Efficacy of Pulmonary Vasodilator Therapy in Patients With Functionally Single Ventricle

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SUMMARY

This study retrospectively evaluated the effectiveness of pulmonary vasodilator therapy with bosentan ($n = 14$) and/or sildenafil ($n = 23$) in 34 patients with a functionally single ventricle. Vasodilator therapy was initiated before the Fontan procedure in 18 patients and after the procedure in 16 patients. The reasons for vasodilator treatment included high pulmonary artery pressure or pulmonary vascular resistance ($n = 8$), high central venous pressure after the Fontan or bidirectional Glenn procedure ($n = 7$), and ventilatory impairment ($n = 8$). In the 11 patients who underwent right heart catheterization before and after the initiation of therapy, the mean pulmonary artery pressure decreased significantly from 19.5 ± 5.5 mmHg to 14.3 ± 3.0 mmHg ($P = 0.023$) and the transpulmonary pressure gradient decreased significantly from 10.9 ± 4.6 mmHg to 7.2 ± 3.3 mmHg ($P = 0.046$). Of the 18 patients who started vasodilator therapy before the Fontan procedure, 10 survived surgery, 4 are awaiting surgery, 3 had not been evaluated for the Fontan procedure at the end of the study period, and 1 died of heart failure after discontinuing bosentan therapy. There were no deaths among the patients who started therapy after the Fontan procedure. Two of the 14 patients receiving bosentan discontinued treatment because of adverse effects (hepatic dysfunction and increased serum brain natriuretic peptide level). Bosentan or sildenafil therapy is usually safe and may contribute to reducing pulmonary vascular resistance in patients with a functionally single ventricle before and after a Fontan type operation. (Int Heart J 2015; 56: S26-S30)

Key words: Pulmonary vascular resistance, Bosentan, Sildenafil, Fontan procedure

The Fontan procedure is a third-stage palliation procedure performed in patients with a functionally single ventricle, to enable flow through the pulmonary circulation without pumping by the ventricle. The decision to perform this procedure depends mainly on the condition of the pulmonary vasculature, particularly pulmonary artery pressure (PAP) and pulmonary vascular resistance (PVR). Three of the 10 criteria for selection for the Fontan procedure described by Choussat, *et al*⁽¹⁾ in 1978 refer to the pulmonary vasculature: mean PAP ≤ 15 mmHg, pulmonary arteriolar resistance < 4 Wood U $\times$ m², and no remodeling of the pulmonary artery.⁽¹⁾ Most subsequent studies reported that high PAP and PVR were associated with lower survival during the early stage after the Fontan procedure.⁽²⁻⁶⁾

Several pulmonary vasodilators such as prostaglandin I₂, endothelin receptor antagonists, and phosphodiesterase-5 (PDE-5) inhibitors have been reported to improve the symptoms and prognosis of patients with idiopathic pulmonary arterial hypertension and Eisenmenger syndrome.⁽⁷⁻¹³⁾ If these agents are also effective in reducing high PAP or PVR in patients with a single ventricle, they may contribute to reducing the risks associated with surgery. This study evaluated the effectiveness of treatment with bosentan (an endothelin receptor antagonist) and/or sildenafil (a PDE-5 inhibitor) in patients with a functionally single ventricle, before and after the Fontan

procedure.

METHODS

Patients: This study included 34 consecutive patients who received bosentan and/or sildenafil therapy between March 2008 and April 2011 at the Sakakibara Heart Institute. Patients were identified by retrospective review of the medical records. The most common primary diagnoses were single ventricle ($n = 6$), unilateral atrioventricular valve atresia ($n = 6$), atrioventricular septal defect ($n = 5$), and complete transposition of the great vessels ($n = 4$) (Table I).

All patients had undergone a palliative operation, followed in most cases by the bidirectional Glenn procedure. The initial palliative procedures included the Blalock–Taussig procedure ($n = 14$, including simultaneous right ventricular exclusion in 1 patient and a simultaneous Blalock–Hanlon procedure in 1 patient), pulmonary artery banding ($n = 16$, including simultaneous aortic reconstruction in 6 patients), the Norwood procedure ($n = 3$), and tricuspid valvuloplasty ($n = 1$) (Table II). Because this was a retrospective study, approval from an institutional ethics review board and patient consent for inclusion were not required (in accordance with Japanese regulations).

