Pulmonary Arterial Hypertension Associated With Tetralogy of Fallot

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Summary

Pulmonary arterial hypertension (PAH) is a common postoperative complication in patients with congenital heart disease (CHD). Although the recent clinical classification of pulmonary hypertension divided PAH associated with CHD (PAH–CHD) into several subclasses, the anatomical and hemodynamic features of postoperative PAH–CHD vary enormously. Therefore, it is still difficult to obtain clinical evidence supporting the indication of pulmonary vasodilators for PAH–CHD. We often encounter patients with PAH occurring after surgical treatment of tetralogy of Fallot (TOF), especially patients with major aortopulmonary collateral arteries (MAPCAs). PAH might be caused by pulmonary agenesis, hypoplasia and/or thrombosis, inadequate closure of the ventricular septal defect, relief of the pulmonic stenosis, or an excessively large prior systemic-to-pulmonary shunt. Moreover, patients with TOF and MAPCAs who are diagnosed as inoperable because of the presence of PAH show similar hemodynamic and clinical features to patients with Eisenmenger syndrome. The MAPCAs in these patients usually show hypoplastic and abnormal arborization. Based on our experience, we believe that PAH-targeted therapies are effective in some patients with PAH occurring after surgical treatment of TOF and MAPCAs, especially as an adjunct to percutaneous pulmonary angioplasty. To help classify patients with PAH associated with TOF, especially with MAPCAs, we propose several new subclassifications: “PAH due to hypoplastic pulmonary arterial beds”, “PAH due to abnormal pulmonary arborization”, or “segmental PAH associated with CHD.” A multicenter registry of patients using a unified protocol is essential to explore the indications and efficacy of pulmonary vasodilators for postoperative PAH–CHD. (Int Heart J 2015; 56: S17-S21)

Key words: Major aortopulmonary collateral artery, Pulmonary vasodilator, Percutaneous pulmonary angioplasty, Pulmonary arterial bed

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fil and tadalafil, are established vasodilators in iPAH. They are also effective in PAH–CHD, although the data are currently limited. It was reported that sildenafil improved exercise capacity and hemodynamic variables in a 12-month open-label study of 514 children with PAH, including 10 with PAH–CHD.\(^6\)

Endothelin is a mediator of vasoconstriction, cell proliferation, vascular hypertrophy, and fibrosis, and is therefore involved in the pathophysiology of PAH and is associated with the severity and outcomes of PAH.\(^9\) The dual endothelin receptor antagonist, bosentan, has the strongest clinical support of all of the targeted therapies for PAH–CHD.\(^6\) The BREATHE-5 trial and its long-term open-label extension study showed that bosentan significantly improved exercise capacity, hemodynamics, and functional class independently of the location of lesions in patients with Eisenmenger syndrome.\(^7\,\,9\) Based on these results, the current guidelines proposed by the European Society of Cardiology recommend that bosentan should be prescribed to patients with Eisenmenger syndrome of functional class III (recommendation class I, evidence level B), although other endothelin receptor antagonists, PDE-5 inhibitors, PGI\(_2\), or combination therapy should also be considered (recommendation class IIa, evidence level C).\(^9\)

**Types of postoperative PAH–CHD:** PAH is a common postoperative complication of CHD, but may also occur preoperatively. The Dana Point Classification\(^11\) divided PAH–CHD into four subclasses: A. Eisenmenger syndrome, B. PAH associated with systemic-to-pulmonary shunts, C. PAH with small defects, and D. PAH after corrective cardiac surgery. These subclasses were recently modified by the Pediatric Task Force of the 5th World Symposium on Pulmonary Hypertension in Nice using the following terms: 1) Eisenmenger syndrome, 2) left-to-right shunts, operable or inoperable; 3) PAH with co-incident CHD; and 4) postoperative PAH.\(^13\) However, the anatomical and hemodynamic features of PAH vary considerably among patients, especially in patients with PAH occurring after surgical treatment of CHD. Therefore, it is difficult to establish clinical support for the use of pulmonary vasodilators for all conditions, even though many types of pulmonary vasodilators have been used to treat postoperative PAH–CHD.

