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Preoperative prostaglandin E1 treatment to prevent right ventricular failure after orthotopic heart transplantation

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Abstract. Elevated pulmonary vascular resistance (PVR) and pulmonary hypertension (PH) are high risk factors for early graft failure in orthotopic heart transplantation (oHTx). The need for an oversized donor in patients with elevated PVR aggravates the shortage of suitable donor organs. To decrease the elevated PVR to values suitable for orthotopic heart transplantation prostaglandin E1 (PGE1) was administered in 11 patients (11 male, mean age 49.2 years, mean dosage 35 ng/kg per min over 6–8 days). Ten days after the discontinuation of the PGE1 therapy, recatheterization was done. All haemodynamic data were determined by right heart catheterization using a Swan Ganz catheter and thermodilution technique before, and 10 days after, PGE1 treatment. The Wilcoxon signed ranks test was used for statistics. PVR significantly decreased in all patients (5.5 to 2.8 Wood units, $P < 0.005$). All patients were considered to be suitable for oHTX and put on the waiting list. At the time of writing, in eight of these patients (eight male, mean age 49.6 years; four ischemic, four dilatative CMP) oHTX had been successfully performed. No right ventricular failure occurred in the postoperative phase. These results sugest that long-term moderation of elevated PVR by PGE1 therapy weeks or months before transplantation enables oHTX in patients with elevated PVR.

Key words: Pulmonary hypertension – Pulmonary vascular resistance – Orthotopic heart transplantation – Prostaglandin E1

Orthotopic heart transplantation (oHTx) in end-stage congestive heart disease is complicated by secondary pulmonary hypertension (PH) and consecutive elevated pulmonary vascular resistance (PVR). PH and elevated PVR are outstanding risk factors for early postoperative mortality in oHTX [9]. Patients with an elevated PVR of 4 to 6 Wood units (WU) are not generally accepted for oHTX. However, no clear definition of the borderline between orthotopic and heterotopic heart transplantation concerning elevated pulmonary pressure and PVR has yet been found [12]. Moreover, the reversibility of elevated PVR to values tolerated by the unconditioned transplanted right ventricle complicates the definition of the borderline indication.

In cases of PVR values higher than 4–6 WU the use of an oversized donor heart is indicated [19]. Some centres prefer the heterotopic transplantation [15] technique or perform heart lung transplantation which are at higher risk and have inferior long-term results compared with oHTx. To enable oHTx in patients with high PVR and to avoid the unindicated implantation of oversized donor hearts for borderline indications we used the selective pulmonary vasculature dilatator prostaglandin E1 (PGE1) to induce a long-lasting moderation of elevated PVR.

Materials and methods

Patients, indication for PGE1 therapy, pretreatment right heart catheterization

In 1990 33 patients were evaluated for cardiac transplantation at the University of Graz, Department of Transplantation. Eleven patients presenting a PVR higher than 3 WU or a mean pulmonary artery pressure higher than 30 mm Hg were considered to be at risk for postoperative right ventricular failure and were included in this study (Table 1). All patients were on digitalis, ACE inhibitors and diuretics. This therapy was continued until recatheterization was done.

Catheterization technique

A Baxter Eduard Swan-Ganz 7F thermodilution catheter was introduced through the right internal jugular vein and advanced to the pulmonary artery wedge position using radiographic and haemodynamic guidance. Haemodynamic data were recorded with a Hellige

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Table 1. Demographic data

Patients	Sex	Age	Diagnosis
1	m	45	dilative
2	m	46	ischaemic
3	m	32	dilative
4	m	61	ischaemic
5	m	57	dilative
6	m	33	dilative
7	m	51	ischaemic
8	m	54	dilative
9	m	60	ischaemic
10	m	61	ischaemic
11	m	42	dilative

Table 2. Haemodynamic data before PGE1 treatment

Patient number	PAPs (mm Hg)	PAPd (mm Hg)	PAPm (mm Hg)	CO (l/min)	PVR (WU)
1	83	27	47	4.7	4.2
2	70	42	52	3.5	3.4
3	69	47	37	3.8	3.0
4	65	24	38	3.7	3.2
5	45	23	35	2.0	5.2
6	47	22	33	3.0	4.3
7	79	31	53	5.9	3.1
8	135	50	94	3.6	13.9
9	78	36	56	2.1	9.5
10	71	19	36	3.5	6.3
11	79	32	50	3.9	4.9