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Data collection: The medical records of all patients were reviewed, and the doses of bosentan and/or sildenafil and any adverse effects were recorded. When available, the PAP, PVR, and transpulmonary pressure gradient on right heart catheterization before and after the initiation of pulmonary vasodilator therapy were recorded.

Statistical analysis: Continuous variables are expressed as mean $\pm$ SD. Pulmonary parameters before and after the initiation of pulmonary vasodilator therapy were compared using Student's *t* test in Microsoft Excel™ (Microsoft, Santa Rosa, California, USA). A value of $P < 0.05$ was considered statistically significant.

RESULTS

Patient characteristics: The patients were 16 males and 18 females with a median age of 4 years (range, 4 months to 30 years) at the time of initiation of bosentan or sildenafil therapy. Vasodilator therapy was initiated before the Fontan procedure in 18 patients and after the Fontan procedure in 16 patients (Table I). Of the 18 patients who received vasodilator therapy before the Fontan procedure, 15 had undergone the bidirectional Glenn procedure, 1 had undergone pulmonary artery banding, 1 had undergone pulmonary artery banding with simultaneous aortic reconstruction, and 1 had undergone the Blalock–Taussig procedure. One of these 18 patients temporarily

stopped and then subsequently resumed vasodilator therapy.

Reasons for pulmonary vasodilator therapy: The most common reasons for bosentan or sildenafil therapy were high PAP or PVR on right heart catheterization ($n = 8$), ventilatory impairment ($n = 8$), high central venous pressure after the Fontan procedure or bidirectional Glenn procedure ($n = 7$), and trisomy 21 ($n = 3$) (Figure 1). The causes of ventilatory impairment were bilateral phrenic nerve paralysis ($n = 3$), recurrent nerve paralysis ($n = 1$), and obstructive tracheobronchial lesions ($n = 4$). The three cases of bilateral phrenic nerve paralysis resulted from previous surgery, and these patients all underwent diaphragmatic plication surgery to treat their ventilatory impairment. The other five patients with ventilatory impairment did not undergo invasive treatment for this. Of the eight patients with ventilatory impairment, six received sildenafil therapy and two received bosentan therapy. Five of these eight patients underwent the Fontan procedure, and the other three underwent only the bidirectional Glenn procedure.

Details of vasodilator treatment: For bosentan, the mean starting dose was 1.3 mg/kg/day (range, 0.3–4.5 mg/kg/day) and the mean highest maintenance dose was 3.0 mg/kg/day (range, 1.0–5.3 mg/kg/day). For sildenafil, the mean starting dose was 0.5 mg/kg/day (range, 0.1–1.4 mg/kg/day) and the mean highest maintenance dose was 1.4 mg/kg/day (range, 0.3–2.1 mg/kg/day).

Of the 14 patients who received bosentan therapy, 2 did not receive other pulmonary vasodilators or supplemental oxygen therapy, 11 received beraprost sodium therapy, and 3 received supplemental oxygen therapy (Figure 2). Of the 23 patients who received sildenafil therapy, 12 did not receive other pulmonary vasodilators or supplemental oxygen therapy, 9 received beraprost sodium therapy, 4 received supplemental oxygen therapy, and 2 received bosentan therapy (Figure 2). Patients also received diuretics and anticoagulants as indicated,

Table I. Patient Characteristics ($n = 34$)

Variable	
Sex, male / female	16 / 18
Start of therapy	
Before Fontan	18
After Fontan	16
Initial Diagnosis	
Functional single ventricle	6
Atrioventricular septal defect	5
Mitral atresia	4
Tricuspid atresia	2
Complete transposition of the great arteries	4
Corrected transposition of the great arteries	1
Hypoplastic left heart syndrome	2
Ebstein anomaly	2
Pulmonary atresia with intact ventricular septum	2
Other	6

Figure 1. Reasons for starting primary vasodilators. CVP indicates central venous pressure; PAP, pulmonary artery pressure; PLE, protein-losing enteropathy; Rp, pulmonary vascular resistance; V–V, veno-venous; and R–L, right-to-left.

Table II. First Palliation Procedure

Procedure	<i>n</i>
Blalock–Taussig procedure	12
Blalock–Taussig procedure + right ventricular exclusion	1
Blalock–Taussig procedure + Blalock–Hanlon procedure	1
Pulmonary artery banding	10
Pulmonary artery banding + aortic reconstruction	6
Norwood procedure	3
Tricuspid valvuloplasty	1

Figure 2. Treatment with pulmonary vasodilators. O2 indicates oxygen; and PGI2, beraprost sodium.

as well as angiotensin-converting enzyme inhibitors ($n = 25$), angiotensin II receptor antagonists ($n = 1$), and β -blockers ($n = 21$) (Table III).

