Prostaglandin E₁ Testing in Heart Failure–associated Pulmonary Hypertension Enables Transplantation: The PROPHET Study

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Background: Elevated pulmonary vascular resistance (PVR) is relevant to prognosis of congestive heart failure and heart transplantation. Proof of reversibility by pharmacologic testing in potential transplantation candidates is important because it indicates a reduced probability of right ventricular failure or death in the early post-transplant period. This study aimed to clarify the possible extent of acute reversibility of elevated PVR in a large, consecutive cohort of heart transplant candidates.

Methods: This study included 208 consecutive patients (age 52 ± 10 years, 89% men and 11% women, ejection fraction 21 ± 9%, VO₂ max 12.6 ± 4.2 ml/kg/min) being evaluated for heart transplantation in 7 transplant centers in Germany and Switzerland. Testing was performed with increasing intravenous doses of prostaglandin E₁ (PGE₁; average maximum dose 173 ± 115 ng/kg/min for at least 10 minutes) in 92 patients exhibiting a baseline PVR of ≥2.5 Wood units (WU) and/or a transpulmonary gradient (TPG) of ≥12 mm Hg.

Results: PGE₁ testing lowered PVR from 4.1 ± 2.0 to 2.1 ± 1.1 WU (p < 0.01), increased cardiac output from 3.8 ± 1.0 to 5.0 ± 1.5 liters/min (p < 0.01), and decreased TPG from 14 ± 4 to 10 ± 3 mm Hg (p < 0.01), mean pulmonary artery pressure (PAM) from 39 ± 9 to 29 ± 9 mm Hg (p < 0.01) and mean pulmonary capillary wedge pressure (PCWP) from 24 ± 7 to 19 ± 9 mm Hg (p < 0.01). Mean aortic pressure (MAP) decreased to 85% and systemic vascular resistance (SVR) to 65% of baseline values (p < 0.01). Symptomatic systemic hypotension was not observed. For the whole population the percentage of patients with PVR ≥2.5 WU was reduced from 44.2% to 10.5% with PGE₁. PVR decreased in each patient; only 2 patients (1%) remained ineligible for listing because of a final PVR of >4.0 WU. TPG, ejection fraction and male gender were independent predictors of reversibility of PVR.

Conclusions: Elevated PVR in heart transplant candidates is highly reversible and can be normalized during acute pharmacologic testing with PGE₁. J Heart Lung Transplant 2006;25:1070–6. Copyright © 2006 by the International Society for Heart and Lung Transplantation.

Heart transplantation is the treatment of choice for end-stage heart failure in some patients. Passive pulmonary hypertension in heart failure may induce an additional pulmonary arteriolar vasoconstriction, leading to a secondary, reactive pre-capillary component of pulmonary hypertension. This vasoconstriction may be caused by hypoxia, catecholamines, an imbalance of vasoconstriction (e.g., endothelin, angiotensin II) and vasodilating mediators (e.g., prostacyclin and nitric oxide), or changes in calcium or potassium channels of vascular smooth muscle cells.1–6

Pulmonary vascular resistance (PVR) in heart transplant candidates is generally significantly elevated to, on average, 2.7 to 3.1 Wood units.7–9 An elevated PVR imposes a substantially increased afterload on the donor right ventricle, potentially leading to right heart failure, which is one of the main causes of death in the early post-transplant period.7,10 A severe, fixed elevation of...
PVR is a contraindication to listing for heart transplantation. Several retrospective studies reported a 2.5- to 3-fold increase in post-transplant mortality for populations with elevated values for pre-transplant PVR or transpulmonary gradient (TPG). Pharmacologic reversibility of high pulmonary vascular resistance and elevated transpulmonary gradient during pre-operative testing has been associated with lower peri-operative mortality, indicating a prognostic benefit if PVR could be manipulated in a favorable direction. Inotropic agents, such as dobutamine or enoximone, and vasodilating agents, such as nitroglycerin, nitroprusside, adenosine, sitaxsentan (an endothelin receptor blocker), prostaglandin I2, prostaglandin E1 and inhaled nitric oxide, have been evaluated in studies with small numbers of patients. At present, there is no clear consensus on the best agent available, but nitric oxide and prostaglandin E1 appear to be the most promising.

