Chapter 5

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 62m (22 - 150 m) from 386 ± 135 to 448 ± 133m (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 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 Figure 1. Four segmental PAH patients had

Table 1A. Baseline characteristics

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>Gender</th>
<th>Defect</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>31</td>
<td>Female</td>
<td>PA+MAPCA+APD stenosis</td>
</tr>
<tr>
<td>B</td>
<td>38</td>
<td>Female</td>
<td>PA+VSD+MAPCA stenosis</td>
</tr>
<tr>
<td>C</td>
<td>42</td>
<td>Female</td>
<td>PA+ASD+ASD stenosis</td>
</tr>
<tr>
<td>D</td>
<td>23</td>
<td>Male</td>
<td>PA+DILV + TAPVC</td>
</tr>
<tr>
<td>E</td>
<td>30</td>
<td>Male</td>
<td>PA+DILV</td>
</tr>
<tr>
<td>F</td>
<td>29</td>
<td>Female</td>
<td>PA+TOF</td>
</tr>
<tr>
<td>G</td>
<td>32</td>
<td>Female</td>
<td>PA+ASD+MAPCA</td>
</tr>
</tbody>
</table>

Abbreviations PA; pulmonary atresia, PS; pulmonary artery stenosis, VSD; ventricular septal defect, TAPVC; total anomalous pulmonary 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

Table 1B. Baseline characteristics

<table>
<thead>
<tr>
<th>Stenosis</th>
<th>Segmental PAH (%)</th>
<th>PAH</th>
<th>SaO2 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>APD 40</td>
<td>90 / 5</td>
<td>16 / 2</td>
</tr>
<tr>
<td>B</td>
<td>MAPCA inf 20</td>
<td>95 / 12</td>
<td>40 / 28</td>
</tr>
<tr>
<td>C</td>
<td>APS 40</td>
<td>129 / 53</td>
<td>50 / 40</td>
</tr>
<tr>
<td>D</td>
<td>APD 60</td>
<td>65 / 40</td>
<td>30 / 20</td>
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<tr>
<td>E</td>
<td>APS 33</td>
<td>65 / 40</td>
<td>*</td>
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<tr>
<td>F</td>
<td>APD+APS 20</td>
<td>80 / 40</td>
<td>40 / 20</td>
</tr>
<tr>
<td>G</td>
<td>APS 105 / 15</td>
<td>56 / 18</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations APD; right pulmonary artery, APS; left pulmonary artery, n/a; not available, PAH; pulmonary arterial hypertension
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 (Figure 2A). Higher baseline exercise heart rate was significantly associated with fewer increase in 6MWD (r = -0.91 P = 0.01), see Figure 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 (β = -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 CHD patients with segmental PAH. Most improvement in exercise capacity was seen in patients with low baseline 6MWD. Higher baseline exercise heart rate was significantly associated with lesser improvement in 6MWD.
Figure 1. Anatomy of segmental PAH patients (available in 6 of the 7 cases)
A: Left Magnetic resonance imaging APD Stenosis, Right Schematic drawing
B: Left Magnetic resonance angiography inferior MAPCA stenosis, Right Schematic drawing
C: Computer tomography stenosis APS
Figure 1. Anatomy of segmental PAH patients (available in 6 of the 7 cases)
D: Left Cardiac catheterisation distal APD stenosis, Right hypertensive APS
E: Magnetic Resonance Imaging APD stenosis
F: Magnetic Resonance Imaging APD stenosis
4.1 Treatment effect of bosentan

For patients with “homogeneous” CHD due to simple underlying lesions, the BREATHE-5 study described a beneficial effect of bosentan therapy in patients with Eisenmenger syndrome. At baseline all patients were in functional class III. The 6MWD resulted in a significant treatment effect of 53 meters. Functional class, albeit seeming subjective, was a common indicator of treatment effect. Changes in exercise heart rate during 6MWD tests was usually not an indicator of treatment effect in patients with homogeneous PAH. Van Loon et al described the long-term effect of bosentan treatment in 20 adults and 10 children with pulmonary arterial hypertension and their heart rate did not change from baseline through last follow-up. In addition, mean maximum heart rate during the 6MWD did not change significantly during follow-up compared to baseline in 64 adult patients with PAH associated with CHD. Our findings of unchanged oxygen saturation were in agreement with the results of the BREATHE-5 study. Bosentan therapy in patients with Eisenmenger syndrome did not compromise the peripheral oxygen saturation.