Outcomes after vasodilator therapy: Mean PAP values before and during bosentan or sildenafil therapy were available for 11 patients. In these patients, the mean PAP decreased significantly from 19.5 ± 5.5 mmHg before therapy to 14.3 ± 3.0 mmHg during therapy ($P = 0.023$) (Figure 3A). The mean transpulmonary pressure gradient decreased significantly from 10.9 ± 4.6 mmHg before therapy to 7.2 ± 3.3 mmHg during therapy in the six patients for whom these data were available ($P = 0.046$) (Figure 3B). PVR values before and during bosentan or silde-

nafil therapy were available for six patients. In these patients, the PVR did not change significantly after the initiation of therapy (Figure 3C).

Of the 18 patients who initially received bosentan or sildenafil therapy before the Fontan procedure, 10 had undergone the Fontan procedure by the end of the study period and 4 were still awaiting surgery. Three of the remaining four patients had not been evaluated for the Fontan procedure at the end of the study period. The other remaining patient, who received bosentan after undergoing simultaneous mitral valve replacement and the Glenn procedure, developed heart failure postoperatively, and bosentan therapy was discontinued. This patient subsequently died of infection and heart failure, 15 months after discontinuation of bosentan therapy. There were no deaths among the patients who started bosentan or sildenafil therapy after the Fontan procedure.

Discontinuation of therapy: Bosentan therapy was discontinued in four patients, for the following reasons: hepatic dysfunction ($n = 1$), increased brain natriuretic peptide level associated with symptoms of heart failure ($n = 1$), changed to sildenafil therapy ($n = 1$, reason unknown), and adequate reduction in PAP ($n = 1$). Sildenafil therapy was discontinued in

Table III. Medications Other Than Pulmonary Vasodilators

Medication	<i>n</i>
Enalapril	24
Imidapril	1
Candesartan	1
Carvedilol	20
Bisoprolol	1

Figure 3. Outcomes after initiation of vasodilator therapy. **A:** Mean PA pressure before and during pulmonary vasodilator therapy in the 11 patients for whom these values were available. **B:** Transpulmonary pressure gradient before and during pulmonary vasodilator therapy in the nine patients for whom these values were available. **C:** Pulmonary vascular resistance before and during pulmonary vasodilator therapy in the six patients for whom these values were available. Red line indicates post-Blalock-Taussig operation; blue lines, post-bidirectional Glenn operation; black lines, post-Fontan operation; and PA, pulmonary artery.

four patients, for the following reasons: dizziness ($n = 1$, changed to bosentan therapy), flushing ($n = 1$), and adequate reduction in PAP ($n = 2$).

DISCUSSION

The condition of the pulmonary vasculature is generally considered to limit the selection of patients for the Fontan procedure.^{2,6} The main pulmonary vascular parameters to consider are the mean PAP, PVR, interruption or stenosis of a pulmonary artery, and cross-sectional areas of the right and left pulmonary arteries. Recent advances have enabled treatment of some cases of interruption or stenosis of a pulmonary artery by pulmonary angioplasty or catheter-based therapy, and these conditions therefore may not be a contraindication to the Fontan procedure.

Preoperative PAP and PVR are considered to be important predictors of prognosis after the Fontan procedure, particularly during the early postoperative period.⁴ Various parameters have previously been used to select patients for the Fontan procedure, such as: mean PAP ≤ 12 mmHg and pulmonary arteriolar resistance < 4 Wood U $\times$ m²,¹ mean PAP ≤ 15 mmHg or pulmonary arteriolar resistance < 2 Wood U $\times$ m²,² and mean PAP < 20 mmHg or pulmonary arteriolar resistance < 3 Wood U $\times$ m².⁶ Gentles, *et al*⁴ conducted a follow-up study of 500 patients who had undergone the Fontan procedure and reported that mean PAP ≥ 19 mmHg was associated with an increased risk of failure.

