RELATIVE CHANGES IN PULMONARY VASCULAR RESISTANCE FOR ASSESSMENT TREATMENT EFFICACY IN PULMONARY ARTERIAL HYPERTENSION.

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ABSTRACT

Rationale: Absolute changes in pulmonary vascular resistance (PVR) are considered as measure of treatment response of the pulmonary vasculature in pulmonary arterial hypertension (PAH). However, since the relation between PVR and arteriolar diameters is nonlinear, it is questionable whether a similar change in the vasculature reflects the same response for high and low baseline PVR.

Objectives: We studied the relation between baseline PVR and PVR response (ΔPVR).

Methods: We investigated reported hemodynamic data of clinical trials with PAH-specific therapy at 3 months and one year follow-up. In addition, we analyzed 80 individual PAH patients treated with PAH-specific therapy with one year follow-up.

Measurements and Main Results: The ΔPVR is larger when PVR at baseline is high (above median), both after 3 months and one year. The response of PVR in the individual PAH patients confirmed the findings of the clinical trials, i.e. larger ΔPVR for high baseline PVR. To quantify the relation between baseline PVR and ΔPVR we analyzed published clinical trials of epoprostenol, and our own patients. We found proportional relationships between baseline PVR and ΔPVR in clinical trials and in individual patient group implying that for epoprostenol the average treatment response can be given as one number, namely ΔPVR/baseline PVR.

Conclusions: We found that a high baseline PVR predicts a larger PVR decrease irrespective of treatment. Given the proportional relationship between change in PVR and baseline PVR, we propose that relative changes rather than absolute changes in PVR should be used to compare treatment effects.
INTRODUCTION

Pulmonary arterial hypertension (PAH) results from excessive remodeling and vasoconstriction of predominantly small pulmonary arteries (i.e., resistance arteries) leading to an increase in pulmonary vascular resistance (PVR).\(^1\)

The aim of current PAH-specific therapy is to lower PVR by targeting the three major pathways involved in the development and progression of PAH.\(^2\) In many PAH studies, an absolute decrease in PVR is considered as a valuable secondary hemodynamic endpoint.\(^3\) Assuming that current PAH-specific therapies cause changes in luminal cross-section of pulmonary resistance vessels, Poiseuille’s law predicts a nonlinear relationship between PVR and arterial dimensions such that a similar change in diameter will cause a larger decrease in PVR when vessels are small (i.e. a higher PVR). In other words, the PVR response will be larger in patients with a high PVR at baseline.

To test the hypothesis whether a high baseline PVR predicts a more pronounced decrease in PVR, regardless of type of PAH-specific treatment, we re-examined the hemodynamic data reported in published clinical studies. To explore whether similar observations can be extrapolated to individual patients, we studied hemodynamic data from PAH patients from our own center. We propose, based on the presented results, to evaluate treatment responses of the pulmonary vasculature to PAH-specific therapy on the basis of relative changes in PVR, i.e. \(\Delta\text{PVR}/\text{baseline PVR}\), rather than absolute changes in PVR.

METHODS

This study consists of two parts.

First, we investigated the PVR response in relation to baseline PVR using reported hemodynamic data on PAH-specific therapy (e.g. prostacycline derivates, endothelin-receptor antagonists and phosphodiesterase-5 inhibitors) in clinical randomized controlled trials (RCT) in PAH. The hemodynamic data were assessed from the tables and/or text of each individual RCT, as summarized in the meta-analysis of Galie et al.\(^8\) These studies had an average follow up of 3 months and comprise the short-term group. Only studies reporting PVR were analyzed (Table 1).\(^5\)\(^\text{-}^9\)\(^19\) RCT’s with non-approved PAH-drugs (i.e. Beraprost\(^10\)\(^20\) and Terbogre\(^21\)), and the RCT on Eisenmenger syndrome patients\(^22\) were excluded. To see whether the results remain the same in the longer-term, we also investigated clinical studies, as summarized by Gomberg-Maitland et al.\(^23\) with an average follow up of 1 year (long-term group). Again, only studies reporting PVR were included (Table 2).\(^24\)\(^30\)

All studies were separated into two groups: high and low PVR, stratified by the median PVR at baseline (i.e. PVR of 1028 dynes·s·mmHg\(^{-1}\) for the short-term studies and 1272 dynes·s·mmHg\(^{-1}\) for long-term studies).
In the second part of our study we investigated whether the results from the clinical PAH studies can be extrapolated to individual PAH patients. Therefore, we retrospectively studied 80 consecutive patients diagnosed with IPAH in our center according to current guidelines from June 2000 till June 2011. The hemodynamic response of PAH-specific treatment (e.g. epoprostenol, treprostinil, sildenafil, bosentan and sitaxentan) was studied during a follow up of approximately 1 year. Again, we stratified the patients by the median PVR.

