Reversible pulmonary hypertension in heart transplant candidates—pretransplant evaluation and outcome after orthotopic heart transplantation

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Abstract

Background: Heart transplantation is the most effective treatment for well-selected patients with endstage heart failure. Unfortunately, transplant candidates with pulmonary hypertension (PHT) are often not considered for heart transplantation. This study was performed to assess the value of prostaglandin E 1 (PG-E 1) for reduction of PHT and to predict the postoperative outcome, compared to patients without PHT. Patients and methods: We studied a group of 151 consecutive heart transplant candidates using right heart catheterization. In patients with PHT (pulmonary vascular resistance, PVR > 2.5 Wood-Units (WU) and/or transpulmonary gradient (TPG) ≥ 12 mmHg) a short-term treatment protocol with PG-E 1 was performed, to achieve PVR < 2.5 WU and TPG < 12 mmHg. Results: 61 patients (40%) had PHT according to our criteria. Reduction of PHT was successful in 71% of patients (n = 43), of these, 18 patients underwent cardiac transplantation and the 1-year mortality rate was 22% (n = 4). The 1-year mortality rate in transplanted patients without PHT was 14% (n = 3). There was no statistical difference in survival between the PHT and the non-PHT group. Outcome in patients without heart transplantation was similar in both groups, except for patients with non-reducible PHT (1-year mortality 50%). Conclusions: Our study demonstrates the efficacy and safety of PG-E 1 in lowering PHT in heart transplant candidates, as well as the need for aggressive evaluation and treatment in these patients. Patients with reversible PHT have comparable post-transplant outcomes and no tendency to higher acute right ventricular failure.

Keywords: Orthotopic heart transplantation; Pulmonary hypertension; Prostaglandin

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1. Introduction

Heart transplantation is the most effective treatment in carefully selected patients with endstage heart failure. Several studies have confirmed that elevated pulmonary vascular resistance (PVR) or transpulmonary gradient (TPG) is a risk factor for mortality in the early and late stages following orthotopic heart transplantation (oHTX). The high risk of right ventricular failure exists because the grafted heart is unable to adapt to significant pulmonary hypertension (PHT) [1–6]. The degree of PHT as an absolute contraindication for orthotopic transplantation is unknown. However, there is a consensus that the risk of death after oHTX is increased if the PVR is greater than 2.5 Wood-Units (WU) and/or the TPG is greater than 12 mmHg [7,8]. In these cases heterotopic transplantation can be performed, but the risk of mortality is elevated [9–11].

Thus, it is extremely important to determine, preoperatively, whether or not PHT can be reversed. Several pharmacologic agents including nitroprusside, nitric oxide, urapidil, milrinone, prostaglandin E 1 (PG-E 1), and I 1 have been used in the assessment of reversibility [1,5,6,12–18]. Some drugs induce severe hypotension because of their vasodilatating action on systemic vascular resistance and large veins, leading to lower filling pressures in the right ventricle. PG-E 1 and prostacyclin...
are more specific drugs, due to inactivation by the pulmonary endothelium [19].

This study was performed to test the hemodynamic effects of PG-E \textsubscript{1} on PVR, to assess outcomes in patients proceeding to oHTX compared to patients without PHT and to compare the 1-year follow-up of patients without heart transplantation, with and without PHT.

2. Patients and methods

One hundred and fifty-one consecutive heart-transplant candidates from our interdisciplinary heart failure and transplant program at Münster University [20] underwent right heart catheterization for hemodynamic evaluation between March 1998 and April 2001. Patients with implanted mechanical assist devices; clinical decompensation or inotropic-support at initial evaluation were excluded from this study. The study protocol was approved by the institution’s investigational review board and all patients gave written informed consent before right heart catheterization and PG-E \textsubscript{1} treatment.

2.1. Right heart catheterization

All patients underwent right heart catheterization with a Swan Ganz catheter (Baxter Healthcare Corp., Irvine, CA) via the right or left internal jugular vein. Cardiac output was measured by thermodilution using rapid bolus injection of 10 cc cold saline. The average of five measurements was used. Systolic (sAP), diastolic (dAP) and mean arterial pressure (mAP) were measured automatically with the non-invasive Dinamap XL (Johnson & Johnson Medical Inc., Arlington, USA).