In patients without interruption or stenosis of a pulmonary artery, the main causes of increased PAP or PVR after the Fontan procedure are: pulmonary venous obstruction, reduced ventricular compliance due to hypertrophy or fibrosis,¹⁴ increased left atrial pressure resulting from regurgitation or stenosis of the atrioventricular valve, remodeling of small lung vessels because of excessive pulmonary blood flow, and microthrombosis and spasm of the small pulmonary arteries due to chronic respiratory disease.¹⁵ Pulmonary venous obstruction may require surgical intervention. To avoid reduced ventricular compliance, the appropriate palliative operation should be chosen and the Fontan procedure should be performed at an appropriate time to avoid excessive hypertrophy. Treatment with β -blockers or vasodilators may improve ventricular compliance^{16,17} or extend ventricular filling time.¹⁸ In patients with moderate to severe atrioventricular valve regurgitation, vasodilators or β -blockers should be administered as first-line therapy, and surgery may be required if there is no significant improvement in the regurgitation.^{19,20}

Vasodilators such as nitric oxide, prostaglandin I₂, endothelin receptor antagonists, and PDE-5 inhibitors have been used to treat pulmonary vascular obstructive disease, and were reported to be effective in a number of studies.²¹⁻²⁵ However, Ovaert, *et al*²⁶ reported that bosentan therapy was not effective in patients with a failing Fontan circulation and reduced left ventricular compliance, and suggested that investigation of the efficacy of vasodilator therapy in Fontan patients should be focused on those with high PAP or PVR due to pathology of the pulmonary vessels. Yamagishi, *et al*²⁷ reported that central venous pressure was correlated with the serum endothelin level, and that high serum endothelin levels were observed during the early period after the Fontan procedure. In addition, Kham-

badkone, *et al*²⁸ reported that nitric oxide reduced PVR after the Fontan procedure in the long term. The Fontan procedure may result in non-pulsatile pulmonary arterial flow, causing pulmonary endothelial dysfunction and reduced production of nitric oxide, which may eventually result in pulmonary vasoconstriction. Mitchell, *et al*²⁹ considered that postoperative increase in pulmonary arteriolar resistance might lead to long-term hemodynamic compromise because PVR was elevated after heart transplantation in patients with late failure of a Fontan procedure. In patients who underwent right heart catheterization before and after initiation of vasodilator therapy in this study, the PAP and transpulmonary pressure gradient decreased significantly after initiation of therapy. Patients who received vasodilator therapy prior to the procedure had favorable outcomes after surgery. Both bosentan and sildenafil may therefore be considered to be effective at reducing high PAP and PVR and reducing the risks associated with surgery.

Eight patients in this study had ventilatory impairment, of which five underwent the Fontan procedure. Sildenafil has been shown to reduce hypoxia-induced pulmonary hypertension, and to be useful for reducing PVR in patients with interstitial pneumonia, without reducing the ventilation-perfusion ratio.³⁰⁻³² Tadalafil has been approved for use as a pulmonary vasodilator in patients with hypoxic pulmonary hypertension, and has also been reported to be effective for the treatment of chronic obstructive pulmonary disease.³³ These findings may help to explain the efficacy of sildenafil treatment in the patients in this study with ventilatory impairment. In patients with respiratory tract involvement since childhood, improvement may also simply reflect the natural course of their disease, which tends to improve with increasing age. Because a number of patients selected for the Fontan procedure have ventilatory impairment, further investigation of the effectiveness of PDE-5 inhibitors for pulmonary vasodilatation in patients with high PVR and ventilatory impairment is warranted. Furthermore, a recent study reported that sildenafil had positive inotropic effects on the right ventricle of a biventricular heart.³⁴ Such inotropic effects may have influenced outcomes in the patients in this study.

This study is limited by its retrospective nature and the small number of subjects with heterogeneous presentations and treatments. Because most patients in this study also received other treatments such as β -blockers, renin-angiotensin-aldosterone system inhibitors, supplemental oxygen therapy, and bi-level positive airway pressure ventilation, it cannot be determined whether the outcomes were specifically related to bosentan or sildenafil therapy. Larger, prospective studies are needed to definitively determine the efficacy of vasodilator therapy before and after surgery in this population. Although the results of this study suggest that bosentan or sildenafil therapy is safe in most patients and may help to reduce PAP and the transpulmonary pressure gradient in patients selected for the Fontan procedure, vasodilator therapy may not be appropriate for every patient with a failing Fontan circulation. Increased understanding of the circulatory dynamics is expected to improve therapeutic choices in these patients.

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