Quality of life should be assessed in the future as an outcome parameter of treatment effect in patients with segmental PAH. Patient focused assessments in clinical PAH studies are important due to possible discrepancies between clinical performance and objective exercise capacity of patients. PAH patients are likely to adapt to decreased needs. In patients with CHD, PAH has been shown a major contributor to reduced functional capacity even among patients with previous defect closure and patients who had not developed Eisenmenger’s physiology.

Table 2. Effects of bosentan in complex CHD patients with segmental PAH

<table>
<thead>
<tr>
<th>FU (mo)</th>
<th>6MWD (m)</th>
<th>BL</th>
<th>Bosentan</th>
<th>Functional class</th>
<th>BL</th>
<th>Bosentan</th>
<th>BL</th>
<th>Bosentan</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>12</td>
<td>594</td>
<td>682</td>
<td>II</td>
<td>I</td>
<td>462</td>
<td>250</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>12</td>
<td>497</td>
<td>530</td>
<td>II</td>
<td>II</td>
<td>419</td>
<td>610</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>12</td>
<td>358</td>
<td>399</td>
<td>II</td>
<td>I</td>
<td>1454</td>
<td>1443</td>
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<tr>
<td>D</td>
<td>6</td>
<td>288</td>
<td>328</td>
<td>III</td>
<td>II</td>
<td>n/a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>12</td>
<td>230</td>
<td>380</td>
<td>III</td>
<td>II</td>
<td>n/a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>12</td>
<td>n/a</td>
<td></td>
<td>II</td>
<td>II</td>
<td>n/a</td>
<td></td>
<td></td>
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<tr>
<td>G</td>
<td>9</td>
<td>348</td>
<td>370</td>
<td>III</td>
<td>II</td>
<td>n/a</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations FU; follow up, 6MWD; six minute walking distance, BL; baseline Mo; months, m; meters, n/a; not available
Figure 2A. Exercise capacity in complex CHD patients with segmental PAH on bosentan treatment
Figure 2B. Heart rate and improvement of exercise capacity
4.2 Mechanisms
The mechanism of bosentan is a competitive dual inhibition of the endothelin-1 receptor. Endothelin-1 is a potent vasoconstrictor, which also mediates cell proliferation, fibrosis and inflammation. The plasma level of endothelin-1 in patients with PAH appeared to be elevated, inducing histopathological changes in the pulmonary vascular bed.17 This endothelin-1 elevation has been shown for patients with PAH having a broad spectrum of underlying diagnoses.18 Endothelin-1 levels in patients with segmental PAH have never been studied. It is assumable that patients with segmental PAH have, despite parts with low pulmonary pressures, elevated endothelin-1 levels accounting for the treatment effect of bosentan.

4.3 Clinical impact
Determining the etiology of PAH is essential to appropriate management.19 The retrospective case observations here suggest efficacy of bosentan treatment in adults with segmental PAH. Left untreated, patients with homogeneous PAH typically have a progressive decline in function with high morbidity ultimately leading to death.20 Whether patients with segmental PAH have a similar prognosis is unknown. Early evaluation and treatment of segmental PAH patients may improve clinical outcome. Early recognition of disease could lead to prompt initiation of diagnostic evaluation and start of therapy. Starting appropriate treatment regimens early in the disease process is expected to improve quality of life.

4.4 Limitations
The major limitations of the study were the small subject numbers and the heterogeneity of underlying post-operative anatomy; however we note the rarity of this condition and the lack of previously published reports describing this patient population. Though these patients benefited from treatment, the retrospective observations should be interpreted with caution.

5. CONCLUSION
This 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.
REFERENCES


