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Sildenafil reduces pulmonary vascular resistance in single ventricular physiology

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ABSTRACT

Background: High pulmonary vascular resistance (PVR) may be a risk factor for early and late mortality in both Glen shunt and Fontan operation patients. Furthermore, PVR may increase long after the Fontan operation. Whether pulmonary vasodilators such as phosphodiesterase 5 inhibitors can decrease PVR in patients with single ventricular physiology remains undetermined.

Methods and results: This was a prospective, multicenter study. Patients with single ventricular physiology who have a PVR index higher than 2.5 Wood units·m^2 (WU) were enrolled. Cardiac catheterization was performed before and after administration of sildenafil in all patients. After the Fontan operation, a six minute walk test (6 MWT) was also performed. A total of 42 patients were enrolled. PVR was significantly decreased in each stage of single ventricular physiology after sildenafil administration: from 4.3 ± 1.5 WU to 2.1 ± 0.6 WU ($p < 0.01$) in patients before a Glenn shunt, from 3.2 ± 0.5 WU to 1.6 ± 0.6 WU ($p < 0.001$) in patients after a Glenn shunt, and from 3.9 ± 1.7 WU to 2.3 ± 0.8 WU ($p < 0.001$) in patients after Fontan. In patients after Fontan, the 6 MWT increased from 416 ± 74 m to 485 ± 72 m ($p < 0.01$), and NYHA functional class improved significantly ($p < 0.05$) after sildenafil administration. No major side effects were observed in any patients.

Conclusions: Sildenafil reduced PVR in patients with single ventricle physiology. Sildenafil increased exercise capacity and improved NYHA functional class in patients after a Fontan operation. This implies that pulmonary vasodilation is a potential therapeutic target in selected patients with elevated PVR with single ventricle physiology. Long-term clinical significance warrants further study.

1. Introduction

The Fontan procedure is the only procedure to eliminate cyanosis in patients with a functionally univentricular heart. In three decades, mortality and morbidity of the Fontan operation have improved dramatically [1,2]. The therapeutic strategy to perform a bidirectional Glenn shunt (a superior cavopulmonary shunt) before Fontan completion may be one of the major reasons for the improved rate of mortality [3,4]. Despite the changes in surgical strategy, relatively high pulmonary arterial pressure and pulmonary vascular resistance may still be risk factors of early and late mortality of both Glenn shunts and Fontan operations. There are several reports suggesting that a mean pulmonary arterial pressure >15–18 mm Hg and pulmonary vascular resistance >2–4 Wood units·m^2 are associated with increased mortality [5–7]. Amelioration of these factors may optimize postoperative management.

Fontan circulation has a unique nature in that it lacks the ventricle to propel pulmonary blood flow. In long-term studies after a Fontan operation, various problems may become apparent, including exercise intolerance, liver dysfunction, protein-losing enteropathy, and arrhythmia [8]. These problems, emanating long after the Fontan operation, may result, at least in part, from increases in pulmonary vascular resistance (PVR), which in turn causes increases in pulmonary arterial pressure, right atrial enlargement, decreases in cardiac output, and liver congestion.

Recently, several pulmonary vasodilators, including endothelin receptor antagonists, prostaglandin I2, and phosphodiesterase 5 inhibitors (PDE5i), have been introduced to treat idiopathic pulmonary arterial hypertension and pulmonary hypertension associated with congenital heart disease. It, however, remains undetermined whether pulmonary

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vasodilators can decrease PVR in patients with single ventricular physiology [9]. Thus, a multicenter, single-arm study was conducted to determine whether sildenafil, PDE5i, reduces pulmonary vascular resistance before and after a Fontan operation.

2. Methods

2.1. Subjects

This study was a prospective, open label, multicenter and single-arm study. Patients with single ventricular physiology between the ages of 1 and 50 years old who undertook cardiac catheterization, and had a PVR index (PVRi) higher than 2.5 Wood units·m^2 (WU) were enrolled. These criteria were adopted in this study because a PVR >2.5 Wood units·m^2 was considered higher than normal [10,11]. In patients after palliative or Fontan operation, cardiac catheterizations were performed more than six months after these operations.

Patients were divided into three groups, according to clinical situations. Patients in Group 1 had not undergone any surgical intervention (including a Glenn shunt), except for a Blalock–Taussig shunt. Patients in Group 2 had received a bidirectional Glenn shunt, but not a Fontan operation. Patients in Group 3 had undergone a Fontan operation.

A total of 42 patients were enrolled in this study (30 patients at Tokyo Women's Medical University, six at Sakakibara Heart Institute, four at Keio University, two at Nagano Children's Hospital, and none at Fukuoka Children's Hospital or Toho University). Group 1 included 7 patients, Group 2, 11, and Group 3, 24. Baseline characteristics are summarized in Tables 1 and 2. In Group 1, sildenafil was started at the age of 12 ± 8 months. Four patients had undergone Blalock–Taussig shunt operation. In Group 2, the Glenn procedure had been performed at 39 ± 82 (median 14) months of age, and sildenafil was started 44 ± 84 (median 9.8) months after the Glenn procedure. In Group 3, the mean age at the time of the Fontan operation was 3.6 ± 2.7 years old, and mean age of sildenafil administration was 9.5 ± 4.6 years after Fontan operation.