Because there is a lack of a guideline-recommended, standardized protocol for pre-transplant reversibility testing of elevated PVR, and a lack of any prospective study evaluating the effectiveness of a potent vasodilator for reversibility of PVR in a large group of heart transplant candidates, the Working Group on Thoracic Organ Transplantation of the German Society of Cardiology designed and performed the PROPHET study.

This study addressed the reversibility of an elevated PVR in a large, homogeneous group of patients with severe left ventricular dysfunction–induced pulmonary hypertension in a short-term hemodynamic study with PGE1, and the safety of this short-term testing.

**METHODS**

**Population**

The study included 208 consecutive heart failure patients undergoing evaluation for potential listing for heart transplantation (Table 1). Patients dependent on intravenous inotropic support were excluded. The study was approved by the ethics committee of each participating study center. Written informed consent was given by each patient.

**Right Heart Catheterization and Testing With PGE1**

All 208 patients underwent right heart catheterization while under continuation of their pre-existing oral therapy (Table 1), which was not changed before and not withheld on the morning of the investigation. A Swan–Ganz thermodilution catheter was positioned in the pulmonary circulation via an 8F cannula in the femoral or internal jugular vein. A 4F cannula in the femoral artery was used for continuous measurement of the systemic artery pressure. Cardiac output (CO) was measured in triplicate by the thermodilution technique. Mean right atrial pressure (RAM), mean pulmonary artery pressure (PAM) and mean pulmonary capillary wedge pressure (PCWP) were measured. The transpulmonary gradient (TPG) was obtained by subtracting the mean PCWP from PAM, and the PVR (in Wood units) was calculated using the standard formula of TPG divided by CO. The baseline data were measured in duplicate, and averaged. Ninety-two of 208 patients exhibited a PVR or TPG above the pre-specified cut-off values (PVR >2.5 WU, TPG >12 mm Hg) and were tested with prostaglandin E1. Prostaglandin E1 infusion was started at a dose of 50 ng/kg/min via 8F vein cannula. Stepwise increasing doses of PGE1 were given over at least 5 minutes at each level (10 minutes at the maximum dose level) until a decrease in PVR to ≤2.5 WU or a decrease in TPG to ≤12 mm Hg was noted. PGE was stopped prematurely, if an arterial systolic blood pressure of 80 mm Hg was reached. The patient became symptomatically hypotensive earlier, or showed other side effects that did not allow continuation of the drug.

Echocardiographic examination and assessment of maximum oxygen consumption (VO2max) were performed within a period of 1 month before or after right heart catheterization.

**Statistics**

Statistics were performed by Omnicare Clinical Research (Cologne, Germany). Data are expressed as mean ± standard deviation. Comparison of hemodynamic variables was made using the paired t-test. The influence of hemodynamic, demographic, echocardiographic and laboratory data on reversibility of PVR and TPG was investigated using stepwise multivariate logistic regression. Statistical significance was established at $p < 0.05$.

**RESULTS**

**Baseline Hemodynamics**

The baseline hemodynamics of the entire population ($n = 208$) and the pre-defined patient cohorts without ($n = 116$) and with ($n = 92$) increased PVR >2.5 WU or TPG >12 mm Hg are given in Table 2.

**PGE1 Testing**

In the 92 patients tested with PGE1, PVR decreased from $4.1 \pm 2.0$ to $2.1 \pm 1.1$ WU ($p < 0.01$), and TPG from $14 \pm 4.0$ to $10 \pm 3.0$ mm Hg ($p < 0.01$). CO increased from $3.8 \pm 1.0$ to $5.0 \pm 1.5$ liters/min ($p < 0.01$). PAM decreased from $39 \pm 9$ to $29 \pm 9$ mm Hg ($p < 0.01$), and mean PCWP from $24 \pm 7$ to $19 \pm 9$ mm Hg ($p < 0.01$). MAP and SVR decreased significantly to 85% and 65% of their respective baseline values (Table 3).
Individual Extent of Reversibility