Early repair of simple CHDs, such as ventricular septal defect, in infancy usually prevents the development of pulmonary vascular remodeling and postoperative PAH. However, prior histological studies suggested that the delayed development of medial hypertrophy in response to PAH in patients with complex CHDs, such as transposition of the great arteries, could increase the susceptibility of pulmonary arteries to moderate pressure load and appears to be responsible for the early development of severe intimal changes.\(^13\) CHDs associated with Down syndrome also seem to have similar characteristics. Therefore, patients with transposition of the great arteries or CHD with Down syndrome, especially those who did not undergo corrective operation at an early age, are likely to develop severe PAH–CHD. Such patients are candidates for pulmonary vasodilators, but they are often refractory to such treatments. We also need to establish some evidence for the effectiveness and safety of pulmonary vasodilators following Glenn- or Fontan-type surgery as part of the treatment of patients with univentricular disorders, as discussed in another chapter of this issue.

**Postoperative PAH associated with tetralogy of Fallot:** Severe PAH is a rare complication after surgical correction of tetralogy of Fallot (TOF), with a prevalence of about 1%.\(^14\) However, we have often encountered patients with postoperative PAH associated with TOF (PAH–TOF), especially patients with major aortopulmonary collateral arteries (MAPCAs). The medical management of PAH, including disease-specific therapy, should target the underlying pathological disorders. Although there have been numerous controlled trials to optimize the treatment of iPAH, no controlled trials have focused on postoperative PAH–TOF. Here, we present our experiences of a few cases with postoperative PAH–TOF, who were treated with PAH-targeted therapies.

**Case Reports**

Case 1 was a 5-year-old girl who presented with cyanosis at 1 month old and was referred to our hospital. She was diagnosed with TOF and MAPCAs by echocardiography. Fluorescence in situ hybridization revealed she had the chromosome deletion 22q11.2. She underwent a left-sided Blalock–Taussig shunt operation at 1 month old, followed by unifocalization of right-sided MAPCAs at 4 months old. Because cardiac catheterization at 10 months old revealed stenosis in the left-sided Blalock–Taussig shunt, she underwent a revised left-sided Blalock–Taussig shunt operation at 11 months old. Home oxygen therapy was started as postoperative therapy. Because cardiac catheterization at 1 year old demonstrated stenosis of the unifocalized right pulmonary arteries, she underwent percutaneous balloon dilation at 1, 2, and 4 years of age. At 5 years of age, she underwent a Rastelli-type intracardiac surgical repair. She experienced postoperative pulmonary hypertension crisis and required inhaled nitric oxide (NO) as a specific pulmonary artery vasodilator. She started a combination of sildenafil and bosentan on postoperative day (POD) 2. The estimated right ventricle pressure caused by tricuspid regurgitation, as determined by echocardiography, gradually decreased and inhaled NO therapy was discontinued on POD 10 (Figure 1A). She was extubated on POD 11 and discharged from hospital on POD 33. Cardiac catheterization 4 months after the Rastelli-type surgery demonstrated residual stenosis in bilateral peripheral pulmonary arteries and she underwent percutaneous balloon dilation to treat the stenosis (Figure 1B). Percutaneous balloon dilation decreased the pressure gradient through the stenotic lesions from 39 mmHg to 20 mmHg in the left peripheral pulmonary artery and from 30 mmHg to 0 mmHg in the right peripheral pulmonary artery (Figure 1C). Her right ventricle pressure decreased from 65/6 mmHg to 27/2 mmHg, while her systemic pressure was maintained at 77/56 mmHg. She continued treatment with sildenafil and bosentan and no adverse effects were observed. She is now asymptomatic and doing well without cyanosis. Her SpO\(_2\) was 99% and a chest X-ray showed a cardiothoracic ratio of 62% with normal pulmonary vascular markings.

Case 2 was a 23-year-old male who was born by vacuum extraction at 37 weeks of gestation with a birth weight of 1572 g. He was the smaller boy of monozygotic twins with twin-to-twin transfusion syndrome. Soon after birth, he was admitted to the neonatal intensive care unit because of cyanosis and respiratory distress. A heart murmur was audible and echocardiography prompted the diagnosis of TOF with MAPCAs. He
had the chromosomal deletion 22q11.2. His pulmonary arteries were hypoplastic and a very narrow confluent central pulmonary artery was fed by a MAPCA from the descending aorta. At 5 months old, he underwent a right-sided Blalock–Taussig shunt operation. Cardiac catheterization and angiography were performed at 3, 6, and 15 years of age. The studies showed no indication of corrective cardiac surgery because of severe hypoplasia and abnormal arborization of his pulmonary arterial trees. Severe stenosis was revealed in the left pulmonary arteries fed by MAPCA. The last study, at 15 years old, showed that the pressures of the hypoplastic central and peripheral pulmonary arteries were 55/6 mmHg (mean: 28 mmHg), indicating PAH. At 18 years old, his functional capacity was class III and he was prescribed bosentan to treat PAH. Bosentan was administered at an initial dose of 62.5 mg/day and increased to 125 mg/day at 4 weeks and continued thereafter. His symptoms, which included fatigue, tiredness, and dyspnea, were alleviated by bosentan. His SpO2 was unchanged at around 75%, but his quality of life appeared to have improved. A chest X-ray still showed a cardiothoracic ratio of 61% as well as decreased pulmonary vascular marking with hyperinflation of the lungs. This patient experienced no adverse events during treatment with bosentan.