Since different treatments were used in the studies we paid special attention to the effects of epoprostenol on PVR in different studies. The reason for choosing epoprostenol is that this drug has been investigated in several studies, and particularly because PVR measured at baseline varies considerably between the different studies, making it possible to investigate the relation between PVR response and baseline PVR. Four studies with epoprostenol were used in the short-term and- long-term group and 19 PAH patients who were treated with epoprostenol with one year follow up.

Statistical analyses
All data are expressed as mean ±SD

Baseline and follow up values between low and high PVR of the Short-term and Long-term group, were compared using Wilcoxon matched pairs test, and for our cohort of patients paired Student's t-test was utilized. For comparisons between low and high PVR of the Short-term and Long-term group we used Mann Whitney test and for our own cohort unpaired Student's t-test was applied. To test for the statistical difference between the relationships of PVR base and PVR change in Fig 2a en b vs. c the slopes of the linear regression analysis were compared.

A p < 0.05 was considered statistically significant.

RESULTS
Table 1 shows the 12 RCT's of the ‘Short-term group’, encompassing 1928 patients. The majority of patients in these studies had IPAH and a minority associated PAH. The PAH-specific drugs tested were epoprostenol (n=3), epoprostenol combined with bosentan (n=1), inhaled iloprost (n=2), treprostinil (n=1), bosentan (n=2), sitaxsentan (n=1), sildenafil (n=2) and sildenafil combined with epoprostenol (n=1). The average study period was 13.3 ± weeks (range 8-24 weeks).

Table 2 shows the 7 clinical studies of the ‘Long-term group’, encompassing 363 patients. The majority of patients in these studies had PAH and a minority associated PAH. The PAH-specific drug tested were epoprostenol (n=4), bosentan (n=1) and ambrisentan (n=1). The average study period was 1.2 years (range 1-2 years).

Figure 1A shows that 3 months of treatment with PAH-specific therapy causes a two times larger decrease in PVR in the high baseline-PVR group (> 1028 dynes·s·mmHg⁻¹) than in the low baseline-PVR group (< 1028 dynes·s·mmHg⁻¹).
Table 1. RCT's with PAH-specific therapy as summarized by Galie et al.8 Randomized clinical trials of PAH-specific therapy with average follow up of 3 months.

<table>
<thead>
<tr>
<th>1st Author</th>
<th>Year</th>
<th>N</th>
<th>Active drug</th>
<th>Comparator</th>
<th>Study period (wks)</th>
<th>Etiology (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Badesch et al.9</td>
<td>2000</td>
<td>111</td>
<td>epoprostenol</td>
<td>randomized controls</td>
<td>12</td>
<td>APAH (100)</td>
</tr>
<tr>
<td>Barst et al.10</td>
<td>1996</td>
<td>81</td>
<td>epoprostenol</td>
<td>randomized controls</td>
<td>12</td>
<td>IPAH (100)</td>
</tr>
<tr>
<td>Rubin et al.17</td>
<td>1990</td>
<td>23</td>
<td>epoprostenol</td>
<td>randomized controls</td>
<td>8</td>
<td>IPAH (100)</td>
</tr>
<tr>
<td>Humbert et al.14</td>
<td>2004</td>
<td>33</td>
<td>epopr + bosentan</td>
<td>epopr + placebo</td>
<td>16</td>
<td>IPAH (82), APAH (18)</td>
</tr>
<tr>
<td>Simmoneau et al.18</td>
<td>2002</td>
<td>470</td>
<td>treprostinil</td>
<td>placebo</td>
<td>12</td>
<td>IPAH (58), APAH (42)</td>
</tr>
<tr>
<td>McLaughlin et al.15</td>
<td>2006</td>
<td>67</td>
<td>inhaled iloprost</td>
<td>placebo</td>
<td>12</td>
<td>IPAH (55), APAH (45)</td>
</tr>
<tr>
<td>Olscheweski et al.16</td>
<td>2002</td>
<td>203</td>
<td>inhaled iloprost</td>
<td>placebo</td>
<td>12</td>
<td>IPAH (50), APAH (22), CTEPH (28)</td>
</tr>
<tr>
<td>Galie et al.5</td>
<td>2008</td>
<td>185</td>
<td>bosentan</td>
<td>placebo</td>
<td>24</td>
<td>IPAH (64), APAH (32), Other (4)</td>
</tr>
<tr>
<td>Channick et al.12</td>
<td>2001</td>
<td>32</td>
<td>bosentan</td>
<td>placebo</td>
<td>12</td>
<td>IPAH (84), APAH (16)</td>
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<tr>
<td>Barst et al.11</td>
<td>2004</td>
<td>178</td>
<td>sitaxsentan</td>
<td>placebo</td>
<td>12</td>
<td>IPAH (53), APAH (47)</td>
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<tr>
<td>Simmoneau et al.19</td>
<td>2008</td>
<td>267</td>
<td>sildenafil+ epopr</td>
<td>placebo + epopr</td>
<td>16</td>
<td>IPAH (79), APAH (21)</td>
</tr>
<tr>
<td>Galie et al.13</td>
<td>2005</td>
<td>278</td>
<td>sildenafil</td>
<td>placebo</td>
<td>12</td>
<td>IPAH (64), APAH (30), Other (6)</td>
</tr>
</tbody>
</table>