PAP, pulmonary artery pressure; s, systolic; d, diastolic; m, mean; CO, cardiac output; PVR, pulmonary vascular resistance; WU, Wood units

Table 3. Haemodynamic data after PGE1 treatment

Patient number	PAPs (mm Hg)	PAPd (mm Hg)	PAPm (mm Hg)	CO (l/min)	PVR (WU)	Outcome
1	98	32	55	4.9	3.1	oHTx
2	63	26	36	5.0	3.0	oHTx[a]
3	50	22	36	4.0	0.5	oHTx
4	58	27	38	4.3	1.8	d.w.w.
5	45	19	29	5.7	1.9	d.w.w.
6	30	15	24	3.0	1.8	oHTx
7	71	27	46	5.9	2.8	oHTx
8	80	39	37	3.9	5.7	d.w.w.
9	73	31	42	4.0	3.8	oHTx[b]
10	52	17	28	5.0	2.5	oHTx
11	78	27	45	3.9	3.6	oHTx[c]

d.w.w., died while waiting for oHTx
[a] died 10 months after oHTx: *Pneumocystis carinii* pneumonia
[b] died 3 months after oHTx: ventricular fibrillation
[c] died on day 20 after oHTx: acute rejection

Table 4. Haemodynamic data ($n = 11$)

	Before PGE1	After PGE1	
PAPsys (mm Hg)	74.6 (45–135)	63.4 (30–98)	$P < 0.05$
PAPdia (mm Hg)	32.3 (19–50)	25.6 (15–39)	$P < 0.05$
PAPm (mm Hg)	48.9 (33–94)	37.8 (24–55)	$P < 0.05$
Wedge (mm Hg)	30.5 (17–44)	27.5 (15–40)	ns
CO (l/min)	3.6 (2–5.9)	4.5 (3–5.7)	$P < 0.05$
PVR (Wood)	5.5 (3–13.9)	2.8 (0.5–5.7)	$P < 0.005$

Servomed. The cardiac output was calculated with a 9520 cardiac output computer of the American Edwards Labaratories. Oxygen and nitroglycerine tests were performed during right heart catheterization.

PGE1 treatment

PGE1 (Minprog, Upjohn) was initiated at a dosage of 5 ng/kg per min. During the first 24 h a stepwise dosage augmentation was performed until a mean dosage of 35 ng/kg per min (25–60 ng) was reached [16]. The PGE1 dosage was maintained continuously for 6–8 days using a motor syringe pump via a central i.v. line. At the expected end of treatment the dosage was tapered during another 24 h. The amount of the dosage increase was dependent on the occurrence of side effects, such as headache, abdominal pain, systemic hypotension, oedema and joint pain. In all patients the dosage increase was performed until side effects appeared. To induce tolerance to high doses of PGE1 intravenous piritamide, diuretics and catecholamines at dosages up to 8 μg/kg per min were administered. After PGE1 therapy all patients were discharged for 10 days.

Recatheterization, statistics

After 10 days all patients were readmitted to our department. In all patients the PGE1 treatment had been discontinued for a minimum of 8 days before recatheterization was done using identical techniques to the investigation before the PGE1 treatment. Statistical evaluation was performed using the Wilcoxon signed ranks tests. Significance was assumed for $P < 0.05$.

Results

The baseline results of right heart catherization are presented in Table 2. The results of the right heart catherization 1 week after the discontinuation of the PGE1 treatment are summarized in Table 3. In all patients the haemodynamic data improved (Tables 3 and 4). The PVR significantly decreased in all 11 patients treated with PGE1. In eight patients the CO increased, in ten patients a reduction in the systolic PAP occurred, and in nine patients the diastolic and the mean PAP decreased. No correlation could be found between the reduction in PVR during right heart catheterization using oxygen or nitroglycerine and the PGE1-induced long-term moderation of PVR.

At the time of writing eight of the PGE1-treated patients had undergone orthotopic heart transplantation according to the techniques described by the Stanford group [13]. The mean interval between PGE1 treatment and oHTx was 2 months (10–152 days). The donor/recipient body weight relationship indicated no use of oversized donors in this patient cohort (Table 5). In the early postoperative period all patients were prophylactically treated with PGE1 starting from the weaning of the cardiopulmonary bypass. No right heart failure or tricuspid valve insufficiency was observed after transplantation. Three patients died due to *Pneumocystis carinii* pneumonia (10 months after oHTx), ventricular fibrillation (3 months after oHTx) and therapy-resistant acute rejection grade 4 (20 days after oHTx).