PVR and TPG were calculated using the following formulas:

\[
\text{PVR (WU)} = \frac{\text{TPG}}{\text{CO}}
\]

\[
\text{PHT was defined as } \text{PVR} \geq 2.5 \text{ WU and/or } \text{TPG} \geq 12 \text{ mmHg according to the Münster Transplant criteria [20].}
\]

2.2. Prostaglandin E\textsubscript{1} treatment

All patients with PHT received a PG-E \textsubscript{1} infusion (Minprog \textsuperscript{®} 500, Pharmacia & Upjohn GmbH, Erlangen, Germany) using an infusion pump (Baxter Healthcare Corp.) and the distal lumen of the Swan Ganz catheter. The infusion started with a dose of 10 ng/kg/min. After 5 min hemodynamic monitoring was repeated. The PG-E \textsubscript{1} infusion was increased every 5 min in six steps as follows: 20, 50, 70, 100, 150, up to the maximum dose of 200 ng/kg/min. Five minutes after each dose up-titration, hemodynamic testing was repeated. After reaching one of the study endpoints the PG-E \textsubscript{1} infusion was stopped and the catheter was removed.

2.3. Study endpoints

The PG-E \textsubscript{1} infusion was stopped if one of the following endpoints was reached: (1) successful decrease of PVR < 2.5 WU and TPG < 12 mmHg, (2) reaching the maximum dose of 200 ng/kg/min, (3) systolic blood pressure < 70 mmHg, (4) heart rate > 130/min, (5) severe side effects like dizziness, nausea, vomiting, severe headache or flash-symptoms. Patients with a successful reduction of PVR < 2.5 WU and TPG < 12 mmHg were called ‘complete-responders’. Patients with PHT in whom reduction of PVR and TPG to normal values was not achieved were called ‘non-responders’.

2.4. Cardiac parameters

In addition to the hemodynamic evaluation, the following cardiac parameters were measured or determined:

Peak VO\textsubscript{2} determined with a cardiac exercise test, left ventricular end-diastolic diameter (LVEDD) and fractional shortening (FS) measured by echocardiography, left ventricular ejection fraction (LVEF) measured by radionuclide ventriculography or by left heart catheterization and the heart failure survival score (HFSS), described by Aaronson et al. [21], as a prognostic score to evaluate 1-year event-free survival.\textsuperscript{1}

2.5. Additional therapy during evaluation

We optimized oral therapy to the maximum dose of angiotensin converting enzyme (ACE) inhibitor. Tailoring of β-adrenergic antagonist, digitalis, diuretics or anticoagulation, in patients at high risk of cardiac embolism, was also attempted. In patients with non-responsive PHT, implantation of a right atrial catheter and administration of prostacyclin as a long-term therapy or treatment with inhaled iloprost was planned. These patients were rescheduled for right heart catheterization in 3 months. Patients with side effects due to PG-E\textsubscript{1} were scheduled for treatment with prostacyclin during the same session or over the following 6 weeks.

3. Statistical analysis

All results are presented as mean values ± standard error. For all pairwise comparisons, the Student’s t-test was employed to assess significance of differences. The test results were considered statistically significant if the

\textsuperscript{1}High risk, 5.80–7.19; medium risk, 7.20–8.09; low risk, 8.10–10.49.
null hypothesis could be rejected with a $P$ value below 0.05. End of follow-up was April 2002.

4. Results

One hundred and fifty-one patients underwent right heart catheterization for hemodynamic monitoring. In 61 patients (40.4%) PVR $\geq$ 2.5 WU and/or TPG $\geq$ 12 mmHg was evident. Treatment with PG-E$_1$ was initiated in all 61 patients. Mean age, gender, etiology, medication and the cardiac parameters LVEDD and FS were comparable in both groups. The peak $V_{O_2}$ (14.8 $\pm$ 4.2 vs. 12.2 $\pm$ 2.9, $P$ = 0.001) and LVEF (23.1 $\pm$ 7.6 vs. 19.3 $\pm$ 6.7, $P$ = 0.02) were significantly lower in the PHT group. In addition, patients with PHT had a medium risk HFSS compared to a low risk for patients in the Non-PHT group. Patient’s characteristics, medication, cardiac parameters and baseline hemodynamics are presented in Table 1.