APAH = associated pulmonary arterial hypertension, IPAH= idiopathic pulmonary arterial hypertension

Table 2. Long-term clinical trials with PAH-specific therapy with average follow up of 1 year. All non-RCT's with a follow up of 1 year as summarized by Gomberg-Maitland et al.23

<table>
<thead>
<tr>
<th>1st Author</th>
<th>Year</th>
<th>N</th>
<th>Active drug</th>
<th>Study period (wks)</th>
<th>Etiology (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blalock et al.25</td>
<td>2010</td>
<td>11</td>
<td>ambrisentan</td>
<td>2</td>
<td>IPAH(99), APAH (1)</td>
</tr>
<tr>
<td>Sitbon et al.30</td>
<td>2003</td>
<td>11</td>
<td>bosentan</td>
<td>1.2</td>
<td>IPAH(81), PH sclerodermia (19)</td>
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<tr>
<td>Provencher et al.28</td>
<td>2006</td>
<td>48</td>
<td>bosentan</td>
<td>1</td>
<td>IPAH (100)</td>
</tr>
<tr>
<td>Kuhn et al.26</td>
<td>2003</td>
<td>57</td>
<td>epoprostenol</td>
<td>1</td>
<td>IPAH(54), APAH(21), other(25)</td>
</tr>
<tr>
<td>McLaughlin et al.27</td>
<td>2002</td>
<td>115</td>
<td>epoprostenol</td>
<td>1.4</td>
<td>IPAH(100)</td>
</tr>
<tr>
<td>Barst et al.24</td>
<td>1994</td>
<td>14</td>
<td>epoprostenol</td>
<td>1</td>
<td>IPAH(100)</td>
</tr>
<tr>
<td>Sitbon et al.29</td>
<td>2002</td>
<td>107</td>
<td>epoprostenol</td>
<td>1</td>
<td>IPAH(100)</td>
</tr>
</tbody>
</table>

APAH = associated pulmonary arterial hypertension, IPAH= idiopathic pulmonary arterial hypertension
The difference in response is significant (p=0.002). Figure 1B shows that at one year follow-up the decrease in PVR is even more than two times larger in the high baseline-PVR group (> 1272 dynes·s·mmHg⁻¹) as compared to the low baseline-PVR group (< 1272 dynes·s·mmHg⁻¹). The difference in response is significant (p=0.03). Limitations of comparing different studies is the limited number of studies and treatment differences between the studies. For this reason, differences in treatments might underlie our findings. Therefore, we also evaluated individual patients on a variety of treatments and observed the same as in the studies (fig 1C). Figure 1C shows that in our own IPAH patients the decrease in PVR is much larger in the high baseline PVR group (p=0.0009) than in the low PVR group (p=NS) and that the difference between the groups is significant.

Figure 1. Absolute changes in PVR after 3 months (A) and one year (B) of PAH-specific therapy, stratified according to a median baseline PVR of 1028 dynes. The effect of PAH-specific therapy on absolute PVR change in individual IPAH patients (n=80) after one year follow up, also stratified according to the same median baseline PVR (C). * p<0.05, ** p<0.01, # p=NS
In Fig. 2 the effect of epoprostenol of the RCT’s on the relation between PVR change and baseline PVR is depicted, at 3 months follow up (A) and after one year follow up (B). The relative change in PVR, i.e. ΔPVR/baseline PVR, is 0.35. Also shown is (C) the effect of epoprostenol on the PVR change in relation to PVR at baseline in individual IPAH patients, where the relative change is 0.54. The relationship shows larger changes in PVR in patients with a higher baseline PVR (A, B and C). The differences between the slopes of the studies (2a en 2b) vs. own patients (2c) were statistically not different (p=0.7).