Table 5. Donor/recipient body-weight ratio

Patient number	PVR before PGE1	PVR after PGE1	Body-weight ratio
1	4.2	3.1	1.0
2	3.4	3.0	1.2
3	3.0	0.5	1.1
4	4.3	1.8	1.0
5	3.1	2.8	1.3
6	9.5	3.8	0.9
7	6.3	2.5	1.2
8	4.9	3.6	1.0

Discussion

Pulmonary vascular resistance of 6–8 WU is generally accepted to be an absolute contraindication for oHTx [8]. In contrast, right ventricular decompensation and failure has also been observed in patients presenting slightly elevated or near normal values [12]. The exposure of the donor heart to the new haemodynamic conditions of the recipient after weaning from bypass leads, in cases of right ventricular afterload mismatch, to a right ventricular overload pattern [3] which results in hypocontractility [14]. To get used to the new right ventricular afterload conditions about 2 weeks of training and adaptation are required. After that time the upper normal range of right and left ventricular filling pressure is reached [3]. The danger of right ventricular failure increases when primary right ventricular dysfunction induced by prolonged ischaemic time [3], preservation damage or body size mismatch complicates the haemodynamic situation [11]. The use of donor hearts which are larger, have reduced ischaemic time and have not undergone any significant trauma while supporting the donor in patients with marginal PVR has been suggested [19]. However, all these factors affecting the function of the transplanted right ventricle contribute to the imprecise limit of PVR beyond which oHTx is contraindicated.

Most centers accept 6 WU as the borderline for oHTx [1, 2]. To overcome these problems prostaglandins are perioperatively used at many centres. PGE1 is a short-acting, potent pulmonary vasodilator which increases myocardial contractility [4], decreases PVR, increases cardiac output [4] and is an immunosuppressive agent [11].

The effect of PGE1 on elevated PVR and PH after mitral valve replacement [5] and after coronary bypass grafting [6] has been reported. The postoperative effect of prostaglandins on acute right ventricular failure after heart transplantation has been proved [17, 20]. Higgenbottam reported successful bridging to heart-lung transplantation with continous prostacycline therapy in patients with fixed primary pulmonary hypertension [10].

We decided on PGE1 because of its short time of action and its 80–90% metabolism at the first lung passage [7]. Because of the application in the upper vena cava the main effects of PGE1 occur in the lesser circuit. Treatment of severe side effects is a simple dosage reduction.

PGE1 decreased PVR in all patients. The pulmonary vasodilating effect of PGE1 results in an improvement in the left ventricular filling pressure. In addition, the increased contractility of the myocardium results in improved cardiac output and in a long-lasting reduction in the right ventricular afterload. Nevertheless, the persistence of the decreased PVR values for weeks after stopping the PGE1 therapy has to be further investigated. The improvement of the left ventricular performance [18] and the sympathomimetic effect of the applied catecholamines might contribute to the long-lasting effect.

Despite seriouly elevated PVR and PAP values before PGE1 treatment, after treatment all patients were suitable for oHTx according to generally accepted criteria. On the one hand we circumvented heterotopic heart transplantation in highly elevated PVR, and on the other hand the waste of oversized donor organs could be avoided as none of the transplanted right ventricles failed.

The use of oxygen or nitroglycerine enables the demonstration of the reversibility of the elevated PVR during right heart catheterization but their effect is not specific to the pulmonary vasculature and it does not result in long-term moderation of the elevated PVR. The influence of the PGE1 treatment on survival time and life quality while on the waiting list cannot be determined yet, but there is a trend towards better working capacity and life expectancy for patients after PGE1 treatment.

In conclusion, we have proved the reversibility of the vasoconstrictive component of the PVR in a model independent of oxygen or nitroglycerine examination. It can be assumed that patients responding to PGE1 therapy while on the waiting list do not develop right ventricular failure under PGE1 therapy after oHTx. There is a long-term moderation of elevated PVR. Patients also presenting with borderline PVR can be accepted for oHTx. We are able to accept donor organs that are not much oversized and might have longer ischaemic times. This increases the probability of obtaining a suitable donor heart and reduces the risk of wasting organs due to right ventricular failure.