A final PVR $\leq 2.5$ WU was reached in 76% of patients ($n = 70$), and a final TPG $\leq 12$ mm Hg in 80% of patients ($n = 74$). Both a final PVR $\leq 2.5$ WU and a final TPG $\leq 12$ mm Hg was achieved in 70% of patients ($n = 64$). In 87% of patients ($n = 80$) either PVR or TPG decreased to below the level of 2.5 WU or 12 mm Hg, respectively. A final PVR between 2.5 and 4.0 WU was found in 22% of patients ($n = 20$), and a final TPG between 12 and 15 mm Hg in 11% of patients ($n = 10$). A final PVR $> 4$ WU was seen in 2 patients only (2.2%) and a final TPG $> 15$ mm Hg in 8 patients (9%), with only 1 patient fulfilling both criteria.

PGE$_1$ testing reduced the number of patients with a PVR $> 4$ WU from 37 (40% of patients tested or 18% of the whole population) to 2 (2.2% of patients tested or 1% of the whole population), and the number of patients with a TPG $> 15$ mm Hg from 30 to 8. Thus, eligibility for transplant listing, defined as final PVR $\leq 4.0$ WU, amounted to 98% (90 of 92 patients tested) or 99% (206 of 208 patients evaluated), respectively (Figure 1).
Table 2. Baseline Hemodynamic Parameters of entire PROPHET Study Cohort (n = 208)*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All patients (n = 208)</th>
<th>Not tested (n = 116)</th>
<th>Tested (n = 92)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mm Hg)</td>
<td>81 ± 12</td>
<td>80 ± 14</td>
<td>82 ± 11</td>
</tr>
<tr>
<td>Heart rate (min⁻¹)</td>
<td>75 ± 16</td>
<td>72 ± 15</td>
<td>79 ± 15</td>
</tr>
<tr>
<td>RAM (mm Hg)</td>
<td>7 ± 4</td>
<td>6 ± 4</td>
<td>9 ± 5</td>
</tr>
<tr>
<td>PAM (mm Hg)</td>
<td>30 ± 12</td>
<td>23 ± 8</td>
<td>39 ± 9</td>
</tr>
<tr>
<td>PCWPmean (mm Hg)</td>
<td>20 ± 8</td>
<td>17 ± 8</td>
<td>24 ± 7</td>
</tr>
<tr>
<td>TPG (mm Hg)</td>
<td>10 ± 5</td>
<td>7 ± 3</td>
<td>14 ± 4</td>
</tr>
<tr>
<td>CO (liters/min)</td>
<td>4.0 ± 1.0</td>
<td>4.2 ± 1.0</td>
<td>3.8 ± 1.0</td>
</tr>
<tr>
<td>PVR (Wood units)</td>
<td>2.7 ± 1.9</td>
<td>1.6 ± 0.7</td>
<td>4.1 ± 2.0</td>
</tr>
<tr>
<td>SVR (dyne/cm²)</td>
<td>1,551 ± 496</td>
<td>1,476 ± 333</td>
<td>1,651 ± 628</td>
</tr>
</tbody>
</table>

MAP, mean aortic pressure; RAM, mean right atrial pressure; PAM, mean pulmonary artery pressure; PCWPmean, mean pulmonary capillary wedge pressure; TPG, transpulmonary gradient; CO, cardiac output; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance.

*Includes patients tested with prostaglandin E₁ due to elevated PVR.

Table 3. Hemodynamic Data at Baseline and During Intravenous Prostaglandin E₁ Testing

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline (n = 92)</th>
<th>After PGE₁ (n = 92)</th>
<th>% of baseline value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mm Hg)</td>
<td>82 ± 11*</td>
<td>70 ± 12</td>
<td>85%</td>
</tr>
<tr>
<td>Heart rate (min⁻¹)</td>
<td>79 ± 15</td>
<td>81 ± 16</td>
<td>103%</td>
</tr>
<tr>
<td>RAM (mm Hg)</td>
<td>9 ± 5</td>
<td>7 ± 5</td>
<td>78%</td>
</tr>
<tr>
<td>PAM (mm Hg)</td>
<td>39 ± 9</td>
<td>29 ± 9</td>
<td>74%</td>
</tr>
<tr>
<td>PCWPmean (mm Hg)</td>
<td>24 ± 7</td>
<td>19 ± 9</td>
<td>79%</td>
</tr>
<tr>
<td>TPG (mm Hg)</td>
<td>14 ± 4</td>
<td>10 ± 4</td>
<td>71%</td>
</tr>
<tr>
<td>CO (liters/min)</td>
<td>3.8 ± 1.0</td>
<td>5.0 ± 1.5</td>
<td>132%</td>
</tr>
<tr>
<td>PVR (Wood units)</td>
<td>4.1 ± 2.0</td>
<td>2.1 ± 1.1</td>
<td>51%</td>
</tr>
<tr>
<td>SVR (dyne/cm²)</td>
<td>1,651 ± 628</td>
<td>1,079 ± 412</td>
<td>65%</td>
</tr>
</tbody>
</table>