**Figure 2.** PVR response to epoprostenol after 3 months (A) and year of follow up (B). Each point reflects the average value from the studies. And the PVR response to epoprostenol in individual patients with IPAH (n=19)(C). The slopes between fig 2a en b vs. c are statistically not different.

**DISCUSSION**

The present study consistently demonstrates that the effect of current approved PAH-specific therapy on the change in PVR is strongly related to baseline PVR both in patient groups (clinical trial data) and individual patients. In other words, the decrease in PVR is larger in patients with higher PVR at baseline, irrespective of choice of therapy. In addition, we showed that for a single drug, both from clinical trial data and individual patients, changes in PVR are linearly proportional to baseline PVR, and all with similar ratio ΔPVR/baseline PVR of about 0.35. This finding implies that in order to compare drug effects the relative change in PVR, i.e. ΔPVR/baseline PVR, rather than absolute changes in PVR should be considered.
Pulmonary vascular effect

PAH-specific treatment decreases PVR by targeting established pathways (i.e. prostacyclin, endothelin and nitric oxide pathway) leading to an increase in the luminal cross-section by counteracting vasoconstriction and, possibly, by reversing vascular remodeling. In present clinical practice, the absolute change in PVR is considered to reflect a treatment response, regardless of the PVR at baseline. Different treatments have been compared on the basis of the differences in absolute PVR responses, irrespective of baseline values. However, Poiseuille’s law (resistance is proportional to 1/radius^4) states that a similar absolute change in luminal cross-section has a larger effect on resistance in small vessels than in vessels with a larger radius. Indeed, based on all published clinical trials, our study confirms that short-term and long-term changes in PVR are larger when baseline PVR is high. The clinical trial data with a short and long term follow up showed a similar pattern as found in individual patients proving that this is a consistent finding, sustained over time, and holding at a patient level.

We have only evaluated epoprostenol treatment because the studies that report on this drug have a sufficiently large variation in baseline PVR. Studies on other PAH-specific drugs (ERA’s and PDE-5 inhibitors and other prostacycline derivates) were less suitable for assessing the single relative change since these studies have a quite similar average baseline PVR. In the trials evaluating epoprostenol we found a proportional relation between baseline PVR and ΔPVR. The individual patients showed a similar trend between ΔPVR and baseline PVR. However, the relationships differed quantitatively: 0.35 for the clinical trials and 0.53 for individual patients, although this difference was not significant. The advantage of using the relative instead of the absolute PVR change is that individual patient response can be compared in terms of a single number.

Our study has several important clinical implications.

First, baseline PVR predicts treatment outcomes in terms of PVR. Thus using PVR as an inclusion criterion in clinical studies has a consequence for the expected changes in PVR. This is illustrated by a recent study by Ghofrani et al. who showed, in a post-hoc analysis, that after separating the patients in groups based on median baseline PVR, significant improvements in PVR were found in the high baseline PVR group and not in the low PVR group. While the results in that paper are in line with the outcomes of our study, these results do not support the notion that imatinib is only effective in high PVR patients due to its antiproliferative effect.

Second, comparison between differences in treatment responses should be made on the basis of relative changes rather than absolute changes. Our results provide a strong rationale for this approach, since relative changes in hemodynamic response make it possible to distinguish treatment efficacy of different PAH-specific drugs of different studies.
The mechanisms which we propose to explain our results may be valid on a general physiological level but may be an oversimplification of the events which occur with treatment at the microscopic level. PAH is a disease of vasoconstriction and vascular remodeling and all studied drugs are primarily vasodilators, with some antiproliferative effects shown in-vitro and in animal models.\textsuperscript{33-35} It would be interesting to know where exactly in the PAH vasculature these drugs exert their effects. However, this study did not aim to find the mechanisms of vascular changes in pulmonary arterial hypertension by PAH-specific treatment. Nor even did the present study distinguish treatment effect on hemodynamics between cardiac and pulmonary vasculature.

In conclusion, in PAH patients treated with PAH-specific therapy, a high baseline PVR predicts a large effect on PVR. For this reason, comparisons of treatment responses should not be made in absolute terms but should be carried out relative to baseline PVR. Therefore, this paper necessitates the need for international convention about standardization of evaluation of the effect cq. response of PAH-specific drugs.

**REFERENCE LIST**


