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Treatment of segmental pulmonary artery hypertension in adults with congenital heart disease

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ABSTRACT

Introduction: Pulmonary arterial hypertension (PAH) in patients with congenital heart disease (CHD) usually has a homogeneous pressure distribution. More rarely, complex CHD patients have segmental PAH. This is often post-surgically. The characteristics of these patients and their responsiveness to specific pulmonary vasodilator therapy have not been described.

Methods: Seven adults with segmental PAH complicating CHD were treated at 3 specialized adult CHD centers between January 2006 and December 2010. Clinical characteristics, six minute walking distances (6MWD), laboratory tests and images were obtained from medical records and the responses to Bosentan, an endothelin-1 receptor antagonist, were assessed.

Results: All patients (mean age 32 (23–42) years, five females) had a primary diagnosis pulmonary atresia (PA), four with major aortopulmonary collateral arteries (MAPCAs). Four segmental PAH patients had a right pulmonary artery stenosis, two a left pulmonary artery stenosis and one a unilateral MAPCA stenosis. All patients were symptomatic (functional class II or III) and bosentan was started empirically. Bosentan treatment led to a significant improvement in functional class compared to baseline (1.7 ± 0.5 versus 2.4 ± 0.5; $p<0.01$). Mean 6MWD (available in 6 patients) increased by 62 m (22–150 m) from 386 ± 135 to 448 ± 133 m ($p=0.03$) after 12 months treatment. Most improvement was seen in patients with low baseline 6MWD. Higher baseline exercise heart rate was significantly associated with lesser improvement in 6MWD ($r=-0.91$ $p=0.01$). Laboratory results did not change after initiation of bosentan treatment.

Conclusion: This small retrospective case series suggested a significant improvement of functional class and exercise capacity after bosentan treatment in patients with segmental PAH. These findings warrant a prospective study of the potential benefit of selective pulmonary vasodilator therapy in these complex patients. Therefore, we call on treating physicians to share similar cases.

1. Introduction

Congenital heart disease (CHD) in adults is associated with pulmonary arterial hypertension (PAH) in 5–10% of cases [1,2]. The characteristic pulmonary pressure distribution in CHD-PAH patients is homogeneous [3]. However, some cases of complex CHD are complicated by segmental PAH. This is often post-surgical with branch pulmonary artery stenosis resulting in local differences in pulmonary artery pressure and pathophysiologic severity [4]. Consequently, some areas of pulmonary tissue have higher pressures than others. The clinical presentation of CHD patients with segmental PAH varies from asymptomatic incidental findings on trans-thoracic echocardiography (TTE) to progressive dyspnoea on exertion or even haemoptysis [5,6].

Initial treatment for these patients with segmental PAH may involve percutaneous intervention or surgical repair [7]. Medical treatment is considered when such interventions are not possible. Three main classes of medical therapies for PAH have been investigated: endothelin-1 receptor antagonists such as bosentan, prostanoids such as epoprostenol and phosphodiesterase 5 inhibitors such as sildenafil [8,9]. Bosentan has been shown to improve six minute walking distance (MWD) in homogenous CHD-PAH [10]. Whether bosentan is effective in CHD patients with segmental PAH is unknown [11,12]. Therefore, we collected case observations from three specialist adult CHD centers to

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evaluate the characteristics of such patients and the potential benefit of bosentan in this clinical condition.

2. Methods

2.1. Data collection

Large adult congenital heart units in Amsterdam, Sydney and London reviewed their databases for symptomatic patients with segmental PAH. Clinical characteristics, 6MWD, laboratory tests and imaging data were obtained where available from medical records. New York Heart Association functional class data was obtained from baseline (pre-treatment) and last visit. For each patient the proportion of segmental PAH was estimated by the anatomy and the location of pulmonary artery stenosis found on advanced imaging.

2.2. Statistics

For statistical analysis SPSS 18.0 (SPSS Inc, Chicago, Illinois) was used. The difference between baseline and treatment was calculated with paired t-test. Correlation between change in 6MWD and baseline 6MWD, functional class, rest saturation, exercise saturation, rest heart rate, exercise heart rate and NT-pro-BNP was evaluated using Pearson correlation analysis (r). Univariate linear regression analysis was performed for each clinical outcome parameter to determine whether it was associated with the estimated proportion of segmental PAH. p-values below 0.05 were considered to be significant.

