Can Pulmonary Vasodilator Therapy Expand the Operative Indications for Congenital Heart Disease?

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SUMMARY

The operability of congenital heart disease with left to right shunt depends on the severity of the pulmonary vascular disease induced by the increased pulmonary blood flow. Although some recommendations exist regarding operative indications according to pathological, hemodynamic, and epidemiological factors, the evidence underlying these recommendations is not conclusive. Recently, oral pulmonary vasodilator therapy has been reported to improve outcomes in patients with idiopathic pulmonary arterial hypertension, and this therapy also appears to be effective in patients with congenital heart disease and pulmonary arterial hypertension, including those with postoperative pulmonary hypertension and Eisenmenger syndrome. It is expected that the availability of novel pulmonary vasodilator therapy will expand the operative indications in patients with congenital heart disease with left to right shunt, but there is currently insufficient evidence to definitively determine this. A multicenter double-blind study should be conducted to further examine this issue. (Int Heart J 2015; 56: S12-S16)

Key words: Pulmonary hypertension, Eisenmenger syndrome, Outcome, Surgical indication

Recent advances in pediatric cardiac surgery techniques have increased the ability to correct congenital heart disease (CHD) at an early age. However, pulmonary arterial hypertension (PAH) associated with CHD is still a serious problem. The operability of CHD with left to right shunt depends on the severity of the pulmonary vascular disease induced by the increased pulmonary blood flow.

Oral pulmonary vasodilator therapy has shown promising results. Pulmonary vasodilator therapy improves outcomes in patients with idiopathic PAH, and has also been reported to be effective in patients with other types of PAH. This therapy may reduce pulmonary vascular resistance (Rp) in patients who were previously thought to have irreversible pulmonary vascular disease.

This review provides an overview of 1) the operative indications in patients with CHD and PAH, 2) the natural history of PAH associated with CHD and Eisenmenger syndrome, 3) advanced therapy targeting PAH, and 4) recent advances in pulmonary vasodilator therapy for patients with CHD and postoperative PAH, to answer the question: “Can pulmonary vasodilator therapy expand the operative indications for CHD with PAH?”

What Are the Operative Indications in Patients With CHD With Left to Right Shunt?

In patients with CHD with left to right shunt and increased pulmonary blood flow, structural changes of the pulmonary vessels such as intimal thickening may progress and become irreversible, resulting in obliteration, adventitial fibrosis, reduced number of intra-acinar arteries, and plexiform lesions. These irreversible vascular changes result in an extremely high operative risk even after complete repair of CHD, with progressive PAH and high Rp. However, it is difficult to determine whether patients have irreversible pulmonary vascular changes and a high risk of poor postoperative outcome.

Some recommendations exist regarding operative indications in patients with a ventricular septal defect (VSD). In 1974, Dushane suggested that VSD surgery could be performed when Rp ≤ 14 Wood U·m−2. Friedli et al. reported that Rp > 6 Wood U·m−2 and a pulmonary-to-systemic resistance ratio (Rp/Rs) > 0.3 were associated with increased mortality after VSD surgery. Rp < 8 Wood U·m−2 has also been suggested as an operative indication for VSD surgery. The ability of the pulmonary vascular bed to dilate is also very important, and can be evaluated by administration of selective pulmonary vasodilators such as oxygen or nitric oxide.

Lung biopsy can provide important information regarding pulmonary vascular changes. Heath-Edward grading is a well-known method of evaluating the progression of pulmonary vascular disease. However, no direct correlation has been shown between Rp and the Heath-Edward grade. Bush et al. reported that patients with Rp > 6 Wood U·m−2 had high mortality after VSD surgery regardless of the Heath-Edward grade. The Heath-Edward grade may provide a different indication of severity compared with other grading scales, such as Yamaki’s index of pulmonary vascular disease. Yamaki, et
reported substantial data regarding the operability of CHD evaluated using their index. However, operability based on the results of open lung biopsy is not necessarily consistent with operability based on the hemodynamic data.\(^{29,30}\)

Kirklin and Dushane\(^{29,30}\) reported that all patients with preoperative Rp < 10 Wood U·m\(^{-3}\) had normal or near-normal Rp on long-term follow-up. Studies of the longitudinal Rp trend in patients of various ages with VSD reported that those with preoperative Rp 4–6 Wood U·m\(^{-3}\) had no postoperative progression of disease.\(^{31,32}\) However, these studies had relatively small patient numbers.

Considering these data, our institute evaluates on VSD patients when Rp < 8 Wood U·m\(^{-3}\) and Rp/Rs < 0.5. VSD patients with high Rp (> 4 Wood U·m\(^{-3}\)) are evaluated for pulmonary vasoreactivity.