4.1. Response to prostaglandin $E_1$

Treatment with PG-E$_1$ with reduction of PVR $<$ 2.5 WU and TPG $<$ 12 mmHg was successful in 43 patients (70.5%), with an average dose of 116 $\pm$ 54 ng/kg/min PG-E$_1$ (Complete responders). Six patients (9.8%) received the maximum dose of 200 ng/kg/min PG-E$_1$ without successful reduction of PVR and TPG (Non-responders). In 12 patients (19.6%) side effects forced termination of the treatment (systolic blood pressure $<$ 70 mmHg in 2 patients, nausea in 7 patients and headache in 3 patients) before normal values of PVR and TPG were reached.

No deaths or severe complications occurred during treatment. Only one total atrioventricular block occurred during catheterization and was evident for 15 min. After finishing the PG-E$_1$ infusion all patients returned to baseline hemodynamic parameters within several minutes.
failure therapy was performed. Two patients received a transferred to the waiting list, alternative surgical heart patients high-risk surgical revascularization ("74.1 for cardiac transplantation, 35 patients were transferred 4.2.1. Non-PHT group

4.1.2. Non-responders

In the 6 patients without successful PG-E1 therapy, PVR was decreased from 3.9±1.4 to 2.1±1.1 WU (−46%, \( P<0.05 \)), TPG from 15.2±6.0 to 10.9±4.9 mmHg (−27%, \( P<0.05 \)). There was an increase in cardiac index (CI) from 2.1±0.5 to 2.8±0.7 l/min/m² (−27%, \( P<0.05 \)). Pulmonary capillary wedge pressure (PCWP) was lowered from 22.1±7.4 to 17.4±7.6 mmHg (−23%, \( P<0.05 \)), mean pulmonary artery pressure (mPAP) from 37.1±8.2 to 28.1±9.7 mmHg (−24%, \( P<0.05 \)) and mAP from 84.8±14.0 to 74.1±13.5 mmHg (−12%, \( P<0.05 \)) (Table 1, Figs. 1 and 2).

4.1.1. Complete responders

PVR was decreased from 3.9±1.4 to 2.1±1.1 WU (−46%, \( P<0.05 \)), TPG from 15.2±6.0 to 10.9±4.9 mmHg (−27%, \( P<0.05 \)). There was an increase in cardiac index (CI) from 2.1±0.5 to 2.8±0.7 l/min/m² (−27%, \( P<0.05 \)). Pulmonary capillary wedge pressure (PCWP) was lowered from 22.1±7.4 to 17.4±7.6 mmHg (−23%, \( P<0.05 \)), mean pulmonary artery pressure (mPAP) from 37.1±8.2 to 28.1±9.7 mmHg (−24%, \( P<0.05 \)) and mAP from 84.8±14.0 to 74.1±13.5 mmHg (−12%, \( P<0.05 \)) (Table 1, Figs. 1 and 2).

4.1.2. Non-responders

In the 6 patients without successful PG-E1 therapy, PVR was decreased using the maximum PG-E1 dose from 4.3±0.5 to 2.9±0.7 WU (−33%, \( P<0.05 \)) and TPG from 16.7±3.6 to 16.6±4.3 mmHg (−0.6%, \( P = 0.95 \)). There was an increase in CI from 2.0±0.3 to 3.1±1.1 l/min/m² (55%, \( P = 0.05 \)). PCWP was lowered from 22.5±5.3 to 15.2±4.5 mmHg (−32%, \( P<0.05 \)), mPAP from 39.7±4.2 to 31.8±4.9 mmHg (−20%, \( P<0.05 \)) and mAP from 83.7±21.4 to 71.3±7.8 mmHg (−15%, \( P = 0.25 \)).

4.2. Outcome

4.2.1. Non-PHT group

Of the 90 patients in the Non-PHT group evaluated for cardiac transplantation, 35 patients were transferred to the waiting list (Fig. 3). In 8 patients who were not transferred to the waiting list, alternative surgical heart failure therapy was performed. Two patients received a high-risk mitral valve-reconstruction (MVR) and one patient high-risk surgical revascularization (CABG).

Two patients underwent Batista procedure and in 3 patients implantation of a biventricular pacing system was performed. The mortality in these surgical heart failure therapy patients was 12.5% (\( n = 1 \)). Forty-four patients were too well to be listed or were not receiving maximal heart failure medication and 3 patients were refused admission to the waiting list due to poor compliance. During follow-up 3 patients died and 12 patients were lost to follow-up (Fig. 3).