Although we felt that the medical treatment of PAH was effective in these two patients, for example, we have experienced some patients who PAH deteriorated during treatment. Case 3 is a 32-year-old male who had TOF and a hypoplastic left pulmonary artery. At 5 years old, he underwent intracardiac repair consisting of right ventricular outflow tract reconstruction with a transannular patch. Cardiac catheterization at 27 years old showed occlusion of the left pulmonary artery and hypertension in the right pulmonary artery (Table). About 2 weeks after starting treatment with bosentan at an initial dose of 125 mg/day, his symptoms, which included fatigue and dyspnea, started to deteriorate and his SpO2 decreased from 90% to 80%. Therefore, bosentan was discontinued after 4 weeks. We think that ventilation–perfusion mismatch and/or volume overload occurred during treatment with bosentan in this patient.

**DISCUSSION**

**Characteristics of TOF with MAPCAs:** TOF with MAPCAs is one of the most severe types of CHD, accounting for about 1% of all cases of CHD. TOF with MAPCAs has a clinical course that is frequently complicated by the development of PAH. The MAPCAs that supply blood to the lungs vary in terms of their size, location, and blood flow volume between patients. Surgical treatment involving unifocalization of the MAPCAs is essential to regulate and maintain adequate blood flow to the lungs. However, some patients are contraindicated to this procedure and require either palliative or medical treatment for their symptoms. These patients tend to have a poor prognosis with worsening of cyanosis and/or dyspnea, and the development of heart failure.

MAPCAs are thought to be derived from the embryonic splanchnic vascular plexus, and contribute to the pulmonary blood supply in approximately 30–40% of patients with TOF and severe stenosis/atrophy of the pulmonary trunk (Figure 2). Maldevelopment of the sixth pharyngeal arch arteries in embryonic stages results in hypoplasia or aplasia of bilateral pulmonary arteries and/or ductus arteriosus. Therefore, to provide blood flow to the lungs, MAPCAs form from remnants of inter-segmental arteries, which originally connect the peripheral pulmonary arteries and the ascending or descending aorta (Figure 2). Collateral arteries, which are highly variable in terms of their number, size, origin, course, arborization, and structure, are sometimes the only source of pulmonary blood or they may supply as little as one lung segment. The size of the distal pulmonary arterial bed supplied by collaterals is generally in-

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**Table.** Results of Cardiac Catheterization in Case 3

<table>
<thead>
<tr>
<th>Site</th>
<th>(O_2) (%)</th>
<th>Blood pressure (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supra vena cava</td>
<td>61</td>
<td>(11)</td>
</tr>
<tr>
<td>Infra vena cava</td>
<td>63</td>
<td>(12)</td>
</tr>
<tr>
<td>Right atrium</td>
<td>61</td>
<td>(12)</td>
</tr>
<tr>
<td>Right ventricle</td>
<td>74</td>
<td>79/EDP 18</td>
</tr>
<tr>
<td>Main pulmonary artery</td>
<td>74</td>
<td>83/11 (34)</td>
</tr>
<tr>
<td>Left pulmonary artery</td>
<td>Occluded</td>
<td>Occluded</td>
</tr>
<tr>
<td>Right pulmonary artery</td>
<td>71</td>
<td>59/3 (25)</td>
</tr>
<tr>
<td>Pulmonary capillary wedge</td>
<td>–</td>
<td>(11) right</td>
</tr>
<tr>
<td>Left ventricle</td>
<td>89</td>
<td>113/EDP 16</td>
</tr>
<tr>
<td>Aorta</td>
<td>92</td>
<td>121/49 (73)</td>
</tr>
</tbody>
</table>

( ) denotes mean pressure. EDP indicates end-diastolic pressure.
versely related to the vascular bed of the true pulmonary arteries, which ranges from normal in size to completely absent. TOF with MAPCAs is highly associated with the chromosome deletion 22q11.2. Patients with TOF, MAPCAs, and the 22q11.2 deletion usually show hypoplastic pulmonary arterial trees.