Sildenafil was started at a dose of 0.5 mg per kilograms and increased to 1 to 2 mg per kilograms within 1–2 months. In adult patients >18 years old, sildenafil was started with a dose of 40 mg/day, and increased to 60 mg/day. Follow-up catheterizations for assessment of hemodynamics were performed three months after sildenafil administration in all patients. Mean pulmonary artery pressure (MPAP, in mm Hg), pulmonary blood flow (Qp, in L/min/m^2), systemic blood flow (Qs, in L/min/m^2) or cardiac index (CI, in L/min/m^2), transpulmonary pressure gradient (TPPG, in mm Hg), and PVR index (PVRi, in Wood units·m^2) were measured. CI and Qp were measured using the Fick method. The grade of atrioventricular valve regurgitation was assessed from ventriculography. In patients after the Glenn shunt, cardiac output and pulmonary blood flow were estimated using calculation method of Salim et al. [12]. Assessment of NYHA functional class and 6 MWT was performed to evaluate exercise capacity in Group 3 patients. All the following blood tests were performed at the time of cardiac catheterization: hemoglobin (Hb), creatinine (Cre), aspartate aminotransferase (AST), alanine aminotransferase (ALT), brain natriuretic peptide (BNP), and estimated glomerular filtration ratio (eGFR).

Exclusion criteria for this study were as follows; 1: Existence of significant arteriopulmonary collateral vessels, 2: Existence of pulmonary artery stenosis and/or pulmonary vein obstruction, 3: Existence of respiratory failure and upper airway obstruction.

The primary outcome investigated in this study was improvement of PVRi. Secondary outcomes in Groups 1 and 2 were whether they were able to proceed to the next surgical step, such as a Glenn shunt or Fontan operation. In Group 3, the secondary outcome was an improvement of exercise capacity and NYHA functional class.

Table 2
Baseline characteristics.

	ALL (n = 42)	Group 1 (n = 7)	Group 2 (n = 11)	Group 3 (n = 24)
Atrioventricular valve regurgitation				
None	25	3	10	12
Mild	11	2	0	9
Moderate	6	2	1	3
Severe	0	0	0	0
Medical therapy				
Furosemide	20	3	4	13
Spironolactone	21	2	4	15
Trichlormethiazide	2	0	0	2
ACE inhibitors/ARB	16	2	4	10
Carvedilol	3	0	2	1
Digoxin	5	0	0	5
Aspirin	20	3	8	9
Warfarin	8	1	3	4
Anti-arrhythmia drug	1	0	0	1
Bosentan	4	0	1	3
Beraprost sodium	8	1	2	5
Home oxygen therapy	6	0	5	1

Table 1
Patient characteristics.

	All (n = 42)	Group 1 (n = 7)	Group 2 (n = 11)	Group 3 (n = 24)
Sex				
Male (n)	18	5	3	10
Female (n)	24	2	8	14
Height(cm)		67.4 ± 5.3	98.7 ± 30.5	135.9 ± 25.5
Weight (Kg)		6.8 ± 1.2	16.7 ± 12.0	36.7 ± 17.0
Age at administration (months or years)		12.0 ± 7.7 months	6.9 ± 9.6 years	12.7 ± 5.7 years
Months or years after final operation (years)		13.0 ± 8.5 months	4.0 ± 7.2 years	9.5 ± 4.6 years
Hb concentration (g/dL)		16.4 ± 2.2	16.7 ± 1.5	15.9 ± 2.4
O2 saturation (%)		81.6 ± 5.1	81.1 ± 4.6	92.4 ± 4.05
Anatomical diagnosis, n				
Tricuspid atresia	5	1	1	3
Hypoplastic left heart syndrome	2	1	0	1
Single ventricle	8	2	1	5
Double outlet right ventricle	19	2	4	13
PA-IVS	8	1	5	2
Operation type (no. of patients, including overlap)				
No palliation prior to Glenn or Fontan		3	0	2
Systemic to pulmonary shunt		2	8	16
Pulmonary artery banding		3	4	4
Norwood procedure		1	0	1
Damus–Kaye–Stansel		0	3	1
TAPVR repair		0	0	1
Pulmonary artery angioplasty		0	2	6
Atrio-ventricular valve plasty		0	0	3
Pace maker implantation		0	0	2
Glenn type				
Original Glenn		–	0	0
Bidirectional Glenn		–	10	6
Kawashima procedure		–	1	1
Fontan type				
APC		–	–	12
LT		–	–	2
TCPC		–	–	10