Of the 35 patients transferred to the waiting list, two died prior to transplantation. Eleven patients deteriorated whilst on the waiting list and received a left ventricular assist device (LVAD). Of these, 7 patients were successfully bridged-to-transplantation, 4 patients died prior to HTX and 8 patients were withdrawn from the waiting list due to improved cardiac function.

Twenty-one patients underwent heart transplantation, including 7 patients with LVAD support; in these patients the 1-year mortality rate was 14% (\( n = 3 \)). The causes of mortality were multi-organ-failure, intracerebral bleeding and acute rejection (Table 2, Fig. 3).

4.2.2. Complete responders

Of the 43 patients with reducible PHT, 22 were transferred to the transplant waiting list (Fig. 4). Six patients who had side effects due to the PG-E1 treatment and 2 patients from the non-reversible PHT group were transferred to the waiting list, following PHT-reduction using prostacyclin. Thirty-one patients were either too well at initial evaluation or had non-reversible PHT; in 5 of these patients Batista procedure, MVR, CABG and biventricular pacing (\( n = 2 \)) was performed. All 5 patients were still alive at the end of follow-up. The remaining 26 patients received tailoring of their oral heart failure medication or were scheduled for a long...

Fig. 1. Mean value, range and standard error at baseline (*) and maximum dose of PG-E1 (**) in patients with PHT. *\( P<0.05 \), —, mean; ■, range (PVR in WU; CI in l/min/m²; TPG, mPAP and PCWP in mmHg).

Fig. 2. Mean value, range and standard error at baseline (*) and maximum dose of PG-E1 (**) in patients with PHT. *\( P<0.05 \), —, mean; ■, range (PVR in WU; CI in l/min/m²; TPG, mPAP and PCWP in mmHg).

Fig. 3. Mean value, range and standard error at baseline (*) and maximum dose of PG-E1 (**) in patients with PHT. *\( P<0.05 \), —, mean; ■, range (PVR in WU; CI in l/min/m²; TPG, mPAP and PCWP in mmHg).
Of these patients, 6 died during follow-up and 5 patients were lost to follow up.

Of the 30 patients on the waiting list, 5 died prior to transplantation, 7 patients were removed from the list due to improved cardiac function and 2 patients received a LVAD as a successful bridge-to-transplantation (Table 2, Fig. 4).

Eighteen patients underwent cardiac transplantation. In all patients with elevated pulmonary pressure, administration of PG-E₁ was performed according to our transplant-protocol. Following right heart catheterization, we administered PG-E₁ in increasing doses prior to transplantation. Nitric oxide inhalation was needed in some patients with post-operative signs of right heart failure to avoid excessively high doses of PG-E₁.

The 1-year post-transplant mortality rate was 22% (n=4). The causes of mortality were acute right ventricular failure, acute rejection, cerebral vascular accident and intracerebral bleeding.

4.2.3. Non-responders

Of the 61 patients with PHT treated with PG-E₁, 6 patients could not be transferred to the waiting list due to non-reduction of PHT according to our orthotopic transplant criteria (TPG<12 mmHg and PVR<2.5 WU). These 6 patients were scheduled for implantation of a right atrial catheter with connection to a long-term prostacyclin pump, however, 2 patients died, 2 and 3 months after the initial evaluation. Of the remaining 4 patients, two had reducible PHT following long-term prostacyclin treatment and increased congestive heart failure medication and were transferred to the transplant waiting list. One patient was withdrawn due to improved cardiac function and 1 patient died prior to transplantation. Three of the 6 patients in whom successful reduction of PHT could not be achieved with PG-E₁ died during follow-up.

5. Discussion

Accurate preoperative assessment of pulmonary hemodynamics to lower the risk of postoperative right ventricular failure is crucial in evaluating the suitability of patients with congestive heart failure for oHTX.

PG-E₁, a naturally occurring substance with an eicosanoid structure is a strong vasodilator drug. It has a half-life of only a few seconds, due to inactivation by 15-hydroxyprostaglandin dehydrogenase and Δ13-reductase in the lung, which acts as a filter and protects, the systemic circulation [19,22]. Previous studies have shown that in patients with congestive heart failure and PHT being assessed for cardiac transplantation, the administration of PG-E₁ significantly decreased PVR and TPG [5,13,15,22–24].

