at 26 weeks of gestation (birth weight, 470 g) was admitted to our hospital, and was treated for respiratory distress with intratracheal surfactant and mechanical ventilation. Screening echocardiography showed a large perimembranous VSD and patent ductus arteriosus with right ventricular hypertrophy (Figure A). After administration of indomethacin, the ductus arteriosus closed at 3 days of age.

At 3 months of age, she required nasal continuous pressure support after weaning from mechanical ventilation, because of respiratory distress and hypercapnia. Chest X-ray showed cardiomegaly (cardiothoracic ratio, 53%) and pulmonary congestion with hazy lung fields. Cardiac catheterization was performed at 6 months of age to evaluate the hemodynamics and severity of her pulmonary hypertension. With nasal oxygen 0.5 L/minute and Fi\(\text{O}_2\) = 1.0, her pulmonary arterial pressure was elevated at 61/15 (mean 39) mmHg, systemic-to-pulmonary blood flow ratio was 2.1, and pulmonary vascular resistance was 4.2 mmHg/L-minute-m\(^2\). She immediately underwent patch closure of the VSD under cardiopulmonary bypass, and developed transient hypotension and bradycardia just after surgery. She was extubated on the first postoperative day and stayed in the intensive care unit for 4 days. Chest X-ray showed that her cardiothoracic ratio decreased to 50%. Repeat cardiac catheterization was performed at 7 months of age to evaluate pulmonary hypertension, and showed a pulmonary arterial pressure of 41/17 (mean 24) mmHg and pulmonary vascular resistance of 3.6 mmHg/L-minute-m\(^2\). An oxygen loading test with 100% oxygen showed a pulmonary arterial pressure of 39/18 (mean 23) mmHg, which was not a significant decrease. Her respiratory symptoms improved after surgery, and she was discharged with home oxygen supplementation.

At 1 year of age (6 months after surgery), echocardiography showed bowing of the interventricular septum into the left ventricle and an estimated right ventricular pressure of > 90 mmHg, suggesting suprasystemic right ventricular pressure.
nary vasodilator therapy is controversial. and bosentan was effective, even though combination pulmo-

We assume that treatment with the combination of prostacyclin and bosentan, follow-up echocardiography showed improvement of the right ventricular hypertrophy and decreased right ventricular pressure. She had no adverse events and did not require further hospitalization. At 4 years of age, echocardiography showed that the estimated right ventricular pressure had decreased to 20 mmHg (Figure E). Her plasma BNP level decreased to 23 pg/dL. She was able to discontinue her home oxygen supplementation and pulmonary vasodilator therapy.

**Discussion**

We present a preterm infant with CHD and concomitant BPD who developed recurrent PAH at 6 months after corrective cardiac surgery. The biphasic pattern suggests heterogeneous pathophysiology of PAH. The first episode of PAH was likely caused by the increased left-to-right shunt and mild elevation of pulmonary vascular resistance, and the second episode was related to changes in the pulmonary vasculature associated with BPD.

PAH associated with BPD is likely to progress gradually over time. The timing of the diagnosis of PAH associated with BPD was reported to vary from 2 months to 70 months (mean, 4.8 months). The pathological changes of the pulmonary vasculature and alveoli are heterogeneous in PAH associated with CHD and BPD. It may therefore be appropriate for infants with CHD and concomitant BPD to be carefully managed with home oxygen supplementation or pulmonary vasodilator therapy even after effective cardiac surgery. In the present case, the pulmonary arterial pressure was still high just after closure of the VSD, which may predict a relatively poor clinical course.

However, the indications for such procedures should be carefully determined by weighing the risks against the benefits. Conclusions: We present a preterm infant with CHD and concomitant BPD who developed recurrent PAH after corrective cardiac surgery. The biphasic pattern of PAH suggests heterogeneous pathophysiology of PAH in preterm infants with CHD and BPD. In these patients, careful management with home oxygen supplementation and/or pulmonary vasodilator therapy is warranted even after corrective cardiac surgery.

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**References**