PAH in patients with TOF and MAPCAs: Progressive PAH is often responsible for the deteriorations in patients with TOF and MAPCAs. The development of PAH, even after surgical treatment, has a significant influence on the long-term prognosis of these patients. Percutaneous intervention and surgical repair are primarily done to repair pulmonary arterial stenosis, and if they are not possible, medical treatment may be an alternative option for the management of PAH.

Elucidating the cause of PAH is essential to help select the most appropriate treatment. PAH is thought to be caused by multiple factors in patients with TOF and MAPCAs. Lesions characteristic of TOF with MAPCAs include hypoplasia of pulmonary arterial beds as a result of decreased pulmonary blood flow, peripheral pulmonary stenosis, vascular spasm in a region of alveolar hypoventilation, and potentially remodeling of the pulmonary vasculature (Figure 3). Pulmonary vascular remodeling is a characteristic of iPAH and is also caused by an increase in pulmonary blood flow through systemic-to-pulmonary shunts in patients with CHD. Histologic analyses of MAPCAs have revealed evidence of medial hypertrophy, fibrous intimal proliferations, rupture of the internal elastic lamina, and plexiform lesions, reminiscent of pulmonary vascular remodeling in iPAH. Considering these findings, PAH could also develop in patients with TOF and decreased pulmonary blood flow. In terms of the underlying mechanisms, hypoplastic and/or segmentally unequal pulmonary arterial beds are susceptible to vascular remodeling despite low blood flow stress (Figure 3). Therefore, further subclassifications of PAH–CHD such as “PAH due to abnormal/hypoplastic pulmonary arterial beds”, “PAH due to normal pulmonary arborization”, or “segmental PAH associated with CHD” may be needed to appropriately recognize the type of PAH associated with TOF, especially in patients with MAPCAs.

Targeted therapy for PAH in patients with TOF and MAPCAs: As described above, there are numerous factors involved in the etiology of PAH in patients with TOF and MAPCAs. Catheter intervention is the first-line treatment for patients with peripheral pulmonary stenosis. Although there is no evidence for the benefits of PAH-targeted therapies in patients with TOF and MAPCAs, a recent paper reported that bosentan was effective in such patients with PAH after intracardiac repair. Another paper showed that sildenafil was well tolerated and improved symptoms and SpO2 in the majority of patients with PAH associated with TOF and MAPCAs when it was used alone or as an adjunct to percutaneous pulmonary angioplasty. We sent a questionnaire to pediatric cardiologists who were treating patients with PAH–TOF at 10 Japanese institutions to obtain their impressions of the efficacy of oral pulmonary vasodilators in these patients (unpublished data). The 10 cardiologists reported on 40 patients (age range 1–36 years) who were treated with oral pulmonary vasodilators, including 27 patients had TOF and MAPCAs and 13 cases with TOF without MAPCAs. All of the cardiologists who responded to our questionnaire thought that oral pulmonary vasodilators should be prescribed to these patients as soon as possible after repairing peripheral pulmonary stenosis.

Medications for PAH play an important role in the structural remodeling process underlying severe PAH. Because the histology of MAPCAs is similar to that of pulmonary vascular
remodeling in iPAH, drugs used to treat iPAH may be effective in patients with PAH associated with TOF and MAPCAs, by reversing pulmonary vascular remodeling. Based on our clinical experience, we believe that pulmonary vasodilators may be effective in patients with postoperative pulmonary hypertension crisis, allowing the discontinuation of inhaled NO. These drugs may improve the quality of life of patients who undergo palliative surgery, although they are not effective in all patients with PAH associated with TOF and MAPCAs. A prospective study is needed to establish ways to predict the extent of the contribution of pulmonary vascular remodeling to the pathogenesis of PAH in patients with TOF and MAPCAs.

Conclusions: The anatomical and hemodynamic characteristics of PAH, especially postoperative PAH–CHD, vary considerably among individual patients. Subclassifications of PAH, such as “PAH due to hypoplastic pulmonary arterial beds”, “PAH due to abnormal pulmonary arborization”, or “segmental PAH associated with CHD”, are necessary to better classify PAH associated with TOF, especially in patients with MAPCAs. Multicenter registries of patients using a unified protocol are essential to explore the indications and efficacy of pulmonary vasodilators for PAH occurring after surgical treatment of CHD, especially in patients with TOF and MAPCAs.

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