Our data confirm PG-E₁ as a potent acute pulmonary vasodilator in patients with PHT caused by congestive heart failure. PG-E₁ was effective in lowering PVR and TPG with a success rate of 71%. Our data are similar to the study by Murali et al., who showed a successful reduction with PG-E₁ in 31 patients (79%), however, side effects occurred in 8 patients (21%) [5].
There were no statistical differences in age, gender or etiology between patients with PHT or without PHT, but a statistically significant lower peak Vo2 and LVEF (P = 0.001 and 0.02) and a higher risk group in the HFSS (median vs. low risk).

From the 151 patients in this study, 65 patients were transferred to the waiting list and HTX was performed in 39 patients. Heart transplantation was performed in 21 patients without PHT and 18 patients with reversible PHT. Immediately prior to transplantation a hemodynamic measurement was performed, to confirm the previously measured degree of PHT, and PG-E1 was administered pre-operatively.

Sixty percent of the patients from the waiting list in both groups were transplanted. The 1-year mortality in patients with reversible PHT and Non-PHT was similar, as was death on the waiting list, despite the lower HFSS in the PHT group. There was no evidence that pronounced PHT contributed to a higher incidence of deterioration, either prior to transplantation or to early graft failure or right ventricular failure post transplant.

The non-waiting list mortality in the Non-PHT group (7%, n = 4) was similar to that in the reversible PHT group (13%, n = 4) (P = 0.39). Of the 6 patients with non-reversible PHT under PG-E1, none could be transplanted and the overall mortality was 50% (n = 3) (P < 0.05 compared to the Non-PHT and PHT-groups).

Although pre-operative PVR is well recognized as being associated with acute right ventricular failure after orthotopic transplantation, no general agreement has been reached on the level of PHT that most accurately predicts a poor postoperative outcome. Elevated pre-operative PVR and TPG seem to be associated with a significant increase in post-transplantation death [2–6, 24–26]. Kirklin et al. reported that elevated preoperative PVR was the most important risk factor for early
and late post-transplant mortality and the risk of death increased in proportion to PVR \[^{27}\]. Heterotopic transplantation might be a preferable alternative in patients with congestive heart failure and fixed severe PHT, but this procedure involves a complex surgical technique and is associated with a worse outcome \[^{9,11,28}\].

There are different treatments for non-reducible PHT, such as long-term prostacyclin administration using an implantable catheter and an infusion pump, inhaled aerosolized iloprost or the new oral vasodilator therapy with sildenafil or bosentan \[^{29–32}\]. Implantation of a left ventricular assist for unresponsive PHT might be a possibility, but is associated with high risks and costs \[^{33}\].

Therefore, knowledge about whether PHT is reversible in transplant candidates is important. Orthotopic transplantation can be performed using vasodilator drugs perioperatively. Nitric oxide inhalation is often used prophylactically for the management of right ventricular heart failure after heart transplantation \[^{34–37}\]. PG-E\(^1\) is also a potent pharmacologic agent for right ventricular failure after oHTX \[^{38}\]. Long-term results after oHTX in patients with reversible PHT are most promising \[^{4,7,12,25,26,39–41}\] and potentially, transplant candidates with PHT may be better treated with an oversized heart transplanted orthotope, than by heterotopic transplantation \[^{39}\].

### 6. Conclusion

Careful evaluation and selection of candidates for cardiac transplantation is essential. Pharmacologic testing of the reversibility of PHT is important in reducing post-operative morbidity and mortality.

We conclude that baseline hemodynamic measurement is not sufficient for evaluation in heart transplant candidates and suggest that transplant candidates must be transferred to a heart transplant center for evaluation, with an aggressive protocol for lowering PHT. If reduction to normal PVR and TPG is possible, orthotopic transplantation can be performed successfully, without increased risk of acute right ventricular failure.

Patients with reversible PHT, who were not transferred to the waiting list, had a similar outcome to patients without PHT. Patients with non-reducible PHT had the highest mortality, despite adequate therapy.

### References

\[^{[1]}\] Chen JM, Levin HR, Michler RM, et al. Reevaluating the significance of pulmonary hypertension before cardiac trans-

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**Fig. 4. Flow Diagram from the PHT-group (WL, waiting list; LVAD, left ventricular assist device; PC-Pump, prostacyclin-pump).**