3. Results

3.1. Baseline characteristics

Seven patients (mean age 32 (23–42) years, five females) had segmental PAH. Table 1 summarizes patients' baseline characteristics. This includes a detailed description of the distribution of pulmonary pressures. All seven patients had the underlying diagnosis of pulmonary atresia (PA), four of whom had major aortopulmonary collateral arteries (MAPCAs). Interventions in the history were central Goretex shunt ($n=1$), Waterston shunt ($n=1$), Blalock Taussig shunt ($n=3$) and Potts shunt ($n=1$), see Fig. 1. Four segmental PAH patients had a right pulmonary artery stenosis, two a left pulmonary artery stenosis and one a unilateral MAPCA stenosis. Pulmonary pressures pre-stenosis were higher (90/5; 95/12; 129/53; 65/50; 65/50; 80/40; 105/15 mmHg) than pressures post stenosis (16/2; 40/28; 50/40; 30/20; 0/0; 40/20; 56/18 mmHg) respectively. Time between onset and diagnosis of PAH was unknown.

3.2. Effects of bosentan treatment

All patients were symptomatic and bosentan was started empirically. Patients remained on monotherapy with bosentan and other medical therapies included diuretics for five patients, antiarrhythmic agents for four patients and oral anticoagulation for four patients. Bosentan treatment showed a significant improvement of functional class compared to baseline (1.7 ± 0.5 versus 2.4 ± 0.5; $p<0.01$), see Table 2.

Six patients had 6MWD available. Mean 6MWD increased with $+62$ m (22–150 m) from 386 ± 135 to 448 ± 133 ($p=0.03$) at 12 months of treatment. Most improvement was seen in patients with low baseline 6MWD (Fig. 2A). Higher baseline exercise heart rate was significantly associated with fewer increase in 6MWD ($r=-0.91$ $p=0.01$), see Fig. 2B. Change in 6MWD was not associated with baseline 6MWD, functional class, rest saturation, exercise saturation and rest heart rate. Mean resting heart rate at baseline (88 ± 11 beats per minute) was unchanged during follow-up (81 ± 17 beats per minute), as was mean maximum heart rate during the 6MWD (110 ± 22 beats per minute versus 114 ± 26 beats per minute). Mean resting oxygen saturation at baseline was 81% and did not change significantly during 12 months follow-up. Mean minimum oxygen saturation during the 6MWD at baseline was 67 ± 16% and did not change significantly at last follow-up to 61 ± 17%.

NT-pro-BNP levels were available for three patients and were unchanged compared to baseline (mean 778 ± 586 versus 768 ± 611 ng/L).

The estimated proportion of segmental PAH was investigated by univariate linear regression analysis to verify whether it could predict clinical outcome. The analysis did not find a clinical outcome parameter to be significantly associated with patients' estimated proportion of segmental PAH. Change in functional class tended to associate with segmental PAH severity without reaching significance ($\beta=-0.027$; $p=0.051$).

Therapy with bosentan was safe and well tolerated for these patients. Mild adverse events were reported by two patients. One patient developed headache and one patient reported nausea and later a syncopal episode. No disturbed liver function tests were found.

4. Discussion

Our observations are the first to show significant improvement of clinical status and exercise tolerance after bosentan therapy in complex

Table 1
Baseline characteristics.

	Age (y)	Gender	Defect	Interventions
A	31	Female	PA + MAPCA + APD stenosis	Patch APD stenosis + ligation MAPCA + closure VSD
B	38	Female	PA + VSD + MAPCA stenosis	Central Goretex shunt
C	42	Female	PA + ASD + ASD stenosis	Waterston shunt
D	23	Male	PA + DILV + TAPVC	Blalock Taussig shunt
E	30	Male	PA + DILV	Blalock Taussig shunt + Potts shunt
F	29	Female	PA + TOF	Blalock Taussig shunt
G	32	Female	PA + ASD + MAPCA	RVOT reconstruction + stenting left lower collateral

	Stenosis	Segmental PAH (%)	PAH		SaO_2 (%)
			Pre (mmHg)	Post (mmHg)	
A	APD	40	90/5	16/2	99–>89
B	MAPCA inf	20	95/12	40/28	81–>65
C	APS	40	129/53	50/40	82–>57
D	APD	60	65/50	30/20	81–>85
E	APD	33	65/50	n/a	65–>58
F	APD + APS	20	80/40	40/20	n/ a
G	APS	n/a	105/15	56/18	83–>56

PA; pulmonary atresia, PS; pulmonary artery stenosis, VSD; ventricular septal defect, TAPVC; total anomalous pumonary venous connection, APD; right pulmonary artery, APS; left pulmonary artery, TOF; Tetralogy of Fallot, DILV; double inlet left ventricle, RVOT; right ventricular outflow tract, MAPCA; major aortopulmonary collateral arteries.
APD; right pulmonary artery, APS; left pulmonary artery, n/a; not available, PAH; pulmonary arterial hypertension.