Pulmonary vascular compliance and the effect of endothelin receptor antagonism

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Background
The Windkessel model of pulmonary circulation has been applied to patients with pulmonary arterial hypertension (PAH) and pulmonary vascular compliance may be an important prognostic factor. The effects of a selective or non-selective endothelin receptor antagonist (ERA) on this model have not been assessed. It may explain the differences reported in outcomes in connective tissue disease associated PAH with selective ERA therapy.

Figure 1. Windkessel circuit diagram

Z – characteristic impedance
C – pulmonary arterial compliance
R – peripheral resistance

Objectives
Assess the effect of the endothelin receptor type A selective agent sitaxentan & the dual receptor antagonist bosentan on pulmonary vascular compliance.

Methods
Retrospective analysis of pre- and post-treatment haemodynamic right heart catheter data of patients with pulmonary arterial hypertension associated with connective tissue disease treated with either sitaxentan or bosentan over a two year period. Calculated values: cardiac index = cardiac output / body surface area, vascular resistance = 80 x (mean PA - wedge pressure) / cardiac output, vascular compliance = stroke volume / PA pulse pressure, R-C time = heart period x (mean PA - wedge pressure) / PA pulse pressure. Calculated difference was given by subtracting the change with sitaxentan from the change with bosentan.

Results & Discussion
Data are presented in the table and graphs shown. Change in haemodynamic parameters was comparable with both therapies (table 1). Overall pulmonary vascular resistance fell (figure 2) and compliance increased (p<0.05 student’s t-test), however the R-C time and hence the relationship between resistance and compliance did not alter significantly.

Table 1. Change in selected haemodynamic parameters with selective and non-selective ERA therapy

<table>
<thead>
<tr>
<th>Change in parameter</th>
<th>Bosentan (n=25)</th>
<th>Sitaxentan (n=19)</th>
<th>Treatment difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Pulmonary Artery Pressure (mmHg)</td>
<td>-3.6 ± 12.1*</td>
<td>-2.9 ± 13.6</td>
<td>-0.7</td>
</tr>
<tr>
<td>Cardiac Index (L/min/m²)</td>
<td>+0.2 ± 1.3</td>
<td>+0.1 ± 1.1</td>
<td>+0.1</td>
</tr>
<tr>
<td>Pulmonary Vascular Resistance (dynes/s/cm⁵)</td>
<td>-116 ± 321*</td>
<td>-86 ± 262</td>
<td>-30</td>
</tr>
<tr>
<td>Pulmonary Vascular Compliance (mL/mmHg)</td>
<td>+0.24 ± 1.0*</td>
<td>+0.17 ± 1.0</td>
<td>+0.07</td>
</tr>
<tr>
<td>R-C time (s)</td>
<td>-0.02 ± 0.4</td>
<td>-0.06 ± 0.3</td>
<td>+0.04</td>
</tr>
</tbody>
</table>

Data quoted with 95% confidence intervals. *p<0.05 paired student’s t-test.

References

Conclusions
Both type A selective and dual endothelin receptor antagonists reduce pulmonary vascular resistance and improve pulmonary vascular compliance. A difference between the effects of bosentan and sitaxentan has not been established with respect to haemodynamic changes.

Conflicts of interest: the Royal Free Hospital pulmonary hypertension service has received educational grants from: Actelion, Glaxo-Smith-Kline, Pfizer & United Therapeutics.