MAP, mean aortic pressure; RAM, mean right atrial pressure; PAM, mean pulmonary artery pressure; PCWPmean, mean pulmonary capillary wedge pressure; TPG, transpulmonary gradient; CO, cardiac output; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance.

*p < 0.01.

Predictors of Reversibility

Stepwise logistic multivariate regression of all parameters listed in Table 1 and Table 2 revealed higher baseline TPG, absence of COPD, male gender and higher left ventricular ejection fraction as predictors for the absolute response to PGE₁.

Side Effects

PGE₁ was well tolerated. Almost all patients had mild flushing. Twenty-three percent of patients had mild nausea. However, no patient suffered side effects requiring premature stoppage of PGE₁ application, such as symptomatic hypotension or emesis.

DISCUSSION

Effectiveness of PVR Reversibility Testing and Implications for Transplant Listing

This multicenter study demonstrates the reversibility of increased PVR with PGE₁ in a large cohort of patients with severe left ventricular dysfunction being evaluated for orthotopic heart transplantation. At baseline, 92 of 208 patients (44%) exhibited a PVR >2.5 WU, and 37 of 208 (18%) a PVR >4.0 WU (a consensus cut-off value for ineligibility for heart transplant listing in Germany). After PGE₁ testing, PVR remained >2.5 WU in only 22 of 208 patients (10.6%), and only 2 of 208 patients (1%) remained ineligible for immediate listing because of persistent PVR >4.0 WU.

More than 90% of patients received angiotensin-converting enzyme (ACE) inhibitors or AT-1 receptor antagonists, 64% received beta-blockers, and 31% were on high-dose loop diuretics. The mean doses of ACE inhibitors and beta-blockers, on average, amounted to only approximately 50% of the maximum dosages recommended by the guidelines. It can be speculated that further optimization of heart failure treatment, especially high-dose ACE-inhibitor and beta-blocker therapy, would have positively influenced the baseline hemodynamics of the pulmonary circulation, thus shifting more patients into the group with initially normal PVR.

The present patient population, however, reflects a typical heart failure cohort seen in transplant centers for initial evaluation and compares favorably with the low adherence to guideline-recommended drug therapy in the EuroHeart Failure survey.

Baseline data reveal that patients with PVR >2.5 WU or TPG >12 mm Hg, when compared with those having levels below this cut-off level, had the following: significantly higher New York Heart Association (NYHA) class; lower ejection fractions and VO₂max; higher bilirubin levels; more often used high-dose diuretics, glycosides, amiodarone and phenprocoumone; less often used beta-blockers; are older; and had a higher percentage of insulin-dependent diabetes. This profile characterizes a more advanced heart failure situation and suggests a less rigorous therapy with beta-blockers despite comparable aortic pressure.
Drugs for Reversibility Testing

Inotropic agents such as dobutamine and enoximone do not decrease the TPG. A true reduction of PVR is therefore questionable according to the opening pressure concept of the pulmonary vasculature in heart failure. Accordingly, these inotropic agents are not useful for testing of reversibility. Inhaled nitric oxide (NO) offers the potential advantage of a complete lack of systemic hypotensive effects. However, it does not reduce or may even increase the pulmonary capillary wedge pressure. This may be dangerous in left ventricular failure because of the risk of pulmonary overflow and edema. In contrast, inhaled NO can be used safely to reduce PVR immediately after transplantation.