References

1. Addonizio LJ, Gersony WM, Robbins RL, Drusin RE, Smith CR, Reison DS, Reemtsma K, Rose EA (1987) Elevated pulmonary vascular resistance and cardiac transplantation. Circulation 76 [Suppl V]: V–52
2. Armitage JM, Hardesty RL, Griffith BP (1987) Prostaglandin E1. An effective treatment of right heart failure after orthotopic heart transplantation. J Heart Transplant 6: 348–351
3. Bathia JSJ, Kirshenbaum JM, Shemin RJ, Cohn LH, Collins JJ, DiSesa VJ, Young PJ, Mudge GH, St. John Sutton M (1987) Time course of resolution of pulmonary hypertension and right ventricular remodeling after orthotopic cardiac transplantation. Circulation 4: 819–826
4. Clayman CB (1975) The prostaglandins. JAMA 8: 904–906
5. D'Ambra MN, LaRaia PJ, Philbin DM, Watkins D, Hilgenberg AD, Buckley MJ (1985) Prostaglandin E1. A new therapy for refractory right heart failure and pulmonary hypertension after mitral valve replacement. J Thorac Cardiovasc Surg 89: 567–572
6. Dewhirst WE (1988) Prostaglandin E1 for refractory right heart failure after coronary artery bypass grafting. J Cardiothorac Anesth 2: 56–59
7. Ferreira (1967) Prostaglandins: their disappearance from and release into circulation. Nature 216: 868

8. Fonger JD, Borkon AM, Baumgartner WA, Achuff SC, Augustine S, Reitz BA (1986) Acute right ventricular failure following heart transplantation: improvement with prostaglandin E1 and right ventricular assist. J Heart Transplant 5: 317–321
9. Heck CF, Shumway SJ, Kaye MP (1989) The Registry of the International Society for Heart Transplantation: sixth Official Report – 1989. J Heart Transplant 4: 271–276
10. Higgenbottam T, Wheeldon D, Wells F, Wallwork J (1984) Long-term treatment of primary pulmonary hypertension with continuous intravenous epoprosterol (Prostacyclin). Lancet II: 1046–1047
11. Iberer F, Wasler A, Tscheliessnigg KH, Metzler H, Rehak P, Kleinert M, Popper H, Auer T, Gombotz H, Petutschnigg B, Rödl S, Giegerl E (1990) Prostaglandin in der Herztransplantation-Prävention des Rechtsherzversagens und der Abstossung. Z Herz, Thorax, Gefäßchir 14: 33–37
12. Kirklin JK, Naftel D, Kirklin JW, Blackstone E, White-Williams C, Bourge R (1988) Pulmonary vascular resistance and the risk of heart transplantation. J Heart Transplant 7: 331–336
13. Lower RR, Shumway NE (1960) Studies on orthotopic heart transplantation of the canine heart. Surg Forum 11: 18–24
14. Pascual JMS, Fiorelli AI, Bellotti GM, Stolf NAG, Jatene AD (1990) Prostacyclin in the management of pulmonary hypertension after heart transplantation. J Heart Transplant 9: 644–651
15. Shumway SJ, Baughman KL, Traill TA, Cameron DE, Fonger JD, Gardner TJ, Achoff SC, Reitz BA, Baumgartner WA (1989) Persistent pulmonary hypertension after heterotopic heart transplantation: a case report. J Heart Transplant 8: 387–390
16. Swan P, Tibballs J, Duncan A (1986) Prostaglandin E1 in primary pulmonary hypertension. Crit Care Med 1: 72–73
17. Tscheliessnigg KH, Iberer F, Zenker G, Kleinert M, Auer T, Gombotz H, Breinl E, Metzler H, Dacar D, Mächler H, Popper H, Lanzer G, Wasler A, Petutschnigg B, Rödl S (1990) Right ventricular failure and tricuspid regurgitation after orthotopic cardiac transplantation. Diagnosis and treatment. Trasplante 1(3): 113–117
18. Virgolini I, Kaliman J, Fitscha P, O'Grady J, Rogatti W, Sinzinger H (1989) Beneficial effect of long-term PGE1 treatment in left ventricular heart failure. Prostaglandins Leukot Essent Fatty Acids 38: 177–180
19. Wahlers TH, Haverich A, Schäfers HJ, Hermann G, Fieguth HG, Borst HG (1987) Risk factors of right heart failure (RHF) after orthotopic heart transplantation (HTX) (abstract). J Am Coll Cardiol 9: 90A
20. Weiss CI, Park JV, Bolman RM (1989) Prostaglandin E1 for treatment of elevated pulmonary vascular resistance in patients undergoing cardiac transplantation. Transplant Proc 21: 2555–2556