Even though many studies have evaluated factors related to the operability of VSD, uncertainties regarding operative indications still exist. The apparent discrepancies between lung biopsy findings and hemodynamic and epidemiological data are relatively small. There are some concerns regarding the results of hemodynamic evaluation by cardiac catheterization.\(^{4,10}\) First, respiratory instability during catheterization, especially in infants, may induce hypercapnia and adversely affect Rp, resulting in underestimation of operability. Second, Rp and Rs are usually calculated using estimated oxygen consumption as described by LaFarge.\(^{33}\) However, these estimated data do not always reflect measured data.\(^{34}\) At our institute, we therefore use measured rather than estimated oxygen consumption values to calculate Rp and Rs during cardiac catheterization.

Numerous studies have evaluated operative indications for atrial septal defect (ASD).\(^{35,36}\) Rahimtoola, et al.\(^{37}\) reported poor operative outcomes when the peak pulmonary arterial pressure was > 60 mmHg, and suggested a cutoff value of Rp 640 dyne·s·cm\(^{-2}\) for operation. Dave, et al.\(^{38}\) reported poor operative outcomes when the peak pulmonary arterial pressure was > 40 mmHg, and suggested a cutoff value of Rp/Rs 0.2 for operation. Koizumi, et al.\(^{39}\) recommended that operation should not be performed if Rp/Rs > 0.4. Yamaki, et al.\(^{40}\) reported their detailed lung biopsy findings in patients with ASD, and strongly recommended open lung biopsy when the peak pulmonary arterial pressure is > 70 mmHg, mean pulmonary arterial pressure is > 44 mmHg, pulmonary-to-systemic pressure ratio is > 0.66, Rp/Rs is > 0.42, or Rp is > 8 Wood U·m\(^{-3}\).

A 4-year follow-up study of patients with ASD conducted in the 1980s found no postoperative progression of disease in patients with preoperative Rp 9–14 Wood U·m\(^{-3}\). A study of the longitudinal Rp trend in 51 adult patients with ASD and PAH at our institute found similar results, and concluded that patients with ASD and PAH who had Rp < 14 Wood U·m\(^{-3}\) could be considered for operation.\(^{41}\) However, it is thought that patients with Rp 8–14 Wood U·m\(^{-3}\) have a high operative risk, and surgery should be carefully considered in these patients.

Despite a number of studies evaluating risk factors, there are still uncertainties regarding the precise operative indications for ASD with PAH. Further investigation is needed to determine the factors indicating operability in patients with ASD with PAH.

**Natural Course of Residual PAH and Eisenmenger Syndrome After Surgery**

If PAH cannot be improved after VSD or ASD closure, the hemodynamics of these postoperative patients are similar to those of patients with idiopathic PAH, because the right to left shunt that could prevent severe hemodynamic deterioration during a PAH crisis. The natural course of residual PAH after cardiac surgery is extremely poor.\(^{42-48}\) However, if surgery is thought to be contraindicated and the left to right shunt remains, pulmonary vascular change progresses and patients develop Eisenmenger syndrome, which is characterized by late complications and poor outcomes.\(^{41}\) These potential outcomes should be considered when deciding whether to perform surgery. However, the above-mentioned studies of postoperative PAH were conducted before the availability of advanced targeted therapy for PAH. Before the availability of pulmonary vasodilator therapy, patients with CHD and postoperative PAH had poorer outcomes than patients with Eisenmenger syndrome. Recent advances in pulmonary vasodilator therapy may change the outcomes in these patients. It is therefore important to reconsider the available outcome data now that novel pulmonary vasodilator therapy is available.

**How Does Pulmonary Vasodilator Therapy Affect Outcomes in Patients With CHD and PAH?**

A decade ago, the pharmacological treatment of PAH in patients with CHD was limited to diuretics, digitalis, and anti-coagulants, which did not significantly improve clinical outcomes or life expectancy. Recently, a number of novel pulmonary vasodilator drugs have become available, including endothelin receptor antagonists and phosphodiesterase-5 inhibitors.\(^{6,42}\) These vasodilators have been shown to improve functional status and survival in patients with idiopathic PAH.\(^{6,43}\)

Pulmonary vasodilator therapy is now being used to treat PAH in patients with CHD, including those with Eisenmenger syndrome. Many reports have indicated that the endothelin receptor antagonist bosentan is effective for improving clinical outcomes and exercise capacity in patients with Eisenmenger syndrome.\(^{6,8,12,41}\) The BREATHE-5 trial (Bosentan Randomized Trial of Endothelin Antagonist Therapy-5)\(^{6}\) is the only double-blind, placebo-controlled trial of pulmonary vasodilator therapy conducted in patients with Eisenmenger syndrome. The results of the BREATHE-5 trial showed that bosentan therapy significantly reduced Rp and improved the 6-minute walk distance compared with placebo. In addition, a follow-up study showed further improvement in functional class and the 6-minute walk distance in these patients.\(^{45}\) There were no significant differences in efficacy between subgroups of patients with ASD, VSD, or both. Long-term follow-up found improvements in functional class and exercise tolerance lasting at least 2 years. A pathological experimental study found that bosentan affected pulmonary vascular disease in rats.\(^{44}\)