The effectiveness of different drugs has been compared in several studies investigating small numbers (n = 7 to 39) of patients. Murali et al tested 39 heart transplant candidates with elevated PVR or TPG with PGE1 (mean dose 50 ng/kg/min). PVR could be reduced from 5.1 to 2.7 Wood units (i.e., 52% of the baseline value), which is identical to our results, although a lower mean dose was used. Nine of 39 patients were also tested with nitroglycerin, 12 of 39 with nitroprusside. PVR was reduced to 86% only of baseline value by nitroglycerin, and to 62% only of baseline value by nitroprusside. Both agents were significantly less effective than PGE1. Compared with nitroglycerin or nitroprusside, the advantage of PGE1 was the more selective pulmonary vasodilation leading to a more pronounced reduction of PVR for a given reduction of SVR or aortic pressure. Inhaled NO was comparably effective as PGI2 and PGE1, and both were more effective than nitroprusside. In a recent study of 19 patients, NO and PGE1 decreased PVR by 47% and 42% (p = 0.87), respectively. There were 4 non-responders to PGE1, who responded to NO, and 4 non-responders to NO, who responded to PGE1.

As PGE1 was documented as one of the most effective PVR-lowering agents, comparison of the effectiveness of different drugs was not addressed in the present study.

Predictors of Reversibility

Male gender and higher ejection fraction predicted a more pronounced PGE1-induced reduction of TPG, as well as a higher baseline TPG. The latter finding is notable because it suggests an association between a more severe baseline hemodynamic situation and its reversibility: the higher the transpulmonary gradient, the higher the effectiveness of PGE1. A correlation between higher baseline PVR and better response to PGI2 was described earlier by our group. This correlation between high baseline PVR and higher relative extent of reversibility was first described by Loh et al using inhaled NO and by Givertz et al using short-term intravenous application of the endothelin-A receptor antagonist sitaxsentan. A potential explanation may be the exhaustion of counterbalancing mediators, such as NO, in high PVR states.

Potential Implications for Heart Failure Therapy

Structural arterial remodeling, present in primary pulmonary hypertension, seems to be uncommon in left heart failure-associated, secondary pulmonary hypertension, as documented by the marked immediate reversibility of pulmonary vasoconstriction in the present study and others, as well as by the almost always complete reversibility of pulmonary hypertension in the first months after heart transplantation or implantation of a mechanical circulatory support device. Heart failure patients with increased PVR may therefore represent a poorly recognized sub-group for potential treatment with specific vasodilators (e.g., endothelin-receptor antagonists, prostaglandins, oral phosphodiesterase inhibitors), which have not been found to be of prognostic relevance in unselected heart failure patients.

Implications for Post-transplant Prognosis

Retrospective studies have documented a correlation between reversibility of an elevated PVR or TPG and improved early post-transplant survival. In a prospective study of a small cohort of transplant patients, the 1-year mortality of those with reversible pulmonary hypertension during PGE1 testing was higher, although not significantly different from that of patients without pulmonary hypertension (22% [4 of 18 patients] vs 14% [3 of 21 patients]).

At present, questions remain with regard to implications of reversibility during PGE1 testing on post-operative mortality. First, after successful PGE1 testing, some patients may be listed and transplanted who would have been ineligible beforehand. This may lead to a higher mortality compared to patients listed with normal baseline PVR or those listed after successful testing with less effective drugs. However, intra-individually these patients most probably would experience a prognostic benefit compared with the natural course of their end-stage heart failure. Furthermore, because early post-transplant mortality in patients with elevated PVR is not only due to right heart failure, elevated PVR may be a marker for a sicker, higher risk population, but is not necessarily the cause of death. Pharmacologic reduction of PVR may therefore reduce right heart failure–related death, but not other causes of death. Available information so far suggests, however, that all-cause mortality in patients with reversible pulmonary hypertension is also reduced. The second phase of the PROPHET study, post-transplant evaluation of mortality, will address these questions.
We conclude that intravenous PGE$_1$ is highly effective and safe for reduction and normalization of elevated pulmonary vascular resistance in heart transplant candidates.

The investigators gratefully acknowledge the willingness of the patients to participate in the study and the cooperation of the technical assistants and nurses.

REFERENCES