Although there are no double-blind, placebo-controlled studies of the effects of phosphodiesterase-5 inhibitors in patients with CHD and PAH, a prospective open-label study found that sildenafil therapy was effective for improving pulmonary hemodynamics, functional class, and exercise tolerance with few significant side effects.\(^{1,12}\)

Unfortunately, evidence of the effectiveness of prostacyclin therapy for Eisenmenger syndrome is limited to small studies and case reports.\(^{45,46}\) Fernandes, et al.\(^{47}\) reported that continuous intravenous epoprostenol therapy improved pulmonary hemodynamics, functional class, and exercise tolerance in patients with Eisenmenger syndrome.
The results of the above-mentioned studies suggest that novel pulmonary vasodilator therapy may be beneficial for patients with Eisenmenger syndrome. If such therapy is also beneficial for patients with CHD and postoperative PAH, it may be appropriate to change the management strategies and operative indicators for these patients.

**Novel Strategies for Patients With CHD and PAH That Is Thought to Be Inoperable**

If it is confirmed that patients with CHD and PAH respond to novel pulmonary vasodilator therapy, three management strategies can be considered for patients who are thought to be inoperable or borderline. First, pulmonary vasodilator therapy can be started before operative repair. If this therapy improves the PAH, surgical repair can be considered. Second, pulmonary vasodilator therapy can be started after operative repair. However, if pulmonary vasodilator therapy is ineffective, the natural progression of disease may then be similar to that of idiopathic PAH. It is therefore important to confirm pulmonary vasoreactivity to both classical vasodilators such as nitric oxide, and novel pulmonary vasodilators such as sildenafil, before surgery. As sildenafil has a fast onset of action, it can be used to test vasoreactivity during cardiac catheterization. Third, the cardiac defect can be partially closed using a patch with a small hole or a one-way flap. This decreases or stops the left to right shunt, but allows right to left shunting during a PAH crisis, especially in the postoperative period. If Rp improves in response to long-term oral pulmonary vasodilator therapy, complete closure can be performed.

All the above management strategies depend on effective reduction of Rp by novel pulmonary vasodilator therapy. However, the long-term outcomes of these strategies are currently unknown. Although there is evidence that oral pulmonary vasodilator therapy is effective in patients with Eisenmenger syndrome, information regarding the effects of such therapy in patients with CHD and postoperative PAH is limited to case reports. The effectiveness of these strategies has therefore not been established.

Hoetzenecker, et al. reported a 71-year-old woman with an ASD and severe PAH (Rp > 400 dyne·s·cm⁻², mean pulmonary arterial pressure 54 mmHg). Bosentan therapy was started at 125 mg/day and was increased to 250 mg/day after 1 month. Ten months later, cardiac catheterization showed a significant reduction in Rp. She was discharged from hospital on postoperative day 28 with ongoing bosentan therapy. After 8 months of follow-up, she remained in good clinical condition.

Kim, et al. reported a 41-year-old woman with a large ASD and severe PAH (Rp 25.0 Wood U·m⁻²). Vasoreactivity testing with oxygen showed a weak response. Sildenafil was started at 25 mg/day and was increased to 50 mg/day after 9 months. After 2 years of sildenafil treatment, cardiac catheterization showed Rp 12.63 Wood U·m⁻² and Rp/Rs 0.43. Vasoreactivity testing with oxygen reduced Rp/Rs to 0.24. She underwent surgical repair of the ASD without significant postoperative problems. Four years after the repair, she had New York Heart Association class I functional status and all medications including sildenafil were discontinued.

Although there is currently no conclusive evidence regarding the effectiveness of pulmonary vasodilator therapy in patients with CHD and PAH, the outcomes in several reported cases, such as those described above, appear to be promising.

The number of adult patients with CHD and PAH is increasing, and it is important to improve the available evidence regarding the effectiveness of such treatment.

**Conclusion:** Considering the currently available evidence regarding the effects of pulmonary vasodilator therapy in patients with Eisenmenger syndrome, oral pulmonary vasodilator therapy may improve outcomes in patients with CHD and postoperative PAH. Advances in treatment may expand the operative indications in patients with CHD and PAH. To further assess this possibility, long-term outcomes should be studied in patients with CHD and postoperative PAH who receive pulmonary vasodilator therapy. A multi-center double-blind study should be conducted to definitively determine the effects of pulmonary vasodilator therapy in these patients.

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